Chiba University Global COE Program

Global Center for Education and Research in Immune System Regulation and Treatment

Final Report 2008-2012

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CONTENTS

1. Messages

Final Report of the MEXT's Global COE Program: Global Center for Education and Research in Immune System Regulation and Treatment

Foreword

There is a long history of efforts by doctors and scientists to overcome immunological diseases, and scientists have long been conducting basic research on the regulation of the immune system, which has led to the development of the field of immune therapy. The fact that many diseases are caused by the dysregulation and malfunction of the immune system has been revealed. It has also become apparent that finding the origin of the disease contributes greatly to the treatment of the disease. However, it is necessary to continually develop new strategies and identify new targets in order to establish effective treatments.

In the clinical field, patients' symptoms are utilized to determine the cause of disease. Techniques based on clinicians' experience have established therapeutic intervention and greatly contributed to efforts in conquering disease. However, a successful systematic treatment approach to conquer intractable diseases has yet to be established. New findings based on biological principles which contribute to curing the cause of the disease will be necessary to overcome these intractable diseases.

During the process of drug development, some drugs which work on animals often do not work on humans. This may be because of unknown or yet-to be-defined mechanisms, or the physiological differences between humans and animals, but without a thorough understanding these mechanisms, effective therapies may never be established. We realized the need to develop human and technical resources to challenge this problem and have established a new department on "Advanced Therapeutics" as a G-COE program to train outstanding personnel who can play critical roles in the research for developing a systematic study of treatment. The field of Immunology was chosen as the center of the G-COE program because of the quality of its research staff. As such, we have so far succeeded in fostering young scientists who devote themselves to both translational research and clinical research in the field of Immune System Regulation.

One of the unique features of this program was the "Chiba Visiting Professor Program (CVPP)" which promoted an exchange of ideas and an opportunity for internationally-based scientists to come to Japan and mentor our young researchers. To date, we have invited more than 20 researchers from the United States to give research guidance to G-COE Research Assistants (RA) and Fellows. Our researchers have also been given an opportunity to study in the foreign laboratories affiliated with those same visiting professors. Various English programs, such as "Presentation Seminars," by expert native English speakers were also conducted. The development of new therapeutics involves a great variety of medical fields, thus, this program is jointly implemented by the Graduate School of Medicine and the Graduate School of Pharmaceutical Sciences, Chiba University, the RIKEN Research Center for Allergy and Immunology (RCAI), and the National Institute of Radiological Sciences (NIRS) in order to enhance and accelerate the training of young researchers at Chiba University.

We have supported PhD students in the relevant fields who are selected as G-COE RAs. A total of about 100 students have participated in this program to date, and have greatly contributed to the research activities.

I am happy to report that our G-COE program "Global Center for Education and Research in Immune System Regulation and Treatment" has achieved great research results and successfully established a system to foster young researchers who will take leadership roles in the future. I believe this achievement led to the adoption of our new program and project by the government. The Exploratory Advanced Therapeutics department will continue work to develop new and effective therapies and advanced medical treatments.

Thank you for your continued support and cooperation.

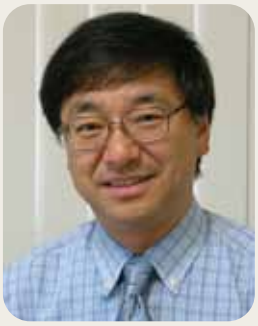
Yasushi Saito

Yasushi Saito, MD, PhD
President, Chiba University

Message from the Program Leader

Chiba University has successfully conducted a Global COE Program called the "Global Center for Education and Research in Immune System Regulation and Treatment" since the 2008 academic year. This program is jointly implemented by the Graduate School of Medicine and the Graduate School of Pharmaceutical Sciences, Chiba University, the Riken Research Center for Allergy and Immunology (RCAI) and the National Institute of Radiological Sciences (NIRS), in order to promote research about the regulation of the immune system and to develop new strategies for the treatment of intractable immune disorders by regulating the immune system. In addition, a major aim of this program is to foster young researchers who are expected to take leadership roles in the fields of therapeutic research in the future. The program is organized and run by the program core members and coordinators. We have implemented various unique programs in order to develop sufficient human resources who will be capable of playing active roles in international settings. These include the G-COE independent young research associates, G-COE postdoctoral fellows, G-COE graduate students, the Annual Best Research Award and the G-COE CVPP (Chiba Visiting Professor Program). In addition to establishing a system for fostering world-class basic and clinical researchers, the establishment of a new department of Exploratory Advanced Therapeutics, and accelerating translational research, clinical trials and drug trials, we are also making efforts to train outstanding personnel and produce leaders who can play critical roles in achieving the goals and objectives of the program.

This final report contains the results of our research activities and efforts for developing human resources that we have so far achieved. We held seven international symposiums, 13 workshops, three summer program jointly organized by RIKEN, and four retreats in the last four and a half years. We sent personnel abroad as many as 13 times for G-COE-related purposes, including both short- and long-term overseas education for graduate students. In addition, we also invited a total of 45 researchers and visiting professors from abroad. Such international exchange activities have led to an increase in the number of high impact research papers published by our young researchers. Another significant result is that an immunotherapy for lung cancer and head and neck cancer that involves activating NKT cells established and approved as an advanced medical technology by the Ministry of Health, Labour and Welfare.



In addition to our original proposal, various new educational approaches have also been introduced to this program, based on both suggestions from graduate students and advice from International Advisory Board Members, including; (1) the BSJM (Basic Science Joint Meeting), research seminars arranged by graduate students on Friday evenings, (2) Special English lectures (Exercises) and scientific presentations in English for graduate students made by expert native English speakers, for which the students obtain credits, (3) the establishment of a course of lectures and seminars entitled "Exploratory Advanced Therapeutics" for the junior year curriculum of medical students, to encourage young physicians to devote themselves to both translational research and clinical research, (4) an Allergy Clinical Conference which comprises joint meetings in the fields of Internal Medicine, Pediatrics, Dermatology and Otorhinolaryngology, with a goal of training young physicians who can conduct both research and treatments for allergy-associated diseases in a comprehensive manner. Therefore, the physicians educated as part of our G-COE program for comprehensive clinical research on Allergy are expected to play a key role at the Chiba University Allergy Center, which was established in October 2012 (Director; Dr. Yoichi Kohno) at Chiba University Hospital.

Another important outcome of this program is the establishment of the "Future Medicine Research Center" (Director; Dr. Toshinori Nakayama) as a center at Chiba University. We are going to develop eight sections with a total of 32 new faculty members. The center aims to develop researchers who are working in the Advanced Therapeutics field. Looking back on the past four and a half years, I think we have achieved major progress. In October 2012, a post-G-COE program called the "Program for Leading Graduate Schools: Nurture of Creative Research Leaders in Immune System Regulation and Innovative Therapeutics at Chiba University" was accepted and approved by the Japanese Government (http://www.isrit-lgp-chiba.jp/jpn/message/index.html). This is a 7-year program. We will continue to strive to produce physician scientists and researchers who will be active in the global arena, while continuing to develop unique and effective strategies and solutions for the plethora of problems and challenges facing us today. I would therefore like to ask for your additional support, guidance and encouragement to further promote this new program.

Toshinori Nakayama

Toshinori Nakayama, MD, PhD
Program Leader

Appreciation of Great Success in Global COE Program

The Chiba University Global COE Program, named the "Global Center for Education and Research in Immune System Regulation and Treatment", has been successfully implemented for the last five years as a result of the great efforts of many people. I greatly appreciate the extensive efforts made by Prof. T. Nakayama, the leader of the Global COE program, and the core members of the Graduate School of Medicine and other institutes, such as the Graduate School of Pharmaceutical Sciences, the Riken Research Center for Allergy and Immunology, and the National Institute of Radiological Sciences. One of the most important aims of this program was to nurture young researchers in this field. In order to accomplish this purpose, we recruited distinguished scientists from over the world as visiting professors or associate professors of Chiba University. The "Chiba Visiting Professor Program (CVPP)" had been very helpful to educate the postdoctoral fellows and doctoral students at our university through international symposia and workshops. Such international activities have led to an increase in the publication of high quality scientific papers by young researchers, concomitantly encouraging the young researchers to devote themselves to translational research.

Allergic diseases such as allergic rhinitis, asthma and atopic dermatitis are very common in Japan. In addition, the immune responses and inflammation are etiologically important for the development of various other diseases, such as heart failure, atherosclerosis and cancer. Therefore, translational research in immune system regulation is important from a therapeutic point of view. The remarkable outcomes of this Global COE program, such as the clinical application of translational research in the Department of Exploratory Advanced Therapeutics, the promotion of clinical trials at the Clinical Research Center and establishment of the Allergy Center at Chiba University Hospital, has led to the acquisition of a budget for the Program for Leading Graduate School, named the "Nurture of Creative Research Leaders in Immune System Regulation and Innovative Therapeutics" in 2012. By carrying out this new program, we will be able to further promote translational research for clinical applications of innovative therapeutics and contribute to progress in medicine.

Finally, I would like to thank the Ministry of Education, Culture, Sports, Science and Technology of Japan for the great and continued support during the duration of this Chiba University Global COE Program.

Haruaki Nakaya, MD, PhD
Dean, Graduate School of Medicine, Chiba University

Greetings

Chiba University Graduate School of Medicine has been promoting a Global COE Program entitled the "Global Center for Education and Research in Immune System Regulation and Treatment", under the leadership of Prof. Toshinori Nakayama in the Department of Immunology. This has taken the form of integrating the research achievements in Immunology and Allergy which we have attained over the past 50 years. This G-COE program is organized by the 17 program core members, who have various affiliations, including the Graduate School of Pharmaceutical Sciences, Chiba University, RIKEN Research Center for Allergy & Immunology and the National Institute of Radiological Sciences. This program is striving to advance unique basic research on the immune system from new perspectives and to develop research on new therapeutic strategies for intractable immune disorders, including allergy, cancer, cardiovascular inflammatory diseases and arteriosclerosis. Translational research and clinical trials resulting from the achievements in this program are conducted mainly at the Center for Advanced Medicine, Chiba University Hospital, after examination in the Clinical Research Center. Through these activities, we are aiming to foster therapeutic researchers with comprehensive knowledge and methodology for the treatment of intractable immune disorders. The Chiba University Graduate School of Medicine has recently established the Future Medicine Research Center to nurture creative medical researchers in developing innovative therapeutics.

Various unique educational programs for young researchers have been carried out, and we focus on promoting the ability to perform creative research from new viewpoints and playing an active role in international settings. One of the educational programs is intended to vigorously promote the G-COE-CVPP (Chiba Visiting Professor Program). Under the CVPP, we invite 18 researchers from eight institutions in the USA (such as the University of California and the NIH), Europe, etc. as visiting professors, in order to provide research guidance, especially to the G-COE-RAs and G-COE Fellows. Furthermore, graduate students and young researchers have an opportunity to study in the foreign laboratories that are mainly affiliated with the visiting professors. Through the increasing mutual exchange and research collaboration, we have been pursuing our goal. Finally, our new program "Nurture of Creative Research Leaders in Immune System Regulation and Innovative Therapeutics" has been accepted as the Program for Leading Graduate Schools this year.

This Final Report described the progress made by the programs for educating young researchers, in addition to the research results we have accomplished thus far in the four and a half years that the program has been running. I hope that this Final Report will serve a role in promoting broad collaborations with other organizations, as well as in helping nurture young researchers at other institutions. We look forward to your continued support and cooperation.

Takeshi Tokuhisa, MD, PhD
Vice President, Chiba University

2. Member and Organization

Outline of the program

Outline of the program

The etiology of allergic diseases and cancer is thought to be the dysregulation and malfunction of the immune system operating in the body, respectively. Recent advances in the fields of immunology provide substantial numbers of candidate molecules and strategies for the treatment of allergic diseases and cancer. Therefore we have now reached the stage for the development of new therapeutic strategies based on “immune system regulation” perspective.

The program was jointly implemented by the Graduate School of Medicine and the Graduate School of Pharmaceutical Sciences, Chiba University, the Riken Research Center for Allergy and Immunology (RCAI) and the National Institute of Radiological Sciences (NIRS). Our goal is to advance therapeutic research for intractable immune disorders including allergy, cancer, cardiovascular inflammatory diseases and arteriosclerosis, creating an internationally unprecedented excellent center for education and research in therapeutics based on immune system regulation. Through the research activities, we fostered young researchers with integrated knowledge and methodology on immune system regulation and immunological treatment, as well as with the general ability to, 1. Accomplish creative research from new perspectives, 2. Conduct comprehensive clinical research on allergy and an interdisciplinary clinical research on cancer and 3. Plan an active role in the global scientific community.

Research Activities

We began research and educational activities in collaboration with 17 program core members (Chiba Univ. Grad. Sch. of Med.:11, the Grad. Sch. of Pharm. Sci.:2, RCAI:2, NIRS:2) and one coordinator, in the 2008 academic year. One program core member from NIRS has changed since the 2009 academic year and two core members joined on 2010. The central pillars of the research are as follows:

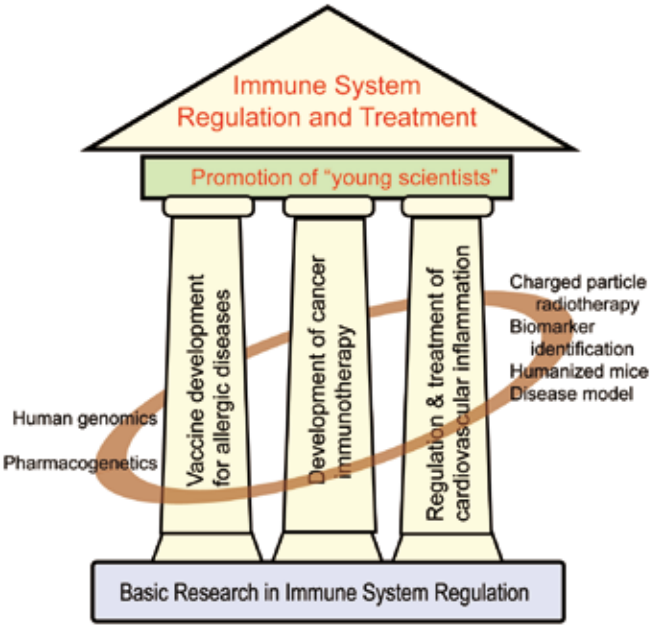
1. Basic research on the immune system regulation, disease genomics, pharmacogenomics and drug metabolism,
   And based on the latest research evidence created from these basic researches,
2. Development of preventive and treatment strategies for allergies by regulating immune system,
3. Development of immune cell therapy for cancer,
4. Identifying the pathogenic mechanisms of cardiovascular inflammatory diseases.

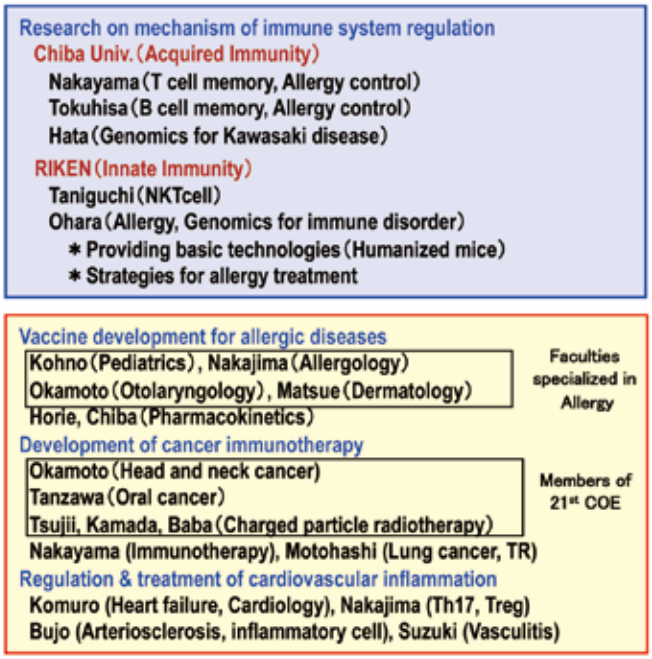
We promoted clinical research on the diseases listed above and established a new field of therapeutics. We have produced 800 original English papers by December 2012. (Figure 1)

Human Resources Training

Education for graduate students and post-doctoral fellows

We supported PhD students who were selected as G-COE-RA (research assistant) graduate students cross-disciplinarily from among various PhD students in the relevant fields. A total of 100 graduate students have participated in this program. In

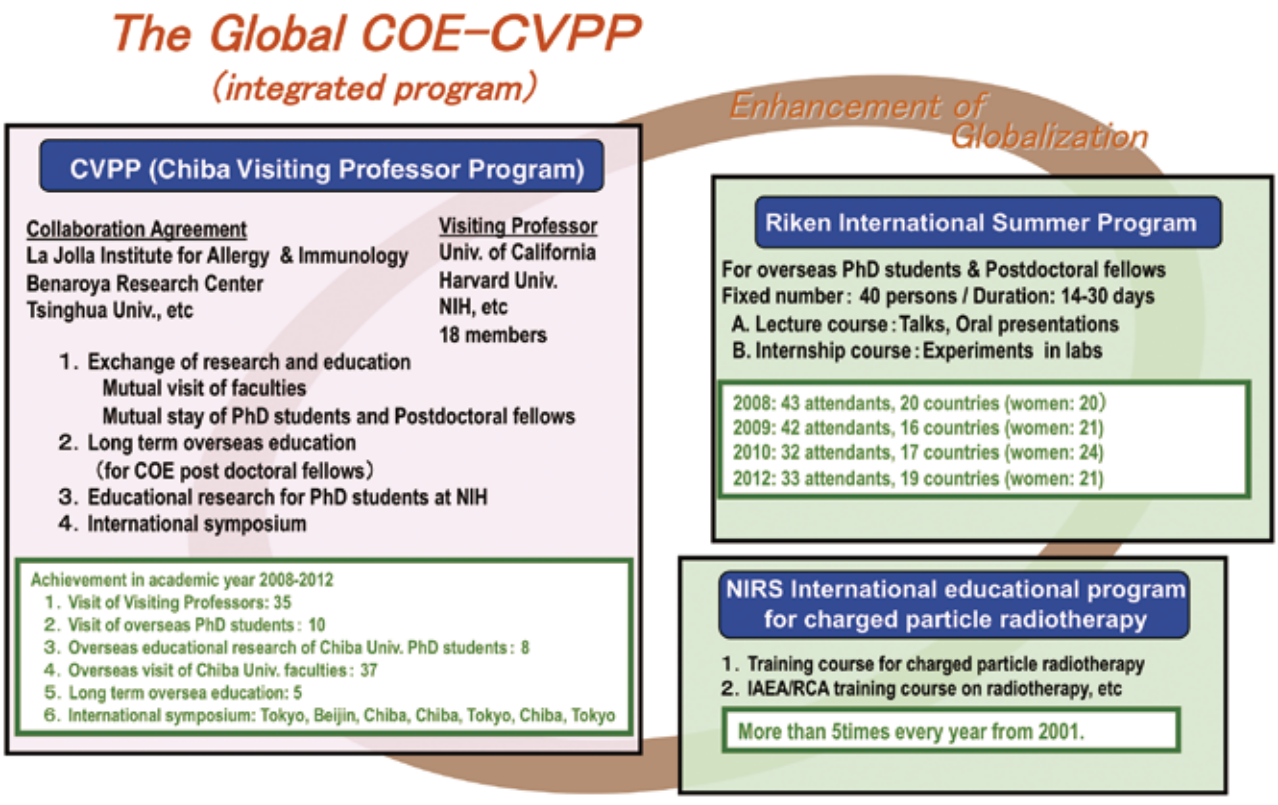




addition to a supervisor, two other university faulty members in a related field were responsible for the education of each G-COE-RA graduate student to thus provide with comprehensive guidance. Special grants for research (young scientist start-up grant level) were provided to certain numbers of excellent students and researchers through the process of reviewing their research proposals. Annual Best Research Awards were given to the most outstanding students in order to enhance their motivation. Nine people won the awards from 2008 through 2012. Employing six G-COE independent young research associates and twenty-two G-COE postdoctoral fellows, we have established a structure for promoting research. In order to encourage PhD students and young researchers to become much more globally active, we accelerated globalization in our education by making the most of the Global COE-CVPP, a unique system in this program. Furthermore, we introduced BSJM (Basic Science Joint Meeting) research seminars arranged by graduate students, and Special English Lectures (Exercises) of Scientific Presentations for graduate students, by expert native English speakers, for which the students obtain credits. We have set up a course of lectures and seminars entitled "Exploratory Advanced Therapeutics" for the junior year curriculum with the view to fostering young doctors who devote themselves to translational research and clinical research, and Allergy Clinical Conference, joint meetings in the fields of internal medicine, pediatric, dermatology and otorhinology, with the goal of training young doctors who can conduct research and treatment for allergy associated diseases in a comprehensive manner.

The Global COE-CVPP

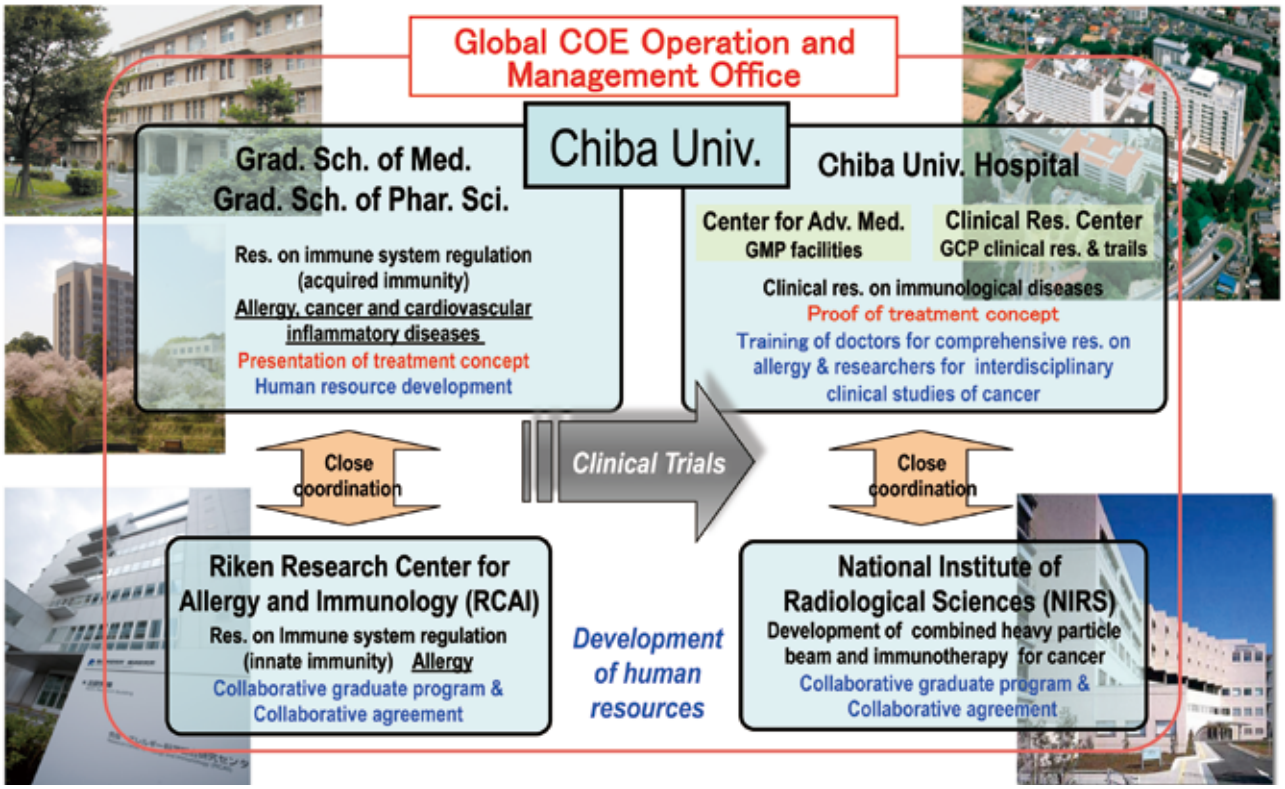
The Graduate School of Medicine, Chiba University has originally established CVPP (Chiba Visiting Professor Program), a collaboration system with foreign researchers. In this program, we encourage PhD students and young researchers to become much more globally active. With the Global COE-CVPP, integrated program of the CVPP and original programs which have been conducted by RCAI or NIRS, we have accelerated the globalization regarding the graduate school education and fostering young researchers. Eighteen visiting professors and visiting associate professors participated in G-COE-CVPP. The visiting professors and the visiting associate professors stayed at Chiba University from periods ranging from a few days to two weeks every year to engage in such activities as giving lectures, leading discussions and small workshops. Meanwhile, PhD students (as a training course with credit) and postdoctoral fellows had the opportunities to present their original research and obtain advice from this faculty. In addition, seven international symposiums and twelve workshops (including eight workshops in "Presentations and discussions by G-COE-RAs") were held, mainly by CVPP coordinators, with a program designed for young researchers to actively participate. We have, in particular, proved effectiveness of the G-COE-RA workshop in the reports of RAs research activities, from various perspectives. (Figure2)



Research Organization

The clinical application of the basic research results, produced by the Graduate School of Medicine and Pharmaceutical Sciences, is conducted mainly at the Chiba University Hospital Clinical Research Center and Center for Advanced Medicine. Since 2007, in recognition of its distinguished achievement, Chiba University Hospital has been designated to be a core hospital for the clinical research (one of only about ten hospitals in Japan) by the Japanese government. In cooperation with RCAI which jointly implements this program, translational research will be strongly promoted, not only in educational aspects, but also for the practical application of new methods of treatment for allergy.

Chiba University and RCAI have collaborated under an agreement made in 2007 to strengthen bilateral relations. Expansion of this relationship has accelerated the training of graduate students and young researchers in Chiba University. NIRS is the No. 1 research institute in the world for highly advanced cancer therapy using heavy ion charged particle beams, and it has promoted the 21st COE Program in close collaboration with Chiba University. This program, with such collaboration, carried out research and developed new low invasive cancer therapies combining heavy ion charged particle therapy with immune cell therapy, which has never yet been attempted in the world, and also promoted and nurtured the young human resources involved with this new approach. (Figure 3)



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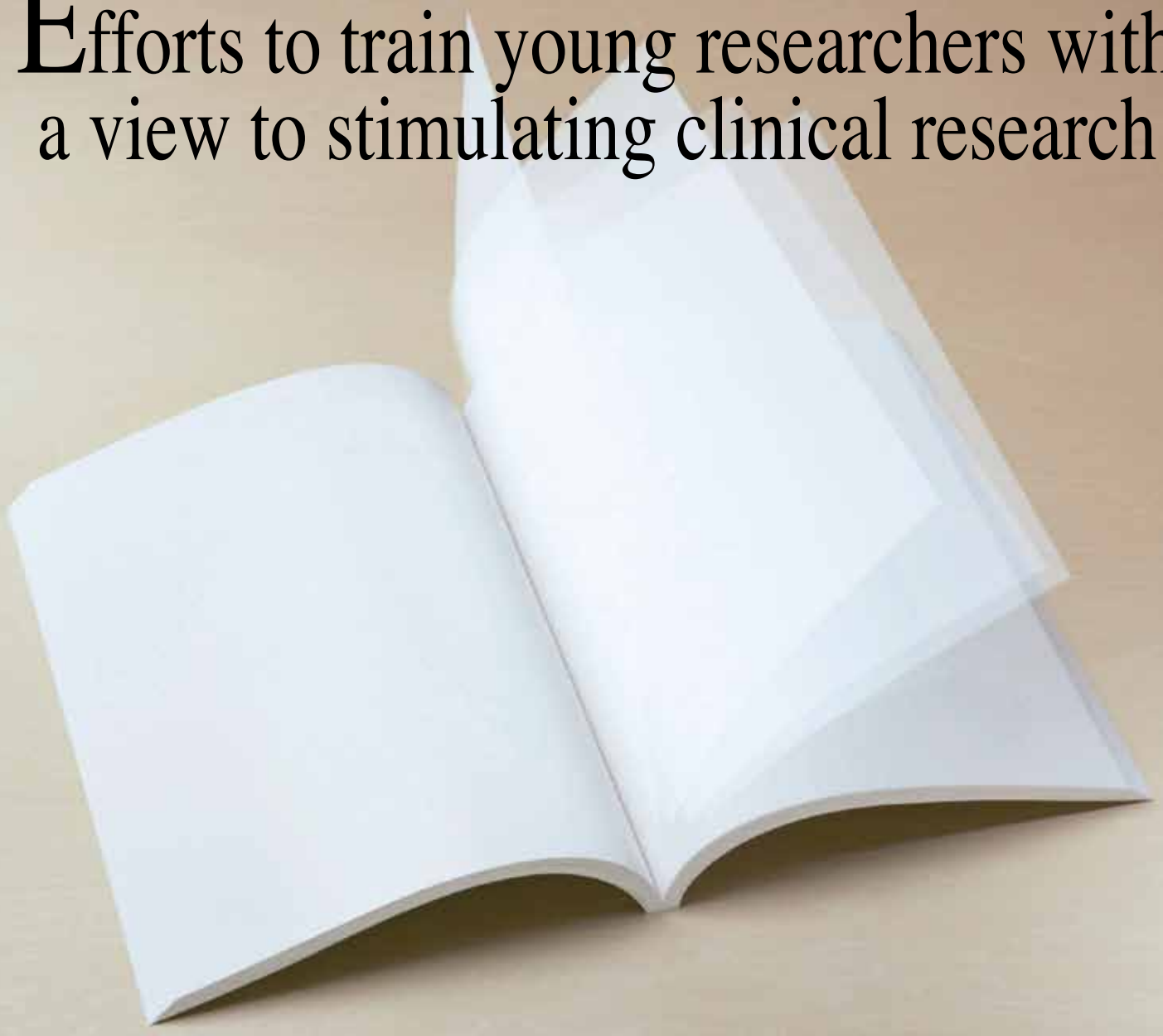
3.

Efforts to train young researchers with a view to stimulating clinical research



Efforts to train young researchers with a view to stimulating clinical research

Summary

As initially proposed, we have conducted various unique programs aimed at young researchers with a view to stimulating clinical research, such as Annual Best Research Award and the establishment of special lectures on 3-1 Clinical Allergology/Clinical Oncology as new subjects of study in the Graduate School of Medicine, while supporting young researchers to have the better study environment and to become more internationally-active by G-COE-CVPP. Furthermore, we have additionally introduced the following new educational approaches to this program: 3-2 For graduate students, Special English Courses (Exercises) of Scientific Presentations were set up as a practical education that enable students to be active in international settings; 3-3 For young doctors, Allergy Clinical Conference was held with the goal of training young doctors who can conduct research and treatment for allergy associated diseases in a comprehensive manner; 3-4 For graduate students and young doctors, a course of lectures entitled "Introduction/Application of Clinical Research" was initiated in collaboration with the Clinical Research Center of Chiba University Hospital; 3-5 For young researchers who strive for doing clinical research, Seed Grant Competitions were held to provide a broad-ranging support; 3-6 For the junior year in the School of Medicine, a course of lectures and seminars entitled "Exploratory Advanced Therapeutics", for which the students obtain credits, was established in 2010 to enlighten them about attraction of the basic research that can be connected with clinical research.

In these various activities, 3-7-1 we established Center for Advanced Medicine in 2008 as a playing field for young researchers aiming at clinical trails to achieve innovative therapeutic strategy, whereas for those who eager to work as a doctor for comprehensive clinical research on Allergy, 3-7-2 we established Chiba University Allergy Center as their playing field in accordance with the Chiba University Hospital Development Plan. The G-COE Program has made great contribution to enrich these various solutions for developing young therapeutic researchers.

Clinical Allergology/ Clinical Oncology

3-1 Clinical Allergology/Clinical Oncology

Special English Lectures for graduate school students

Outline of the program

Subject: Special Lectures of Clinical Allergology
Organizer: Hiroshi Nakajima

Lecture 1 : Toshinori Nakayama
Subject : Allergic responses regulated by T cells

GIO: Th1/Th2 cell differentiation and the maintenance of memory Th1/Th2 cell function

SBO: To be able to explain the following subjects;

1. Processes required for the generation of Th1/Th2 cells.
2. Molecular mechanisms that regulate Th1/Th2 cell differentiation.
3. Chromatin remodeling events governing the Th1/Th2 cell differentiation and maintenance.

Lecture 2 : Takeshi Tokuhisa
Subject : Differentiation of immune memory IgE B cells

Germinal center (GC) is a complex cellular microenvironment that directs generation of high affinity memory B cells with somatic hypermutation of Ig-V genes. Although high-affinity IgE memory B cells should be developed in GCs, IgE+ B cells are hardly detected in GCs. Thus, high-affinity IgE memory B cells may be differentiated from high-affinity IgG1 B cells developed in GCs by sequential class switching outside of GCs. We discuss molecular mechanisms of the high-affinity IgE memory B cell development in GCs.

Lecture 3 : Kazuo Suzuki
Subject : Contribution of neutrophils to host-defense and chronic diseases

Neutrophils contribute to host defense in the initial steps of infection by killing bacteria, viruses, and fungi which are highly pathogenic agents. In addition, the cells show cross-talk with macrophages and lymphocytes in the early phase of host defense through the cytokines-chemokines produced. Dysfunction of neutrophils induces opportunistic infection and severe syndrome, resulting in death. Mechanisms of dynamic action and molecular events of the cells have been investigated. Recently, neutrophils also recognized to induce chronic diseases, and are to be involved in influenza infection. Thus, it is important for infectious diseases and chronic diseases that neutrophil functions must be regulated.

Lecture 4 : Shinichiro Motohashi
Subject : NKT cell-based immune regulation

NKT cells have been reported to play important roles in various diseases such as malignant tumor or allergic diseases.

A new subject of study, Special Lectures of Clinical Allergology/Clinical Oncology, was initiated in our graduate school from 2009. Clinical Allergology and Clinical Oncology, were held alternatively. All the lectures were given in English, by core members of this program.

In the lecture of Clinical Allergology, fundamentals of allergy were introduced by basic immunologists. Advanced clinical researches aim to conquer the allergic diseases were introduced by the clinical immunologists specialized in allergy. In the lecture of Clinical Oncology, immunological aspects of oncology were introduced by basic researchers. The development of novel advanced treatment such as immunotherapy or charged particle radiotherapy in patients with various cancers were reviewed by the clinical immunologists specialized in oncology.

In this lecture, progress to date in the clinical studies of NKT cell-based immunotherapy is reviewed and the role of NKT cells in immunotherapy highlighted.

Lecture 5 : Yoshitaka Okamoto
Subject : Present situation of allergic rhinitis and its immune responses

Recent observations have suggested a significant worldwide increase in the prevalence of allergic rhinitis and in Japan, Japanese cedar *(Cryptometria japonica)* and Japanese cypress *(Chamaecyparis obtusa)* pollens are considered to be the major unique allergens. Allergic rhinitis is a typical type 1 allergic disease by an adaptive immune response that occurs through the induction of allergen-specific effector T cells from naïve T cells. In the lecture, the immune responses observed in patients with allergic rhinitis will be discussed.

Lecture 6 : Hiroyuki Matsue
Subject : Dendritic cell-based immune regulation

Dendritic cells (DC) are special subsets of professional antigen-presenting cells that play a dual role of initiating and silencing acquired immune responses. Thus, it should be feasible to control the magnitude and direction of immune responses by experimental manipulation of DC function. We will overview the recent progress in the development of DC-based immuno-stimulatory and immuno-suppressive strategies, which are potentially applicable to the treatment of cancer, allergy, autoimmune disease, allograft rejection, and graft-versus-host disease.

Lecture 7 : Yoichi Kohno
Subject : Food allergy

Food allergy is one of the most common allergic diseases in childhood. In this lecture, clinical features and diagnosis of food allergy will be discussed.

Lecture 8 : Hiroshi Nakajima
Subject : Allergic airway inflammation

Asthma is a chronic airway inflammation that is characterized by intense eosinophil infiltrates, mucus hypersecretion, and airway hyperresponsiveness. These pathognomonic features are mediated mainly by antigen-specific Th2 cells. In addition, recent studies have shown that Th17 cells are involved in causing airway inflammation. In this lecture, the role of helper T cells in the regulation of allergic airway inflammation will be discussed.

Subject: Special Lectures of Clinical Oncology
Organizer: Motohashi Shinichiro

Lecture 1 : Toshinori Nakayama
Subject : Anti-tumor immunity mediated by memory T cells

GIO: Understanding the mechanisms on anti-tumor immunity mediated by memory Th1/Th2 cells.
SBO: To be able to explain the following subjects;
1. Processes required for the generation of memory Th cells.
2. Molecular mechanisms that regulate memory Th cell function.
3. Mechanisms on anti-tumor immunity mediated by memory Th cells.

Lecture 2 : Takeshi Tokuhisa
Subject : Germinal center and B cell lymphoma-genesis

Germinal centers (GCs) are a complex cellular microenvironment that directs generation of high affinity memory B cells with somatic hypermutation (SHM) of Ig-V genes and Ig class-switch recombination (CSR). B cell lymphoma can be developed from these GC-B cells by the SMH of various oncogenes and the chromosomal translocation including the oncogene. We discuss molecular mechanisms of the B cell lymphoma-genesis in GCs.

Lecture 3 : Hiroyuki Matsue
Subject : Dendritic Cells and Tumor

In this lecture, I will review roles of dendritic cells (DC) in the process of tumor formation especially in the context of “Cancer-Immunosurveillence”(Burnet) and the new concept “Cancer-Immunoediting”(Schreiber). In addition, I will focus on discussing DC-based cancer immunotherapies: Their past, present and future.

Lecture 4 : Yoshitaka Okamoto
Subject : Current situation and treatment of head and neck cancer

Head and neck cancer has been estimated to be the sixth most common malignancy worldwide, with about 500,000 patients diagnosed annually. The management of advanced head and neck cancer has generally involved the combined-modalities of chemotherapy, radiation therapy and surgery. However, the increased toxicity and extensive functional morbidity induced by these combined therapies can severely impair the quality of life (QOL), and, at the same time, the prognosis still remains poor. In this lecture, the development of new treatment strategies to improve the prognosis and QOL of patients will be discussed.

Clinical Allergology/Clinical Oncology & Presentation Seminar, Intermediate/Advanced

Lecture 5 : Hideki Tanzawa
Subject : The mechanism of resistance to chemotherapy and radiotherapy of cancer
GIO: To understand the mechanism of resistance to chemotherapy and radiotherapy of cancer.
SBO: To be able to explain the following subjects;
1. The mechanism of resistance to chemotherapy of cancer.
2. The mechanism of resistance to radiotherapy of cancer. entiation.
3. The practical method of translational research.

Lecture 6 : Yasunori Akutsu, Hisahiro Matsubara
Subject : Translational research for esophageal cancer
Esophageal cancer is still the worst malignant disease, and its prognosis is miserable. First, clinical diagnosis and treatments will be reviewed, and second, translational research for esophageal cancer will be presented. In our department, cancer vaccine therapy using heat shock protein and cancer specific antigen peptide are progressing. We will present the results and discuss the future.

Lecture 7 : Shinichiro Motohashi
Subject : NKT cell-based immunotherapy for cancer
NKT cells have been reported to play important roles in various diseases such as malignant tumor or allergic diseases. In this lecture, the progress to date in the clinical studies of NKT cell-based immunotherapy for cancer is reviewed and the role of NKT cells in immunotherapy highlighted

Lecture 8 : Tadashi Kamada
Subject : Carbon ion radiotherapy for malignant disease
Carbon ion radiotherapy (CIRT) is a unique radiotherapy, which possesses well localized, and superior depth dose distribution in addition to uniform, less repairable radiobiological effects. The use of CIRT for various diseases has been explored as clinical trials at the Heavy Ion Medical Accelerator in Chiba (HIMAC), Japan, since 1994. In this lecture, the up to date results of carbon ion radiotherapy in various cancers at the National institute of Radiological sciences will be discussed.

3-2 Presentation Seminar

For scientific presentation in English

Lecturer: Berlitz Instructor

A new subject of study, Presentation seminor, started in our graduate school to promote young basic and clinical immunologists skills and abilities of international scientific interaction with researchers in foreign countries. In this course, all the lectures and practices were given in English, by the special instructor. Two courses including intermediate course and advanced course were provided according to the English skills. In these courses, students aimed at learning how to deliver an effective and memorable English presentation.

Subject: Presentation seminar/Advanced class
Organizer: Takeshi Tokuhisa, Hiroshi Nakajima

Content and Specific Behavioral Objectives (SBO)

Lecture 1 : Prof.Tokuhisa, Prof.Nakajima, Berlitz Instructor
Subject : Review Essential Elements of a Presentation
SBO: This is the first lesson focusing on reviewing the essential elements of a presentation. You will review language and techniques for: Introduction – Purpose – Outline.
We will consider the important steps of:
1. Starting your presentation;
2. Moving on to your next point;
3. Closing and summarizing your presentation.
We will also consider – "How should I adapt my message to my audience? Types of audiences and types of presentations". Using language effectively in an oral presentation.

Lecture 2 : Berlitz Instructor
Subject : Review ways to effectively handle a Q&A session
SBO: This lesson focuses on ways to effectively handle a post-presentation Q&A. You will review and practice:
1. Inviting questions from the audience;
2. Answering questions effectively;
3. Handling difficult situations.
Class pair and group practice.
We will also consider the topic of our mini presentation for the next class.

Lecture 3 : Berlitz Instructor L
Subject : First Presentation
SBO: You will deliver a mini presentation on a topic of your choice that will be expanded to become your final presentation later on in the final class. Your classmates will participate as the audience, asking you questions in your Q&A, and afterwards, providing positive and constructive feedback on your performance. You will be able to recognize and evaluate your strengths and weaknesses, thus allowing you to focus on making improvements in your overall presentation skills.

Lecture 4 : Berlitz Instructor
Subject : First Presentation – continued feedback
SBO: Our focus will be to make improvements in your overall presentation skills. You will consider your presentation from the

perspective of an academic setting: What is the purpose of an academic presentation? Is it basically to inform the audience and/or persuade the audience? When we inform our audience. We are aiming to help our audience understand something – ex. our research. When we persuade our audience we are aiming to influence the behaviors and/or attitudes of our audience with the information we have presented.

Lecture 5 : Berlitz Instructor Lecturer
Subject : Did you Communicate Effectively in Your Presentation?
Vary voice and use non – verbal communication.
SBO: This lesson will critique how you used body language, tone of voice and intonation to make your English presentation more natural and confident.
1. Use of eye contact and body language;
2. Use of tone and intonation for emphasis;
3. Involving your audience.
Class pair and group practice.

Lecture 6 : Berlitz Instructor
Subject : Did you Make Your Presentation More Memorable?
SBO: This lesson will review tips for how to create and use visual aids in oral presentations and explain them to give your presentation more impact.
1. Introducing and explaining a visual aid;
2. Making effective slides;
3. Giving examples to support your points;
4. Stating interesting facts and figures.
This lesson will also contain - Explaining a Research Project Review. Did you organize your research to present it coherently? We will briefly review language you can use to explain estimations, schedules and ideas in an academic presentation about a research project.
1. Giving estimations;
2. Explaining a timeline;
3. Connecting ideas.
Class pair and group practice.

Lecture 7 : Berlitz Instructor
Subject : Review, Re-do, Feedback, Do again
SBO: What can I do to practice for my final presentation? Here you will try to critically incorporate everything you have thus far studied and reviewed in the course.
Everything + 1 – we will consider the concept of everything + 1, whereby you will try to expand upon and develop the elements of your presentation to an Advanced level.
Class pair and group practice.

Lecture 8 : Berlitz Instructor
Subject : Review, Re-do, Feedback, Do again
Final Feedback before your last presentation
SBO: What can I do to prepare for my final presentation? Overcoming anxiety in an oral presentation.
Here you will prepare for your final presentation by considering how to overcome anxiety. You will also critically break down your presentation in terms of:
- Presentation Analysis
- Presentation Practice
- Presentation Performance
You will also remember ways to effectively handle a post-presentation Q&A. Thus increasing your confidence from the perspective of preparedness and the concept of Everything +1
Class pair and group practice.

Lecture 9 & 10 : Berlitz Instructor
Subject : Final presentation
SBO: This is the lesson in which you will deliver your presentation one final time. Your classmates will participate as the audience, asking you questions in your Q&A, and afterwards, providing positive and constructive anonymous feedback on your performance. You will be able to recognize and evaluate your achievements in this course through your work in this final lesson.

Allergy Clinical Conference

3-3 Allergy Clinical Conference

Joint Meeting
- **Dept. of Allergy and Clinical Immunology**
- **Dept. of Pediatrics**
- **Dept. of Otorhinolaryngology**
- **Dept. of Dermatology**

Organizer: Hiroshi Nakajima

About 30% of the Japanese population is suffering from allergic diseases such as bronchial asthma, allergic rhinitis, and atopic dermatitis. However, only symptomatic therapy is presently available, and curative therapeutic strategy has long been desired. Chiba University Global COE Program named "Global Center for Education and Research in Immune System Regulation and Treatment" focused on creating an internationally unprecedented excellent center for education and research to promote therapeutic research for intractable immune disorders including allergy by governing the regulation of immune system. In addition, this program aimed to foster young scientists in the field of therapeutic research, who have the abilities to accomplish creative research and to take leadership roles in the field of therapeutic research on allergy. To achieve the purpose, Chiba University Global COE Program held Allergy Clinical Conference in Chiba (ACCC) quarterly. More than 50 people of basic scientists, medical students, clinicians, and specialist in the field of basic immunology, internal medicine, pediatrics, otorhinolaryngology, and dermatology attended the ACCC every time. In the ACCC, researchers from Department of Allergy and Clinical Immunology, Department of Pediatrics, Department of Otorhinolaryngology, and Department of Dermatology provided hot topics in the field of basic research, clinical research, and translational research. Each topic was discussed actively and profoundly. We trained outstanding personnel and produced leaders, who play critical roles in achieving therapeutic research for allergic diseases.

Content and Specific Behavioral Objectives G-COE

Lecture 1 : January 28, 2009

- **Shinichiro Kagami**
  (Department of Allergy and Clinical Immunology)
- **Yoshinori Morita**
  (Department of Pediatrics)
- **Shigetoshi Horiguchi**
  (Department of Otorhinolaryngology, Head and Neck Surgery)
- **Naotomo Kambe**
  (Department of Dermatology)

Lecture 2 : April 15, 2009

- **Ayako Ohno**
  (Japanese Red Cross Narita Hospital)
- **Kei Ikeda**
  (Department of Allergy and Clinical Immunology)
- **Shuji Yonekura**
  (Department of Otorhinolaryngology, Head and Neck Surgery)
- **Takayasu Arima**
  (Department of Pediatrics)

Lecture 3 : July 15, 2009

- **Akira Suto**
  (Department of Allergy and Clinical Immunology)
- **Kouichi Kobayashi**
  (Department of Otorhinolaryngology, Head and Neck Surgery)
- **Akiko Yamaide**
  (Chiba Children's Hospital)
- **Takashi Satoh**
  (Department of Dermatology)

Lecture 4 : November 4, 2009

- **Noriaki Kamada**
  (Department of Dermatology)
- **Masaya Yokota**
  (Department of Allergy and Clinical Immunology)
- **Yoshinori Morita**
  (Department of Pediatrics)
- **Go Sasahara**
  (Department of Otorhinolaryngology, Head and Neck Surgery)

Lecture 5 : March 10, 2010

- **Yoshihisa Kobayashi, Hirotoshi Kawashima, Daiki Nakagomi**
  (Department of Allergy and Clinical Immunology)
- **Hiroaki Takatori**
  (Department of Allergy and Clinical Immunology)
- **Heizaburo Yamamoto**
  (Department of Otorhinolaryngology, Head and Neck Surgery, Chiba Rosai Hospital)
- **Yaei Togawa**
  (Department of Dermatology)
- **Yoichi Suzuki**
  (Department of Public Health)

Lecture 6 : July 23, 2010

- **Makiko Oikawa**
  (Department of Dermatology)
- **Chieko Kato**
  (Department of Allergy and Clinical Immunology)
- **Yuzaburo Inoue**
  (Department of Pediatrics)
- **Heizaburo Yamamoto**
  (Department of Otorhinolaryngology, Head and Neck Surgery)

Lecture 7 : December 15, 2010

- **Shigetoshi Horiguchi**
  (Department of Otorhinolaryngology, Head and Neck Surgery)
- **Noriaki Kamata**
  (Department of Dermatology)
- **Chiaki Inagaki**
  (Department of Allergy and Clinical Immunology)
- **Ken Yamamoto**
  (Department of Pediatrics)

Lecture 8 : July 13, 2011

- **Naotomo Kambe**
  (Department of Dermatology)
- **Takayasu Arima**
  (Department of Pediatrics)
- **Mizuki Sakata, Yoshie Suzuki**
  (Department of Allergy and Clinical Immunology)
- **Heizaburo Yamamoto**
  (Department of Otorhinolaryngology, Head and Neck Surgery)

Lecture 9 : December 14, 2011

- **Rena Ota**
  (Department of Dermatology)
- **Tomohisa Iinuma**
  (Department of Otorhinolaryngology, Head and Neck Surgery)
- **Yuzaburo Inoue**
  (Department of Pediatrics)
- **Kotaro Suzuki**
  (Department of Allergy and Clinical Immunology)

Lecture 10 : April 18, 2012

- **Toshioki Sakurai**
  (Department of Otorhinolaryngology, Head and Neck Surgery)
- **Shoichiro Wakabayashi**
  (Department of Dermatology)
- **Kentaro Takahashi**
  (Department of Allergy and Clinical Immunology)
- **Taiji Nakano**
  (Department of Pediatrics)

Lecture 11 : July 11, 2012

- **Yugo Maru**
  (Department of Dermatology)
- **Shigeru Tanaka**
  (Department of Allergy and Clinical Immunology)
- **Hiroshi Kido**
  (The Institute for Enzyme Research, the University of Tokushima)

Lectures of Introduction and Application of Clinical Research

3-4 Lectures of Introduction and Application of Clinical Research

co-organized with Clinical Resarch Center, Chiba University Hospital

Organizer: Hideki Hanaoka

A new series of lectures focused on the clinical research was started in our Chiba University Hospital. The aim of these lectures was to learn basic and application about clinical trials and deeply understand clinical trials through practice. We fostered young researchers through these systematic lectures and promoted young basic and clinical researches skills and abilities to conduct translational research with GCP compliance.

Lecturer	Subject
Mitsukazu Kitada	Drug development and advance
Shinichiro Motohashi	Practice side of translational research
Kanako Katayama	To perform better clinical trial
Shunsuke Ono	The clinical trial and GCP
Akihiro Hirakawa	Roles of statistician in the examination of the new medicine
Maki Murakami	Roles of clinician in the examination of the new medicine
Yuichi Maru	Informed consent
Fumitaka Nagamura	The present situation of translational research
Kaoru Kanazawa	Clinical trial: From the point of view of CRC
Issei Komuro	Development of advanced medical care
Itaru Shimadu	Morals of life and study
Kaori Muto	Morals of life and study 2
Hideki Suganuma	An interim analysis for clinical trial
Noritaka Ariyoshi	PGx in clinical research
Fumihiko Kanai	Clinical trial: From the point of view of doctor
Toshinori Nakayama	The general introduction of translational research
Yasuhiro Fujiwara	Doctor-initiated clinical trial
Masaaki Hanawa	On-site point of view; Clinical trial watching from drug industry
Hideki Hanaoka	Role of the IRB in the clinical trial
Biostatistician	Biostatistics
Taro Shibata	Training class on clinical trial

Lectures of Exploratory Advanced Therapeutics

3-5 Lectures of Exploratory Advanced Therapeutics

A course of lectures and seminars for the junior year in the School of Medicine

Organizer: Shinichiro Motohashi

The exceptional basic research has produced many innovating treatments through translational research. All excellent treatments were exploratory advanced medicine at their developmental stage. Students learned the process that basic research is bridged to translational research and to standard treatment through advanced therapeutic development research. Part of the lecture was conducted as a presentation by students, which was a great opportunity to actively learn cutting-age medical development.

Lecturer	Subject
Toshinori Nakayama, Yasushi Saito, Hideki Hanaoka	Overview of TR
Shigetoshi Horiguchi, Yoshitaka Okamoto	TR for nasal allergy
Naoki Shimojo, Yoichi Kohno	Pathogenesis of food allergy in children and TR
Hiroshi Nakajima, Akira Suto	Pathogenic mechanism of bronchial asthma and TR
Norihiko Watanabe, Kei Ikeda	Rheumatoid arthritis and antibody therapy
Kazuo Suzuki, Takeyuki Sato	Basic research and clinical study of Influenza
Hideaki Bujo, Masayuki Kuroda	Protein replacement therapy using gene therapy
Koutaro Yokote, Tomoaki Tanaka, Minoru Takemoto	New development of research in Endocrinology, metabolism and geriatric disease
Tohru Minamino, Issei Komuro	Regeneration therapy for vessels and cardiac muscle
Goro Matsumiya	Organ transplantation
Tomoaki Nakaseko	Bone marrow transplantation
Shinichiro Motohashi	Immunotherapy for lung cancer
Yoshitaka Okamoto	Advanced clinical research for head and neck cancer
Hisahiro Matsubara	Advanced clinical research for esophageal cancer
Yuichiro Takiguchi	Paradigm shift of chemotherapy
Mitsutoshi Yoneyama	Viral infection and natural immunity
Itsuko Ishii	Drug efficasies and side effects

Seed Grant Competition

3-6 Seed Grant Competition

co-organaized with Chiba University COE start-up program "Center for Translational Research in Advanced Medicine"

Program leader:
Shinichiro Motohashi

We performed seeds grant competitions for advanced medicine as part of the global COE program activity, for the purpose of seeds exploitation, acceleration of translational research and enhancing young researchers' motivation for clinical study, at Chiba University.

The competitions were held for small research groups or individuals that were conducting research for innovative treatments which had a possibility to progress translational research (TR) stage in the near future, against intractable diseases including allergic disease, cancer and auto immune disease. The proposals we evaluated were in various stages of research.

Each time, the number of applications was largely exceeded we had expected since the applications were submitted a lot from various other departments than those in the Graduate School of Medicine, at Chiba University. This indicated that TR was sure to be a matter of concern for our young researchers. We supported excellent study proposals which were recommended by the selection committee, in providing research grants and time for regular discussions, in order to accelerate the realization of TR. In addition, we gave practical advice and supports on documentary arrangement required for TR execution, if a proposal was close to translating in clinical research. An open seminar was held every year to report the progress of all the studies and contributed to vitalize clinical research.

2009

Name	Affiliation	Title
Masahiro Mori	Graduate School of Medicine	Clinical application of MM-101, a novel enhancer of axonal elongation, for neuroimmunological diseases
Minoru Takemoto	Chiba University Hospital	Identification of novel diagnostic and therapeutic strategies for podocytopathy
Ayako Inamine	Graduate School of Medicine	Clinical aspect for Lactobacillus paracasei KW3110 oral adjuvant immunotherapy
Shigetoshi Yoshida	Chiba University Hospital	Investigation for therapeutic pulmonary regeneration by human type II alveolar epithelial cells
Shinichi Sakamoto	Chiba University Hospital	NKT based immunotherapy against homone refractory prostate cancer via targetting tissue associated macrophage derived IL-6.
Kunikazu Moribe	Graduate School of Pharmaceutical Sciences	Ascorbyl dipalmitate/PEG-lipid nanoparticles as a novel drug delivery carrier for hydrophobic drugs
Fumio Sakane	Graduate School of Science	Anti-cancer agent comprising diacylglycerol kinase a inhibitor -Diacylglycerol kinases as emerging potential drug targets for a variety of intractable diseases-
Tomomi Furihata	Graduate School of Pharmaceutical Sciences	Identification and characterization of a cancer-type variant of organic anion transporting polypeptide 1B3

2010

Name	Affiliation	Title
Daiju Sakurai	Graduate School of Medicine	α-Galactosylceramide pulsed DC therapy in patients with Head and Neck SCC after the standard therapy

Tomoro Hishiki	Graduate School of Medicine	Development of novel therapeutic strategy using NKT cell-based immunotherapy for pediatric solid tumors
Akiko Suganami	Graduate School of Medicine	Detecting and Treating of Anti-diabetic and Anti-cancer Drugs using High-throughput Diacylglycerol Kinase Assay
Takeshi Murata	Graduate School of Science	Structural basis for drug design of neurodegenerative diseases against the adenosine A2a receptor
Kunikazu Moribe	Graduate School of Pharmaceutical Sciences	Preparation of PEG-lipid-based nano-complex as a drug delivery carrier
Kazuyuki Matsushita	Graduate School of Medicine	Peptides from splicing variants as novel gastrointestinal tumor markers detected by protenomics
Fumio Sakane	Graduate School of Science	Discovery and Development of Anti-diabetic and Anti-cancer using High-throughput Diacylglycerol Kinase Assay
Moriya Yasumitsu	Graduate School of Medicine	Identification of anti-proliferative miRNA expression in squamous cell carcinoma of the lung: Pursue for the common therapeutic targets of tobacco-related cancer

2011

Name	Affiliation	Title
Takeshi Murata	Graduate School of Science	Structural analysis of active state of human A2a adenosine receptor using functional antibody
Eun-Young Lee	Graduate School of Medicine	A search for curative therapy of Type1 diabetes through Beta-cell Regeneration
Kazuyuki Matsushita	Graduate School of Medicine	SAP155-mediated splicing of FUSE-binding protein-interacting repressor (FIR) serves as a molecular switch for c-myc gene expression
Shinichiro Kagami	Chiba University Hospital	Induction of CD62Lhigh regulatory T cells by geranylgeranyl-transferase inhibitor I
Tomomi Furihata	Graduate School of Pharmaceutical Sciences	Biochemical characterization of newly identified cancer-type organic anion transporting polypeptide 1B3 in human cancerous tissues and cells

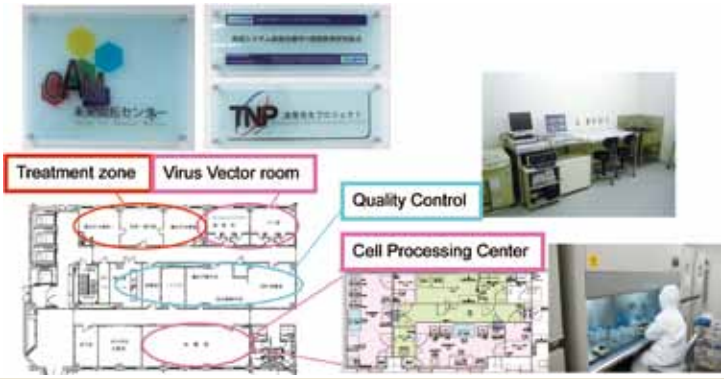
2012

Name	Affiliation	Title
Shunichiro Onishi	Clinical Cell Biology and Medicine, Graduate School of Medical and Pharmaceutical Sciences	Investigation of the roles of semaphorin 3g in the regulation of glucose metabolism
Hiroshi Hasegawa	Department of Cardiovascular Medicine, Graduate School of Medicine	Cardioprotective effects of dipeptidyl peptidase-4 inhibition on heart failure
Tomomi Furihata	Laboratory of Pharmacology and Toxicology, Graduate School of Pharmaceutical Sciences	Expressio profile of cancer-type OATP1B3 in human lung cancer tissues and exploration of its biological functions
Naoki Kunii	Department of Immunology, Graduate School of Medicine	Adoptive Cell Therapy of human T cells expressing a Chimeric Antigen Receptor for Salivary Gland Tumor
Yasunori Akutsu	Department of Frontier Surgery, Graduate School of Medicine	A newly developed hyperthermia, "Oncothermia" induces immunoreaction by abscopal effect for squamous cell carcinoma
Hiromichi Sakai	Laboratory of Biofunctional Chemistry, Department of Chemistry, Graduate School of Science	A comprehensive approach to development of type 2 diabetes therapy targeting diacylglycerol kinase δ

Center for Advanced Medicine/ Allergy Center

3-7-1 Center for Advanced Medicine

Director: Issei Komuro (2008 May - 2010 March)
Yoshitaka Okamoto (2010 April - present)



Center for Advanced Medicine was opened at the East Ward of Chiba University Hospital on May 29, 2008 designed to collectively conduct research activities at many levels ranging from research for development of therapeutic strategies to clinical applications in advanced medicine. Professor Issei Komuro, who is a core member of the G-COE Program, was appointed the Director of the Center.

The center plays a key role as the core of research facilities to create innovative treatment for intractable diseases which are considered to be impossible to realize with the traditional medicine, as well as to expand research and development in advanced medical technology that has been energetically conducted so far in each department of Chiba University Hospital.

We built the unified and efficient structure in the center to pursue the research covering from basic research to clinical applications in the fields of cell therapy, regenerative medicine and gene therapy, with setting up facilities including Cell Processing room with a high-level aseptic condition, Gene regulatory room (Virus Vector Processing room), Treatment room, and Material and sample room, while establishing Clinical Trial Division, Administrative Division and Quality Management Division for its organization.

At the center, we are performing clinical trails primarily at Center for Advanced Medicine and Research, and Clinical Research Center for new strategies derived from the therapeutic research for intractable immune disorder which has been advanced mainly under the G-COE Program. NKT cell immunotherapy for cancer (Motohashi, Okamoto, Nakayama) promoted by our core members was approved as the advanced medicine for lung cancer and head & neck cancer. Also peripheral blood mononuclear cell implantation for therapeutic angiogenesis (Komuro) and protein supplement therapy using adipose cells (Bujo) have been strongly promoted. Center for Advanced Medicine also serves another important role as an educational institution where young researchers and doctors can receive on-the-job training through hands-on activities on clinical research. The research being originating in Chiba University to develop new therapeutic strategies, which is carried on primarily by the G-COE members, is aiming to make further progress by not only collaborative research with all other graduate schools at Chiba University, especially the Graduate School of Pharmaceutical Sciences and the Graduate School of Engineering, but expanding collaboration with other universities and outside research institutions as well including Kazusa DNA Research Institute and pharmaceutical companies.

3-7-2 Allergy Center

Among the doctors educated by various activities of our G-COE Program, those for comprehensive clinical research on Allergy are actively involved in the operation of Chiba University Allergy Center which is established based on the basic concept of Chiba University Hospital Development Plan at Oct 1st, 2012. Under the leadership of Prof. Yoichi Kohno, Director of the Allergy Center, who is also a core member of the G-COE Program, comprehensive treatments that enables to obtain high value and patient's high satisfaction are realized by assembling clinical departments responsible for allergic diseases such as that of Allergy and Clinical Immunology, Pediatric, Otolaryngology, and Dermatology. This G-COE Program will greatly contribute toward producing medical specialists of Allergic diseases necessary for attaining that purpose.

4.

Research activity

Memory Th2 cell differentiation and regulation of allergic responses

Core Member

Toshinori Nakayama

Department of Immunology
Graduate School of Medicine,
Chiba University

Summary

The quality of adaptive immune responses depends on the size of the antigen-specific memory T cell pool, which is regulated through specific homeostatic mechanisms controlling both cell survival and proliferation. Upon antigen recognition, naïve CD4 T cells undergo a rapid clonal expansion, followed by differentiation into functionally distinct helper T (Th) cell subsets, such as effector Th1, Th2 and Th17 cells. These effector T cells undergo a dramatic contraction in numbers after antigen clearance, with 90-95% succumbing to apoptosis within weeks. However, some of the effector T cells are maintained as memory T cells for long periods *in vivo*. The maintenance of memory T cells is central to the establishment of immunological memory, although the molecular details of the process are poorly understood (ref. 1, 2). Asthma is a major public health problem that has increased markedly in prevalence in the past two decades. Asthma is characterized by a chronic inflammation of the lower airways that causes airway hyperresponsiveness (AHR) to a wide variety of specific and non-specific stimuli. The cardinal features of acute asthma are airway inflammation predominated by eosinophils, hyper-secretion of mucus and AHR. A critical role for Th2 cells in the pathogenesis of allergic asthma has been demonstrated in studies of human asthma, as well as of animal models of allergic airway inflammation. In Japan, 4,000 asthma patients died every year. The aim of our studies is to clarify the mechanisms governing the asthma phenotype and to develop a new therapy for this disease. We also foster young researchers to accomplish this aim.

1. Establishment and maintenance of Th2 cell memory

We investigated the role of the *Polycomb* group (PcG) gene in the establishment and maintenance of memory Th2 cells. Our results indicate that the PcG gene plays a crucial role in the generation and maintenance of memory Th2 cells. In Th2 cells, *Bmi1* appears to bind to the *Noxa* gene locus and directly represses its transcription to promote memory Th2 cell survival. The antigen-induced allergic airway inflammatory responses were compromised in *Bmi1*$^{-/-}$ memory Th2 mice, suggesting a physiological role for Bmi1 in the establishment of Th2 cell-mediated memory responses (ref. 3, 4). In addition, another PcG gene, *Ring1B*, plays a crucial role in allergic airway inflammation by controlling the Bim-dependent apoptosis of effector Th2 cells in the lungs (G-COE-RA, fellow, Suzuki et al., ***J. Immunol,*** 2010: ref. 3). Taken together, our results and those obtained by other investigators demonstrate an essential role for the PcG genes in the establishment and maintenance of memory Th2 cells. In addition, we have started the identification of a memory CD4 T cell niche in the body using a newly introduced laser microscopy technique (ref.5).

2. Regulation of the transcriptional expression of GATA3, a master regulator of Th2 cells

During development, PcG and *Trithorax* group (TrxG) molecules form multimeric and heterogeneous complexes, and act as antagonistic regulators in the maintenance of the transcriptional status of developmentally-regulated genes, such as the *Hox* genes. We demonstrated that the activation of STAT6 induced the dissociation of the PcG complex and association of the TrxG complex with the GATA3 gene locus during Th2 cell development. In addition, the maintenance of GATA3 expression is regulated in a STAT6-independent manner (G-COE-independent research associate, Onodera et al., ***J Exp Med.*** 2010: ref. 6). We identified Gfi1 (growth factor independent-1) as a downstream target of the ERK-MAPK cascade involved in Th2 cell differentiation. We also reported that the T cell receptor-mediated induction of Gfi1 controls Th2 cell differentiation through the regulation of GATA3 protein stability (Shinnakasu et al., ***J. Immunol***, 2008 ref. 7)

3. Regulation of allergic airway inflammation and development of a new treatment

The cardinal features of acute asthma are airway inflammation, hyper-secretion of mucus and airway hyperreactivity. A critical role for Th2 cells in the pathogenesis of allergic asthma has been demonstrated in studies performed both in humans and in animal models. Repressor of GATA (ROG) represses GATA3, which is a key transcriptional factor for Th2 differentiation. We have found that ROG and Zfp35 are negative regulators of allergic asthma (Hirahara JACI, 2008, Kitajima, ***J. Immunol.*** 2009 ref. 8). The expression of Zfp35 was detected in IL-4^{low}-producing Th2 cells. A color-corded real-time imaging model using a laser

microscope in the lung was developed to visualize the cellular dynamics of the migration of Th2 cells into the lungs of living animals using a mouse model of asthma. This new method enables the study of the *in vivo* cell biology of inflammation diseases (ref. 9). CD69 is an early activation marker on leukocytes. However, the expression of CD69 is required for the development of allergic asthma. Furthermore, the administration of anti-CD69 antibodies attenuated asthma symptoms (ref. 10).

4. Role of GATA3 in developing Th2 cells

To investigate the role of GATA3 on developing Th2 cells, we performed chromatin immunoprecipitation with a high-throughput sequencing (ChIP-Seq) analysis in developing Th2 cells. The ChIP-seq analysis combines chromatin immunoprecipitation (ChIP) with massively parallel DNA sequencing to identify the binding sites of DNA-associated proteins. It can be used to precisely map the global binding sites for any protein of interest. A genome-wide unbiased ChIP-Seq analysis revealed 24 GATA3-binding genes specific to Th2 cells. This study provides a platform for understanding how GATA3 regulates the transcription of Th2-specific genes during Th2 cell differentiation (G-COE-RA, Horiuchi et al., ***J. Immunol.*** 2011: ref. 9).

5. Identification of pathogenic memory Th2 cells and clarification of the molecular mechanisms controlling IL-5 production in memory Th2 cells

Recently, we found that memory Th2 cells express CXCR3, a well-known marker for Th1 cells, and that the cells could be subdivided into four distinct subpopulations according to their expression of CD62L and CXCR3. IL-5-producing cells were predominantly detected in the $CD62L^{lo}CXCR3^{lo}$ population in memory Th2 cells, and this population played a critical role in the memory Th2-dependent allergic airway inflammation as “pathogenic memory Th2 cells”. Furthermore, a T-box transcription factor, *Eomesodermin* (Eomes), was upregulated in memory Th2 cells and suppressed the GATA3-dependent IL-5 production, which resulted in reduced airway inflammation (G-COE-RA, fellow, Endo et al., ***Immunity***, 2011: ref. 10). In this study, we have identified pathogenic memory Th2 cells and clarified the molecular mechanisms underlying their induction of memory Th2-dependent eosinophilic airway inflammation.

6. Regulation of Th2 differentiation by the Sox4 transcription factor

TGF-β is a pleiotropic cytokine that inhibits the proliferation, differentiation, activation and effector function of cells of the immune system and induces the differentiation of peripheral $CD4^+$ T cells into anti-inflammatory regulatory T cells (Treg cells). Although both Th1 differentiation and Th2 differentiation are inhibited by TGF-β, Th2 differentiation is preferentially inhibited. The IL-4 mediated activation of STAT6 plays an important role in the induction of Th2 cells, as well as in the inhibition of Th1 cell generation. We showed that a combination of IL-4 and TGF-β augments the development of Th1 cells (G-COE-RA, Tofukuji et al., ***J. Immunol.*** 2012: ref. 11). However, the molecular mechanisms underlying the TGF-β-mediated inhibition of Th2 differentiation remain unclear.

We have identified transcription factor Sox4 as a molecule that is induced by TGF-β and downregulates Th2 differentiation. Sox4 is a member of the Sry- related high-mobility group box (Sox) family of transcription factors that plays a key role in the regulation of transcription during developmental processes. To assess the involvement of Sox4 in the TGF-β-mediated inhibition of Th2 differentiation, we performed a series of knockdown experiments. Inhibition of Th2 differentiation by TGF-β was restored significantly by knockdown of Sox4. Next, we analyzed T-cell specific Sox4 transgenic mice and T cell–specific Sox4-deficient mice **(Figure 2)** and showed that Sox4 functions as a critical regulator of Th2 differentiation and Th2 cell–dependent immune responses by *in vitro* and *in vivo* experiments. We also showed that Sox4 bound directly to GATA-3, preventing its binding to GATA-3 consensus DNA sequences, and that it inhibited the differentiation of Th2 cells. In summary, Sox4 is a downstream target of TGF-β, and through its role as a negative regulator of GATA-3, functions a critical regulator of Th2 differentiation and Th2 cell–dependent immune responses (G-COE-RA, fellow Kuwahara et al., ***Nat. Immunol***. 2012: ref. 14).

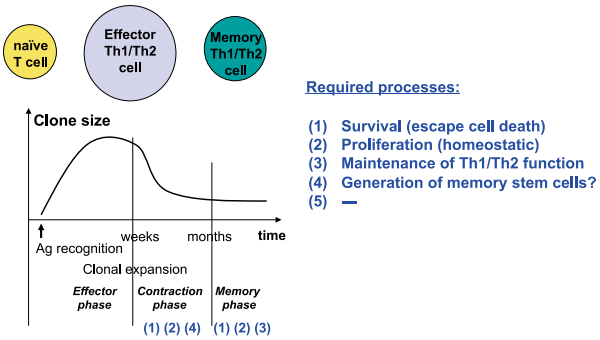


Figure 1. Cellular processes required for the generation of functional memory Th1/Th2 cells.
After antigen recognition by a TCR, naïve CD4 T cells undergo clonal expansion and differentiate into effector Th1/Th2 cells within a couple of weeks. After antigen clearance, most of the effector Th1/Th2 cells are thought to undergo apoptotic cell death during the contraction phase. However, some of the effector cells escape cell death and differentiate into memory type Th1/Th2 cells, and survive for a long time *in vivo*. Several processes, including cell survival/escape from cell death, proliferation/homeostatic proliferation, and the maintenance of Th1/Th2 cell function are required for the successful generation of functional memory type Th1/Th2 cells. The concept of memory stem cells has also been proposed, but this has not been experimentally proven at this time. (See Ref. 1)

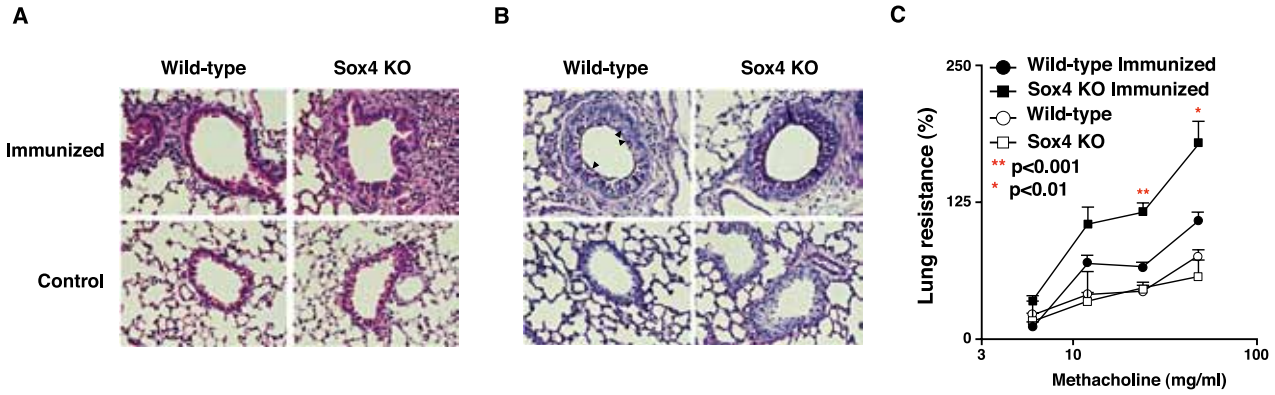


Figure 2. Enhanced OVA-induced allergic airway inflammation in mice with CD4$^+$ T cell–specific Sox4 deficiency.
(A) Microscopy of the lungs from wild-type or *Sox4*$^{fl/fl}$CD4-Cre mice unimmunized (lower) or immunized with OVA (upper) that were fixed and stained with hematoxylin and eosin. (B) Microscopy of the lungs from the mice in (A), fixed and stained with periodic acid–Schiff reagent. (C) The airway resistance of the mice treated as in (A), after treatment with various concentrations of methacholine (horizontal axis), presented as the lung resistance relative to the lung resistance without methacholine treatment.

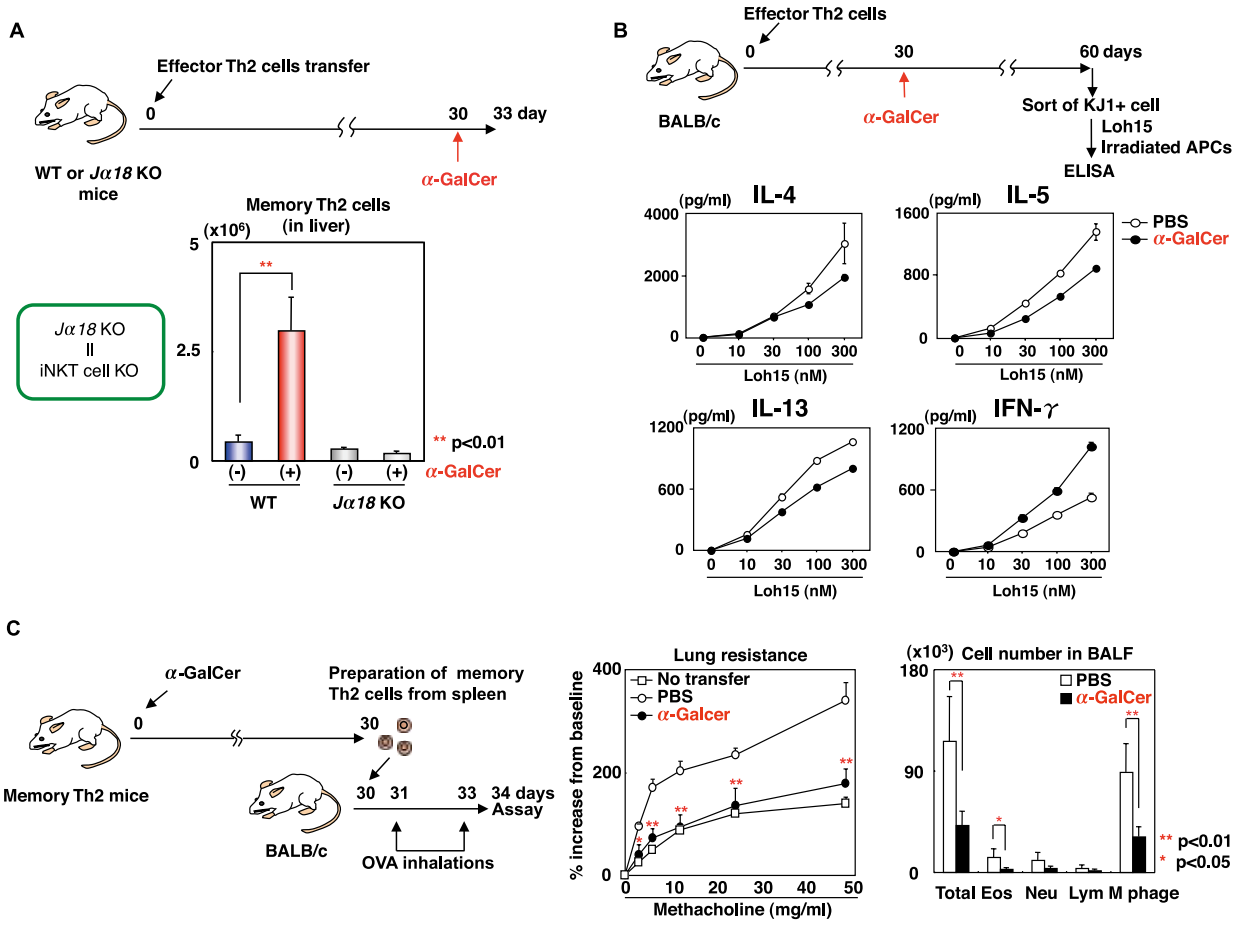


Figure 3. The activation of NKT cells induced the proliferation and altered the function of memory Th2 cells.
(A) The numbers of memory Th2 cells in the livers of WT and Jα18 KO mice at 3 d after α-GalCer administration. (B) Memory Th2 cells were purified from memory Th2 mice treated with or without α-GalCer (100 μg/kg) 30 d before the analysis. Memory Th2 cells (4 × 10^4) were purified from the spleens of these mice and then stimulated with irradiated splenocytes (2 × 10^5) and antigenic peptide (Loh15) at the indicated concentrations. Three days later, culture supernatants were collected, and the cytokine levels were determined by ELISA. (C) Thirty days after α-GalCer administration, memory Th2 cells were transferred as shown, and mice were exposed to OVA aerosol to induce airway inflammation. One day after the last OVA challenge, the AHR was assessed by measuring the lung resistance. The absolute numbers of leukocytes in the bronchoalveolar lavage fluid are shown.

7. Functional modulation of memory Th2 cells induced by activated NKT cells

Natural killer T (NKT) cells belong to a novel lymphoid lineage distinct from T cells, B cells or NK cells. Upon activation, NKT cells produce a large amount of cytokines (IL-2, IFN-γ, IL-4, IL-17, IL-21) and play critical roles in the regulation of various immune responses. A recent study indicated that NKT cells recognize glycolipids from bacteria and play a role as sensors of bacterial pathogens (ref. 15). We have demonstrated that the activation of NKT cells induces the proliferation of memory Th1 and Th2 cells, but not naïve CD4 T cells, through the production of IL-2, IL-4 and IL-21 (ref. 16). This may occur during infection and also under steady state conditions to control the antigen-independent maintenance of the memory CD4 T-cell pool in the body. In addition, activated NKT cells alter the function of memory Th2 cells to a Th1 cell phenotype (Figure 3). Therefore, polarized Th cells display a degree of functional plasticity, and NKT cells control the quality of memory Th2 cells *in vivo*.

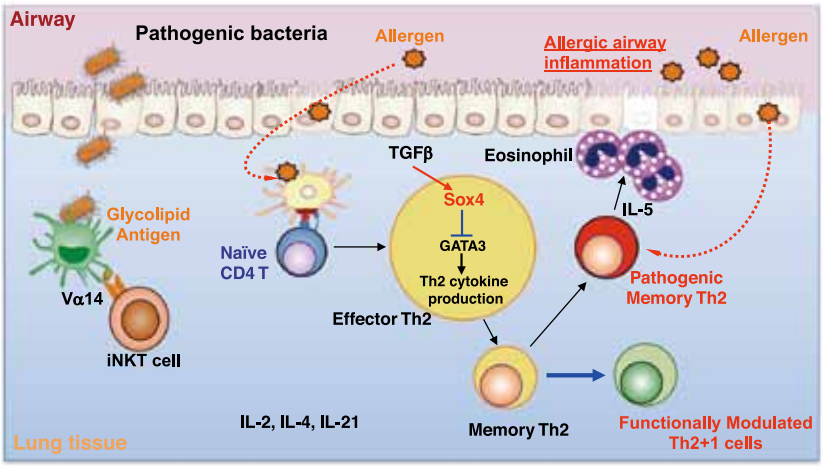


Figure 4. A schematic diagram of our recent research on allergic asthma.
Sox4 is a downstream target of TGF-β, and through its role as a negative regulator of GATA3, it functions as a critical regulator of Th2 differentiation and Th2 cell-dependent immune responses. In addition, activated NKT cells alter the function of memory Th2 cells to induce a Th1 cell phenotype (functionally modulated). We have identified pathogenic memory Th2 cells and clarified the molecular mechanisms required for the induction of memory Th2-dependent eosinophilic airway inflammation. (See Refs. 12, 14 and 16)

Recent publications

1. Nakayama T, and Yamashita M.: Initiation and maintenance of Th2 cell identity. *Curr. Opin. Immunol.* 20: 265-271 (2008)
2. Nakayama T, and Yamashita M.: Critical role of the Polycomb and Trithorax complexes in the maintenance of CD4 T cell memory. *Semin. Immunol.* 21: 78-83 (2009).
3. Yamashita M, Kuwahara M, Suzuki A, Hirahara, K, Shinnakasu R, Hosokawa H, Hasegawa A, Motohashi S, Iwama A, and Nakayama T.: Bmi1 regulates memory CD4 T cell survival via repression of the *Noxa* gene. *J. Exp. Med.* 205: 1109-1120 (2008).
4. Tokoyoda K, Hauser E.A, Zehentmeier S, Hanazawa A, Nakayama T. and Radbruch A.: Organization of immunological memory by stroma. *Nat. Rev. Immunol.* 10(3): 193-200 (2010).
5. Onodera A, Yamashita M, Endo Y, Kuwahara M, Tofukuji S, Hosokawa H, Kanai A, Suzuki Y, Nakayama T. STAT6-mediated displacement of polycomb by trithorax complex establishes long-term maintenance of GATA3 expression in T helper type 2 cells. *J Exp Med.* 207(11): 2493-506 (2010).
6. Hasegawa A, Hayashi K, Kishimoto H, Yang M, Tofukuji S, Suzuki K, Nakajima H, Hoffman R. M, Shirai M, and Nakayama T.: Color-coded real-time cellular imaging of T lymphocyte accumulation and focus formation in mouse asthma model. *J. Allergy Clin. Immunol.* 125(2): 461-468 (2010).
7. Endo Y, Iwamura C, Kuwahara M, Suzuki A, Sugaya K, Tumes DJ, Tokoyoda K, Hosokawa H, Yamashita M, Nakayama T. Eomesodermin controls interleukin-5 production in memory T helper 2 cells rough inhibition of activity of the transcription factor GATA3. *Immunity* 35(5): 733-45 (2011).
8. Kuwahara M, Yamashita M, Shinoda K, Tofukuji S, Onodera A, Shinnakasu R, Motohashi S, Hosokawa H, Tumes D, Iwamura C, Lefebvre V, Nakayama T. The transcription factor Sox4 is a downstream target of signaling by the cytokine TGF-β and suppresses T(H)2 differentiation. *Nat Immunol.* 13(8): 778-86 (2012).
9. Iwamura C, Nakayama T. Role of NKT cells in allergic asthma. *Curr Opin Immunol.* 22(6): 807-13 (2010).
10. Iwamura C, Shinoda K, Endo Y, Watanabe Y, Tumes J. D, Motohashi S, Kawahara K, Kinjo Y, and Nakayama T.: Regulation of memory CD4 T-cell pool size and function by natural killer T cells *in vivo*. *Proc. Natl. Acad. Sci. USA* 109(42): 16992-16997 (2012).

Novel strategies targeting immune and inflammatory pathways for the prevention of cardiovascular diseases

Core Member

Issei Komuro

Cardiovascular Medicine,
Graduate School of Medicine,
The University of Tokyo

Summary

Despite considerable progress in the field of modern medicine, cardiovascular diseases are still the leading cause of death in Western communities. There is a crucial need to elucidate the precise pathology of each disease in order to improve the clinical outcomes. Our research has recently focused on the role of immune cells in the cardiovascular system. We herein show that several types of dysregulation of the immune system play important roles in the onset of atrial fibrillation (AF), congestive heart failure and atherosclerosis. We also have revealed the molecular mechanisms underlying these processes. By targeting these molecules, we could successfully inhibit the initiation of these cardiovascular diseases in mouse models of heart diseases. Our findings opened up a new avenue that will permit the development of new strategies to treat these diseases.

Our next goal is to train research leaders who could extent these findings into clinical practice. We have been promoting a program of translational research in therapeutic angiogenesis to treat ischemic heart diseases, and have recently initiated a clinical trial. We encourage young researchers to be involved in the entire processes of these investigations, including their planning and execution. Such on-the-job training will hopefully create research leaders who are competent in designing and promoting future translational research.

1. Role of cardiac mast cells in the initiation of atrial fibrillation

Atrial fibrillation (AF) is a common arrhythmia that significantly increases the risk of stroke and heart failure. Prevention of AF is therefore a crucial issue. This study demonstrated that mast cells are critically involved in the pathogenesis of AF in stressed hearts. Pressure overload induced mast cell infiltration and fibrosis in the atrium, and enhanced AF susceptibility following atrial burst stimulation under Langendorff perfusion. The induction of both atrial fibrosis and AF was attenuated by the stabilization of mast cells with cromolyn, or by bone marrow reconstitution from mast cell-deficient WBB6F1-Kit$^{W/W\text{-}V}$ mice. Bone marrow-derived mast cells co-cultured with cardiac myocytes or fibroblasts increased the PDGF-A synthesis and promoted cell proliferation and collagen expression in cardiac fibroblasts, which was abolished by treatment with an anti-PDGF α-receptor neutralizing antibody. Consistently, the upregulation of atrial PDGF-A expression in pressure overloaded hearts was suppressed by bone marrow reconstitution from WBB6F1-Kit$^{W/W\text{-}V}$ mice. Furthermore, injection of the anti-PDGFα-receptor neutralizing antibody attenuated the atrial fibrosis and induction of AF in pressure-overloaded hearts. Our results revealed a crucial role for mast cells in AF, and highlighted a potential application of controlling the mast cell-PDGF-A axis to achieve upstream prevention of AF in stressed hearts.

2. The role of 12-lipoxygenase in heart failure

Our previous study showed that 12-lipoxygenase (12-LO) was markedly upregulated during heart failure. We established transgenic mice that overexpressed 12-LO in cardiomyocytes to determine whether increased expression of 12-LO causes heart failure. Echocardiography showed that 12-LO transgenic mice developed systolic dysfunction. Cardiac fibrosis increased in 12-LO transgenic mice with the infiltration of macrophages. The cardiac expression of MCP-1 was upregulated in 12-LO transgenic mice in comparison to wild-type mice. Inhibition of MCP-1 reduced the infiltration of macrophages into the myocardium and prevented systolic dysfunction in 12-LO transgenic mice. Likewise, a disruption of 12-LO significantly reduced the cardiac MCP-1 expression and macrophage infiltration, thereby improving the systolic dysfunction induced by chronic pressure overload. Our results suggest that cardiac 12-LOX is involved in the development of heart failure.

3. Therapeutic angiogenesis by peripheral blood mononuclear cells

The results of a clinical trial of therapeutic angiogenesis for critical limb ischemia revealed that the implantation of peripheral blood mononuclear cells (PBMNC) stimulates skeletal muscle to secrete angiogenic growth factors. These mechanisms could therefore theoretically be applied to ischemic heart diseases (IHD).

Pre-clinical research using a large animal model revealed that this is feasible and safe. We therefore designed a clinical phase I/II trial of PBMNC therapy to treat patients with severe IHD. The trial was started as soon as it was approved by the Ethics Committee of Chiba University. With help from the Division of Clinical Research, we have educated young researchers in the

planning and execution of translational research. These researchers received on-the-job training that involved the entire processes of these investigations. These activities will hopefully create research leaders who are competent in planning and promoting future translational research.

While the new clinical trial was successful, a population of patients ended up being resistant to this approach. We compared the profiles of the treatment-resistant group with the treatment-responsive group, and found a decrease in Notch signaling activity in the PBMNCs of the treatment- resistant group. We validated the therapeutic efficacy of the transfer of the PBMNCs overexpressing a Notch ligand and of an agonistic antibody for Notch signaling in a mouse model of limb ischemia. These results suggest that the activation of Notch signaling in the treatment-resistant group might improve the clinical efficacy of the treatment.

4. Role of C1q-Wnt signaling in hypertension-induced atherosclerosis

Hypertension is the leading risk factor for many cardiovascular diseases. High blood pressure induces the structural remodeling of arteries (hypertensive arterial remodeling), which leads to arteriosclerosis and end-organ damage. However, the signaling cascade that triggers arterial remodeling after blood pressure elevation remains elusive. We have recently reported that complement C1q activates Wnt signaling and induces aging-associated impairment of skeletal muscle regeneration.

We identified a critical role for complement C1q-induced activation of Wnt signaling in hypertensive arterial remodeling. The proliferation of vascular smooth muscle cells (VSMCs) and activation of Wnt signaling in VSMCs were observed after blood pressure elevation. *β-catenin* gene deletion and chemical inhibition of Wnt signaling attenuated the hypertension-induced VSMC proliferation. Macrophages were recruited, and C1q was highly expressed in the vessel wall following blood pressure elevation. Macrophage depletion, C1s inhibition, and *C1qa* gene deletion suppressed the hypertension-induced activation of Wnt signaling and proliferation of VSMCs, and prevented hypertensive arterial remodeling. Our findings collectively indicate that macrophage-derived C1q triggers hypertensive arterial remodeling through the activation of Wnt signaling in VSMCs and suggest that there is a previously unknown link between innate immunity and Wnt signaling. Inhibition of the C1q-induced activation of Wnt signaling may provide a novel therapeutic strategy to prevent arteriosclerosis in patients with hypertension.

5. Senescent vascular endothelial cells and chronic inflammation in cardiovascular diseases

We share the honor of being one of the pioneers in studying the link between cellular senescence and cardiovascular diseases. Senescent vascular endothelial cells show several types of dysfunction associated with cardiovascular diseases. One important characteristic is their persistent upregulation of inflammatory genes. Prolonged invasion of inflammatory cells, such as macrophages and T cells, into the internal structure of blood vessels and adipocytes exacerbates atherosclerosis and diabetes. This immune response is called chronic inflammation, and is considered to be the major cause of not only cardiovascular diseases, but also most age-related diseases, such as cancer and cognitive decline. Our working hypothesis is that cellular senescence largely contributes to chronic inflammation and the progression of cardiovascular diseases. Thus far, this hypothesis seems to be correct.

We studied the pathways that regulate the cellular senescence of vascular endothelial cells. We identified Notch signaling as a protective pathway against cellular senescence in this cell type. Overexpression of a Notch ligand slowed down the process of cellular senescence of cultured human vascular endothelial cells, apparently by blocking the expression of the senescence inducer, p16. This was done by two mechanisms. First, Notch signaling enhanced the expression of MKP1. MKP1 inactivated MAPK p38, an activator of p16. Thus, MKP1 increase led to p16 downregulation and blocked the cellular senescence of vascular endothelial cells. The second mechanism was the activation of transcription factor Id1 by Notch signaling. Id1 is an inhibitor of p16. Thus, Id1 activation led to an additive effect on decreasing p16 and enhanced the prevention of cellular senescence. Therefore, Notch activation, in addition to limb ischemia therapy, might have a therapeutic effect by protecting vascular cells against cellular senescence, and thereby preventing chronic inflammation.

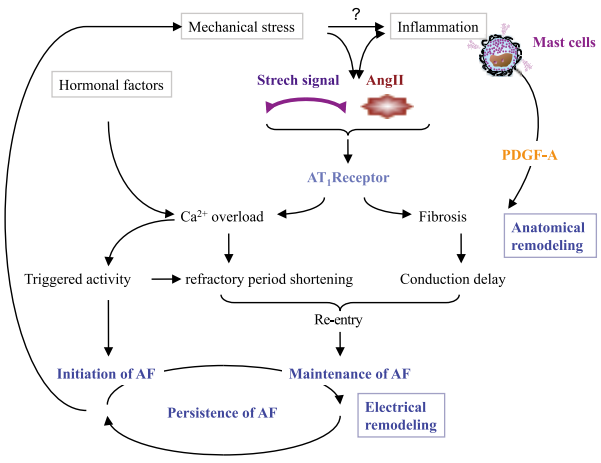


Figure 1. The role of mast cells in the pathogenesis of atrial fibrillation.
Mast cells produce PDGF-A and promote fibrosis of the atrial wall, which subsequently increases the susceptibility of the heart to stimuli that initiate atrial fibrillation.

We also found that obese mice that had been fed a high calorie diet had an increased number of senescent endothelial cells. This was caused by the activation of p53, a major stimulator of cellular senescence. In addition to the increased food consumption, these mice consumed fewer calories than wild type mice. This was attributable to a decrease of the energy expenditure in the muscle. In endothelial-specific p53 conditional knockout mice, the energy consumption in the muscle was rescued, and the mice were leaner than wild type mice when fed with high calorie diet. These results led us to conclude that vascular endothelial cells controlled the energy consumption in the muscle. We identified two pathways that mediate the signaling from blood vessels to the muscle. Vascular endothelial cells produced NO synthesized by eNOS, which promoted mitochondrial biogenesis and energy consumption. The endothelial cells transported glucose from the blood to the muscle via the glucose transporter, GLUT1, which led to increased consumption of glucose in the muscle. These two pathways were dampened by cellular senescence. These results suggest that the senescence of endothelial cells leads to decreased energy consumption and obesity, which eventually induces chronic inflammation, leading to metabolic and cardiovascular diseases, such as diabetes and atherosclerosis.

We also identified the molecular mechanisms by which pro-inflammatory signals were retained in senescent endothelial cells. This should contribute to the future development of therapeutic technologies for multiple cardiovascular diseases, since chronic inflammation is a major cause of such diseases, and our previous reports suggest that the inflammatory signaling by senescent endothelial cells contributes to this process. We identified the CDC42 and NF-κB pathways as the pro-inflammatory signaling pathways in senescent endothelial cells. We confirmed these results in several mouse models. Interestingly, these mechanisms were conserved in roundworms, which do not have a blood vessel system. Knockdown of the homologs of CDC42 blocked the expression of inflammatory gene-like genes in roundworms, and extended their lifespan. This suggests that the knockdown of inflammatory pathways may extend the lifespan of patients of age-related diseases with chronic inflammation. Therefore, our results indicate that the pathways identified to underlying the senescence of endothelial cells can modulate the lifespan by regulating chronic inflammation. We are now investigating the role of CDC42 in the chronic inflammation and atherosclerosis in several mouse models.

In summary, we studied the cell signaling leading to cellular senescence and how senescent endothelial cells contributed to chronic inflammation and cardiovascular diseases. These findings have the potential to lead to the development of novel treatments for age-related diseases, including cardiovascular diseases, by targeting their common mechanism, chronic inflammation.

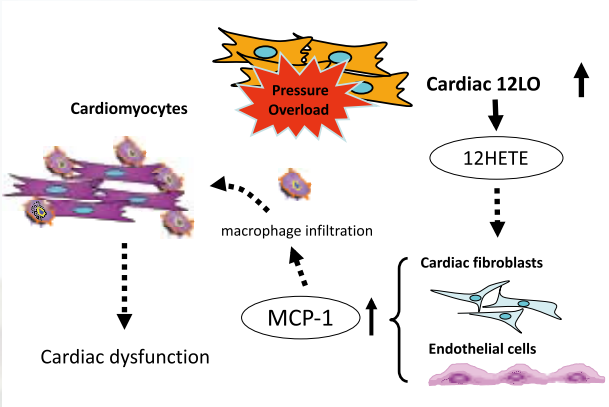


Figure 2. 12-LO expression is upregulated in cardiomyocytes by various stimuli, such as pressure overload.
The enhanced production of 12-HETE by 12-LO increases the expression of MCP-1 by cardiac fibroblasts and endothelial cells, thereby inducing the infiltration of macrophages into the myocardium. This infiltration in turn induces cardiac fibrosis and systolic dysfunction.

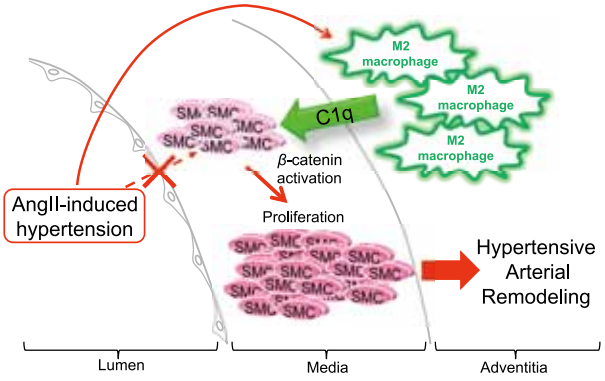


Figure 3. The C1q-induced activation of Wnt signaling causes hypertensive arterial remodeling.
M2 macrophages infiltrate into the aortic adventitia soon after blood pressure elevation and secrete complement C1q, which activates canonical Wnt signaling and induces the proliferation of VSMCs.

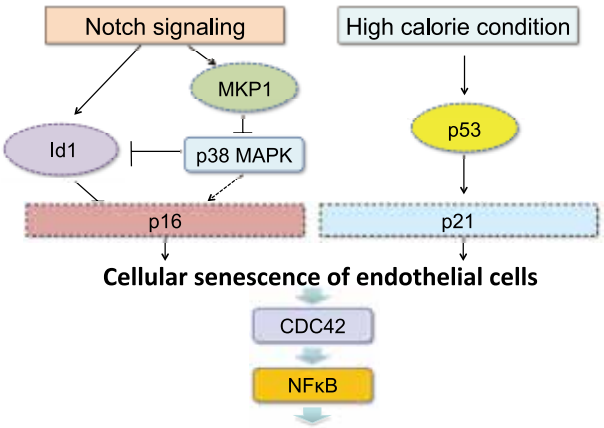


Figure 4. Inactivation of Notch signaling promotes cellular senescence in a p16-dependent manner.
Consumption of a high calorie diet promotes cellular senescence in a p21-dependent manner. Senescent endothelial cells activate the CDC42 and NFκB pathways. These pathways induce chronic inflammation and contribute to the progression of cardiovascular diseases.

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Control of memory B cell development and its application to immunotherapy

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Summary

The aim of our study is to elucidate the molecular mechanisms that govern the differentiation and maintenance of immune memory B cells. Since we have previously studied the role of the *Bcl6* gene product in high-affinity memory B cell development through germinal centers, we will continue to study these molecular mechanisms. We will also attempt to expand our research on vaccine development for infectious diseases and allergies. Through these research activities, we will eagerly train and promote young doctoral and postdoctoral researchers in the field of basic immunology.

1. A role for Bcl6 in high-affinity IgE antibody-producing B cells

Germinal centers (GCs) are the sites of development of high-affinity memory B cells and long-lived plasma cells. After antigen-activated B cells collaborate with activated T follicular helper (Tfh) cells on the follicular border, some of the activated B cells rapidly proliferate in the follicle to generate GCs. These proliferating B

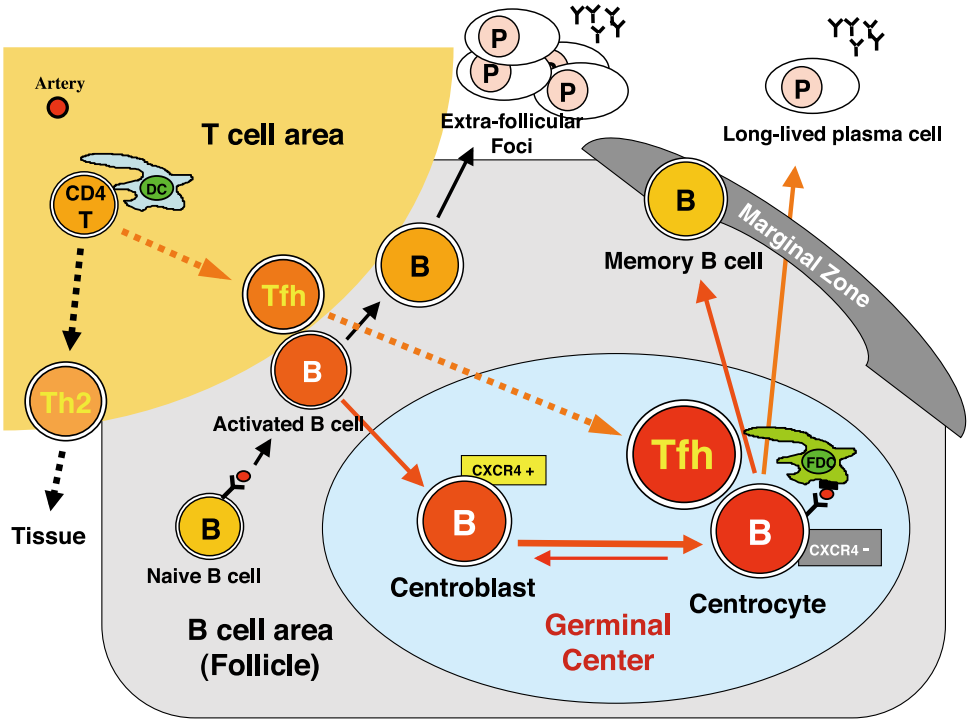

Figure 1. High-affinity antibody-producing B cells develop in germinal centers.
After Ag-activated B cells collaborate with activated T follicular helper (Tfh) cells, some of the activated B cells rapidly proliferate in the follicle to generate germinal centers (GCs). These proliferating B cells, called centroblasts, undergo somatic hypermutation. Then, the centrocytes express high-affinity IgG Abs that competitively bind to Ags on follicular dendritic cells (FDCs) and also collaborate with GC-Tfh cells. These activated centrocytes scarcely proliferate and differentiate into high-affinity memory B cells or long-lived plasma cells.

cells, called centroblasts, undergo somatic hypermutation (SHM) and form the dark zone of GCs. Then, the centroblasts turn to differentiate into centrocytes with Ig class-switching to IgG. The centrocytes migrate to areas adjacent to the dark zone of the GCs. In the area called the light zone of the GCs, the centrocytes express high affinity IgG Abs that competitively bind to antigens on follicular dendritic cells and also collaborate with GC-Tfh cells. These activated centrocytes scarcely proliferate and differentiate to memory B cells or long-lived plasma cells.

Since Bcl6 is highly expressed in GC B cells and suppresses the expression of Cε germline transcript, high-affinity IgE memory B cells are suggested to be differentiated from IgG1 B cells developed in GCs by a sequential Ig class switch from IgG1 to IgE. However, the role of Bcl6 in the inhibition of the sequential Ig class switch in GC B cells is unknown. In this study, when splenic B cells from Bcl6-deficient (KO) and Bcl6-transgenic (Tg) mice were stimulated with anti-IgM and anti-CD40 Abs plus IL-4, $IgG1^{+}IgE^{+}$ B cells were detected in KO B cell cultures, but not in Tg B cell cultures. When activated B cells were simultaneously stimulated with IL-4 and IL-21, the expression of Cγ1 germline transcript in wild-type (WT) and KO B cells was enhanced by IL-21 stimulation. IL-21 stimulation suppressed the Cε expression in WT B cells. However, this suppression was not observed in KO B cells, suggesting that the IL-21-mediated suppression of the Cε expression is due to Bcl6. Therefore, Bcl6 controls the Cγ1 and Cε expressions and stabilizes the Ig class switch to IgG1 in activated B cells simultaneously stimulated with IL-4 and IL-21.

2. The role of PHF11 in the activation of murine B cells

Plant homeodomain finger protein-11 (PHF11) is a novel asthma-susceptibility gene, as confirmed by the linkage study for allergic diseases, and is highly expressed in B cells. In order to elucidate the role of PHF11 in the activation of B cells, we generated Tg mice. When splenic B cells were stimulated with anti-IgM and anti-CD40 Abs plus IL-4, the absolute cell numbers and percentages of IgG1 B and IgE B cells in the Tg B cell culture were higher than those in the WT B cell culture until day 6 of culture. The Tg B cells produced larger amounts of IgG1 and IgE Abs as compared with the WT B cells in the culture supernatants. When Tg

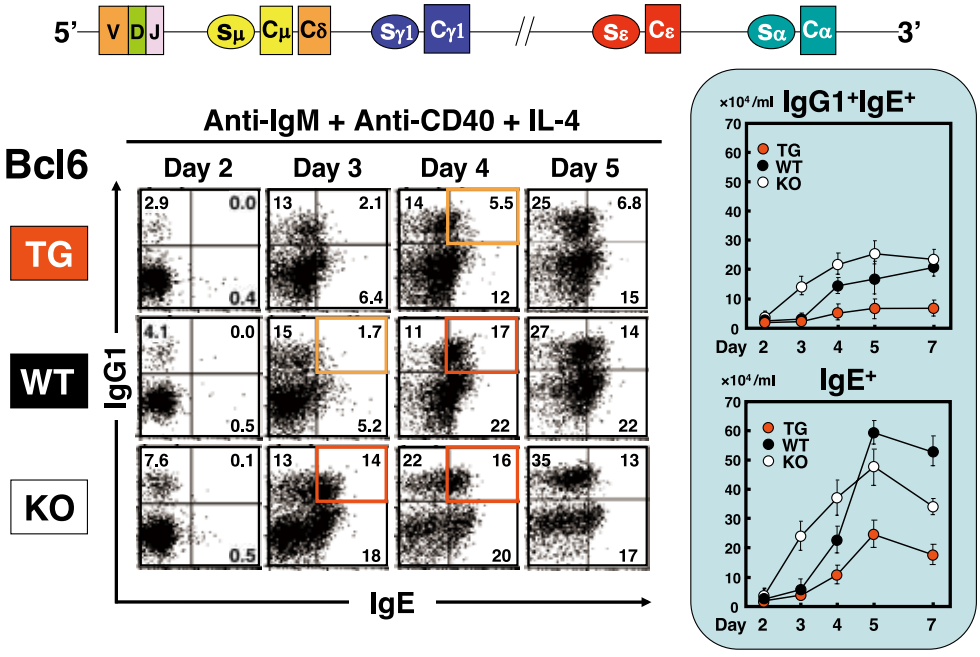

Figure 2. The role of Bcl6 in the Ig class switch to IgE in activated B cells.
When splenic B cells from wild-type (WT), Bcl6-deficient (KO) and Bcl6-transgenic (TG) mice were stimulated with anti-IgM and anti-CD40 Abs plus IL-4, $IgG1^{+}IgE^{+}$ B cells were detected in the WT B cell culture and the KO B cell culture, but not in the TG B cell culture. (These results were modified from publication 2.)

mice were immunized intraperitoneally with NP16-CG, the absolute numbers of total NP-binding GL7$^+$ B cells in the spleens of the Tg mice were similar to those in the WT mice 10 days after immunization. However, the percentages of NP-binding IgG1 B cells in the Tg mice were higher than those in the WT mice. These results suggest that PHF11 plays a role in the development of IgG1 and IgE B cells.

3. IL-4 and IL-21 inversely regulate the CXCR4 expression in activated B cells

In GC B cells, CXCR4 is upregulated in centroblasts where it is required for dark zone localization. Centrocytes, which localize in the light zone, exhibit a lower CXCR4 expression compared with centroblasts. IL-4 and IL-21 from follicular helper T cells are important for GC formation. However, little is known about their precise roles in the differentiation of GC B cells. We stimulated splenic B cells with anti-IgM and anti-CD40 Abs plus IL-4 on day 0 of culture, then sequentially stimulated the cells with IL-4 or IL-21 on day 2 of culture. Stimulation of wild-type B cells with IL-4 induced larger amounts of CXCR4 on activated B cells on day 4 of culture. Although Bcl6-deficient B cells expressed as much CXCR4 as wild-type B cells on day 2 of culture, they could not preserve the expression until day 4 of culture. When IL-21 was sequentially added to the culture, the CXCR4 expression was reduced in the activated wild-type B cells. Therefore, the inverse effects of IL-4 and IL-21 on the CXCR4 expression in activated B cells with a Bcl6 expression may explain their distinct roles in the differentiation of GC B cells.

4. The role of ADAR1 in the induction of somatic hypermutation in GC B cells

Somatic hypermutations (SHMs) of immunoglobulin genes accumulate in GC B cells. Bcl6, which functions as a transcriptional repressor, plays a role in GC B cells; however, the role of Bcl6 in the accumulation of SHMs remains unclear. Ig class-switch recombination (CSR) simultaneously induces somatic mutations in the IgM class-switch (Ig-Sμ) region of IgG B cells. Surprisingly, in this study, mutations were detected in the Ig-Sμ region of Bcl6-deficient IgM B cells without CSR and were primarily generated by conversion of adenosine to guanosine, suggesting the presence of a novel DNA mutator in B cells. Activation-induced cytidine deaminase (AID) is a cell-intrinsic source and belongs to the RNA-editing cytidine deaminase family. We looked for adenosine-targeted RNA-editing genes as a novel

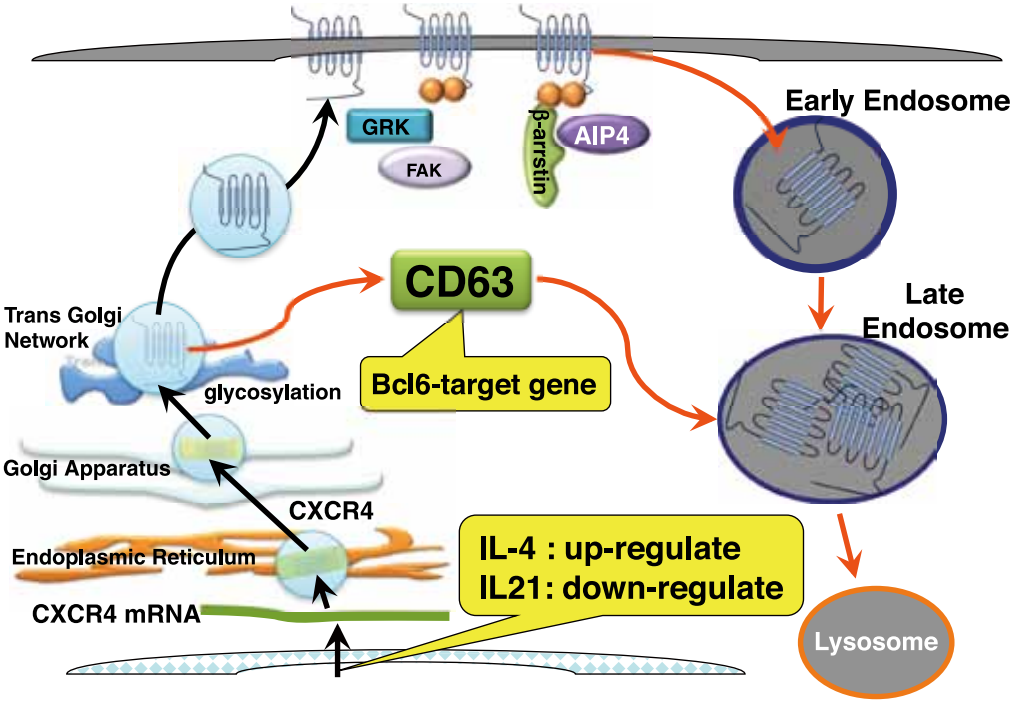

Figure 3. IL-4 and IL-21 inversely regulate the CXCR4 expression in activated B cells.
The CXCR4 expression was upregulated and downregulated in activated B cells by stimulation with IL-4 and IL-21, respectively. In germinal center B cells, the CXCR4 expression was upregulated in centroblasts not only by IL-4 stimulation, but also by reduction of the CD63 expression by Bcl6.

inducer. The adenosine deaminase acting on RNA (ADAR) family converts the adenosine of pre-mRNA into inosine, which is subsequently translated into guanosine; thus, we examined the expression of ADAR family genes in various cells obtained from Bcl6-deficient mice. The *adenosine deaminase acting on RNA1 (ADAR1)* gene was found to be overexpressed in the Bcl6-deficient cells, and its promoter analysis revealed that *ADAR1* is a molecular target of Bcl6. Exogenous *ADAR1* induced adenosine-targeted DNA mutations in IgM B cells obtained from ADAR1-transgenic mice. We are currently examining the physiologic role of ADAR1 in the induction of SMH in GC B cells.

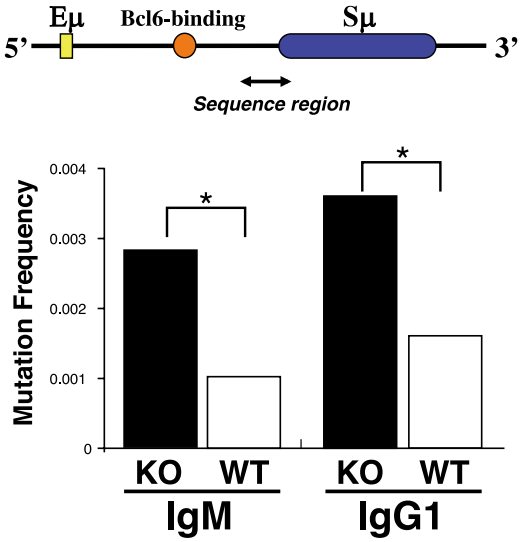

Figure 4. Somatic mutations in the Ig-Sμ region of Bcl6-KO B cells.
Splenic IgM B cells obtained from wild-type (WT) and Bcl6-deficient (KO) mice were stimulated with LPS and IL-4 for four days. The Ig-Sμ region of the IgM B cells and the IgG1 B cells was sequenced. The frequency of mutations is described. *: $p < 0.005$/

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Identification of risk factors for allergies and Kawasaki disease

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I. Risk factors for allergic diseases

Summary

The cause of allergic diseases is generally traced to the interplay between genetic and environmental factors. Over the last decade, the prevalence of allergic diseases has rapidly increased. This rapid increase is unlikely to have been caused by genetic factors, but rather by environmental factors. Genetic factors, however, are important because they confer individual differences in responses to environmental factors. The aim of our study was to clarify the interactions between genes and environmental factors in the development of atopy and allergic diseases.

1. Genetic epidemiology of atopy and allergic diseases in Japanese children

We began to investigate the environmental and genetic factors involved in the development of atopy and allergic diseases in Japanese school children in 2006. We investigated the interactive relationships between day care attendance and genetic polymorphisms and their effects on the serum total and specific IgE levels. Children with the C/T or T/T genotype of CD14-550C/T who attended day care exhibited significantly lower total IgE levels (P=0.000097). Day care showed little effects on the total IgE levels in children with the C/C genotype. Children with the Val/Ile genotype of IL4R who attended day care exhibited significantly lower total IgE levels (P=0.0012). After correcting for confounding factors, the interaction between day care and CD14-550C/T was significant for the total IgE level (P=0.0046) and the mite-specific IgE level (P=0.00047) as well as for atopy (P=0.0097). Moreover, the interaction between day care and IL4R Ile50Val was significant for the total IgE level (P=0.019) and the mite-specific IgE level (P=0.0025). The effects of day care on the total and specific serum IgE levels appeared to be affected by the children's genetic backgrounds.

2. Study of the association between the C3 gene and adult and childhood asthma

The complement system plays an important role in the immunological response against invading microorganisms. We previously reported the existence of an association between single nuclear proteins (SNPs) in the C3 gene and asthma. However, no functional SNPs associated with susceptibility to asthma have been identified.

We analyzed 26 SNPs in the C3 gene and its promoter region to narrow down the regions associated with childhood and adult asthma. Childhood and adult atopic asthma patients and healthy controls were recruited from urban cities in Japan and genotyped. A single SNP analysis revealed that a SNP (SNP24, rs11569562) located in intron 31 of the C3 gene was associated with adult asthma (corrected P (Pcor)=0.030). In the linkage disequilibrium (LD) block 4 spanning exons 24 to 41, the frequency of the CCC haplotype in the adult asthma patients was significantly higher than that in the adult controls (Pcor=0.038). Our results suggest that LD block 4 confers susceptibility to adult asthma.

3. Roles of matrix metalloproteinase genes in the development of allergic airway diseases

Matrix metalloproteinases (MMP) genes consist of a family of 24 genes in humans that are involved in various biological processes. Nine MMP genes (MMP7, 20, 27, 8, 10, 1, 3, 12, 13) are clustered on chromosome 11.

We investigated the association between the IgE levels and SNPs of MMP9 in school children. Two SNPs associated with childhood asthma were found to be associated with cedar pollinosis. The ORs for pollinosis were higher than those for asthma. Our results suggest that the MMP9 gene confers susceptibility to cedar pollinosis in Japanese children. The SNP association tests of the MMP gene cluster region revealed associations between SNPs located in the MMP3, MMP7, MMP8, MMP12 and MMP13 genes. Among these associations, we obtained findings that may elucidate the pathophysiological roles of MMP12.

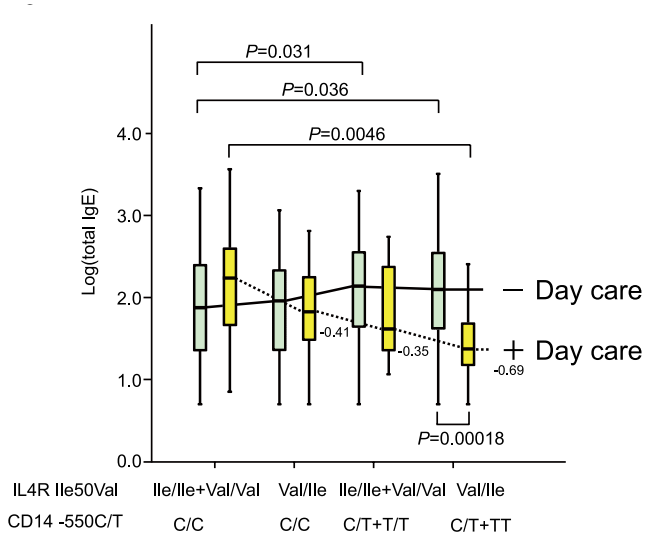

Figure 1. Interactions between specific genotypes and day care attendance were observed with respect to the total IgE levels in school children.
The school children were grouped according to a combination of CD14-550C/T and IL4R Ile50Val genotypes, as shown in the graph. A box plot of log10 (total IgE) is shown for children who attended day care (+Day care) and for those who did not (-Day care). Children with the C/T or T/T genotype of CD14-550C/T who attended day care exhibited significantly lower total IgE levels. Day care exerted a slight effect on the total IgE levels among children with the C/C genotype. Children with the Val/Ile genotype of IL4R who attended day care exhibited significantly lower total IgE levels. Day care exerted slight effects on the total IgE levels among children with the Val/Val genotype.

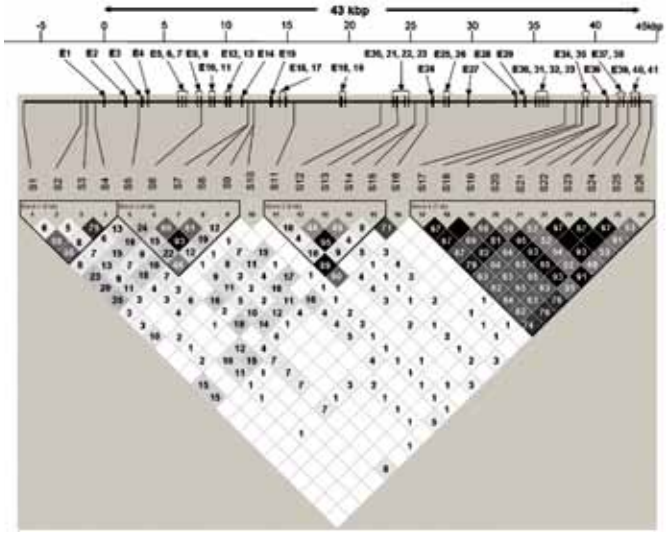

Figure 2. Structure of the C3 gene and the location of SNPs and their linkage equilibrium map.
Exons are indicated by black boxes. Numbers starting with E stand for exons, while those starting with S stand for SNPs. Pairwise linkage disequilibrium (LD) (r^2) was estimated from 96 control subjects. LD blocks were defined by the solid spine of LD using the "Haploview" program. The number in each cell represents r^2 (×100), the black cells represent r^2=1 and the white cells represent r^2=0. Each cell is colored in a graduated manner according to the strength of LD. A haplotype of LD block 4 was found to be significantly associated with adult atopic asthma.

Ⅱ. Identification of susceptibility genes for Kawasaki disease

Summary

Kawasaki disease (KD) is a systemic vasculitis syndrome of childhood that is characterized by a high fever, skin rashes and so on. Previously, we conducted a genome-wide linkage study of KD using the affected sib-pair method and identified 10 candidate chromosomal regions harboring susceptibility variants for KD. After performing systematic screening of single nucleotide polymorphisms (SNPs) in these candidate regions using case-controlled association studies, we identified a functional SNP of the *ITPKC* gene located at 19q13.2 that confers KD in both Japanese and American children. With the aim of further identifying susceptibility SNPs, we carried out a positional candidate gene study of the 4q35 region and a genome-wide association study.

Positional candidate gene study of the 4q35 region

1. Screening of HapMap tagSNPs and fine mapping of the CASP3 gene region

We focused on *CASP3*, which is located at 185.8Mb on chromosome 4 close to the linkage peak at 4q35 (184.9Mb). We selected four tagging SNPs (rs4647693, rs2696057, rs2720378 and rs2705881) representing haplotypes at the *CASP3* region. For the first stage of screening, the genotypes at these four locations were determined in 638 KD patients and 1,031 controls. Because three SNPs exhibited significant associations with KD ($P < 0.05$ after the Bonferroni correction for the

four tests), we then resequenced the 36kb of the *CASP3* gene region in 24 Japanese subjects (12 KD subjects and 12 controls) and genotyped the first case-controlled panel for 34 additional variants and compared allele frequencies. Twenty-five of the 46 variants (12 tagging SNPs + 34 additional variants) exhibited P values < 0.001 (P < 0.05 after a conservative Bonferroni correction for 46 tests) and most were clustered in the 5' region of *CASP3* (Figure 3). To validate the associations and identify the causative variants, these 25 loci were further examined in an independent Japanese case-controlled panel with 282 KD patients and 378 controls. Again, all of the 25 variants showed the same trend of association, and rs2720378 was found to be the most significant in a meta-analysis using the Mantel-Haenszel method ($P = 3.5 \times 10^{-9}$).

2. Determination of the responsible SNP with a functional effect among associated SNPs

We next assessed the functional significance of the variants in *CASP3*. We screened for possible enhancer activity around the associated variants using a reporter gene assay and found that the sequence surrounding rs72689236 located in the 5' untranslated region of *CASP3* exhibited an enhancer activity level that was significantly lower for the risk allele (A) than for the protective allele (G). In order to further elucidate the enhancer element that may lie near rs72689236, we conducted an electrophoretic mobility shift assay (EMSA) using nuclear extract from PBMCs and rs72689236 oligonucleotides as probes. We observed a band shift using the probe specific to the G allele. Using a supershift assay with antibodies against transcription factors, we confirmed that the protein was NFATc2.

Genome-wide association study (GWAS)

1. GWAS and follow-up of associated SNPs

To identify additional risk loci, we conducted a GWAS using 428 KD patients and 3,379 controls. We found an association with genome-wide significance ($P < 5.0 \times 10^{-8}$) at an intergenic region between *FAM167A* and *BLK* on 8p22-23 ($P = 3.3 \times 10^{-11}$, Figure 4). We prepared two case-controlled panels (panel 1: 470 cases and 378 controls, panel 2: 284 cases and 569 controls) independent from those used in the GWAS and performed genotyping for the top 100 SNPs exhibiting *P* values smaller than 5.8×10^{-5}. In both panels, SNPs in the *FAM167A-BLK* region showed an association with KD, and the lowest *P* value in a meta-analysis was 8.2×10^{-21} (rs2254546). In the follow-up association studies of the top ranked SNPs, two additional susceptibility loci, the *CD40* gene in 20q12-13.2 (rs4813003) and the HLA class II region in 6p21 (rs2857151), were identified. SNPs near *ITPKC* and *CASP3* also showed a trend of an association, and the *P* values in the meta-analyses of the GWAS and follow-up studies achieved genome-wide significance levels.

2. Replication of a previously reported association of a functional SNP of the FCGR2A gene

An association of a functional SNP of *Fc fragment of IgG, low affinity IIa, receptor (FCGR2A)* located on chromosome 1 has been reported in a GWAS of European KD patients. The SNP, rs1801274, alters the amino acid translation of the 131st codon from histidine to arginine (H131R). We confirmed that the same risk allele (H) of rs1801274 conferred KD in our Japanese Kawasaki disease samples ($P = 1.6 \times 10^{-6}$).

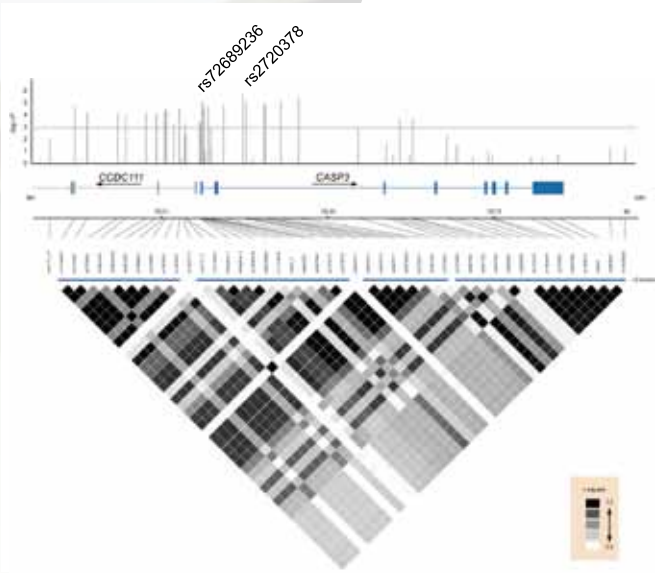

Figure 3. Linkage disequilibrium (LD) structure of the *CASP3* locus and the association of the variants with KD in Japanese subjects.
Pairwise LD plots with 46 variants distributed across the 36 kb region in and surrounding *CASP3* are illustrated using the Haploview software program. Values for r^2 were calculated using genotype data obtained from Japanese control samples (n=1031). The blue horizontal bars under the SNP IDs represent LD blocks defined by Gabriel's rule. The genomic organizations of *CASP3* and the *coiled-coil domain containing 111 (CCDC111*; only the 5' region is shown) are illustrated with blue and gray boxes representing the exons. The arrows under the gene names indicate the orientation of transcription. The position and negative log of the P values obtained from the genetic association study (637 KD cases and 1,031 controls; allelic frequency comparison) for each variant tested are indicated by vertical bars in the upper panel. The threshold for statistical significance ($P = 0.001$) is indicated by a gray horizontal line in the upper panel.

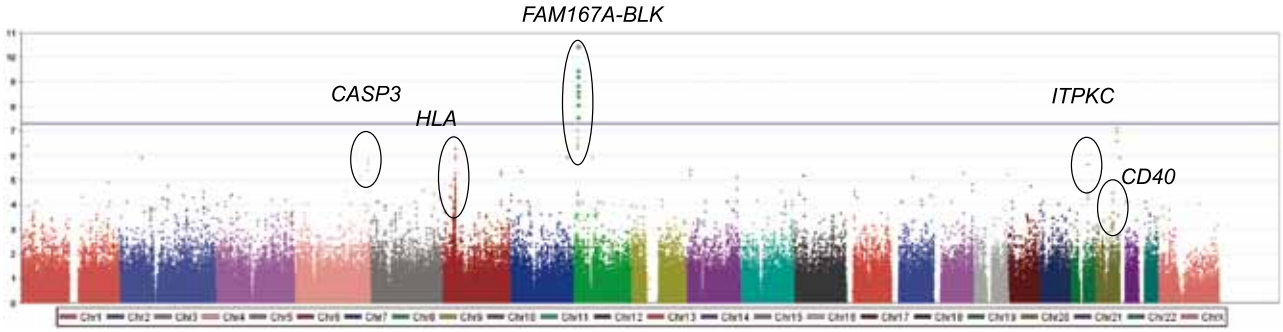

Figure 4. Genome-wide association results.
P values for the 463,793 SNPs on autosomes obtained using the Cochran-Armitage trend test and the 10,010 SNPs on chromosome X obtained using meta-analyses of allele frequency comparisons for both genders. The red and blue horizontal lines indicate the significance threshold of the GWAS ($P < 5.0 \times 10^{-8}$) and the P value cut-off level for selecting the top 100 SNPs for the follow-up studies ($P < 5.8 \times 10^{-5}$), respectively.

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T Cell-mediated Immune Regulation in Allergic and Autoimmune Diseases

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INTRODUCTION

Accumulating evidence indicates that T helper (Th) 2 cell-derived cytokines play critical roles in orchestrating and amplifying allergic inflammation in asthma. In addition, newly identified cytokines including TSLP, IL-25 and IL-33 are involved in the induction of allergic inflammation in patients with asthma. On the other hand, a new subtype of $CD4^+$ T cells characterized by the production of interleukin 17 (Th17 cells) has recently been described. The major feature of this subpopulation is that the cells can generate significant amounts of pro-inflammatory cytokines, therefore, they appear to be critically involved in the pathogenesis of autoimmune diseases. Our group is interested in the regulatory mechanisms of allergic airway inflammation in asthma and in the regulation of T cell differentiation, and we hope to contribute to the development of a new therapeutic approach against asthma and autoimmune diseases. I herein summarize the recent discoveries made by our group.

1. Roles of the IL-23-Th17 Cell Axis in the Regulation of Th2 Cell-Mediated Eosinophilic Airway Inflammation in Mice

The IL-23-IL-17A producing $CD4^+$ T cell (Th17 cell) axis plays important roles in the development of chronic inflammatory diseases, including autoimmune diseases. However, the role of the IL-23-Th17 cell axis in the regulation of allergic airway inflammation is still largely unknown. We employed a mouse model of asthma to examine whether the IL-23-Th17 cell axis was involved in inducing antigen-induced allergic airway inflammation. We found that IL-23 mRNA was expressed in the lungs of sensitized mice upon antigen inhalation, and that neutralization of IL-23 decreased antigen-induced eosinophil recruitment into the airways. In accordance with these findings, the enforced expression of IL-23 in the airways significantly enhanced antigen-induced eosinophil recruitment and Th2 cytokine production in the airways. Moreover, adoptive transfer of antigen-specific Th17 cells significantly enhanced the antigen-induced, Th2 cell-mediated eosinophil recruitment into the airways (Figure 1).

In addition, we found that IL-22, one of Th17 cell-derived cytokines, was produced by $CD4^+$ T cells upon antigen challenge, that the neutralization of IL-22 by an anti-IL-22 antibody in the effector phase enhanced antigen-induced eosinophil recruitment into the airways, and that intranasal administration of recombinant IL-22 inhibited antigen-induced eosinophil recruitment into the

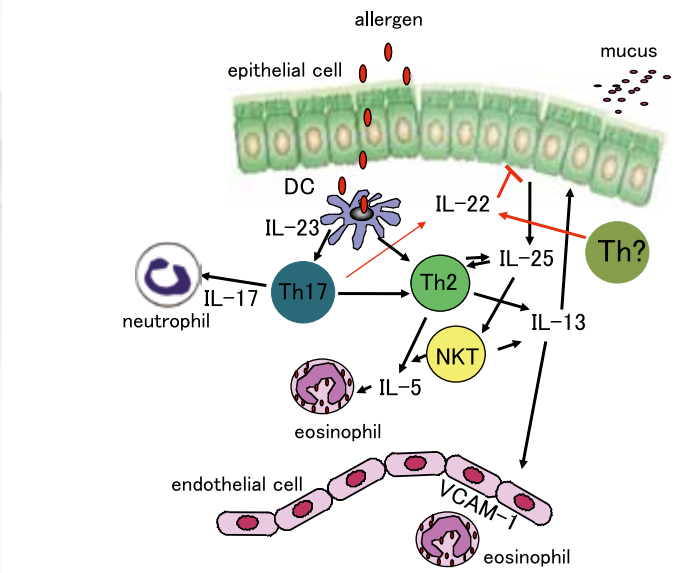

Figure 1. A schematic illustration of the roles of the IL-23-Th17 cell axis in airway inflammation
Upon stimulation with antigens and some pathogens, DCs produce IL-23, which enhances the development and maintenance of Th17 cells. Th17 cell-derived cytokines, such as IL-17A and IL-17F, enhance the recruitment of neutrophils into the airways. In addition, Th17 cells enhance the Th2 cell-mediated allergic airway inflammation. The effector cytokines of Th17 cells, such as TNF-α, may collaborate with IL-13 to recruit more eosinophils into the airways through the production of chemokines. On the other hand, IL-22, one of Th17 cell-derived cytokines, inhibits Th2 cell-mediated allergic airway inflammation by inhibiting the IL-25 production from epithelial cells.

airways. We also found that the anti-IL-22 antibody enhanced antigen-induced IL-25 production in the airways, and that co-injection of the anti-IL-25 antibody reversed the enhancing effect of the anti-IL-22 antibody on antigen-induced eosinophil recruitment into the airways. Our results indicate that the IL-23-Th17 cell axis plays multiple roles in regulating antigen-induced eosinophilic airway inflammation (Figure 1).

2. Regulation of IL-21 Production in CD4$^+$ T Cells

It has been shown that IL-21 is produced by Th17 cells, functions as an autocrine growth factor for Th17 cells, and plays critical roles in autoimmune diseases. In this study, by establishing a method for the intracellular staining of IL-21, we found that, although IL-21-producing CD4$^+$ T cells developed preferentially under Th17-polarizing conditions, a considerable number of IL-21-producing CD4$^+$ T cells were negative for intracellular IL-17A and IL-17F. We also found that IL-6 potently induced the development of IL-21-producing CD4$^+$ T cells without the induction of IL-4, IFN-γ, IL-17A or IL-17F production. On the other hand, TGF-β inhibited the IL-6-induced development of IL-21-producing CD4$^+$ T cells. In addition, IL-21 itself induced the development of IL-21-producing CD4$^+$ T cells. The IL-21-producing CD4$^+$ T cells exhibited a stable phenotype of IL-21 production in the presence of IL-6, but still had the potential to produce IL-4 under Th2-polarizing conditions and IL-17A under Th17-polarizing conditions.

Furthermore, we addressed the mechanisms underlying the transcriptional regulation of IL-21 production in CD4$^+$ T cells. We found that IL-6 induced c-Maf expression in CD4$^+$ T cells, and that the enforced expression of c-Maf induced IL-21 production in CD4$^+$ T cells even in the absence of IL-6 or IL-4/STAT6 signaling, or an autocrine effect of IL-21. Moreover, we found that c-Maf directly bound to and activated the IL-21 promoter and CNS-2 enhancer through MARE sites (Figure 2). On the other hand, we also found that, although TGF-β upregulated the IL-6-induced c-Maf expression in CD4$^+$ T cells, TGF-β inhibited the c-Maf-induced IL-21 production in CD4$^+$ T cells. Taken together, these results suggest that IL-6-induced c-Maf directly enhances the IL-21 production in CD4$^+$ T cells by activating the IL-21 promoter and CNS-2 enhancer, and that TGF-β suppresses c-Maf-induced IL-21 production in CD4$^+$ T cells.

3. Protein Geranylgeranylation Regulates the Balance Between Th17 Cells and Foxp3$^+$ Regulatory T Cells

Recent studies have suggested that statins, inhibitors of HMG-CoA reductase in the mevalonate pathway, exhibit anti-inflammatory effects. However, the immunomodulatory effects of statins on the differentiation of CD4$^+$ T cells and their underlying mechanisms are still largely unknown. To address these issues, we examined the effect of simvastatin and inhibitors of protein farnesylation and geranylgeranylation on the differentiation of Th17 cells and Foxp3$^+$ CD4$^+$ T cells. Simvastatin inhibited the differentiation of Th17 cells but enhanced the differentiation of Foxp3$^+$ CD4$^+$ T cells. A geranylgeranyltransferase I inhibitor, GGTI-298, but not a farnesyltransferase inhibitor, FTI-277, mimicked the effects of simvastatin, indicating that the inhibition of protein geranylgeranylation is responsible for the effects of the statins. Moreover, Foxp3$^+$ CD4$^+$ T cells developed in the presence of TGF-β and GGTI-298 functioned as regulatory T cells in an *in vitro* T cell proliferation assay, as well as in an autoimmune colitis model. Furthermore,

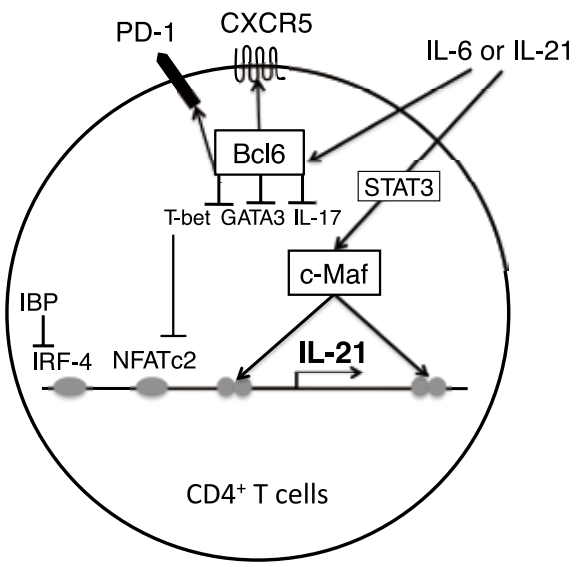

Figure 2. A schematic drawing of the development of IL-21-producing CD4$^+$ T cells
IL-21-producing CD4$^+$ T cells exhibit distinct characteristics from Th17 cells and develop preferentially in an IL-6-rich environment devoid of TGF-β, and IL-21 functions as an autocrine growth factor for IL-21-producing CD4$^+$ T cells. IL-6 induces c-Maf expression in CD4$^+$ T cells, and c-Maf directly binds to and activates the IL-21 promoter and CNS-2 enhancer through MARE sites.

GGTI-298 induced SOCS3 expression and inhibited IL-6-induced STAT3 phosphorylation in $CD4^+$ T cells.

We also compared the characteristics of GGTI-298-induced Treg cells and conventional Treg cells and found that GGTI-298-induced Treg cells expressed higher levels of CD62L and lower levels of CD69 than conventional Treg cells. A DNA microarray analysis of GGTI-298-induced Treg cells and conventional Treg cells revealed that GGTI-298-induced Treg cells expressed higher levels of Kruppel-like factor 2 (KLF2), which has been reported to induce CD62L expression, than conventional Treg cells. Taken together, these results indicate that protein geranylgeranylation enhances the differentiation of Th17 cells and inhibits the differentiation of $CD62L^{low}$ Treg cells, at least partly via the inhibition of SOCS3 and KLF2 expression.

4. Prediction of the Clinical Response to Tocilizumab Therapy with a Comprehensive Gene Expression Analysis of Peripheral Blood Mononuclear Cells in Patients with Rheumatoid Arthritis

Tocilizumab (TCZ) is a biological agent which is highly efficacious for rheumatoid arthritis (RA). Although predicting the treatment response to TCZ would be especially beneficial, since TCZ takes a longer time to demonstrate efficacy compared with anti-TNFα agents, such methods have not been established. On the other hand, previous reports showed the usefulness of a DNA array analysis of peripheral blood to predict the clinical response to infliximab in RA patients. Therefore, we sought to establish a method to predict the clinical response to tocilizumab therapy with a comprehensive gene expression analysis of PBMCs in patients with RA. A total of 18 patients who received TCZ for inadequately controlled RA (CDAI > 10) were analyzed as a training cohort. RNA was extracted from PBMCs before the first administration of tocilizumab, and was analyzed for comprehensive gene expression using the Human Whole Genome 4×44K format. The clinical response was assessed over six months using the CDAI category improvement and physician's global assessment. After six months of TCZ treatment, responders and non-responders were identified by two different measures (13 responders and three non-responders for CDAI category improvement; 17 responders and three non-responders for physician's global assessment). A clustering analysis in the training cohort showed a distinct pattern between responders and non-responders (Figure 3), suggesting that the comprehensive gene expression analysis of PBMCs has promise for predicting the clinical response of RA patients to TCZ therapy.

5. β-glucan Curdlan Induces IL-10-producing $CD4^+$ T Cells and Inhibits Allergic Airway Inflammation

Although several pathogen-derived products have been shown to possess therapeutic potential for allergic diseases, it remains largely unknown whether β-glucan, a cell wall component present in a variety of fungi, yeasts and bacteria, has regulatory potential for allergic diseases. We examined the effects of curdlan, a linear β-(1-3)-glucan, on the development of allergic airway inflammation. We found that intraperitoneal injection of curdlan significantly inhibited the antigen-induced eosinophil recruitment and Th2 cytokine production in the airways. The activation of $CD4^+$ T cells in the presence of curdlan induced IL-10-producing $CD4^+$ T cells with high levels of c-Maf expression. The curdlan-induced development of IL-10-producing $CD4^+$ T cells required the presence of antigen-presenting cells and the ICOS-ICOSL interaction (Figure 4). The curdlan-induced

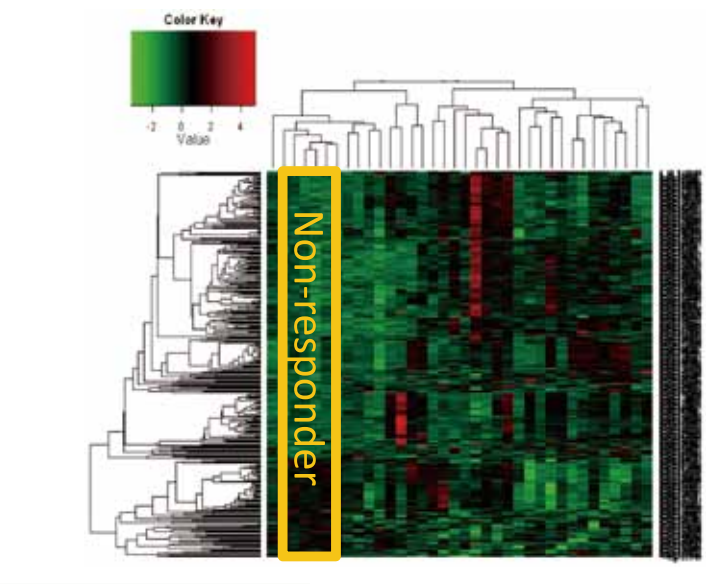

Figure 3. Predicting the clinical response to tocilizumab with a comprehensive gene expression analysis of PBMCs in patients with RA
A clustering analysis in the training cohort showed a distinct pattern between responders and non-responders.

development of IL-10-producing CD4$^+$ T cells also required intrinsic expression of STAT6. Furthermore, the transfer of antigen-specific CD4$^+$ T cells that were stimulated in the presence of curdlan inhibited antigen-induced eosinophil recruitment into the airways. Taken together, these results suggest that curdlan is capable of inducing IL-10-producing CD4$^+$ T cells and inhibiting the development of eosinophilic airway inflammation, underscoring the therapeutic potential of curdlan for allergic diseases.

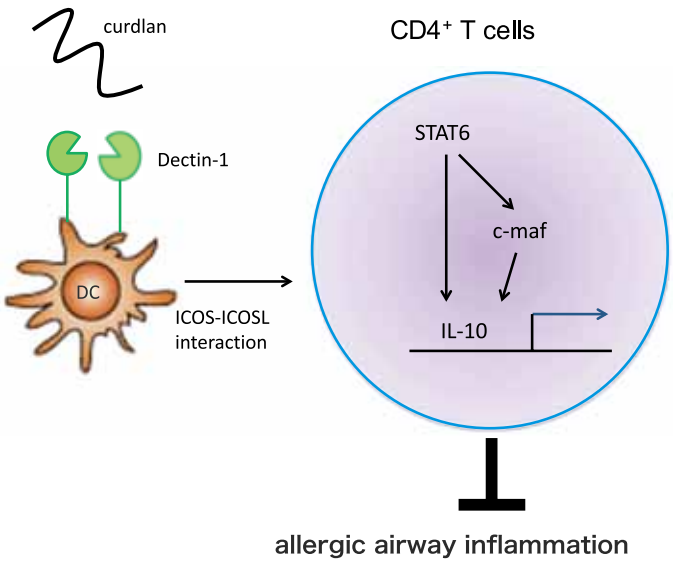

Figure 4. Curdlan induces IL-10-producing CD4$^+$ T cells
The activation of CD4$^+$ T cells in the presence of curdlan induces IL-10-producing CD4$^+$ T cells. The curdlan-induced development of IL-10-producing CD4$^+$ T cells requires the presence of antigen-presenting cells and the ICOS-ICOSL interaction. The curdlan-induced development of IL-10-producing CD4$^+$ T cells also requires intrinsic expression of STAT6.

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Role of microRNA in the regulation of VEGF-A in childhood asthma, antibodies to pneumococci basophils as a marker of IgE-mediated L-asparaginase allergy, and the involvement of oxidative

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Summary

1. The role of microRNA in the regulation of VEGF-A in childhood asthma

Airway inflammation and airway remodeling are thought to be the major contributors to the pathogenesis of asthma. Recently, it has been proposed that one of the key players in the pathogenesis of airway remodeling in asthma is vascular endothelial growth factor-A (VEGF-A). Although the expression of VEGF-A is regulated by many factors such as epigenetics and specific transcription factors, it is not clear whether microRNAs (miRNAs) are involved in the regulation of VEGF during airway remodeling in asthma. We therefore analyzed the expression of VEGFA mRNA and the miRNAs which are predicted to target VEGFA mRNA in CD4-positive T cells. Our results suggest that hsa-mir-15a might play an important role in the pathogenesis of pediatric asthma via the regulation of VEGFA expression. In the future, hsa-mir-15a might be a clinical marker and/or therapeutic target for pediatric bronchial asthma.

2. The association between pneumococcal antibodies and pneumococcal conjugate vaccine in Japanese subjects

The seven-valent pneumococcal conjugate vaccine (PCV7) was introduced as the national immunization for children under 5 years old in many countries to protect infants against invasive pneumococcal diseases (IPDs). After the introduction of the PCV7, the incidence of IPDs by non-PCV7 serotypes increased. Therefore, PCV13 instead of PCV7 has subsequently been used in several countries. In Japan, PCV7 was introduced as voluntary immunization for children under 10 years old in 2010. There are currently no data available about the serotype-specific pneumococcal IgG antibodies in Japanese subjects acquired through natural exposure. It is therefore unclear whether PCV13 should be introduced, and what the most appropriate age cut-off is for children in Japan. We elucidated the seroprevalence of IgG antibodies against PCV13 serotypes in Japanese subjects acquired through natural exposure. Our study suggests that children, especially those < 2 years old, should be recommended to receive the PCV. The current study reported that pneumococcal nasopharyngeal carriage shortly before the first infant dose of PCV7 resulted in hyporesponsiveness to the capsular polysaccharide of the carried strain. In the future, we will investigate the association between pneumococcal carriage and IgG antibodies induced by pneumococcal

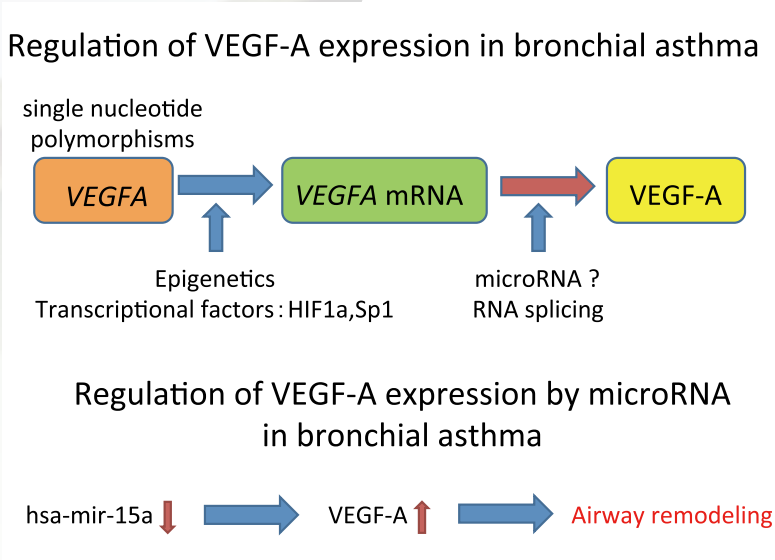


Figure 1. Regulation of VEGF-A expression in patients with bronchial asthma.
Although the expression of VEGF-A is regulated by many factors, such as epigenetic factors, specific transcription factors and RNA splicing, it was not clear whether microRNAs (miRNAs) are involved in VEGF-A regulation under airway remodeling in asthma. We revealed that the expression of hsa-mir-15a, which regulates VEGF-A expression, was lower in pediatric bronchial asthma patients. Our data suggest that hsa-mir-15a might play an important role in airway remodeling via its regulation of VEGFA.

in Japanese subjects after injection of the pneumococcal conjugate vaccine, CD203c on stress-induced JNK1 phosphorylation in hedgehog signaling and osteoblast differentiation

conjugate vaccine serotypes in Japanese children.

3. The expression of CD203c on basophils as a marker of IgE-mediated L-asparaginase allergy

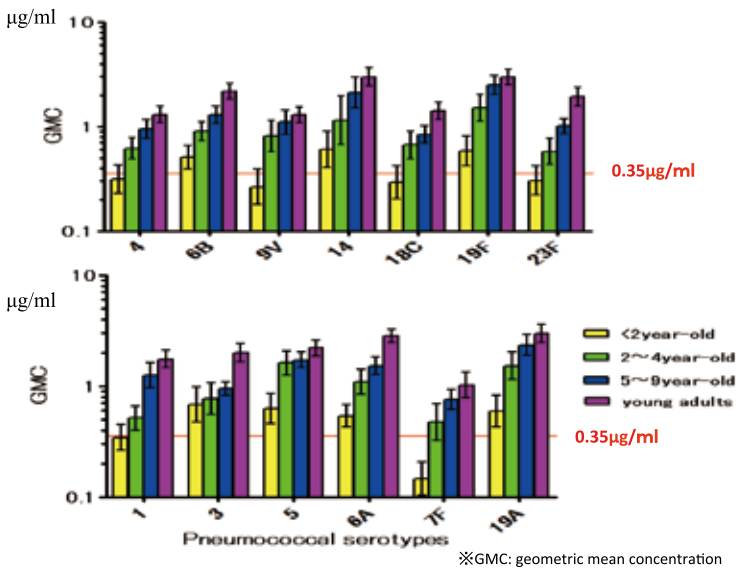
L-asparaginase (ASP) has been widely used to treat acute lymphoblastic leukemia (ALL) for more than 25 years. Because ASP is derived from bacterial sources, about 45% of patients develop type 1 allergies to this compound, which is a major limitation to its clinical use. Although type 1 drug allergies are usually related to IgE, it has been reported that the detection of ASP-specific IgE is very difficult because of its low level, and ASP-specific IgG is currently used as a marker of allergic reactions in the clinical setting. Recently, CD203c basophil activation tests (BAT) have been reported to be a reliable tool for the diagnosis of IgE-mediated allergic diseases. This study assessed the diagnostic value of CD203c-BAT compared to ASP-specific IgG in patients with ALL who suffered from an ASP allergy, and demonstrated that CD203c-BAT is a reliable marker to monitor IgE-mediated ASP allergies.

4. Involvement of oxidative stress-induced JNK1 phosphorylation in hedgehog signaling and osteoblast differentiation

Hedgehog, which is a morphogenic and oncogenic factor promoting medulloblastoma and basal cell carcinoma, plays a pivotal role in the early phase of osteoblast differentiation. The bone mass maintains equilibrium with a balance between bone formation and bone absorption. During the development of osteoporosis, oxidative stress has been progressively recognized as a key mediator, which is especially noted in aging, proximal renal tube acidosis, and iron overload due to red blood cell transfusion. The effect of oxidative stress on hedgehog signaling and subsequent osteoblast differentiation has been proposed as a pathogenic mechanism underlying osteoporosis. In this study, we evaluated hedgehog signaling under oxidative stress conditions using C3H10T1/2 murine embryonic mesenchymal cells. The result may contribute to identifying novel therapeutic targets for osteoporosis.

1. The role of microRNA in the regulation of VEGF-A in childhood asthma

The serum VEGF-A levels were significantly higher in pediatric asthma patients compared to non-atopic pediatric controls. This result suggests that VEGF-A may be involved in the pathogenesis of pediatric asthma. Although VEGF-A is produced by several types of cells, we focused on CD4-positive T cells, which play an important role in the pathogenesis of asthma. We analyzed the VEGFA mRNA expression of CD4-positive T cells in pediatric asthma patients, atopic controls and non-atopic controls. **The VEGFA expression was significantly higher in pediatric asthma patients compared to atopic controls or non-atopic controls, suggesting that VEGF-A might play an important role in the pathogenesis of asthma in an IgE-independent manner.** We searched for microRNAs that regulate VEGFA expression by using an *in silico* analysis. We revealed that the expression of hsa-mir-15a, one of the miRNAs predicted to regulate VEGFA expression, was significantly lower in pediatric asthma patients compared to atopic controls and non-atopic controls. We further revealed that hsa-mir-15a targets VEGFA mRNA by using a luciferase assay, and also found that transfection of mature hsa-mir-15a downregulates VEGFA expression in HEK293 cells.



※GMC: geometric mean concentration

Figure 2. The serotype-specific pneumococcal IgG level for each of the PCV13 serotypes stratified by age.
It was revealed that overall, infants aged < 2 years had low IgG levels, especially against serotypes 1, 4, 7F, 9V, 18C and 23F. The IgG levels against almost all serotypes increased with age.

2. The association between pneumococcal antibodies and pneumococcal conjugate vaccine in Japanese subjects

We measured the serotype-specific IgG antibodies in non-immunized Japanese subjects by an ELISA protocol, as recommended by the WHO. The WHO recommended serotype-specific antibody concentration of 0.35 μg/ml was estimated as the threshold concentration for protection against IPD. In this study, we found that overall, infants aged < 2 years had low IgG levels, especially against serotypes 1, 4, 7F, 9V, 18C and 23F. The IgG levels against almost all serotypes increased with age. The proportion of children with IgG concentrations ≧ 0.35 μg/ml increased with age and reached almost 100% in the 5 to 9-year-old cohort. Recently, the incidence of IPDs by non-PCV7 serotypes has been increasing in Japan. PCV13 should be introduced in Japan in the near future.

3. The expression of CD203c on basophils as a marker of IgE-mediated L-asparaginase allergy

Thirty-three children (eight with allergies, 25 non-allergic) who were diagnosed with ALL were evaluated. We collected blood samples and performed a skin prick test (SPT) before ASP treatment, and prospectively observed them for ASP allergies. We measured the ASP-specific immunoglobulin level by an ELISA. As previously reported, the ASP-specific IgG level was higher in ASP allergy patients. The ASP-specific IgE level was almost undetectable by the ELISA in our study. The ASP-specific IgG4 level was very low in both groups. The skin prick test was positive in three of the eight allergic patients, and only one of the 25 non-allergic patients. The expression of CD203c-BAT in patients with an ASP allergy was higher than that of non-allergy patients. The area under the ROC curve (AUC) of CD203c-BAT was similar to that of ASP-specific IgG. The IgE crosslinking-induced luciferase expression (EXiLE) assay was positive in a patient with an ASP allergy whose expression of CD203c-BAT was very high, confirming the presence of specific IgE against ASP. The expression of CD203c-BAT changed dynamically during ALL treatment, and CD203c-BAT was a better marker than ASP-specific IgG to predict IgE-mediated ASP allergy. Further investigations will be needed to confirm our results, along with the changes during the clinical course.

4. Involvement of oxidative stress-induced JNK1 phosphorylation in hedgehog signaling and osteoblast differentiation

Oxidative stress due to hydrogen peroxide inhibited the mRNA expression of hedgehog target genes and osteoblast-associated genes, and the subsequent mineralization in C3H10T1/2 murine embryonic mesenchymal cells. Since oxidative stress-induced phosphorylation of Jnk1 occurred at the same time, we hypothesized that Jnk1 activation in response to oxidative stress leads to inhibition of hedgehog signaling. The hedgehog signaling activity was determined by a luciferase assay using a gli response element reporter construct. Interestingly, the inhibitory effect of hydrogen peroxide on hedgehog signaling was blocked by a Jnk inhibitor. Moreover, anysomycin treatment (a Jnk stimulator), or transient overexpression of a constitutively active form of Jnk1 inhibited hedgehog activity. These data suggest that oxidative stress inhibits hedgehog signaling and osteoblast differentiation due to the phosphorylation of Jnk1, and this seemed to have a role in the pathogenesis of

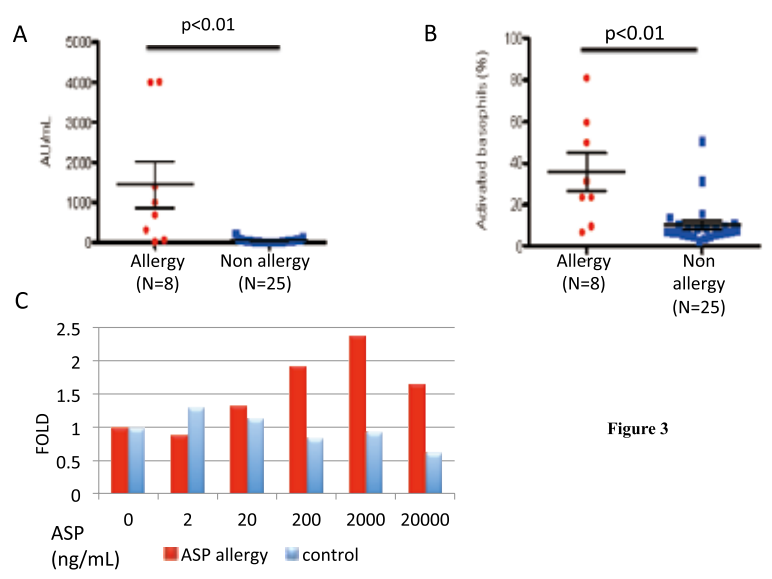


Figure 3

Figure 3. The ASP-specific immune response.
The ASP-specific IgG level, as measured by an ELISA (A), and the activated basophil rate (B), were significantly increased in allergic patients. (Mann Whitney test). (C)The axis bar represents the luminescence ratio in stimulated (ASP antigen) versus non-stimulated (ASP=0) patients. The horizontal line represents the ASP concentration. A luminescence ratio > 2.0 was considered to be positive. The EXiLE for ASP showed dose dependency, and the EXiLE value was positive (at 2,000 ng/mL) for ASP in a patient with an ASP allergy whose BAT level was 31.4%.

osteoporosis. To evaluate the protein interaction in detail, immunoprecipitation and intracellular localization studies were performed in HEK 293 cells transiently overexpressing Gli1 and Jnk1.

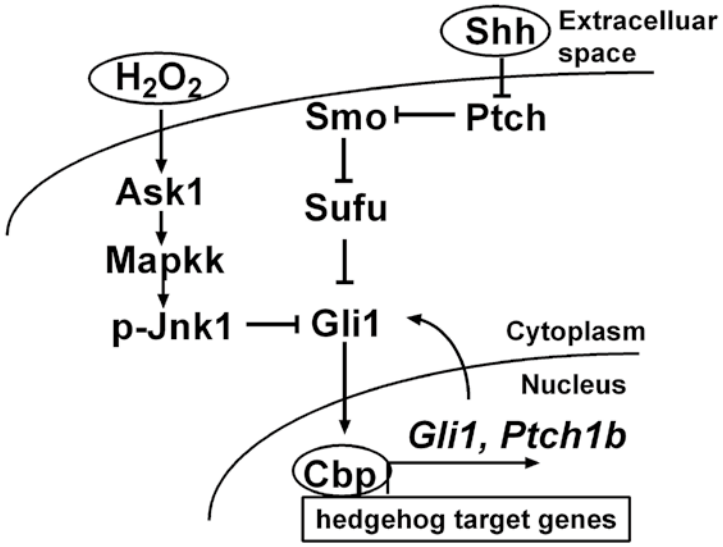


Figure 4. The effect of oxidative stress on hedgehog signaling.
Oxidative stress inhibits Gli1 mRNA expression and osteoblast differentiation in the early phase though the phosphorylation of Jnk1.

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An analysis of autoinflammatory syndromes with the constitutively active mutation of intracellular pattern recognition receptors for the pathogenesis of skin disorders

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Summary

Among the periodic fever syndromes that develop in the early infant period, autoinflammatory syndromes based on mutations of innate immunity-associated molecules recently attracted our attention. Like periodic fevers and arthritis/arthralgia, these genetic diseases are accompanied by phenotypically characteristic skin eruptions that resemble those that accompany infectious conditions. We investigated two autoinflammatory syndromes based on mutations encoding the intracellular pattern recognition receptor NLRs. The first is cryopyrin-associated periodic fever syndrome (CAPS), which includes three overlapping syndromes: familial cold auto-inflammatory syndrome (FCAS, MIM #120199), Muckle-Wells syndrome (MIM #191900) and CINCA syndrome (chronic infantile neurologic cutaneous and articular syndrome (MIM #607115). The other is autosomal-dominant Blau syndrome (MIM #186580) and early-onset sarcoidosis (EOS, MIM #609464), a set of sporadic granulomatous disorders that phenotypically resemble Blau syndrome. Even though the number of affected patients in Japan is restricted to less than 50, analyses of these autoinflammatory syndromes with characteristic clinical manifestations are expected to provide useful information for understanding the pathophysiological mechanisms of common disorders with similar symptoms.

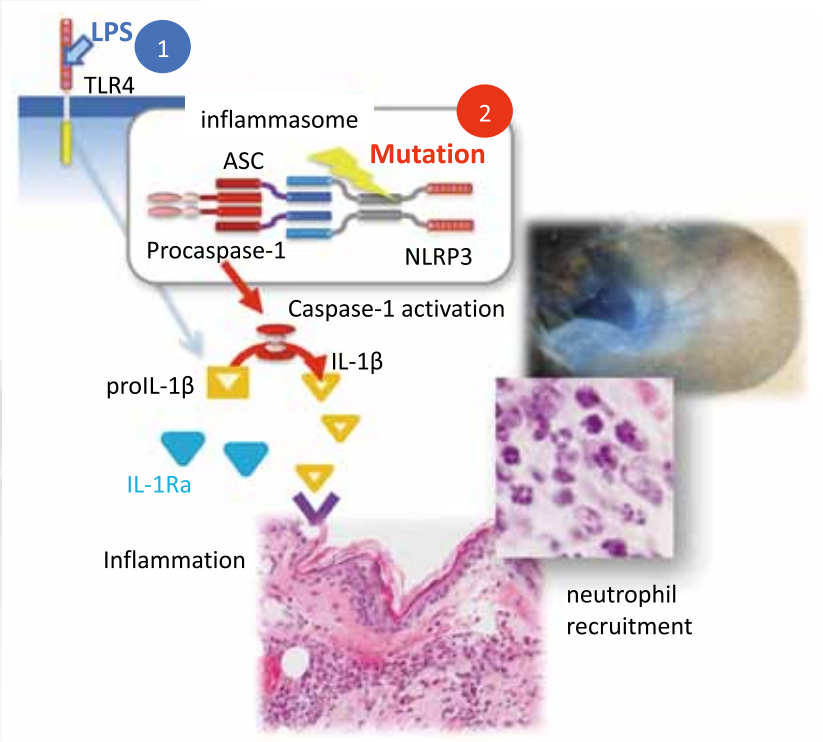

Figure 1. The mechanism underlying the development of the urticaria-like rash in CAPS is mediated by IL-1β produced via the activation of NLRP3-inflammasome.
The inflammasome is composed of an NLR protein and an adaptor protein called ASC, which can bridge the NLR to pro-caspase-1. Activation of the inflammasome results in self-cleavage and activation of pro-caspase-1 into the active protease. Next, activated caspase-1 cleaves its target molecules, including pro-IL-1β, into biologically active forms. We determined that IL-1β activated through the NLRP3 inflammasome in mast cells mediates neutrophil recruitment and vascular leakage in histamine-independent urticaria.

1. An analysis of CAPS with an NLRP3 mutation as a model of antihistamine-refractory urticaria

Background: The development of an urticarial rash in the neonatal or early infant period is one of the clinical manifestations characteristic of CAPS caused by a mutation in the gene encoding *NLRP3*. The urticarial rash observed in CAPS is similar to that associated with common urticaria. However, unlike ordinary urticaria, the rash observed in most CAPS patients responds to therapy with an IL-1 receptor antagonist rather than antihistamines.

Results: After performing immunohistochemical staining of the affected skin samples, we traced IL-1β in CAPS to a surprising source: mast cells (MCs). Primary MCs derived from murine bone marrow expressed inflammasome components, including Nlrp3. Microbial ligands such as LPS triggered the synthesis of the IL-1β precursor in the MCs, while a second ATP or R837-triggered signal activated the inflammasome. No IL-1β secretion was detected in the MCs obtained from Nlrp3- or Asc-deficient mice in response to LPS plus ATP or R837. Murine Nlrp3 mutants corresponding to those observed in human CAPS induced constitutive Asc-dependent NF-κB activation and IL-1β secretion. Transfer of MCs expressing an R258W mutant corresponding to R260W of human CAPS-associated NLRP3 induced perivascular neutrophil-rich inflammation in the murine skin, a histological hallmark of the urticaria observed in CAPS patients (Figure 1). Our paper is introduced on the cover of *The Journal of Experimental Medicine* accompanied by the caption: "Mast cells make a hive-inducing cytokine" (Figure 2).

The activation of the inflammatory cytokine IL-1β requires two stimuli: microbial ligands mediated by TLR4 signaling such as LPS induce the production of the preform of IL-1β, while activation of NLRP3 converts the proIL-1β into its bioactive mature form. In cases of FCAS, the mildest form of CAPS, systemic cold exposure induces skin eruptions, suggesting that cold exposure may work as the first signal for the production of IL-1β. In CINCA syndrome, the most severe type of CAPS, however, the clinical symptoms start within the first week after birth; however, the trigger for IL-1β production remains unknown. Nakamura Y., a former graduate student of our department, continued the study on CAPS and found that, using CAPS-associated mutation knock-in mice, nonpathological microbiota on the skin surface work as the first signal of IL-1β

Figure 2. On the cover of *The Journal of Experimental Medicine*.
Our paper is introduced by the caption, "Mast cells make a hive-inducing cytokine," in the JEM (ref. 8).

production via TNF-α production from skin MCs.

In addition, we previously reported that, in CINCA syndrome, almost half of all patients have the NLRP3 mutation as the somatic mosaicism; however, this concept is not widely accepted. Therefore, in order to establish the biological relevance of somatic mosaicism in CAPS, we performed international multicenter surveillance for a genetic analysis and analyzed the cellular functions of iPS cells established from patients with the NLRP3 mutation as their somatic mosaicism.

Discussion: Our findings implicate MCs as the IL-1β producers in the skin of CAPS patients. It is possible that skin rashes associated with histamine resistance are mediated via inflammasome activation in MCs because many cases of non-CAPS urticaria are unresponsive to histamine H1-receptor antagonists. Therefore, understanding the pathophysiology of CAPS may provide critical insight into more common diseases, such as antihistamine-refractory urticaria.

2. An analysis of EOS/Blau syndrome with a NOD2 mutation as a model of granulomatous disorders

Background: Systemic inflammatory granulomatosis, EOS/Blau syndrome, is associated with mutations in the *NOD2* gene, another member of the intracellular pattern recognition receptor NLRs family. We collected data on all patients in Japan in order to describe the clinical manifestations of EOS/Blau syndrome and to determine whether the *NOD2* genotype and its activity predict the clinical phenotype.

Results: All nine mutations, including E383G, a novel mutation that was identified in 20 patients, were detected in the centrally located NOD region and found to be associated with ligand-independent NF-κB activation. Attention was focused on the two most frequent mutations at the amino acid position of. R334W tended to cause more obvious visual impairments than R334Q, in line with the NF-κB activation potential of these two mutants.

Discussion: NOD2 genotyping may help to predict disease progression in patients with EOS/Blau syndrome. We plan further studies to determine whether constitutive NF-κB activation occurs in the patients followed in our clinic and how NOD2 mutants and NF-κB activation lead to granuloma formation in order to identify the pathological mechanisms underlying granulomatous disorders.

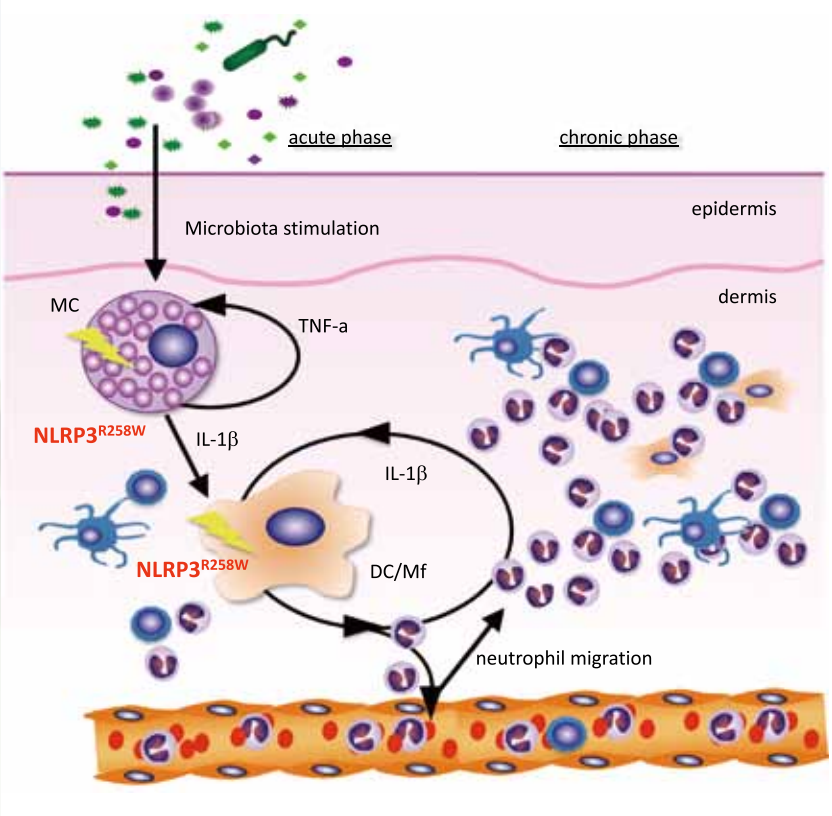

Figure 3. The first signal for IL-1β mediated inflammation in CAPS.
Nonpathological microbiota residing on the skin surface initiate the production of TNF-α from the mast cells and induce the preform of IL-1β as the first signal. This proIL-1β converts into the mature IL-1β form through the constitutively active NLRP3 mutant, then IL-1β itself induces the production of its preform.

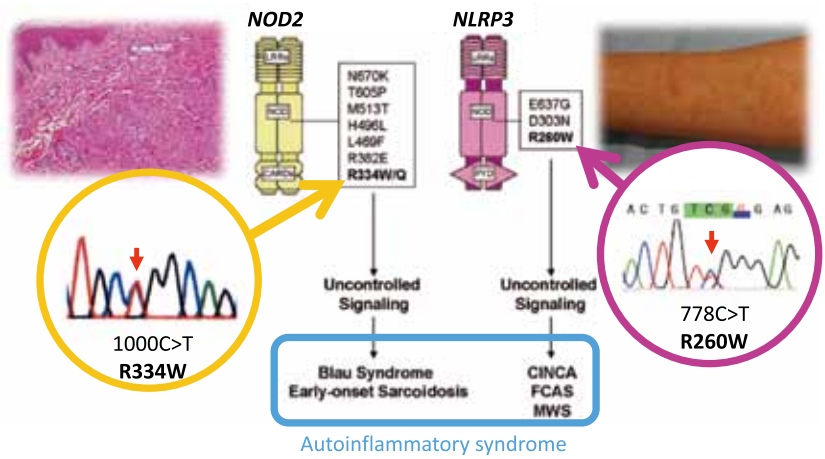

Figure 4. The NLRP3 mutation in CAPS and the NOD2 mutation in EOS/Blau syndrome.
NOD2 and NLRP3, both of which belong to the family of genes of the intra-cellular pattern recognition receptor NLR, are activated as a result of a constitutively active mutation located at the central NOD domain, resulting in the development of characteristic clinical symptoms. Interestingly, amino acid residues of the disease-associated mutations of R334W in NOD2 and R260W in NLRP3 are at analogous sequence positions in each of the NOD domains, suggesting a common molecular mechanism for the development of autoinflammatory syndromes.

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Translational research to develop immunotherapies against allergic rhinitis and head and neck cancer

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1. Clinical efficacy of sublingual immunotherapy for Japanese cedar pollinosis and its mechanisms of action

A recent review of randomized controlled studies of sublingual immunotherapy (SLIT) for allergic rhinitis suggests that this approach is safe and may be effective as an alternative route of administration.

To clarify the efficacy of sublingual immunotherapy in Japanese cedar pollinosis, which is a unique type of pollinosis in Japan, we conducted several double blind, randomized, placebo-controlled trials. No major adverse effects were observed in any of the studies. This slide shows the results of one of the studies done in Chiba. A total of 103 patients with cedar pollinosis were enrolled and received standardized pollen crude extract or placebo sublingually once a week for 16 months from October 2007 to the end of April 2008. The nasal symptom scores during the cedar pollen season were evaluated using a symptom diary. The dose of pollen extract was 2000 JAU/ml, which was the highest currently available. Although there was no significant difference in the nasal symptoms score in the first pollen season, the group of patients treated with cedar pollen extract exhibited significantly lower symptom scores compared to the placebo group in the second pollen season, and the percentage of mild subjects in the active SLIT group was around 30% higher than that in the placebo group, and the symptom medication score was reduced by 21% in the active SLIT group compared with the placebo group. We suspected that the lack of improvement of the symptoms in the first season was caused by the low frequency of dosing with the cedar pollen extract.

In the next study, daily administration, rather than once a week administration, of the allergen was carried out. The study was performed as a double-blind clinical trial for six months in 2008. The Japanese cedar pollen dispersion level in 2009 was extremely high, but mild improvement was found in the treatment group.

Based on the results of these clinical trials performed by physicians, Japanese pharmaceutical companies have started clinical studies for sublingual immunotherapy, and a phase III clinical study registered by the Health and Welfare Ministry of Japan was performed for 16 months from 2010 to 2012 in the same way as our study had been done. The results of the study were promising, and it is likely that such immunotherapy will be widely performed as a standard treatment in the near future in Japan.

However, there are still some problems associated with the wider use of sublingual immunotherapy, including the identification of objective biomarkers of the therapeutic effects of the immunotherapy. We have been examining candidate biomarkers in a clinical study. We found that the changes in the levels of cedar antigen Cryj-specific Th2 cell clones and Cryj-specific regulatory T cells might be candidate markers. Cryj is the major allergen of cedar pollen. Responders and non-responders to sublingual immunotherapy were also identified based on an examination of symptoms, the same as for other treatments. Since this therapy needs to be performed over a long period of time, it reduces the burden on the patients and is likely that wider use of the therapy will occur if the therapeutic effects can be predicted at the beginning or in an early period of the therapy.

The relationship between the ratio of cedar-specific IgE antibodies and the total IgE level in the serum of the patients just before the starting the SLIT, with the severity of the symptoms of these patients during the pollen dispersion season after treatment by SLIT for two years was examined. The ratio of cedar-specific IgE antibodies and the total IgE in serum before therapy were inversely correlated with the severity of symptoms during the pollen dispersion season in patients treated with sublingual immunotherapy. The therapeutic effects were higher in patients with a ratio lower than the average (0.19) in all patients, thus suggesting that this ratio could be used as a predictor indicating a good response to the immunotherapy.

In addition, we compared the changes in gene expression from before to two months after sublingual immunotherapy, with the goal of identifying genes that predict the response to the sublingual immunotherapy. The gene expression patterns in peripheral mononuclear cells was examined by a microarray analysis from four groups of patients: responders and non-responders in the sublingual immunotherapy and placebo groups. The results showed that several genes that were increased in expression eight weeks after the beginning of sublingual immunotherapy were predictive of a therapeutic effect. Further examinations are now ongoing to verify the changes of these genes just after sublingual immunotherapy as predictors of the effects of treatment.

2. An adjuvant immunotherapy with intramucosal administration of α-galactosylceramide-pulsed antigen-presenting cells for head and neck carcinoma

The management of head and neck cancer has generally involved the combined modalities of chemotherapy, radiation therapy and surgery. However, the increased toxicity and extensive functional morbidity induced by these combined therapies can severely impair the quality of life (QOL) of patients, and despite advances in these treatments, the prognosis still remains poor. In order to improve the prognosis and QOL of patients with head and neck cancer, the development of new treatment strategies is therefore of critical importance.

Cancer immunotherapy has been suggested as a new combination modality as an adjuvant for cancer therapy; however, its efficacy still needs to be improved.

Natural killer T (NKT) cells represent a unique lymphocyte subpopulation. After activation, humanVα24NKT cells show a strong anti-tumor activity against various malignant tumors both *in vivo* and *in vitro*. Previous studies have demonstrated that α-galactosylceramide (αGalCer) is an exogenous ligand that activates NKT cells.

The migration pattern of αGalCer-pulsed antigen presenting cells (APCs) and the immune responses after the administration by different routes was assessed using indium-labeled APCs and single photon emission computed tomography (SPECT) images. These In-labeled APCs were injected into the subnasal mucosa of the inferior turbinate in the patients with Head and Neck cancer. APC spots were observed at the primary injection sites and ipsilateral to the upper neck lymph nodes.

Based on these studies, we conducted a phase I study with α-GalCer-pulsed APCs administered in the nasal submucosa of patients with head and neck cancer, and evaluated the safety and feasibility of such a treatment. Nine patients with unresectable or recurrent head and neck cancer received two treatments one week apart with 1×10^8 of α-GalCer-pulsed autologous APCs into the nasal submucosa. To prepare the 1×10^8 APCs, only 150 mL of peripheral blood extract was sufficient, so it was easy for patients, because no apheresis was necessary. After the first and second administrations of α-GalCer-pulsed APCs, an increased number of NKT cells was observed in four patients, and enhanced natural killer activity was detected in the peripheral blood of eight patients. Regarding the clinical outcome, one patient, five patients and three patients exhibited PR, SD, and PD, respectively. This outcome does not rule out the clinical efficacy of the treatment,

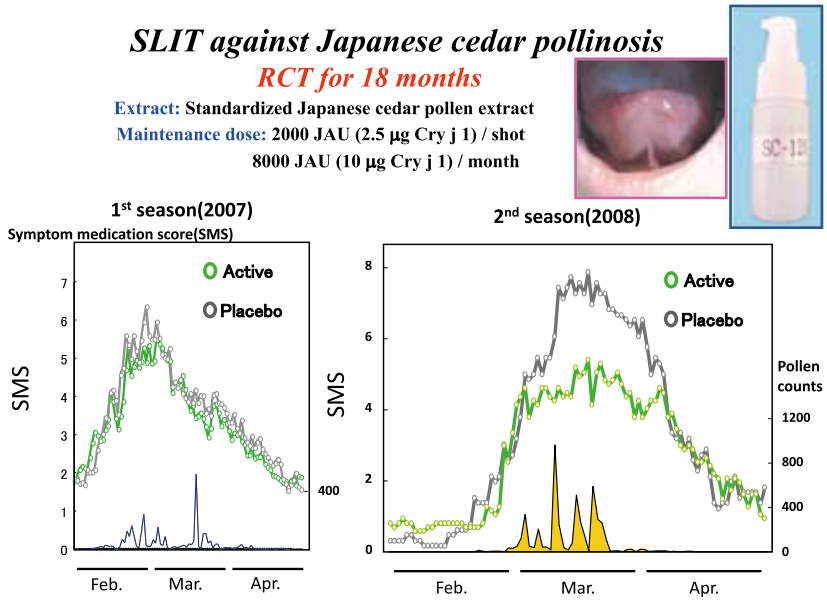

Figure 1.
To clarify the efficacy of sublingual immunotherapy against Japanese cedar pollinosis, which is a unique type of pollinosis in Japan, we conducted several double-blind, randomized, placebo-controlled trials. No major adverse effects were observed in any of the studies. This slide shows the result of a study done for 16 months from 2007 to 2008 in Chiba. A total of 103 patients with cedar pollinosis were enrolled and received standardized pollen crude extract or placebo sublingually once a week for 16 months from 2007 to 2008. The nasal symptom scores during the cedar pollen season were evaluated using a symptom diary. Although there was no significant difference in the nasal symptoms score in the first pollen season, the group of patients treated with cedar pollen extract exhibited significantly lower symptom scores compared to the placebo group in the second pollen season.

because the status of the patients enrolled in this study, who had either unresectable or recurrent cancer, must be categorized as very serious. The important finding of this study was that the nasal submucosal administration of α-GalCer-pulsed APCs for patients with head and neck cancer was safe, and a small number of these APCs could be collected without the inconvenience of apheresis, without any adverse effects, and these pulsed APCs exhibited significant immune responses and some positive clinical effects.

Several clinical studies have been performed on the basis of these results; the nasal submucosal administration of α-GalCer-pulsed APCs as an adjuvant immunotherapy for the prevention of recurrence of mucosal melanoma following carbon iron radiotherapy and of advanced hypopharyngeal cancer following the combined standard therapies are both being examined. These clinical studies are in progress to examine the potential of mucosal immunotherapy based on NKT cells.

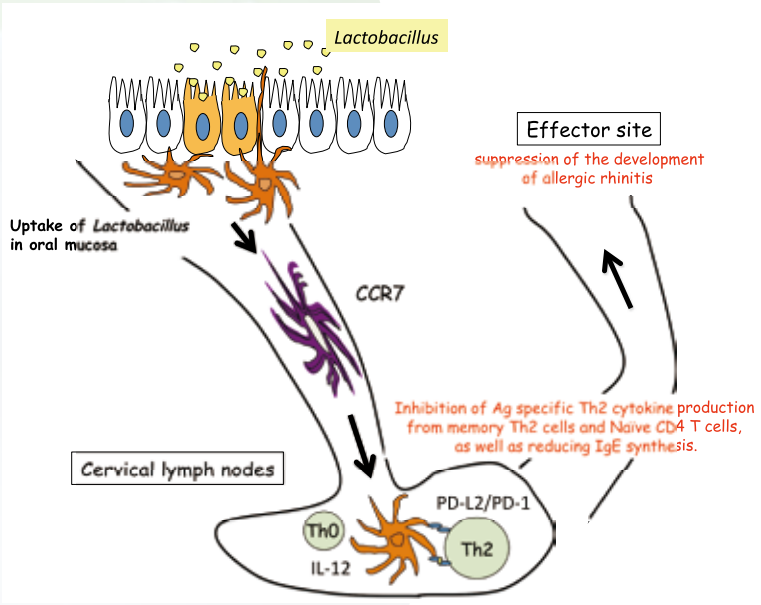

Figure 2.
The sublingual administration of Lactobacillus (KW3110 strain) decreased the IgE production and nasal symptoms after nasal provocation with antigen. The lactobacillus accelerates the migration of these DCs into the regional lymph nodes and inhibits the production of Th2 cytokines through the enhancement of CCR-7 and PD-L2 expression. As the anti-allergic effects of sublingual administration of Lactobacillus were enhanced by simultaneous stimulation with antigen in this study, improved efficacy of SLIT may be achieved by adjuvant therapy with the sublingual administration of Lactobacillus.

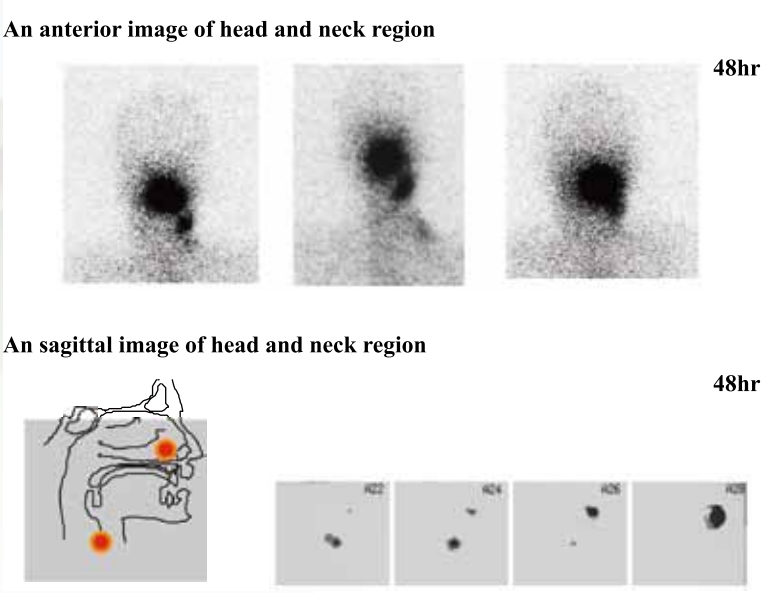

Figure 3.
The migration pattern of αGalCer-pulsed APCs and the immune responses after administration by different routes using indium-labeled APCs and single photon emission computed tomography (SPECT) images. These In-labeled APCs were injected into the subnasal mucosa of the inferior turbinate in patients with head and neck cancer. APC spots were observed at the primary injection sites and ipsilateral to the upper neck lymph nodes.

Clinical effects

	clinical outcome	adverse events
Case 001	SD	–
Case 002	SD	–
Case 003	PR	Anemia (grade 2)
Case 004	PD	–
Case 005	PD	–
Case 006	SD	–
Case 007	SD	–
Case 008	SD	–
Case 009	PD	–

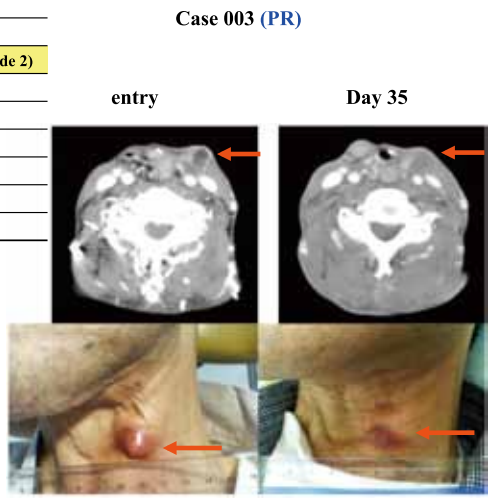

Figure 4.
The APCs pulsed with α-GalCer were administered into the nasal mucosa twice a week. The time course effects on the NKT cell counts and IFN-γ-inducing cell counts were investigated. Three representative cases are shown.
We observed upregulation of the NKT cell count and IFN-γ-inducing cell count after APC injection. Furthermore, there was one case with regression of a skin metastatic tumor.

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Filing date: 2009-08-28.
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Development of enhanced chemotherapy by overcoming an anti-cancer resistance mechanism

Core Member

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Objective

Cisplatin (CDDP) is a platinum formulation commonly used for chemotherapy, which is effective either alone or in combination with other drugs for the treatment of a wide variety of malignant solid tumors, including oral squamous cell carcinoma (OSCC). Resistance to CDDP is a major obstacle to effective cancer therapy, because clinically relevant levels of resistance emerge quickly after the start of chemotherapy. The aim of this study was to identify genes associated with CDDP resistance in order to help develop methods to overcome the resistance.

1. Identification of novel CDDP resistance genes

We performed a microarray analysis using CDDP-resistant cell lines (H1-R, Sa3-R, and KB-R) and their parental OSCC cell lines (H1, Sa3, and KB) to identify genes associated with CDDP resistance. We compared the average fold changes in gene expression for the three cell lines, and identified 199 genes that were differentially expressed by 1.5-fold or more, 164 of which were upregulated and 35 of which were downregulated. The 199 genes were then analyzed using a pathway analysis. Forty-one of these genes were mapped to genetic networks, and four networks were identified. We validated the mRNA expression of these genes by quantitative RT-PCR. Among them, *PDE3B* and *AKR1C* were upregulated in all CDDP-resistant cell lines compared with CDDP-sensitive cell lines, and showed excellent concordance with the microarray data. Therefore, we investigated the effect of knocking down *PDE3B* and *AKR1C* on the chemosensitivity of CDDP-resistant cells.

2-1. Effect of a PDE3B inhibitor on the in vitro CDDP sensitivity *(Figure 1)*

Since we found that *PDE3B* knockdown increased the CDDP chemosensitivity, a putative selective PDE3B inhibitor, cilostazol, which has been used to treat human diseases, was evaluated for its effects on CDDP chemosensitivity. CDDP-resistant cells were exposed to cilostazol to investigate whether the reduction of PDE3B alters CDDP resistance. As in the *PDE3B* knockdown cells, both CDDP-resistant cell lines had enhanced CDDP chemosensitivity in the presence of cilostazol. We found no such improvement in the parental cells with a low mRNA level of the *PDE3B* gene. These data are consistent with the possibility that cilostazol might be a novel cancer drug, and that it may exert its anti-cancer effects by inhibiting PDE3B activity in CDDP-resistant cells.

2-2. In vivo effects of the PDE3B inhibitor on CDDP sensitivity *(Figure 2)*

We then determined if cilostazol affects the tumor response to CDDP *in vivo* by evaluating the effects of cilostazol on tumor xenografts in mice. The Sa3/Sa3-R and H1/H1-R cells were inoculated subcutaneously into female athymic nude mice and grew to a mean volume of 100 mm^3. The response of each target xenograft to CDDP plus cilostazol was enhanced significantly ($P < 0.01$, Mann-Whitney U-test) only in the CDDP-resistant cell lines (Sa3-R, H1-R), compared to controls and mice treated with CDDP alone and cilostazol alone. In the parental cell lines (Sa3, H1), systemic cilostazol reduced the mean tumor volume by 32.2% in Sa3 cells and by 16.1% in H1 cells. CDDP alone reduced the mean tumor volume by 89.0% in Sa3 cells and 85.5% in H1 cells. The effect of systemic cilostazol combined with CDDP did not differ from that of the single administration. In contrast, the resistant cells had consistently smaller tumors than control animals following combined treatments; the tumor volume decreased by about 90.0% in Sa3-R cells and 84.9% in H1-R cells. Our findings suggest that the enhanced CDDP sensitivity resulting from the combination of CDDP and cilostazol was attributable at least partly to the increased apoptosis and reduced tumor cell proliferation. We also found that the average mouse body weight in the cilostazol-treated group never decreased below that of the control group (data not shown), indicating that the treatment does not have any overt toxicity greater than that of either agent alone.

3-1. Impact of AKR1C on the CDDP sensitivity in vitro *(Figure 3)*

We carried out knockdown experiments to determine whether AKR1C was related to the sensitivity of cells to CDDP treatment. A MTS assay revealed that *AKR1C* knockdown cells were much more susceptible to CDDP chemotherapy. These results suggest that AKR1C is also related to the efficacy of CDDP-based chemotherapy against OSCC. NSAIDs are inhibitors of

the AKR1C family. Among them, we focused on mefenamic acid, because it is the most effective inhibitor against all AKR1C family members. To examine the effect of mefenamic acid on the chemosensitivity of the cells, we treated the CDDP-resistant cells and parental cells with mefenamic acid prior to the CDDP chemotherapy. Cell viability in the mefenamic acid-treated CDDP-resistant cells was decreased after CDDP treatment ($P < 0.01$).

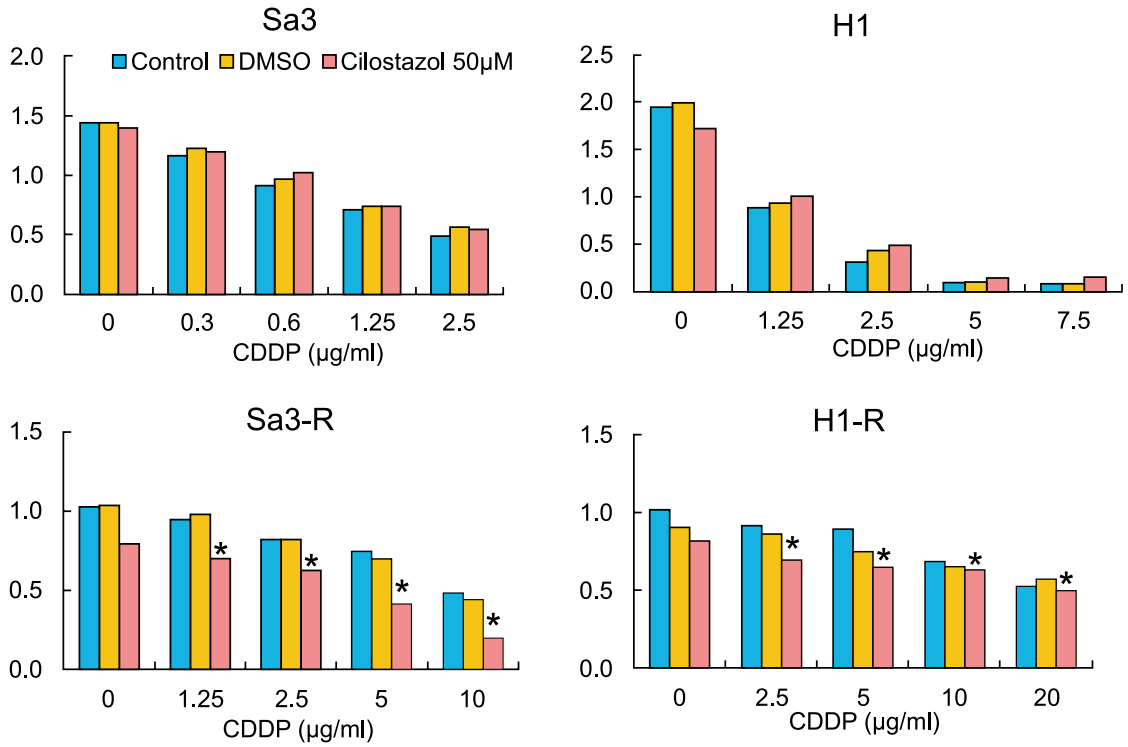

Figure 1. The effects of cilostazol on the sensitivity of cells to CDDP.
To examine the effect of a PDE3B inhibitor, cilostazol, on the chemosensitivity of the cells, we treated the CDDP-resistant cell lines (Sa3-R, H1-R) and their parental cell lines (Sa3, H1) with cilostazol prior the CDDP chemotherapy. The cells were cultured for 24 hours with or without cilostazol, then CDDP was added and the cells were incubated for another 72 hours. The viability of the cilostazol-treated CDDP-resistant cells was decreased after CDDP treatment (*$P < 0.05$).

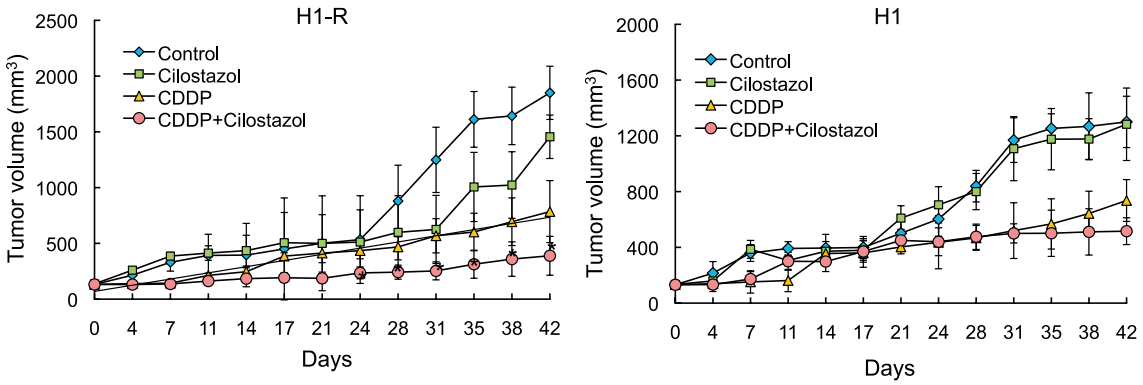

Figure 2. Antitumor activity of cilostazol combined with CDDP *in vivo*.
(A) The H1-R and H1 cells were injected subcutaneously into the lower limbs of female athymic nude mice (BALB/cAnNcrj-nu-/nu). The animal experiments included four treatment groups: control, cilostazol alone, CDDP alone, and CDDP combined with cilostazol. In the mice implanted with CDDP-resistant cells, cilostazol combined with CDDP resulted in consistently downregulated tumor growth compared to that in control mice (*$P < 0.05$).

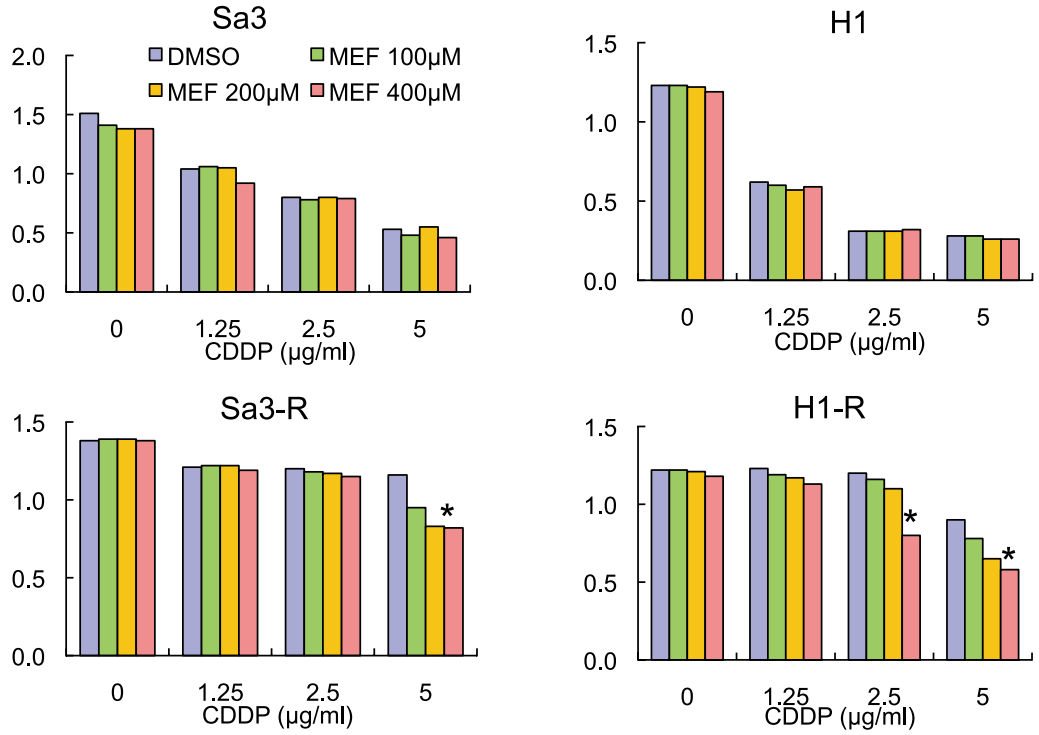

Figure 3. The effects of mefenamic acid on the sensitivity of cells to CDDP.
To examine the effects of an AKR1C inhibitor, mefenamic acid, on the chemosensitivity of cells, we treated the CDDP-resistant cell lines (Sa3-R, H1-R) and their parental cell lines (Sa3, H1) with mefenamic acid prior to treatment with CDDP. The cells were cultured for 24 hours with or without mefenamic acid, and then CDDP was added and cells were incubated for another 72 hours. The viability of the mefenamic acid-treated CDDP-resistant cells was decreased after CDDP treatment (*$P < 0.05$).

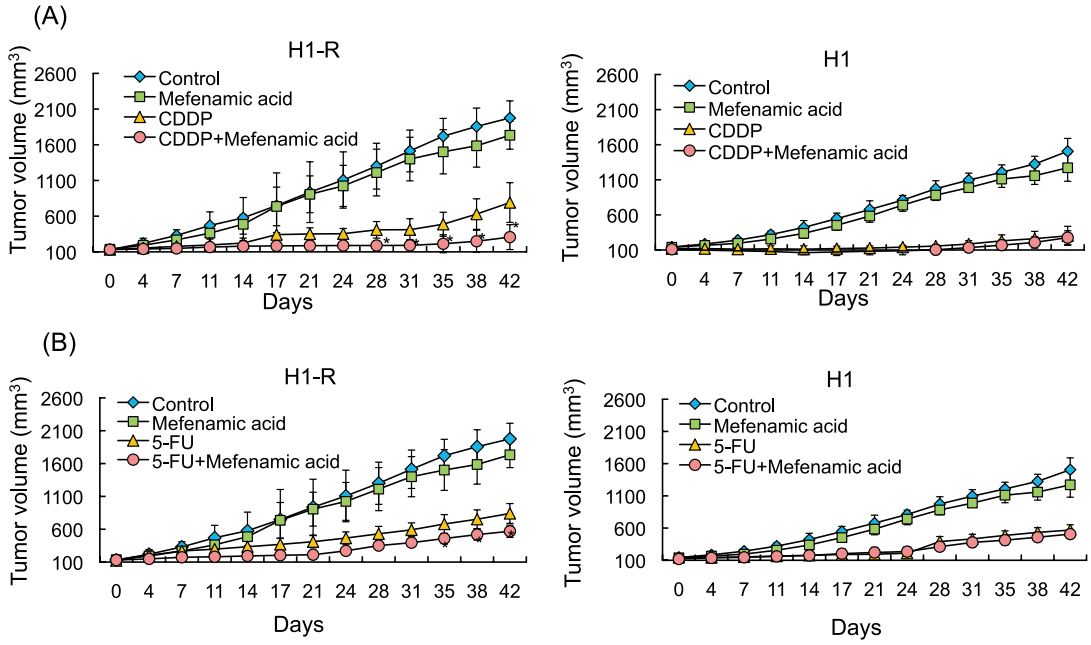

Figure 4. Antitumor activity of mefenamic acid combined with CDDP or 5-FU *in vivo*.
(A) The H1-R and H1 cells were injected subcutaneously into the lower limbs of female athymic nude mice (BALB/cAnNcrj-nu-/nu). The animal experiments included four treatment groups: control, mefenamic acid (500 μg/day) alone, CDDP (2 mg/kg/i.p.) alone and CDDP combined with mefenamic acid. In CDDP-resistant cells, mefenamic acid combined with CDDP resulted in consistently downregulated tumor growth compared to that in control mice (*$P < 0.05$).
(B) The animal experiments included four treatment groups: control, mefenamic acid alone, 5-FU (7.5 mg/kg/i.p.) alone and 5-FU combined with mefenamic acid. In CDDP-resistant cells, mefenamic acid combined with 5-FU resulted in consistently decreased tumor growth compared to that in control mice (*$P < 0.05$).

3-2. *In vivo* effects of an AKR1C inhibitor on the CDDP sensitivity *(Figure 4A)*

We subcutaneously inoculated CDDP-resistant cell lines and parental cell lines into female athymic nude mice to validate the inhibitory effect of mefenamic acid *in vivo*. When the volume of the transplanted tumors reached 100 mm^3, the mice were treated with mefenamic acid and/or CDDP. The effect of mefenamic acid combined with CDDP on tumor growth inhibition was enhanced significantly compared with the control, no treatment, CDDP alone, and mefenamic acid alone groups. These results suggest that combination CDDP chemotherapy with mefenamic acid might be useful for CDDP-resistant OSCC.

3-3. Effects of an AKR1C inhibitor on 5-FU sensitivity *(Figure 4B)*

Combination chemotherapy comprising CDDP and 5-fluorouracil (5-FU) is also used for patients with OSCC. Therefore, we also investigated the 5-FU chemosensitivity after inhibiting AKR1C activity *in vitro* and *in vivo*. Similar to CDDP, mefenamic acid increased the chemosensitivity to 5-FU in chemoresistant cells.

4. Conclusion.

1. The inhibition of PDE3B activity increased the chemosusceptibility of CDDP-resistant OSCCs to CDDP.
2. The combination of CDDP and 5-FU chemotherapy with mefenamic acid might be useful for chemoresistant OSCCs.

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[Others: 2011, 5 articles; 2010, 4 articles; 2009, 8 articles; 2008, 6 articles]

Development of immunotherapy for lung cancer

Core Member

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Summary

Primary lung cancer is often an intractable disease even when the primary tumor lesion is small and diagnosed at early stage. Lung cancer is currently the leading cause of cancer death in industrialized countries. The aim of our study was to develop a novel immunotherapy targeting the invariant natural killer T (iNKT) cell immune system in patients with lung cancer. iNKT cells possess potent anti-tumor effects after activation with a specific glycolipid antigen, α-galactosylceramide (α-GalCer). In addition to direct killing, iNKT cells mediate adjuvant activity through the production of IFN-γ, which in turn activates NK cells and CD8 T cells. Recently, the Japanese Ministry of Health, Labour and Welfare approved our NKT cell-based immunotherapy as a "Highly Advanced Medical Technology", which is one of the important steps to establish it as a standard treatment. The establishment of this new, minimally-invasive, immunotherapy with few adverse events may improve the therapeutic outcome of lung cancer and contribute to improving the health and social welfare of the population.

We also foster young researchers through an on-the-job training system in the clinical research field and promote their ability to conduct translational research that is GCP compliant.

1. Analysis of tumor infiltrating iNKT cells after iNKT cell-based immunotherapy

A phase I-II clinical study of α-GalCer-pulsed dendritic cells (DCs) to activate endogenous iNKT cells was previously performed in patients with inoperable advanced or recurrent non-small cell lung cancer (NSCLC). The administration of α-GalCer-pulsed DCs increased the number of IFN-γ producing cells in the peripheral blood, which appeared to be associated with prolonged survival. A new study protocol was designed to evaluate the preoperative administration of α-GalCer-pulsed DCs in patients with lung cancer to clarify the anti-tumor mechanisms, while especially focusing on the tumor site.

Patients with operable advanced NSCLC received an intravenous injection of α-GalCer-pulsed DCs one week before surgery. In the resected lung tissue, tumor infiltrating lymphocytes (TILs), lymphocytes in the normal lung, mononuclear cells in the draining lymph nodes, as well as the peripheral blood mononuclear cells, were collected, and the iNKT cell-specific immune responses were analyzed. Four patients completed the study protocol. A significant increase in iNKT cell numbers in the TILs (Figure 1) and augmented IFN-γ production in the α-GalCer-stimulated TILs were observed in comparison to the non-injected control group. In

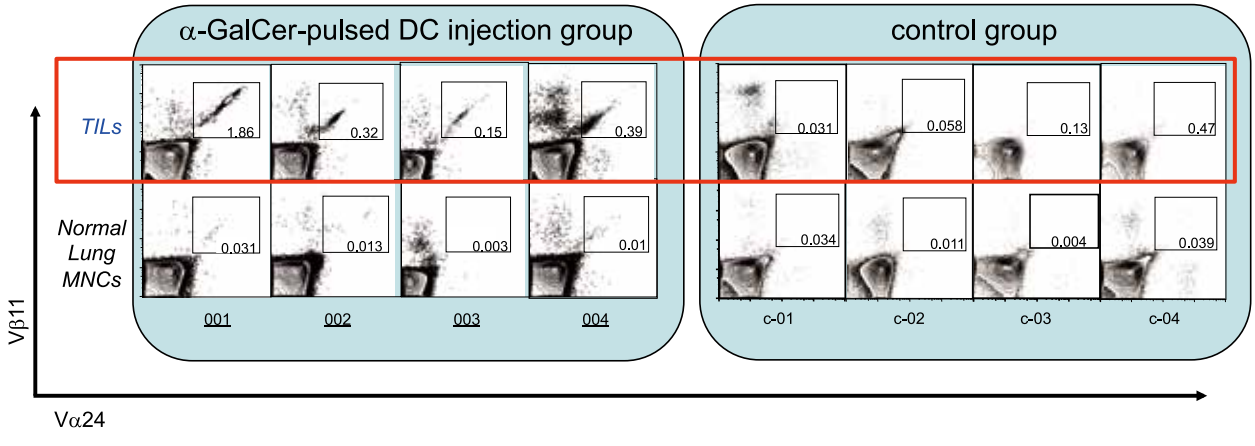

Figure 1. The proportion of iNKT cells ($V\alpha24^{+}V\beta11^{+}$ cells) in TILs and normal lung MNCs in the α-GalCer-pulsed DC administration group and the control group were assessed by flow cytometry.

conclusion, the administration of α-GalCer-pulsed DCs successfully induced the dramatic infiltration and activation of iNKT cells in the tumor microenvironment (Figure 2).

2. Loco-regional immunotherapy by trans-bronchial injection of α-GalCer-pulsed DCs in patients with advanced or recurrent NSCLC

To activate the iNKT cells in the tumor microenvironment more efficiently, we performed a trans-bronchial injection of α-GalCer-pulsed DCs in patients NSCLC. We established the study protocol, and prepared the essential documents, such as case report forms, cell processing record and other protocols, with young scientists to promote their ability to conduct translational research that is GCP compliant and adheres to ethical guidelines.

This immunotherapy includes the direct injection of α-GalCer-pulsed DCs into the lung tumor or draining lymph nodes via bronchoscopy, which is a novel technique for cell administration. Advanced or recurrent non-small cell lung cancer patients received intranodal or intra-tumoral injections of α-GalCer-pulsed DCs (level 1, $1\times10^8/m^2$; level 2, $5\times10^8/m^2$; level 3, $1\times10^9/m^2$) by endobronchial ultrasound (EBUS) to test the safety, feasibility and clinical response. Immunomonitoring was also performed in all cases. Twenty-one patients were enrolled in this study. No severe adverse events related to the α-GalCer-pulsed DC injection were observed in any of the patients. After the α-GalCer-pulsed DCs were administered, an increased NKT cell number in the PBMCs was observed in eight cases, and the number of IFN-γ producing cells in peripheral blood increased in 10 cases. Regarding the clinical responses, one patient exhibited a partial response and eight were classified as having stable disease. In this clinical trial, trans-bronchial α-GalCer-pulsed DCs were well tolerated and could be administered safely in patients with advanced disease.

3. Detection of a biomarker for NKT cell-based immunotherapy

The previous clinical trial of α-GalCer-pulsed DCs showed that the patients with increased IFN-γ production in PBMCs after the DC treatment (good responder group) experienced a prolonged overall survival time in comparison to the poor responder group. We extended the previous study and performed a microarray-based gene expression analysis using peripheral blood NK cells and T cells from the patients enrolled in the above-mentioned clinical study (Figure 3). We sought to identify biomarkers associated with good or poor responders in this immunotherapy trial.

Six patient samples corresponding to three subjects in the good responder group and three subjects in the

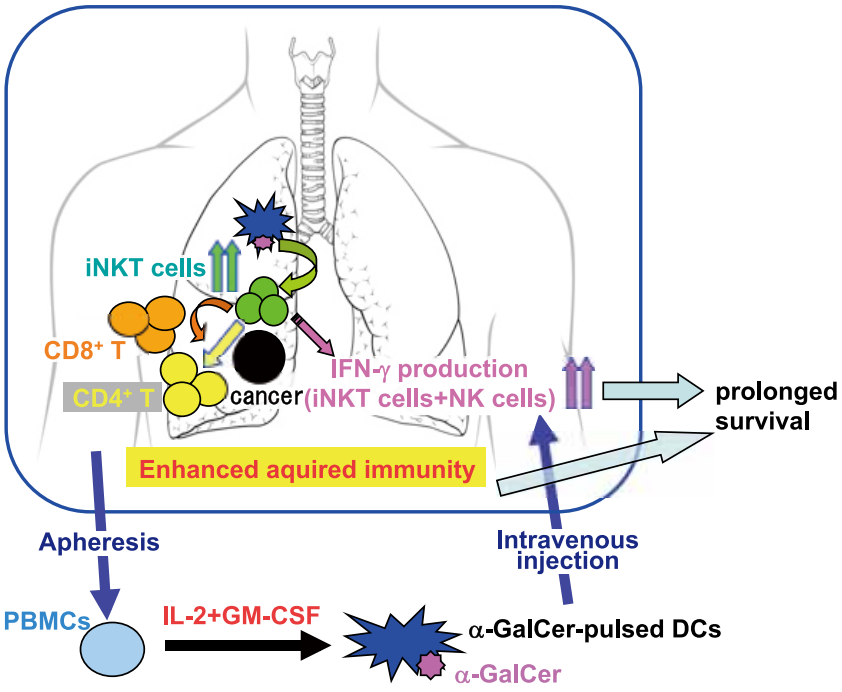

Figure 2. Functionally sufficient antigen presenting cells can be induced from patients' PBMCs, with the use of IL-2 and GM-CSF.
Intravenously injected α-GalCer-pulsed DCs reach the lung parenchyma and stimulate endogenous iNKT cells. The stimulated iNKT cells expand and preferentially produce IFN-γ, which correlated with a prolonged survival. We are now investigating the adjuvant effects of acquired immunity in the tumor microenvironment, such as tumor specific $CD8^+$ T cells or $CD4^+$ T cells, which may also correlate with prolonged survival.

poor responder group were included in the microarray analysis. Genes that were differentially expressed between the pre-treatment and post-treatment samples were selected for the analysis. Subsequently, genes that were only expressed in the good responder group or poor responder group were chosen for the analysis. After these procedures, 14 selected genes were quantified by reverse transcriptase-polymerase chain reaction in another eight patient samples, and three genes, *LTB4DH*, *DPYSL3* and *C13orf15*, were confirmed to be candidate genes. The expression profile of these three genes may be associated with the responsiveness of IFN-γ production and survival time after α-GalCer-pulsed DC treatment.

4. α-GalCer-pulsed DC treatment as a Highly Advanced Medical Technology

The previous phase I/II clinical trial of α-GalCer-pulsed DCs in patients with NSCLC refractory to standard treatment showed that it led to a prolonged overall survival time (median survival time of 17.4 months in all 23 enrolled cases). From these data, we applied this treatment as part of the Highly Advanced Medical Technology System, and the Japanese Ministry of Health, Labour and Welfare (MHLW) approved "intravenous injection of α-GalCer-pulsed DCs for the treatment of inoperable advanced or recurrent non-small cell lung cancer" as a Highly Advanced Medical Technology on September 28, 2011. We started a phase II clinical study in February 2012 under the support of the Clinical Research Center in Chiba University Hospital (Figure 4). The aim of the phase II study was to establish a novel second-line treatment in patients with advanced or recurrent NSCLC. The entry criteria were patients with first-line chemotherapy for advanced or recurrent non-small cell lung cancer. Further inclusion criteria were no chemotherapy or radiotherapy received for at least 4 weeks before enrollment, age between 20 and 80 years, performance status of 0, 1, or 2; and normal or near normal renal, hepatic and hematopoietic function. $V\alpha24^{+}V\beta11^{+}$ invariant NKT cells were detected in enrolled patients at a level of over 10 cells in 1 ml of peripheral blood by flow cytometry. The primary endpoint is to investigate the overall survival time and the secondary endpoints are to evaluate the progression free survival time, objective response rate, disease control rate, invariant NKT cell-specific immune responses and the safety

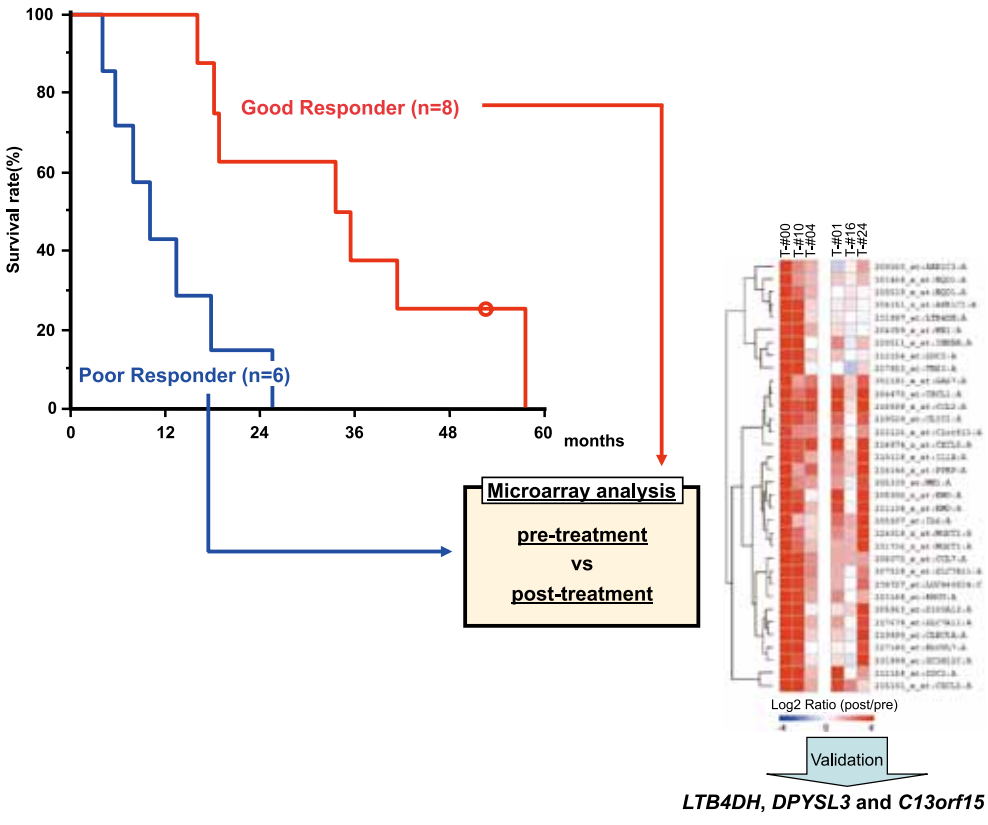

Figure 3. After α-GalCer-pulsed DC treatment, the good responder group showed a significantly better survival rate in comparison to the poor responder group.
We attempted to identify biomarkers associated with good or poor responders following this iNKT cell-based immunotherapy with the use of a microarray analysis.

profile. This study is an open label, single arm study and 35 patients total will be enrolled in the study protocol. We will complete the patient enrollment within three years and finish the protocol study within five years.

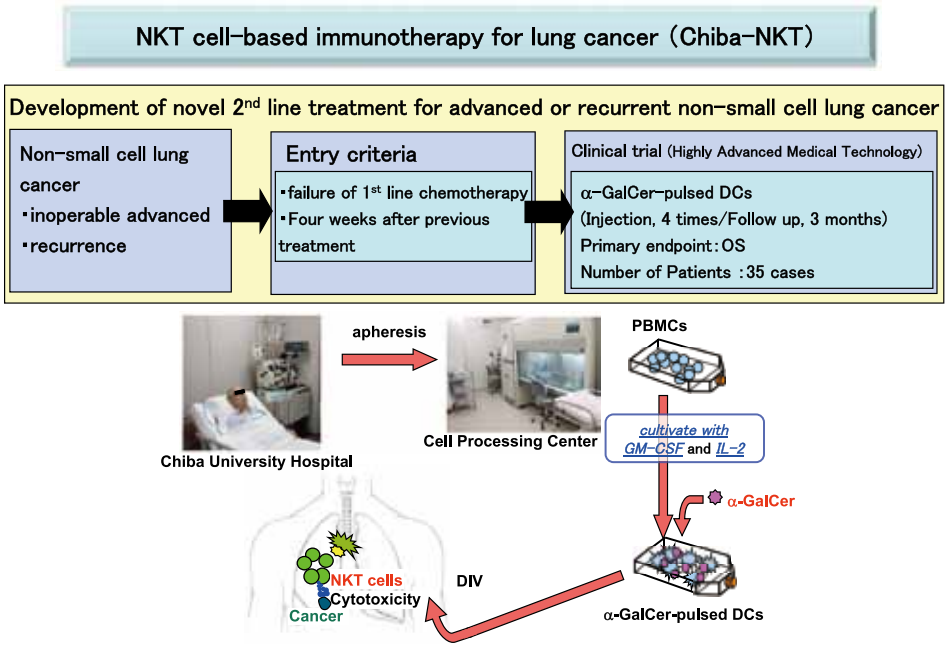

Figure 4. Outline of the phase II study of α-GalCer-pulsed DC treatment as a Highly Advanced Medical Technology.

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Development of *ex vivo* gene therapy for intractable serum enzyme deficiencies

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Summary

Familial lecithin: cholesterol acyltransferase (LCAT) deficiency is an autosomal recessive disorder caused by mutations of the *lcat* gene. LCAT is responsible for the conversion of plasma unesterified cholesterol into cholesteryl ester. LCAT plays a central role in the formation and maturation of high-density lipoprotein (HDL), which is involved in reverse cholesterol transport. The primary symptoms of this disease are hypo-α-lipoproteinemia, corneal opacities, anemia and renal dysfunction caused by impaired reverse cholesterol transport from various organs. Thus far, approximately 100 *lcat* gene mutations have been identified with recent genome-based analyses. Recently, patients with heterozygous *lcat* mutations were reported to exhibit an increased risk of atherosclerosis. The aim of our study was to develop a cell-based gene therapy to deliver functional LCAT proteins via autotransplantation of *lcat*-gene transduced pre-adipocytes (Fig. 1).

We focused on human pre-adipocytes, which are propagated from subcutaneous fat by ceiling culture of processed adipose tissue (designated as ceiling culture-derived proliferative adipocytes, ccdPAs). ccdPAs are homogeneous and exhibit highly adipogenic potential, suitable for transplantation therapy into the subcutaneous space. The suitability of ccdPAs as recipients for retrovirus vector-mediated gene transduction was examined. The ccdPAs stably expressed transduced genes for the duration of the culture period. LCAT proteins obtained from the gene-transduced ccdPAs exhibited cholesterol esterifying activity and ameliorated impaired lipid metabolism in the sera of LCAT-deficient patients, as well as in a LCAT-deficient mice model, suggesting that the ectopic secretion of LCAT, which is physiologically secreted by hepatocytes, could serve as a therapeutic option for treating serum enzyme deficiencies such as LCAT deficiency. The gene-transduced ccdPAs did not exhibit any abnormal phenotypes in *in vitro* or *in vivo* evaluations.

We submitted our clinical gene therapy research to the Ministry of Health, Labour and Welfare (MHLW) upon approval by the committee for gene therapy at Chiba University Hospital. Our clinical research protocols are now under deliberation by the MHLW. Our study showed that ccdPAs are a possible platform for enzyme replacement therapy for *ex vivo* gene therapy purposes. We also train young researchers during preclinical studies to establish GMP-based cell propagation in order to promote their ability to conduct translational research with GCP compliance.

Introduction

Among the clinical trials conducted thus far, inherited monogenic disorders represent approximately 10% of the diseases targeted by gene therapy applications. The most impressive outcomes of *ex vivo* gene therapy trials have been reported in subjects with immunodeficiencies as a result of monogenic disorders, including adenosine deaminase deficiency (ADA-SCID) and γc chain deficiency (X-SCID). To correct the immune disorders present in these patients, it is necessary to correct the functions of the target immune cells in order for the cells to grow, differentiate into multiple hematopoietic lineages and reconstruct the immune system. On the other hand, genetic and acquired disorders causing secreted serum enzyme deficiencies have also been postulated to be ideal targets for gene therapy applications. In these diseases, the deficient proteins function systemically, and the protein defects cause severe complications in target organs. Therapeutic genes expressed by a viral vector are directly infused into the target tissues (*in vivo* gene therapy) or therapeutic gene-transduced cells are transplanted (*ex vivo* gene therapy) and, subsequently, functional proteins are produced systemically in order to improve symptoms through protein replacement therapy. We have been developing such *ex vivo* gene therapy for LCAT deficiency syndromes (Fig. 2) as the first target disease.

Characteristics of human pre-adipocytes, ccdPAs

In this study, we focused on pre-adipocytes committed to mature adipocytes as therapeutic gene delivery vehicles. After performing collagenase digestion of adipose tissue, stromal vascular fractions (SVF) were removed and lipid-containing cells were subjected to ceiling culture. The propagated ccdPAs showed highly adipogenic potentials in comparison to SVF-derived adipose tissue stem cells (ASC). The ccdPAs spontaneously differentiated into adipocytes in *in vitro* three-dimensional culture, suggesting that ccdPAs are committed to mature adipocytes. The ccdPAs were evaluated as recipients and vehicles of the *lcat* gene. We evaluated the effects of culture conditions in order to optimize the gene transduction protocol, which resulted in high efficiency

with a minimal integrated copy number per cell, suitable for *ex vivo* gene therapy purposes. The transduced *lcat*-gene was expressed in the ccdPAs, and the secreted LCAT proteins exhibited free cholesterol-esterifying activities. The gene transduction resulted in no significant changes in cell characteristics. No cell populations with an abnormal phenotype were ever observed in the *in vitro* and *in vivo* experiments. Based

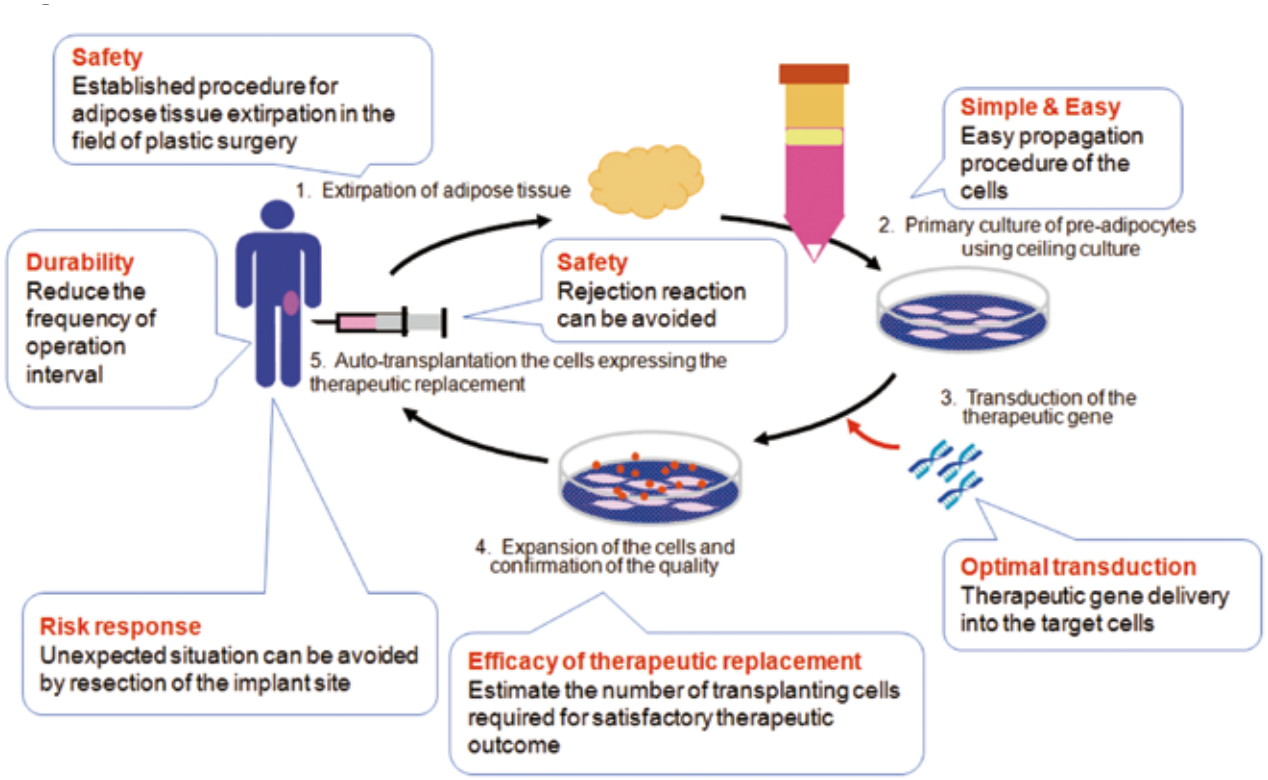

Figure 1. Enzyme replacement therapy using therapeutic gene-transduced pre-adipocytes.
An outline of established *ex vivo* gene therapy for the treatment of LCAT-deficient patients is depicted. Subcutaneous fat obtained from patients was treated with collagenase and human ccdPAs were propagated using the ceiling culture method. The cells were transduced with an *lcat* gene-expressing retrovirus vector and expanded. After GMP production, including quality control, the cells were harvested and transplanted subcutaneously into the patients.

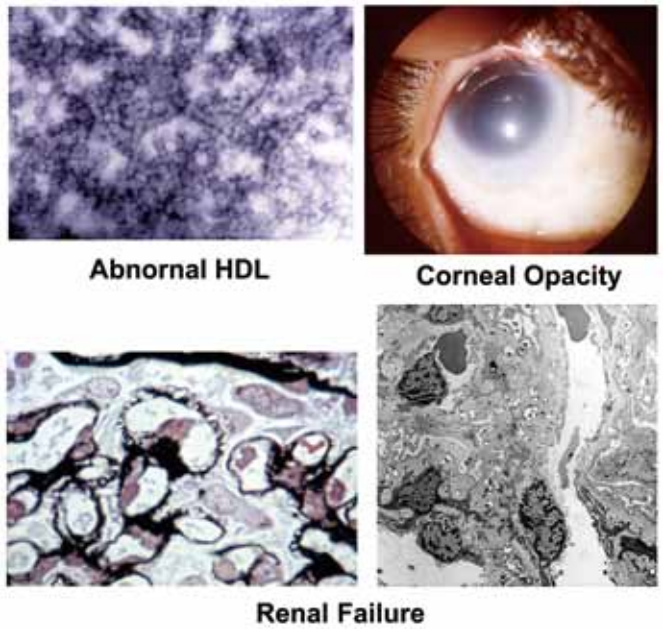

Figure 2. LCAT deficiency
LCAT is involved in the removal of free cholesterol from various tissues and maturation of HDL. Lecithin:cholesterol acyltransferase (LCAT) deficiency has been identified as a genetic metabolic disorder. LCAT dysfunction results in abnormal HDL particles. The cholesteryl ester levels are markedly reduced in lipoproteins and abnormal cholesterol deposition is observed in the tissues of these patients, who often develop severe complications, including corneal opacity, anemia, proteinuria and renal failure.

on these experiments, we developed a GMP-based production protocol of *lcat* gene-expressing ccdPAs.

Efficacy studies of *lcat* gene-transduced ccdPAs

Renal insufficiency is a life-shortening complication of FLD that does not develop in fish-eye disease (FED), another congenital disease with different gene mutations in the *lcat* gene. Efficacy studies were performed in the *lcat* gene-transduced ccdPAs to evaluate the possibility of LCAT replacement therapy via auto-transplantation.

Five patients with FLD and four patients with FED were analyzed. Abnormal lipid metabolisms in these patients's sera were ameliorated by incubation with recombinant LCAT produced by ccdPAs, as demonstrated by improved maturation of HDL (Fig. 3). In order to identify the causative abnormal lipoproteins in renal insufficiency, lipoproteins in FLD and FED patients' sera were analyzed using gel permeation chromatography with concomitant determination of the lipid concentrations. The lipoprotein profiles showed that large-sized lipoprotein particles corresponding to, VLDL and LDL were associated with the degree of renal insufficiency. Interestingly, the LDL particles in the FLD and FED patients were larger in size than those in the unaffected subjects. Therefore, abnormal LDL in FLD is distinct from that of FED in terms of lipid composition and is suggested to be one of the causative lipoproteins involved in progressive renal insufficiency in FLD patients.

Human *lcat* gene-transduced murine ccdPAs were subcutaneously transplanted into LCAT gene knock-out mice (KO-mice). The transplanted ccdPAs stably survived from 14 days after transplantation and differentiated into mature adipocytes. hLCAT was continuously supplied into the mice sera. The impaired lipid metabolism observed in the KO-mice was in part ameliorated by the transplantation of the *lcat* gene-transduced ccdPAs. These results suggest that the ectopic expression and secretion of LCAT in transplanted engineered ccdPAs can improve abnormal lipid metabolism in LCAT-deficient patients and may thereby prevent the progression of renal insufficiency, which determines the prognosis of these patients.

Development of a transplantation cocktail for clinical application

Establishing a transplantation therapy requires that the procedure increase the survival of transplanted pre-adipocytes. In this study, the survival of adipocytes after transplantation was significantly improved by the secretion of VEGF by the host adipose tissue. Secretion of VEGF was affected by host conditions. We also demonstrated that matrix metalloproteinase 3 is involved in the VEGF secretion by adipose tissue. Basic FGF improved the survival of transplanted adipocytes through the actions of matrix metalloproteinase 2.

The development of clinically applicable scaffolds is another important issue for the application of cell transplantation. We focused on fibrin glue as a clinically applicable scaffold in LCAT replacement therapy via the transplantation of *lcat*-gene transduced ccdPAs. Fibrin glue increased cell viability, which was accompanied by decreased apoptotic cell death. The serum LCAT concentrations in the transplanted mice with fibrin gel were comparable to those observed in the mice with the experimental scaffold, Matrigel. To further apply the fibrin-based scaffold to cell transplantation therapy, we examined the potency of platelet-rich plasma (PRP) in the apoptosis of ccdPAs *in vitro*. PRP stimulated the proliferation of ccdPAs and prevented serum starvation- and TNF-α/cycloheximide-induced apoptosis. These results indicate that ccdPAs exhibit anti-apoptotic activities in addition to increased proliferation when cultured in PRP. Therefore, PRP may improve the outcomes of transplantation of adipose tissue by enhancing the anti-apoptotic activities of implanted pre-adipocytes.

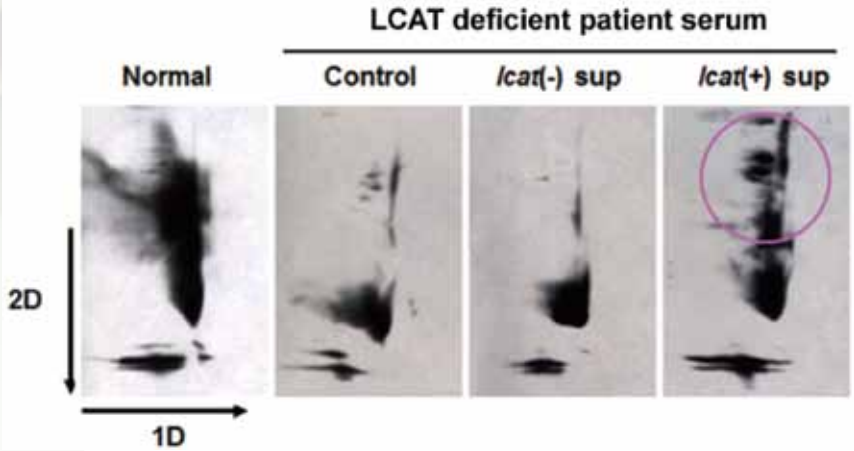

Figure 3. Amelioration of impaired HDL maturation by rLCAT produced by ccdPAs
2D gel electrophoresis to detect the HDL functions showed that the disturbed high-density lipoprotein subpopulation profile was clearly ameliorated by *in vitro* incubation with ccdPA/*lcat*-derived rLCAT.

Conclusion

We developed the basic technologies of adipocyte-based enzyme replacement therapy using ccdPAs. Our research projects may shed light on the development of therapeutic applications for a variety of intractable serum enzyme deficiencies (Fig. 4).

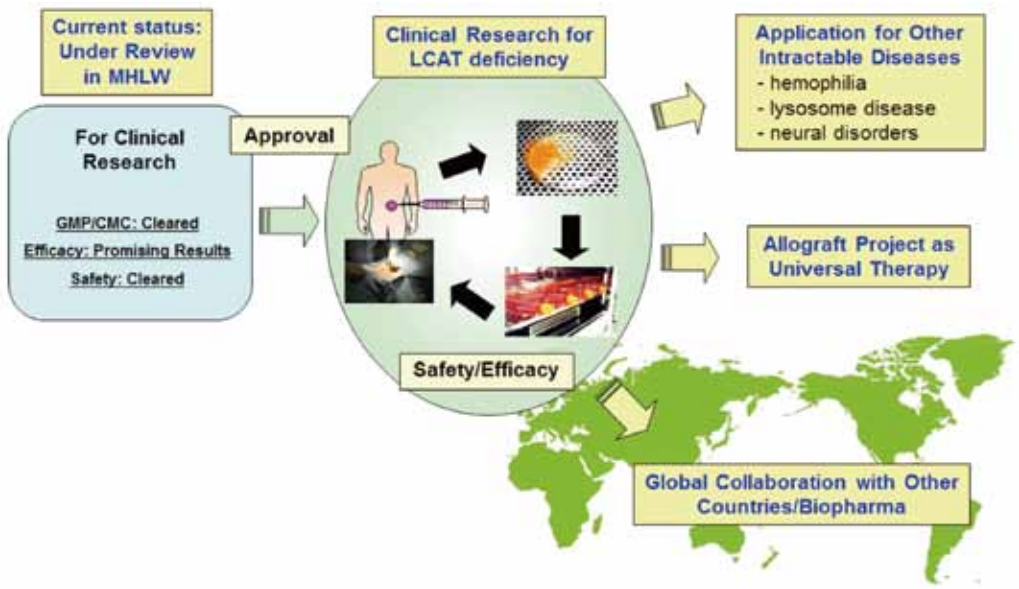

Figure 4. Perspectives on *ex vivo* gene therapy using technical platforms with ccdPAs
Protocols for clinical research at Chiba University are now under the review by the MHLW. Upon approval, clinical research will be conducted (2013-). Based on the POC obtained by clinical research together with the results of preclinical studies in GLP regulation, a clinical trial will be conducted to develop gene therapy products. We are applying these techniques to treat other intractable diseases. We are considering global collaborations with other researchers/pharmaceuticals to spread this novel enzyme replacement therapy using gene transduced-adipocytes.

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Identification of the causal factors of alteration of the functions and expressions of pharmacokinetics-related genes

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Summary

Drug metabolizing enzymes, drug transporters and nuclear receptors play important roles in determining drug pharmacokinetics. The gain or loss of function among these factors results in the aberrant pharmacokinetic profiles of various drugs, eventually leading to lower pharmacological efficacy or unexpected adverse effects. Therefore, identifying the genes that are responsible for the pharmacokinetics of candidate drugs as well as developing tools to clarify the functions of genes are crucial issues in drug development. It is also important in the clinical setting to characterize the causal factors that alter the expression levels of genes and the mechanisms of drug-drug interactions.

Based on the above background, we are working on several research projects aimed at clarifying the mechanisms of function and the transcriptional regulation of human pharmacokinetics-related genes as well as developing advanced tools for evaluating the functions of genes. Through involvement in these research projects, we have offered graduate students opportunities to learn experimental techniques and to engage in the logical thinking process. We have also encouraged students to attend domestic and international congresses to hone their presentation abilities and English skills.

List of representative research projects

1. Characterization of ribavirin transport systems in human hepatocytes
2. Development of human artificial chromosome-based humanized mice for *in vivo* pharmacokinetic evaluations of drugs in the preclinical stage
3. Characterization of the function and expression of the newly-identified cancer-type organic anion transporting polypeptide 1B3 in cancer cells
4. Clarification of the mechanisms underlying benzbromarone-induced hepatotoxicity
5. Development of an advanced *in vitro* human blood-brain barrier model for the evaluation of drug penetration into the brain
6. A functional analysis of a mutation in the *SLCO1B1* gene (c.1628T>G)
7. Clarification of the transcriptional regulation mechanisms of the constitutive androstane receptor
8. Identification of the role of epigenetics in the regulatory mechanisms controlling the *cytochrome P450 1A2* gene expression
9. Evaluation of a method to predict drug-drug interactions via inhibition of cytochrome P450 3A

We herein briefly describe the current progress in three of the above projects (1, 3, 5).

1. Characterization of ribavirin transport systems in human hepatocytes

Ribavirin is a nucleoside analogue that inhibits hepatitis C virus (HCV) replication in human hepatocytes. Ribavirin is such a hydrophilic molecule that it is transported into cells via plasma membrane transporters. Because the uptake process into human hepatocytes is a prerequisite step that allows ribavirin to target HCV, ribavirin uptake transporters should play a critical role in ribavirin's action. However, uptake of ribavirin by human hepatocytes has not been fully characterized. Therefore, the aims of the present study are to identify hepatic ribavirin uptake transporters and to clarify their functional importance in ribavirin's antiviral actions. The results of the uptake experiments showed that equilibrative nucleoside transporter 1 (ENT1) is the primary ribavirin uptake transporter in human hepatocytes (Figure 1A). We then examined the role of ENT1 in ribavirin's antiviral actions using OR6 cells, a HCV replication cell system, in which ENT1 was exclusively responsible for ribavirin uptake. Our results clearly showed that functional disturbance of ENT1 in OR6 cells induced by nitrobenzylmercaptopurine riboside, an ENT1 inhibitor, significantly attenuates ribavirin's antiviral activities (Figure 1B).

Based on the above results, we concluded that ENT1 plays the determinant role in the antiviral efficacy of ribavirin in OR6 cells. We believe that these findings will encourage further studies aimed at understanding the functions and expression mechanisms of ENT1 in human hepatocytes, the results of which may greatly contribute to identifying the predictive factors of treatment efficacy and establishing more effective therapeutic regimens.

2. Characterization of the function and expression of the newly-identified cancer-type organic anion transporting polypeptide 1B3 in cancer cells

Organic anion transporting polypeptide 1B3

(OATP1B3) is a hepatocyte plasma membrane transporter of which the substrates include not only endogenous anionic compounds, but also numerous xenobiotic compounds. Under normal conditions, OATP1B3 is exclusively expressed in the human liver; however, it can also be expressed in various human cancer tissues and is associated with both prognosis and clinical outcomes. Therefore, it is believed that OATP1B3 holds a potential significance for cancer therapy as well as cancer biology. Recently, we reported the identification of a new OATP1B3 mRNA isoform expressed in human colon and lung cancer tissues, which we named cancer-type OATP1B3 (Ct-OATP1B3). Ct-OATP1B3 mRNA was generated from a previously unidentified transcription start site using an alternative promoter region localized at intron 2 **(Figure 2)**. We also showed that the Ct-OATP1B3 mRNA level is strikingly higher than that of liver type-OATP1B3 (Lt-OATP1B3) mRNA in these cancer tissues **(Figure 3)**. Therefore, we demonstrated that the newly-identified Ct-OATP1B3 (but not Lt-OATP1B3) is the primary mRNA isoform in human colon and lung cancer tissues. In line with the possibility that its translation products play important biological roles in cancer cells, we strongly believe that the existence of Ct-OATP1B3 should be taken into account during future studies of OATP1B3 associated with cancer prognosis and clinical outcomes.

3. Development of an advanced *in vitro* human blood-brain barrier model for the evaluation of drug penetration into the brain

The blood-brain barrier (BBB), which is composed of brain microvascular endothelial cells (BMEC) together with astrocytes and pericytes, strictly regulates penetration of diverse small/large compounds into the brain. *In vitro* BBB models are considered to be highly useful for central nervous system (CNS) drug development. In this study, we succeeded in establishing a new cell line, hereinafter referred to as human BMEC conditionally immortalized clone β (HBMEC/ciβ), as part of our ongoing efforts to develop an *in vitro* human BBB model.

Our results showed that HBMEC/ciβ proliferates well and exhibits a similar mRNA expression profile to that of primary HBMEC. Furthermore, we found that HBMEC/ciβ forms tight junctions and possesses an effective efflux transporter function, both of which are essential to a functioning BBB **(Figure 4)**. Therefore, our data indicate that the newly established HBMEC/ciβ offers a promising tool for use in the development of a practical *in vitro* human BBB model.

To enhance the usefulness of our cells, we are currently investigating several methods of improving the cellular functional properties. One is the development of a specific culture method for our cells using a feature in which higher temperatures can terminate proliferation signals in conditionally immortalized cells. When we examined the effects of higher temperatures on the HBMEC/ciβ differentiation status, higher temperatures stimulated HBMEC/ciβ differentiation marked by morphological alterations and increases in several mRNA levels. Therefore, while it is still premature to state it categorically, it is possible that inducing differentiation by shifting culture temperatures will provide a feasible method of improving the HBMEC/ciβ

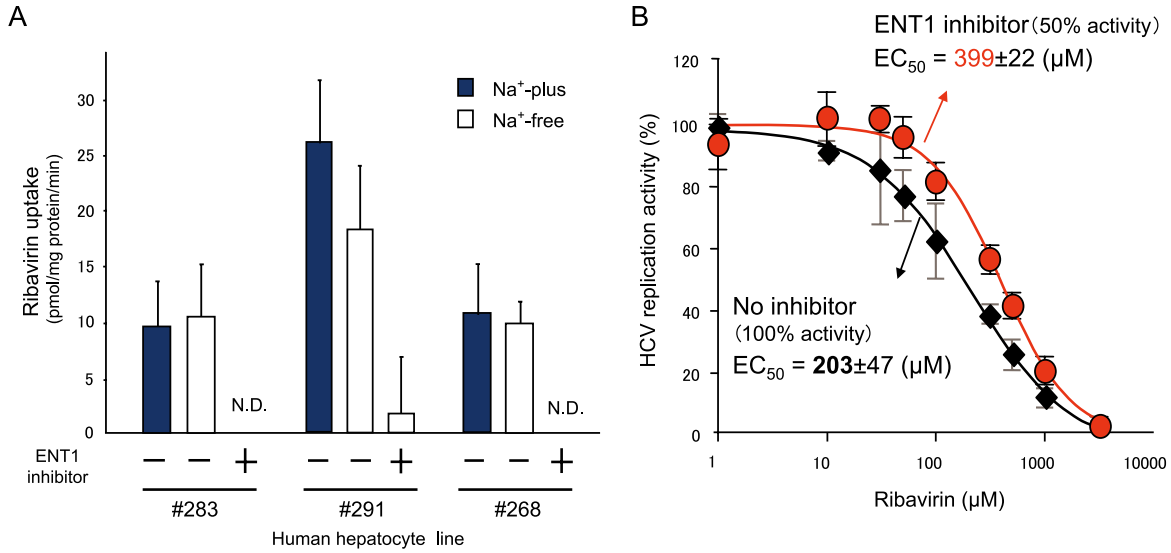

Figure 1. Identification of ribavirin uptake transporters in human hepatocytes and their roles in ribavirin's pharmacological actions.
A: A ribavirin uptake analysis in human hepatocytes. The ribavirin uptake activity in human hepatocytes was Na^+-independent and sensitive to an ENT1 inhibitor, suggesting that ENT1 is the primary ribavirin uptake transporter in human hepatocytes. Each value represents the mean ± S.D. of three independent analyses, each performed in duplicate. B: The role of ENT1 in ribavirin's pharmacological actions in an HCV replication system, OR6 cells. ●, cells treated with the ENT1 inhibitor (the ENT1 activity level was estimated to be 50%). ◆, non-treated cells. Inhibition of the ENT1 function resulted in attenuation of ribavirin efficacy, suggesting that ENT1 plays a critical role in ribavirin's actions in OR6 cells. Each value represents the mean ± S.D. of five independent analyses, each performed in duplicate.

functions.

Another method involves the establishment of human conditionally immortalized astrocytes, as cumulative evidence shows that human astrocytes strengthen the BBB properties of HBMEC *in vivo* as well as *in vitro*. We have just introduced the immortalized gene into human primary astrocytes, and the cells showed high proliferation activity. The cells retained several astrocyte-enriched mRNA expressions along with a high adenosine uptake activity level, which is one of the important functions of mature astrocytes. Therefore, it can be expected that immortalized human astrocytes are useful for developing a co-cultured *in vitro* BBB model.

Considering our data obtained thus far, it is highly expected that a combination of HBMEC/ciβ, immortalized astrocytes and dedicated culture conditions will mark the establishment of a novel immortalized cell-based BBB model, which we call "an advanced" *in vitro* BBB model. We believe that the model holds promise in making significant contributions to CNS drug development.

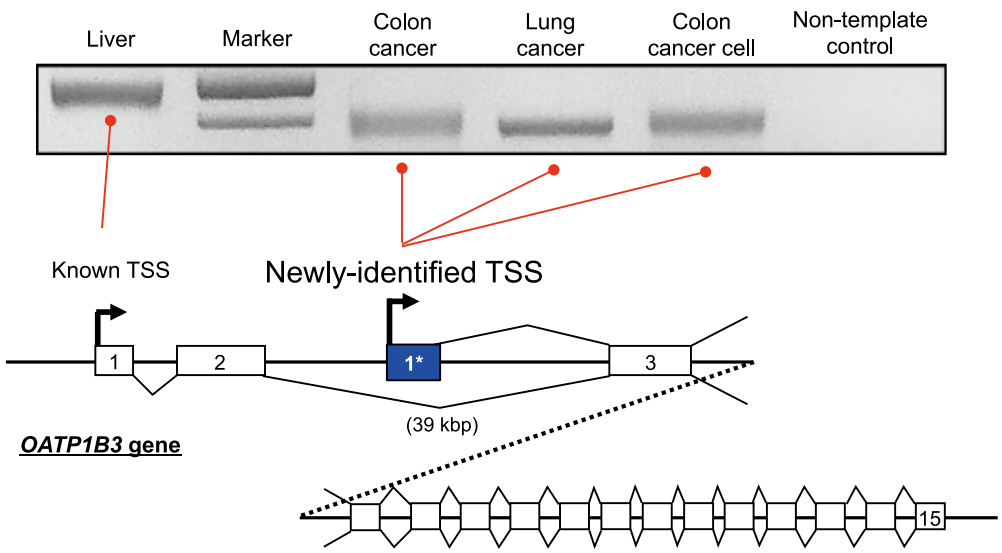

Figure 2. Identification of ct-OATP1B3 mRNA in human cancerous tissues and cells.
The transcription start sites (TSS) in human liver, human colon cancer tissue, human lung cancer tissue and human colon cancer cells were determined. The TSS in the cancerous tissues were located within intron 2, different from that observed in the human liver. Ct-OATP1B3 mRNA contains the newly-identified exon 1 that is spliced to the reported exon 3. Ct-OATP1B3 mRNA and Lt-OATP1B3 mRNA share the residual exons (4 to 15).

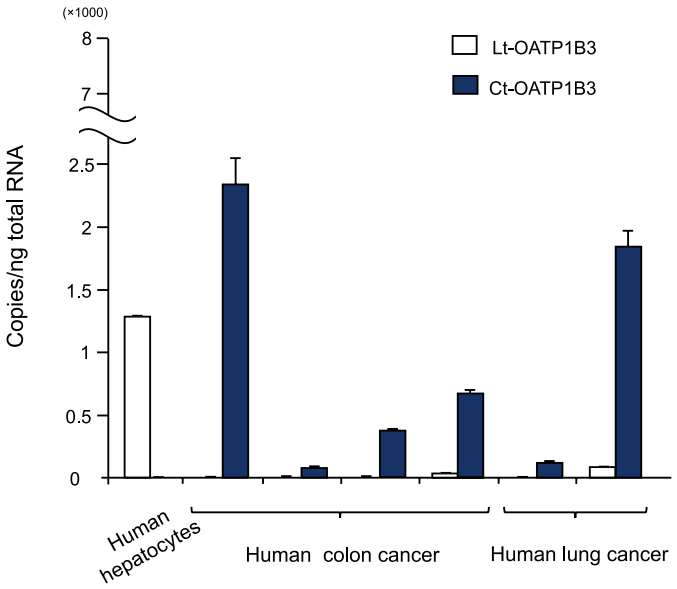

Figure 3. Comparison of the Ct-OATP1B3 mRNA level to the Lt-OATP1B3 mRNA level in human hepatocytes and human cancerous tissues.
Quantification of the Ct-OATP1B3 mRNA and Lt-OATP1B3 mRNA levels in human hepatocytes, human colon cancer tissues (n=4) and human lung cancer tissues (n=2) was performed using a standard curve method. Each value represents the mean ± S.D. of three independent analyses, each performed in duplicate. Ct-OATP1B3 mRNA was hardly expressed in the human hepatocytes, whereas it was a predominant form in the human cancerous tissues.

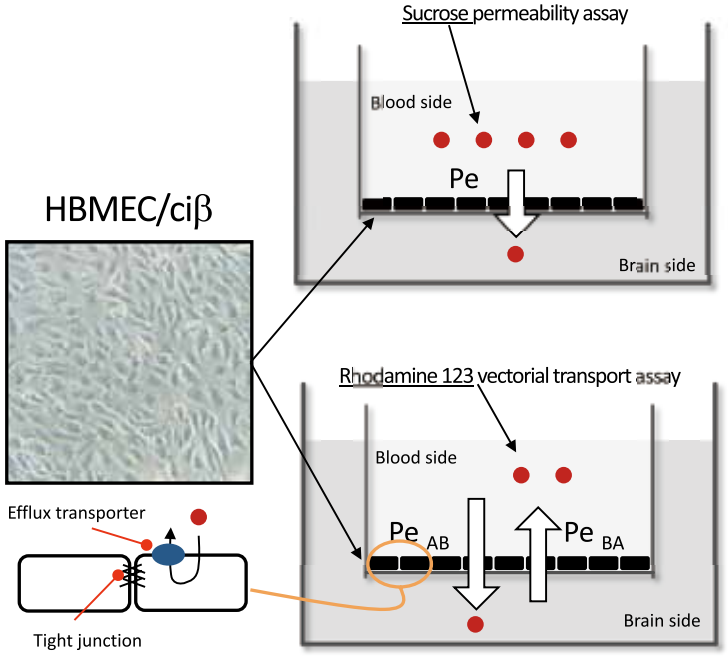

Figure 4. A schematic illustration of the HBMEC/ciβ-based *in vitro* human BBB model.
HBMEC/ciβ shows a similar morphology to that of human primary BMEC. An *in vitro* human BBB model can be developed using HBMEC/ciβ cultured in the transwell system, in which the insert well and the bottom well mimic the blood side and the brain side, respectively. HBMEC/ciβ forms tight junctions between the cells to shut down the paracellular route for drug penetration and expresses various drug efflux transporters, including P-glycoprotein, that prevent drug penetration across the BBB. The sucrose permeability rate is often determined to evaluate the tight junction function, and the rhodamine 123 efflux ratio, which is calculated using the bidirectional permeability assay, is often determined to evaluate the efflux transporter function.

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Analysis of a novel mechanism of drug-induced liver and intestinal injury to improve clinical pharmacotherapy

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Summary

Adverse drug reactions are a major problem in clinical pharmacotherapy. Although pharmacotherapy is regarded as an important way to cure diseases, it is often discontinued because of these harmful adverse reactions. Unfortunately, most of the mechanisms underlying the drug-induced adverse reactions remain to be elucidated. We have been investigating the mechanism(s) of drug-induced liver or intestinal injury.

Although the majority of our studies have focused on the mechanism of drug-induced liver and intestinal injury in experimental animals, the obtained information can be extrapolated to humans by additional studies after confirming the findings by human *in vitro* studies. Therefore, an analysis of these mechanisms will lead to a safer application of clinical pharmacotherapy. These studies also allow our graduate students to learn how to apply their research in clinical applications, to improve pharmacotherapy in the clinical setting.

1. Mechanism of methotrexate (MTX)-induced intestinal injury

Although MTX is widely used in clinical practice, severe intestinal injury sometimes forces patients to discontinue using this drug. We investigated the molecular mechanism underlying the MTX-induced intestinal injury in an experimental animal model. The administration of MTX causes intestinal injury in rats, which is characterized by enhanced paracellular permeability in the small intestine. This intestinal injury is associated with oxidative stress and is attenuated by treatment with an antioxidant, N-acetyl cysteine (NAC). More recent studies showed that the MTX-induced intestinal injury is partly caused by the altered phosphorylation status of zonula occludens-1 (ZO-1), which is a scaffolding protein that plays a pivotal role in the formation of tight junctions. We detected a reduction of ZO-1 immunostaining along the apical membrane of intestinal villi exposed to MTX. Decreased claudin-4 immunostaining was also observed in the intestinal villus tips of MTX-treated rats. In addition, the injury is also partly caused by inflammatory cytokines. Therefore, MTX-induced intestinal injury also involves immune responses. Our study suggests a novel mechanism of MTX-induced intestinal injury, which may contribute to the safer application of MTX in clinical practice.

2. Molecular mechanism of drug-induced cholestasis caused by the internalization of transporters in the bile canalicular membrane

Transporters in the bile canalicular membrane play an important role in the biliary excretion of xenobiotics, including therapeutic agents, as well as bile salts. Therefore, bile canalicular transporters are a determinant of bile flow. We found that exposure of isolated rat hepatocytes to a high concentration of ethacrynic acid caused the internalization and dysfunction of bile canalicular transporters. We investigated the mechanism responsible for the altered localization of bile canalicular transporters. The internalization of transporters was associated with oxidative stress. It followed an elevation of the intracellular Ca^{2+} concentration and the activation of novel protein kinase C (nPKC). Treatment with tertiary butyl hydroperoxide also induced an internalization of bile canalicular transporters associated with oxidative stress, and the addition of glutathione ethyl ester, an antioxidant, induced the relocalization of the transporters to the canalicular membrane. This relocalization process depends on intracellular microtubules and is followed by the activation of protein kinase A. The internalization of transporters was also observed in the rat intestine, although it was followed by the activation of conventional PKC (cPKC), not the nPKC. This suggests that the mechanism of transporter internalization differs between the liver and intestine. However, the putative phosphorylation targets of these protein kinases involved in reversible Mrp2 trafficking remain unclear. We investigated the effect of changing the intrahepatic redox status on the C-terminal phosphorylation status of radixin (p-radixin), which links Mrp2 to F-actin, and the interaction of p-radixin with Mrp2 in rat hepatocytes. We detected a significant decrease in the amount of p-radixin that co-immunoprecipitated with Mrp2 after tertiary-butylhydroperoxide (t-BHP) treatment. After treatment with GSH-ethylester (GSH-EE), the phosphorylation level was the same as that of the control. From these observations, we concluded that the interaction of p-radixin with Mrp2 was decreased by the activation of PKC and under oxidative stress conditions, which subsequently led to Mrp2 internalization, whereas the interaction of p-radixin and Mrp2 was increased by the activation of PKA during the recovery from oxidative stress. Moreover, when there

was sustained internalization of Mrp2, the hepatic MRP2 protein expression was decreased, and the canalicular localization of MRP2 was disrupted without changing its mRNA expression level. This reduction in MRP2 protein expression was suppressed by pretreatment with N-benzyloxycarbonyl (Cbz)-Leu-Leu-leucinal (MG-132), a proteasome inhibitor. Furthermore, the modification of MRP2 by small ubiquitin-related modifier 1 (SUMO-1) was impaired in BSO-treated rat livers, while that by ubiquitin (Ub) and MRP2 was enhanced. These observations suggest that sustained periods of low GSH content, coupled with altered modifications of MRP2 by Ub/SUMO-1 were accompanied by the proteasomal degradation of MRP2.

Although bile salt export pump (BSEP) dysfunction is considered to be susceptibility factor for drug-induced liver injury (DILI), little is known about the relationship between drug-induced BSEP dysfunction and BA-dependent hepatotoxicity. We demonstrated that BA-dependent toxicity was observed for 11 test compounds in sandwich-cultured hepatocytes (SCHs) treated in the presence of BAs, while no signs of toxicity were observed in SCHs treated in the absence of BAs. Of the 11 compounds, nine were known BSEP inhibitors. Moreover, for some compounds, an increase in the severity of BA-dependent toxicity was observed in SCHs that were co-treated with 1-aminobenzotriazole, a non-selective inhibitor of cytochrome P450-mediated drug metabolism. These results indicate that the SCH-based model is likely to prove useful for the evaluation of BA-dependent DILI, including the effects of drug metabolism and BSEP inhibition on liver injury.

3. Transporter-mediated drug-drug interactions

Cyclosporine A (CsA), an immunosuppressant, reportedly inhibits the hepatic uptake transporters of the organic anion transporting polypeptide (OATP/Oatp) family. Therefore, the administration of this drug sometimes increases the plasma concentration of other concomitantly administered drugs that are substrates of OATPs, resulting in transporter-mediated drug-drug interactions. We investigated the mechanism underlying the inhibition of OATPs by CsA. The administration of CsA to rats inhibited the hepatic uptake transporters for several days. In addition, exposure of a primary culture of rat hepatocytes to CsA caused a stable inhibition of these transporters. However, the expression levels of hepatic uptake transporters remained unchanged in CsA-treated hepatocytes. The long-lasting inhibition of hepatic uptake transporters was observed in human OATP-expressing systems. These results suggest that the administration of CsA to humans may inhibit the hepatic uptake transporters, leading to severe drug-drug interactions in clinical situations.

The potential for P-glycoprotein (P-gp)-mediated drug-drug interactions (DDIs) between antimalarials and P-gp substrates was examined using Caco-2 cells. Selected antimalarials were screened for an interaction with P-gp. Lumefantrine, amodiaquin and artesunate blocked P-gp-mediated transport. Several herbal medicines are also used in African traditional medicine for the treatment of malaria. The extracts of phytomedicines *Tapinanthus sessilifolius* Blume, *Vernonia amygdalina* Delile and *Carica papaya* inhibited P-gp in Caco-2 cells. Interactions of the phytomedicines with conventional P-gp substrate drugs are likely to occur upon their coadministration, which may result in altered therapeutic outcomes.

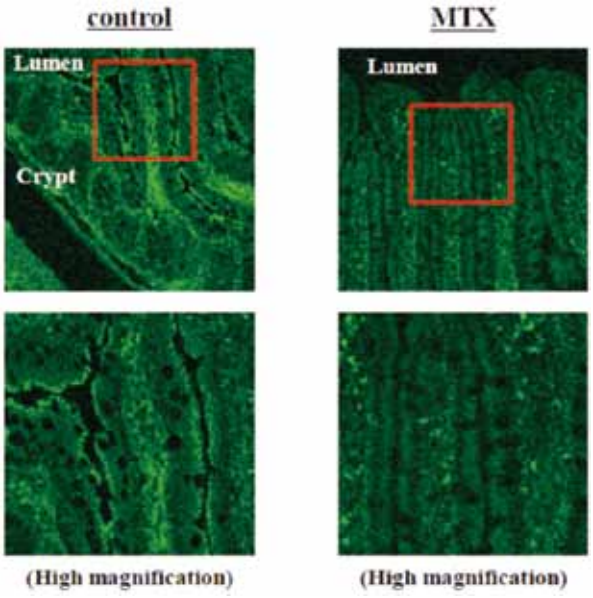

Figure 1. Immunohistochemical localization of ZO-1 in the villus epithelia of the small intestine of untreated (control) and MTX-treated rats.

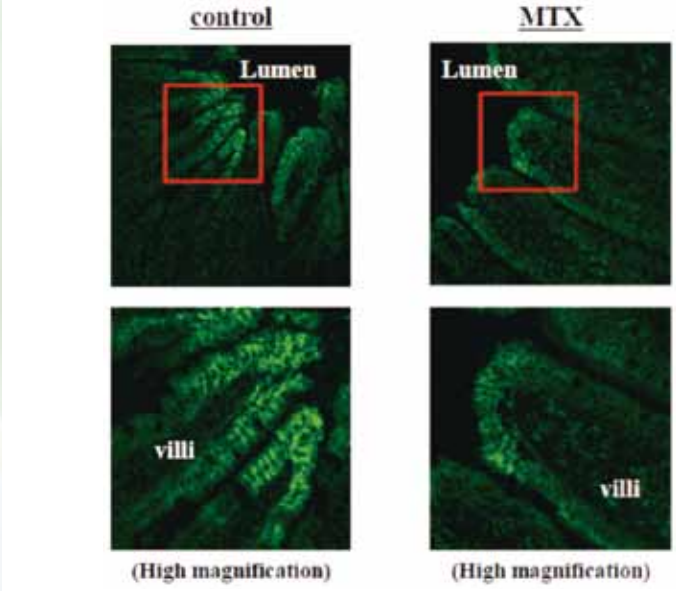

Figure 2. Immunohistochemical localization of Claudin-4 in the villus epithelia of the intestine of untreated (control) and MTX-treated rats.

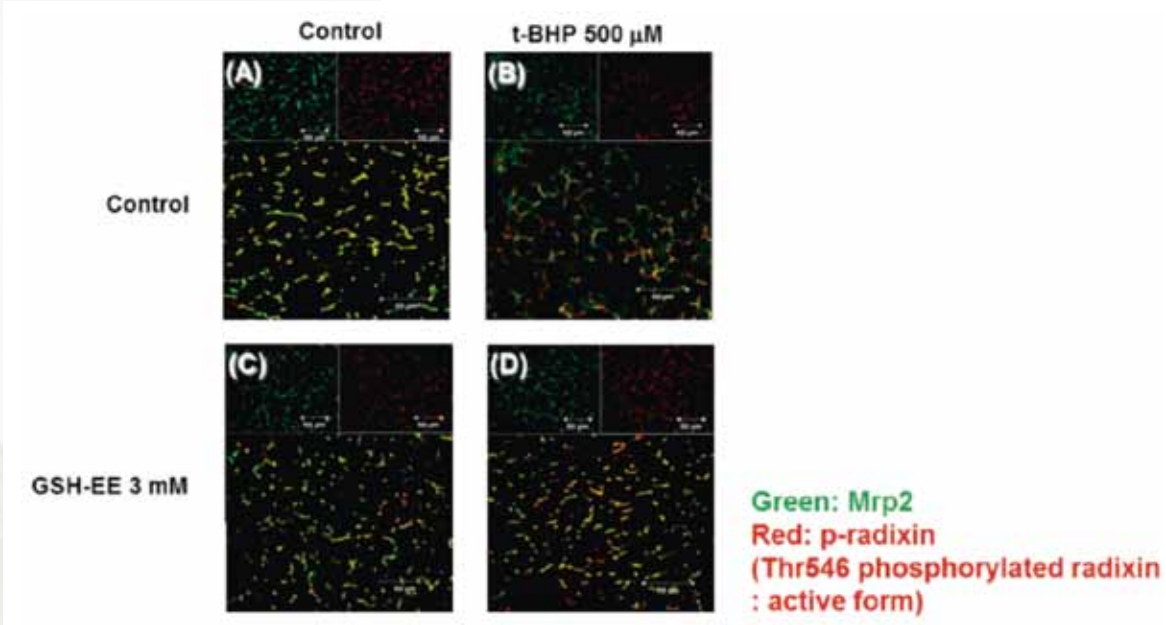

Figure 3. Reversible changes in the localization of Mrp2 on the bile canalicular membrane induced by the change in the cellular redox status.

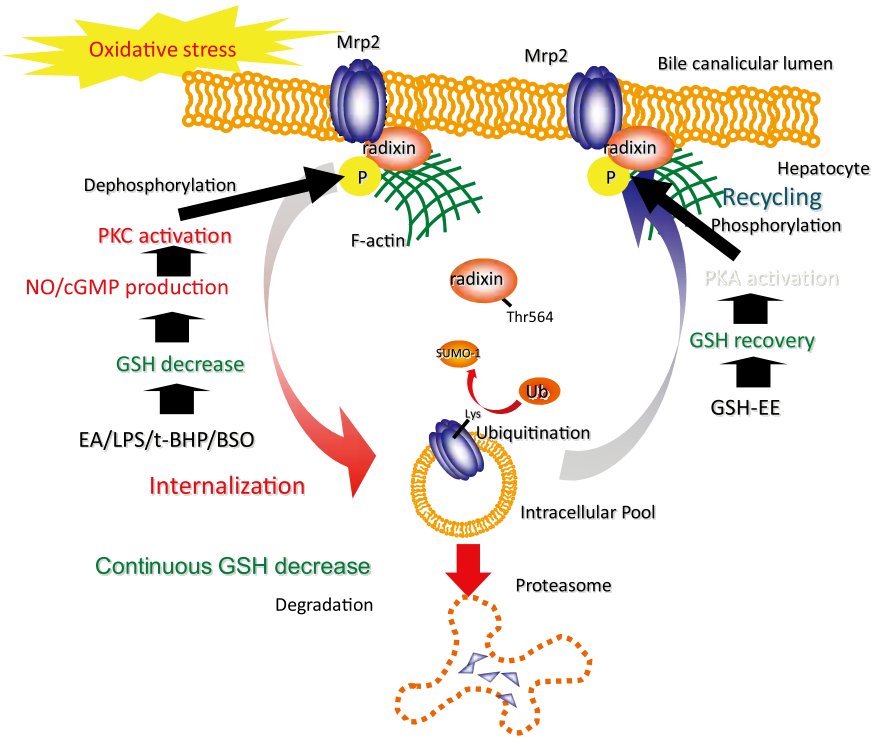

Figure 4. The molecular mechanism underlying the oxidative stress-induced internalization of bile canalicular transporters and their relocalization to the membrane

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The mechanisms underlying NKT cell-mediated adjuvant effects

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Summary

For effective anti-tumor responses, an increase in the function and number of CD8 killer T cells and NK cells is essential. However, the tumor-specific CD8 killer T cells and NK cells mediating anti-tumor responses do not generally increase in number, because tumor cells do not have any adjuvant activity, which is important for the activation of anti-tumor responses, and therefore, these cells fail to activate the immune system. Moreover, the tumor cells themselves produce immunosuppressive cytokines, such as TGF-beta and IL-10, which suppress the functions of dendritic cells, CD8 killer T cells and/or NK cells.

NKT cells mediate adjuvant activity by their production of IFN-gamma, which in turn activates and increases the number of both NK cells and tumor-specific CD8 killer T cells. Therefore, the activation of NKT cells in a tumor-bearing host inhibits tumor growth and leads to the rejection of the tumor.

Tumors contain two types of tumor cells; MHC positive and negative. Therefore, the elimination of both MHC positive and MHC negative tumor cells at the same time is essential to fully eradicate the tumor. CD8 killer T cells only kill MHC positive cells through their recognition of the MHC, while NK cells only kill MHC negative target cells. Therefore, both CD8 killer T cells and NK cells need to be activated during anti-tumor responses in order to obtain complete eradication of a tumor. Only NKT cells can activate both CD8 killer T cells and NK cells at the same time.

This process is known as NKT cell-mediated adjuvant therapy, and has been developed to treat patients with cancer. Although we have started to treat patients with advanced lung cancer using this method in Phase I/IIa

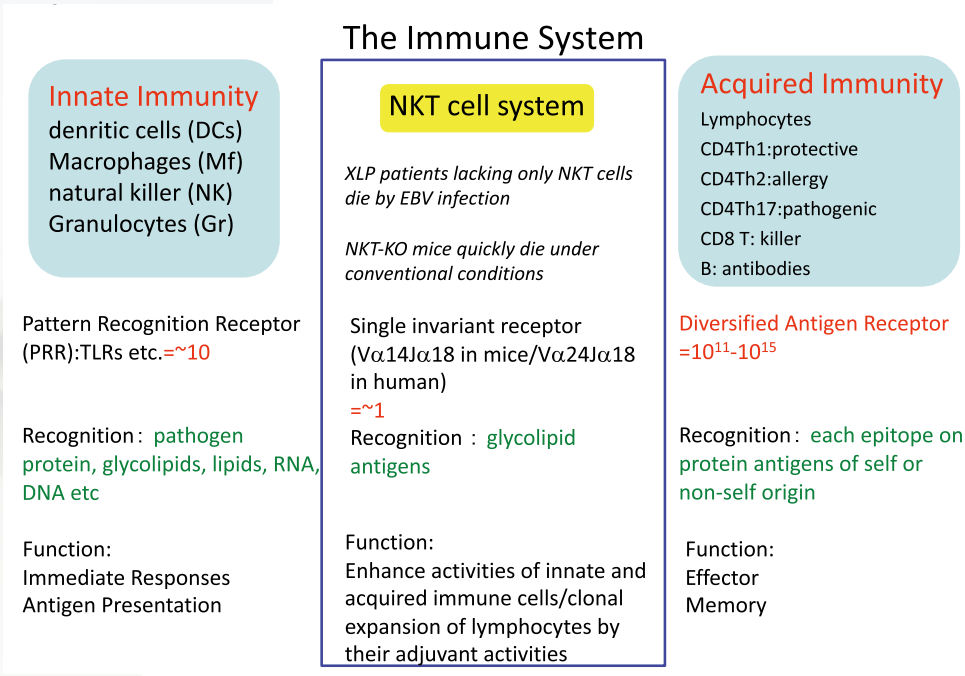


Figure 1. The role of NKT cells in the immune system
The immune system is composed of two systems to mediate innate responses and effector/memory responses. NKT cells are essential for both innate and acquired immune responses, because XLP patients lacking only NKT cells easily die from an EB virus infection, and because mice lacking only NKT cells quickly die under conventional conditions just after birth. Therefore, NKT cells are essential for immune responses.

clinical trials, this report describes the theoretical background and rationale for the establishment of this therapy.

Achievements

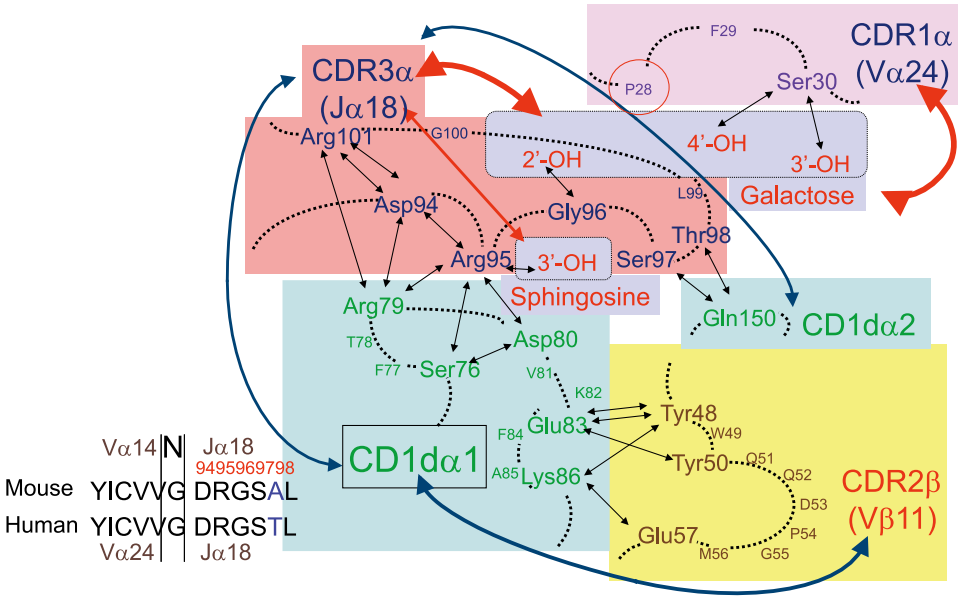
1. Neoglycolipid synthesis based on the crystal structure of the human NKT cell antigen receptor/alpha-galactosylceramide/CD1d triple complex

Based on our discovery that alpha-galactosylceramide (alpha-GalCer) is a NKT cell ligand in 1997, researchers (Borg et al.) in Australia successfully crystallized the triple complex of Valpha24/Vbeta11/alpha-GalCer/CD1d. We successfully generated new alpha-GalCer analogs with strong adjuvant activity based on this crystal structure. A new molecule with an alpha-linked carba-galactosyl moiety was produced by replacing the 5a'-oxygen atom of the pyranose ring of D-galactose of alpha-GalCer with a methylene group.

This modification generates an ether-bond on the pyranose ring, which is resistant to glycosidase, making it more stable than alpha-GalCer *in vivo*, and also creating a new hydrophobic interaction with Pro28 on the invariant Valpha14-Jalpha18 TCR alpha, resulting in more stable binding. Alpha-carba-GalCer induces enhanced production of Th1 cytokines and augmented iNKT-cell-mediated adjuvant effects *in vivo* in comparison to alpha-GalCer. Therefore, the generation of neoglycolipids may provide optimal therapeutic reagents for generating protective or regulatory immune responses.

2. Effects of NKT cell-mediated adjuvant activity on anti-tumor responses

The IFN-gamma produced by IL-12-activated NKT cells results in the activation and clonal expansion of $CD4^+$ Th1 cells, as well as cytotoxic $CD8^+$ T cells in the acquired immune system, leading to memory or secondary immune responses. This also activates NK cells in the innate immune system. In general, MHC positive target cells are eliminated by the $CD8^+$ T cells, whereas MHC negative target cells are killed by NK cells. Since both MHC positive and MHC negative tumor cells are present in tumors and both need to be eliminated, NKT-cell-mediated adjuvant activity affecting both the innate and acquired immune responses is an important strategy for the treatment of cancer. In fact, the treatment of tumor-bearing mice with alpha-GalCer-pulsed DCs leads to the eradication of established metastatic tumors. Therefore, the manipulation of DCs to produce IL-12 might be a promising strategy for the treatment of cancer to selectively trigger protective anti-tumor immunity through the NKT cell system. We also developed ES-derived NKT cells or iPS-derived NKT cells *in vitro* by nuclear transfer and iPS technologies,



First 4 aa, DRGS sequences in Jα18, are critical for the binding with with both CD1d and the sugar head group of α-GalCer.

Figure 2. The crystal structure of the triple complex of human Va24/Vb11 NKT cell receptor/alpha-GalCer/CD1d molecules
The mode of ligand recognition by the NKT cell receptor is distinct from that of the conventional T cell receptor: 1) The first five amino acids of the Ja18 region in the invariant Va24 chain, which is almost equivalent in both humans and mice, are essential for the ligand binding to CD1d and the ligand, alpha-GalCer. 2) Because of the similarity of the first five amino acids in both human and mice, alpha-GalCer can be used for both species, especially for NKT cell-targeted immune therapy on anti-tumor therapy.

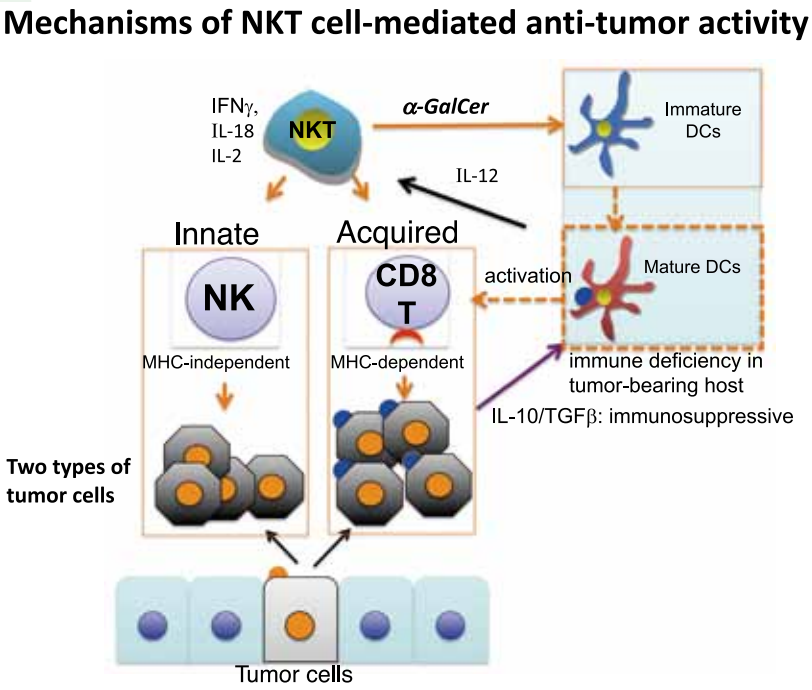


Figure 3. The mechanisms of NKT cell-mediated adjuvant therapy
NKT cells have three major functions: 1) Unlike conventional T cells, NKT cells can interact with immature DCs in the presence of alpha-GalCer to induce the maturation of immature DCs and help the host recover from immunodeficiency. 2) alpha-GalCer-activated NKT cells produce IFN-gamma, which in turn activates NK cells to kill MHC negative tumor cells and CD8 killer T cells to kill MHC positive tumor cells at the same time. Therefore, to eradicate a tumor, the activation of NKT cells is essential. This is the mechanism of "Adjuvant NKT Cell Targeted Therapy" that we developed.

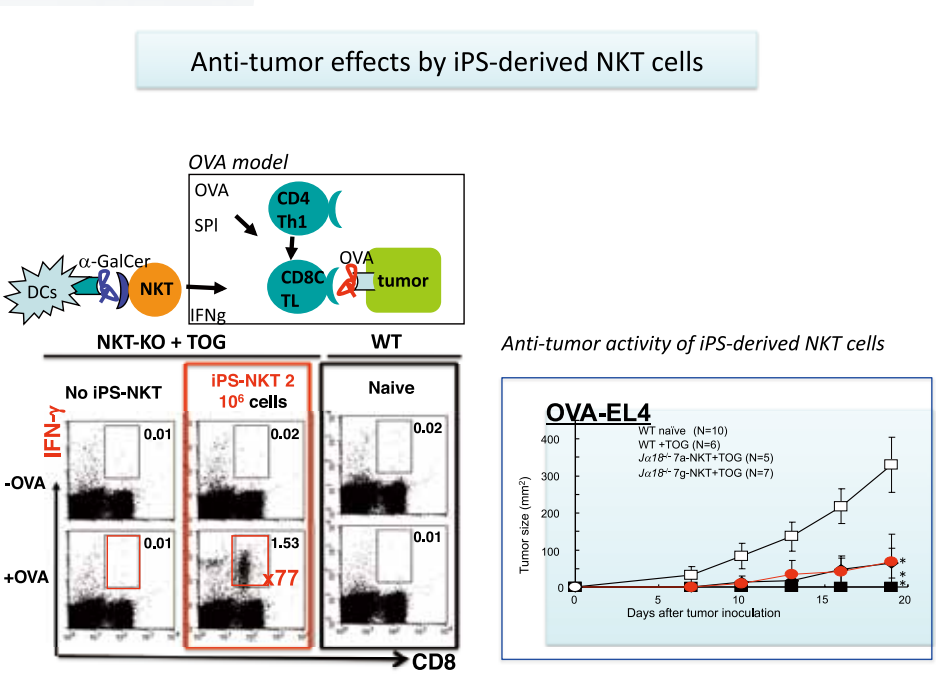


Figure 4. The mechanisms of NKT cell-mediated adjuvant therapy
NKT cells have three major functions: 1) Unlike conventional T cells, NKT cells can interact with immature DCs in the presence of alpha-GalCer to induce the maturation of immature DCs and help the host recover from immunodeficiency. 2) alpha-GalCer-activated NKT cells produce IFN-gamma, which in turn activates NK cells to kill MHC negative tumor cells and CD8 killer T cells to kill MHC positive tumor cells at the same time. Therefore, to eradicate a tumor, the activation of NKT cells is essential. This is the mechanism of "Adjuvant NKT Cell Targeted Therapy" that we developed.

respectively, both of which led to IFN gamma-mediated adjuvant effects and anti-tumor immune responses.

In fact, the establishment of a system for the efficient generation of NKT cells from ESCs or iPS would enable the development of NKT cells to investigate the mechanisms of IFN gamma-mediated adjuvant activity induced by NKT cells. For this purpose, we used NKT cell-derived iPSCs generated using the Yamanaka factors or cloned ES (NKT-ES) cells generated by the transfer of nuclei from mature NKT cells, and established a culture system that preferentially developed functional NKT cells producing mainly interferon gamma and exhibiting strong adjuvant activity. This cloned ES or iPS culture system offers a new opportunity to elucidate the molecular events in NKT cell development and for the establishment of NKT cell-based therapy.

In conclusion, we developed a novel NKT cell targeted adjuvant therapy by administering alpha-GalCer-pulsed DCs on the basis of the NKT cell-mediated adjuvant effects on the anti-tumor responses in mice.

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Invited Lectures

1. **Taniguchi M**. What NKT cell brings and where it will go. G-COE program summer retreat, Chiba, Sep. 6 2009.
2. **Taniguchi M**. Clinical application of NKT cell-targeted therapy and its future direction. University of Palermo. Lecturer, Sep. 10 2009.
3. **Taniguchi M**. A novel subset of mouse NKT cells bearing the IL-17 receptor B responds to IL-25 and contributes to airway hyperreactivity. The 2nd European Congress of Immunology, invited speaker, Berlin, Germany, Sep. 13-16 2009.
4. **Taniguchi M**. iPS-derived NKT cell with adjuvant activity. World Immune regulation Meeting –V. invited speaker, Davos (Switzerland), Mar. 25 2010.
5. **Taniguchi M**. NKT cell-targeted adjuvant cell therapy-from basic to clinic. the 14th International Congress of Immunology (ICI 2010), invited speaker, KOBE, Aug. 23 2010.
6. **Taniguchi M**. iPS-derived NKT cells in the 40th Annual Meeting of the German Society for Immunology, Leipzig (Germany), invited speaker, Sep. 26-29 2010.
7. **Taniguchi M**. iPS-Derived NKT Cells and their Adjuvant Effects. 2011 Keystone Symposia on NK and NKT Cell Biology, invited speaker, Breckenridge / Colorado (USA), Jan. 2011.
8. **Taniguchi M**. NKT cell subsets and their function. The International PhD Program in Immunopharmacology. University of Palermo, Palermo (Italy), Mar. 28-29, 2011.
9. **Taniguchi M**. Early NKT Precursor. 6th International Symposium on CD1 and NKT Cells. invited speaker, Chicago (USA), Sep. 23-27 2011.
10. **Taniguchi M**. NKT Cell-mediated Adjuvant Activity on Antitumor Responses. FOCIS2012, invited speaker, Vancouver (Canada) Jun. 19-23 2012.

Construction of an Infrastructure for Immunogenomics

Core Member

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Summary

Genomics inevitably requires an informational/material infrastructure because it is based on data-driven approaches. In particular, a data sharing system accordingly plays a crucial role in genomics. In addition, interdisciplinary collaboration is highly critical and serves as a key point in obtaining meaningful results through such integrative approaches. In this context, we attempted to demonstrate the power of genomic approaches in immunology in a collaborative framework with clinical and basic immunologists. The first thing we had to do was to establish various platforms to share clinical and basic immunological data in the research community. Thereafter, we became positively involved in the network of researchers of primary immunodeficiency diseases (PIDs) and constructed new PID clinical archives as well as a mutation analysis system based on immunogenomics to actively apply the genomic approaches in order to address clinical problems in immunology. This provided us with many important lessons for further development of immunogenomics in the medical field.

1. Construction of a Reference Database of Immune Cells, RefDIC

The creation of a reliable database of various "omics" data in immunology is necessary in order to realize genomic approaches in immunology. Therefore, we previously constructed a reference database of immune cells (RefDIC: http://refdic.rcai.riken.jp/welcome.cgi). We have also been accumulating cytokine/chemokine profiles of various immune cells under various conditions and, in parallel with the new data accumulation, upgraded the data browsing functions of the RefDIC to further enhance its database function (Figure 1). Collectively, the RefDIC serves as a unique database in immunogenomics that enables researchers to cross-reference the mRNA and protein profiles of immune cells on the same platform. The RefDIC provides researchers with a wealth of information regarding the genome-wide gene expression in immune cells.

2. Construction of Informational Infrastructures for PID Studies: Clinical Data Repository and Mutation Analysis Tools

We began to closely collaborate with experts in the field of PIDs at 13 universities in Japan and genome scientists at the Kazusa DNA Research Institute because our ultimate goal is to apply genomic approaches to tackle medical problems. As a first step, we constructed a clinical data repository, termed PIDJ (http://pidj.rcai.riken.jp/index.html). More than 1,000 clinical data sets have been deposited in the PIDJ as of December 2009, and the PIDJ functions as a gateway to seamlessly connect to genetic tests of PID-causative candidate genes when PID experts believe that a patient should be subjected to genetic testing. More than 300 PID patient samples have been analyzed in a year, and the number of patient samples to be analyzed has continuously increased. One of the most time-consuming steps in genetic testing to search for disease-causative genes is to interpret newly identified genetic variations. Therefore, we generated a new mutation analysis platform, Mutation@A Glance (http://rapid.rcai.riken.jp/mutation/: Figure 2), in order to expedite the interpretation of identified genetic variations in candidate genes in patients. Mutation@A Glance enables researchers to discriminate between newly identified genetic variations from single nucleotide

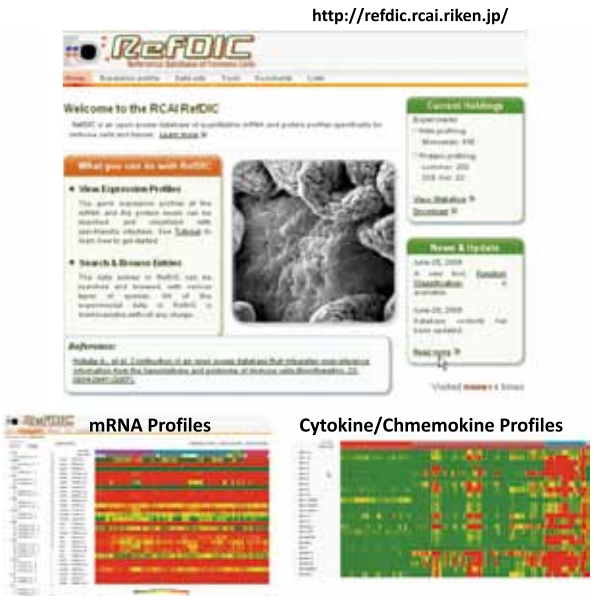

Figure 1. RefDIC Database: Immunogenomics database that enables researchers to cross-reference the mRNA and protein profiles of various immune cells.

polymorphisms as well as known disease-causative mutations and greatly facilitates the evaluation of the effects of genetic variations in terms of the protein structure and function.

3. Collaborations with Other Groups in the G-COE Project

We have assisted members of the G-COE in conducting comprehensive gene expression profiling and data analyses. In the course of these collaborations, we intentionally tried to educate young students regarding various genomic methods and data analyses because one of the important missions of the G-COE is to develop human resources who are familiar with genomic methodology as well as medical science.

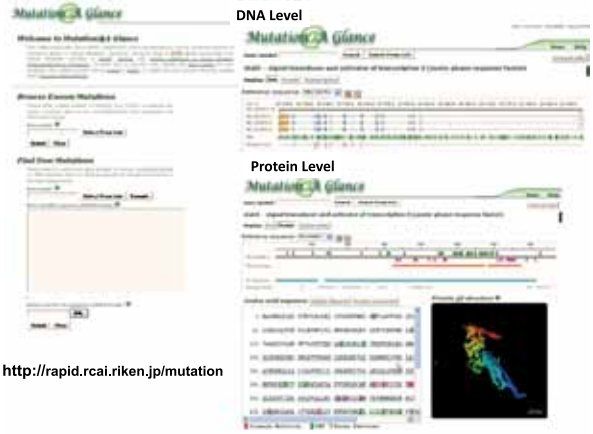

Figure 2. Mutation@A Glance: Facilitates interpretation of newly identified genetic variations.

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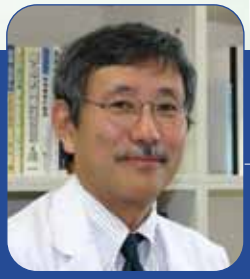
Carbon Ion Radiotherapy and Immunotherapy for Bone and Soft Tissue Sarcomas



Core Member

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Summary

Tumors arising from bones, muscles and vessels are referred to as bone and soft tissue sarcomas. While the incidence of these tumors is extremely low, they are capable of occurring ubiquitously throughout the body. Therefore, they are occasionally detected too late, or their accurate diagnosis presents difficulty and incomplete treatment is administered on the false recognition of their being benign. While tumor resection is the most common treatment modality for such bone and soft tissue sarcomas, major progress has been made in their management, thanks to the development of combined therapy modalities. These methods combine chemotherapy and radiotherapy with new imaging diagnostic techniques, such as MR, CT and PET. However, chemotherapy may often not be effective, and curative surgery may therefore be difficult to perform for tumors that develop in or near the spinal cord or in the pelvis, as well as in patients with advanced limb tumors and postoperative recurrent tumors. Moreover, most bone and soft tissue sarcomas are resistant to conventional radiation. Therefore, despite the significant progress seen in the treatment of bone and soft tissue sarcomas, patients judged to be intractable for surgery are less likely to find an effective treatment option. Carbon ion beams, with their superior dose conformity and potent biological effects, holds significant promise for achieving outstanding results with radio-resistant bone and soft tissue sarcomas.

A dose escalation trial using carbon ion beams was carried out on 64 lesions of 57 bone or soft tissue sarcoma patients from June 1996 to February 2000. A fixed-dose phase II trial was then initiated in April 2000, and 537 patients have been treated as of February 2012. A dose escalation trial (phase I/II trial) with a total dose ranging from 52.8 GyE to 73.6 GyE administered in 16 fractions over four weeks (single radiation doses of 3.3 - 4.6 GyE) was carried out on 64 lesions of 57 bone and soft tissue sarcoma patients between June 1996 and February 2000. Dose escalation was halted at 73.6 GyE, because 7 of the 17 patients treated were found to have grade 3 RTOG acute reactions (of the skin; no other grade 3 or worse acute reactions were detected). These findings made it clear that with a fractionation regimen of 16 fractions over four weeks, for a total dose of 70.4 GyE, was the maximum applicable dose. The overall local control rate was 89% at 1 year, 62% at 3 years, and 62% at 5 years. A significant difference was found between the local control rates achieved with a total dose of 57.6 GyE or less and those with 64.0 GyE or more.

A fixed-dose phase II trial was then initiated in April 2000, and as of February 2012, 537 patients have been enrolled for treatment. The 5-year local control rates are currently 70%, and the overall survival rates are 60%. Grade 3 or worse toxic reactions included two patients with acute skin toxicities (grade 3) and seven patients with late skin toxicities (grade 3: 6 patients; grade 4: 1 patient). These late skin reactions suggest that there may be risk factors in addition to the total dose, including: 1) subcutaneous tumor invasion, 2) tumor volume, 3) sacral involvement of the tumor, 4) previous surgery, 5) additional chemotherapy, and 6) irradiation from two portals. It was possible, however, to prevent these reactions by aiming for a standard dose of 70.4 GyE and by modifying the irradiation method to include irradiation from three portals, in order to reduce the dose delivered to the skin. These modifications dramatically reduced the incidence of the high-grade skin reactions.

The 5-year overall survival rate for the 88 patients with osteosarcoma of the trunk was 31%. The response to neo-adjuvant chemotherapy was found to be a prognostic factor in this series (Figure 1). The tumor size also could be a determining factor for local control and survival. The 185 chordoma patients (excluding patients with base of the skull primaries) in this cohort had a 5-year local control rate of 78% and a 5-year overall survival rate of 85%. Carbon ion radiotherapy was well tolerated and demonstrated substantial activity against sarcomas in this study.

Carbon ion radiotherapy is seen as a valid alternative to surgery not only for patients disqualified from surgery, but also for elderly patients and patients with major functional loss consequent to a surgical resection. Although the treatment results after carbon ion radiotherapy have so far been satisfactory, it is imperative to continue long-term follow-up observations and carry out further analyses to assess the local control, toxicities and survival rates. Research will also be needed to clarify the role of heavy particle radiotherapy in the context of combination therapy, including immunotherapy for bone and soft tissue sarcomas.

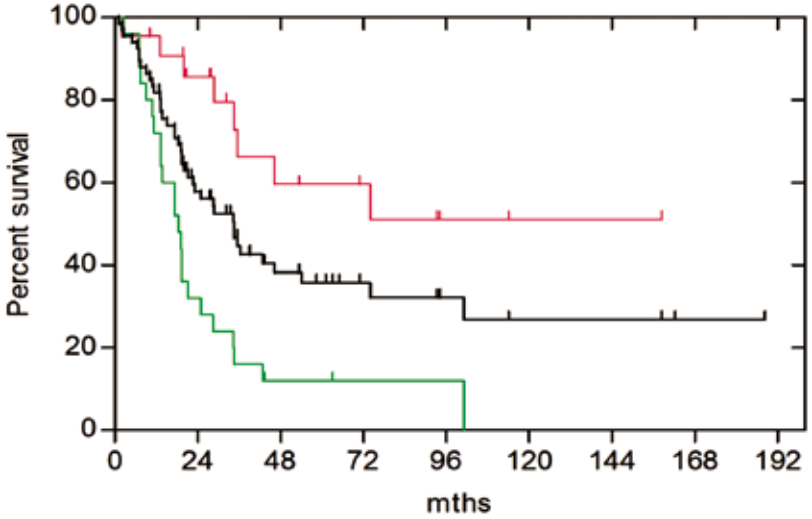

Figure 1. Overall survival curves in patients with unresectable osteosarcoma of the axial bone (70 new cases).
Red line: cases with a SD/PR response to adjuvant chemotherapy (n=22); black line: all new cases (n=70); green line: cases with a PD response to adjuvant chemotherapy (n=25).
SD: stable disease PR: partial response PD: progressive disease

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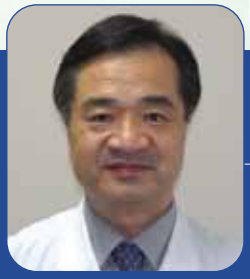
Carbon ion radiotherapy for clinical stage I non-small cell lung cancer



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Summary

Carbon ion radiotherapy (CIRT) is a promising modality because of its excellent dose localization and high biological effect on the tumor. Our clinical trials led us to conclude that irradiation with heavy particle beams, notably carbon ion beams, offers a significant potential for improving tumor control without increasing the toxicity risks.

A phase I/II study of the treatment of stage I non-small cell lung cancer (NSCLC) by CIRT was first conducted between 1994 and 1999 using a dose escalation method to determine the optimal dose [1, 2]. Furthermore, definite tumor control was also confirmed by the autopsies of CIRT-treated patients and in cases treated by surgery [3].

The present study was a phase II clinical trial and a phase I/II dose escalation clinical trial. The total dose in the phase II clinical trial was fixed at 72.0GyE in 9 fractions over 3 weeks [4], and at 52.8GyE for stage IA NSCLC and 60.0GyE for stage IB NSCLC in 4 fractions in one week [5]. In addition, elderly patients 80 years and older can be treated safely by CIRT [6].

The phase I/II dose escalation clinical trial in one day CIRT was initiated in April 2003. The total dose was initially 28.0GyE, and it was raised to 50.0GyE in 2011. This article describes the intermediate steps (Figure 1).

The local control rate for all patients (#9802 and #0001) was 91.8%, and those for T1 and T2 tumors were 96.7% and 85.0%, respectively. While there was a significant difference (p=0.0156) in tumor control rate between T1 and T2, there was no significant difference (P=0.1516) between squamous cell carcinomas and non-squamous cell carcinomas. The 5-year cause-specific survival rate was 71.8% (IA: 82.7, IB: 55.6), and overall survival was 42.3% (IA: 50.7, IB: 32.2) (Figure 2). No adverse effects greater than grade 2 occurred in the lung.

In a single fractionation trial, the 5-year local control rate for 131 patients was 80.5%, and the control rates for T1 and T2 tumors were 82.8% and 78.4%, respectively (Figure 3). No adverse effects greater than grade 2 occurred in the lung.

Carbon beam radiotherapy, an excellent new modality in terms of high QOL and ADL, was proven to be a valid alternative to surgery for stage I cancer, especially for elderly and inoperable patients.

Analysis in the results of Carbon ion radiotherapy for peripheral clinical stage I non-small cell lung cancer

[Phase II clinical trial]

One hundred and thirty-one primary lesions were treated with CIRT. Fifty-one primary tumors were treated by carbon ion beam irradiation alone using a fixed total dose of 72GyE in 9 fractions over 3 weeks. The remaining 80 stage I tumors, the IA and IB stage tumors were treated with fixed doses of 52.8GyE and 60.0GyE in 4 fractions in one week, respectively. The mean age was 74.5 years, and gender breakdown was 94 males and 37 females. The tumors were 72 T1 and 59 T2. There were 85 adenocarcinomas, 43 squamous cell carcinomas, 2 large cell carcinomas and 1 adenosquamous cell

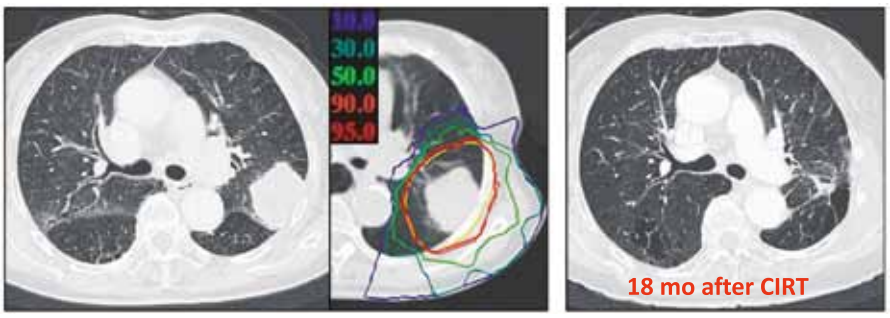

Figure 1. Stage IB, squamous cell carcinoma. Single fractionation carbon ion radiotherapy was performed with 40GyE.
Prior CT (A), dose distribution map (B), and CT at 18 months after carbon ion radiotherapy (C). CT scan at 18 months shows tumor shrinkage and slight lung fibrosis.

carcinoma. Medical inoperability stood at 76%.

Toxicities to the lung caused by CIRT were assessed according to RTOG (early) and RTOG/EOTRC (late). No reactions higher than grade 2 lung reaction were observed.

The local control, cause-specific, and overall survival rates for the patients in the phase II clinical trial were 91.8%, 71.8%, and 42.3%, respectively. The 5-year cause-specific survival rate of the patients was 71.8%, breaking down into 82.7% for stage IA and 55.6% for stage IB tumors. The 5-year overall survival rate was 42.3%, breaking down into 50.7% for stage IA and 32.2% for stage IB tumors.

With clinical stage I NSCLC, our 5-year overall survival results were somewhat inferior to the surgical ones (77.0% in surgical resected c-stage IA cases and 60.1% in c-stage IB cases, data from Japanese Joint Committee of Lung Cancer Registry, 1999) (Table 1). The incidence of death due to intercurrent diseases in the surgical groups was 19% or a few[7,8], but our patients showed a higher incidence of death due to intercurrent diseases (60%). Generally, such a high frequency of intercurrent death might be related to many of the medically inoperable patients and the advanced age of our patients, as they were on average 10 years older than the surgical patients.

A comparison of stage IA with stage IB revealed a large difference in stage IA between the overall (50.7%) and cause-specific (82.7%) survival, while there was a smaller difference in stage IB between the overall (32.2%) and cause-specific (55.6%) survival. Such large and small survival differences in the two stage I subgroups might well be explained by the low incidence of recurrence death in stage IA (24%) and its high incidence in stage IB (63%). Nine of the 10 patients (90%) with malignant pleurisy and 17 of the 23 patients (74%) with distant metastasis died of disease progression. The poor prognosis of stage IB cases was based on the high incidence of pleural and distant metastasis.

Adjuvant chemotherapy may improve the prognosis of stage IB cases, but not all patients will be suitable for chemotherapy because a standard chemotherapy frequently causes the unfavorable complications. Therefore, the establishment of a novel adjuvant therapy with minimal-invasive and low-toxicity, such as immunotherapy, is highly desirable.

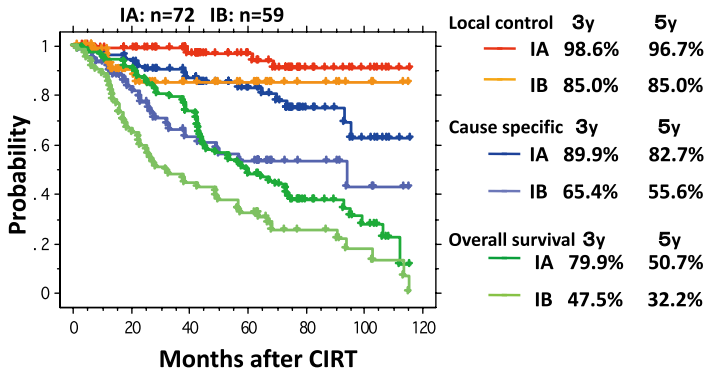

Figure 2. Survival for peripheral c Stage I NSCLC

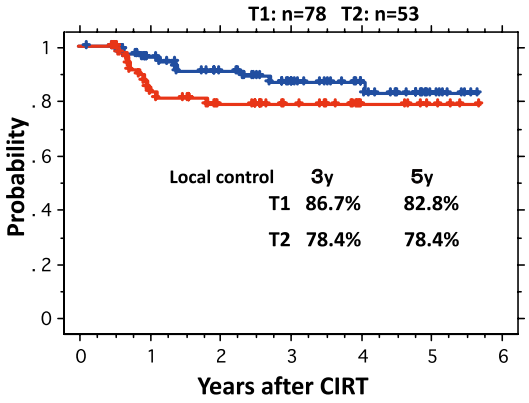

Figure 3. Local control rate for Stage I NSCLC treated with CIRT single fractionation in T1/T2

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The pathophysiology and treatment of Werner syndrome, a hereditary disorder of premature aging

Core Member

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Summary

Progressive functional decline and gradual deterioration of the physiological function with age (physiological aging) are inevitable. However, when such changes occur in early stages or are more progressive than usual, they are referred to as pathological aging. Atherosclerosis, osteoporosis and Alzheimer's disease can be considered to be caused by pathological aging of the arteries, bone and brain, respectively. Progeroid syndrome includes a group of diseases in which pathological aging phenotypes appear systemically. Werner syndrome (WS) and Hutchinson-Gilford Progeria Syndrome (HGPS) are representative progeroid disorders.

WS was initially reported in 1904 by a German ophthalmologist Otto Werner as "a case of scleroderma with cataracts." It is an autosomal recessive disorder caused by a mutation in the gene encoding the RecQ type DNA helicase. More than 60% of all WS cases reported worldwide involve Japanese patients. It has been reported that patients tend to die in their 40s primarily due to coronary artery disease and malignant neoplasms. We have previously reported that the prognosis of WS can be improved with adequate therapeutic intervention. We herein conducted a survey of 396 newly identified WS cases at 3,166 departments in Japanese hospitals with more than 200 beds in which we collected and analyzed clinical information in detail.

Our data showed that the prevalence of epithelial malignant neoplasms (cancer) was increased in the WS patients with diabetes, whereas mesenchymal malignant neoplasms (sarcoma) were more common in the WS patients without diabetes (ref. 1). The prevalence of coronary artery disease was higher in the WS patients, while the incidences of stroke and dementia were lower in these patients compared with those observed in the general population (ref. 2).

The major clinical symptoms of WS included progeroid changes in the hair (98.5% prevalence), the development of cataracts (95.7%) and atrophic skin changes/intractable skin ulcers (96.9%). Although the disease is known to be inherited in an autosomal recessive manner, parental consanguinity was confirmed in only 43% of all cases. We also discovered that WS subjects exhibit specific calcifications in the Achilles tendon. Taking these findings together, new diagnostic

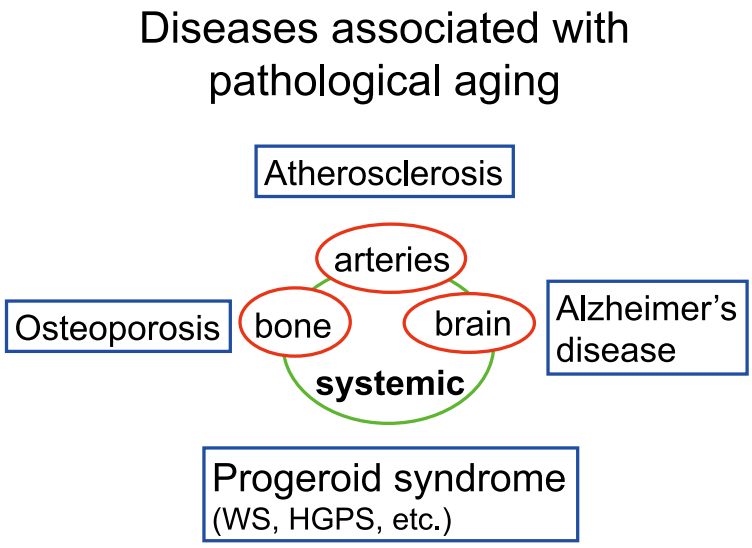

Figure 1. Diseases related to pathological aging and progeroid syndrome

criteria for WS with high objectivity were established (ref. 3). Moreover, the "Patients Association for WS (Werner syndrome KANJA-KAZOKU NO KAI)" was formed to facilitate communication among patients as well as encourage interaction between patients and researchers (http://www.justmystage.com/home/8nkazoku/). The activities of this association are widely broadcasted in Japan (refs. 5, 6).

In order to elucidate the mechanisms underlying premature aging phenotypes in WS patients, basic research projects, *e.g.* generation of WRN/Tert double knockout mice and inducible pluripotent stem cells derived from WS skin fibroblasts, are under way. Moreover, the function of the novel growth inhibitory factor CCN3/NOV and the roles of the TGF-β/Smad3 pathway in adipocyte differentiation and insulin sensitivity were elucidated in relation to the etiology of cancer, atherosclerosis and metabolic diseases, which are major complications of WS.

Diagnostic criteria for Werner syndrome 2012

I Major symptoms (Appears after 10 and before 40 years of age)

1. Graying and loss of hair
2. Bilateral cataracts
3. Skin changes: atrophy, sclerosis and ulcer
4. Soft tissue calcification including Achilles tendon
5. Bird-like face

II Other symptoms and findings

1. High-pitched hoarseness
2. Glucose and lipid abnormality
3. Osteoporosis and other bone abnormality
4. Non-epithelial tumor or thyroid cancer
5. Parental consangial marriage
6. Premature coronary artery diseases
7. Primary hypogonadism
8. Short stature

III Presence of WRN mutations

Diagnostic procedure
Confirmed: all major symptoms or 3 or more major symptoms and identification of gene mutations
Suspected: Mafor symptoms 1 and 2 plus other major symptoms or 2 or more other symptoms.

Figure 2. New diagnostic criteria for Werner syndrome (ref. 3)

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1. Onishi S, Takemoto M, Ishikawa T, Okabe E, Ishibashi R, He P, Kobayashi K, Fujimoto M, Kawamura H, Yokote K. Japanese diabetic patients with Werner syndrome exhibit high incidence of cancer. *Acta Diabetol*. in press.
2. Okabe E, Takemoto M, Onishi S, Ishikawa T, Ishibashi R, He P, Kobayashi K, Fujimoto M, Kawamura H, Yokote K. Incidence and characteristics of metabolic disorders and vascular complications in individuals with Werner syndrome in Japan. *J Am Geriatr Soc*. 60: 997-998 (2012).
3. Takemoto M, Mori S, Kuzuya M, Yoshimoto S, Shimamoto A, Igarashi M, Tanaka Y, Miki T, Yokote K. Diagnostic criteria for Werner syndrome based on Japanese nationwide epidemiological survey. *Geriatr Gerontol Int*. in press.
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8. Shimoyama T, Hiraoka S, Takemoto M, Koshizaka M, Tokuyama H, Tokuyama T, Watanabe A, Fujimoto M, Kawamura H, Sato S, Tsurutani Y, Saito Y, Perbal B, Koseki H, Yokote K. CCN3 inhibits neointimal hyperplasia through modulation of smooth muscle cell growth and migration. *Arterioscler Thromb Vasc Biol*. 30: 675-82 (2011).
9. Suzuki S, Tanaka T, Poyurovsky MV, Nagano H, Mayama T, Ohkubo S, Lokshin M, Hosokawa H, Nakayama T, Suzuki Y, Sugano S, Sato E, Nagao T, Yokote K, Tatsuno I, Prives C. Phosphate-activated glutaminase (GLS2), a p53-inducible regulator of glutamine metabolism and reactive oxygen species. *Proc Natl Acad Sci USA*.107: 7461-6 (2010).

Newly developed therapies for esophageal cancer

Core Member

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Summary

Esophageal cancer is one of the most malignant neoplasms and is treated primarily with surgery, chemotherapy and radiotherapy. The outcomes of this disease have been improved in recent decades; however, further progress and the development of new strategies for the treatment of esophageal cancer are strongly required.

Several modalities are available to develop new approaches to achieve our aims. One method is immunological and the other is genetic. We developed a combination therapy with radiation and intratumoral administration of dendritic cells, for which we have demonstrated good results. Currently, we are trying to develop a combination therapy with thermotherapy and dendritic cell therapy. Furthermore, we evaluated the function of non-coding RNA (micro-RNA) and developed a new strategy for a drug delivery system to bring drugs to target lesions. Through this research, many young researchers can accomplish their goals and develop their careers.

1. Immunotherapy for esophageal cancer

First, we assessed the outcomes of the antitumor effects of combined therapy with radiation and dendritic cells. Following radiation therapy, the expression of heat shock protein gp96 was markedly increased and the population of cytotoxic T-cells was increased. Furthermore, antitumor effects beyond the radiation field were observed. This phenomenon was thought to be the “abscopal effect,” and the combination of radiation and dendritic cell therapy effectively elicited an immunoreaction. Based on these basic data, we are planning to conduct a clinical trial of combination therapy with radiation and dendritic cells for esophageal squamous cell carcinoma.

Additionally, we considered therapies that are more effective and less toxic for patients. Instead of radiation, we evaluated the effectiveness of the newly developed hyperthermia therapy created by Oncotherm (Hungary). This hyperthermia therapy has several characteristics, one of the most important of which is the accumulation of energy into tumors. Tumor-specific hyperthermia can induce effective immunotherapy.

2. MicroRNA in esophageal cancer

We previously identified downregulated miRNAs in our comprehensive miRNA profiling study of ESCC specimens (ref. 1, Table 1). We analyzed the effects of miR-203, a downregulated miRNA, on ESCC. Of the candidate target genes of miR-203, we selected LASP1 for a further analysis and verified that miR-203 inhibits the migration and invasion of ESCC cells by regulating LASP1. Furthermore, the expression of miR-203 was found to be inversely correlated with the LASP1 expression in the ESCC specimens. Moreover, we found that there was a significant correlation between the expression levels of miR-203 and the relapse-free survival rate (ref. 2, **Figure 1**). Secondly, we identified serum miRNAs as candidate novel diagnostic and prognostic biomarkers for ESCC. We performed an miRNA array using serum samples obtained from ESCC patients and healthy controls. Serum miR-1246 was the most significantly elevated marker in the ESCC patients.

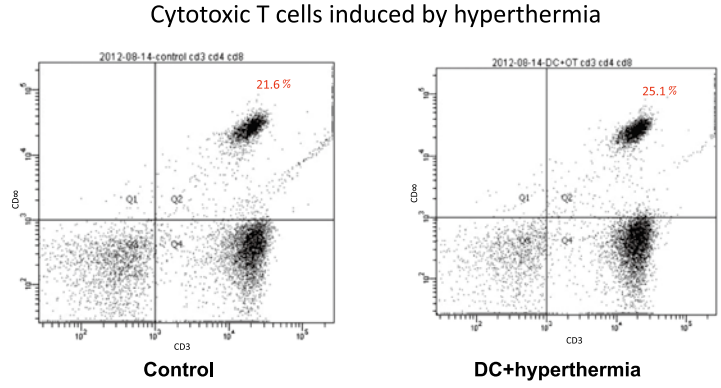

Figure 1.
Left: A population of cytotoxic T-lymphocytes (CTL) in the tumor-drainage lymph nodes (TDLN) of a control mouse. Right: A population of CTL in the TDLN of a mouse treated with dendritic cells and hyperthermia.

Serum miR-1246 exhibited superior discriminatory power compared to SCC-Ag, and the serum expression levels of miR-1246 were found to be correlated with the TNM stage. Furthermore, according to the multivariate analysis, the serum level of miR-1246 was the strongest independent poor prognostic factor (Takeshita et al. in submitting, Table 2). These data support our contention that the expression levels of miRNAs in serum and tissue have a strong potential as novel diagnostic and prognostic biomarkers for ESCC.

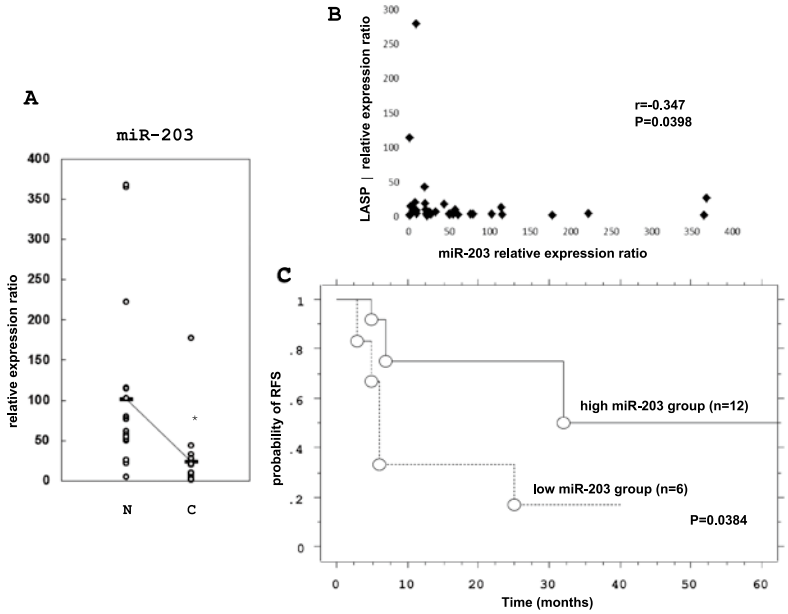

Figure 2.
A: The expression levels of miR-203 in the ESCC clinical specimens. N, noncancerous tissues; C, cancer tissues. *P < 0.05.
B: The correlation between the LASP1 and miR-203 expression levels in the ESCC clinical specimens.
C: The results of the Kaplan-Meier analysis of relapse-free survival (RFS) in the patients with ESCC. The prognostic impact of miR-203 was further tested using the log-rank test.

Research activity

Recent publications

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2. Matsubara, H.(2011)Session Surgical Treatment of Esophageal Cancer: Present Aspects and New Trends. The third Symposium, Stomach Cancer: *Diagnosis and Treatment*. 2011.8.25-26 Mongolia.
3. Takeshita N, Mori M, Kano M, Hoshino I, Akutsu Y, Hanari N, Yoneyama Y, Ikeda N, Isozaki Y, Maruyama T, Akanuma N, Miyazawa Y, Matsubara H. miR-203 inhibits the migration and invasion of esophageal squamous cell carcinoma by regulating LASP1. *Int J Oncol*. 2012 Nov; 41(5): 1653-61.
4. Akutsu Y, Uesato M, Shuto K, Kono T, Hoshino I, Horibe D, Sazuka T, Takeshita N, Maruyama T, Isozaki Y, Akanuma N, Matsubara H. The Overall Prevalence of Metastasis in T1 Esophageal Squamous Cell Carcinoma: A Retrospective Analysis of 295 Patients. *Ann Surg*. 2012 Oct 26. (in press)
5. Kono K, Iinuma H, Akutsu Y, Tanaka H, Hayashi N, Uchikado Y, Noguchi T, Fujii H, Okinaka K, Fukushima R, Matsubara H, Ohira M, Baba H, Natsugoe S, Kitano S, Takeda K, Yoshida K, Tsunoda T, Nakamura Y. Multicenter, phase II clinical trial of cancer vaccination for advanced esophageal cancer with three peptides derived from novel cancer-testis antigens. *J Transl Med*. 2012 Jul 9; 10: 141.
6. Usui A, Hoshino I, Akutsu Y, Sakata H, Nishimori T, Murakami K, Kano M, Shuto K, Matsubara H. The molecular role of Fra-1 and its prognostic significance in human esophageal squamous cell carcinoma. *Cancer*. 2012 Jul 1; 118(13): 3387-96.
7. Akutsu Y, Shuto K, Kono T, Uesato M, Hoshino I, Shiratori T, Isozaki Y, Akanuma N, Uno T, Matsubara H. The number of pathologic lymph nodes involved is still a significant prognostic factor even after neoadjuvant chemoradiotherapy in esophageal squamous cell carcinoma. *J Surg Oncol*. 2012 Jun 15; 105(8): 756-60.
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9. Akutsu Y, Hanari N, Yusup G, Komatsu-Akimoto A, Ikeda N, Mori M, Yoneyama Y, Endo S, Miyazawa Y, Matsubara H. COX2 expression predicts resistance to chemoradiotherapy in esophageal squamous cell carcinoma. *Ann Surg Oncol*. 2011 Oct; 18(10): 2946-51.
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A new biomarker anti-moesin antibody for the development of vasculitis and infectious diseases and their treatment

Coordinator

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Summary

1. Analysis of the development of ANCA-associated vasculitis:

The myeloperoxidase(MPO)-specific anti-neutrophil cytoplasmic antibody (MPO-ANCA) and neutrophils are associated with the development of vasculitis. In our country, the prevalence of this disease is higher in aged people as microscopic polyangiitis (MPA) and rapidly progressive glomerulonephritis (RPGN) showing MPO-ANCA. We are investigating the analysis and treatment for the disease with graduated students.

1)MPO-ANCA epitope analysis: Based on the observations of risk epitopes of MPO-ANCA in sera patients with various MPO-ANCA-associated vasculitis (MAAV), risk epitopes in its model mice were correlated with levels of cytokines/chemokines (1).

2)Stimulation of glomerular endothelium (mGEC) with MPO-ANCA: Treatment with anti-MPO IgG increased the expression of mRNAs for ICAM-1, VCAM-1, and E-selectin. In addition, production of several cytokines/chemokines in mGEC were also stimulated with anti-rmMPO IgG.

3) Damage of endotherila cells by anti-moesin antibody in MAAV: We found moesin targeted by MPO antibody which is located on the surface of stimulated endothelial cells in mouse (Figure 1), suggesting in serum of the patients with MAAV(2). IFN-γ, MCP-1, IL-2, IL-7, IL-12p70, IL-13, GM-CSF, and G-CSF were significantly higher in the positive group of MAAV. Serum creatinine in the anti-moesin-positive group was higher than that in the negative group. We detected secretion of IL-8, MCP-1 and IFN-γ from neutrophils stimulated with anti-

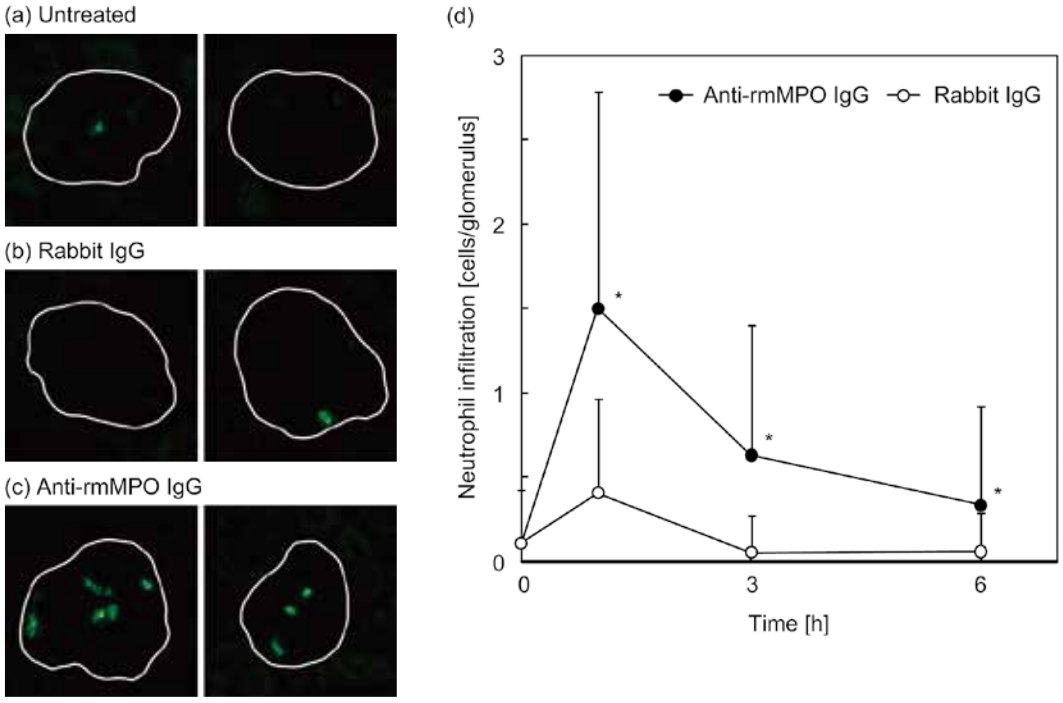

Figure 1. Anti-rmMPO IgG induced neutrophil infiltration to glomeruli.
C57BL/6N micewere injected with rabbit IgG or anti-rmMPO IgG (0.5 mg/mouse). After 1h, the mice were sacrificed and frozen section of kidney was stained for Gr-1. Representative immunofluorescence images with outlined glomeruli were shown. Untreated control mice (a) were used as negative control. (b) Rabbit IgG, (c) Anti-rmMPO IgG. (d) Quantification of anti-rmMPO IgG-induced neutrophil infiltration to glomeruli. The number of infiltrated Gr-1$^+$ neutrophils per glomerulus was counted out of more than 50 randomly selected glomeruli. The data are expressed as mean number of neutrophils per glomerulus +/- SD. *$p < 0.05$ vs. rabbit IgG-treated mice at same time points.

moesin antibody, and TNF-α, IL-6, IL-8, MCP-1 from monocytes. Additionally, fluorescence-labeled anti-moesin reacted with the intra-cellular region of neutrophils, showing as cytoplasmic profile (Figure 2c-e). Anti-moesin antibody seems to be associated with production of inflammatory cytokine/chemokine targeting neutrophils with cytoplasmic profile.

4) Model mice for MAAV:

4-1) PRGN Model - SCG/Kj mouse: Response region for MPO-ANCA production has been named as *Man-1*. A) Anti-IL-6R antibody treatment, which is effective in rheumatic arthritis, showed recovery of renal failure. B) Mizoribin treatment also showed recovery of renal failure. C) $CD4^{+}CD3^{+}B220^{+}$(major=CD4-CD8) cells decreased.

4-2) *Candida albicans* extract (CADS/CAWS)-induced coronary arteritis: We demonstrated that MPO-ANCA-activated neutrophils allowed the local environment to differentiate Th17 cells through IL-6, IL-17A, and IL-23 production.

5) *In vivo* imaging: Using anti-MPO IgG conjugated with quantum dots(QD) QD-aMPO were shown to bind to endothelium in kidney using *in vivo* imaging (Figure 2a, b).

6) International epidemiology and standardization and international congress:

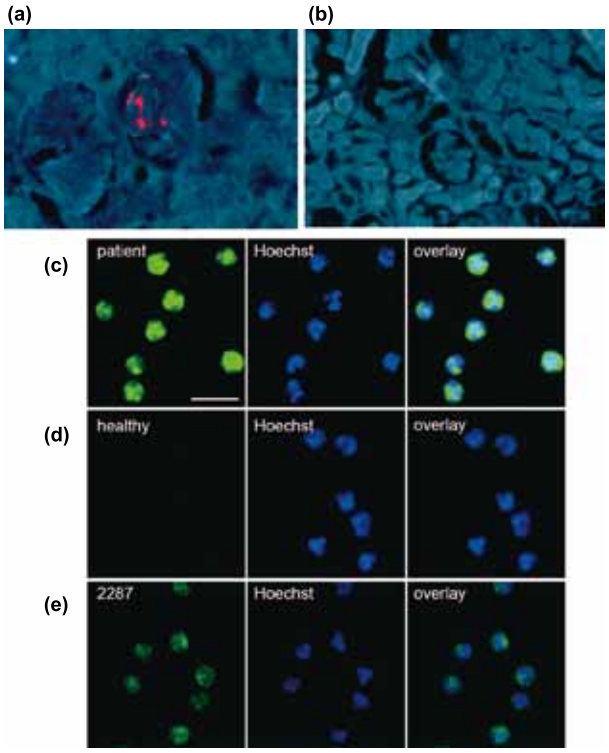

Figure 2. Accumulation of Quantum dots-conjugated anti-rmMPO on glomerular resion and immunofluorescence profile of anti-moesin antibody in neutrophils.
(a) anti-rmMPO, (b) control rabbit IgG, human neutrophils fixed by 4% paraformaldehyde and were permeabilized by 0.01% Triton- × 100, stained with anti-moesin positive patient's serum (c), healthy serum (d), or anti-moesin 2287 (e) (green), and nuclei stained by Hoechst 33342 dye (blue). Scale bar is 20 μm.

6-1) Definition criteria and validation (DCVAS) has been studied in the world (3,4).

6-2) The Asia Pacific Meeting of Vasculitis and ANCA Workshop – 2012 (AP-VAS 2012, March 28-31, 2012 in Shinagawa, Tokyo): The meeting was first held in Asia-Pacific area, focusing on vasculitis and ANCA-associated vasculitis organized by Prof. Kazuo Suzuki as the president. Scientists and physicians studying on ANCA and related diseases: 469 members from 21 countries. This meeting was able to extend insights into Kawasaki disease, Takayasu arteritis, and MPO-associated vasculitis. The programme addressed the multi-disciplinary nature of vasculitis, including genomics, genetics, pathogenesis, epidemiology, biomarkers, clinical features, and therapeutic trials, in particular the specialities of rheumatology, nephrology, and others. This meeting was co-operated with 18 societies, EUVAS, VCRC, British Embassy, and MHLW projects.

2. Development of synthetic immunoglobulins

It has been requested that development of synthetic immunoglubilins, because high-dose immunoglubilin (IVIg) treatment has been used for severe infectious diseases, autoimmune diseases, vasculitis and rheumatoid arthritis, showing increase of usage recently.

Synthetic immunoglobulin: A) The products were effective for the treatment in model mice of Kawasaki disease-like coronary arteritis. B) SCG/Kj mouse is useful for evaluation of IVIg treatment. According to the good results of synthetic mouse-type immunoglobulins was lead to the development for human-type immunoglobulins.

3. Analysis of clinical pictures of influenza and its treatments

1) Avian H5N1 flu (Hanoi):

A clinical picture of patients with acute respiratory distress syndrome (ARDS) was induced by highly pathogenic avian influenza A (H5N1) (5). Lower survival rate of patients with H5N1 infection was reported (6). We measured risk factors were analyzed in both National Hospital of Pediatrics in Hanoi and Chiba University, MPO and IL-6sR in nasal wash fluid significantly increased, suggesting that these cytokines and MPO may be associated with severity of H5N1 infection (7).

2) Pathogenic mechanism of influenza-induced FARDS and drug development for influenza infection:

2-1) Mouse model of fluminant ARDS for analysis and treatment for flu: We analyzed risk factors of lung injury caused by H5N1 infection using mouse model. Influenza (H1N1)–infected mouse showed infiltration of inflammatory cells at day 3-4, epithelial cells were detected in BAL. IL-1α, β and GM-CSF, KC, and RANTES in BALF at day 2. MCP-1, and later TNF-α, Eotaxin, and MIP-1α increased. In addition, MPO activity in BALF was associated with nutrophil infiltration. Taken together of analysis using MPO-KO mice, MPO was clearly associated with lung injury (Figure 3). These results suggest that these

cytokine/chemokines and MPO in the mice may be risk molecules in patient with H5N1 infection (8).

2-2) Drug development for influenza infection: When 3 selected macrolides were administered into mice showing fulminate pneumonia by influenza virus infection, the viral nucleotide expression in whole-lung tissue was significantly decreased.

2-3) Contribution of influenza virus NS1 and MPO to sequential cytokine-chemokine induction: We examined cytokine/chemokine production in A549 human epithelial cells infected with influenza A/H1N1 virus (PR-8) or nonstructural protein 1 (NS1) plasmid *in vitro*. TNF-α and RANTES were predominantly produced from the cells infected with PR-8 virus. siTNF-α down-regulated RANTES expression and secretion of RANTES, IL-8, and MCP-1. In addition, siRANTES suppressed IFN-γ expression and the secretion of RANTES, IL-8, and MCP-1. In addition, the cells transfected with viral NS1 plasmid showed production of a large amount of IL-8 and MCP-1 in the presence of the H_2O_2-MPO system, suggesting that NS1 of PR-8 may induce a "cytokine storm" from the epithelial cells (Figure 4) (9).

3) Contribution of NKT cells associated with IL-5 and IL-6 receptor in ventilation-induced lung injury (VILI) in mice: The lung injury in VILI was developed with high score of histological findings, elevation the ratio of neutrophils and macrophages in BALF. The number of NKT cells increased in the lung. Jα18KO mice showed the lung injury with elevation of total protein in BALF, and low PaO2 associated with elevation of IL-5, IL-6, IL-23, IL-12p40, GM-CSF and KC in BALF. Treatment with anti-IL-5 mAb and anti-IL-6R

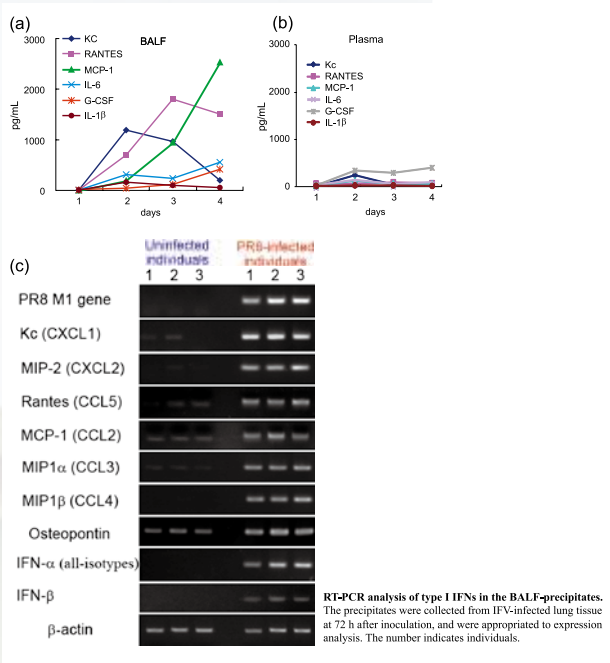

Figure 3. Time course of cytokines/chemokines after influenza inoculation and expression of cytokines/chemokines.
(a) in BALF, (b) in plasma, (c) RT-PCR analysis of type I IFNs in the BALF-precipitates. The precipitates were collected from IFV-infected lung tissue at 72 h after inoculation, and were appropriated to expression analysis. The number indicates individuals.

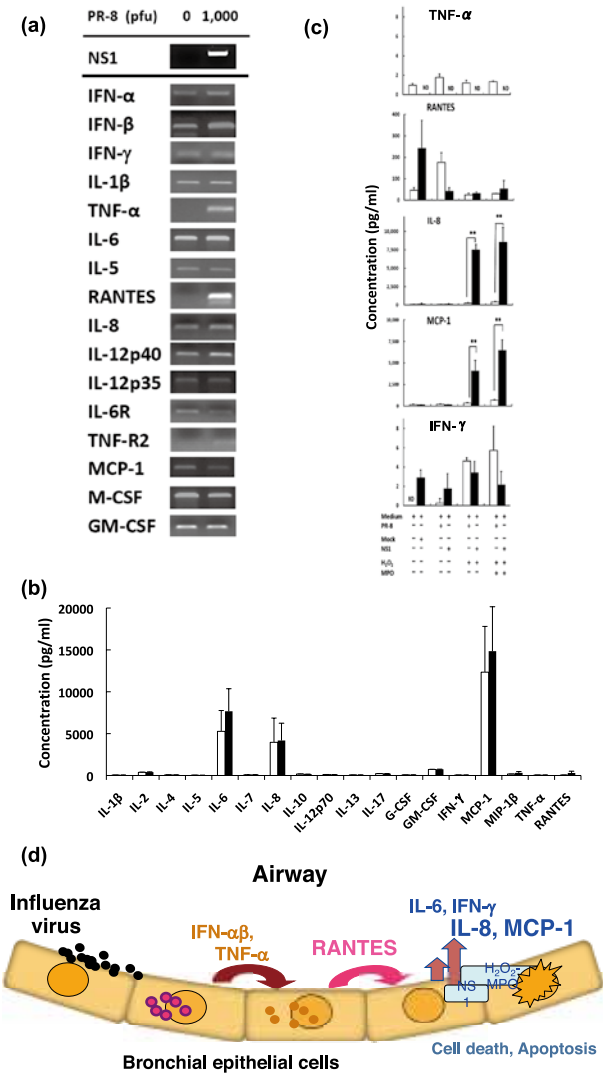

Figure 4. Expression and secretion of cytokines/chemokines from epithelial cell A-549 cells infected with influenza virus PR-8 or NS1-plasmic *in vitro*.
(a) Expression of cytokines/chemokines, (b) secretion of cytokines/chemokines from epithelial cell A-549 cells infected with influenza viruses PR-8, (c) production of TNF-α, RANTES, IL-8, MCP-a, and IFN-γ stimulated with PR-8 or NS1 plasmid in the presence of H_2O_2 and MPO. (d) Scheme for sequential secretion of cytokines/chemokines from cultured bronchial epithelial cells infected with influenza viruses.

mAb in 5hr-MV-Jα18KO mice resulted in significant improvement in oxygenation and lung injury.

4) *in vivo* imaging: Using anti-MPO IgG conjugated with quantum dots(QD) QD-aMPO were shown to bind to endothelium in kidney using *in vivo* imaging.

5) Efficacy of pandemic influenza AH1N1 vaccine in health care workers (HCWS) of a university hospital in Japan: An inactivated, split-virus, unadjuvanted AH1pdm (10) vaccine was initiated for HCWs. Retrospective observation was conducted for evaluating efficacy of a single-dose vaccine for HCWs in a hospital in Japan. 5.2% of 250 HCWs without vaccination were infected, a significantly higher rate than 1.5% of 1,567 HCWs with vaccination (11).

6) Simulation of infection spreading:

We analyzed the simulated spread of influenza in commuter towns in the Tokyo suburbs. School closure delayed the epidemic and reduced the peak of the disease, but it was not as effective in decreasing the number of infected people. Vaccination of school children decreased the numbers not only of infected children but also of infected adults in the regional communities.

Recent publications

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Role of memory CD4 T cells *in vivo*

Independent Research Associate

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Summary

Understanding and controlling the system of immunological memory may lead to the development of new treatments for autoimmune diseases and allergy or tumors. CD4 T cells are the key to immunological memory. However, little is known about the role of memory CD4 T cells. We have demonstrated that memory CD4 T cells reside in the bone marrow (BM) after their generation. We are now attempting to clarify the role of memory CD4 T cells *in vivo* by using memory-CD4-T cell-deficient mice and an intravital microscopy system (Figure 1).

As a Global COE independent assistant professor, I started to analyze the role of memory CD4 T cells in the excellent research environment of the Global COE program. I provide instruction on research and have discussions with graduate students. In addition, to promote international education, we have invited foreign scientists or graduate students to our laboratory, and sent our graduate students to foreign laboratories, and provide opportunities for young scientists present their research in the international seminars of the Global COE program.

1. Molecular mechanisms of reactivation of memory CD4 T cells *in vivo*

Memory CD4 T cells are maintained in the BM with high reactivity. They are reactivated by antigen presented by antigen-presenting cells, leave the BM quickly, and induce efficient help to B cells in secondary lymphoid tissues. However, the molecular mechanisms remain unclear. We have identified a subpopulation of the antigen-presenting cells and observed their dynamics and the interaction with memory CD4 T cells in the BM *in vivo*. We will examine the molecular mechanisms on the dynamics of memory CD4 T cells.

2. Role of memory CD4 T cells *in vivo*

We have found that CD69-deficient mice lack only memory CD4 T cells (Figure 2). To clarify the role of memory CD4 T cells, we are now evaluating the ability to help B cells in the deficient mice and exploring the possibility of new and unexpected roles of memory CD4 T cells. In addition, we also analyze the role of CD69 in the maintenance of memory CD4 T cells.

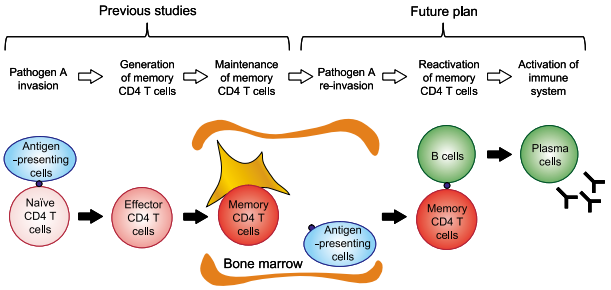

Figure 1. A flow chart of our research.
We have examined how memory CD4 T cells are generated and maintained in the body. We are now analyzing the reactivation of memory CD4 T cells and their regulation of B cell maturation in secondary immune response.

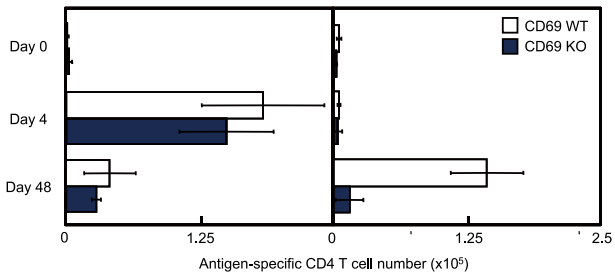

Figure 2. Defects of memory CD4 T cells in CD69-deficient mice.
48 days after immunization few memory CD4 T cells were maintained in the spleen and BM of CD69-deficient mice.

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Role of NF-κB Signaling in Allergic Reactions

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Summary

The aim of our study was to clarify the mechanism regulating mast cell exocytosis, which is also called degranulation. Because mast cell granules contain many chemical mediators causing early phase allergic reactions, such as histamine, the prevention of mast cell degranulation would be an ideal therapeutic approach for the treatment or prevention of allergic diseases such as asthma, atopic rhinitis and atopic dermatitis. We have shown the importance of IKK2, also called IKKβ, in mast cell degranulation. I was appointed as a Global COE independent associate professor and started research on the role of mast cell NF-κB signaling with funds for independent activities. I am working on revitalizing the research environment through discussions with graduate students. Furthermore, my graduate students and I have been conducting positive discussions with prominent foreign lectures invited to contribute to various projects in the Global COE program.

Tumor suppressor p53 functions as a negative regulator in IgE-mediated mast cell activation

Mast cells are recognized as the major effector cells of the type I hypersensitivity reactions, and they are known to play a pivotal role in allergic diseases, such as allergic rhinitis, asthma and atopic dermatitis. Engagement of FceRI by IgE, followed by the aggregation of multiple IgE-bearing FceRI molecules by polyvalent antigens, leads to degranulation and the release of histamine, LTC4, and other preformed chemical mediators. Additionally, multiple cytokine genes are transcribed, and newly synthesized arachidonic acid metabolites are secreted.

The tumor suppressor p53 is a sequence-specific transcription factor that is critical for maintaining genomic stability. In the absence of cellular stress, the protein levels of p53 in cells are maintained at low levels, and the majority of p53 remains in the cytoplasm. Upon the induction of various stresses, such as apoptosis, cell cycle arrest, senescence, DNA repair, cell metabolism, and autophagy, the half-life of p53 increases from minutes to hours. p53 then translocates into the nucleus and activates the transcription of its target genes. Although the roles of p53 in stress-associated stimulation have been well studied, the roles of p53 in antigen receptor-mediated stimulation are poorly understood.

We examined the anaphylactic reaction using mast cell knock-in mouse models and IgE-mediated degranulation using p53-deficient mast cells to clarify the role of mast cell p53 in the early phase of allergic reactions. We found that the protein levels of p53 were upregulated upon IgE-mediated stimulation in mast cells without the induction of apoptosis. We also found that a lack of p53 in mast cells results in enhanced IgE-induced degranulation and cytokine production, leading to enhanced responses in both the early phase and late phase of IgE-mediated anaphylaxis *in vivo*. These results suggest that p53 is involved in the negative feedback regulation of IgE-mediated mast cell activation (Figure 1).

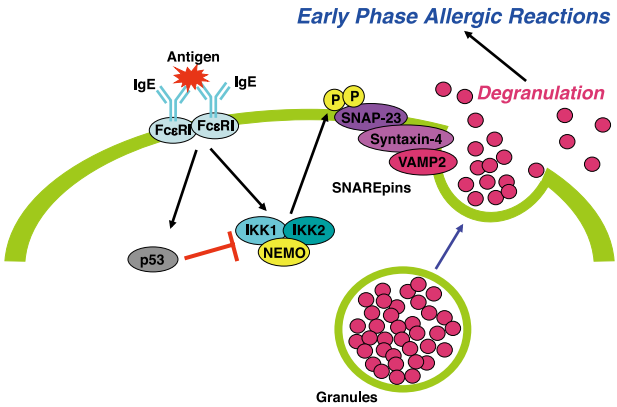

Figure 1: IKK2 phosphorylates SNAP-23 in response to FceRI-stimulation, leading to the formation and promotion of vesicle fusion with the plasma membrane, resulting in the degranulation of mast cells and subsequently, in the early phase allergic reaction. FceRI stimulation up-regulates the p53 expression, and p53 represses the IKK2 kinase activity. Therefore, p53 is involved in the negative feedback regulation of IgE-mediated mast cell activation.

Recent publications

1. Suzuki K, Murphy SH, Xia Y, Yokota M, Nakagomi D, Liu F, Verma IM, Nakajima H. Tumor suppressor p53 functions as a negative regulator in IgE-mediated mast cell activation. *PLos One*. 6(9): e25412 (2011).
2. Murphy SH, Suzuki K, Downes M, Welch GL, De Jesus P, Miraglia LJ, Orth AP, Chanda SK, Evans RM, Verma IM. Tumor suppressor protein (p)53, is a regulator of NF-kappaB repression by the glucocorticoid receptor. *Proc Natl Acad Sci USA*. 108(41): 17117-22 (2011).
3. Nakagomi D, Suzuki K, Hosokawa J, Kobayashi Y, Suto A, Takatori H, Watanabe N, Matsue H, Murphy TL, Murphy KM, Shimada S, Nakajima H. Therapeutic potential of B and T lymphocyte attenuator expressed on CD8+ T cells for contact hypersensitivity. *J Invest Dermatol*. in press.

Development of a new approach to therapeutic angiogenesis

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Summary

Mechanistic knowledge regarding blood vessel regeneration has made therapeutic angiogenesis come of age. We established peripheral blood mononuclear cell (MNC) implantation therapy as a method to treat patients with severe limb ischemia. We are intensively bringing clinical data back into basic experiments to develop an even better way to treat such patients. Going back and forth between bench and bedside is quite a sophisticated style to promote medical investigations, which was made possible by support from the G-COE program. This led me to uncover a molecular mechanism of MNC treatment induced therapeutic angiogenesis. Through such studies, I wish to build my career as a Physician Scientist, and show graduate students, who have just started their research career, how wonderful it is to be involved in the process of science and medicine.

1. Cellular behaviors in therapeutic angiogenesis

We previously reported that therapeutic limb angiogenesis by MNC transplantation was accomplished through enhancement of the muscle regeneration process, which essentially coincides with massive production of angiogenic growth factors by regenerating myotubes (MT). We closely examined the samples and found robust proliferation of myoblasts (MB), MCP-1 secretion, and macrophage (MΦ) accumulation just after cell therapy. Treatment of muscle tissue with an inhibitor of MCP-1 resulted in reduction of MΦ followed by marked attenuation of blood flow recovery. These effects by MNC were also abolished in MB null Pax7 knockout mice, thus indicating that MB is the direct target of transplanted MNC. The co-culture of MT with MΦ resulted in production of various angiogenic and myogenic growth factors by MT. These results suggest that MNC induce MB to secrete paracrine factors, which induce MΦ accumulation into regenerating muscle tissue. It is also suggested that this MΦ accumulation would further enhance differentiated MT to produce growth factors, establishing a positive feedback loop that will last until the regeneration process is completed.

2. Molecular mechanism of therapeutic angiogenesis

It is necessary to elucidate the precise molecular mechanism in order to apply these findings in clinical settings. Among such factors that influence MB activation, We focused on Notch signaling, for its ligand Jagged-1 is highly expressed in MNC. We found that MNC activated Notch signaling in ischemic tissue, predominantly among MB. Importantly, the treatment of a wild type ischemic host with a Notch inhibitor markedly impaired blood flow recovery. Notch-1 conditional knockout (CKO) mice showed similar results after PBMNC transplantation, further confirming the importance of host Notch signaling. Interestingly, deletion of a Notch ligand Jagged-1 from the donor PBMNC resulted in marked attenuation of neovascularization. Conversely, the overexpression of Jagged-1 in the implanted cells significantly increased the efficacy of this treatment. Therefore, we provide a model showing that exogenous introduction of Notch ligands could be a novel strategy to enhance therapeutic angiogenesis.

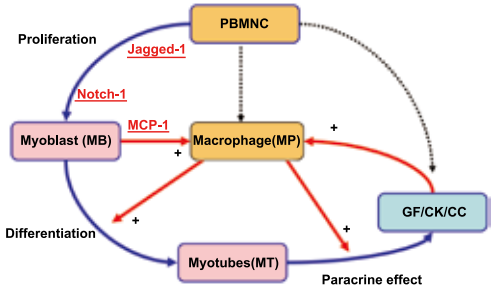

Figure 1. Mechanism of Therapeutic Angiogenesis following Cell transplantation.
Peripheral blood mononuclear cells (PBMNC) activate myoblasts (MB) via Notch signaling when transplanted into ischemic muscle. MBs recruit macrophage (MΦ) to induce their differentiation into myotubes (MT). MΦs also enhance production of angiogenic growth factors, cytokines, and chemokines (GF/CK/CC) by MT, establishing a positive feedback loop which will last until the process of muscle regeneration is completed.

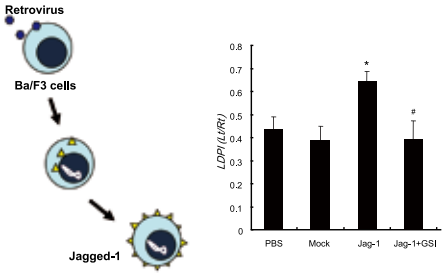

Figure 2. Notch Ligand as a Novel Tool to induce Therapeutic Angiogenesis.
Notch ligand Jagged-1 was induced into a hematopoietic cell line. When transplanted into mice hind limb ischemia, these cells exhibited significant ability to enhance blood flow recovery. The effect was abolished by a Notch inhibitor (GSI), suggesting that the cells target against Notch signaling. Therefore, Notch ligand can be a new tool to induce therapeutic angiogenesis.

Recent publications

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2. Moriya J, Minamino T, Tateno K, Shimizu N, Kuwabara Y, Sato Y, Saito Y, and Komuro I. Long-Term Outcome of Therapeutic Neovascularization Using Peripheral Blood Mononuclear Cells for Limb Ischemia. *Circ Cardiovasc Intervent*. 2: 245-254, 2009

Molecular mechanisms in heart failure

Independent Research Associate

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Summary

Heart failure is an important cause of morbidity and mortality in many industrial countries. Although treatment for heart failure has progressively improved, both in pharmacological and non-pharmacological aspects, the mortality of patients with severe heart failure remains very high, and the only treatment for DCM patients with severe symptoms is a heart transplantation. Many novel therapies have been anticipated since the number of heart transplantations is limited. I initially examined the molecular mechanisms in heart failure in an attempt to develop novel therapies. After I was employed as a Global COE independent assistant professor, I clarified the role of 12-lipoxygenase in heart failure with a graduate student, and established a new mouse model of dilated cardiomyopathy. I am working with graduate students to clarify the molecular mechanisms of how gene mutations cause dilated cardiomyopathy using the new model. Discussions with other Global COE members, who have specialties in different fields are crucial in this research.

1. The role of 12-lipoxygenase in heart failure

Our previous study confirmed that 12-lipoxygenase (12-LO) was markedly up-regulated in heart failure; however, the role of 12-LO in heart failure has not been examined. We established transgenic mice that overexpressed 12-LO in cardiomyocytes to determine whether increased expression of 12-LO causes heart failure. Echocardiography showed that 12-LO transgenic mice developed systolic dysfunction. Cardiac fibrosis increased in 12-LO transgenic mice with the infiltration of macrophages. The cardiac expression of MCP-1 was up-regulated in 12-LO transgenic mice in comparison to wild-type mice. The inhibition of MCP-1 reduced the infiltration of macrophages into the myocardium and prevented systolic dysfunction in 12-LO transgenic mice. Likewise, the disruption of 12-LO significantly reduced the cardiac MCP-1 expression and macrophage infiltration, thereby improving systolic dysfunction induced by chronic pressure overload. Our results suggest that cardiac 12-LOX is involved in the development of heart failure.

2. The molecular mechanism of dilated cardiomyopathy caused by gene mutations

Dilated cardiomyopathy (DCM) is characterized by dilatation and impaired contraction of the left ventricle and patients with DCM often develop heart failure. Various mutations have been identified in DCM patients, but how such mutations lead to DCM remains unknown. We generated transgenic mice (Tg) that overexpress the mutated cardiac α-actin in the heart to examine how gene mutations cause DCM. This mutation has been reported in patients with DCM. Left ventricular dimension and systolic function were gradually increased and decreased, respectively, in the Tg mice in comparison to the wild-type mice. The activities of CaMKIIδ were increased in Tg mice. Inhibition of CaMKIIδ activation by KN-93 prevented an increase in left ventricular dimension and preserved cardiac function. We established a murine model of DCM that has a mutation similar to that of human DCM. The activation of CaMKIIδ therefore plays a critical role in the development of heart failure in this model.

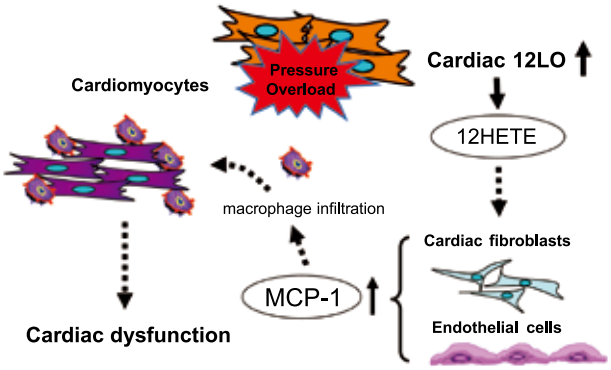

Figure 1. 12-LO expression is upregulated in cardiomyocytes by various stimuli such as pressure overload.
Enhanced production of 12-HETE by 12-LO increases expression of MCP-1 by cardiac fibroblasts and endothelial cells, thereby inducing infiltration of macrophages into the myocardium. This infiltration in turn induces cardiac fibrosis and systolic dysfunction.

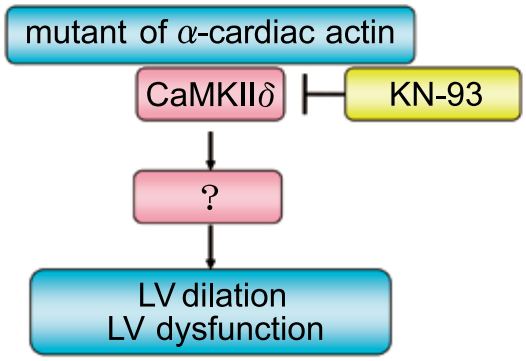

Figure 2. The activation of CaMKIIδ in the DCM model mice induced cardiac dysfunction.

Recent publication

1. Kayama Y, Minamino T, Toko H, Sakamoto M, Shimizu I, Takahashi H, Okada S, Tateno K, Moriya J, Yokoyama M, Nojima A, Yoshimura M, Egashira K, Aburatani H, Komuro I. Cardiac 12/15 lipoxygenase-induced inflammation is involved in heart failure. *J Exp Med*. 206(7): 1565-74 (2009)

Epigenetic of CD4 T cell differentiation

Independent Research Associate

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Summary

Before moving to Chiba I performed Ph.D. studies at the University of Adelaide, Australia. At that time we were investigating factors important in the control of eosinophilic inflammation in allergic asthma. Another prominent cell-type contributing to allergic inflammation are CD4 T lymphocytes, and I subsequently became interested in how expression of the cytokines that control inflammation are regulated at the genetic level in these cells. I was attracted to post-doctoral studies in the G-COE program at the Department of Immunology at Chiba University due to the groundbreaking research being performed in the area of effector and memory functions of CD4 T cells in diseases such as allergic asthma. Shortly after arriving in Chiba in 2009 I was awarded a Japanese Society for The Promotion of Science post-doctoral fellowship to support my studies for a period of 24 months and in 2011 was subsequently appointed as a G-COE Independent Assistant Professor.

As a G-COE Independent Assistant Professor and native English speaker I contribute to the preparation and discussion of G-COE Student RA presentations that provide an ideal setting for the development of important presentation skills. I also provide instruction to graduate students in the laboratory and frequently participate in discussions about global employment opportunities and career development with recent Ph.D. graduates.

Control of CD4 T cell function by Ezh2:

Upon encountering antigen, naïve CD4 T cells differentiate into discrete subsets of effector T helper (Th) cells, producing cytokines that direct immune responses to different types of infection (Figure 1). Specialization into interferon gamma (IFN-γ)-producing Th1 cells is essential for immunity to intracellular pathogens, whereas differentiation into interleukin (IL-)4, -5 and -13-producing Th2 cells promotes immunity to parasitic worms but can also cause allergic disorders. It has recently become clear that epigenetic modifications (i.e. changes in DNA conformation and accessibility) can regulate lymphocyte function. Trithorax and polycomb proteins are essential for epigenetic gene regulation at several stages during development and are particularly important during cellular differentiation. Our current research involves investigation of trithorax and polycomb group proteins and their roles in controlling gene expression in CD4 T cells.

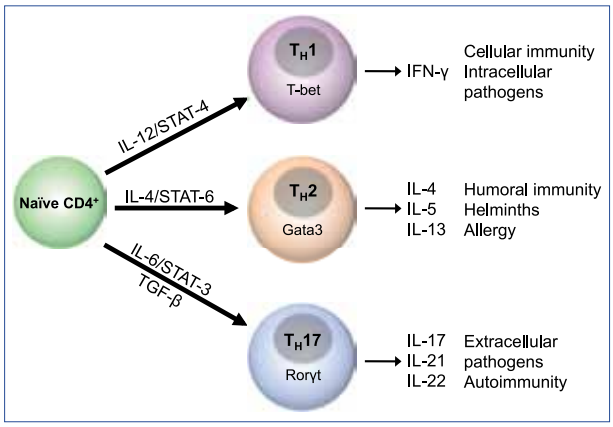

Figure 1.
Naïve CD4 T cells rapidly specialize into different types of effector cells that direct immune responses. Each subset is required for protection against different types of pathogens.

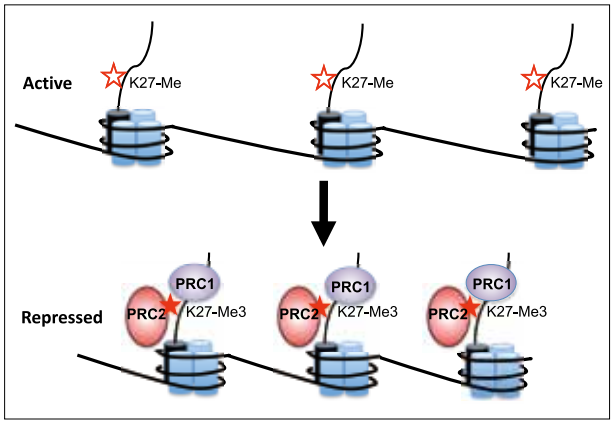

Figure 2.
Genetic regulation by polycomb proteins: DNA is packaged in the nucleus wrapped around core histones. Members of polycomb repressive complex (PRC)1 and PRC2 associate with the DNA, di and trimethylate histone 3 at lysine 27, and repress gene expression.

Recent publications

1. Kuwahara M, Yamashita M, Shinoda K, Tofukuji S, Onodera A, Shinnakasu R, Motohashi S, Hosokawa H, Tumes DJ, Iwamura C, Lefebvre V, Nakayama T. The transcription factor Sox4 is a downstream target of signaling by the cytokine TGF-β and suppresses T(H)2 differentiation. *Nat Immunol*. 1; 13(8): 778-786 (2012).
2. Kitajima M, Ito T, Tumes D.J, Endo Y, Onodera A, Hashimoto K, Motohashi S, Yamashita M, Nisimura T, Ziegler F. S., Nakayama T. Memory type 2 helper T cells induce long-lasting anti-tumor immunity by activating natural killer cells. *Cancer Res*. 71: 4790-4798 (2011).

Epigenetic regulation of helper T cells by Polycomb and Trithorax complexes

Independent Research Associate

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Summary

It is becoming clear that the immune system is regulated not only by its own machinery, but also by mechanisms involving general cellular memory. Histone modifications and DNA methylation form the molecular basis of the epigenetic regulation of cellular memory. We have focused on Polycomb and Trithorax complexes, which are called epigenetic regulators, and investigated their roles in Th2 cell function. In a recent study, we found that Th2 cells failed to maintain their function in the absence of Menin, a component of the Trithorax complex. Additionally, we successfully used a ChIP-Seq analysis to identify genome-wide targets of GATA3, the master transcription factor for Th2 cell differentiation.

I started this epigenetic study of helper T cells as a Ph.D. student. After I was employed as a G-COE independent assistant professor, I expanded my previous study and performed a genome-wide analysis. I am able to concentrate on my research projects thanks to the excellent support from the G-COE program. It also has allowed me to participate in the G-COE symposiums and workshops (presentations and discussions by G-COE student RAs), and I have been able to have positive discussions with prominent foreign scientists and innovative young scientists. I also provide instructions on research and have discussions with graduate students to improve the research environment in our laboratory.

1. Epigenetic regulation of the *Gata3* gene expression by Polycomb and Trithorax complexes

Polycomb group (PcG) and Trithorax group (TrxG) molecules act as antagonistic regulators to maintain the transcriptional status of the developmentally regulated *Hox* genes. Various nuclear factors, including PcG and TrxG molecules, regulate T helper type 2 (Th2) cells, which play an important role in humoral immunity and allergic reactions. We herein show that the activation of STAT6 induces displacement of the PcG complex by the TrxG complex at the upstream region of the *Gata3* gene encoding a transcription factor essential for Th2 cell differentiation. Once Th2 cells are developed, the TrxG complex associated with Menin binds to the whole *Gata3* gene locus, and this binding is required for the long-term maintenance of *Gata3* expression and Th2 cytokine expression. Thus, STAT6-mediated displacement of PcG by the TrxG complex establishes a subsequent STAT6-independent regulation of *Gata3* expression in Th2 cells via the recruitment of the Menin/TrxG complex.

2. Genome-wide analysis of GATA3 target genes

We successfully used a ChIP-Seq analysis to identify the genome-wide targets of GATA3, the master transcription factor for Th2 cell differentiation. We also performed a DNA microarray analysis and a ChIP-Seq analysis of histone modifications, and finally identified a set of GATA3-regulated genes. The GATA3 dependency of these genes was validated by qPCR with high reproducibility, thus indicating that the combination of the ChIP-Seq and DNA microarray analyses was effective for the selection of target genes. In summary, our study revealed that GATA3 was required for the induction and maintenance of the expression of the majority of Th2-specific genes in Th2 cells.

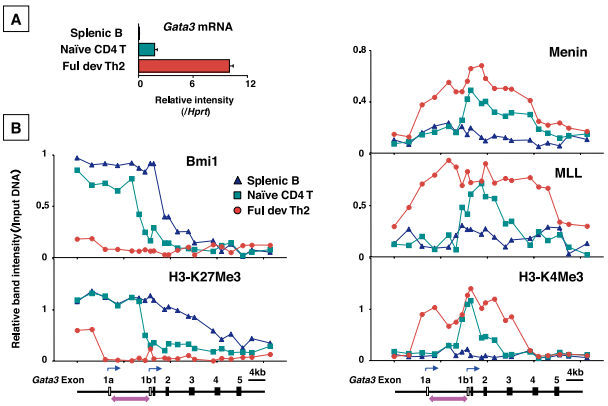

Figure 1. Epigenetic status of splenic B cells, naïve CD4 T cells, and fully developed Th2 cells at the *Gata3* locus
(A) The *Gata3* mRNA level was measured by quantitative RT-PCR. Splenic B cells, naïve CD4 T cells and fully developed Th2 cells (Full dev Th2) were examined. (B) A representative result of a ChIP assay using antibodies specific for the indicated proteins, with a series of primer pairs covering the *Gata3* locus, is shown. The PCR product band intensities relative to the input in each primer pair are shown. A schematic representation of the mouse *Gata3* gene locus is shown below each graph. In splenic B cells, the Bmi1 and H3-K27Me3 signals are detected from the upstream region of the proximal promoter and the region around exons 1 and 2. However, in naïve CD4 T cells, the Bmi1 and H3-K27Me3 signals are enriched only in the upstream region of the proximal promoter, and have low signals at the proximal promoter and the coding region. Menin and MLL binding and H3-K4Me3 signals were enriched from the downstream region of the proximal promoter to exon 2. Fully developed Th2 cells show strong enrichment of Menin and MLL signals from the beginning of the distal promoter to exon 5 and H3-K4Me3 signals to exon 3. In summary, the signals for H3-K4Me3 show a similar pattern to those of Menin and MLL in all cells, whereas the H3-K27Me3 profile is similar to that of Bmi1.

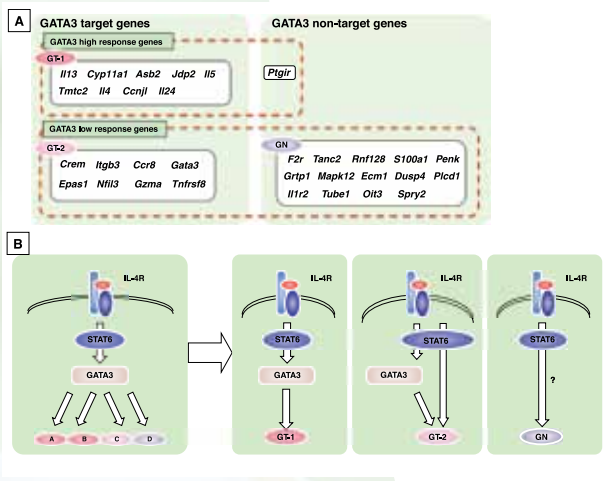

Figure 2. Classification of Th2-specific genes according to the mechanism of regulation
(A) Classification of Th2-specific genes according to the mechanism of regulation
GATA3 target genes are classified into two groups; a GATA3 high response group and low response group. Therefore, although GATA3 has been recognized as a master regulator of Th2 cell differentiation, some Th2-specific genes are not regulated by GATA3 itself, but in collaboration with STAT6.
(B) A schematic representation of the mechanism regulating the Th2-specific inducible genes
The old model is shown in the left panel and a new model that we propose is shown in the right panel. Almost all Th2-specific inducible genes were thought to be controlled by GATA3 (old model). Indeed, the genes encoding Th2 cytokines are shown to be included in the GT-1 group in our analysis. On the other hand, we identified genes that were regulated by a collaboration between GATA3 and STAT6 (GT-2). We also identified a set of genes whose expression was regulated in a GATA3-independent manner (GN), suggesting that GATA3 does not upregulate all of Th2-specific inducible genes.

Recent publication

1. Onodera A, Yamashita M, Endo Y, Kuwahara M, Tofukuji S, Hosokawa H, Kanai A, Suzuki Y, Nakayama T. STAT6-mediated displacement of polycomb by trithorax complex establishes long-term maintenance of GATA3 expression in T helper type 2 cells. *J. Exp. Med*. 207(11): 2493-506 (2010).
2. Horiuchi S, Onodera A, Hosokawa H, Watanabe Y, Tanaka T, Sugano S, Suzuki Y, Nakayama T. Genome-Wide Analysis Reveals Unique Regulation of Transcription of Th2-Specific Genes by GATA3. *J. Immunol*. 186(11): 6378-89 (2011).

Sox4 acts as a downstream target of TGFβ and suppresses GATA3-induced immune responses

Fellow

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T helper type 2 (Th2) cells produce IL-4, IL-5, and IL-13 and play an important role in humoral immunity and allergic reactions. To establish new treatment for allergic diseases, we are investigating the mechanisms of Th2 cell differentiation. Such an approach was evaluated, and I was employed as a Global COE fellow and started research about the mechanisms of Th2 cell differentiation.

The commitment of naïve CD4 T cells to distinct effector Th cells requires changes in the expression of transcription factors. Sox4 is a member of the Sry-related high-mobility group box (Sox) family of transcription factors that plays a key role in the regulation of transcription during developmental processes. Here we show that Sox4 negatively regulates GATA3, the master regulator of Th2 cell function, and we describe two distinct mechanisms by which it does so (Figure 1). First, Sox4 binds directly to GATA3, preventing GATA3 binding to DNA. Second, Sox4 binds a DNA sequence in the IL-5 promoter that overlaps the GATA3 binding sequence, preventing GATA3 binding. By inhibiting GATA3, Sox4 blocks Th2 cell differentiation both *in vitro* and *in vivo*, resulting in the amelioration of Th2 cell-driven airway inflammation in mice expressing transgenic Sox4. TGFβ-induced inhibition of Th2 cell differentiation was mediated by Sox4 whose expression is induced by TGFβ. Thus, Sox4 acts as a downstream target of TGFβ to inhibit GATA3 function and Th2 cell differentiation.

Moreover, I am trying to activate the G-COE program by discussing with graduate students while advancing the present study, and studying hard with each other.

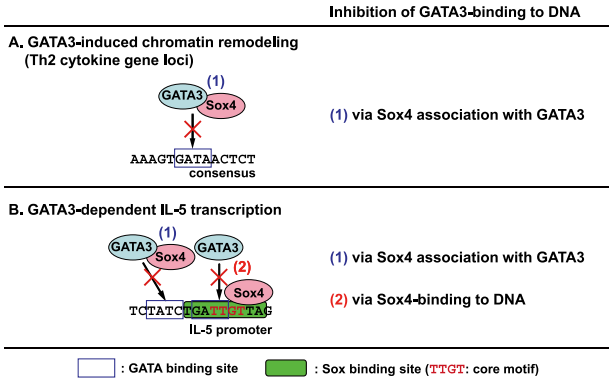

Figure 1. Sox4 down-regulates Th2 cell differentiation through its role in the negative regulation of GATA3 function via two distinct mechanisms.
First, Sox4 associates with GATA3 and inhibits GATA3 binding to its DNA binding sequence resulting in impaired GATA3-induced chromatin remodeling of the Th2 cytokine gene loci (Figure 1A). This mechanism may operate also in the inhibition by Sox4 in GATA3-dependent IL-5 transcription (Figure 1B upper panel). Second, Sox4 directly binds to the IL-5 promoter and interferes with GATA3 DNA binding, thus leading to the repression of IL-5 transcription (Figure 1B lower panel).

Crucial role of CD8αα for T cell memory survival

Fellow

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A hallmark of immune T cell memory is that repeated infections with a pathogen are met with more rapid and enhanced protective immunity against that organism. On the other hand, allergic responses are caused by an abnormal immunoresponse to antigens which are originally non-pathogenic.

I have performed basic research on the development of prevention and cures for allergies by controlling the immune system, which was the one of the goals of the global COE, but further technical improvement in the future is necessary for my research. I was appointed as a Global COE fellow and started research to obtain new technology under Dr. Hilde Cheroutre of La Jolla Institute for Allergy & Immunology.

Effector memory T cells are located in various tissues and have a heightened and immediate effector function. In contrast, central memory T cells reside within lymphoid tissues and require proliferation and differentiation to become effector cells. In our previous study, it was clarified that CD8αα is a key component involved in maintaining the effector memory T cells, and

in my latest molecular analysis I found that a major function of CD8αα is to modulate the TCR signaling to avoid the induction of apoptosis (Figure 1).

I have strived to share my experiences and technical education through discussions with graduate students. In addition, from the viewpoint of globalized education for the graduate students, I want to pass on my experiences performing research in the U.S. and to educate students about the differences in planning and conducting research in Japan and the U.S.

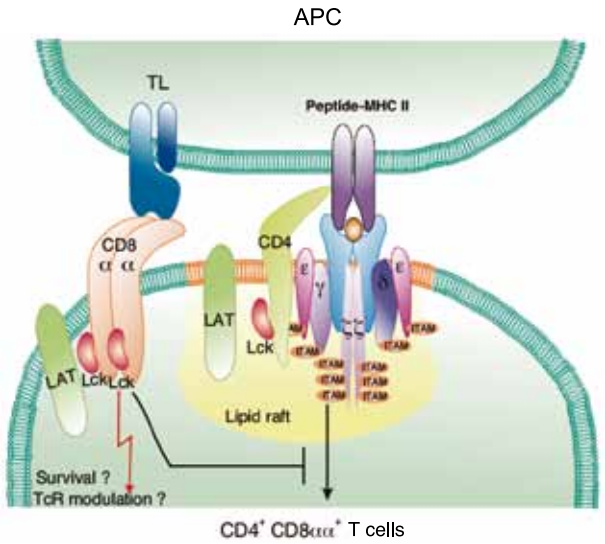

Figure 1: Unlike the conventional coreceptors, CD8αβ and CD4, the CD8αα repressor is excluded from lipid rafts. The CD8αα corepressor negatively regulates TCR activation by disrupting lipid rafts and by sequestering the signaling molecules required for TCR-initiated downstream signaling. Although the detailed mechanism has not been clarified, the constitutive presence of CD8αα indicates that it may interact with its ligand, TL, and promote the long-term survival of memory T cells.

TSLP and Th2 cells in allergic diseases

Fellow

Masayuki Kitajima

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Thymic stromal lymphopoietin (TSLP) has been implicated in the development and progression of allergic inflammation in both humans and mice. However, the direct effect of TSLP on effector Th cells has not been extensively investigated. Recently, with collaborators and graduate students, we reported enhanced Th2 differentiation and allergen-induced airway inflammation in Zfp35-deficient mice (Kitajima *et al*, J Immunol, 2009), with the hope to continue the international collaboration cultivated in those research activities, initiated a program as a fellow researcher in unison with the idea of Global COE program.

In this study, we show that the level of TSLPR expression on effector Th2 cells is higher than on Th1 and Th17 cells. TSLPR expression in Th2 differentiation was up-regulated in an IL-4 dose dependent manner. Functionally, TSLP treatment of Th2 cells, but not Th1 or Th17, significantly induced proliferation (Figure 1). Therefore, the novel function of TSLP suggests that TSLP is directly involved in the homeostasis of Th2 cells in allergic inflammation.

Our research activities keep evolving with the globalization, and research collaboration with overseas research laboratories will strongly benefit the postgraduates that will drive research activities in Japan in the future. Moreover, the process of sharing discussion and study results with a worldwide research community has contributed to the growth of postgraduates and their collaborative activities.

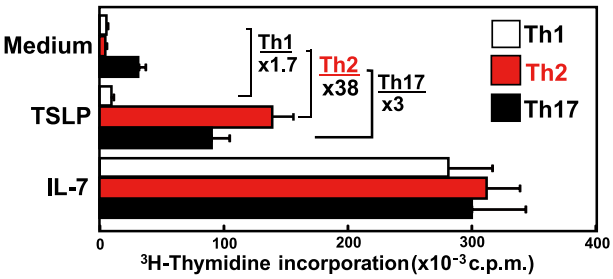

Figure 1. Th1, Th2, and Th17 cells were stimulated with medium, TSLP, or IL-7 for 24 hours. Cell proliferation was examined by a ^{3}H-Thymidine incorporation assay. TSLP stimulation of Th2 cells induced higher proliferation than on Th1 and Th17 cell. We tried to find other TSLP functions on Th2 cells and to confirm physiological functions *in vivo*.

A short comment from Dr. Steven Ziegler, a supervisor and a visiting professor Chiba University

Masayuki is doing quite well, and has begun to write up his work on TSLP effects on Th2 effector cells.

NKT cell precursors in the CD4/CD8 double-negative (DN) thymic fraction

Fellow

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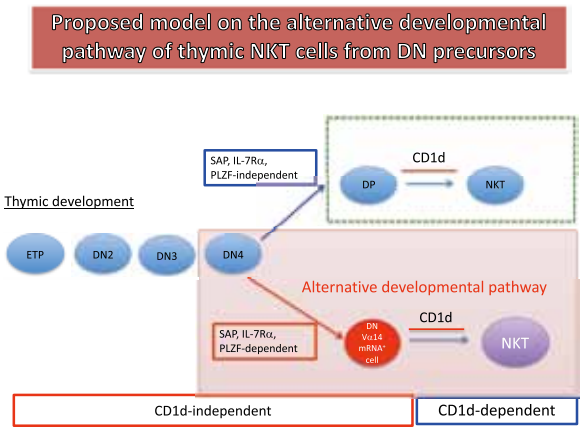
Department of Immunology, Graduate School of Medicine, Chiba University
Laboratory for Immune Regulation, Research Center for Allergy and Immunology, RIKEN

CD1d-restricted natural killer T (NKT) cells represent a distinct subset of T lymphocytes expressing both αβT cell receptors (Vα14-Jα18/Vβ8 in mice, Vα24-Jα18/Vβ11 in humans) and natural killer (NK) cell-associated receptors. The unique ability of NKT cells to secrete large amounts of effector cytokines immediately upon activation implies that NKT cells play important immunoregulatory roles. The development of these cells is of particular interest because of their unusual phenotype and behavior. Currently, the majority opinion postulates that NKT cells diverge from the conventional T cell ontogeny after the $CD4^+CD8^+$ double-positive (DP) stage upon agonistic selection with CD1d and endogenous glycolipid ligand(s). However, we recently found the presence of NKT cell precursors in the DN4 stage thymocytes, that is, before the cells reached the DP stage, in both wild-type and CD1d-deficient mice. These results provided new insights into the early development of NKT cells prior to surface expression of the invariant Vα14 antigen receptor, and suggested a unique differentiation pathway for NKT cells that is different from that of conventional T cells. Based on these findings, I was appointed as a Global COE fellow in 2008, which made it possible for me to continue my research on the DN NKT precursors, which will hopefully lead to the elucidation of the unique developmental pathway of NKT cells. During my appointment, regular discussions with graduate students were held to assist them in pursuing their scientific careers. The Global COE program has provided me with various opportunities to meet with leading scientists, which was very helpful for stimulating my research.



The DN4-fraction 2 (Fr2,) but not DN4-fraction 1 (Fr1), thymocytes have the potential to generate NKT cells *in vitro* on both OP9/control and OP9/Dll-1 stromal monolayers. Wild-type C57BL/6-derived DN4 thymocyte subsets were highly purified using a FACSAria cell sorter and were co-cultured with stromal cells for eight days. The values indicate the percentage of αGC/CD1d dimer$^+$ NKT cells within the viable lymphocyte gated cells.

Figure 1. A proposed model of the alternative developmental pathway of thymic NKT cells from DN precursors.
It is well established that CD4 and CD8 double-positive (DP) thymocyte precursors give rise to NKT cells. However, we have previously shown the presence of cells with NKT lineage potential in the DN4 stage thymocytes, that is, before the cells reach the DP stage, in both wild type and CD1d-deficient mice. The data obtained by *in vitro* and *in vivo* methods showed that these DN cells develop into mature NKT cells only upon engagement with their selecting molecule, CD1d. Furthermore, the development of these DN cells seems to require IL7Ra, SAP and PLZF. In summary, our study reveals a novel thymic differentiation pathway for DN NKT cell precursors before positive selection with CD1d, and suggests the possibility that there is an alternative developmental pathway for NKT cells in the thymus.

A new oral adjuvant approach for the treatment of Japanese cedar pollen allergy

Fellow

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Japanese cedar pollinosis, caused by the pollen of the Japanese cedar tree, is the most common seasonal allergic disease in Japan. Allergic immunotherapy is indicated in patients with allergic rhinitis, which is a typical IgE-mediated disease with an increasing prevalence worldwide. A recent review of randomized controlled studies of sublingual immunotherapy (SLIT) suggests that this approach is safe. However, the clinical improvement is limited, and the development of an effective and safe adjuvant for SLIT is needed. Under these circumstances, I was employed as a Global COE fellow and started research about allergic immunotherapy.

I have attempted to elucidate clinical biomarkers correlated with the improvement of clinical symptoms

by SLIT, with a focus on the mechanism underlying the inhibition of allergic responses (Patent Pending: 2012-210167).

All lactic acid bacteria influence the maturation of DCs as a result of their uptake of antigen, but the patterns differed significantly among the strains. KW3110 led to strong induction of CCR-7 and PD-L2 by mature DCs. In OVA-sensitized mice, sublingual administration of low doses of KW3110 with OVA decreased the IgE production and nasal symptoms induced by nasal OVA provocation. These results suggested that the upregulation of CCR7 and PD-L2 expression on DCs by KW3110 plus an antigenic stimulus reduced the memory Th2 cell responses at allergic inflammatory sites. Thus, we have demonstrated that sublingual administration by KW3110 is of clinical interest as a new oral mucosal immunotherapy for allergic rhinitis (*Clin Immunol*. 2012, 2010-190842).

In addition, I have been working on revitalizing the research environment through active discussions with G-COE graduate students.

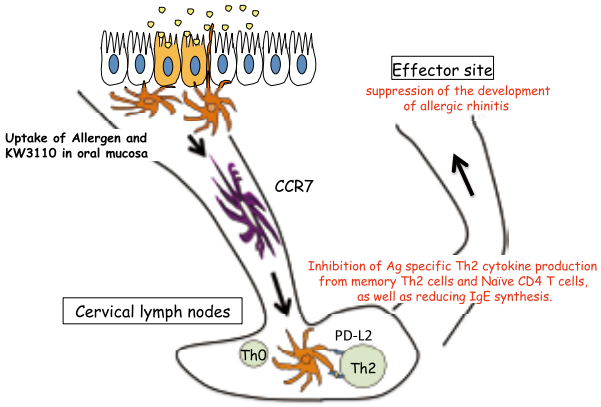

Figure 1. KW3110 is of clinical interest as a new oral adjuvant immunotherapy for allergic rhinitis

Analysis of therapeutic efficacy and its biomarkers for sublingual immunotherapy against Japanese cedar pollinosis

Fellow

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Graduate School of Medicine, Chiba University

Japanese cedar *(Cryptomeria japonica)* pollinosis is one of the most prevalent allergies in Japan. We have identified and characterized novel allergens in Japanese cedar pollen and have been working to develop a novel approach for immunotherapy. The goal of developing immunotherapy inspired us to join the Global COE program to investigate the therapeutic efficacy and safety of sublingual immunotherapy (SLIT) against Japanese cedar pollinosis, which is the most promising treatment to cure the pollinosis.

We recruited volunteers with Japanese cedar pollinosis in Kanto area. We instructed them to take the vaccine sublingually for one and a half years. An active treatment of SLIT significantly ameliorated the symptom-medication score in comparison to those in the placebo group. The mild symptom group in the active treatment group showed significant decrease of Th2-type cytokine production in comparison to those in both the severe symptom group in the active treatment group and the placebo group. Furthermore, patients who showed upregulation of antigen-specific regulatory T cells after the pollen season in the active treatment group showed significant amelioration of their subjective symptom score in comparison to those who showed downregulation of the regulatory T cells in the active treatment group and in the placebo group. We concluded the downregulation of Th2-type cytokine production and the upregulation of regulatory T cells may be a biomarker correlated with therapeutic effects by SLIT.

I have discussions with young scientists in our or collaborating laboratories to advise them from the viewpoint of a biochemist.

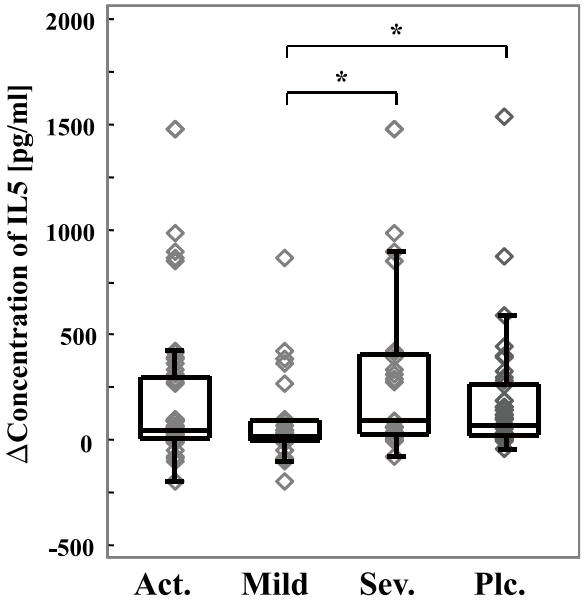

Figure 1. The upregulation of Th2-type cytokine production after the pollen season in the mild symptom group (Mild) in the active treatment group (Act.) was significantly attenuated in comparison to that in both the severe symptom group (Sev.) in the active treatment group and the placebo group (Plc.).

The role of NOD-like receptors in mast cells

Fellow

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CAPS (cryopyrin-associated periodic syndromes) is caused by gain of functional mutations in the gene, nucleotide-binding oligomerization domain (NOD)-leucine rich repeats containing pyrin domain 3 (NLRP3), whose product is a component of the inflammasome that includes the adaptor protein, ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) and procaspase-1. We identified mast cells as the main cell population responsible for IL-1β production through *NLRP3* inflammasome in the skin of CAPS patients (Nakamura Y *et al*, J Exp Med. 2009). This research was selected as the 1st Annual Best Research Award, Chiba University G-COE Program. In this year, I joined G-COE program as research fellow and started my work in Gabriel Nunez laboratory at University of Michigan.

Specifically, the research in Nunez Lab focuses on mechanistic studies to understand the role of proteins of the Nod-like receptor and Toll-like receptor families in the host immune response against bacterial pathogens. In my recent work, we found an unknown protein secreted from some kind of bacteria induced mast cell activation. Now, we are working on identified this novel mast cell activator in Nunez Lab. We believe identified the novel mast cell activator contribute to understanding the mechanism of allergy and microbial-host defense.

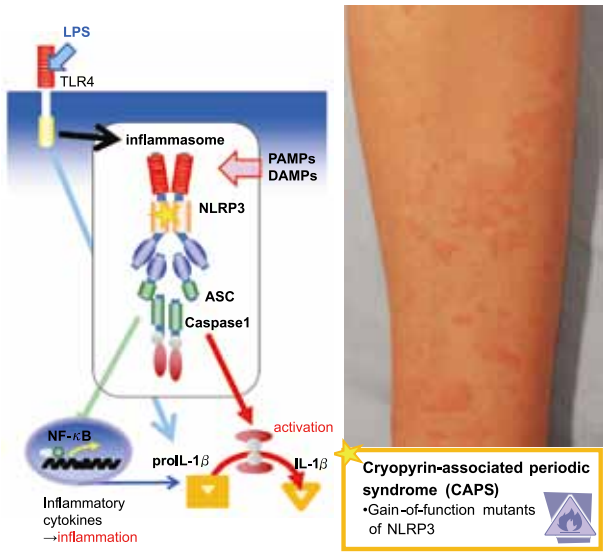

Figure 1. The mechanism of urticaria-like rash in CAPS mediated by IL-1β produced through the activation of NLRP3-inflammasome.

A short comment from Dr. Gabriel Nunez.
I am happy to work with her in my laboratory at University of Michigan. Her research project will deal with studies to understand the role of Nod-like receptors (NLRs) in mediating the function of mast cells. I was impressed by her outstanding work that she did in which she provided clear evidence for a link between mast cells and the inflammasome.

Granulocyte-colony stimulating factor (G-CSF) therapy attenuates the development of atherosclerotic lesion formation by modulating the regulatory T cell function

Fellow

Masashi Yoshida

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Graduate School of Medicine,
Chiba University

It is important to attenuate the progression of atherosclerotic lesions to reduce morbidity and death in patients with ischemic heart disease. We previously reported that Granulocyte-colony stimulating factor (G-CSF) therapy prevents progression of atherosclerosis in myocardial infarction-prone Watanabe heritable hyperlipidemic rabbits and vascular injury models. However, the precise mechanism by which G-CSF prevents the progression of atherosclerosis is largely unknown. I was approved to become a Global COE fellow to address this issue, and started to work on atherosclerosis and G-CSF.

Atherosclerosis results from chronic inflammation, which is caused via immune reactions in atherosclerotic lesions. Excessive responses of the type 1 helper T cells play a major role in the immune reactions associated with atherosclerosis and these responses are controlled by regulatory T cells. Therefore we examined effects of G-CSF on atherosclerosis in apolipoprotein E-deficient mice. Apolipoprotein E-deficient mice treated with G-CSF showed a reduction in atherosclerotic lesions of the aortic

sinus and an increase in the number of Foxp3-positive regulatory T cells in those lesions (Figure 1). Further study is required to reveal the mechanism of G-CSF-mediated attenuation of atherosclerotic region formation. Unfortunately, I had to leave Global COE program in 2009. But Uchiyama, a former research assistant in this Global COE program, and I work collaborated on this research, and he has continued this research.

Aside from this project, we reported 'Chronic doxorubicin cardiotoxicity is mediated by oxidative DNA damage-ATM-p53-apoptosis pathway and attenuated by pitavastatin through the inhibition of Rac1 activity' during a Global COE seminar.

I often had meaningful discussions with postgraduates concerning not only research but their future plans.

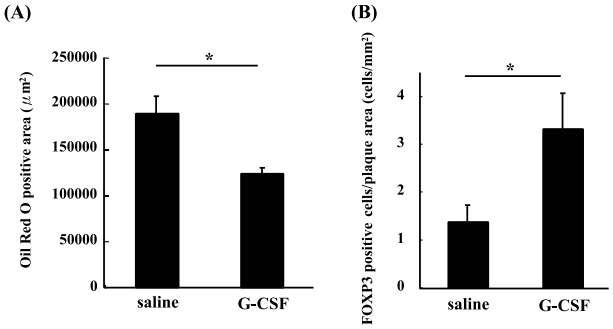

Figure 1. Apolipoprotein E-deficient mice treated with G-CSF showed A) a reduction in atherosclerotic lesions of aortic sinus and B) an increase in the number of Foxp3-positive regulatory T cells in those lesions. The p value is < 0.05 vs. saline.

Cardiac mast cells cause atrial fibrillation through PDGF-A-mediated fibrosis in pressure-overloaded hearts

Fellow

Kaoru Ito

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Graduate School of Medicine, Chiba University

Atrial fibrillation (AF) is a common arrhythmia that increases the risk of stroke and heart failure. We performed research assuming that mast cells, which are associated with allergies and immune responses, might play a significant role in the development of AF. Because our approach to elucidate the relationship between immune cells and cardiovascular disease went hand in hand with the philosophy of the Global COE, I was accepted as a Global COE fellow and started my research as part of the program. We first employed a pressure overload model and tried to estimate the contribution of mast cells to AF by administrating cromolyn and using genetically modified mice. Pressure overload induced mast cell infiltration and fibrosis in the atrium, and enhanced the susceptibility to AF following atrial burst stimulation under Langendorff perfusion. Both atrial fibrosis and AF inducibility were attenuated by stabilization of the mast cells with cromolyn, or by bone marrow reconstitution from mast cell-deficient WBB6F1-Kit$^{W/W-V}$ mice. When they were co-cultured with cardiac myocytes or fibroblasts, bone marrow-derived mast cells increased PDGF-A synthesis and promoted cell proliferation and collagen expression in cardiac fibroblasts, which was abolished by treatment with an anti-PDGF α-receptor neutralizing antibody. Consistently, the upregulation of atrial PDGF-A expression in pressure overloaded hearts was suppressed by bone marrow reconstitution from WBB6F1-Kit$^{W/W-V}$ mice. Furthermore, the injection of an anti-PDGF α-receptor neutralizing antibody attenuated the atrial fibrosis and AF inducibility in pressure-overloaded hearts. Our results revealed a crucial role for mast cells in AF, and highlight a potential application of controlling the mast cell-PDGF-A axis to achieve the upstream prevention of AF in stressed hearts.

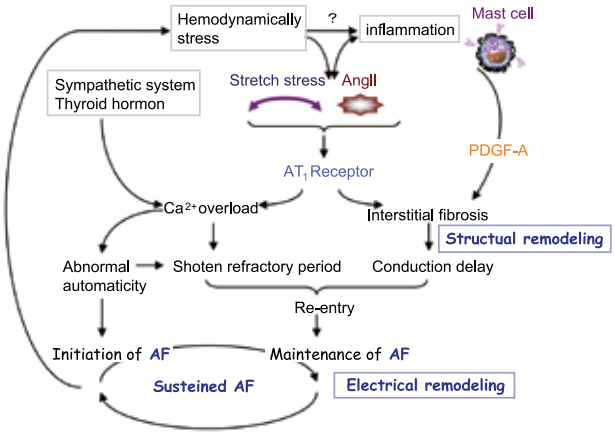

Figure 1. The role of mast cells in the pathogenesis of atrial fibrillation.
Mast cells produce PDGF-A and promote fibrosis of the atrial wall, which subsequently increases the susceptibility of the heart to stimuli that initiate atrial fibrillation.

The role of the Polycomb-related gene, Dmap1 in the maintenance of genome stability

Fellow

Masamitsu Negishi

Department of Cellular and Molecular Medicine
Graduate School of Medicine, Chiba University

I have investigated Polycomb-mediated epigenetic regulation, focusing on the maintenance of genome stability in stem (cancer) cells. Through this attempt, I was appointed as a COE fellow and thereafter I came to launch this research in a Global COE program.

We previously reported that the NuA4 complex components, *DNA methyltransferase 1-associated protein 1 (Dmap1)* is a novel binding partner of Polycomb Bmi1 and that Dmap1 cooperates with the Polycomb complex to maintain gene silencing through epigenetic regulation (Negishi *et al*, BBRC 2007). We further sought to explore the cellular function of Dmap1 in mammalian cells. We found that the Dmap1-PCNA interaction is essential for DNA replication fork progression and the PCNA-related DNA repair pathways and that knockdown of Dmap1 in p53-deficient mouse embryonic fibroblasts causes genome instability due to aberrant DNA repair, resulting in tumor formation in immunodeficient mice (Negishi *et al*, Genes Cell 2009). Furthermore, human DMAP1 located at Chromosome 1p34, a region frequently deleted in human tumors with 1p deletions, so we have been studying whether human DMAP1 can function as a *bona fide* tumor suppressor in 1p deletion tumors.

With regard to educational activities, I actively contribute to the implementation and discussion with graduate students on their research activities. In addition, I make an effort to take the initiative in promoting international research activities, by participating in international meetings twice during this period in addition to the COE programs.

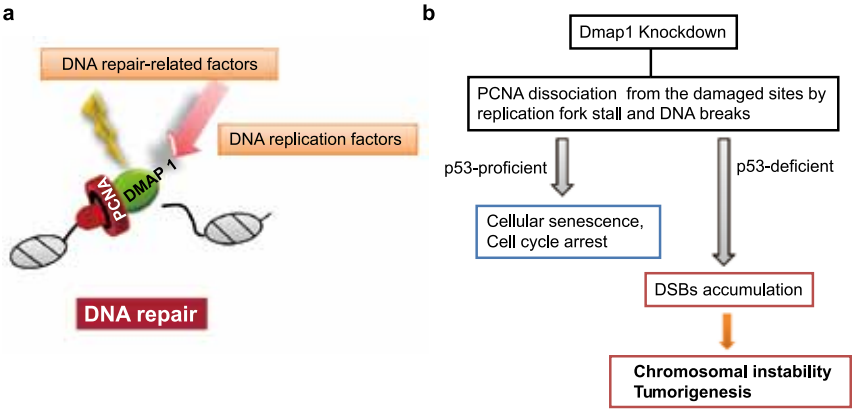

Figure 1.
a. NuA4 complex component, Dmap1 interacts with PCNA and accumulates at damaged sites in the DNA repair process.
b. Knockdown of Dmap1 led to dissociation of PCNA from damaged sites, which causes cellular senescence in p53-proficient cells or chromosomal instability due to DSBs accumulation in p53-deficient cells.

CDC42 and NFκB signaling contribute to the pro-inflammatory phenotype of senescent endothelial cells

Fellow

Takashi Ito

Department of Cardiovascular Medicine
Graduates School of Medicine, Chiba University

Risk factors for atherosclerosis, such as aging and lifestyle-related stresses, induce the senescence of endothelial cells, leading to the accumulation of senescent cells within atherosclerotic lesions. One of the phenotypes of senescent cells is the persistently elevated expression of pro-inflammatory genes responsible for atherosclerotic progression, such as MCP-1, E-selectin and VCAM-1. However, the mechanisms by which senescent endothelial cells retain the pro-inflammatory phenotype remain largely unknown. Using an RNAi-based screening method, we found that CDC42 and NFκB signaling are responsible for the sustained induction of pro-inflammatory genes.

Knockdown of either the CDC42-PAK2 or IKK-p65 pathway impaired the expression of MCP-1, E-selectin and VCAM-1 in three types of senescent cells induced by p16, p21, or replicative exhaustion. The introduction of active CDC42 into young cells induces NFκB activation and a pro-inflammatory phenotype similar to senescent cells, indicating that CDC42 functions upstream of NFκB. In a Cre-lox mouse model with endothelial-specific senescent cells, inflammatory genes were induced in several organs, which was blocked by CDC42 gene deletion. The CDC42-induced inflammatory signal is characteristic of senescent cells, since the blockade of CDC42 signaling in endothelial cells does not abrogate the acute inflammatory responses induced by TNF-alpha or LPS. Furthermore, CDC42 knockdown in an immune active mutant of *C. elegans* blocks immunostimulatory gene expression and restores the short lifespan of the strain. Thus, the cell-autonomous CDC42 activation in senescent cells serves to induce sterile inflammation and may contribute to chronic inflammation and organismal aging. These mechanisms appear to be conserved across species.

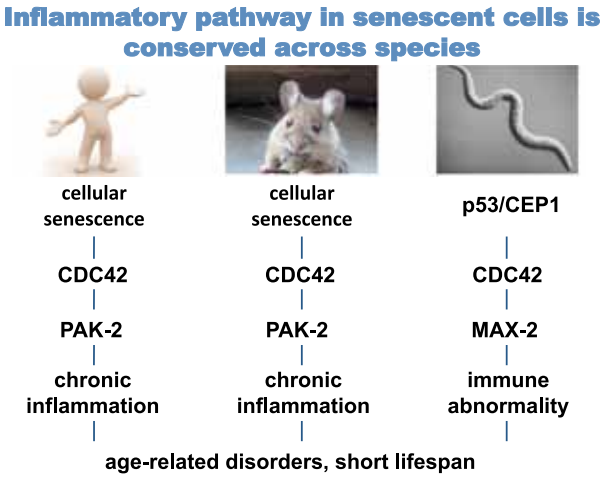

Figure 1. CDC42 is induced in senescent endothelial cells.
This results in the induction of pro-inflammatory genes, leading to chronic inflammation and organismal aging in multiple species, such as humans, mice and worms.

Generation of memory Th17 cells involved in the induction of steroid-resistant asthma

Fellow

Akane Suzuki

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Graduate School of Medicine,
Chiba University

After antigen recognition, naive CD4 helper T (Th) cells undergo differentiation into effector Th cells, and some of the effector cells differentiate into memory Th cells. Since memory Th cells are involved in chronic airway inflammation, it is important to clarify the mechanism(s) of memory Th cell generation in order to establish new treatment strategies for allergic diseases. I started working on this mechanism after I was employed as a Global COE fellow.

As part of these studies, we examined the role of memory Th17 cells in steroid-resistant asthma. The airway hyperresponsiveness was increased in memory pathogenic Th17 mice, compared with memory non-pathogenic Th17 mice. The expression of the TNFR family member CD30 was observed on effector pathogenic Th17 cells. Four weeks after the transfer of $CD30^{Hi}$ or $CD30^{Lo}$ effector Th17 cells into syngenic mice, the number of memory cells formed was increased in mice that received the $CD30^{Hi}$ cells. In addition, the production of IL-17A was higher in memory Th17 cells generated from $CD30^{Hi}$ effector Th17 cells than from $CD30^{Lo}$ effector Th17 cells. Moreover, we found that $CD30^{Lo}$ effector Th17 cells expressed higher levels of the pro-apoptotic genes Bim and FasL compared to $CD30^{Hi}$ effector Th17 cells (**Figure 1**). Therefore, our findings suggest that the reduction of Bim and FasL through CD30 signaling is critical for the generation of memory Th17 cells.

I have also tried to activate the G-COE program by discussing my project with graduate students at seminars and retreats.

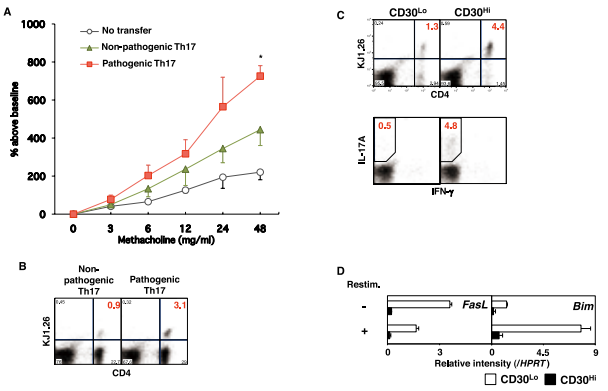

Figure 1.
The airway hyperresponsiveness was increased in memory pathogenic Th17 mice, compared with memory non-pathogenic Th17 mice (A). The number of memory cells formed was increased in mice that received pathogenic Th17 cells (B). The number of memory cells formed and the production of IL-17A were also increased in mice that received $CD30^{Hi}$ pathogenic Th17 cells (C). Furthermore, $CD30^{Lo}$ effector Th17 cells expressed higher levels of the pro-apoptotic genes Bim and FasL compared to $CD30^{Hi}$ effector Th17 cells (D).

The role of tumor suppressor candidate 5 (TUSC5) in adipocyte regulation and the immune response

Fellow

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Brain endothelial cell-derived gene 1 (bec-1), which we identified, is a homolog of a tumor suppressor candidate gene, *TUSC5*. *TUSC5* was identified as a gene present in the LOH region of human lung cancer. It contains the CD225 domain and is highly expressed in adipose tissue. These characteristics suggest that TUSC5 is involved in the immune response, metabolism and cancer suppression; however its functions are not well understood. The aim of my research is to elucidate the physiological role of TUSC5 through the analyses of adipocytes and TUSC5 knockout mice.

We found that the hTUSC5 protein was detected in human white adipose tissues, supporting its expression profile in mouse tissue. In human preadipocytes, the expression of hTUSC5 mRNA and protein were induced drastically during their differentiation, followed by PPARγ accumulation. Furthermore, pioglitazone, a PPARγ ligand, dose-dependently facilitated the induction of TUSC5, as well as the differentiation of human preadipocytes. A ChIP assay with an anti-PPARγ antibody suggested that PPARγ protein associates with the hTUSC5 promoter region, and genome-wide ChIP sequencing supported this association.

In addition, we generated TUSC5 knockout mice using gene targeting methods. We found that the fat tissue weights and fat cell size were decreased in TUSC5 knockout mice compared to wild type mice. A genome-wide transcription start site analysis using primary cultured adipocytes revealed that obesity-related genes, such as MCP-1 and IL-6, were decreased in TUSC5 KO mice compared with wild type mice. These results strongly suggest that TUSC5 plays a physiological role in obesity and the underlying chronic inflammation.

Eomesodermin controls the function of IL-5-producing pathogenic memory Th2 cells

Fellow

Yusuke Endo

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Recent reports have suggested that memory Th cells display high levels of heterogeneity compared to effector Th cells according to the function and the tissue localization in the body. However, due to the limited number of memory Th cells, very few studies have focused on which functional subpopulations are associated with diseases. When I was a graduate student, I was served as a G-COE research assistant from 2008 to 2010. After graduation, I was employed as a G-COE research fellow and was consistently engaged in research about pathogenic memory Th2 cells that induce chronic airway inflammation. Last year, I published my thesis in ***Immunity***, as described below.

1. Memory Th2 cells were subdivided into four distinct subpopulations according to their expression of CD62L and CXCR3. IL-5 producing cells were selectively detected in the CD62L^{lo}CXCR3^{lo} population. 2. A permissive chromatin conformation at the IL-5p region was specifically observed in the CD62L^{lo}CXCR3^{lo} population of memory Th2 cells. 3. Memory Th2-dependent airway inflammation was attenuated in the absence of the CD62L^{low}CXCR3^{low} population. 4. Eomesodermin was shown to interact with GATA3, preventing GATA3-dependent IL-5 production in memory Th2 cells. According to these observations, we identified IL-5 producing pathogenic memory Th2 cells that induce allergic asthma. Furthermore, in memory Th2 cells, IL-5 is uniquely regulated by two distinct mechanisms; (i) the chromatin conformation at the IL-5 locus, and (ii) the expression of eomesodermin, which prevents GATA3-dependent transcriptional activity (Endo

et al., *Immunity*, 2011) (Figure 1).

Currently, I teach graduate students from abroad and make an effort to inspire and support their research while discussing with them in English.

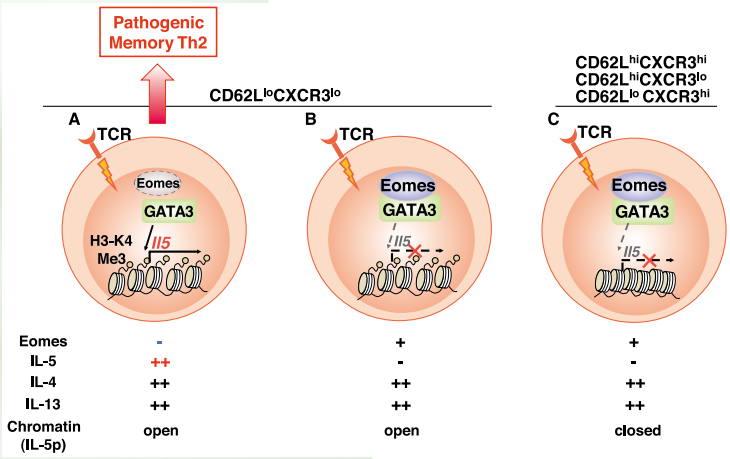

Figure 1. A schematic representation of the regulation of IL-5 expression in memory Th2 cells.
The expression levels of eomesodermin, GATA3 and that of IL-4, IL-13 and IL-5 after TCR stimulation in the four CD62L/CXCR3 subpopulations are shown. High levels of H3-K4 methylation markers were observed at the *IL-5* promoter in the CD62L^{low}CXCR3^{low} population of memory Th2 cells (A and B). The other three subpopulations (CD62L/CXCR3) showed low levels of H3-K4 methylation markers (C). The population A expressed limited levels of eomesodermin, and could induce IL-5 expression upon TCR stimulation. Population B did not induce IL-5 expression due to the high expression of eomesodermin. Eomesodermin interacts with GATA3 and inhibits the ability of GATA3 to induce IL-5 transcription.

Role of CD69 in the generation of memory T helper lymphocytes

Fellow

Kenta Shinoda

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Immunity defends the body from infection by bacteria and viruses, and by memorizing the antigen information, can more quickly and strongly remove pathogens that can previously infected the body. Memory T helper (Th) lymphocytes play an essential role in immunological memory. Despite their importance for the regulation of immune reactions and immunological memory, little is known about the molecular mechanisms of the generation and maintenance of memory Th cells. I was employed as a Global COE fellow to clarify the mechanisms underlying the regulation of immunological memory, and focused my research on the mechanisms underlying the generation of memory Th cells.

We have shown that effector Th cells relocated to the bone marrow (BM) after their activation in secondary lymphoid organs, and were maintained as memory Th cells in the BM. Under steady state conditions, resting memory Th cells mostly express CD69, which is a well-known early activation marker of lymphocytes. We focused on CD69 and clarified the role of CD69 in memory Th cells. We enumerated the memory Th cells in CD69-deficient mice. Although CD69 does not appear to be required for the development of effector Th cells, the number of antigen-specific memory Th cells in CD69-deficient mice was dramatically decreased compared to wild-type mice. In addition, CD69-deficient Th cells failed to induce an efficient production of high-affinity antibodies *in vivo*. With regard to the generation of memory Th cells, we found that CD69 regulates the homing of effector Th cells to the BM as an adhesion molecule (Figure 1). These data suggest that CD69 plays a crucial role in the generation of memory Th cells, and that the relocation of effector Th cells to the BM is essential for the generation of memory Th cells (Shinoda et al., *Proc Natl Acad Sci USA*., 109: 7409-14, 2012).

I am presently working on revitalizing the research environment through active discussions with graduate students and by contributing to discussions and collaborations with graduate students on their research activities.

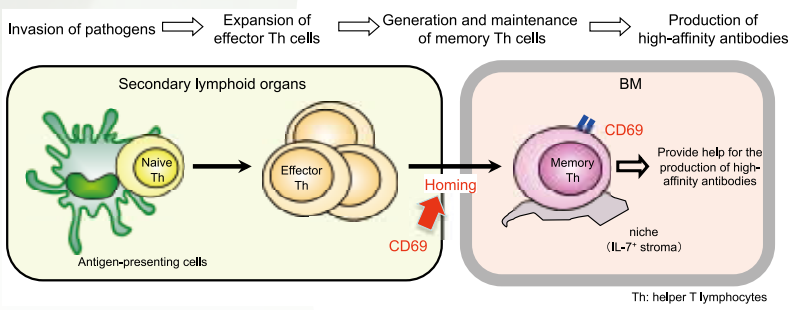


Figure 1. CD69 regulates the generation of memory Th cells

My experience at Duke Clinical Research Institute learning about global clinical research and translational research

Fellow

Masaya Koshizaka

Clinical Research Center
Chiba University Hospital

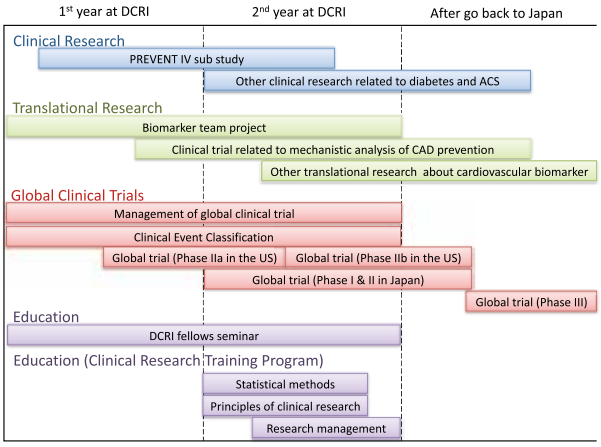
I have been engaging in clinical research at Duke Clinical Research Institute (DCRI) since July 2011, in order to promote Japanese participation in global clinical studies, and to learn how to manage clinical studies, as a solution for the “Drug lag”.

We reanalyzed the PREVENT IV trial, as a post-hoc analysis of a CABG clinical trial. Despite similar rates of 1-year graft failure, diabetic patients, particularly those receiving insulin, had worse 5-year clinical outcomes than non-diabetics. (Submitted)

I also participated in clinical trials related to identifying biomarkers of cardiovascular disease (CAD), in order to learn about Translational Research (TR). We planned a clinical trial of s new drug to evaluate the mechanism by which it can prevent CAD, and wrote the protocol for the study. The study will be started soon.

I have been joining in the team meetings for a global clinical trial related to diabetes, and am learning how to manage global clinical trials. I am also doing Clinical Event Classification for three global clinical trials. I cannot describe these in detail yet; however, I am participating in another global clinical trial, which we are planning to join in as a Japanese academic research organization (ARO). I am also taking classes as part of a Clinical Research Training Program in order to systematically learn more about clinical research.

I have been learning about American thought processes and negotiation skills through these studies, and also am keeping a relationship with the Chiba University Clinical Research Center ARO by weekly meeting using Skype. I would like to keep contributing to improvements in TR and clinical research, both as a G-COE, at Chiba University, and in Japan.



My experiences at the DCRI and the future plan
PREVENT IV: The project of Ex-vivo Vein graft Engineering via Transfection IV, ACS: acute coronary syndrome, CAD: coronary artery disease

Comparison of microscopic polyangiitis patients between Japan and Europe

Fellow

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Microscopic polyangiitis (MPA) is an autoimmune disease characterized by small vessel vasculitis and antineutrophil cytoplasm antibody (ANCA). Regarding the findings of clinical trials for MPA, recently most such trials tend to be performed with an international and multicenter design because of its rareness. Indeed, Japanese centers are now taking part in the ongoing PEXIVAS trial. However, the geoepidemiological study that was performed in 2000 suggested a difference in the phenotype of MPA between Japan and Europe. Consequently it has been recognized that comparison studies of the phenotypes and outcomes in MPA are needed to accurately interpret the findings of future international clinical trials. I and Dr. David Jayne, a G-COE visiting professor from Cambridge University Hospital, investigated the difference in the phenotypes and outcomes in MPA between Japan and Europe during my visit to his department from January, 2012 (We continued this study even after the end of the G-COE program in March, 2012.). In the analysis, based on the findings of 761 MPA patients from Japan and Europe, we found Japanese MPA patients to have a higher onset age, a higher degree of MPO-ANCA positivity, milder renal dysfunction and more frequent pulmonary involvement than European patients. However, the

patient survival and renal survival were similar between both groups despite the presence of phenotypic differences. A multivariate analysis suggested that the differences in age and pulmonary involvement canceled out the difference in renal function. These results are therefore useful not only for interpreting the findings of international trials, but also for exploring the disease mechanism with planed genetic studies. In addition, I discussed these findings with graduate students who helped us to collect data in Japan, and such discussions were very stimulating for all participants.

Apart from this study, two papers in this field have been successfully accepted during my stay in Dr Jayne's department (Switching of anti-TNF-α agents in Behcet's disease. ***Cli Exp Rheumatol***. 2012; 30 (3 Suppl72): S62-8, Antineutrophil cytoplasm antibodies-associated vasculitis: recent developments. ***Kidney Int***. In Press).

(A)

	EU	Japan
Median age at onset	64.8 y	70.5 y
MPO-ANCA positive	69.4%	95.8%
PR3-ANCA positive	22.4%	3.2%
Median Cre (mg/dl)	2.51	1.80

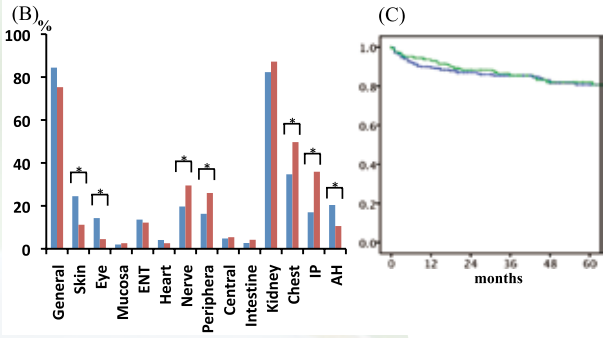

Figure 1.
(A): This table shows the baseline characteristics. Japanese MPA patients had higher onset age, higher MPO-ANCA positivity and milder renal dysfunction than European patients(All $p<0.01$ by chi-square test or Mann-Whitney U test).
(B): This figure shows the proportions of organ involvement at disease onset. The blue bar indicates the European data, while the red one shows the Japanese data. Japanese MPA patients had more frequent pulmonary and neurological involvement than European patients, and they also had less eye and skin involvement (All $p<0.05$ by chi-square test or Fisher exact test).
(C): This figure shows the Kaplan-Meier survival curves. The blue line indicates the Japanese data, while the green shows the means of the European data. The curves were not substantially different between Japan and Europe ($p=0.71$ by Log-Rank test).

CD49b regulates the establishment and maintenance of T helper cell memory

Fellow

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Chiba University

Memory CD4 T cells play a key role in acquired immunity. We have demonstrated that professional memory CD4 T cells reside and rest in the bone marrow (BM). However, how CD4 T cells migrate to the BM and are maintained there as memory cells remains unclear. Therefore, I started research focused on the molecular mechanisms underlying the establishment and maintenance of memory CD4 T cells in the BM as a Global-COE Research fellow this year.

We found that memory CD4 T cells in the BM express high levels of CD49b, which is one of adhesion molecules, and that CD49b-deficient effector CD4 T cells fail to migrate from the spleen into the bone marrow via the sinusoids, specifically inhibiting their transmigration through sinusoidal endothelial cells (Figure 1). In the marrow, effector and memory CD4 T cells contact stromal cells expressing collagen II, which are specific ligands for CD49b. Interestingly, memory CD4 T cells dock onto IL-7^{+}/collagen XI^{+} cells of the BM, whereas effector CD4 T cells do not adhere. The injection of blocking antibodies to CD49b in the late phase of an immune response eliminated memory CD4 T cells from the BM. These results indicate that the collagen-receptor CD49b is required for the migration of memory CD4 T cells onto their survival niches and their maintenance there.

In addition, while attending to my studies, I worked to improve the research environment at Chiba University by positively discussing my projects with Ph.D. students at the G-COE Workshop and Retreat, which was sponsored by the G-COE program.

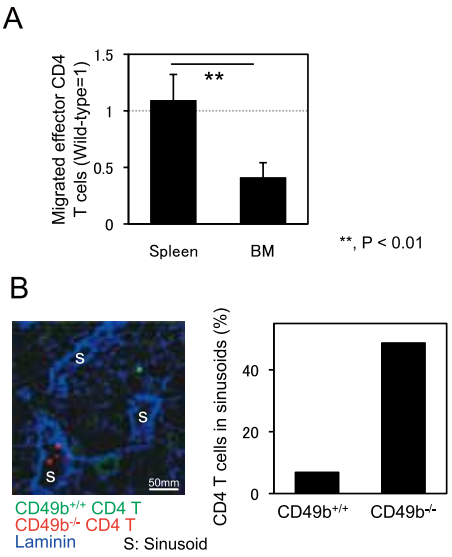

Figure 1.
The loss of CD49b on CD4 T cells reduces their migration into the BM via the sinusoids. (A) CD49b-deficient effector CD4 T cells fail to migrate into the BM. (B) CD49b-deficient CD4 T cells under steady state conditions fail to migrate into the BM remaining in the sinusoids.

Responses to cedar pollen in environmental challenge chambers

Fellow

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Graduate School of Medicine, Chiba University

Environmental challenge chambers (ECC) have been used to expose people to pollen allergens within a stable atmosphere and to examine the efficacy of treatment. To establish a new treatment for allergic diseases, we examined the correlation between the nasal symptoms and the expression of inflammatory mediators using this chamber. Such an approach was evaluated while I was employed as a Global COE fellow and starting my research.

Volunteers with Japanese cedar pollinosis were exposed to cedar pollen (8000 grains/m^3) in the chamber for three hours. Most of the patients who were exposed to Japanese cedar pollen for only a limited number of hours in the ECC outside of the pollen season exhibited nasal symptoms both during the pollen exposure in the chamber, as well as after they had left the chamber, i.e., a late phase reaction. These symptoms continued in all subjects for about three days after leaving the chamber (Figure 1).

We also collected and examined the nasal washings before and six hours after pollen exposure in the chamber. Increased concentrations of Th-2 cytokines, eotaxin, leukotrienes, and eosinophilic cationic protein were observed in the nasal washings collected six hours after pollen exposure in the chamber compared with those collected immediately prior to the pollen exposure.

I am currently trying to activate the G-COE program by discussing it with graduate students while advancing the present study.

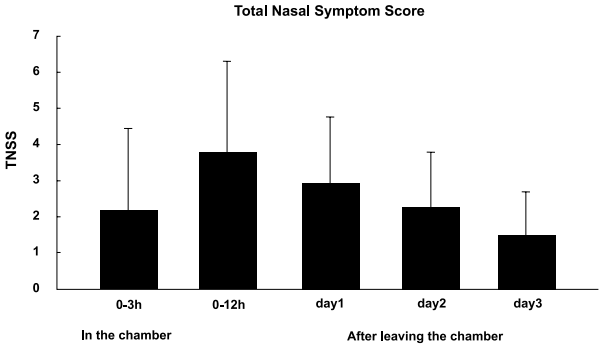

Figure 1. Total nasal symptom score using the Environmental challenge chamber.
Most of the patients who are exposed to Japanese cedar pollen for only a limited number of hours in the ECC outside of the pollen season, exhibited nasal symptoms both during the pollen exposure in the chamber, as well as after they have left the chamber. These symptoms continued for about 3 days after leaving the chamber in all subjects.

Enhanced function of redirected human T cells expressing a ubiquitylation-resistant linker for activation of T-cells

Fellow

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It is likely that the enhancement of signaling after antigenic stimulation, particularly in the tumor microenvironment, would improve the function of adoptively transferred T cells. Linker for activation of T cells (LAT) plays a central role in T-cell activation. We hypothesized that the expression of an ubiquitylation-resistant form of LAT in cells would enhance T cell signaling, and thus augment the anti-tumor activity of the cells. To test this hypothesis, human $CD4^+$ or $CD8^+$ T cells were electroporated with siRNA to repress endogenous LAT, and a ubiquitylation-resistant LAT 2KR or wild-type LAT mRNA was introduced into the cells. Significantly enhanced phosphorylation of LAT and PLCγ was observed, and augmented calcium signaling after T cell receptor (TCR) triggering was observed in the LAT 2KR-expressing T cells. The TCR-induced calcium signaling was abrogated in LAT knockdown cells, but the basal level was higher than that of the control siRNA electroporated cells, suggesting that there is a fundamental requirement for LAT to maintain calcium homeostasis. Redirected LAT 2KR T cells expressing a chimeric antigen receptor or an MHC class I restricted TCR showed augmented function, as

indicated by enhanced cytokine secretion and cytotoxicity (Figure 1). These results indicate that the interruption of LAT ubiquitylation is a promising strategy to augment the effector T cell function for adoptive cell therapy.

In addition, I have been trying to activate the G-COE program by discussing my research with graduate students while advancing the present study, and by studying hard with the other students.

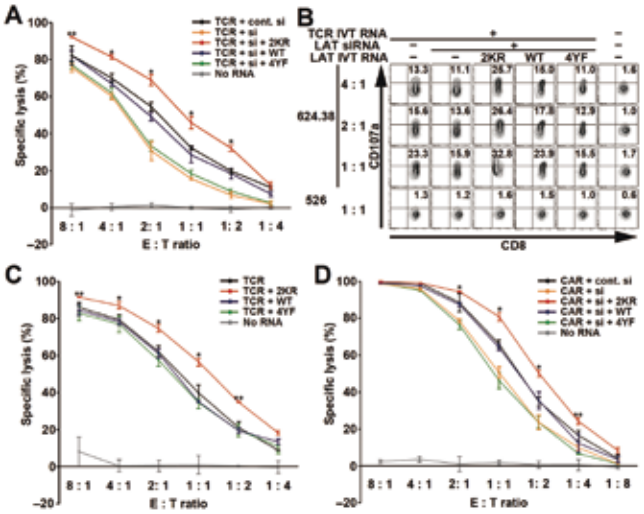

Figure 1. Enhanced cytotoxicity of TCR$^-$ and CAR-redirected CD8$^+$ T cells expressing LAT ubiquitylation-resistant mutants.
(A, C and D) Flow-based cytotoxicity assays against NY-ESO-1-transduced Nalm-6 target cells were performed after a 4 hr incubation with effector cells. The effector cells were: anti-NY-ESO-1 TCR expressing CD8$^+$ T cells with endogenous LAT knockdown (A); anti-NY-ESO-1 TCR expressing CD8$^+$ T cells with the indicated LAT mutants without endogenous LAT knockdown (C) and anti-CD19-ζ CAR expressing CD8$^+$ T cells with endogenous LAT knockdown (D). The average +/- S.D. of triplicate samples was plotted. The statistical significance of differences is indicated by asterisks: *, P<0.01 (Student's t-test); **, P<0.05 (Cochran-Cox). (B) CD107a mobilization assay against 624.38 (NY-ESO-1$^+$ and HLA-A2$^+$) or 526 (NY-ESO-1$^-$ and HLA-A2$^+$) melanoma target cells was performed with anti-NY-ESO-1 TCR expressing LAT-substituted T cells. CD8$^+$ gated cells are shown.

Development of a novel postoperative adjuvant immunotherapy for lung cancer

Fellow

Kaoru Nagato

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Graduate School of Medicine, Chiba University

The aim of our study is to develop a novel postoperative adjuvant immunotherapy targeting invariant natural killer T (NKT) cells in patients with non-small cell lung cancer. NKT cells possess potent anti-tumor effects after activation with a specific glycolipid antigen, α-Galactosylceramide (α-GalCer). A previous phase I/II study of αGalCer-pulsed dendritic cells (DCs) revealed that intravenous injection of αGalCer-pulsed DCs increased the number of IFN-γ producing cells in the peripheral blood, which appeared to be associated with prolonged survival. We performed an exploratory study with the preoperative administration of αGalCer-pulsed DCs to clarify the NKT cell-specific immune responses at the tumor site more precisely. Patients with operable advanced lung cancer received an intravenous injection of αGalCer-pulsed DCs before surgery. The resected lung- and tumor-infiltrating lymphocytes (TILs) were collected, and the invariant NKT cell-specific immune responses were analyzed. There was a significant increase in the number of NKT cells in the TIL population in pre-treated patients in comparison to the non-injected control group (Figure 1) and there was an augmented IFN-γ production in the αGalCer-stimulated TILs. In conclusion, the administration of αGalCer-pulsed DCs successfully induced the dramatic infiltration and activation of NKT cells in the tumor microenvironment (Nagato et al, *J Clin Immunol*. 2012). During my term as a G-COE fellow, I tried to inspire the G-COE students through discussions at the G-COE RA workshop and other G-COE program events.

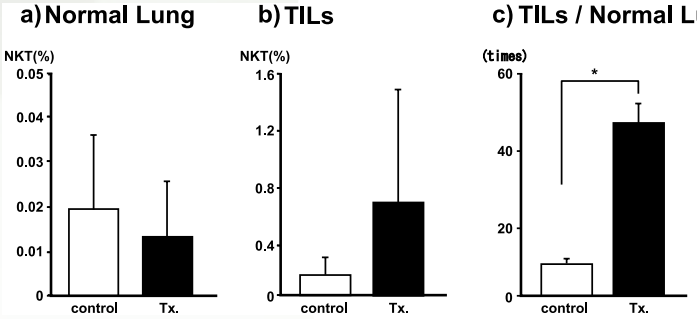

Figure 1. The comparison between the NKT cells in normal lung MNCs (a) and TILs (b) in the αGalCer-pulsed DC treatment group and the control group. Control, control group; Tx, αGalCer-pulsed DC administration group; * p=0.0008

Epigenetic regulation of pharmacokinetics-associated gene expression by DNA methylation

Research Assistant

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Graduated School of Pharmaceutical Science
Chiba University

Drug metabolizing enzymes and drug transporters play important roles in drug disposition. Pharmacokinetics-associated (PK) gene expression is regulated by various transcription factors such as nuclear receptors. Recently, epigenetic regulation including DNA methylation has been attracting a lot of attention as a novel gene regulation mechanism and has been reported to regulate the gene expression levels. However, the epigenetic regulatory mechanism of the expression of various PK genes is unclear. I investigated the effect of DNA methylation on the regulation of PK gene expression to elucidate the mechanism of epigenetic regulation of PK gene expression. In addition, I was appointed as a Global COE-RA because our study could contribute to the Global COE entitled “Immune System Regulation and Treatment”.

I analyzed the effect of 5-aza-2’-deoxycytidine (AZA), a DNA methylating enzyme inhibitor, on mRNA expression levels of the PK genes in human cell lines derived from human liver, intestine and kidney to identify the PK genes that are regulated by DNA methylation. The expression levels of more than half of the PK genes I analyzed were up-regulated by AZA. Moreover, the patterns of the genes up-regulated by AZA were dependent on the cells. These results suggested that DNA methylation significantly contributes to the –regulation the expression of PK genes, and regulation mechanism was dependent on the cell types.

The presentations and discussions at the Global COE-RA workshop were conducted in English. I had the rare opportunity present my research in English. The presentations were recorded and distributed to the participants, allowed me to review my presentation. In particular, the comments from two advisers provided me with good opportunity to improve my presentation and English skill.

Molecular mechanisms of cell-cell communication in pancreatic islets -A clue essential for renovating islets in autoimmune diabetes

Research Assistant

Jiro Terada

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Type 1 diabetes mellitus is an autoimmune disease caused by insulin secretory failure due to the destruction of most pancreatic β-cells. Islet cell transplantation has drawn significant interest in regenerative medicine, as it is the only radical treatment of the intractable disease. However, the mechanism of effective and continuous insulin secretion in the islets remains mostly unknown. Pancreatic islets are composed of thousands of pancreatic β-cells, and the cell-cell contacts play a crucial role in efficient insulin secretion. Therefore an investigation of the three-dimensional structure in differentiated pancreatic β-cells is extremely important for the development of the regenerative medicine for this disease.

The purpose of our study was to assess the molecular mechanism of cell-cell communication in pancreatic islets by using the pseudo-islets from insulin-secreting MIN6 cells. Based on this research project I was assigned to be a Global COE-RA, and I started the studies described below.

1. A novel method to form highly advanced pseudo-islets from MIN6 cells was established.

2. A new experimental system using transfection of two different genes in MIN6 cells cultured separately was designed to analyze cell-cell communication with intracellular calcium signal in pancreatic β-cells. Briefly, the MIN6 cells were stimulated with metabolic glutamate receptor-5 agonist and growth hormone secretion was monitored as a tracer from the other co-cultured MIN6 cells.

These experiments required techniques that were new to me because my previous specialty was clinical respirology. However, this opportunity to be a COE-RA enabled me to work on this study and participate in the various COE programs. Now I am engaged in basic respiratory research at the University of Wisconsin-Madison in the United States. The experience at Chiba University broadened my current study. I am deeply grateful to all people involved in this program, especially Professor Toshinori Nakayama.

The mechanism of tissue-specific imprinting in human *GNAS* gene

Research Assistant

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Chiba University

GNAS is a complex imprinted gene that uses multiple promoters to generate several gene products. Inactivating Gsα mutations leads to pseudo-hypoparathyroidism (PHP). Gsα is imprinted in a tissue-specific manner, being primarily expressed from the maternal allele in the renal tubules, thyroid, pituitary, and ovary. Patients with PHP1B show loss of CpG methylation in exon 1A of the maternal allele. This region is thought to be essential for the mechanism of tissue-specific imprinting. The mechanism of paternal allele specific suppression of *GNAS* expression is unknown; however, it is hypothesized that the interaction between the tissue-specific silencing factor and this differentially methylated region may play a key role. The factor is not identified and the regulation system is still unclear. I was appointed as a Global COE-RA and started research into tissue-specific imprinting.

We are going to elucidate the mechanism of tissue-specific imprinting in *GNAS* by using the megakaryotic cell line, CMS which has imprinted expression of *GNAS* exon 1A and exon 1. We performed a chromatin immunoprecipitation assay to clarify the allele-specific gene silencing through histone modification.

The histone modification pattern in the Gsα promoter and exon 1 differed between the imprinted and non-imprinted cell lines. Histone acetylation and methylation at Lysine4 were predominant in the CMS cell line. They are related to active transcription. Histone methylation at Lysine9 was predominant in the non-imprinted LCL63 cell line. They are related to inactive transcription. Next we performed DNaseI footprinting to find the specific binding site for the unknown silencing protein which is specifically expressed in the imprinted cell line, but we could not find a difference between the two cell lines.

I had chance to conduct a presentation and discussion in English, and received advice from doctors in other laboratories. That was a great experience for me. I would like to apologize for not attending the meeting due to my father's illness.

Identification of a novel angiogenic regulator involved in vasculitis and/or atherosclerosis

Research Assistant

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Graduate School of Medicine,
Chiba University

Semaphorin3E (sema3E) and its specific receptor plexinD1 regulate the patterning of vessels during embryogenesis. However, it is unclear whether these molecules are involved in postnatal angiogenesis. We performed an *in vitro* assay using human umbilical vein endothelial cells (HUVECs) to elucidate the role of sema3E/plexinD1. Treatment with vascular endothelial growth factor (VEGF) increased the proliferation and tube formation and this increase was significantly inhibited by sema3E. Moreover, treatment with the plexinD1-Fc fusion protein antagonized this anti-angiogenic activity of sema3E. Western blot analyses revealed that sema3E suppressed VEGF-induced phosphorylation of VEGFR2, suggesting that sema3E negatively regulates angiogenesis by inhibiting the VEGF signaling pathway. The expression of sema3E and plexinD1 was markedly upregulated in ischemic limbs. Immunohistochemistry showed that sema3E was expressed by the arterioles, myocytes, and capillary endothelial cells in ischemic tissue. Introduction of the plexinD1-Fc gene into ischemic limbs led to a significant improvement of blood flow recovery and an increase in the number of CD31-positive cells. Other members of the sema3 family are transcriptionally regulated by p53, a tumor suppressor protein that inhibits neovascularization in tumors. Consistent with these reports, the forced expression of p53 upregulated sema3E expression in HUVECs. We also found that the expression of p53 was markedly increased in ischemic limbs and that this increase was further enhanced in ischemic tissues of diabetic mice. Consequently, the expression of sema3E was significantly higher in the ischemic limbs of diabetic mice than in control mice, and the blood flow recovery after ischemia was strongly impaired in these mice even though treated with VEGF. In contrast, treatment with both VEGF and PlexinD1-Fc markedly improved blood flow recovery in diabetic mice. These results indicate that sema3E/plexinD1 negatively regulates postnatal angiogenesis under the regulation of p53 and suggest that inhibition of sema3E would be a novel strategy for therapeutic angiogenesis, especially when VEGF treatment is ineffective.

Role of regulatory T cells in the atheroprotective effects of granulocyte colony-stimulating factor

Research Assistant

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Chiba University

We and others have recently reported that granulocyte colony-stimulating factor (G-CSF) prevents left ventricular remodeling and dysfunction after myocardial ischemia in animal models and humans. We have also reported that G-CSF prevents the progression of atherosclerosis in rabbit, but the precise mechanism is still elusive. This study supports the concept that modulation of regulatory t cell (Treg) subset might be useful strategy for patients with atherosclerotic disease. I was appointed as a Global COE-RA and initiated research of the role of Tregs in atherosclerosis.

We examined the effects of G-CSF on atherosclerosis in apolipoprotein E-deficient ($ApoE^{-/-}$) mice. Twelve-week-old male $ApoE^{-/-}$ mice were treated with G-CSF at a dose of 200 $\mu g \cdot kg^{-1} \cdot d^{-1}$ or the same volume of saline subcutaneously 5 days per week for 4 weeks. Atherosclerotic lesions in the aortic sinus were significantly reduced in G-CSF-treated mice (31% reduction, $p<0.05$). G-CSF reduced the level of interferon-gamma by 31% and increased the level of interleukin-10 by 20% in atherosclerotic lesions of aortic sinus. G-CSF triggered marked recruitment of $CD4^+CD25^+$ regulatory T cells in spleen and inguinal lymph nodes. G-CSF markedly increased the number of Foxp3-positive regulatory T cells in atherosclerotic lesions of the aortic sinus. The administration of anti-CD25 antibody (PC61) that depletes regulatory T cells abrogated these atheroprotective effects of G-CSF. These findings suggest that regulatory T cells mediate the atheroprotective effects of G-CSF.

I obtained a great deal of information from several immunology specialists at the Global COE-RA workshop. Afterwards, I received particularly useful instruction from my advisers. These interactions have stimulated numerous ideas for further research.

Migration after administration of αGalCer-pulsed Antigen presenting cells into submucosa of patients with head and neck cancer

Research Assistant

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Antigen-presenting cells (APCs) play a crucial role in the induction of immune responses. However, the optimal administration route of tumor-specific APCs to induce effective immunological responses in cancer immunotherapy remains to be elucidated. Human NKT cells have strong antitumor activities and are activated by a specific ligand, namely, α-galactosylceramide (αGalCer).

Patients with head and neck squamous cell carcinoma (HNSCC) received an injection of αGalCer-pulsed and ^{111}In labeled APCs into the nasal, the oral floor submucosa and then the total body image and single photon emission computed tomography (SPECT) images were examined. The immunological responses, such as the number of peripheral blood NKT cells, anti-tumor activities, and the $CD4^+$ $CD25^{high}$ $Foxp3^+$ T cells (Treg) induced following administration of these APCs were also compared.

The APCs injected into the nasal submucosa quickly migrated to the lateral lymph nodes and those injected into the oral floor submucosa dominantly migrated to submandibular nodes than to the lateral lymph nodes. An increase in the absolute number of NKT cells and the IFN-γ producing cells was observed in the peripheral blood after injection of the APCs into the nasal submucosa, however, these antitumor activities were not detected and the increased frequency of Treg cells were observed after administration into the oral floor.

These results indicate that a different administration route of APCs has the potential to bring a different immunological reaction. Submucosal administration of αGalCer into oral submucosa tend to induce immunological suppression.

The presentation and discussions at the Global COE-RA workshop were held in English. Presentations were recorded and distributed to participants later. It was a valuable experience to be able review my presentation.

Novel immune gene therapy for malignant tumors

Research Assistant

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Activation of DCs is a vital step to link tumor destruction and induction of immunity. We found that immature DCs expressed Fas, which plays a major role in an apoptotic process. Ligation of Fas molecules of DCs with FasL expressed on tumors increased cell-to-cell interactions, which subsequently activated T cell-mediated immunity. We also found forced expression of CD40L in tumors enhanced the interaction between DCs and the tumors, induced secretion of cytokines and consequently produced T-cell-dependent systemic immunity. Therefore specific transfer FasL or CD40L into tumor cells is a possible way to induce the systemic immune response.

In this study, type 5 adenoviral (Ad) vectors were used as a vehicle to transfer *FasL* and *CD40L* genes into tumor cells. To make the Ad specific transfer immune genes into tumors, we have been investigated on transcriptional regulatory regions of the genes that are preferentially expressed in tumors. In particular we focused on *midkine*, *survivin* and *cyclooxygenase-2* genes. We found the regulatory regions of these genes transcribed a linked reporter gene better than the SV40 promoter in several source tumors. The transcriptional regulatory regions of the tumor specific genes were then filled into Ad E1 region which is up-stream of the *FasL* or *CD40L* genes. Therefore, the transcriptional regulatory regions can alter tumors susceptible to the recombinant adenoviruses and the adenoviruses force the tumors express FasL or CD40L which induce the anti-tumor effects through the induction of systemic immunity.

Since it is beneficial to have a biomarker to predict the efficacy prior to the treatment in clinical settings, we also examined the correlation between the Ad infectivity and the coxsackie virus adenovirus receptor (CAR) expression levels or between Ad infectivity and the p53 status of target cells. Nine human esophageal carcinoma cell lines were chosen as target cells. The results showed that the Ad infectivity was linked with CAR expression level but not the p53 status. The anti-tumor effects of the novel recombinant Ad containing immune genes will be tested *in vitro* and *in vivo*.

Role of BTLA on NKT cells

Research Assistant

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NKT cells rapidly produce both Th1 and Th2 cytokines upon activation and play a crucial role in various immune responses, including anti-tumor immunity, infection, transplantation, allergic reaction, and autoimmune diseases. For the control of these responses, elucidation of mechanisms underlying NKT cell activation is expected. Fortunately, I got an opportunity to join the Global COE program as a RA and studied the role of recently-identified inhibitory co-receptor BTLA (B and T Lymphocyte Attenuator) in the regulation of NKT cell function.

In this project, I found that BTLA was expressed on NKT cells at the levels similar to those on T cells and that BTLA-deficient NKT cells produced larger amounts of cytokine upon α-GalCer stimulation as compared with wild-type (WT) NKT cells. I also found that BTLA-deficient mice were more susceptible to Concanavalin A (ConA) - induced hepatitis than WT mice. The augmentation of ConA-induced hepatitis in BTLA-deficient mice was cancelled in BTLA/NKT-double deficient mice. Moreover, NKT-deficient mice reconstituted with BTLA-deficient NKT cells were significantly more susceptible to ConA-induced hepatitis as compared with NKT-deficient mice reconstituted with WT NKT cells. These results suggest that BTLA functions as the inhibitory co-receptor of NKT cells and plays a critical role in the prevention of NKT cell-mediated liver injury.

At the Global COE-RA workshop, I made a first-time presentation and discussion in English. Instructive advice offered by the guest professors (specialists in NKT cells) and senior researchers improved the quality of my project. I thank the Global COE program for the valuable experience and all the advice and support.

Trafficking of Lyn tyrosine kinase to the Golgi and the nucleus

Research Assistant

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In immune system, receptor-mediated signaling is critical for regulation of cellular function. Src-family tyrosine kinases (SFKs) have been implicated as critical regulators of a large number of intracellular signaling pathways such as cell growth and differentiation. It is suggested that dysfunction of SFKs result in immune disorders including allergy and cancer. SFKs, classified as cytosolic enzymes, are localized at the cytoplasmic surface of the plasma membrane, but an appreciable fraction is found at intracellular compartments, implying that a correlation of SFKs localization with their various functions.

Lyn, one of the abundant in immune cells, is found not only at the plasma membrane but also at the Golgi and the nucleus. Recently, we showed that newly synthesized Lyn transported through the Golgi to the plasma membrane along the secretory pathway, depending on its kinase domain. From the examination of subcellular localization of Lyn mutants, it is suggested that the N-terminal lipid modification and the kinase domain of Lyn also play a role in the Golgi targeting of newly synthesized Lyn. Nuclear Lyn levels are increased upon treatment with inhibitor of SFKs, suggesting that kinase activity of Lyn is involved in regulation of localization of Lyn to the nucleus. Our results suggest that Lyn trafficking to the Golgi and the nucleus is strictly regulated, implying that the distinct localization of Lyn is important for its function.

It was really a good experience for me to participate in the Global COE program. Through attending symposiums and seminars, I managed to access wide variety of recent findings from basic research to clinical one, and the occasion encouraged me toward further progress in our research. I also had a chance to make presentation at the Global COE-RA workshop. It was a fruitful time to deepen our discussions.

Development and characterization of IL-21-producing CD4$^+$ T cells

Research Assistant

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The pathogenesis of autoimmune diseases is still unknown. It is imperative to elucidate the mechanism of autoimmune diseases to establish an effective therapy. Recently, many groups including ours have shown that IL-21 plays critical roles in the development of autoimmune diseases. I have been appointed as a G-COE-RA and have started research on IL-21-producing CD4$^+$ T cells.

Recent studies have shown that IL-21 is produced by Th17 cells and functions as an autocrine growth factor for Th17 cells. We investigated the differentiation and characteristics of IL-21-producing CD4$^+$ T cells by intracellular staining. We have shown that IL-21-producing CD4$^+$ T cells exhibit characteristics distinct from Th17 cells and develop preferentially in an IL-6-rich environment devoid of TGF-b, and that IL-21 functions as an autocrine growth factor for IL-21-producing CD4$^+$ T cells (Kashiwakuma, Suto, et al. *J. Exp. Med.* 2008).

Follicular helper T (Tfh) cells are a subset of effector T cells that produce IL-21 and stimulate immunoglobulin production in B cells. BTLA, an inhibitory co-receptor, is expressed on Tfh cells. We examined the regulatory role of BTLA in the development and function of Tfh cells using BTLA$^{-/-}$ Tfh cells. We have shown that BTLA signaling suppresses IL-21 production from Tfh cells and subsequent Tfh cell-mediated IgG responses (Kashiwakuma, Suto, et al. submitted).

In addition to research environment, the Global COE program provides us a tremendous educational environment. I had a chance to present my recent research at a Global COE-RA workshop, and Global COE stuff scientists provided instructive comments on our work and my presentation. A number of eminent investigators presented special lectures at the Global COE symposium and retreat, and provided ideas for the future directions of my research. I also had a chance to discuss my research with prominent foreign investigators. It was a good opportunity for my faculty development.

The study of tumor suppressive microRNA in head and neck squamous cell carcinoma

Research Assistant

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The survival rate of patients with head and neck squamous cell carcinoma (HNSCC) has shown little improvement, despite recent advances in surgery, radiotherapy and chemotherapy. Further understanding of the new molecular oncogenic pathways in HNSCC is urgently needed. Under these circumstances, I was appointed as a Global COE-RA and started research on the use of microRNA in HNSCC.

MicroRNAs (miRNAs) are endogenous short non-coding RNA molecules, which negatively regulate protein-coding genes expression. miRNAs are aberrantly expressed in cancer cells and down-regulated miRNAs might be lead to activation of oncogenes. The aim of this study was to identify the tumor suppressive miRNAs based on miRNA expression signatures in HNSCC and to predict biological target genes.

We successfully identified differentially expressed miRNAs from HNSCC miRNA expression signatures using surgical specimens with HNSCC. A gain-of-function analysis of down-regulated miRNAs revealed that miR-489 inhibited cell growth in all cancer cell lines tested. We identified PTPN11 as a target gene of miR-489 by using genome-wide gene expression analysis. Tumor suppressive miRNAs and target oncogenes may provide new insights in the understanding of the potential mechanisms in HNSCC. Our findings have therapeutic implications and may be exploited for future treatment of HNSCC.

Presentations and discussions were held in English at the Global COE-RA workshop. The English presentation provided training for the international congress of oncology next year. In addition, the valuable comments from advisers were very useful for preparing my research article. My participation in this program was very valuable experience.

Development of a novel cancer vaccine using heat shock protein

Research Assistant

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The prognosis of esophageal and head and neck cancer with lymph node or distant metastasis remains poor, despite recent improvements in local treatment such as surgery or chemoradiotherapy. There are currently few treatment options. Cancer immunotherapy is anticipated to provide systemic treatment contribute to the current treatment methods by activating an anti-tumor immune response. On the other hand, there could be a remote effect (abscopal effect) against non-irradiation tissue following radiation therapy, and the possibility of a systemic immunoreaction. Synergy was induced for a remote tumor when we administered a local injection of dendritic cells (DC) and the radiation exposure to the double cancer mouse models. The injection of the dendritic cells together with irradiation activated the CTL in lymph nodes around the tumor (tumor draining lymph nodes; TDLNs). In addition, this process involved increased expression of heat shock protein (HSP) in response to the radiation exposure. Furthermore, we confirmed that HSP has an anticancer activity in an independent localized injection. A recent report revealed a cancer vaccine using HSP derived from the cancer cells, and we are expanding our research to further investigate this activity. The isolation of this HSP derived from the cancer cells could provide a novel cancer treatment.

The G-COE provides me the opportunity to attend international immunology presentations, discuss the contents, and present my research by English twice a year. Such opportunities are normally difficult in Japan.

The role of matrix metalloproteases in the pathophysiology of bronchial asthma and Kawasaki disease (MCLS)

Research Assistant

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Matrix metalloproteinases (MMPs) are a class of extracellular and membrane-bound proteases involved in a wide array of physiological and pathological processes such as cytokine activation, organogenesis, cancer invasion/metastasis, inflammation, and atherosclerosis, which are the targets of "immune system regulation and treatment" in the Global COE. An ongoing project in our laboratory investigates the involvement of MMPs in allergic diseases. Epidemiological studies of genetic polymorphisms in MMP genes have demonstrated significant associations between bronchial asthma and several MMP genes. I was accepted as a Global COE because the focus of this study matched the aim of the Global COE. I am trying to verify the role of MMP-3, which shows a significant association with adult asthma, in the pathophysiology of inflammation in asthma both *in vitro* using human primary culture and *in vivo* using mouse models.

Primary cultured cells of airway tissue, including epithelial cells, smooth muscle cells, and fibroblasts were stimulated with various types of cytokines and pathogen-associated molecular patterns (PAMPs), and the reactive changes in MMP-3 mRNA expression level and cytokine production were investigated. Stimulation of smooth muscle cells and fibroblasts with IL-1 beta induced marked elevations in MMP-3 mRNA expression and cytokine levels in culture media, whereas no significant changes were observed in epithelial cells, suggesting the possible involvement of MMP-3 in airway tissues other than the epithelia.

The symposiums and workshops associated this Global COE were unexceptionally inspiring in content, and remarkably helpful in training young researchers. Presentation in English was a good experience and I received valuable comments. In particular, the video recording of the presentation will help to improve my presentation technique.

Development of enhanced chemotherapy by overcoming anti-cancer resistant mechanisms

Research Assistant

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Cisplatin (CDDP) is a commonly used chemotherapeutic agent in the treatment of various malignant tumors, including oral squamous cell carcinoma (OSCC); however, resistance to CDDP is a major obstacle to effective cancer therapy. Therefore, the aim of this study is to identify genes associated with CDDP resistant mechanisms to overcome CDDP resistance. I started my research as Global COE-RA to conduct that study.

We performed microarray analysis and pathway analysis using parental OSCC cell lines (CDDP-sensitive) and CDDP-resistant cell lines established from parental cell lines to identify genes associated with CDDP resistant mechanism. The expression status of selected genes was validated using quantitative RT-PCR, Western blot analysis, and immunohistochemical staining in OSCC cells and clinical samples. Furthermore, we confirmed whether CDDP sensitivity would be enhanced by down-regulation of the candidate genes using small interfering RNA (siRNA) or inhibitors.

We identified 199 genes differentially expressed in the CDDP-resistant cell lines by microarray analysis, and 51 candidate genes were selected using pathway analysis. Increased mRNA and protein expression of five genes; *Lumican, NRG1, PKD2, PDGF-C, and PDE3B,* were observed in all CDDP-resistant cell lines in comparison to the parental cell lines. The protein expression levels of five molecules were up-regulated in primary OSCC in a patient with an unresponsive cases tumor. Down-regulation of the expression of five genes by siRNA enhanced the CDDP-sensitivity of OSCC cells. These results suggested that these five novel genes have great potential for predicting the efficacy of CDDP-based chemotherapy against OSCC. Moreover, we focused on PDE3B, first. Combination therapy with a PDE3B inhibitor and CDDP had a synergic or additive inhibitory effect on tumor cell activity.

The Global COE program presents various symposiums by foreign CVPP. I tried to present my research and discussions in English at the Global COE-RA workshop, That was not easy, but it was a very valuable experience. Two professors made very important suggestions, which were helpful for my research.

A role for plant homeodomain finger protein 11 (*PHF11*) in IgE production by activated B cells

Research Assistant

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Polymorphisms of the *PHF11* gene are highly associated with high serum IgE levels and the clinical severity of asthma. We investigated the role of Phf11 in IgE production by activated B cells. We generated transgenic (Tg) mice carrying the murine *phf11* gene under the control of a distal lck promoter. When splenic naïve B cells were stimulated with anti-IgM Abs and anti-CD40 Abs with IL-4 *in vitro*, the percentage of IgE^+ B cells and the IgE titer in the culture of Tg B cells were significantly higher than those of wild type (Wt) B cells. In contrast, knockdown of the endogenous *phf11* by siRNA reduced the frequency of class-switch to IgE by activated Wt B cells. The germline transcript (GLT) ε mRNA expression in activated Tg B cells was significantly higher than that in activated Wt B cells. The levels of Phf11 and H3K4me3 protein bound to the GLT ε promoter region in the Tg B cells were higher than those in the Wt B cells. In an OVA-induced allergic model, the serum IgE anti-OVA Ab titer in Tg mice was significantly higher than that in Wt mice. Long-lived plasma cells producing high affinity IgE anti-NP Abs were clearly detected in the spleens of Tg mice immunized with NP-CG in alum. Based on these results, it can be concluded that the Phf11 in activated B cells augments the frequency of class-switch to IgE and generation of high affinity IgE-secreting long-lived plasma cells.

I deeply appreciate having had ample opportunities to present my research in English, with my supervisor's advice, at the G-COE RA workshops. In addition, many events associated with the G-COE program provided me opportunities to discuss my work and future career with many other young investigators. The experience will help me a lot during my stay in the USA as a research fellow. I will continue to engage in medical research and would like to contribute to progress in medicine.

Lethal myelofibrosis induced by *Bmi1*-deficient hematopoietic cells unveils a tumor suppressor function of the polycomb group genes

Research Assistant

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Research in the field of epigenetic regulation of hematopoietic stem and progenitor cells has made dramatic progress. As a Global COE-RA, I studied the role of Bmi1 in the proliferation and differentiation of megakaryocytes

Polycomb-group (PcG) proteins form the multiprotein polycomb repressive complexes (PRC) 1 and 2, and function as transcriptional repressors by inducing histone modifications. They maintain the proliferative capacity of hematopoietic stem and progenitor cells by repressing the transcription of tumor suppressor genes, namely *Ink4a* and *Arf*, and thus have been characterized as oncogenes. However, the identification of inactivating mutations of a PcG gene, *EZH2*, unveiled a tumor suppressor function for this molecule in myeloid malignancies, including primary myelofibrosis (PMF). We showed that loss of another PcG gene, *Bmi1*, causes pathological hematopoiesis similar to PMF. In a mouse model, loss of *Bmi1* in *Ink4a-Arf*$^{-/-}$ hematopoietic cells induced abnormal megakaryocytopoiesis accompanied by marked extramedullary hematopoiesis, which eventually resulted in lethal myelofibrosis. The absence of Bmi1 caused de-repression of a cohort of genes, including *Hmga2*, an oncogene overexpressed in PMF. Chromatin immunoprecipitation assays revealed that Bmi1 directly represses the transcription of *Hmga2*. Of note, the overexpression of *Hmga2* in hematopoietic stem cells induced a myeloproliferative state with enhanced megakaryocytopoiesis in mice. Our findings provide the first genetic evidence of a tumor suppressor function of Bmi1, and uncover the role of PcG proteins in restricting growth by silencing oncogenes.

My appointment as a Global COE-RA has provided me with many opportunities to present and discuss my data. In particular, all the presentations and discussions at the Global COE meeting were in English, which provided a very good opportunity for me to improve my English. I was also able to exchange ideas with other students about my research and obtain many opinions and suggestions from the senior staff. It was a really valuable experience for me. With the support of Global COE, I received a 2011 American Society of Hematology (ASH) Outstanding Abstract Achievement Award and a 2011 Award of the Japan Hematology Society. I also published two articles during my time as a Global COE-RA.

Epigenetic regulation of the tissue-specific transcription of the human *GNAS* gene

Research Assistant

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Recently, many studies have shown that epigenetic transcriptional regulation plays important roles in gene expression. Some data suggest that some epigenetic changes are regulated in a tissue-specific manner. Uncovering the mechanisms underlying this regulation is important in many research areas. We have been investigating them through our research on pseudo hypoparathyroidism type 1b (PHP1b) which is one of the representative diseases considered to be epigenetically regulated. Our research aim met the requirements of the COE, so that I had an opportunity to work on my research as a COE-RA.

We made several constructs including the promoter region of the *GNAS* gene, which is the gene that causes PHP1b, to reveal the region and binding proteins which regulate its tissue-specific epigenetic regulation. A Luciferase assay was performed in both the imprinted cells and the non-imprinted cells, and the results were compared.

All constructs showed lower transcriptional activity than the positive control. There were no differences between the imprinted and the non-imprinted cells. These results suggested that the enhancer(s) and insulator(s) may regulate the transcription of this gene, rather than the repressor binding the unmethylated region, as has generally been expected.

The Global COE workshops in which we presented and discussed our research in English were good opportunities for me to improve my presentations. These experiences were also useful for preparing to make presentations at international meetings. Joining the retreats where I could discuss my work with other RAs expanded my horizons and made it easier to collaborate with other labs. The experiences as a Global COE-RA were very helpful for my research.

The impact of Hepatitis B virus e antigen on the immune signaling pathway in hepatitis B

Research Assistant

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Although the HBeAg is thought to be involved in immune tolerance, the precise function of HBeAg is still unknown. We assumed that the HBeAg blocks aberrant immune responses, and the roles of the HBeAg in cytokine production and the interaction between HBeAg and the immune system were examined in human hepatocytes. We found that the HBeAg might modify the disease progression by inhibiting inflammatory cytokines and IFN gene expression via the suppression of NF-κB signaling and IFNβ promoter activation [Wu S et al. *Viral Immunol*. 2010 Oct; 23(5): 467-76; Wu S et al. *Cancer Lett*. 2011 Dec 15; 312(1): 33-42]. Consequently, we further examined the molecular mechanism underlying the cytokine production regulated by HBeAg. We identified novel molecular mechanisms, whereby HBeAg modulates the NF-κB signaling pathways through RIPK2, supporting the concept that HBeAg could impair both the innate and adaptive immune responses to promote chronic HBV infection [Wu S et al. *J Infect Dis*. 2012 Aug; 206(3): 415-20].

I greatly appreciate being able to participate in the G-COE project. The G-COE events were always in English, which give us a lot of opportunities to practice our skills in English presentation. I think I benefited significantly from this, because it will help me make future presentations in English at international academic meetings.

Two external mentors gave me valuable comments at the G-COE RA workshop. My mentors' comments inspired me to explore the molecular mechanism underlying the effects of the HBeAg.

To train the RAs, the COE project held a variety of events such as seminars, workshops, symposiums and lectures given by famous researchers and experts. I thought that my two years as a RA were the most instructive two years during my time as a graduate student. It is a very valuable experience for students to be able to participate in a G-COE project.

Mechanisms underlying the trafficking of Src-family kinases from the Golgi apparatus to the plasma membrane

Research Assistant

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Src-family tyrosine kinases (SFKs) play important roles in signal transduction at the cytoplasmic face of the plasma membrane upon extracellular ligand stimulation. In immune cells, SFKs play crucial roles in regulating cell proliferation, differentiation and migration, and disruption of SFK regulation leads to the development of cancer and aberrant immune responses. We recently showed that SFKs are localized at the cytoplasmic face of the plasma membrane; however, an appreciable fraction of SFKs are also found in intracellular compartments such as endosomes and the Golgi apparatus. Although the localization of SFKs is critical for their function, the mechanisms underlying the intracellular trafficking of SFKs remain elusive. Elucidating the mechanisms involved in SFK trafficking is important for understanding the regulation of immune cell functions.

Recently, we showed that Lyn, a member of the SFK family, is transported to the plasma membrane through the Golgi apparatus in a manner dependent on its kinase domain. We investigated the actions of a Lyn kinase domain-binding protein to elucidate the mechanisms underlying Lyn trafficking from the Golgi apparatus. We identified acyl-CoA synthetase 3 (ACSL3) to be a Lyn kinase domain-binding protein using GST-pulldown and MALDI/TOF/MS. Golgi exportation of Lyn was blocked by knockdown of ACSL3. We demonstrated the significance of the Lyn kinase domain for Golgi exportation of Lyn via an association with ACSL3. Given that Lyn plays a critical role in signal transduction primarily at the cytoplasmic face of the plasma membrane upon extracellular ligand stimulation, ACSL3 is indispensable for Lyn signaling at the plasma membrane.

I was able to learn cutting-edge research in immunology at the Global COE symposiums and seminars. I received a large amount of advice at the Global COE research assistant workshop and retreat program, which greatly helped to advance my research.

The role of TGF-β/Smad3 signaling in the pathogenesis of obese fat tissue

Research Assistant

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Obesity is serious problem because it causes many kind of life-style related illness. In recent years, obesity has been shown to be closely associated with inflammation, because hypertrophic visceral adipose tissue secretes a variety of inflammatory cytokines that lead to insulin resistance. TGF-β has a wide range biological effect, and we have previously reported the role of TGF-β on atherosclerosis and diabetic nephropathy, using mice lacking Smad3, a major mediator of TGF-β signaling. However, the role of TGF-β/Smad3 signaling in the pathogenesis of obese fat tissue is not fully understood. Therefore, as a Global COE-RA, I started research on obesity.

Analyzing visceral fat of obese *ob/ob* mice revealed that TGF-β/Smad3 signaling was increased in obese fat tissue. Moreover, we proved that TGF-β inhibits adipocytogenesis dependent on Smad3 by inducing wild type (WT) and Smad3 KO mouse embryo fibroblasts to differentiate into adipocytes. Finally, obesity was induced in WT and Smad3 KO mice with a high fat diet, and we discovered that Smad3 KO mice were more insulin-sensitive than WT mice *in vivo*. These data suggest that TGF-β is highly expressed in obese fat tissue, and it inhibits adipocytogenesis via Smad3 and contributes to development of insulin-resistance.

Global COE-RA workshops provides a great opportunity to conduct presentations and discussions in English. In addition, I could review my presentation objectively by watching recorded DVD, so it was very useful. G-COE retreats provide the opportunity to develop relationships with other G-COE RAs, and obtain motivation for research.

Vascular inflammation and endothelial insulin signaling in atherosclerosis

Research Assistant

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Atherosclerotic diseases such as coronary heart diseases and cerebrovascular diseases, together with cancer, comprise three major disease categories with a high mortality rate, and vascular inflammation plays a crucial role in atherosclerotic lesion formation. Vascular inflammation also plays an important role in the pathogenesis of diabetes and obesity. Moreover, endothelial damage associated with inflammatory changes in the vascular wall is observed in animal models of diabetes and insulin resistance, and it is suggested that immune responses contribute to the development of such inflammatory reactions in the vasculature. We therefore hypothesized that insulin signaling in endothelial cells plays a role in the development of vascular inflammation and atherosclerosis and tested this hypothesis in mouse models of diabetes.

We found that an increase in serum insulin concentration induces activation of PI3K/Akt pathway in endothelial cells and induces apoptosis or senescence of endothelial cells in mouse models of diabetes and insulin resistance. We also found that the expression of inflammatory cytokines is also induced in these animals. These observations suggest that endothelial cell damage and vascular inflammation contribute to the progression of atherosclerosis in the diabetic state. Currently we are trying to generate endothelial cell-specific insulin receptor knockout mice, and will examine the effect of the loss of insulin signaling in endothelial cells on the formation of atherosclerotic lesions in ApoE knockout mice.

It was a great honor for me to be selected as a RA in this Global COE program. In particular, conducting a presentation and discussion in English as well as obtaining comments and advice from people outside the laboratory were extremely valuable for me.

The role of matrix metalloproteinase 8 in allergic inflammation

Research Assistant

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Allergic disease such as asthma is caused by interplay of many genes and environment factors. The primary interest of our department is genetic variations that affect the susceptibility to allergic diseases.

We are studying matrix metalloproteinases (MMPs) because they are associated with inflammation and allergic diseases. I was appointed as a Global COE-RA, and I am now studying the human *MMP-8* gene.

MMPs are proteinases involved the degradation of the extracellular matrix, and inflammation. Twenty-four MMPs have been identified in humans. MMP-8 contributes to the solubilization of IL-13 $R\alpha_2$ *in vivo* and attenuates allergic inflammation elicited by IL-13.

We analyzed the correlation between 8 SNPs in the *MMP8* gene and the development of asthma, and found that two non-synonymous amino acid changes were significantly associated with childhood asthma. Currently, I am investigating the differences in substrate specificity and protease activity of two different types of MMP-8.

Research presentations in English at Global COE-RA are a valuable experience for me, because I have little experience discussing my research in English. Instruction by 2 Global COE advisers was very helpful to advance my study. I participated in a Global COE seminar, and I also learned the details of recent studies about immunology and allergy. It was very useful.

Characterization of the mechanisms of intestinal barrier dysfunction in methotrexate-treated rats

Research Assistant

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Methotrexate (MTX) is widely used in clinical practice for the treatment of autoimmune disease and cancer chemotherapy. However, its adverse effects, such as intestinal mucosal injury, are major factors limiting its use. We aimed to clarify the mechanisms underlying MTX-induced intestinal barrier dysfunction, specifically focusing on the immune responses associated with MTX-treatment. The Global COE project has significant interest in this research; I was therefore appointed as a Global COE-RA and started the work.

Intestinal barrier function is regulated by tight junctions (TJ), multiprotein complexes which are located at the most apical part of the lateral membrane. The current study was undertaken to determine how intestinal TJ proteins, such as zonula occludens-1 (ZO-1) and claudins, are altered in relation to mucosal immune responses to MTX-treatment.

In MTX-treated rats showed increased intestinal permeability, as indicated by enhanced fluorescein isothiocyanate-dextran flux. At the same time, the intestinal mucosa of MTX-treated rats showed increased myeloperoxidase activity, reactive oxygen species, TNF-α, IL-1β, MIP-2 and TLR4. MTX decreased tyrosine phosphorylation of ZO-1 and its localization to cell-cell contact. Claudin-2 was upregulated in the crypt of small intestine. Immunostaining of claudin-4 at the villous tips of the small intestine was detected weakly, in comparison to control rats. MTX disrupted the interaction between ZO-1 and claudin-4. We found that inhibition of ZO-1 binding to claudin-4 is associated with enhanced intestinal permeability, under inflammatory conditions.

Global COE project provided many attractive opportunities, such as seminars, workshops and educational symposium. They also provided interesting ideas, which contributed to my own original research. I realize that this outcome is largely due to the Global COE project.

Inhibitory effect of disodium cromoglycate on respiratory syncytial virus infection in epithelial cells

Research Assistant

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Respiratory syncytial virus (RSV) is one of the major causative pathogens of upper and lower respiratory tract infections in children. Currently, the conventional pharmacologic treatment is far from optimal. Disodium cromoglycate (DSCG) is a drug widely used for the treatment of bronchial asthma and allergic rhinitis. DSCG is also often used for the treatment of acute infantile wheezing and exacerbation of asthma, which are often related to RSV infections. However, the effects of this drug against RSV infections is still controversial. We have demonstrated that DSCG has antiviral effects *in vitro*. The aim of this study was to investigate the effects of DSCG on RSV and reveal the mechanism underlying its antiviral effect.

DSCG had no virucidal effect, and pre-treatment of Hep-2 cells with DSCG did not affect their RSV infection. The results of a time-dependent drug addition experiment showed that DSCG strongly inhibited the life cycle of RSV at around 0-2 h post-infection, suggesting an inhibitory effect on the early stage of infection; RSV-cell binding and/or fusion events. RSV binds cells at both 4°C and 37°C, but fusion occurs only when the temperature is raised above 18°C.DSCG inhibited both virus attachment at 4°C and virus attachment and fusion at 37°C, but the inhibitory effect was stronger at 37°C. DSCG strongly inhibited syncytium formation, which occurs in the late stage of infection. Syncytium formation is an F protein-mediated cell-to-cell fusion event, similar to a virus-to-cell fusion event. Our results indicate that DSCG inhibits RSV infection mainly by blocking virus-to-cell and cell-to-cell fusion.

The Global COE RA workshop was a good opportunity to learn how to write a manuscript and make a presentation in English. The advisors at this workshop asked many questions and provided useful advice, which helped me to evaluate my research and consider the project from a different point-of-view.

Transcriptional regulation of *MYCN* in human neuroblastoma

Research Assistant

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MYCN is the most important determinant that influences the prognosis of patients with neuroblastoma and is frequently amplified in high-risk tumors. *MYCN* overexpression in neuroblastoma cells contributes to immune escape by inhibiting their ability to attract NKT cells. Despite its clinical significance, it remains unclear how *MYCN* expression is regulated in neuroblastomas. Therefore, I investigated the transcriptional regulation of *MYCN* as a Global COE-RA.

We have found that TAp63, a member of the p53 family, directly represses the expression of both *MYCN* and *NCYM*, a natural antisense transcript of *MYCN*, whereas *MYCN* stimulates *MYCN* and *NCYM* mRNA. A luciferase assay and ChIP analysis revealed that TAp63 and *MYCN* are directly recruited onto the overlapping genomic region between *MYCN* and *NCYM* genes, and the region was required for the TAp63- or *MYCN*-mediated regulation of the bidirectional promoter activity. In addition, our results show that *NCYM* encodes a nuclear protein which is highly expressed in *MYCN*-amplified neuroblastoma cells, and the *NCYM* protein induces expression of *MYCN* mRNA through the direct recruitment onto *MYCN* promoter.

As a Global COE-RA, I had a good opportunity to consider my own research in a more independent manner, since we should carefully plan how to use the research funding. We generated a specific antibody against *NCYM*, and this led us to the surprising finding that the natural antisense gene of *MYCN* encodes a functional nuclear protein. Presentation and discussion in English at Global COE-RA workshop also provided good trainings for me. Indeed, I repeatedly checked my own presentation by watching the recorded movie. In addition, I was able to concentrate on research because of the financial support, and two papers were accepted for publication in this year (Suenaga *et al. BBRC* 2009 and Suenaga *et al. JBC* 2009). Collectively, this program provided me with a great chance to improve the ability to think and act as a scientific researcher.

The research for individualization of warfarin therapy

Research Assistant

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Arteriosclerosis is an intractable immunity-related disease and causes cerebral and myocardial infarction. Warfarin is widely used for the prevention and treatment of the infarction. However, it is known that warfarin has a narrow therapeutic index and a large interpatient variability in dose.

This study can contribute to development of prevention and treatment of the infarction. Therefore, I was appointed as a Global COE-RA and started research focused on the individualization of warfarin therapy.

We reported that white blood cell count (WBC) and taking allopurinol have a significant association with the warfarin maintenance dose. Additionally, an evaluation of the algorithms by Akaike's Information Criteria (AIC) revealed that taking allopurinol and the WBC may be useful to predict the warfarin maintenance dose. Especially, association between WBC and warfarin dose have not been reported in any previous report. We further investigating the association between the WBC and warfarin dose.

We investigated the WBC, PT-INR and warfarin dose in patients' medical records. There was an association between the WBC and PT-INR in each patient with a constant warfarin dose. Therefore, the WBC has a significant positive association with PT-INR.

We are currently conducting basic research with rats to confirm the association between the WBC and PT-INR.

The Global COE-RA workshop was held in English. It was my first opportunity to present my research in English. Workshops or retreats with small groups of scientists allow friendly discussion. The opinions of other RAs are very useful for our research.

Identification of active ingredient(s) in a protein-bound polysaccharide, polysaccharide Kureha (PSK), for stimulating dendritic cells

Research Assistant

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A protein-bound polysaccharide, polysaccharide Kureha (PSK) has been used as an immunostimulatory anti-cancer agent for over 30 years. However, little is known about the molecular mechanisms and active ingredient(s) in PSK. I was appointed as a Global COE-RA and started an investigation of PSK.

Progenitor populations of murine dendritic cells (mDCs; derived from young adult C57BL6 mice bone marrow) were obtained by an appropriate negative selection method, followed culture for DC differentiation using GM-CSF and IL-4. The expression of proinflammatory cytokines (IL-6, TNF-α) as well as a chemokine (MCP-1) in response to PSK were assessed by an enzyme immune-sorbent assay (ELISA). Low molecular compounds were used to specifically inhibit intracellular signal transduction pathways and fractions of protein or polysaccharide in PSK were also used.

PSK stimulated the expression of cytokines (IL-6, TNF-α) and chemokine (MCP-1) in dose-dependent manner. Signal transduction pathway inhibitor assays were analyzed to reveal the molecular mechanisms of PSK. Wortmannin and JAK inhibitor blocked the enhanced expression of IL-6, TNF-α and MCP-1 by PSK. The protein and polysaccharide fractions of PSK was analyzed to identify the active ingredient(s) in PSK. The protein fraction enhanced the expression of IL-6, TNF-α but not polysaccharide fraction. These findings suggested that the PI3K and JAK/STAT pathways were essential for PSK dependent increase of IL-6, TNF-α as well as MCP-1 and the protein in PSK was essential for stimulating DCs.

The presentations and discussions at the Global COE-RA workshop were held in English. The presentations were recorded and distributed to the participants later. I had an opportunity to objectively review my presentation. The Global COE seminar provided me with the opportunity to learn from presentations by various professors. These experiences were very useful to me.

The HAS2-HYAL2/CD44 system regulates spontaneous chemokinesis of cancer cells by an autocrine mechanism

Research Assistant

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Hyaluronan (HA) is a major glycosaminoglycan present in the extracellular matrix. HA is synthesized on the cell surface by hyaluronan synthase (HAS) 1, HAS2 and HAS3, and is degraded by hyaluronidase1 (HYAL1) and HYAL2 in a CD44-dependent manner. It is well known that the HA levels were frequently elevated in many cancers such as breast, colorectal, lung and ovarian cancers, and it is associated with the invasiveness of cancer. Furthermore, it has been reported that the overexpression of HAS2, HYAL2 and CD44 is related to the invasiveness of breast cancer cells. The objective of this study was to determine the role of the HAS2-HYAL2/CD44 system on cell motility (chemokinesis) in cancer cells.

In this study, we used HeLa-S3 cells showing spontaneous chemokinesis. First, siRNA-mediated knockdown of HAS2 was found to result in a reduction of spontaneous chemokinesis in HeLa-S3 cells. However, exogenously added high molecular weight (HMW)-HA (920 kDa), which is believed to be synthesized by HAS2, did not enhance spontaneous chemokinesis. Next, we investigated the effect of siRNA-mediated knockdown of HYAL2 or CD44 on the spontaneous chemokinesis of HeLa-S3 cells. Knockdown of either molecule reduced the spontaneous chemokinesis of the cells. To further verify the involvement of HYAL2 in the spontaneous chemokinesis, we used MDA-MB-231 cells, which express lower levels of HYAL2 protein than HeLa-S3 cells. Overexpression of HYAL2 in the MDA-MB-231 cells resulted in enhancement of their spontaneous chemokinesis. Furthermore, low molecular weight (LMW)-HA (23kDa) cancelled the HYAL2 siRNA-mediated reduction of spontaneous chemokinesis in the HeLa-S3 cells to the control level. These findings suggest that the HAS2-HYAL2/CD44 system may support the spontaneous chemokinesis of human cancer cells by an autocrine mechanism via auto-degradation of HMW-HA to produce LMW-HA.

This work was supported in Global COE program, and published in 2011 in the *International Journal of Oncology*.

English presentations and discussions are required at the Global COE RA workshop. It will be useful for the improvement of my international communication in future. The Global COE retreat program has provided many useful discussions about my presentation with other RAs and many tutors. I would like to express my gratitude to the Global COE program for the opportunity to expand my academic knowledge and improve my ability to communicate in English.

Human IL-10 receptor 1/IgG1-Fc Fusion Protein: Immunoadhesins for potential immunotherapy of melanoma

Research Assistant

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The development of malignant disease might be seen as a failure of immune surveillance. One of the potential immune escape mechanisms is the production of immunosuppressive factors such as interleukin 10 (IL-10) by the tumor cells themselves or the induction of such factors in tumor-infiltrating cells. IL-10 can suppress immune responses via a signaling cascade by decreasing MHC class II on antigen presenting cells and down-regulating the expression of TNF-alpha or IFN-gamma. IL-10 secretion was preferentially detected in metastatic melanoma cell lines and metastatic lesions. We have developed human IL-10 R1/IgG fusion molecules to regulate IL-10 activity, and investigated these compounds in an *in vitro* system. This research allowed me to be accepted as a research assistant in Global COE.

Monomeric and dimeric immunoadhesin constructs were tested for their ability to capture human IL-10 which was produced from a melanoma cell line. The IL-10 immunoadhesins transfected into human melanoma cell captured exogenously as well as endogenously produced IL-10. Transfection of IL-10 producing melanoma cells with the monomeric IL-10 immunoadhesin enhanced T cell responses and produced more IFN-gamma. These results suggest that IL-10 immunoadhesins were effective in blocking the biological activity of human IL-10 and may be useful in reversing immunosuppression induced by tumor cells. With these results, I am going to move forward to confirm the activity of immunoadhesins *in vivo* and make the protein for further experiments with my collaborators.

Although it was challenging, I was very pleased to participate in the Global COE program. The workshop was held in English and I prepared my oral presentation in English. There were many constructive discussions and my advisors provided effective suggestions. My depth of knowledge was expanded by my participation in the workshop, and immersion in the symposium and lectures on immunology.

Anti-tumor effects of replication-competent adenoviruses with enhanced antigen presentation

Research Assistant

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A new therapeutic strategy for refractory tumors, such as malignant mesothelioma and pancreatic cancer, needs to be established in order to improve the patient prognosis. We constructed adenoviruses (Ad) which are designed to selectively replicate in tumors, but not in non-tumorous cells. These Ad are unlikely to impair systemic immunity, in contrast to most other current cancer therapies. Under the global COE program, we planned to construct a novel Ad to adequately capture putative tumor antigens and subsequently to enhance antigen presentation. We have examined whether these Ad produce anti-tumor effects against refractory tumors.

Our Ad contains the transcriptional regulatory region of the *cyclooxygenase-2*, the *midkine* or the *survivin* gene, which is highly expressed in a number of tumor cells, and the region regulates the transcription of early response genes *E1A and E1B*. We further constructed an Ad that can express the *Fas ligand* or *CD40 ligand* gene, since Fas/Fas ligand interactions enhance the antigen capture of dendritic cells and CD40/CD40 ligand ligations activate them. We examined a combination of the oncolytic Ad with tumor-specific viral replication and a dendritic cell-activating Ad, and found that the combination was effective against refractory tumors.

I presented my data in English at the global COE-RA workshop. It was a good opportunity for me to improve my English and presentation skills during the discussion with my advisory board members, and the experience will be helpful in future international conferences. The symposium gave me a good chance to explore immunology research other than that associated with cancer research. Moreover, my advisers kindly provided significant advice about my study.

Development of cancer immunotherapy (Head and Neck cancer)

Research Assistant

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In general, the management of patients with head and neck squamous cell carcinoma (HNSCC) involves a combination therapy of chemotherapy, radiation therapy and surgery. However, the increased toxicity and extensive functional morbidity induced by such combination therapy can severely impair the quality of life (QOL) and the prognosis for these patients still remains poor. Persistent invasion or micro metastasis frequently leads to local recurrence and distant metastasis.

Vα24 natural killer T (NKT) cells have potent anti-tumor activity. In order to develop new treatment strategies, I have participated in the clinical studies of NKT cell-based immunotherapy in the patients with HNSCC. Fortunately, I was appointed as a Global COE-RA and could continue the study.

A clinical study of intra-arterial infusion of *ex vivo* expanded Vα24 NKT cells combined with submucosal injection of α-galactosylceramide (αGalCer)-pulsed antigen-presenting cells (APCs) was performed in patients with locally recurrent and operable HNSCC. Half cases achieved objective tumor regression and Vα24 NKT cells increased in peripheral blood in most cases. The number of Vα24 NKT cells increased in cancer tissues in some cases and was associated with tumor regression. No severe adverse event was observed.

We had to give a talk and discuss in English at Global COE-RA workshop and at the small group discussion with foreign CVPP. The discussions were friendly, and it was valuable for me to listen to experts' opinions.

The role of Notch signaling in vascular aging

Research Assistant

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The features of the aged vasculature include an increase in inflammation and a decline in the regenerative potential, which cause vascular dysfunction and atherosclerosis. Although these phenomena are known to be associated with cellular senescence, the molecular mechanisms underlying these age-related changes remain unclear. We herein demonstrate that Notch signaling has a crucial role in endothelial cell senescence. We found that inhibition of Notch signaling using a Notch1 short hairpin RNA (shRNA) in human umbilical vein endothelial cells (HUVEC) reduced the maximum population doublings, increased the activity of senescence-associated beta-galactosidase, and induced the expression of aging-associated molecules such as p53, p21 and p16. Knockdown of the Notch ligand, Jagged1, resulted in the attenuation of Notch signaling in the neighboring cells, thereby inducing premature senescence similar to the knockdown of Notch1. In contrast, overexpression of Notch1 or Jagged1 extended the replicative lifespan of HUVECs and decreased the expression of aging-associated molecules. In addition, using a microarray analysis, we found that Notch1 positively regulated the expression of inhibitor of DNA binding 1 (Id1) and MAP kinase phosphatase1 (MKP1), while MKP1 further upregulated Id1 expression by inhibiting its p38MAPK-induced protein degradation. Overexpression of Id1 downregulated p16 expression, thereby inhibiting the premature senescence of Notch1-deleted endothelial cells. These findings indicate that Notch1 signaling has a role in the regulation of endothelial cell senescence via a p16-dependent pathway, and suggest that the activation of Notch1 could be a new therapeutic target for treating age-associated vascular diseases.

Through my activities as an RA of the Global COE, I obtained my valuable experiences. The discussions with researchers who had different specialties was really helpful for taking a larger view. At the Global COE workshop, the presentations in English were very useful as training activities for future activity abroad.

The roles of Wnt signaling and immune cells in hypertensive arterial remodeling

Research Assistant

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Hypertension is the leading risk factor for many cardiovascular diseases. High blood pressure induces structural remodeling of arteries (hypertensive arterial remodeling), which leads to arteriosclerosis and end-organ damage. However, the signaling cascade that triggers arterial remodeling after blood pressure elevation remains elusive.

We recently reported that complement C1q activates Wnt signaling and induces aging-associated impairment of skeletal muscle regeneration. In the G-COE program, we identified a critical role for macrophage-derived complement C1q, which activates Wnt signaling in vascular smooth muscle cells (VSMCs) during hypertensive arterial remodeling. The proliferation of VSMCs and activation of Wnt signaling in VSMCs were observed following blood pressure elevation. Macrophages were recruited and C1q was highly expressed in the vessel wall following blood pressure elevation. Macrophage depletion, C1s inhibition and *C1qa* gene deletion suppressed hypertension-induced activation of Wnt signaling and proliferation of VSMCs and prevented hypertensive arterial remodeling. Our findings collectively indicate that macrophage-derived C1q triggers hypertensive arterial remodeling by activating Wnt signaling in VSMCs and suggest the existence of a previously unknown link between innate immunity and Wnt signaling. Th einhibition of C1q-induced activation of Wnt signaling may become a novel therapeutic strategy for preventing arteriosclerosis in patients with hypertension.

In the workshop, the G-COE advisers' comments and remarks on various aspects of our study were useful for improving the quality of our research. Additionally, I was able to improve my English skills through the process of making presentations and holding discussions in English.

At the retreat, having the opportunity to converse with researchers of various fields and be exposed to different values, I was able to enlarge my worldview and establish relationships with other scientists. The G-COE program provided me valuable experience that I am sure will be of great help to my future career.

Chromatin dynamics and the transcriptional regulatory networks in cardiac mesoderm specification

Research Assistant

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Heart failure due to cardiomyocyte dysfuction is a leading cause of death worldwide. Although the heart has limited regenerative capacity, heart regenerative medicine has recently come of age, and would be facilitated by knowing how cardiomyocytes can be efficiently generated *in vitro*. Our group has found that Wnt signaling regulates cardiomyocyte differentiation, and recently reported that this signaling is controlled by complement C1q, which is associated with an aging-related phenotype. I applied to be a Global COE-RA, and after being selected, started research about how Wnt signaling regulates differentiation.

Cell differentiation is regulated by transcriptional regulatory networks consisting of thousands of interactions of *trans*-regulatory factors and *cis*-regulatory elements. We performed a genome-wide epigenome analysis of the chromatin dynamics during cardiomyocyte differentiation, and constructed phase-specific transcriptional regulatory networks that were altered during differentiation. We found that Wnt signaling not only activates the *trans*-regulatory factors in the nucleus, but also cooperates with pre-existing key regulatory factors, regulating phase-specific enhancer switch during cardiac mesoderm specification.

I am grateful to the Global COE program for the great opportunity to engage in interactions with interdisciplinary scientists. In particular, the objective comments made at workshops have led to advances in my research.

Involvement of Endothelial Inflammation and Senescence Induced by Arteriosclerosis in Patients with Metabolic Disorders

Research Assistant

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Various stimuli can induce irreversible cell growth arrest, termed cellular senescence. This response is controlled by negative regulators of the cell cycle such as p53. Accumulating evidence suggests the existence of a potential relationship between cellular senescence and age-associated diseases, including type 2 diabetes. We investigated the role of endothelial p53 as a senescence-associated molecule under high-calorie conditions. We found that treatment of endothelial cells with high levels of glucose and palmitate synergistically increased the p53 expression. Consistent with the *in vitro* results, the endothelial expression of p53 was markedly upregulated when the mice were fed a high-calorie diet, thus suggesting that an excessive calorie intake promotes endothelial senescence. To investigate the role of endothelial p53 in type 2 diabetes, we analyzed metabolic parameters in endothelial cell-specific p53 conditional knockout (ECp53CKO) mice on a high-fat high-sucrose diet. In spite of the lack of difference in dietary intake, the ECp53CKO mice exhibited significantly smaller weights and lower amounts of fat accumulation than the control mice. Moreover, the ECp53CKO mice exhibited better insulin sensitivity and glucose tolerance than their control littermates. The ECp53CKO mice demonstrated significant increases in oxygen consumption and higher core body temperatures compared with the control mice. We next investigated the potential mechanisms by which endothelial p53 regulates glucose metabolism and found that the ECp53CKO mice possessed higher levels of mitochondrial DNA content and glucose transport in skeletal muscles than the control mice.

These results suggest that endothelial p53 regulates glucose metabolism by modulating mitochondrial biogenesis and glucose uptake in skeletal muscles. For this reason, inhibition of endothelial p53 may be a novel therapeutic target to block the vicious cycle of cardiovascular and metabolic abnormalities occurring in diabetic patients.

I was able to join some discussions beyond the field of research and received a large amount of objective opinions regarding my study in this program. At the workshop, I learned how to obtain the understanding of audiences from different fields and to prepare presentations in English. These opportunities were meaningful for my research.

Anti-inflammatory peptides secreted from cardiac progenitor cells ameliorate cardiac dysfunction following myocardial infarction

Research Assistant

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Regenerative therapy based on cell engraftment into infarct hearts has been proposed as a new strategy to treat myocardial infarction. Although several reports have shown that engrafted cells improve the function of ischemic hearts, the effects of cell therapy vary among these studies and the mechanisms underlying the observed beneficial effects remain unknown. Based on the engraftment of various cell types, we found that clonal stem cell antigen-1-positive cardiac progenitor cells (CPC) are the only cells that exert therapeutic effects. Therefore, we elucidated the mechanisms underlying these beneficial effects. In this study, we focused on anti-inflammatory effects. Under these circumstances, I was appointed as a Global COE-RA to initiate this research. By using antibody array analyses, we found that the soluble form of JAM-A (Junctional Adhesion Molecule-A) is abundantly secreted from CPC. JAM-A is a constituent of tight junctions and its soluble form is known to block transendothelial migration. In this study, pretreatment of neutrophils with CPC CM inhibited TNF-α-induced transendothelial migration. This inhibitory effect was attenuated by neutralizing anti-JAM-A antibodies. Injection of CPC into infarct hearts attenuated neutrophil infiltration and the expression of inflammatory cytokines in comparison with a control. Injection of JAM-A proteins into the infarct areas prevented cardiac remodeling and reduced the size of fibrotic areas in comparison with that observed in the non-treated group. Therefore, the soluble form of JAM-A secreted from CPC blocks transendothelial migration of inflammatory cells after myocardial infarctions and ameliorates tissue damage to infarct hearts by preventing any excess inflammation. Our findings may lead to the establishment of new therapies for cardiovascular disease by utilizing the anti-inflammatory effects of JAM-A.

At the Global COE-RA workshop, presentations and discussions were held in English. Therefore, it was a good opportunity for me to improve my English skills. Attending small discussions at the workshop was an unforgettable experience for me.

Identification of a new pathway for Th1 cell development induced by cooperative stimulation with IL-4 and TGFβ

Research Assistant

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After antigen stimulation, naïve CD4 T cells differentiate into distinct helper T cell (Th) subsets, such as Th1, Th2, Th17 and inducible regulatory T (iTreg) cells. In the presence of TGFβ, Th1 cell differentiation is inhibited, whereas both Th1 and Th17 cells are involved in the onset and symptoms of inflammatory diseases. We hypothesized that a different pathway for Th1 cell differentiation may exist in the presence of TGFβ. I initiated my research on this project as a Global COE-RA.

We found that a combination of IL-4 and TGFβ augmented the development of Th1 cells that express CD103 ($CD103^+$ Th1 cells) if IFNγ is present. The T-box containing transcription factor eomesodermin (Eomes) is preferentially expressed in $CD103^+$ Th1 cells, and is involved in IFNγ production. The induction of T-bet during early T cell activation is essential for the formation of the active chromatin at both the Eomes and IFNγ gene loci. TGFβ is required for the induction of Eomes and CD103, as well as the inhibition of Th2 cytokine expression. In addition, IL-4 induces *EOMES* transcription through activation of the Stat6 signaling pathway. $CD103^+$ Th1 cells are detected in the IEL of normal mice and may play an important role in the immune response in the epithelial mucosa.

The Global COE-RA workshop conducted presentations and discussions in English. It was a good opportunity for me to improve my presentation skills in English. At the IMSUT/RCAST-Chiba University Global COE Joint Retreat 2011, the ability to communicate with researchers from other universities through poster sessions and receptions encouraged me in my research. I also received the Best Poster Award, which further motivated me in my research.

Epigenetic regulation of Th2-specific genes by the Menin/TrxG complex

Research Assistant

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CD4 T cells play an important role in allergic inflammatory diseases. Many studies have been conducted to clarify the molecular mechanisms underlying the actions of these cells. In the present study, we examined Menin/TrxG molecules that are known to maintain GATA3 transcription in Th2 cells using DNA microarray and ChIP-seq analyses. Based on the results of the DNA microarray and ChIP-seq analyses, we identified 24 genes that are highly expressed specifically in Th2 cells. We also examined the dependence of GATA3 and Menin by analyzing the data obtained from the GATA3 and Menin ChIP-seq analyses and conducting overexpression and knockdown analyses in Menin KO Th2 cells. The results showed that some of the genes (example: IL-4, IL-13) were normaly induced in Menin KO effector Th2 cells but not in developed Th2 cells.

The G-COE workshop, which is held two times a year, was a great opportunity for me to give a presentiation in English. The suggestions from my adviser were not only about my presentiation, but also about how to answer questions and how to make slides for my presentation. It was an excellent opportunity for me to improve my English skills as well as my research. At the G-COE symposium, I was able to listen to many top scientists from all over the world. It was a very stimulating experience.

Role of the Menin/TrxG complex in Th17 cell differentiation

Research Assistant

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Epigenetic modifications, such as methylation of DNA and various post-translational modifications of histones, play an important role in Th2 gene expression and regulation. These modifications are partly mediated by the Trithorax group (TrxG) complex, which activates transcription, and the Polycomb group (PcG) complex, which represses transcription. Previously, our data suggested that, after Th2 cell differentiation, the binding of the menin/TrxG complex was required for the maintenance of GATA3 expression and Th2 cytokine production. However, it remains unclear how menin regulates allergic reactions such as asthma, in which both Th2 and Th17 cells are reported to be involved *in vivo*. Furthermore, its involvement in Th17 cell differentiation has not been well understood. This study investigated the effects of epigenetic regulation on Th17-mediated diseases, and I started this work as a Global COE-RA.

Menin was initially identified as a product of the *Men1* tumor suppressor gene. A reduction in the generation of IL-17-producing cells and the expression of *Il17a* mRNA were observed in menin-deficient cells. To further elucidate the role of menin in Th17 cell differentiation, the binding of menin and histone modifications at the *Il17a* gene locus were assessed by ChIP assays. The recruitment of menin at the locus was observed in Th17 cells. In addition, the levels of H3-K4Me3 and H3-K9Ac were decreased in menin-deficient Th17 cells at the *Il17a* gene locus. These results indicate that histone modification via the recruitment of menin plays a crucial role in Th17 cell differentiation.

Next, we evaluated the role of menin in the development of allergic airway inflammation. The total numbers of infiltrating leukocytes, especially neutrophils, in the BAL fluid samples were significantly decreased in mice receiving menin-deficient Th17 cells compared with those receiving WT Th17 cells. *In vivo*, we found that allergic airway inflammation was attenuated in the mice transferred menin-deficient Th17 cells.

At the Global COE-RA symposium, not only was I able to learn about the most recent findings in immunology, but the seminar also increased my motivation with regard to my own study. In addition, I had the chance to make a presentation and discussion in English at the Global COE-RA workshop. I keenly felt the importance of improving my English for communication and discussion, which was very useful. The retreat in September also provided opportunities to meet and become better acquainted with other G-COE RAs. It was a fruitful time for me.

A mouse model of spinal metastasis-induced neuropathic pain and the mechanism underlying cancer-related pain

Research Assistant

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Cancer-related pain is a very complicated pain syndrome, including bone cancer pain and bone metastasis-induced neuropathic pain. Cancer-related pain is difficult to control and the patient response to existing treatments is often inadequate. We were planning to establish a reproducible mouse model of spinal metastasis-induced neuropathic pain, and I was appointed as a Global COE-research assistant and started research about cancer pain as part of the G-COE program.

Experiments were conducted using adult male C57BL/6J mice. We initially injected the medium containing NCTC2472 mouse fibrosarcoma cells into the tibia bone marrow using a microsyringe. Two weeks after injection, we detected the erosion and destruction of the tibia bone three 3-dimensional computed tomography (3D-CT), and the darkly-stained bone marrow cells were replaced with the more lightly-stained sarcoma cells in the sarcoma-bearing tibia. During the next stage of the project, we are planning to develop a spinal-metastasis model and to investigate the mechanism of bone metastasis-induced neuropathic pain. There are currently no reports about spinal metastasis animal models. Therefore, this study might provide a major step in the development of a clinical treatment for cancer pain.

After completing graduate school, I came to the United States and have been doing research at the University of California, San Diego. The experience as a G-COE RA was one of the reasons I decided to study abroad. The presentation in English at the G-COE workshop and summer G-COE retreat (IMSUT/RCAST-Chiba University joint retreat 2011) was a rare and great opportunity for me. It was a very important experience, and I was greatly inspired by the other researchers, especially by my peers.

The efficacy of platelet-rich plasma for the treatment of metastatic cancer pain

Research Assistant

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It is difficult to treat metastatic tumors that cause severe pain due to bone destruction. Platelet-rich plasma (PRP) was reported to be clinically effective for pain relief and promoting bone union. I have already obtained results showing its benefits for spine surgery. Based on these previous findings, the global COE program selected me as an RA, which permitted me to conduct further studies.

In order to create a model of metastatic tumors, we used NCTC2472 tumor cells and injected them into the tibias of B57/CL6 mice. The engraftment and growth of tumor cells were confirmed about three weeks after the injection. Specifically, the invasion of tumor cells into the cortex of the tibial bone, and the partial erosion of the same area with local swelling was observed. We also treated these mice with PRP after the engraftment of tumor, and carried out measurements of pain behavior in treated and untreated mice using the Catwalk gait analysis system.

In the control (tumor-bearing) mice, a significant reduction in contact pressure and contact area was observed in the injected paw, whereas these changes were not observed in the treated tumor-bearing mice. These findings indicated that PRP could decrease the pain caused by metastatic bone tumors.

As a RA of the G-COE, I had several opportunities to make presentations in English. This made me to realize the importance of practicing such presentations, because I hope to make presentations all over the world in the future. It was also inspiring to hear the presentation made by other RAs, and the interactions with the other RAs helped motivate me to improve my research.

The efficacy of a nerve growth factor antibody for cancer neuropathic pain in model mice

Research Assistant

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The occurrence of spinal metastases can cause significant morbidity, with pain and neurological deficits adversely affecting the patient's quality of life. Cancer-related neuropathic pain is caused by tumors compressing the spinal nerve root. Surgery is currently the most effective treatment for cancer-related neuropathic pain, however, it is invasive, especially for advanced cancer patients whose general condition is poor. Recently, many clinicians have paid attention to anti-nerve growth factor (NGF) therapy, which has been reported to be more effective than opioids for knee osteoarthritis pain based on a clinical trial in the U.S.A. As a Global COE-RA, I started my research project about the efficacy of anti-NGF therapy for cancer neuropathic pain using a mouse model.

In this study, cancer-related neuropathic pain was successfully induced in mice by prepared injecting murine sarcoma cells into the left sciatic nerve. Two weeks after surgery, we detected a painful gait using the CatWalk walk analysis system, and upregulation of pain-related molecules was observed in the dorsal root ganglia and spinal dorsal horn. After anti-NGF therapy, the painful gait was improved and the upregulation of pain-related molecules were suppressed. These findings may indicate the possibility of using anti-NGF therapy for cancer-related neuropathic pain in the future.

My presentations and discussions at the Global COE RA workshop were held in English only. It was a great experience for me, because I am now working at a laboratory in Canada as a postdoctoral fellow. In addition, meeting and discussing my work many other young researchers who were investigating other areas was an amazing experience for me.

A tumor suppressive microRNA-133a-mediated molecular mechanism in head and neck squamous cell carcinoma

Research Assistant

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The presence of non-coding RNA in the human genome was revealed by the Human Genome Project in 2004. Among these sequences, single-stranded RNA consisting with 19-21 bases are classified as microRNAs (miRNAs), which have attracted attention because they control the expression of multiple protein-coding genes. We profiled the expression of miRNAs in head and neck squamous cell carcinoma (HNSCC). I was appointed as a Global COE-RA and started research about the functional significance of miRNAs in HNSCC.

First of all, we examined the miRNA expression profiles in maxillary sinus and hypopharyngeal squamous cell carcinoma (SCC) from clinical paired normal and cancer tissues. We found that 23 and 31 miRNAs were significantly downregulated in maxillary sinus and hypopharyngeal SCC, respectively ($P<0.05$). Among these miRNAs, the significant downregulation of microRNA-133a (miR-133a) in cancer tissues was confirmed by qRT-PCR. Ectopic expression of miR-133a significantly suppressed HNSCC cell proliferation, migration and invasion *in vitro*. A genome-wide gene expression and bioinformatic analysis identified that tumor suppressive miR-133a directly regulated caveolin-1 (*CAV1*) and glutathione S-transferase pi 1 (*GSTP1*). Silencing of the *CAV1* gene led to significant inhibition of cell migration and invasion in HNSCC cells, whereas silencing of *GSTP1* showed a significant induction of cell apoptosis. These results indicated that *CAV1* and *GSTP1* may have oncogenic functions in HNSCC cells.

Presentations and discussions were held in English at the Global COE-RA workshop. My presentations were recorded and evaluated by advisers later. This provided a very helpful experience for me as a graduate student.

Role of HMGB1 in esophageal squamous cell carcinoma

Research Assistant

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Esophageal cancer is one of the worst malignant digestive malignancies and its prognosis is quite poor. To treat this disease, surgery, radiotherapy and chemotherapy are usually applied. Although the outcomes of this disease have been improved at a certain level in recent decades, the development of a new modality is strongly required for further progress in this field.

HMGB1 is known to be a cytokine of inflammation and a substance that is related to p53 in the nucleus; however, its function remains unclear. We therefore aimed to clarify the function of this molecule. Using surgical specimens that had not been treated preoperatively, immunohistochemical staining of HMGB1 was performed. When positivity for HMGB1 was greater than 50%, the case was defined as being positive. After this evaluation, the correlations between the HMGB1 expression and the clinicopathological features were analyzed. Then, using shHMGB1, we knocked down HMGB1 in TE2 cells using the lipofection method. After performing selection with puromycin, we selected stable HMGB1-knockdown TE2. Next, we compared the sensitivity for 5-FU between HMGB1-knockdown TE2 and control TE2. Consequently, 122 of 153 (79.7%) cases exhibited positivity for HMGB1. In a univariate analysis, the HMGB1-negative cases were found to exhibit significantly worse survival ($P=0.004$). A multivariate analysis revealed that HMGB1 is an independent prognostic factor for survival (hazard ratio: 1.9409; $p=0.002$). Sensitivity to 5-FU was lower in the shHMGB1-induced TE2 cells compared to that observed in the control TE2 cells.

It was a great opportunity for me to be a research assistant for the G-COE. Based on this research, I was able to show that HMGB1 is an independent prognostic factor and that is closely related to sensitivity to 5-FU. Additionally, I was able to recognize the importance of giving presentations in English. Although it was not familiar for me, I was able to take a step forward. I will continue to make further efforts to improve my research and language skills.

Functional variations in the thromboxane A2 receptor gene are associated with the lung function in asthma patients

Research Assistant

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We have studied the relationships between asthma-related gene polymorphisms and the disease susceptibility and lung function in Japanese childhood-onset asthma patients, and found a suggestive association of a single nucleotide polymorphism (SNP), c.795T>C, in the thromboxane A2 receptor gene (*TBXA2R*) with a lung function parameter in the patients. The c.795T>C SNP has previously been reported to be associated with the asthma susceptibility and lung function in asthma patients. Because c.795T>C is a synonymous SNP, it is not likely to be of functional importance. We hypothesized that other *TBXA2R* gene polymorphism(s) in linkage disequilibrium (LD) with c.795T>C would be functional.

We comprehensively sequenced the *TBXA2R* gene in 48 control subjects and found SNPs (rs2238633 T>G, rs2238632 C>T) which were located in intron 1 of this gene and in LD with c.795T>C. In a luciferase assay, the combination of both mutant alleles of these two SNPs showed higher promoter activity compared to that of both wild-type alleles. Homozygotes for a haplotype consisting of both mutant alleles of these two SNPs were associated with lower lung function (FEV1/FVC, %MMEF) in patients, compared to other combinations of alleles. We also found associations of the haplotype with the mRNA expression level in peripheral whole blood cells and with the eosinophil fraction of peripheral blood. These findings suggest that the variations in intron 1 are implicated in regulating *TBXA2R* gene expression and affect the lung function in asthma patients, and may also result in other phenotypes.

At the Global COE-RA workshop, I had the valuable opportunity to present and discuss my research in English and received a lot of useful advice. At the G-COE retreat, I had a good opportunity to communicate with other G-COE RAs. These were all valuable experiences for me.

c-Maf activates the promoter and enhancer of the IL-21 gene, while TGF-b inhibits c-Maf-induced IL-21 production in $CD4^+$ T cells

Research Assistant

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Previous studies have shown that IL-6 potently induces IL-21 production in $CD4^+$ T cells, whereas TGF-b inhibits IL-6-induced IL-21 production in $CD4^+$ T cells. In this study, we addressed the mechanisms underlying the transcriptional regulation of IL-21 production in $CD4^+$ T cells. We found that IL-6 induced c-Maf expression in $CD4^+$ T cells and that the enforced expression of c-Maf induced IL-21 production in $CD4^+$ T cells without IL-6, IL-4/STAT6 signaling or an autocrine effect of IL-21. Moreover, we found that c-Maf directly bound to and activated IL-21 promoter and CNS-2 enhancer through Maf recognition element (MARE) sites. On the other hand, we also found that although TGF-b upregulated IL-6-induced c-Maf expression in $CD4^+$ T cells, TGF-b inhibited c-Maf-induced IL-21 production in $CD4^+$ T cells. Finally, we found that Foxp3 bound to both IL-21 promoter and CNS-2 enhancer, and thus modestly but significantly inhibited c-Maf-induced IL-21 production in $CD4^+$ T cells. Taken together, these results suggest that c-Maf directly induces IL-21 production in $CD4^+$ T cells by activating IL-21 promoter and CNS-2 enhancer, while TGF-b suppresses c-Maf-induced IL-21 production in $CD4^+$ T cells.

At the Global COE-RA workshop, all presentations and discussions were held in English and this program has therefore become a truly precious experience for me.

Investigation of the roles of CCN3 signaling in the pathogenesis of podocytopathy

Research Assistant

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Recently, it has been suggested that glomerular diseases can be considered to be a consequence of podocyte dysfunction ('podocytopathy') caused by a wide variety of factors, including diabetes, hypertension, autoimmune diseases and so on. It has also been reported that transforming growth factor beta (TGF-β) is an important downstream mediator, not only of the development of renal hypertrophy, but also of the accumulation of mesangial extracellular matrix components. However, the role of TGF-β signaling in the pathogenesis of podocytopathy has not yet been elucidated.

We analyzed the roles of CCN3, a member of the CCN family, in the pathogenesis of atherosclerosis and found that CCN3 inhibits the development of atherosclerosis (*Arterioscler Thromb Vasc Biol*. 2010; 30: 675-82). In the kidneys, the expression of CCN3 is localized in the glomerular podocytes *in vivo*. We therefore focused on the roles of CCN3, a possible mediator of TGF-β signaling, in the pathogenesis of podocytopathy.

We examined the effects of TGF-β signaling on the CCN3 expression in cultured podocytes and found that the CCN3 expression is decreased in the presence of TGF-β in a dose-dependent manner. On the other hand, the expression of CCN3 in Smad3, an intracellular TGF-β signaling molecule, significantly increased in knockout mouse glomeruli. These results indicate that the expression of CCN3 is regulated by TGF-β signaling in podocytes. We also found that CCN3 significantly inhibits the expression of fibronectin, a component of the glomerular basement membrane, which was induced by TGF-β in cultured podocytes. Since an increased expression of fibronectin is frequently observed within glomeruli under diabetic conditions, our findings may be significant and could open up new therapeutic strategies for treating diabetic complications in the future.

It was an extremely nice experience to be able to present my work and discuss my research in English at the Global COE-RA workshop. I also received wonderful suggestions and participated in discussions with external experts in science, which was very useful for my research. The Global COE research program has given me the motivation to participate in big conferences in the future.

The DMAP1 tumor suppressor activates the MYCN/ATM/p53 pathway

Research Assistant

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Because I was accepted as a research assistant by the G-COE program, I was able to concentrate on my research project. First, I would like to describe our research progress.

It is known that p53 is mutated or inactivated in many cancers, and that the inactivation of p53 contributes to carcinogenesis and tumorigenesis. Elucidation of the p53 activation machinery may help to develop immune cell therapy for cancer, because p53 is reported to contribute to the tumor regression induced by immune cells.

Recently, a functional relationship between p53 and our target gene, DMAP1, was reported. We then studied the role of DMAP1 on p53 activation in neuroblastoma cell lines, which usually retain inactivated p53. As a result, a correlation between low expression of DMAP1 and a poor prognosis of neuroblastoma, and p53 activation by DMAP1 via ATM in the presence of the anti-tumor drug doxorubicin were observed.

Interestingly, *MYCN*, a homolog of the *MYC* oncogene in neuroblastoma, stabilized DMAP1 and upregulated ATM/p53 activation under doxorubicin treatment. Further, the participation of DMAP1 in the ATM/p53 activation by MYCN was observed. Together, these findings suggested that DMAP1 may have a tumor-suppressive role in response to oncogene overexpression.

My final thesis came about through the presentations at the G-COE workshop and retreat and based on the many constructive comments from my adviser, teachers and other RAs, which finally allowed me to submit my work to a scientific journal.

I was able to practice presenting my research in English at the "presentation seminar" and workshop hosted by the G-COE program. This training helped me engage in discussions at international conferences. I will further utilize this experience when I study abroad.

Finally, I would like to report that I made many friends at several G-COE events, and these friendships have helped bolster my professional development.

Developing enhanced chemotherapy by overcoming cancer-resistant mechanisms

Research Assistant

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Cisplatin (CDDP) is a commonly used chemotherapeutic agent in the treatment of various malignant tumors, including oral squamous cell carcinoma (OSCC). However, resistance to CDDP is a major obstacle to providing effective cancer therapy. The aim of this study was to identify genes associated CDDP-resistant mechanisms. This research fits well with the concepts of the Global COE, and I was appointed as a Global COE-RA to initiate this research.

We performed a microarray analysis using parental OSCC cell lines and CDDP-resistant cell lines established from parental cell lines to identify genes associated with CDDP-resistant mechanisms. We found seven genes that were upregulated by 2.0-fold and differentially expressed in the CDDP-resistant cell lines and validated the mRNA expressions of these genes using quantitative RT-PCR. Among these genes, the AKR1C family (AKR1C1, AKR1C2, AKR1C3 and AKR1C4) was upregulated in all of the CDDP-resistant cell lines compared with that observed in the CDDP-sensitive cell lines. We assume that inhibition of the AKR1C activity influences CDDP-resistant mechanisms. Consistent with our hypothesis, CDDP chemosensitivity increased in the cells treated with AKR1C siRNA or a specific AKR1C inhibitor, mefenamic acid. In addition to the *in vitro* experiments, we subcutaneously inoculated CDDP-resistant cells and parental cells into female athymic nude mice to validate the inhibitory effects of mefenamic acid *in vivo*. The response of the CDDP-resistant cell xenografts to CDDP plus mefenamic acid was significantly enhanced compared with that observed in the controls and that observed in response to systemic therapy with CDDP alone or mefenamic acid alone. These results suggest that combination CDDP chemotherapy with mefenamic acid might be an effective therapeutic system for treating CDDP-resistant OSCC.

The Global COE-RA workshop was a good opportunity to learn how to write a manuscript and make a presentation in English. The instruction provided by two Global COE advisers was very helpful in advancing my study.

Growth arrest and re-differentiation of vascular smooth muscle cells cultured in type I collagen matrix honeycombs

Research Assistant

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Although the phenotypic change in vascular smooth muscle cells (SMC) is a crucial event for the progression of atherosclerosis, the mechanism underlying this change is not fully understood. Researching the SMC phenotype change is difficult because it is not possible to maintain SMCs for an extended time in the differentiated state. We previously reported that dedifferentiated SMCs displayed similar features to differentiated SMCs when cultured in three-dimensional matrices of type-I collagen called “honeycombs”, but the mechanisms underlying the development of these features are unknown. The purpose of my study as a Global COE-RA was to clarify the mechanism responsible for the growth arrest and re-differentiation of SMCs cultured in honeycombs.

The SMCs cultured in honeycombs showed lower protein synthesis and stopped proliferating. We focused on the regulation of eukaryotic initiation factors (eIFs), which, together with RNA molecules, regulate translation initiation. The phosphorylation of eIF2α was increased in SMCs after culturing them in honeycombs, and this may be regulated by the intracellular spermine (one of the major polyamines) level. Among the various eIFs, the protein levels but not the mRNA levels, of eIF4B and 4G were dramatically decreased in SMCs cultured in honeycombs. We showed that the synthesis of eIF4B might be regulated by polyamines at the level of translation in SMCs cultured in honeycombs. Moreover, we confirmed that the degradation of eIF4B and 4G was promoted in SMCs cultured in honeycombs. These data suggest that the regulation of eIFs (phosphorylation, translation and degradation) decreases protein synthesis, inhibiting the proliferation of SMCs cultured in honeycombs.

The presentations and discussions in English at the Global COE-RA workshop were really good experiences for me. I was able to receive valuable advice from participants, which encouraged me to carry out the research.

Nuclear function of the proto-oncogene product, c-Abl tyrosine kinase

Research Assistant

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The c-Abl tyrosine kinase is a proto-oncogene product that is ubiquitously expressed. Cytoplasmic c-Abl plays important roles in cell proliferation, differentiation and adhesion. c-Abl translocates into the nucleus in response to DNA damage. However, the function of nuclear c-Abl is poorly understood. The chromatin structure dynamically changes as a result of histone modifications, and chromatin dynamics regulate gene expression. As a Global COE-RA, I examined the relationship between nuclear c-Abl and histone modifications and chromatin structural changes.

To examine the involvement of nuclear c-Abl in histone modifications and chromatin structural changes, cells were transfected with NLS-c-Abl, a c-Abl mutant tagged with a nuclear localization signal (NLS). Compared with intact c-Abl, NLS-c-Abl induced an increase number of chromatin structural changes and histone modifications, including a decrease in histone H4 acetylated on lysine 16 (H4K16Ac). Nuclear c-Abl-induced chromatin structural changes, and the downregulation of H4K16Ac was inhibited by trichostatin A, an inhibitor of histone deacetylases. Furthermore, c-Abl knockdown or treatment with an Abl inhibitor significantly repressed the chromatin structural changes and H4K16 hypoacetylation in response to the DNA damage mediated by Adriamycin, an anti-cancer drug. These results showed that nuclear c-Abl changes the chromatin structure through histone deacetylation.

I am grateful to the Global COE program. I used the grant to purchase antibodies to examine the histone modification, which enabled me to reveal the involvement of nuclear c-Abl in histone modifications (Aoyama et al., *Exp. Cell Res.*, 317: 2874-2903, 2011). At the workshop and English presentation seminar, I made presentations and engaged in discussions in English for the first time. These experiences improved my English presentation skills and motivated me to apply for a presentation at an international academic meeting (52nd American Society for Cell Biology annual meeting). These were valuable experiences which will influence my academic career.

β-glucan curdlan induces IL-10-producing $CD4^+$ T cells and inhibits allergic airway inflammation

Research Assistant

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A number of studies have suggested a correlation between a decreased incidence of infectious diseases and an increased incidence of allergic diseases, including asthma. Although several pathogen-derived products have been shown to possess therapeutic potential for allergic diseases, it remains largely unknown whether β-glucan, a cell wall component of a variety of fungi, yeasts, and bacteria, has therapeutic or regulatory potential for allergic diseases. In this study, we examined the effect of curdlan, pure 1-3 linked β-glucan, on allergic airway inflammation. These studies were done under the philosophy of the Global COE program. I was appointed as a Global COE-RA and started my planned research under the program.

We found that the intraperitoneal injection of curdlan significantly inhibited antigen-induced eosinophil recruitment and Th2 cytokine production in the airways. The activation of $CD4^+$ T cells in the presence of curdlan induced IL-10-producing $CD4^+$ T cells. The curdlan-induced development of IL-10-producing $CD4^+$ T cells required the presence of antigen-presenting cells and an ICOS-ICOSL interaction. It also required intrinsic expression of STAT6. Furthermore, adoptive transfer of antigen-specific $CD4^+$ T cells that were stimulated in the presence of curdlan inhibited antigen-induced eosinophil recruitment into the airways. Taken together, these results suggest that curdlan is capable of inducing IL-10-producing $CD4^+$ T cells and inhibiting the development of eosinophilic airway inflammation.

I did not previously have very many opportunities to present my work in English. At the Global COE-RA workshop, presentations and discussions were held in English. It was a good experience for me. At the workshop, we received advice on our research project and presentation from an adviser. This advice was very helpful.

The efficacy of Foxp3$^+$ CD4$^+$ T cells induced in the presence of a geranylgeranyltransferase inhibitor in the regulation of T cell-dependent B cell responses

Research Assistant

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Statins inhibit HMG-CoA reductase, a key rate-limiting enzyme in the mevalonate pathway. Accumulating data suggest that statins exhibit anti-inflammatory effects on a number of experimental models, including experimental autoimmune encephalomyelitis and antigen-induced allergic airway inflammation. In a previous study, we showed that simvastatin inhibits the differentiation of Th17 cells, but enhances the differentiation of Foxp3$^+$ regulatory CD4$^+$ T cells (Tregs). We have also shown that a geranylgeranyltransferase inhibitor (GGTI-298), which inhibits protein geranylgeranylation in the mevalonate pathway, mimics the effect of simvastatin. In addition, we found that while the Tregs induced in the presence of GGTI-298 (GGTI-298-induced Tregs) exhibit normal cell cycle progression, GGTI-298-induced Tregs express higher levels of CD62L and lower levels of CD69 compared with conventional Tregs.

It is well established that Tregs are potent immunoregulatory cells. Importantly, the CD62L$^+$ subset of Tregs has been shown to preferentially migrate to secondary lymphoid organs. Moreover, CD69$^-$ Tregs in humans have been reported to efficiently suppress germinal center (GC)-T helper cells and GC T helper cell-induced B cell responses. However, the efficacy of GGTI-298-induced Tregs in the regulation of T cell-dependent B cell responses remains unknown.

To determine the efficacy of GGTI-298-induced Tregs in the regulation of T cell-dependent B cell responses, we investigated the T cell-dependent B cell responses in Balb/c mice that received a transfer of GGTI-298-induced Tregs or conventional Tregs, together with naïve CD4$^+$ T cells from OVA-specific DO11.10 mice. The recipient mice were immunized with OVA, and the differentiation of follicular helper T cells from the transferred OVA-specific KJ1-26$^+$ T cells and the development of GC B cells were evaluated by flow cytometry. The adoptive transfer of GGTI-298-induced Tregs suppressed follicular helper T cell differentiation and GC B cell development more strongly than that of conventional Tregs. Additionally, OVA-specific IgG production was significantly reduced in mice that received GGTI-298-induced Tregs compared with those that received conventional Tregs. These results indicate that GGTI-298-induced CD62L^{high} Tregs may have distinct therapeutic potential from conventional Tregs.

At the global COE-RA workshop, I had the opportunity to present our data in English and obtained suggestions from researchers in other fields. As a result, this experience was very valuable for me.

Identification and Characterization of DPYSL4, a Novel p53-dependent Regulator of Energy Production and Oxygen Consumption in Tumor and Nontumor Cells

Research Assistant

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p53 has recently been shown to control the energy balance and metabolic homeostasis, suggesting that it has a wide variety of functions and roles in the pathogenesis of various diseases, including cancer and diabetes. To clarify this novel function of p53, we have performed a genome-wide analysis to characterize p53 target genes related to cell metabolism using both non-tumor and cancer cells.

The RNA-seq analysis using human adipocytes and cancer cells identified 454 candidate genes that were upregulated by DNA damage in a p53-dependnent manner. We identified more than 30 genes that were related to cellular metabolism as p53 targets based on a KEGG pathway and gene ontology analysis. We found that dihydropyrimidinase-like 4 (DPYSL4), which has high homology to an enzyme involved in purine/pyrimidine metabolism, was strongly affected by p53. Knockdown of DPYSL4 inhibited ATP production and oxygen consumption in accordance with an elevation of the NAD+/NADH ratio in both non-tumor and cancer cells. The overexpression of DPYSL4 in cancer cells suppressed the matrigel matrix invasion and migration *in vitro*, as well as the growth of tumor xenografts *in vivo*. Thus, DPYSL4, a unique p53-inducible gene in both adipocytes and tumor cells, may control energy production, possibly linking the tumor suppressor function of p53 to its role in energy function.

It was a good opportunity to be able to present my research in English at the Global COE-RA workshop. I was excited about the interactions with many graduate students who were engaged in various research fields. Thanks to the many workshops and seminars provided as part of the Global COE program, I was able to expand my view of both my own research and that in various fields.

An association study of matrix metalloproteinase-12 gene polymorphisms and asthma in a Japanese population

Research Assistant

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Asthma is an inflammatory lung disease that is caused by a combination of genetic and environmental factors. There are lines of evidence indicating that genetic variations influencing tissue remodeling and the host defense system are involved in the development of asthma and its symptoms. Matrix metalloproteinases (MMPs) degrade various molecules (ex. extracellular matrix or cytokines) and play important roles in tissue remodeling and the host defense system.

The MMP12 gene has been shown to be associated with asthma in Caucasian populations. The primary aim of our study was to investigate whether genetic variations in MMP12 are associated with the risk of developing asthma in a Japanese population.

N357S exhibited a P value <0.05 for childhood and combined adult plus childhood asthma in the dominant model. This risk variant is associated with asthma severity in adult patients. In the functional assay, the minor allele enzyme exhibited a significantly lower activity level than the major allele enzyme. MMP12-specific siRNA suppressed IP-10 secretion from airway epithelial cells upon stimulation with IFN-β. Our results suggest that MMP12 confers susceptibility to asthma and is associated with asthma severity in the Japanese population. MMP12 may be associated with asthma via the inappropriate attraction of leukocytes to inflamed tissue.

It was very helpful to our study that I had the chance to present our findings and to communicate with researchers from other laboratories and other universities at the Global COE-RA workshop and many other Global COE events. At most Global COE events, the presentations and discussions were held in English. This was a very rewarding experience for me. I would like to thank the organizers for giving me this valuable opportunity.

SH-2251, a novel thioamide-related small compound, inhibits the differentiation of IL-5-producing Th2 cells by attenuating Gfi1 expression

Research Assistant

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IL-5 is a key cytokine that plays an important role in the development of pathological conditions in chronic allergic inflammation. The identification of a strategy to inhibit IL-5 production is important to establish of new therapies for allergic inflammation.

SH-2251, a novel thioamide-related compound, selectively inhibits IL-5 production from T lymphocytes. We found that SH-2251 inhibits the generation of IL-5-producing Th2 cells. I joined the Global COE as a research assistant and started investigating the molecular mechanism by which SH-2251 inhibits the generation of IL-5-producing Th2 cells.

We investigated the effect of SH-2251 on active histone markers at the Th2 cytokine gene locus in Th2 cells, and found that SH-2251 inhibited the induction of the histone H3K4me3, H3K9ac, and H3K27ac at the *Il5* gene locus during Th2 cell differentiation. Furthermore, Th2 cell-driven airway inflammation in mice was suppressed by oral administration of SH-2251.

A DNA microarray analysis was performed to identify the gene(s) that contributed to the SH-2251-mediated inhibition of IL-5 production. We identified Gfi1 as a downstream target of SH-2251. The Gfi1 expression dramatically decreased in SH-2251-treated Th2 cells, and the SH-2251-mediated inhibition of IL-5-producing Th2 cell differentiation was restored by transduction of cells with Gfi1. Based on these results, we concluded that SH-2251 inhibits the differentiation of IL-5-producing Th2 cells, at least in part, by attenuating the expression of Gfi1.

At the Global COE workshop, I had to deliver a presentation about the study in English. The post-presentation discussion also had to be conducted in English. This was challenging for me. However, I thankfully had sufficient time to frame my answers and respond clearly. The discussion was very helpful for conducting this study.

Haploinsufficiency of Akt1 prolongs the lifespan in mice

Research Assistant

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There is increasing evidence that nutrient-sensing machinery is critically involved in the regulation of aging. The insulin/insulin-like growth factor-1 signaling pathway is the best characterized pathway with an influence on longevity in a variety of organisms, ranging from yeast to rodents. Reduced expressions of the receptor for this pathway have been reported to prolong lifespans. We herein show that haploinsufficiency of *Akt1* leads to an increased lifespan in mice. In this study, the $Akt1^{+/-}$ mice exhibited lower body weights than their littermates with lower amounts of fat mass and normal glucose metabolism. The degree of ribosomal biogenesis and the amount of mitochondrial DNA content were significantly reduced in these mice, along with decreases in oxidative stress. Consistent with the results obtained in mice, inhibition of Akt1 has been found to promote longevity in nematodes (*Caenorhabditis elegans*), whereas activation of Akt1 shortens the lifespan of this species. The inhibition of Akt1 leads to decreases in the ribosomal gene expression and mitochondrial DNA content in both human cells and nematodes. Moreover, the deletion of the ribosomal gene expression results in a decrease in the mitochondrial DNA content and an increase in lifespan in nematodes. These results suggest that increases in mitochondrial numbers and energy expenditure associated with enhanced protein synthesis accelerate both aging and the onset of age-associated diseases.

I am grateful to the G-COE program for providing me the opportunity to present my findings.

The expression of CD203c on basophils as a marker of IgE-mediated L-asparaginase allergy

Research Assistant

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L-asparaginase (ASP) is a key drug used to treat acute lymphoblastic leukemia (ALL). However, approximately 45% of patients develop type 1 allergic reactions to ASP. Although type 1 allergies are usually related to IgE, it has been reported that the ASP-specific IgE level is too low to measure, and IgG might be associated with allergic reactions to ASP. Recently, CD203c-basophil activation tests (BAT) have been reported to be a more reliable tool than IgE assays. We assessed the diagnostic value of the BAT compared to ASP-specific IgG tests and the skin prick test (SPT) and found that ASP allergy is IgE-mediated.

Thirty-three children (eight with allergies, 25 non-allergic) were evaluated. We collected blood samples and checked them by the SPT before ASP treatment, and prospectively observed them for ASP allergies. We measured the ASP-specific IgG level by ELISA. The ASP-specific IgG was higher in ASP allergy patients than those without ($p<0.01$). The SPT correlated with the finding of an ASP allergy ($p<0.01$). The expression of CD203c-BAT was higher in ASP allergy patients ($p=0.02$). The area under the ROC curve of CD203c-BAT (0.87) was similar to that of ASP-specific IgG (0.9). An IgE crosslinking-induced luciferase expression (EXiLE) assay was a recently developed and has high sensitivity to detect IgE. The EXiLE was positive in a patient with ASP allergy whose CD203c-BAT was very high. Moreover, we found that the CD203c-BAT or SPT became negative after an ASP allergy reaction. We demonstrated successful readministration of ASP to two previously allergic patients.

The BAT, SPT and EXiLE suggested the presence of ASP-specific IgE in the sera of ASP allergy patients. The CD203c-BAT is a useful marker to predict an ASP allergy. ASP re-administration to ASP allergy patients was safe after using the BAT.

Although I have made many presentations in Japanese in the past, it was a great experience to be able to make English presentations at the G-COE Workshop. I have broadened my horizons after exchanging comments and suggestions with other young researchers at the G-COE retreat. The financial support provided by the G-COE allowed me to concentrate on my academic research.

Research on micro RNAs that regulate the VEGF-A expression in patients with pediatric asthma

Research Assistant

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Recently, it has been supposed that one of the key players in the pathogenesis of airway remodeling in asthma is vascular endothelial growth factor-A (VEGF-A). Although the expression of VEGF-A is regulated by many factors such as epigenetics and transcriptional factors, it is unclear whether microRNAs (miRNAs) are involved in the VEGF regulation underlying airway remodeling in patients with asthma. Under these circumstances, I was appointed as a Global COE-RA to initiate research on micro RNA that regulates the VEGF-A expression in patients with pediatric asthma.

We analyzed the VEGF-A mRNA expression of CD4-positive T-cells in pediatric asthma patients, atopic controls and non-atopic controls. The VEGF-A expression was significantly higher in the pediatric asthma patients than in the atopic and non-atopic controls, suggesting that VEGF-A plays an important role in the pathogenesis of asthma. Micro RNAs that regulate the VEGF-A expression were evaluated using an in silico analysis. We revealed that hsa-mir-15a, one of the predicted miRNAs that regulates the VEGF-A expression, was significantly lower in the pediatric asthma patients than in the atopic and non-atopic controls. Our results suggest that hsa-mir-15a plays an important role in the pathogenesis of pediatric asthma by regulating the VEGF-A expression. In the future, hsa-mir-15a might be used as a clinical marker or a target of therapy in pediatric bronchial asthma.

By participating in the presentation seminar and the Global COE-RA workshop, both of which were held in English, I learned a significant amount regarding English presentations. The opportunity to make an English presentation allowed me to gain more confidence in making presentations at international conferences. At the G-COE retreat, I had the chance to talk with other G-COE RAs. It was a very rewarding experience for me.

Oxidative stress-induced JNK1 phosphorylation inhibits hedgehog signaling and osteoblast differentiation

Research Assistant

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Hedgehog, which is a morphogenesis factor and oncogenic factor promoting medulloblastoma and basal cell carcinoma, plays a pivotal role in the early phase of osteoblast differentiation. Molecular targeted therapy against hedgehog signaling as a novel antineoplastic approach has been progressing, while an animal study has shown the possibility of decreased bone mass as a side effect of this treatment. To prevent or relieve this side effect induced by hedgehog-targeted therapy, we focused on the facets of hedgehog signaling that induce osteoblast differentiation. I was appointed as a Global COE-RA, and started studying about hedgehog-induced osteoblast differentiation under this program.

The inhibitory effect of oxidative stress on hedgehog signaling and subsequent osteoblast differentiation has been proposed as a pathogenic mechanism for osteoporosis. However, the mechanism by which oxidative stress inhibits hedgehog signaling remains unclear. Therefore, we evaluated hedgehog signaling under oxidative stress conditions using murine embryonic mesenchymal cells (C3H10T1/2 cells).

Oxidative stress induced by hydrogen peroxide inhibited the expression of hedgehog target genes and osteoblast-associated genes, and the subsequent bone mineralization. Moreover, the inhibitory effect was blocked by a JNK inhibitor. Transient overexpression of the wild type or constitutively active form of JNK1 strongly inhibited the hedgehog activity. These data suggested that the inhibition of hedgehog signaling by oxidative stress-activated JNK1 is involved in the pathogenesis of osteoporosis.

I had several opportunities to present and discuss in English at the Global COE-RA workshops. This was a prime opportunity to gain feedback from advisors about my research and to communicate with other participants, which was also useful to motivate me in my own research. The lectures held by G-COE seminar were also informative and interesting.

A role for Bcl6 in the differentiation of memory precursor CD8 T cells

Research Assistant

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Bcl6, a sequence-specific transcriptional repressor, is important for the generation and maintenance of central memory CD8 T cells, which are differentiated from memory precursor cells, but not from effector cells. However, the molecular mechanism involved in the generation of these cells is largely unknown. Recent studies reported that prolonged IL-2 signals promote effector CD8 T cell differentiation, and that activated CD8 T cells that expressed a larger amount of CD25 efficiently differentiated into effector cells. When naïve CD8 T cells from IL-2-KO and WT mice were stimulated with anti-CD3 and anti-CD28 antibodies, the WT CD8 T cells differentiated into both CD25lo and CD25hi CD8 T cells. However, the IL-2-KO CD8 T cells did not differentiate into CD25hi CD8 T cells, and the amount of Bcl6 mRNA in the IL-2-KO CD8 T cells was significantly higher than that in WT CD8 T cells. When IL-2 was added in the IL-2-KO CD8 T cell culture, CD25hi CD8 T cells were differentiated, and the amount of Bcl6 mRNA in the T cells was reduced.

To investigate whether Bcl6 negatively regulates the CD25 expression in activated CD8 T cells, naive CD8 T cells were sorted from the spleens of Bcl6-KO and WT mice. The level of CD25 on Bcl6-KO naive CD8 T cells was similar to that on WT naive CD8 T cells. These naive CD8 T cells were then stimulated with anti-CD3 and anti-CD28 antibodies. The majority of Bcl6-KO CD8 T cells differentiated into CD25hi CD8 T cells. The amounts of CD25 and IL-2 mRNA in Bcl6-KO CD8 T cells were significantly higher than those in WT CD8 T cells. Furthermore, we identified putative Bcl6-binding DNA sequences around the CD25 and IL-2 genes, and the binding of Bcl6 to these sequences was confirmed in naïve, but not in activated, CD8 T cells by a ChIP assay. Taken together, these data indicate that Bcl6 is responsible for the differentiation of memory precursor CD8 T cells by repressing the expression of the CD25 and IL-2 genes.

I was honored to be a RA in this Global COE program. It provided me with a great opportunity to present and discuss my work in English at the COE-RA workshop. I was able to obtain some valuable advice about my research and presentation skills from the supervisors. The events associated with the Global COE program also provided an opportunity to learn about cutting-edge research in immunology being conducted by prominent professors from around the world. It was an extremely valuable experience for me.

Naïve CD4 T cells are instructed to differentiate into effector or memory CD4 T cells

Research Assistant

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Ly6C is a marker of memory CD4 T cells. We recently detected Ly6C in a portion of naïve CD4 T cells. However, the differentiation of Ly6C^{hi} and Ly6C^{lo} naïve CD4 T cells remains largely unknown. In this study, we examined the heterogeneity of naive CD4 T cells. The aim of this research fits well with the concepts of the Global COE, and I was appointed as a Global COE-RA to initiate this study.

In vitro, when Ly6C^{lo} and Ly6C^{hi} T cells were sorted from naïve (CD62L^{+}CD44^{-}) CD4 T cells obtained from the spleens of wild-type mice and stimulated with anti-CD3 and anti-CD28 Abs, the Ly6C^{hi} naïve CD4 T cells differentiated largely into CD25^{hi} CD4 T cells within six hours after stimulation. *In vivo*, Ly6C^{hi} naïve CD4 T cells, but not Ly6C^{lo} naïve CD4 T cells, obtained from OT II-Tg mice transferred into Ly5.1 mice differentiated largely into CD25^{hi} CD4 T cells on one day after immunization with OVA. The Ly6C^{hi} naïve CD4 T cells produced more IFNγ and TNFα and became Th1-like effector cells following anti-CD3 and anti-CD28 Ab stimulation. Moreover, Ly6C^{lo} naïve CD4 T cells, but not Ly6C^{hi} naïve CD4 T cells, aided high-affinity antibody production after both primary and secondary immunization. Therefore, Ly6C^{hi} and Ly6C^{lo} naïve CD4 T cells have the potential to differentiate into different kinds of cells following activation. These data indicate that naïve CD4 T cells are instructed to differentiate into effector or memory CD4 T cells before antigen stimulation.

Giving a presentation and discussion in English at the Global COE-RA workshop provided me with a great opportunity to enhance my training. These experiences were very useful to me and will advance my research at international conferences. Two of my Global COE advisers gave me good advice regarding my research. As a Global COE-RA, the Global COE program gave me a grant to conduct my own research and provided me a good opportunity to evaluate my research in an independent manner. Moreover, the Global COE workshop and symposiums gave me a chance to meet prominent professors from around the world. This valuable experience has enhanced my training and career. I am honored to be a Global COE-RA member.

A randomized phase II trial of adjuvant immunotherapy with α-Galactosylceramide-pulsed dendritic cells for advanced oropharyngeal and hypopharyngeal cancer following standard therapy

Research Assistant

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The management of head and neck cancer has generally involved the combined modalities of chemotherapy, radiation therapy and surgery. However, the prognosis for these patients still remains poor. Persistent invasion or micrometastasis frequently leads to the development of local recurrence and distant metastasis. The development of new treatment strategies for the prevention of recurrence of head and neck cancer is therefore of critical importance. Immunotherapy could be expected to be one of the combined modalities that could be used as an adjuvant for cancer therapy.

Invariant natural killer T (iNKT) cells represent a unique lymphocyte subpopulation. Human iNKT cells activated by α-Galactosylceramide (α-GalCer) show strong anti-tumor activity against various malignant tumors. We have conducted a phase I study with α-GalCer-pulsed dendritic cells (DCs) administered in the nasal submucosa of patients with head and neck cancer, and evaluated the safety and feasibility of such a treatment.

Based on these results, the randomized phase II study of α-GalCer-pulsed or α-GalCer non-pulsed DCs as an adjuvant immunotherapy was initiated to prevent the recurrence of advanced oropharyngeal and hypopharyngeal cancer after treatment with the combined standard therapies. This clinical study is in progress to examine the potential of mucosal immunotherapy based on iNKT cells. At present, 16 patients are enrolled in the clinical trial. NKT cell-specific immune responses have been confirmed in some cases. We will assess the correlation between the immune response after injection of α-GalCer-pulsed DCs and the clinical effects.

At the Global COE-RA workshop, I made a presentation in English for the first time. At a later date, the evaluation of the presentation by the advisor was very helpful. I also participated in many workshops and symposia. They were a valuable experience for me and will be very useful for my future studies.

Functional analysis of the polycomb group protein, *Ezh2*, in *MLL-AF9*-induced acute myeloid leukemia

Research Assistant

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The function of the polycomb group proteins in various cancers is now gaining attention. In the course of the treatment of leukemias, the micro-residual leukemia stem cells that cause recurrence are one of the biggest problems. We started this research project to clarify the function of *Ezh2*, the methyltransferase of H3K27me3, in leukemia stem cells.

We sorted granulocyte-macrophage progenitors from *Ezh2* conditional knockout mice that were transduced the cells with *MLL-AF9*, which strongly promote leukemias, and analyzed the function of *Ezh2*. The deletion of *Ezh2* compromised the proliferative capacity of *MLL-AF9*-transformed GMPs *in vitro*, induced the differentiation of *MLL-AF9*-induced acute myeloid leukemia (AML) and significantly prolonged the survival of recipient mice *in vivo*. Furthermore, deletion of *Ezh2* caused a reduction in the frequency of leukemia-initiating cells. To elucidate the mechanism underlying how *Ezh2* regulates the progression of *MLL-AF9*-induced AML, we examined the genome-wide distribution of H3K27me3 by a ChIP-seq analysis and a microarray analysis, and clarified that *Ezh2* regulates genes relevant to differentiation, apoptosis and stem cell function through its modification of H3K27me3 in *MLL-AF9*-induced AML.

We have had several Global COE-RA workshops each year, and presented our recent progress in English. Through the good discussions at these workshops, we were able to improve our presentation skills in English, and these experiences will be good training for giving presentations at international meetings. I also published my thesis paper during my appointment as a Global COE-RA. I had a really fruitful time as a Global COE-RA.

Effect of inflammatory cell damage on atherosclerosis

Research Assistant

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Atherosclerosis is a chronic inflammatory disease of the blood vessels. Macrophages are present at all stages of the disease, and facilitate cholesterol accumulation and inflammation, which can lead to an infarction. Acrolein is a highly reactive α, β-unsaturated aldehyde produced by polyamine oxidation following endogenous cell damage. Since our preliminary study showed that acrolein might be related to atherogenesis, I was appointed as a Global COE-RA and started research to determine whether acrolein mediated atherosclerosis.

Our study about plasma low density lipoprotein (LDL), a carrier of cholesterol, showed that LDL from healthy subjects was modified by acrolein, suggesting that LDL was modified by acrolein in the plasma. I then examined whether acrolein-conjugated LDL (Acro-LDL) induces macrophage foam cell formation using a cell culture technique. This study revealed that Acro-LDL induced higher cholesterol accumulation in macrophages than oxidized LDL, which is an atherogenic lipoprotein. Moreover, an uptake inhibition assay using a neutralizing antibody showed that the scavenger receptor-dependent endocytic pathway was the major route of Acro-LDL uptake by macrophages. A confocal microscopy analysis also indicated that the macrophages incubated with Acro-LDL accumulated a lot of cholesterol in lipid droplets. These are new findings on the macrophage foam cell formation, an important step of atherosclerosis and atherogenesis.

The Global COE-RA workshop was my first chance to give a research presentation in English, and it was a motivational experience for me. Discussing my work with an advisor was very helpful for my study, because I had not considered their viewpoint. It was also a good experience for me to meet the other your researchers involved in this program.

Uptake of estrogen precursors and induction of PI-9 in ER-positive breast cancer

Research Assistant

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About two-thirds of breast cancers express an estrogen receptor (ER-positive breast cancer), and estrogen (mainly estradiol, E2) plays a key role in the proliferation of breast cancer cells. I have focused on the uptake transporters for estrogen precursors (estrone sulfate and dehydroepiandrosterone sulfate) and proteinase inhibitor 9 (PI-9, which is known as an endogenous inhibitor of granzyme B) to establish new biomarkers and drug targets for ER-positive breast cancer, and I started to investigate these topics after being appointed as a Global-COE (G-COE) RA.

Our results suggest that not only estrogen, but also estrogen precursors, play a key role in the proliferation of breast cancer cells, and that some transporters with the ability to transport estrogen precursors into cells are expressed in ER-positive breast cancer cells. In particular, the expression level of organic anion transporting polypeptide 2B1 may be strongly related to the proliferation of breast cancer cells. PI-9 may be induced by not only by E2, but also by estrogen precursors, and the expression level of PI-9 may also be related to the proliferation of breast cancer cells.

After I was appointed as a G-COE-RA, I have made foreign friends and have been studying English, since the presentations at the G-COE workshops are all made in English. The G-COE program was extremely useful for me to expand my global vision, and I now want to study abroad after graduation. Moreover, it was a really valuable experience for me, because there were a lot of opportunities to talk to other G-COE-RAs and to learn about a lot of other research topics, which helped me obtain a more global view of research.

Nuclear ErbB4-induced histone methylation is inhibited by Src

Research Assistant

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Protein tyrosine phosphorylation is a one of the post-translational modifications, and has important roles in tumorigenesis and the regulation of the immune systems. It has been reported that ErbB4 tyrosine kinase is involved in inhibiting the growth of tumor cells and in immune responses, but little is known about nuclear ErbB4 signaling through tyrosine phosphorylation. Because I was trying to understand the regulation of nuclear ErbB4 signaling by tyrosine phosphorylation, the Global COE program selected me as a Global COE-RA to help support and improve my research.

Our study determined that nuclear ErbB4 increased H3K9me3, a repressive histone marker, in a kinase activity-dependent manner. Moreover, the levels of hTERT gene expression, which is repressed by H3K9me3, were decreased by nuclear ErbB4 signaling. On the other hand, the ErbB4-mediated increase in H3K9me3 and decrease in hTERT gene expression were antagonized by EGFR, another member of the ErbB family, in a manner dependent on a downstream tyrosine kinase, Src. We also found that Src inhibited the nuclear translocation of ErbB4. Taken together, these results suggest that nuclear ErbB4 signaling is regulated by tyrosine phosphorylation and has important roles in histone modification.

The Global COE-RA workshop was carried out in English, and gave me the opportunity to improve my ability to present my research in English. After the presentation, advisers evaluated my study, and then pointed out points that could use improvement. The comments and suggestions were precise and very useful. Additionally, the Global COE retreat allowed me to discuss my research and goals with other Global COE-RAs. In this way, the Global COE program supported my research and improved my abilities as a researcher. I recently succeeded in publishing my studies (*J. Cell Sci.*, in press, 2012).

The histamine H4 receptor as a novel therapeutic target for intractable pruritic dermatosis

Research Assistant

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Chronic pruritus is a major and distressing symptom of many autoimmune skin diseases, and can significantly impair the quality of life for patients with these diseases. The histamine H4 receptor (H4 receptor) is expressed on several hematopoietic cells, and a number of studies have shown that it is involved in both the innate and adaptive immune responses. In addition, recent *in vivo* studies have shown that the H4 receptor may contribute to pruritic responses. We have previously reported that an H4 receptor antagonist, JNJ7777120, significantly reduced both the histamine- and substance P-induced scratching behavior in mice. We also reported that JNJ7777120 attenuated the scratching behavior and improved the skin lesions in an experimental model of atopic dermatitis. These results indicate that H4 receptor antagonists might have the potential to be new drugs for both skin inflammation and pruritus due to allergic dermatitis, such as atopic dermatitis. As part of this research program, we tried to clarify the mechanisms responsible for the anti-pruritic and anti-inflammatory effects of H4 receptor antagonists.

We have investigated the H4 receptor expression in human epidermal tissues and found it to be greater in keratinocytes in the epidermal upper layer than in the lower layer. We then examined the expression of the H4 receptor during differentiation in a human keratinocyte cell line, HaCaT. Quantitative reverse transcription polymerase chain reaction showed that the levels of H4 receptor mRNA in HaCaT cells were increased during the culture period. These results suggest that a previously unknown pruritic mechanism may exist, driven by the response of H4 receptors expressed in keratinocytes.

Giving a presentation at the Global COE-RA workshop was a very valuable experience for me. I was able to gain experience making presentations and engaging in discussions in English. In the second year, I presented my work at a congress of immunology held in England. In addition, thanks to the expertise of the advisers, I was able to expand my views about my research.

Regulation of mast cell functions by cellular lipid balances

Research Assistant

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Mast cells are known to produce inflammatory mediators, such as histamine and prostaglandin D_2. However, there is limited information about the activation pathway of degranulation in mast cells. We have been investigating the cellular effects of bioactive lipids, specifically sphingolipids. Recently, cellular lipids, including sphingolipids, have been demonstrated to have important roles in the activation of immune cells. We have started to investigate the effects of bioactive lipids on the activation of mast cells as a G-COE-RA project.

As part of this project, we examined the effects of cholesterol depletion (using methyl-β-cyclodextrin (MβCD)) on the degranulation in RBL mast cells. Treatment of RBL2H3 cells with MβCD significantly increased the IgE- and A23187-induced degranulation compared to control cells. Interestingly, the effects of MβCD on the RBL2H3 cells were offset by the repletion of cholesterol. Thus, the increased degranulation from MβCD-treated mast cells appeared to be dependent on phospholipase D signaling.

At the G-COE workshop, I was able to improve my English presentation skills, because I made several presentations of my research and answered questions in English. Furthermore, in the joint retreat with researchers from other universities, I was encouraged by discussions with so many researchers from different fields. I am grateful to have been able to have valuable experiences as a G-COE-RA.

Glutathione S-transferase P1 (GSTP1) suppresses cell apoptosis and is regulated by miR-133a in head and neck squamous cell carcinoma (HNSCC)

Research Assistant

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MicroRNAs (miRNAs) are small non-coding RNAs of approximately 19-22 nucleotides that negatively regulate gene expression and can function as oncogenes or tumor suppressors. We previously demonstrated that miR-133a is a tumor-suppressive miRNA, and is commonly downregulated in head and neck squamous cell carcinoma (HNSCC). The aim of this study was to determine the oncogenic gene(s) targeted by miR-133a in HNSCC. I was appointed as a Global COE-RA and started my research on this topic.

Molecular target searches for miR-133a showed that glutathione S-transferase P1 (GSTP1) was directly regulated by miR-133a. GSTP1 is a member of the glutathione S-transferase enzyme superfamily, and catalyzes the conjugation of electrophiles with glutathione in the process of detoxification. Overexpression of GSTP1 has been observed in many types of cancer, including HNSCC. However, the role of *GSTP1* in HNSCC is not well understood. Transient transfection of miR-133a repressed the expression of *GSTP1* at both the mRNA and protein levels. The signal from a luciferase reporter was significantly decreased at one miR-133a target site at the 3'UTR of *GSTP1*, suggesting that miR-133a directly regulates *GSTP1*. We investigated the role of *GSTP1* in two HNSCC cell lines, HSC3 and SAS. Silencing of *GSTP1* revealed that cancer cell proliferation was significantly decreased in both cell lines. In addition, the frequency of apoptotic cells increased following si-*GSTP1* transfection of both the HSC3 and SAS cell lines. Our data indicate that *GSTP1* may have an oncogenic function and may be regulated by miR-133a, a tumor suppressive miRNA, in HNSCC. The identification of a novel oncogenic pathway could provide new insights into potential mechanisms of HNSCC carcinogenesis.

After being chosen to be a research assistant (RA) of the global COE program, I was able to participate in different events, such as the global COE-RA workshop. This allowed me to engage in a variety of discussions and exchange views with numerous other Japanese graduate students about the content of our research. It was a valuable experience for me as an international student. I think this valuable experience will be very helpful for my future research work after I return to my home country.

Gain and maintenance of cancer stem properties in neuroblastoma

Research Assistant

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Neuroblastoma (NB) is one of the most common solid tumors in childhood. *MYCN* is frequently amplified in unfavorable NBs, and the survival rate of patients with malignant NB is less than 30%. It is therefore necessary to find new therapies for this disease. Recently, models involving cancer stem cells have been proposed to explain the mechanisms of relapse, immune evasion, invasion and metastasis of cancers. As our work on NB is based upon such stem cell research, which aligns with the ethos of the Global COE, I was accepted as a Global COE-RA.

NCYM, a natural antisense gene of *MYCN*, is encoded by the *MYCN* locus. *NCYM* is 100% co-amplified with *MYCN* in *MYCN*-amplified NBs. It has been reported that *MYCN* is involved in the functions of several stem cells and that it enhances the efficiency of iPS cell generation. Based on these findings, we focused on the relationship between *MYCN/NCYM* amplification and the cancer stem cell properties. In NB cell lines, *NCYM* induces the expression of OCT4, which is one of the most important genes required to generate iPS cells. The induction of OCT4 by *NCYM* enhances the stem-like properties of the cells, such as their invasion and cell sphere formation. We also checked the expression of *NCYM* and *OCT4* in NB clinical samples. The expression of *NCYM* was significantly correlated with that of *OCT4* in the clinical samples. Our results suggest that *NCYM* might be involved in the development of NB cancer stem cells via the induction of *OCT4*.

It was a good opportunity to learn how to present an effective English presentation in the classes managed by Global COE. In addition, the discussions at almost all of the Global COE workshops were conducted in English. Our presentations at workshops were video-recoded for us to evaluate and improve our presentation skills. This opportunities provided by the Global COE program were very useful.

A radiometal labeling reagent for antibody fragments to reduce the renal radioactivity levels

Research Assistant

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Radiolabeled antibody fragments, such as Fab and Fv fragments, have been found to be useful for diagnostic and therapeutic applications due to their rapid pharmacokinetics and even distribution in a tumor mass in a size-related manner. However, high and persistent localization of radioactivity is observed in the kidneys, which compromises the diagnostic accuracy of tumors around the kidneys, and decreases the therapeutic effectiveness of such agents. To solve this problem, we designed and synthesized a new trifunctional chelating agent (TFCA) for ^{111}In and ^{90}Y that possesses a substrate for renal brush border enzymes so that the radiolabeled compound targeted for urinary excretion is liberated from the antibody molecule during its short contact with the renal brush border membrane.

Our previous study showed that the brush border membrane vesicles isolated from the rat kidney cortex are suitable for the evaluation of the enzyme–mediated cleavage of peptide linkers. Using this technique, we selected some peptide sequences recognized by the enzymes, and synthesized TFCAs. The ^{111}In-labeled Fab fragments using a TFCA, however, still exhibited high renal radioactivity levels. The use of another TCA with more enzyme-sensitive linkage also exhibited high renal radioactivity levels. These findings, along with the findings of a ^{99m}Tc-labeled Fab fragment with another TFCA, suggest that a radiometal chelate of a net neutral charge would be essential to reduce the renal radioactivity levels, which would provide a good basis for the future design of alternative TFCAs that would meet the requirements.

It was a good opportunity for me to make English presentations at the Global COE-RA workshops. In addition, since the presentations were recorded, I was able to use the videos to improve my presentation skills. Furthermore, the Global COE retreat provided me with chances to talk to other RA members, which helped inspire my research.

Role of IL-21 in the development of autoimmune inflammation in the scurfy mouse

Research Assistant

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Foxp3$^+$ T-cell-deficient Scurfy (Sf) mice rapidly develop severe autoimmune inflammation in the skin, liver and lungs, and die within 4 weeks after birth. Many inflammatory cytokines, including IL-21, are highly upregulated in the CD4$^+$ T cells of Sf mice. IL-21 is a pleiotropic cytokine produced by CD4$^+$ T cells, which affects the proliferation, differentiation and effector function of T cells, B cells, NK cells and dendritic cells, and a blockade of IL-21 signaling ameliorates the symptoms in mouse models of rheumatoid arthritis, lupus and type I diabetes. However, the role of IL-21 in the development of multiorgan inflammation in the Sf mouse is unknown. In this study, we examined the role of IL-21 in multiorgan inflammation by generating Sf IL-21 receptor (IL-21R)-deficient mice. We found that the Sf IL-21R-deficient mice showed an extended lifespan compared to Sf mice or Sf IL-21R-heterozygous (Het) mice. The multiorgan inflammation, especially interstitial lung inflammation, was ameliorated in Sf IL-21R-deficient mice, suggesting that IL-21 is involved in the phenotype in Sf mice. In addition, the number of effector CD8$^+$ T cells was significantly reduced in the lungs of Sf IL-21R-deficient mice compared to Sf IL-21R-Het mice. We are currently investigating the role of CD8$^+$ T cells in IL-21-mediated lung inflammation in Sf mice.

At the Global COE-RA workshop, presentations and discussions were held in English, which was a very valuable experience for me. In addition, I had a chance to receive great suggestions from Global COE advisers, which will be very useful for our future research.

Predicting the treatment response of rheumatoid arthritis patients by a comprehensive gene expression analysis of peripheral blood mononuclear cells

Research Assistant

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Rheumatoid arthritis (RA) is a systemic inflammatory disease with a high prevalence characterized by destructive polyarthritis. The treatment outcome of the disease has considerably improved in recent years based on the availability of biological therapies which target inflammatory cytokines, such as tumor necrosis factor α (TNFα) and interleukin-6 (IL-6). However, these drugs are expensive and not efficacious in a proportion of patients. Therefore, a strategy to predict responders and non-responders is needed. However, such methods have not been established. We started a study using a comprehensive gene expression analysis to predict the clinical response to these therapies and to reveal the mechanism underlying the variable response in individual patients. Based on this proposed research study, I was appointed as a Global COE-RA.

A total of 39 patients who received tocilizumab (TCZ), a humanized monoclonal IL-6 receptor antibody, for inadequately controlled RA were recruited. We extracted mRNA from their peripheral blood mononuclear cells (PBMCs) before the first administration of TCZ, and analyzed them for their comprehensive gene expression pattern. We have identified the genes that have significantly different expression levels between responders and non-responders and are now validating the mRNA expression using real-time PCR.

In addition, in order to identify the specific mode of action for each drug, we are comparing the gene expression profiles in purified CD4$^+$ T cells obtained from the peripheral blood of RA patients before and after they received anti-rheumatic drugs.

At the Global COE-RA workshop, I had the opportunity to present our data in English and received suggestions from researchers in other fields. The experience was valuable and helped keep me motivated with this research project.

Cardioprotective effects of dipeptidyl peptidase-4 inhibitors on diabetes in mice following myocardial infarction

Research Assistant

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Heart failure is the second leading cause of death in Japan, and the rate of death due to heart failure is increasing. The prognosis of heart failure has been improved by drug therapies such as β-blockers and ACE-Is and the development of revascularization therapy to treat myocardial infarction. However, these therapies remain insufficient. Recently, incretin-related drugs such as GLP-1 analogues and DPP-4 inhibitors have become available as novel therapeutic agents for treating diabetes. It is unclear whether DPP-4 inhibitors exert cardioprotective effects. Therefore, we conducted an *in vivo* study to elucidate whether DPP-4 inhibitors exhibit cardioprotective effects.

C57BL/6 mice fed a high-fat diet (HFD) were injected with streptozotocin to induce diabetes. The mice were subjected to permanent ligation of the left coronary artery and randomized to treatment with either HFD alone or HFD plus a DPP-4 inhibitor. The cardiac function was assessed using echocardiography five days after coronary ligation. The infarct size, number of vessels and presence of myocardial ischemia were also assessed on day 5. The levels of phosphorylated Akt, ERK, STAT-3 and BCL-2 in the heart lysates measured on day 3 were analyzed using a Western blot analysis. The results showed that the DPP-4 inhibitor improved the cardiac function, decreased the infarct size, increased the number of endothelial cells and decreased hypoxiprobe-1-positive ischemic areas on day 5. The Western blot analysis showed increased levels of phosphorylated STAT-3 and BCL-2. Therefore, DPP-4 inhibitors may exert cardioprotective effects via the STAT-3 signaling pathway.

The Global COE-RA workshop was a good opportunity to give a presentation and discussion in English. The G-COE gave us the opportunity to hear presentations from outside of our field and the chance to change ossified ways of thinking.

Association between pneumococcal carriage and IgG antibodies induced by the 13-valent pneumococcal conjugate vaccine in Japanese children

Research Assistant

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The seven-valent pneumococcal conjugate vaccine (PCV7) was introduced as the national immunization for children under 5 years old in many developed countries to protect infants against invasive pneumococcal diseases (IPDs). After the introduction of the PCV7, the incidence of IPDs due to non-PCV7 serotypes increased. Therefore, the PCV13 was introduced in several countries. The current study found that pneumococcal nasopharyngeal carriage shortly before the first infant dose of PCV7 resulted in hyporesponsiveness to the capsular polysaccharide of the carried strain. I was appointed as a Global COE-RA to investigate the association between pneumococcal carriage and hyporesponsiveness, and started my research under this program.

We revealed the seroprevalence of IgG antibodies against PCV13 serotypes in Japanese through natural exposure. This is the first time such data have been assessed. We measured the serotype-specific IgG antibodies in one hundred sixty non-immunized Japanese by the ELISA protocol recommended by the WHO. The WHO recommended a serotype-specific antibody concentration of 0.35 μg/ml as the estimated threshold concentration for protection against IPD. In this study, it was revealed that overall, infants aged under 2 years had low IgG levels, especially against serotypes 1, 4, 7F, 9V, 18C and 23F. The IgG levels against almost all of the serotypes increased with age. The proportion of children with IgG concentrations ≧ 0.35 μg/ml increased with age and reached almost 100% in the 5 to 9-year-old cohort.

In the future, we will investigate the association of pneumococcal carriage and IgG antibodies induced by pneumococcal conjugate vaccine serotypes in Japanese children.

At the Global COE-RA workshop, I presented and discussed my research in English for the first time. This helped motivate me to work on my English training for the presentation. In addition, the valuable comments from advisers were very useful for my study. It was a very valuable experience for me.

Study of mechanisms underlying osteoporotic pain without fractures

Research Assistant

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Osteoporosis often induces low back pain (LBP), even in patients without fractures. In a previous study, we reported that inflammatory mediators such as tumor necrosis factor-α (TNFα) secreted by osteoclasts increase the expression of calcitonin gene-related peptide (CGRP) in the dorsal root ganglia (DRG) neurons innervating the lumbar vertebrae of osteoporotic rats.

The purpose of this study was to evaluate pain behavior in an osteoporosis model using rats and to perform osteoclast cultures in order to elucidate the mechanisms underlying osteoporotic pain without fractures.

1. Sensory innervated lumbar vertebrae in osteoporotic rats

As an osteoporosis model, we used female rats ovariectomized (OVX) at five weeks. We evaluated the levels of CGRP, a marker of inflammatory pain immunoreactive (-ir), and Tuj-1, a marker of nerve axon immunoreactive (-ir) sensory neurons innervating the lumbar vertebrae, in osteoporotic rats using immunohistochemistry. The proportions of CGRP-ir and Tuj-1-ir neurons were significantly elevated in the lumbar vertebrae of the osteoporotic rats.

2. Study of cocultures of osteoclasts and DRG cells *in vitro*

We performed cocultures using the culture supernatant of osteoclasts and DRG cells.

The proportions of CGRP-ir and Tuj-1-ir neurons were significantly elevated in the cocultured DRG cells.

These results suggest that sensory nerve ingrowth might increase in the bone marrow of osteoporotic vertebral bodies compared to that observed in normal rats.

3. Evaluation of pain behavior

Currently, we are attempting to assess pain by using CatWalk to evaluate the pain behavior of osteoporotic rats.

At the G-COE workshop, I had a very special academic experience. In particular, giving an English presentation and participating in a Q and A session enhanced my skills. In addition, I am honored to have been elected to receive the G-COE Special Research Award for 2012.

Identification of novel molecular targets regulated by tumor suppressive miR-375 induced by histone acetylation in esophageal squamous cell carcinoma

Research Assistant

Yuka Isozaki

Department of Frontier Surgery
Graduate School of Medicine,
Chiba University

The aim of this study was to determine whether histone acetylation regulates tumor suppressive microRNAs (miRNAs) in esophageal squamous cell carcinoma (ESCC) and to the identify genes regulated by these miRNAs. We identified an miRNA that was highly upregulated in an ESCC cell line by cyclic hydroxamic acid-containing

peptide 31 (CHAP31), a histone deacetylase inhibitor (HDACI), using a miRNA array analysis. miR-375 was strongly upregulated by CHAP31 treatment in an ESCC cell line. The expression level of the most upregulated miRNA, miR-375, was analyzed using quantitative real-time PCR in human ESCC specimens. The tumor suppressive function of miR-375 was revealed by restoring miR-375 in the ESCC cell lines. We performed a microarray analysis to identify the target genes of miR-375. The mRNA and protein expression levels of these genes were verified in the ESCC clinical specimens. LDHB and AEG-1/MTDH were detected as miR-375-targeted genes. Restoration of miR-375 suppressed the expressions of LDHB and AEG-1/MTDH. The ESCC clinical specimens exhibited a high level of the LDHB expression at both the mRNA and protein levels. A loss-of-function assay using an siRNA analysis was performed to examine the oncogenic function of the gene. Knockdown of LDHB by RNAi revealed a tumor suppressive function in the ESCC cells. The correlation between the gene expression and clinicopathological features was investigated using immunohistochemistry in 94 cases of ESCC. Positive staining of LDHB correlated significantly with the presence of lymph node metastasis and the tumor stage. Positive staining also exhibited a tendency to be associated with a poor prognosis. Our results indicate that HDACIs upregulate miRNAs, some of which act as tumor suppressors. LDHB, which is regulated by the tumor suppressive miR-375, may therefore act as an oncogene in ESCC.

Development of a new therapy for cardio-renal interaction through the anti-inflammatory and anti-oxidative effects of cilostazol/probucol

Research Assistant

Peng He

Department of Clinical Cell Biology and Medicine
Graduate School of Medicine, Chiba University

The number of patients with diabetic nephropathy (DN) has been increasing dramatically, largely due to the increase in diabetic patients. It is well known that the dysfunction of podocytes, one of the cell types composing renal glomeruli, are important for the development and progression of DN, and that inflammation plays a key role in the development of podocyte injury. Therefore, anti-inflammatory treatment may be useful for preventing the development and progression of DN. Based on our work on the protective effects of cilostazol/probucol against inflammatory kidney injury, I was appointed as a G-COE-RA and received generous scientific and economic support.

In our studies, we demonstrated that cilostazol, an antiplatelet drug, and probucol, an anti-hyperlipidemia drug, have an additive protective effect against LPS-induced acute inflammation of the kidneys though their anti-inflammatory and anti-oxidative properties. With regard to the molecular mechanism underlying these effects, cilostazol can repress the phosphorylation of p44/42 MAPK, and probucol can repress the increase in oxidative stress, which additively protect the renal glomeruli from inflammatory injury. Therefore, with these two drugs working together, it may be possible to prevent the development and progression of DN.

The support from the G-COE program was important for our findings. At the G-COE workshop and English presentation class, we presented our research in English to prepare us for international conferences in the future. Moreover, the comments and the advice of the advisers helped me a lot in my research. In addition, events like the retreat and G-COE seminar provided good opportunities to discuss my researcher with investigators from different fields. These events opened my eyes and encouraged me to search for new ideas.

The role of ESET in hematopoietic stem cells

Research Assistant

Shuhei Koide

Department of Cellular and Molecular Medicine
Graduate School of Medicine, Chiba University

Stem cells can divide and differentiate into diverse specialized cell types, and can self-renew to produce more stem cells. The cell populations that make up the tissues and organs are closely involved in the maintenance of hierarchy. On the other hand, the presence of cancer stem cells continues to supply tumorigenic cells while differentiating and undergoing limited self-renewal. It is believed that the cause of these cancer stem cells is a failure in an epigenetic regulatory mechanism. I was appointed as a Global COE-RA to study the mechanisms of stem cell maintenance in normal stem cells, so that we could apply these finding to destroy cancer stem cells.

ESET is a histone H3 Lys 9 (H3K9) methyltransferase that suppresses gene expression. We hypothesized that the methylation of H3K9 by ESET was important for the maintenance of the undifferentiated state of the stem cells. To assess this, we performed a conditional loss analysis *in vivo*. We also performed bone marrow transplantation in mice conditionally deficient in ESET after the C57BL/6 wild-type mice were lethally irradiated. As a result, a significant reduction of bone marrow hematopoietic cell populations was observed, and ESET was therefore concluded to be essential for the maintenance of hematopoietic stem cells.

The Global COE-RA workshop was conducted in English. In addition, I received objective advice from different senior advisers. This was a great experience for me, and will help me make a presentation at an international conference in the future. At the Global COE retreat, I had the opportunity to talk with people from various fields, which was very helpful for expanding my appreciation of the various types of immunology-related research.

Elucidation of intercellular communication of pancreatic β-cells: A fundamental basis for islet transplantation in autoimmune diabetes mellitus

Research Assistant

Asuka Morita

Department of Medical Physiology
Graduate School of Medicine, Chiba University

Type 1 diabetes mellitus is an autoimmune disease caused by pancreatic β-cell destruction. Currently, only allotransplantation of pancreatic islets or the pancreas is capable of freeing patients from supplementary insulin injections. Although recent progress in stem cell biology has enabled the generation of pancreatic β-cells from stem/progenitor cells, these differentiated β-cells must be assembled prior to transplantation into three-dimensional structures, namely islets. Islets are a functional unit of the insulin secretory machinery that are known to exhibit better insulin secretory responses than dispersed β-cells due to cell-to-cell communication. Nevertheless, the mechanisms underlying this intercellular communication have not been studied in detail. In this study, we aimed to clarify the molecular mechanisms underlying cell-to-cell communication using newly developed pseudoislets generated from a pancreatic β-cell line.

The pseudoislets generated in this study using a new method were superior to those generated by conventional methods with respect to having a similar size and round shape. In addition, we were able to precisely control the ratio of composing cells in a single pseudoislet, which allowed us to develop a novel experimental system for monitoring cell-to-cell communication. We generated pseudoislets composed of two types of β-cells: sensing cells with a stimulus-sensing apparatus (S-cell) and reporter cells equipped with a secretion monitoring gene (R-cell). Using this system, we succeeded in monitoring the secretion from R-cells by stimulating S-cells in the same pseudoislet. These systems are beneficial for clarifying the mechanisms underlying synchronization of insulin secretion and protection from cell death, both of which are required to establish effective and long-lasting regenerative medicine for patients with type 1 diabetes mellitus.

During the course of the Global COE-RA program, I was given many opportunities to present our research data in English. In addition, I would also like to express my gratitude to this program for giving me a chance to meet many highly motivated colleagues.

Phosphorylation of ATF2 during mitosis

Research Assistant

Hitomi Hasegawa

Department of Molecular Cell Biology
Graduate School of Pharmaceutical Sciences, Chiba University

Cancer cells undergo abnormal division and progress indefinitely. We would like to learn more about cancer cell growth by studying mitosis. Protein phosphorylation plays significant roles in cellular signaling, and research on the phosphorylation-related signaling in cancer cells constitutes an important step in the development of anti-cancer agents. Activating transcription factor 2 (ATF2) is known as a transcription factor that is activated by stress stimulation, and its transcriptional activity requires phosphorylation in the G1 phase. ATF2 regulates the expression of genes related to the cell cycle and immune responses. Better understanding ATF2 phosphorylation will be useful for cancer- and immune-related therapies. However, little is known about the phosphorylation of ATF2 in the mitotic phase.

In this study, we examined the phosphorylation of ATF2 during mitosis. We found that ATF2 is phosphorylated during mitosis. To identify the kinase that phosphorylates ATF2 in mitosis, we collected mitotic phase cells and treated these cells with several specific kinase inhibitors. The phosphorylation of ATF2 was decreased by RO-3306, a cyclin-dependent kinase 1 (Cdk1) inhibitor. Moreover, we found colocalization of ATF2 and Cdk1 in mitotic phase cells. Next, we examined the role of ATF2 in mitotic progression using shRNA. Cells with ATF2 knocked down exhibited an increased proportion of anaphase and telophase cells during mitosis. These results suggest that the phosphorylation of ATF2 by Cdk1 has important roles in mitosis.

At the Global COE-RA workshop, I was very nervous about making a presentation and discussion in English, but I think it was a good experience. The comments and suggestions given about my presentation were very useful, and provided a further impetus for my research. I want to devote myself to research based on the experiences gained at the Global COE-RA workshop.

Regulation of the activity of Src-family kinases in cancer cell detachment

Research Assistant

Takao Morinaga

Department of Molecular Cell Biology
Graduate School of Pharmaceutical Sciences,
Chiba University

Src-family kinases belong to a family of non-receptor type tyrosine kinases. Although there are many reports showing that activated Src-family kinases promote metastasis, one of the important steps of cancer malignancy, little is known about how Src is activated in metastasis. Our research, centered on the activity of Src-family kinases and metastasis, fit with the aim of Global COE program, so I was appointed as a Global COE-RA and started my research.

We established HeLa S3 cells stably expression Lyn, a member of the Src-family kinases. Using these cells and the parental cell line, we found that Lyn was activated during cell detachment. We also analyzed the membrane distribution of Lyn during cell detachment by sucrose-density gradient fractionation. As a result of the fractionation, we found that Lyn changed its membrane fraction on the plasma membrane from the low density fraction to the high density fraction during cell detachment, and Lyn showed hyper-activity when it was localized in the high density fraction. These results suggest that Src-family kinases are activated by changing their membrane distribution in metastasis, and that this activation likely contributes to cancer malignancy.

In the poster session at the global COE retreat, we were able to have a fruitful discussion with researchers of the same generation while getting acquainted. At the global COE workshop, many senior researchers from a variety of fields gave us valuable comments about our presentations. This was the first time that I conducted a presentation and Q&A session in English, but it was a good experience that helped sharpen my ability to explain my work. Some of the meaningful ideas obtained from these discussions were reflected in my research.

Nuclear tyrosine phosphorylation signals by Src-family tyrosine kinase

Research Assistant

Sho Kubota

Department of Molecular Cell Biology
Graduate School of Pharmaceutical Sciences,
Chiba University

The regulation of chromatin structure is important to control a wide variety of cellular events. The chromatin structure is changed in some types of cancer and is related to cancer malignancy. We recently we that nuclear-localized tyrosine kinases play roles in regulating the chromatin structure and histone modifications through tyrosine phosphorylation. To identify a new therapeutic target for cancer, we tried to understand the mechanism underlying the chromatin structural changes induced by tyrosine phosphorylation. I was selected as a Global COE-RA and started my project on this topic.

To identify tyrosine-phosphorylated proteins in the nucleus, we established cell lines expressing Lyn tyrosine kinase tagged with a nuclear localization signal (NLS-Lyn). The proteins that were affinity-purified from cell lysates using an anti-pTyr antibody were excised from an SDS-PAGE gel and subjected to proteolytic cleavage followed by LC/MS/MS.

We identified KAP1, a component of the heterochromatin structure, as a nuclear tyrosine-phosphorylated protein. The tyrosine phosphorylation of KAP1 was induced by various tyrosine kinases that are localized within the nucleus. We next investigated the major tyrosine phosphorylation sites of KAP1, and found that these sites are common tyrosine phosphorylation sites for various tyrosine kinases. Furthermore, the tyrosine phosphorylation of KAP1 inhibits its association with heterochromatin. These results suggest that tyrosine phosphorylation regulates the chromatin structure through the tyrosine phosphorylation of KAP1.

At the Global COE workshop, I presented and discussed my data in English. It was my first time to give a presentation in English, and I had good experiences. In addition, at the workshop, we were able to discuss our research with other investigators, and I obtained important opinions about the function of KAP1 from these other professors. At the Global COE Retreat, I had an opportunity to discuss various topics with other Global COE-RAs. The opinions from the other members were very useful for my research, and I was also able to learn about the other members' research in detail. I am grateful to the G-COE program for giving me such a valuable opportunity.

Development of a human blood-brain barrier model

Research Assistant

Atsuko Kamiichi

Laboratory of Pharmacology and Toxicology
Graduate School of Pharmaceutical Sciences,
Chiba University

The permeability across the blood-brain barrier (BBB) is one of the important factors affecting whether a drug can exert its effects on the central nervous system. Therefore, precise prediction of the permeability of drug candidates across the BBB is crucial for their successful development. To achieve such precise prediction, we aimed to develop a new human BBB model. Because this model is expected to contribute to the development of novel anti-allergy drugs, which is one of the aims of the G-COE program, my research project has been accepted as part of the G-COE program.

In the present study, two immortalization genes were introduced into human primary brain microvascular endothelial cells (BMECs) and human primary astrocytes (both are known as major components of the BBB) to establish new immortalized cell lines. These were named HBMEC/ciβ and HASTR/ci-1, respectively.

The HBMEC/ciβ and HASTR/ci-1 showed a higher proliferation capacity compared with the corresponding primary cells. HBMEC/ciβ showed a BMEC-specific mRNA expression profile and possessed properties essential for a functioning BBB (tight junction function and effective efflux transporter function). In addition, the cells showed transcytotic receptor function. We also found that HASTR/ci-1 cells showed an astrocyte-specific mRNA expression profile, and exhibited adenosine uptake activity, which is one of important functions of mature astrocytes. Therefore, it can be expected that HBMEC/ciβ and HASTR/ci-1 cells will be useful for development of an easy-to-use and highly functional human BBB model.

As a member of the G-COE program, I have worked enthusiastically and aggressively published my research results in English. I gave a presentation in English at the 12th European ISSX Meeting in the Netherlands, as well as at the G-COE workshop. These experiences have made me realize that I still need to work on my English presentation skills. Therefore, in addition to working hard on my research, I will keep brushing up on my English.

5. Events

We established Annual Best Research Award to enhance young researchers' motivation to pursue research. The award was given to Ph.D. students in the G-COE relevant fields whose research was recognized to be the most outstanding through evaluation in the committee of the G-COE Operation and Management Office. The winners gained research fund with a certificate and a commemorative gift.

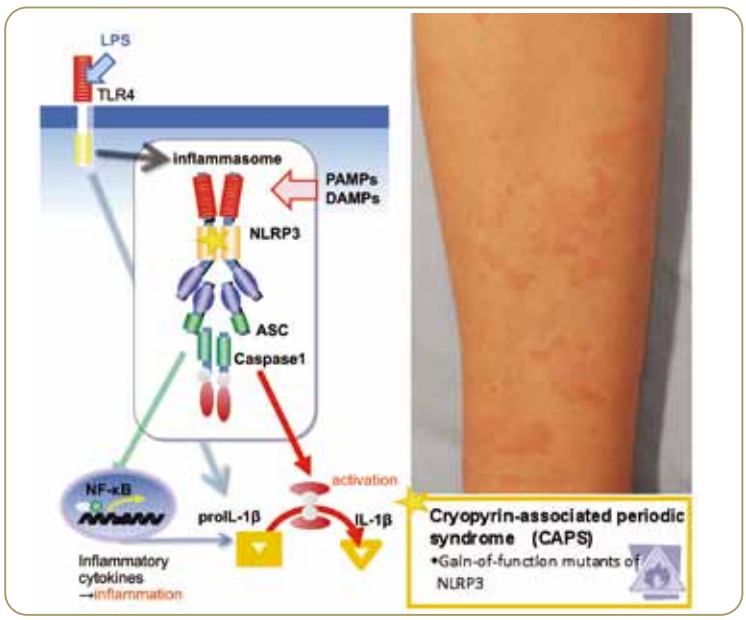
The 1st Annual Best Research Award

The 1st Annual Best Research Award

Yuumi Nakamura
Graduate Student,
Department of Dermatology, Graduate School of Medicine,
Chiba University

Mast cells mediate neutrophil recruitment and vascular leakage through the NLRP3 inflammasome in histamine-independent urticaria

Urticarial rash observed in cryopyrin-associated periodic syndrome (CAPS) caused by NLRP3 mutations is effectively suppressed by anti-IL-1 treatment, suggesting a pathophysiological role of IL-1β in the skin. We identified mast cells (MCs) as the main cell population responsible for IL-1β production in the skin of CAPS patients. Unlike normal MCs that required stimulation with proinflammatory stimuli for IL-1β production, resident MCs from CAPS patients constitutively produced IL-1β. Primary MCs expressed inflammasome components and secreted IL-1β via NLRP3 inflammasome. Furthermore, MCs expressing disease-associated but not wild-type NLRP3 secreted IL-1β and induced neutrophil migration and vascular leakage, the histological hallmarks of urticarial rash, when transplanted into mouse skin. Our findings implicate MCs as IL-1β producers in the skin and mediators of histamine-independent urticaria through the NLRP3 inflammasome.



The 2nd Annual Best Research Award

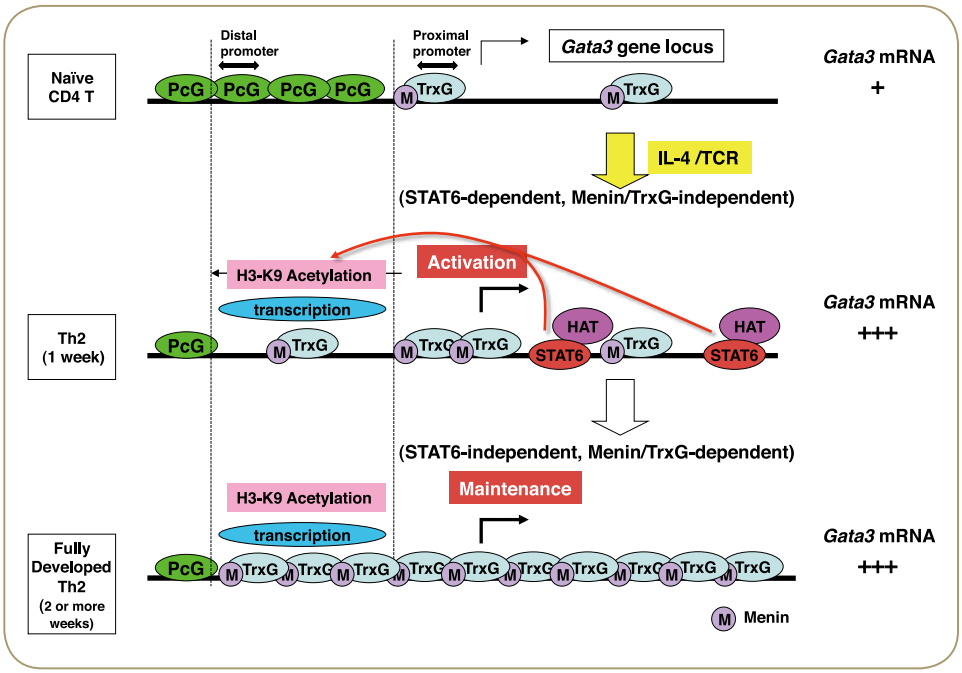
The 2nd Annual Best Research Award

Atsushi Onodera
G-COE Independent Research Associate,
Department of Immunology, Graduate School of Medicine,
Chiba University

STAT6-mediated displacement of Polycomb by the Trithorax complex establishes long-term maintenance of *Gata3* expression in Th2 cells

Polycomb group (PcG) and Trithorax group (TrxG) molecules act as antagonistic regulators to maintainen the transcriptional status of the developmentally regulated *Hox* genes. Various nuclear factors, including the PcG and TrxG molecules, regulate T helper type 2 (Th2) cells, which play an important role in humoral immunity and allergic reactions. We found that the activation of STAT6 induces the displacement of the PcG complex by the TrxG complex at the upstream region of the *Gata3* gene encoding a transcription factor essential for Th2 cell differentiation. Once Th2 cells are developed, the TrxG complex associated with Menin binds to the whole *Gata3* gene locus, and this binding is required for the long-term maintenance of *Gata3* expression and Th2 cytokine expression. Thus, STAT6-mediated displacement of PcG by the TrxG complex establishes a subsequent STAT6-independent regulation of *Gata3* expression in Th2 cells via the recruitment of the Menin/TrxG complex.

(*J. Exp. Med.* 207(11): 2493-506 (2010))



The 3rd Annual Best Research Award

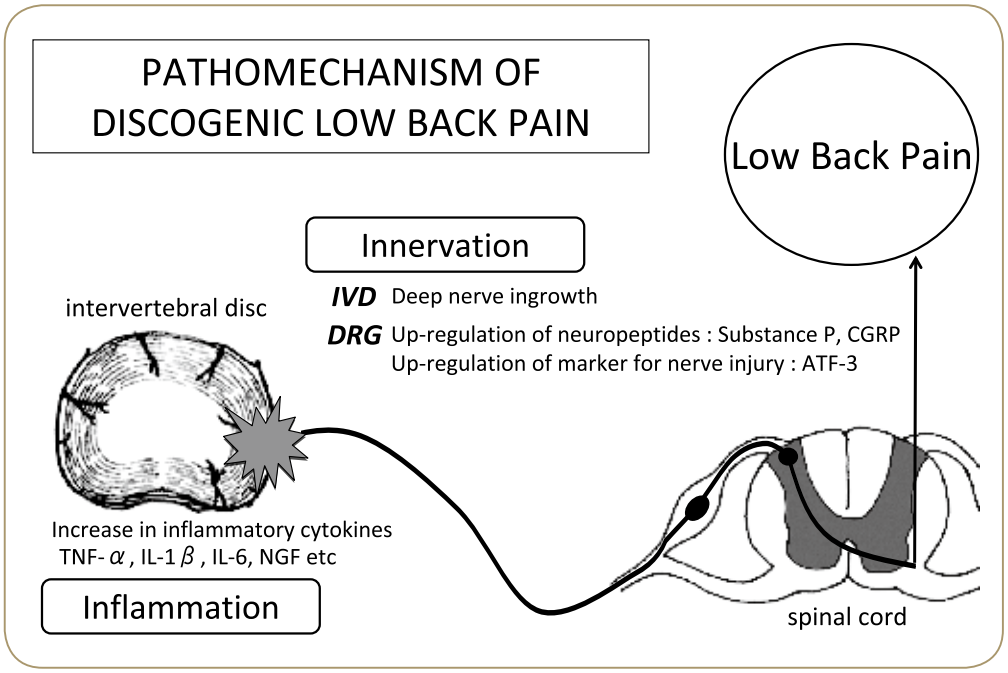
The 3rd Annual Best Research Award

Masayuki Miyagi
G-COE Research Assistant,
Department of Orthopaedic Surgery,
Graduate School of Medicine,
Chiba University

Disc dynamic compression in rats produces long-lasting increases in inflammatory mediators in the discs, and induces long-lasting nerve injury and regeneration of the afferent fibers innervating discs: A pathomechanism for chronic discogenic low back pain

Low back pain is one of the most common and important medical problems. Intervertebral disc (IVD) pathology is thought to be a significant contributor to low back pain. However, its pathophysiology remains incompletely understood. We elucidated and compared the inflammatory mediators in the IVDs in rats, and the responses of the sensory nervous system in a newly developed IVD dynamic compression model. In this study, IVD compression in rats produced a long-lasting increase in inflammatory mediators, including NGF, TNFα, IL-1β and IL-6 in IVDs, and neuropeptides (including CGRP) in the dorsal root ganglia. Moreover, IVD compression induced long-lasting nerve injury and regeneration of the afferent fibers innervating IVDs. These results may help to further elucidate the causes of persistent discogenic low back pain in humans.

(Spine 2012 37(21): 1810-8)



The 3rd Annual Best Research Award

The 3rd Annual Best Research Award

Yusuke Endo
G-COE Fellow,
Department of Immunology,
Graduate School of Medicine,
Chiba University

Eomesodermin controls the function of IL-5-producing pathogenic memory Th2 cells

Many Japanese people (approximately 1/3 of the Japanese population) suffer from allergic diseases of the upper and lower respiratory tracts, such as chronic rhino-sinusitis and chronic bronchial asthma. However, these diseases are generally resistant to steroids, and no effective treatment has yet been developed. Chronic allergic airway inflammation is thought to be induced by allergen-specific $CD4^+$ helper T (Th) cells, mainly by Th2 cells. In particular, memory Th2 cells survive for a long time in the body and play a crucial role in maintaining many allergic diseases, including allergic asthma.

We identified pathogenic memory Th2 cells within the $CD62L^{lo}CXCR3^{lo}$ population of memory Th2 cells. The pathogenic population selectively produced IL-5 and induced allergic airway inflammation. We also clarified the unique molecular mechanisms of IL-5 in memory Th2 cells (**Figure 1**). In memory Th2 cells, IL-5 is regulated by two distinct mechanisms: (i) chromatin conformation at the IL-5 locus, and (ii) the expression of eomesodermin, which prevents GATA3-dependent transcriptional activity.

Recently, we and other groups have reported that allergic airway inflammation or chronic dermatitis are induced and maintained by pathogenic Th2 populations. In particular, the IL-5-producing Th2 population plays a critical role in these allergic diseases and is expected to provide a target for the treatment of these severe diseases.

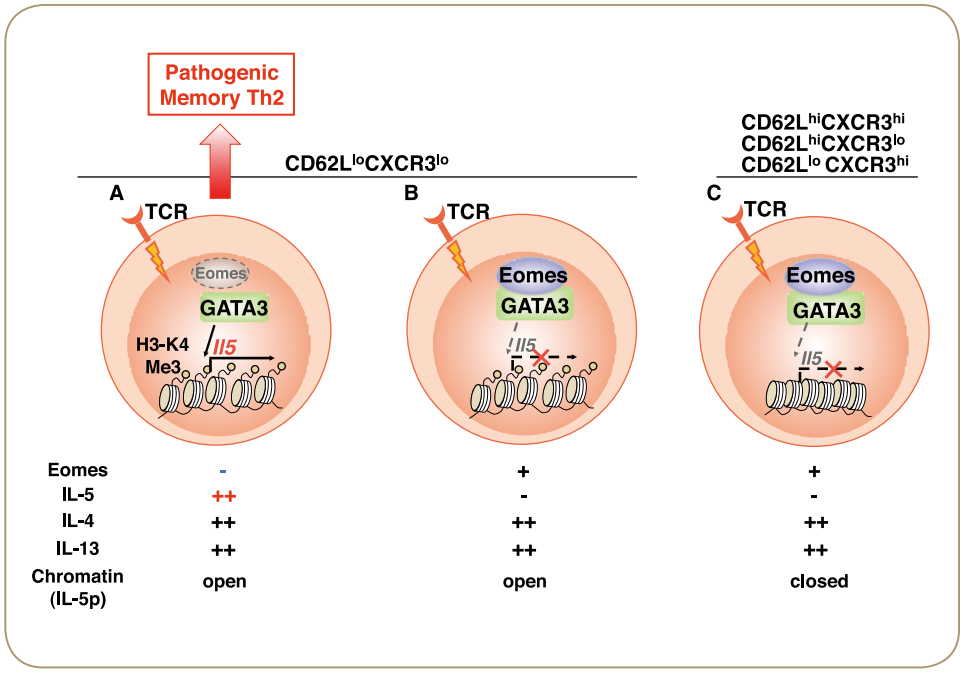


Figure 1: A schematic representation of the regulation of IL-5 expression in memory Th2 cells.
The expression of Eomes, GATA3 and that of IL-4, IL-13 and IL-5 after TCR stimulation in the four CD62L/CXCR3 subpopulations are shown. High H3-K4 methylation was observed at the *IL-5* promoter in the $CD62L^{low}CXCR3^{low}$ population of memory Th2 cells (**A and B**). The other three subpopulations (CD62L/CXCR3) showed low H3-K4 methylation (**C**). The population **A** expressed limited levels of Eomes, and could induce IL-5 expression upon TCR stimulation. Population **B** did not induce IL-5 expression due to its high expression of Eomes. Eomes interacts with GATA3 and inhibits the ability of GATA3 to induce IL-5 transcription.

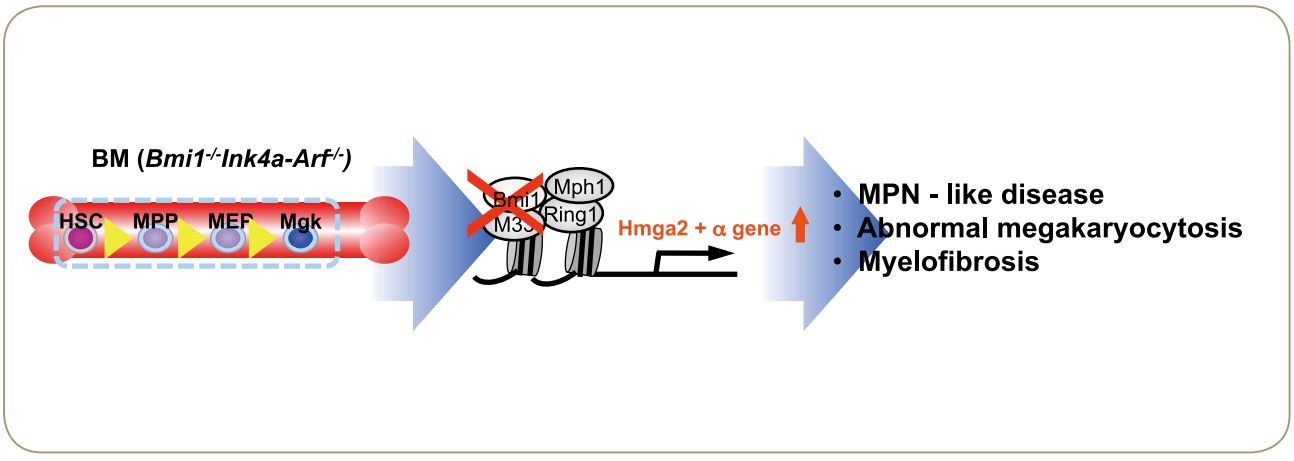
The 4th Annual Best Research Award

The 4th Annual Best Research Award

Yuan Jin
G-COE Research Assistant,
Department of Cellular and Molecular Medicine,
Graduate School of Medicine,
Chiba University

Lethal myelofibrosis induced by *Bmi1*-deficient hematopoietic cells unveils a tumor suppressor function of the polycomb group genes

Polycomb-group (PcG) proteins form the multiprotein polycomb repressive complexes (PRC) 1 and 2, and function as transcriptional repressors through histone modifications. They maintain the proliferative capacity of hematopoietic stem and progenitor cells by repressing the transcription of tumor suppressor genes, namely *Ink4a* and *Arf*, and thus have been characterized as oncogenes. However, the identification of inactivating mutations of a PcG gene, *EZH2*, unveiled a tumor suppressor function in myeloid malignancies, including primary myelofibrosis (PMF). We recently found that the loss of another PcG gene, *Bmi1*, causes pathological hematopoiesis similar to PMF. In a mouse model, loss of *Bmi1* in *Ink4a-Arf*$^{-/-}$ hematopoietic cells induced abnormal megakaryocytopoiesis, which was accompanied by marked extramedullary hematopoiesis, which eventually resulted in lethal myelofibrosis. The absence of *Bmi1* caused de-repression of a cohort of genes, including *Hmga2*, an oncogene overexpressed in PMF. Chromatin immunoprecipitation assays revealed that *Bmi1* directly represses the transcription of *Hmga2*. Of note, the overexpression of *Hmga2* in hematopoietic stem cells induced a myeloproliferative state with enhanced megakaryocytopoiesis in mice. Our findings provide the first genetic evidence of a tumor suppressor function of *Bmi1*, and also uncovered the role of PcG proteins in restricting growth by silencing oncogenes.



The 4th Annual Best Research Award

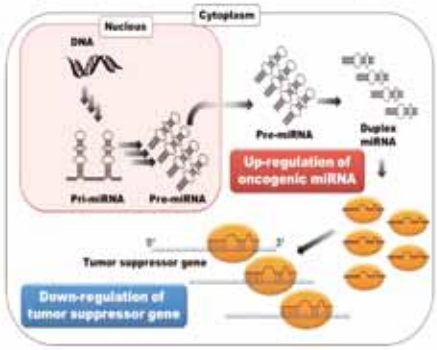
The 4th Annual Best Research Award

Nijiro Nohata
G-COE Research Assistant,
Department of Otolaryngology, Head and Neck Surgery,
Graduate School of Medicine,
Chiba University

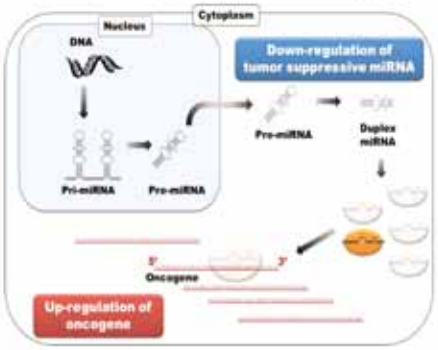
Tumor suppressive microRNAs regulate novel cancer pathways in head and neck squamous cell carcinoma

MicroRNAs (miRNAs) are a class of endogenous non-protein coding short RNA molecules. The miRNAs regulate the expression of multiple genes by degrading messenger RNA or repressing their translation in a sequence-specific manner. We first examined the miRNA expression profiles in maxillary sinus and hypopharyngeal squamous cell carcinoma (SCC) from clinical paired normal and cancer tissues. We found that 23 and 31 miRNAs were significantly downregulated in maxillary sinus and hypopharyngeal SCC, respectively, from these differential miRNA expression signatures (P<0.05). The downregulation of *miR-1*, *miR-133a*, *miR-375* and *miR-874* in cancer tissues was confirmed by qRT-PCR. Ectopic expression of *miR-1*, *miR-133a*, *miR-375* or *miR-874* significantly suppressed the HNSCC cell proliferation, migration and invasion activity. A genome-wide gene expression and bioinformatic analysis identified the molecular networks of these tumor suppressive miRNAs. These novel tumor suppressive miRNA-mediated pathways provide new insights into the potential mechanisms of HNSCC oncogenesis.

Hypothesis in cancer cell:
1) miRNAs function as oncogenes



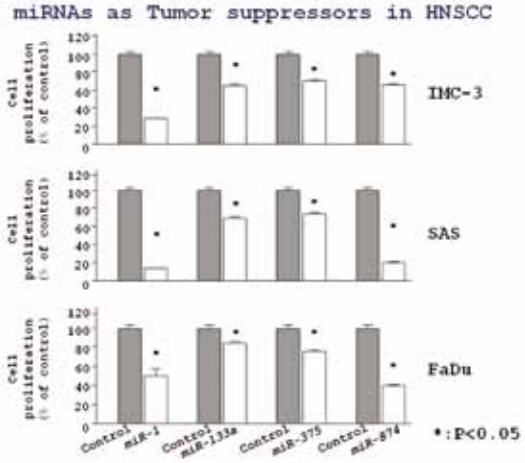
Hypothesis in cancer cell:
2) miRNAs function as tumor suppressors



Most down-regulated miRNAs in human SCC

Rank	Hypopharyngeal SCC	Maxillary sinus SCC	Esophageal SCC	Lung SCC
1	miR-1	miR-874	miR-375	miR-133a
2	miR-375	miR-133a	let-7c	miR-1247
3	miR-139-5p	miR-375	miR-145	miR-206
4	miR-504	miR-204	miR-143	miR-99b*
5	miR-125b	miR-1	miR-100	miR-139-5p
6	miR-199b	miR-139-5p	miR-133a	miR-30a-3p
7	miR-100	miR-145	miR-99a	miR-138
8	miR-497	miR-143	miR-133b	miR-126
9	let-7c	miR-486-3p	miR-1	miR-30e-3p
10	miR-30a*	miR-146a	miR-30a-3p	miR-26a-1*
11	miR-218	miR-410	miR-504	miR-140-3p
12	miR-10b	miR-126	miR-139-5p	miR-34b
13	miR-126*	miR-539	miR-204	miR-574-3p
14	miR-378	miR-134	miR-203	miR-628-5p
15	miR-328	miR-218	miR-326	miR-186

miRNAs as Tumor suppressors in HNSCC



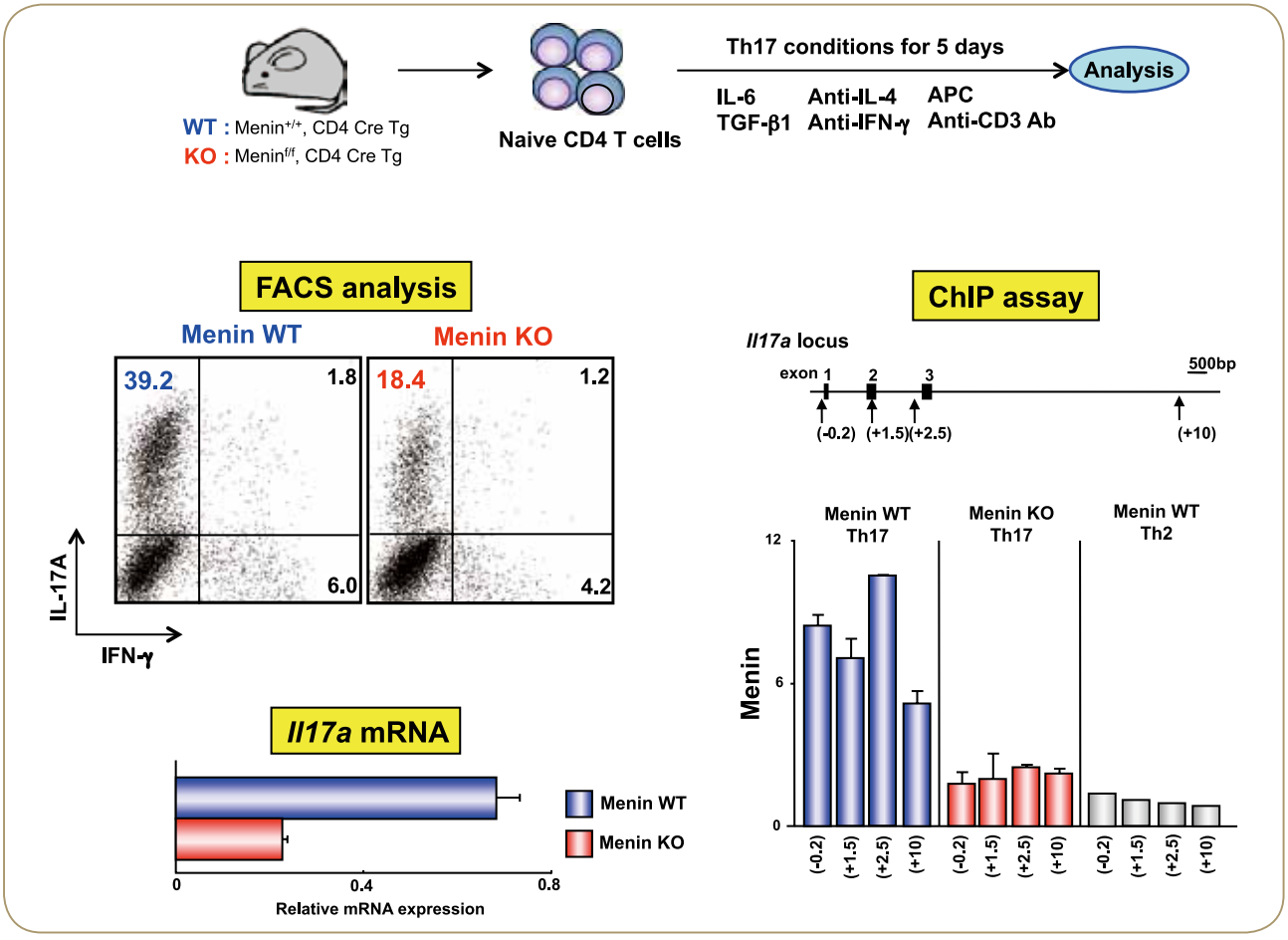
The 5th Annual Best Research Award

The 5th Annual Best Research Award

Yukiko Watanabe
G-COE Research Assistant,
Department of Immunology,
Graduate School of Medicine,
Chiba University

Role of Menin/TrxG in the differentiation and maintenance of Th17 cells

The Menin protein is known to be an essential component required for the DNA binding of the TrxG/MLL complex. Our previous data suggested that Menin controls the *Gata3* and *Il4* gene expression in Th2 cells. However, it remains unclear whether the Menin/TrxG complex is involved in Th17 cell differentiation. In this study, we show that Menin recruitment at the *Il17a* gene locus plays an important role in histone modification, RNAPII accumulation, and the subsequent expression of *Il17a* mRNA. Interestingly, the binding of Menin to the *Il17f* and *Rorc* gene loci is indispensable for maintaining the expression of these genes. Additionally, the binding of Menin to the Th17-related genes loci was dependent on STAT3 recruitment. *In vivo*, both allergic airway inflammation and mucus production were found to be attenuated in the mice transferred Menin-deficient Th17 cells. Therefore, Menin orchestrates the Th17 cell function *in vitro* and *in vivo*, thereby regulating the "induction" or "maintenance" of the target gene expression.



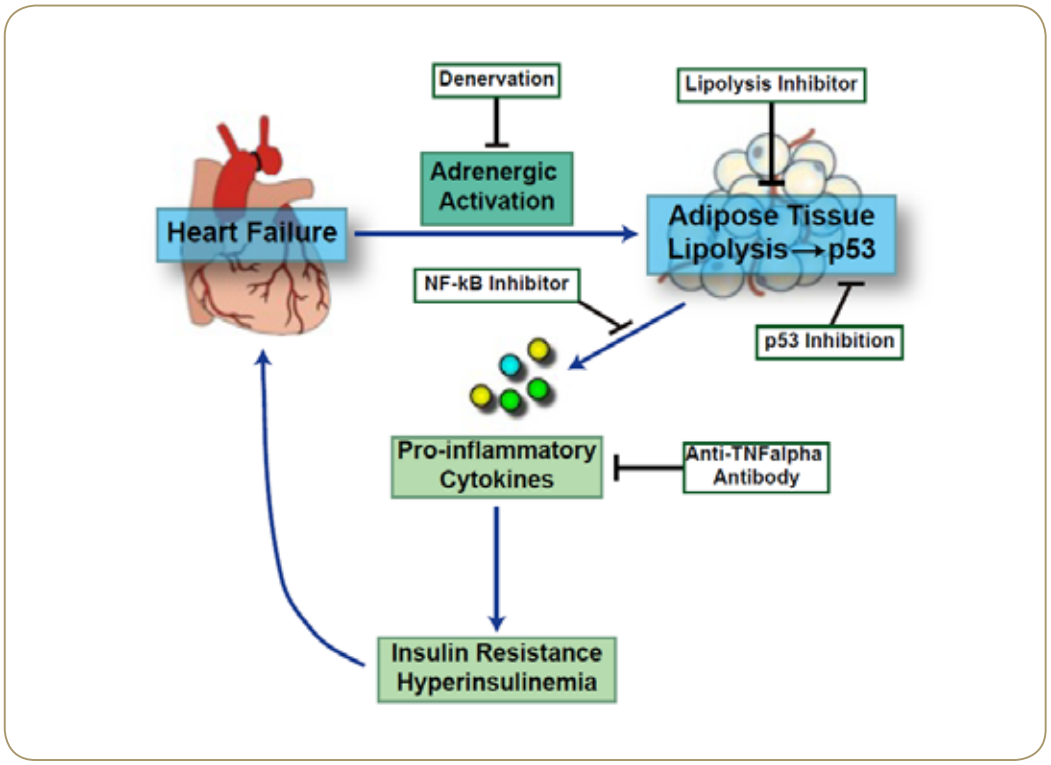
The 5th Annual Best Research Award

The 5th Annual Best Research Award

Yoko Yoshida
G-COE Research Assistant,
Department of Cardiovascular Medicine,
Graduate School of Medicine,
Chiba University

A crucial role for p53 in regulating adipose remodeling in heart failure and diabetes

Accumulating evidence has indicated that there is a close link between insulin resistance and heart failure (HF). In the present study, we show that p53-induced adipose tissue inflammation is critically involved in insulin resistance during HF, and that inhibition of adipose tissue p53 improves the progression of cardiac dysfunction, as well as metabolic abnormalities (Yoshida Y et al. Cell Metab. 15(1): 51-64, 2012). Although we previously reported that p53-induced adipose inflammation in obesity led to systemic insulin resistance (Nat Med 2009), its molecular mechanisms was unclear. In this study, we clarified that class 3 semaphorin E (Sema3E) acts as a chemoattractant for macrophages, with p53-induced upregulation of Sema3E expression provoking adipose tissue inflammation and systemic insulin resistance in association with dietary obesity (Yoshida Y et al., Nature in revision). Our results suggest that inhibition of p53-induced adipose tissue inflammation could be a novel therapeutic target to block the vicious cycle of metabolic dysfunction in patients with HF and obesity.



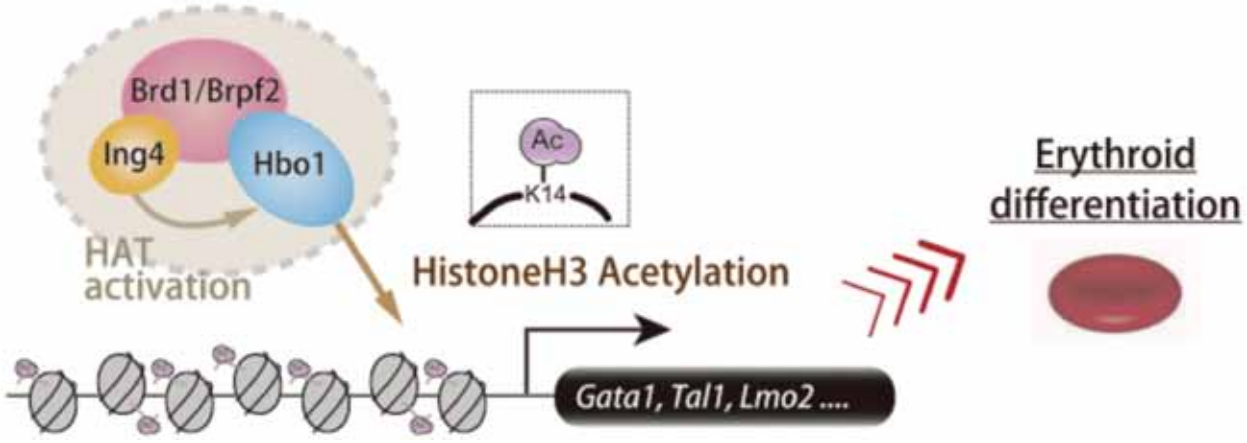
The 5th Annual Best Research Award

The 5th Annual Best Research Award

Yuta Mishima
Graduate Student,
Department of Cellular and Molecular Medicine,
Graduate School of Medicine,
Chiba University

The Hbo1-Brd1/Brpf2 complex is responsible for the global acetylation of H3K14 and is required for fetal liver erythropoiesis

Bromodomain-containing protein 1 (BRD1), also known as BRPF2, has been considered to be a subunit of the MOZ/MORF H3 HAT complex based on analogy with BRPF1 and BRPF3. In this study, we showed that BRD1 forms a novel HAT complex with HBO1 and regulates erythropoiesis. Brd1-deficient embryos showed severe anemia due to impaired fetal liver erythropoiesis. The biochemical analyses revealed that BRD1 bridges HBO1 and its activator protein, ING4. Genome-wide mapping in erythroblasts demonstrated that BRD1 and HBO1 are largely co-localized in the genome, and target key developmental regulatory genes. Of note, the levels of global acetylation of histone H3 at lysine 14 (H3K14) were profoundly decreased in Brd1-deficient erythroblasts, and depletion of Hbo1 similarly affected H3K14 acetylation. Impaired erythropoiesis in the absence of Brd1 was accompanied by a reduced expression of key erythroid regulator genes. Our findings suggest that the Hbo1-Brd1 complex is the major H3K14 HAT required for the transcriptional activation of erythroid developmental regulatory genes in the fetal liver.



The Hbo1-Brd1/Brpf2 complex is responsible for global acetylation of H3K14 and required for fetal liver erythropoiesis

Blood. 2011 Sep 1;118(9):2443-53. Epub 2011 Jul 13.

The 1st Chiba University G-COE Symposium

"Immune System Regulation and Treatment"

Date: January 6, 2009
Venue: Sapia Hall, Tokyo Station Conference, Tokyo
Chair: Kazuo Suzuki, Toshinori Nakayama, Takeshi Tokuhisa, Stephen P. Schoenberger, Masaru Taniguchi, Steven F. Ziegler, Hiroshi Nakajima, Hiroyuki Matsue, Hideki Tanzawa, Toshiaki Kawakami

The 1st Chiba University Global COE Symposium "Immune System Regulation and Treatment" was held in cooperation with La Jolla Institute for Allergy & Immunology (LIAI) and RIKEN Research Center for Allergy and Immunology (RCAI).

Following opening addresses by Dr. Yasushi Saito, President of Chiba University, and Dr. Takeshi Tokuhisa, Dean, Graduate School of Medicine, and a presentation of Global COE outline by Dr. Toshinori Nakayama, Program Leader, Dr. Mitchell Kronenberg, President, LIAI, presented the keynote lecture entitled "Activation of invariant NKT cells by microbes and microbial products".

One hundred twenty participants attended the symposium. We invited six foreign researchers from LIAI and Benaroya Research Institute (BRI) with which we have made a collaborative agreement under this program, so that core members in three research fields of this program presented the current research activities. During each session we had a valuable discussion. This symposium was significant as the kick-off activity of this program and gave great momentum to our future research promotion.

Opening remarks

Yasushi Saito (President, Chiba University)
Takeshi Tokuhisa (Dean, Graduate School of Medicine, Chiba University)

G-COE outline

Toshinori Nakayama (Program Leader)

Keynote Lecture

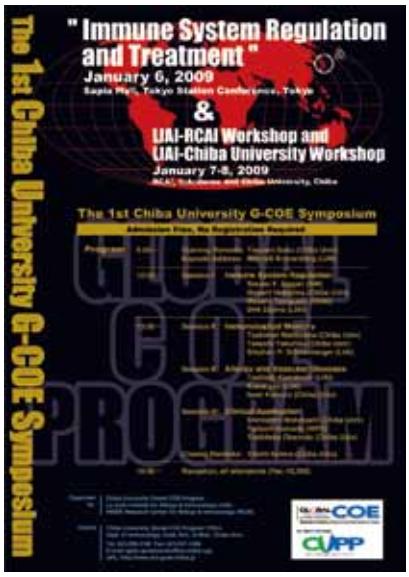
Mitchell Kronenberg (Division of Developmental Immunology, La Jolla Institute for Allergy & Immunology)
"Activation of invariant NKT cells by microbes and microbial products"

Lectures

Steven F. Ziegler (Immunology Program, Benaroya Research Institute)
"TSLP and Allergic Inflammation"
Hiroshi Nakajima (Dept. of Molecular Genetics, Graduate School of Medicine, Chiba University)
"Similarities and differences between IL-21-producing CD4$^+$ T cells and Th17 cells"
Masaru Taniguchi (RIKEN Research Center for Allergy & Immunology)
"A novel subset of mouse NKT cells bearing the IL-17 receptor B contributes to the development of airway hyperreactivity"
Alex Sette (Center for Emerging Diseases and Biodefense, La Jolla Institute for Allergy & Immunology)
"Structural features of immunodominance in antibody, helper and cytotoxic responses to vaccinia virus"
Toshinori Nakayama (Dept. of Immunology, Graduate School of Medicine, Chiba University)
"Regulation of memory Th1/Th2 cell survival and function by the Polycomb group and Trithorax group gene products"
Takeshi Tokuhisa (Dept. of Developmental Genetics, Graduate School of Medicine, Chiba University)
"Possible roles for Bcl6 in differentiation of germinal center B cells"
Stephen P. Schoenberger (Laboratory of Cellular Immunology, La Jolla Institute for Allergy & Immunology)
"Programming of CD8$^+$ T cell tolerance versus immunity by B cell APC"
Toshiaki Kawakami (Division of Allergy, La Jolla Institute for Allergy & Immunology)
"Skin inflammation regulated by mast cells"
Klaus Ley (Autoimmune Research; Inflammation Biology, La Jolla Institute for Allergy & Immunology)
"Inflammatory cell recruitment to atherosclerotic lesions"
Issei Komuro (Dept. of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University)
"Critical roles of muscle-secreted angiogenic factors in therapeutic neovascularization using peripheral mononuclear cells"
Shinichiro Motohashi (Dept. of Immunology, Graduate School of Medicine, Chiba University)
"Accumulation of activated Vα24 invariant natural killer T cells in the tumor microenvironment after α-Galactosylceramide-pulsed IL-2/GM-CSF-cultured peripheral blood mononuclear cell treatment"
Tadashi Kamada (Research Center for Charged Particle Therapy, National Institute of Radiological Sciences)
"Carbon ion radiotherapy for bone and soft tissue sarcomas"
Yoshitaka Okamoto (Dept. of Otorhinolaryngology, Graduate School of Medicine, Chiba University)
"Immunotherapy of nasal submucosal injection of α-Galactosylceramide-pulsed antigen presenting cells or with combination of intra-arterial infusion of activated natural killer T cells in patients with head and neck squamous cell cancer"

Closing remarks

Yoichi Kohno (Director, Chiba University Hospital, Chiba University)



The 2nd Chiba University G-COE Symposium

"Differentiation and Function of Lymphocytes"

Date: May 29, 2009
Venue: The 1st Auditorium, Chiba University Hospital 3F
Director: Takeshi Tokuhisa
Chair: Toshinori Nakayama, Takeshi Tokuhisa, Kazuo Suzuki, Hiroshi Nakajima

The 2nd Chiba University Global COE Symposium "Differentiation and Function of Lymphocytes", organized by Dr. Takeshi Tokuhisa, was held at the 1st Auditorium, Chiba University Hospital, on May 29, 2009. Six foreign researchers including three from the U.S. National Institutes of Health (NIH), and one researcher from Japan gave talks as invited speakers. One hundred thirty people, including both clinicians and basic researchers, gathered to learn and discuss their latest studies.

Following opening remarks by Dr. Toshinori Nakayama, Program Leader, and the plenary lecture by Dr. Alfred Singer, National Institutes of Cancer, NIH entitled "Circumventing Thymic Selection of MHC-Restricted T Cells", three sessions were held. During the second session, entitled G-COE fellow presentation, a young scientist at Chiba University and G-COE-RA in this program described their studies. Discussions during each session were so lively, and the atmosphere so exciting, that many participants seemed to be disappointed when Dr. Haruaki Nakaya, Dean, Graduate School of Medicine, gave closing remarks.

Opening remarks

Toshinori Nakayama (Program Leader)

Plenary lecture

Alfred Singer (Experimental Immunology Branch, National Cancer Institute, NIH)
"Circumventing Thymic Selection of MHC-Restricted T Cells"

Lectures

Sonoko Habu (Department of Immunology, Juntendo University School of Medicine)
"Thymus is an Essential Environment for T Cell Specification Through Notch Signaling"
Rémy Bosselut (Laboratory of Immune Cell Biology, National Cancer Institute, NIH)
"Transcriptional Control of CD4 T Cell Lineage Differentiation in the Thymus"
Daniel Campbell (Benaroya Research Institute)
"T-bet Controls Regulatory T Cell Homeostasis and Function During Type-1 Inflammation"
Dinah Singer (Experimental Immunology Branch, National Cancer Institute, NIH)
"Complex Regulatory Mechanisms Govern MHC Class I Transcription in vivo"
Junji Moriya (Department of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University)
"Inhibition of Semaphorin as a Novel Strategy for Therapeutic Angiogenesis"
Daisuke Kashiwakuma (Department of Molecular Genetics, Graduate School of Medicine, Chiba University)
"Development and Characterization of IL-21-producing CD4$^+$ T Cells"
Koji Tokoyoda (Department of Immunology, Graduate School of Medicine, Chiba University, DRFZ Berlin, Germany)
"Professional Memory CD4$^+$ T Lymphocytes Preferentially Reside and Rest in the Bone Marrow"
Rose Zamoyska (Institute for Immunology and Infection Research, The University of Edinburgh)
"The Influence of Signal Strength on the Differentiation of Effector and Memory T Cells"
Hiroyuki Matsue (Department of Dermatology, Graduate School of Medicine, Chiba University)
"Murine Skin-derived Cultured Mast Cells: A Useful Tool for Discovering Functions of Skin Mast Cells"
Stephen P Shoenberger (La Jolla Institute for Allergy and Immunology)
"Molecular Determinants of CD8$^+$ T Cell Memory"

Closing remarks

Haruaki Nakaya (Dean, Graduate School of Medicine, Chiba University)

The 3rd Chiba University G-COE Symposium

"Molecular Dynamics of Immune System Regulation"

Date: November 6, 2009
Venue: The 1st Auditorium, Chiba University Hospital 3F
Chair: Masakatsu Yamashita, Kazuo Suzuki, Toshinori Nakayama, Shinichiro Motohashi, Issei Komuro, Atsushi Iwama, Hiroshi Nakajima, Koutaro Yokote, Tomoaki Tanaka, Ichiro Taniuchi

The 3rd Chiba University Global COE Symposium "Molecular Dynamics of Immune System Regulation" was held at the 1st Auditorium, Chiba University Hospital, on November 6. At this symposium, to be also held as part of commemorating the 60th anniversary of Chiba University, which began with an address by Dr. Yasushi Saito, President of Chiba University, three invited speakers from abroad, Dr. Ken G. C. Smith (University of Cambridge), Dr. Dale T. Umetsu (Children's Hospital Boston, Harvard Medical School) and Dr. James K. Liao (Brigham & Women's Hospital, Harvard Medical School) gave special lectures. Joined by six domestic invited speakers they presented the most recent studies about signaling pathways and transcriptional regulation in their own research fields from a wide range of fields, not only immunology, as well as new trends in immunology such as immunogenomics, humanized mouse, and real-time cellular imaging. The presentations and discussions in a cross-disciplinary approach stimulated all the participants. Dr. Haruaki Nakaya, Dean, Graduate School of Medicine, gave closing remarks.

Opening remarks

Yasushi Saito (President, Chiba University)

Special lectures

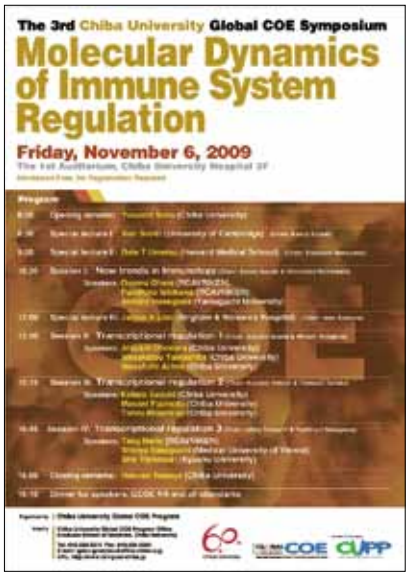
Kenneth G. C. Smith (Cambridge Institute for Medical Research, University of Cambridge)
"Fc receptors: immune regulation, autoimmunity and evolution"
Dale T. Umetsu (Children's Hospital Boston, Harvard Medical School)
"Microbes, apoptosis and TIM-1 in the development of asthma"
James K. Liao (Brigham & Women's Hospital and Harvard Medical School)
"Akt/mTOR: a potential link between altered circadian rhythm, obesity, and vascular senescence"

Lectures

Osamu Ohara (Laboratory for Immunogenomics, RIKEN Research Center for Allergy and Immunology; Department of Human Genome Research, Kazusa DNA Research Institute)
"From transcriptome analysis to immunogenomics: current status and future direction"
Fumihiko Ishikawa (Research Unit for Human Disease Models, RIKEN Research Center for Allergy & Immunology)
"Humanized mouse for biomedical research"
Akihiro Hasegawa (Department of Microbiology and Immunology, Yamaguchi University School of Medicine)
"Real-time cellular imaging of T lymphocyte migration in mouse asthma model"
Atsushi Onodera (Department of Immunology, Graduate School of Medicine, Chiba University)
"The dynamic exchange of Polycomb and Trithorax molecules binding to the GATA3 gene locus controls the Th2-specific GATA3 expression"
Masakatsu Yamashita (Department of Immunology, Graduate School of Medicine, Chiba University)
"Regulation of the GATA3-induced immune responses by the transcription factor Sox4"
Masafumi Arima (Department of Developmental Genetics, Graduate School of Medicine, Chiba University)
"A critical role of the intron enhancer element of the IL-4 gene in Th2 cytokine expression"
Kotaro Suzuki (Department of Molecular Genetics, Graduate School of Medicine, Chiba University; Laboratory of Genetics, Salk Institute)
"Roles of mast cell IKK/NF-κB pathway in allergic reactions"
Masaki Fujimoto (Department of Clinical Cell Biology, Graduate School of Medicine, Chiba University)
"Twist-1: new negative-feedback regulator of peroxisome proliferator-activated receptor γ co-activator-1 α (PGC-1α)"
Tohru Minamino (Department of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University)
"Lifestyle-related disease and cellular aging signal network"
Taku Naito (Laboratory for Transcriptional Regulation, RIKEN Research Center for Allergy & Immunology)
"Ikaros-mediated epigenetic regulation of Notch signaling in T cell development and leukemeogenesis"
Shinya Sakaguchi (Division of Immunobiology, Institute of Immunology, CePPI, Medical University of Vienna)
"The zinc finger protein MAZR is part of the transcription factor network controlling CD4/CD8 cell fate decision of DP thymocytes"
Sho Yamasaki (Division of Molecular Immunology, Medical Institute of Bioregulation, Kyushu University)
"Self and non-self recognition through C-type lectin Mincle"

Closing remarks

Haruaki Nakaya (Dean, Graduate School of Medicine, Chiba University)



The 4th Chiba University G-COE Symposium

"Regulation of Immune Disorders"

Date: August 20, 2010
Venue: The 1st Auditorium, Chiba University Hospital 3F
Chair: Toshinori Nakayama, Atsushi Iwama, Ichiro Taniuchi, Shinichiro Motohashi, Naoki Shimojo, Andreas Radbruch, Takeshi Tokuhisa, Hiroshi Nakajima, Steven F. Zieglar, Hisahiro Matsubara

The 4th Chiba University Global COE Symposium "Regulation of Immune Disorders" was held at the 1st Auditorium, Chiba University Hospital, on August 20. The symposium focused on "Regulation of Immune Disorders" by the 7 invited speakers, who presented big topics in their current researches in the form of educational lectures for RA students. Following opening remarks by Dr. Yasushi Saito, President of Chiba University, and the plenary lecture by Dr. Anjana Rao, Harvard Medical School, entitled "Leukemia-associated mutations in TET2 diminish catalytic activity", five sessions were held. All attendees were able to engage in discussions with prominent investigators from all over the world and learned about their current activities. These discussions with symposium speakers are sure to show G-COE-RAs in high level research in immunology.

Opening remarks

Haruaki Nakaya (Dean, Graduate School of Medicine, Chiba University)

Plenary lecture

Anjana Rao (Department of Pathology, Harvard Medical School; Immune Disease Institute; and Program in Cellular and Molecular Medicine, Children's Hospital Boston)
"Leukemia-associated mutations in TET2 diminish catalytic activity"

Lectures

Ichiro Taniuchi (Laboratory for Transcriptional Regulation, RCAI, RIKEN)
"Transcriptional regulation of CD4/CD8 lineage choice"
Toshinori Nakayama (Department of Immunology, Graduate School of Medicine, Chiba University)
"STAT6-mediated displacement of Polycomb by the Trithorax complex establishes long-term maintenance of GATA3 expression in Th2 cells"
Atsushi Iwama (Department of Cellular and Molecular Medicine, Graduate School of Medicine, Chiba University)
"Unexpected role for the polycomb gene Bmi1 in lymphoid commitment"
Mitchell Kronenberg (La Jolla Institute for Allergy and Immunology)
"Recognition of microbial and environmental antigens by invariant natural killer T cells"
Chiaki Iwamura (Department of Immunology, Graduate School of Medicine, Chiba University)
"Antigen-specific memory CD4 T cells selectively expanded by NKT cell activation *in vivo*"
Hilde Cheroutre (La Jolla Institute for Allergy and Immunology)
"Omitting Felony by Switching Fate: Lineage Conversion of CD4 Th cells to CD8 CTLs"
Takeshi Tokuhisa (Department of Developmental Genetics, Graduate School of Medicine, Chiba University)
"Roles for Bcl6 in differentiation of germinal center B cells"
Shane Crotty (La Jolla Institute for Allergy and Immunology)
"Differentiation and function of follicular helper CD4 T cells (T_{FH})"
Andreas Radbruch (Deutsches Rheumaforschungszentrum Berlin)
"Protective and pathogenic immunological memory"
Steven F. Ziegler (Immunology Program, Benaroya Research Institute)
"TSLP and Allergic Inflammation"
Erwin W. Gelfand (National Jewish Health)
"The Dual Role of $CD8^+$ T cells in the Regulation of Lung Allergic Responses"
Yoichi Suzuki (Department of Public Health, Graduate School of Medicine, Chiba University)
"Matrix metalloproteinase genes in the pathogenesis of allergic airway diseases"
Yoshitaka Okamoto (Department of Otorhinolaryngology, Head and Neck Surgery, Chiba University Hospital)
"NKT cell-based immunotherapy for cancer: Nasal submucosal administration of antigen-presenting cells may induce effective anti-tumor immune responses"
Kazuo Suzuki (Inflammation Program, Department of Immunology, Graduate School of Medicine, Chiba University)
"Approach to clinical trial of synthetic immunoglobulin treatment for vasculitis"

Closing Remarks

Yoichi Kohno (Director, Chiba University Hospital)

The 5th Chiba University G-COE Symposium

"Development and Maintenance of Immune Memory"

Date: December 4, 2010
Venue: Sapia Hall, Tokyo Station Conference, Tokyo
Director: Takeshi Tokuhisa
Chair: Koji Tokoyoda, Toshinori Nakayama, Takashi Saito, Kazuo Sugamura, Koji Matsushima, Masayuki Miyasaka, Hiroshi Kiyono, Ichiro Taniuchi, Tomohiro Kurosaki, Toshitada Takemori

The 5th Chiba University Global COE Symposium "Development and Maintenance of Immune Memory" was held at Tokyo on September 4, co-organized by IMSUT&RCAST G-COE Program, The University of Tokyo.

This time, the theme was confined to immunological memory, though, more than 150 participants got together, which may suggest that immunological research in this area is receiving more attention. A total of 21 talks including one given by an invited researcher from the U.S. were presented in the symposium, starting with a session on Memory CD4 T cells and ending with one on Memory B/Plasma cells. At the end, Dr.Tasuku Honjo, Kyoto University, logically and energetically presented the latest studies on the mechanism of class switch recombination in the plenary lecture, and many participants were very impressed.

Opening remarks

Toshinori Nakayama (Program Leader, Chiba University Global COE Program)
Hiroshi Kiyono (IMSUT & RCAST G-COE Program, The University of Tokyo)

Lectures

Toshinori Nakayama (Department of Immunology, Graduate School of Medicine, Chiba University)
"CD4 T cell memory controlled by Polycomb and Trithorax molecules"
Naoto Ishii (Department of Microbiology and Immunology, Tohoku University School of Medicine)
"OX40 and IL-7 independently contribute to the proliferative homeostasis of effector memory $CD4^+$ T cells"
Yutaka Kurebayashi (Department of Microbiology and Immunology, Keio University School of Medicine)
"Regulation of Th17 differentiation by PI3K-Akt-mTORC1 axis"
Chiaki Iwamura (Department of Immunology, Graduate School of Medicine, Chiba University)
"Antigen-specific memory CD4 T cells selectively expanded by NKT cell activation *in vivo*"
Yusuke Endo (Department of Immunology, Graduate School of Medicine, Chiba University)

"Eomesodermin controls IL-5 production in memory Th2 cells through the inhibition of GATA3 activity"
Akemi Sakamoto (Department of Developmental Genetics, Graduate School of Medicine, Chiba University)
"Roles of Bcl6 in memory T cell development"
Keishi Fujio (Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo)
"$CD4^+CD25^-LAG3^+$ regulatory T cells in the treatment of inflammatory diseases"
Yasuhiro Nakashima (Department of Immunology and Cell Biology, Graduate School of Medicine and Faculty of Medicine, Kyoto University)
"PD-1+ memory phenotype $CD4^+$ T cells underlying impaired immune system in leukemia"
Kouji Matsushima (Department of Molecular Preventive Medicine, Graduate School of Medicine, The University of Tokyo)
"Spatial and temporal regulation of memory $CD8^+$ T cell response"
Makoto Kurachi (Department of Molecular Preventive Medicine & MD Student Training Program, Graduate School of Medicine, Center for NanoBio Integration (CNBI), The University of Tokyo)
"Chemokine receptor CXCR3 facilitates $CD8^+$ T cell differentiation into short-lived effector cells leading to memory degeneration"
Michio Tomura (Department of Molecular Preventive Medicine, Graduate School of Medicine, The University of Tokyo)
"Revealing of spatiotemporal regulation of memory T cell generation and maintenance in the whole body by Kaede-Tg mice"
Ruka Setoguchi (Laboratory for Immune Regulation, RIKEN Research Center for Allergy and Immunology)

"Maintenance of memory CD8 T cells"
Shiki Takamura (Department of Immunology, Kinki University Faculty of Medicine)
"Friend virus evasion of $CD8^+$ T cell immunity"
Koichi Araki (Emory Vaccine Center and Department of Microbiology and Immunology, Emory University School of Medicine)
"mTOR and memory CD8 T cell differentiation"
Takeshi Tokuhisa (Department of Developmental Genetics, Graduate School of Medicine, Chiba University)
"Role for Bcl6 in differentiation of high affinity IgE B cells"
Toshitada Takemori (Laboratory for Immunological Memory, RIKEN Research Center for Allergy and Immunology)
"Memory B cell generation and functional maturation; distinct cellular pathways establish B cell memory"
Yoshimasa Takahashi (Department of Immunology, National Institute of Infectious Diseases)
"Protective memory B cells against influenza virus infection in the lungs"
Takuya Nojima (Research Institute for Biological Science, Tokyo University of Science)
"Role of IL-21 in memory-versus-plasma cell fate decision of germinal center B cells induced *in vitro*"
Kohei Kometani (Laboratory for Lymphocyte Differentiation, RIKEN Research Center for Allergy and Immunology)
"Plasma cells differentiation from memory B cells"
Jun Kunisawa (Division of Mucosal Immunology, Institute of Medical Science, The University of Tokyo)
"Regulation of IgA antibody responses by immunological crosstalk with intestinal environmental factors"
Ayako Inamine (Department of Otolaryngology, Graduate School of Medicine, Chiba University)
"Establishment of the high affinity B cell memory by IL-21"

Plenary Lecture

Tasuku Honjo (Department of Immunology and Genomic Medicine, Graduate School of Medicine, Kyoto University)
"Evolutional origin of class switch recombination"

Closing Remarks

Takeshi Tokuhisa (Symposium Director, Chiba University Global COE Program)

The 6th Chiba University G-COE Symposium

"Immune System Regulation toward Disease Control"

Date: November 30, 2011
Venue: Hotel New Otani Makuhari, Chiba
Chair: Taishin Akiyama, Toshinori Nakayama, Takeshi Tokuhisa, Koji Tokoyoda, Masato Kubo, Akemi Sakamoto, Hiroshi Nakajima, Susumu Nakae

The 6th Chiba University Global COE Symposium "Immune System Regulation toward Disease Control" was held at Makuhari on November 30, co-organized by IMSUT&RCAST G-COE Program, The University of Tokyo.

This symposium focused on immune system regulation and immune-related diseases. A total of 15 talks were presented in the symposium, starting with the lecture by Dr. Alfred Singer, NIH, U.S., on lymphocyte development and homeostasis, followed by sessions in immunological memory and T lymphocyte function, and ending with one on allergy and inflammation by young researchers. The fact the hall was fully packed with audience suggests that we successfully lined up attractive researchers from home and abroad. The symposium ended successfully with the closing remarks by Dr. Hiroshi Kiyono, Professor, The University of Tokyo.

Opening remarks

Toshinori Nakayama (Program Leader, Chiba University Global COE Program)

Lectures

Alfred Singer (Experimental Immunology Branch, National Cancer Institute)
"Generation of T cells that recognize conformational antigenic epitopes independently of MHC"

Meinrad Busslinger (Research Institute of Molecular Pathology, Vienna Biocenter)
"Lineage commitment and plasticity of B lymphocytes"

Taishin Akiyama (Department of Cancer Biology, The Institute of Medical Science, The University of Tokyo)
"Molecular mechanisms to establish the thymic microenvironment essential for central tolerance"

Motoko Y. Kimura (Experimental Immunology Branch, National Cancer Institute)
"IL-7 signaling must be intermittent and not continuous to maintain naïve CD8 T cells and avoid cytokine induced cell death"

David Tarlinton (The Walter and Eliza Hall Institute of Medical Research)
"The Nature of B and T Cell Memory Generated in Germinal Centers"

Toshinori Nakayama (Department of Immunology, Graduate School of Medicine, Chiba University)
"Eomesodermin controls IL-5 production in memory Th2 cells through the inhibition of GATA3 activity"

Toshiaki Ohteki (Department of Biodefense Research, Medical Research Institute, Tokyo Medical and Dental University)
"Prominent role for pDCs in mucosal IgA induction"

Chen Dong (Department of Immunology and Center for Inflammation and Cancer, MD Anderson Cancer Center)
"Novel T cell subsets in immunity and diseases"

Hilde Cheroutre (Division of Developmental Immunology, La Jolla Institute for Allergy & Immunology)
"Mucosal Immunity: At the Borders, It Matters Who You Are"

Akihiko Yoshimura (Department of Microbiology and Immunology, Keio University School of Medicine)
"Role of SOCS1 in Treg plasticity and functions"

Masato Kubo (Research Institute for Biological Science, Tokyo University of Science RCAI, RIKEN Yokohama Institute)
"Regulation of IL-4 mediated humoral immunity by Follicular helper T cells"

Shinobu Saijo (Division of Molecular Immunology, Medical Mycology Research Center, Chiba University, PRESTO JST)
"C-type lectin and fungal infections"

Susumu Nakae (Laboratory of Systems Biology, Center for Experimental Medicine and Systems Biology and Frontier Research Initiative, The Institute of Medical Science, The University of Tokyo)
"Roles of IL-25 and IL-33 in allergic airway inflammation"

Koichi Hirose (Department of Allergy and Clinical Immunology, Chiba University Hospital)
"Roles of IL-22 in the regulation of allergic airway inflammation"

David Artis (Perelman School of Medicine, University of Pennsylvania)
"Regulation of Innate and Adaptive Immunity at Barrier Surfaces"

Closing Remarks

Hiroshi Kiyono (Project Leader, Global COE Program, The University of Tokyo)

The 7th Chiba University G-COE Symposium

"Current and Future Trends in Genome-based Immunity, Infection and Cancer"

Date: January 28, 2013
Venue: Sapia Hall, Tokyo Station Conference, Tokyo
Master chair: Shinichiro Motohashi
Chair: Hiroshi Nakajima, Toshinori Nakayama, Atsushi Iwama, Yoichi Furukawa, Naoya Kato

The 7th Chiba University Global COE Symposium "Current and Future Trends in Genome-based Immunity, Infection and Cancer" was held in Tokyo on January 28th, co-sponsored by the University of Tokyo IMSUT & RCAST G-COE Program.

The symposium centered around basic immunology research based on genome and post-genome studies, infection and cancer research. The symposium began with G-COE program activity reports by two program leaders, Dr. Toshinori Nakayama (Chiba University) and Dr. Hiroshi Kiyono (The University of Tokyo). Then, Dr. William E Paul (U.S. NIH) and Dr. Sean M. Grimmond (The University of Queensland, Australia) gave keynote lectures. In the three sessions that followed, research reports were presented and active discussions ensued.

The symposium ended with closing remarks by Dr. Takeshi Tokuhisa, vice president of Chiba University.

Overview of G-COE Program

Hiroshi Kiyono (Division of Mucosal Immunology, International Research Center for Infectious Diseases, The Institute of Medical Science, The University of Tokyo (IMSUT)
Toshinori Nakayama (Department of Immunology, Graduate School of Medicine, Chiba University)

Keynote Lecture

William E. Paul (Laboratory of Immunology, National Institute of Allergy and Infectious Diseases, National Institutes of Health)
"IL-1 Family Members: Potent Regulators of Cytokine Production and T Cells Responses to Antigen"
Sean M. Grimmond (Queensland Centre for Medical Genomics, Institute for Molecular Bioscience, The University of Queensland)
"Cohort and personalized Cancer Genome Analysis of Pancreatic Adenocarcinoma
Naoya Kato (Unit of Disease Control Genome Medicine, The Institute of Medical Science, The University of Tokyo)
"A Genome Wide Association Study for Hepatitis C Virus-Induced Liver Cirrhosis and Hepatocellular Carcinoma"

Lectures

Yoshihiro Kawaoka (International Research Center for Infectious Diseases and Division of Virology, Department of Microbiology and Immunology, The Institute of Medical Science, The University of Tokyo)
"An epic journey to publish ferret H5N1 transmission studies"
Ai Kawana-Tachikawa (Division of Infectious Diseases, Advanced Clinical Research Center, The Institute of Medical Science, The University of Tokyo)
"Mechanisms underlying disruption of T cell immunity during chronic HIV-1 infection"
Toshinori Nakayama (Department of Immunology, Graduate School of Medicine, Chiba University)
"Pathogenic memory Th2 cells in the airway"
Yoshitaka Okamoto (Department of Otorhinolaryngology, Graduate School of Medicine, Chiba University)
"Immunological changes after immunotherapy for cedar pollinosis and their clinical uses"
Tohru Minamino (Department of Cardiovascular Biology and Medicine, Niigata University Graduate School of Medical and Dental Sciences)
"Lifespan regulatory system as a potential therapeutic target for cardiovascular disease"
Shinichiro Motohashi (Department of Medical Immunology, Graduate School of Medicine, Chiba University)
"NKT cell-targeting therapy for lung cancer"
Makoto Otsu (Stem Cell Bank, Center for Stem Cell Biology and Regenerative Medicine, The Institute of Medical Science, The University of Tokyo)
"Pleiotropic nature of hematopoietic stem cell responses to an inflammatory niche environment"
Atsushi Kaneda (Genome Science Division, Research Center for Advanced Science and Technology (RCAST), The University of Tokyo, Core Research for Evolutional Science and Technology (CREST), Japan Science and Technology Agency.)
"Accumulation of epigenetic alteration involved in gastrointestinal carcinogenesis"
Atsushi Iwama (Department of Cellular and Molecular Medicine, Graduate School of Medicine, Chiba University)
"Tumor suppressor function of the polycomb-group genes in myelodysplastic disorders"
Akira Hata (Department of Public Health, Graduate School of Medicine, Chiba University)
"Identification of susceptibility genes for Kawasaki disease"

Closing remarks

Takeshi Tokuhisa (Vice President, Chiba University. Department of Developmental Genetics, Graduate School of Medicine, Chiba University)

Chiba University G-COE Workshop

The 1st Chiba University G-COE Workshop
"LIAI-RCAI Workshop and LIAI-Chiba University Workshop"

Date: January 7-8, 2009
Venue: The 1st Auditorium, Chiba University Hospital 3F
Chair: Kazuo Suzuki, Shinichiro Motohashi, Takeshi Tokuhisa, Hiroshi Nakajima, Toshinori Nakayama, Atsushi Iwama, Masakatsu Yamashita

This workshop was held at two venues, RIKEN and Chiba University, having 73 participants in Chiba University. We held this activity as part of CVPP (Chiba Visiting Professor Program), the core system for developing human resources in our Global COE Program. In addition to Chiba Visiting Professors' talks young scientists including the graduate student who was selected via a call for contribution made the oral presentation. Chiba Visiting Professors visited immunology-related labs to discuss and give advice on our research activities. We were so impressed with the ambitious remark our students made as to believe in the future progress.

Opening remarks
Toshinori Nakayama (Program Leader)

Lectures by invited speakers
Mitchell Kronenberg (Division of Developmental Immunology, La Jolla Institute for Allergy & Immunology)
"Innate immune function of NKT cells in the response to diverse microbes"
Toshiaki Kawakami (Division of Allergy, La Jolla Institute for Allergy & Immunology)
"Models of atopic dermatitis–characteristics and use"
Steven F. Ziegler (Immunology Program, Benaroya Research Institute)
"Regulation of Th2-type inflammation by TSLP"
Klaus Ley (Autoimmune Research; Inflammation Biology, La Jolla Institute for Allergy & Immunology)
"Chemokine-independent neutrophil arrest"
Stephen P. Schoenberger (Laboratory of Cellular Immunology, La Jolla Institute for Allergy & Immunology)
"Programming of tolerance versus activation of $CD8^+$ T cells by B cell APC"

Presentation by young scientists
Masafumi Arima (Dept. of Developmental Genetics, Graduate School of Medicine, Chiba University)
"Role of the intron enhancer element of the IL-4 gene in Th2 cytokine expression"
Norihiko Watanabe (Dept. of Allergy and Clinical Immunology, Graduate School of Medicine, Chiba University)
"The Role of B and T Lymphocyte Attenuator (BTLA) in the Prevention of Autoimmune Diseases"
Hideaki Bujo (Dept. of Genome Research and Clinical Application, Graduate School of Medicine, Chiba University)
"Establishment of a novel biomarker for smooth muscle cell migration in atherogenesis"
Takayasu Arima/Naoki Shimojo (Dept.of Pediatrics, Graduate School of Medicine, Chiba University)
"Impaired innate immune response at birth is associated with development of eczema in infancy"
Yuumi Nakamura (Graduate Student, Dept. of Dermatology, Graduate School of Medicine, Chiba University)
"Mast cells mediate neutrophil recruitment and vascular leakage through the NLRP3 inflammasome in histamine-independent urticaria"
Takashi Fujimura (COE Fellow, Dept. of Otolaryngology, Head and Neck Surgery, Graduate School of Medicine, Chiba University)
"Analysis of the therapeutic bio-markers for sublingual immunotherapy against Japanese cedar pollinosis"
Masakatsu Yamashita (Dept. of Immunology, Graduate School of Medicine, Chiba University)
"Epigenetic regulation of Th2 cell differentiation"
Hiroyuki Takano (Dept. of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University)
"Cardioprotective Effects of G-CSF on Heart Failure after Acute Myocardial Infarction"
Tomoaki Tanaka (Dept. of Clinical Cell Biology, Graduate School of Medicine, Chiba University)
"Nuclear export factor hCAS/CSE1L associates with chromatin and regulates expression of selective p53 target genes"

Discussion with invited speakers

The 2nd Chiba University G-COE Workshop
"Presentation and discussion by G-COE-RA"

Date: February 21, 2009
Venue: the 2nd Lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

The program was totally carried out in English, which aimed to nourish the ability internationally-active. The C-COE-RA made an oral presentation on his or her research activity with discussion. As part of education for G-COE-RAs, in addition to a supervisor, two other university faculty members in related fields have been appointed as Advisor to each RA. Afterward they gave advice on the studies presented in the workshop, regarding research planning, progress, future plan, the

Chiba University G-COE Workshop

presentation itself and so on. The feedback based on different perspectives can inspire RAs and provide motivation to advance their research studies. Some RA gave feedback that it was a good opportunity to continue studying how to make a presentation in English. The participants stood out 92 showing the great interests in our Global COE program among graduate students.

In addition, video recording their presentations was delivered to each RA in order to help RA not only for improve English communication but also learn positive behavior at international settings.

We look forward to the next time.

The 3rd Chiba University G-COE Workshop

"Presentation and discussion by G-COE-RA"

Date: May 30, 2009
Venue: Data Sessions in each Laboratory

The 3rd Chiba University Global COE Workshop was held on May 30, in the form of a discussion tour. Drs Habu, Schoenberger, Zamoyska, Bosselut and Campbell, invited speakers in the symposium held on the previous day, participated in this workshop. Each visited several laboratories involved with this G-COE Program in order to conduct discussions with the young researchers and the graduate students. During these small group sessions all present were able to share their own views; thus, this workshop was very productive. In the Department of Immunology in particular, introducing the research results just before the submission of a paper, researchers received many significant comments and suggestions for the direction of their future research.

The 4th Chiba University Global COE Workshop

"Presentation and discussion by G-COE-RA"

Date:June 13, 2009
Venue: 1st Lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

The 4th Global COE Workshop was held on Saturday, June 13. This was the second workshop in "Presentation and Discussion by G-COE-RA", following that of February 2009. More than 110 participants attended the workshop. All the G-COE-RAs made presentations and discussed on their research studies in English, except Dr. Kashiwakuma who gave his presentation in the 2nd symposium on May 29. Each talk created an active discussion. The participants gathered from various fields of research including clinical medicine and pharmaceutical sciences, as well as immunology-related fields. The result was a wide-ranged of questions, which sometimes exceeded G-COE-RAs' expectation; we realized difficulty in responding in English adequately in a question-and-answer period. Such opportunities can help improve RAs' preparation and mental attitude to presentation as well as the overall impression. Besides the supervisory professor, two advisers, who are appointed from this faculty for each RA, gave advice and comments to the presentation. It is also worth mentioning that the G-COE-RAs autonomously prepared and managed this workshop. Led by Ms. Akane Suzuki, Mr. Kenta Shinoda and Mr. Yusuke Endo, they expertly ran the workshop including the video recording.

Chiba University G-COE Workshop

The 5th Chiba University G-COE Workshop (Joint workshop with Uppsala Faculty)
"Presentation and discussion by G-COE-RA"

Date: February 20, 2010
Venue: 1st lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

The 5th Chiba University Global COE Workshop was held on February 20, in cooperation with Uppsala University in Sweden. This was the third workshop in "Presentation and Discussion by G-COE-RA". Five faculty members from Uppsala University, who were invited for the first project on the academic and research collaboration, joined the workshop as discussion leaders. They brought a new and more global perspective to the workshop, encouraging stimulating discussions. The atmosphere closely paralleled that of making a presentation overseas, which was a precious experience for RA.

The 6th Chiba University G-COE Workshop
"Presentation and discussion by G-COE-RA"

Date: June 26, 2010
Venue: 1st lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

The 6th Global COE workshop was held on June 26. This was the fourth workshop in "Presentation and Discussion by G-COE-RA". All the G-COE-RAs presented their experimental plan and results in English. Some RAs selected this year again joined sessions as RA discussers to be actively involved in the discussions. The workshop ended fruitfully, being upgraded to a higher level.

The 7th Chiba University G-COE Workshop
"Presentation and discussion by G-COE-RA"

Date: August 21, 2010
Venue: Laboratories, Faculty of Medicine and Pharmaceutical sciences

The 7th Chiba University Global COE Workshop was held on August 21, in the form of a discussion tour. Six world's leading researchers who were invited speakers in the symposium held the previous day, participated in this workshop. Each of them visited several laboratories involved with this G-COE program in turn, in order to have discussions with young researchers and graduate students. It was so productive that a lot of significant comments and suggestions were provided for examining the direction of their future research.

Chiba University G-COE Workshop

The 8th Chiba University G-COE Workshop

“Presentation and discussion by G-COE-RA”

Date: February 19, 2011
Venue: 1st lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

The 8th Global COE workshop was held on February 19. This was the fifth workshop in “Presentation and Discussion by G-COE-RA”. Thirty-three G-COE RAs presented the progress of each research. The audiences were drawn into their presentations that were full of each RA’s characteristics and charm, while also being impressed with their research quality. Most of the presentations were assertive and sophisticate. Students took English Presentation Seminar in the previous summer; we believe it has contributed a lot for their improvement. The participants enjoyed discussions through a barrage of questions made by the students in the Q and A periods. This workshop was very active and fruitful. We saw the RA grow by increasing experience in presentation and discussion in this manner.

The 9th Chiba University G-COE Workshop

“Presentation and discussion by G-COE-RA”

Date: June 4, 2011
Venue: 1st lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

The 9th Global COE workshop was held on June 4. This was the sixth workshop in “Presentation and Discussion by G-COE-RA”.

The RAs have been widely recruited from the related research field of this program, thus the increasing number of departments have been involved in this program each year. New RAs made a presentation on their experimental plan, and the RAs selected again this year on research results and progresses additionally in English. In the Q and A periods, each RA was pelted with questions. To respond them smoothly actually requires higher English communicative ability.

The 10th Chiba University G-COE Workshop

“Presentation and discussion by G-COE-RA”

Date: February 11, 2012
Venue: 1st lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

The 10th Global COE workshop was held on February 11. This was the seventh workshop in “Presentation and Discussion by G-COE-RA”. Thirty RAs presented the progress of their research. The participants from various research fields made questions and

Chiba University G-COE Workshop

gave advices from a different point of view, which made the discussion very exciting. We once again realized that G-COE-RA workshop is a great opportunity to have a good effect on each other.

The 11th Chiba University G-COE Workshop

"Presentation and discussion by G-COE-RA"

Date: July 14, 2012
Venue: 2nd lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

The 11th Global COE workshop was held on July 14. This was the 8th workshop in "Presentation and Discussion by G-COE-RA".

Thirty-one COE-RAs including newly selected 13 RAs presented their research in English. New RAs made presentations on their experimental plans, and the RAs selected again this year gave presentations on the results of their research and continuing progresses. Many of the presentations were bold, complex, and well done. The animated discussions with other RAs and the comments from the advisors were useful to help improve their research. We saw the RAs' growth in ability to respond the questions smoothly in Q and A periods.

The 12th Chiba University G-COE Workshop

Date: January 29, 2013
Venue: Sapia Hall, Tokyo Station Conference, Tokyo

The 12th international Workshop of Chiba University Global COE program & The 1st Symposium of International Immunological Memory and Vaccine Forum (IIMVF) is held.

The 13th Chiba University G-COE Workshop

"Presentation and discussion by G-COE-RA"

Date: February 16, 2013
Venue: 1st Lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

Chiba University Global COE Retreat 2009

Date: September 5 and 6
Venue: Seimei-no-Mori Resort
Director: Hiroshi Nakajima
Chair: Masakatsu Yamashita, Toshinori Nakayama, Masahiko Hatano, Takeshi Tokuhisa, Shinichiro Motohashi, Koutaro Yokote

Chiba University G-COE Retreat 2009 was held on September 5 and 6, at the Seimei-no-mori Resort. Eighty graduate students and PI researchers involved in this G-COE program participated and had the opportunity for in-depth discussion at a quiet place. The program consisted of two special lectures, 13 oral presentations, and 14 poster presentations. On the first day, Dr. Tatsuhiko Kodama, Research Center for Advanced Science and Technology, University of Tokyo, gave a special lecture in which he explained the latest studies about the epigenome. It gave us an insight for our future research. The next day, for a special lecture, Dr. Masaru Taniguchi, Research Center for Allergy and Immunology, RIKEN, gave a talk about NKT cells from discovery to a future vision including therapeutic use. This talk had a great impact on our students and young researchers. In the general presentations, topics touched on a variety of subjects and we had discussions on each topic, which were very meaningful for new development in our research. In the poster presentations held in a congenial atmosphere, each poster was discussed profoundly. Dr. Nyambayar Dashtsoodol (G-COE fellow) got the best poster award. We believe that this program provided mutual understanding between students and researchers.

Opening remarks
Toshinori Nakayama (Program Leader)

Orientation
Hiroshi Nakajima (Department of Molecular Genetics, Graduate School of Medicine, Chiba University)

Special lectures
Tatsuhiko Kodama (Systems Biology and Medicine, Research Center for Advanced Science and Technology, University of Tokyo)
Masaru Taniguchi (RIKEN Research Center for Allergy and Immunology)

Lectures
Haruhiro Toko (Department of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University)
Koji Tokoyoda (Department of Immunology, Graduate School of Medicine, Chiba University)
Kotaro Suzuki (Department of Molecular Genetics, Graduate School of Medicine, Chiba University)
Kaoru Tateno (Department of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University)
Masamitsu Negishi (Department of Cellular and Molecular Medicine, Graduate School of Medicine, Chiba University)
Takashi Fujimura (Department of Otorhinolaryngology, Head and Neck Surgery, Graduate School of Medicine, Chiba University)
Kaoru Ito (Department of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University)
Makoto Kuwahara (Department of Immunology, Graduate School of Medicine, Chiba University)
Yusuke Endo (Department of Immunology, Graduate School of Medicine, Chiba University)
Daisuke Kashiwakuma (Department of Molecular Genetics, Graduate School of Medicine, Chiba University)
Yuuki Obata (Department of Molecular Cell Biology, Graduate School of Pharmaceutical Sciences, Chiba University)
Yuya Tsurutani (Department of Clinical Cell Biology, Graduate School of Medicine, Chiba University)
Yusuke Suenaga (Department of Molecular Biology and Oncology, Graduate School of Medicine, Chiba University)

Party & Poster Session

Closing remarks
Toshinori Nakayama (Program Leader)

Chiba University Global COE Retreat 2010

Date: September 4 and 5
Venue: Seimei-no-Mori Resort
Director: Hiroshi Nakajima
Chair: Atsushi Onodera, Suzuki Kotaro, Shinichiro Motohashi, Toshinori Nakayama, Yoshitaka Okamoto, Ayako Inamine, Takashi Ito, Tomozumi Takatani, Shinya Okamoto, Akane Suzuki

Chiba University G-COE Retreat 2010 was held on September 4 and 5, at the Seimei-no-mori Resort. Sixty graduate students and PI researchers involved in this G-COE program participated and had the opportunity for in-depth discussion on a quiet place. The program consisted of two special lectures, 8 oral presentations, 8 poster presentations, and 36 one-minute presentations. On the first day, Dr. Kenji Tanaka, Director of The Tokyo Metropolitan Institute of Medical Science, gave a special lecture in which he explained not only the latest studies on but also a history of proteasome. It gave us a great insight into future research. On the following day, as a special lecture, Dr. Takeshi Tokuhisa, Chiba University, gave a talk about a required ability for mentor. This talk had a great impact on our students and young researchers. In the presentations by G-COE Fellows, topics touched on a variety of subjects and we had discussions on each topic, which were very meaningful for new development in our research. In the poster presentations held on a congenial atmosphere, each poster was discussed profoundly. Dr. Yuusuke Endo (G-COE-RA) got the best poster award. We believe that this program provided mutual understanding between students and principal investigators.

Opening remarks
Toshinori Nakayama (Program Leader)
Haruaki Nakaya (Dean, Graduate School of Medicine, Chiba University)

Orientation
Hiroshi Nakajima (Department of Molecular Genetics, Graduate School of Medicine, Chiba University)

Special lecture
Keiji Tanaka (Director General, Tokyo Metropolitan Institute of Medical Science)
Takeshi Tokuhisa (Department of Developmental Genetics, Graduate School of Medicine, Chiba University)

Lecutures
Kotaro Suzuki (Department of Molecular Genetics, Graduate School of Medicine, Chiba University)
Jun Onodera (Department of Immunology, Graduate School of Medicine, Chiba University)
Nyambayar Dashtsoodol (Department of Immunology, Graduate School of Medicine, Chiba University)
Ayako Inamine (Department of Otorhinolaryngology, Hand and Neck Surgery, Graduate School of Medicine, Chiba University)
Takashi Ito (Department of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University)
Akane Suzuki (Department of Immunology, Graduate School of Medicine, Chiba University)
Tomozumi Takatani (Department of Pediatrics, Graduate School of Medicine, Chiba University)
Shinya Okamoto (Department of pediatrics, Graduate School of Medicine, Chiba University)

One minute speech by all G-COE-RAs

Party & Poster Session

Closing remarks
Toshinori Nakayama (Program Leader)

Chiba University Global COE Retreat 2011

Date: September 17 and 18
Venue: Oiso Prince Hotel
Director: Hiroshi Nakajima
Chair: Yoshiyuki Goto, Shinichiro Motohashi, Hiroshi Kiyono, Toshio Suda, Yoshiko Fukuyama, Kotaro Suzuki, Shintaro Sato, Akane Suzuki, Ayuko Sato-Kimura, Takashi Ito, Naoto Koyanagi, Takafumi Mayama

Chiba University G-COE Retreat 2011 was held on September 17 and 18, at the Oiso Prince Hotel. This was our first joint Retreat with The IMSUT (Institute of Medical Science and Technology, The University of Tokyo) Global COE Program titled "Center of Education and Research for the Advanced Genome-Based Medicine: For personalized medicine and control of worldwide infectious diseases". The program was organized by the program committee, which included Dr. Taishin Akiyama and Jun Kunisawa from the IMSUT and Dr. Hiroshi Nakajima from Chiba University. One-hundred and ten graduate students and researchers from the both G-COE programs gathered and studied together for two days, developing new interactions and stimulating active discussion. The program consisted of one special lectures as well as 16 oral presentations, poster presentations, and one-minute presentations. Dr. Toshio Suda, Professor at Keio University, gave a keynote lecture entitled "Stem Cells and Cancer Stem Cells" about Immune cell metabolism. In the general presentations, almost all the presentations in each field were of very high quality. During this two-day meeting, the communication that developed among researchers from other universities through poster sessions and the reception encouraged and motivated the participants strive even harder in their research.

Opening remarks
Toshinori Nakayama (Program Leader)

Session1 : One minute presentation
Chairs: Y oshiyuki Goto (IMSUT) **& Shinichiro Motohashi** (Chiba Univ.)
Outline of poster presentation and One minute presentation

Session 2 : Keynote Lecture
Chair: Hiroshi Kiyono (IMSUT)
Toshio Suda (Department of Cell Differentiation, School of Medicine, Keio University)

Session 3: Poster Presentation
Chairs: Yoshiko Fukuyama (IMSUT) **& Kotaro Suzuki** (Chiba Univ.)

September 18 (Sunday)

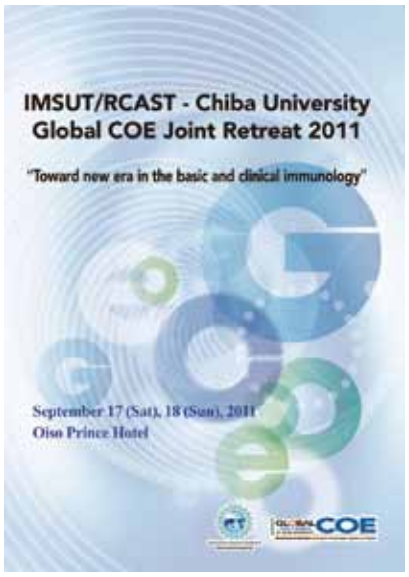
Session 4: Oral presentation 1
Chairs: Shintaro Sato (IMSUT) **& Akane Suzuki** (Chiba Univ.)

1) Kotaro Suzuki (Department of Molecular genetics, Graduate School of Medicine, Chiba University)
2) Hiroshi Ashida (Division of Bacterial Infection, IMSUT)
3) Atsushi Onodera (Department of Immunology, Graduate School of Medicine, Chiba University
4) Shin Kaneko (Division of Stem Cell Therapy, IMSUT)

Session 5 : Oral presentation 2
Chairs: Ayuko Sato-Kimura (IMSUT) **& Takashi Ito** (Chiba Univ.)
1) Takeharu Sakamoto (Division of Cancer Cell Research, IMSUT)
2) Yusuke Endo (Department of Immunology, Graduate School of Medicine, Chiba University)
3) Yusuke Kurashima (Division of Mucosal Immunology, IMSUT)
4) Kenta Shinoda (Department of Immunology, Graduate School of Medicine,Chiba University)
5) Hirotake Ichise
(Laboratory of Developmental Genetics, IMSUT)
6) Nyambayar Dashtsoodol
(Department of Immunology, Graduate School of Medicine, Chiba University)

Session 6: Oral presentation 3 by graduate students
Chairs: Naoto Koyanagi (IMSUT) **& Takafumi Mayama** (Chiba Univ.)
1) Masataka Yokoyama (Department of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University)
2) Ryuta Uraki (Division of Virology, IMSUT)
3) Fumiya Yamaide (Department of Public Health, Graduate School of Medicine, Chiba University)
4) Masahiro Onji (Division of Infectious Genetics, IMSUT)
5) Satomi Tanaka (Department of Cellular and Molecular Medicine, Graduate School of Medicine, Chiba University)
6) Takahiko Imai (Division of Viral Infection, IMSUT)

Closing remarks
Hiroshi Kiyono (Project Leader, Global COE Program, The University of Tokyo)



Chiba University Global COE Retreat 2012

Date: September 8 and 9
Venue: Seimei-no-Mori Resort
Director: Hiroshi Nakajima
Chair: Shinichiro Motohashi, Toshinori Nakayama, Hiroshi Nakajima, Atsushi Onodera, Damon Tumes, Kotaro Suzuki, Akane Suzuki, Takashi Ito, Kenta Shinoda, Asami Hanazawa, Yusuke Endo

The Chiba University G-COE Retreat 2012 was held on September 8 and 9, at the Seimei-no-mori Resort. Sixty graduate students and PI researchers involved in this G-COE program participated and had the opportunity for in-depth discussions in a quiet place. The program consisted of 2 special lectures, 8 oral presentations, 25 poster presentations, and 25 one-minute presentations.

On the first day, Dr. Tadatsugu Taniguchi, Professor, Institute of Industrial Science, the University of Tokyo, gave a special lecture in which he explained the latest studies on immune response directed by immune receptor signals from a view point of the link between natural immunity and adaptive immunity. It gave us a great insights into our future research. Also Dr. Taniguchi gave young researchers a message about it really means to be a researcher in this kind of program. His talk had a great impact on our students and young researchers.

On the following day, as a special lecture, Dr. Toshinori Nakayama, the Chiba University G-COE program leader, gave a talk titled "PhD course leading program, Nurture leadership to promote creative research on Immune system regulation and innovative therapeutics". The presentations by G-COE Fellows, touched on a variety of subjects and we had discussions on each topic, which were very meaningful for new development in our research. Poster presentations were held on a congenial atmosphere, and each poster was discussed in detail. Dr. Yukiko Watanabe (G-COE-RA) got the best poster award. This program enhanced mutual understanding between students and principal investigators.

Opening remarks
Toshinori Nakayama (Program Leader)

Orientation
Hiroshi Nakajima (Department of Molecular Genetics, Graduate School of Medicine, Chiba University)

Special lecture
Tadatsugu Taniguchi (Professor, Department of Molecular Immunology, Institute of Industrial Science, the University of Tokyo)
Toshinori Nakayama (Program Leader)

Lecutures
Kotaro Suzuki (Department of Molecular Genetics, Graduate School of Medicine, Chiba University)
Atsushi Onodera (Department of Immunology, Graduate School of Medicine, Chiba University)
Damon Tumes (Department of Immunology, Graduate School of Medicine, Chiba University)
Takashi Ito (Department of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University)
Akane Suzuki (Department of Immunology, Graduate School of Medicine, Chiba University)
Yusuke Endo (Department of Immunology, Graduate School of Medicine, Chiba University)
Kenta Shinoda (Department of Immunology, Graduate School of Medicine, Chiba University)
Asami Hanazawa (Department of Immunology, Graduate School of Medicine, Chiba University)

One minute speech by all G-COE-RAs

Party & Poster Session

Closing remarks
Toshinori Nakayama (Program Leader)

Basic Science Joint Meeting (BSJM)

Basic Science Joint Meeting (BSJM) is a research seminar, coordinated by graduate students working group on Friday evenings (chief coordinator is Atsushi Onodera, graduate student). BSJM was started from November 2008 and held 25 times.

1.	Nov 21, 2008 17:00-18:00	Takashi Miki, Professor, Dept. of Autonomic Physiology
2.	Dec 5, 2008 17:00-18:00	John Joseph O'Shea Jr, Scientific Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH, USA Visiting Professor, Chiba Univ.
3.	Dec 12, 2008 17:00-18:00	Shinichiro Motohashi, Associate Professor, Dept.of Medical Immunology
4.	Jan 9, 2009 18:00-19:00	Kayo Inaba, Professor, Lab. of Immunobiology, Grad. Sch. of Biostudies, Kyoto Univ.
5.	Jan 16, 2009 17:00-18:00	Daisuke Tohyama, Graduate Student, Dept. of Neurobiology
6.	Feb 13, 2009 17:00-18:00	Masafumi Arima, Lecturer, Dept. of Developmental Genetics
7.	Feb 27, 2009 17:00-18:00	Damon Tumes, G-COE Fellow, Dept of Immunology
8.	Mar 6, 2009 17:00-18:00	Arifumi Iwata, G-COE-RA, Dept. of Allergy and Clinical Immunology
9.	Apr 3, 2009 17:00-18:00	Shiki Takamura, Assistant Professor, Dept. of Immunology, Kinki Univ. Sch. of Med.
10.	Apr 10, 2009 17:00-18:00	Lisa Fujimura, Assistant Professor, Biomedical Research Center
11.	Apr 17, 2009 17:00-18:00	Koji Tokoyoda, G-COE Independent Research Associate, Dept. of Immunology
12.	Apr 24, 2009 17:00-18:00	Koji Yasutomo, Professor, Dept. of Immunology & Parasitology Institute of Health Biosciences, The Univ. of Tokushima Grad. Sch.
13.	May 1, 2009 17:00-18:00	Mitsujiro Osawa, Lecturer, Dept. of Cellular and Molecular Medicine
14.	May 15, 2009 17:00-18:00	Naohiko Seki, Associate Professor, Dept. of Functional Genomics
15.	Jun 12, 2009 17:00-18:00	Harukiyo Kawamura, Assistant Professor, Dept. of Autonomic Physiology
16.	Jun 19, 2009 17:00-18:00	Tomokazu Nagao, Assistant Professor, Dept. of Immunology
17.	Jun 26, 2009 17:00-18:00	Ichiro Taniuchi, Team Leader, RCAI, RIKEN
18.	Jul 17, 2009 17:00-18:00	Atsushi Onodera, Graduate Student, Dept. of Immunology
19.	Jul 24, 2009 17:00-18:00	Takeaki Sugawara, Research Fellow, Dept. of Cellular and Molecular Medicine
20.	Sep 11, 2009 17:00-18:00	Tatsuya Sato, Assistant Professor, Dept. of Developmental Biology
21.	Sep 24, 2009 17:00-18:00	Hiroshi Ohno, Team Leader, RCAI, RIKEN
22.	Oct 9, 2009 17:00-18:00	Yoshimi Takai, Dean, Graduate School of Medicine, Kobe University
23.	Oct 23, 2009 17:00-18:00	Kazuki Yamasaki, G-COE-RA, Dept. of Immunology
24.	Oct 30, 2009, 17:00-18:00	Atsushi Yamaguchi, Associate Professor, Dept. of Neurobiology
25.	Nov 27, 2009, 17:00-18:00	Nobuya Yoshida, Graduate Student, Dept. of Developmental Genetics
26.	Dec 18, 2009 17:00-18:00	Yuki Kinjo, Head, Laboratory of Biodefense, Department of Bioactive Molecules, National Institute of Infectious Disease
27.	Jan 22, 2010 17:00-18:00	Chiaki Iwamura, Assistant Professor, Dept. of Immunology
28.	Feb 12, 2010 17:00-18:00	Hiroaki Takatori, Assistant Professor, Dept. of Molecular Genetics
29.	Apr 2, 2010 09:30-10:30	Tetsuichiro Saito, Professor, Dept. of Developmental Biology
30.	Apr 9, 2010 09:30-10:30	Satoru Miyagi, Assistant Professor, Dept of Cellular and Molecular Medicine
31.	Apr 16, 2010 09:30-10:30	Saki Kawashima, G-COE RA, Dept of Molecular Genetics
32.	Apr 23, 2010 09:30-10:30	Atsushi Onodera, Assistant Professor, Dept. of Immunology
33.	May 7, 2010 09:30-10:30	Haruko Takano, Post Doctoral Fellow, Biomedical Research Center
34.	May 14, 2010 09:30-10:30	Akio Matsumoto, Associate Professor, Dept. of Pharmacology
35.	May 21, 2010 09:30-10:30	Ryuichi Sugamata, Assistant Professor, Dept. of Immunology
36.	May 28, 2010 09:30-10:30	Naohiko Seki, Associate Professor, Dept. of Functional Genomics
37.	Jun 4, 2010 09:30-10:30	Toshinao Oyama, Post Doctoral Fellow, Dept. of Molecular and Tumor Pathology
38.	Jun 11, 2010 09:30-10:30	Asuka Morita, Graduate Student, Dept. of Autonomic Physiology
39.	Jun 18, 2010 09:30-10:30	Shinichiro Motohashi, Associate Professor, Dept. of Medical Immunology

40.	Jun 25, 2010 09:30-10:30	Jun Ikari, G-COE-RA, Dept of Developmental Genetics
41.	Jul 2, 2010 09:30-10:30	Tomoaki Tanaka, Assistant Professor, Dept. of Clinical Cell Biology and Medicine
42.	Jul 9, 2010 09:30-10:30	Satoshi Fujimoto, Assistant Professor, Dept. of Developmental Biology
43.	Jul 16, 2010 09:30-10:30	Akira Suto, Assistant Professor, Dept. of Molecular Genetics
44.	Jul 23, 2010 09:30-10:30	Hiroyuki Hosokawa, Assistant Professor, Dept. of Immunology
45.	Sep 3, 2010 09:30-10:30	Kenta Shinoda, G-COE-RA, Dept. of Immunology
46.	Sep 10, 2010 09:30-10:30	Makiko Kashio, Graduate Student, Dept of Cellular and Molecular Medicine
47.	Sep 17, 2010 09:30-10:30	Tomokazu Nagao, Lecturer, Dept. of Immunology
48.	Sep 24, 2010 09:30-10:30	Hiroyuki Ishikawa, Associate Professor, Dept. of Biology, Graduate School of Science
49.	Oct 1, 2010 09:30-10:30	Hiroshi Ishii, Graduate Student, Dept. of Neurobiology
50.	Oct 8, 2010 09:30-10:30	Masakatsu Yamashita, Head of Laboratory, Kazusa DNA Research Institute
51.	Oct 15, 2010 09:30-10:30	Shigetoshi Horiguchi, Lecturer, Dept. of Otorhinolaryngology, Head and Neck Surgery
52.	Oct 22, 2010 09:30-10:30	Yusuke Endo, G-COE-RA, Dept. of Immunology
53.	Nov 5, 2010 09:30-10:30	Yuko Muroyama, Assistant Professor, Dept. of Developmental Biology
54.	Nov 12, 2010 09:30-10:30	Takashi Miki, Professor, Dept. of Medical Physiology
55.	Nov19, 2010 09:30-10:30	Tohru Minamino, Lecturer, Dept. of Cardiovascular Science and Medicine
56.	Nov 26, 2010 09:30-10:30	Nobuya Yoshida, Graduate Student, Dept. of Developmental Genetics
57.	Dec 17, 2010 09:30-10:30	Yasunori Sato, Lecturer, Chiba University Hospital Clinical Research Center
58.	Dec 24, 2010 09:30-10:30	Naohiko Seki, Associate Professor, Dept. of Functional Genomics
59.	Jan 7, 2011 09:30-10:30	Yuichi Michikawa, Senior Researcher, RadGenomics Project, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences
60.	Jan 14, 2011 09:30-10:30	Harukiyo Kawamura, Assistant Professor, Dept. of Medical Physiology
61.	Jan 21, 2011 09:30-10:30	Kentaro Takahashi, Graduate Student, Dept. of Molecular Genetics
62.	Jan 28, 2011 09:30-10:30	Chiaki Iwamura, Assistant Professor, Dept. of Immunology
63.	Feb 4, 2011 09:30-10:30	Akira Matsuura,Professor, Div. of Nanoscience, Graduate School of Advanced Integration Science/Department of Biology, Faculty of Science
64.	Feb 18, 2011 17:00-18:00	Shinichiro Motohashi, Associate Professor, Dept. of Medical Immunology
65.	Feb 25, 2011 17:00-18:00	Ayako Inamine, G-COE Fellow, Dept. of Otolaryngology, Head and Neck Surgery
66.	Apr 1, 2011 17:00-18:00	Haruko Takano, Post Doctoral Fellow, Biomedical Research Center
67.	Apr 8, 2011 17:00-18:00	Mitsujirou Osawa, Lecturer, Dept. of Cellular and Molecular Medicine
68.	Apr 15, 2011 17:00-18:00	Kouya Suzuki, Graduate Student, Dept. of Immunology
69.	Apr 22, 2011 17:00-18:00	Junji Yamashita, Research Fellow, Dept. of Immunology
70.	May 6, 2011 17:00-18:00	Ayako Matsumoto, JSPS Fellow, Dept. of Pharmacology/Dept. of Neurobiology
71.	May 13, 2011 17:00-18:00	Koji Onomoto, Assistant Professor, Div. of Molecular Immunology, Medical Mycology Research Center
72.	May 20, 2011 17:00-18:00	Hideki Hanaoka, Director/Professor, Chiba University Hospital Clinical Research Center
73.	May 27, 2011 17:00-18:00	Jing Pan, G-COE-RA, Dept. of Developmental Genetics
74.	June 4, 2011 17:00-18:00	Hiroyuki Ishikawa, Associate Professor, Dept. of Biology, Graduate School of Science
75.	Jun 10, 2011 17:00-18:00	Akio Matsumoto, Associate Professor, Dept. of Pharmacology
76.	Jun 17, 2011 17:00-18:00	Masayuki Kuroda, Associate Professor, Center for Advanced Medicine
77.	Jun 24, 2011 17:00-18:00	Atsushi Onodera, Assistant Professor, Dept. of Immunology
78.	Jul 1, 2011 17:00-18:00	Tatsuya Sato, Assistant Professor, Dept. of Developmental Biology
79.	Jul 8, 2011 17:00-18:00	Takaaki Konuma, Graduate Student, Dept. of Cellular and Molecular Medicine
80.	Jul 15, 2011 17:00-18:00	Masaya Yokota, Graduate Student, Dept. of Molecular Genetics
81.	Jul 22, 2011 17:00-18:00	Nobuhide Tsuruoka, Clinical Fellow, Dept. of Reproductive Medicine/Dept. of Developmental Genetics

82.	Sep 2, 2011 17:00-18:00	Takeshi Murata, Associate Professor, Graduate School of Science
83.	Sep 9, 2011 17:00-18:00	Tomoaki Tanaka, Lecturer, Dept. of Clinical Cell Biology and Medicine
84.	Sep 16, 2011 17:00-18:00	Tohru Minamino, Lecturer, Dept. of Cardiovascular Science and Medicine
85.	Oct 7, 2011 17:00-18:00	Shunsuke Nakamura, Graduate Student, Dept. of Cellular and Molecular Medicine
86.	Oct 14, 2011 17:00-18:00	Arifumi Iwata, Clinical Fellow, Dept. of Molecular Genetics
87.	Oct 28, 2011 17:00-18:00	Asami Hanazawa, Graduate Student, Dept. of Immunology
88.	Nov 4, 2011 17:00-18:00	Motoo Kitagawa, Associate Professor, Dept. of Molecular and Tumor Pathology
89.	Nov 11, 2011 17:00-18:00	Tetsuhiro Chiba, Assistant Professor, Dept. of Medicine and Clinical Oncology
90.	Nov 18, 2011 17:00-18:00	Daiju Sakurai, Lecturer, Dept. of Otolaryngology, Head and Neck Surgery
91.	Nov 25, 2011 17:00-18:00	Naohiko Seki, Associate Professor, Dept. of Functional Genomics
92.	Dec 2, 2011 17:00-18:00	Susumu Kawamoto, Professor, Molecular Biology, Medical Mycology Research Center
93.	Dec 9, 2011 17:00-18:00	Soichi Tofukuji, Graduate Student, Dept. of Immunology/Kazusa DNA Research Institute
94.	Dec 16, 2011 17:00-18:00	Fumihiro Ishibashi, Graduate Student, Dept. of Immunology/Dept. of Thoracic Surgery
95.	Jan 6, 2012 09:30-10:30	Akira Matsuura, Professor, Graduate School of Advanced Integration Science
96.	Jan 13, 2012 09:30-10:30	Yaeko Nakajima, Research Associate, Dept. of Cellular and Molecular Medicine
97.	Jan 20, 2012 09:30-10:30	Yuka Shiga, Graduate student, Dept. of Immunology
98.	Jan 27, 2012 09:30-10:30	Tetsuya Sasaki, Graduate Student, Dept. of Immunology
99.	Feb 3, 2012 09:30-10:30	Naoto Yonezawa, Associate Professor, Dept. of Chemistry
100.	Feb 10, 2012 09:30-10:30	Jin Yuan, G-COE-RA, Dept. of Cellular and Molecular Medicine
101.	Feb 17, 2012 09:30-10:30	Tomomi Furihata, Assistant Professor, Laboratory of Pharmacology and Toxicology
102.	Feb 24, 2012 09:30-10:30	Masashi Arima, Lecturer, Dept. of Developmental Genetics
103.	Apr 6, 2012 09:30-10:30	Naoki Kunii, G-COE Fellow, Center of Advanced Medicine
104.	Apr 13, 2012 09:30-10:30	Koji Onomoto, Assistant Professor, Medical Mycology Research Center
105.	Apr 20, 2012 09:30-10:30	Hiroyuki Hosokawa, Assistant Professor, Dept. of Immunology
106.	May 11, 2012 09:30-10:30	Tomohiro Tamaji, Assistant Professor, Dept. of Molecular Genetics
107.	May 18, 2012 09:30-10:30	Yuta Mishima, Graduate Student, Dept. of Cellular and Molecular Medicine
108.	May 25, 2012 09:30-10:30	Akemi Sakamoto, Assistant Professor, Dept. of Developmental Genetics
109.	Jun 1, 2012 09:30-10:30	Hidemi Suzuki, Assistant Professor, Dept. of Thoracic Surgery
110.	Jun 8, 2012 09:30-10:30	Seiichiro Hirono, Graduate Student, Dept. of Medical Physiology
111.	Jun 15, 2012 09:30-10:30	Chiaki Iwamura, Assistant Professor, Dept. of Immunology
112.	Jul 13, 2012 09:30-10:30	Risa Fujimura, Assistant Professor, BioMedical Center
113.	Jul 20, 2012 09:30-10:30	Goro Sashida, Assistant Professor, Dept. of Cellular and Molecular Medicine
114.	Jul 27, 2012 09:30-10:30	Pan Jing, Graduate student, Dept. of Developmental Genetics
115.	Sep 7, 2012 09:30-10:30	Hiroyuki Ishikawa, Associate Professor, Dept. of Biology
116.	Sep 14, 2012 09:30-10:30	Satoshi Miyagi, Assistant Professor, Dept. of Cellular and Molecular Medicine
117.	Sep 21, 2012 09:30-10:30	Damon Tumes, G-COE Independent Research Associate
118.	Oct 5, 2012 09:30-10:30	Lee Unyong, Assistant Professor, Dept. of Medical Physiology
119.	Oct 12, 2012 09:30-10:30	Motoyuki Ito, Professor, Dept. of Biochemistry
120.	Oct 19, 2012 09:30-10:30	Naohiko Seki, Department of Functional Genomics
121.	Oct 2, 2012 09:30-10:30	Tatsuya Sato, Department of Biology
122.	Nov. 9, 2012, 09:30-10:30	Tomoaki Tanaka, Dept. of Clinical Cell Biology and Medicine
123.	Nov.16, 2012, 09:30-10:30	Tsuyoshi Endo, Dept. of Geosystem and Biological Sciences

G-COE Seminar

Date: December 5, 2008

Lecturer:
John Joseph O'Shea Jr.
Scientific Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health (NIH)
Chief, Molecular Immunology and Inflammation Branch, NIAMS, NIH

Date: March 30, 2009

Lecturer:
Laurent Gapin
Associate Professor, University of Colorado Hearth Science Center and National Jewish Health

Date: March 31, 2009

Lecturer:
Mark Exley
Assistant Professor of Medicine, Cancer Biology, Beth Israel Deaconess Medical Center, Harvard Medical School

Date: April 3, 2009

Lecturer:
Shiki Takamura
Assistant Professor, Department of Immunology, Kinki University School of Medicine

Date: April 24, 2009

Lecturer:
Koji Yasutomo
Professor, Department of Immunology & Parasitology, Institute of Health Biosciences, The University of Tokusima Graduate School

Date: May 14, 2009

Lecturer:
Carl H June
Translational Research Professor, Department of Pathology and Laboratory Medicine, University of Pennsylvania

Date: May 20, 2009

Lecturer:
Anja Hauser
Group leader, Department of Immunodynamics Deutsches Rheumafors-chungzentrum Berlin (DRFZ)

Date: June 11, 2009

Lecturer:
Motoko Kimura
Fellow, Experimental Immunology Branch, NCI, National Institutes of Health (NIH)
Ryoji Yagi
Fellow, Laboratory of Immunology, NIAID, National Institutes of Health (NIH)

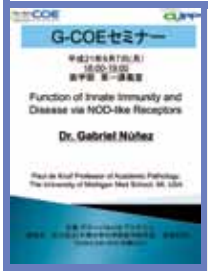
Date: June 26, 2009

Lecturer:
Ichiro Taniuchi
Team Leader, Laboratory for Transcriptional Regulation, RIKEN Research Center for Allergy and Immunology (RCAI)

Date: July 14, 2009

Lecturer:
James Scott-Browne
Graduate Student, University of Colorado at Denver
Mark Headley
Graduate Student, Benaroya Research Institute

Date: September 7, 2009



Lecturer:
Gabriel Núñez
Paul de Kruif Professor of Academic Pathology, The University of Michigan Med School

Date: September 30, 2009

Lecturer:
Akihiko Yoshimura
Professor, Department of Microbiology and Immunology, Keio University School of Medicine

Date: October 9, 2009

Lecturer:
Yoshimi Takai
Dean, School of Medicine, Kobe University

Date: November 10, 2009

Lecturer:
Tatsuya Togashi
Associate Professor, Environmental Science and Landscape Architecture Course, Landscape Science, Chiba University

Date: December 8, 2009

Lecturer:
Philippa Marrack
Distinguished Professor, University of Colorado
Investigator, Howard Hughes Medical Institute at Denver
Professor, Integrated Department of Immunology, University of Colorado Denver and National Jewish Health

Date: December 18, 2009

Lecturer:
Yuki Kinjo
Head, Laboratory of Biodefense, Department of Bioactive Molecules, National Institute of Infectious Diseases

Date: January 15, 2010

Lecturer:
Dr. David Jayne
Visiting Professor, Chiba University
Professor Cambridge University
Addenbrookes Hospital, UK

Date: January 15, 2010

Lecturer:
Dr. Ming-hui Zhao
Visiting Professor, Chiba University
Professor Peking University
First Hospital, Beijing, China

Date: February 18, 2010

Lecturer:
Michiyuki Yamada
Professor emeritus, Yokohama City University

Date: March 29, 2010

Lecturer:
Seema Ahuja
Associate Professor, Department of Medicine, Texas Health Science Center San Antonio, Texas, USA.

Date: April 6, 2010

Lecturer:
Kojiro Yano
Astra Zeneca Senior Research Fellow in Systems Biology, Department of Physiology, Development and Neuroscience, University of Cambridge

Date: April 8, 2010

Lecturer:
Yasushi Ishihama
Associate Professor, Institute for Advanced Biosciences, Keio University

Date: April 15, 2010

Lecturer:
Fumio Sakane
Professor, Laboratory of Biofunctional Chemistry, Fundamental Science, Graduate School of Science, Chiba University

Date: April 15, 2010

Lecturer:
Koichi Kobayshi
Department of Cancer Immunology & AIDS, Dana-Farber Cancer Institute, Assistant Professor of Pathology, Harvard Medical School

Date: May 18, 2010

Lecturer:
Naoto kawakami
Max Planck Institute of Neurobiology, Department of Neuroimmunology

Date: June 7, 2010

Lecturer:
Sachiko Tsukita
Professor, Biological Science, Department of Pathology, Graduate School of Medicine, Osaka University

Date: July 7, 2010

Lecturer:
Takao Kobayashi
Associate Professor, Center for Integrated Medicine Research, Keio University

Date: July 15, 2010

Lecturer:
Mitutoshi Yoneyama
Professor, Molecular Immunology, Medical Mycology Research Center, Chiba Uniersity
Researcher, Japan Science and Technology Agency SAKIGAKE
"RNA and Biofunctions"

Date: August 31, 2010

Lecturer:
DeBroski Herbert
Assistant Professor, Division of Immunobiology Cincinnati Children's Research Foundation

Date: September 2, 2010

Lecturer:
Masayuki Kitajima
Postdoctoral Fellow, Immunology Program, Benaroya Research Institute at Virginia Mason

G-COE Seminar

Date: September 17, 2010

Lecturer:
Kiyoshi Takeda
Professor, Laboratory of Immune Regulation, Osaka University

Date: October 8, 2010

Lecturer:
Yoshimi Takai
Dean, Kobe University Graduate School of Medicine/School of Medicine

Date: October 15, 2010

Lecturer:
Tatsuo Kinashi
Professor, Kansai Medical University

Date: October 28, 2010

Lecturer:
Makoto Suematsu
Professor, Department of Biochemistry & Integrative Medical Biology, School of Medicine, Keio University

Date: November 1, 2010

Lecturer:
Makio Iwashima
Associate Professor, Department of Microbiology and Immunology, Stritch School of Medicine, Loyola University, Chicago, USA

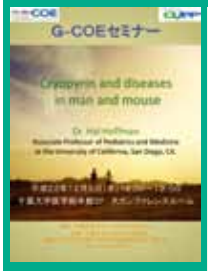
Date: November 29, 2010

Lecturer:
Fred Finkelman
McDonald Professor of Medicine and Professor of Pediatrics, University of Cincinnati College of Medicine

Date: December 6, 2010

Lecturer:
Koichi Araki
Department of Microbiology and Immunology , Emory University School of Medicine

Date: December 9, 2010



Lecturer:
Hal Hoffman
Associate Professor of Pediatrics and Medicine at the University of California, San Diego, CA

Date: January 13, 2011

Lecturer:
Koji Matsushima
Professor, Department of Molecular Preventative Medicine, Faculty of Medicine, University of Tokyo

Date: March 8, 2011

Lecturer:
Haruhiko Koseki
Group Director, Developmental Genetics Laboratory, Riken RCAI

Date: April 6, 2011

Lecturer:
Shinobu Saijo
Independent assistant professor, Molecular Immunology, Medical Mycology Research Center, Chiba University

Date: April 13, 2011

Lecturer:
Koichi Kobayashi
Assistant Professor of Pathology, Harvard Medical School

Date: May 12, 2011

Lecturer:
Kihito Takahashi
Deputy Director, Development & Medical Affairs, GlaxoSmithKline

Date: August 25, 2011

Lecturer:
Teruyuki Nakanishi
Professor, Department of Veterinary Medicine, College of Bioresource Science, Nihon University

Date: October 7, 2011

Lecturer:
Yoshimi Takai
Professor, Kobe University Graduate School of Medicine

Date: January 19, 2012

Lecturer:
Motonari Kondo
Professor, Department of Immunology, Toho University School of Medicine

Date: March 19, 2012

Lecturer:
Dale T. Umetsu
Children's Hospital, Harvard Medical School

Date: April 9, 2012

Lecturer:
Omid Akbari
Associate Professor, University of Southern California, Keck School of Medicine

Date: July 19, 2012

Lecturer:
Matthew Buechler
Graduate student, University of Washington, Department of Immmunology

Date: August 21, 2012

Lecturer:
Hiroo Ueno
Professor, Department of Stem Cell Pathology, Kansai Medical University

Date: September 14, 2012

Lecturer:
Yoshimi Takai
Professor, Kobe University, Graduate School of Medicine

Date: October 1, 2012

Lecturer:
Frank C. Schroeder
Assistant Professor, Boyce Thompson Institute and Department of Chemistry and Chemical Biology, Cornell University

Date: October 3, 2012

Lecturer:
Hisashi Narimatsu
Director, Research Center for Medical Glycoscience, National Institute of Advanced Industrial Science and Technology

Date: November 5, 2012

Lecturer:
Makio Iwashima
Associate Professor, Loyola University Chicago, Stritch School of Medicine, Department of Microbiology and Immunology

Date: November 20, 2012

Lecturer:
Atsushi Hirao
Professor, Division of Molecular Genetics, Cancer and Stem Cell Research Program, Cancer Research Institute, Kanazawa University

Date: December 17, 2012

Lecturer:
Yoshiaki Kubota
Center for Integrated Medical Research, Keio University (Kairinmaru Project)

Date: January 8, 2013

Lecturer:
Hideshi Ishii
Department of Gastroenterological surgery, Graduate School of Medicine, Osaka University

RCAI International Summer Program co-organized by the G-COE Program

Date: July 3-10, 2009
August 17-27, 2010
June 22-27, 2012
Place: RIKEN Research Center for Allergy and Immunology (RCAI)

In 2009, 2010 and 2012, the RCAI International Summer Program (RISP) took place at the RIKEN Research Center for Allergy and Immunology (RCAI), jointly organized by RCAI and the G-COE Program, targeting graduate students and postdoctoral fellows overseas. This Summer Program had 42 participants from 16 countries including 21 women in 2009, 44 participants from 9 countries including 24 women in 2010 and 41 participants from 19 countries including 21 women in 2012. In the early part of lecture course, besides oral and poster presentations, participants attended intensive lectures on the basic concepts to leading-edge study of immunology by distinguished researchers invited from home and abroad. Later in the program, the participants attended the RCAI-JSI International symposium held at Yokohama in 2009, 14th International Congress of Immunology held at Kobe in 2010 and the RCAI-JSI International symposium held at Tokyo in 2012. RISP invited promising young researchers from all over the world, who became better acquainted and deepened their mutual exchange; this can be an invaluable asset for building a network for advancing research. Some of the participants stayed on at RCAI for a 1-month internship. The overall results of the questionnaire given to participants showed a high level of satisfaction with this program. RCAI and Chiba University have promoted collaboration including activities for development of human resources. This relationship was sure to be enhanced by jointly organizing RISP.

The 8th & 9th NIRS Research Center for Charged Particle Therapy Symposium

"Standardization and optimization of charged particle therapy"

Date: January 16, 2009
Venue: Auditorium, 2F Research Building for Charged Particle Therapy National Institute of Radiological Sciences

Chiba University G-COE Program has been promoted collaboratively with the National Institute of Radiological Sciences (NIRS), focusing on development of young researchers, as well as research and development on new less-invasive cancer treatments with minimal side effect, especially the one combining heavy ion charged particle therapy with immunotherapy. Furthermore NIRS is working together for graduate education under Chiba University Collaborative Graduate Studies Program.

NIRS Research Center for Charged Particle Therapy Symposium was held on January 16, 2009, jointly organized with Chiba University Global COE Program. The symposium aims to disseminate research results on charged particle therapy, and this time participants mainly shared the recent research results particularly on standardization and optimization of charged particle therapy, and basic research results to support clinical results. In addition, a presentation on NKT cell-based immunotherapy and a lecture about appropriate procedure of the clinical trail were also given as a topic related to collaborative work with NIRS and the G-COE Program.

Date: January 15, 2010
Venue: Auditorium, 2F Research Building for Charged Particle Therapy National Institute of Radiological Sciences

The NIRS-Chiba University G-COE Joint Symposium on Carbon-Ion Therapy and Immunotherapy was held on January 15. The program was designated for encouraging much discussion on basic and clinical research results toward future development of novel less-invasive therapeutic strategies, searching for common ground between carbon iron therapy and the immunological mechanism from what has been known until now. Dr. Ken-ichiro Seino (Institute of Medical Science St. Mariannna University School of Medicine) presented a keynote lecture on tumor immunity from the basics to a future vision including the potential of regenerative immunotherapy by using iPS cells, in an easy-to understand manner. For a special lecture, Dr. Kazuhiro Kamiki (Dept.of Immunotherapeutics (Medinet), Graduate School of Medicine, the University of Tokyo) presented results of clinical trials of immunotherapy and also explained the problems of current immunotherapy including the basic research results, in terms of creating immunosuppressive environment. His talk was suggestive enough to provide an important direction toward a breakthrough to the current immunotherapy, which does not sufficiently meet many patients' expectations. Much heated and fruitful discussion was generated by the 97 participants in this symposium, which was concluded with great success.

The 1st & 2nd NZ-RIKEN-CHIBA Joint Workshop

The 1st NZ-RIKEN-CHIBA Joint Workshop

"Recent advances in immune regulation and immunotherapy"

Date & Venue: June 14, 2010, Research Center for Allergy and Immunology (RCAI)
June 16, 2010, Libray Hall 3F, Library of Health Sciences, Chiba University

The NZ-RIKEN-CHIBA Joint Workshop "Recent advances in immune regulation and immunotherapy" was held in cooperation with the RIKEN Research Center for Allergy and Immunology (RCAI), the Ministry of Research, Science & Technology, New Zealand, and The G-COE program. This event was launched by the Ministry's proposal for continuous exchange of research and personnel among researchers from New Zealand, this G-COE program and others, involved in immunological and clinical studies. This time seven researchers in New Zealand visited Japan to introduce and discuss ongoing research studies with domestic researchers with a view to seeking collaboration in the future.

The joint workshop was held on Monday, June 14, at RCAI. The meeting covered issues on "Immune activation and regulation", "Infection, autoimmune, allergy and vaccine" and "Immunotherapy", providing an opportunity for scientists from both countries to learn the latest developments in their respective fields. On Wednesday, June 16, another meeting for presentation and discussion with the researchers from New Zealand took place at Chiba University. Following the welcome address by Dr. Haruaki Nakaya, Dean, Graduate School of Medicine, and greetings from Dr. John Fraser, Head School of Medical Sciences, University of Auckland, the six New Zealand researchers presented their studies such as 'Strategies to enhance CD8+ T cell responses to vaccination', related investigations on bacterial infection stimulating CD8+ T cells in lymph node for responses to vaccination and so on, to our faculty and graduate students. In the afternoon, after a site visit to the Center for Advanced Medicine, they made individual visit to laboratories for further discussions. We expected progress in this exchange, with the possibility for increasing the collaboration we found in this workshop.

Researchers from New Zealand

Anne Camille La Flamme (Senior Lecturer, Victoria University of Wellington)
Rod Dunbar (Associate Professor, University of Auckland)
Gavin F Painter (Principal Scientist, Team Leader, Industrial Research Ltd)
Gib Bogle (Senior Research Fellow, Auckland Bioengineering Institute)
Ian F. Hermans (Doctor, Malaghan Institute of Medical Research, Wellington)
John Fraser (Head, School of Medical Sciences, University of Auckland)
Sarah Hook (Associate Professor, School of Pharmacy, University of Otago)

The 2nd NZ-RIKEN-CHIBA Joint Workshop

"Recent advances in immune regulation and immunotherapy"

Date: February 26 and 27, 2013
Venue: The University of Auckland

The 2nd NZ-RIKEN-CHIBA Joint Workshop was held on February 26 and 27, 2013 at The University of Auckland, New Zealand.

Five researchers from RIKEN and four researchers from Chiba University including three Chiba University G-COE program core members joined the workshop.

The workshop covered four topics; Allergy, Autoimmunity & Tolerance, Immune Regulation & Immunodynamics, Immunotherapy and Infectious Immunity and featured presentations by leading researchers from Japan and New Zealand.

Creating the future of medicine to improve patients' health

Date: March 19, 2012
Venue: Chiba University Hospital Clinical Research Center

The CCRC 10th Anniversary and CFMRC Inauguration Symposium was held to commemorate the launch of the Chiba University Future Medicine Research Center (CFMRC) in March 2012 and the 10th anniversary of Chiba University Hospital Clinical Research Center (CCRC). The Memorial Hall (which seats 300) was full to capacity. Guests from the Japanese Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labour, and Welfare were in attendance for the symposium.

Lecturers from Harvard Medical School and Duke University gave keynote speeches on their academia-launched development research. A panel discussion was held under the theme of "Our Roles, Human resources, and Collaboration." A detailed discussion was held to find a direction of Chiba University. The symposium ended on a high note with the Celebration party.

Summary of the Panel discussion

It is difficult to be an expert for both basic research and clinical research, and for physicians to cover the entire area of medicine. The cooperation and information exchange between clinical researchers, the regulatory authority, and the pharmaceutical industry are necessary participants to the developmental process. Furthermore we should nurture human resources for the next generation, which is the mission of the FMCR. We expect these efforts will bear fruit in the future.

Opening Remarks

Yasushi Saito, MD: President of Chiba University
Keiji Yamamoto, PhD: Vice President of Chiba University
Masaru Miyazaki, MD: Director of Chiba University Hospital
Akira Tamagami: Ministry of Education, Culture, Sports, Science and Technology
Masanobu Yamada: Ministry of Health, Labor, and Welfare

Keynote addresses

Chairpersons/Hideki Hanaoka, MD, PhD,Sinichiro Motohashi, MD, PhD

Toshinori Nakayama, MD, PhD, Professor of Chiba Univ. Director of CFMRC
"Our goals as Chiba University Future Medicine Research Center"

Dale T. Umetsu, MD, PhD, Professor of Harvard Medical School
"Innate Lymphoid Cells Shape Immunity in the Lungs"

John H. Alexander, MD, MHS, Associate Professor of Duke University
"Academic Physician Involvement in New Drug Development: Lessons from ARISTOTLE"

Panel Discussion "Our roles, human resources, and collaboration"

Chairpersons / Yasushi Saito, Toshinori Nakayama
Panelists / Dale T. Umetsu, John H. Alexander, Keiji Yamamoto and the presenters

Presentations

1) Hideki Hanaoka, Director of CCRC
"Our 10 years history and new roles to create the future of medicine"
2) Yoshiaki Uyama, Visiting Professor of Chiba Univ., PMDA,
"A bridge to collaboration between academic investigators and government regulators"
3) Kazuki Saito, Professor of Pharmaceutical Sciences, Chiba Univ.
"Translational research in pharmaceutical sciences at Chiba University"
4) Shinichiro Motohashi
"Targeting lung cancer with NKT cells"

Discussion and Summary

Joint Program, Overseas Official Trips and Invited Researchers

◆ G-COE Joint Program

November 5-25, 2008	Introductory Seminar of Biostatistics(5 times in all) Lecturer: Yasunori Sato
November 13, 2008	The 266th Chiba Bioscience Seminar Shouichi Ohga · Kyushu University
November 17, 2008	The 4th Chiba Basic and Clinical Immunology Seminar Toru Miyazaki · The University of Tokyo
November 27, 2008	The 267th Chiba Bioscience Seminar Naoto Hirano · Harvard Medical School
January 7-March 24, 2009	Lectures of Exploratory Advanced Therapeutics(12 times in all) Organizer: Hideki Hanaoka (Lecturer, Clinical Research Center, Chiba University Hospital)
January 12, 2009	Joint Forum of University educational Reform Program Poster Session Organized by Bunkyo Kyoukai
March 2, 2009	The 6th Chiba Basic and Clinical Immunology Seminar Hiroshi Takayanagi · Tokyo Medical and Dental University
June 23, 2009	The 7th Chiba Basic and Clinical Immunology Seminar Kiyoshi Takeda · Osaka University
July 2, 2009	The 268th Chiba Bioscience Seminar Janet Pope · St.Joseph Health Care London, Ontario, Canada
September 3, 2009	The 8th Chiba Basic and Clinical Immunology Seminar Toshiro Hara · Kyushu University
December 15, 2009	The 9th Chiba Basic and Clinical Immunology Seminar Yoichiro Iwakura · The Institute of Medical Science, The University of Tokyo
March 24, 2010	The 10th Chiba Basic and Clinical Immunology Seminar Sho Matsushita · Saitama Medical University
May 13, 2010	The 11th Chiba Basic and Clinical Immunology Seminar Kohei Miyazono · The University of Tokyo
November 18, 2010	The 12th Chiba Basic and Clinical Immunology Seminar Akira Takashima · University of Toledo, USA
December 8, 2010	The 13th Chiba Basic and Clinical Immunology Seminar Takao Koike · Hokkaido University
May 11, 2011	The 14th Chiba Basic and Clinical Immunology Seminar Fumihiko Ishikawa · Riken Research Center for Allergy and Immunology
May 24, 2011	The University of Tokyo G-COE Seminar Gordon D. Brown · University of Aberdeen, UK
June 24, 2011	The 15th Chiba Basic and Clinical Immunology Seminar Takayuki Sumida · University of Tsukuba
July 8, 2011	The 16th Chiba Basic and Clinical Immunology Seminar Akihiro Yachie · Kanazawa University
August 25, 2011	The 1st Infection & Immunity seminar Osamu Takeuchi · Osaka University
September 16, 2011	The 2nd Infection & Immunity seminar Glen N Barber · University of Miami, USA
December 13, 2011	The 17th Chiba Basic and Clinical Immunology Seminar Atsushi Kumanogoh · Osaka University
May 11, 2012	The 18th Chiba Basic and Clinical Immunology Seminar Shimon Sakaguchi · Immunology Frontier Research Center, Osaka University
June 13, 2012	The 19th Chiba Basic and Clinical Immunology Seminar Chie Kudo · Keio University School of Medicine
November 21, 2012	The 20th Chiba Basic and Clinical Immunology Seminar Toshifumi Mikayama · Kyowa Hakko Kirin Co., Ltd.

◆ Overseas Official Trips

Name	Affiliation	From	To	Place(Purpose)
Faculty and Fellow				
Toshinori Nakayama	Program Leader	August 14, 2008	August 21, 2008	Oxford University (Magdalen College), UK (Research presentation)
Kazuo Suzuki	Coordinator	July 21, 2008	July 26, 2008	National Hospital of Pediatrics, Hanoi, Vietnam National Institute of Infectious and Tropical Diseases, Hanoi, Vietnam (The G-COE research program introduction)
Toshinori Nakayama	Program Leader	September 23, 2008	October 1, 2008	LIAI, NIH, USA (The Program Promotion Conference with the G-COE overseas collabolative Institutes)
Masayuki Kitajima	G-COE Fellow	September 24, 2008	March 31, 2010	Benaroya Research Institute, Virginia, USA (Long term overseas study)
Katsunori Ogawara	Assistant Professor	October 7, 2008	October 14, 2008	13th World Congress on Advances in Oncology and 11th International Symposium on Molecular Medicine, Greece (The G-COE research presentation)
Kazuo Suzuki	Coordinator	November 18, 2008	November 21, 2008	Xiamen University, China (The G-COE research introduction)
Toshinori Nakayama	Program Leader	November 19, 2008	November 20, 2008	Grand Hilton Hotel, Soul, Korea (The G-COE research program introduction)
Toshinori Nakayama	Program Leader	December 5, 2008	December 7, 2008	Tsinghua University, Peking, China (The G-COE research program introduction)
Chang He	Research Fellow	December 5, 2008	December 7, 2008	Tsinghua University, Peking, China (The G-COE research program introduction)
Zou Jun	Research Fellow	December 5, 2008	December 7, 2008	Tsinghua University, Peking, China (The G-COE research program introduction)
Toshinori Nakayama	Program Leader	February 8, 2009	February 15, 2009	Loyola University of Chicago, USA (The G-COE research introduction)
Koji Tokoyoda	G-COE independent research associate	February 17, 2009	March 15, 2009	Deutsches Rheuma-Forschungszentrum, Berlin, Germany (Collaborative research)
Ryo Shinnakasu	G-COE Fellow	April 27, 2009	March 31, 2010	LIAI, USA (Long term overseas study)
Yuumi Nakamura	G-COE Fellow	May 1, 2009	October 31, 2009	Department of Pathology, University of Michigan, USA (Long term overseas study)
Toshinori Nakayama	Program Leader	May 7, 2009	May 12, 2009	Benaroya Research Institute, Seattle, USA (The Program Promotion Conference and the G-COE research presentation with collaborative institutes)
Koji Tokoyoda	G-COE independent research associate	July 10, 2009	July 30, 2009	Deutsches Rheuma-Forschungszentrum, Berlin, Germany (Collaborative research)
Nyambayar Dashtsoodol	G-COE Fellow	July 25, 2009	August 2, 2009	University of Minnesota, USA (Research presentation)
Toshinori Nakayama	Program Leader	August 28, 2009	August 30, 2009	Bangkok Convention Center, Thailand (Lecture and the G-COE research introduction in JSPS-NRCT Seminar at Research Expo 2009 hosted byJSPS Bangkok Office)
Koji Tokoyoda	G-COE independent research associate	September 8, 2009	September 25, 2009	International Congress Center, Deutsches Rheuma-Forschungszentrum, Berlin, Germany (Research presentation and collaborative research)
Ayako Inamine	G-COE Fellow	September 10, 2009	September 19, 2009	Langenbeck-Virchow-Haus GbR, International Congress Center, Berlin, Germany (Research presentation and collaborative research)
Toshinori Nakayama	Program Leader	September 13, 2009	September 24, 2009	International Congress Center Berlin, Hamburg, Germany, University of London (Research presentation)
Kazuo Suzuki	Coordinator	October 6, 2009	October 9, 2009	Peking University, China (The G-COE research introduction)
Toshinori Nakayama	Program Leader	November 15, 2009	November 25, 2009	Hilton Papagayo Resort Costa Rica, NIH, University of Pensylvania, USA (The G-COE research presentation and research program introduction)
Takashi Fujimura	G-COE Fellow	December 4, 2009	December 13, 2009	Sheraton Buenos Aires Hotel & Convention Center, Argentina (The G-COE research presentation)
Koji Tokoyoda	Assistant Professor	April 15, 2010	April 27, 2010	Deutsches Rheuma-Forschungszentrum, Berlin, DEU (Collaborative research)

Joint Program, Overseas Official Trips and Invited Researchers

◆ Overseas Official Trips

Name	Affiliation	From	To	Place(Purpose)
Faculty and Fellow				
Toshinori Nakayama	Program Leader	May 19, 2010	May 26, 2010	CIS Annual Meeting, The First CIS North American Primary Immune Deficiency National Conference, NIH, USA
Ryo Shinnakasu	G-COE Fellow	April 1, 2010	September 30, 2010	La Jolla Institute for Allergy & Immunology, USA
Kaoru Ito	G-COE Fellow	July 18, 2010	July 25, 2010	Basic Cardiovascular Sciences 2010 Scientific Sessions, USA
Koji Tokoyoda	Assistant Professor	September 15, 2010	October 2, 2010	Deutsches Rheuma-Forschungszentrum, Berlin, DEU (Collaborative research), 40th Annual Conference of the German Society of Immunology,
Toshinori Nakayama	Program Leader	September 30, 2010	October 6, 2010	ASBMB Special Symposia(Granlibakken conference center and lodge), USA
Atsushi Onodera		September 30, 2010	October 8, 2010	ASBMB Special Symposia(Granlibakken conference center and lodge), USA · La Jolla Institute for Allergy & Immunology, USA
Ayako Inamine	G-COE Fellow	September 25, 2010	October 5, 2010	Deutsches Rheuma-Forschungszentrum, Berlin, DEU
Ryo Shinnakasu	G-COE Fellow	October 1, 2010	March 31, 2011	La Jolla Institute for Allergy & Immunology, USA
Tokoyoda Koji	Assistant Professor	November 7, 2010	November 14, 2010	Deutsches Rheuma-Forschungszentrum, Berlin, DEU (Collaborative research)
Kaoru Ito	G-COE Fellow	November 13, 2010	November 18, 2010	AHA Scientific Sessions 2010 McCormick Place, USA
Kazuo Suzuki	Coordinator	December 19, 2010	December 25, 2010	NIH-NIAID, Boston University, USA
Shinichiro Motohashi	Associate Professor	January 11, 2011	January 21, 2011	University of Pennsylvania(Pathology and Laboratory Medicine), USA
Fumihiro Ishibashi		January 11, 2011	January 21, 2011	University of Pennsylvania(Pathology and Laboratory Medicine), USA
Kenichi Harigaya	Professor	January 21, 2011	January 27, 2011	Keystone Symposia, Fairmont Waterfront, CAN
Toshinori Nakayama	Program Leader	February 6, 2011	February 13, 2011	Keystone Symposia, Fairmont Waterfront, CAN, Fairmont Banff Springs, Benaroya Research Institute, USA
Kazuo Suzuki	Coordinator	May 11, 2011	May 28, 2011	NIH, UNC Chapel Hill, USA Royal Blu Radisson Hotel, BLE, Cambridge University Hospitals, GBR
Toshinori Nakayama	Program Leader	May 14, 2011	May 25, 2011	NIH, University of Pennsylvania,Swissôtel Chicago, USA, NH Conference Centre, NLD
Shinichiro Motohashi	Associate Professor	May 19, 2011	May 25, 2011	Swissôtel Chicago, University of Pennsylvania, USA
Kazuki Yamasaki		May 19, 2011	May 25, 2011	Swissôtel Chicago, University of Pennsylvania, USA
Toshinori Nakayama	Program Leader	June 12, 2011	June 23, 2011	Istanbul Congress Center, TUR, La Jolla Institute of Allergy and Immunology, Stanford University, USA
Atsushi Onodera		June 23, 2011	July 2, 2011	National Institutes of Health, USA
Masaya Koshizaka	G-COE Fellow	July 3, 2011	March 31, 2012	Duke Clinical Research Institute, USA
Kazuo Suzuki	Coordinator	September 25, 2011	September 30, 2011	Cambridge University Hospitals, GBR
Toshinori Nakayama	Program Leader	September 23, 2011	September 29, 2011	Gleacher Center, The University of Chicago, USA
Toshinori Nakayama	Program Leader	December 19, 2011	December 21, 2011	Zhejiang University School of Medicine, CHN
Toshinori Nakayama	Program Leader	January 29, 2012	February 7, 2012	1. California Institute of Technology, USA 2. LIAI, USA 3. Fairmont Hotel New Port Beach, USA
Yusuke Endo	G-COE Fellow	January 29, 2012	February 7, 2012	1. California Institute of Technology, USA 2. LIAI, USA 3. Fairmont Hotel New Port Beach, USA
Kenta Shinoda	G-COE Fellow	January 29, 2012	February 7, 2012	1. California Institute of Technology, USA 2. LIAI, USA 3. Fairmont Hotel New Port Beach, USA
Takashi Ito	G-COE Fellow	March 25, 2012	March 31, 2012	Big Sky Resort, Montana, USA
Shunsuke Furuta	G-COE Fellow	January 16, 2012	March 31, 2012	Addenbrooke's Hospital, University of Cambridge, GBR
Masaya Koshizaka	G-COE Fellow	April 1, 2012	March 1, 2013	Duke Clinical Research Institute, USA
Naoki Kunii	G-COE Fellow	April 1, 2012	April 1, 2012	Graduate School of Medicine, Chiba University

◆ Overseas Official Trips

Name	Affiliation	From	To	Place(Purpose)
Faculty and Fellow				
Toshinori Nakayama	Program Leader	May 16, 2012	May 20, 2012	Swissotel Chicago, NIH, USA
Shinichiro Motohashi	Associate Professor	May 17, 2012	May 21, 2012	Swissotel Chicago, USA
Kaoru Nagato	G-COE Fellow	May 17, 2012	May 21, 2012	Swissotel Chicago, USA
Toshinori Nakayama	Program Leader	June 13, 2012	June 21, 2012	Deutsches Rheuma-Forschungszentrum, Berlin, DEU
Heizaburo Yamamoto	G-COE Fellow	July 1, 2012	March 31, 2013	La Jolla Institute for Allergy & Immunology, USA
Students				
Masanobu Yamatoji	Graduate Student	October 7, 2008	October 14, 2008	13th World Congress on advances in Oncology and 11th International Symposium on Molecular Medicine, Greece (Research presentation)
Kentarou Sakuma	Graduate Student	October 7, 2008	October 14, 2008	13th World Congress on advances in Oncology and 11th International Symposium on Molecular Medicine, Greece (Research presentation)
Yoshiro Hirasaki	Graduate Student	December 5, 2008	December 7, 2008	Tsinghua University, Peking, China (The G-COE research introduction, interaction between students)
Asami Hanazawa	RA	July 14, 2009	July 24, 2009	Deutsches Rheuma-Forschungszentrum, Berlin, Germany (Short term overseas study)
Akane Suzuki	RA	November 18, 2009	December 6, 2009	NIH, Washington DC, USA (Short term overseas study)
Tomokazu Sumida	RA	July 19, 2010	July 24, 2010	Basic Cardiovascular Sciences 2010 Scientific Sessions, USA
Kenta Shinoda	RA	September 15, 2010	September 28, 2010	Deutsches Rheuma-Forschungszentrum, Berlin, Germany (Collaborative research), 40th Annual Conference of the German Society of Immunology, Germany
Yuan Jin	RA	September 14, 2010	September 19, 2010	Annual Society for Hematology and Stem Cells (ISEH) Meeting (Melbourne Convention & Exhibition Centre), AUS
Yusuke Endo	RA	September 30, 2010	October 8, 2010	ASBMB Special Symposia (Granlibakken conference center and lodge), USA · La Jolla Institute for Allergy & Immunology, USA
Hiroto Kamoda	RA	November 13, 2010	November 17, 2010	Society for Neuroscience 2010 (San Diego Convention Center), USA
Tomokazu Sumida	RA	October 26, 2010	November 1, 2010	WNT2010, Karolinsla Institutet Stockholm, SWE
Tomokazu Sumida	RA	November 13, 2010	November 18, 2010	AHA Scientific Sessions 2010 McCormick Place, USA
Tetsuhiro Ishikawa	RA	November 13, 2010	November 17, 2010	Neuroscience 2010 San Diego Convention Center, USA
Teruyoshi Saito	RA	January 21, 2011	January 27, 2011	Keystone Symposia, Fairmont Waterfront, CAN
Wu Shuang	RA	February 16, 2011	February 20, 2011	The 21st Conference of the Asian Pacific Association for the Study of the Liver, Queen Sirikit National Convention Center, THA
Masataka Yokoyama	RA	July 17, 2011	July 23, 2011	The Ritz-Catlton New Orleans, LA, USA
Satomi Tanaka	RA	December 9, 2011	December 15, 2011	San Diego Convention Center, USA
Moeko Hino	RA	December 9, 2011	December 15, 2011	San Diego Convention Center, USA
Yohko Yoshida	RA	February 12, 2012	February 18, 2012	Ventura Beach Marriott, USA
Yoshiki Kaneko	RA	June 17, 2012	June 24, 2012	The Fairmont Royal York (Toronto), CAN
Yohko Yoshida	RA	July 21, 2012	July 27, 2012	Basic Cardiovascular Sciences 2012 Scientific Sessions
Eriko Suwa	RA	September 4, 2012	September 12, 2012	Scottish Exhibition & Conference Centre, GBR

Joint Program, Overseas Official Trips and Invited Researchers

◆ Invited Researchers

Name	Affiliation	From	To	Place
Faculty				
John Joseph O'Shea Jr.	Scientific Director, NIAMS, NIH	December 1, 2008	December 6, 2008	Graduate School of Medicine, Chiba University
Mitchell Kronenberg	President and Scientific Director, Member and Division Head, La Jolla Institute for Allergy & Immunology	January 4, 2009	January 10, 2009	Tokyo Station Conference Sapia Hall, Graduate School of Medicine, Chiba University
Toshiaki Kawakami	Member, Division of Allergy, La Jolla Institute for Allergy & Immunology	January 1, 2009	January 12, 2009	Tokyo Station Conference Sapia Hall, Graduate School of Medicine, Chiba University
Steven F. Ziegler	Member and Director, Immunology Program, Benaroya Research Institute	January 1, 2009	January 12, 2009	Tokyo Station Conference Sapia Hall, Graduate School of Medicine, Chiba University
Stephen Philip Schoenberger	Member, Laboratory of Cellular Immunology, La Jolla Institute for Allergy & Immunology	January 4, 2009	January 12, 2009	Tokyo Station Conference Sapia Hall, Graduate School of Medicine, Chiba University
Klaus Ley	Head and Member, Autoimmune Research, Inflammation Biology, La Jolla Institute for Allergy & Immunology	January 4, 2009	January 13, 2009	Tokyo Station Conference Sapia Hall, Graduate School of Medicine, Chiba University
Thierry Mallevaey	Researcher, University of Colorado at Denver	March 29, 2009	March 31, 2009	Graduate School of Medicine, Chiba University
Laurent Gapin	Associate Professor, University of Colorado at Denver, National Jewish Health	March 29, 2009	March 31, 2009	Graduate School of Medicine, Chiba University
Mark Exley	Associate Professor, Harvard University	March 30, 2009	April 1, 2009	Graduate School of Medicine, Chiba University
Anja Hauser	Group Leader, Department of Immunodynamics Deutsches Rheumaforschungzentrum Berlin (DRFZ)	May 16, 2009	June 6, 2009	Graduate School of Medicine, Chiba University
Daniel J. Campbell	Assistant Member, Immunology Program, Benaroya Research Institute	May 27, 2009	June 5, 2009	Graduate School of Medicine, Chiba University
Alfred Singer	Chief, Experimental Immunology Branch, NIH	May 26, 2009	June 4, 2009	Graduate School of Medicine, Chiba University
Rose Zamoyska	Professor, Immune Cell Biology, University of Edinburgh	May 27, 2009	June 5, 2009	Graduate School of Medicine, Chiba University
Dinah Singer	Senior Investigator, Head, Molecular Regulation Section, NIH	May 26, 2009	June 1, 2009	Graduate School of Medicine, Chiba University
Stephen Philip Schoenberger	Member, Laboratory of Cellular Immunology, La Jolla Institute for Allergy & Immunology	May 27, 2009	June 5, 2009	Graduate School of Medicine, Chiba University
Rémy Bosselut	Senior Investigator, Laboratory of Immune Cell Biology, NCI, NIH	May 28, 2009	June 4, 2009	Graduate School of Medicine, Chiba University
Carl H. June	Professor, University of Pennsylvania	May 14, 2009	May 15, 2009	Graduate School of Medicine, Chiba University
Motoko Kimura	Research Fellow, Experimental Immunology Branch, NCI, NIH	May 27, 2009	May 29, 2009, June 11, 2009	Graduate School of Medicine, Chiba University
Ryoji Yagi	Research Fellow, Laboratory of Immunology, NIAID, NIH	May 28, 2009	May 29, 2009, June 11, 2009	Graduate School of Medicine, Chiba University
Jessy Deshane	Post-Doctoral Researcher, University of Alabama at Birmingham	July 1, 2009	July 12, 2009	RIKEN RCAI
Cindy Ma	Post-Doctoral Researcher, Garvan Institute of Medical Research	July 1, 2009	July 12, 2009	RIKEN RCAI
Marian Turner	Post-Doctoral Researcher, Walter and Eliza Hall Institute of Medical Research	July 1, 2009	July 13, 2009	RIKEN RCAI
Susan Johnson	Post-Doctoral Researcher, University of Geneva	July 1, 2009	July 12, 2009	RIKEN RCAI
Andreia Lino	Post-doctoral Researcher, Institute Gulbenkian de Ciência	July 1, 2009	July 12, 2009	RIKEN RCAI
Aaron Tyznik	Post-Doctoral Researcher, La Jolla Institute for Allergy and Immunology	July 1, 2009	July 12, 2009	RIKEN RCAI
Todd Suscovich	Post-Doctoral Researcher, Benaroya Research Institute	July 1, 2009	July 12, 2009	RIKEN RCAI
Carrie Arnold	Post-Doctoral Researcher, The Scripps Research Institute	July 1, 2009	July 12, 2009	RIKEN RCAI
Dipayan Rudra	Post-doctoral Researcher, Memorial Sloan, Kettering Cancer Center	July 1, 2009	July 12, 2009	RIKEN RCAI

Name	Affiliation	From	To	Place
Faculty				
Joseph Reynolds	Post-doctoral Researcher, M.D. Anderson Cancer Center	July 1, 2009	July 12, 2009	RIKEN RCAI
Jennifer Walker	Post-Doctoral Researcher, Walter and Eliza Hall Institute of Medical Research	July 1, 2009	July 13, 2009	RIKEN RCAI
Ricardo Weinlich	Post-Doctoral Researcher, Institute of Biomedical Sciences, University of Sao Paulo	June 30, 2009	August 9, 2009	RIKEN RCAI
Clifford Lowell	Professor and Chair, University of California, San Francisco	July 1, 2009	July 10, 2009	RIKEN RCAI
Ellen Rothenberg	Professor, California Institute of Technology	July 4, 2009	July 8, 2009	RIKEN RCAI
Cristian Munz	Professor, Viral Immunobiology Institute of Experimental Immunology University of Zurich	July 5, 2009	July 10, 2009	RIKEN RCAI
Gabriel Nunez	Professor, University of Michigan	September 5, 2009	September 12, 2009	Graduate School of Medicine, Chiba University
Kenneth G. C. Smith	Genzyme Professor, Experimental Medicine, Cambridge Institute of Medical Research, University of Cambridge School of Clinical Medicine	November 3, 2009	November 8, 2009	Graduate School of Medicine, Chiba University
Dale T. Umetsu	Prince Turki Bin Abdul Azis al Saud Professor, Pediatrics, Children's Hospital Boston, Harvard Medical School	November 5, 2009	November 6, 2009	Graduate School of Medicine, Chiba University
Shinya Sakaguchi	Postdoctoral fellow, Prof. Ellmeier's laboratory, Institute of Immunology, Medical University of Vienna	November 6, 2009	November 7, 2009	Graduate School of Medicine, Chiba University
James K. Liao	Director, Brigham & Women's Hospital	November 5, 2009	November 7, 2009	Graduate School of Medicine, Chiba University
Philippa Marrack	Professor, University of Colorado	December 2, 2009	December 9, 2009	Graduate School of Medicine, Chiba University
Naoto Kawakami	Max Plank Institute of Neurobiology-Group Leader	May 14, 2010	June 7, 2010	Graduate School of Medicine, Chiba University
Koichi Kobayashi	Department of Cancer Immunology & AIDS Dana-Farber Cancer Institute Pathology, Harvard Medical School-Assistant Professor	April 9, 2010	April 18, 2010	Graduate School of Medicine, Chiba University
Erwin W. Gelfand	National Jewish Health-Professor	August 18, 2010	August 21, 2010	Graduate School of Medicine, Chiba University
Steven F. Ziegler	Benaroya Research Institute-Professor	August 17, 2010	September 2, 2010	Graduate School of Medicine, Chiba University
Shane Crotty	La Jolla Institute for Allergy & Immunology-Assistant Member	August 17, 2010	August 21, 2010	Graduate School of Medicine, Chiba University
Anjana Rao	Harvard Medical School-Professor, La Jolla Institute for Allergy & Immunology	August 18, 2010	August 28, 2010	Graduate School of Medicine, Chiba University
Mitchell Kronenberg	La Jolla Institute for Allergy & Immunology-Assistant Member	August 18, 2010	August 27, 2010	Graduate School of Medicine, Chiba University
Andreas Radbruch	German Rheumatology Research Center Berlin-Scientific Director	August 18, 2010	August 27, 2010	Graduate School of Medicine, Chiba University
Hilde Cheroutre	La Jolla Institute for Allergy & Immunology-Assistant Member	August 18, 2010	September 5, 2010	Graduate School of Medicine, Chiba University
DeBroski Herbert	Cincinnati Children's Research Foundation-Assistant Professor	August 20, 2010	September 1, 2010	Graduate School of Medicine, Chiba University
Masayuki Kitajima	Benaroya Research Institute-Postdoctoral Fellow	August 30, 2010	September 12, 2010	Graduate School of Medicine, Chiba University
Lisa Ma	Sanford-Burnham Medical Research Institute-Post-Doctoral Researcher	August 15, 2010	August 28, 2010	RIKEN RCAI
Annick Van De Ven	Wilhelmina Children's Hospital, University Medical Center Utrecht-M.D received	August 15, 2010	August 28, 2010	RIKEN RCAI
Jonathan Clingan	Wilhelmina Children's Hospital, University Medical Center Utrecht-M.D Received	August 15, 2010	August 28, 2010	RIKEN RCAI
Hae-Young Park	Gachon University of Medicine and Science-Post-Doctoral Researcher	August 16, 2010	August 28, 2010	RIKEN RCAI
Frederick Masson	The Walter and Eliza Hall Institute of Medical Research-Post-Doctoral Researcher	August 15, 2010	August 29, 2010	RIKEN RCAI
Nicholas Clarkson	Oxford University Post-Doctoral Researcher	August 15, 2010	August 28, 2010	RIKEN RCAI
Monica Leung	Genomics Institute of the Novartis Research Foundation-Postdoctoral Fellow	August 15, 2010	August 28, 2010	RIKEN RCAI

Joint Program, Overseas Official Trips and Invited Researchers

Name	Affiliation	From	To	Place
Faculty				
Gerge Gesteiger	Memorial Sloan-Kettering Institute Post-Doctoral Researcher	August 15, 2010	August 28, 2010	RIKEN RCAI
Luisa Cimmino	Walter and Eliza Hall Institute Post-Doctoral Researcher	August 15, 2010	August 29, 2010	RIKEN RCAI
Eduardo Villablanca	Massachusetts General Hospital, Harvard Medical School Post-Doctoral Researcher	August 15, 2010	August 28, 2010	RIKEN RCAI
Steven Josefowicz	Memorial Sloan Kettering Cancer Center, Post-Doctoral Researcher	August 15, 2010	August 28, 2010	RIKEN RCAI
Fernando Sepulveda	Institute Curie, U932	August 15, 2010	August 28, 2010	RIKEN RCAI
Anastasia Tikhonova	IGG University of Pennsylvania, National Cancer Institute	August 15, 2010	August 28, 2010	RIKEN RCAI
Fred Finkelman	University of Cincinnati-Professor	November 23, 2010	November 30, 2010	Tokyo Station Conference Sapia Hall
Koichi Araki	School of Medicine, Emory University	December 2, 2010	December 8, 2010	Tokyo Station Conference Sapia Hall
Hal Hoffman	University of California San Diego-Associate Professor	December 2, 2010	December 11, 2010	Graduate School of Medicine, Chiba University
Alfred Singer	National Institutes of Health-Chief	November 25, 2011	December 1, 2011	Hotel New Otani Makuhari
Hilde Cheroutre	La Jolla Institute for Allergy and Immunology-Division Head and Professor	November 25, 2011	December 6, 2011	Hotel New Otani Makuhari
Meinrad Busslinger	The Research Institute of Molecular Pathology-Senior Scientist (Professor)	November 26, 2011	December 1, 2011	Hotel New Otani Makuhari
Motoko Kimura	National Institutes of Health-Research Fellow	November 19, 2011	December 4, 2011	Hotel New Otani Makuhari
Chen Dong	MD Anderson Cancer Center-Professor	November 28, 2011	December 6, 2011	Hotel New Otani Makuhari
David Tarlinton	Walter and Eliza Hall Institute of Medical Research-Associate Professor	November 24, 2011	December 2, 2011	Hotel New Otani Makuhari
David Artis	University of Pennsylvania-Associate Professor	November 27, 2011	December 1, 2011	Hotel New Otani Makuhari
Dale Umetsu	Harvard Medical School-Professor	March 17, 2012	March 20, 2012	Graduate School of Medicine, Chiba University
Omid Akbari	University of Southern California-Associate Professor	April 8, 2012	April 10, 2012	Graduate School of Medicine, Chiba University
Natalia Zietara	Hannover Medical School-Postdoc	June 20, 2012	July 28, 2012	RIKEN RCAI
Iliyan Iliev	Cedars-Sinai Medical Center-Postdoc	June 20, 2012	June 30, 2012	RIKEN RCAI
Andy Tsun	Institute Pasteur of Shanghai-Postdoc	June 21, 2012	June 30, 2012	RIKEN RCAI
Ruth Etzensperger	National Cancer Institute, National Institutes of Health-Postdoc	June 20, 2012	June 30, 2012	RIKEN RCAI
Roy Ramiscal	John Curtin School of Medical Research, Australian National University-PhD Scholar	June 20, 2012	July 1, 2012	RIKEN RCAI
Irene Bonaccorsi	University of Messina-Postdoc	June 20, 2012	June 30, 2012	RIKEN RCAI
Nicholas Arpaia	Memorial Sloan-Kettering Cancer Center-Postdoc	June 20, 2012	June 30, 2012	RIKEN RCAI
Carl H June	University of Pennsylvania-Professor	September 17, 2012	September 21, 2012	Graduate School of Medicine, Chiba University
Frank C.Schroeder	Boyce Thompson Institute-Assistant Professor	September 25, 2012	October 25, 2012	Graduate School of Medicine, Chiba University

◆ Invited Researchers

Name	Affiliation	From	To	Place
Students				
Sandra Zehentmeiner	Graduate Student, Department of Immunodynamics Deutsches Rheumaforschungzentrum Berlin (DRFZ)	April 28, 2009	June 11, 2009	Graduate School of Medicine, Chiba University
Juandy Jo	Graduate Student, Spemann Graduate School of Biology and Medicine	July 1, 2009	July 12, 2009	RIKEN RCAI
Hemanth Ramaprakash	Graduate Student, University of Michigan	July 1, 2009	July 12, 2009	RIKEN RCAI

Name	Affiliation	From	To	Place
Students				
Ramon Mayoral	Graduate Student, Institute for Research in Biomedicine	July 1, 2009	July 12, 2009	RIKEN RCAI
Hakim Yadi	Graduate Student, The Babraham Institute	July 1, 2009	July 12, 2009	RIKEN RCAI
Doo-Hee Shim	Graduate Student, International Vaccine Institute	July 2, 2009	July 12, 2009	RIKEN RCAI
Diego Mourao Sa	Graduate Student, Cancer Research UK, London Research Institute	July 1, 2009	July 12, 2009	RIKEN RCAI
Gabriel Victora	Graduate Student, New York University School of Medicine	July 1, 2009	July 12, 2009	RIKEN RCAI
Matthew Meredith	Graduate Student, The Rockefeller University	July 1, 2009	July 12, 2009	RIKEN RCAI
Thomas Tiller	Graduate Student, Max Planck Institute for Infection Biology	July 1, 2009	July 12, 2009	RIKEN RCAI
Jessica Moffat	Graduate Student, The Walter and Eliza Hall Institute of Medical Research	July 1, 2009	July 13, 2009	RIKEN RCAI
Jaclyn McAlees	Graduate Student, The Ohio State University, Integrated Biomedical Gradutae Program	July 1, 2009	July 12, 2009	RIKEN RCAI
Niklas björkström	Graduate Student, Karolinska Institutet	July 1, 2009	July 12, 2009	RIKEN RCAI
Rosa Maria Barreira da Silva	Graduate Student, Institute of Experimental Immunology, University of Zurich	July 1, 2009	July 11, 2009	RIKEN RCAI
Yvonne Vercoulen	Graduate Student, Center for Molecular and Cellular Intervention, Wilhelmina Children's Hospital, UMC Utrecht	July 1, 2009	July 12, 2009	RIKEN RCAI
Andrea Reboldi	Graduate Student, Institute for Research in Biomedicine	July 1, 2009	July 12, 2009	RIKEN RCAI
Marko Knoll	Graduate Student, Max Planck Institute for Infection Biology	July 1, 2009	July 12, 2009	RIKEN RCAI
James Scott-Browne	Graduate Student, University of Colorado Denver	July 1, 2009	July 15, 2009	RIKEN RCAI/Graduate School of Medicine, Chiba University
Duncan Sutherland	Graduate Student, Australian National University	July 1, 2009	August 10, 2009	RIKEN RCAI
Sunita Singh	Graduate Student, National Centre for Cell Science (NCCS)	July 1, 2009	August 9, 2009	RIKEN RCAI
Aranzazu Cruz-Adalia	Graduate Student, National Centre of cardiovascular Diseases (CNIC)	July 1, 2009	August 9, 2009	RIKEN RCAI
Yingting Mok	Graduate Student, University of Cambridge	July 1, 2009	July 12, 2009	RIKEN RCAI
Heidi Snider	Graduate Student, The Ohio State University, Columbus, OH	July 1, 2009	July 12, 2009	RIKEN RCAI
Meghan Koch	Graduate Student, University of Washington, Benaroya Research Institute	July 1, 2009	July 12, 2009	RIKEN RCAI
Swantje Hammerschmidt	Graduate Student, Institute of Immunology, Medical School Hannover	July 1, 2009	July 12, 2009	RIKEN RCAI
John Altin	Graduate Student, John Curtin School of Medical Research	July 1, 2009	July 13, 2009	RIKEN RCAI
Priya Dedhia	Graduate Student, Immunology Graduate Group, University of Pennsylvania	June 29, 2009	July 12, 2009	RIKEN RCAI
Mark Headley	Graduate Student, Benaroya Research Institute	July 1, 2009	July 15, 2009	RIKEN RCAI/Graduate School of Medicine, Chiba University
Joaquim Carreras	Graduate Student, University of Cambridge, U.K., Hospital Clinic, University of Barcelona	July 1, 2009	July 16, 2009	RIKEN RCAI
Annie Xin	The Walter and Eliza Hall Institute of Medical Research-Graduate Student	August 15, 2010	August 29, 2010	RIKEN RCAI
Byung-seok Kim	Seoul National University-Graduate Student	August 16, 2010	August 28, 2010	RIKEN RCAI
Vera Schwierzeck	University of Cambridge, CIMR-Graduate Student	August 15, 2010	August 28, 2010	RIKEN RCAI
Robert Johnston	La Jolla Institute for Allergy & Immunology-Graduate Student	August 15, 2010	August 28, 2010	RIKEN RCAI
Caroline Prado Terrazas	Universidad Andrés Bello, Fundación Ciencia Para la Vida-Graduate Student	August 14, 2010	August 29, 2010	RIKEN RCAI
David Dilillo	Duke University Medical Cente-Graduate Student	August 15, 2010	August 28, 2010	RIKEN RCAI
Olga Schulz	Hannover Medical School, Institute of Immunology-Graduate Student	August 15, 2010	August 28, 2010	RIKEN RCAI

Joint Program, Overseas Official Trips and Invited Researchers

Name	Affiliation	From	To	Place
Students				
Stephan Halle	Hannover Medical School-Graduate Student	August 15, 2010	August 28, 2010	RIKEN RCAI
Jean Charton	University of Lausanne-Graduate Student	August 15, 2010	August 28, 2010	RIKEN RCAI
Catharina Elssen	Maastricht University Medical Center-Graduate Student	August 15, 2010	August 28, 2010	RIKEN RCAI
Tyani Chan	Garvan Institute of Medical Research-Graduate Student	August 15, 2010	August 29, 2010	RIKEN RCAI
Stephanie Grabow	The Walter and Eliza Hall Institute-Graduate Student	August 15, 2010	August 29, 2010	RIKEN RCAI
Santi Suryani	Garvan Institute of Medical Research-Graduate Student	August 15, 2010	August 29, 2010	RIKEN RCAI
Dmitriy Kolodni	Harvard Medical School-Graduate Student	August 15, 2010	August 28, 2010	RIKEN RCAI
John Yi	University of Alabama at Birmingham-Graduate Student	August 15, 2010	August 28, 2010	RIKEN RCAI
Joseph Bardi	Johns Hopkins University-Graduate Student	August 15, 2010	August 28, 2010	RIKEN RCAI
Margot Cucchetti	Centre d'Immunologie Marseille-Luminy (CIML)-PhD Student	June 20, 2012	July 28, 2012	RIKEN RCAI
Huizhong Xiong	New York University Medical Center-Graduate Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Stefania Raimondo	University of Palemro, Italy-PhD Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Zahra Sabouri	The Australian National University, John Curtin School of Medical Research-PhD Student	June 20, 2012	July 1, 2012	RIKEN RCAI
Alex Delbridge	The Walter and Eliza Hall Institute-Graduate Student	June 20, 2012	July 1, 2012	RIKEN RCAI
Dylan Johnson	University of Tronto-Graduate Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Francisco Contreras	Fundacion Ciencia para la Vida/Universidad Andres Bello-Graduate Student	June 19, 2012	July 1, 2012	RIKEN RCAI
Francisca Almeida	Singapore Immunology Network-PhD Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Ellen Wehrens	University Medical Center Utrecht (UMCU)-Graduate Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Charles Tran	Campbell Family Institute/University of Tronto-Graduate Student	June 20, 2012	July 28, 2012	RIKEN RCAI
Chaoran Li	Duke University-Graduate Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Zuojia Chen	Institute Pasteur of Shanghai, Chinese Academy of Sciences-Graduate Student	June 21, 2012	July 28, 2012	RIKEN RCAI
Aras Toker	Helmholtz Centre for Infection Research-PhD Student	June 20, 2012	July 28, 2012	RIKEN RCAI
Fernanda Duraes	University of Geneva-Ph.D Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Maria De Obaldia	Perelman School of Medicine, Univ. of Pennsylvania-Graduate Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Lucille Rankin	The Walter and Eliza Hall Institute of Medical Research-PhD Student	June 20, 2012	July 1, 2012	RIKEN RCAI
HyeJeong KIM	University of Ulsan-Graduate Student	June 21, 2012	June 30, 2012	RIKEN RCAI
Kevin Man	University of Melbourne-PhD Student	June 20, 2012	July 1, 2012	RIKEN RCAI
Kamalvishnu Gottimukkala	Indian Institute of Science Education and Research-Pune-Graduate Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Jerneja Mori	National Institute of Chemistry-PhD Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Shivani Srivastava	University of Washington-Graduate Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Anthony Bonito	The Mount Sinai School of Medicine-Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Antony Raubitschek	Benaroya Research Institute (University of Washington)-Graduate Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Yudong Liu	The University of Alabama at Birmingham-Graduate Student	June 20, 2012	June 30, 2012	RIKEN RCAI
Qifeng Han	Emory University-Graduate Student	June 20, 2012	January 0, 1900	RIKEN RCAI
Somayeh Sabouri	Kyoto University-Graduate Student	June 21, 2012	June 30, 2012	RIKEN RCAI
Matthew Buechler	University of Washington-Graduate Student	July 19. 2012	July 19. 2012	Graduate School of Medicine, Chiba University

News Letter

We issued our News Letter four times between April 2009 and February 2012.
These newsletters were filled with articles on events, such as symposia and workshops, reports from young researchers studying abroad, and an introduction of our Annual Best Research Award winners.

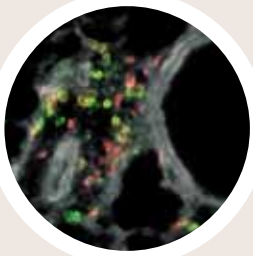
GLOBAL COE

News Letter vol.1 4.2009

Chiba University Global COE Program

Global Center for Education and Research in Immune System Regulation and Treatment

CONTENTS



Message from Program Leader

Program leader
Toshinori Nakayama

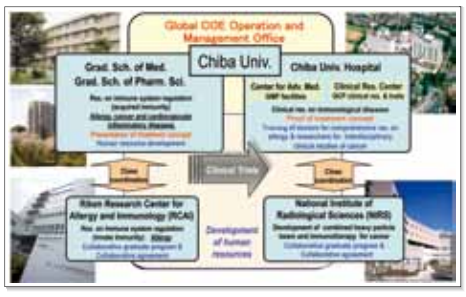
Chiba University initiated a Global COE Program named the "Global Center for Education and Research in Immune System Regulation and Treatment" during the 2008 academic year. The program is jointly implemented by the Graduate School of Medicine and the Graduate School of Pharmaceutical Sciences, Chiba University, RCAI (Riken Research Center for Allergy and Immunology) and NIRS (National Institute of Radiological Sciences). The aim is to promote research in the regulation of the immune system, develop strategies for the treatment of intractable immune disorders regulating the immune system and foster young researchers who will take leadership roles in the field of therapeutic research through this program. The program is operated by 17 program core members, 20 collaborators and a few coordinators. In addition, various unique programs such as G-COE independent young research associates, G-COE postdoctoral fellows, G-COE graduate students, Annual Best Research Award and G-COE-CVPP (Chiba Visiting Professor Program: 18 visiting professors are appointed) have all been established in order to develop sufficient human resources capable of playing active roles in international settings. Along with establishing a developmental system for world-level therapeutic researchers, transmitting new treatment strategies to the world, setting up a Department of Immune System Regulation and Treatment in our graduate school and accelerating translational research, clinical trials and drug trails, to the program will train outstanding personnel and produce leaders, who can play critical roles in achieving those targets.

The complete details of this program and recruitment will be presented on our website (http://www.isrt-gcoe-chiba.jp/). I sincerely hope the students and young researchers, who are interested in our research and this program, will be able to visit our research center at Chiba University.

Toshinori Nakayama

Outline of Global COE Program

Global Center for Education and Research in Immune System Regulation and Treatment



Outline of the program

About 30% of the Japanese population is suffering from allergic diseases. However, only symptomatic therapy is presently available, and no curative therapeutic strategy has yet been developed. In addition, one out of three Japanese people die of cancer.

As more elderly people are afflicted with these diseases, the development of low invasive treatments which enable such patients to obtain a good QOL is desired. Allergic diseases and cancer have the common etiological characteristic that is thought to be the dysregulation and malfunction of the immune system operation in the body. To date, concerning the pathogenic mechanism of these diseases, immunological study has produced remarkable achievements on the molecular and genetic level. As a result, we have now reached the stage for the development of new therapeutic strategies based on "immune system regulation" perspectives. Hence, this program focuses on creating an internationally unprecedented excellent center for education and research, in therapeutics based on immune system regulation, in order to promote therapeutic research for intractable immune disorders including allergy, cancer, cardiovascular inflammatory diseases and arteriosclerosis. In addition, this program aims to foster the development of young scientists in the field of therapeutic research, who have the abilities to, 1. Accomplish creative research from new perspectives, 2. Conduct comprehensive clinical research on allergy and an interdisciplinary clinical research on cancer and 3. Play an active role in the global scientific community after obtaining integrated knowledge and methodology on immune system regulation and immunological treatment.

The clinical application of the basic research results will be conducted mainly at the Chiba University Hospital Clinical Research Center and Center for Advanced Medicine. Since 2007, in recognition of its distinguished achievement, Chiba University Hospital has been designated to be a core hospital for the clinical research (one of only about ten hospitals in Japan) by the Japanese government. In cooperation with RCAI (Riken Research Center for Allergy and Immunology) which jointly implements this program, translational research will be strongly promoted, not only in educational aspects, but also for the practical application of new methods of treatment for allergy.

Chiba University and RCAI have collaborated under an agreement made in 2007 to strengthen bilateral relations. Expansion of this relationship will accelerate the training of graduate school students and young researchers in Chiba University. NIRS, National Institute of Radiological Sciences is the No. 1 research institute in the world for highly advanced cancer therapy using heavy ion charged particle beams, and it has promoted the 21st COE Program in close collaboration with Chiba University. This program, with such collaboration, intends to carry out research and develop new low invasive cancer therapies combining heavy ion charged particle therapy with immune cell therapy, which has never yet been attempted in the world, and also promote and nurture the young human resources involved with this new approach.

Members

Core Members

Toshinori Nakayama
Professor and Chairman, Department of Immunology, Graduate School of Medicine, Chiba University

Issei Komuro
Professor and Chairman, Department of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University

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Akira Hata
Professor and Chairman, Department of Public Health, Graduate School of Medicine, Chiba University

Hiroshi Nakajima
Professor and Chairman, Department of Molecular Genetics, Graduate School of Medicine, Chiba University

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Professor and Chairman, Department of Pediatrics, Graduate School of Medicine, Chiba University

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Professor and Chairman, Department of Otorhinolaryngology, Head and Neck Surgery, Graduate School of Medicine, Chiba University

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Shinichiro Motohashi
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Hideaki Bujo
Professor and Chairman, Department of Genome Research and Clinical Application, Graduate School of Medicine, Chiba University

Kan Chiba
Professor and Chairman, Department of Pharmacology and Toxicology, Graduate School of Pharmaceutical Sciences, Chiba University

Toshiharu Horie
Professor and Chairman, Department of Biopharmaceutics, Graduate School of Pharmaceutical Sciences, Chiba University

Masaru Taniguchi
Director, RIKEN, Research Center for Allergy and Immunology
Professor Emeritus, Chiba University

Osamu Ohara
Group Director, Laboratory for Immunogenomics, RIKEN, Research Center for Allergy and Immunology
Visiting Professor, Department of Pharmacogenomics, Graduate School of Pharmaceutical Sciences, Chiba University

Hirohiko Tsujii
Executive Director, National Institute of Radiological Sciences
Visiting Professor, Graduate School of Medicine, Chiba University

Tadashi Kamada
Director, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences
Visiting Professor, Graduate School of Medicine, Chiba University

Masayuki Baba
Head, Clinical Oncology Section, Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Sciences

Coordinator

Kazuo Suzuki
Professor and Chairman, Inflammation program, Department of Immunology, Graduate School of Medicine, Chiba University

News Letter

Members

G-COE Collaborators

Atsushi Iwama
Professor and Chairman, Department of Cellular and Molecular Medicine, Graduate School of Medicine, Chiba University

Tetsuichiro Saito
Professor and Chairman, Department of Developmental Biology, Graduate School of Medicine, Chiba University

Masahiko Hatano
Professor and Chairman, Department of Biomedical science, Graduate School of Medicine, Chiba University

Hisahiro Matsubara
Professor and Chairman, Department of Frontier Surgery, Graduate School of Medicine, Chiba University

Kenichi Harigaya
Professor and Chairman, Department of Molecular and Tumor Pathology, Graduate School of Medicine, Chiba University

Osamu Yokosuka
Professor and Chairman, Department of Medicine and Clinical Oncology, Graduate School of Medicine, Chiba University

Mitsukazu Kitada
Head, Department of Hospital Pharmacy, Chiba University Hospital

Ichiro Yoshino
Professor and Chairman, Department of Thoracic Surgery, Graduate School of Medicine, Chiba University

Haruaki Nakaya
Professor and Chairman, Department of Pharmacology, Graduate School of Medicine, Chiba University

Masakatsu Yamashita
Associate Professor, Department of Immunology, Graduate School of Medicine, Chiba University

Naoki Shimojo
Associate Professor, Department of Pediatrics, Graduate School of Medicine, Chiba University

Yoichi Suzuki
Associate Professor, Department of Public Health, Graduate School of Medicine, Chiba University

Naotomo Kambe
Lecturer, Department of Dermatology, Graduate School of Medicine, Chiba University

Hideki Hanaoka
Lecturer, Clinical Reserch Center, Chiba University Hospital

Norihiko Watanabe
Lecturer, Department of Allergy and Clinical Immunology, Chiba University Hospital

Koutaro Yokote
Professor and Chairman, Department of Clinical Cell Biology, Graduate School of Medicine, Chiba University

Tomoaki Tanaka
Assistant Professor, Department. of Clinical Cell Biology, Graduate School of Medicine, Chiba University

Naoto Yamaguchi
Professor and Chairman, Department of Molecular Cell Biology, Graduate School of Pharmaceutical Sciences, Chiba University

Hiroshi Kobayashi
Professor and Chairman, Department of Biochemistry, Graduate School of Pharmaceutical Sciences, Chiba University

Akira Nakagawara
President of Chiba Cancer Center, Director of the Research Institute
Visiting Professor, Graduate School of Medicine Chiba University

International Advisory Board Members

Alfred Singer
Chief, Experimental Immunology Branch, National Institutes of Health (NIH)

Dinah Singer
Senior Investigator, Head, Molecular Regulation Section,
National Institutes of Health (NIH)

Andreas Radbruch
Scientific Director, German Rheumatology Research Center Berlin (DRFZ)

Steven L Reiner
Professor, Division of Infectious Diseases and Abramson Family Cancer Research Institute, University of Pennsylvania

James Kuang-Jan Liao
Director, Vascular Medicine Research, Brigham & Women's Hospital
Associate Professor of Medicine, Harvard Medical School

Sonoko Habu
Professor, Graduate School of Medicine, Juntendo University

Kazuhiko Yamamoto
Professor, Graduate School of Medicine, The University of Tokyo

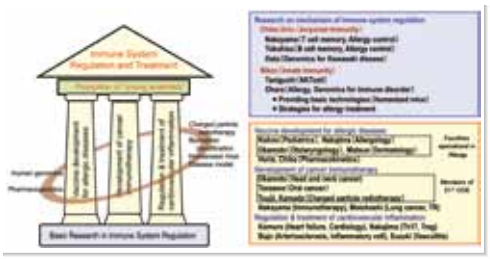
Takao Koike
Professor, Graduate School of Medicine, Hokkaido University

Hiroshi Kiyono
Professor, The Institute of Medical Science, The University of Tokyo

Yoshihiko Saito
Professor, Nara Medical University

Research Activities and Education

In the Graduate School of Medicine at Chiba University, there are several domestically and internationally top-level basic researchers in immunology and allergology. There are also expert groups in clinical fields such as internal medicine, pediatrics, otolaryngology and dermatology, who are able to conduct highly advanced clinical research on allergy. In terms of the research in cancer, this Global COE Program follows and extends the 21st Century COE Program at Chiba University (2003-2007). We plan to eagerly promote basic research and establish a new field of therapeutics by focusing the following four projects. (1) Basic research on the immune system regulation, disease genomics, pharmacogenomics and drug metabolism, and based on the latest research evidence, (2) Development of preventive and treatment strategies for allergies by regulating immune system, (3) Development of immune cell therapy for cancer, and (4) Identifying the pathogenic mechanisms of cardiovascular inflammatory diseases. The following figure shows the outline of the research and staff members of each discipline.



Development of Human Resources

Education for graduate school and postdoctoral fellows

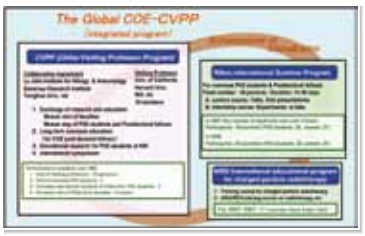
We support Ph.D. students who are selected as G-COE RA (research assistant) graduate students cross-disciplinarily from among various Ph.D. students in the relevant fields and invite them to participate in this program. In addition to a supervisor, two other university teachers in a related field will be responsible for the education of the G-COE RA graduate students to thus provide them with comprehensive guidance.

A special grant for research (young scientist start-up grant level) will be provided to certain numbers of excellent students through the process of reviewing their research proposals. Furthermore, Annual Best Research Awards will be given to the most outstanding students in order to enhance their motivation. In addition, we will select and hire about 10 COE fellows. The Global COE Operation and Management Office will directly advise these students and evaluate their research reports. We have introduced the CVPP (Chiba Visiting Professor Program, an exchange program that enables students, young researchers and faculty to mutually visit each other, with 18 visiting professors and associate professors participating from abroad) based on our president's discretionary budget to enhance the education for Ph.D. students and young researchers in order to enable them to become more internationally minded. In addition, we will also expand the CVPP into a Global COE-CVPP by combining this program with other programs originally established by the Riken Research Center for Allergy and Immunology and the National Institute of Radiological Sciences.

Support for the independence of young researchers

We will appoint several COE independent young research associates, who can thus be assured to remain independent in terms of their research environment, thereby enhancing their promotion to Research Associate Professor or Research Professor (tenure track) at Chiba University, or Associate Professor or Professor (tenure) when they finish their research in three to five years. The Global COE Operation and Management Office is responsible for developing an effective career path strategy for those young researchers who desire to follow careers in other directions.

The Global COE-CVPP



The Graduate School of Medicine, Chiba University has originally established CVPP (Chiba Visiting Professor Program), a collaboration system with foreign researchers. In this program, we encourage PhD students and young researchers to become much more globally active. In Global COE program, we co-host the "RCAI international summer program", held primarily at the Riken Research Center for Allergy and Immunology, and also an international training program on charged particle therapy", which is primarily held at the National Institute of Radiological Sciences.

CVPP

A total of 18 visiting professors and visiting associate professors from the University of California, University of Washington, University of Colorado, Harvard University, University of Cambridge, University of Geneva, Peking University and National Institutes of Health are presently participating in CVPP. We will organizationally collaborate with some of these institutions and Asian universities including Chinese ones. Under the auspices of CVPP, the above visiting professors and visiting associate professors have stayed at Chiba University from periods ranging from a few days to two weeks every year to engage in such activities as giving lectures, leading discussions and small workshops.

Meanwhile, Ph.D. students (as a training course with credit) and postdoctoral fellows have the opportunities to present their original research and obtain advice from this faculty. Moreover G-COE program provides them an opportunity at an early stage in their research to stay abroad for periods ranging from two weeks to three months in order to gain valuable experience to study in the labs abroad that are mainly affiliated with the visiting professors and visiting associate professors. A long-term stay for two to three years is also offered to extend their studies. An international symposium is held every year, mainly by CVPP coordinators, with a program designed for young researchers to actively participate.

RCAI international summer program

A summer program for two to four weeks is held mainly by the Riken Research Center for Allergy and Immunology (RCAI), as the core institution, every year, targeting Ph.D. students and postdoctoral fellows from abroad and consists of about 40 participants. This lecture course offers talks by lecturers and oral and poster presentations by the participants, and the internship course provides an opportunity for young researchers to stay in a lab to conduct their experiments. In 2007, due to the high popularity of this program, the number of students applying to this program was over 3 times the number of available openings, including 43 participants coming from 19 countries and comprising 26 Ph.D. students and 21 women. In 2008, the participants came from 20 countries, consisting of 28 Ph.D. students and 20 women. This program helps to broaden the interactive mobility of young researchers by opening the door to the world, which, we believe, will thus lead to the recruitment of excellent young researchers from other countries.

International training program on charged particle therapy

The goal of this program is to internationally promote the development of charged particle therapy including an IAEA/RCA training course on radiation therapy and workshops on charged particle therapy, which are held every year, and mainly carried out by the National Institute of Radiological Sciences (NIRS), as the core institution.

Since 2000, this training course has been held 17 times with more than 220 foreign researchers participating this short-term training program. We plan to enhance these activities by expanding this program and establishing a new "Global COE- training course on charged particle therapy".

CVPP Members

Visiting Professor

Mitchell Kronenberg
President and Scientific Director, Member and Division Head, Division of Developmental Immunology, La Jolla Institute for Allergy & Immunology
Adjunct Professor of Biology, University of California, San Diego

Hilde Cheroutre
Member, Division of Developmental Immunology, La Jolla Institute for Allergy & Immunology

Toshiaki Kawakami
Member, Division of Allergy, La Jolla Institute for Allergy & Immunology
Adjunct Professor, Department of Medicine, University of California, San Diego,
Associate Member, Hematologic Malignancies Program, The Moores UCSD Cancer Center

Stephen Philip Schoenberger
Member, Laboratory of Cellular Immunology, La Jolla Institute for Allergy & Immunology
Adjunct Associate Professor, Division of Hematology and Oncology, Department of Medicine, University of California, San Diego

Shane Crotty
Assistant Member, Division of Vaccine Discovery, La Jolla Institute for Allergy & Immunology
Adjunct Assistant Professor, Department of Medicine, University of California, San Diego

Steven F Ziegler
Member and Director, Immunology Program, Benaroya Research Institute
Affiliate Professor, Department of Immunology, University of Washington

Daniel J Campbell
Assistant Member, Immunology Program, Benaroya Research Institute

Erwin W Gelfand
Professor and Chairman, Department of Pediatrics, Division of Cell Biology, National Jewish Health,
Professor of Pediatrics and Immunology, University of Colorado School of Medicine, Denver Colorado

Philippa Marrack
Distinguished Professor of the University of Colorado
Professor, Integrated Department of Immunology, University of Colorado Hearth Science Center (UCHSC) and National Jewish Health
Professor, Department of Biochemistry and Molecular Genetics, UCHSC

Laurent Gapin
Assistant Professor, University of Colorado Hearth Science Center and National Jewish Health

Dale T Umetsu
Prince Turki Bin Abdul Azis al Saud Professor of Pediatrics, Children's Hospital Boston, Harvard Medical School

Anjana Rao
Senior Investigator, Immune Disease Institute (IDI), Harvard Medical School
Professor, Department of Pathology, Harvard Medical School

William E Paul
Chief, laboratory of Immunology, National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Health (NIH)

John Joseph O'Shea Jr.
Scientific Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Health (NIH)
Chief, Molecular Immunology and Inflammation Branch,

Remy Bosselut
Senior Investigator, Laboratory of Immune Cell Biology, National Cancer Institute, National Institute of Health (NIH)

David R W Jayne
Consultant in Nephrology and Vasculitis, Department of Medicine, Addenbrooke's Hospital, University of Cambridge, UK

Karl-Heinz Krause
Professor of Medicine, Department of Pathology and Immunology, Faculty of Medicine, University of Geneva

Ming-hui Zhao
Chief, Renal Division, Department of Medicine, Peking University First Hospital
Institute of Nephrology, Peking University
Key Laboratory of Renal Disease, Ministry of Health of China

The 1st Annual Best Research Award

Yuumi Nakamura
Graduate Student, Dept. of Dermatology, Graduate School of Medicine, Chiba University

Mast cells mediate neutrophil recruitment and vascular leakage through the NLRP3 inflammasome in histamine-independent urticaria

Urticarial rash observed in cryopyrin-associated periodic syndrome (CAPS) caused by NLRP3 mutations is effectively suppressed by anti-IL-1 treatment, suggesting a pathophysiological role of IL-1β in the skin. We identified mast cells (MCs) as the main cell population responsible for IL-1β production in the skin of CAPS patients. Unlike normal MCs that required stimulation with proinflammatory stimuli for IL-1β production, resident MCs from CAPS patients constitutively produced IL-1β. Primary MCs expressed inflammasome components and secreted IL-1β via NLRP3 inflammasome. Furthermore, MCs expressing disease-associated but not wild-type NLRP3 secreted IL-1β and induced neutrophil migration and vascular leakage, the histological hallmarks of urticarial rash, when transplanted into mouse skin. Our findings implicate MCs as IL-1β producers in the skin and mediators of histamine-independent urticaria through the NLRP3 inflammasome.

G-COE Research Assistant Members

G-COE-RA 2008

Atsushi Miyajima Lab. of Pharmacology and Toxicology	**Akane Suzuki** Dept. of Immunology
Jiro Terada Dept. of Autonomic Physiology	**Yusuke Endo** Dept. of Immunology
Kaori Kinoshita Dept. of Pediatrics	**Kenta Shinoda** Dept. of Immunology
Naoko Kikkawa Dept. of Otorhinolaryngology	**Arifumi Iwata** Dept. of Allergy & Clin. Immunol., Chiba Univ. Hospital
Daisuke Kashiwakuma Dept. of Molecular Genetics	**Masako Kimura-Sato** Dept. of Public Health
Masayuki Kano Dept. of Frontier Surgery	**Keiji Shinozuka** Dept. of Clinical Molecular Biology
Junji Moriya Dept. of Cardiovascular Science and Medicine	**Jun Ikari** Dept. of Developmental Genetics
Raita Uchiyama Dept. of Cardiovascular Science and Medicine	**Jin Yuan** Dept. of Cellular and Molecular Medicine
Motoyoshi Kurosaki Dept. of Otorhinolaryngology	**Makoto Kuwahara** Dept. of Immunology
Guangyu Ma Dept. of Environmental Biochemistry	**Kikuko Ikeda** Dept. of Molecular Cell Biology

The 1st Chiba University G-COE Symposium

Immune System Regulation and Treatment

January 6, 2009, Sapia Hall, Tokyo Station Conference, Tokyo


Yasushi Saito
(Chiba Univ)


Mitchell Kronenberg
(LIAI)

The 1st Chiba University Global COE Symposium "Immune System Regulation and Treatment" was held in cooperation with La Jolla Institute for Allergy & Immunology (LIAI) and RIKEN Research Center for Allergy and Immunology (RCAI).

Following opening addresses by Dr. Yasushi Saito, President of Chiba University, and Dr. Takeshi Tokuhisa, Dean, Graduate School of Medicine, and a presentation of Global COE outline by Dr. Toshinori Nakayama, Program Leader, Dr. Mitchell Kronenberg, President, LIAI, presented the keynote lecture entitled "Activation of invariant NKT cells by microbes and microbial products".

The participants stood at around 120. We invited six foreign researchers from LIAI and Benaroya Research Institute (BRI) with which we have made a collaborative agreement under this program, so that core members in three research fields of this program presented the current research activities, leading to valuable discussion. This symposium was significant as the kick-off activity of this program and gave great momentum to our future research promotion.

Program

Opening Remarks
Yasushi Saito(Chiba Univ)
Takeshi Tokuhisa(Chiba Univ)
Toshinori Nakayama(Chiba Univ)

Keynote Address
Mitchell Kronenberg(LIAI)

Session I: Immune System Regulation
Steven F. Ziegler(BRI)
Hiroshi Nakajima(Chiba Univ)
Masaru Taniguchi(RCAI)
Dirk Zajonc(LIAI)

Session II: Immunological Memory
Toshinori Nakayama(Chiba Univ)
Takeshi Tokuhisa(Chiba Univ)
Stephen P. Schoenberger(LIAI)

Session III: Allergy and Vascular Diseases
Toshiaki Kawakami(LIAI)
Klaus Ley(LIAI)
Issei Komuro(Chiba Univ)

Session IV: Clinical Application
Shinichiro Motohashi(Chiba Univ)
Tadashi Kamada(NIRS)
Yoshitaka Okamoto(Chiba Univ)

Closing Remarks
Yoichi Kohno(Chiba Univ)


Steven F. Ziegler


Toshinori Nakayama


Takeshi Tokuhisa


Issei Komuro


Yoichi Kohno


Masaru Taniguchi


Tadashi Kamada


Kazuo Suzuki

The 1st Chiba University G-COE Workshop

LIAI-RCAI Workshop and LIAI-Chiba University Workshop
January 7-8, 2009, RCAI, Yokohama and Chiba University, Chiba

This workshop was held at two venues, RIKEN and Chiba University, having 73 participants in Chiba University. We held this activity as part of CVPP (Chiba Visiting Professor Program), the core system for developing human resources in our Global COE Program. In addition to Chiba Visiting Professors' talks, young scientists including the graduate student who was selected via a call for contribution made the oral presentation. They obtained practical and suggestive advice in the discussion.

On the next day, as a discussion tour, Chiba Visiting Professor visited immunology-related labs to discuss and give advice on our research activities. We were so impressed with the ambitious remarks our students made as to believe in the future progress.

Program Coordinated by Kazuo Suzuki

January 7

Lecture and Discussion I
Chair: S. Motohashi, K. Suzuki, T. Tokuhisa
Speaker: M. Kronenberg, T. Kawakami, S. Ziegler

Presentation and Discussion I
Chair: H. Nakajima
Speaker: M. Arima, N. Watanabe, H. Bujyo

Presentation and Discussion II
Chair: T. Nakayama
Speaker: N. Shimojyo, T. Arima, Y. Nakamura, T. Fujimura, G-COE graduate students*

Presentation and Discussion III
Chair: A. Iwama
Speaker: H. Yamashita, H. Takano, T. Tanaka G-COE graduate students*

*Call for contributions

January 8

Lecture and Discussion II
Chair: K. Suzuki, M. Yamashita
Speaker: K. Ley, S. Schoenberger

Small Group Discussion
Five groups, 1 hour per each visiting professor
Free discussion

The 2nd Chiba University G-COE Workshop

February 21, 2009, the 2nd Lecture Hall, Main Building 1F,
Faculty of Medicine, Chiba University

"Presentation and discussion by G-COE-RA"

All the programs were carried out in English, which aimed to nourish the ability internationally-active. The G-COE-RA made an oral presentation on his or her research activity with discussion. Besides the supervisory professor, two advisers, who are appointed from this faculty for each RA, gave advice and comments to the presentation. Some RA gave feedback that it was a good opportunity to continue studying how to make a presentation in English. The participants stood out 92 showing the great interests in our Global COE program among gradu-ate students.

In addition, video recording their presentations was delivered to each RA in order to help RA not only for skill-up English communication but also learn positive behavior at international settings. We look forward to the next time.


D. Kashiwakuma


J. Yuan


J. Moriya


M. Kuwahara


R. Uchiyama


N. Kikkawa


J. Ikari


K. Shinozuka

PROGRAM Coordinated by Kazuo Suzuki

Saturday, February 21 Chair: Kazuo Suzuki

Opening remarks by Toshinori Nakayama
Program Leader

Session I Chair: Toshinori Nakayama

Atsushi Miyajima
Lab. of Pharmacology and Toxicology
"Epigenetic regulation of pharmacokinetics-associated gene expression by DNA methylation"

Jiro Terada
Dept. of Autonomic Physiology
"Molecular mechanisms of cell-cell communication in pancreatic islets -A clue essential for renovating islets in autoimmune diabetes mellitus-"

Kaori Kinoshita
Dept. of Pediatrics
"Research on the mechanism of tissue-specific imprinting in human GNAS gene"

Naoko Kikkawa
Dept. of Otorhinolaryngology, Head and Neck Surgery
"Identification of novel therapeutic microRNAs in head and neck squamous cell carcinoma"

Daisuke Kashiwakuma
Dept. of Molecular Genetics
"Development and characterization of IL-21-producing CD4+ T cells"

Session II Chair: Kazuo Suzuki

Masayuki Kano
Dept. of Frontier Surgery
"Development of a novel cancer vaccination using heat shock protein Gp96"

Junji Moriya
Dept. of Cardiovascular Science and Medicine
"A pathological role of Semaphorin3E/PlexinD1 in impaired angiogenesis of diabetes"

Raita Uchiyama
Dept. of Cardiovascular Science and Medicine
"Effect of granulocyte colony-stimulating factor on atherosclerosis in Apolipoprotein E-deficient mice"

Motoyoshi Kurosaki
Dept. of Otorhinolaryngology
"Migration of α-Galcer-pulsed antigen presenting cells after submucosal or subcutaneous injection in patients with head and neck cancer"

Guangyu Ma
Dept. of Environmental Biochemistry
"Novel immune gene therapy for malignant tumors"

News Letter

Session III Chair: Takeshi Tokuhisa

Akane Suzuki
Dept. of Immunology
"Polycomb group gene product Ring1B regulates Th2-dependent airway inflammation through the control of Th2 cell differentiation and apoptosis"

Yusuke Endo
Dept. of Immunology
"Identification of IL-5 producing CD62L$^-$ CXCR3$^-$ memory Th2 cells and their roles in allergic airway inflammation"

Kenta Shinoda
Dept. of Immunology
"Role of CD69 for the generation and function of memory CD4 T cells"

Arifumi Iwata
Dept. of Allergy and Clinical Immunology
"Protective roles of B and T lymphocyte attenuator (BTLA) in NKT cell-mediated experimental hepatitis"

Masako Kimura-Sato
Dept. of Public Health
"The role of matrix metalloproteinase (MMP)-3 in the pathophysiology of bronchial asthma"

Session IV Chair: Hiroshi Nakajima

Keiji Shinozuka
Dept. of Clinical Molecular Biology
"Identification of Cisplatin-resistance related genes in head and neck squamous cell carcinoma"

Jun Ikari
Dept. of Developmental Genetics
"A critical role of Bcl6 in expression of the CC-type chemokine genes and pulmonary epithelial cell-mediated inflammation"

Jin Yuan
Dept. of Cellular and Molecular Medicine
"Role of Bmi1 in leukemic stem cell"

Makoto Kuwahara
Dept. of Immunology
"Regulation of GATA3-dependent immune responses by the transcription factor Sox4"

Kikuko Ikeda
Dept. of Molecular Cell Biology
"Trafficking of Lyn tyrosine kinase to the Golgi and the nucleus"


Y. Endo


K. Ikeda


M. Kurosaki


M. Kimura-Sato


A. Iwata


G. Ma


A. Miyajima


K. Shinoda


A. Suzuki


J. Terada


M. Kano

G-COE Seminar





Allergy Clinical Conference

Coordinated by Hiroshi Nakajima


Basic Science Joint Meeting (BSJM)

Coordinated by PhD student working group, Chief:Atsushi Onodera

1. **Nov 21, 2008** 17:00-18:00
Takashi Miki, Professor, Dept. of Autonomic Physiology

2. **Dec 5, 2008** 17:00-18:00
John Joseph O'Shea Jr, Scientific Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH, USA Visiting Professor, Chiba Univ.

3. **Dec 12, 2008** 17:00-18:00
Shinichiro Motohashi, Associate Professor, Dept. of Medical Immunology

4. **Jan 9, 2009** 18:00-19:00
Kayo Inaba, Professor, Lab. of Immunobiology, Grad. Sch. of Biostudies, Kyoto Univ.

5. **Jan 16, 2009** 17:00-18:00
Daisuke Tohyama, Graduate Student, Dept. of Neurobiology

6. **Feb 13, 2009** 17:00-18:00
Masafumi Arima, Assistant Professor, Dept. of Developmental Genetics

7. **Feb 27, 2009** 17:00-18:00
Damon Tumes, G-COE Fellow, Dept of Immunology

8. **Mar 6, 2009** 17:00-18:00
Arifumi Iwata, G-COE RA, Dept. of Allergy and Clinical Immunology

9. **Apr 3, 2009** 17:00-18:00
Shiki Takamura, Assistant Professor, Dept. of Immunology, Kinki Univ. Sch. of Med.

10. **Apr 10, 2009** 17:00-18:00
Lisa Fujimura, Assistant Professor, Biomedical Research Center

11. **Apr 17, 2009** 17:00-18:00
Koji Tokoyoda, G-COE Assistant Professor, Dept. of Immunology

12. **Apr 24, 2009** 17:00-18:00
Koji Yasutomo, Professor, Dept. of Immunology & Parasitology, Institute of Health Biosciences, The Univ. of Tokushima Grad. Sch.

Upcoming Events

The 2nd Chiba University G-COE Symposium "Differentiation and Function of Lymphocytes"
Date: May 29, 2009
Venue: The 1st auditorium, University Hospital 3F

The 3rd Chiba University G-COE Workshop
Date: May 30, 2009
Venue: Main Building, Faculty of Medicine, Chiba University

The 4th Chiba University G-COE Workshop (Presentation and discussion by G-COE-RA)
Date: June 13, 2009
Venue: The 1st Lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

RCAI International Summer Program 2009 (co-organized by G-COE Program)
Date: July 3 - 10, 2009
Venue: Riken Research Center for Allergy and Immunology

Chiba University G-COE Retreat 2009
Date: September 5 - 6, 2009
Venue: Nihon Aerobics Center

The 3rd Chiba University G-COE Symposium
Date: November 6, 2009
Venue: Chiba University

The 5th Chiba University G-COE Workshop (Presentation and discussion by G-COE-RA)
Date: February 20, 2010
Venue: The 1st Lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

Office

Global COE Program Office was opened this April, next to the office of the management group Main Building 1F, Faculty of Medicine. Please feel free to inquiry.

Global COE Program Office
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URL: http://www.isrt-gcoe-chiba.jp


T. Nakasato, Y. Takayanagi, S. Nakamura

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GLOBAL COE

News Letter

vol.2
12.2009

Chiba University Global COE Program

Global Center for Education and Research in Immune System Regulation and Treatment

CONTENTS

Research Highlights

Dr. Tohru Minamino (Department of Cardiovascular Science and Medicine) and Dr. Masakatsu Yamashita (Department of Immunology) both involved in this program, received the 1st Chiba Medical Society Award.

Tohru Minamino
Department of Cardiovascular Science and Medicine

A crucial role for adipose tissue senescence in the regulation of insulin resistance

Most somatic cells have a finite lifespan and eventually enter an irreversible growth arrest, termed cellular senescence. Telomeres are TTAGGG repeats at the end of the chromosome and play a crucial role in its integrity. As a consequence of semi-conservative DNA replication, telomere length is shortened by cell division, and critically short telomeres are recognized as DNA damage, thereby inducing p53-dependent senescence (Fig. 1). Telomerase is an enzyme that adds telomeres onto chromosome ends. It is known that primary cultured cells from aged individuals or patients with premature aging syndrome have a shorter lifespan, and there is evidence that age-associated telomere shortening occurs in humans. These reports suggest a crucial role for cellular senescence in organismal aging and age-associated disease. We have also demonstrated that telomere-dependent vascular cell senescence contributes to vascular aging and atherogenesis, and that p53 is critically involved in the development of heart failure. In the current study, we hypothesize that cellular aging influences insulin resistance and accelerates the development of diabetes, because aging is known to increase the prevalence of metabolic disorders like diabetes. To test our hypothesis, we utilized telomerase-deficient mice with short telomeres. These mice developed insulin resistance when fed a high-caloric diet, and their adipose tissue showed senescence-like changes such as an increased expression level of p53, up-regulation of p53-induced expression of pro-inflammatory adipokines, and accumulation of macrophages in adipose tissue, thereby promoting insulin resistance (Fig. 2, 3). Resection of senescent adipose tissue improved insulin resistance in telomerase-deficient mice, whereas implantation of senescent adipose tissue into wild-type mice led to impairment of insulin sensitivity in the recipients. The adipose tissue of type 2 diabetic mice also exhibited senescence-like changes. Inhibition of p53 activity in adipose tissue significantly improved the senescence-like changes of adipose tissue, dysregulated expression of pro-inflammatory adipokines, and insulin resistance of type 2 diabetic mice. Conversely, up-regulation of p53 in adipose tissue caused an inflammatory response that led to insulin resistance. Adipose tissue from diabetic patients also showed senescence-like features (Fig. 4). Our results demonstrate a previously unappreciated role of adipose tissue p53 in the regulation of insulin resistance and suggest that cellular aging signals in adipose tissue could be a novel target for the treatment of diabetes.

This study was published in the September issue of Nature Medicine. (*Nat Med 2009; 15: 1082-1087.*)

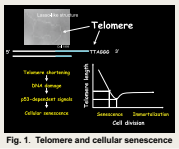


Fig. 1. Telomere and cellular senescence

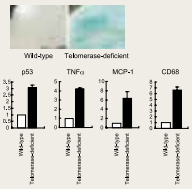


Fig. 2. Staining for cellular senescence and real time PCR in adipose tissue of telomerase-deficient mice

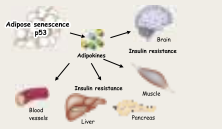


Fig. 3. Adipose senescence and insulin resistance

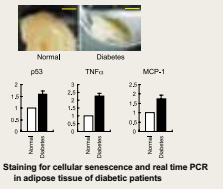


Fig. 4. Staining for cellular senescence and real time PCR in adipose tissue of diabetic patients

Masakatsu Yamashita
Department of Immunology

Epigenetic regulation of Th2 cell differentiation and allergic diseases

Approximately 30% of the Japanese population suffers from allergic diseases. However, only symptomatic therapies are presently available, and no curative therapeutic strategies have been developed. We are attempting to elucidate the underlying molecular mechanisms of allergic diseases, with a focus on the role of CD4-positive helper T (Th) cells. Th cells play the role of conductor in immune responses and are subdivided into at least three populations–Th1, Th2, and Th17–based on their cytokine production profile (Figure 1). Th cells typically balance each other and regulate protective immune responses. However, if the balance shifts towards a type2 bias, allergic diseases can develop. Th2 cells are involved in the earliest step of allergic reactions (Figure 2). They regulate the production of antibodies and the recruitment of eosinophils through secretion of interleukin (IL)-4, IL-5, and IL-13, the so-called Th2 cytokines. We hypothesized that the control of Th2 cell differentiation and function results in the inhibition of allergic responses, such as IgE production, recruitment of eosinophils at inflammatory lesions, and airway hyper-responsiveness. Therefore, we have investigated the molecular mechanisms involved in the induction of Th2 cell differentiation and the maintenance of Th2 cell identity. As a result, we found that transcription factor GATA3 regulates Th2 cell differentiation via epigenetic regulation of Th2 cytokine expression. Epigenetic regulation of gene expression is an acquired regulatory mechanism of gene expression and is controlled by various factors, including cellular environment and stress. It has been reported that the onset of metabolic syndromes and cardiovascular inflammation also developed via epigenetic mechanisms (Figure 3). Recently, we found that a histone methyltransferase, MLL (Mixed lineage leukemia), plays a crucial role in the development of chronic allergic responses. MLL maintains GATA3 expression and the ability to produce Th2 cytokines in memory Th2 cells via epigenetic mechanisms (Figure 4). Furthermore, we demonstrated that down-regulation of MLL expression results in improvement of symptoms in a model of allergic airway inflammation. We hope to find new strategies for the treatment of allergic disorders by defining the molecular mechanisms that underlie disease.

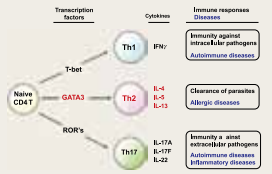


Figure 1. Differentiation and functions of helper T cell subsets

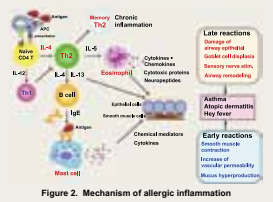


Figure 2. Mechanism of allergic inflammation

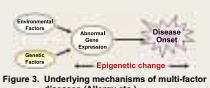


Figure 3. Underlying mechanisms of multi-factor diseases (Allergy etc,)

Figure 4. Difference in the regulatory mechanism of GATA3 and Th2 cytokine expression between effector and memory Th2 cells

The 2nd Chiba University Global COE Symposium

Differentiation and Function of Lymphocytes

May 29, 2009, The 1st Auditorium, Chiba University Hospital 3F

Alfred Singer　Dinah Singer　Sonoko Habu

The 2nd Chiba University Global COE Symposium "Differentiation and Function of Lymphocytes", organized by Dr. Takeshi Tokuhisa, was held at the 1st Auditorium, Chiba University Hospital, on May 29, 2009. Six foreign researchers including three from the U.S. National Institutes of Health (NIH), and one researcher from Japan gave talks as invited speakers. One hundred thirty people, including both clinicians and basic researchers, gathered to learn and discuss their latest studies. Following opening remarks by Dr. Toshinori Nakayama, Program Leader, and the plenary lecture by Dr. Alfred Singer, National Institute of Cancer, NIH entitled "Circumventing Thymic Selection of MHC-Restricted T Cell", three sessions were held. During the second session, entitled G-COE fellow presentation, a young scientist at Chiba University and G-COE-RA in this program described their studies. Discussions during each session were so lively, and the atmosphere so exciting, that many participants seemed to be disappointed when Dr. Haruaki Nakaya, Dean, Graduate School of Medicine, gave closing remarks. Followings are brief summaries and impressions of plenary lecture and sessions by each chair.

PROGRAM　Symposium Director: Takeshi Tokuhisa

- **Opening remarks**
  Toshinori Nakayama (Chiba University)
- **Plenary lecture**
  Alfred Singer (National Cancer Institute, NIH)
- **Session I: Regulation of immune system development**
  Sonoko Habu (Juntendo University)
  Rémy Bosselut (National Cancer Institute, NIH)
  Daniel Campbell (Benaroya Research Institute)
  Dinah Singer (National Cancer Institute, NIH)
- **Session II: G-COE fellow presentation**
  Junji Moriya (Chiba University)
  Daisuke Kashiwakuma (Chiba University)
- **Session III: Immune response and memory**
  Koji Tokoyoda (Chiba University)
  Rose Zamoyska (University of Edinburgh)
  Hiroyuki Matsue (Chiba University)
  Stephen P Schoenberger (The La Jolla Institute for Allergy and Immunology)
- **Closing remarks**
  Haruaki Nakaya (Chiba University)

Plenary lecture :

Dr. Alfred Singer gave an elegant lecture about the concept of MHC restriction, the phenomena associated with the fundamentals of antigen recognition in immune response by T cells. He introduced his own research in which thinking is very important and this was very meaningful for young graduate students.　*–By Toshinori Nakayama*

Session I: Regulation of immune system development :

Four lecturers gave talks on the subject of T cell differentiation. Dr. Habu (Juntendo University) reported that Dll4 expressed on thymic epithelial cells is a key Notch ligand for T cell differentiation in the thymus. Dr. Bosselut (NIH) reported the functions of Thpok, a key transcription factor for intrathymic CD4-T cell differentiation. He demonstrated that GATA3, which has long been considered important for CD4-T cell differentiation, induces CD4-T cell differentiation through promoting Thpok expression, and also that Thpok promotes CD4-T cell differentiation by repressing CD8 expression in CD4CD8 double positive T cells. After lunch, Dr. Campbell (BRI) described the functional differentiation of Regulatory T cells (Treg), which are involved in Th1-mediated inflammatory responses. By inducing the expression of chemokine receptor CXCR3 via the expression of T-bet transcriptional factor, Treg accumulate at sites of Th1-mediated inflammation and control its inflammatory response negatively. Dr. D Singer (NIH) presented the latest research results on regulatory mechanisms governing the gene expression of MHC class I that is essential to antigen recognition by CD8-T cells. All cells constantly express MHC Class I molecule. As its mechanism, she demonstrated the existence of a region that functions to block the suppression of gene expression in the 3' side of MHC Class I gene. Each subject dealt with the most recent results of the research fields that have been rapidly advancing recently. This session resulted in active discussions.　*–By Takeshi Tokuhisa*

News Letter


Daisuke Kashiwakuma

Session II: G-COE fellow presentation :

Dr. Moriya gave a talk entitled "Inhibition of Semaphorin as a Novel Strategy for Therapeutic Angiogenesis". It was interesting that, based on analysis of Semaphorin3E and its receptor PlexinD1, cell growth with VEGF and tube formation was down-regulated by a signal with Semaphorin3E. His study on proliferation and/or recruitment of endothelial cells, which were regulated with these molecules on recovery from damage of blood vessels is valuable. We hope this evidence will be applied to clinical research in the near future. Dr. Kashiwakuma presented a talk entitled "Development and Characterization of IL-21-producing CD4$^+$T Cells." His study is valuable, because he found a large amount of IL-21, which is related to autoimmune diseases and lupus, was produced in CD4$^+$T cells stimulated with IL-6, but not in Th17 cells. The novel evidence strongly suggests IL-21-producing CD4$^+$T cells are different subsets from Th17 cells. These findings are expected to elucidate of mechanisms of autoimmune diseases and to result in useful treatments for the diseases. We look forward to further studies of this type. *–By Kazuo Suzuki*

Session III: Immune response and memory :

Dr. Tokoyoda (Chiba University) stated that bone marrow plays an important role in maintaining immunological memory by T cells. Dr. Matsue (Chiba University) said that skin mast cells are powerful tools for investigating the innate immune system. Dr. Zamoyska (University of Edinburgh) focused on the relation between LCK and memory T cells and Dr. Schoenberger (LIAI) described the relation between CD27-CD70 binding and memory T cells. Each topic was discussed in detail and provided a new impetus for research staffs as well as graduate students. *–By Hiroshi Nakajima*


Remy Bosselut


Stephen P Schoenberger

The 3rd Chiba University G-COE Workshop

May 30, 2009, Data Sessions in each Laboratry

The 3rd Chiba University Global COE Workshop was held on May 30, in the form of a discussion tour. Drs Habu, Schoenberger, Zamoyska, Bosselut and Campbell, invited speakers in the symposium held on the previous day, participated in this symposium. Each visited several laboratories involved with this G-COE Program in order to conduct discussions with the young researchers and the graduate students. During these small group sessions all present were able to share their own views; thus, this workshop was very productive. In the Department of Immunology in particular, introducing the research results just before the submission of a paper, researchers received many significant comments and suggestions for the direction of their future research.

The 4th Chiba University Global COE Workshop

Presentation and Discussion by G-COE-RA

June 13, 2009, 1st Lecture Hall, Main Building 1F,
Faculty of Medicine, Chiba University

The 4th Global COE Workshop was held on Saturday, June 13. This was the second workshop in "Presentation and Discussion by G-COE-RA", following that of February 2009. More than 110 participants attended the workshop. All the G-COE-RAs made presentations and discussed on their research studies in English, except Dr. Kashiwakuma who gave his presentation in the 2nd symposium on May 29. Each talk created an active discussion. The participants gathered from various fields of research including clinical medicine and pharmaceutical sciences, as well as immunology-related fields. The result was a wide-ranged of questions, which sometimes exceeded G-COE-RAs' expectation; we realized difficulty in responding in English adequately in a question-and-answer period. Such opportunities can help improve RAs' preparation and mental attitude to presentation as well as the overall impression. As part of education for G-COE-RAs, in addition to a supervisor, two other university faculty members in related fields have been appointed as Advisor to each RA. Afterward they gave advice on the studies presented in the workshop, regarding research planning, progress, future plan, the presentation itself and so on. The feedback based on different perspectives can inspire RAs and provide motivation to advance their research studies. It is also worth mentioning that the G-COE-RAs autonomously prepared and managed this workshop. Led by Ms. Akane Suzuki, Mr. Kenta Shinoda and Mr. Yusuke Endo, they expertly ran the workshop including the video recording.

PROGRAM Coordinator: Kazuo Suzuki

Saturday, June 13 Chair: Kazuo Suzuki

Opening remarks by Toshinori Nakayama
Program Leader

Session 1 Chair: Toshinori Nakayama

Naoko Kikkawa
Dept. of Otorhinolaryngology
"Identification of differentially expressed microRNAs based on expression signature of hypopharyngeal squamous cell carcinoma"

Tomozumi Takatani
Dept. of Pediatrics
"Research on the epigenetic regulation of tissue-specific transcription in human GNAS gene"

Wu Shuang
Dept. of Medicine and Clinical Oncology
"Functional analysis of hepatitis B virus proteins: the effects on immunological signal pathways"

Yuuki Obata
Dept. of Molecular Cell Biology
"Mechanism of the trafficking of Lyn from the Golgi apparatus to the plasma membrane"

Yuya Tsurutani
Dept. of Clinical Cell Biology and Medicine
"The role of TGF-β/Smad3 signaling in the pathogenesis of obese fat tissue"

Session 2 Chair: Kazuo Suzuki

Zhi Li
Dept. of Cardiovascular Science and Medicine
"Cardiovascular diseases and immune reaction"

Masako Kimura-Sato
Dept. of Public Health
"The role of matrix metalloproteinase (MMP)-3 in the pathophysiology of bronchial asthma"

Satoshi Hattori
Dept. of Public Health
"The role of matrix metalloproteinase 8 in allergic inflammation"

Kazuma Hamada
Dept. of Biopharmaceutics
"Protective effect and mechanisms of rebamipide on the methotrexate- induced intestinal epithelial barrier dysfunction in rats"

Junko Ogita
Dept. of Pediatrics
"Disodium cromoglycate inhibits respiratory syncytial virus replication in epithelial cells"

Session 3 Chair: Takeshi Tokuhisa

Kenta Shinoda
Dept. of Immunology
"Role of CD69 for the generation and function of memory CD4 T cells"

Yusuke Endo
Dept. of Immunology
"Identification of IL-5 producing CD62L$^-$ CXCR3$^-$ Memory Th2 cells and their roles in allergic airway inflammation"


A. Hanazawa


J. Yuan


J. Ikari


A. Suzuki


J. Ogita


K. Yamasaki

Asami Hanazawa
Dept. of Immunology
"In vivo dynamics of memory T cell reactivation"

Akane Suzuki
Dept. of Immunology
"*Polycomb* group gene product Ring1B regulates Th2-dependent airway inflammation through the control of Th2 cell differentiation and apoptosis"

Jin Yuan
Dept. of Cellular and Molecular Medicine
"Role of Bmi1 in hematopoiesis and leukemogenesis"

Session 4 Chair: Hiroshi Nakajima

Jun Ikari
Dept. of Developmental Genetics
"The role of PHF11 in activation of murine B cells"

Yusuke Suenaga
Dept. of Molecular Biology and Oncology
"TAp63 suppresses MYCN expression in favorable neuroblastomas"

Takumi Harada
Lab. of Clinical Pharmacology
"The research for individualization of warfarin therapy"

Satoru Saito
Dept. of Frontier Surgery
"Identification of active ingredient(s) in a protein-bound polysaccharide, polysaccharide Kureha (PSK), for stimulating murine and human dendritic cells"

Keiji Shinozuka
Dept. of Clinical Molecular Biology
"Inhibition of PDE3B improves CDDP-sensitivity in head and neck squamous cell carcinoma"

Session 5 Chair: Shinichiro Motohashi

Teruyoshi Saito
Dept. of Molecular and Tumor Pathology
"Hyaluronidase-2 is a motility-inducing enzyme of human cancer cell lines"

Mizue Terai
Dept. of Molecular and Tumor Pathology
"Human IL-10 receptor 1/IgG1-Fc fusion protein: Immunoadhesins for human IL-10 with theraputic potential"

Shinya Okamoto
Dept. of Biochemistry
"Enhanced immune responses against tumors followed by adenoviruses-mediated cell death"

Masayuki Kano
Department of Frontier Surgery
"Development of a novel cancer vaccination using heat shock protein Gp96"

Kazuki Yamasaki
Dept. of Otorhinolaryngology
"Phase II study of administration of ex vivo expanded NKT cells and α-galactosylceramide-pulsed antigen-presenting cell before salvage surgery in patients with recurrent head and neck carcinoma"


K. Hamada


K. Shinozuka


K. Shinoda


M. Kimura-Sato


M. Kano


M. Terai


N. Kikkawa


S. Saito


S. Hattori


S. Okamoto


T. Harada


T. Saito


T. Takatani


W. Shuang


Y. Endo


Y. Suenaga


Y. Obata


Y. Tsurutani


Z. Li

Education Report

Special English Lectures for graduate school students

A new subject of study, Special Lectures of Clinical Allergology, was initiated in our graduate school from this academic year. This and another subject, Special Lectures of Clinical Oncology, are held alternatively. All the lectures are given in English, by core members of this program.

Subject: Special Lectures of Clinical Allergology
Organizer: Hiroshi Nakajima

General Instruction Objective (GIO):
Allergic diseases including food allergy, asthma, allergic rhinitis, and atopic dermatitis are caused by the dysregulation of the immune system. In these special lectures, the mechanisms of immune cell regulation and allergic diseases will be introduced. Through the lectures, students will be motivated to start their own medical research.

Content and Specific Behavioral Objectives (SBO)

Lecture 1 : Monday, August 10, 10:30-12:00
Subject : Allergic responses regulated by T cells
by Toshinori Nakayama
GIO: Th1/Th2 cell differentiation and the maintenance of memory Th1/Th2 cell function
SBO: To be able to explain the following subjects;
1.Processes required for the generation of Th1/Th2 cells.
2.Molecular mechanisms that regulate Th1/Th2 cell differentiation.
3.Chromatin remodeling events governing the Th1/Th2 cell differentiation and maintenance.

Lecture 2 : Monday, August 10, 12:50-14:20
Subject : Differentiation of immune memory IgE B cells
by Takeshi Tokuhisa
Germinal center (GC) is a complex cellular microenvironment that directs generation of high affinity memory B cells with somatic hypermutation of Ig-V genes. Although high-affinity IgE memory B cells should be developed in GCs, IgE+ B cells are hardly detected in GCs. Thus, high-affinity IgE memory B cells may be differentiated from high-affinity IgG1 B cells developed in GCs by sequential class switching outside of GCs. We discuss molecular mechanisms of the high-affinity IgE memory B cell development in GCs.

Lecture 3 : Monday, August 10, 14:30-16:00
Subject : Contribution of neutrophils to host-defense and chronic diseases
by Kazuo Suzuki
Neutrophils contribute to host defense in the initial steps of infection by killing bacteria, viruses, and fungi which are highly pathogenic agents. In addition, the cells show cross-talk with macrophages and lymphocytes in the early phase of host defense through the cytokines-chemokines produced. Dysfunction of neutrophils induces opportunistic infection and severe syndrome, resulting in death. Mechanisms of dynamic action and molecular events of the cells have been investigated. Recently, neutrophils also recognized to induce chronic diseases, and are to be involved in influenza infection. Thus, it is important for infectious diseases and chronic diseases that neutrophil functions must be regulated.

Lecture 4 : Monday, August 10, 16:10-17:40
Subject : NKT cell-based immune regulation
by Shinichiro Motohashi
NKT cells have been reported to play important roles in various diseases such as malignant tumor or allergic diseases. In this lecture, progress to date in the clinical studies of NKT cell-based immunotherapy is reviewed and the role of NKT cells in immunotherapy highlighted.

Lecture 5 : Tuesday, August 11, 10:30-12:00
Subject : Present situation of allergic rhinitis and its immune responses
by Yoshitaka Okamoto
Recent observations have suggested a significant worldwide increase in the prevalence of allergic rhinitis and in Japan, Japanese cedar (*Cryptomeria japonica*) and Japanese cypress (*Chamaecyparis obtusa*) pollens are considered to be the major unique allergens. Allergic rhinitis is a typical type 1 allergic disease by an adaptive immune response that occurs through the induction of allergen-specific effector T cells from naïve T cells. In the lecture, the immune responses observed in patients with allergic rhinitis will be discussed.

Lecture 6 : Tuesday, August 11, 12:50-14:20
Subject : Dendritic cell-based immune regulation
by Hiroyuki Matsue
Dendritic cells (DC) are special subsets of professional antigen-presenting cells that play a dual role of initiating and silencing acquired immune responses. Thus, it should be feasible to control the magnitude and direction of immune responses by experimental manipulation of DC function. We will overview the recent progress in the development of DC-based immuno-stimulatory and immuno-suppressive strategies, which are potentially applicable to the treatment of cancer, allergy, autoimmune disease, allograft rejection, and graft-versus-host disease.

Lecture 7 : Tuesday, August 11, 14:30-16:00
Subject : Food allergy
by Yoichi Kohno
Food allergy is one of the most common allergic diseases in childhood. In this lecture, clinical features and diagnosis of food allergy will be discussed.

Lecture 8 : Tuesday, August 11, 16:10-17:40
Subject : Allergic airway inflammation
by Hiroshi Nakajima
Asthma is a chronic airway inflammation that is characterized by intense eosinophil infiltrates, mucus hypersecretion, and airway hyperresponsiveness. These pathognomonic features are mediated mainly by antigen-specific Th2 cells. In addition, recent studies have shown that Th17 cells are involved in causing airway inflammation. In this lecture, the role of helper T cells in the regulation of allergic airway inflammation will be discussed.

Notes
Textbook: Reference books are shown, and handouts are provided when required.
Evaluation: Judged by attendance and reports, etc.

RCAI International Summer Program 2009

co-organized by the G-COE Program

Date: July 3-10, 2009 (Lecture course)
July 13-August 7, 2009 (Internship course)
Place: Research Center for Allergy and Immunology (RCAI)

RCAI International Summer Program (RISP) 2009 was held at Research Center for Allergy and Immunology (RCAI), July 3-10, jointly organized by RCAI and the G-COE Program, targeting graduate students and postdoctoral fellows overseas. This fourth Summer Program had 42 participants from 16 countries including 21 women, selected from among 104 applicants worldwide. In the Lecture Course, besides oral and poster presentations, participants attended intensive lectures on basic concept to leading-edge study of immunology for 4 days by 14 distinguished researchers invited from home and abroad. In the latter stage of this program, participants attended RCAI-JSI International Symposium held at Pacifico Yokohama. Through RISP the participants became better acquainted with fellows from all over the world; this can be a valuable asset for building a network for advancing research. Four of the participants stayed on at RCAI for a 1-month internship. The results of our questionnaire given to participants showed a high level of satisfaction with this program. RCAI and Chiba University have promoted collaboration including activities for development of human recourses. This relationship was sure to be enhanced by jointly organizing RISP 2009.

Lecture Course Program

Friday, July 3
Orientation Dr. Masaru Taniguchi, Director, RIKEN RCAI
Dr. Masato Tanaka, RIKEN RCAI
Central Facility Tour
Lecture: 1 **Dr. Hiroshi Kawamoto, RIKEN RCAI**
Lineage Restriction Pathway in Hematopoiesis:revision of the classical concept of myeloid-lymphoid dichotomy
Lecture: 2 **Dr. Clifford Lowell, University of California**
The STIM1 calcium sensor is required for activation of the phagocyte oxidase during inflammation and host defense
Lecture: 3 **Dr. Hiroshi Nakajima, Chiba University**
Th2 cells, Th17 cells, and allergic airway inflammation
Welcome Party

Saturday, July 4 Tokyo Sightseeing Tour

Monday, July 6
Oral Presentation 1 by Group A
Lecture: 4 **Dr. Takeshi Tokuhisa, Chiba University**
Role for Bcl6 in development and maintenance of germinal center B cells
Lecture: 5 **Dr. Sidonia Fagarasan, RIKEN RCAI**
T cell-independent and T cell-dependent f IgA synthesis in gut
Lecture: 6 **Dr. Ellen Rothenberg, California Institute of Technology**
Gene regulatory guidance mechanisms for early lymphocyte development
Discussion with leaders

Tuesday, July 7
Oral Presentation 2 by Group B
Lecture: 7 **Dr. Masaru Taniguchi, RIKEN RCAI**
NKT cell-mediated adjuvant cell therapy for cancer patients
Lecture: 8 **Dr. Diane Mathis, Harvard Medical School**
Central tolerance
Lecture: 9 **Dr. Alexander Rudensky, Memorial-Sloan Kettering Cancer Center**
Class Struggle and Regulatory T-Cells
Lecture: 10 **Dr. Thomas Tedder, Duke University Medical Center**
Regulatory B Cells and B10 Cells During Immune Responses, Inflammation, Autoimmunity and Cancer

Wednesday, July 8
Oral Presentation 3 by Group C
Lecture: 11 **Dr. Vijay Kuchroo, Harvard Medical School**
Differentiation of Th17 cells
Lecture: 12 **Dr. Yong-Jun Liu, The University of Texas**
Negative feedback regulation of type 1 IFN response by pDC specific receptor IL17 and Igand
Lecture: 13 **Dr. Takaharu Okada, RIKEN RCAI**
Lymphocyte migration and interactions during the antibody response
Lecture: 14 **Dr. Christian Münz, University Hospital of Zürich**
Macroautophagy in innate and adaptive immunity

July 9 and 10 RCAI-JSI International Symposium on Immunology







Chiba University G-COE Retreat 2009

September 5 and 6, 2009, Seimei-no-Mori Resort


Tatsuhiko Kodama
Professor
Research Center for Advanced Science and Technology, University of Tokyo


Masaru Taniguchi
Director
Research Center for Allergy and Immunology, RIKEN

Chiba Global COE Program Retreat 2009 was held at Seimei-no-Mori Resort on September 5 and 6, and was directed by Prof. Hiroshi Nakajima. Many activities were planned, including two special lectures, four oral sessions, and a poster session. All involved in this program gathered, getting away from their laboratories. Surrounded by the beauties of nature, participants relaxed and enjoyed themselves with the interaction created in various scenes. Particularly in the poster session held during the dinner party, graduate students exchanged their own views freely with professors and researchers in a friendly atmosphere. Dr. Nyambayar Dashtsoodol, G-COE Fellow from Mongolia, studying at RCAI, RIKEN, received the Best Poster Award. The followings are impressions of some participants.


Nyambayar Dashtsoodol
G-COE Fellow RCAI, RIKEN

Hiroshi Nakajima

Professor and Chairman, Department of Molecular Genetics

On the occasion of Chiba University G-COE Retreat 2009, I put the most importance on strengthening relationships among members. Research is basically an individual task and relationships among researchers tend to be poor, eventually resulting in repeated failures of experiments and wasting important time and money for doing research. Thus, I think this retreat serves as a place where we can know what other members are studying in their labs and promote collaborative activities and improve efficiency in performing research. This concept is just like that of Immunology Retreat, which has long been held by the NIH Immunology Group, where Dr. Nakayama and I were studying.
Staying the night was also important. There may be some discoveries when we talk in a relaxed manner without worrying time. In this way, the poster session after the buffet party or midnight discussions in the cottages may have been the main program.
Another important thing was having an opportunity to broaden the scope of research by contact with different research areas. Dr. Tatsuhiko Kodama's talk on the epigenome, the first special lecture, gave us an insight for our future research. In the second special lecture, we got a hint for our stance as a researcher from Dr. Masaru Taniguchi's talk on his life's work, research into NKT cells. In addition, the topics for oral and poster presentations were chosen from a variety of research fields. I hope that this retreat produces a number of exciting and fruitful researches at Chiba University.

Takeshi Tokuhisa

Professor and Chairman, Department of Developmental Genetics

Chiba University G-COE Retreat 2009 was held on September 5 and 6, staying at the Seimei-no-mori Resort. Eighty graduate students and PI researchers involved in this G-COE program participated. The program consisted of two special lectures, 13 oral presentations and 14 poster presentations. On the first day, Dr. Tatsuhiko Kodama, Research Center for Advanced Science and Technology, University of Tokyo, gave a special lecture in which he explained, in an easy-to-understand manner, the latest studies about the regulation mechanism of functional gene expression in cells by epigenomes. It was tremendously valuable for our future researches in Immunology. The next day, for a special lecture, Dr. Masaru Taniguchi, Research Center for Allergy and Immunology, RIKEN, gave a passionate talk about NKT cells from discovery to a future vision of its research activities. This talk had a great impact on our students and young researchers. In the general presentations, topics touched on a variety of subjects, not only Immunology, from pathologic analysis of cardiovascular and metabolic diseases to translational researches. We had lively discussions on each topic, which were very meaningful for new development in our researches. In the poster presentations held during the evening, as discussions went on enthusiastically in a congenial atmosphere, there was a likely increase in mutual understanding between students and researchers.

PROGRAM Director: Hiroshi Nakajima

Saturday, September 5
Opening remarks Toshinori Nakayama
Orientation Hiroshi Nakajima
Session 1 Haruhiro Toko, Koji Tokoyoda
Special Lecture 1 Tatsuhiko Kodama
Professor, Systems Biology and Medicine, Research Center for Advanced Science and Technology, University of Tokyo
Session 2 Kotaro Suzuki, Kaoru Tateno
Party & Poster Session

Sunday, September 6
Special Lecture 2 Masaru Taniguchi
Director, RIKEN Research Center for Allergy and Immunology
Session 3 Masamitsu Negishi, Takashi Fujimura, Kaoru Ito, Makoto Kuwahara
Session 4 Yusuke Endo, Daisuke Kashiwakuma, Yuuki Obata, Yuya Tsurutani, Yusuke Suenaga

Koji Tokoyoda

G-COE Independent Assistant Professor

I enjoyed this program very much, although the schedule was quite intense. The presentations and discussions in this program were most fruitful, and I think that this program provided a nice environment to develop research. In particular the free time after dinner gave me an opportunity to talk with some researchers involved with clinical subjects. We had many talks over beer. I realized the joy of research, and will be very glad if this program is held again next year. I appreciate having such this opportunity, which I enjoyed very much, both scientifically and personally.

Ayako Inamine

G-COE Fellow

The first retreat of the Chiba University G-COE Program was held at the Seimeinomori Resort Nihon Aerobics Center, Chosei-gun, Chiba, on September 5-6. Most of the participants involved in this program were young researchers in the field of basic or clinical research on intractable immune disorders. During this retreat, there were presentations and active discussions for two days.
I am conducting translational research to develop radical treatment strategies for allergic disease. With regard to my poster presentation, I received advice from various perspectives and obtained a considerable amount of information. Furthermore, there were active discussions in addition to the scientific topics.
I appreciate that I could be away from the laboratory and spend considerable time in discussions with many young researchers during the retreat.

Daisuke Kashiwakuma

G-COE RA, Department of Molecular Genetics

Because the majority of graduate students spend a lot of time in their laboratories, there is little chance to communicate with other students in different laboratories. The retreat gave us a chance to discuss a number of issues with other students and researchers in magnificent surroundings. We also learned the history of NKT cell research from Dr. Taniguchi and most recent findings in epigenome research from Dr. Kodama. The retreat was valuable for my future research.



The 3rd Chiba University Global COE Symposium

Molecular Dynamics of Immune System Regulation

November 6, 2009, the 1st Auditorium, Chiba University Hospital 3F

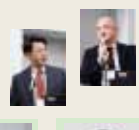

Yasushi Saito
President

The 3rd Chiba University Global COE Symposium "Molecular Dynamics of Immune System Regulation" was held at the 1st Auditorium, Chiba University Hospital, on November 6. At this symposium, to be also held as part of commemorating the 60th anniversary of Chiba University, which began with an address by Dr. Yasushi Saito, President of Chiba University, three invited speakers from abroad, Dr. Ken G. C. Smith (University of Cambridge), Dr. Dale T. Umetsu (Children's Hospital Boston, Harvard Medical School) and Dr. James K. Liao (Brigham & Women's Hospital, Harvard Medical School) gave special lectures. Joined by six domestic invited speakers they presented the most recent studies about signaling pathways and transcriptional regulation in their own research fields from a wide range of fields, not only immunology, as well as new trends in immunology such as immunogenomics, humanized mouse, and real-time cellular imaging. The presentations and discussions in a cross-disciplinary approach stimulated all the participants. Dr. Haruaki Nakaya, Dean, Graduate School of Medicine, gave closing remarks. Feedback from some of the participants is given on the next page.

Program

Opening remarks
Yasushi Saito (Chiba University)
Special lecture I
Ken G. C. Smith (University of Cambridge)
Special lecture II
Dale T. Umetsu (Harvard Medical School)
Session I: New trends in Immunology
Osamu Ohara (RCAI/RIKEN)
Fumihiko Ishikawa (RCAI/RIKEN)
Akihiro Hasegawa (Yamaguchi University)
Special lecture III
James K. Liao (Brigham & Women's Hospital)
Session II: Transcriptional regulation 1
Atsushi Onodera (Chiba University)
Masakatsu Yamashita (Chiba University)
Masafumi Arima (Chiba University)
Session III: Transcriptional regulation 2
Kotaro Suzuki (Chiba University)
Masaki Fujimoto (Chiba University)
Tohru Minamino (Chiba University)
Session IV: Transcriptional regulation 3
Taku Naito (RCAI/RIKEN)
Shinya Sakaguchi (Medical University of Vienna)
Sho Yamasaki (Kyushu University)
Closing remarks
Haruaki Nakaya (Chiba University)





News Letter

Yasushi Saito
President, Chiba University

Immune system functions to protect the body from external attack by microorganism.
This G-COE project is planned in order to develop novel therapeutic methods for various diseases by use of immune mechanisms. We believe that the project will greatly contribute to the progress in this research field and also to development of human resource.

Koutaro Yokote
Professor, Dept. of Clinical Cell Biology

In the 3rd Global COE Symposium entitled "Molecular Dynamics of Immune System Regulation", new trends in immunology as well as a wide variety of topics on transcriptional regulation were discussed. In our session, Drs. Kotaro Suzuki, Masaki Fujimoto and Tohru Minamino gave wonderful presentations which reminded me that inflammation is deeply involved not only in the process of allergic reactions but also in metabolic disorders and cardiovascular aging. I sincerely hope that new findings obtained in this G-COE program will lead to novel therapeutic methods to overcome yet untreatable disorders.

Atsushi Iwama
Professor, Dept. of Cellular and Molecular Medicine

The 3rd Chiba University G-COE Symposium was full of various well balanced topics from immunology to circulation, metabolism and obesity. These topics successfully reminded us of the implication of immune systems in a wide range of phenomena in steady state and disease. The topics were also varied from the receptor function to the signaling, transcription, and epigenetics. We could see amazing progress in science in many fields. Among the speakers, many young scientists did very good presentations and particularly, one graduate student made his debut in this symposium. New generations are emerging in Chiba University! The president Dr. Saito gave opening remarks, Dean Prof. Nakaya gave a closing remark, and the director of the University Hospital Prof. Kohno made a toast during the reception. It's great that all the leading figures got together in this symposium. Finally I'd like to thank Prof. Nakayama and the G-COE staff for a successful symposium. We look forward to participating in the next symposium.

Haruaki Nakaya
Dean, Graduate School of Medicine

The 3rd Global COE Symposium was held at Chiba University Hospital on November 6, 2009. The title of the symposium was "Molecular Dynamics of Immune System Regulation". Many distinguished speakers were invited from abroad and universities/institutes of Japan, and all gave us provocative lectures. Dr. K.G.C. Smith from University of Cambridge indicated the role of genetic variations in Fc receptors in development of autoimmune disease and responses to malaria infection. Dr. D.T. Umetsu from Harvard Medical School reported that infection with the hepatitis A virus protects against asthma. Dr. J.K. Liao from Harvard Medical School reported that obesity and altered circadian rhythm increase vascular senescence through activation of Akt/mTOR pathway. I was really impressed that many young researchers from our university gave excellent presentations of original papers. I hope these young scientists become established researchers with further progress in their research in the future.

Yoichi Kohno
Director, Chiba University Hospital

Shinichiro Motohashi
Associate Professor, Dept. of Medical Immunology

In the 3rd Chiba University Global COE Symposium "Molecular Dynamics of Immune System Regulation", three invited speakers from foreign countries attended this international symposium. Not only the famous scientists but also the graduate school student gave the lectures, since the aim of the Global COE program is to foster young researchers.
Dr. Umetsu discussed the correlation between human hepatitis A virus (HAV) infection and asthma. According to the hygiene hypothesis, improved hygiene, which partially explains the reduced rate of infections in industrialized countries, is at the origin of increased incidence of allergic and autoimmune diseases. He described the protection mechanisms of asthma through the cellular receptor for HAV, TIM-1, which leads to disclosing the important regulatory mechanisms of allergic diseases.

G-COE Seminar

Allergy Clinical Conference

Basic Science Joint Meeting (BSJM)

Coordinated by PhD student working group, Chief: Atsushi Onodera

13. May 1, 2009 17:00-18:00
Mitsujiro Osawa, Lecturer, Dept. of Cellular and Molecular Medicine

14. May 15, 2009 17:00-18:00
Naohiko Seki, Associate Professor, Dept. of Functional Genomics

15. June 12, 2009 17:00-18:00
Harukiyo Kawamura, Assistant Professor, Dept. of Autonomic Physiology

16. June 19, 2009 17:00-18:00
Tomokazu Nagao, Lecturer, Dept. of Immunology

17. June 26, 2009 17:00-18:00
Ichiro Taniuchi, Team Leader, RCAI, RIKEN

18. July 17, 2009 17:00-18:00
Atsushi Onodera, Graduate Student, Dept. of Immunology

19. July 24, 2009 17:00-18:00
Takeaki Sugawara, Research Fellow, Dept. of Cellular and Molecular Medicine

20. September 11, 2009 17:00-18:00
Tatsuya Sato, Assistant Professor, Dept. of Developmental Biology

21. September 24, 2009 17:00-18:00
Hiroshi Ohno, Team Leader, RCAI, RIKEN

22. October 9, 2009 17:00-18:00
Yoshimi Takai, Dean, Graduate School of Medicine, Kobe University

23. October 23, 2009 17:00-18:00
Kazuki Yamasaki, G-COE RA, Dept. of Immunology

24. October 30, 2009 17:00-18:00
Atsushi Yamaguchi, Associate Professor, Dept. of Neurobiology

Members Studying Abroad

Under Chiba Visiting Professor Program (CVPP), the core system for developing human resources in our Global COE Program, Ph.D. students and postdoctoral fellows have an opportunity to study abroad at an early stage in their research, gaining valuable experience by studying in the laboratories that are mainly affiliated with visiting professors.

Name	Position	Visit duration	Hosting organization	Country
Masayuki Kitajima	G-COE Fellow	April 1, 2009-March 31, 2010	Benaroya Research Institute Virgria	USA
Ryo Shinnakasu	G-COE Fellow	April 27, 2009-March 31, 2010	La Jolla Institute for Allergy & Immunology	USA
Yuumi Nakamura	G-COE Fellow	May 1, 2009-October 31, 2009	Dept. of Pathology, University of Michigan	USA

G-COE Research Assistant Members

G-COE-RA 2009

Jin Yuan	Dept. of Cellular and Molecular Medicine	**Keiji Shinozuka**	Dept. of Clinical Molecular Biology
Jun Ikari	Dept. of Developmental Genetics	**Kenta Shinoda**	Dept. of Immunology
Yusuke Endo	Dept. of Immunology	**Yusuke Suenaga**	Dept. of Molecular Biology and Oncology
Shinya Okamoto	Dept. of Biochemistry	**Akane Suzuki**	Dept. of Immunology
Junko Ogita	Dept. of Pediatrics	**Tomozumi Takatani**	Dept. of Pediatrics
Yuuki Obata	Dept. of Molecular Cell Biology	**Yuya Tsurutani**	Dept. of Clinical Cell Biology
Masayuki Kano	Dept. of Frontier Surgery	**Mizue Terai**	Dept. of Molecular and Tumor Pathology
Daisuke Kashiwakuma	Dept. of Molecular Genetics	**Satoshi Hattori**	Dept. of Public Health
Naoko Kikkawa	Dept. of Otorhinolaryngology	**Asami Hanazawa**	Dept. of Immunology
Wu Shuang	Dept. of Medicine and Clinical Oncology	**Kazuma Hamada**	Dept. of Biopharmaceutics
Satoru Saito	Dept. of Frontier Surgery	**Takumi Harada**	Lab. of Clinical Pharmacology
Teruyoshi Saito	Dept. of Molecular and Tumor Pathology	**Kazuki Yamasaki**	Dept. of Otorhinolaryngology
Masako Kimura-Sato	Dept. of Public Health	**Zhi Li**	Dept. of Cardiovascular Science and Medicine

New Members

G-COE Collaborators

Naruhiko Ishiwada
Lecturer, Department of Pediatrics, Chiba University Hospital

Masanori Minagawa
Lecturer, Department of Pediatrics, Graduate School of Medicine, Chiba University

Yutaka Tamura
Associate Professor, Department of Bioinformatics, Graduate School of Medicine, Chiba University

Upcoming Events

Symposium on Carbon Ion Radiotherapy and Immunotherapy
Co-organized by National Institute of Radiological Sciences (NIRS) and Chiba University G-COE Program
Date: January 15, 2010
Venue: National Institute of Radiological Sciences (NIRS)

Chiba-Uppsala Academia Joint Workshop
Co-organized by Uppsala University, Dept. of Clinical Cell Biology, Graduate School of Medicine, Chiba University, and the G-COE Program
Date: February 19, 2010
Venue: The 1st Auditorium, Chiba University Hospital 3F

The 5th Chiba University G-COE Workshop (Presentation and Discussion by G-COE-RA)
Date: February 20, 2010
Venue: The 1st Lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

New Zealand-Japan Workshop "Immunotherapy (tentative)"
Co-organized by New Zealand Ministry of Research, Science & Technology and Chiba University G-COE Program
Date: April 2010

The 4th Chiba University G-COE Symposium
Date: August 20, 2010
Venue: The 1st Auditorium, Chiba University Hospital 3F

Office

Ms. Ayaka Ohno, a staff member, has joined our office from this past May. She is greatly contributing to our activities. Your further cooperation and assistance will be much appreciated. Best wishes for a happy holiday season.

Editor's Note

We have wonderful decorations for Christmas season in town as the end of year is approaching. This issue contains activities of new trials in research and education in the Chiba University Global COE Program. In addition, descriptions are also given of the symposium held as part of commemorating the 60th anniversary of Chiba University are covered. We appreciate all contributors taking the time to creating this issue. Readers are encouraged to submit descriptions and pictures for the next issue. This cover page is designed with colors of Christmas and the New Year.
Chiba University Global COE Program
Coordinator Kazuo Suzuki

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GLOBAL COE

News Letter

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Chiba University Global COE Program

Global Center for Education and Research in Immune System Regulation and Treatment

CONTENTS

Dr. Koji Tokoyoda, Assistant Professor, Dept. of Immunology, who was also Independent Research Associate of the G-COE Program last academic year, recently won two notable awards, ***the 2010 Robert Koch Postdoctoral Awards for Young Scientists*** and ***the 2010 JSI (Japanese Society for Immunology) 5th Young Investigator Awards*** for his work regarding the generation and maintenance of the immunological memory. Following is a brief introduction to his work.

Koji Tokoyoda
Assistant Professor, Dept. of Immunology

Life-style of memory helper T cells in immune memory

"Immunity" defends our body from infection of bacteria and virus and also, by memorizing the antigen information, more quickly and strongly removes the re-invaded pathogen. The ability to memorize the information has been a key factor in the development of vaccines. Studies on vaccine began about 200 years ago. It is well-known that immune memory system used by vaccine is constructed by memory lymphocytes in the body. However, it had been unclear how memory lymphocytes are maintained in the body.

Memory lymphocytes are categorized into memory plasma cells which produce functional antibodies, memory cytotoxic T cells which survey infected cells, and memory helper T cells which control the generation and maintenance of the other memory lymphocytes. Our previous studies had shown that memory plasma cells are maintained on CXCL12-expressing stromal cells of the bone marrow (Tokoyoda et al., *Immunity*, 20: 707-718, 2004). Moreover, we recently reported that memory helper T cells who play a central role in immune memory are also maintained in the bone marrow and reside on IL-7-expressing stromal cells but not CXCL12-expressing cells (**Tokoyoda et al., *Immunity*, 30: 721-730, 2009,** Figure 1 and 2). BM memory helper T cells are long-lived, functional *in vitro* and *in vivo*, and resting (Figure 3). These findings indicated that memory plasma cell and memory helper T cell reside on a distinct stromal cell, respectively, and rest there with high function. We suggested that the specified microenvironment for memory lymphocytes like for example CXCL12- and IL-7-expressing stromal cells are called "niche", and these memory lymphocytes are like stem cells who rest there with high function, and multi-potency (**Tokoyoda et al., *Nat. Rev. Immunol.*, 10: 193-200, 2010**).

This concept may change the goal of vaccination, because it is not only for making a lot of antibodies but for maintaining memory lymphocytes in their niches. Namely, by monitoring memory lymphocytes in their niches, vaccination can be further improved. In addition, a bad memory in the case of chronic autoimmune diseases and allergy may also take advantage of similar mechanisms to a good memory like infection and vaccination. Our short-time goal is to clarify the role of memory helper T cells in immune memory, especially when the former antigen re-invades, namely in the secondary immune response, contributing the understanding of the systemic immune system (Figure 4).

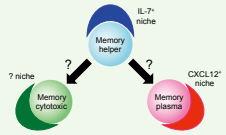


Figure 1. Memory lymphocytes are maintained on their distinct niches

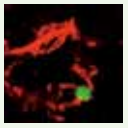


Figure 2. Memory helper T cells (green) reside on stromal cells (red)

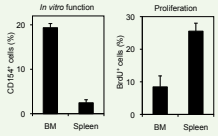


Figure 3. BM memory CD4 T cells are resting with high responsiveness

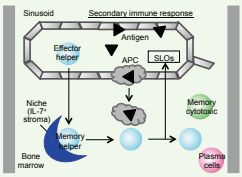


Figure 4. Systemic mechanisms in immune memory and secondary immune response. APC: antigen-presenting cells, SLO: secondary lymphoid organs

Annual Best Reseach Award 2010

This award is given to Ph.D. students in the G-COE relevant fields whose research is recognized as most outstanding through the year. The winner for the Annual Best Research Award 2010 went to Dr. Atsushi Onodera, who is now G-COE Independent Research Associate. His award-winning research is shown below.

Atsushi Onodera
G-COE Independent Research Associate
Dept. of Immunology

Regulation of Th2 cell differentiation and function by polycomb and trithorax complex

The number of allergy sufferers is increasing each year in Japan. However, no curative therapeutic strategies have been developed. We have focused on the role of CD4-positive helper T (Th) cells, which play a role of conductor in immune responses and are subdivided into at least three populations-Th1, Th2, and Th17, based on their cytokine production profile (Figure 1). Th cells typically balance each other and regulate protective immune responses. However, if the balance shifts towards a type2 bias, allergic diseases can develop. Th2 cells regulate the production of antibodies and the recruitment of eosinophils through secretion of interleukin (IL)-4, IL-5, and IL-13, so-called Th2 cytokines. According to these observations, Th2 cells are thought to be central players in the allergic response. We hypothesized that the control of Th2 cell differentiation and function results in the inhibition of allergic responses. Therefore, we have investigated the molecular mechanism involved in the induction of Th2 cell differentiation and the maintenance of Th2 cell identity. As a result, we found that the epigenetic regulation of transcription factor GATA3 and Th2 cytokine expression are critical for Th2 cell differentiation. Epigenetic regulation of gene expression is an acquired regulatory mechanism of gene expression. Epigenetics is becoming a key concept to understanding cell differentiation and gene regulation. Polycomb (PcG) and trithorax (TrxG) complex are known to be involved in the epigenetic regulation of their target genes (Figure 2). PcG and TrxG were originally identified in Drosophila. They play crucial roles in cancer formation and stem cell maintenance in humans. In contrast, their roles in the immune system are poorly understood. We performed further analysis of epigenetic regulation of Th2 differentiation with a focus on PcG and TrxG. Recently, we found the Th2-specific displacement of PcG by TrxG at the upstream region of the GATA3 gene, a transcription factor essential for Th2 cell differentiation (Figure 3). After Th2 cell differentiation, the recruitment of TrxG complex was required for the maintenance of GATA3 expression, because increased GATA3 expression was not maintained in the absence of Menin, a critical molecule for DNA binding in the TrxG complex (Figure 4). This study was published in the Journal of Experimental Medicine (***J Exp Med. 2010; 207: 2493-506***). Now, we are proceeding with a new project to identify genome-wide PcG and TrxG target genes using a next generation ChIP-seq technology. Finally, we hope to find new strategies for the treatment of allergic disorders by defining the molecular mechanisms that underlie the diseases.

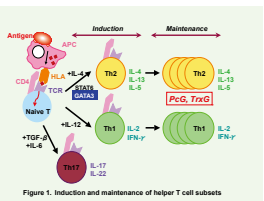


Figure 1. Induction and maintenance of helper T cell subsets

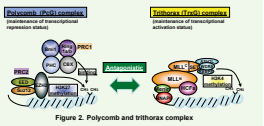


Figure 2. Polycomb and trithorax complex

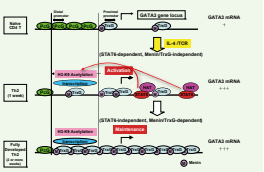


Figure 3. Displacement of PcG by TrxG at the GATA3 gene locus

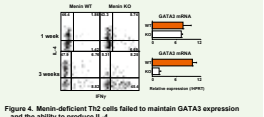


Figure 4. Menin-deficient Th2 cells failed to maintain GATA3 expression and the ability to produce IL-4

Mast cell research progresses!

Kotaro Suzuki
G-COE Independent Research Associate
Dept. of Molecular Genetics

Role of STATs in Mast Cells

Many cytokines transmit their signals through the activation of the member of signal transducers and activators of transcription (STATs). There are seven STAT proteins, STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. A variety of physiological roles of STAT proteins has been clarified not only in T cells and B cells but also in mast cells. In this letter, I show the roles of STAT proteins in murine mast cells.

STAT5a

IL-3 is known to be an inducer of proliferation and survival of murine mast cells. STAT5a plays critical roles in these IL-3-mediated functions (1). Figure 1 shows that IL-3-mediated proliferation of bone marrow-derived mast cells (BMMCs) is severely impaired in STAT5a-deficient mice. And STAT5a is also essential for mast cell survival through upregulation of bcl-x(L) (1).

STAT6

The IL-4–STAT6 pathway induces mast cell apoptosis (2,3) and inhibits TNF-α production through the induction of tristetraprolin which regulates mRNA rapid degradation (4). Figure 2 shows that IL-4 inhibits IgE-induced neutrophil recruitment into the peritoneal cavity through a STAT6-dependent mechanism (4).

STAT4

Given that previous studies have shown that STAT4 is expressed in limited cell types, including NK cells and Th1 cells. We recently found that STAT4 is expressed in BMMCs and activated by IFN-β but not IL-12 or IL-23 (5). Figure 3 shows that IFN-β-induced expression of monocyte chemoattractant protein-1 (MCP-1), a chemokine that preferentially attracts monocyte/macrophage, was severely impaired in STAT4$^{-/-}$ BMMCs as compared with WT BMMCs. These results suggest that STAT4 is essential for IFN-β-induced MCP-1 expression in BMMCs (5). Because mast cells are distributed in almost all tissues, our results suggest that mast cells may be involved in the enhancement of the antiviral responses initiated by pDC by producing MCP-1 in response to type I IFNs-STAT4 signals (Figure 4).

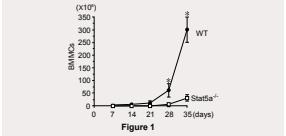


Figure 1

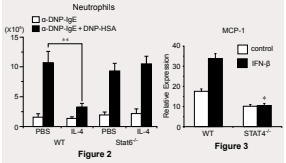


Figure 2

Figure 3

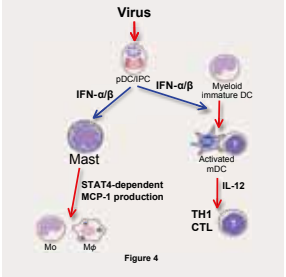


Figure 4

References

1) Ikeda K et al. Stat5a is essential for the proliferation and survival of murine mast cells. Int. Natl. Allergy and Immunol. 137 S1: 45, 2005.
2) Suzuki K et al. Proteolytic processing of Stat6 signaling in mast cells as a negative regulatory mechanism. J. Exp. Med. 196: 27, 2002.
3) Nakajima H et al. Lineage-specific negative regulation of STAT-mediated signaling by proteolytic processing. Cytokine & Growth Factor Reviews. 14: 375, 2003.
4) Suzuki K et al. IL-4-Stat6 signaling induces tristetraprolin expression and inhibits TNF-α production in mast cells. J. Exp. Med. 197: 1717, 2003.
5) Iida K et al. STAT4 is required for IFN-β-induced MCP-1 expression in mast cells. Submitted.

News Letter

Research Highlights

TR in allergy

Ayako Inamine
G-COE Fellow
Dept. of Otorhinolaryngology

A new Immunotherapeutic approach to Japanese cedar pollen allergy

Japanese cedar pollinosis, caused by the pollen of the Japanese cedar tree, is the most common seasonal allergic disease in Japan. In recent years, our country has experienced an increase in the prevalence of allergic rhinitis. A variety of medications has been administered to improve symptoms. Anti-histamines, anti-leukotrienes and intranasal steroids are most widely prescribed to relieve sneezing, nasal discharge and nasal obstruction. These drugs reduce symptoms, but do not treat the underlying disease and have a high risk of associated some adverse events.

Antigen-specific immunotherapy is effective for changing the natural course of allergic diseases, preventing the development of other allergic diseases, and reducing new allergic sensitization, particularly taken over a long period. However, conventional administration by the subcutaneous route is associated with a risk, albeit low, of anaphylactic shock and the inconvenience of frequent visits to a physician.

A recent review of randomized controlled studies of sublingual immunotherapy (SLIT) for allergic rhinitis suggests that this approach has the benefit of allowing treatment to be carried out in the home environment and has been found to be safety and effective treatment strategy as an alternative route of administration. However, clinical improvement is limited and development of an effective and safe adjuvant for SLIT is needed (Figure 1).

We are attempting to elucidate clinical biomarkers correlated with clinical symptoms in preparation for a future double-blind, placebo-controlled study of SLIT, with a focus on the mechanism of inhibition against allergic responses.

Lactobacillus are cultures of potentially beneficial bacteria of healthy gut microflora that are reported to be effective in treatment of various allergic diseases as immunomodulators. Heat-killed Lactobacillus influenced the maturation of DCs induced by uptake of antigen, but the patterns differed significantly among strains. KW3110 strongly induced expression of CCR-7 and PD-L2 in mature DCs (Figure 2). In OVA-sensitized mice, sublingual administration of low doses of KW3110 decreased IgE production and nasal symptoms induced by nasal OVA provocation (Figure 3). Thus, we have demonstrated that sublingual administration by KW3110 is of clinical interest as a new oral mucosal immunotherapy for allergic rhinitis. A clinical study in patients with Japanese cedar pollinosis is in progress to examine this hypothesis and may yield further information on the potential of Lactobacillus (Figure 4).

We hope to find new developmental strategies for SLIT by defining the regulatory mechanisms of allergic disease, and also to investigate IgE+ B cell memory with a view to developing new treatments for allergic disease. These strategies would provide a new target for allergic immunotherapy.

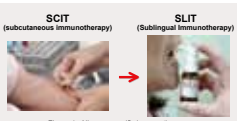


Figure 1. Allergen specific immunotherapy

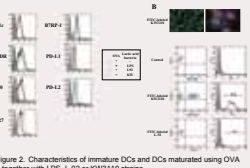


Figure 2. Characteristics of immature DCs and DCs maturated using OVA together with LPS, L-92 or KW3110 strains

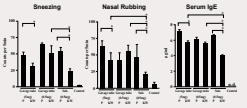


Figure 3. Influence of intragastric administration via a gavage tube or sublingual administration of lactic acid bacteria on nasal symptoms and serum IgE

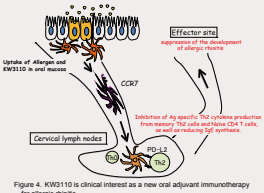


Figure 4. KW3110 is clinical interest as a new oral adjuvant immunotherapy for allergic rhinitis

Research Highlights

Interface between Immunology and Cardiology

Kaoru Ito
G-COE Fellow
Dept. of Cardiovascular Science and Medicine

Cardiac Mast Cells and Macropages Play Crucial Roles in the Genesis of Atrial Fibrillation in Angiotensin II-infused Mouse Hearts

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, and worsens heart failure and causes stroke, contributing to increased morbidity and mortality. Although the pathophysiology of AF remains incompletely understood, clinical and experimental studies have suggested that inflammation underlies a susceptible AF substrate.

To elucidate how inflammation is linked to the development of structural remodeling as a susceptible AF substrate in stressed hearts, we first administered angiotensin II (Ang II) (2mg/kg/day) subcutaneously via an osmotic mini-pump for 14 days. (Figure 1A) After AngII infusion, we applied electrical stimulation to the hearts under Langendorff perfusion, and found that AF was induced more frequently in Ang II-infused mice than in vehicle-infused control mice. (Figure 1C) Masson trichrome staining revealed that Ang II-infusion promoted atrial fibrosis. (Figure 1B) In addition, toluidine blue staining and immunostaining using anti-Mac3 antibody revealed that the atrium was infiltrated by mast cells (Figure 2A) and macrophages (Figure 2B) in Ang II-infused mice.

First, to elucidate the role of mast cells in the pathogenesis of AF, we administered cromolyn, which is a mast cell stabilizer and abrogates mast cell degranulation. In Ang II infused mice hearts, cromolyn treatment didn't change the number of mast cells in the atria (Figure 3A), but reduced macrophage infiltration into the atria. (Figure 3B) As a result, the atrial structural remodeling (Figure 3C) and AF inducibility (Figure 3D) in Ang II-infused mice were suppressed by cromolyn.

Next, to elucidate the role of macrophages, we used an expressing vector encoding a dominant-negative human MCP-1 with deletion of N-terminal amino acids (7ND) to inhibit macrophage recruitment. In Ang II infused mouse hearts, 7ND injection didn't suppress mast cell infiltration into the atria (Figure 4A), but inhibited macrophage accumulation in the atria (Figure 4B), resulting in reduced atrial fibrosis (Figure 4C) and decreased AF inducibility. (Figure 4D)

These results suggest that an inflammatory cascade involving mast cells and macrophages contributes to the pathogenesis of AF in Ang II-infused mouse hearts. This study highlights a potential application of stabilization of the mast cell-macrophage cascade to achieve upstream prevention of AF in stressed hearts.

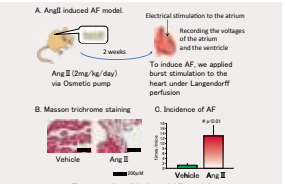


Figure 1. Ang II induced AF model

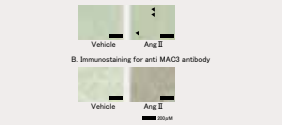


Figure 2. The numbers of mast cells and macrophages were increased in the atria of Ang II-infused mice hearts.

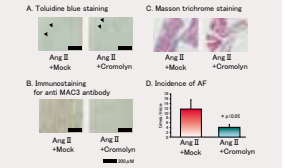


Figure 3. Cromolyn treatment suppressed AF inducibility in Ang II-infused mice.

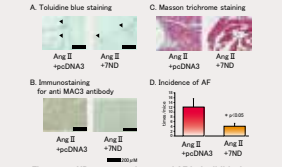


Figure 4. 7ND treatment decreased AF inducibiltiy in Ang II-infused mice.

Education Report

Inauguration of Two New Programs

1. Presentation seminar Intermediate/Advanced

Presentation seminar Intermediate/Advanced, new subjects for graduate students, was introduced into the curriculum. All lectures and practices were given in English, by expert native English speakers. The seminars focus on scientific presentations in English, and students intensively learned and practiced not only the basics necessary for presentations but also techniques for improving these presentations, such as how to respond to a difficult situation in a question and answer period, effective body language and so on. The results of a questionnaire given to the students in both Intermediate and Advanced courses showed a high level of satisfaction with the lectures. Followings is a summary of the seminar (Advanced) and feedback from students (excerpts from the questionnaire).

General Instruction Objective (GIO) :
In this course, you will learn how to deliver an effective and memorable English presentation. Not only will you learn about the structure of a presentation, but you will also obtain the essential techniques and elegant language skills to achieve your presentation goals. In addition, you will participate in the course both as a presenter and as an audience member, giving you the opportunity to practice asking and responding to questions smoothly.

Content and Specific Behavioral Objectives (SBO) Summry:

◆Date:August 2-5, 2010

[No.1]
Subject:The Opening and Body
You will learn language and techniques for introducing yourself, stating the purpose and the outline, beginning your presentation, and moving on to your next point.

[No.2]
Subject: The Closing and Q&A Session
You will learn language and techniques for closing and summarizing, and inviting and answering questions in a Q&A.

[No.3]
Subject:Making Your Presentation Special
This lesson focuses on ways to make your presentation more memorable and effective using visuals and giving examples.

[No.4]
Subject:Introducing Your University and Studies
This lesson focuses on presentations to introduce yourself, your school, faculty and/or department, stating the organizational structure and your responsibilities and obligations.

[No.5]
Subject:Explaining Charts and Figures
Today's lesson will give you the tools you need to explain and refer to numbers, charts and data, and help your audience to follow them.

[No.6]
Subject:Making a Proposal
This lesson focuses on techniques used in making effective proposal presentations explaining a work plan, schedule and budget.

[No.7]
Subject:Putting it All Together
Today's "role play" focused lesson gives you the opportunity to use what you have learned throughout the course to make presentations.

[No.8]
Subject:Final Presentation
This is the lesson in which you will deliver a presentation on a topic of your choice. Your classmates will participate as the audience, asking you questions in your Q&A and, afterwards, providing positive and constructive feedback on your performance.

Comments from students

•I learned how to deliver a presentation for the first time and learned a lot from the lectures. We studied 90 min×2 lessons for a fourth straight day, which was much harder than I had expected, and I felt we were short of time in preparing for the final presentation. Due to small-group (15 or so students) guidance, I got better acquainted with other G-COE RAs. (Name plates and changing seating worked very well!!) If there is another opportunity like this next year, I will surely take it again. I hope all graduate students can take the seminar since it is very useful.

•I appreciate leaning the lessons with G-COE RAs in a friendly atmosphere. My hope is that it will have more practical content specifically for scientific presentations.

2. Clinical Oncology

A new subject of study, Special lectures of Clinical Oncology, was initiated in our graduate school.
All the lectures are given in English, by core members of the G-COE program.

General Instruction Objective (GIO) :
Malignant diseases are manifested by the dysregulation and malfunction of the immune system. In these special lectures, the mechanisms of immune cell regulation and cancer will be introduced. Through the lectures, students will get a good motivation to start their medical research.

Content and Specific Behavioral Objectives (SBO) Summary:

◆Date:August 9-10, 2010

[No.1] **Lecturer: Nakayama Toshinori**
Subject:Anti-tumor immunity mediated by memory T cells
Understanding the mechanisms on anti-tumor immunity mediated by memory Th1/Th2 cells.

[No.2] **Lecturer:Tokuhisa Takeshi**
Subject:Germinal center and B cell lymphoma-genesis
Germinal centers (GCs) are a complex cellular microenvironment that directs generation of high affinity memory B cells. We discuss molecular mechanisms of the B cell lymphoma-genesis in GCs.

[No.3] **Lecturer: Matsue Hiroyuki**
Subject:Dendritic Cells and Tumor
In this lecture, I will review roles of dendritic cells (DC) in the process of tumor formation especially in the context of "Cancer-Immunosurveillance" (Burnet) and the new concept "Cancer-Immunoediting"(Schreiber), and I will focus on discussing DC-based cancer immunotherapies: Their past, present and future.

[No.4] **Lecturer: Okamoto Yoshitaka**
Subject:Current situation and treatment of head and neck cancer
The management of advanced head and neck cancer has generally involved the combined-modalities of chemotherapy, radiation therapy and surgery. However, the prognosis still remains poor. The development of new treatment strategies to improve the prognosis and QOL of patients will be discussed.

[No.5] **Lecturer: Tanzawa Hideki**
Subject:The mechanism of resistance to chemotherapy and radiotherapy of cancer
This lecture will lead to understand and explain the mechanism of resistance to chemotherapy and radiotherapy of cancer, and the practical method of translational research.

[No.6] **Lecturer: Akutsu Yasunori, Matsubara Hisahiro**
Subject:Translational research for esophageal cancer
Esophageal cancer is still the worst malignant disease, and its prognosis is miserable. First, clinical diagnosis and treatments will be reviewed, and second, translational research for esophageal cancer will be presented.

[No.7] **Lecturer: Motohashi Shinichiro**
Subject:NKT cell-based immunotherapy for cancer
In this lecture, the progress to date in the clinical studies of NKT cell-based immunotherapy for cancer is reviewed and the role of NKT cells in immunotherapy highlighted.

[No.8] **Lecturer: Kamada Tadashi**
Subject:Carbon ion radiotherapy for malignant disease
Carbon ion radiotherapy (CIRT) is a unique radiotherapy, which possesses well localized, and superior depth dose distribution in addition to uniform, less repairable radiobiological effects. In this lecture, the up to date results of carbon ion radiotherapy in various cancers at the National institute of Radiological sciences will be discussed.

Event One

NIRS-Chiba University G-COE Joint Symposium on Carbon-Ion Therapy and Immunotherapy

January 15, 2010
Auditorium, Research Builing for Charged Particle Therapy 2F
National Institute of Radiological Sciences (NIRS)

The NIRS-Chiba University G-COE Joint Symposium on Carbon-Ion Therapy and Immunotherapy was held on January 15. The program was designed for encouraging much discussion on basic and clinical research results toward future development of novel less-invasive therapeutic strategies, searching for common ground between carbon ion therapy and the immunological mechanism from what has been known until now. Dr. Ken-ichiro Seino (Institute of Medical Science St. Marianna University School of Medicine) presented a keynote lecture on tumor immunity from the basics to a future vision including the potential of regenerative immunotherapy by using iPS cells, in an easy-to-understand manner. For a special lecture, Dr. Kazuhiro Kakimi (Dept. of Immunotherapeutics (Medinet), Graduate School of Medicine, the University of Tokyo) presented results of clinical trials of immunotherapy and also explained the problems of current immunotherapy including the basic research results, in terms of creating immunosuppressive environment. His talk was very suggestive enough to provide an important direction toward a breakthrough to the current immunotherapy, which does not sufficiently meet many patients' expectations.

Much heated and fruitful discussion was generated by the 97 participants in this symposium, which was concluded with great success. We would like to strengthen our partnership with the National Institute of Radiological Sciences in order to develop less invasive cancer therapy with fewer side effects, combining carbon ion therapy with immunotherapy.

Shinichiro Motohashi

Event Two

The 1st Chiba-Uppsala Academia Joint Workshop "Inflammation/Immunity and Cancer"

February 19, 2010, the 1st Auditorium
Chiba University Hospital 3F

"The 1st Chiba-Uppsala Academia Joint Workshop" was held on February 19, 2010 at the 1st Auditorium at Chiba University Hospital. This was the first project on the academic and research collaboration agreed on in 2008 between Uppsala University in Sweden and Chiba University. This workshop was also one of events to celebrate the 60th anniversary of Chiba University.

Dr. Claesson-Welsh from Uppsala University and Dr. Yokote from Chiba University organized this project and invited five leading researchers, including Dr. Welsh herself, from Uppsala University. The workshop began with the opening remarks by Dr. Kohno, director of University Hospital. The focus of this workshop was on "Inflammation/Immunity and Cancer", and the workshop was divided into four different topics. The first session was on "Inflammatory Regulation." At first, Dr. Heyman made a presentation on regulation of antibody responses. Dr. Nakajima, Department of Molecular Genetics, then spoke about the role of IL-17 in asthma. The last presentation of the first session was on the characterization of p53 associated proteins by proteomic approach by Dr. Tanaka (Department of Clinical Cell Biology and Medicine).

The second session was on "Inflammatory Diseases." Dr. Kämpe, Dr. Takemoto (Department of Clinical Cell Biology and Medicine), and Professor Suzuki (Department of Immunology, G-COE coordinator) made presentations on autoimmune polyendocrine syndrome, R3h-domain containing like, and ANCA-associated vasculitis. Because these presentations concerned different organs, we had an opportunity to learn a wide range of recent results in inflammatory disease.

The third session was on "Angiogenesis and Vascular Inflammation." Drs. Welsh, Dimberg and Minamino (Department of Cardiovascular Science and Medicine) made their presentations about VEGF, αB-crystallin, and vessel formation of cardiovascular disease, respectively.

The fourth session was on "Immunity and Cancer." Drs. Essand, Yoshitomi (Department of General Surgery and Molecular Diagnosis) and Iwama (Department of Cellular and Molecular Medicine) made presentations on T cells and viruses in cancer therapy, revealing the molecular mechanisms underlying the pancreatic cancer by proteomic and conventional approach, and on regulation of normal and cancer stem cell self-renewal by the polycomb complexes. Lively discussions took place throughout the workshop, and it was very interesting to experience the different approaches the Swedish researchers made to the study.

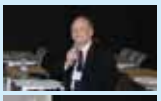
We greatly appreciate the more than 70 participants who came to this workshop. We were also happy to be able to further discuss joint research projects. This workshop was a great opportunity for us to build the first step of our relationship with Uppsala University. We have decided to hold a joint workshop every other year, hopefully next time at Uppsala University.

Masaki Fujimoto
Chiba-Uppsala Academia Joint Workshop Office

Event Three

Chiba University G-COE Joint Workshop with Uppsala Faculty

February 20, 2010, 1st Lecture Hall, Main Building 1F
Faculty of Medicine, Chiba University


The Chiba University G-COE Joint Workshop with Uppsala Faculty was held on Saturday, February 20, in cooperation with Uppsala University in Sweden. This was the third workshop in "Presentation and Discussion by G-COE-RA". Five faculty members from Uppsala University, who were invited for the first project on the academic and research collaboration, joined the workshop as discussion leaders. They brought a new and more global perspective to the workshop, encouraging stimulating discussions. The atmosphere closely paralleled that of making a presentation overseas. Each successive workshop has increased the desired results. The comments below were made by the Uppsala faculty team.

It was a great honor to participate as a discussion leader in the Chiba University Global COE Joint workshop with Uppsala Faculty, and a delight to listen to the PhD students presenting their work. I was very much impressed by the clarity of the presentations and the pure excellence of the science. The work presented was creative and novel, of a high international level, and brought many new ideas that I will try to incorporate into my research at Uppsala University. Importantly, this workshop provided an opportunity for the PhD-students to practice giving a lecture to an international audience. Without exception, they performed superbly. Congratulations to Dr. Nakayama and Dr. Suzuki for organizing this successful program.

–By Anna Dimberg

My main impression of the G-COE workshop held on Feb 20, 2010 was that of very high ambition. Clearly, the PhD students had prepared excellently for their talks, which were held in English. Many presentations were on challenging translational project, often in the absolute forefront in their fields. Most of the talks were also very well planned to be within time, which is essential for an event like this. It was sometimes a challenge for the PhD students to respond to questions from the audience. It is vital to constantly improve the skills in communication in English, for all of who do not have English as our first language. I would like to encourage the PhD students to continue to practice to present in English and for their fellow students in the audience to ask questions in English. This will ensure success when participating in international exchange of all kinds. My best wishes to all the PhD students: Good luck with your research!

–By Lena Claesson-Welsh

The presentations of the research projects by the graduate students were generally very well performed. It was obvious that a lot of effort had been taken in preparing excellent powerpoint presentations with high quality pictures. The oral presentations had been well rehearsed and were easy to understand. The students also kept the allotted time very well, much appreciated by the chairmen. The scientific quality of the projects was excellent. An area where some improvement could be made is to train the students in understanding spoken scientific English in a stressful situation, since some of the young investigators had problems answering the questions they got after their presentations. Usually, this was just a matter of not understanding the English, because when they were asked in Japanese they could reply adequately. Thus, my overall comment is that the programme is very impressive in the quality both of the students and of their scientific achievements. To reach excellence in an international setting, it is recommended that the ability of the students to communicate in spoken English is improved.

–By Birgitta Heyman

On the 20th of February 2010, 3rd year PhD students presented their scientific work at a joint workshop at Chiba University together with representatives from the Uppsala University. First of all, the day as such must be regarded as a success. It was a pleasure to listen to and discuss the science presented at the workshop. The overall level of the presentations was very high, which was reflected by the fact that much of the presented work had already been accepted in or submitted to renounced medical journals. I would like, in particular point out the presentations on the development and role of CD4 T cells, which I regard as highly innovative and in the scientific front line.

Credits also to Dr. Nakayama and Dr. Suzuki for a well-organized day.

Finally, I would like to thank everyone involved for making the stay in Chiba such a pleasant experience.

–By Magnus Essand

Event Four

Advanced Medicine Progress Seminar

by Seeds Grant Competition Winners 2009

Co-organized by Chiba University COE start-up program
February 23, 2010, Library Hall 3F, Library of Health Sciences, Chiba University


We held a seed grant competition for advanced medicine for the purpose of seed exploitation, acceleration of Translational Research (TR) and enhancing young researchers' motivation to do clinical study, at Chiba University. We have been supporting eight selected excellent study proposals in providing research grants and regular discussions, in order to accelerate the realization of TR. An open seminar took place on February 23, 2010 to report progress in these studies.

Each of the studies is aimed at developing diagnostic biomarkers, or novel therapeutic agents and treatments targeting various diseases including neurodegenerative diseases, nasal allergy and prostate cancer. From the reports at the seminar, we recognized that the stage of research varied greatly among the studies, however, energetic efforts have been made to promote them toward realizing TR. The support offered by this event has led to acceleration in TR, thus we will cooperatively strive for patients to have effective diagnosis or remedies as soon as possible.

Shinichiro Motohashi, Program leader, Seeds Grant Competition

Event Five

NZ-RIKEN-CHIBA Joint Workshop

"Recent advances in immune regulation and immunotherapy"

June 14, 2010, Research Center for Allergy and Immunology (RCAI)
June 16, 2010, Library Hall 3F, Library of Health Sciences, Chiba University

The NZ-RIKEN-CHIBA Joint Workshop "Recent advances in immune regulation and immunotherapy" was held in cooperation with the RIKEN Research Center for Allergy and Immunology (RCAI), the Ministry of Research, Science & Technology, New Zealand, and The G-COE program. This event was launched by the Ministry's proposal for continuous exchange of research and personnel among researchers from New Zealand, this G-COE program and others, involved in immunological and clinical studies. This time seven researchers in New Zealand visited Japan to introduce and discuss ongoing research studies with domestic researchers with a view to seeking collaboration in the future.

The joint workshop was held on Monday, June 14, at RCAI. The meeting covered issues on "Immune activation and regulation", "Infection, autoimmune, allergy and vaccine" and "Immunotherapy", providing an opportunity for scientists from both countries to learn the latest developments in their respective fields. On Wednesday, June 16, another meeting for presentation and discussion with the researchers from New Zealand took place at Chiba University. Following the welcome address by Dr. Haruaki Nakaya, Dean, Graduate School of Medicine, and greetings from Dr. John Fraser, Head School of Medical Sciences, University of Auckland, the six New Zealand researchers presented their studies such as 'Strategies to enhance CD8+ T cell responses to vaccination', related investigations on bacterial infection stimulating CD8+ T cells in lymph node for responses to vaccination and so on, to our faculty and graduate students. In the afternoon, after a site visit to the Center for Advanced Medicine, they made individual visit to laboratories for further discussions. We expect progress in this exchange, with the possibility for increasing the collaboration we found in this workshop.


John Fraser

Researchers from New Zealand

Anne Camille La Flamme, Senior Lecturer, Victoria University of Wellington
Rod Dunbar, Associate Professor, University of Auckland
Gavin F Painter, Principal Scientist, Team Leader, Industrial Research Ltd
Gib Bogle, Senior Research Fellow, Auckland Bioengineering Institute
Ian F. Hermans, Doctor, Malaghan Institute of Medical Research, Wellington
John Fraser, Head, School of Medical Sciences, University of Auckland
Sarah Hook, Associate Professor, School of Pharmacy, University of Otago


at the Chiba University Inohana Library


at the RIKEN Research Center for Allergy and Immunology

Event Six

The 6th Global COE Workshop

Presentation and Discussion by G-COE-RA

June 26, 2010, 1st Lecture Hall, Main Building 1F
Faculty of Medicine, Chiba University

The 6th Global COE Workshop that was the fourth workshop in "Presentation and Discussion by G-COE-RA" took place on June 26. This year 36 graduate students selected as G-COE-RA, increasing the number of the RAs by 10 from the 2009 academic year, including the 26 RAs newly selected. They presented their experimental plan and results in English in this workshop. Two advisory professors, in addition to the student's mentors, evaluated each presentation. For many of them it was their first time to make a presentation in English, however the results were very impressive and exceeded expectations. Better preparation may have resulted from hearing about this event from friends and senior staff. Some RAs selected this year again joined sessions as RA discussers to be actively involved in the discussions. They actually led each discussion period, thereby showing their ability to communicate in English. The workshop ended fruitfully, being upgraded to a higher level.



Event Seven

RCAI International Summer Program 2010 Co-organized by the G-COE Program

Date: August 17-27, 2010 (Lecture course)
August 30-September 26, 2010 (Internship course)
Place: RIKEN Research Center for Allergy and Immunology (RCAI)



The RCAI International Summer Program (RISP) 2010 took place at the RIKEN Research Center for Allergy and Immunology (RCAI), August 17-27, jointly organized by RCAI and the G-COE Program, targeting graduate students and postdoctoral fellows overseas. This fifth Summer Program had 44 participants from 10 countries including 24 women, selected from among 141 applicants worldwide. In the early part of lecture course, besides oral and poster presentations, participants attended intensive lectures on the basic concepts to leading-edge study of immunology by 14 distinguished researchers invited from home and abroad. Later in the program, June 22-27, the participants attended the 14th International Congress of Immunology held at Kobe. In this summer program, all the participants were going to make poster presentations at the ICI, however more than 10 of them were selected to make oral presentations, reflecting the high level of their research. RISP invites promising young researchers from all over the world, who become better acquainted and deepen their mutual exchange; this can be an invaluable asset for building a network for advancing research. Three of the participants stayed on at RCAI for a 1-month internship. The overall results of the questionnaire given to participants showed a high level of satisfaction with this program: 100% answered "yes" to the question, "Would you encourage your colleagues to attend the RCAI Summer Program?"

Event Eight

The 4th Chiba University Global COE symposium

Regulation of Immune Disorders

August 20, 2010
The 1st Auditorium, Chiba University Hospital 3F

The 4th Chiba University Global COE symposium was held on August 20, 2010 in the auditorium at Chiba University Hospital. The symposium focused on "Regulation of Immune Disorders" by the invited speakers, who presented big topics in their current researches in the form of educational lectures for RA students.


Anjana Rao
LIAI, Harvard Medical School
(Plenary Lecture)

The plenary lecture by Dr. Anjana Rao (Department of Pathology, Harvard Medical School; Immune Disease Institute and Program in Cellular and Molecular Medicine, Children's Hospital Boston) entitled "Leukemia-associated mutations in TET2 diminish catalytic activity" was exciting for all attendees including RA graduate students. After her lecture, **gene expression and regulation** in epigenetics study were discussed in the talks of "transcriptional regulation of CD4/CD8 lineage choice", "STAT6-mediated displacement of Polycomb by the Trithorax complex establishes long-term maintenance of GATA3 expression in Th2 cells" presented by Dr. Toshinori Nakayama, and "Unexpected role for the polycomb gene Bmi1 in lymphoid commitment". In the second session on **NKT cells and mucosal immunity**, Dr. Mitchell Kronenberg (La Jolla Institute for Allergy and Immunology) described "Recognition of microbial and environmental antigens by invariant natural killer T cells", followed by presentations on"Antigen-specific memory CD4 T cells selectively expanded by NKT cell activation *in vivo*"and "Omitting felony by switching fate: Lineage conversion of CD4 Th cells to CD8 CTLs", which were highlighted in the current NKT study. Next, Dr. Takeshi Tokuhisa focused on **memory cells** in his talk entitled "Roles for Bcl6 in differentiation of germinal center B cells" followed by lectures on "Differentiation and function of follicular helper CD4 T cells (Tfh)" and "Protective and pathogenic immunological memory". **Regulation of allergic disorders** was also discussed with RA students. Finally, **translational researches** on "NKT cell-based immunotherapy for cancer: Nasal submucosal administration of antigen- presenting cells may induce effective anti-tumor immune responses" and "Approach to clinical trial of synthetic immunoglobulin treatment fovasculitis" were discussed.

Thus, all attendees were able to engage in discussions with prominent investigators from all over the world and learn about their current research activities. These discussions with symposium speakers are sure to show attendees how to engage in high level research in immunology.

–By Kazuo Suzuki


I could learn the latest and broad immunological knowledge at the 4th G-COE symposium. In particular, the seminar of Dr. Andreas who is one of authorities on immunological memory was very impressive and beneficial for advancing my research. In addition, it was very useful for me, as a respiratory physician, to learn about the roles of TSLP and CD8+T cells in the pathogenesis of bronchial asthma. Contents of this symposium considered the pathogenesis of allergic diseases and were very useful for both medical researchers and clinicians. It was my great pleasure to attend this symposium.

Jun Ikari, G-COE-RA, Dept. of Developmental Genetics

I obtained a great deal of information from several immunology specialists at the 4th Chiba University Global COE Symposium. Through attending this symposium, I learned of a wide variety of recent findings from basic research to clinical findings. Discussions with foreign researchers at the symposium will be remarkably helpful for the development of their research fields. I think that Chiba University Global COE Symposiums will greatly activate immunology research.

Yuuki Obata, G- COE-RA, Dept. of Molecular Cell Biology

Event Nine

The 7th Chiba University G-COE Workshop

August 21, 2010

The 7th Chiba University Global COE Workshop was held on August 21, in the form of a discussion tour. Drs Rao, Crotty, Ziegler, Kronenberg, Cheroutre and Radbruch who were invited speakers in the symposium held the previous day, participated in this workshop. Each of them visited several laboratories involved with this G-COE Program in turn, in order to have discussions with young researchers and graduate students. It was so productive that a lot of significant comments and suggestions were provided for examining the direction of their future research.

News Letter

Event Ten

Chiba University G-COE
Retreat 2010

September 4 and 5, 2010, Seimei-no-Mori Resort

The Chiba University G-COE Retreat 2010 was held on September 4 and 5 at the Seimei-no-mori Resort. Sixty graduate students and PI researchers involved in this G-COE program participated and had the opportunity for in-depth discussion at a quiet place. The program consisted of two special lectures, 8 oral presentations, 8 poster presentations, and 36 one-minute presentations. On the first day, Dr. Keiji Tanaka, Director of The Tokyo Metropolitan Institute of Medical Science, gave a special lecture in which he explained not only the latest studies on but also a history of proteasome. It gave us a great insight into future research. The next day, for a special lecture, Dr. Takeshi Tokuhisa, Chiba University, gave a talk about a required ability for mentor. This talk had a great impact on our students and young researchers. In the presentations by G-COE Independent Research Associates and G-COE Fellows, topics touched on a variety of subjects and we had discussions on each topic, which were very meaningful for new developments in our research. In the poster presentations held in a congenial atmosphere, each poster was discussed profoundly. Dr. Yuusuke Endo (G-COE-RA) got the best poster award. We believe that this program provided mutual understanding between students and principal investigators.

Hiroshi Nakajima
Director, G-COE Retreat

Keiji Tanaka
Director,
The Tokyo Metropolitan Institute of Medical Science

Takeshi Tokuhisa
Professor,
Dept. of Developmental Genetics

The G-GOE Retreat 2010 was held at Seimei-no-mori Resort on September 4-5. This is my second time participating in this retreat. In the magnificent and relaxed surroundings, the retreat gave us a chance to discuss a number of issues, deepen mutual understanding, and I have spent two enriched days. Different from last year, most of the RAs gave self-introduction, showing their personality and interests and so on to participants. From this, we could get clear impressions of the young researchers. In the poster presentation held in the evening, presenters were requested to give oral presentation in 5 min. Dr. Motohashi played as a time-keeper using his iPhone. The presentation became interesting because his iPhone's bell ringing. It's difficult for me to explain my presentation in 5 min. I received valuable advice from participants. In the special lecture, I think I got a hint from Prof. Tanaka's talk about the treasure for him. Prof. Tokuhisa gave a talk about developing a mature personality according research based on his experience. For me, as an international student, I was also deeply impressed by his lectures, especially about what he learned and felt during overseas study. For the international student benefiting from the G-COE program such as me, it's so lucky to have a chance to hear the wonderful lectures given by famous professors. This experience became a treasure for me. I really appreciated having such opportunity.

Wu Shuang, G-COE-RA, Dept. of Medicine and Clinical Oncology

It was very useful for me to make a presentation of my research at the Chiba University G-COE Retreat 2010. I received a lot of advice after my presentation, which has been of great help for my future study. At night, I got acquainted with many researchers and discussed a wide range of issues, including some not familiar to me. This helped me expand my knowledge. This program increased my motivation and was very a fruitful experience for me. I think the beauties of nature in the Seimei-no-mori Resort helped us to relax and communicate with each other. I appreciate the opportunity to join the retreat.

Tomozumi Takatani, G-COE-RA, Dept. of Pediatrics

Poster presentation by Mr Endo, the best poster award winner

Event Eleven

The 5th Chiba University Global COE Symposium
Development and Maintenance of Immune Memory

December 4, 2010
Sapia Hall, Tokyo Station Conference, Tokyo

The G-COE Program held the 5th Chiba University Global COE Symposium at Tokyo, on Saturday, December 4, co-organized by IMSUT & RCAST G-COE Program, The University of Tokyo. This fifth symposium, entitled "Development and Maintenance of Immune Memory", featured topics relating to immunological memory. Since the regular annual meeting of the Japanese Society for Immunology did not take place this year, with the idea of being a substitute for that, the symposium was held the next day after the general meeting of the Japanese Society for Immunology took place at Tokyo. This time, the theme was confined to immunological memory, though, more than 150 participants got together, which may suggest that immunological research in this area is receiving more attention. A total of 21 talks including one given by an invited researcher from the U.S. were presented in the symposium, starting with a session on Memory CD4 T cells and ending with one on Memory B/Plasma cells. All lectures were given in English including a question and answer period, dealing with the latest findings in the field where studies are progressing rapidly. The symposium was very fruitful with lively and stimulating discussion on each talk. At the end, Dr. Tasuku Honjo, Kyoto University, logically and energetically presented the latest studies on the mechanism of class switch recombination in the plenary lecture, and many participants were very impressed not only with the research results he demonstrated but also his attitude to ward doing research. I believe this symposium will lead to progress in the research of immunological memory in the future.

–Takeshi Tokuhisa, Symposium Director

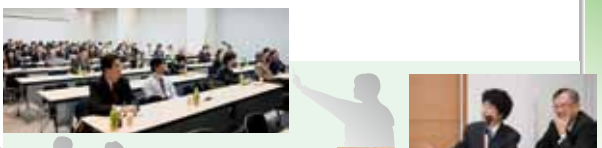
Participating as a speaker

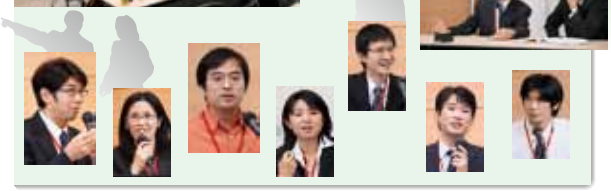
Having felt relieved because my PhD thesis defense was finished, I had a big job to round off the year, English presentation in the 5th G-COE Symposium on December 4. I attended this symposium with a bit different tension because it was held at the Tokyo station conference, and there was a large audience, though I have given English presentations in G-COE-RA workshop several times in the past. I managed to finish the presentation, but in the question period… I muttered, "I couldn't understand the meaning of the question well" in the mind. I got into a panic and answered in English, but in a incomplete sentence. However, thanks to this experience, I recognized again the difficulty of answering questions in English, and of telling correctly people in other fields in English. I kept in mind that I'd speak better next time.

I had a lot of fun to attend this symposium because 'immunological memory', which is closely related to my research, was the main theme and there were a lot of interesting presentations. I was really excited to hear the presentations by various speakers from the young to leading figure's professors. It was valuable to participate and talk in this symposium, including my failure.

Yusuke Endo
G-COE-RA, Dept. of Immunology

Tasuku Honjo, Kyoto University
(Plenary Lecture)





TOPICS

Robert Koch Postdoctoral Awards for Young Scientists

Dr. Koji Tokoyoda, Assistant Professor, Dept. of Immunology

In cooperation with the German Societies of Hygiene and Microbiology, Immunology and Virology, the Robert Koch Foundation in Germany annually presents postdoctoral awards to outstanding work by young scientists. This year Dr. Koji Tokoyoda, Assistant Professor, Dept. of Immunology received the award for immunology for his work on the generation and maintenance of the immunological memory. Dr. Tokoyoda attended the award ceremony held in Berlin on November 12 to be honored with the other winners for the Robert Koch Award and the Robert Koch Gold Medal, along with receiving a diploma and prize money. He is the first Japanese scientist to win this award. The award-winning study is reported on page 2 of this newsletter.

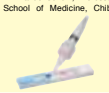
At the award ceremony Dr. Koji Tokoyoda (left), Prof. Jörg Hacker, Präsident der Deutschen Akademie der Naturforscher Leopoldina (right)

Best poster award at the International ISSX Ms Mio Watanabe, second-year student of master course, Laboratory of Pharmacology and Toxicology, Graduate School of Medical and Pharmaceutical Sciences

Ms Mio Watanabe, second-year student of master course, Graduate School of Medical and Pharmaceutical Sciences, won the best poster award of International ISSX (International Society for the Study of Xenobiotics) Meeting held in Istanbul in September. She studied drug metabolism using humanized CYP3A mouse constructed with human artificial chromosome. The title of her poster was Humanized CYP3A Mice: (2) Functional Expression of Human CYP3A Isoforms in CYP3A-HAC Mice and Inhibition of CYP3A via Mechanism-Based Inactivation.

A jointly developed New Influenza Simple Test Kit won Minister of Science and Technology Policy Award in recognition for industry-academia-government collaboration performance

This simple test kit for detection of new Influenza H1N1 won the Minister of Science and Technology Policy Award in June. The kit was jointly developed by the National Center for Global Health and Medicine, Mizuho Medy Co.,Ltd., Chiba University Hospital, University of Miyazaki Hospital and Dr. Kazuo Suzuki, Professor, (Dept. of Immunology, Graduate School of Medicine, Chiba University). Without any special devices, this kid enables to give a diagnosis in clinical practice and contributes to the people's health and medical care cost containment.



A related article on H5N1 influenza appeared in the Medical Tribune

Dr. Thuy T. B. Phung (Researcher, National Hospital of Pediatrics, Hanoi, Vietnam)
Dr. Kazuo Suzuki, Professor, Dept. of Immunology

This study conducted by Dr. Thuy T. B. Phung, who visited Chiba University Graduate school of Medical and Pharmacology Sciences under the JSPS RONPAKU (Dissertation PhD) Program, was reported as a topic in "the 14th International Congress of Immunology" section of Medical Tribune. The title of her research project was "Key cytokines/chemokines in acute respiratory distress syndrome with avian influenza (H5N1) infection in Vietnamese children".

G-COE Seminar

Almost biweekly pace!

For our graduate students, top-ranked world researchers gave lectures including recent findings of their studies. The seminar has been held a total of 23 times after the last report in vol.2.




Allergy Clinical Conference

Go beyond the borders

In the conference researchers from Dept. of Allergy and Clinical Immunology, Dept. of Pediatrics, Dept. of Otorhinolaryngology and Dept. of Dermatology discuss allergic diseases across disciplines.



Basic Science Joint Meeting (BSJM)

This seminar has been held every week coordinated by graduate students working group.

25. November 27, 2009
Nobuya Yoshida, Graduate Student, Dept. of Developmental Genetics

26. January 22, 2010
Chiaki Iwamura, Assistant Professor, Dept. of Immunology

27. Febrary 12, 2010
Hiroaki Takatori, Assistant Professor, Dept. of Molecular Genetics

28. April 2, 2010
Tetsuichiro Saito, Professor, Dept. of Developmental Biology

29. April 9, 2010
Satoru Miyagi, Assistant Professor, Dept of Cellular and Molecular Medicine

30. April 16, 2010
Saki Kawashima, G-COE RA, Dept of Molecular Genetics

31. April 23, 2010
Atsushi Onodera, Assistant Professor, Dept. of Immunology

32. May 7, 2010
Haruko Takano, Post Doctoral Fellow, Biomedical Research Center

33. May 14, 2010
Ako Matsumoto, Associate Professor, Dept. of Pharmacology

34. May 21, 2010
Ryuichi Sugamata, Assistant Professor, Dept. of Immunology

35. May 28, 2010
Naohiko Seki, Associate Professor, Dept. of Functional Genomics

36. June 4, 2010
Toshinao Oyama, Post Doctoral Fellow, Dept. of Molecular and Tumor Pathology

37. June 11, 2010
Asuka Morita, Graduate Student, Dept. of Autonomic Physiology

38. June 18, 2010
Shinichiro Motohashi, Associate Professor, Dept. of Medical Immunology

39. June 25, 2010
Jun Ikari, G-COE RA, Dept of Developmental Genetics

40. July 2, 2010
Tomoaki Tanaka, Assistant Professor, Dept. of Clinical Cell Biology and Medicine

41. July 9, 2010
Satoshi Fujimoto, Assistant Professor, Dept. of Developmental Biology

42. July 16, 2010
Akira Suto, Assistant Professor, Dept. of Molecular Genetics

43. July 23, 2010
Hiroyuki Hosokawa, Assistant Professor, Dept. of Immunology

44. September 3, 2010
Kenta Shinoda, G-COE RA, Dept. of Immunology

45. September 10, 2010
Makiko Kashio, Graduate Student, Dept of Cellular and Molecular Medicine

46. September 17, 2010
Tomokazu Nagao, Lecturer, Dept. of Immunology

47. September 24, 2010
Hiroyuki Ishikawa, Associate Professor, Dept. of Biology, Graduate School of Science

48. October 1, 2010
Hiroshi Ishii, Graduate Student, Dept. of Neurobiology

49. October 8, 2010
Masakatsu Yamashita, Head of Laboratory, Kazusa DNA Research Institute

50. October 15, 2010
Shigetoshi Horiguchi, Lecturer, Dept. of Otorhinolaryngology, Head and Neck Surgery

51. October 22, 2010
Yusuke Endo, G-COE RA, Dept. of Immunology

52. November 5, 2010
Yuko Muroyama, Assistant Professor, Dept. of Developmental Biology

53. November 12, 2010
Takashi Miki, Professor, Dept. of Medical Physiology

54. November 19, 2010
Tohru Minamino, Lecturer, Dept. of Cardiovascular Science and Medicine

55. November 26, 2010
Nobuya Yoshida, Graduate Student, Dept. of Developmental Genetics

56. December 17, 2010
Yasunori Sato, Lecturer, Chiba University Hospital Clinical Research Center

57. December 24, 2010
Naohiko Seki, Associate Professor, Dept. of Functional Genomics

G-COE Research Assistant Members

As part of graduate students education, The G-COE Program has adopted G-COE-RAs every year. These positions are competitive and selected across disciplines from among various Ph.D. students in the relevant fields. This year, 36 G-COE-RAs are studying with the special supports and guidance designed to nurture the ability to be internationally active. The accompanying photos are all of the members of G-COE-RAs in 2010, most of which were taken at the 6th Global COE Workshop held on June 26.


Kazuhide Takeuchi
Dept. of Public Health


Mei-Lan Liu
Dept. of Cardiovascular Science and Medicine


Tetsuhiro Ishikawa
Dept. of Orthopedic Surgery


Masayuki Miyagi
Dept. of Orthopedic Surgery


Masataka Yokoyama
Dept. of Cardiovascular Science and Medicine


Yoshihito Kameda
Dept. of Cardiovascular Science and Medicine


Masashi Uchida
Dept. of Clinical Pharmacology


Tomokazu Sumida
Dept. of Cardiovascular Science and Medicine


Yohko Ogasawara
Dept. of Cardiovascular Science and Medicine


Nijiro Nohata
Dept. of Otorhinolaryngology


Yusuke Endo
Dept. of Immunology


Kenta Shinoda
Dept. of Immunology


Yukiko Watanabe
Dept. of Immunology


Shu Horiuchi
Dept. of Immunology


Soichi Tofukuji
Dept. of Immunology


Yukiko Hiramatsu
Dept. of Molecular Genetics


Jun Ikari
Dept. of Developmental Genetics


Jin Yuan
Dept. of Cellular and Molecular Medicine


Seitaro Nomura
Dept. of Cardiovascular Science and Medicine


Shuang Wu
Dept. of Medicine and Clinical Oncology


Morito Mezawa
Dept. of Clinical Cell Biology and Medicine


Kazumasa Aoyama
Dept. of Molecular Cell Biology


Yuuki Obata
Dept. of Molecular Cell Biology


Hiroto Kamoda
Dept. of Orthopedic Surgery


Norimasa Ikeda
Dept. of Frontier Surgery


Teruyoshi Saito
Dept. of Molecular and Tumor Pathology


Yohko Yamaguchi
Dept. of Molecular Biology and Oncology


Shinya Okamoto
Dept. of Biochemistry


Ayumi Yamamoto
Dept. of Clinical Molecular Biology


Saki Kawashima
Dept. of Molecular Genetics


Yukari Saito
Dept. of Molecular Genetics


Tomozumi Takatani
Dept. of Pediatrics


Junko Tanaka
Dept. of Pediatrics

Hidekazu Nagano
Dept. of Clinical Cell Biology and Medicine

Fumiya Yamaide
Dept. of Public Health

Junpei Suzuki
Dept. of Pharmacogenomics

New Members

Core Members

Hisahiro Matsubara
Professor and Chairman, Department of Frontier Surgery, Graduate School of Medicine, Chiba University

Koutaro Yokote
Professor and Chairman, Department of Clinical Cell Biology and Medicine, Graduate School of Medicine, Chiba University

G-COE Independent Research Associate

Atsushi Onodera
Department of Immunology

G-COE Fellow

Takashi Ito
Department of Cardiovascular Science and Medicine

Akane Suzuki
Department of Immunology

Takafumi Mayama
Department of Clinical Cell Biology and Medicine

JSPS Fellow (G-COE)

Asami Hanazawa
Department of Immunology

Upcoming Events

The 8th Chiba University Global COE Workshop (Presentation and Discussion by G-COE-RA)
Date: February 19, 2011
Venue: The 1st Lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

Advanced Medicine Progress Seminar by Seeds Grant Competition Winners 2010
Date: March 8, 2011
Venue: The 3rd Auditorium, Chiba University Hospital 3F

G-COE Retreat jointly organized with IMSUT & RCAST G-COE Program and Chiba University G-COE Program (tentative)
Date: September 17-18, 2011
Venue: Naito Seminar House, Tokyo University Yamanaka-Ryou

Editor's Note

Vol. 3 of the newsletter contains many news items. In particular, some of the research activities are featured as highlights since our young researchers have produced plenty of results in their fields. We fill our newsletter with articles on events like international conferences with numerous visitors from abroad, symposia or workshops with a view to collaboration, education for RAs to be active internationally, which including a retreat, a newly established training course for improving the ability of discussion in international settings and so on. We are delighted to report that the G-COE program has made the steady progress as a global center. Please feel free to inform us of any comments or requests you may have about the newsletter; we welcome your feedback.

Kazuo Suzuki
G-COE Coordinator
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News Letter

GLOBAL COE

News Letter vol.4 2.2012

Chiba University Global COE Program

Global Center for Education and Research in Immune System Regulation and Treatment

CONTENTS

Research Highlights

Dr. Tomoaki Tanaka (Department of Clinical Cell Biology and Medicine) and Dr. Shinichiro Motohashi (Department of Medical Immunology) both involved in this program, received the Chiba Medical Society Award (2011). Dr. Motohashi's research also received the 16th Inohana Alumni Award.

Tomoaki Tanaka
Lecturer, Dept. of Clinical Cell Biology and Medicine

"The p53 world", a wide variety of physiological functions and common pathogenesis of cancer, diabetes, and age-related disease

〜Forefront of Molecular Biology of "Life-Aging-Disease-Death"〜

While many processes in biology, for instance, temporal and spatial control of gene profile during the development of organisms, increase complexity, the aging process increases entropy and culminates in the death of animals. Recent genetic studies have indicated that the aging process is subjected to a regulatory network. It is now well appreciated that the network includes the nutrient-sensing pathways (such as insulin and AKT/mTOR signals), and transcriptional and chromatin regulation (sirtuins, etc) with profound consequences. Importantly as well, it is also evident that key molecules that regulate cellular senescence and apoptosis, such as tumor suppressor p53, are critically involved in the aging process and pathogenesis of its associated diseases such as cancer, cardiovascular disease, and metabolic disorders, a testament to the importance and crosstalk of transcriptional and epigenetic regulators in the four inevitable events in our lives (Figure 1).

Tumor suppressor p53 receives multiple forms and a diverse range of stress signals such as DNA damage and oxidative or metabolic stress, and then initiates different cellular outcomes, including cell-cycle arrest, apoptosis, and/or cellular senescence. Recently several lines of evidence have suggested that p53 pathway is linked to the reprogramming process by pluripotent factors and oncogenic signals, and p53 systematically regulates intracellular metabolic pathways to preserve anti-oxidant and bioenergetic function (Figure 2). To elucidate the p53 mechanisms, we have attempted to isolate and characterize p53 chromatin complexes *in vivo* by manipulating biochemical techniques and mass-spectrometry, and to perform genome-wide screening of RNA-seq and ChIP-seq using tumor and non-tumor cells, including senescent cells and ES/iPS cells. We found several chromatin regulators and transcriptional coactivators such as CAS/CSE1 (chromosome segregation factor), Sp110 (component of PML nuclear body protein forming a multiprotein complex), and zinc finger proteins in association with p53 chromatin complexes (Figure 3). Given that they are components of intranuclear structures and have functional domains such as the bromodomain and PHD zinc finger motif that potentially function as "reader" for histone codes in epigenetic and chromatin-mediated transcriptional regulation, p53 is a bona-fide epigenetic regulators acting as "the guardian of the genome" and "the cellular gatekeeper". Further, genome-wide analyses revealed that p53 can actively and/or repressively control cell-cycle regulators, metabolic regulators, senescence-associated secretary proteins (SASPs), and linc RNAs in cancer, senescent and ES/iPS cells. Thus, our study suggests that p53 exerts multiple functions with a complexity of crosstalk to intranuclear structure and transcriptional regulation for a wide variety of transcripts, including linc RNAs in senescent and ES/iPS cells, linking to a common mechanism of cancer, life-style-related disease, and age-related disease such as diabetes and cardiovascular disorders (Figure 4).

Figure 1. Epigenetic Regulators and Disease

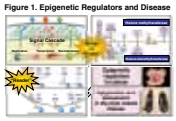


Figure 3. Our Research Work about Tumor Suppressor p53

Figure 2. Wide Variety Function of p53 and its Metabolic Role

Figure 4. Forefront of Molecular Biology of "Life-Aging-Disease-Death"

Research Highlights

Shinichiro Motohashi
Associate Professor, Dept. of Medical Immunology

NKT cell-based Immunotherapy for non-small cell lung cancer

Invariant natural killer T (iNKT) cells are activated by a specific ligand, α-Galactosylceramide (α-GalCer), in a CD1d-dependent manner, and upon activation iNKT cells modulate the function of a wide variety of other immune cells, including anti-tumor effector cells in both a direct and an indirect manner (Figure 1). Early clinical trials of iNKT cell-based immunotherapy demonstrated that the infusion of ligand-pulsed antigen presenting cells (APCs) or *in vitro* activated iNKT cells was safe and well tolerated in patients with non-small cell lung cancer (NSCLC). Intravenous injection of α-GalCer-pulsed APCs, which induces the activation of endogenous NKT cells and NKT cell-dependent responses, was well tolerated. In this clinical trial, whole PBMCs cultured with GM-CSF and IL-2 are used as antigen presenting cells (Figure 2). These APCs include DCs that can activate iNKT cells efficiently. The number of IFN-γ-producing cells in PBMCs after restimulation with α-GalCer in vitro was detected to evaluate the functional iNKT cells and NK cells that were subsequently activated by activated iNKT cells. The number of IFN-γ-producing cells was clearly elevated (good responder group) in 10 patients, while the remaining 7 patients did not show any increased IFN-γ production (poor responder group). The median survival time (MST) of the good responder group was significantly better than that of the poor responder group (Figure 3). This result suggested IFN-γ might be a valuable biological marker for predicting the clinical course in response to α-GalCer-pulsed APC administration. Two candidate biomarkers that might be associated with immune responses were also detected (Figure 4). From these results, "intravenous injection of α-GalCer-pulsed APCs for the treatment of non-small cell lung cancer" was approved by the Japanese Ministry of Health, Labour and Welfare as "Highly Advanced Medicine" (Sep. 28th, 2011). In addition, the phase I study of trans-bronchial intratumoral or intranodal α-GalCer-pulsed APC injection was initiated in patients with advanced NSCLC to activate iNKT cells in the tumor microenvironment more efficiently. Further investigation to clarify the mechanisms of iNKT cell-mediated anti-tumor immunity is in progress. It would be advantageous to identify biomarkers that may predict the clinical outcome before the treatment, and select subgroup(s) of patients who will most likely have a significant clinical benefit in any or a specific type of iNKT cell-based immunotherapy.

Figure 1

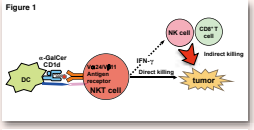


Figure 2

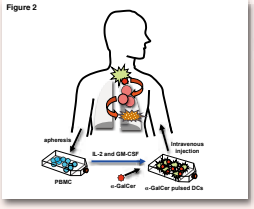


Figure 3

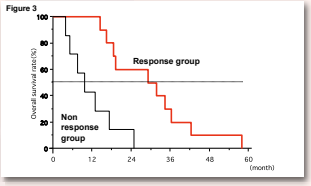
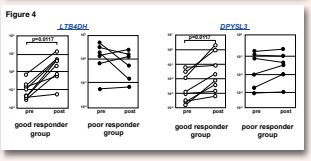


Figure 4



Research Highlights

Annual Best Research Award 2011

This award is given to Ph.D. students in the G-COE relevant fields whose research is recognized as most outstanding through the year. The Annual Best Research Award 2011 went to Dr. Masayuki Miyagi (G-COE-RA) and Dr. Yusuke Endo who is now a G-COE Fellow.

Masayuki Miyagi
G-COE Research Assistant
Dept. of Orthopaedic Surgery

The pathomechanism of chronic diskogenic low back pain

Low back pain is one of the most common and important medical problems. Intervertebral disk (IVD) pathology is thought to be a significant contributor to low back pain. However, its pathophysiology remains incompletely understood. Shinohara first reported the presence of nerve fibers in the deep layers of IVDs in diskogenic low back pain patients. Further investigations have found high levels of inflammatory mediators in degenerated human IVDs. The results of these studies suggest that the presence of sensory nerve fibers in IVDs and the persistent production of inflammatory mediators in degenerated IVDs may lead to diskogenic low back pain.

However, the pathomechanism of "chronic" diskogenic low back pain was not absolutely clear. We compared in rats the behavior of the sensory nervous system (neuropeptides in dorsal root ganglion (DRGs) and glia in the spinal dorsal horn) and inflammatory mediators (nerve growth factor: NGF, TNF-alpha, IL-6) in experimentally injured IVDs over the first eight weeks following experimental IVD injury. In this study, inflammatory mediator levels in injured IVDs were significantly higher than control levels for four days but by the end of second week no longer significantly differed from control levels (Figure 1). On the other hand, the up-regulation of neuropeptides in DRG neurons and the microglia and astrocytes in the spinal dorsal horn remained significantly higher in the injured group than in the non-injured group for the entire eight weeks studied (Figure 2). Thus, in this lumbar IVD injury model, local inflammation calmed down to normal levels within two weeks, but activation of the sensory nervous system continued for at least eight weeks. ***(Miyagi M, et al., Spine 2011 in press)***

There are two limitations to this study. First, there are some differences in the findings between animal models such as the IVD injury model and human specimens. When considering diskogenic low back pain, not only injury but also mechanical stress such as dynamic compression may be an important factor in human degenerated IVDs. Now, we are proceeding with a new project to investigate in a newly developed IVD dynamic compression model (Figure 3). Second, the evaluation of low back pain behavior is a limitation of most basic research animal models. We previously reported the gait changes using the CatWalk system (Figure 4) in a rat model of lumbar myofascial inflammation and suggested that we may be able to apply this system to the evaluation of low back pain behavior in rats. ***(Miyagi M, et al., Spine, 36(21):1760-4, 2011.)*** Now we are proceeding with a new project to investigate the low back pain behavior using the CatWalk system in a rat model of the IVD injury model.

Figure 1. The production of inflammatory mediators in IVDs

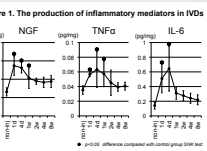
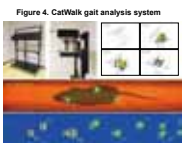


Figure 3. IVD injury or/and dynamic compression model

Figure 2. Immunohistochemistry

Figure 4. CatWalk gait analysis system



Research Highlights

Annual Best Research Award 2011

Dr. Endo also received the Dean's Excellent Record Award, Graduate School of Medical and Pharmaceutical Sciences, Chiba University.

Yusuke Endo
G-COE Fellow
Dept. of Immunology

Identification of pathogenic memory Th2 cells, which are required for allergic inflammation and clarification of molecular mechanisms controlling IL-5 production in memory Th2 cells.

Approximately 30% of the Japanese population suffers from allergic disease. However, only symptomatic therapies are presently available, and no curative therapeutic strategies have been developed. We are trying to clarify the underlying molecular mechanisms of allergic disease, focusing on the role of CD4-positive helper T (Th) cells. Effector Th cells are subdivided into at least three distinct subsets (Th1, Th2, and Th17 cells) according to their cytokine production profiles (Figure 1). Among them, Th2 cells produce IL-4, IL-5, and IL-13 (so-called Th2 cytokines) and are thought to play a critical role in allergic disease.

After antigen clearance, some of the effector Th cells are maintained as memory Th cells for long periods in vivo through the contraction phase (Figure 2). Memory Th cells play an important role in 'immunological memory' that is central in immune responses, and they are involved in a wide variety of diseases. Memory Th cells displayed higher heterogeneity as compared to effector Th cells and are subdivided into several subpopulations according to the expression of cell surface molecules, cytokine production, and expression of transcription factors even in the same Th subsets. However, functional difference of each subpopulation in memory Th cells remains to be analyzed in detail. Therefore, this study is an important subject that needs to be further analyzed to understand the development of disease including allergic disorders.

Recently, we found that memory Th2 cells expressed CXCR3, a well-known marker for Th1 cells, and were subdivided into four distinct subpopulations according to the expression of CD62L and CXCR3. IL-5-producing cells were predominantly detected in the CD62L^{L}CXCR3^{lo} population in memory Th2 cells (Figure 3) and this population played a critical role in the memory Th2-dependent allergic airway inflammation. Furthermore, T-box transcription factor, *Eomesodermin* (Eomes) was up-regulated in memory Th2 cells and suppressed GATA3-dependent IL-5 production, which resulted in reduced airway inflammation (Figure 4). This study was published in the November issue of Immunity (Endo et al., *Immunity* 35, 733).

In this study, we have identified pathogenic memory Th2 cells and clarified molecular mechanisms, which are required for the induction of memory Th2-dependent eosinophilic airway inflammation. We will apply this study to human memory CD4 T cells for the treatment of allergic disorders.

Figure 1. Differentiation and function of helper T cell (Th) subsets

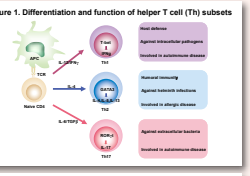


Figure 2. Overview of memory Th cell generation

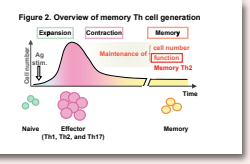


Figure 3. The CD62L^{lo}CXCR3^{lo} population of memory Th2 cells selectively produces IL-5

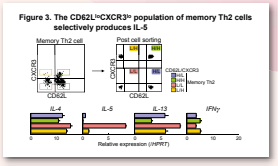
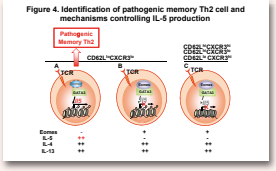


Figure 4. Identification of pathogenic memory Th2 cell and mechanisms controlling IL-5 production



Research Highlights

Dr. Kenta Shinoda, who is now a G-COE Fellow, was awarded the Dean's Excellent Record Award, Graduate School of Medical and Pharmaceutical Sciences, Chiba University, at the graduation ceremony. His research is shown below.

Kenta Shinoda
G-COE Fellow
Dept. of Immunology

Role of CD69 for the generation of memory T helper lymphocytes

Immunity is said to have a memory for most invading agents encountered before, because a second encounter with the same agent prompts a rapid and vigorous response. Memory T helper (Th) lymphocytes play an essential role in immunological memory. In their absence, the generation of long-lived plasma cells and the maintenance and secondary expansion of memory cytotoxic T cells are impaired. Despite their eminent importance for the regulation of immune reactions and immunological memory, little is known about the molecular mechanisms of the generation and maintenance of memory Th cells.

After antigen recognition, naive Th cells activate and expand into a large pool of effector Th cells in secondary lymphoid organs, such as spleen and lymph nodes. Most of the effector Th cells die during a phase of contraction; however, a small proportion survive and differentiate into memory Th cells in body. To date, we have showed that effector Th cells relocated to the bone marrow (BM) after their activation in secondary lymphoid organs, and were maintained as memory Th cells in the BM. In addition, memory Th cells persist as resting in the BM, next to IL-7-secreting stromal cells, suggesting that IL-7 is the prime survival signal for these memory cells. Upon challenge with the antigen, they could efficiently induce the production of high-affinity antibodies by B lymphocytes. Taken together, these results suggest that effector Th cells relocate to the BM and maintain on a survival niche for a long period. However, mechanisms involved in this process remain unknown.

In the steady states, resting memory Th cells mostly express CD69 (Figure 1), which is well-known as an early activation marker of lymphocytes. We focused on CD69 and examined to clarify the role of CD69 in memory Th cells. We enumerated memory Th cells in CD69-deficient mice. Although CD69 does not appear to be required for the development of effector Th cells, the number of antigen-specific memory Th cells in CD69-deficient mice dramatically decreased compared to wild-type mice (Figure 2). In addition, CD69-deficient Th cells failed to induce an efficient production of high-affinity antibodies in vivo (Figure 3). In the way of generation of memory Th cells, we show that CD69 regulates the homing of effector Th cells to BM as an adhesion molecule. These data suggest that CD69 plays a crucial role in the generation of memory Th cells and that the relocation of effector Th cells to the bone marrow is essential for generation of memory Th cells (Figure 4). In the case of allergy or autoimmune diseases, we think there are similar mechanisms underlying the generation and maintenance of harmful memory Th cells. We will clarify the mechanisms involved in the maintenance of harmful memory Th cells in chronic diseases.

Figure 1. Memory Th cells (red) reside on stromal cells (blue) and express CD69 (green)

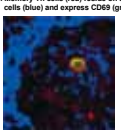


Figure 2. CD69 is required for the generation of antigen-specific memory Th cells

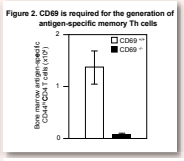


Figure 3. CD69-deficient Th cells fail to provide efficient help for B cells

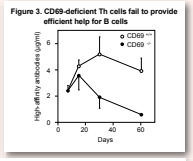
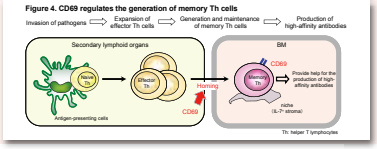


Figure 4. CD69 regulates the generation of memory Th cells



Reports of Study Abroad

Eight young researchers involved in this program contributed reports of study abroad. Let's hear their experience and advice.

TSLP in Allergic Diseases

Masayuki Kitajima
Immunology Program
Benaroya Research Institute at Virginia Mason
(from October 2008)

With collaborators and graduate students, we reported that enhanced Th2 differentiation and allergen-induced airway inflammation in Zfp35-deficient mice (Kitajima *et al*, J Immunol, 2009) and memory Th2 cells induce antitumor immunity by activating NK cells (Kitajima *et al*, Cancer Res, 2011). With strong hope in international collaboration cultivated in the research activities I have begun research activities as a fellow researcher in unison with the idea of Global COE program. After a year and half as G-COE fellow, now I am a postdoctoral fellow in the same laboratory (that of Dr. Steven Ziegler).

The cytokine thymic stromal lymphopoietin (TSLP) has been implicated in the development and progression of allergic inflammation in both humans and mice. We reported that TSLP enhances the function of Th2 cells as a result of studying as a G-COE fellow (Kitajima *et al*, Eur J Immunol, 2011). Thus, the novel function of TSLP suggests that TSLP is involved in homeostasis of Th2 cells in allergic inflammation directly. Next, I am investigating TSLP-activated DCs, which have not been extensively investigated. In this study, using CCL17-eGFP transgenic mouse-derived FLT3L-induced bone marrow DC subsets (CD11b^{High} DC, CD24^{High} DC, and pDC), we found that CCL17-eGFP-expressing DCs induced by TSLP were part of CD11b^{High} DCs. And the GFP-positive DCs had a high level of costimulatory molecules and MHCII expression compared to the GFP-negative DCs, and they had increased Th2 differentiation *in vitro*. Taken together, these results may indicate identification of TSLP-targeted DCs and establishment of the DC assay system, and suggest that it has a potential for providing new information on the role of TSLP-activated DCs in allergic inflammation.

In research activities that keep evolving with the globalization, learning the research form of real overseas research laboratories is sure to become a provision of the postgraduate who conducts research activities of Japan in the future. Moreover, I am convinced that the process of piling discussion and study results with a worldwide researcher has touched off the growth of the postgraduate who has the connection with the fellow researcher's own growth.

With members of the laboratory
Masayuki Kitajima (first from left in top raw), Steven F. Ziegler (third from left in middle raw)

Study at University of Wisconsin-Madison

Jiro Terada
Dept. of Respirology, Graduate School of Medicine, Chiba University
[Dept. of Comparative, University of Wisconsin Madison (from April 2009 to March 2011)]

I'd like to express my appreciation of the opportunity to have worked as a G-COE-RA. I'll briefly present my research life from 2005 to 2011.

My PhD study started after I had worked as a respiratory physician for five years. The goal of my research was to study basic science in respiratory medicine. The first half of my PhD research was respiratory neuro-regulation using physiological methods under professors Fukuda and Kuwaki in Dept. of Autonomic Physiology, while the second half was cell-cell communication using pancreas cell-line with molecular technique. After the completion of my PhD study, I went to the University of Wisconsin Madison with my sons and wife. I worked there for two years under Gordon Mitchell who is well known in the study of respiratory neuroplasticity. My research projects were 1) Diaphragm long-term facilitation during sleep in unanesthetized rats and 2) Respiratory neuroplasticity for respiratory failure in spinally injured rats. Madison is a beautiful and safe capital city of the state of Wisconsin in the midwestern U.S. It was more difficult at first to understand the culture and English than I expected. But thanks to my boss, colleagues and friends in Japan, I've finished my projects there.

Now I think I had great and irreplacable experience with my family. So I think it would be good challenge for young researchers to do some research in foreign countries. Again, I was deeply grateful to everyone who encourages my research life in Chiba and Madison, especially the members of the G-COE program.

With members of the laboratory
Jiro Terada (second from right in front raw), Gordon Mitchell (third from right in middle raw)

A research project report: from University of Michigan

Yuumi Nakamura
Department of Pathology, University of Michigan
(from May 2009)

I had finished a graduate degree, and then worked as G-COE research fellow at Chiba University in 2009. During that period, my research project was focused on the role of the NLRP3-inflammasome in mast cells. After that, to investigate this more deeply, I started to work as a research fellow in Dr. Gabriel Nunez's lab at the University of Michigan. I'm now using a "human disease-associated Nlrp3 mutant knock-in mouse" that is a very powerful tool for analyzing the role of Nlrp3-inflammasome *in vivo*. Recently, many studies have suggested the activation of the NLRP3 inflammasome is involved in a variety of metabolic diseases including obesity, atherosclerosis and type 2 diabetes. I believe our current project in this field may have the potential to lead to better treatment for inflammasome-associated diseases.

At Dr. Nunez's home
(from left, Gabriel Nunez, Nakamura's family)

Crucial role of CD8αα for T cell memory survival

Ryo Shinnakasu
Division of Developmental Immunology
La Jolla Institute for Allergy & Immunology
(from May 2009)

A hallmark of immune T cell memory is that repeated infections with a pathogen are met with more rapid and enhanced protective immunity against that organism. Effector memory T cells (EM) are located in various tissues and have a heightened and immediate effector function. By contrast, central memory T cells (CM) reside within lymphoid tissues and require proliferation and differentiation to become effector cells.

On the other hand, allergy responses are caused by an abnormal immunoresponse to antigens that are non-pathogen originally. Memory T cells are known to affect these allergy responses.

When I belonged to Chiba University I performed my basic researches about generation of EM and CM for the development of the allergic prevention and cure by the immune system.

Currently, I belong to the laboratory of Dr. Hilde Cheroutre at the La Jolla Institute for Allergy & Immunology. It becomes clear from our past study gradually that CD8αα serve as key components for maintain the intraepithelial lymphocytes which is a kind of effector memory T cells and now I am performing the analysis from a molecule level about the function mechanism of CD8αα.

I have had a lot of precious experience since I started research in U.S. 2 years ago. I want to make the most of these experiences for my future research in Japan and I want to tell students what I felt through research life in U.S for about the differences of how to lead and the way of thinking for research in comparison to Japan.

With members of the laboratory
Ryo Shinnakasu (third from left), Hilde Cheroutre (third from right)

With members of the laboratory
Haruhiro Toko (fifth from left), Mark Sussman (center in back raw)

Heart Institute in San Diego State University

Haruhiro Toko
Department of Biology
San Diego State University
(from February 2010)

I belonged in Cardiovascular Science and Medicine, Chiba University Graduate School of Medicine. From Feb., 2010, I have studied at Heart Institute in San Diego State University (P.I. Mark Sussman). In this lab., almost all researchers study about the role of kinases such as Akt and Pim1, or the role of cardiac progenitor cells in the pathological heart.

Before coming here, I studied about the molecular mechanisms of how some gene mutations induce dilated cardiomyopathy. I clarified that a kinase, CaMKII, is an important factor to induce cardiac dysfunction in dilated cardiomyopathy. From the results, I was interested in the role of kinases in the heart diseases. Kinases / phosphatases regulate crucial aspects of growth and survival through phosphorylation / dephosphorylation of target substrates. Many reports involved in my study demonstrated that processes of cardiac hypertrophy, myocardial infarction, and heart failure are dictated in part by which kinases / phosphatases are involved and also by the intensity and duration of specific enzymatic activities. While research has identified numerous critical regulatory kinases and phosphatases in the myocardium, the intracellular mechanism for temporal regulation of signaling duration and intensity remains obscure. I would like to clarify the mechanism, so I decided to come here. Now, I have focused on an enzyme, which regulates phosphorylated kinases / phosphatases, and have examined the role of the enzyme in the physiological and pathological heart.

News Letter

Reports of Study Abroad

My professional and cultural experiences in the United States

Jun Ikari
Pulmonary, Critical Care, Sleep and Allergy Medicine, Department of Internal Medicine, University of Nebraska Medical Center
(from April 2011)

I have researched at The University of Nebraska Medical Center since April 2011 under the supervision of Professor Stephen I. Rennard who is one of the leading authorities on chronic obstructive pulmonary disease (COPD) around the world.

In Japan, I researched on 'A role of PHF11 in activated B cells'. Polymorphism of the PHF11 is highly associated with high serum IgE levels and clinical severity of asthma. We found exogenous murine Phf11 in activated B cells augments frequencies of class switch recombination to IgE and generation of IgE-secreting long-lived plasma cells.

In the United States, I am evaluating the altered repair function of lung fibroblast that contributes to the development of COPD. Also I am exploring the therapeutic approach to restore the repair function in COPD. As for my advice for studying abroad, I recommend cultivating the ability to research independently, because the autonomy of the individual is valued in the United States. I also think it is important to improve discussion skills in English, because researchers are requested to actively join discussions at a meeting. The experience of communicating in English at the G-COE conferences and the laboratory meetings at the Department of Developmental Genetics has been really great help for me professionally.

I live in the city of Omaha, Nebraska. Omaha is a very quiet, safe and serene place to live. I enjoy watching sports, sharing meals with friends at my home and travelling. I can feel America's dynamism through the vast extent of land and diverse cultures. I want to grow as a person and a researcher utilizing these experiences. I'm deeply grateful that my position here will afford me that opportunity.

With members of the laboratory
Jun Ikari (second from right), Stephen I Rennard (second from left)

How solve the drug lag and how improve Translational Research

Masaya Koshizaka
Duke Clinical Research Institute, Duke University
(from July 2011)

Since 2007, I engaged in improving the management of the clinical trials scientifically and ethically at the Chiba University Clinical Research Center. It is necessary to have the objective data center for clinical trials. I involved in setting up and operating the data center, in order to manage large clinical data properly.

Japan lags behind the other countries in clinical trials.

It is told that it takes more time and money to do clinical trials in Japan than the other Asian countries. It is one reason of the drug lag, the delay of domestic introduction of overseas innovative medicine.

It is necessary to clear up the drug lag, in order to use new drugs for Japanese patients as soon as possible. Thus we have to participate in the global clinical trials. For this goal, I participate in the actual global clinical trials of cardiovascular diseases and diabetes, as a researcher at Duke Clinical Research Institute (DCRI), the top level research institute.

DCRI is in North Carolina, which has nature and enough resources of study. In DCRI there are many research fellows, who came from Australia, Brazil, Canada, China, Denmark, Holland, Italy, and Taiwan.

I could learn not only clinical trials, but also western communication and culture.

After going back to Japan, I would like to improve Japanese clinical researches.

IN DCRI I also participate in the Biomarker project in order to learn about Translational Research (TR). I would like to contribute to TR of Chiba University in the future, too.

At the home of Dr. John H. Alexander (Koshizaka's mentor)
(From left, Koshizaka's family, Alexander's family, and Hideki Hanaoka)

A report of studying abroad at Haverd Medical School

Kaoru Ito
Department of Genetics, Harvard Medical School
(from April 2011)

I did the research about heart failure and its pathophysiology in Chiba University. Since the mechanisms of heart failure are diversified, I studied a molecular biological approach. At the same time, I got interested in the genetic approach. Next generation sequencer (NGS) and the new methods which can be performed in NGS might increase my interest in genetics. And I thought it was a good idea to pursue the pathophysiology of heart failure by investigating cardiomyopathy which is an extreme model of genetic heart failure. So I asked my boss and my superiors where the best lab was to study cardiomyopathy by genetic approach and I got valuable advices. Fortunately, now I work for the lab which is famous for cardiomyopathy.

Our research subjects are familial heart diseases, the large cohort study regarding cardiac hypertrophy and mouse models of heart failure. Now I am engaged in the first and second ones. Because we deal with huge data of genome, RNAseq and ChIPseq and so on, our lab members are divided into two groups, a dry group which is engaged in the computer work and a wet group which is engaged in small animal experiments. Because I am curious about the new technique, I also do some work which is related with a small animal experiment though I am in a dry group.

In our lab, when we conduct experiments which are concerned with NGS, what I need to do is just to prepare the samples because our research assistants and technicians do the other experiments.

I thought that division of labor improves the efficiency. But I make an effort to watch the experiment because I am a beginner in the field. Our lab uses human samples mainly and we can get human samples easier than we do so in Japan, not only blood samples for DNA extraction but also fresh organ samples for RNA extraction. In addition, a lot of collaborations with other institutes are being made and many labs provide their ideas to advance the research. I was surprised at the systematic and effective research environment.

Finally, just before I went to the US to study abroad, the biggest earthquake we have ever experienced hit Japan. So being in anguish over whether I should leave Japan or not, I came to Boston. Now I still think about it. But I believe that I must do what I should do in the US and I will find a way to give something back to Japan after returning to my country.

With members of the laboratory
Kaoru Ito (first from left in top raw), Jonathan.G.Seidman (Professor, first from right in top raw), Cristine.E.Seidman (Professor, third from right in top raw)

The 8th Global COE Workshop

February 19, 2011

Presentation and Discussion by G-COE-RA

1st Lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

The 8th Global COE Workshop that was the fifth workshop in "Presentation and Discussion by G-COE-RA" took place on February 19. Thirty-three G-COE-RAs presented the progress of each research. Some of them talked coolly about the results in an assuming tone, and some kept on talking with much enthusiasm that might be brought from passion to their own research studies, or other might have got nervous for their first experience of presentation in English. The audiences were drawn into their presentations that were full of each RA's characteristics and charm, while also being impressed with the research quality on which each RA is working. Most of the presentations were assertive and sophisticate. Students took English Presentation Seminar, which was introduced at the Graduate School of Medicine and Pharmaceutical Science last summer; we believe it has contributed a lot for their improvement. The participants enjoyed discussions through a barrage of questions made by the students in the Q and A periods. This workshop was very active and fruitful. We have seen the RA grow by increasing experience in presentation and discussion in this manner, and realized the significance and evident progress of the workshop as well as the Global COE Program.

Advanced Medicine Progress Seminar by Seeds Grant Competition Winners 2010

March 8, 2011

The 3rd Auditorium, Chiba University Hospital 3F

We held a seed grant competition for advanced medicine for the purpose of seed exploitation, acceleration of Translational Research (TR) and enhancing young researchers' motivation to do clinical study, at Chiba University. We have been supporting eight selected excellent study proposals in providing research grants and regular discussions, in order to accelerate the realization of TR. An open seminar took place on March 8, 2011 to report progress in these studies.

Each of the studies is aimed at developing tumor markers, diagnostic drug for tumor localization, or novel therapeutic agents and treatments targeting various diseases including neurodegenerative diseases and malignant tumors. From the reports at the seminar, we recognized that the stage of research varied greatly among the studies, however, energetic efforts have been made to promote them toward realizing TR. Two studies we make a continuing support were reported the steady progress compared to last year. We will continue to support by holding this seed grant competition until we will establish a clear trend to promote the research for diagnostic or therapeutic development generated from Chiba University starting from this in-house seed exploitation.

Shinichiro Motohashi
Program Leader,
Seeds Grant Competition

March 29, 2011

Inaugural Joint Scientific Meeting – Medical University of Vienna and Chiba University –

Conference Room, Main Building 2F, Faculty of Medicine, Chiba University

Inaugural Joint Scientific Meeting –Medical University of Vienna (MUV) and Chiba University– was held on March 29, 2011. This was the first event on the academic and research collaboration activities agreed on in 2010 between Medical University of Vienna in Austria and Chiba University. The symposium program was designed by the Chiba University Graduate School of Medicine and Chiba University Hospital in order to encourage the medical research activities between both universities, with supports by Chiba University G-COE program and the Health and Labor Science Research programs for Translational Research.

The symposium began with the opening remarks by Dr. Yoichi Kohno, director of University Hospital. The focus of this workshop was on "The LDL receptor to immature cell diseases". At first, Dr. Hideaki Bujo, Graduate School of Medicine (Chaired by Dr. Takashi Miki, Graduate School of Medicine) made a presentation on the LDL receptor family study overview. Dr. Chiaki Nakaseko, Graduate School of Medicine and University Hospital (Chaired by Dr. Atsushi Iwama, Graduate School of Medicine), then spoke about the prognostic impact of serum soluble LR11 on acute leukemia. The last presentation was on the adipocyte-based gene therapy for interactive serum protein deficiencies by Dr. Masayuki Kuroda, Chiba University Hospital (Chaired by Dr. Koutaro Yokote, Graduate School of Medicine). The symposium finished with the closing remarks by Dr. Haruaki Nakaya, dean of Graduate School of Medicine.

The symposium was much productive with the enthusiastic discussion by many participants for the future collaborative research projects. The joint meeting will be next held at MUV.

Hideaki Bujo
Joint Program Chiba University Office

Message with Selected Slides

Dear President Dr. Saito, dear Colleagues!
I deeply regret that unfortunate events bringing sadness to many Japanese people preclude my participation in this Inaugural Joint Scientific Meeting of our Universities.
My thoughts and hopes are with all of you.
I wish you and your colleagues a successful meeting now, and a rapid recovery from the dire consequences of the powers of nature.
Hoping that we will be able to meet soon,
With best regards,

Wolfgang J. Schneider

The 9th Global COE Workshop

June 4, 2011

Presentation and Discussion by G-COE-RA

1st Lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

The 9th Global COE Workshop that was the sixth workshop in "Presentation and Discussion by G-COE-RA" was held on Saturday, June 4. This year 33 graduate students selected as G-COE-RAs, including the 17 RAs newly selected. The RA has been widely recruited from the related research field of this program, thus the increasing number of departments has been involved in this program every year. In particular, in the Graduate School of Pharmaceutical Sciences, the number of the RAs has doubled from last year to 10 and consequently three departments have newly involved. New RAs made a presentation on their experimental plan, and the RAs selected again this year on research results and progresses additionally in English. In the Q and A periods, each RA was pelted with questions. To respond them smoothly actually requires higher English communicative ability. We are sure that the RAs will further improve the ability making use of program designed for that purpose, including a video of the presentation and Presentation Seminar for scientific seminar in English, in addition to experience in the workshop. Besides the student's mentors, two advisory professors evaluated each presentation. The increasing number of advisory professors newly involved could be a sign for fulfillment and progress of this program.

IMSUT/RCAST - Chiba University Global COE Joint Retreat 2011

"Toward new era in the basic and clinical immunology"

Date: September 17-18, 2011
Place: Oiso Prince Hotel

Toshio Suda
Professor
Department of Cell Differentiation, Keio University School of Medicine

IMSUT/RCAST - Chiba University Global COE Joint Retreat was held for the first time in cooperation with The IMSUT (Institute of Medical Science, The University of Tokyo) & RCAST (Research Center for Advanced Science and Technology, The University of Tokyo) Global COE Program "Center of Education and Research for the Advanced Genome-Based Medicine: For personalized medicine and the control of worldwide infectious diseases". One-hundred and ten graduate students and researchers from the both G-COE programs gathered and studied together for two days, developing new interaction and stimulating active discussion. Dr. Toshio Suda, Professor of Keio University, gave a keynote lecture entitled "Stem Cells and Cancer Stem Cells". The program was organized by the program committee in which members are Drs. Taishin Akiyama and Jun Kunisawa from the IMSUT and Dr. Hiroshi Nakajima from Chiba University. The followings are reports from some participants.

At the poster session, Soichi Tofukuji, G-COE-RA, Department of Immunology, Graduate School of Medicine, Chiba University, received the Best Poster Award.

Kotaro Suzuki

Department of Molecular Genetics, Graduate School of Medicine, Chiba University

The Chiba University G-COE Retreat 2011 was held on September 17 and 18 at Oiso Prince Hotel. This was our 3rd Retreat and IMSUT/RCAST-Chiba University G-COE Joint Retreat. The maximum number of graduate students and PI researchers participated compared with the past 2 times of conventions. Also in the contents, almost all presentations in each field were high quality. In Poster Presentation as well as Oral Presentation, we had in-depth discussion. We believe that this program provided mutual understanding between students and PI.

Hiroshi Ashida

Division of Bacterial infection, The Institute of Medical Science, The University of Tokyo

I attended the "IMSUT/RCAST - Chiba University Global COE Joint Retreat 2011" at Oiso. In this retreat, young scientists and graduate students, who specialize in immunology, from Chiba University and IMSUT presented recent data on oral presentations or poster sessions. Although I am unfamiliar to immunology (I am a bacteriologist), it was good opportunity to motivate myself through discussion and communicate with same generation. In particular, advises and questions from another field specialists to my research subject will provide me turning points to further execute research.

Finally, I thank retreat secretaries, executive committees, and all participants for their support and participation.

Ryuta Uraki

Division of Virology, The Institute of Medical Science, The University of Tokyo

I am a master course's student researching the pathogenicity of influenza virus. I was so nervous because the theme of this seminar was immunology, not virology which is my major. However, in spite of my anxiety, this seminar was so attractive and exciting for me to get fruitful advice about the interesting phenomenon I have focused on from wonderful professors and seniors. Further, this seminar gave me fine chance to present my research orally in English and to communicate with researchers in other fields. I would like to make use of what I learned in this seminar to perform more creative research.

Tomokazu Sumida

Department of Cardiovascular Science and Medicine, Graduate School of Medicine, Chiba University

The G-COE retreat was held at Oiso overlooking the blue ocean and the white beach. As this year's retreat was co-hosted by IMSUT/RCAST and Chiba University, more programs became available and it seemed there was educational consideration for training young researchers.

Many of the presentation based on the latest immunological research provided me with great learning experience, since I usually study about cardiology and do not have much opportunity to encounter basic immunological study. Learning that the immunological system was associated with so many pathophysiological conditions and also finding the possibility of its relevance with cardiovascular diseases, I developed deeper interest in medical science.

During this 2-day meeting, the communication with researchers from other universities through poster sessions and reception, encouraged and motivated me to research harder and deeper. I really appreciate having the opportunity to join this occasion.

Satomi Tanaka

Department of Cellular and Molecular Medicine, Graduate School of Medicine, Chiba University

This year's Global COE Joint Retreat was held in a hotel that faced on Oiso long beach. I felt quite nervous because I had to present our recent work in English in front of a large audience. However, we had a social gathering the night before and dressed in plain clothes, unlike an ordinary academic conference, so we were able to have a more lively discussion in a pleasant atmosphere. It was also a good chance to talk to a lot of researchers from other departments. Furthermore, I was very impressed with the lecture on normal and cancer stem cells presented by Dr. Suda. Thank you for giving me the valuable opportunity.

Yosuke Kurashima

Division of Mucosal Immunology, The Institute of Medical Science, The University of Tokyo

I was participated in the Global COE Joint Retreat on September 17 to 18th. It was a great opportunity for me to learn recent research direction in the medical fields such as Immunology, Infection, and Cancer at once. In the keynote lecture, Prof. Suda from Keio Univ. presented the data indicating the importance of hypoxic microenvironment for the maintenance of hematopoietic stem cells in the stem cell niche. Because "Immune Cell Metabolism" is becoming one of the recent notable fields in the immunology, the experimental results indicating the importance of H1F1a for the regulation of TCA cycle in stem cell niche was very impressive for me. Last but not least, I would like to express my sincere appreciation for setting up this wonderful meeting to the organizers and administrators. I'd definitely want to participate next time, if there is a chance like this time.

The 6th Chiba University Global COE Symposium

Immune System Regulation toward Disease Control

November 30, 2011
Hotel New Otani Makuhari, Chiba











The G-COE Program held the 6th Chiba University Global COE Symposium at Makuhari, on Wednesday, November 30th, co-organized by IMSUT & RCAST G-COE Program, The University of Tokyo. This sixth symposium, entitled "Immune System Regulation toward Disease Control", focused on immune-related diseases. Since the regular annual meeting of the Japanese Society for Immunology was held for 3 days until the preceding day at the Makuhari Messe, the symposium was filled with enthusiasm. Participants listened intently to presentations and discussed topics of mutual interest heatedly. The fact that the hall was fully packed with audience suggests that we successfully lined up attractive researchers from home and abroad. A total of 15 talks were presented in symposium, starting with a session on lymphocyte development and homeostasis, followed by those on immunological memory and T lymphocyte function, and ending with one on allergy and inflammation. Personally, I was most interested in Dr. Meinrad Busslinger's presentation about a genome-wide analysis of the transcriptional regulation in B cells by ChIP-Seq and RNA-Seq. His lecture provided me with useful information to precede my study based on the same technology he used. At lunchtime, I happened to sit next to him and fortunately talked with him directly. I asked him some questions and discussed new insights into the genome-wide study. Additionally, I led the symposium as MC and made several announcements in English. I also took over the management of the symposium cooperating with G-COE office members. This was my first time to do MC work and management, so I found some points to improve at next chance. However, it was a great experience for me. I believe this symposium will transmit new information toward the rest of the world from Chiba University, and lead to progress in the research of immunological field in the future.

Atsushi Onodera
G-COE Independent Research Associate, Dept. of Immunology

The G-COE Program held the 6th Chiba University Global COE Symposium at Makuhari in Chiba prefecture and I could learn the latest immunological knowledge. At this symposium, the seminar of Dr. Chen Dong who is one of the authorities on Th17 cell research was very impressive. Not only could I learn the most recent findings in Th17 cells from his study, but this seminar also increased my motivation for my study. Additionally, I could gain a further understanding of signaling pathway and cytokines for the immune system. Overall, this seminar was beneficial for advancing my research. Moreover, when I saw the researchers vigorously discussing on the newest topics, I persuaded myself that research in the immunological field made further progress in the near future. By using the knowledge acquired at this symposium, I would like to work hard and contribute to the development of medicine and bioscience.

I worked as a staff member in this symposium and had the opportunities to speak with some researchers directly. However, I keenly felt the importance of English speaking ability for communication. I will make a conscious effort to study English in order to be able to communicate more smoothly when participating in the next symposium.

Yukiko Watanabe
G-COE-RA
Dept. of Immunology







G-COE Seminar

Learn from the forefront
For our graduate students, top-ranked world researchers gave lectures including recent findings of their studies.







Allergy Clinical Conference

Go beyond the borders
In the conference researchers from Dept. of Allergy and Clinical Immunology, Dept. of Pediatrics, Dept. of Otorhinolaryngology and Dept. of Dermatology cross-disciplinarily discuss allergic diseases.


Basic Science Joint Meeting (BSJM)

Coordinated by PhD student working group

This seminar has been held every week coordinated by graduate students working group.

59. January 7, 2011
Yuichi Michikawa, Senior Researcher, RadGenomics Project, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences

60. January 14, 2011
Harukiyo Kawamura, Assistant Professor, Dept. of Medical Physiology

61. January 21, 2011
Kentaro Takahashi, Graduate Student, Dept. of Molecular Genetics

62. January 28, 2011
Chiaki Iwamura, Assistant Professor, Dept. of Immunology

63. February 4, 2011
Akira Matsuura, Professor, Div. of Nanoscience, Graduate School of Advanced Integration Science/Department of Biology, Faculty of Science

64. February 18, 2011
Shinichiro Motohashi, Associate Professor, Dept. of Medical Immunology

65. February 25, 2011
Ayako Inamine, G-COE Fellow, Dept. of Otolaryngology, Head and Neck Surgery

66. April 1, 2011
Haruko Takano, Post Doctoral Fellow, Biomedical Research Center

67. April 8, 2011
Mitsujirou Osawa, Lecturer, Dept. of Cellular and Molecular Medicine

68. April 15, 2011
Kouya Suzuki, Graduate Student, Dept. of Immunology

69. April 22, 2011
Junji Yamashita, Research Fellow, Dept. of Immunology

70. May 6, 2011
Ayako Matsumoto, JSPS Fellow, Dept. of Pharmacology/Dept. of Neurobiology

71. May 13, 2011
Koji Onomoto, Assistant Professor, Div. of Molecular Immunology, Medical Mycology Research Center

72. May 20, 2011
Hideki Hanaoka, Director/Professor, Chiba University Hospital Clinical Research Center

73. May 27, 2011
Jing Pan, G-COE RA, Dept. of Developmental Genetics

74. June 4, 2011
Hiroyuki Ishikawa, Associate Professor, Dept. of Biology, Graduate School of Science

75. June 10, 2011
Akio Matsumoto, Associate Professor, Dept. of Pharmacology

76. June 17, 2011
Masayuki Kuroda, Associate Professor, Center for Advanced Medicine

77. June 24, 2011
Atsushi Onodera, Assistant Professor, Dept. of Immunology

78. July 1, 2011
Tatsuya Sato, Assistant Professor, Dept. of Developmental Biology

79. July 8, 2011
Takaaki Konuma, Graduate Student, Dept. of Cellular and Molecular Medicine

80. July 15, 2011
Masaya Yokota, Graduate Student, Dept. of Molecular Genetics

81. July 22, 2011
Nobuhide Tsuruoka, Clinical Fellow, Dept. of Reproductive Medicine/Dept. of Developmental Genetics

82. September 2, 2011
Takeshi Murata, Associate Professor, Graduate School of Science

83. September 9, 2011
Tomoaki Tanaka, Lecturer, Dept. of Clinical Cell Biology and Medicine

84. September 16, 2011
Tohru Minamino, Lecturer, Dept. of Cardiovascular Science and Medicine

85. October 7, 2011
Shunsuke Nakamura, Graduate Student, Dept. of Cellular and Molecular Medicine

86. October 14, 2011
Arifumi Iwata, Clinical Fellow, Dept. of Molecular Genetics

87. October 28, 2011
Asami Hanazawa, Graduate Student, Dept. of Immunology

88. November 4, 2011
Motoo Kitagawa, Associate Professor, Dept. of Molecular and Tumor Pathology

89. November 11, 2011
Tetsuhiro Chiba, Assistant Professor, Dept. of Medicine and Clinical Oncology

90. November 18, 2011
Daiju Sakurai, Lecturer, Dept. of Otolaryngology, Head and Neck Surgery

91. November 25, 2011
Naohiko Seki, Associate Professor, Dept. of Functional Genomics

92. December 2, 2011
Susumu Kawamoto, Professor, Molecular Biology, Medical Mycology Research Center

93. December 9, 2011
Soichi Tofukuji, Graduate Student, Dept. of Immunology/Kazusa DNA Research Institute

94. December 16, 2011
Fumihiro Ishibashi, Graduate Student, Dept. of Immunology/Dept. of Thoracic Surgery

New Members

RAs Newly Selected in 2011


Kenta Watanabe
Department of Clinical Pharmacology


Taiji Nakano
Department of Pediatrics


Satomi Tanaka
Department of Cellular and Molecular Medicine


Aika Nojima
Department of Cardiovascular Science and Medicine


Mani Kohno
Department of Developmental Genetics


Go Sasahara
Department of Otorhinolaryngology, Head & Neck Surgery


Tomohiko Makiyama
Laboratory of Chemical Pharmacology


Jing Pan
Department of Developmental Genetics


Muradil Mutallip
Department of Otorhinolaryngology, Head & Neck Surgery

Jun Matsumoto
Department of Clinical Pharmacology

Xin Wang
Department of Biochemistry

Yoshiki Kaneko
Department of Molecular Biology and Oncology

Eriko Suwa
Department of Geriatric Pharmacology and Therapeutics

Kenichi Ishibashi
Department of Molecular Cell Biology

Hiroyuki Suzuki
Department of Molecular Imaging and Radiotherapy

Moeko Hino
Department of Pediatrics

Tadashi Shiohama
Department of Pediatrics

G-COE Collaborators

Itsuko Ishii
Associate Professor, Department of Clinical Pharmacology

Noritaka Ariyoshi
Associate Professor, Division of Pharmacy, Chiba University Hospital

Koichi Ueno
Professor, Department of Geriatric Pharmacology and Therapeutics

Toshihiko Murayama
Professor, Laboratory of Chemical Pharmacology

Mitsutoshi Yoneyama
Professor, Division of Molecular Immunology, MMRC

Shinobu Saijo
Associate Professor, Division of Molecular Immunology, MMRC

G-COE Independent Research Associate

Tumes Damon
Department of Immunology

G-COE Fellows

Yusuke Endo
Department of Immunology

Kenta Shinoda
Department of Immunology

Masaya Koshizaka
Chiba University Hospital Clinical Research Center

Shunsuke Furuta
Department of Molecular Genetics

Upcoming Events

The 10th Chiba University G-COE Workshop (Presentation and Discussion by G-COE-RA)
Date: February 11, 2012
Venue: The 1st Lecture Hall, Main Building 1F, Faculty of Medicine, Chiba University

CCRC 10th Anniversary and CFMRC Inauguration Symposium
Date: March 19, 2012
Venue: The Auditorium, Medical and Pharmaceutical Science Building II 1F, Chiba University

The 11th Chiba University G-COE Workshop (Presentation and Discusslon by G-COE-RA)
Date: June 2012

G-COE Retreat 2012
Date: September 8-9, 2012
Venue: Seimei-no-Mori Resort

The University of Auckland – RCAI – Chiba University Symposium (tentative)
Date: Autumn 2012 / Venue: New Zealand

The 7th Chiba University G-COE Symposium
Date: January 2013

The 12th Chiba University G-COE Workshop (Presentation and Discussion by G-COE-RA)
Date: February 2013

Editor's Note

Here is vol.4 of our newsletter. There were earthquakes, tsunami and a nuclear power plant accident last year, but medical and clinical researches have steadily progressed. Seeing from vol. 1, you may recognize how the promotion of this G-COE program has contributed to provide a better environment for young researchers who aim to do medical research or develop treatments. Also events have expanded in many different directions from an international perspective. We are sure that this G-COE program will produce many young researchers capable of working on the international stage. (Kazuo Suzuki, G-COE Coordinator)

Chiba University Global COE Program
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6. Achievements

Publications by Core Members (Selected)

2008

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8. Cervigni F, Suzuki Y, Ishii T, Hata A. Spatial accessibility to pediatric services. ***J Community Health***. 2008; 33(6): 444-448.

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International Conference Presentations by Core Member's Group

2008 Speakers	Title
Bujo H, Takahashi M, Jiang M, Ohwaki K, Noike H, Schneider WJ, Saito Y, Shirai K.	Circulating levels of soluble form of LR11, a novel migration regulator of intimal SMC, are increased in subjects with coronary stenosis.
Nakayama T.	Initiation and maintenance of Th2 cell identity: Regulation by Polycomb and Trithorax group molecules.
Nakayama T.	Bmi1 regulates memory Th2 cell survival via repression of the Noxa gene.
Kambe N, Nakamura Y, Okafuji I, Nishikomori R, Kanazawa N, Matsue H.	A case of early-onset sarcoidosis who showed spontaneous regression of his clinical manifestations but inherited skin eruption to his baby: What should we call this systemic inflammatory granulomatosis associated with NOD2 mutation?
Taniguchi M.	Identification of IL-17RB+ NKT cells preferentially producing IL-13 as a novel subset responsible for development of AHR.
Shimizu A, Kambe N, Togowa Y, Kamada N, Ohki K, Tomiita M, Matsue H.	A case of idiopathic thrombocytopenic purpura suggesting an initial manifestation of systemic lupus erythematosus.
Kambe N, Ma F, Nakahata T.	Direct development of primate connective tissue-type mast cells from immature state of $CD34^{+}$ hemangioblastic progenitors, independently from the development pathway of mucosal-type mast cells.
Nakamura Y, Kambe N, Matsue H.	Cryopyrin-associated IL-1β secretion in mast cells and a role played by mast cells in autoinflammatory disorders.
Motohashi S, Nagato K, Fujiwara T, Taniguchi M, Nakayama T.	Phase I/II study of αGalCer-pulsed dendritic cell in patients with advanced or recurrent non-small cell lung cancer.
Kamada T.	Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas.
Jiang M, Motomura K, Bujo H, Saito Y.	Deficiency of LR11, an urokinase receptor signal enhancer, accelerates adiposity in mice through the acceleration of adipocyte differentiation.
Kitamura H, Ito M, Yuasa T, Kikuguchi C, Hijikata A, Ohara O.	Genome-wide characterization of transcripts translationally regulated by bacterial LPS.
Fushimi K, Uzawa K, Ishigami T, Saito K, Shimada K, Murano A, Nakatsuru M, Ogawara K, Shiiba M, Tanzawa H.	Identification of Genes Related to Radioresistance of Oral Cancer.
Shiiba M, Ishigami T, Nomura H, Fushimi K, Yamano Y, Shinozuka K, Sakamoto Y, Ono K, Ogawara K, Bukawa H, Yokoe H, Uzawa K, Tanzawa H.	Clinical Observations of Postoperative Delirium After Surgery for Oral Carcinoma.
Shinozuka K, Uzawa K, Kato Y, Ono K, Hayashi Y, Koike H, Higo M, Yokoe H, Tanzawa H.	Overexpression of Septin1 in Oral Carcinoma.
Yamano Y, Uzawa K, Nomura H, Nakashima D, Kouzu Y, Endo Y, Kawasaki K, Watanabe T, Bukawa H, Tanzawa H.	Grp94 as a Target in Human Oral Carcinogenesis.
Hata A, Onouchi Y.	A possible personalized medicine with a functional polymorphism in ITPKC to prevent coronary artery complications in Kawasaki disease.
Ito K, Akazawa H, Tamagawa M, Ogawa W, Kasuga M, Nakaya H, Komuro I.	PDK-1 is required for β-adrenergic response and cell survival in the hearts.
Tateno K, Moriya K, Miura K, Minamino T, Komuro I.	In-situ Activation of Constituent Platelets Enhance the Therapeutic Capacity of Peripheral Blood Mononuclear Cell Implantation.
Toko H, Kayama Y, Takahashi H, Minamino T, Komuro I.	Activation of CaMKIIdelta is Critically Involved in Mutated Cardiac Alpha-Actin Induced Dilated Cardiomyopathy.
Uchiyama R, Takano H, Ueda K, Niitsuma Y, Hasegawa H, Komuro I.	Erythropoietin promotes angiogenesis and prevents heart failure after myocardial infarction.
Yoshida M, Shiojima I, Komuro I.	Pitavastatin attenuates doxorubicin-induced cardiotoxicity through anti-oxidant effect.
Komuro I.	A Novel Cardiomyocyte Differentiation.
Yasuda H, Suzuki K.	Preparedness of Influenza in the commuter towns of Tokyo; Analysis of model cities; Analysis of model cities and a metaphor model.
Nakayama T.	Regulation of memory Th2 cell survival and function by the Polycomb group and Trithorax group gene products.
Okamoto Y.	Present situation and treatment of allergic rhinitis.
Komuro I.	Myocardial and Vascular Rebirth.
Kamada T.	Carbon Ion Radiotherapy for Unresectable Primary Bone Sarcoma of the Spine.
Keerthikumar S, Raju R, Kandaswamy K, Hijikata A, Ramabadran S, Balakrishnan L, Ahmed M, Rani S, Selvan LD, Somanathan DS, Ray S, Bhattacharjee M, Gollapudi S, Ohara O, Pandey A, Mohan S.	Primary Immunodeficiency disease database: A discovery tool for the genomics research.
Tsujii H.	Carbon Ion RT at NIRS: Clinical protocols and fractionation regimen.
Tsujii H.	Current indications for proton and carbon ion RT, Part III: Sarcoma.
Saito K, Imai MA, Uzawa K, Ogawara K, Tanzawa H, Shirasawa H.	Oncolytic Activity of Sindbis Virus for Oral Cancer Cells.
Sakuma K, Uzawa K, Ishigami T, Sakamoto Y, Ogawara K, Shiiba M, Bukawa H, Yokoe H, Tanzawa H.	Enhancement of Radiation Sensitivity in oral Squamous Cell Carcinoma by Inhibition of ICAM2.
Yamatoji M, Uzawa K, Ono K, Ogawara K, Onda T, Shibahara T, Nakajima D, Saito K, Kasamatsu A, Shiiba M, Bukawa H, Yokoe H, Tanzawa H.	Gelsolin-like Actin-Capping Protein(CapG) may Serve as Useful Target to Identify and Treat Patients with Advanced Oral Squamous-Cell Carcinoma.
Yasuda H, Suzuki K.	Preparedness of Influenza in the commuter towns of Tokyo; Analysis of model cities; Analysis of model cities and a metaphor model.
Bujo H, Saito Y.	Mechanisms by which fat cells become villains.
Ono Y, Nakamura Y, Kambe N, Kamada N, Matuse H.	A case of psoriasis-like eczematous drug eruption due to etanercept.

	Meeting	City	Country	Month・Year
	American College of Cardiology Scientific Sessions	Chicago	U.S.A.	Apr.08
	Allergy Symposium Program La Jolla Institute for Allergy and Immunology (LIAI)	San Diego	U.S.A.	Apr.08
	Experimental Biology 2008	San Diego	U.S.A.	Apr.08
	V International Congress on Familial Mediterranean Fever and Systemic Autoinflammatory Diseases	Rome	Itary	Apr.08
	Collegium Internationale Allergologicum 2008	Curacau	Netherland	May.08
	2nd International Conference on Cutaneous Lupus Erythematosus	Kyoto	Japan	May.08
	International Investigative Dermatology 2008	Kyoto	Japan	May.08
	International Investigative Dermatology 2008	Kyoto	Japan	May.08
	2008 American Society of Clinical Oncology Annual Meeting	Chicago	U.S.A.	May.08
	44th ASCO Annual Meeting	Chicago	U.S.A	May.08
	American Diabetes Association 68th Scientific Sessions	San Francisco	U.S.A.	Jun.08
	33rd FEBS Congress and 11th IUBMB Conference	Athens	Greece	Jun.08
	The IADR 86th General Session & Exhibition	Toronto	Canada	Jul.08
	The IADR 86th General Session & Exhibition	Toronto	Canada	Jul.08
	The IADR 86th General Session & Exhibition	Toronto	Canada	Jul.08
	The IADR 86th General Session & Exhibition	Toronto	Canada	Jul.08
	The 2008 EAUHGS Symposium	Sapporo	Japan	Jul.08
	5th Annual Symposium of the American Heart Association Council on Basic Cardiovascular Sciences	Keystone	U.S.A.	Jul.08
	5th Annual Symposium of the American Heart Association Council on Basic Cardiovascular Sciences	Keystone	U.S.A.	Jul.08
	5th Annual Symposium of the American Heart Association Council on Basic Cardiovascular Sciences	Keystone	U.S.A.	Jul.08
	5th Annual Symposium of the American Heart Association Council on Basic Cardiovascular Sciences	Keystone	U.S.A	Jul.08
	5th Annual Symposium of the American Heart Association Council on Basic Cardiovascular Sciences	Keystone	U.S.A.	Jul.08
	Hearts of Japan	San Diego	U.S.A.	Aug.08
	The second China-Japan Colloquium of mathematical biology	Okayama	Japan	Aug.08
	Immunochemistry & Immunobiology	Oxford	U.K.	Aug.08
	Confence in Dalian Developing Area	Dalian	China	Aug.08
	Stems of the Heart	Boston	U.S.A.	Sep.08
	ASTRO The 50th Annual Meeting	Boston	U.S.A	Sep.08
	Human Genome Meeting (HGM2008)	Hyderabad	India	Sep.08
	Radiotherapy with proton and Ions ESTRO	Heidelberg	Germany	Oct.08
	Radiotherapy with proton and Ions ESTRO	Heidelberg	Germany	Oct.08
	The 13th World Congress on Advances in Oncology and 11th International Symposium on Molecular Medicine	Creta	Greece	Oct.08
	The 13th World Congress on Advances in Oncology and 12th International Symposium on Molecular Medicine	Creta	Greece	Oct.08
	The 13th World Congress on Advances in Oncology and 11th International Symposium on Molecular Medicine	Creta	Greece	Oct.08
	The NIMS 2008 Conference & The 4th East Asia SIAM Conference	Daejeon	Korea	Oct.08
	US-Japan medical joint cooperation program meeting	Hanoi	Vietnam	Oct.08
	The 10th China-Japan Joint Meeting of Dermatology	Hangzhou	China	Oct.08

International Conference Presentations by Core Member's Group

2008

Speakers	Title
Taniguchi M.	Role of NKT cell in innate and acquired immunity.
Kamada T.	Carbon Ion Radiotherapy at NIRS.
Ito K, Akazawa H, Tamagawa M, Ogawa W, Kasuga M, Nakaya H, Komuro I.	PDK1 plays crucial roles in beta-adrenergic response and cell survival in the heart.
Moriya J, Minamino T, Tateno K, Orimo M, Miyauchi H, Okada S, Shimizu I, Nojima A, Yokoyama M, Komuro I.	Semaphorin3E is a Novel Angiogenic Regulator.
Bujo H, Jiang M, Motomura K, Ohwaki K, Yamazaki H, Saito Y.	sLR11, an enhancer of intimal smooth muscle cell migration, inhibits fat accumulation in mice as a novel adipogenesis regulator.
Hattori S, Mashimo Y, Funamizu M, Shimojo N, Okamoto Y, Kohono Y, Hata A, Suzuki Y.	CD14 -550C/T polymorphism modifies the effect of daycare attendance on total and specific IgE levels in children.
Kamada T.	Carbon Ion Radiotherapy for Sacral Chordoma.
Suzuki K.	Xiamen University Medical School.
Nakayama T.	Combination therapy of In vitro expanded natural killer T cells and αGalactosylceramide pulsed APCs in patients with recurrent head and neck carcinoma.
Suzuki K.	Imaging of Vasculitis.
Suzuki K.	Steering Meeting on EUVAS/EULAR.
Moriya J, Minamino T, Komuro I.	A pathological role of Semaphorin3E/PlexinD1 in impaired angiogenesis of diabetes.
Ohara O.	Symposium for PID in Asia.

2009

Speakers	Title
Motohashi S.	Activation of tumor infitrating Vα24 NKT cells after preoperative α-Galactosylceramide-pulsed dendritic cell treatment.
Nakayama T.	Regulation of memory Th1/Th2 cell survival and function by the Polycomb group and Trithorax group gene products.
Okamoto Y, Kunii N, Horiguchi S, Uchida T, Sakurai D, Motohashi S, Taniguchi M, Nakayama T.	Immunotherapy of nasal submucosal injection of α-Galactosylceramide-pulsed antigen presenting cells or with combination of intra-arterial infusion of activated natural killer T cells in patients with head and neck squamous cell cancer.
Terashima A, Watarai H, Inoue S, Sekine E, Nakagawa R, Hase K, Iwamura C, Nakajima H, Nakayama T, Taniguchi M.	A novel subset of mouse NKT cells bearing the IL-17 receptor B contributes to the development of airway hyperreactivity.
Tokushisa T, Sakamoto A, Arima M, Hatano M.	Possible roles for Bcl6 in differentiation of germinal center B cells.
Aratani Y, Suzuki K.	Phagocyte NADPH-oxidase deficiency promotes zymosan-induced acute lung inflammation.
Chang He T, Nagao T, Nakayama K, Suzuki K.	Modulation of endothelial cell functions by intravenous immunoglobulin in vitro.
Furutani M, Kameoka Y, Takahashi K, Aratani Y, Nagi-Miura N, Ohno N, Nagao T, Suzuki K.	Synthetic polyclonal immunoglobulin.
Hirahashi J, Kawahata K, Hishikawa K, Fujita T, Arita M, Nagao T, Suzuki K, Nakakuki M, Saiga K.	Dietary enrichment with eicosapentanoic acid (EPA) prevents antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.
Kameoka Y, Furutani M, Suzuki K.	Evaluation of variety of artificial poly-clonal γ-globulin.
Kawachi S, Nunoi H, Suzuki K.	Treatment of severe ARDS (including H5N1-FARDS) with IVIg -From the Cases of NHP-Hanoi-.
Kobayashi S, Suzuki K, Fujimoto S.	New consensus, definition, classification and system for diagnosis of vasculitis from EULAR and ACR meeting held in Zurich.
Muso E, et al.	IVIg therapy for MPO-ANCA positive MPA-For further effort to establish the evidence in Japan-.
Ohno N, Suzuki K.	Analysis of Cytokine Production by PBMC in Vitor Stimulated with Solid Phase IVIg.
Suzuki K.	Immunomodulatory therapy for vasculitis with synthetic IVIG.
Tomizawa K, Nagao T, Osahima M, Kobayashi K, Suzuki K.	Decreased of Risk Epitpies of MPO-ANCA with Remission: Preliminary Analysis.
Uno K, Mso E, Ihara T, Suzuki K.	Comparison of plasma cytokine/chemokine levels and IFN-α production capacity amongst healthy subjects, MPO-ANCA nephritis patients, and IgA nephritis patients.
Nakayama T.	Regulation of memory Th1/Th2 cell survival and function by the Polycomb group and Trithorax group gene products.
Suzuki K.	Preparedness for the spread of influenza: Prohibition of Traffic, school closure, and vaccination of children in the commuter towns of Tokyo.
Bujo H.	Oxidized LDL and atherosclerosis; Expected role of probucol.
Suzuki K.	Clinical pictures and risk parameters of avian influenza (H5N1) infection in Vietnam.
Shimojo N, Inoue Y, Suzuki Y, Kohno Y.	Association of RANTES Promoter Gene Polymorphisms with Respiratory Syncytial Virus Bronchiolitis in The Japanese Population.
Maehara Y, Kawachi S, Nagao T, Todaka R, Jun Z, Oshima M, Suzuki K.	Cytokines and chemokines in the early phase of mice ventilator-induced lung injury model in mice.
Kamada T, Sugahara S, Tsuji H, Serizawa I, Imai R, Okada T, Tsujii H.	Carbon Ion Radiotherapy in Bone and Soft Tissue Sarcomas.
Kamada T, Tsujii H.	Carbon Ion Radiotherapy: Clinical Study the Japanese Way.

Meeting	City	Country	Month・Year
Japan-German Immunology Seminar 2008 Immune Regulation in Health and Disease	Fukuoka	Japan	Nov.08
1st National Innovation Forum for Medicine 2008	Berlin	Germany	Nov.08
American heart association Scientific Sessions 2008	New Orleans, Louisiana	U.S.A.	Nov.08
American heart association Scientific Sessions 2008	New Orleans, Louisiana	U.S.A.	Nov.08
American Heart Association Scientific Sessions 2008	New Orieans	U.S.A.	Nov.08
Annual meeting of ASHG	Philadelphia	U.S.A.	Nov.08
14th Annual Meeting of the Connective Tissue Oncology Society	London	U.K.	Nov.08
Xiamen University Medical School Meeting	Xiamen	China	Nov.08
The Second International Cell Therapy Conference Present and Future of Cell Therapy	Seoul	Korea	Nov.08
2nd Intenational Symposium for Bioimaging in Queenstown	Queenstown	New Zealand	Nov.08
Steering Meeting on EUVAS/EULAR	Zurich	Switzerland	Dec.08
The 6th Korea-Japan Joint Symposium on Vascular Biology	Kanazawa	Japan	Dec.08
PIDJ network: DNA Analysis	Yokohama	Japan	Dec.08

Meeting	City	Country	Month・Year
The 1st Chiba University G-COE Symposium	Tokyo	Japan	Jan.09
The 1st Chiba University G-COE Symposium	Tokyo	Japan	Jan.09
The 1st Chiba University G-COE Symposium	Tokyo	Japan	Jan.09
The 1st Chiba University G-COE Symposium	Tokyo	Japan	Jan.09
The 1st Chiba University G-COE Symposium	Tokyo	Japan	Jan.09
International Forum on Inflammation-2009, IVIg treatment and development of synthetic IgG	Tokyo	Japan	Jan.09
International Forum on Inflammation-2009, IVIg treatment and development of synthetic IgG	Tokyo	Japan	Jan.09
International Forum on Inflammation-2009, IVIg treatment and development of synthetic IgG	Tokyo	Japan	Jan.09
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International Forum on Inflammation-2009, IVIg treatment and development of synthetic IgG	Tokyo	Japan	Jan.09
International Forum on Inflammation-2009, IVIg treatment and development of synthetic IgG	Tokyo	Japan	Jan.09
International Forum on Inflammation-2009, IVIg treatment and development of synthetic IgG	Tokyo	Japan	Jan.09
2009 International Symposium-Nutritional, Medical and Social Sciences for Children-	Tokushima	Japan	Jan.09
International Symposium Infectious Diseases	Tokyo	Japan	Feb.09
PICASSO investigator meeting	Seoul	Korea	Mar.09
Infectious Diseases Workshop Modeling	Murramarang	Australia	Mar.09
American Academy of Allergy, Asthma and Immunology 2009	Washington DC	U.S.A.	Mar.09
2009 International Anesthesia Research Society Annual Meeting	San Diego	U.S.A.	Mar.09
NIRS-ETOILE Joint Symposium 2009 on Carbon Ion Radiotherapy	Lyon	France	Mar.09
NIRS-ETOILE Joint Symposium 2009 on Carbon Ion Radiotherapy	Lyon	France	Mar.09

International Conference Presentations by Core Member's Group

2009 Speakers	Title
Taniguchi M.	Case study: Establishing a translational platform for development of novel therapeutics to allergy in Japan.
Dashtsoodol N, Watarai H, Sakata S, Taniguchi M.	NKT precursor cells in adult thymus.
Kunii N, Motohashi S, Yamamoto H, Okita K, Nagato K, Horiguchi S, Taniguchi M, Okamoto Y, Nakayama T.	Combination therapy of activated NKT cells and αGalCer-pulsed antigen presenting cells in patients with recurrent head and neck cancer.
Motohashi S, Nagato K, Yoshino I, Taniguchi M, Nakayama T.	A Phase I-II study of αGalCer-pulsed antigen presenting cells in patients with advanced or recurrent non-small cell lung cancer.
Nakayama T.	iNKT cell based immunotherapy for cancer.
Tashiro T, Inoue S, Chiba T, Kakimoto K, Omori-Miyake M, Nakagawa R, Fujii S, Shimizu K, Hirokawa T, Watarai H, Mori K, Taniguchi M.	Newly synthesized glycolipids potentiate to produce large amount of IFN-γ in vivo.
Terashima A, Watarai H, Inoue S, Sekine E, Nakagawa R, Hase K, Iwamura C, Watarai H, Nakayama T, Taniguchi M.	Novel NKT cell subset bearing IL-17RB is responsible for induction of AHR.
Watarai H, Iida M, Sakata S, Nagata Y, Dashtsoodol N, Sekine E, Inoue S, Hongo N, Fujii S, Shimizu S, Kawamoto H, Koseki H, Taniguchi M.	Generation of NKT cells with desired function from embryonic stem cells and induced pluripotent stem cells.
Watarai H, Nagata Y, Sakata S, Rybouchkin A, Koseki H, Fujii S, Dashtsoodol N, Taniguchi M.	Generation of NKT cells in vitro from Cloned ES cell line.
Sakuma K, Uzawa K, Nomura H, Ogoshi K, Kato Y, Koike H, Ono K, Shiiba M, Bukawa H, Yokoe H, Tanzawa H.	Overexpression and Altered Subcellular Localization of ATG16L1 in Squamous cell Carcinoma.
Yamano Y, Uzawa K, Shinozuka K, Fushimi K, Ishigami T, Kouzu Y, Higo M, Iyoda M, Ogawara K, Shiiba M, Bukawa H, Yokoe H, Tanzawa H.	Decreased Expression of CEACAM1 in Oral Squamous Cell Carcinoma.
Yamatoji M, Uzawa K, Onda T, Shibahara T, Nakajima D, Saito K, Kasamatsu A, Sakamoto Y, Shiiba M, Bukawa H, Yokoe H, Tanzawa H.	LIN-7C/VELI3/MALS-3 is an Essential Component in Metastasis of Oral Cancer.
Suzuki K, Hamano Y.	Role of the 'Man-1' cluster gene region on chromosome-1 in response in MPO-ANCA vasculitis genetic dissection of vasculitis, MPO-ANCA production, and related traits in scg/kj mice.
Suzuki K.	Myeloperoxidase and the heart.
Tomizawa K, Nagao T, Saiga K, Oshima M, Kobayashi K, Nakayama T, Tanokura M, Suzuki K.	Association of risk epitopes of MPO-ANCA with renal failure in SCG/Kj mice showing crescentic glomerulonephritis.
Kamada T.	The past, present, and future of carbon ion radiotherapy at NIRS-HIMAC.
Kohno Y.	Factors Related with Atopic Dermatitis in Early Childhood: a Birth Cohort Study.
Nakayama T, Hirahara K, Yamashita M.	ROG, repressor of GATA, regulates Th2-driven allergic airway inflammation and airway hyperresponsiveness.
Hijikata A, Raju R, Keerthikumar S, Ramabadran S, Balakrishnan L, Pandey A, Mohan S, Ohara O.	Mutation@A Glance: A New Bioinformatics Tool for Mutation Analusis in Primary Immunodeficiency Diseases.
Imai K, Nonoyama S, Oshima K, Kanegane H, Miyawaki T, Ohara O, Takemori T, Hara T.	Primary Immunodeficiency Database Network in Japan.
Keerthikumar S, Ramabadran S, Raju R, Balakrishnan L, Hijikata A, Pandey A, Ohara O, Mohan S.	RAPID: Resource of Asian Primary Immunodeficiency Diseases An Integrated Informational Platform.
Furutani M, Kameoka Y, Takahashi K, Aratani Y, Nagi-Miura N, Ohno N, Nagao T, Suzuki K.	Synthetic polyclonal immunoglobulin.
Iwasawa M, Miyakawa T, Takahashi Y, Inafuku K, Matsue H, Nishimura K.	Chromoblastomycosis and subcutaneous phaeohyphomycosis caused by Exophiala bergeri and E. Xenobiotica in immunocompromised patients.
Bujo H.	Translational research started from two pathological cells - intimal smooth muscle cell and abdominal adipocyte.
Yoshida N, Sakamoto A, Kitayama D, Arima M, Hatano M, Koike T, Tokuhisa T.	IL-4 and IL-21 inversely regulate CXCR4 expression on activated B cells.
Bujo H, Jiang M, Ohwaki K, Saito Y.	Circulating sLR11, essential for the angiotensin II-induced intimal smooth muscle cell migration, is a biomarker of carotid atherosclerosis.
Fujimoto S, Kobayashi S, Suzuki K.	Incidence and clinical phenotype of ANCA-associated renal vasculitis: comparison between Japan and the UK.
Hirahashi J, Kuwahara K, Arita M, Nagao T, Suzuki K, Hishikawa K, Fujita T.	Dietary enrichment with eicosapentanoic acd (EPA) prevents anti-neutrophils cytoplasmic antibody (ANCA)-associated vasculiits.
Ito-Ihara T, Muso E, Kobayashi S, Uno K, Tamura N, Yamanishi Y, Fukatsu A, Watts RA, Scott DG, Jayne DR, Suzuki K, Hashimoto H.	A comparative study of the diagnostic accuracy of ELISA systems for the detection of anti-neutrophil cytoplasm antibodies available in Japan and Europe.
Muso E, Joh K, Ihara T, Iwasaki Y, Komiya T, Suzuki K.	Specific cytokines and chemokines as the predictor of clinical and pathological activity and chronicity in patients with ANCA-ANCA-positive MPA.
Oharaseki T, Yokouchi Y, Wakayama M, Ihara F, Yamada H, Suzuki K, Naoe S, Takahashi K.	Histopathology of late-stage arteritis in murine systemic vasculitis induced by polysaccharide of Candida albicans, as animal model of Kawasaki disease.
Suzuki K, Tomizawa K, Nagao T, Kobayashi S, Muso E, Yumura W, Sasaki T, Hotta O, Harabuchi Y, Homma S, Yamanishi Y, Lund, Sweden and Copenhagen, DenmarkNishii M, Jayne D, Rasmussen N, Nakayama T, Hashimoto H.	Japan-UK-EU Project Members. Risk Epitopes of MPO-ANCA in Patients with MPA in Japan.

Meeting	City	Country	Month・Year
Biomedical Asia 2009-Translatioonal Research Asia Summit	Singapore	Singapore	Mar.09
The 5th International Symposium on CD1/NKT Cells	Kamakura	Japan	Mar.09
The 5th International Symposium on CD1/NKT Cells	Kamakura	Japan	Mar.09
The 5th International Symposium on CD1/NKT Cells	Kamakura	Japan	Mar.09
The 5th International Symposium on CD1/NKT Cells	Kamakura	Japan	Mar.09
The 5th International Symposium on CD1/NKT Cells	Kamakura	Japan	Mar.09
The 5th International Symposium on CD1/NKT Cells	Kamakura	Japan	Mar.09
The 5th International Symposium on CD1/NKT Cells	Kamakura	Japan	Mar.09
The 5th International Symposium on CD1/NKT Cells	Kamakura	Japan	Mar.09
IADR/AADR/CADR 87th General Session and Exhibition	Miami	U.S.A.	Apr.09
IADR/AADR/CADR 87th General Session and Exhibition	Miami	U.S.A.	Apr.09
IADR/AADR/CADR 87th General Session and Exhibition	Miami	U.S.A.	Apr.09
6th International Human Peroxidase Meeting	Chapel Hill, North Carolina	U.S.A.	Apr.09
Myeloperoxidase and the heart, 6th International Human Peroxidase Meeting	Chapel Hill, North Carolina	U.S.A.	Apr.09
6th International Human Peroxidase Meeting	Chapel Hill, North Carolina	U.S.A.	Apr.09
ESF-EMBO Symposium Spatio-Temporal Radiation Biology: Transdisciplinary Advances for Biomedical Applications	Sant Feliu de Guixols	Spain	May.09
2009 KAAACI-KAPARD Joint Congress	Seoul	Korea	May.09
96th Annual Meeting the American Association of Immunologists Immunology 2009	Seattle	U.S.A.	May.09
Keystone Symposia Human Immunology and Immunodeficiencies	Beijing	China	May.09
Keystone Symposia Human Immunology and Immunodeficiencies	Beijing	China	May.09
Keystone Symposia Human Immunology and Immunodeficiencies	Beijing	China	May.09
International Forum on Inflammation-2009, IVIg treatment and development of synthetic IgG	Tokyo	Japan	May.09
International Society for Human and Animal Mycology 2009	Tokyo	Japan	May.09
University of Cambridge Addenbrooke's Hospital IMS Seminar	Cambridge	U.K.	May.09
Kyoto T cell conference 2009	Kyoto	Japan	Jun.09
American Diabetes Association 69th Scientific Sessions	New Orieans	U.S.A.	Jun.09
14th International Vasculitis and ANCA Workshop	Lund, Sweden and Copenhagen	Denmark	Jun.09
14th International Vasculitis and ANCA Workshop	Lund, Sweden and Copenhagen	Denmark	Jun.09
14th International Vasculitis and ANCA Workshop	Lund, Sweden and Copenhagen	Denmark	Jun.09
14th International Vasculitis and ANCA Workshop	Lund, Sweden and Copenhagen	Denmark	Jun.09
14th International Vasculitis and ANCA Workshop	Lund, Sweden and Copenhagen	Denmark	Jun.09
14th International Vasculitis and ANCA Workshop	Lund, Sweden and Copenhagen	Denmark	Jun.09

International Conference Presentations by Core Member's Group

2009 Speakers	Title
Suzuki K.	Lecture on Epitope of MPO-ANCA in Workshop-I: Epitope specificity.
Takahashi K, Oharaseki T, Yokouchi Y, Yamada H, Mamada H, Naoe S, Saji T, Ohno N, Suzuki K.	Effect of anti-TNF-α medicaments in mice vasculitis model caused by Candida albicans water soluble fraction.
Tomizawa K, Nagao T, Saiga K, Oshima M, Kobayashi K, Nakayama T, Tanokura M, Suzuki K.	Risk Epitopes of MPO-ANCA in SCG/Kj mice.
Uno K, Muso E, Ito-Ihara T, Yagi K, Fujita S, Suzuki K.	Comparison of plasma cytokine/chemokine levels and IFN-α production capacity amongst healthy subjects, patients with MPO-ANCA positive MPA, and IgA nephritis.
Bujo H, Jiang M, Ohwaki K, Schneider WJ, Saito Y.	LR11, a novel circulating marker of carotid atherosclerosis, is essential for angiotensin II -induced intimal smooth muscle cell migration.
Kazuki Y, Abe S, Takiguchi M, Hoshiya H, Kajitani N, Yoshino T, Oshima T, Tomizuka K, Aueviriyavit S, Kobayashi K, Chiba K, Oshimura M.	HUMANIZED P450 MOUSE:(1) CONSTRUCTION OF HUMANIZED MODEL MICE CONTAINING THE CYP3A CLUSTER FOR DRUG SCREENING.
Aueviriyavit S, Kobayashi K, Wataanbe M, Kameyama N, Kazuki Y, Oshimura M, Chiba K.	HUMANIZED P450 MOUSE:(2) FUNCTIONAL EXPRESSION OF HUMAN CYP3A ISOFORMS IN CYP3A-HACNICE AND THEIR APPLICATION IN DRUG-DRUG INTERACTION STUDY VIA MECHANISM-BASED INACTIVATION.
Kobayashi K, Tkagi S, Ohtsuki T, Yoshida A, Ishibashi M, Chiba K.	A compound in fetal bovine serum modulates the activation of pregnane X receptor.
Nakajima H.	Th2 cells, Th17 cells, and allergic inflammation.
Kamada T.	Carbon Ion Radiotherapy - Chiba Experience.
Kanazawa N, Nishiyama M, Li H-J, Okafuji I, Kambe N, Furukawa F.	Long-term ICAM-1 expression on PMA-activated THP-1 cells harboring disease-associated NOD2 mutations.
Iyoda M, Uzawa K, Sakuma K, Yamano Y, Sakamoto Y, Ogawara K, Shiiba M, Bukawa H, Yokoe H, Tanzawa H.	Overexpression of RHAMM in Oral Squamous Cell Carcinoma.
Nakajima H.	Th2, Th17, and allergic inflammation.
Ogoshi K, Uzawa K, Yamatoji M, Kasamatsu A, Negoro K, Wada T, Fujita S, Shiiba M, Bukawa H, Yokoe H, Tanzawa H.	Cross-resistance of platinum derivatives in H-1R, a cisplatin-resistant cell line.
Shiiba M, Fushimi K, Shinozuka K, Sakamoto Y, Ono K, Ogawara K, Bukawa H, Yokoe H, Uzawa K, Tanzawa H.	Clinical Characteristics of Oral Carcinomas with Multiple Primary Malignancies 2.
Shinozuka K, Uzawa K, Fushimi K, Saito K, Ono K, Ogawara K, Shiiba M, Bukawa H, Yokoe H, Tanzawa H.	Overexpression of NRG1 Correlating to Cisplatin-Resistance in Oral Squamous Cell Carcinoma.
Satoh T, Kambe N, Nakamura Y, Kanazawa N, Matsue H.	The clinical difference in early-onset sarcoidosis between father and his baby with same NOD2 mutation.
Toko H.	ER Stress-Response Transcription Factor ATF6 Plays a Critical Role in Maintaining Cardiac Function under Physiological and Pathological Conditions.
Yoshida M, Shiojima I, Ikeda H, Komuro I.	Pitavastatin attenuates doxorubicin-induced cardiotoxicity through the inhibition of oxidative stress-DNA damage-ATM-p53 pathway.
Motohashi S, Nagato K, Taniguchi M, Nakayama T, Yoshino I.	α-Galactosylceramide-pulsed antigen presenting cell treatment in patients with advanced NSCLC.
Yamamoto N, Baba M, Nakajima M, Miyamoto T, Kandatsu S, Yoshikawa K, Mizoe J, Kamada T, Tsujii H.	Serial radiographic changes on CT for long survivors after carbon ion radiotherapy in non-small cell lung cancer.
Baba M, Yamamoto N, Nakajima M, Yoshikawa K, Imai R, Matsufuji N, Minohara S, Miyamoto T, Tsuji H, Kamada T, Mizoe J, Tsujii H.	Carbon Ion Radiotherapy in Hypofraction Regimen for Stage I Non-Small Cell Lung Cancer.
Kamada T.	Carbon Ion Radiotherapy: Clinical study.
Kamada T.	Carbon Ion Radiotherapy in Bone and soft Tissue Sarcomas.
Yamada S, Shinoto M, Yasuda S, Imada H, Katou H, Kamada T, Tsujii H, Tsuji H, Baba M, Mizoe J, Yoshikawa K, Kandatsu S, Ochiai T.	Carbon Ion Therapy for Patients with Locally Recurrent Rectal Cancer.
Nakayama T.	Development of new immunotherapy for cancer: iNKT cell-based immunotherapy.
Taniguchi M.	NKT cells bridging innate and acquired immunity.
Taniguchi M.	IL-17RB+ NKT subset responsible for development of AHR.
Taniguchi M.	Islet transplantation.
Inamine A, Okawa T, Horiguchi S, Okamoto Y.	DC stimulated by Lactobacillus paracasei KW3110, inhibits local inflammation of allergic rhinitis.
Taniguchi M.	A novel subset of mouse NKT cells bearing the IL-17 receptor B responds to IL-25 and contributes to airway hyperreactivity.
Yoshino M, Suzuki M, Moriya Y, Hoshino H, Motohashi S, Yoshida S, Shibuya K, Yoshino I.	Promoter hypermethylation of p16 and Wif-1 genes as an independent prognostic marker in stage IA non-small cell lung cancers.
Toubaru S, Yoshikawa K, Ohashi S, Hasebe M, Ishikawa H, Sagou K, Tamura K, Tanimoto K, Kandatsu S, Baba M, Fukumura T, Saga T, Kawaguchi K, Tsujii H.	Usefulness of C-11 methionine PET/CT for predicting recurrence, metastasis and prognosis of patients with lung cancer treated by carbon ion radiotherapy.
Hamano Y, Yumura W, Kusano E, Suzuki K.	Genetic dissection of leukocytosis related to spontaneously occurring crescentic glomerulonephritis in a model of SCG/Kj mice.
Ohara O.	From transcriptome analysis to immunogenomics
Nakajima H, Wakashin H, Hirose K.	Role of IL-23-Th17 cell axis in Th2 cell-mediated allergic airway inflammation
Kamada T.	Impact of Carbon Ion Radiotherapy on Outcome in Unresectable High-grade Osteosarcoma of the Trunk.

	Meeting	City	Country	Month・Year
	14th International Vasculitis and ANCA Workshop	Lund, Sweden and Copenhagen	Denmark	Jun.09
	14th International Vasculitis and ANCA Workshop	Lund, Sweden and Copenhagen	Denmark	Jun.09
	14th International Vasculitis and ANCA Workshop	Lund, Sweden and Copenhagen	Denmark	Jun.09
	14th International Vasculitis and ANCA Workshop	Lund, Sweden and Copenhagen	Denmark	Jun.09
	15th International Symposium on Atherosclerosis	Boston	U.S.A.	Jun.09
	16th International Conference on Cytochrome P450	Okinawa	Japan	Jun.09
	16th International Conference on Cytochrome P450	Okinawa	Japan	Jun.09
	16th International Conference on Cytochrome P450	Okinawa	Japan	Jun.09
	RCAI international summer program 2009	Yokohama	Japan	Jul.09
	Heavy Ions in Therapy and Space Symposium 2009	Köln	Germany	Jul.09
	The 9th World Congress on Inflammation	Tokyo	Japan	Jul.09
	Second World Congress of International Academic of Oral Oncology	Toronto	Canada	Jul.09
	6th BIENNIAL INTERNATIONAL SYMPOSIUM “EOSINOPHILS 2009” of the International Eosinophil Society	Bruges	Belgium	Jul.09
	Second World Congress of International Academic of Oral Oncology	Toronto	Canada	Jul.09
	Second World Congress of International Academic of Oral Oncology	Toronto	Canada	Jul.09
	Second World Congress of International Academic of Oral Oncology	Toronto	Canada	Jul.09
	The 4th Joint Meeting of Japanese Dermatological Association and Australasian College of Dermatologists	Sapporo	Japan	Jul.09
	6th Annual Symposium of the American Heart Association’s Council on Basic Cardiovascular Sciences	Las Vegas	U.S.A.	Jul.09
	Basic Cardiocascular Science 2009	Las Vegas	U.S.A.	Jul.09
	13th World Conference on Lung Cancer	San Francisco	U.S.A.	Jul.09
	13th World Conference on Lung Cancer 13th World Conference on Lung Cancer	San Francisco	U.S.A.	Aug.09
	NIRS-IMP Joint Symposium on Carbon Ion Therapy	Lánzhōu	China	Aug.09
	NIRS-IMP Joint Symposium on Carbon Ion Therapy	Lánzhōu	China	Aug.09
	NIRS-IMP Joint Symposium on Carbon Ion Therapy	Lánzhōu	China	Aug.09
	NIRS-IMP Joint Symposium on Carbon Ion Therapy	Lánzhōu	China	Aug.09
	Thailand Research Expo 2009	Bangkok	Thailand	Aug.09
	University of Palermo	Palermo	Italy	Sep.09
	University of Palermo	Palermo	Italy	Sep.09
	University of Palermo	Palermo	Italy	Sep.09
	Satellite Symposium of the European Congress of Immunology 2009	Berlin	Germany	Sep.09
	European Congress on Immunology (ECI) 2009	Berlin	Germany	Sep.09
	13th World Conference on Lung Cancer	San Francisco	U.S.A.	Sep.09
	The 2009 EANM Congress	Barcelona	Spain	Oct.09
	The American Society of Nephrology The 42nd Annual Meeting and Scientific Exposition	San Diego	U.S.A.	Oct.09
	US-Japan International Cancer Systems Biology Meeting	Yokohama	Japan	Oct.09
	International symposium: Eosinophil‚ other inflammatory cells and molecules in allergy.	Akita	Japan	Oct.09
	The 51st ASTRO Annual Meeting	Chicago	U.S.A.	Nov.09

International Conference Presentations by Core Member's Group

2009

Speakers	Title
Ohara O.	From transcriptome analysis to immunogenomics: current status and future direction
Tokuhisa T, Sakamoto A, Arima M, Hatano M.	Roles for Bcl6 in differentiation of germinal center B cells
Nakajima H.	IL-23-Th17 cell axis enhances Th2-cell-mediated allergic airway inflammation in mice
Komuro I.	The Third International Conference on Cell Therapy(IRICT)
Tateno K, Minamino T, Komuro I.	Notch Signaling in Intrinsic Stem Cell is a Prerequisite for Therapeutic Angiogenesis
Ohara O.	Functional genomics focused on immune systems
Komuro I.	Zhongshan Lecture
Fujimura T, Yonekura S, Horiguchi, Sakaguchi M, Okamoto Y.	IL10+Foxp3+ cells in CD25+CD4+ leukocytes are available as therapeutic biomarker for sublingual immunotherapy against Japanese cedar pollinosis.
Komuro I.	SIRIC International Forum 2009: Theme: Imaging for Shedding light to Atherosclerosis
Kamada T.	KIDS workshop 2009 in NIRS IAEA NIRS Joint Workshop & NIRS Symposium on Radiation Protection for Children

2010

Speakers	Title
Nakayama T.	Dual negative regulation of GATA3 function by Sox4. Adaptive and Innate Immune Responses to Neglected Tropical Diseases Conference.
Hamano Y, Yumura W, Kusano E, Nagao T, Suzuki K.	Genetic dissection of aberrant T cell activation related to the pathogenesis of ANCA related systemic vasculitis in a model of SCG/Kj mice.
Nagao T, Aratani Y, Nakayama T, Suzuki K.	Development of murine crescentic glomerulonephritis model using anti-MPO and anti-LAMP-2 antibodies.
Takahashi K, Oharaseki T, Yokouchi Y, Yamada H, Mamada H, Miura NN, Ohno N, Murata H, Naoe S, Suzuki K.	CAWS-induced murine vasculitis and Kawasaki disease.
Muso E, Uno K, Iwasaki Y, Tateishi Y, Komiya T, Ihara T, Suzuki K.	IVIg therapy for acute phase MPO-ANCA positive systemic vasculitis—New horizon of therapy with evidence of Suppresive effect on acute cytokine and chemokine storm.
Suzuki K.	Role of Neutrophils and Myeloperoxidase in Severe Lung Injury in Mice with A/H1N1 (PR-8) and Patients with Avian Flu (H5N1).
Suzuki K, Sugamata R, Nagao T, Tomizawa H, Yamamoto K, Nakajima N, Sato Y, Aratani Y, Todaka R, Oshima M, Sata T, Kobayashi K, Kawachi S, Phung T. T. B, Nguyen L, Nakayama T.	Role of neutrophils and myeloperoxidase in severe lung injury in mice with influenza A/H1N1 (PR-8) and in patients with avian flu (H5N1).
Hasegawa A, Nakayama T.	Real-time cellular imaging of T lymphocyte migration in a mouse asthma model.
Ohara O.	Exploration of PID-causative mutations: An Japan model and the future direction
Kikkawa N.	MicroRNA expression signature in hypopharyngeal squamous cell carcinoma (HSCC): miR-489 inhibits cell proliferation by targeting PTPN11.
Nakajima H, Wakashin H, Hirose K, Iwamoto I.	Th2 cells‚ Th17 cells‚ and allergic airway inflammation.
Komuro I.	2010 Angiotensin Gordon Conference.
Sugamata R, Nagao T, Dobashi H, Tomizawa K, Yamamoto K, Nakajima N, Sato Y, Aratani Y, Todaka R, Oshima M, Sata T, Kobayashi K, Kawachi S, Nakayama T, Suzuki K.	Role of neutrophils and myeloperoxidase in lung injury induced by influenza A/H1N1 (PR-8) infection in mice.
Fujikawa A, Okamoto Y.	Nasal submucosal administration of antigen-presenting cells induces effective immunological responses in immunotherapy.
Okamoto Y.	Early intervention for allergic rhinitis.
Tadashi Kamada.	Carbon ion radiotherapy for bone and soft tissue sarcomas.
Takatani T, Saitoh T, Nishii Y, Minamaitani K, Minagawa M, Nishioka T, Yasuda T, Fukumoto S, Kohno Y.	Development of tertiary hyperparathyroidism in patients with X-linked hypophosphatemic vitamin D resistant rickets: Contribution of high FGF23 level before treatment.
Nobata N.	MicroRNA expression signatures in hypopharyngeal squamous cell carcinoma (HSCC): miR-489 inhibits cell proliferation by targeting PTPN11.
Fujii K, Miyashita T, Endo M, Uchikawa H, Kohno Y	Germline and somatic PTCH1 mutations in Japanese basal cell nevus syndrome.
Endo M, Fujii K, Miyashita T, Uchikawa H, Tanabe R, Yamada Y, Kohno Y.	Clinical manifestations in Japanese Gorlin syndrome patients.
Kanazawa N, Nishiyama M, Li HJ, Okafuji I, Kambe N, Furukawa F.	2010 Annual Meeting of the Society for Investigative Dermatology.
Kamada T, Tsujii H.	Recent and Long Term Clinical Results in Carbon Ion Radiotherapy at NIRS-HIMAC.
Kamada T, Imai R, Tsujii H.	Bone & soft tissue sarcomas.
Nakayama T.	iNKT cell-based immunotherapy for cancer.
Kamada T, Tsujii H.	Carbon Ion Radiotherapy at the NIRS, HIMAC.
Shimojo N, Arima T, Suzuki S, Matsumoto K, Kohno Y.	Impairment of Toll like receptor signaling in cord blood mononuclear cells of children who later develop atopic eczema.

	Meeting	City	Country	Month・Year
	The 3rd Chiba University Global COE symposium "Molecule Dynamics of Immune System"	Chiba	Japan	Nov.09
	LAH 50th Symposium	Stanford	U.S.A	Nov.09
	The 2009 Fall Conference of The Korean Association of Immunologists	Seoul	Korea	Nov.09
	Long-Term Outcome of Therapeutic Neovascularization Using Peripheral Blood Mononuclear Cells for Limb Ischemia	Seoul	Korea	Nov.09
	Scientific Session 2010 American Heart Association	Orlando	U.S.A	Nov.09
	World Allergy Congress Argentina 2009	Buenos Aires	Argentina	Dec.09
	The Role of Statin in the Treatment of Heart Failure	Shanghai	China	Dec.09
	The XXI World Allergy congress	Buenos Aires	Argentina	Dec.09
	Senescenec as a cause of atherosclerosis and therapeutic angiogenesis using peripheral blood mononuclear cells	Seoul	Korea	Dec.09
	Plans for Radiotherapy	Chiba	Japan	Dec.09

	Meeting	City	Country	Month・Year
	US-JAPAN Joint Immunology Board&Parastic Disease Panel Conference	San Diego	U.S.A	Jan.10
	Inflammation Program	Chiba	Japan	Jan.10
	Inflammation Program	Chiba	Japan	Jan.10
	Inflammation Program	Chiba	Japan	Jan.10
	Inflammation Program	Chiba	Japan	Jan.10
	Phagocyte Imaging joint with 3th International Symposium for Bioimaging. 3rd International Symposium on Bioimaging	Okazaki	Japan	Jan.10
	3rd International Bioimaging Symposium	Okazaki	Japan	Jan.10
	3rd International Bioimaging Symposium	Okazaki	Japan	Jan.10
	The 2nd Symposium for PID in Asia	Kisarazu	Japan	Feb.10
	Cancer genomics, epigenetics, and the development of novel therapeutics 2010	Waikoloa	U.S.A.	Feb.10
	1st Chiba-Uppsala Academia joint Workshop	Chiba	Japan	Feb.10
	Molecular & Therapeutic implications of stretch-sensing by the AT1R	California	U.S.A.	Feb.10
	Annual scientific meeting of the European Society for Clinical Investigation	Bari	Italy	Feb.10
	39th meeting of Korean Rhinologic Society	Daejeon	Korea	Mar.10
	39th meeting of Korean Rhinologic Society	Daejeon	Korea	Mar.10
	II NISR-CNAO Joint Symposium on Hadrontherapy	Pavia	Italy	Mar.10
	14th International Congress of Endocrinology	Kyoto	Japan	Mar.10
	101st American Cancer Society	Washington DC	U.S.A	Apr.10
	11th International Child Neurology Congress	Cairo	Egypt	May.10
	11th International Child Neurology Congress	Cairo	Egypt	May.10
	Long-term ICAM-1 and transient PDGF-B expression on PMA-activated THP-1 cells harboring early-onset sarcoidosis/Blau syndrome-associated NOD2 mutations.	Atlanta	U.S.A	May.10
	49th Annual Meeting of the Particle Therapy Co-Operative Group	Maebashi	Japan	May.10
	49th Annual Meeting of the Particle Therapy Co-Operative Group	Chiba	Japan	May.10
	Corporate Thursday Clinical Immunology Society	Philadelphia	U.S.A	May.10
	From cancer biology to photon and carbon ion radiation therapy; A Joint Symposium of NIRS, CSU and U.C.	Colorado	U.S.A	May.10
	Congress of the European Academy of Allergy and Clinical Immunology 2010	London	UK	Jun.10

International Conference Presentations by Core Member's Group

2010 Speakers	Title
Suzuki K, Kobayashi S, Fujimoto S, Hirahashi J.	Discussion in DCVAS.
Suyama K, Suzuki S, Tanaka T, Terano T, Yokote K, Prives C, Tatsuno I.	Interactive Life Style Intervention Program by Monitoring the Internet-Based Acquisition of Daily Physical Data with Highly Functional Pedometer and Weighing Machine in Japanese Male Patients with Metabolic Syndrome.
Suzuki S, Tanaka T, Suyama K, Yokote K, Prives C, Tatsuno I.	Phosphate Activated Glutaminase (GLS2) & sbquo; a Novel p53-Inducible Regulator of Glutamine Metabolism and Reactive Oxygen Species.
Yasuda H, Yoshizawa N, Matsumoto M, Kawachi S, Suzuki K.	Transmission of Pandemic H1N1 Influenza in Japan in 2009: Simulated Measures and Post-Analysis.
Taniguchi M.	Discovery of NKT cells with adjuvant activity and their clinical application in patients with advanced lung cancer.
Tachibana K, Sakurai K, Yokoh H, Ishibashi T, Tanaka. A, Ishikawa K, Yokote K.	Mutation (P1195L) of the insulin receptor attenuates oxidative stress and apoptosis in pancreatic β-cells induced by high fat diet.
Okamoto Y.	Allergic rhinitis-comparison of the practical guideline for management of allergic rhinitis in Japan with ARIA
Inamine A, Horiguchi S, Yonekura S, Hanazawa T, Hosokawa H, Matuura-Suzuki A, Nakayama T, Okamoto Y.	Sublingual administration of Lactobacillus paracasei KW3110 inhibits Th2-dependent allergic responses via the up-regulation of PD-L2 on dendritic cells.
Yamada Y, Tomiita M, Ichimoto K, Nakano T, Morita Y, Arima T, Shimojo N, Kohno Y, Kawaguchi S, Hashimoto Y, Kanazawa M.	The first Japanese case of Protracted Febril Myalgia Syndrome (PFMS): a form of myalgia associated with Familial Mediterranean Fever (FMF).
Tomiita M, Saito K, Shimojo N, Kohno Y.	Serum IgG4 levels in juvenile onset Sgren'syndrome-Is there any "systemic IgG4-related diseases" patients in pediatric age?
Ito K.	Cardiac Mast Cells Cause Atrial Fibrillation in Angitensin II-infused Hearts.
Sumida T, Naito A, Nagai T, Shiojima I, Komuro I.	Activation of β-catenin signaling by macrophage-derived MMP-9 is critical for AngII-induced vascular remodeling.
Akutsu Y, Shuto K, Shiratori T, Uesato M, Kano M, Usui A, Ochiai T, Matsubara H.	Evaluation of neoadjuvant chemoradiation therapy for esophageal cancer.
Kamada T, Tsujii H.	Carbon Ion Radiotherapy at NIRS-HIMAC.
Morita Y, Shimojo N, Ohnishi H, Kawamoto M, Matsui E, Kondo N, Kohno Y.	Relationship between development of eczema and the content of the cytokines in breast milk.
Inamine A, Sakamoto A, Yoshida N, Arima M, Ikari J, Hatano M, Okamoto Y, Tokuhisa T.	IL-21 is essential for Long-lived Plasma Cell differentiation.
Taniguch M, Fujii S, Motohashi S, Nakayama T.	NKT cell-targeted adjuvant cell therapy-from basic to clinic.
Ohara O.	What is "Systems Immunology" for?
Watanabe N, Oya Y, Ikeda K, Suto A, Kagami S, Hirose K, Kishimoto T, Nakajima H.	Lack of B and T lymphocyte attenuator exacerbates autoimmune disorders and induces Fas-independent liver injury in MRL-lpr/lpr mice.
Kawashima S, Hirose K, Takahashi K, Wakashin H, Suto A, Kagami S, Iwamoto I, Nakajima H.	dectin-1 signaling instructs dendritic cells to induce the development of IL-10-producing CD4+ T cells by ICOS- and TGF-β-dependent mechanisms.
Nishiyama M, Li HJ, Okafuji I, Kambe N, Furukawa F, Kanazawa N.	Long-term ICAM-1 and transient PDGF-B expression on PMA-activated THP-1 cells harboring early-onset sarcoidosis/Blau syndrome-associated NOD2 mutations.
Thuy T.B, Phung, San T. Luong, Kawach S, Nunoi H, Liem T. Nguyen, Nakayama T, Suzuki K.	Key cytokines/chemokines in acute respiratory distress syndrome with avian influenza (H5N1) infection in Vietnamese children.
Sugamata R, Nagao T, Dobashi H, Yamamoto K, Tomizawa K, Nakajima N, Sato Y, Aratani Y, Zou J, Todaka R, Oshima M, Tetsutaro S, Kobayashi K, Kawachi S, Nakayama T, Suzuki K.	Investigation of pathogenic mechanism of influenza pneumonia and therapeutic approach involved in MPO function with novel macrolides.
Shiga Y, Tomizawa T, Nagao T, Sugamata R, Kawachi S, Nakayama T, Suzuki K.	Risk cytokines/chemokines in the early phase of diffuse alveolar damage (DAD) of the ventilator induced lung injury (VILI) in mice.
Mabuchi A, Ishiwata T, Tanaka Y, Kakiuchi T, Suzuki K, Wheatley A.M.	Role of F4/80+Mac-1high cells in Con A induced hepatitis.
Suzuki K, Nagao T, Aratani Y, Wang P, Nakayama T, Suzuki K.	Mechanism of neutrophil extracellular traps formation by anti-myeloperoxidase antibodies.
Nagao T, Suzuki K, Aratani Y, Wang P, Nakayama T, Suzuki K.	Murine crescentic glomerulonephritis model using anti-MPO and anti-LAMP2 antibodies.
Kusunoki R, Nagao T, Iwamura C, Kobayashi S, Yumura W, Nakayama T, Suzuki K.	Treatments for MPO-ANCA-associated vasculitis in SCG/Kj mouse.
Bujo H.	Novel gene therapy using the autologous preadipocyte transplantation for the patients with LCAT deficiency.
Taniguchi M.	NKT cell-targeted adjuvant cell therapy-from basic to clinic.
Yoshida N, Sakamoto A, Kitayama D, Arima M, Hatano M, Koike T, Tokuhisa T.	IL-4 and IL-21 inversely regulate CXCR4 expression on activated B cells.
Ikari J, Fujimura L, Sakamoto A, Hatano M, Tatsumi T, Tokuhisa T, Arima A.	The role of PHF11 in activation of murine B cells.
Pan J, Sakamoto A, Yamashita K, Kohno M, Arima M, Hatano M, Tokuhisa T.	A role of Bcl6 in differentiation of memory precursor CD8 T cells.
Inamine A, Sakamoto A, Yoshida N, Arima M, Okamoto Y, Tokuhisa T.	IL-21 is essential for Long-lived Plasma Cell differentiation.
Sakamoto A, Pan J, Kohno M, Arima M, Hatano M, Tokuhisa T.	Role of Bcl6 in the generation and maintenance of follicular helper T cells.
Arima M, Ikari J, Sakamoto A, Hatano M, Tokuhisa T.	A critical role of the intron enhancer element of the IL-4 gene in Th2 cytokine expression.
Ikeda N, Akutsu Y, Shuto K, Shiratori T, Uesato M, Miyazawa Y, Sakata H, Yoneyama Y, Usui A, Kano M, Akimoto A, Matsubara H.	Significance of expression of HMGB1 in esophageal squamous cell carcinoma.

	Meeting	City	Country	Month · Year
	EUVAS Meeting	Parma	Italy	Jun.10
	The Endocrine Society 92nd Annual Meeting & Expo	San Diego	U.S.A	Jun.10
	The Endocrine Society 92nd Annual Meeting & Expo	San Diego	U.S.A	Jun.10
	Applied Mathematics International Conference 2010 (AMIC2010) & The 6th EASIAM Conference June	KualaLumpur	Malaysia	Jun.10
	Second International Conference-Current Advances in Microbiology‚ Immunology and Allergology	Ulaanbaatar	Mongol	Jun.10
	American Diabetes Association 70th Scientific Sessions	Orlando	U.S.A	Jun.10
	20th Congress of International Japan/North Asia	Tokyo	Japan	Jul.10
	7th International Symposium on Tonsils and Mucosal Barriers of the Upper Airways	Asahikawa	Japan	Jul.10
	14th Congress of Asia Pacific League of Associations for Rheumatology	Hong Kong	China	Jul.10
	14th Congress of Asia Pacific League of Associations for Rheumatology	Hong Kong	China	Jul.10
	Basic Cardiovascular Sciences Conference 2010	California	U.S.A	Jul.10
	Basic Cardiovascular Sciences 2010	Rancho Mirage, CA	U.S.A	Jul.10
	12th World Congress of the ISDE	Kagoshima	Japan	Aug.10
	21st International Conference on the Application of Accelerators in Research & Industry	Texas	U.S.A	Aug.10
	14th INTERNATIONAL CONGRESS OF IMMUNOLOGY	Kobe	Japan	Aug.10
	14th International Congress of Immunology	Kobe	Japan	Aug.10
	14th International Congress of Immunology	Kobe	Japan	Aug.10
	14th International Congress of Immunology	Kobe	Japan	Aug.10
	14th International Congress of Immunology	Kobe	Japan	Aug.10
	14th International Congress of Immunology	Kobe	Japan	Aug.10
	14th International Congress of Immunology.	Kobe	Japan	Aug.10
	14th International Congress of Immunology	Kobe	Japan	Aug.10
	14th International Congress of Immunology	Kobe	Japan	Aug.10
	Risk cytokines/chemokines in the early phase of diffuse alveolar damage (DAD) of the ventilator induced lung injury (VILI) in mice.	Kobe	Japan	Aug.10
	14th International Congress of Immunology	Kobe	Japan	Aug.10
	14th International Congress of Immunology	Kobe	Japan	Aug.10
	14th International Congress of Immunology	Kobe	Japan	Aug.10
	14th International Congress of Immunology	Kobe	Japan	Aug.10
	Amsterdam University Academic Medical Center (AMC) Vascular Medicine Symposium	Amsterdam	Netherlands	Aug.10
	the 14th International Congress of Immunology	Kobe	Japan	Aug.10
	14th International Congress for Immunology	Kobe	Japan	Aug.10
	14th International Congress for Immunology	Kobe	Japan	Aug.10
	14th International Congress for Immunology	Kobe	Japan	Aug.10
	14th International Congress for Immunology	Kobe	Japan	Aug.10
	14th International Congress for Immunology	Kobe	Japan	Aug.10
	14th International Congress for Immunology	Kobe	Japan	Aug.10
	12th World Congress of the ISDE	Kagoshima	Japan	Sep.10

International Conference Presentations by Core Member's Group

2010 Speakers	Title
Kano M, Hoshino I, Akutsu Y, Usui A, Ikeda N, Miyazawa Y, Matsubara H.	Comparison between DWIBS positive nodes and negative of esophageal squamous cell cancer with histological findings and postoperative outcome.
Kono T, Shuto K, Shiratori T, Akutsu Y, Uesato M, Matsubara H.	Can standardized uptake value of 18F-fluorodeoxyglucose positron emission tomography(FDG-PET) predict the outcome of esophageal cancer?
Saito H, Shuto K, Ota T, Sato A, Toma T, Natsume T, Ohira G, Kono T, Uesato M, Akutsu Y, Okazumi S, Matsubara H.	Long-term survival after resection of a solitary postoperative adrenal metastasis from esophageal adenocarcinoma: a case report.
Kawahira H, Shuto K, Akutsu Y, Uesato M, Shiratori T, Ochiai T, Matsubara H.	A case report: reconstructed gastric tube recurrence after radical esophagectomy for esophageal squamous cell cancer.
Akutsu Y, Shuto K, Uesato M, Kono T, Hayashi H, Matsubara H.	Novel technique of the laparoscopic surgery for achalasia.
Saito H, Shuto K, Ota T, Sato A, Narushima K, Aoyagi T, Hayano K, Tohma T, Natsume T, Ohira G, Kono T, Matsubara H.	Depth assessment of superficial esophageal cancer based on high-barium double-contrast esophagography with flat panel X-ray detector.
Sato A, Akutsu Y, Shuto K, Uesato M, Miyazawa Y, Shiratori T, Matsubara H.	Primary small cell carcinoma of the esophagus: report of 5 cases and review of the literature.
Kano M, Hoshino I, Akutsu Y, Usui A, Ikeda N, Miyazawa Y, Matsubara H.	miR-145, miR-133a and miR-133b: tumor suppressive miRNAs target FSCN1 in esophageal squamous cell carcinoma.
Shuto K, Saito H, Kono T, Ohira G, Natsume T, Toma T, Sato A, Ota T, Uesato M, Akutsu Y, Matsubara H.	Preoperative N-staging of esophageal squamous cell cancer by DWIBS in comparison with PET.
Shuto K, Okazumi S, Kono T, Ohira G, Natsume T, Tohma T, Sato A, Ota T, Saito H, Uesato M, Akutsu Y, Matsubara H, Yanagawa N.	Enhanced pattern of metastatic node of esophafeal cancer by thin-section MDCT image.
Hayano K, Shuto K, Kono T, Ohira G, Natsume T, Tohma T, Saito H, Matsubara H.	The usefulness of Perfusion CT to predict response to CRT and survival in patients with esophageal squamous cell carcinoma,
Akutsu Y, Komatsu A, G. Yusup, Ikeda N, Usui A, Kano M, Sakata H, Yoneyama Y, Ochiai T, Matsubara H.	Novel cancer vaccine, gp96, for esophageal squamous cell carcinoma.
Nishiyama M, Li HJ, Okafuji I, Kambe N, Furukawa F, Kanazawa N.	Long-term ICAM-1 and transient PDGF-B expression on PMA-activated THP-1 cells harboring early-onset sarcoidosis/Blau syndrome-associated NOD2 mutations.
Satoh T, Kambe N, Saito M, Nishikomori R, Matsue H.	Enhanced NF-κB activation after the stimulation with NLRP3 activator correlates with disease activities in cryopyin-associated periodic syndrome.
Kishida S, Furihata T, Kamiichi A, Ohta Y, Saito K, Chiba K.	HIBMEC/KYAS, A NEWLY IMMORTALIZED HUMAN BRAIN MICROVASCULAR ENDOTHELIAL CELL LIME, IS A PROMISING TOOL FOR AN IN VITRO BLOOD-BRAIN BARRIER MODEL.
Ishii S, Furihata T, Iikura M, Fukuchi Y, Hashizume M, Nagai N, Chiba K.	CHARACTERIZATION OF THE NOVEL TISSUE-SPECIFIC PROMOTER OF THE SLC29A1 GENE.
Furihata T, Fukuchi Y, Iikura M, Hashizume M, Chiba K.	HUMAN HEPATIC RIVABIRIN TRASPORTER MOLECULAR CHARACTERIZATION AND EXPRESSION PROFILE IN HEPATOCYTES.
Yoshida A, Kobayashi K, Ejiri Y, Takagi S, Mimura H, Hosoda M, Chiba K.	INDUCED EXPESSIONS AND ACTIVITIES OF DRUG-METABOLIZING ENZYMES IN THE HUMAN HEPATOCELLULAR CARCINOMA CELL LINE CULTURED ON THE MICRO-SPACE CELL CULTURE PLATES.
Tsukazaki Y, Nishi M, Senda N, Yasuhiro K, Kubo K, Kobayashi K, Chiba K, Yamada S, Kokji T, Takahashi M, Igarashi H, Oshimura M.	HUMANIZED CYP3A MICE: (3) METABOLISM OF CYP3A4 SUBSTRATES DETECTED BY LC/MS SYSTEM.
Kazuki Y, Abe S, Takiguchi M, Hoshiya H, Kajitani N, Yoshino T, Takehara S, Ishihara C, Kubo K, Oshima T, Tomizuka K, Aueviyavit S, Kobayashi K, Chiba K, Tsukazaki Y, Senda N, Oshimura M.	HUMANIZED CYP3A MICE: (1) CONSTRUCTION OF HUMANIZED MODEL MICE CONTAINING THE CYP3A CLUSTER FOR DRUG SCREENING.
Nagai M, Furihata T, Matsumoto S, Ishii S, Chiba K.	A NOVEL MRNA SPLICING ISOFORM IS A REAL CANCER-TYPE ORGANIC ANION TRANPORTING POLYPEPTIDE 1B3 MRNA.
Iikura M, Furihata T, Ikeda M, Kato N, Chiba K.	RIBAVIRIN UPTAKE SYSTEMS ARE REQUIGED FOR THE ANTI-HEPATITIS C VIRUS ACTIVITY OF RIBAVIRIN.
Watanabe M, Aueviriyavit S, Kobayashi K, Iuchi N, Kazuki Y, Oshimura M, Chiba K.	HUMANIZED CYP3A MICE: (2) FUNCTIONAL EXPRESSION OF HUMAN CYP3A ISOFORMS IN CYP3A-HAC MICE AND INHIBITION OF CYP3A VIA MECHANISM, BASED INACTIVATION.
Nakayama T.	CD4 T cell memory controlled by Polycomb and Trithorax molecules.
Kamada T, Tsujii H.	Carbon Ion Radiotherapy: Clinical Studies and Future Prospects
Kamada T, Imai R, Tsuji H, Imaizumi T, Matsunobu A, Okada T, Tsujii H.	Carbon Ion Radiotherapy in Bone and Soft Tissue Sarcomas
Satoh T, Kambe N, Matsue H.	Enhanced NF-κB activation with NLRP3 activator correlates with disease activities in cryopyin-associated periodic syndrome.
Yamasaki K, Katada K, Kikkawa N, Yonekura S, Okamoto Y.	Phase II study of Activated NKT Cells and α-GalCer-pulsed DCs in Patients with recurrent and operable Head and Neck Carcinoma.
Yonekura S, Yamasaki K, Katada K, Kikkawa N, Okamoto Y.	Present Situation of Allergic Rhinitis in Japan.
Matsubara H, Usui A, Akutsu Y, Hoshino I, Murakami K, Kano M.	Preoperative dental brushing can reduce the risk of postoperative pneumaonia in esophageal cancer patients.
Ohara O.	From transcriptome analysis to systems immunology.
Tsurutani Y, Fujimoto M, Takemoto M, Yokote K.	The role of TGF-β/Smad3 signaling in the pathogenesis of obese fat tissue.
Honda Y, Ishiwada N, Tanaka J, Hishiki H, Kohno Y.	Polyribosylribitol phosphate antibody of the pediatric patients with Haemophilus influenzae type b systemic infection.
Ishiwada N, Hishiki H, Tanaka J, Kurosaki T, Kohno Y.	The incidence of pediatric invasive Haemophilus influenzae diseases and invasive pneumococcal diseases in Chiba prefecture, Japan.

Meeting	City	Country	Month・Year
12th World Congress of the ISDE	Kagoshima	Japan	Sep.10
12th World Congress of the ISDE	Kagoshima	Japan	Sep.10
12th World Congress of the ISDE	Kagoshima	Japan	Sep.10
12th World Congress of the ISDE	Kagoshima	Japan	Sep.10
12th World Congress of the ISDE	Kagoshima	Japan	Sep.10
12th World Congress of the ISDE	Kagoshima	Japan	Sep.10
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12th World Congress of the ISDE	Kagoshima	Japan	Sep.10
12th World Congress of the ISDE	Kagoshima	Japan	Sep.10
12th World Congress of the ISDE	Kagoshima	Japan	Sep.10
Autoinflammation 2010	Amsterdam	Netherlands	Sep.10
Autoinflammation 2010	Amsterdam	Netherlands	Sep.10
9th Interntional ISSX Meeting	Istanbul	Turkey	Sep.10
9th Interntional ISSX Meeting	Istanbul	Turkey	Sep.10
9th Interntional ISSX Meeting	Istanbul	Turkey	Sep.10
9th Interntional ISSX Meeting	Istanbul	Turkey	Sep.10
9th Interntional ISSX Meeting	Istanbul	Turkey	Sep.10
9th Interntional ISSX Meeting	Istanbul	Turkey	Sep.10
9th Interntional ISSX Meeting	Istanbul	Turkey	Sep.10
9th Interntional ISSX Meeting	Istanbul	Turkey	Sep.10
9th Interntional ISSX Meeting	Istanbul	Turkey	Sep.10
The 10th Awaji International Forum on Infection and Immunity	Awaji	Japan	Sep.10
The 4th Japanese-European Joint Symposium on Ion Cancer Therapy and KI-NIRS Joint Symposium on Ion-Radiation Sciences	Stockholm	Sweden	Sep.10
The 4th Japanese-European Joint Symposium on Ion Cancer Therapy and KI-NIRS Joint Symposium on Ion-Radiation Sciences	Stockholm	Sweden	Sep.10
40th Annual ESDR Meeting	Helsinki	Finland.	Sep.10
13th KJ Joint Meeting of Otorhinolaryngology Head & Neck Surgery	Seoul	Korea	Sep.10
13th KJ Joint Meeting of Otorhinolaryngology Head & Neck Surgery	Seoul	Korea	Sep.10
18th China-Japan Joint Congress for Gastroenterological Surgery	Wuxi	China	Sep.10
The 5th Indo-Japan International Symposium on Innovative Molecular Approaches in Global Health Research (IJS-2010)	Jaipur	India	Sep.10
46th European association the study of diabetes annual meeting	Stockholm	Sweden	Sep.10
The 5th Congress of Pediatric Infectious Diseases	Taipei	Taiwan	Sep.10
The 5th Congress of Pediatric Infectious Diseases	Taipei	Taiwan	Sep.10

International Conference Presentations by Core Member's Group

2010 Speakers	Title
Taniguchi M.	iPS-derived NKT cells.
Inamine A, Horiguchi S, Yonekura S, Hanazawa T, Hosokawa H, Matuura-Suzuki A, Nakayama T, Okamoto Y.	Sublingual administration of Lactobacillus paracasei KW3110 inhibits Th2-dependent allergic responses via the up-regulation of PD-L2 on dendritic cells.
Taniguchi M.	iPS-derived NKT cells.
Okamoto Y, Fujikawa A, Inamine A.	Nasal submucosal administration of antigen-presenting cells indued effective immunological response in cancer immunotherapy.
Yoshikawa K, Ohashi S, Toubaru S, Hasebe M, Ishikawa H, Tamura K, Shinoto M, Yamada S, Kandatsu S, Shiraishi T, Tanimoto K, Fukumura T, Saga T, Kamada T.	A preliminary investigation of Cu-62-ATSM tumor hypoxia PET/CT imaging comparing with FDG PET/CT for pancreas cancer.
Yoshida T, Sugiyama T, Suzuki S, Nagano N, Imada E, Hashimoto N, Mayama T, Suyama K, Tanaka T, Yokote K, Sueishi M, Tatsuno I.	Prevalence of Symptomatic Vertebral Fractures in Premenopausal Women Newly Treated with High-Dose Glucocoriticoid.
Yokote K.	Inhibitory effect of CCN3 on arterial neointimal hyperplasia though modulation of smooth muscle cell growth migration.
Ando Y, Kamada T, Fuwa N, Sakurai H, Ogino T, Murayama S, Yamamoto K, Hishikawa Y, Murakami M, Nakano T.	How did the particle therapy grow in the Japanese radiation therapy.
Hasegawa A, Jingu K, Takagi R, Morikawa T, Mizoe J, Kamada T, Tsujii H.	Carbon Ion Radiotherapy For Malignant Head-and-Neck Tumors Invading the Skull Base.
Shinoto M, Yamada S, Yasuda S, Imada H, Kamada T, Tsujii H.	Clinical Results of Carbon Ion Radiotherapy for Lymph Node Recurrence from Resected Colorectal Cancer.
Kamada T, Imai R, Tsuji H, Imaizumi T, Tsujii H.	Carbon ion radiotherapy for primary malignant bone tumors of the sacrum.
Bujo H.	Dyslipidemia and cardiovascular disease.
Bujo H.	Dyslipidemia and cardiovascular disease.
Ogita M, Miyauchi K, Dohi T, Miyazaki T, Nakajima N, Yokoyama T, Kojima T, Yokoyama K, Kurata T, Bujo H, Daida H.	Impact of Soluble LR11 on Target Lesion Revascularization After Coronary Intervention in Patients with Stable Coronary Artery Disease.
Imai R, Kamada T, Imaizumi T, Matsunobu A, Tsuji H.	Carbon ion radiotherapy for chondrosarcoma.
Ito K.	Cardiac Mast Cells Cause Atrial Fibrillation in Angitensin II-infused Hearts.
Sumida T, Naito A.T, Nagai T, Shiojima T, Komuro I.	Activation of β-catenin signaling by macrophage-derived factor is critical for Angiotensin II-induced vascular remodeling.
Akutsu Y, Matsubara H.	Fra-1 is an independent prognostic factor in esophageal squamous cell carcinoma and related to cell proliferation, migration and invasion in vitro.
Ishikawa T, Takemoto M, Akimoto Y, Yan K, Betsholtz C, Tryggvason K, Yokote K.	R3h–Domain Containing Like Protein Is a Novel Regulator of Glomerular Basement Membrane.
Ohwada C, Takeuchi M, Sakai S, Takeda Y, Abe&sbquo D, Shimizu N, Sakaida E, Kawaguchi T, Takubo K, Ebinuma H, Fukamachi I, Yokote K, Iwama A, Schneider WJ, Bujo H, Nakaseko C.	Prognostic Impact of a Novel Biomarker, Serum Soluble LR11 on Acute Leukemias.
Takeuchi M, Ohwada C, Sakai S, Takeda Y, Abe D, Shimizu N, Sakaida E, Kawaguchi T, Takubo K, Ebinuma H, Fukamachi I, Yokote K, Iwama A, Schneider WJ, Bujo H, Nakaseko C.	LR11 is a novel surface marker for normal leukocytes and leukemia cells.
Tokuhisa T, Arima M, Sakamoto A, Hatano M.	Role for Bcl6 in differentiation of high affinity IgE B cells.
Sugamata R, Suzuki K.	The contribution of neutrophil-derived myeloperoxidase in the early phase of acute respiratory distress syndrome induced by influenza virus infection.
Sugamata R, Suzuki K.	Discussion in infectious diseases and vasclulitis.

2011 Speakers	Title
Taniguchi M.	iPS-Derived NKT Cells and their Adjuvant Effects.
Kamada T.	Carbon ion radiotherapy at NIRS-clinical protocols and fractionation regimen.
Nakayama T.	Epigenetic control of memory Th2 cell function via Polycomb and Trithorax molecules.
Suzuki K, Oharaseki T, Yamada H, Nagi-Miura N, Ohno N, Takahashi K.	Application of synthetic IgGs for IVIg Treatment in Kawasaki Disease.
Nakayama T.	Epigenetic control of memory Th2 cell function via Polycomb and Trithorax molecules.
Suzuki K, Iida K, Wakashin H, Yokota M, Nakajima H.	The Role of STAT4 in Mast Cells.
Oonishi K, Imada H, Yasuda S, Yamada S, Shinoto M, Kamada T, Yokosuka O.	Outcomes after short-course carbon ion radiotherapy for patients with hepatocellular carcinoma according to tumor size.
Imada H, Yasuda S, Oonishi K, Yamada S, Shinoto M, Kamada T, Yokosuka O.	Comparison of efficacy and safety of short-course carbon ion radiotherapy for patients with hepatocellular carcinoma depending on the histological differentiation.
Imada H, Yasuda S, Oonishi K, Yamada S, Shinoto M, Kamada T, Yokosuka O.	Comparison of efficacy and safety of short-course carbon ion radiotherapy for patients with hepatocellular carcinoma depending on the histological differentiation.
Kanoh M, Kameda N, Miyake Y, Yoshida M, Komoda S, Kawahira H, Natsume T, Hayashi H, Matsubara H.	First experience of laparoscopic sleeve gastrectomy for morbid obesity in our OR.

	Meeting	City	Country	Month・Year
	40th Annual Meeting of the German Society for Immunology	Leipzig	Germany	Sep.10
	The 10th International Symposium on Dendritic Cells	Lugano	Switzerland	Sep.10
	8th German-Japan Symposium	Cuxhaven	Germany	Sep.10
	7th International Symposium on Tonsils and Mucosal Barriers of the Upper Airways	Asahikawa	Japan	Oct.10
	The 2010 EANM Congress	Vienna	Austria	Oct.10
	The American Society for Bone and Mineral Research 2010 Annual Meeting	San Diego	U.S.A	Oct.10
	6th INTERNATIONAL CCN WORKSHOP	Northern Ireland	UK	Oct.10
	ASTRO 52nd Annual Meeting	San Diego	U.S.A	Oct.10
	ASTRO 52nd Annual Meeting	San Diego	U.S.A	Oct.10
	ASTRO 52nd Annual Meeting	San Diego	U.S.A	Oct.10
	ASTRO 52nd Annual Meeting	San Diego	U.S.A	Oct.10
	Ho Chi Minh City University of Medicine and Pharmacy Topic Course on dyslipidemia and diabetes	Ho Chi Minh City	Vietnam	Nov.10
	Vietnam Nutrition Association The 5th National Nutrition Scientific Conferenc	Ho Chi Minh City	Vietnam	Nov.10
	American Heart Association Scientific Sessions 2010	Orlando	U.S.A.	Nov.10
	CTOS 16th Annual Meeting	Paris	France	Nov.10
	American Heart Association Scientic Sessions 2010	Chicago	U.S.A	Nov.10
	AHA scientific sessions 2010	Chicago IL	U.S.A	Nov.10
	22nd EORTC-NCI-AACR Symposium on Molecular Targerts and Cancer Therapeutics	Berlin	Germany	Nov.10
	American Society of Nephrology Renal Week 2010	Denver	U.S.A	Nov.10
	The 52th American Society of Hematology	Orlando	U.S.A	Dec.10
	The 52th American Society of Hematology	Orlando	U.S.A	Dec.10
	5th Chiba University G-COE symposium	Chiba	Japan	Dec.10
	Seminar in NIAID	Bethesda	U.S.A	Dec.10
	VCRC meeting in Boston University Medical School	Boston	U.S.A	Dec.10

	Meeting	City	Country	Month・Year
	2011 Keystone Symposia on NK and NKT Cell Biology	Colorado	U.S.A	Jan.11
	First International Conference on Real-time Tumor-tracking Radiation Therapy with 4D Molecular Imaging Technique	Kyoto	Japan	Feb.11
	40th Keystone Symposia	Banff	Canada	Feb.11
	10th International Kawasaki disease symposium	Kyoto	Japan	Feb.11
	Kenneth R. Wilske lecture series in science and medicine	Seattle	U.S.A	Feb.11
	14th International Congress of Immunology	Kobe	Japan	Feb.11
	The 21st Conference of the Asian Pacific Association for the Study of the Liver	Bangkok	Thailand	Feb.11
	The 21st Conference of the Asian Pacific Association for the Study of the Liver	Bangkok	Thailand	Feb.11
	The 21st Conference of the Asian Pacific Association for the Study of the Liver	Bangkok	Thailand	Feb.11
	The IFSO-APC&JSSO Congress 2011	Hokkaido	Japan	Feb.11

International Conference Presentations by Core Member's Group

2011 Speakers	Title
Kawahira H, Kawamura I, Kodama M, Hayashi H, Natsume T, Akai T, Mori M, Miyazawa Y, Matsubara H.	Retrospective analysis from 99 Japanese cases of bariatric surgery at Chiba University Hospital.
Akutsu Y, Hanari N, Mori M, Yoneyama Y, Ikeda N, Komatsu-Akimoto A, Endo S, Miyazawa Y, Yusup G, Matsubara H.	COX2 expression predicts resistance to chemoradiotherapy in esophageal squamous cell carcinoma.
Bujo H.	LR11, a novel biomarker for cardiovascular diseases.
Shimizu N, Nakaseko C, Takeuchi M, Ohwada C, Nishi K, Jiang M, Fukamachi I, Bujo H.	Soluble LR11, a modulator of G-CSF-mediated migration of HL-60 cells, is a potential circulating marker indicating the G-CSF-induced mobilization of hematopoietic stem cells.
Shimizu N, Nakaseko C, Takeuchi M, Ohwada C, Jiang M, Yokote K, Fukamachi I, Iseki T, Bujo H.	Soluble LR11, an inhibitor of SDF-1-mediated attachment of HL-60 cells, is a potential circulating marker indicating the G-CSF- induced mobilization of hematopoietic stem cells.
Arima T, Shimojo N, Nakano T, Morita Y, Suzuki S, Tomiita M, Kohno Y.	Presymptomatic differences of gene expression in cord blood mononuclear cells stimulated through Toll-like receptors in infants who have atopic dermatitis.
Ogoshi K, Uzawa K, Yamatoji M, Sakamoto Y, Koike H, Ogawara K, Shiiba M, Tanzawa H.	Aberrant expression of HOXA10 in oral squamous cell carcinoma.
Iyoda M, Uzawa K, Sakuma K, Kouzu Y, Kasamatsu A, Ogawara K, Shiiba M, Tanzawa H.	Identification of ZIC2 as a molecular target for oral cancer.
Suzuki K.	Host defense against Influenza (H5N1 and H1N1) infection.
Taniguchi M.	iPS-derived NKT cell with adjuvant activity.
Taniguchi M.	NKT cell-mediated adjuvant activity.
Nohata N.	miR-133a as a tumor suppressive microRNA targeting multiple oncogenes in head and neck squamous cell carcinoma (HNSCC).
Kishida S, Furihata T, Sugiura H, Kamiichi A, Chiba K.	Ribavirin Metabolism By Purine Nucleoside Phosphorylase:Potential Implications For Ribavirin First-Pass Metabolism In Human Small Intestine.
Kamiichi A, Furihata T, Kishida S, Ohta Y, Saito K, Chiba K.	Functional Characterization And Differentiation Potential of Conditionally Immortalized Human Brain Microvascular Endothelial Cells.
Mizuguchi M, Furihata T, Iikura M, Chiba K.	The uptake transporters are required for ribavirin to exert its pharmacological action in the OR6 cells.
Nagai M, Firihata T, Matsumoto S, Ishii S, Chiba K.	Characterization of a cancer specific organic anion transporting polypeptide 1B3 mRNA splice isoform.
Tanaka S, Sashida G, Nakaseko C, Yokote K, Iwama A.	Ezh2 plays a critical role in the progression of acute leukemia mediated by MLL-AF9.
Yokote K.	Statin in treatment of metabolic syndrome.
Ohara O.	Integration of New Technologies for Accurate and Rapid Molecular Diagnosis of Primary Immunodeficiencies.
Ando Y, Kamada T, Fuwa N, Sakurai H, Ogino T, Murayama S, Yamamoto K, Hishikawa Y, Murakami M, Nakano T.	How did the particle therapy grow from 2002 to 2010 in Japan?; Current Status of Proton and Carbon Ion Radiotherapy.
Kusunoki R, Nagao T, Iwamura C, Kobayashi S, Yumura W, Nakayama T, Suzuki K.	Treatments for MPO-ANCA-associated vasculitis in SCG/Kj mouse.
Tomizawa K, Nagao T, Kusunoki R, Saiga K, Oshima M, Kobayashi K, Nakayama T, Tanokura M, Suzuki K.	Reduction of MPO-ANCA epitopes in SCG/Kj mice by 15-Deoxyspergualin treatment restricted by IgG2b associated with crescentic glomerulonephritis.
Suzuki K, Nagao T, Itabashi M, Sugamata R, Yamazaki Y, Yumura Y, Tsukita S, Wang P-C, Nakayama T, Suzuki K.	A novel anti-neutrophil antibody in serum of patients with MPO-ANCA associated vasculitis.
Nagao T, Suzuki K, Utsunomiya K, Matsumura M, Saiga K, Wang P-C, Minamitani H, Aratani Y, Nakayama T, Suzuki K.	Direct activation of glomerular endothelial cells by anti-moesin activity of anti-myeloperoxidase antibody.
Suzuki K.	Activities of Japanese vasculitis investigators.
Yamasaki K, Motohashi S, Nakayama T.	Induction of NKT Cell-Specific Immune Responses in Cancer Tissues after NKT Cell-Targeted Adoptive Immunotherapy.
Sugamata R, Dobashi H, Nagao T, Tomizawa K, Yamamoto K, Nakajima N, Sato Y, Aratani Y, Oshima M, Yamazak Y, Tsukita S, Sata T, Kobayashi K, Kawachi S, Nakayama T, Suzuki K.	Neutrophil-derived myeloperoxidase contribution in early phase of fulminant acute respiratory distress syndrome (FARDS) induced by influenza virus infection.
Bujo H.	Pharmacologic treatment for PAD in Japan, Cilostazol, and expected effects of lipid lowering drugs and probucol.
Nakayama T, Onodera A.	Epigenetic control of memory Th2 cell function via Polycomb and Trithorax molecules.
Kambe N.	Mastocytosis and mast cell development depending on Kit.
Kambe N, Nakamura Y.	Mast cells mediate neutrophil recruitment and vascular leakage through the NLRP3 inflammasome.
Nakagomi D, Ikeda K, Okubo A, Iwamoto T, Suzuki Y, Takatori T, Suzuki S, Takabayashi K, Nakajima H.	The impact of ultrasonography on the classification of RA with 2010 ACR/EULAR criteria.
Komuro I.	Molecular mechanisms of diabetes and diabetic vasculopathy.
Yoshida T, Hirota Y, Yokoo H, Higuchi S, Sakuma I, Nagano H, Imada E, Hashimoto N, Suzuki S, Mayama T, Suyama K, Tanaka, Nakasa K, Yokote K, Tatsuno I.	Effective Treatment of Hypothyroidism with Intravenous Infusion of Levothyroxine in a Patient with Multidrug Resistance.
Inoue Y, Shimojo N, Suzuki Y, Nakano T, Morita Y, Arima T, Tomiita M, Kohno Y.	Serum levels of human chitinase-like protein YKL-39 but not YKL-40 was lower in childhood asthma.
Nakano T, Inoue Y, Shimojo N, Okamoto Y, Kohno Y.	The use of complementary and alternative medicine by pediatric patients with food allergy in Japan.
Nakano T, Inoue Y, Shimojo N, Okamoto Y, Kohno Y.	The use of complementary and alternative medicine by pesatric patients with food allergy in Japan.
Inoue Y, Shimojo N, Suzuki Y, Nakano T, Morita Y, Arima T, Tomiita M, Kohno Y.	Serum levels of human chitinase-like protein YKL-39 but not YKL-40 was lower in childhood asthma.

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	The IFSO-APC&JSSO Congress 2011	Hokkaido	Japan	Feb.11
	Society of surgical Oncology 64th Annual Cancer Symposium	Texas	U.S.A	Mar.11
	Amsterdam University Academic Medical Center (AMC) Vascular Medicine Symposium	Amsterdam	Holland	Mar.11
	Keystone Symposia - Stem cells, cancer and metastasis-	Kestone	U.S.A	Mar.11
	Cancer Stem Cell Symposia	Keystone	U.S.A	Mar.11
	14th International Congress of Immunology in Kobe. 2010.	Kobe	Japan	Mar.11
	The IADR 89th General Session & Exhibition	San Diego	U.S.A	Mar.11
	The IADR 89th General Session & Exhibition	San Diego	U.S.A	Mar.11
	14th International Congress of Immunology	Kobe	Japan	Mar.11
	World Immune regulation Meeting -V	Davos	Switzerland	Mar.11
	World Immune regulation Meeting -V	Davos	Switzerland	Mar.11
	102st AACR	Orlando	U.S.A	Apr.11
	4th ASIA PACIFIC REGIONAL MEETING OF ISSX(2011)	Tainan	Taiwan	Apr.11
	4th ASIA PACIFIC REGIONAL MEETING OF ISSX(2011)	Tainan	Taiwan	Apr.11
	4th ASIA PACIFIC REGIONAL MEETING OF ISSX(2011)	Tainan	Taiwan	Apr.11
	4th ASIA PACIFIC REGIONAL MEETING OF ISSX(2011)	Tainan	Taiwan	Apr.11
	Japanese Society of Hematology International Symposium	Nagasaki	Japan	Apr.11
	The Royal College of Physician of Thailand	Pattaya	Thailand	Apr.11
	The 7th Congress of Asian Society for Pediatric Research	Denver	U.S.A	Apr.11
	Particle Therapy Co-Operative Group Meeting 50	Philadelphia	U.S.A	May.11
	15th International Vasculitis and ANCA Workshop	Chapel Hill, NC	U.S.A	May.11
	15th International Vasculitis and ANCA Workshop	Chapel Hill, NC	U.S.A	May.11
	15th International Vasculitis and ANCA Workshop	Chapel Hill, NC	U.S.A	May.11
	15th International Vasculitis and ANCA Workshop	Chapel Hill, NC	U.S.A	May.11
	Vasculitis Clinical Research Investigators Meeting - The Vasculitis Clinical Research Consortium (Vcrc) & The European Vasculitis Study Group	Chapel Hill, NC	U.S.A	May.11
	CIS 2011 Annual Meeting	Chicago	U.S.A	May.11
	7th International Peroxidase Meeting	Brussels	Belgium	May.11
	1st Joint APSAVD-PLAS-PSVM Athersclerotic Prophrral Arterial Disease Forum	Manila	Phillipine	May.11
	EUThyme-Rolduc Meeting	Leeuwenhorst	Netherland	May.11
	22nd World Conference of Dermatology 2011	Seoul	Korea	May.11
	22nd World Conference of Dermatology 2011	Seoul	Korea	May.11
	EULAR (European League Against Rheumatism) Congress 2011	London	UK	May.11
	SIRIC International Symposium 2011	Seoul	Korea	Jun.11
	The Endocrine Society 93nd Annual Meeting & Expo	Boston	U.S.A	Jun.11
	EAACI 2011	Istanbul	Turkey	Jun.11
	EAACI Congress 2011	Isutanbul	Turkey	Jun.11
	European Academy of Allergy and Clinical Immunology 2011	Istanbul	Turkey	Jun.11
	European Academy of Allergy and Clinical Immunology	Istanbul	Turkey	Jun.11

International Conference Presentations by Core Member's Group

2011 Speakers	Title
Shimojo N, Ochiai S, Kohono Y, Morita Y. Milk.	Cytokine/chemokine biomarkers associated with the development of eczema in infants at the age of 6 month.
Bujo H.	Circulating soluble LR11 -a novel molecule representing pathological immature cells-.
Bujo H.	Circulating soluble LR11 -a novel molecule representing pathological immature cells-.
Nakayama T, Onodera A.	Regulation of memory Th2 cell function and allergic airway inflammation via polycomb and trithorax molecules.
Nakayama T.	Epigenetic regulation of GATA3 expression and its target genes in Th2 cells.
Kamiichi A, Furihata T, Kishida S, Ohta Y, Saito K, Kawamatsu S, Chiba K.	Functional characterization and differentiation Potential of conditionally immortalized Human brain microvascular endothelia cells.
Ando Y, Tanikawa T, Mukai M, Kamada T, Uemura K, Tsukamoto N, Masuzawa T, Ohnuki K, Osada M, Seki M.	Synthesis of Overall Dose Distribution for Multiple Radiation Therapy by Nonlinear Registration Method.
Kuroda M, Asada S, Aoyagi Y, Tanaka S, Konno S, Tanio M, Aso M, Saito Y, Bujo H.	Proliferative Adipocytes as Therapeutic Gene Vehicle toward Sustained Protein Replacement Therapy.
Yokote K.	Pitavastatin: Eight years of successful lipid management.
Hanazawa T.	Identification of tumor suppressive microRNAs in maxillary sinus squamous cell carcinoma based on microRNA expression signature.
Yokoyama M.	Inhibition of endothelial senescence ameliorates insulin resistance of obese mice.
Sakurai K.	Effect of an α-glucosidase inhibitor acarbose on glucagon-like peptide-1 secretion and postprandial lipid profile.
Matsubara H.	Surgical Treatment of Esophageal Cancer: Present Aspects and New Trends.
Mori M, Akutsu Y, Hayashi H, Kawahira H, Hanari N, Sadahiro T, Oda S, Matsubara H.	A case of 100-year-old woman successfully treated for upside down stomach with laparoscopic surgery.
Ikeda N, Akutsu Y, Mori M, Hanari N, Komatsu A, Miyazawa Y, Matsubara H.	Expression of HMGB1 is associated with 5FU sensitivity in esophageal squamous cell carcinoma.
Shuto K, Kono T, Saito H, Hayano K, Imanishi S, Akutsu Y, Matsubara H.	Comparison between DWIBS and PET in preoperative N-staging of esophageal squamous cell cancer.
Shuto K, Saito H, Kono T, Shiratori T, Akutsu Y, Uesato M, Matsubara H.	DWIBS positive nodes and negative of esophageal squamous cell cancer and the difference of postoperative outcome.
Yoneyama Y, Miyauchi H, Ohira G, Tohma T, Kuboshima M, Akutsu Y, Hanari N, Matsubara H.	The efficacy of intraoperative irrigation and colonoscopy for obstructed left-sided colorectal cancer.
Miyauchi H, Matsubara H, Ohira G.	Is chemoradiotherapy for lower rectal carcinoma able to be a substitute for preventive lateral lymph node dissection ?
Akutsu Y, Hanari N, Mori M, Yoneyama Y, Ikeda N, Endo S, Komtasu-Akimoto A, Matsubara H.	COX2 expression predicts resistance to chemoradiotherapy in 499 esophageal squamous cell carcinoma.
Akutsu Y, Hanari N, Mori M, Gulbostan Yusup, Komatsu-Akimoto A, Ikeda N, Endo S, Matsubara H.	Correlation between gp96 expression and the surgical outcome in 498 patients with esophageal squamous cell carcinoma.
Natsume T, Shuto K, Aoyama H, Kawahira H, Akai T, Mori M, Hayashi H, Matsubara H.	Full scale volume-rendering and left lateral position CT improve the diagnosis of the pancreas invasion of gastric cancer.
Matsubara H.	Treatment of locally advanced esophageal cancer Salvage surgery after definitive chemo/radiation therapy.
Sai S, Oonishi K, Yamada S, Kamada T.	Effects of carbon ion and X-ray irradiation on pancreatic cancer stem cells.
Kambe N, Satoh T, Matsue H.	Peripheral CD14+ monocytes from early-onset sarcoidosis associated with NOD2 mutation do not show the molecular signature of NF-κ B signaling.
Satoh T, Kambe N, Matsue H.	Homopolymerization of ASC using FKBP12 chimeric protein induced rapid cell death accompanied with IL-1 β processing.
Kamada T.	Carbon Ion RT at NIRS: Clinical protocols and fractionation regimen.
Ishikawa T.	R3h–Domain Containing Like Protein Is a Novel Regulator of Glomerular Basement Membrane.
Hoshino I, Isozaki Y, Akutsu Y, Komatsu A, Hanari N, Mori M, Yoneyama Y, Ikeda N, Akanuma N, Maruyama T, Takeshita N, Wei Q, Yusup G, Matsubara H.	Antitumor effects of histone demethylase inhibition on esophageal squamous cell carcinoma.
Yokote K.	Studies on normal aging and progeric disorders.
Nakayama T.	NKT-Induced Antigen-Specific Memory Th2 Response.
Taniguchi M.	Early NKT Precursor.
Motohashi S, Ishibashi F, Taniguchi M, Yoshino I, Nakayama T.	NKT cell-based Immunotherapy for non-small cell lung cancer.
Horie T.	Antitumor drug (methotrexate) induced small intestinal toxicity.
Inoue Y, Yoshida M, Ando K, Hino M, Ochiai H, Nakano T, Morita Y, Arima T, Tomiita M, Shimojo N, Kohno Y.	Two cases of newly-onset post-cord blood stem cell transplantation food allergy.
Hasegawa A, Koto M, Takagi R, Morikawa T, Kamada K, Mizoe J, Tsujii H.	Carbon Ion Radiotherapy for Adenoid Cystic Carcinoma of the Head-and-Neck.
Onodera A, Horiuchi S, Hosokawa H, Watanabe Y, Suzuki Y, Nakayama T.	Genome-wide analysis reveals unique regulation of transcription of Th2-specific genes by GATA3.
Nohata N.	Tumor suppressive microRNA-1/-133a regulates multiple oncogenes in maxillary sinus squamous cell carcinoma.

Meeting	City	Country	Month • Year
European 30th Academy of Allergy and Clinical Immunology 2011	Istanbul	Turkey	Jun.11
Medical University of Vienna Biocenter Symposium	Vienna	Austria	Jun.11
Berlin Max-Delbr, ck-Center for Molecular Medicine symposium	Berlin	Germany	Jun.11
30th Congress of the European Academy of Allergy and Clinical Immunology, 2011	Istanbul	Turkey	Jun.11
45th joint Working Conference on Immunology and Viral Diseases	Stanford, CA	U.S.A	Jun.11
9th International Conference on Cerebral Vascular Biology (CVB2011) Leiden/The Netherlands	Leiden	Leiden/The Netherlands	Jun.11
CARS2011 (25th International Congress and Exhibition)	Berlin	Germany	Jun.11
American Society of Gene & Cell Therapy 14th annual meeting	Seattle	U.S.A	Jun.11
European Atherosclerosis pre-symposium	Gothenburg	Sweden	Jun.11
102nd AACR	Orlando	U.S.A	Jul.11
Basic Cardiovascular Sciences 2011	New Orleans	U.S.A	Jul.11
The 3rd Annual Scientiﬁc Meeting of the Asian Association for the Study of Diabetes	Beijing	China	Jul.11
The third Symposium‚ Stomach Cancer: Diagnosis and Treatment	Ulaanbaatar	Mongolia	Aug.11
International Surgical Week/ISW 2011	Yokohama	Japan	Aug.11
International Surgical Week/ISW 2011	Yokohama	Japan	Aug.11
International Surgical Week/ISW 2011	Yokohama	Japan	Aug.11
International Surgical Week/ISW 2011	Yokohama	Japan	Aug.11
International Surgical Week/ISW 2011	Yokohama	Japan	Aug.11
International Surgical Week/ISW 2011	Yokohama	Japan	Aug.11
International Surgical Week/ISW 2011	Yokohama	Japan	Aug.11
International Surgical Week/ISW 2011	Yokohama	Japan	Aug.11
International Surgical Week/ISW 2011	Yokohama	Japan	Aug.11
International Surgical Week/ISW 2011	Yokohama	Japan	Aug.11
The 4th Asian-Oceanic Pancreatic Association (AOPA)	Saishuu	Korea	Sep.11
41th Annual ESDR Meeting	Barcelona	Spain	Sep.11
41th Annual ESDR Meeting	Barcelona	Spain	Sep.11
ESTRO Teaching Course on Protons and Ions	Paris	France	Sep.11
EASD: European Association for the Study of Diabetes	Lisbon	Portugal	Sep.11
8th International Symposium on Mineral Residual Cancer	Osaka	Japan	Sep.11
Conference on Ageing Societies – a Japanese-Swedish Research Cooperation	Uppsala	Sweden	Sep.11
6th International Symposium on CD1 and NKT cells	Chicago	U.S.A	Sep.11
6th International Symposium on CD1 and NKT Cells	Chicago	U.S.A	Sep.11
6th International Symposium on CD1 and NKT cells.	Chicago	U.S.A	Sep.11
The 2nd International Conference on Gastroenterology	Prague	Czech Republic	Sep.11
APAPARI 2011	Fukuoka	Japan	Sep.11
ASTRO 53rd Annual Meeting	Maiami	U.S.A	Oct.11
NCI Symposium on Chromosone Biology	Washington	U.S.A	Oct.11
16th World Congress on Advances in Oncology and 14th International Symposium on Molecular Medicine	Rhodes	Greece	Oct.11

International Conference Presentations by Core Member's Group

2011 Speakers	Title
Hoshino I, Isozaki Y, Takeshita N, Akutsu Y, Komatsu A, Hanari N, Mori M, Yoneyama Y, Ikeda N, Akanuma N, Maruyama T, Wei Q, Yusup G, Seki N, Matsubara H.	microRNA expression profiling regulated by histone deacetylase inhibitor on esophageal squamous cell carcinoma.
Komuro I.	Harmful Effects of Excenssive Insulin Signaling in a Setting of Pressure Overload.
Tanimoto, Yoshikawa K, Shiraishi T, Inagaki E, Toubaru S, Ohashi S, Obata T, Saga T, Watanabe K, Tsuji H, Ando Y, Kamada T, Miyazaki M, et.al	PPre-surgery SUV and ADC as prognostic factor for outcome in pancreatic cancer.
Yoshikawa K, Ohashi S, Toubaru S, Hasebe M, Ishikawa H, Tamura K, Shinoto M, Yamada S, Kandatsu S, Shiraishi T, Tanimoto K, Fukumura T, Saga T, Kamada T.	Cu-62-ATSM hypoxic imaging of uterine cervical cancer and outcome of carbon ion radiotherapy.
Shiraishi T, Yoshikawa K, Fukumura A, Mizuno H, Tanimoto K, Ishii N, Inagaki E, Omatsu M, Ohashi S, Toubaru S, Kamada T, Ando Y, Tsuji H, Watanabe K, et al.	Experimental PET/CT study of imaging the small amount of positron emitters generated by carbon ion beam irradiation.
Toubaru S, Yoshikawa K, Ohashi S, Hasebe M, Ishikawa H, Sagou K, Tamura K, Tanimoto K, Kandatsu S, Mizoe J, Fukumura T, Saga T, Kawaguchi K, Kamada T.	Multivariate analyses for prognostic evaluation with C-11 methionine PET for head and neck adenoid cystic carcinoma treated by carbon ion radiotherapy.
Koto M, Hasegawa A, Takagi R, Fujikawa A, Morikawa N, Tsujii H, Kamada T.	Carbon Ion Radiotherapy for Skull Base and Paracervical Tumors.
Tsuji H, Mizoguchi N, Toyama S, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Prostate Cancer.
Yamada S, Shinoto M, Yasuda S, Imada H, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Patients with Locally Recurrent Rectal Cancer.
Shinoto M, Yamada S, Yasuda S, Imada H, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Pancreatic Cancer.
Imada H, Yasuda S, Yamada S, Shinoto M, Oonishi K, Endo S, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Liver Cancer.
Komuro I.	p53 inhibits angiogenesis .
Sakurai D.	Immunotherapy for Allergic Rhinitis; up-to-date findings.
Suzuki K.	Role of Myeloperoxidase in Vasculitis and Crescentic Glomerulonephritis.
Hanazawa T.	Tumor suppressive microRNA-1 and -133a regulates multiple oncogenes in maxillary sinus squamous cell carcinoma.
Hoshino I, Akutsu Y, Komatsu A, Hanari N, Mori M, Yoneyama Y, Ikeda N, Akanuma N, Isozaki Y, Maruyama T, Takeshita N, Qin Wei, Gulbostan Yusup, Suzuki T, Matusbara H.	Antitumor effects of histone demethylase inhibition on esophageal squamous cell carcinoma.
Hoshino I, Ikeda N, Akutsu Y, Komatsu A, Hanari N, Mori M, Yoneyama Y, Akanuma N, Isozaki Y, Maruyama T, Takeshita N, Qin Wei, Gulbostan Yusup, Matusbara H.	Expression of HMGB1 in esophageal squamous cell carcinoma.
Kawahira H, Hayashi H, Natsume T, Akai T, Hanari N, Mori M, Horibe D, Hayano K. Matsubara H.	A nove liver retraction avoiding post-surgical liver dysfunction.
Matsubara H, Akutsu Y, Shuto K, Shiratori T, Uesato M, Kohno T, Hanari N, Hoshino I, Miyazawa Y, Yasuda S, Yamada S, Kamata T.	Trial of new preoperative therapy for esophageal cancer.
Kawaguchi T.	Serum soluble LR11 is a promising novel biomarker for B cell lymphoma.
Yoshida Y.	Notch signaling regulates vascular endothelial cell senescence.
Yokoyama M.	Inhibition of endothelial senescence ameliorates insulin resistance of obese mice.
Yokote K.	Eight years of experience with pitavastatin.
Hanazawa T.	A clinical analysis of combination therapy of radiation and intra-arterial chemotherapy for stage III and IV maxillary sinus squamous cell carcinoma.
Hanazawa T.	Carbon Ion Radiotheapy.
Kamada T.	Overview of the Carbon Ion Radiotherapy at HIMAC.
Yamamoto N, Baba M, Nakajima M, Yoshikawa K, Matsufuji N, Minohara S, Tsuji H, Kamada T, Tsujii H.	Carbon Ion Radiotherapy in a Hypofraction Regimen for Stage I Non-Small Cell Lung Cancer.
Hasegawa A, Koto M, Takagi R, Fujikawa A, Morikawa T, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Malignant Head-and-Neck Tumors.
Imai R, Kamada T, Tsuji H, Maruyama K, Matsumoto K, Tsujii H.	Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas.
Yamamoto N, Baba M, Nakajima M, Yoshikawa K, Matsufuji N, Minohara S, Tsuji H, Kamada T, Tsujii H.	Carbon Ion Radiotherapy in a Hypofraction Regimen for Stage I Non-Small Cell Lung Cancer.
Hasegawa A, Koto M, Takagi R, Fujikawa A, Morikawa T, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Skull Base and Head-and-Neck Tumors.
Tsuji H, Mizoguchi N, Toyama S, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Prostate Cancer Up-to-date results.
Yamada S, Shinoto M, Endo S, Yasuda S, Imada H, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Patients with Locally Recurrent Rectal Cancer and Carbon Ion Radiotherapy for Pancreatic Cancer.
Yasuda S, Imada H, Yamada S, Shinoto M, Oonishi K, Endo S, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Liver Cancer.
Imai R, Kamada T, Tsuji H, Maruyama K, Matsumoto K, Tsujii H.	Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas.
Komuro I.	Molecular Mechanisms and Novel Treatments of Heart Failure.

	Meeting	City	Country	Month · Year
	21st World Congress of the International Association of Surgeons‚ Gastroenterologists and Oncologists/IASGO2011	Tokyo	Japan	Oct.11
	American Heart Association 2011	Orlando	U.S.A	Oct.11
	EANM Annual Congress 2011	Birmingham	England	Oct.11
	EANM Annual Congress 2011	Birmingham	England	Oct.11
	EANM Annual Congress 2011	Birmingham	England	Oct.11
	EANM Annual Congress 2011	Birmingham	England	Oct.11
	2th NIRS-ETOILE Joint Symposium on Carbon Ion Therapy	Lyon	France	Oct.11
	2th NIRS-ETOILE Joint Symposium on Carbon Ion Therapy	Lyon	France	Oct.11
	2th NIRS-ETOILE Joint Symposium on Carbon Ion Therapy	Lyon	France	Oct.11
	2th NIRS-ETOILE Joint Symposium on Carbon Ion Therapy	Lyon	France	Oct.11
	2rd NIRS-ETOILE Joint Symposium on Carbon Ion Therapy	Lyon	France	Oct.11
	The Second Pacific Symposium on Vascular Biology	Jeju Island	Korea	Oct.11
	Kyung Hee Internation Rhinology Symposium	Seoul	Korea	Nov.11
	American society of nephrology-2011 Kidney week	Philadelphia, PN	U.S.A	Nov.11
	11th Japan-Taiwan Conference on Otolaryngology-Head and Neck Surgery	Kobe	Japan	Nov.11
	21st World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists/IASGO2011	Tokyo	Japan	Nov.11
	21st World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists/IASGO2011	Tokyo	Japan	Nov.11
	21st World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists/IASGO2011	Tokyo	Japan	Nov.11
	21st World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists/IASGO2011	Tokyo	Japan	Nov.11
	The 53rd American Society of Hematology	San Diego	U.S.A	Nov.11
	American Heart Association Scientific Sessions 2011	Orlando	U.S.A	Nov.11
	American Heart Association Scientific Meeting 2011	Orlando	U.S.A	Nov.11
	The 27th Mexican Congress of Cardiology	Puerto Vallarta	Mexico	Nov.11
	14th International Rhinologic Society, 30th International Symposium Infection and Allergy of the Nose	Tokyo	Japan	Nov.11
	14th International Rhinologic Society, 30th International Symposium Infection and Allergy of the Nose	Tokyo	Japan	Nov.11
	2th NIRS-ETOILE Joint Symposium on Carbon Ion Therapy	Lyon	France	Nov.11
	2th NIRS-ETOILE Joint Symposium on Carbon Ion Therapy	Lyon	France	Nov.11
	2th NIRS-ETOILE Joint Symposium on Carbon Ion Therapy	Lyon	France	Nov.11
	2nd NIRS-ETOILE Joint Symposium on Carbon Ion Therapy	Lyon	France	Nov.11
	Symposium of Carbon Ion Radiotherapy in Taipei	Taipei	Taiwan	Dec.11
	Symposium of Carbon Ion Radiotherapy in Taipei	Taipei	Taiwan	Dec.11
	Symposium of Carbon Ion Radiotherapy in Taipei	Taipei	Taiwan	Dec.11
	Symposium of Carbon Ion Radiotherapy in Taipei	Taipei	Taiwan	Dec.11
	Symposium of Carbon Ion Radiotherapy in Taipei	Taipei	Taiwan	Dec.11
	Symposium of Carbon Ion Radiotherapy in Taipei	Taipei	Taiwan	Dec.11
	The Korean Society of Cardiology	Daejeon	Korea	Dec.11

International Conference Presentations by Core Member's Group

2011

Speakers	Title
Inoue Y, Shimojo N, Suzuki Y, Nakano T, Morita Y, Arima T, Tomiita M, Kohno Y.	Serum Levels of Human Chitinase-Like Protein YKL-39 but Not YKL-40 Was Lower in Childhood Asthma.
Shimizu N, Nakaseko C, Takeuchi M, Ohwada C, Tsukamoto S, Kawaguchi T, Nishii K, Jiang M, Yokote K, Fukamachi I, Bujo H.	Soluble LR11/SorLA, a potential circulating marker indicating the G-CSF-induced mobilization of hematopoietic stem cells, is a modulator of G-CDF-mediated migtration of HL-60 cells.
Kawaguchi T, Ohwada C, Higashi M, Takeuchi M, Sakai S, Takeda Y, Shimizu N, Sakaida E, Takubo K, Ebinuma H, Fukamachi I, Tamaru J, Yokote K, Bujo H, Nakaseko C.	Serum soluble LR11 as a novel biomarker for B cell lymphoma.
Tanaka S.	Ezh2 plays a critical role in the progression of MLL-AF9-induced acute myeloid leukemia.
Shimizu N.	Soluble LR11, a potential circulating marker indicating the G-CSF-induced mobilization of hematopoietic stem cells, is a modulator of G-CSF-mediated migration of HL-60 cells.

2012

Speakers	Title
Furihata T, Nagai M, Ishii S, Matsumoto S, Motohashi S, Yoshino I, Chiba K.	A novel variant is a bona fide organic anion transporting polypeptide 1B3 in cancer cells.
Kishida S, Furihata T, Kamiichi A, Kawamatu S, Chiba K.	Establishment and functional characterization of a novel conditionally immortalized human brain microvascular endothelial cell line.
Endo Y.	Eomesodermin controls IL-5 production in memory Th2 cells through the inhibition of GATA3 activity.
Okabe E.	Incidence and characteristics of metabolic disorders and vascular complications in Werner syndrome patients in Japan.
Taniguchi M.	Subsets of NKT cells.
Onouchi Y.	Genome-wide association study identified new susceptibility loci for Kawasaki disease -We have found milestones but still have far to go-.
Yoshida Y, Minamino T	Notch signaling positively regulates vascular endothelial cell senescence.
Oonishi K, Imada H, Yasuda S, Yamada S, Shinoto M, Endo E, Kamada T, Yokosuka O.	Efficacy and safety of short-course carbon ion radiotherapy for elderly hepatocellular carcinoma patients.
Watanabe K, Suzuki H, Haniu H, Numano F, Saitoh A, Uchiyama M, Bujo H.	Soluble LR 11: a novel biomarker for vascular lesion development late after Kawasaki disease.
Onishi K, Imada H, Yasuda S, Yamada S, Shinoto M, Endo S, Kamada T, Yokosuka O.	Efficacy and safety of short-course carbon ion radiotherapy for elderly hepatocellular carcinoma patients.
Ikeuchi T, Hirayama S, Miida T, Tokutake T, Yajima R, Jiang M, Bujo H, Nishizawa M.	Quantification of soluble LR11/SorLA in CSF and plasma of patients with Alzheimer disease
Yamamoto N, Baba M, Nakajima M, Yoshikawa K, Matsufuji N, Minohara S, Tsuji H, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas.
Tsuji H, Mizoguchi N, Toyama S, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas.
Yamada S, Shinoto M, Yasuda S, Imada H, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas.
Hasegawa A, Koto M, Takagi R, Fujikawa A, Morikawa T, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas.
Imai R, Kamada T, Tsuji H, Maruyama K, Matsumoto K, Tsujii H.	Carbon Ion Radiotherapy for Bone and Soft Tissue Sarcomas.
Shinoda K.	CD69 regulates the formation of resting T helper memory.
Okamoto Y.	Research and development of the new treatment against allergic rhinitis in Japan.
Onouchi Y, Ozaki K, Suzuki H, Terai M, Hata A, Tanaka T.	ITPKC and CASP3 polymorphisms and risks for IVIG unresponsiveness and coronary artery lesion formation in Kawasaki disease.
Horie T.	Oxidative stress and Hepatotoxicity.
Kamada T.	arbon Ion RT at NIRS: Clinical protocols and fractionation regimen.
Ito T.	CDC42 and NFκB signaling contribute to pro-inflammatory phenotype of senescent endothelial cells.
Yokote K.	Lipid management guideline in Japan.
Taniguchi M.	NKT cell subsets and their function.
Ikeda K, Nakagomi D, Hosokawa J, Yamagata M, Nakajima H.	Optic neuropathy associated with Churg-Strauss syndrome: a report of two cases.
Hanazawa T.	microRNA-874 as a tumor suppressor in maxillary sinus squamous cell carcinoma based on microRNA expression signature.
Kinoshita T.	Molecular networks regulated by tumor suppressive microRNA-375 in head and neck squamous cell carcinoma.
Nohata N.	Molecular networks regulated by tumor suppressive microRNA-1 and microRNA-133a in head and neck squamous cell carcinoma.
Yokote K.	Cellular regulation in diabetic complications.
Okamoto Y.	Alternatie Medicine for allerge rhinitis.
Nohata N.	Identification of Novel Tumor Suppressive microRNAs, in Head and Neck Squamous Cell Carcinoma.
Nakayama T.	Pathogenic memory Th2 cells in airway inflammation.

Meeting	City	Country	Month・Year
WAC 2011	Cancun	Mexico	Dec.11
The 53rd American Society of Hematology	San Diego	U.S.A	Dec.11
The 53rd American Society of Hematology	San Diego	U.S.A	Dec.11
The 53rd American Society of Hematology	San Diego	U.S.A	Dec.11
The 53rd American Society of Hematology	San Diego	U.S.A	Dec.11

Meeting	City	Country	Month・Year
International Symposium on PPF of Molecular Pharmacokinetics	Tokyo	Japan	Jan.12
International Symposium on PPF of Molecular Pharmacokinetics	Tokyo	Japan	Jan.12
14th International Conference on Lymphocyte Activation and Immune Regulation	Newport Beach	U.S.A	Feb.12
International Conference on Orphan Drugs and Rare Diseases	Tokyo	Japan	Feb.12
The 4th Joint RCAI-LIAI Workshop Program	San Diego	U.S.A	Feb.12
10th International Kawasaki Disease Symposium	Kyoto	Japan	Feb.12
Gordon Research Conference Aging Biology of	Ventura	U.S.A	Feb.12
The 22nd Congress of the Asian Pacific Association for the Study of the Liver	Taipei	Taiwan	Feb.12
The 10th International Kawasaki Disease Symposium	Kyoto	Japan	Feb.12
The 22nd Congress of the Asian Pacific Association for the Study of the Liver	Taipei	Taiwan	Feb.12
Keystone Symposia - Apo, Alzheimer's and lipoprotein biology	Keystone	U.S.A	Feb.12
NIRS-KFSHRC Joint Symposium on Carbon Ion Radiotherapy and Radiation Emergency Medicine	Riyadh	Saudi Arabia	Feb.12
NIRS-KFSHRC Joint Symposium on Carbon Ion Radiotherapy and Radiation Emergency Medicine	Riyadh	Saudi Arabia	Feb.12
NIRS-KFSHRC Joint Symposium on Carbon Ion Radiotherapy and Radiation Emergency Medicine	Riyadh	Saudi Arabia	Feb.12
NIRS-KFSHRC Joint Symposium on Carbon Ion Radiotherapy and Radiation Emergency Medicine	Riyadh	Saudi Arabia	Feb.12
NIRS-KFSHRC Joint Symposium on Carbon Ion Radiotherapy and Radiation Emergency Medicine	Riyadh	Saudi Arabia	Feb.12
14th International Conference on Lymphocyte Activation and Immune Regulation	NewPort Beach	U.S.A	Mar.12
The 43rd Korea Otolaryngology meeting	Seoul	Korea	Mar.12
Human Genome Meeting 2012	Sydney	Australia	Mar.12
The 5th International Symposium for Future Technology Creating Better Human Health and Society	Okayama	Japan	Mar.12
ESTRO Teaching Course on Protons and Ions	Uppsala	Sweden	Mar.12
Keystone Symposia symposium:Molecular Basis of Vascular Inflammation and Atherosclerosis (C7)	Big Sky	U.S.A	Mar.12
XVI International Symposium on Atherosclerosis	Sydney	Australia	Mar.12
Meeting of the International PhD Program in Immunopharmacology	Palermo	Italy	Mar.12
APVAS	Tokyo	Japan	Mar.12
AACR2012	Chicago	U.S.A	Mar.12
AACR2012	Chicago	U.S.A	Mar.12
AACR2012	Chicago	U.S.A	Mar.12
2012 Shanghai Symposium on Obesity and Diabetes	Shanghai	China	Apr.12
The 14th Japan-Korea Joint Meeting of Otorhinolaryngology/Head & Neck Surgey	Kyoto	Japan	Apr.12
The 14th Japan-Korea Joint Meeting of Otorhinolaryngology/Head & Neck Surgey	Kyoto	Japan	Apr.12
Novo nordisk innovation summit Tokyo 2012 chronic inflammation and autoimmune diseases	Tokyo	Japan	Apr.12

International Conference Presentations by Core Member's Group

2012 Speakers	Title
Yamada S, Shinoto M, Endo S, Yasuda S, Imada H, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Patients with Locally Recurrent Rectal Cancer and Pancreatic Cancer.
Kamada T.	Current Status and Future Prospects for Carbon Ion Therapy World-wide.
Yamamoto N, Baba M, Nakajima M, Yoshikawa K, Matsufuji N, Minohara S, Tsuji H, Kamada T, Hirohiko Tsujii	Carbon Ion Radiotherapy in a Hypofraction Regimen for Stage I Non-Small Cell Lung Cancer.
Tsuji H, Mizoguchi N, Toyama S, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for prostate cancer.
Yamada S, Shinoto M, Endo S, Terashima K, Yasuda S, Imada H, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Patients with Locally Recurrent Rectal Cancer.
Yamada S, Shinoto M, Terashima K, Yasuda S, Imada H, Kamada T, Tsujii H.	Carbon Ion Radiotherapy for Pancreatic Cancer.
Tanzawa H.	Targeting gene therapies enhance sensitivity in chemo- and/or radio-therapy of oral cancer.
Kamada T.	Carbon ion radiotherapy at NIRS-HIMAC.
Yokota M, Suzuki K, Tokoyoda K, Nakagomi D, Nakayama T, Kohsaka H, Iwamoto I, Nakajima H.	Crucial Roles of Mast Cells in a Murine Model of Polymyositis.
Takahashi K, Hirose K, Kawashima S, Niwa Y, Wakashin H, Iwata A, Nakajima H.	IL-22 Attenuates IL-25 production by lung epithelial cells and inhibits antigen-induced eosinophilic inflammation.
Koto M, Hasegawa A, Takagi R, Fujikawa A, Morikawa T, Tsujii H, Kamada T.	Risk factors for brain injury after carbon ion radiotherapy for skull base tumors.
Wakatuki M, Kato S, Ohno T, Karasawa K, Ando K, Kiyohara H, Nakano T, Kamada T, Syozu M.	Carbon ion Radiotherapy for locally advanced adenocarcinoma of the uterine cervix.
Shinoto M, Yamada S, Yoshikawa K, Yasuda S, Imada H, Kamada T.	Role of FDG-PET as a predictor of distant failure in preoperative Carbon-ion radiotherapy for pancreatic cancer.
Kamiichi A, Furihata T, Nagai M, Matsumoto S, Ishii S, Motohashi S, Yoshino I, Chiba K.	A novel variant is a bona fide organic anion trasporting polypeptide 1B3 in cancer cells.
Karasawa K, Wakatuki M, Ando K, Kato S, Kiyohara H, Kamada T.	Carbon Ion Radiotherapy For Gynecological Melanoma.
Yamada S, Shinoto M, Terashima K, Yasuda S, Imada H, Kamada T, Tsujii H.	Shinichiro Mori: Pancreas / Rectum.
Sai S, Oonishi K, Yamada S, Kamada T.	Effects of Carbon Ion Beam on Pancreatic Cancer Stem-Like Cells In Vitro and In Vivo.
Kamada T.	Pencil Beam Scanning with Carbon Ion at NIRS-HIMAC.
Nagato K, Motohashi S, Nakayama T.	Accumulation of activated invariant NKT cells in the tumor microenvironment after α-galactosylceramide-pulsed antigen presenting cells.
Ito T.	CDC42 and NFκB signaling contribute to pro-inflammatory phenotype of senescent endothelial cells.
Komuro I.	Angiogenesis and heart failure.
Sanayama Y, Ikeda K, Kagami S, Furuta S, Kashiwakuma D, Iwamoto I, Umibe T, Matsumura R, Sugiyama T, Sueishi M, Nawata Y, Hiraguri M, Saito Y, Kanari H, Nonaka K, Ohara O, Nakajima H.	Prediction of clinical response to tocilizumab therapy with comprehensive gene expression analysis of peripheral blood mononuclear cells in patients with rheumatoid arthritis.
Nakagomi D, Ikeda K, Okubo A, Iwamoto T, Sanayama Y, Takahashi K, Yamagata M, Takatori H, Suzuki K, Takabayashi K, Nakajima H.	Ultrasonographic assessment of synovitis improves the accuracy of 2010 American College of Rheumatology/ European League Against Rheumatism classification criteria for rheumatoid arthritis to predict development of a methotrexate-requiring disease.
Shimojo N, Kumemura N, Morita Y, Tada H, Suzuki K, Takao I, Kohno Y, Kido H.	Allergen sensitization develops in utero:analysis of allergen-specific antibodies by ahighly-sensitive new allergen microarray.
Sai S, Oonishi K, Yamada S, Kamada T, et al.	Effects of Carbon Ion Beams on Liver Cancer Stem-Like Cells and Its Comparison with X-rays.
Shimojo N. Kumemura N, Morita Y, Tada H, Suzuki K, Takao I, Kohno Y, Kido H.	Allergen sensitization develops in utero:analysis of allergen-specific antibodies by ahighly-sensitive new allergen microarray.
Endo Y, Nakayama T.	Identification of pathogenic memory Th2 cells that produce IL-5 and regulate allergic airway inflammation.
Okamoto Y, Inamine A, Yonekura S.	Lactic acid bactera as an effective adjuvant with sublingual immunotherapy for allergic rhinitis.
Kamiichi A, Furihata T, Kishida S, Kawamatsu S, Chiba K.	ESTABLISHMENT OF NOVEL CONDITIONALLY IMMORTALIZED HUMAN ASTROCYTES:A PROMISING TOOL FOR DEVELOPMENT OF A NEW IN VITRO CO-CULTURE MODEL OF THE BLOOD-BRAIN BARRIER
Kishida S, Furihata T, Kamiichi A, Kawamatsu S, Chiba K.	EXAMINATION OF TRANSCYTOTIC RECETOR GENES EXPRESSION IN A NEWLY-DEVELOPED CONDITIONALLY IMMORTALIZED HUMAN BRAIN MICROVASCULAR ENDOTHELIAL CELL LINE
Taniguchi M.	NKT Cell-mediated Adjuvant Activity on Antitumor Responses
Yoshida T.	Effective treatment of hypothyroidism with powdered medicine and its involvement of efflux transporter BCRP in a patient with multidrug resistance
Sakuma I.	An Adult Case of Fructose-1, 6-Bisphosphatase (FBPase) Deficiency with Novel Compound Heterozygous Mutations in FBP1 Gene.
Komuro I.	Wnts in development in other pathways“Complement C1q activates canonical Wnt signaling and Promotes aging-related phenotypes.
Mukai M, Ando Y, Okuda Y, Tsuji H, Kamada T.	Prototype of the Radiation Oncology Teaching Files System for Charged Particle Radiotherapy.
Horie T.	Reversible canalicular Mrp2 localization induced by intracellular redox status.
Nomiya T, Kawashiro S, Harada M, Sudo H, Ota I, Ichikawa M, Kuroda Y, Murakami M, Nemoto K, Tsuji H, Kamada T.	Analyses of inter- and intra-fractional target motion in the lung using respiratory gating device.

	Meeting	City	Country	Month · Year
	New Frontiers in Cancer Treatment	Colorado	U.S.A	Apr.12
	New Frontiers in Cancer Treatment	Colorado	U.S.A	Apr.12
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	New Frontiers in Cancer Treatment	Colorado	U.S.A	Apr.12
	New Frontiers in Cancer Treatment	Colorado	U.S.A	Apr.12
	New Frontiers in Cancer Treatment	Colorado	U.S.A	Apr.12
	The 53th Congress of the Korean Society of Oral and Maxillofacial Surgeons	Gangwon	Korea	Apr.12
	Clinical protocols and fractionation regimen, Department of radiation oncology grand rounds	New York	U.S.A	May.12
	AAI Annual Meetings 2012	Honolulu	U.S.A	May.12
	AAI Annual Meetings 2012	Honolulu	U.S.A	May.12
	European Society for Therapeutic Radiology and Oncology 31	Barcelona	Spain	May.12
	European Society for Therapeutic Radiology and Oncology 31	Barcelona	Spain	May.12
	European Society for Therapeutic Radiology and Oncology 31	Barcelona	Spain	May.12
	The 2nd Japan-China Symposium on Cancer Research	Chiba	Japan	May.12
	51st Annual Meeting of Particle Therapy Co-Operative Group	Seoul	Korea	May.12
	53rd Annual Meeting of Particle Therapy Co-Operative Group	Seoul	Korea	May.12
	52nd Annual Meeting of Particle Therapy Co-Operative Group	Seoul	Korea	May.12
	51st Annual Meeting of Particle Therapy Co-Operative Group	Seoul	Korea	May.12
	Clinical Immunology Society (CIS) Annual Meeting	Chicago	U.S.A	May.12
	41st Annual Meeting of The American Aging Association	Dallas	U.S.A	May.12
	17th International Vascular Biology Meeting	Wiesbaden	Germany	Jun.12
	EULAR congress 2012	Berlin	Germany	Jun.12
	EULAR congress 2012	Berlin	Germany	Jun.12
	EAACI2012	Geneva	Switzerland	Jun.12
	International Society for Stem Cell Research (ISSCR) 10th Annual Meeting	Yokohama	Japan	Jun.12
	EAACI2012	Geneva	Switzerland	Jun.12
	European Academy of Allergy and Clinical Immunology Congress 2012	Geneva	Switzerland	Jun.12
	24 ISIAN	Tolouse	France	Jun.12
	19th International Symposium on Microsomes and Drug Oxidations (MDO) and 12th European Regional ISSX Meeting	Noordwijk aan Zee	The Netherlands	Jun.12
	19th International Symposium on Microsomes and Drug Oxidations (MDO) and 12th European Regional ISSX Meeting	Noordwijk aan Zee	The Netherlands	Jun.12
	FOCIS2012	Vancouver	Canada	Jun.12
	ENDO2012	Houston	U.S.A	Jun.12
	ENDO2012	Houston	U.S.A	Jun.12
	EMBO Conference : 30 Years of Wnt Signalling	Egmond aan Zee	Netherlands	Jun.12
	CARS2012	Pisa	Italy	Jun.12
	The 3rd International Conference on Gastroenterology	Kos Island	Greece	Jul.12
	The 6th S. Takahashi Memorial Symposium & The 6th Japan-US Cancer Therapy international Joint Symposium	Hiroshima	Japan	Jul.12

International Conference Presentations by Core Member's Group

2012 Speakers	Title	
Nohata N.	Tumor suppressive microRNA-1 and microRNA-133a cluster regulating molecular targets in head and neck squamous cell carcinoma	
Akutsu Y, Mori M, Matsubaram H.	A novel Peptide Vaccine Therapy for Esophageal Squamous Cell Carcinoma.	
Ishibashi R.	Semaphorin3g regulates endothelial cell fenestration and the structure of podocyte foot processes	
Ishikawa T.	Investigation of the podocyte-secreted protein R3h domain containing-like in diabetic nephropathy	
Nakano T, Inoue Y, Shimojo N, Kohno Y.	Expression of hsa-mir15a, which is a candidate microRNA regulating VEGFA expression, is lower in CD4+ T cells in pediatric asthma patients	
Okazumi S, Shuto K, Matsubara H, Kato R.	Preoperative estimation of curative resection for advanced esophageal cancer with adjacent organ invasion after chemoradiation by qualitative response evaluation using 3D-volume rendered MD-CT.	
Okazumi S, Shuto K, Matsubara H, Kato R.	The cancer cell amont in lymph node metastasis of esophageal cancer evaluated by contrast enhanced MD-CT pattern or fdg-pet uptake and its clinical significance.	
Akutsu Y, Shuto K, Uesato M, Kono T, Hoshino I, Shiratori T, Isozaki Y, Akanuma N, Matsubara H.	The number of metastati lns is a significant prognostic factor for esophageal cancer patients treated with neoadjuvant chemoradiotherapy.	
Akutsu Y, Yasuda S, Nagata M, Izumi Y, Okazumi S, Shimada H, Nakatani Y, Tsujii H, Kamada T, Yamada S, Matsubara H.	A phase I/II clinical trial of preoperative short-course carbon-ion radiotherapy for patients with squamous cell carcinoma of the esophagus.	
Akutsu Y, Hanari N, Hoshino I, Kono T, Uesato M, Shuto K, Natsume T, Hayashi H, Mori M, Matsubara H.	The outcome of laparoscopic surgery with and without short gastric vessel division for achalasia.	
Hoshino I, Maruyama T, Akutsu Y, Komatsu A, Hanari N, Mori M, Yoneyama Y, Akanuma N, Isozaki Y, Takeshita N, Hayashi, H, Tamura Y, Toyota T, Matsubara H.	Staging laparoscopy with near-infrared flourescence imaging using synthesized indocyanine green liposomal derivative.	
Hoshino I, Akutsu Y, Komatsu A, Hanari N, Mori M, Yoneyama Y, Akanuma N, Isozaki Y, Maruyama T, Takeshita N, Matsubara H.	Antitumor effects of novel histone demethylase inhibitor on esophageal squamous cell carcinoma.	
Ohara O.	Integra1ve Medical Sciences at RIKEN RCAI: to understand the process of disease development	
Matsubara H.	Surgical treatment of gastric cancer: Current situation in Japan.	
Nishimori T, Miyauchi H, Suzuki K, Ohira G, Tohma T, Hanari N, Mori M, Matsubara H.	Preoperative chemoradiotherapy for advanced lower rectal cancer.	
Mori M, Hanari N, Horibe D, Gunji H, Kawahira H, Hayashi H, Matsubara H.	Current status of laparoscopic surgery for gastric submucosal tumors in our institution.	
Hanari N, Mori M, Horibe D, Gunji H, Kawahira H, Hayashi H, Matsubara H.	Intracorporeal reconstraction after laparoscopic distal gastrectomy and total gastrectomy for gastric cancer.	
Yokote K.	Familial hypercholesterolemia, model of care in Asian-Pacific region.	
Yokote K.	Lipid management guideline in A-P region.	
Motegi H.	1,5-anhydroglucitol is useful for an assessment of glycemic excursion and short-term improvement of glycemic control correlating with an evaluation by continuous glucose monitoring system.	

Meeting	City	Country	Month・Year
8th International Conference on Head and Neck Cancer	Toronto	U.S.A.	Jul.12
Fourth Japanese-Mongolian International Cancer Joint Symposium	Ulaanbaatar	Mongolia	Sep.12
48th EASD Annual Meeting	Berlin	Germany	Oct.12
48th EASD Annual Meeting	Berlin	Germany	Oct.12
29th Symposium of the Collegium Internationale Allergolgicum	Cheju	Korea	Oct.12
13th World Congress of the International Society for Diseases of the Esophagus	Venice	Italy	Oct.12
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13th World Congress of the International Society for Diseases of the Esophagus	Venice	Italy	Oct.12
Australia-Japan workshop on biomedical breakthroughs and systems biology	Tokyo	Japan	Oct.12
19th China-Japan Joint Congress for Gastroenterological Surgery	Shanghai (Congress in print)	China	Oct.12
19th China-Japan Joint Congress for Gastroenterological Surgery	Shanghai (Congress in print)	China	Oct.12
19th China-Japan Joint Congress for Gastroenterological Surgery	Shanghai (Congress in print)	China	Oct.12
19th China-Japan Joint Congress for Gastroenterological Surgery	Shanghai (Congress in print)	China	Oct.12
8th Asian-Pacific Society of Atherosclerosis and Vascular Disease	Phuket	Thailand	Oct.12
8th Asian-Pacific Society of Atherosclerosis and Vascular Disease	Phuket	Thailand	Oct.12
8th Asian-Pacific Society of Atherosclerosis and Vascular Disease	Phuket	Thailand	Oct.12

Editor's Note

Final Report is completed, compiled on the activities we have done over the past four and half years since the launch of Chiba University Global COE Program. From the manuscripts we received I realize that so many productive activities have been successfully conducted. I'd like to express my deepest appreciation to all the core members striving to organize and run the program, and people involved as well. Our G-COE program ended this year, however I hope our efforts to educate young researchers will bear rich fruits in the future.

Shinichiro Motohashi

Chiba University Global COE Program
Final Report 2008-2012

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