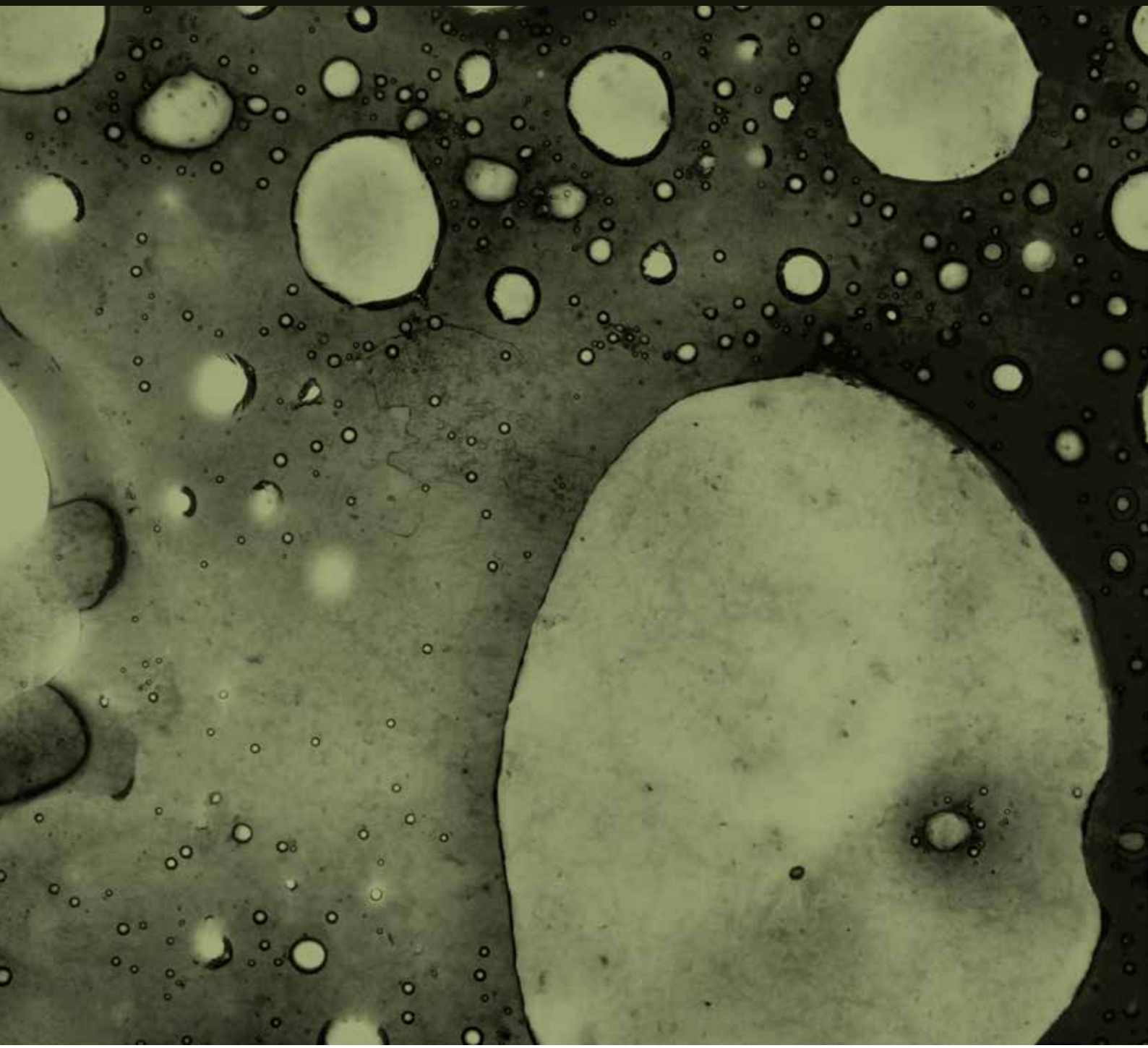
IMPACT

UNRAVELING THE SECRETS OF IMMUNOLOGY



IIMVF

LGS AT CHIBA UNIVERSITY

CHIBA UNIVERSITY

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Impact Objectives

- Basic research on immunological memory
- Translational research on allergic and chronic airway inflammation
- Development of immunotherapy for cancer
- Development of guidance to 'cultivate professional researchers'

Keen collaborator

Professor Toshinori Nakayama has been working to improve the collaborative and teaching efforts of the Department of Immunology at Chiba University in order to tackle key questions in immunology

Can you share a little about how your own career has developed? Have there been any key moments that have changed the pathway?

There are two people who have influenced my life the most: Dr Tomio Tada, my PhD advisor in the Graduate School of Medicine at the University of Tokyo; and Dr Alfred Singer, my supervisor at the National Institutes of Health. As a student, I was awe-struck by Dr Tada's presentations and fascinated by the world of immunology. I decided to enter Dr Tada's lab right after graduating from medical school. Immune system research was still unknown territory at the time (early 1980s). I found it thrilling and challenging to discover new processes and to expand the field. Dr Tada taught me a wide range of knowledge and skills: from the joy of science to the pleasure of new cultural discoveries. Dr Singer taught me how to promote research and how to deliver a successful presentation: even an academic presentation should be entertaining!

In what ways are international collaborations important to the projects you are involved with?

The most important thing about collaboration is conducting a thorough study to see the whole picture of a problem. In that sense, it does not matter if the collaboration is domestic or international. However, Japanese research and technology is sometimes criticised for its inward-looking tendencies. International collaborations provide us with different perspectives and opportunities to develop networks, and also help us to maintain global standards and prevent the pursuit of Galapagos technologies and domestically focused research.

You have a number of joint research projects underway. How important is the relationship with other academic institutions as well as healthcare organisations to this research?

Through collaborations we can share resources such as genetically modified mice and then each researcher can study the event from his/her own standpoint. For example, a pharmacologist can provide materials by creating one chemical or reagent and then researchers can test its effect using a knockout mouse or mouse model of a certain disease. Based on the animal study, we can conduct a clinical study in collaboration with researchers from clinical departments. By doing so, we can maximise the specialty of each researcher.

How does the Japanese Global Centers of Excellence (COE) Program support and cultivate professional researchers within your Department?

In Japan, the scholarship system for graduate students remains unsatisfactory. I believe the Global COE Program has helped students concentrate on their research. In Global COE, we use various measures to encourage our students to be professional researchers. These include providing extra opportunities including workshops or study abroad so that students can collaborate with overseas researchers; establishing an annual prize for the best student to inspire a deeper commitment to research; and providing broad educational and research support from basic science to clinical research.

Can you talk a little about what the International Immunological Memory and Vaccine Forum (IIMVF) meeting is and its importance to your work?

We hold the IIMVF meeting once a year in order to promote three key areas: 1) information exchange and mutual professional and social friendship among junior researchers, and between junior and senior researchers; 2) dissemination of junior researchers' studies to the world community by making presentations and discussions in the presence of world-class research leaders; and 3) industry-academia joint research at the international level, and procurement of research funds.

What do you foresee your Department's research themes will be going forward?

One of my goals is to clarify pathogenesis of intractable chronic inflammatory disease at the molecular, genetic and cellular level in order to develop a novel treatment. We can then apply our findings to research in many fields including autoimmune disease, allergy, tumour immunology and cancer.

Breathe easy

Through her work in the ***Department of Immunology*** *at* ***Chiba University****,* ***Dr Motoko Y Kimura*** *hopes to offer relief to sufferers of refractory allergic diseases*

What drives you to continue your research into immunology?

I love Mother Nature and living creatures and am curious how creatures develop and continue to live; these curiosities drove me to become a scientist. As immunology is one of the well-organised systems that are essential for life, I chose this area and have been studying T lymphocytes, which are crucial for acquired immunity. I would like to engage in research on fundamental life phenomena. I would feel enormous pleasure if a discovery of mine is applied to the treatment of patients who are suffering from refractory diseases in the future.

Can you talk about the CD69 antibody project you are currently involved in?

I am looking at the role of CD69 on immune cell development and on immune responses. CD69 has been identified as an early activation marker; however, it was not really known if there were any biological roles of its expression except for its regulation of S1P1 expression. Due to our extended efforts, we now know that CD69 is not a simple activation marker and actually has a crucial role in immune responses, especially inflammation. We found that CD69 antibody treatment efficiently ameliorates allergic responses in mouse models, and that it is due to failure of recruitment of CD69 expressing inflammatory cells into lung tissues. We are currently working on the mechanisms how CD69 antibody works, and getting to know the existence of functional CD69 ligands in inflamed lung.

How did the idea for your research on CD69 antibody treatment for refractory allergic diseases come about?

Our lab has been working on CD69 biology for a long time. In the early 1990s, CD69 was known as a simple early activation marker on leucocytes such as T cells, but was not thought to have crucial functions for immune responses. When I was doing my Master's, I had a chance to analyse CD69 knockout mice that our lab had made for the first time in the world. At that time, we thought that CD69 should have some roles on thymocyte development since CD69 expression is specifically upregulated during thymocyte development. Unfortunately, we couldn't find any significance in the thymus at that time, but eventually we found that CD69 expression on activated leukocytes is crucial for inflammation in the periphery. I was very excited to be involved in these discoveries.

What are your views on the current situation around gender equality in science?

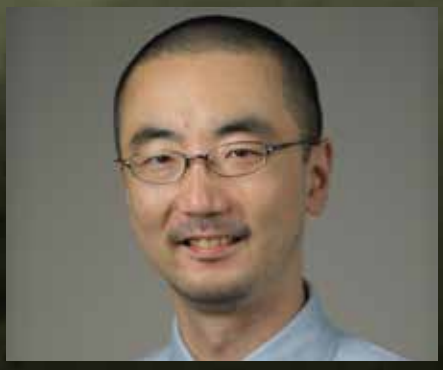
Considering the fact that female faculty members make up less than 10 per cent of Chiba University's Medical School, I consider myself fortunate to be a faculty member and to have the opportunity to proceed with my science. I know many smart and dedicated female PhD students who quit science before becoming a faculty member. I think it is due to the conservative society pressures on women to take care of the household and to raise children and so on which makes it difficult for women to continue to work. On the other hand, female scientists can benefit from being a minority, since academic societies are trying to have more female scientists and are giving more opportunities to them. I hope more female students decide to work in academia because I think women can be excellent scientists!

How are you supporting graduate students and young researchers in the Department of Immunology through your research?

I think deep discussion of the data is most important, not only to advance each project, but also to educate students in how to be an independent scientist. I try to create an environment where all students can freely talk their thoughts and ideas. Each student has his/her own unique character; therefore I try to get to know each student well so that we develop good relationships and communicate well. This is a necessary step to enable deep discussion. I enjoy discussing data with my students and learning many things from them too.

Controlling inflammation

By analysing the involvement of Th2 cells in chronic inflammatory diseases, ***Associate Professor Kiyoshi Hirahara*** *of the* ***Department of Immunology at Chiba University*** *is aiming to develop new treatments for pulmonary fibrosis*



How has your career in basic medical research developed?

After obtaining my medical doctor's licence in Japan, I was engaged in clinical practice as a physician, specifically in respiratory medicine, for more than five years. During that time, I saw many cases that current treatments could not cure and keenly felt the desperate need for new treatments. Aware of the importance of basic research, I decided to become a basic medical researcher. This led me to explore immune responses in the respiratory apparatus (upper and lower respiratory tract) and intractable respiratory diseases, including pulmonary fibrosis. I have conducted various research activities focusing on CD4+ T cells throughout my graduate studies under the instruction of Professor Toshinori Nakayama at Chiba University and postdoc under Dr John J O'Shea at the Molecular Immunology and Inflammation Branch of the US National Institute of Arthritis and Musculoskeletal and Skin Diseases. Currently I am carrying out research mainly on the identification of the roles of CD4+ T cells in intractable respiratory diseases.

Do you think there any key questions about immunity that need addressing?

Currently, it is considered that abnormality of the immune system might be contributing to pathological process of various intractable diseases. Therefore, medical agents with a variety of immunosuppressive properties, such as steroids, are used in treating these diseases. However, these types of treatments can only cure a limited number of cases. This means that the development of a novel therapy by elucidation of pathological conditions involving the immune system is a pressing task.

What topics are you currently investigating?

Pulmonary fibrosis is a disease in which the alveolar epithelium – responsible for gas exchange in the lungs – becomes harder and harder due to chronic inflammation of the lungs from various causes. As pulmonary fibrosis worsens, it progressively leads to respiratory failure. Above all, idiopathic pulmonary fibrosis is an extremely poor-prognosis disease and 50 to 70 per cent of patients die within five years of diagnosis. Over 10,000 patients are currently suffering from idiopathic pulmonary fibrosis in Japan and there is no curative treatment for the disease. It has substantial resistance to existing drugs including steroids, and its mechanism in pathological conditions remains unknown. As such, I am undertaking research focusing on the fibrosis of the lung tissue with a goal of pathological clarification of the disease.

In what ways will the functional analysis of pathogenic Th2 cells impact on the healthcare sector?

Currently, most of the major immunosuppressive agents used in the world have low specificity and are classified either as drugs with limited therapeutic effects or as drugs with curative properties and strong side effects. It is my belief that research on pathogenic Th2 cells will result in a more specific drug target or novel biomarker.

How valuable is the strength of the Department of Immunology's existing collaborations for achieving the outcomes from your research?

We are currently conducting a joint research project with Professor Yoshitaka Okamoto from the Department of Otorhinolaryngology, Head and Neck Surgery here at Chiba University. Under this study, we are translating the concept, which we created based on the outcomes from our mouse study, into humans. We use samples of patients with various types of diseases to analyse how tissue fibrosis becomes advanced at local inflamed sites in humans. This joint research is making great progress and giving an additional boost to our study on pathological clarification of various diseases. We are committed to producing concrete results every day.

Unraveling the secrets of immunology

*Researchers in the **Department of Immunology** at **Chiba University** are using an expanded network of collaborators to further understand the role of Tpath2 cells in chronic inflammation*

Immunology is an extremely complex subject. The interactions between the thousands of cell types within the two immune systems – innate and adaptive – allow for huge flexibility in tackling foreign invaders and domestic pathogens such as cancer. Given the complexity of the system, it is not surprising that mistakes arise.

Such mistakes range from the hugely destructive responses to certain pathogens through allergic reactions to an inability to recognise cancerous cells. The cell types involved in these processes often have multiple functions, regularly altering themselves to meet different functional requirements. Type 2 helper cells (Th2 cells) are one such cell type. Most of the Th2 cells detected in our peripheral blood are immunological memory cells that are stimulated when the body is exposed to the same antigens that it has previously encountered. These can be from microorganisms and viruses, but can equally be from allergens. This means that pathogenic forms of these cells (Tpath2 cells) are often responsible for chronic inflammatory responses where epithelia react recurrently to a long-past antigen. Professor Toshinori Nakayama of the Department of Immunology at Chiba University has directed his research to discovering the causes of, and finding solutions to, chronic inflammation.

Graduate Student sitting at the clean bench to adjust the reagent and to determine quantity of Cytokine-producing cells

Nakayama and his team were the first to identify Tpath2 cells and have recently discovered their key role in chronic inflammation. The researchers take an all-encompassing approach, looking at the issue from several different biological angles. These include investigating the molecular changes occurring in Th2 cells as they become pathogenic, the location and effects of these cells in mice models, and identifying their location in patient samples. This approach allows Nakayama to focus on his ultimate aim: 'The results of our work will be the evidence required to develop a new treatment or vaccine utilising immunological memory. My hope is that our research will result in a vaccine with which you can never get a disease and which has no major side effects.' In order to further these aspirations, Nakayama has also set up a growing network of international collaborations and has steered the focus of the department to aiding young researchers.

THE PATH TO A VACCINE

The story of pathogenic Th2 cells begins with a desire to know the causes of chronic lung inflammation in some asthma sufferers. A key cause of asthmatic inflammation is a group of cells called eosinophils that are normally responsible for tackling parasite infection. Eosinophils are activated by the presence of interleukin 5 (IL-5), a soluble protein called cytokine. Nakayama and his team identified a subpopulation of Tpath2 cells that produce abundant IL-5, stimulating eosinophils and creating the allergic response. Additionally, they found Tpath2 cells persisted and therefore led to chronic inflammation in the region where the cells

Main Building of the Faculty of Medicine built in 1936

were present. This is a particular problem because, unlike regular asthma, chronic asthma can't be treated with steroids. However, these discoveries left many questions unanswered. Chief amongst these were how Th2 cells were activated and how they maintained this activation state.

After extensive investigation, Nakayama and his team discovered that Tpath2 cells were stimulated to produce IL-5 by another cytokine – IL-33. This second cytokine is released by epithelial cells (in the lung for asthma) and causes a change in the organisation of the DNA containing the gene for IL-5. The structural change in the DNA causes IL-5 to be highly expressed in Tpath2 cells. This explains how the cells are activated to recruit eosinophils in the first place; however IL-33 signalling by the epithelial cells is not constant and therefore this did not explain the chronic aspect of the inflammation. Further work in mouse models and using human samples helped uncover the chronicity of the pathology. The team discovered that a combination of two other interleukins, IL-2 and IL-25, was capable of producing the same DNA remodelling as IL-33. Additionally, these two proteins are both produced by the same eosinophils previously activated by Tpath2 cells. It is therefore easy to see that an exacerbating cycle is created

‘The results of our work will be the evidence required to develop a new treatment or vaccine utilising immunological memory. My hope is that our research will result in a vaccine with which you can never get a disease and which has no major side effects’

by the two cell types leading to chronic inflammation at the site of this interaction. These foundational findings are an essential step to finding a way to treat chronic inflammation. Nakayama is continually working closely with clinicians in order to develop means through which this knowledge can be applied to patients. Additionally, he and his team are pursuing several other research angles which show promise of finding a solution. Nakayama and the Department of Immunology are clearly seeing the research benefits of increased national and international collaboration, with a regular stream of thorough scientific investigation into chronic inflammation and other immunological issues.

International collaborations

The sharing of discoveries and expertise is essential to all good scientific research. Japan has often stood accused of focusing too heavily on research and technology aimed solely at tackling domestic issues. This insular approach is one many researchers are keen to shed. Led by Professor Nakayama, the Department of Immunology at Chiba University is attempting to reverse this impression. In order to do so, Nakayama has initiated several programmes and collaborations aimed at engaging the international community and drawing in foreign researchers to work in the department. He is taking four key and interlinked approaches to tackling the issue.

The Japanese Global Centers of Excellence (COE) Program was a national programme designed to increase international competitiveness. Most of the departments in Chiba University’s Graduate School of Medicine, including the Department of Immunology, benefited directly from this funding by being able to advance and expand their research. Particularly, there was a focus on making funds available to develop young talent. Traditionally, funding for students has been tough in Japan, as Nakayama explains: ‘The scholarship system for graduate students remains unsatisfactory. It is common that students or their parents pay for tuition and living expenses. Global COE enabled us to pay US$1,000 per month to about 50 students every year, additionally, the programme allowed the recruitment of talented foreign researchers who helped to provide new perspectives to the Department’s work. Another important aspect to the student development process is the Leading Graduate School (LGS). The LGS aims to create international leaders who will contribute significantly to research in immune-related diseases as well as to the development of new drugs and methods of treatment. This is achieved through providing students with a multidisciplinary approach to their learning and offering extra funding opportunities.

In order to further the aim of increasing international involvement in immunological research, Nakayama has instigated two essential initiatives. Firstly, the university has recently announced a new joint partnership with the University of California, San Diego. A joint Research Centre has been designed to create preventative vaccines against a range of infectious diseases, allergies and cancers. Included in this remit is a focus on academic exchanges – giving young researchers a chance to experience a different, yet still high-quality, research experience. Additionally, exchanges of senior staff allow a closer sharing of ideas and direction between these two world-leading institutions, as Nakayama explains: ‘Through these efforts, I believe we can foster international-standard researchers who can produce cutting-edge findings.’ Secondly, Nakayama is heavily involved in the International Immunological Memory and Vaccine Forum (IIMVF). The IIMVF is an annual conference with a focus on young researchers’ work. The conference aims specifically to help information exchange between all involved; to promote friendships between researchers at all levels; to highlight the work of early-stage scientists; and to facilitate the expansion of industry-academia partnerships. Chiba University will host the next iteration of the conference in 2017.

Project Insights

TOPICS OF CURRENT RESEARCH PROJECTS

- Generation and maintenance of immune system
- Clarification of mechanism of allergy onset and therapeutic development

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PROJECT COORDINATOR BIO

Professor Toshinori Nakayama leads the Department of Immunology in the Graduate School of Medicine at Chiba University, Japan. After studying the field of immunology for many years he is now focused on basic research into immunological memory and translational research on allergy and cancer. Nakayama has written a number of published papers on these topics. He has also received a number of awards recognising his work in this field, including the 3rd Japanese Society for Immunology Award in 2000 and the 14th Abbott Japan Allergy Research Award in 2004. Nakayama is member of a number of societies including the American Association of Immunologists, the American Society for Biochemistry and Molecular Biology and the Molecular Biology Society of Japan.

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