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Chiba University Global COE Program

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

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- The 3rd Symposium: Molecular Dynamics of Immune System Regulation, November 6, 2009

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.



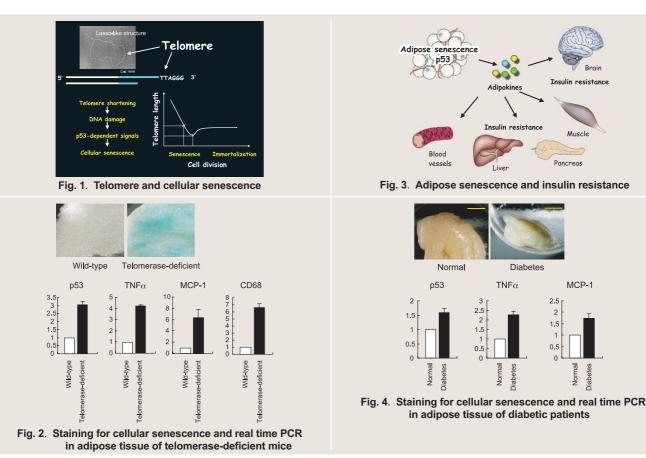
Tohru Minamino Department of Cardiovascular Science and Medicine

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 highcalorie diet, and their adipose tissue showed senescence-like changes such as an increased expression level of p53, up-regulation of p53induced 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 senescencelike changes of adipose tissue, dysregulated expression of proinflammatory 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.*)





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.

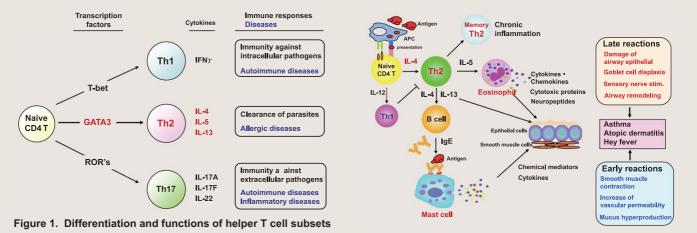


Figure 2. Mechanism of allergic inflammation

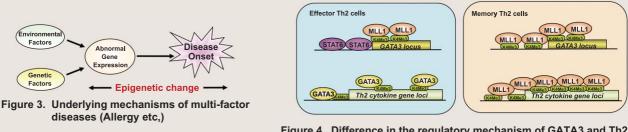


Figure 4. Difference in the regulatory mechanism of GATA3 and Th2 cytokine expression between effector and memory Th2 cells

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Differentiation and Function of Lymphocytes

May 29, 2009, The 1st Auditorium, Chiba University Hospital 3F





Alfred Singer

Singer



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) 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.

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



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*



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-andanswer 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"

Asami Hanazawa

Dept. of Immunology "In vivo dynamics of memory T cell reactivation"

Akane Suzuki

Dept. of Immunology

"Polycomb group gene product Ring1B regulates Th2dependent 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"

"The role of PHF11 in activation of murine B cells"

Dept. of Molecular Biology and Oncology "TAp63 suppresses MYCN expression in favorable

"The research for individualization of warfarin therapy"

"Identification of active ingredient(s) in a protein-bound

polysaccharide, polysaccharide Kureha (PSK), for stimulating

"Inhibition of PDE3B improves CDDP-sensitivity in head and

"Hyaluronidase-2 is a motility-inducing enzyme of human

Immunoadhesins for human IL-10 with theraputic potential"

"Enhanced immune responses against tumors followed by

"Development of a novel cancer vaccination using heat shock

"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

Session 4

Yusuke Suenaga

neuroblastomas" Takumi Harada

Satoru Saito Dept. of Frontier Surgery

Keiji Shinozuka

Session 5

Teruyoshi Saito

cancer cell lines"

Shinya Okamoto

Masayuki Kano

protein Gp96' Kazuki Yamasaki Dept. of Otorhinolaryngology

and neck carcinoma"

Dept. of Biochemistry

Mizue Terai

Dept. of Developmental Genetics

Lab. of Clinical Pharmacology

murine and human dendritic cells"

Dept. of Clinical Molecular Biology

neck squamous cell carcinoma"

Dept. of Molecular and Tumor Pathology

Dept. of Molecular and Tumor Pathology "Human IL-10 receptor 1/IgG1-Fc fusion protein:

adenoviruses-mediated cell death

Department of Frontier Surgery

Jun Ikari

Chair: Hiroshi Nakajima

Chair: Shinichiro Motohashi

















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S. Hattori



S. Okamoto



T. Harada



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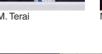




































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ducation Report

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 (*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 : 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 DCbased immuno-stimulatory and immuno-suppressive strategies, which are potentially applicable to the treatment of cancer, allergy, autoimmune disease, allograft rejection, and graftversus-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	y 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 Part	, 3		
Saturdav. Julv	4 Tokyo Sightseeing Tour		
Monday, July	6		
	tion 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 wit			
21000001011			
Tuesday, July	7		
	, tion 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 Procentation 2 by Gr

Oral Present	ation 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 ILT7 and ligand
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-nomori 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-tounderstand 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.

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.

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 & Post	er Session		
Sunday, Sep	tember 6		
Special Lect	ure 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		

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.





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)











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

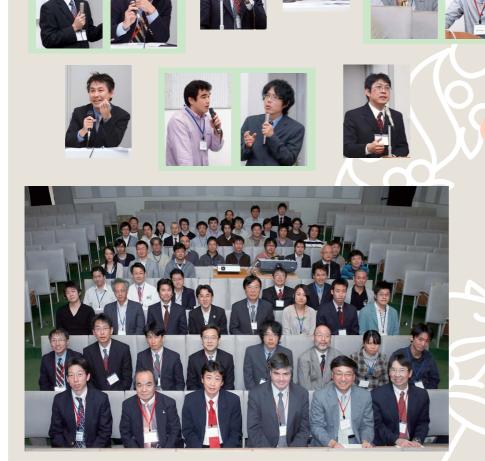
The 3rd Chiba University G-COE Symposium was full of various well balanced topics from immunology to circulation, metabolism and obesity. These topics successfully reminded us of the implication of immune systems in a wide range of phenomena in steady state and disease. The topics were also varied from 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

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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. 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

Chiba University Global COE Program Graduate School of Medicine, Chiba University

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