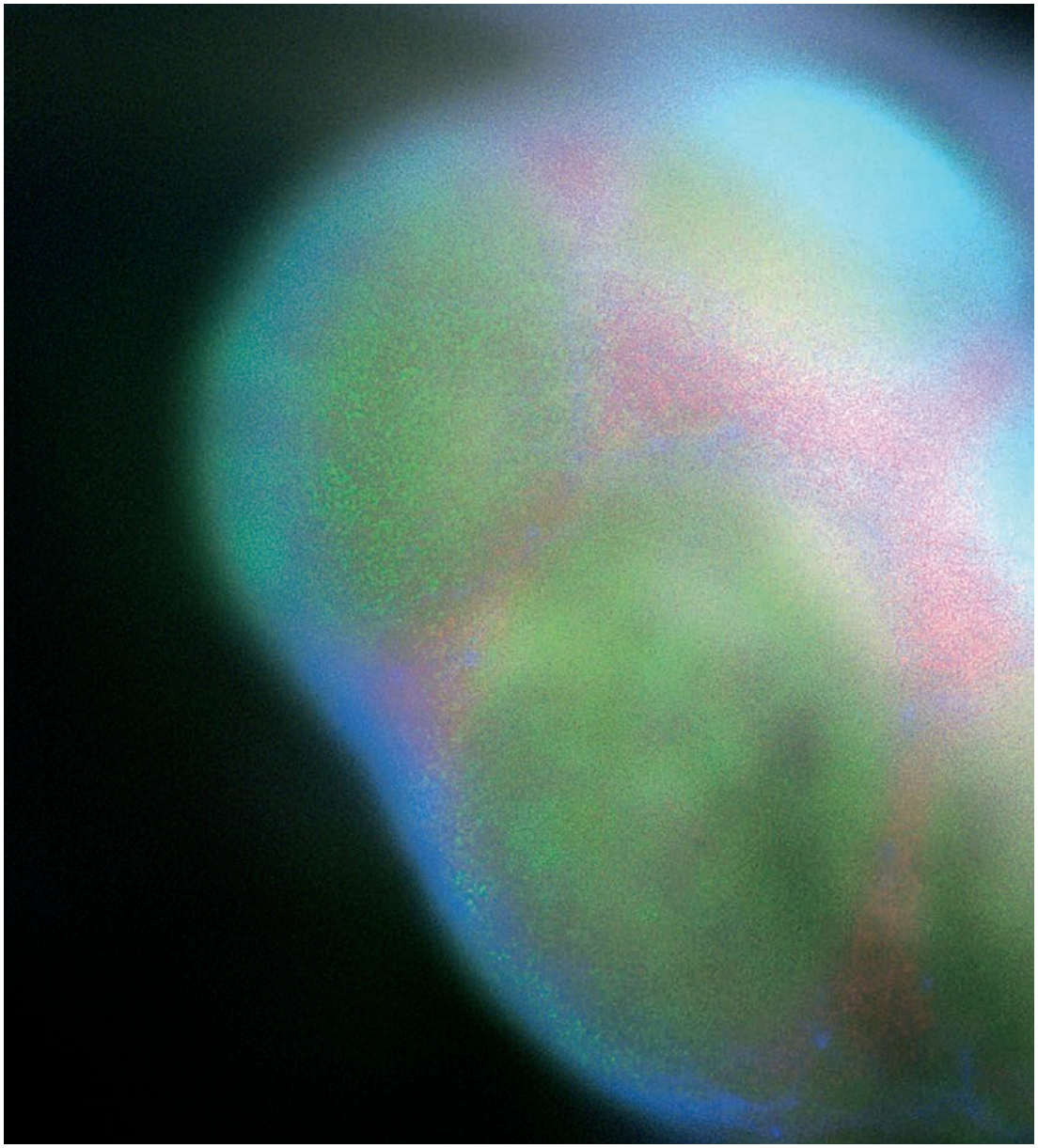
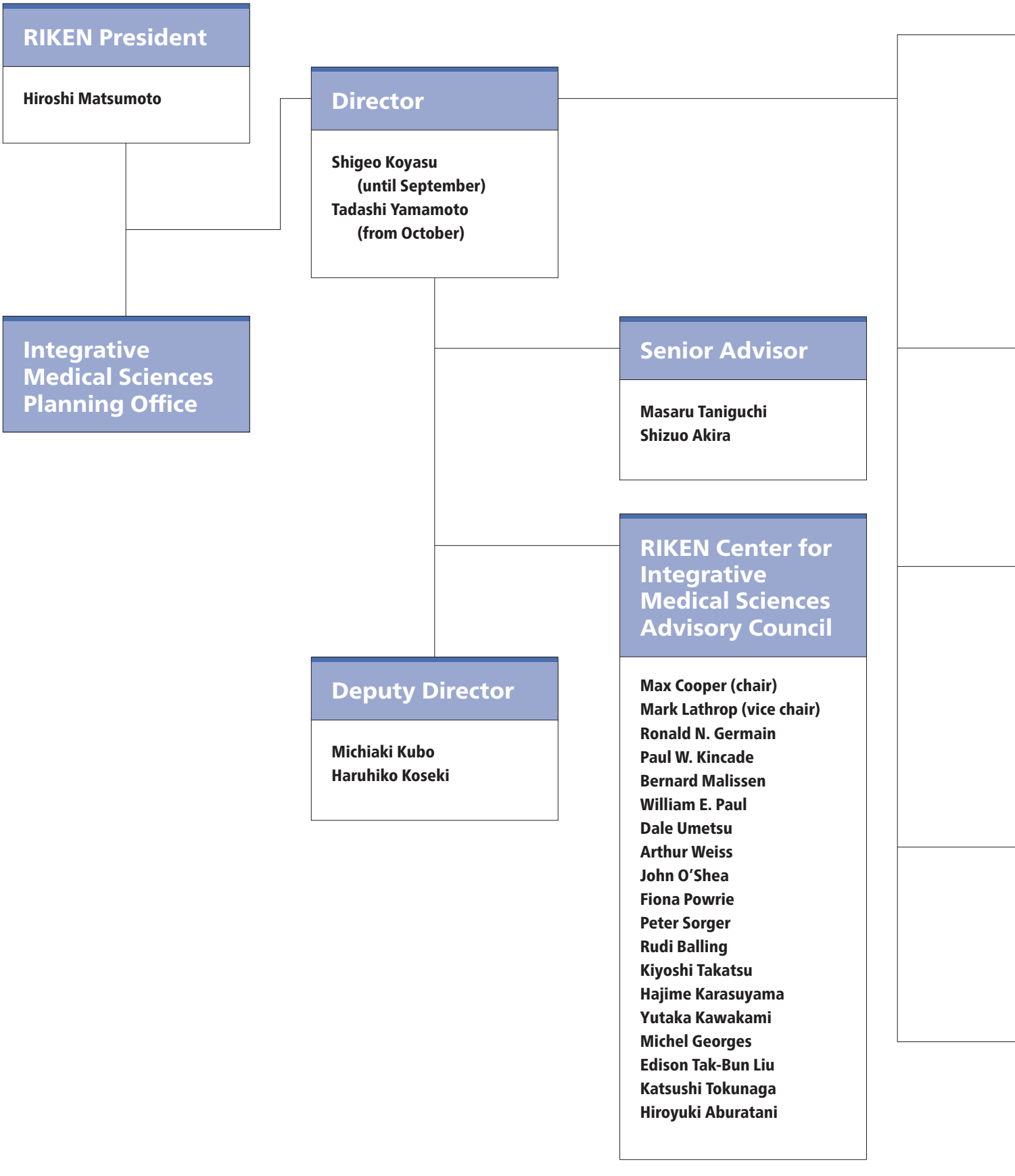


RIKEN IMS
Annual Report 2015

RIKEN Center for Integrative Medical Sciences

RIKEN Center for Integrative Medical Sciences Organization Chart



Core for Homeostatic Regulation

- Lab. for Cell Signaling: **Takashi Saito**
- Lab. for Lymphocyte Differentiation: **Tomohiro Kurosaki**
- Lab. for Transcriptional Regulation: **Ichiro Taniuchi**
- Lab. for Immune Cell Systems: **Shigeo Koyasu**
- Lab. for Human Disease Models: **Fumihiko Ishikawa**
- Lab. for Intestinal Ecosystem: **Hiroshi Ohno**
- Lab. for Mucosal Immunity: **Sidonia Fagarasan**
- Lab. for Gut Homeostasis: **Kenya Honda**
- Lab. for Immune Homeostasis: **Shohei Hori**
- Lab. for Skin Homeostasis: **Masayuki Amagai**
- Lab. for Metabolic Homeostasis: **Naoto Kubota**
- Lab. for Immune Crosstalk: **Hilde Cheroutre**
- Lab. for Inflammatory Regulation: **Takashi Tanaka**
- Lab. for Cytokine Regulation: **Masato Kubo**
- Lab. for Innate Immune Systems: **Kazuyo Moro**

Core for Precise Measuring and Modeling

- Lab. for Developmental Genetics: **Haruhiko Koseki**
- Lab. for Integrative Genomics: **Osamu Ohara**
- Lab. for Disease Systems Modeling: **Hiroaki Kitano**
- Lab. for Immunogenetics: **Hisahiro Yoshida**
- Lab. for Integrated Bioinformatics: **Todd Duane Taylor**
- Lab. for Tissue Dynamics: **Takaharu Okada**
- Lab. for Integrated Cellular Systems: **Mariko Okada**
- Lab. for Metabolomics: **Makoto Arita**

Core for Genomic Medicine

- Lab. for Genotyping Development: **Yukihide Momozawa**
- Lab. for Genome Sequencing Analysis: **Hidewaki Nakagawa**
- Lab. for Medical Science Mathematics: **Tatsuhiko Tsunoda**
- Lab. for Statistical Analysis: **Yoichiro Kamatani**
- Lab. for Pharmacogenomics: **Taisei Mushiroda**
- Lab. for International Alliance on Genomic Research: **Ming Ta Michael Lee**
- Lab. for Cardiovascular Diseases: **Toshihiro Tanaka**
- Lab. for Autoimmune Diseases: **Kazuhiko Yamamoto**
- Lab. for Digestive Diseases: **Kazuaki Chayama**
- Lab. for Bone and Joint Diseases: **Shiro Ikegawa**
- Lab. for Endocrinology, Metabolism and Kidney Diseases: **Shiro Maeda**
- Lab. for Respiratory and Allergic Diseases: **Mayumi Tamari**

Program for Medical Innovations

- Lab. for Immune Regulation: **Masaru Taniguchi**
- Lab. for Immunotherapy: **Shin-ichiro Fujii**
- Lab. for Vaccine Design: **Yasuyuki Ishii**
- Lab. for Allergic Disease: **Toshiaki Kawakami**
- Drug Discovery Antibody Platform Unit: **Toshitada Takemori**

Young Chief Investigator Program

- YCI Laboratory for Stem Cell Competency: **Hayato Kaneda**
- YCI Laboratory for Immune Regeneration: **Tomokatsu Ikawa**
- YCI Laboratory for Quantitative Omics: **Katsuyuki Shiroguchi**
- YCI Laboratory for Cellular Bioenergetic Network: **Toshimori Kitami**

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Director's Report

This is my first annual report since becoming Director of RIKEN Center for Integrative Medical Sciences (IMS) in October 2015. I assumed this responsibility from former Director Shigeo Koyasu, who was promoted to RIKEN Executive Director. It is my great honor to work at IMS, one of the leading research institutes in medical life sciences in Japan. When I moved to IMS, I visited each laboratory and talked with all the principal investigators. My first impression was that IMS has a core of remarkably good and solid scientists.

IMS was established in 2013 by the integration of two former RIKEN Centers, the Research Center for Allergy and Immunology (RCAI) and the Center for Genomic Medicine (CGM), both of which had independently achieved outstanding reputations in their respective fields. I am a molecular biologist and have been working in the field of oncogene research and signal transduction, so my background and approaches did not fit perfectly with either genomics or immunology, but science is science. My interests in studying how gene expression is controlled in a context-dependent manner, and how cells respond to their environment to maintain homeostasis, were also common topics at IMS. During my first discussions with IMS researchers, I felt that genomic and immunology research had been well-integrated beyond my expectations. They talked about how to tackle the existing research boundaries to create new future directions. I believed that the efforts by each IMS member to understand their different scientific cultures would push collaborations and move the Center forward.

IMS is a unique Center in RIKEN, because of its mandate to connect basic medical and life science research with clinical medicine. Researchers are aspiring to understand the relationships between genes and diseases, environment and homeostatic regulation, internal body changes and disease onset, and are modeling and stratifying these processes. IMS has a strong support system for research conducted in the Center as well as for external collaborative research. This includes state of the art technologies in the Animal Facility, GWAS studies, and metabolomics. We continue to strengthen and expand support activities for studying internal and external triggers of diseases and the delicate equilibrium existing in times of health.

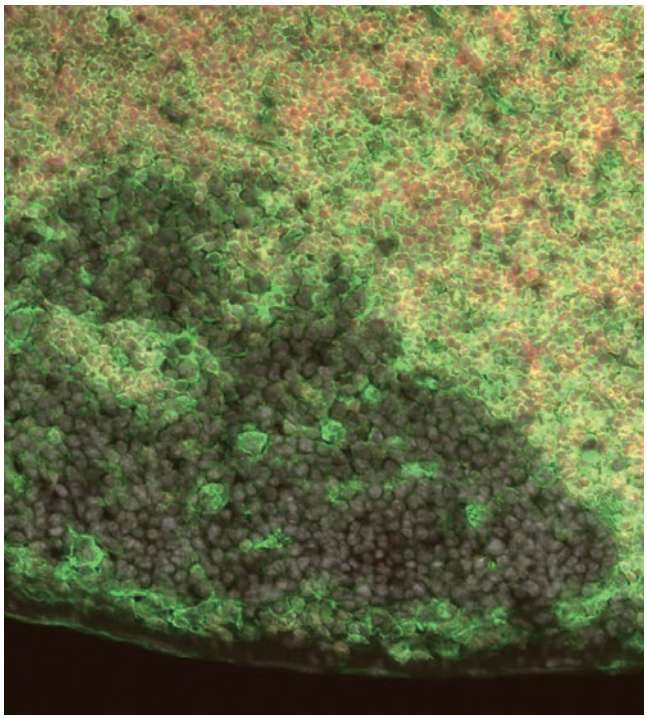
Healthy aging is a concerning issue in Japan. Living in Okinawa for the past five years, I became interested in the aging problem in relation to diet and lifespan. Okinawa is rich in herbs, vegetables, and seafood, and Okinawans used to have the longest life expectancy in the world. However, this is no longer true due to lifestyle changes, particularly the choice of diet. Yet, no national institution has been investigating the relationship between Okinawan lifespan and diet, and there is not even a pharmaceutical school in Okinawa. RIKEN is going to promote an aging research program that should be complementary to our ongoing microbiota research in IMS. I would also like to keep in mind that there is a lot to do in Okinawa in aging research.

To nurture young researchers who will become leaders in future multidisciplinary research, IMS established its unique Young Chief Investigator (YCI) system, which was approved as RIKEN's official system in 2015. In this program, the selected YCI heads an independent research laboratory and has access to mentoring by multiple senior specialists in related research fields. The YCI laboratory shares space, equipment and facilities with a host laboratory within IMS. In the 5th year, each YCI is reviewed for promotion. In 2016, YCI Katsuyuki Shiroguchi, was promoted to PI at the RIKEN Quantum Biology Center.

IMS also promoted three young leaders in 2015. Yoichiro Kamatani, Yukihide Momozawa, and Kazuyo Moro became Team Leaders of the Laboratory for Statistical Analysis, Laboratory for Genotyping Development and the Laboratory for Innate Immune System, respectively.

IMS researchers continue to perform outstanding research, publishing papers in significant journals in 2015. Kenya Honda reported Th17 cell induction by adhesion of microbes to intestinal epithelial cells (*Cell*, 2015). Yukinori Okada and Michiaki Kubo reported a population-specific HLA imputation reference panel and its application to Graves' disease risk in Japanese (*Nature Genetics*, 2015). Kazuyo Moro reported that IFN and IL-27 antagonize ILC2 function (*Nature Immunology*, 2015). There were 279 papers published from IMS in 2015. I believe that with our continuous challenges, we will flourish as pioneers in integrative medical sciences.

Tadashi Yamamoto
Director,
RIKEN Center for Integrative Medical Sciences



Part 1

Research Highlights

Good neighbors make good defenses

A tight physical association between gut bacteria and the intestinal wall helps establish robust immune defenses

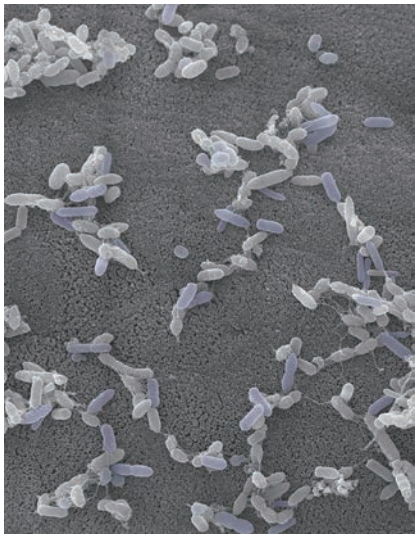


Figure: Electron micrograph showing T_H17-inducing bacteria isolated from the human intestine.

A recent study by RIKEN researchers has shed light on the conundrum of how microbes in the gut can influence the host's immune system, despite being separated by the gut lining.

The intestinal wall is a major entry point for infection, and immune cells known as T_H17 cells reinforce this barrier and fend off pathogens. Certain 'commensal' bacteria in the guts of mammals stimulate the proliferation of T_H17 cells.

In rodents, one subset of gut bacteria plays a particularly strong role in this process. "We had previously identified segmented filamentous bacteria (SFB) as one of the most potent inducers of T_H17 cells," explains Takeshi Tanoue, a member of the team, which was led by Kenya Honda of the RIKEN Center for Integrative Medical Science. "Tight adhesion to intestinal epithelial cells is a remarkable characteristic of these microbes."

The researchers explored whether this adhesion plays a major role in activating immunity in the gut. They began by exploiting the strikingly distinct SFB populations in rats and mice. "About 5–10 percent of the genes are specific to each strain," notes Tanoue. Although rat-derived SFBs could proliferate in the mouse intestine and vice-versa, neither population was able to adhere tightly to the intestinal wall after transplantation. This reduced adhesion correlated with a sharp decrease in T_H17 induction, indicating that the mere presence of these commensals is insufficient—a tight epithelial interaction is essential. Indeed, pathogenic bacteria that bind to the surface of the intestinal wall during infection also stimulate T_H17 proliferation, apparently via a similar mechanism.

These results offer only limited insights into humans, however. "SFBs haven't been found in the human intestine, and the counterpart T_H17-inducing bacteria have not yet been identified," says Tanoue. The researchers therefore collected fecal samples from human subjects and examined which specimens could act on T_H17 cells when transplanted into mice. The results enabled them to identify 20 bacterial strains that appear to play a similar role to mouse SFBs (Figure).

Abnormalities in T_H17 activation can contribute to inflammatory bowel disease, and hence a detailed bacterial census may help to diagnose or treat this disorder.

Since the human commensals isolated in the present study came from a patient with inflammatory bowel disease, further experiments are needed to identify the 'optimal' gut bacterial community. "We don't know if these bacteria are pathogenic or beneficial to the host," explains Tanoue. "We're now trying to isolate T_H17-inducing bacteria from healthy human samples." In principle, such bacteria could be delivered clinically as 'probiotics' to help normalize disease-associated disruptions of gut immunity.

This article was reproduced from RIKEN Research with permission
http://www.riken.jp/en/research/rikenresearch/highlights/8168/

Original article:
Atarashi, K., Tanoue, T., Ando, M., Kamada, N., Nagano, Y., Narushima, S., Suda, W., Imaoka, A., Setoyama, H., Nagamori, T. et al. Th17 cell induction by adhesion of microbes to intestinal epithelial cells. ***Cell*** 163, 367–380 (2015)

Global genes for gut disorders

People with inflammatory bowel disease share the same genetic risk factors the world over

Figure: Inflammatory bowel disease is increasingly afflicting people of Asian ethnicity.

The genetic regions that underlie susceptibility to inflammatory bowel disease (IBD) are almost the same in people of diverse ancestries around the world, a recent international study has found. One implication of this finding is that drugs developed to target the genetic causes of the two forms of IBD—ulcerative colitis and Crohn's disease—should prove effective for sufferers regardless of their ethnicity or genetic background.

"The basic mechanisms of IBD are common across populations," says Atsushi Takahashi, a bioinformatics researcher at the RIKEN Center for Integrative Medical Sciences and a member of the International IBD Genetics Consortium that led the project. He added that since the mechanisms of other diseases are also shared across populations, international collaborations are important for developing insights into these diseases.

Unlike most previous investigations, which considered only individuals of one descent, the present study explored the genetic underpinnings of ulcerative colitis and Crohn's disease in populations of four ancestries—East Asian, Indian, Iranian and European.

The researchers analyzed close to 200,000 DNA letters of each person from about 43,000 people with IBD and 53,500 healthy controls. Of these DNA samples, just under 10 percent were from people of East Asian, Indian or Iranian descent, while the others were from people from Europe, North America and Oceania.

The results confirmed many genetic variants previously recognized as risk factors for IBD as well as revealing 38 regions of the genome that had not been implicated before. Of these newly identified regions, 27 were associated with both Crohn's disease and ulcerative colitis, 7 with Crohn's alone and 4 only with colitis.

Their findings bring the number of gene regions known to be linked to IBD to 200. Notably, the vast majority of the newly discovered gene regions were found in people with IBD from diverse ancestry groups. "Almost all the genes associated with IBD are shared between European and non-European populations," Takahashi says.

With IBD increasing around the world–especially in Asia, where lifestyle changes brought about by economic growth have dramatically increased the incidence of these gut disorders—new treatments options are urgently needed.

The 38 new gene regions offer a range of potential avenues for drug development. Some genes are involved in cell degradation pathways, while others are responsible for activating specialized immune cells known as T cells. "Scientists can now investigate these gene loci in more detail, and new drugs may be developed," Takahashi says.

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http://www.riken.jp/en/research/rikenresearch/highlights/8110/

Original paper:
Liu, J. Z., van Sommeren, S., Huang, H., Ng, S. C., Alberts, R., Takahashi, A., Ripke, S., Lee, J. C., Jostins, L., Shah, T. et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. ***Nature Genetics*** 47, 979–986 (2015)

Immune gene map for Japan

New resource enables scientists to find immunity genes linked to Graves' disease

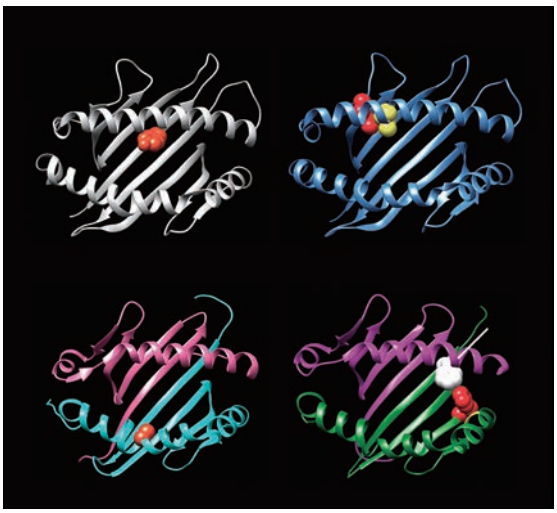

Figure: Three-dimensional ribbon models of the four HLA proteins that the study associated with Graves' disease risk. The colored spheres indicate residues at the amino acid positions associated with Graves' disease risk.

A comprehensive panel of the common gene variants that affect the immune system among Japanese individuals has been established by a RIKEN-led team. The researchers have used this new resource to identify specific immune-related genes that are most strongly associated with the risk of a person developing Graves' disease, an autoimmune disorder that affects about 30 million people around the world.

"These biomarkers are the best candidates for personalized or precision medicine," says Yukinori Okada, a genetic epidemiologist at the RIKEN Center for Integrative Medical Sciences, who led the study. He notes that these immune-related genes affect disease risk much more than the other types of gene variants usually used by researchers when searching for predictors of disease.

The stretch of DNA known as the major histocompatibility complex (MHC) includes more than 200 genes that help the immune system recognize foreign substances. It is one of the most genetically diverse regions of the genome. The variation contained within the MHC—specifically in genes that code for the human leukocyte antigen (*HLA*) genes—underlie individual susceptibility to many diseases, including cancers, mental illnesses, infectious diseases and autoimmune disorders.

Fine mapping of risk variants within *HLA* genes has mostly been limited to people of European ancestry. Consequently, the resulting databases are not representative of populations found elsewhere in the world. To address this imbalance, Okada, in collaboration with RIKEN geneticist Michiaki Kubo and other colleagues, decided to build a reference dataset of HLA gene variation among individuals of Japanese origin. They did so by inspecting more than 7,000 single DNA polymorphisms in the genomic region encoding the MHC.

The researchers then used this new resource to analyze the association of *HLA* genes with Graves' disease, a disorder of the immune system that results in the overproduction of thyroid hormones. Also known as Basedow's disease, this condition additionally causes bulging eyes, heat intolerance and weight loss. Okada's team combined their immune gene map with data from a genome-wide association study that included close to 2,000 Japanese individuals with Graves' disease and around 7,000 healthy controls. They discovered that common variants in four *HLA* genes (Figure) each independently increase the risk of a person developing the disease.

This knowledge can now help doctors to more effectively identify patients that are most likely to suffer the autoimmune disorder. The Japanese map of *HLA* genes can also be used to discover risk variants associated with other disorders.

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http://www.riken.jp/en/research/rikenresearch/highlights/8086/

Original article:
Okada, Y., Momozawa, Y., Ashikawa, K., Kanai, M., Matsuda, K., Kamatani, Y., Takahashi, A. & Kubo, M. Construction of a population-specific HLA imputation reference panel and its application to Graves' disease risk in Japanese. ***Nature Genetics*** 47, 798–802 (2015)

How the body stops an immune response from triggering allergic diseases

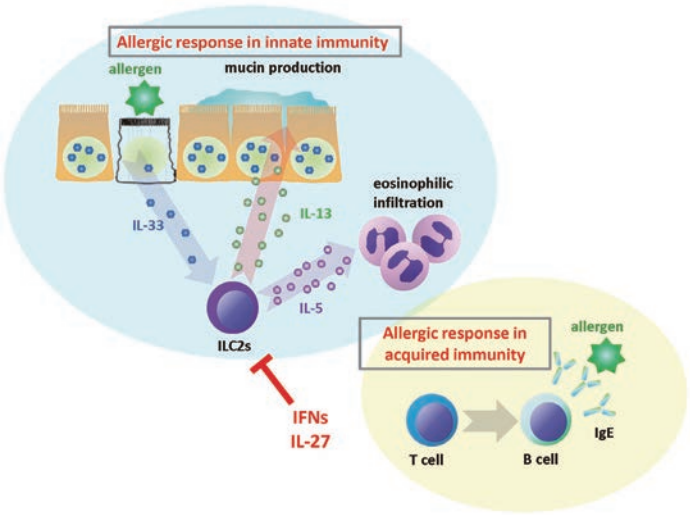

Figure: IFN and IL-27 suppress ILC2s-induced allergic response in innate immunity

The innate immune response, which is the body's rapid and non-specific response to pathogens, was once believed to be a simple system relying on short-lived effector cells alone, but it is now known to be more complex, involving long-lived lymphoid cells. Researchers from the RIKEN Center for Integrative Medical Sciences (IMS) in Japan have now shown how the body suppresses the activation of the long-lived cells after infection, preventing the response from continuing when it is no longer needed.

Parasitic worms, known as helminths, are a formidable challenge to human health, being a major cause of mortality in the developing world. The body's key first-line defense against these parasites and some fungal infections is called the type 2 innate immune response, which is preceded by a more specific one called the type 2 adaptive immune response. It actually turns out to be a double-edged sword, as it has been implicated in allergic inflammatory responses such as asthma caused by fungal infections.

"This immune response is important, but also can be dangerous if it lasts beyond its necessity," says Kazuyo Moro, team leader of the Laboratory for Innate Immune Systems in IMS, "It was once believed that the response was mainly mounted by short-lived cells, but now we know that it also involves a population of longer-lived innate lymphoid cells. Since a continuing response is associated with allergic inflammation, it is important for us to understand how these cells are turned off."

A key finding of the study, published in *Nature Immunology*, are that these innate lymphoid cells can be shut off by certain cytokines—interferon-beta, -gamma and interleukin-27—to end the immune response and ensure that the inflammation does not last. In addition, the scientists helped clear up a mystery about these cells by showing that they do not circulate to tissues that require an immune response but are actually located in the tissues, and are only turned on when a threat is detected. "This shows," says Moro, "that the response is mounted locally in a very specific way. This may be another way for the body to prevent the lasting inflammation that can be associated with the response."

According to Shigeo Koyasu, group director of the Laboratory for Immune Cell Systems, who led the group, "These findings are helpful in understanding how the type 2 innate response changes to be both beneficial and harmful. Learning how these cells are activated and inactivated can give us clues for understanding and treating how the body reacts to such infections."

He continues, "We are beginning to gain insights into the innate immune response, which was previously thought to be simpler than our understanding today. I hope that our work will encourage researchers to look for similar regulatory mechanisms in type 1 and type 3 innate immune responses as well, as this will help us to gain a broader understanding of the complexity of our immune response."

This article was reproduced from RIKEN Press Release
http://www.riken.jp/en/pr/press/2015/20151124_1/

Original paper:
Kazuyo Moro, Hiroki Kabata, Masanobu Tanabe, Satoshi Koga, Natsuki Takeno, Miho Mochizuki, Koichi Fukunaga, Koichiro Asano, Tomoko Betsuyaku, and Shigeo Koyasu. Interferon and IL-27 antagonize ILC2 function and type 2 innate immune responses. ***Nature Immunology*** 17, 76–86 (2015)

Research on 377,000 people worldwide highlights the role of genes in eczema

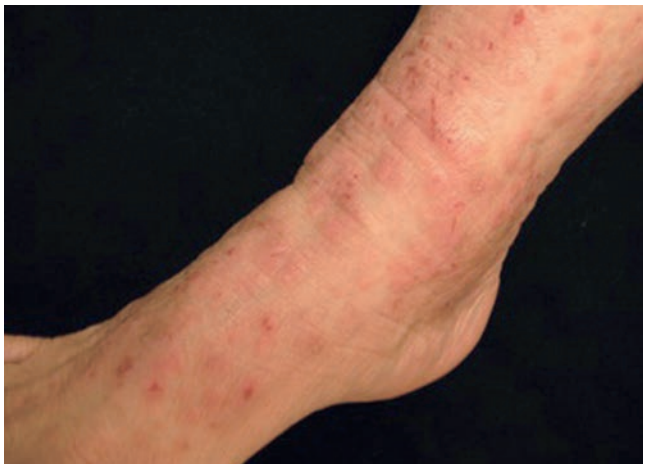

Figure: Atopic dermatitis is the most common form of eczema that causes dry and itchy skin condition.
Copyright: Dr.Tamotsu Ebihara, Department of Dermatology, Keio University School of Medicine

Eczema – an itchy dry-skin condition – affects an estimated one in five children and one in 12 adults in the UK. Genes play an important role in determining how likely we are to develop eczema but the majority of the genes that cause the condition have yet to be detected.

Now, in the largest genetic study of eczema in the world to date, a group of international researchers including Drs. Tomomitsu Hirota, Mayumi Tamari and Michiaki Kubo of RIKEN Center for Integrative Medical Sciences (IMS) and Dr. Lavinia Paternoster from the University of Bristol, has combined data on 377,000 participants involved in 40 research studies worldwide.

The team used a technique called 'genome-wide association analysis' to look at the genomes of these 377,000 people and to identify small changes (variants) in the genes commonly found in people with eczema. They found 10 new variants, bringing the total number of variants known to be related to eczema to 31.

What all these new genetic variants have in common is that they all play a role in regulating our immune system, highlighting potential new targets for therapeutic research for eczema.

The researchers also found some evidence of genetic overlap between eczema and other diseases like inflammatory bowel disease. This suggests that studying these diseases together in the future could give important insights into the mechanisms of disease and potentially identify new treatments.

Speaking about the discovery, Dr. Paternoster said: "Though the genetic variants identified in this current study represent only a small proportion of the risk for developing eczema (they are in no way deterministic, rather they slightly increase your risk), they do give new insights into important disease mechanisms and through on-going research in this area these findings could be turned into treatments of the future."

Dr. Sara Brown, an academic dermatologist who contributed to the research from the University of Dundee, said: "Eczema runs in families so we know that genetic factors are an important part of the cause. The very large numbers of participants in this research has allowed us to 'fine-tune' our understanding of eczema genetic risk, providing more detail on how the skin immune system can go wrong in eczema."

This article was edited from the University of Bristol Press Release with permission http://www.bristol.ac.uk/news/2015/october/eczema-genes.html

Original paper:
Paternoster L, Standl M, Waage J, Baurecht H, Hotze M, Strachan DP, Curtin JA, Bønnelykke K, Tian C, Takahashi A, et al. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. ***Nature Genetics*** 47, 1449–56 (2015)

Controlling inflammation in fat cells

A signaling mechanism that controls inflammation in fat cells could offer a way to prevent obesity-induced diabetes Controlling inflammation in fat cells

Figure: Administering interleukin-33 increased the number of Treg cells in fat tissue in obese mice, improving glucose tolerance.

The excess fat tissue associated with obesity causes inflammation and reduces glucose tolerance, which increases the risk of diabetes. The mechanism responsible for these physiological effects, however, has been unclear. An international team including researchers from the RIKEN Center for Integrative Medical Sciences (IMS) has now identified a signaling pathway that is crucial for controlling obesity-associated inflammation, offering hope for a therapeutic target to prevent glucose intolerance.

The researchers focused on immune cells called regulatory T (T_{reg}) cells. These cells respond to inflammation and proliferate within inflamed tissue. "Whereas most T cells are activated by a specific antigen and induce inflammation, T_{reg} cells suppress inflammatory responses," explains Shigeo Koyasu from the Laboratory for Immune Cell Systems at the IMS.

Previous work by the Walter and Eliza Hall Institute (WEHI) of Medical Research in Australia showed that T_{reg} cells can be in either an activated state in which they suppress inflammation, or a resting state. In collaboration with the WEHI, Koyasu and his RIKEN colleagues searched for genetic differences between resting and activated T_{reg} cells. By analyzing gene expression in the two states, they discovered approximately 2,700 differences.

Interestingly, the researchers discovered that T_{reg} cells in fat tissue, known as visceral adipose tissue (VAT), expressed an exceptionally high level of a receptor called ST2 for the signaling molecule interleukin-33 (IL-33). By genetically manipulating the expression of ST2 in mice, the researchers showed that IL-33 signaling is crucial for the development of VAT-T_{reg} cells. When applied to cultured cells and injected into mice, IL-33 was found to induce the proliferation of VAT-T_{reg} cells, increasing their population by over ten fold.

"T_{reg} cells suppress inflammation, which improves glucose tolerance, so an increase in T_{reg} cells is beneficial," says Koyasu. "A lack of IL-33 greatly reduced VAT-T_{reg} numbers, resulting in impaired glucose tolerance. Administration of IL-33 restored glucose tolerance."

Finally, the team administered IL-33 to mice that were either genetically obese or obese owing to a high fat diet. In both cases, IL-33 increased the number of VAT-T_{reg} cells and improved glucose tolerance. The findings have therapeutic potential.

"Human T_{reg} cells in fat tissue also express IL-33 receptors, so it is possible that IL-33 could increase T_{reg} cells in humans," explains Koyasu. As a possible therapy, however, IL-33 comes with strings attached. "IL-33 also induces allergic inflammation, so it is critical to control the dose to avoid an allergic response while maintaining the ability to control VAT-T_{reg} cells."

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http://www.riken.jp/en/research/rikenresearch/highlights/7988/

Original paper:
Vasanthakumar, A., Moro, K., Xin, A., Liao, Y., Gloury, R., Kawamoto, S., Fagarasan, S., Mielke, L. A., Afshar-Sterle, S., Masters, S. L. et al. The transcriptional regulators IRF4, BATF and IL-33 orchestrate development and maintenance of adipose tissue-resident regulatory T cells. ***Nature Immunology*** 16, 276–285 (2015)

Genome-wide homozygosity influences stature and cognition

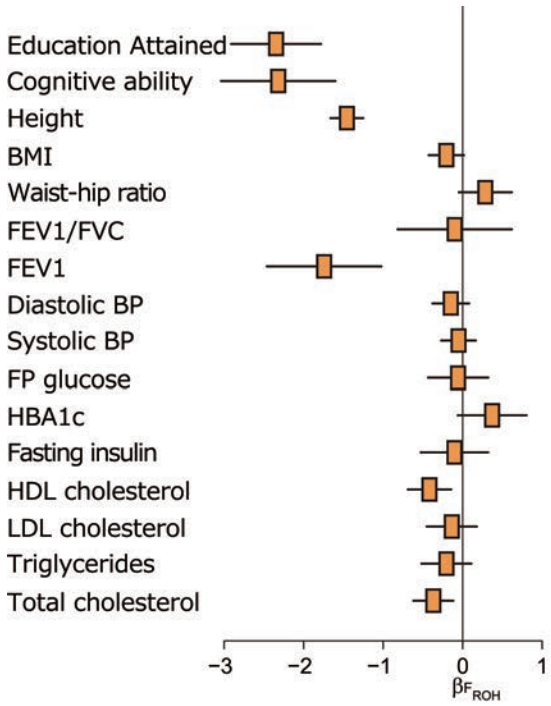


Figure: Effects of genome-wide homozygosity on 16 traits

An international research project including researchers from RIKEN Center for Integrative Medical Sciences (IMS), revealed that greater genetic diversity is linked to increased height and lung capacity, as well as to better cognitive skills and educational attainment.

Inbreeding within related populations increases the number of inherited identical copies of genes from both parents. These genomic regions, where the copies inherited from parents are identical, are called "runs of homozygosity (ROH)", and are used as indicators that an individual's ancestors were related.

To investigate the influence of genetic diversity, researchers from more than one hundred research institutions worldwide launched an international project "Runs of Homozygosity Genetics (ROHgen) Consortium" in 2013. Using the medical records and genetic information of more than 350,000 people, the Consortium members determined if there was any correlation between genome-wide homozygosity and a variety of phenotypic traits, including body measurement (height, body mass index, waist-hip ratio), blood chemistry (blood glucose, HbA1c, insulin, cholesterol, triglycerides), physiological parameters (blood pressure and lung function), cognitive functions and educational attainment.

The researchers found that a decrease in homozygosity tends to correlate with an increase height, lung capacity, and cognitive skills and to higher levels of educational attainment. However, the study found no link between genetic diversity and high blood pressure or cholesterol levels. It had been thought that close family ties would raise a person's risk of complex diseases, but the researchers found this not to be the case in general.

"The ROHgen consortium highlighted the power of large-scale genetic analyses to uncover the link between genetic homozygosity and phenotypic traits," says Yukinori Okada of RIKEN IMS.

"Our research answers questions first posed by Darwin as to the benefits of genetic diversity. Our next step will be to hone in on the specific parts of the genome that most benefit from diversity," commented Peter Joshi of The University of Edinburgh.

Original paper:
Peter K. Joshi, Tonu Esko, Hannele Mattsson, Niina Eklund, Ilaria Gandin, Teresa Nutile, Anne U. Jackson, Claudia Schurmann, Albert V. Smith, Weihua Zhang, Yukinori Okada, Alena Stančáková, Jessica D. Faul, Wei Zhao, Traci M. Bartz, Maria Pina Concas, Nora Franceschini, Stefan Enroth, Veronique Vitart, Stella Trompet, Xiuqing Guo, Daniel I. Chasman, Jeffery R. O'Connel,

Tanguy Corre, Suraj S. Nongmaithem, et al. Directional dominance on stature and cognition in diverse human populations. ***Nature*** 523, 459–62 (2015)

The genetic roots of adolescent scoliosis

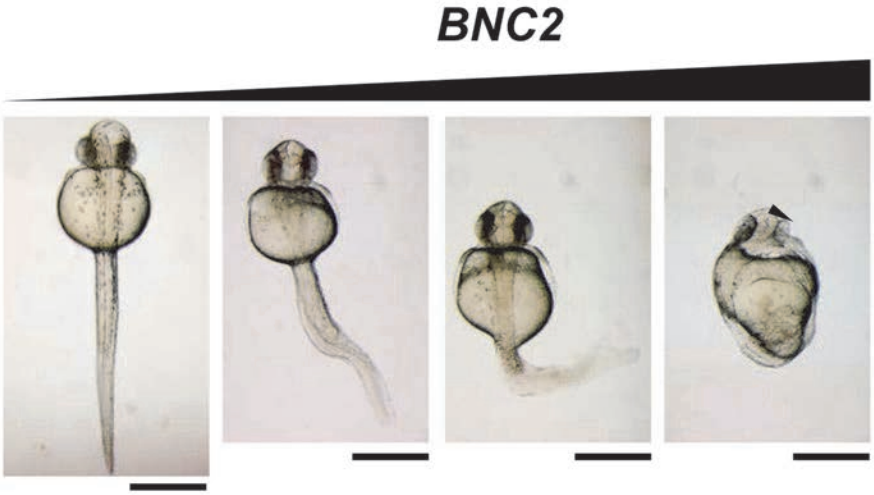


Figure: The effect of BNC2 on zebrafish development

Adolescent idiopathic scoliosis (AIS)—a condition featuring curvature of the spine—affects tens of millions of children worldwide, but does not have a known cause. Now, scientists at the RIKEN Center for Integrative Medical Sciences in collaboration with Keio University in Japan have discovered a gene that is linked to susceptibility to the condition. Published in the American Journal of Human Genetics, the work details how the susceptibility gene is associated with increased expression of the protein BNC2, which is in turn regulated by another protein called YY1.

"AIS is a complex and mysterious disease with awkward spinal deformities that can be a nightmare for affected people," explains team leader Shiro Ikegawa. "We were excited to find a single nucleotide polymorphism located on human chromosome number nine that is significantly associated with the disease."

The discovery began with a genome-wide association study using more than ten thousand volunteers with and without scoliosis. This type of study looks for small differences in genes—called single nucleotide polymorphisms, or SNPs—that occur more frequently in people with a certain disease. After confirming the association between a particular SNP (pronounced "snip") in two additional independent populations—one in Japan and one in China—they determined that it is located near the part of the DNA that codes for the protein BNC2.

The team then examined where BNC2 is expressed in humans. Using quantitative RT-PCR, they found that it is most highly expressed in the uterus, spinal cord, bone, and cartilage. "This result told us that we were on the right track," says Ikegawa, "and evidence that the SNP variation associated with the disease led to higher levels of BNC2 expression told us that this SNP has the potential to regulate expression of BNC2."

The team tested this hypothesis and found that not only was BNC2 expression triggered by the protein YY1—which binds to the DNA around the SNP—but that for genes with the at-risk SNP variant, the amount of BNC2 produced when YY1 was present was much greater than for genes with the non-risk variant.

The BNC2 gene is highly conserved across diverse species, and plays roles in a variety of tissues. To test how over-expression of BNC2 affects development, the team expressed it in zebrafish embryos and found that it resulted in severe body curvature that was positively correlated to the amount of BNC2.

These results and the abundance of BNC2 in the human spine and bones make it likely that adolescents with the disease-associated SNP variant may begin to produce excess BNC2 at puberty if other genetic or environmental factors are also present.

The next step is to understand how BNC2 causes scoliosis and why it is so much more prevalent in women than in men. "The expression of BNC2 in the uterus and changes that occur during puberty could help explain the large sex difference," explains Ikegawa. "Additionally, knowing what genes are downstream of BNC2 will provide us with potential targets for therapeutic interventions."

This article was reproduced from RIKEN Press Release
http://www.riken.jp/en/pr/press/2015/20150724_1/

Original paper:
Yoji Ogura, Ikuyo Kou, Shigenori Miura, Atsushi Takahashi, Leilei Xu, Kazuki Takeda, Yohei Takahashi, Katsuki Kono, Noriaki Kawakami, Koki Uno, Manabu Ito, Shohei Minami, Ikuho Yonezawa, Haruhisa Yanagida, Hiroshi Taneichi, Zezhang Zhu, Taichi Tsuji, Teppei Suzuki, Hideki Sudo, Toshiaki Kotani, Kota Watanabe, Naobumi Hosogane, Eijiro Okada, Aritoshi Iida, Masahiro Nakajima, Akihiro Sudo, Kazuhiro Chiba, Yuji Hiraki, Yoshiaki Toyama, Yong Qiu, Chisa Shukunami, Yoichiro Kamatani, Michiaki Kubo, Morio Matsumoto and Shiro Ikegawa. A functional SNP in BNC2 is associated with adolescent idiopathic scoliosis. ***American Journal of Human Genetics*** 97, 337–42 (2016)

Blocking differentiation is enough to give cells "stemness"

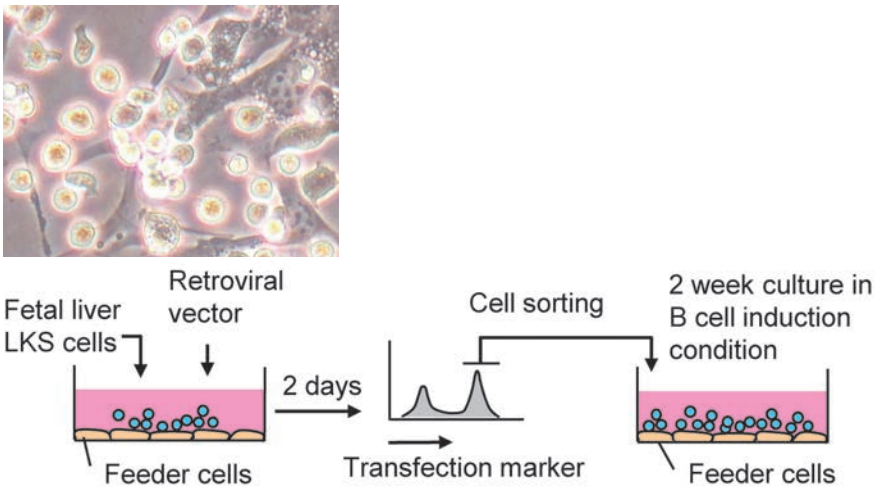


Figure: Schematic representation of the method for the production of Id3-induced hematopoietic progenitor (IdHP) cells (*lower*) and photomicrograph of IdHP cells (*upper*)

Though immune therapy and regenerative medicine are promising areas of research for future medical therapies, they are limited today by the difficulty of creating stem cells, and scientists around the world are searching for ways to create somatic stem cells in the easiest way possible. Now, a collaboration between the RIKEN Center for Integrative Medical Science (IMS) and other institutions in Japan and Europe have found that in immune cells, simply blocking a transcription factor that leads to differentiation is sufficient to keep cells in a multipotent stem cell-like state where they can continue to proliferate and can later differentiate into various cell types.

Efforts in the past to create stem cells have typically involved finding ways to take target cells and "dedifferentiate" them into multipotent cells, but this is typically a painstaking process.

According to Tomokatsu Ikawa, the first and corresponding author of the paper published in Stem Cell Reports, "We decided to look at the possibility that somatic stem cells could be maintained in a stem cell-like state where they could proliferate without undergoing differentiation." To test this, the team took mouse hematopoetic progenitor cells—cells that give rise to all white blood cells—and modified them to overexpress a protein called Id3. Id3 inhibits the expression of E-proteins, which are involved in differentiation in somatic cells. They then placed the cells into culture conditions containing certain cytokines, and instead of differentiating into B-cells, the cells continued to divide as stem cells. When placed in a culture that did not contain those cytokines, the cells differentiated into various immune cells. To test whether the cells would maintain their multipotency in living animals, the researchers transplanted them into mice whose white blood cells had been depleted, and showed that the new cells could expand and differentiate into various types of white blood cells.

To explore the potential for therapeutic application, the group then attempted a similar experiment using human blood stem cells taken from umbilical cords, which they transfected with a vector encoding human Id3. They found that, like the mouse cells, these human cells could be maintained in a dividing state and then prompted to differentiate by changing the conditions.

"With this work we have succeeded in showing," says Ikawa, "that the cells can be kept in a state of undifferentiation where they will proliferate extensively. This is both a useful tool for giving us a better understanding of the genetic and epigenetic program controlling the self-renewal of stem cells, and on a practical side, it could allow us to inexpensively produce large numbers of immune cells, which could then be used for regenerative medicine or immune therapy."

The research was done by RIKEN in collaboration with Kyoto University, Maastricht University Medical Centre in the Netherlands, Osaka University, and Nihon University School of Medicine.

This article was reproduced from RIKEN Press Release
http://www.riken.jp/en/pr/press/2015/20151023_1/

Original article:
Tomokatsu Ikawa, Kyoko Masuda, Mirelle J. A. J. Huijskens, Rumi Satoh, Kiyokazu Kakugawa, Yasutoshi Agata, Tomohiro Miyai, Wilfred T. V. Germeraad, Yoshimoto Katsura, and Hiroshi Kawamoto. Induced developmental arrest of early hematopoietic progenitors leads to the generation of leukocyte stem cells. ***Stem Cell Reports*** 5, 716–727 (2015)

Determination of the CD4+ cytotoxic T lymphocyte lineage

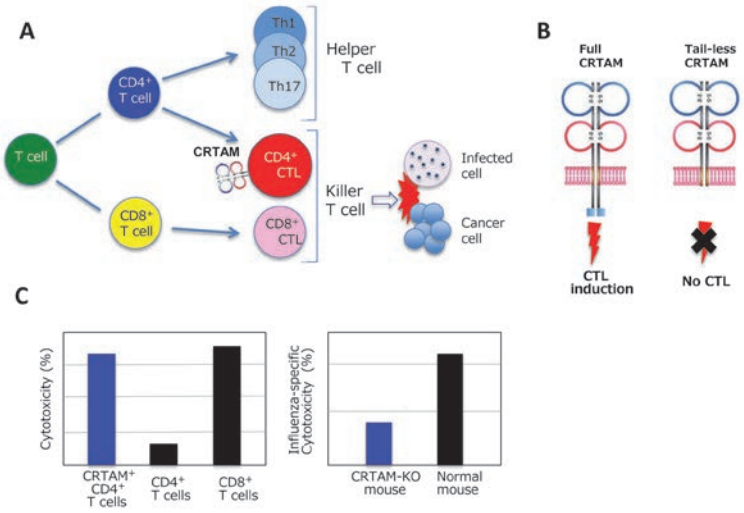


Figure: CRTAM determines the CD4+ cytotoxic T lymphocyte lineage

A. CD4+ CTL are generated from CRTAM-expressing CD4+ T cells.
B. Full-length CRTAM- but not tail-less CRTAM-expressing T cells generate CD4+ CTL.
C. CRTAM+ but not CRTAM- CD4+ T cells exhibit cytotoxicity similar to CD8+ T cells (left). Upon influenza virus infection, lung T cells from CRTAM-deficient mice showed reduced influenza-specific killing of infected target cells compared to normal mice (right).

T cell precursors differentiate into CD4+ and CD8+ T cells during their development in the thymus. The CD4+ T cells then differentiate into various helper T cells that help activation of B cells for antibody production, and the CD8+ T cells differentiate into cytotoxic T cells that kill cancer cells and virus-infected cells.

However, there have been reports that some CD4+ T cells could acquire cytotoxic ability and directly kill infected cells. These CD4+ cytotoxic T cells were identified in the peripheral blood of human and mouse after chronic viral infections, but little was known about how CD4+ T cells differentiate into cytotoxic lymphocytes.

The research group led by Takashi Saito in RIKEN IMS discovered that a protein called "class I-restricted T cell-associated molecule (CRTAM)" has an essential role in the differentiation of CD4+ T cells to acquire cytotoxic abilities.

The research group previously reported in 2009 that CRTAM regulates the immune response by CD8+ cytotoxic T cells. Recently, they found that CRTAM is expressed not only in CD8+ T cells but also in a small fraction of CD4+ T cells, and they decided to study the function of CRTAM-expressing CD4+ T cells.

First, they isolated CRTAM-expressing CD4+ T cells (CRTAM+CD4+ T cells) and compared their gene expression pattern with CD4+ T cells and CD8+ T cells. Although CD4+ T cells and CD8+ T cells had different gene expression patterns, they found that the CRTAM+CD4+ T cells share some characteristics of both CD4+ and CD8+ T cells.

Next, they analyzed cytotoxic functions of CRTAM+CD4+ T cells and found that they have cytotoxic activity in vitro similar to CD8+ T cells, while the CRTAM-CD4+ T cells did not exhibit cytotoxicity. More importantly, when mice were infected with influenza virus, CRTAM+CD4+ T cells were increased in their lungs and exhibited influenza-specific cytotoxic activity. On the other hand, CRTAM-deficient mice had much diminished cytotoxic activity compared to normal mice (Figure.)

To study the role of CRTAM in cytotoxic activity, they generated transgenic mice in which all T cells expressed CRTAM. In this mouse, all CD4+ T cells immediately expressed CRTAM upon stimulation, and efficiently differentiated into CD4+ cytotoxic T cells. However, when a truncated CRTAM mutant lacking its cytoplasmic domain was expressed, CD4+ T cells did not develop cytotoxic functions.

"The results indicate that CRTAM-mediated signal is critical for differentiation of CD4+ cytotoxic T cells and CRTAM is the first marker of CD4+ cytotoxic T cells. Regulation of CRTAM expression would be useful for therapeutic aims, such as in chronic virus infection, antitumor responses or inflammatory diseases," says Takashi Saito of IMS.

Original paper:
Takeuchi A, Badr Mel S, Miyauchi K, Ishihara C, Onishi R, Guo Z, Sasaki Y, Ike H, Takumi A, Tsuji NM, Murakami Y, Katakai T, Kubo M, Saito T. CRTAM determines the CD4+ cytotoxic T lymphocyte lineage. ***Journal of Experimental Medicine*** 213, 123–38 (2016)

In memory of Dr. William Paul

Photo: Dr. William E. Paul at RCAI in 2005

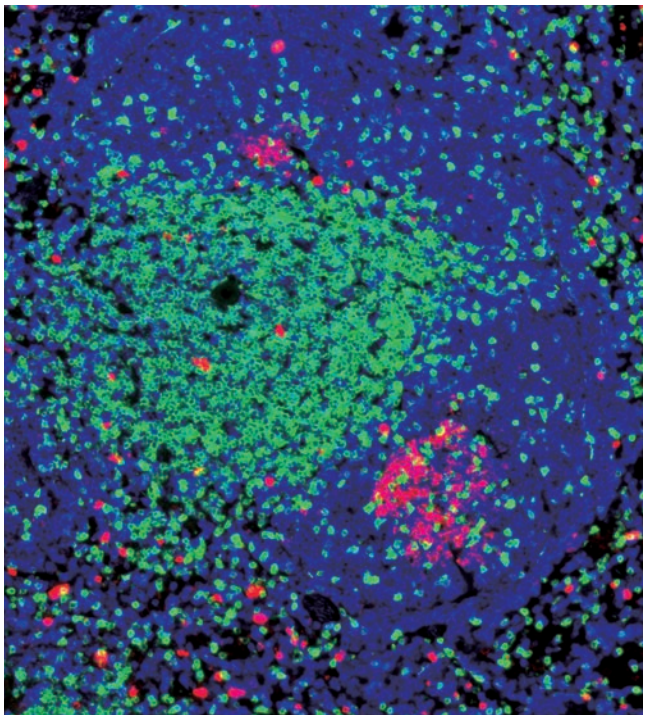
It is very sad and a great loss to IMS that Dr. William E. Paul passed away on September 18th, 2015. Dr. Paul was a member of the Advisory Council of the Center for Integrative Medical Sciences (IMS, 2013–2015) and of the former Research Center for Allergy and Immunology (RCAI, 2004–2013). In his role as an advisory council member, he visited the Center in Tsurumi, Yokohama almost every year.

Because of his expertise in the fields of cytokine biology and allergy, Dr. Paul was an invaluable supporter of the Center's allergy-related research projects and researchers. He was a textbook of knowledge of immunology and maintained a global view of the field, thus he was always able to give critical but encouraging comments and advice on any research project. We learned from him the importance of basic science and the establishment of proof of concept in translating basic research findings to humans. We always had to consider how to tackle global cutting edge science and to compete with major laboratories throughout the world with our limited resources. Following his advice, IMS created strong central research facilities (Animal Facility, FACS Lab, Imaging Lab and Genomics Lab) that gave IMS laboratories access to state-of-the-art technologies and excellent experimental support. For our ENU (N-ethyl-N-nitrosourea) mutagenesis project, without his critical advice on how to deal with the low mutation rate we would not have succeeded in isolating the *Spade* mutant mouse, which has an atopic dermatitis phenotype. We also learned from him the importance of considering human immunology, even though most of our experiments were done with mice.

Dr. Paul was a wonderful advisor, not only to IMS researchers but also to many other Japanese immunologists. The Japanese Society for Immunology was established in 1970 and Japanese immunologists started to study abroad in the 70's. Many of those pioneering Japanese immunologists visited Dr. Paul in his NIH laboratory at the National Institute of Allergy and Infectious Diseases because of his deep knowledge of immunology and because he was very fair and open to anyone, even young inexperienced researchers. Without his help, immunology would not have flourished in Japan like now. Dr. Paul was a very compassionate human being. In 2011, we experienced the Great East Japan magnitude 9.0 earthquake. Dr. Paul was one of the advisory council members who immediately contacted Dr. Taniguchi, then Director of RCAI, and with their help, the Center launched a systematic effort to provide research supplies, biological samples, and mice to the affected laboratories, as well as support for graduate students and researchers to attend immunology meetings.

We will never forget what Dr. Paul taught us and his warm words always with a smile. In his honor, IMS will move forward to pioneer a new era of human immunology research in combination with human genetics and genomics.

Shigeo Koyasu
Director,
RIKEN Center for Integrative Medical Sciences



Part 2

Lab Activities

Core for Homeostatic Regulation

The ultimate goal of the Core for Homeostatic Regulation is to elucidate the mechanisms of onset of human diseases and to create new scientific paradigms. This Core clarifies the regulation of homeostasis in individuals, focusing on their immune, metabolic and environmental response systems. In addition, the Core for Homeostatic Regulation will validate the disease models established by the Core for Precise Measuring and Modeling in a multitier timeframe from before to after the onset of diseases.

The Core for Homeostatic Regulation is composed of 15 laboratories, which are divided into four areas:

[1] Immune homeostasis

Cell signaling (T. Saito), Lymphocyte differentiation (T. Kurosaki), Immune homeostasis (S. Hori), Metabolic homeostasis (N. Kubota)

[2] Lymphocyte development

Transcriptional regulation (I. Taniuchi), Human disease models (F. Ishikawa)

[3] Mucosal immunity

Intestinal ecosystem (H. Ohno), Mucosal immunity (S. Fagarasan), Immune cell systems (S. Koyasu), Gut homeostasis (K. Honda), Immune crosstalk (H. Cheroutre)

[4] Allergy and inflammation

Skin homeostasis (M. Amagai), Inflammatory regulation (T. Tanaka), Cytokine regulation (M. Kubo), Innate immune systems (K. Moro)

All of these areas elucidate the basic mechanisms of immune regulation at cellular tissue and systemic levels. We ultimately aim to analyze the onset of autoimmune diseases, metabolic disorders [1], primary immunodeficiency [2], inflammatory bowel disease and colitis [3], and atopic dermatitis and allergic diseases [4].

Laboratory for Cell Signaling

Group Director: Takashi Saito

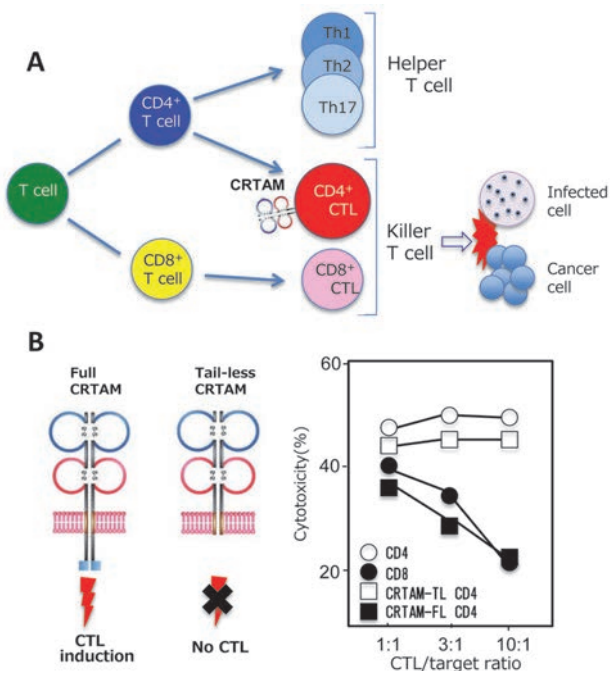


Figure: CRTAM determines the CD4⁺ CTL lineage
[A] CD4⁺CTLs are generated from CRTAM-expressing CD4⁺T cells
[B] Full-length CRTAM (FL)- but not tail-less CRTAM (TL)-expressing T cells induce cytotoxic CD4⁺ CTL.

The objective of our group is to determine the molecular mechanisms of T cell activation, differentiation and homeostasis. Toward this goal, basic mechanisms such as antigen recognition, T cell activation, T cell differentiation, and functional regulation have been studied from a signaling perspective. Both processes of recognition and activation at the single cell level and T cell development/homeostasis within clonal populations are being investigated.

After our finding of TCR-microclusters (MC), which initiate T cell activation, we began to understand that formation of signal clusters in a single cell is a key event for signal regulation. Thus, we analyzed clustering of CARMA1 for regulating NF-κB activation for T cell activation and tumorigenesis, and also the unique clustering of RasGRP1 for Ras activation formed by assembly with cytoskeletal linker molecules. These analyses have provided a dynamic view of signal regulation within a single cell as well as new insights into how to modify the various signaling pathways upon activation through TCR-MC.

In addition, we have analyzed several molecules, isolated as early expressed genes upon T cell activation, as possible targets to modulate T cell activation and function. These are adhesion molecules, transcription factors, nucleic acid-sensors, and cytoskeletal molecules, all of which may regulate T cell-specific functions. CRTAM, which was cloned as an adhesion receptor, is now found to play a critical role in development of CD4⁺ cytotoxic T cells (Figure).

The ultimate aim of our these approaches is to elucidate the onset of T cell function/activation and to be able to modulate it in order to inhibit/prevent immune diseases such as autoimmunity and allergic inflammation by development of effective modulators of T cell activation.

Recent Major Publications

Hashimoto-Tane A., Sakuma M., Ike H., Yokosuka T., Kimura Y., Ohara O. and Saito T. The Micro adhesion-ring surrounding each TCR microclusters forms synapse-like structure essential for T cell activation. ***J Exp Med*** 213, 1609–1625 (2016)

Takeuchi A, Badr MESG, Miyauchi K, Ishihara C, Onishi R, Guo Z, Sasaki T, Ike H, Takumi A, Tsuji NM, Murakami Y, Katakai T. and Saito T. CRTAM determines the CD4+ cytotoxic T lymphocyte lineage. ***J Exp Med*** 213, 123–138 (2016)

Hara H, Yokosuka T, Hirakawa H, Ishihara C, Yasukawa S, Yamazaki M, Koseki H, Yoshida H and Saito T. Clustering of CARMA1 through SH3-GUK domain interactions is required for its activation of NF-κB signaling. ***Nat Commun*** 6, 5555 (2015)

Invited Presentations

Saito T. "Development and function of CD4⁺CTL in inflammation diseases" SICORP Japan-New Zealand Joint Research on Functional Foods (Wellington, New Zealand) February, 2016

Saito T. "Regulation of T cell activation at Immune synapse" Advanced Seminar Series on Microbiology and Immunology (Osaka, Japan) November, 2015

Saito, T. "Microsynapse is an essential structure for T cell activation" FASEB Science Research Conference (Big Sky, USA) June, 2015

Saito, T. "Spatiotemporal regulation of T cell activation" OIST Seminar (Okinawa, Japan) April, 2015

Saito, T. "Spacial regulation of T cell activation at Immune synapse" The Fourth Bizan Immunology Symposium at University of Tokushima (BISUT4) (Tokushima, Japan) January, 2015

Laboratory for Lymphocyte Differentiation

Group Director: Tomohiro Kurosaki

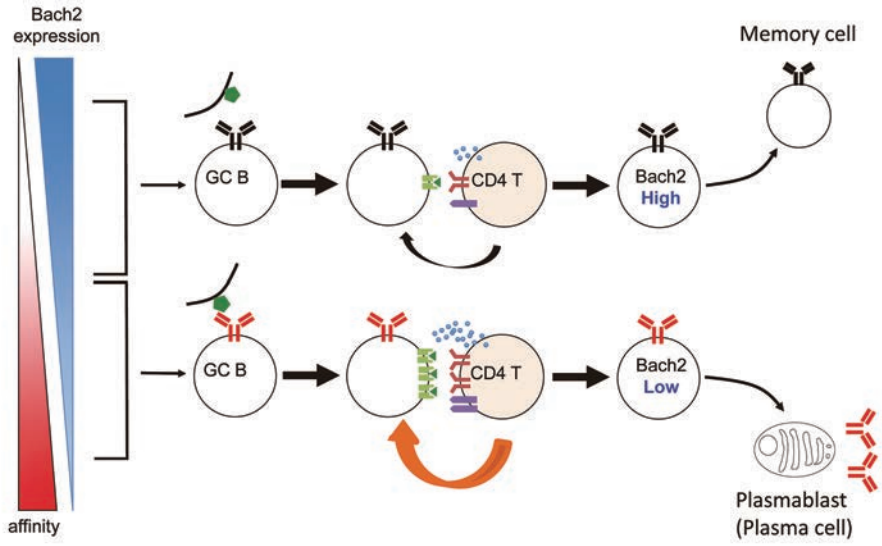


Figure: An instructive model for how memory B cells are selected and generated
Once light zone (LZ) GC cells with high-affinity BCRs (shown in red) begin receiving 'strong' help from T cells, the level of the transcription factor Bach2 goes down, thereby facilitating their differentiation toward plasmablasts (lower). In contrast, selection of LZ GC cells into the memory cells with low-affinity BCRs (shown in black) requires a specific range of T cell help of a weaker magnitude than that needed for plasmablast differentiation. The relatively weak help from T cells keeps Bach2 expression relatively high, a state advantageous for entry into the memory B cell compartment (upper).

Humoral memory relies on the development of memory B cells and long-lived plasma cells. Our lab has been focusing on characterizing of these two types of cells and on clarifying how these cells are generated, maintained, and activated. Most memory B cells responding to T cell-dependent antigens arise from the germinal center (GC) reaction. However, how such memory B cells are selected and developed during GC reactions remains unclear. By employing GC-specific fate mapping mice, we found that light-zone (LZ) GC B cells with BCRs of lower affinity were prone to enter the memory pool. Mechanistically, cells in this memory-prone fraction had higher expression of the transcriptional repressor Bach2 than in the cells bearing higher affinity BCRs. The importance of high Bach2 was underscored by the fact that Bach2 haploinsufficiency resulted in suppression of memory B cell generation. Given our evidence that Bach2 expression was inversely correlated with the strength of T cell help, we propose an instructive model in which weak help from T cells maintains relatively high expression of Bach2, which predisposes GC cells to enter the memory pool (Figure).

After secondary exposure to antigens, memory B cells rapidly generate high-affinity antigen-specific antibodies (Abs), mostly of the IgG isotypes in the case of systemic immune responses. It has been thought that the unique cytoplasmic domain of IgG causes the prompt activation of antigen-experienced IgG memory B cells. By establishing a mouse containing IgG1 B cells that have never encountered antigen, we show that antigen-experienced IgG1 memory B cells rapidly differentiated into plasma cells, whereas non-experienced IgG1 B cell did not, suggesting the importance of the stimulation history, rather than the IgG cytoplasmic domain. Moreover, in addition to the differentiation activity of IgG1 memory B cells, their antigen presentation activity is critical for rapid activation of the T_{FH} memory T cells residing in the follicular region, which, in turn, contributes to activation of the memory B cells.

Recent Major Publications

Shinnakasu R, Inoue T, Kometani K, Moriyama S, Adachi Y, Nakayama M, Takahashi Y, Fukuyama H, Okada T, Kurosaki T. Regulated selection of germinal-center cells into the memory B cell compartment. ***Nat Immunol*** 17, 861–869 (2016)

Inoue T, Morita M, Hijikata A, Fukuda-Yuzawa Y, Adachi S, Isono K, Ikawa T, Kawamoto H, Koseki H, Natsume T, Fukao T, Ohara O, Yamamoto T, Kurosaki T. CNOT3 contributes to early B cell development by controlling Igh rearrangement and p53 mRNA stability. ***J Exp Med*** 212, 1465–1479 (2015)

Kometani K, Kurosaki T. Differentiation and maintenance of long-lived plasma cells. ***Curr Opin Immunol*** 33, 64–69 (2015)

Invited Presentations

Kurosaki T. "Instructive selection of germinal center B cells into the memory compartment" The 3rd Symposium of International Immunological Memory and Vaccine Forum (IIMVF) "What´s Immunological Memory?" (Berlin, Germany) October, 2015

Kurosaki T. "Selection of germinal centre B cells into memory compartment" International Symposium on B cells: Immunity and Autoimmunity (Erlangen, Germany) October, 2015

Kurosaki T. "Regulatory functions of B lineage cells" Institute of Molecular Medicine University Hospital Düsseldorf (Düsseldorf, Germany) September, 2015

Kurosaki T. "Calcium Signaling in B lymphocytes" FASEB Signal Transduction in the Immune System (Big Sky, USA) June, 2015

Laboratory for Transcriptional Regulation

Group Director: Ichiro Taniuchi

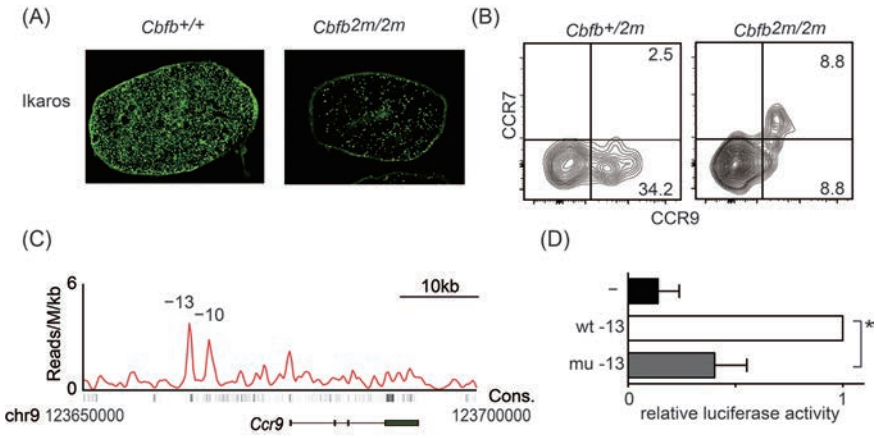


Figure: Role of Cbf*β*2 in regulation of thymic homing activity via activation of an enhancer in the *Ccr9* gene
Migration of Ikaros$^+$ hematopoietic cells into fetal thymus was decreased in Cbfβ2-deficient mice (A) due to impaired induction of CCR9 in IL7R$^+$PIR$^+$ fetal liver cells (B). ChIP-Seq detected binding of Runx/Cbfβ complexes to -13 and -10kb upstream regions in the *Ccr9* gene (C). Runx-site dependent enhancer activity was detected in reporter transfection assay.

One of the major questions in developmental biology is how environmental cues are sensed and integrated into developmental programs encoded by the genome. My laboratory has been addressing how shaping of the primary T lymphocyte pool in the thymus upon receiving T-cell receptor (TCR) signals is regulated at the layer of gene regulation. For this purpose, we have mainly been studying mechanisms that control helper versus cytotoxic lineage dichotomy as a model. Our previous findings showed that antagonistic interplay between two transcription factors, ThPOK and Runx3, serves as a key regulation point to dissect these two lineages. To further understand how expression of the *Zbtb7b* gene (hereafter referred to as the Thpok gene) encoding ThPOK is controlled, we first isolated both transcriptional enhancer and silencer in the *Thpok* locus, and are examining how these two regulatory elements with opposite function operate to control helper-lineage specific *ThPOK* expression under TCR signals. To this aim, we are testing the positional effect of regulatory elements on *Thpok* expression and are characterizing the function of their trans-acting factors, Bcl11b and Satb1. Our current results suggest that coupling of TCR signaling with mechanisms that activate regulatory regions in the genes encoding lineage-specification factors requires prior priming by Bcl11b, which is followed by Satb1-dependent activation.

Our second objective is to unravel functions of Runx transcriptional factor complexes, which consist of a Runx protein and non-DNA binding Cbfβ protein. Runx complexes act as both transcriptional activators and repressors in a context-dependent manner, and play multiple important roles to control differentiation of many types of hematopoietic cells. Our goal is to reveal regulatory mechanisms that modulate the function of Runx complexes, as well as to provide insights into how Runx complexes regulate immune system development and immune responses. We are addressing these questions mainly by analyzing a series of mutant mouse strains harboring specific mutations in the Runx family genes and by identification and characterization of Runx interacting molecules, including functional RNA.

Recent Major Publications

Hao B, Naik AK, Watanabe A, Tanaka H, Chen L, Kondo M, Taniuchi I, Kohwi Y, Kohwi-Shigematus T and Krangel MS. An anti-silencer- and SATB1-dependent chromatin hub regulates Rag1 and Rag2 gene expression during thymocyte development. ***J Exp Med*** 212, 809–24 (2015)

Mishima Y, Wang C, Miyagi S, Saraya A, Hosokawa H, Mochizuki-Kashio M, Nakajima-Takagi Y, Koide S, Negishi M, Sashida G, Naito T, Ishikura T, Onodera A, Nakayama T, Tenen D.G, Yamaguchi N, Koseki H, Taniuchi I, Iwama A. Histone acetylation mediated by Brd1 is crucial for Cd8 gene activation during early thymocyte development. ***Nat Commun*** 5, 5872 (2014)

Tanaka H, Naito T, Muroi S, Seo W, Chihara R, Miyamoto C, Kominami R and Taniuchi I. Epigenetic Thpok silencing limits the time window to choose CD4+ helper-lineage fate in the thymus. ***EMBO J*** 32, 1183–94 (2013)

Invited Presentations

Taniuchi I. "Molecular mechanisms that control thymocyte differentiation" Seminar at Mie University (Tsu, JAPAN) October, 2015

Taniuchi I. "Repression of CCL5 by Runx/Cbfb is essential to prevent lung infiltration" RUNX 2015 (Rehovot, Israel) October, 2015

Taniuchi I. "Roles of Bcl11b and SATB1 during thymocyte differentiation" Venice Thymus Meeting (Venice, Italy) April, 2015

Taniuchi I. "Transcriptional Regulation of T Cell Development in the Thymus" Keystone Symposium "T Cells: Regulation and Effector Function" (Utah, USA) March, 2015

Taniuchi I. "Transcriptional Regulation of T Cell Development in the Thymus" Functional Genomics and Experimental Medicine (Sendai, JAPAN) February, 2015

Laboratory for
Immune Cell Systems

Group Director: Shigeo Koyasu

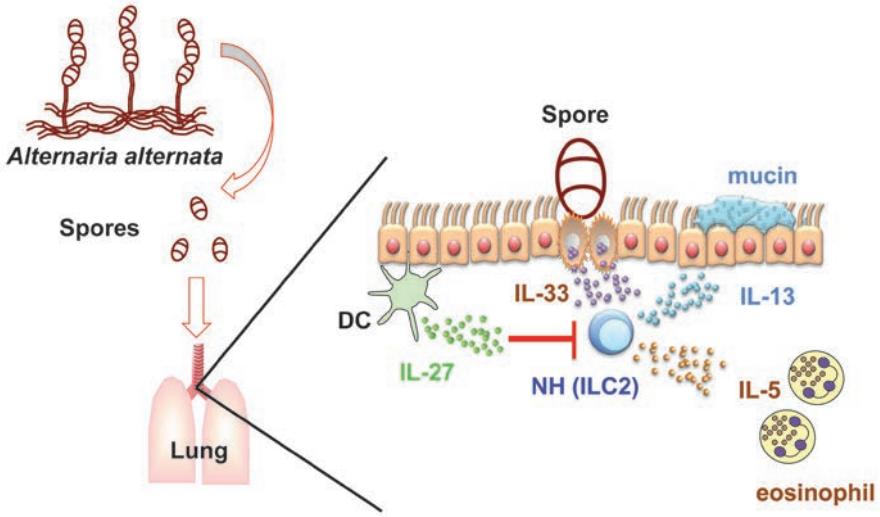


Figure: IL-27 suppresses lung inflammation triggered by *Alternaria alternata*.
Alternaria alternata induces IL-33 production by damaged epithelial cells. IL-33 activates lung NH cells and induces production of IL-5 and IL-13, which cause eosinophilia and goblet cell hyperplasia with mucin production, respectively, and allergic inflammation in the lung. IL-27 is known to be produced by dendritic cells (DC) and acts on NH cells to suppress their proliferation and cytokine production.

We have been working on the role of the natural helper (NH) cell, one of the group 2 innate lymphoid cells (ILC2). We have already shown that NH cells are involved in anti-helminth innate immune responses and in the innate phase of allergic inflammation, such as in protease-induced lung inflammation. Because NH cells are lymphocytes and have a long lifespan in the body, it was important to understand how NH cell-mediated responses are terminated. We employed a fungal infection model to determine the mechanisms used to terminate NH cell functions. *Alternaria alternata* is a fungus that causes allergic asthma-like symptoms in humans. It has been shown that *Alternaria* extract strongly induces IL-33 in airways and triggers lung inflammation. As a result, both NH cells and Th2 cells are activated and induce type 2 immune responses with eosinophilia and mucin production in the airways. We examined the activity of various cytokines on NH cells and found that IL-27 strongly suppressed NH cell proliferation and cytokine production in a Stat1-dependent manner. *In vivo* administration of IL-27 was able to suppress the induction of NH cells in the lung. Interestingly, IL-27 showed stronger activity on NH cells than on Th2 cells, partly because NH cells express the IL-27 receptor, composed of WSX-1 and gp130, at higher levels than Th2 cells. We thus conclude that IL-27 produced by dendritic cells acts on NH cells as an important suppressive mechanism for downregulating NH cell functions and contributing to the termination of innate type 2 responses.

Recent Major Publications

Moro K, Kabata H, Tanabe M, Koga S, Takeno N, Mochizuki M, Fukunaga K, Asano K, Betsuyaku T, Koyasu S. Interferon and IL-27 antagonize group 2 innate lymphoid cell function and type 2 innate immune responses. ***Nat Immunol*** 17, 76–86 (2016)

Morita H, Arae K, Unno H, Miyauchi K, Toyama S, Nambu A, Oboki K, Ohno T, Moromura K, Matsuda A, Yamaguchi S, Narushima S, Kajiwara N, Iikura M, Suto H, McKenzie AN, Takahashi T, Karasuyama H, Okumura K, Azuma M, Moro K, Akdis C, Galli SJ, Koyasu S, Kubo M, Sudo K, Saito H, Matsumoto K, Nakae S. An interleukin-33-mast cell-interleukin 2 axis suppresses papain-induced allergic airway inflammation by promoting the expansion of regulatory T cell numbers. ***Immunity*** 43, 175–186 (2015)

Moro K, Ealey KN, Kabata H, Koyasu S. Methods for isolation and analysis of group 2 innate lymphoid cells in mice. ***Nat Protoc*** 10, 792–806 (2015)

Invited Presentations

Koyasu S. "Innate lymphoid cells in allergic inflammation" The 24th World Allergy Congress (Seoul, Korea) October, 2015

Koyasu S. "Regulation of activities of group 2 ILCs (ILC2s) in allergic inflammation" The 6th FIMSA Congress (Singapore, Singapore) July, 2015

Koyasu S. "Group 2 innate lymphoid cells and allergic inflammation" Tsinghua Symposium on Immunity and Infection (Beijing, China) May, 2015

Koyasu S. "Group 2 innate lymphoid cells and Th2-type innate immunity" The 9th World Immune Regulation Meeting (Davos, Switzerland) March, 2015

Laboratory for Human Disease Models

Group Director & Chief Scientist: **Fumihiko Ishikawa**

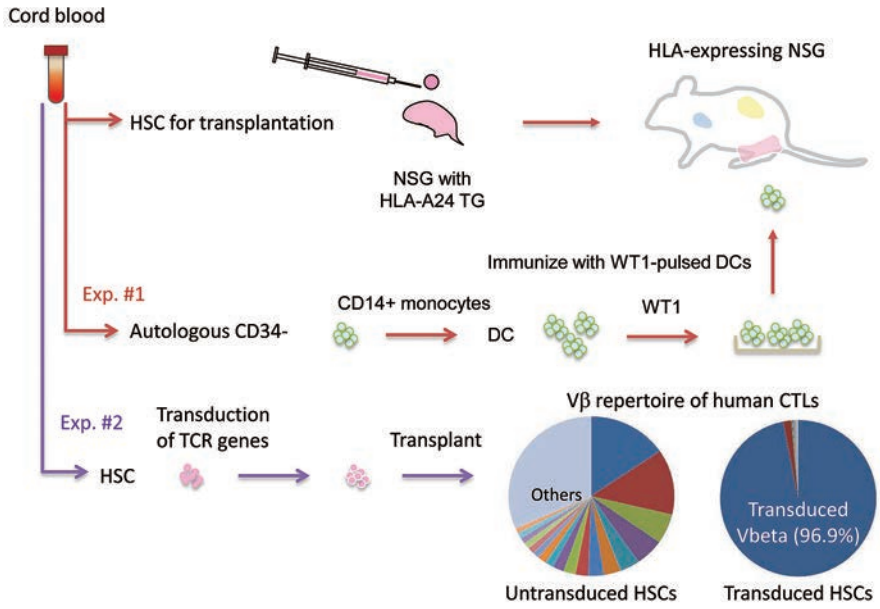


Figure: Modeling immune-therapy with NSG humanized mice.

We have developed a humanized mouse model by intravenously injecting human hematopoietic stem cells (HSCs) into immune-compromised NOD/SCID/Il2rgKO (NSG) newborns. The humanized mouse model has allowed us to investigate how human myeloid and lymphoid cells differentiate from HSCs in multiple organs. One of the limitations of the humanized mouse could be the species barrier between human hematopoietic cells and the mouse environment. To address this issue, we have created an NSG mouse strain expressing human environmental factors and are assessing to what extent humanized mice can recapitulate physiological human hematopoietic and immune systems.

We have also been studying the pathogenesis of acute myeloid leukemia (AML). By understanding malignant hematopoiesis in this disease entity, we further aim to identify the leukemic cells that are resistant to therapy and are responsible for AML relapse. Our long-term goal is to create novel therapeutic strategies targeting the therapy-resistant leukemic cells and to achieve long-term survival of leukemia patients. The NOD/SCID/IL2rgKO mouse transplantation model of human primary AML has enabled us to conduct the following: 1. Prospective isolation of AML initiating stem cells 2. Characterization of genes and gene mutations in leukemogenesis, and 3. Evaluation of novel anti-leukemia agents by developing a sensitive *in vivo* bioassay.

Through integrative analyses of normal and diseased human hematopoiesis and immunity, we continue our best efforts to help patients in the future.

Recent Major Publications

Najima Y, Tomizawa-Murasawa M, Saito Y, Watanabe T, Ono R, Ochi T, Suzuki N, Fujiwara H, Ohara O, Shultz LD, Yasukawa M, Ishikawa F. Induction of WT1-specific human CD8+ T cells from human HSCs in HLA class I Tg NOD/SCID/IL2rgKO mice. ***Blood*** 127, 722–734 (2016)

Saito Y, Yuki H, Kuratani M, Hashizume Y, Takagi S, Honma T, Tanaka A, Shirouzu M, Mikuni J, Handa N, Ogahara I, Sone A, Najima Y, Tomabechi Y, Wakiyama M, Uchida N, Tomizawa-Murasawa M, Kaneko A, Tanaka S, Suzuki N, Kajita H, Aoki Y, Ohara O, Shultz LD, Fukami T, Gogo T, Taniguchi S, Yokoyama S, Ishikawa F. A pyrrolo-pyrimidine derivative targets human primary AML stem cells in vivo. ***Sci Transl Med*** 5, 181ra52 (2013)

Invited Presentations

Ishikawa F. "Dissecting leukemia initiation and creating therapeutic strategies in FLT3-ITD+ human acute myeloid leukemia" Tenth AACR-JCA Joint Conference on Breakthroughs in Cancer Research: From Biology to Therapeutics (Maui, Hawaii) February, 2016

Ishikawa F. "Exploring complexity and heterogeneity of human acute myeloid leukemia using humanized mice" 5th International Workshop on Humanized Mice (Zurich, Switzerland) January, 2016

Ishikawa F. "Exploring complexity and heterogeneity of human hematopoiesis *in vivo*" Deutsches Krebsforschungzentru(dkfz) seminar (Heidelberg, Germany) November, 2015

Ishikawa F. "Understanding *in vivo* kinetics of human hematopoietic stem/progenitor cells" The 3rd Symposium of International Immunological memory and Vaccine Forum (IIMVF) (Berlin, Germany) October, 2015

Ishikawa F. "Developing Therapeutic Strategies Targeting Poor Prognosis Acute Myeloid Leukemia" ISEH 44th Annual Scientific Meeting (Kyoto, Japan) September, 2015

Ishikawa F. "Chemotherapy-resistance of human acute myeloid leukemia" 2015 US-Japan Meeting on Malignant Hematopoiesis and Stem Cells (Hawaii, USA) March, 2015

Laboratory for Intestinal Ecosystem

Group Director: Hiroshi Ohno

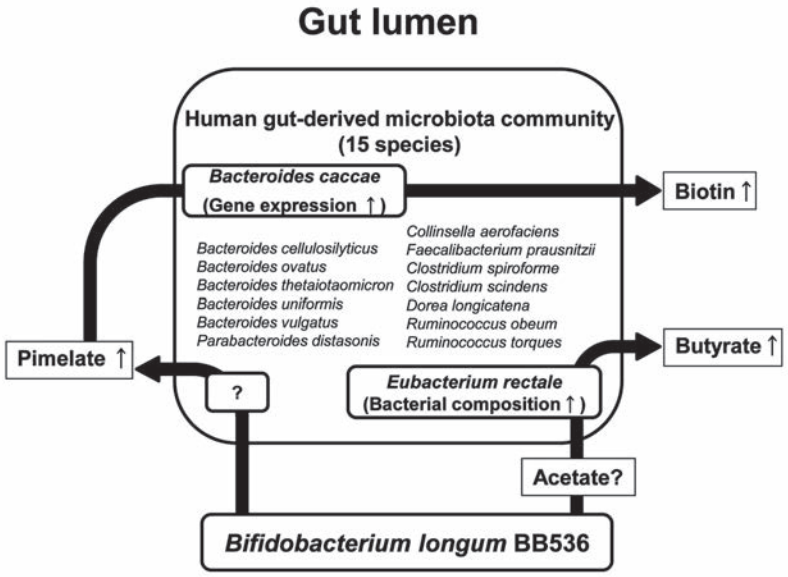


Figure: Effect of *Bifidobacterium longum* BB536 on the metabolism of the human gut-derived microbiota in gnotobiotic mice.
Orally administered *B. longum* BB536 increases the fecal level of butyrate by increasing the proportion of butyrate-producing *Eubacterium rectale*. By contrast, the number of biotin-producing *Bacteroides caccae* is not affected, but instead the genes involved in biotin synthesis are upregulated in the bacterium in the presence of BB536, resulting in the increase of biotin in the feces.

Gut microbiota significantly impact physiology and pathology of the host; nevertheless, the gut does not unconditionally accept commensal microorganisms. Our intestinal immune system somehow senses the type and quantity of bacteria existing in the gut lumen and tries to contain them. The aim of this laboratory is to understand the mechanisms by which the host and its gut commensal microbiota interact, especially focusing on how gut microbes are delivered across the intestinal epithelial barrier to be recognized by the intestinal immune system, how gut microbiota shape host defense and immune systems, and how host-gut microbiota interactions affect host health and disease status.

The delivery of particulate antigens such as bacteria is thought to be mainly achieved by a unique subset of epithelial cells, M cells, residing in a limited region of the epithelial layer called the follicle-associated epithelium (FAE), which covers the lymphoid follicles of gut-associated lymphoid tissue (GALT) such as Peyer's patches (PP). We are studying the function and differentiation of M cells at the molecular level. Identified M cell-specific bacterial uptake receptors could serve as a vaccine delivery target, and we have also been studying this possibility.

Regarding the host-gut microbiota interactions, we are employing a comprehensive multiple omics approach, combining exhaustive (meta) genomic, (meta) transcriptomic, and metabolomic analyses. This approach is applied to understand the molecular basis for regulation of the host by gut microbiota in mice, as well as the impact of gut microbiota on human diseases such as infantile allergic diseases and type 2 diabetes.

Recent Major Publications

Watanabe T, Kawakami E, Shoemaker JE, Lopes TJ, Hashimoto M, Bhuyan F, Hiyoshi M, Noyori O, Nasseer H, Miyazaki M, Saito T, Kondo Y, Osada H, Kimura S, Hase K, Ohno H, Suzu S. Potential role of the formation of tunneling nanotubes in HIV-1 spread in macrophages. ***J Immunol*** 196, 1832–1841 (2016)

Sugahara H, Odamaki T, Fukuda S, Kato T, Xiao JZ, Abe F, Kikuchi J, Ohno H. Probiotic Bifidobacterium longum alters gut luminal metabolism through modification of the gut microbial community. ***Sci Rep*** 5, 13548 (2015)

Matsumura T, Sugawara Y, Yutani M, Amatsu S, Yagita H, Kohda T, Fukuoka S-I, Nakamura Y, Fukuda S, Hase K, Ohno, H., Fujinaga, Y. Botulinum toxin A complex exploits intestinalM cells to enter the host and exert neurotoxicity. ***Nat Commun*** 6, 6255 (2015)

Invited Presentations

Ohno H. "Colonic Treg induction by butyrate produced by gut microbiota" 14th Transplantation Science Symposium (Lorne, Australia) November, 2015

Ohno H. "Integrated Omics Approach for Understanding the Gut Ecosystem" International Scientific Conference on Probiotics and Prebiotics 2015 (Budapest, Hungary) June, 2015

Ohno H. "Structure and function of M-Sec-mediated tunneling nanotube" EMBO Workshop "Cellular synapsis for cell-cell signalling" (Madrid, Spain) May, 2015

Ohno H. "Gut microbiome in the host defense and gut immune regulation" 6th Congress of the Korean Society of Surgical Metabolism and Nutrition & 2015 International Symposium (Seoul, Korea) March, 2015

Ohno H. "Gut microbiome in the host defense and gut immune regulation" The Microbiome Forum: Asia (Kuala Lumpur, Malaysia) January, 2015

Laboratory for Mucosal Immunity

Team Leader: Sidonia Fagarasan

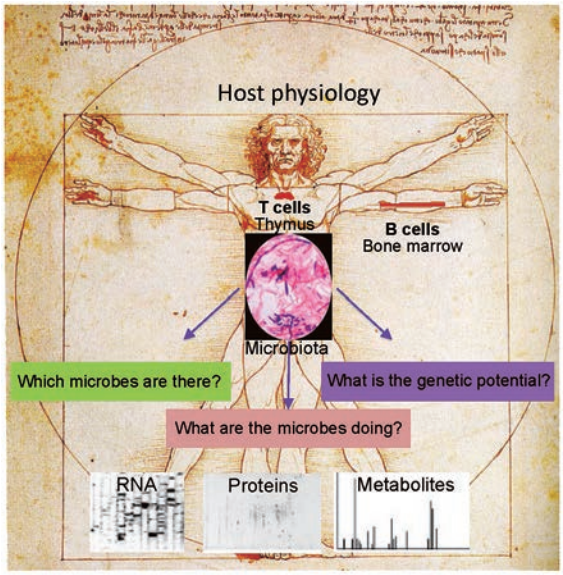


Figure: System immunology.
An image scheme portraying the superorganism and presenting a few questions relevant to achieving a global understanding of the physiology of the superorganism. We aim at understanding the role of the immune system in symbiosis, by asking how the immune cells modify the microbiota structure and function. We further wish to elucidate how the microbiota feedback to the system, by asking how molecules or signaling pathways originating from the microbiota modulate the development and function of the immune system and the implications for the homeostasis of other major physiological systems of the body.

Dysfunction of normal homeostasis leads to diseases, whose pathogenesis includes genetic and environmental factors. For example, epidemiological studies suggested that adult disease risk is associated with adverse environmental conditions early in development (nutrition, chemicals, stress caused by maternal separation, etc.) that cause epigenetic changes persisting throughout life. We aim at understanding the role of the "internal environment", represented by commensal bacteria inhabiting mucosal surfaces, for host health and disease through the lens of the immune system. Although the individual's primary microbiota may reflect maternal hand-over during or immediately after birth, the subsequent shaping of the microbial landscape is driven by complex interactions with the host immune system. Indeed, central to our research is the concept that the emergence of the adaptive immune system with its diversified antigen-recognition receptors contributes to the establishment of advanced symbiotic relationships with the gut microbiota.

We are interested in exploring the bidirectional flux of information between the host immune system and bacterial communities contributing to the establishment of symbiotic and beneficial relationships, as a basis to understand the causes of breakdown in this cooperation that lead to diseases. Our objectives are: 1) to understand the factors that forge the establishment and stability in the function of the microbiota of host organisms, focusing on the question of how the adaptive immune system mediates this complex host-bacterial mutualism; 2) to integrate the immune-bacteria crosstalk in the context of whole body physiology. In our quest to decipher the basic principles of symbiosis and systems immunology we employ approaches that combine genetic and immunologic methods with metagenomic, mass spectrometry-based proteomic and metabolomic approaches, together with extensive phenotypic and functional studies *in vivo*.

Recent Major Publications

Kumar R, Bach MP, Mainoldi F, Maruya M, Kishigami S, Jumaa H, Wakayama T, Kanagawa O, Fagarasan S, Casola S. Antibody repertoire diversification through VH gene replacement in mice cloned from an IgA plasma cell. ***Proc Natl Acad Sci U S A*** 112, E450–457 (2015)

Kawamoto S, Maruya M, Kato LM, Suda W, Atarashi K, Doi Y, Tsutsui Y, Qin H, Honda K, Okada T, Hattori M, Fagarasan S. Foxp3(+) T cells regulate immunoglobulin a selection and facilitate diversification of bacterial species responsible for immune homeostasis. ***Immunity*** 41, 152–165 (2014)

Magri G, Miyajima M, Bascones S, Mortha A, Puga I, Cassis L, Barra CM, Comerma L, Chudnovskiy A, Gentile M, Llige D, Cols M, Serrano S, Aróstegui JI, Juan M, Yagüe J, Merad M, Fagarasan S, Cerutti A. Innate lymphoid cells integrate stromal and immunological signals to enhance antibody production by splenic marginal zone B cells. ***Nat Immunol*** 15, 354–364 (2014)

Invited Presentations

Fagarasan S. "On germinal centers, IgA synthesis and the intestinal ecosystem" Keystone T Follicular Helper Cells and Germinal Centers (Monterey, USA) March, 2016

Fagarasan S. " How adaptive immune system contributes to maintenance of diversified and balanced microbiota in the gut", *Keynote Lecture*, The 17th International Congress of Mucosal Immunology (Berlin, Germany) July, 2015

Fagarasan S. "Symbiotic regulatory loop between Foxp3+ T cells, IgA and microbiota in the gut" Microbe-host mutualism in the shaping of host immunitythe109th International Titisee Conference (Titisee, Germany), April, 2014

Fagarasan S. "TFR/TFH cells in mucosal immunity" Gordon Research Conferences: T follicular Helper Cells (Hong-Kong, China) July, 2013

Laboratory for Gut Homeostasis

Team Leader: Kenya Honda

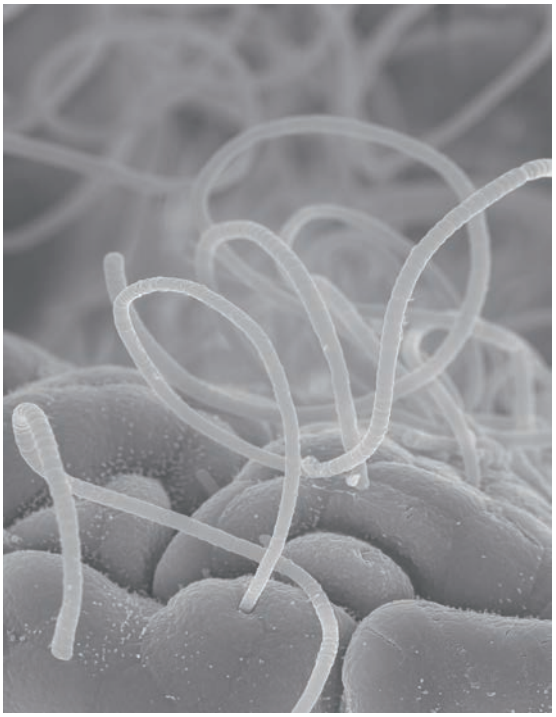


Figure: Th17 cell induction by adhesion of microbes to intestinal epithelial cells.
Scanning electron micrograph showing the small intestine of germ-free mice colonized with segmented filamentous bacteria (SFB) (magnification ~2,500x). SFB elicit a strong T helper 17 (Th17) response, which contributes to enhancement of mucosal barrier function and has been implicated in several immune disorders. Adhesion of SFB to intestinal epithelial cells (ECs) is one of the critical cues for Th17 induction. Photo taken by Seiko Narushima and Kiminori Toyooka.

Our team has been aiming to identify members of the gut microbiota that have a deep impact on the immune system. We have succeeded in isolation of 17 human gut-associated commensal bacterial strains belonging to the class Clostridia that can potently trigger accumulation of colonic $CD4^{+}Foxp3^{+}$ regulatory T (Treg) cells. The collected genomes of the 17 Treg-inducing strains of Clostridia contain abundant genes predicted to be involved in the biosynthesis of short-chain fatty acids (SCFAs), and our results suggest that SCFAs contribute to the induction of Treg cell accumulation. The induced Treg cells expressed RORγt and IL-10 and had strong suppressive activity for effector T cells, and introducing the 17 Clostridia strains reduced GVHD severity.

We have also focused on Th17 cells, which are known to accumulate in response to colonization with a subgroup of intestinal microbes such as segmented filamentous bacteria (SFB). SFB indigenous to mice and rats are genetically distinct host-specific members of the gut microbiota. Upon monocolonization of germ-free (GF) mice or rats, mouse SFB and rat SFB expanded in the gut lumen irrespective of species, but bound to SI epithelial cells (ECs) and induced Th17 cells strictly in a host-specific manner. The physical interaction of SFB with the gut epithelium is thus likely to be essential for Th17 cell differentiation. The causality of the relationship between epithelial adhesion and induction of Th17 cells is further supported by the analysis of Th17 cell induction by the intestinal pathogens, *Citrobacter rodentium* and *Escherichia coli* O157:H7. Upon monocolonization of mice, these pathogens triggered Th17 responses, but adhesion-defective mutants failed to do so. Moreover, a mixture of 20 bacterial strains isolated from fecal samples of a patient with ulcerative colitis on the basis of their ability to robustly induce Th17 cells in the mouse colon also exhibited EC-adhesive characteristics.

Recent Major Publications

Atarashi K, Tanoue T, Ando M, Kamada N, Nagano Y, Narushima S, Suda W, Imaoka A, Setoyama H, Nagamori T, Ishikawa E, Shima T, Hara T, Kado S, Jinnohara T, Ohno H, Kondo T, Toyooka K, Watanabe E, Yokoyama S, Tokoro S, Mori H, Noguchi Y, Morita H, Ivanov II, Sugiyama T, Nuñez G, Camp JG, Hattori M, Umesaki Y, Honda K. Th17 Cell Induction by Adhesion of Microbes to Intestinal Epithelial Cells. ***Cell*** 163, 367–380 (2015)

Narushima S, Sugiura Y, Oshima K, Atarashi K, Hattori M, Suematsu M, Honda K. Characterization of the 17 strains of regulatory T cell-inducing human-derived Clostridia. ***Gut Microbes*** 5, 333–339 (2014)

Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, Fukuda S, Saito T, Narushima S, Hase K, Kim S, Fritz JV, Wilmes P, Ueha S, Matsushima K, Ohno H, Olle B, Sakaguchi S, Taniguchi T, Morita H, Hattori M, Honda K. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. ***Nature*** 500, 232–236 (2013)

Invited Presentations

Honda K. "Th17 cell induction by adhesion of microbes to intestinal epithelial cells" Cold Spring Harbor Laboratory Meeting on Fundamental Immunology & its Therapeutic Potential (Cold Spring Harbor, USA) April, 2015

Honda K. "Regulation of T Cells by the Gut Microbiota" Keystone Symposia, Gut Microbiota Modulation of Host Physiology: The Search for Mechanism (Keystone, USA) March, 2015

Honda K. "Regulation of Th17 and Treg cells by the gut microbiota" The 109th International Titisee Conference, Microbiome-host mutualism in the shaping of host immunity (Titisee, Germany) April, 2014

Honda K. "Regulation of Th17 and Treg cells by the gut microbiota" International Congress of Immunology (Milan, Italy) Aug, 2013

Honda K. "Clostridia strains from human microbiota for Treg induction" Cell Symposia Microbiome and Host Health (Lisbon, Portugal) May, 2013

Laboratory for Immune Homeostasis

Team Leader: Shohei Hori

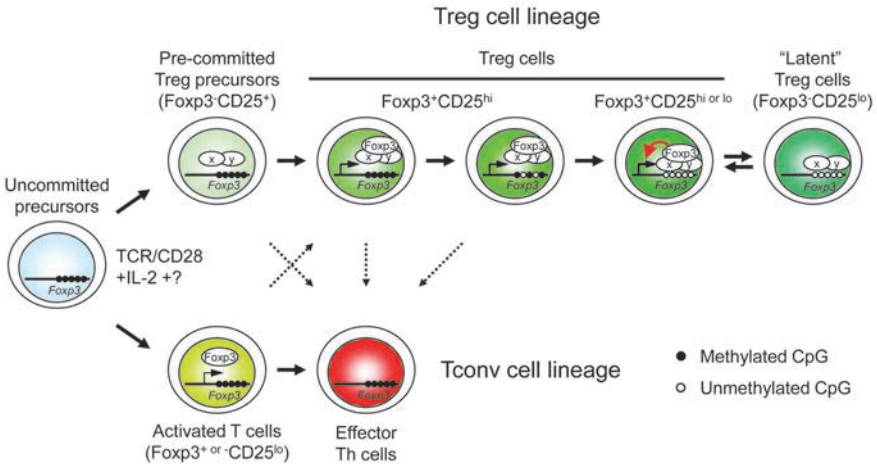


Figure: A model of regulatory T cell fate determination and maintenance
During Treg cell differentiation, uncommitted precursor cells adopt either Treg cell or conventional T (Tconv) cell fates. The commitment to the Treg cell fate is made before (and thus independently of) Foxp3 expression and executed by a transcription factor network elicited by extrinsic signals from the extracellular environment. The same signals also induce epigenetic changes, including DNA demethylation of the *Foxp3* locus. Foxp3 is incorporated into the pre-existing transcription factor network and the resulting "Foxp3 interactome" establishes the characteristic Treg cell phenotype and function in cooperation with the epigenetic modifications. Although Treg cells may down-regulate Foxp3 expression under certain circumstances, these "latent" Treg cells retain the epigenetic memory of, and thus remain committed to, the Treg cell fate. On the other hand, when expressed in activated T cells without engagement of the epigenetic changes and the Foxp3 interactome, Foxp3 by itself cannot establish the characteristic Treg cell phenotype.

Recent Major Publications

Hori S. Lineage stability and phenotypic plasticity of Foxp3+ regulatory T cells. ***Immunol Rev*** 259, 159–172 (2014)

Furusawa Y, Obata Y, Fukuda S, Endo TA, Nakato G, Takahashi D, Nakanishi Y, Uetake C, Kato K, Kato T, Takahashi M, Fukuda NN, Murakami S, Miyauchi E, Hino S, Atarashi K, Onawa S, Fujimura Y, Lockett T, Clarke JM, Topping DL, Tomita M, Hori S, Ohara O, Morita T, Koseki H, Kikuchi J, Honda K, Hase K and Ohno H. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. ***Nature*** 504, 446–450 (2013)

Toker A, Engelbert D, Garg G, Polansky JK, Floess S, Miyao T, Baron U, Duber S, Geffers R, Giehr P, Schallenberg S, Kretschmer K, Olek S, Walter J, Weiss S, Hori S, Hamann A and Huehn J. Active demethylation of the Foxp3 locus leads to the generation of stable regulatory T cells within the thymus. ***J Immunol*** 190, 3180–3188 (2013)

Invited Presentations

Hori S. "Foxp3-dependent control of Treg cell function and homeostasis in tissues." 44th Japanese Society for Immunology (Sapporo, Japan) November, 2015

Hori S. "Foxp3-dependent control of regulatory T cell function and homeostasis." Academy of Immunology and Microbiology seminar series (Pohang, Korea) March, 2015

Hori S. "Genetic control of regulatory T cell fitness in tissues" 7th International Leukocyte Signal Transduction Conference (Kos, Greece) September, 2013

Regulatory T (Treg) cells expressing the transcription factor Foxp3 play an indispensable role in the establishment and maintenance of immunological self-tolerance and tissue homeostasis, a concept well illustrated by the finding that defective generation or function of Treg cells underlies the development of a fatal autoimmune disease in Foxp3-mutant mice and in humans suffering from the IPEX syndrome. Findings that Foxp3+ Treg cells exert tissue-protective or immune-suppressive functions under diverse circumstances have raised the question of what mechanisms ensure the robustness of Treg cell functions, and thus of immunological self-tolerance, in the face of unpredictable perturbations in the extracellular environment. To answer this question, we have focused on the mechanisms that control lineage stability and adaptability of Treg cells in changing environments.

We have previously shown that Foxp3 expression alone does not specify the Treg cell lineage in that activated conventional T cells can promiscuously and transiently express Foxp3 while committed Treg cells can transiently and reversibly down-regulate Foxp3. Despite this phenotypic plasticity, Treg cells retain epigenetic memory of, and thus remain committed to, Foxp3 expression and regulatory functions. We are now addressing the mechanisms underlying this epigenetic memory of Treg cell phenotype and function.

Another focus of our research is to understand how Foxp3 and Treg cells control immunological self-tolerance and tissue homeostasis in changing environments. To address this question, we have addressed how Foxp3 gene mutations found in human IPEX impinge on Treg cells *in vivo* using knock-in mutagenesis in mice. Our analysis revealed that, while many mutations are amorphic or hypomorphic, one particular mutation acts as a gain-of-function mutation that alters DNA binding specificity of Foxp3 and preferentially impairs the ability of Treg cells to adapt to certain non-lymphoid tissue environments. By taking advantage of this unique animal model, we are currently investigating how Treg cells adapt to diverse and fluctuating tissue environments.

Laboratory for Skin Homeostasis

Team Leader: Masayuki Amagai

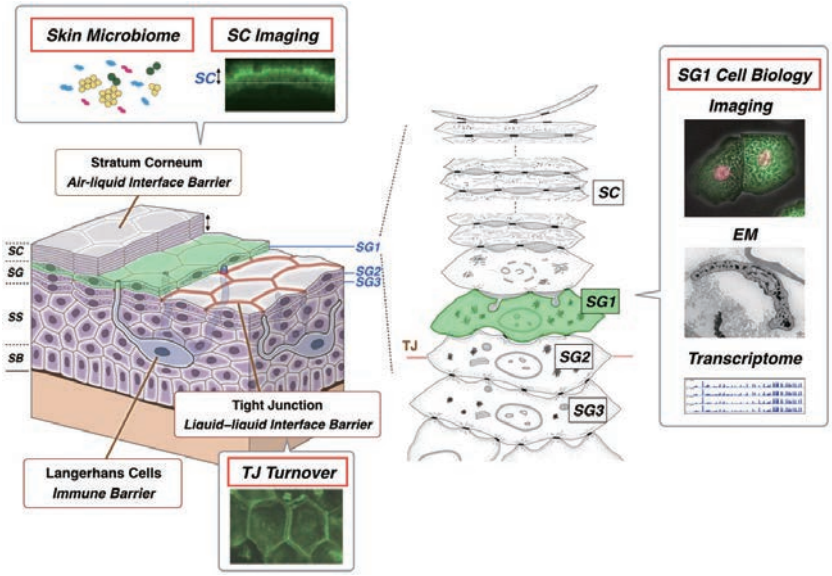


Figure: Comprehensive analyses of skin barrier homeostasis.
Our team is trying to clarify the mechanisms of skin barrier homeostasis by focusing on stratum corneum (SC), tight junction (TJ), and SG1 cells.

Skin is the place where immunity meets external antigens. Cutaneous sensitization has now been considered to the initial key step for many allergic disorders, not only atopic dermatitis (AD), but also asthma, food allergy and anaphylaxis. Skin harbors several barriers to prevent easy penetration of external antigens into the body; however, the exact molecular mechanisms by which the skin barriers form and are maintained are largely unknown.

The epidermis is keratinized stratified squamous epithelia and is the outermost component of the skin. From bottom to top, the epidermis is composed of the stratum basale, stratum spinosum, stratum granulosum (SG) and stratum corneum (SC). Our group has been focusing on SC as an air-liquid barrier and tight junction (TJ) and as a liquid-liquid barrier formed between SG2 cells, among many other skin barriers. There is a fundamental biophysical paradox regarding the function of the epidermis, namely, how it can maintain the barrier, but still constantly replace and shed cells.

Our group is trying to clarify how epidermal barrier homeostasis is maintained under normal conditions and how impaired barrier function occurs and affects microenvironments of the skin in various disease conditions. We use comprehensive approaches combining molecular biology, biochemistry, ultrastructural anatomy, live imaging, microbiology, and systems biology. For example, we have recently succeeded in isolating and culturing SG1 cells, which enables us to perform several unique experiments to understand SC homeostasis.

Another of our strengths is to be able to go back and forth between the basic science findings in mice and those in clinical science in humans with various skin diseases. Our goal is to understand skin barrier homeostasis in health and diseases and to provide patients suffering from severe allergic diseases with more targeted ideal therapeutic approaches with fewer side effects.

Recent Major Publications

Kobayashi T, Glatz M, Horiuchi K, Kawasaki H, Akiyama H, Kaplan DH, Kong HH, Amagai M, Nagao K: Dysbiosis and *Staphyloccus aureus* Colonization Drives Inflammation in Atopic Dermatitis. ***Immunity*** 42, 756–766 (2015)

Yoshida K, Kubo A, Fujita H, Yokouchi M, Ishii K, Kawasaki H, Nomura T, Shimizu H, Kouyama K, Ebihara T, Nagao K, Amagai M: Distinct behavior of human Langerhans cells and inflammatory dendritic epidermal cells at tight junctions in atopic dermatitis. ***J Allergy Clin Immunol*** 134, 856–864 (2014)

Sasaki T, Shiohama A, Kubo A, Kawasaki H, Ishida-Yamamoto A, Yamada T, Hachiya T, Shimizu A, Okano H, Kudoh J, Amagai M: A homozygous nonsense mutation in the gene for Tmem79, a component for the lamellar granule secretory system, produces spontaneous eczema in an experimental model of atopic dermatitis. ***J Allergy Clin Immunol*** 132, 1111–1120 (2013)

Invited Presentations

Amagai M. "Skin barrier homeostasis by stratum corneum and tight junction" Keystone Symposia Conference: Immunity in Skin Development, Homeostasis and Disease (Tahoe, USA) February–March, 2016

Amagai M. "Dissecting Skin Barrier Dysfunction as a Cause of Dermatitis" Gordon Research Conferences on Barrier Function of Mammalian Skin (Waterville Valley, USA) August, 2015

Amagai M. "Skin Barrier Homeostasis in Stratum Corneum and Granulosum" Gordon Research Conferences on Epithelial Defferentiation & Keratinization (Newry, USA) July, 2015

Amagai M. "Towards antigen-specific immune suppression in pemphigus" Inflammatory Skin Disease Summit: The Translational Revolution (Vienna, Austria) November, 2014

Amagai M. "Epidermal barrier function and its dysfunction in atopic diseases" Singapore International Conference on Skin Biology (Singapore, Singapore) March, 2014

Laboratory for Metabolic Homeostasis

Team Leader: Naoto Kubota

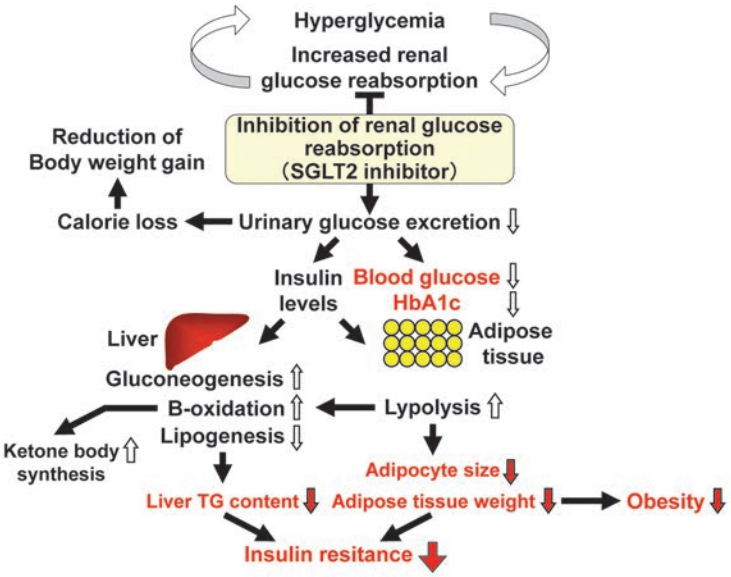


Figure: Mechanisms underlying the anti-diabetic and anti-obesity effects of tofogliflozin

In recent years, there has been a rapid growth in the incidence of type 2 diabetes in both Western and Asian countries. However, the precise molecular mechanisms leading to the progression of type 2 diabetes remain poorly understand. The goal of our team is to identify molecular mechanisms of insulin secretion and insulin resistance.

Molecular mechanism of insulin secretion

Impaired insulin secretion, which leads the development of type 2 diabetes, is thought to be partially caused by genetic factors. Most of the common variant single-nucleotide polymorphisms (SNPs) identified by genome-wide association study (GWAS) have been reported to be associated with defective pancreatic islet function. However, the functional role of genes identified by GWAS remains unclear. To elucidate the physiological and pathophysiological role of these genes *in vivo*, we have generated genetically engineered mice. Specifically, we are investigating common variants in a potassium channel KCNQl and a ubiquitin conjugating enzyme UBE2E2, which confer the largest effect on the risk of type 2 diabetes in Asians.

Molecular mechanism of insulin resistance

Obesity-induced insulin resistance plays a crucial role in the pathogenesis of lifestyle-related diseases, including metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and type 2 diabetes. Insulin resistance is defined as a condition in which physiological insulin signals are impaired for some reason, such as chronic inflammation. Once insulin binds to the insulin receptor, insulin receptor substrate (IRS)-1 and IRS-2 are activated, and mediate intracellular insulin signaling. We have been studying IRS-1 and IRS-2, which show ubiquitous expression patterns (Diabetes 2000, Circulation 2003, J Clin Invest 2004, Cell Metab 2008, Cell Metab 2011, Cell 2012), to clarify their role in the underlying mechanisms of insulin resistance.

Recent Major Publications

Obata A, Kubota N, Kubota T, Iwamoto M, Sato H, Sakurai Y, Takamoto I, Katsuyama H, Suzuki Y, Fukazawa M, Ikeda S, Iwayama K, Tokuyama K, Ueki K, Kadowaki T. Tofogliflozin Improves Insulin Resistance in Skeletal Muscle and Accelerates Lipolysis in Adipose Tissue in Male Mice. ***Endocrinology*** 157, 1029–1042 (2016)

Hashimoto S, Kubota N, Sato H, Sasaki M, Takamoto I, Kubota T, Nakaya K, Noda M, Ueki K, Kadowaki T. Insulin receptor substrate-2 (Irs2) in endothelial cells plays a crucial role in insulin secretion. ***Diabetes*** 64, 876–886 (2015)

Shibata S, Tada Y, Hau CS, Mitsui A, Kamata M, Asano Y, Sugaya M, Kadono T, Masamoto Y, Kurokawa M, Yamauchi T, Kubota N, Kadowaki T, Sato S. Adiponectin regulates psoriasiform skin inflammation by suppressing IL-17 production from γδ-T cells. ***Nat Commun*** 6, 7687 (2015)

Invited Presentations

Kubota N. "Insulin action and insulin resistance" The 53rd Annual Meeting of Kantokoshinetsu Association of the Japan Diabetes Society (Yokohama, Japan) January, 2016.

Kubota N. "Clarification of molecular mechanisms of type 2 diabetes using genetic engineering techniques in mice" 7th AASD Scientific Meeting and Annual Scientific Meeting of the Hong Kong Society of Endocrinology, Metabolism and Reproduction (Hong Kong, China) November, 2015

Kubota N. "Approach for diabetic complication via endothelial cells" The 30th Annual Meeting of the Japan Society of Diabetic Complications (Nagoya, Japan) November, 2015

Kubota T. "The regulation mechanisms of glucose homeostasis via endothelial insulin signaling" The 88th Annual Meeting of the Japan Endocrine Society (Tokyo, Japan) April, 2015

Kubota N. "Identification of molecular mechanisms of type 2 diabetes and obesity by using genetically-engineering technology" The 29th Annual Meeting of the Japan Society of Experimental Diabetes and Obesity (Kyoto, Japan) February, 2015

Laboratory for Immune Crosstalk

Team Leader: Hilde Cheroutre

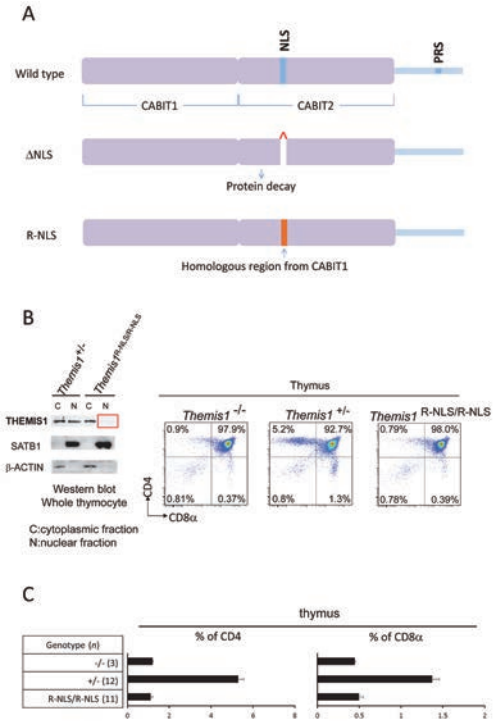


Figure: Nuclear localization of Themis is essential for its function.
(A) Putative structure and mutant schemes of Themis. Themis consists of two homologous parts (CABIT1 and CABIT2), which contain a Nuclear Localization Signal (NLS) and a Proline Rich Sequence (PRS). Since deleting the NLS caused Themis protein instability, the NLS (330-RHFLIPISYKGKFKRRPR-347) in CABIT2 was replaced with the homologous amino acids from CABIT1 (75-KPFELPMNFPGLFKVMAD-92) to stabilize Themis protein and inactivate the NLS. (B) Total thymocytes were fractionated into cytoplasmic (C) and nuclear (N) fractions. Actin and SATB1 were used as loading controls for the cytoplasmic and nuclear fractions, respectively. (C) CD4 and CD8 expression pattern of the R-NLS mutant thymocytes. (D) Percentage of CD4 single positive (SP) cells and CD8SP cells in the thymus of an R-NLS mutant mouse.

Recent Major Publications

Larange A, Cheroutre H. Retinoic Acid and Retinoic Acid Receptors as Pleiotropic Modulators of the Immune System. ***Annu Rev Immunol*** 34, 369–394 (2016)

Mayans S, Stepniak D, Palida SF, Larange A, Dreux J, Arlian BM, Shinnakasu R, Kronenberg M,Cheroutre H, Lambolez F. αβT cell receptors expressed by CD4(-)CD8αβ(-) intraepithelial T cells drive their fate into a unique lineage with unusual MHC reactivities. ***Immunity*** 41, 207–218 (2014)

Fu G, Casas J, Rigaud S, Rybakin V, Lambolez F, Brzostek J, Hoerter JA, Paster W, Acuto O,Cheroutre H, Sauer K, Gascoigne NR. Themis sets the signal threshold for positive and negative selection in T-cell development. ***Nature*** 504, 441–445 (2013)

Invited Presentations

Cheroutre H. "How the Gut Primes the Immune System" 2014 Annual Scientific Meeting of the American College of Rheumatology (ACR). (Boston, USA) November, 2014

Cheroutre H. "Environmental and Cell-Intrinsic Factors Governing the Immune Response" 2014 Pittsburgh Immunology Symposium (Pittsburgh, USA) May, 2014.

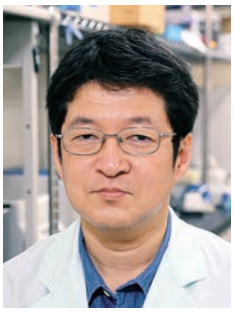
Cheroutre H. "Mucosal Immunity: Taking Strategic Planning a Step Further" Dutch Society for Immunology Annual Symposium (Lunteren, the Netherlands) April, 2014

Cheroutre H. "New Emerging Transcription Factor and Cytokine Networks at the Mucosal Interface of the Intestine" Keystone Symposium (J3) (Vancouver, Canada) January, 2014

Cheroutre H. "Protective Immunity: It Takes More Than Memory" Harvard Medical School (HMS) Immunology Seminar Series (Boston, USA) October, 2013

With our previous research we discovered that not all self-reactive thymocytes are deleted during negative selection, but that many auto-reactive T cells instead are rescued during "agonist" selection and redirected in their functional fate to become beneficial specialized T cells. In collaboration with Dr. Taniuchi's group (p17) we also showed that the lineage commitment in the thymus is not fixed and that mature CD4 T helper cells can functionally reprogram to cytotoxic T lymphocytes (CTL) in response to cognate antigen. The factors and molecular mechanisms that control these decisive processes are not understood and they form a major goal of our research.

By phenotype screening of ENU-induced mutant mice, we newly identified Themis as an essential gene for T cell development. Themis functions by interacting with Grb2 and SHP1, thus reducing TCR signals and allowing positive selection of thymocytes that further mature to naïve T cells. We found that although Themis deletion impaired conventional selection it did not affect agonist selection. By generating specific nuclear localization signal mutants we now find that the nuclear localization of Themis is critical and essential for its function. Therefore, in addition to its function in proximal TCR signaling, Themis also plays a role in the nucleus to control gene expression. Since GWAS studies identified Themis as associated with celiac disease and atopic dermatitis, and since Themis was linked with inflammatory bowel disease, and furthermore, since Themis is essential for pathogenesis of cerebral malaria and for protection against pulmonary tuberculosis, it must also play central roles for peripheral T cells. We are therefore investigating Themis and linked nuclear factors for the functional fate of mature T cells as well. In addition, we are trying to understand the role of Themis and other factors in controlling and translating pre-TCR and TCR signal strength during thymic selection and fate decisions of mature T cells. We are using unique and novel loss-and gain–of-function approaches, designed in collaboration with Dr. Taniuchi's laboratory. These studies also led to the milestone discovery that the nuclear retinoic acid receptor alpha functions as a partner of ZAP70 and plays a critical role in the proximal TCR signaling complex. We are now elucidating these pioneer findings using sophisticated new tools and approaches.



Laboratory for Inflammatory Regulation

Team Leader: Takashi Tanaka

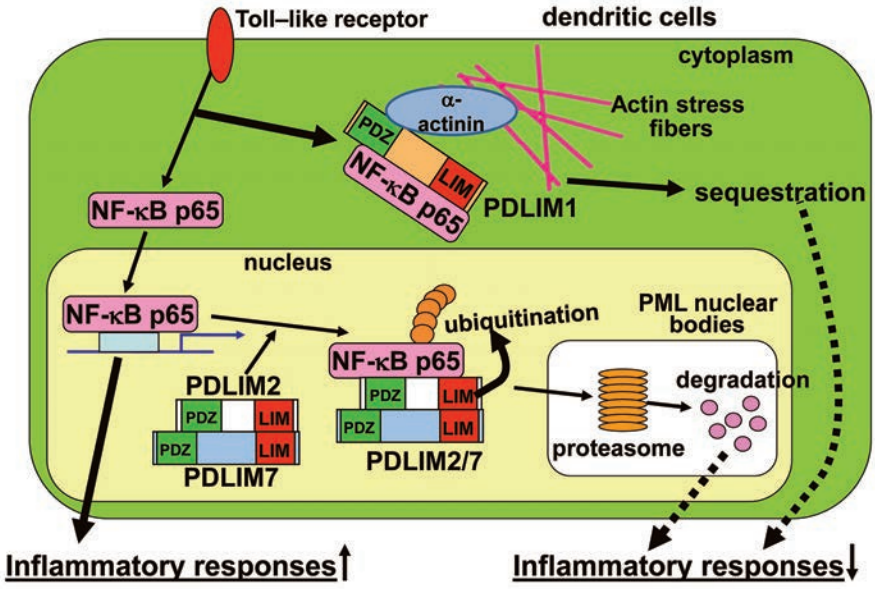


Figure: LIM proteins constitute a new family of negative regulators of NF-κB signaling.
PDLIM2 and PDLIM7 are ubiquitin E3 ligases for the p65 subunit of NF-κB, form heterodimers and cooperatively promote p65 degradation. By contrast, PDLIM1 sequesters p65 in the cytoplasm and inhibits its nuclear translocation, thereby also suppressing NF-κB signaling.

The inflammatory response is an important host defense mechanism to sense and eliminate invading microbial pathogens, and is initiated and conducted by the cooperation of dendritic cells and T-helper cells. However, these inflammatory responses must be terminated at the appropriate time point, otherwise excessive responses can damage normal tissue and may lead to autoimmune diseases. Our research goal is to identify a series of key negative regulators of inflammation-related signal transduction pathways and clarify the complete picture of the molecular mechanisms for regulating inflammatory responses. We predict that dysfunction of these negative regulators might be the cause of human autoimmune diseases.

We previously identified PDLIM2 (PDZ and LIM domain-containing protein-2), a nuclear protein that belongs to a large family of LIM protein, as one of the key factors negatively regulating inflammatory responses. PDLIM2 is a ubiquitin E3 ligase for the STAT4 and STAT3 transcription factors in CD4+T cells, suppressing Th1 and Th17 cell differentiation, and for the p65 subunit of NF-κB in dendritic cells, negatively regulating NF-κB-mediated inflammation. We recently found that LIM proteins constitute a new family that negatively regulates inflammatory responses through different mechanisms. For example, PDLIM1 binds to and sequesters p65 in the cytoplasm, thereby inhibiting NF-κB activation in dendritic cells, whereas PDLIM4, which is predominantly expressed in CD4+T cells, suppresses STAT3 signaling by recruiting PTPBL, a protein tyrosine phosphatase, and facilitating dephosphorylation of a STAT3 tyrosine residue. Notably, a single nucleotide polymorphism (SNP) in human *PDLIM4* is associated with rheumatoid arthritis susceptibility. We have also identified novel negative regulators of inflammatory responses by isolating PDLIM2-associated proteins. Moreover, to elucidate the mechanisms by which initially helpful inflammation leads to pathogenic chronic inflammation, we analyzed the regulation of *in vivo* inflammatory responses using PDLIM2-deficient mice. These studies should help clarify the pathogenesis of human autoimmune and inflammatory diseases and may lead to the development of new therapeutic tools for these diseases.

Recent Major Publications

Ono, R., Kaisho, T., Tanaka, T. PDLIM1 inhibits NF-κB-mediated inflammatory signaling by sequestering the p65 subunit of NF-κB in the cytoplasm. ***Sci Rep*** 5, 18327 (2015)

Tanaka T, Shibazaki A, Ono R, Kaisho T. HSP70 mediates degradation of the p65 subunit of nuclear factor κB to inhibit inflammatory signaling. ***Sci Signal*** 7, ra119 (2014)

Yamazaki C, Sugiyama M, Ohta T, Hemmi H, Hamada E, Sasaki I, Fukuda Y, Yano T, Nobuoka M, Hirashima T, Iizuka A, Sato K, Tanaka T, Hoshino K, Kaisho T. Critical roles of a dendritic cell subset expressing a chemokine receptor, XCR1. ***J Immunol*** 190, 6071–6082 (2013)

Invited Presentations

Tanaka T. "From Molecules to Diseases. Clarification of the molecular mechanisms that negatively regulate inflammatory responses and association analysis of autoimmune diseases by GWAS" The 6th Rheumatology winter seminar in St Luke's International Hospital (Tokyo, Japan) February, 2015

Tanaka T. "From Molecules to Diseases. Clarification of the molecular mechanisms that negatively regulate inflammatory responses and association analysis of autoimmune diseases by GWAS." The 3rd Akashi-cho rheumatic collaborative seminar in St Luke's International Hospital (Tokyo, Japan) October 2014

Tanaka T. "Negative regulation for inflammatory responses and its association with autoimmune diseases" Monash Univ. & RIKEN IMS Workshop (Yokohama, Japan) August, 2014

Tanaka T. "Regulation of inflammatory responses by LIM proteins" The 5th LJI-RCAI Workshop "New Horizon in Immune Regulation towards Disease Intervention" (Yokohama, Japan) October, 2013

Tanaka T. "Clarifying the molecular mechanisms that regulate inflammatory responses" The Osaka Minami Medical Center: Talk with the expert seminar (Osaka, Japan) October, 2013

Laboratory for Cytokine Regulation

Team Leader: Masato Kubo

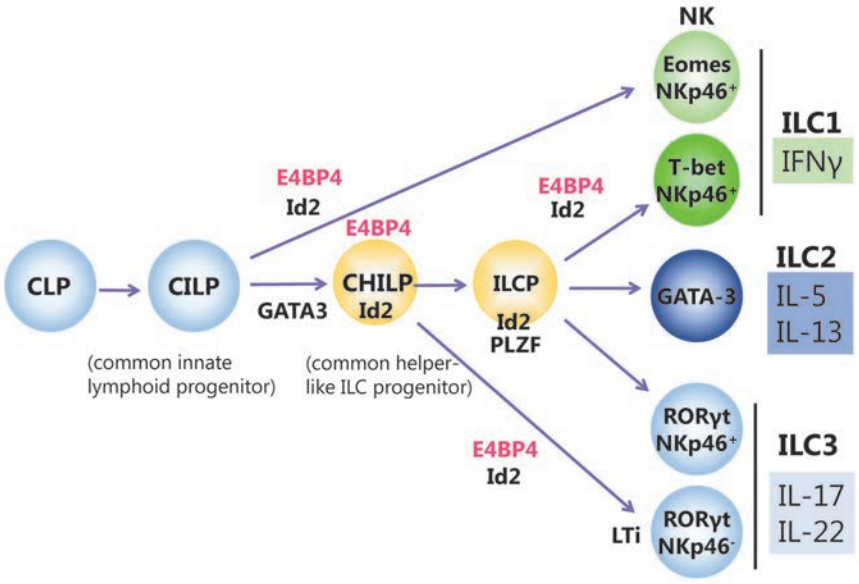


Figure: E4BP4 has a role in the development of all subsets of ILCs by controlling Id2 expression levels.

T cells play a central role in the effector and regulatory functions of the immunological surveillance system, and aberrations in these functions can lead to various immunological disorders. Cytokines are critical factors in the transmission of information from the receptor to the nucleus as well as in the establishment of communication networks among cells. Our overall long-term goal is to understand how effector cytokine genes are epigenetically controlled during cell lineage commitment and how cytokine networks control cell lineage commitment and pathogenic states.

We have focused on Th2 cytokines and generated a series of genetically targeted mice disrupting the *cis*-acting regularly elements in the *Il13/Il4* locus to understand lineage-specific regulation. This mouse system provided evidence that a specific enhancer controlled IL-4 expression in T follicular helper (Tfh) cells, which provide B cell help for humoral immunity. Recently, we found that Th2 cytokines are also secreted from several innate immune cells, including mast cells, basophils, eosinophils, and group 2 innate lymphoid cells (ILC2s). IL-4 production by innate immune cells is controlled by a distinct enhancer in each different lineage, which led us to investigate the precise role of cell type-specific IL-4 expression.

Recent Major Publications

Motomura Y, Morita H, Moro K, Nakae S, Artis D, Koyasu S, Kubo M. Basophil-derived interleukin-4 controls the function of natural helper cells, a member of ILC2s, in lung inflammation. ***Immunity*** 40, 758–771 (2014)

Kurashima Y, Amiya T, Fujisawa K, Shibata N, Suzuki Y, Kogure Y, Hashimoto E, Otsuka A, Kabashima K, Sato S, Sato T, Kubo M, Akira S, Miyake K, Kunisawa J, Kiyono H. The enzyme Cyp26b1-mediates Inhibition of mast cell activation by fibroblasts to maintain skin-barrier homeostasis. ***Immunity*** 40, 530–541 (2014)

Noti M, Wojno ED, Kim BS, Siracusa MC, Giacomin PR, Nair MG, Benitez AJ, Ruymann KR, Muir AB, Hill DA, Chikwava KR, Moghaddam AE, Sattentau QJ, Alex A, Zhou C, Yearley JH, Menard-Katcher P, Kubo M, Obata-Ninomiya K, Karasuyama H, Comeau MR, Brown-Whitehorn T, de Waal Malefyt R, Sleiman PM, Hakonarson H, Cianferoni A, Falk GW, Wang ML, Spergel JM, Artis D. Thymic stromal lymphopoietin-elicited basophil responses promote eosinophilic esophagitis. ***Nat Med*** 19, 1005–1013 (2013)

Invited Presentations

Kubo M. "Role of T follicular helper cells in influenza virus protection" France-Japan Immunology meeting (Cassis, France) October, 2014

Kubo M "Notch regulates reciprocal expression of CCR7 versus CXCR5 to control central memory T cell generation" The 2nd Symposium of International Immunological Memory and Vaccine Forum (La Jolla, USA) August, 2014

Kubo M. "Regulation of allergic airway inflammation by basophil and innate lymphoind cells" The 79th Annual Meeting of the Japanese Society of Interferon & Cytokine Research (Sapporo, Japan) June, 2014

Kubo M. "Understanding a role of cytokine signaling in homeostatic skin regulation" Shanghai Immunodermatology Forum 2014 (Shanghai, China) May, 2014

Kubo M. "Regulation of allergic airway inflammation by basophil and innate lymphoind cells" Dry-eye allergy joint seminer (Tokyo, Japan) January, 2014

Laboratory for
Innate Immune Systems

Team Leader: Kazuyo Moro

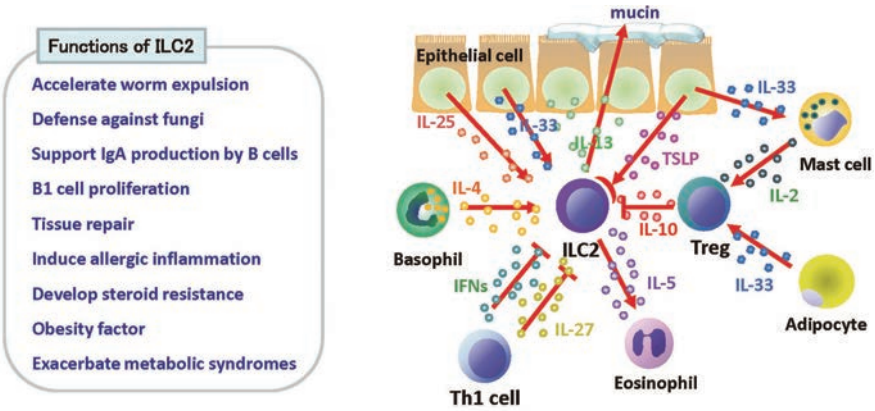


Figure: Group 2 innate lymphoid cells and the cytokine network.
Group 2 innate lymphoid cells (ILC2s) are known to induce type 2 immune responses during helminth infection and allergic inflammation. ILC2s produce large amounts of IL-5 and IL-13 in response to IL-25 or IL-33 and induce eosinophilia and goblet cell hyperplasia that not only attacks the worm but also exacerbates allergic symptoms. Recently, we found that TSLP induces steroid resistance of ILC2s, and that IL-4 from basophils is important for activation of ILC2s during allergic inflammation such as in asthma. ILC2s are suppressed by IFN and IL-27, which might be critical for the conversion from an innate to an acquired type 2 immune response during helminth or fungal infection and allergic inflammation.

Our team has been focused on group 2 innate lymphoid cells (ILC2s), which we originally reported as natural helper cells. ILC2s localize to a variety of tissues such as fat, lung, intestine, liver and skin, and mediate immunity to helminth and fungal infections via strong type 2 cytokine production. Infection with helminths or fungi induces IL-25 and IL-33 production from epithelial cells or endothelial cells and activates ILC2s, leading to eosinophilia and goblet cell hyperplasia resulting from the production of IL-5 and IL-13, respectively. These immune responses are extremely important for defense against infection, but recent studies have shown that ILC2s exacerbate allergic inflammation using the same mechanisms.

We think that it is particularly important to determine the activation and suppression mechanisms of ILC2s during infection and inflammation in order to develop effective treatments for ILC2-related allergic diseases. Recently, we found that ILC2s are involved in obesity, which leads to a variety of metabolic syndromes. Therefore, an additional goal of our research group is to demonstrate the dynamics of ILC2s in obesity, and understand the role of ILC2s in adipose tissue inflammation.

Recent Major Publications

*Moro K, Kabata H, Tanabe M, Koga S, Takeno N, Mochizuki M, Fukunaga K, Asano K, Betsuyaku T, Koyasu S. Interferon and IL-27 antagonize the function of group 2 innate lymphoid cells and type 2 innate immune responses. ***Nat Immunol*** 17, 76–86 (2016) (*corresponding)

*Moro K, Koyasu S. Innate lymphoid cells, possible interaction with microbiota. ***Semin Immunopathol*** 37, 27–37 (2015) (*corresponding)

Motomura Y, Morita H, Moro K, Nakae S, Artis D, Takaho A. Endo, Kuroki Y, Ohara O, Koyasu S, Kubo M. Basophil-derived interleukin-4 controls the function of natural helper cells, a member of ILC2s, in lung inflammation. ***Immunity*** 40, 758–771 (2014)

Invited Presentations

Moro K. "Interferon and IL-27 antagonize ILC2 function and type 2 innate immune responses" Annual Meeting of the Japanese Society for Immunology (Sapporo, Japan) November, 2015

Moro K. "Innate lymphoid cells and inflammation" Annual Meeting of the Japanese Society for Immunology (Kyoto Japan) December, 2014

Moro K. "Natural Helper Cell-a new player in innate immune system-" Annual Meeting of the Japanese Society for Immunology (Chiba, Japan) December, 2013

Core for Precise Measuring and Modeling

Toward the ultimate goal of obtaining a comprehensive understanding of the pathogenesis of human diseases, the functions of the Core for Precise Measuring and Modeling are three pronged: production of mouse models, multiomics measurements and quantitative bioimaging, and bioinformatics/modeling of human disease processes. Through close interactions among these three branches of the core, we aim to collect a wide variety of quantitative data in order to build a computational and predictive network of the disease process. As for the production of genetically engineered mice that will be used as models of human diseases, the laboratory for Developmental Genetics has begun to apply recent advances in genome engineering technology, e.g., CRISPR/Cas9-based genome editing, and thereby considerably enhance the production capacity and power of the disease models. Regarding the precise quantitative measurements branch, one focus in 2014 has been to enhance the power of metabolite analysis by the Laboratory for Metabolomics. Together with mRNA/protein profiling by the Laboratory for Integrative Genomics, the enhanced multiomics measurements and bio-imaging (Laboratory for Tissue Dynamics) will greatly contribute to exploration of the etiology of human diseases. After being processed by bioinformatics (Laboratory for Integrated Bioinformatics), the datasets are used for modeling (Laboratories for Disease Systems Modeling and Integrated Cellular Systems). As a leading IMS project, an atopic dermatitis model mouse, provided by the Laboratory for Immunogenetics, has been extensively analyzed from several different angles, fully exploiting the analysis powers of this core. These efforts should enable us to identify new biomarkers for early diagnosis and prevention of atopic dermatitis in the very near future.

Laboratory for Developmental Genetics

Group Director: Haruhiko Koseki

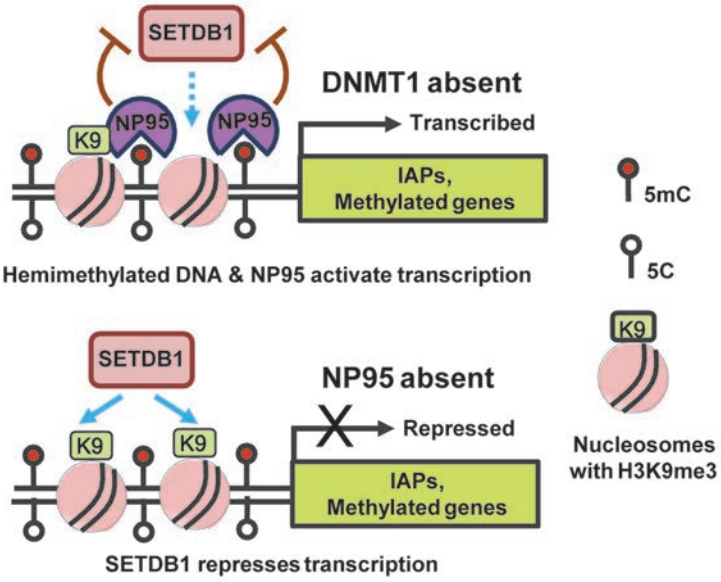


Figure: Protracted binding of NP95 to hemimethylated DNA disrupts transcriptional silencing. The upper panel shows protracted binding of NP95 onto ectopic hemimethylated DNA. NP95 binding inhibits chromatin-mediated transcriptional silencing, in particular, in the retrotransposon associated IAP (intracisternal A particles) loci. The lower panel shows preferential binding of the epigenetic repressor SETDB1 to the same sites, leading to robust transcriptional silencing. In this case, although hemimethylated DNA is present, NP95 is not, which allows SETDB1 to silence these loci.

The Developmental Genetics Research Group is pursuing a research program to elucidate the molecular mechanisms underlying organ development and stem cell functions. Particular emphasis has been put on epigenetic regulation mediated by the combinatorial actions of Polycomb group (PcG) proteins and DNA methylation related proteins.

Repression of endogenous retroviruses (ERVs) in mammals involves several epigenetic mechanisms. For example, acute loss of the maintenance methyltransferase *Dnmt1* induces widespread DNA demethylation and transcriptional activation of ERVs, including CpG-rich IAP (intracisternal A particle) proviruses. We have recently shown that this effect is not due simply to a loss of DNA methylation. Our conditional deletions experiments revealed that both *Dnmt1* and *Np95* are essential for maintenance DNA methylation. However, while IAPs are derepressed in *Dnmt1*-ablated embryos and embryonic stem cells (ESCs), these ERVs remain silenced when *Np95* is deleted alone or in combination with *Dnmt1*. This paradoxical phenotype results from an ectopic interaction between NP95 and the H3K9 methyltransferase SETDB1. Normally, SETDB1 maintains silencing of IAPs, but in the absence of DNMT1, prolonged binding of NP95 to hemimethylated DNA transiently disrupts SETDB1-dependent H3K9me3 deposition. Thus, our observations reveal an unexpected antagonistic interplay between two repressive pathways involved in retroviral silencing in mammalian cells.

Recent Major Publications

Sharif J, Endo TA, Nakayama M, Karimi MM, Shimada M, Katsuyama K, Goyal P, Brind'Amour J, Sun M-A, Sun Z, Ishikura T, Mizutani-Koseki Y, Ohara O, Shinkai Y, Nakanishi M, Xie H, Lorincz MC, Koseki H. Activation of Endogenous Retroviruses in Dnmt1−/− ESCs Involves Disruption of SETDB1-Mediated Repression by NP95 Binding to Hemimethylated DNA. ***Cell Stem Cells*** (in press)

Kondo T, Isono K, Kondo K, Endo TA, Itohara S, Vidal M, Koseki H. Polycomb potentiates meis2 activation in midbrain by mediating interaction of the promoter with a tissue-specific enhancer. ***Dev Cell*** 28, 94–101 (2014)

Isono K, Endo TA, Ku M, Yamada D, Suzuki R, Sharif J, Ishikura T, Toyoda T, Bernstein BE, Koseki H. SAM Domain Polymerization Links Subnuclear Clustering of PRC1 to Gene Silencing. ***Dev Cell*** 26, 565–577 (2013)

Invited Presentations

Koseki, H. "Protoracted NP95 binding to hemimethlated 1 DNA disrupts SETB1-mediated proviral silencing" International Sympojium on "Chromosome Orchestration System," Osaka University (Awajishima, Japan) March, 2016

Koseki, H. "Protracted NP95 binding to hemimethylated DNA disrupts proviral silencing" BMB2015 Biochemistry and Molecular Biology (Kobe, Japan) December, 2015

Koseki, H. "Visualization of genes and epigenetic information in cells" The 67th Annual Meeting of the Japan Society for Cell Biology (Tokyo, Japan) July, 2015

Koseki, H. "iPS-mediated induction of human NKT cells and their application for cancer therapy" The 35th Annual Meeting of the Japanese Society of Inflammation and Regeneration (Okinawa, Japan) July, 2014

Koseki, H. "Activation of polycomb-repressed genes" Mouse Molecular Genetics conference (Cambridge, UK) September, 2013

Laboratory for Integrative Genomics

Group Director: Osamu Ohara

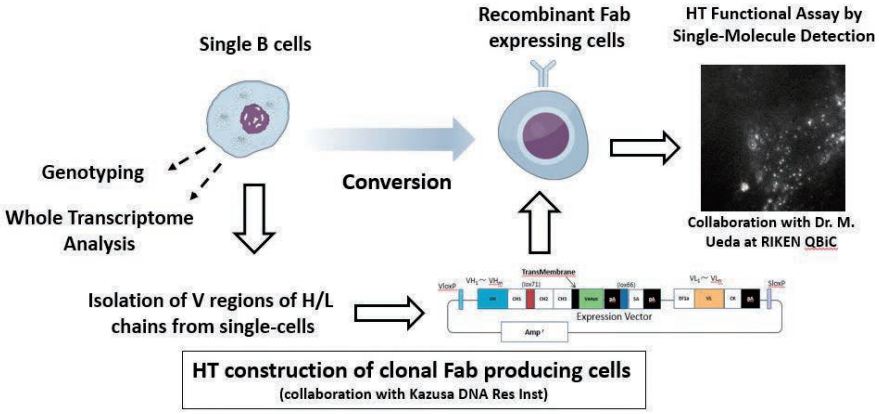


Figure: High-Throughput pipeline for immune repertoire analysis
This figure shows a method for high-throughput (HT) generation of a cell line that stably produces an Fab molecule identified from a single B cell, on the cell surface. After sequencing variable regions in heavy and light chains of immunoglobulin genes, they are cloned into an expression module by a ligation-free high-throughput method. The resultant expression module is then inserted into the genome of a host cell using a high-throughput dual recombinase-mediated cassette exchange method modified at the Kazusa DNA Research Institute. Using this approach, the immune repertoire on the original single B cell is eventually recaptured on the recombinant cell. The functionality of the recombinant Fab molecule will be examined using a single-molecule analysis with an automated robotic system developed at RIKEN Quantitative Biology Center (QBiC, Dr. M. Ueda).

A basic mission of the Laboratory for Integrative Genomics is to function as a "Gateway" to genomics. To achieve this, we have taken a three-pronged approach to our research activities: (1) central support activities; (2) strategic and collaborative research activities; and (3) exploratory research activities aimed at new technology development.

As for the central support activities in category (1), we have made every effort to update new technologies with the least delay, but only after they become mature and robust enough. We believe that these activities will be a big help for medical scientists.

We have made a special effort in category (2) because it is crucial to enhance the research activities of the center as a whole. In the strategic research activities, our group plays the role of "workhorse" to drive the measurement and bioinformatics pipelines of the center projects such as the Atopic Dermatitis project, the Autoimmune project, and the Metabolic disorder project, and so on. The primary bioinformatics analyses are done in our laboratory. As for the collaborative research activities, we have also participated in many intramural as well as extramural collaborations on a laboratory-to-laboratory basis.

As for research category (3), we are now focusing our efforts in the development of single-cell measurement technologies and their applications. In general, there are two measurement types in analysis of population dynamics at the single-cell resolution - snapshot vs real-time monitoring. In our group, we have made a special effort to develop optofluidics methods to monitor individual cells in real-time. This approach will provide us with indispensable lines of information to interpret single-cell snapshot data from the viewpoint of systems biology.

Recent Major Publications

Najima Y, Tomizawa-Murasawa M, Saito Y, Watanabe T, Ono R, Ochi T, Suzuki N,Fujiwara H, Ohara O, Shultz LD, Yasukawa M, Ishikawa F. Induction of WT1-specifi-chuman CD8+ T cells from human HSCs in HLA class I Tg NOD/SCID/IL2rgKO mice. ***Blood*** 127, 722–734 (2016)

Yakushiji-Kaminatsui N, Kondo T, Endo TA, Koseki Y, Kondo K, Ohara O, Vidal M, Koseki H. RING1 proteins contribute to early proximal-distal specification of the fore limb bud by restricting Meis2 expression. ***Development*** 143, 276–285 (2016)

Inoue T, Morita M, Hijikata A, Fukuda-Yuzawa Y, Adachi S, Isono K, Ikawa T, Kawamoto H, Koseki H, Natsume T, Fukao T, Ohara O, Yamamoto T, Kurosaki T. CNOT3 contributes to early B cell development by controlling Igh rearrangement and p53 mRNA stability. ***J Exp Med*** 212, 1465–1479 (2015)

Oda H, Sato T, Kunishima S, Nakagawa K, Izawa K, Hiejima E, Kawai T, YasumiT, Doi H, Katamura K, Numabe H, Okamoto S, Nakase H, Hijikata A, Ohara O, Suzuki H, Morisaki H, Morisaki T, Nunoi H, Hattori S, Nishikomori R, Heike T. Exon skipping causes atypical phenotypes associated with a loss-of-function mutationin FLNA by restoring its protein function. ***Eur J Hum Genet*** 24, 408–414 (2016)

Invited Presentations

Ohara O. "From genotype to phenotype: Mind the gap in multiscale structure of the phenotype" 4th Sardinian Summer School From genome-wide association studies (GWAS) to function (Pula, Italy) June, 2015

Ohara O. "Advances in Clinical Sequencing Technologies for Primary Immunodeficiency Diseases" The 11th Congress of Asian Society for Pediatric Research (ASPR 2015) (Osaka, Japan) April, 2015

Laboratory for Disease Systems Modeling

Group Director: Hiroaki Kitano

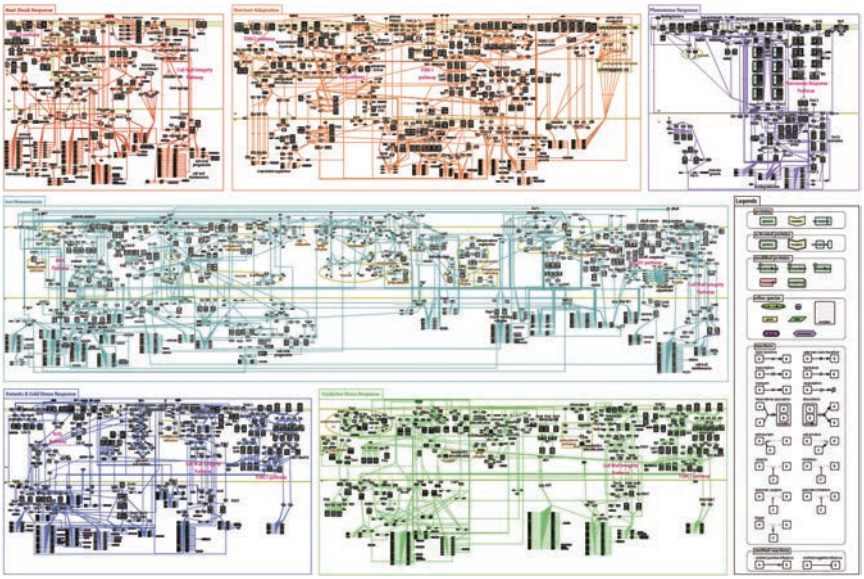


Figure: Comprehensive maps of the stress response pathways for the budding yeast.
Pathways were categorized into six groups and contain multiple layers of information, which are not included in simple interaction networks such as protein-protein interaction (PPI).

The Laboratory for Disease Systems Modeling (LDSM) aims at in-depth understanding of several biological processes relevant to disease systems, and possible applications to clinical practice. There are three interrelated projects: (1) Skin Homeostasis, (2) Aging, and (3) Precision systems biology using budding yeast. Skin homeostasis is linked with IMS's center project on atopic dermatitis. We are striving to create computational models combined with a rage of cell-based experiments at LDSM together with mouse data from other IMS teams. Aging is a new topic with long-range objectives to understand possible control of aging process and uncovering molecular mechanisms behind it. We are focusing on the effect of SIRT1 (mammalian) and Sir2 (budding yeast), and NMN as a chemical substance to affect these genes. We are linking skin homeostasis and aging with low-grade chronic inflammation as the common thread. Precision systems biology using budding yeast strengthens our understanding of key biological process by providing deeper insights on detailed molecular processes with our original gTOW genome-wide assay system.

In addition, the LDSM have has extensive involvement with the Medical Innovation Hub project in its feasibility study stage, but that will not be reported here.

Recent Major Publications

Kawakami E, Nakaoka S, Tazro Ohta T, Kitano H. Weighted enrichment method for prediction of transcription regulators from transcriptome and global chromatin immunoprecipitation data. ***Nucleic Acids Res*** 44, 5010–5021 (2016)

Kitano H. Artificial intelligence to win the Nobel Prize and beyond: Creating the engine of scientific discovery. ***AI Magazine*** 37, 39–49 (2016)

Kawakami E, Singh VK, Matsubara K, Ishii T, Matsuoka Y, Hase T, Kulkarni P, Siddiqui K, Kodilkar J, Danve N, Subramanian I, Katoh M, Shimizu-Yoshida Y, Ghosh S, Jere A, Kitano H. Network analyses based on comprehensive molecular interaction maps reveal robust control structures in yeast stress response pathways. ***Npj Systems Biology and Applications*** 2, 15018 (2016)

Invited Presentations

Kitano H. "Artificial Intelligence for Scientific Discovery in Biomedical Sciences" GET Conference (Boston, USA) April, 2016

Kitano H. "Cellular systems" The 3rd EMBO Conference on Visualizing Biological Data (VIZBI 2016) (Heidelberg, Germany) March, 2016

Kitano H. "Systems Biology and Applications" ICSB 2014-15th International Conference on Systems Biology (Melbourne, Australia) September, 2014

Kitano H. "Software platform for systems drug discovery" Workshop on Translational Knowledge Management in Pharmaceutical R&D, Innovative Medicines Initiative (IMI) (Brussels, Belgium) July, 2013

Laboratory for Immunogenetics

Team Leader: Hisahiro Yoshida

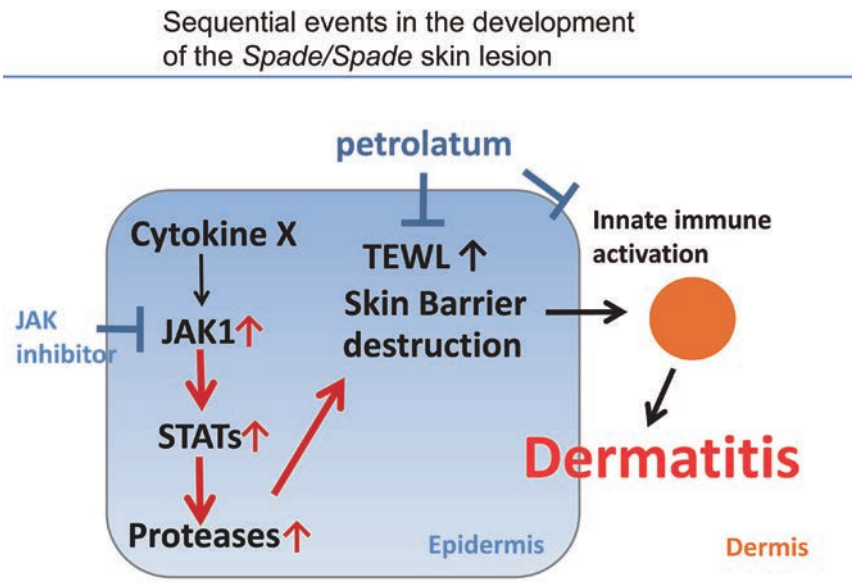


Figure: Dermatitis developmental steps in the *Spade* mutant.

Before the onset of an inflammatory disease, there must be an accumulation of many imperceptible pathogenic events in the human body as part of pre-symptomatic disease development under the influence of genetic and environmental factors. If one could precisely monitor and understand these multiple pre-symptomatic longitudinal events occurring in a healthy individual, it should be possible to predict the timing of disease onset and to take measures to prevent it. This strategy will be beneficial for many individuals in the coming era, when everyone can know their own genome sequence information and genetic risk factors shortly after birth.

In our laboratory, we had been working to identify the genetic factors for allergic or immune disease development by phenotype screening of a chemical mutagen [N-ethyl N-nitrosourea (ENU)] -induced mutant mice on a C57BL/6J background. Among the mutants identified, we have focused on a dermatitis model in which the disease develops at approximately 8 weeks after birth, as detected by ear skin desquamation and subsequent scratching of the skin a few days after the initial symptoms. This phase is followed by a Th2-biased immune response detected by elevated serum IgE, IgG1 and histamine levels 3 weeks later. Then, 8 weeks after that, a Th1 immune biased response ensues, with elevated serum IgG2b and IgG2c. At this final stage, the pathological findings led to the diagnosis of a chronic inflammatory condition of the skin. These symptoms are in part compatible with those of human atopic dermatitis; therefore we named this mutant *Spade* (Stepwise progressive atopic dermatitis).

This phenotype was induced by a gain of function point mutation (R878H) in the JAK1 tyrosine kinase molecule, which is usually activated by several cytokines. As expected, this disease was prevented by painting a JAK inhibitor on the skin, however, petrolatum painting also blocked the dermatitis onset even the presence of the JAK1 activated molecular event. Using this disease model, we have precisely analyzed the pre-symptomatic pathological events as shown in the figure. The accumulation of all these events leads to the onset of dermatitis in the late stage.

Recent Major Publications

Yasuda T, Fukada T, Nishida K, Nakayama M, Matsuda M, Miura I, Dainichi T, Fukuda S, Kabashima K, Nakaoka S, Bin BH, Kubo M, Ohno H, Hasegawa T, Ohara O, Koseki H, Wakana S, Yoshida H. Hyperactivation of JAK1 tyrosine kinase induces stepwise, progressive pruritic dermatitis. ***J Clin Invest*** 126, 2064–2076 (2016)

Satoh R, Kakugawa K, Yasuda T, Yoshida H, Sibilia M, Katsura Y, Levi B, Abramson J, Koseki Y, Koseki H, van Ewijk W, Hollander GA, Kawamoto H. Requirement of Stat3 Signaling in the Postnatal Development of Thymic Medullary Epithelial Cells. ***PLoS Genet*** 12, e1005776 (2016)

Miyai T, Hojyo S, Ikawa T, Kawamura M, Irie T, Ogura H, Hijikata A, Bin BH, Yasuda T, Kitamura H, Nakayama M, Ohara O, Yoshida H, Koseki H, Mishima K, Fukada T. Zinc transporter SLC39A10/ZIP10 facilitates antiapoptotic signaling during early B-cell development. ***Proc Natl Acad Sci U S A*** 111, 11780–11785 (2014)

Invited Presentations

Yoshida H. "Genetic factors and atopic dermatitis disease model" The 10th Tokyo Scientific Forum for Atopic Dermatitis and Psoriasis (Tokyo, Japan) December, 2014

Yoshida H. "Genetic factors and onset of atopic dermatitis in murine disease model" The 113th Annual Meeting of the Japanese Dermatological Association (Kyoto, Japan) May, 2014

Laboratory for Integrated Bioinformatics

Team Leader: Todd D. Taylor

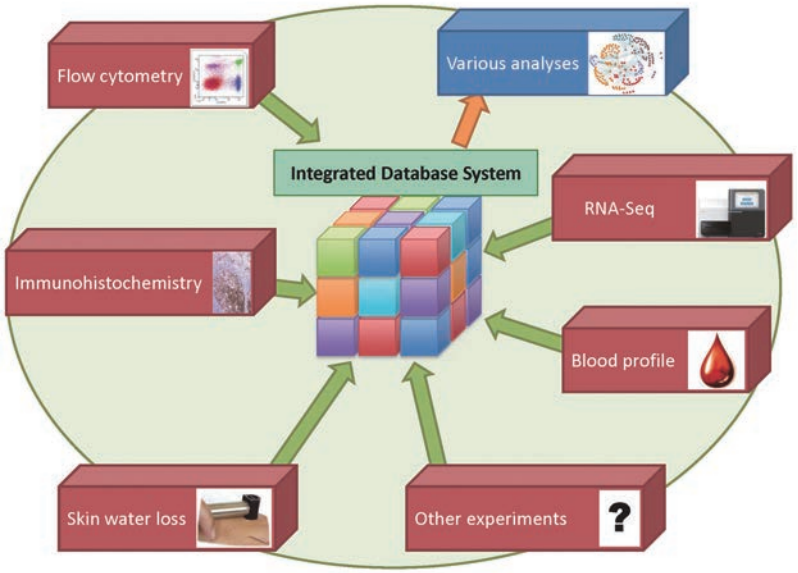


Figure: Overview of the Integrated Database System
Data generated by participating labs for a variety of wet-lab experimental types, including flow cytometry data, immunohistochemistry images, skin water loss measurements, blood profiles, RNA-Seq data, and others, are automatically or manually imported into the database. These data are then easily accessible for downstream analysis.

Large volumes of many different types of data are being generated as part of the core projects being conducted in IMS, and our team provides the necessary bioinformatic support. We are developing an integrated database and sample-tracking system to handle both small-scale and large-scale datasets of various types of experimental outputs. The system currently brings together a variety of wet-lab experimental types being generated by various labs. We are establishing common protocols for transferring massive datasets from different data management systems. For data being generated on a smaller scale, modules are being developed for a database web interface so that researchers or technicians can directly input their data by hand, or by some other simple means. As per user requests, we plan to provide a variety of integrated views of the data, automatically perform calculations and generate graphs, charts and tables, and even assist in data analysis. Most critically, users and collaborators will be able to extract whatever data they need, in the format they need, to perform downstream analyses. The ultimate goal is to develop a flexible system that makes it easy to manage, access, analyze, integrate, and visualize various data types as per user requirements.

In addition, our lab continues to develop general-purpose bioinformatic tools capable of efficiently processing and analyzing data from a variety of sources, with an emphasis on metagenomic data (e.g., taxonomic classification, phylogenic tree visualization, 16S rRNA curation), host-microbiome interactions, and scientific discovery through big data curation. With the advent of high-throughput next-generation sequencers and subsequent massive data output, we anticipate the need for better means of visualizing and understanding the results, and our overall long-term goal is the integration of such tools to ease the analytical burden of non-bioinformatician scientists.

Recent Major Publications

Lau N-S, Makita Y, Kawashima M, Taylor TD, Kondo S, Othman AS, Shu-Chien AC, Matsui M. The rubber tree genome shows expansion of gene family associated with rubber biosynthesis. ***Sci Rep*** 6, 28594 (2016)

Jinda W, Poungvarin N, Taylor TD, Suzuki Y, Thongnoppakhun W, Limwongse C, Lertrit P, Suriyaphol P, Atchaneeyasakul L. A novel start codon mutation of the MERTK gene in a patient with retinitis pigmentosa. ***Mol Vis*** 22, 342–351 (2016)

Nishijima S, Suda W, Oshima K, Kim SW, Hirose Y, Morita H, Hattori M. The gut microbiome of healthy Japanese and its microbial and functional uniqueness. ***DNA Res*** 23, 125–133 (2016)

Invited Presentations

Taylor TD. "Turning 'big data' into 'small data' through crowdsourced curation: integrating all types of medical and scientific knowledge." 3rd AIST-RIKEN Joint Bioinformatics Seminar (Yokohama, Japan) June, 2016

Taylor TD. "Introduction to metagenomics; Metadata management, sampling considerations, experimental approaches, workflow summary." CCB-USM Workshop on Metagenomics. Centre for Chemical Biology, Universiti Sains Malaysia (Penang, Malaysia) December, 2014

Kim SW. "Microbial community analysis using 16S rRNA." CCB-USM Workshop on Metagenomics. Centre for Chemical Biology, Universiti Sains Malaysia (Penang, Malaysia) December, 2014

Taylor TD. "Online resources: databases, tools and pipelines; Introduction to the human genome project and metagenomics." 1st Workshop in Bioinformatics. School of Biological Sciences, University Sains Malaysia (Penang, Malaysia) December, 2013

Taylor TD. "Metagenomics and barcoding." Poznan Summer School of Bioinformatics: Molecular Evolution & Phylogenomics. Collegium Biologicum at Campus UAM Morasko, Adam Mickiewicz University (Poznan, Poland) August, 2013

Laboratory for Tissue Dynamics

Team Leader: Takaharu Okada

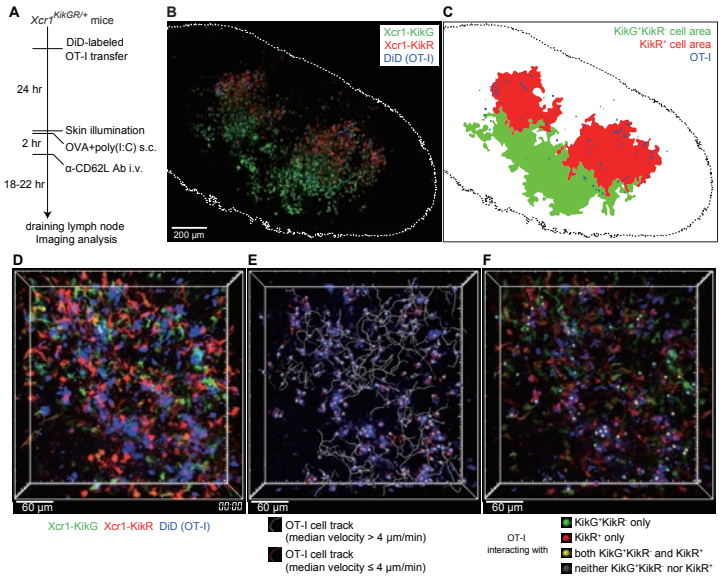


Figure: Imaging Analysis of Antigen-Specific CD8⁺ T Cells interacting with *Xcr1*⁺ Cross-Presenting DC Subsets Using the Photochromic Fluorescent Protein KikGR.
(Modified from Kitano et al. Proc Natl Acad Sci USA 113, 1044–1049, 2016).
(**A**) Experimental design. Cross-presenting DCs that have arrived in the lymph nodes after immunization are visualized as KikR⁺ cells while the other cross-presenting DCs in the lymph nodes are visualized as KikG⁺KikR⁻ cells. (**B**) Fluorescence image of half of an inguinal LN sagittal slice from an Xcr1$^{KikGR/+}$ mouse treated as described in (**A**). A maximal projection image of six confocal sections (35 μm depth) is shown. The dotted line demarcates the LN boundary. "c" and "m" indicate the cortical and medullary sides, respectively (**C**) Demarcation of the KikG⁺KikR⁻ area, KikR⁺ area, and OT-I T cell-occupied area in the image shown in (**B**). (**D**) An intravital two-photon image of an inguinal LN of an *Xcr1*$^{KikGR/+}$ mouse treated as in (**A**). A 3D-rendered fluorescence image is shown. Image depth: 100 μm. (**E**) OT-I T cell tracks. Imaging duration: 30 min. (**F**) The interaction partners of low-motility OT-I T cells (median velocity ≤ 4 μm). The colored dots were placed on low-motility OT-I T cells interacting with the indicated cells.

The goal of the laboratory is to mechanistically understand the *in vivo* cellular dynamics that shape immune responses and inflammation. Currently, we have limited understanding of how immunological memory and tolerance, two central features of adaptive immunity, are controlled by dynamic interactions among immune cells. As a strategy for tackling this problem, we use multi-dimensional fluorescent imaging, in particular two-photon microscopy, to analyze cellular migration and interactions in the tissues. This microscopy method has been revealing the striking dynamics of immune cells in various organs, underlining the importance of this approach to resolve the complexity of the immune system. By applying this imaging strategy to relevant mouse models, we aim to reveal immune cell dynamics that are critical for generation of immunological memory and tolerance. For this aim, we have been developing and studying mouse strains, in which (1) dynamics of helper T cells specialized for B cell immune responses are perturbed, (2) cross-presenting dendritic cells (DCs) are fluorescently labeled for *in vivo* imaging, and (3) dynamics and function of regulatory T (Treg) cell subsets are perturbed to break peripheral tolerance of autoreactive B cells and CD8+ T cells.

In addition, we have recently started projects to study the roles for the peripheral nervous system in modulation of inflammation. Particularly, we are interested in structural and functional changes in sensory neurons in dermatitis. In this study as well, the imaging approaches are very powerful for deciphering the diversity and dynamics of cellular activities. Through this study, we aim to find strategies to suppress chronic inflammation based on the modulation of neuronal activities.

Recent Major Publications

Kitano M, Yamazaki C, Takumi A, Ikeno T, Hemmi H, Takahashi N, Shimizu K, Fraser SE, Hoshino K, Kaisho T, Okada T. Imaging of the cross-presenting dendritic cell subsets in the skin-draining lymph node. ***Proc Natl Acad Sci U S A*** 113, 1044–1049 (2016)

Daniels N., Hyde E, Ghosh S, Seo K, Price KM, Hoshino K, Kaisho T, Okada T, Ronchese F. Antigen-specific cytotoxic T lymphocytes target airway CD103+ and CD11b+ dendritic cells to suppress allergic inflammation. ***Mucosal Immunol*** 9, 229–239 (2016)

Lin WW, Adams WC, Nish SA, Chen YH, Yen B, Rothman NJ, Kratchmarov R, Okada T, Klein U, Reiner SL. Asymmetric PI3K signaling driving developmental and regenerative cell fate bifurcation. ***Cell Rep*** 13, 1–16 (2015)

Invited Presentations

Okada T. "Imaging of cellular dynamics shaping the adaptive immune system" The 44th Annual Meeting of Japanese Society for Immunologists, GlaxoSmithKline K. K. Clinical Seminar (Sapporo, Japan) November, 2015

Okada T. "Fluorescence imaging of immune cell dynamics in the immunological disease model" The 10th Invited Immunologist Seminar at The Shonan Research Center of Takeda Pharmaceutical Company (Fujisawa, Japan) October, 2015

Okada T. "Imaging of Immune Cell Dynamics" The 65th Annual Meeting of the Japan Society for Cell Biology (Tokyo, Japan) July, 2015

Laboratory for Integrated Cellular Systems

Team Leader: Mariko Okada

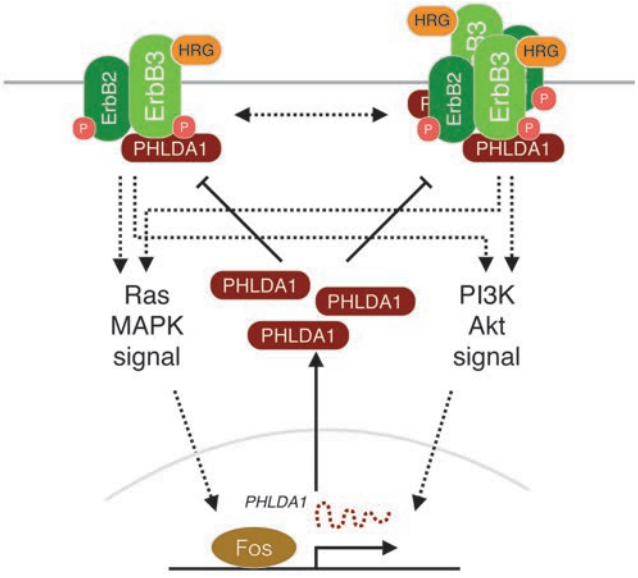


Figure: Negative feedback regulation of ErbB receptor signaling by PHLDA1
PHLDA1 is transcriptionally induced upon activation of Ras-ERK and PI3K-Akt pathways and suppresses high-order oligomerization of the receptor complex.

The aims of the laboratory are to determine the general regulatory rules in the dynamic behavior of signal transduction-transcriptional networks in cell determination processes and to apply this knowledge of regulatory principles for understanding and treatment of human diseases. For this purpose, we perform quantitative measurements of the target biological system using various experimental methods and then integrate these heterogeneous data using mathematical models. A biological system is often dissected with its time, size and data derived from each experimental platform, and integration of such heterogeneous data is only possible using informatics and mathematical modeling. In particular, we have strength in developing data-driven kinetic models, and this approach is being applied to various biological phenomena related to different aspects of cell regulation. In particular, we have been working on signaling and transcription dynamics in proliferation and differentiation of cancer and immune cells *in vitro* and applying these data acquisition strategies and data analysis methods to *in vivo* mouse models. To understand the regulatory layers between signaling and transcription regulation, we have recently analyzed dynamics of epigenetic regulation. We collaborate with single molecule imaging experts to identify the critical kinetic parameters in the regulation. We also develop computational and theoretical methods with collaborators in different research fields that can be applied for the analysis of real biological data. These collaborative efforts are complementary to our kinetic modeling approach and could uncover the regulatory relationships of the molecules in the network in an unbiased manner.

Recent Major Publications

Mina M, Magi S, Jurman G, Itoh M, Kawaji H, Lassmann T, Arner E, Forrest ARR, Carninci P, Hayashizaki Y, Daub CO, the FANTOM Consortium, Okada-Hatakeyama M*, Furlanello C*. Promoter-level expression clustering identifies time development of transcriptional regulatory cascades initiated by ErbB receptors in breast cancer cells. ***Sci Rep*** 5, 11999 (2015) * Corresponding authors.

Nagashima T, Inoue N, Yumoto N, Saeki Y, Magi S, Volinsky N, Sorkin A, Kholodenko BN and Okada-Hatakeyama M. Feedforward regulation of mRNA stability by prolonged ERK activity. ***FEBS J***. 282, 613–629 (2015)

Shinohara H, Behar M, Inoue K, Hiroshima M, Yasuda T, Nagashima T, Kimura S, Sanjo H, Maeda S, Yumoto N, Ki S, Akira S, Sako Y, Hoffmann A, Kurosaki T, Okada-Hatakeyama M. Positive feedback within a kinase signaling complex functions as a switch mechanism for nuclear factor-κB activation. ***Science*** 344, 760–764 (2014)

Invited Presentations

Okada-Hatakeyama M. "Mechanisms of dynamics behaviors of NF-κB signaling in B cell" 16th International Conference of Systems Biology (ICSB) 2015 (Singapore, Singapore) November, 2015

Okada-Hatakeyama M. "Data-based modeling of signal-transcription network for cell fate control" BioNetVista Workshop-ICSB2015 (Singapore, Singapore) November, 2015

Okada-Hatakeyama M. "Data-based modeling of on/off switch mechanism arising from biochemical network" EquaDiff 2015 (Lyon, France) July, 2015

Okada-Hatakeyama M. "On/off switching mechanisms in signaling network" cBio Meeting (Tsuruoka, Japan) May, 2015

Okada-Hatakeyama M. "A switch in NF-kappaB immune signaling" The first Q-Bio Winter Meeting (Hawaii, USA) February, 2013

Laboratory for Metabolomics

Team Leader: Makoto Arita

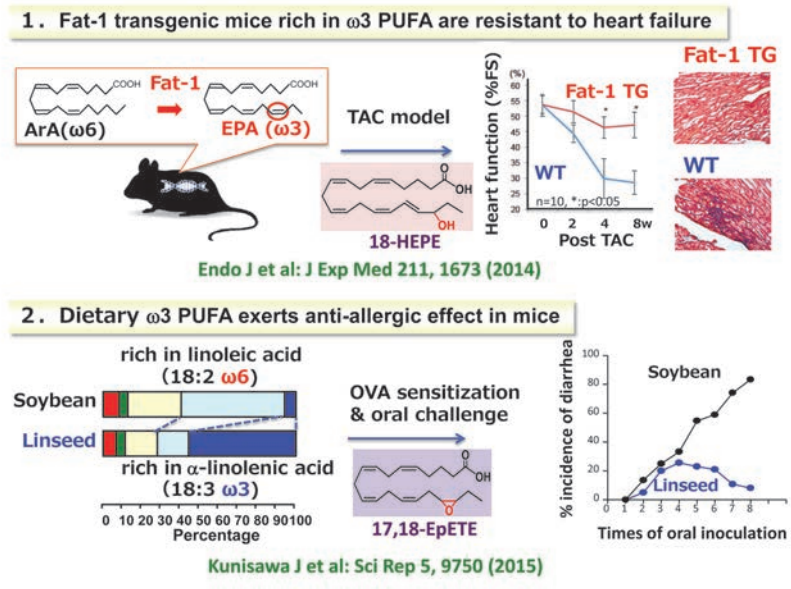


Figure: Anti-inflammatory mechanisms of Omega-3 PUFAs and their bioactive metabolites.
Genetic and lipidomic analyses identified 18-hydroxyeicosapentaenoic acid (18-HEPE) as a cardioprotective and anti-fibrotic metabolite generated by macrophages in the heart. We also identified 17,18-epoxyeicosatetraenoic acid (17,18-EpETE) as an anti-allergic metabolite generated in the gut from dietary omega-3 alpha-linolenic acid.

Recent Major Publications

Sakayori N, Kikkawa T, Tokuda H, Kiryu E, Yoshizaki K, Kawashima H, Yamada T, Arai H, Kang JX, Katagiri H, Shibata H, Innis SM, Arita M, *Osumi N. Maternal dietary balance between omega-6 and omega-3 polyunsaturated fatty acids impairs neocortical development via epoxy metabolites. ***Stem Cells*** 34, 470–482 (2016)

*Kunisawa J, *Arita M, Hayasaka T, Harada T, Iwamoto R, Nagasawa R, Shikata S, Nagatake T, Suzuki H, Hashimoto E, Kurashima Y, Suzuki Y, Arai H, Setou M, Kiyono H. Dietary 3 fatty acid exerts anti-allergic effect through the conversion to 17,18-epoxyeicostetraenoic acid in the gut. ***Sci Rep*** 5, 9750 (2015)

Masterson JC, McNamee EN, Fillon SA, Hosford L, Harris R, Fernando SD, Jedlicka P, Iwamoto R, Jacobsen E, Protheroe C, Eltzschig HK, Colgan SP, Arita M, Lee JJ, *Furuta GT. Eosinophil-mediated signaling attenuates inflammatory responses in experimental colitis. ***Gut*** 64, 1236–1247 (2015)

Invited Presentations

Arita M. "Advanced lipidomics to understand the quality difference of fatty acids in biological systems" The 96th Chemical Society of Japan Annual Meeting (Kyoto, Japan) March, 2016

Arita M. "Quality of Lipids in Health and Disease" Academia Sinica IBMS-RIKEN IMS Joint Workshop (Yokohama, Japan) March, 2016

Arita M. "Lipidomic approach to uncover anti-inflammatory properties of omega-3 polyunsaturated fatty acids" 14th International Conference of Bioactive Lipids in Cancer, Inflammation and Related Diseases (Budapest, Hungary) July, 2015

Arita M. "Lipidomic approach to uncover anti-inflammatory properties of omega-3 polyunsaturated fatty acids" IMS-JSI International Symposium on Immunology 2015 (Yokohama, Japan) June, 2015

Arita M. "Lipo-quality in biological systems" The 57th Annual Meeting of Japanese Conference on the Biochemistry of Lipids (Tokyo, Japan) May, 2015

Lipids are recognized as extremely diverse molecules. Precise determination of each molecular species of lipid, namely Lipo-Quality (Quality of Lipids), becomes a prerequisite not only to understand their biological functions in physiology and disease, but also to discover novel bioactive lipids that may link lipid metabolism and biological phenotypes. A powerful method for the analysis of lipid metabolites is liquid chromatography tandem mass spectrometry (LC-MS/MS). Our research is aimed at elucidating the structure and function of endogenous lipid metabolites that regulate inflammation and tissue homeostasis.

Polyunsaturated fatty acid (PUFA)-derived mediators are formed by enzymatic oxidation through the action of cyclooxygenases (COX), lipoxygenases (LOX), and cytochrome P450 monooxygenases (CYP). By using LC-MS/MS-based lipidomics, we provided new insights into the cellular and molecular mechanisms of inflammatory resolution, especially the functional roles of 12/15-LOX-expressing eosinophils and macrophages in controlling the resolution of inflammation. Our research is also focused on understanding the function of omega-3 PUFAs using genetic and lipidomic approaches, and has identified novel metabolic pathways and bioactive metabolites that may link to omega-3 PUFA's anti-inflammatory actions. Identification of endogenous mediators with potent anti-inflammatory activity could lead to the development of novel therapeutics for disease when sustained inflammation is suspected as a key component of pathogenesis.

We also put a lot of effort into development and application of targeted and non-targeted lipidomics platforms to discover novel links between lipid metabolism and biological phenotypes. By taking advantage of Q-TOF (global lipid screening) and TripleQ (quantitative analyses) mass spectrometers, our new approach has a strong potential to search for lipids of interest globally, or to identify unknown lipid species in a non-biased fashion.

Core for Genomic Medicine

The Core for Genomic Medicine is performing genomic research on human diseases, especially the common diseases. The aims of Core for Genomic Medicine are 1) to identify genetic variations related to disease susceptibility, disease outcome and drug responses (efficacy/adverse reaction), 2) to provide useful information about possible molecular targets for drug discovery, 3) to examine the interactions between genetic and environmental factors to understand the pathogenesis and the progression of diseases, and 4) finally to construct the evidence base for the implementation of personalized medicine.

To identify genetic variations related to disease susceptibility and drug responses, the Core for Genomic Medicine first showed the proof of concept of the genome-wide association study (GWAS) in 2002. To advance this strategy, the Core for Genomic Medicine has organized laboratories to facilitate comprehensive genomic research on common diseases. To produce comprehensive genomic information, the Laboratory for Genotyping Development is mainly working on large-scale SNP genotyping and genome sequencing for various diseases. The resulting huge amount of genomic variation data was mainly analyzed at the Laboratory for Statistical Analysis to extract significant genomic variations related to disease susceptibility and drug responses. These laboratories are in close communication with the research group of pharmacogenomics (Laboratory for Pharmacogenomics and Laboratory for International Alliance on Genomic Research), laboratories for disease-causing mechanisms (Laboratory for Cardiovascular Diseases, Autoimmune Diseases, Digestive Diseases, Bone and Joint Diseases, Endocrinology, Metabolism and Kidney Diseases, and Respiratory and Allergic Diseases) and many other collaborators worldwide for further analyses. In addition to this strategy, the Laboratory for Genome Sequencing Analysis is mainly working on whole genome sequencing of cancer genomes to clarify the pathogenesis of carcinogenesis.

Laboratory for Genotyping Development

Team Leader: Yukihide Momozawa

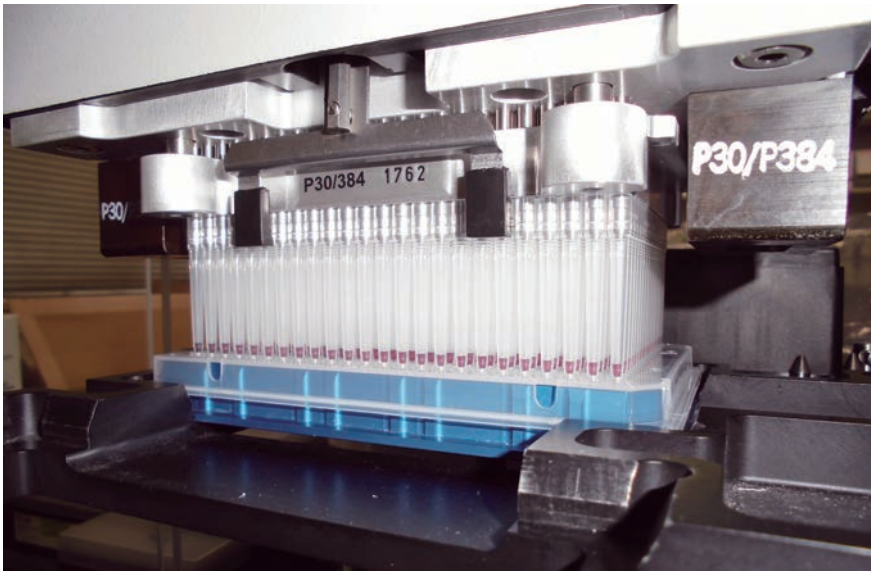


Figure: High throughput dispensing system necessary for large scale genomic analysis.

The aims of the Laboratory for Genotyping Development from FY2013 to FY2016 are 1) to produce precise and large-scale genomic data to identify genetic variants related to diseases susceptibility, outcomes, and drug responses in tight collaboration with the Laboratory for Statistical Analysis and 2) to develop methods and database useful for clinical sequencing.

For these purposes, we newly installed a high-throughput whole genome sequencing (WGS) method, a whole exome sequencing (WXS) method and a target sequencing (TS) method, in addition to the genome wide SNP genotyping that we have previously used. We applied these methods to different projects in collaboration with the BioBank Japan project, the PGRN-RIKEN IMS Global Alliance, and other researchers. In total, between FY2013 and FY2016, we performed genome wide SNP genotyping of 215,446 individuals in 80 projects, WGS of 1,782 individuals in 10 projects, WXS of 644 individuals in seven projects, and TS of 122,472 individuals in 12 projects.

We also contributed to construction of a Japanese population-specific reference panel (n = 908) for human leukocyte antigen (HLA) alleles. We performed high-resolution (four-digit) genotyping of three class I HLA genes and four class II HLA genes and the Laboratory for Statistical Analysis developed the reference panel and applied this panel to genome-wide association study data for Graves' disease. We found that amino acid polymorphisms of multiple class I and class II HLA genes independently contribute to disease risk.

We have published 117 papers between FY2013 and 2016. We will continue these efforts to contribute to the implementation of personalized medicine.

Recent Major Publications

Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, Ripke S, Lee JC, Jostins L, Shah T, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. ***Nat Genet*** 47, 979–986 (2015)

Okada Y, Momozawa Y, Ashikawa K, Kanai M, Matsuda K, Kamatani Y, Takahashi A, Kubo M. Construction of a population-specific HLA imputation reference panel and its application to Graves' disease risk in Japanese. ***Nat Genet*** 47, 798–802 (2015)

Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, Powell C, Vedantam S, Buchkovich ML, Yang J, et al. Genetic studies of body mass index yield new insights for obesity biology. ***Nature*** 518, 197–206 (2015)

Invited Presentations

Kubo M. "The Biobank Japan project" 2013 Taiwan Human Genetics Society Spring Symposium & Annual Meeting: Taiwan-Japan Joint Symposium on BioBank and Genomic Medicine (Taipei, Taiwan) May, 2013

Kubo M. "From genomic research to genomic medicine and prevention" The 59th Annual Meeting of the Japan Society of Human Genetics (Society award) (Tokyo, Japan) November, 2014

Kubo M. "Cancer pharmacogenomics in the Biobank Japan Project" UK-Japan Collaborative Meeting (Cambridg, UK) February, 2015

Kubo M. "Pharmacogenetics in the BioBank Japan project" The 3rd Meeting of South East Asian Pharmacogenomics Research Network (SEAPharm) (Jakarta, Indonesia) April, 2014

Kubo M. "Biobank Japan Project" Finland-Japan BioBank session (Tokyo, Japan) October, 2015

Momozawa Y. "BioBank Japan: future direction" The 6th International Workshop on Genomic Epidemiology (London, UK) May, 2015

Laboratory for Genome Sequencing Analysis

Team Leader: Hidewaki Nakagawa

Recent Major Publications

Fujimoto A, Furuta M, Totoki Y, Tsunoda T, Kato M, Shiraishi Y, Tanaka H, Taniguchi H, Kawakami Y, Ueno M, Gotoh K, Ariizumi S, Wardell CP, Hayami S, Nakamura T, Aikata H, Arihiro K, Boroevich KA, Abe T, Nakano N, Maejima K, Sasaki-Oku A, Ohsawa A, Shibuya T, Nakamura H, Hama N, Hosoda F, Arai Y, Ohashi S, Urushidate T, Nagae G, Yamamoto S, Ueda H, Tatsuno K, Ojima H, Hiraoka N, Okusaka T, Kubo M, Marubashi S, Yamada T, Hirano S, Yamamoto M, Ohdan H, Shimada K, Ishikawa O, Yamaue H, Chayama K, Miyano S, Aburatani H, Shibata T, and Nakagawa H (corresponding). Whole genome mutational landscape and characterization of non-coding and structural mutations in liver cancer. ***Nat Genet*** 48, 500–509 (2016)

Fujimoto A, Furuta M, Shiraishi Y, Gotoh K, Kawakami Y, Arihiro K, Nakamura T, Ueno M, Ariizumi S, Hai Nguyen H, Shigemizu D, Abe T, Boroevich KA, Nakano K, Sasaki A, Kitada R, Maejima K, Yamamoto Y, Tanaka H, Shibuya T, Shibata T, Ojima H, Shimada K, Hayami S, Shigekawa Y, Aikata H, Ohdan H, Marubashi S, Yamada T, Kubo K, Hirano S, Ishikawa O, Yamamoto M, Yamaue H, Chayama K, Miyano S, Tsunoda T, Nakagawa H. Whole-genome mutational landscape of liver cancers displaying biliary phenotype reveals hepatitis impact and molecular diversity. ***Nat Commun*** 6, 6120 (2015)

Ono A, Fujimoto A, Yamamoto Y, Akamatsu S, Hiraga N, Imamura M, Kawaoka T, Tsuge M, Abe H, Hayes CN, Miki D, Furuta M, Tsunoda T, Miyano S, Kubo M, Aikata H, Ochi H, Kawakami Y, Nakagawa H (corresponding), and Chayama K. Circulating tumor DNA analysis for liver cancers and its usefulness as a liquid biopsy. ***Cell Mol Gastroenterol Hepatol*** 1, 516–534 (2015)

Invited Presentations

Nakagawa H. "Cancer whole genome and clinical sequencing for precision medicine" Commemorative Symposium for the opening of Personalized Cancer Medicine Care, SNU Cancer Hospital (Seoul, Korea) October, 2015

Nakagawa H. "Cancer genome profiling by NGS of archives and liquid biopsy samples" The 74th Annual meeting of the Japanese Cancer Association (Nagoya, Japan) October 2015

Nakagawa H. "Whole genome sequencing analysis for iver cancer and genome medicine" (Sapporo, Japan) June 2015

Nakagawa H. "International collaboration for cancer whole genome sequencing and super-computer" Symposium of Supercomputer "KEI" and Life Science (Okayama, Japan) June 2015

Nakagawa H. "Decoding whole genomes of liver cancer toward genomic medicine and impact of chronic inflammation to cancer genome" 2015 SNU Cancer Research Institute Symposium (Jeollanam, Korea) April 2015

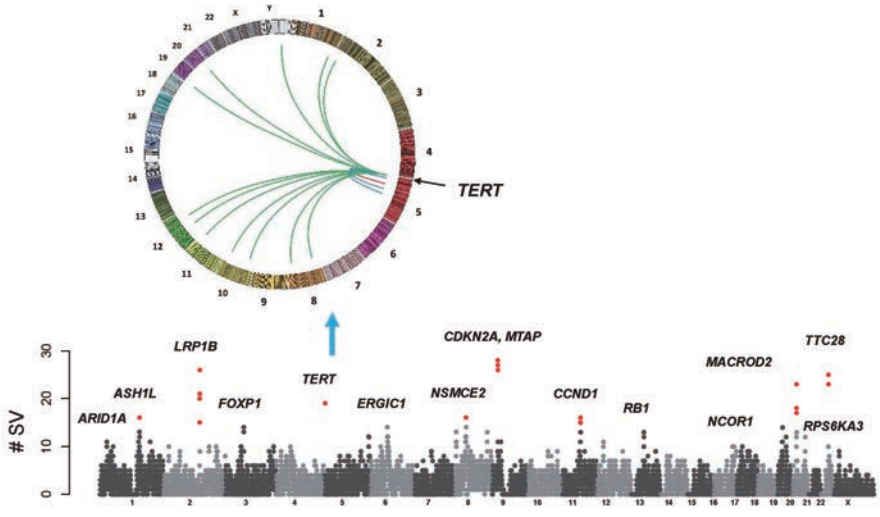


Figure: Number of samples with a SV breakpoint across chromosome (chr1-22, X). Bins with STV breakpoints ≥3% frequency are shown in red. Significantly mutated genes (frequency ≥2%) are annotated. TERT was frequently affected by SVs and HBV integration.

Cancer is essentially a "disease of the genome" which evolves with the accumulation of diverse mutations in the background of germline variants. We now recognize just how diverse human cancer biology and its underlying genomic changes are. Germline variants are biomarkers predisposing to cancer development and genetic analysis of certain specific genes, such as *BRCA1/2*, is commonly performed for cancer risk. Somatic mutations of driver genes have been targeted for cancer treatment, and genotype-based personalized cancer therapy is now a reality. Understanding of and attention to the underlying genetic diversity in cancer is, therefore, likely to increase the success of new cancer treatment modalities. Recent explosive advances in next-generation sequencing (NGS) and bioinformatics enable a systematic, genome-wide identification of all somatic abnormalities by whole genome sequencing (WGS), whole exome sequencing, and RNA sequencing (RNA-Seq). It is important to analyze the likely implications of the huge genome datasets from NGS and to reach a consensus about how to interpret the biological and clinical aspects of somatic and germline variants. Our research objectives are to understand the cancer genome, including germline and somatic events, by utilizing NGS, to identify novel genomic biomarkers and to develop analysis platforms that can be used in clinics for precision medicine.

Laboratory for Medical Science Mathematics

Group Director: Tatsuhiko Tsunoda

Recent Major Publications

Fujimoto A+, Furuta M+, Totoki Y+, Tsunoda T+, Kato M+ (+: co-first), Shiraishi Y, Tanaka H, Taniguchi H, Kawakami Y, Ueno M, Gotoh K, Ariizumi S, Wardell CP, Hayami S, Nakamura T, Aikata H, Arihiro K, Boroevich KA, Abe T, Nakano K, Maejima K, Sasaki-Oku A, Ohsawa A, Shibuya T, Nakamura H, Hama N, Hosoda F, Arai Y, Ohashi S, Urushidate T, Nagae G, Yamamoto S, Ueda H, Tatsuno K, Ojima H, Hiraoka N, Okusaka T, Kubo M, Marubashi S, Yamada T, Hirano S, Yamamoto M, Ohdan H, Shimada K, Ishikawa O, Yamaue H, Chayama K, Miyano S, Aburatani H, Shibata T, Nakagawa H. Whole genome mutational landscape and characterization of non-coding and structural mutations in liver cancer. ***Nat Genet*** 48, 500–509 (2016)

Miya F, Kato M, Shiohama T, Okamoto N, Saitoh S, Yamasaki M, Shigemizu D, Abe T, Morizono T, Boroevich KA, Kosaki K, Kanemura Y, Tsunoda T. A combination of targeted enrichment methodologies for whole-exome sequencing reveals novel pathogenic mutations. ***Sci Rep*** 5, 9331 (2015).

Fujimoto A, Furuta M, Shiraishi Y, Nguyen HH, Shigemizu D, Gotoh K, Kawakami Y, Nakamura T, Ueno M, Ariizumi S, Shibata T, Abe T, Boroevich KA, Nakano K, Sasaki A, Kitada R, Maejima K, Yamamoto Y, Tanaka H, Shibuya T, Ojima H, Shimada K, Hayami S, Shigekawa Y, Aikata H, Arihiro K, Ohdan H, Marubashi S, Yamada T, Ishikawa O, Kubo M, Hirano S, Yamamoto M, Yamaue H, Chayama K, Miyano S, Tsunoda T*, Nakagawa H* (*: co-last). Whole-genome mutational landscape of liver cancers displaying biliary phenotype reveals hepatitis impact and molecular diversity. ***Nat Commun*** 6, 6120 (2015)

Invited Presentations

Tsunoda T. "Big data analysis frontiers personalized medicine" Software Japan 2016, (Tokyo, Japan) February 2016

Tsunoda T. "Omics big data analysis and artificial intelligence for personalized/preemptive medicine" Biomedical workshop (Osaka, Japan) October, 2015

Tsunoda T. "Whole Genome Big Data Analysis for Complex Diseases" 3rd Global COE Workshop between BGI and University of Tokyo – Advances in Medical Genomics (Tokyo, Japan) March, 2014

Tsunoda T. "Whole Genome Approach Is Revolutionizing Medicine" The 10th International Workshop on Advanced Genomics (Tokyo, Japan) May, 2013

Tsunoda T. "Whole genome sequencing and comprehensive mutation analysis of liver cancer" SNUCRI & SNUCH Cancer Symposium (Seogwipo, Korea) May, 2013.

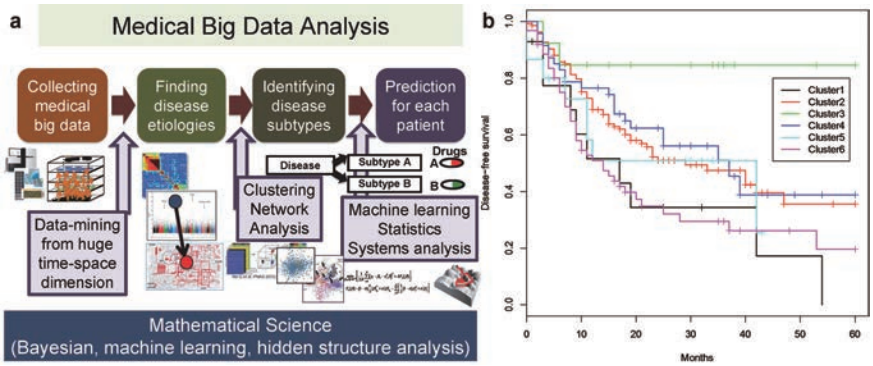


Figure: Medical Big Data Analysis for Precision Medicine.
(a) Common analysis steps and methodologies. (b) Application to omics data from 300 hepatocellular carcinoma cases revealed six clusters, which showed significantly different disease-free survival rates (***Nat Genet*** 48, 500–509 (2016)).

The medical application of rapidly progressing omic profiling technologies and, in particular, the promotion of personalized/precision/preventive medicine have recently become major goals of medical researchers. Traditional therapies do not adequately take into account the individuality of each patient. Our laboratory develops strategies to overcome such medical science issues through a combination of mathematics and computational sciences. Nowadays, biomedical big data, consisting of both clinical and omic profiles, are collected from hospitals and medical institutions. First, by applying data-mining methodologies, we explore etiologies of intractable diseases, e.g., cancer, common diseases, and neurodegenerative diseases. Next, we classify each disease into finer categories through molecular profiles, and clarify disease-causing mechanisms through a systems approach. In this way, we can develop knowledge of disease incidence and progression based on clinical and omic data. Last, we apply mathematical methods, e.g, machine learning techniques, to optimize therapy prediction for each patient when she/he visits a hospital/medical institute. We can also apply these methods to disease prevention based on an individual's medical history. Our laboratory does biomedical research and genomic medicine research driven by prediction through complete utilization of advanced mathematics and computational sciences with the goal of developing personalized/precision/preventive medicine strategies. Our research topics include: (1) exploration of disease etiologies driven by integrative analysis of clinical and omic data, (2) molecular classification of, and a systems approach to, understanding disease based on omic profiling, (3) prediction for personalized/precision/preventive medicine, and (4) the development of methodologies for the above goals.

Laboratory for Statistical Analysis

Team Leader: Yoichiro Kamatani

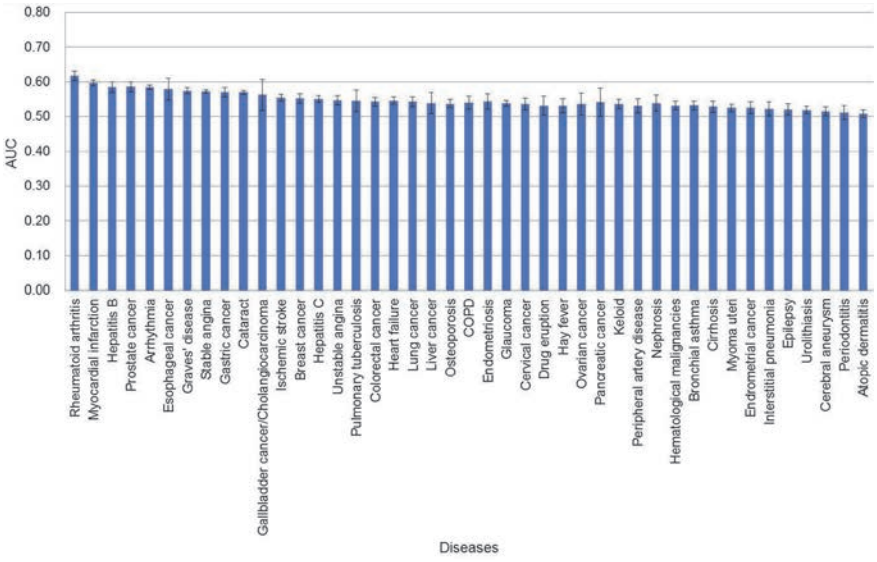


Figure: Predictive power of Random Forest models.
We constructed prediction models for 43 BioBank Japan diseases by using the Random Forest method. The predictive power was estimated by the Area Under the Curve (AUC), which was calculated by 10-fold cross-validation for each model. We observed the highest predictive power in rheumatoid arthritis; however, that was still low and an improved model is required.

Our laboratory aims at analyzing genomic data to identify disease susceptibility genes, as well as developing new statistical methods. Until now, we have used genome-wide SNP array data and performed genome wide association studies (GWAS) of dozens of traits including cancers, metabolic diseases, immunological diseases, psychiatric disorders, and so on. These findings will lead to further understanding of disease mechanisms, drug discovery, and the possibility to predict occurrences of complex diseases by using genetic information. We are continuing GWAS of the samples from ~200,000 BioBank Japan subjects with ~30,000 population controls genotyped for nearly a million genetic variants.

We are also trying to address three key issues in this field; missing heritability, a functional interpretation of the identified genetic variants, and the polygenic nature of the diseases in question. Firstly, CGM began whole genome sequencing (WGS) of thousands of individuals. By using this data, we could evaluate risk effects of rare variants and structural variations, which are not covered well by SNP array data and are possible sources of missing heritability. In 2016, three diseases will be analyzed; myocardial infarction, type 2 diabetes, and gastric cancer.

Secondly, we will focus on the interpretation of GWAS signals. Since it is estimated that the majority of the susceptibility variants for complex diseases will be in gene regulatory regions, evaluation of amino acid changes is not enough, and experimental validation is necessary. We will use public databases and eQTL data of lymphocyte subtypes generated by the Laboratory for Autoimmune Diseases to help the functional impact of these variants.

Lastly, we plan to use machine- learning techniques to reveal non-additive effects of genomic variants, such as dominance or epistasis effects, which have not been investigated well in this field. The novel machine-learning techniques will facilitate detecting such effects.

Recent Major Publications

Joshi PK, Esko T, Mattsson H, Eklund N, Gandin I, Nutile T, Jackson AU, Schurmann C, Smith AV, Zhang W, Okada Y, Stančáková A, Faul JD, Zhao W, Bartz TM, Concas MP, Franceschini N, Enroth S, Vitart V, Trompet S, Guo X, Chasman DI, O'Connel JR, Corre T, Nongmaithem SS, Chen Y, Mangino M, Ruggiero D, Traglia M, Farmaki AE, …, Kamatani Y, et al. Directional dominance on stature and cognition in diverse human populations. ***Nature*** 523, 459–62 (2015)

Okada Y, Momozawa Y, Ashikawa K, Kanai M, Matsuda K, Kamatani Y, Takahashi A, Kubo M. Construction of a population-specific HLA imputation reference panel and its application to Graves' disease risk in Japanese. ***Nat Genet*** 47, 798–802 (2015)

Debette S, Kamatani Y, Metso TM, Kloss M, Chauhan G, Engelter ST, Pezzini A, Thijs V, Markus HS, Dichgans M, Wolf C, Dittrich R, Touzé E, Southerland AM, Samson Y, Abboud S, Béjot Y, Caso V, Bersano A, Gschwendtner A, Sessa M, Cole J, Lamy C, Medeiros E, Beretta S, Bonati LH, Grau AJ, Michel P, Majersik JJ, Sharma P, et al. Common variation in PHACTR1 is associated with susceptibility to cervical artery dissection. ***Nat Genet*** 47, 78–83 (2015)

Invited Presentations

Kamatani Y. "The largest Asian GWAS of ischemic stroke" International Stroke Genetics Consortium 2016 (Boston, USA) May, 2016

Kamatani Y. "Finding disease susceptibility genes and genome cohort study" NGS Field 4th meeting (Tsukuba, Japan) June, 2015

Kamatani Y. "Statistical analyses used for gene mapping of human diseases" Tokyo Workshop on Statistically Sound Data Mining (Tokyo, Japan) February, 2015

Kamatani Y. "Missing heritability, and a premise in heritability estimates" The 3rd annual meeting of Informatics in Biology, Medicine and Pharmacology 2014 (Sendai, Japan) October, 2014.

Kamatani Y, "How genome cohort study could contribute to reveal disease susceptible genes?" The 58th annual meeting of Japanese Society of Human Genetics (Tokyo, Japan) November, 2013.

Laboratory for Pharmacogenomics

Group Director: Taisei Mushiroda

Recent Major Publications

Mushiroda T, Yanai H, Yoshiyama T, Sasaki Y, Okumura M, Ogata H, Tokunaga K. Development of a prediction system for anti-tuberculosis drug-induced liver injury in Japanese patients. ***Hum Gen Var*** 3, 16014 (2016)

Saito T, Ikeda M, Mushiroda T, Ozeki T, Kondo K, Shimasaki A, Kawase K, Hashimoto S, Yamamori H, Yasuda Y, Fujimoto M, Ohi K, Takeda M, Kamatani Y, Numata S, Ohmori T, Ueno SI, Makinodan M, Nishihata Y, Kubota M, Kimura T, Kanahara N, Hashimoto N, Fujita K, Nemoto K, Fukao T, Suwa T, Noda T, Yada Y, Takaki M, Kida N, Otsuru T, Murakami M, Takahashi A, Kubo M, Hashimoto R, Iwata N. Pharmacogenomic Study of Clozapine-Induced Agranulocytosis/Granulocytopenia in a Japanese Population. ***Biol Psychiatry*** (2016) in press

Low SK, Fukunaga K, Takahashi A, Matsuda K, Hongo F, Nakanishi H, Kitamura H, Inoue T, Kato Y, Tomita Y, Fukasawa S, Tanaka T, Nishimura K, Uemura H, Hara I, Fujisawa M, Matsuyama H, Hashine K, Tatsugami K, Enokida H, Kubo M, Miki T, Mushiroda, T. Association Study of a Functional Variant on ABCG2 Gene with Sunitinib-Induced Severe Adverse Drug Reaction. ***PLoS One*** 11, e0148177 (2016).

Invited Presentations

Mushiroda T, "Pharmacogenomics-based individualization of drug therapy" The 89th Annual Meeting of The Japanese Pharmacological Society (Yokohama, Japan) March, 2016

Mushiroda T, "Identification of genomic biomarkers associated with drug responses for individualization of drug therapy" The 36th Annual Meeting of The Japanese Society of Clinical Pharmacology and Therapeutics (Tokyo, Japan) December, 2015

Mushiroda T, "Clinical utility of genetic testing to avoid carbamazepine-induced skin rash" The 114th Annual Meeting of the Japanese Dermatological Association (Yokohama, Japan) May, 2015

Mushiroda T, "Prediction of risk of severe adverse drug reactions by genetic testing and validation of the clinical utility" The 32nd Annual Meeting of The Japaneseociety of Therapeutic Drug Monitoring (Matsumoto, Japan) May, 2015

Mushiroda T, "Individualization of anticancer therapeutics based on pharmacogenomics" The 2015 Golden Helix Symposium "Next-generation Pharmacogenomics" (Kuala Lumpur, Malaysia) March, 2015

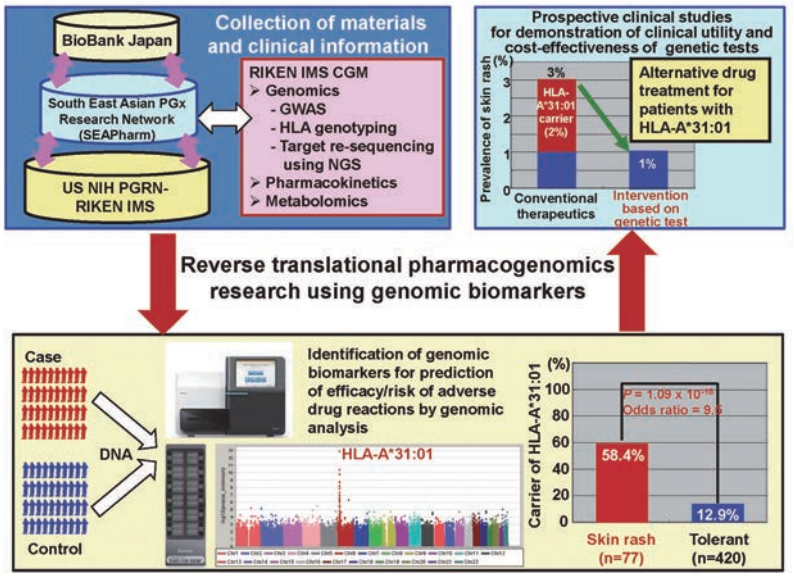


Figure: Scheme of reverse translational pharmacogenomics research for implementation of genetic tests in clinical practice.
We previously reported that carbamazepine-induced skin rash was strongly associated with the HLA-A*31:01 allele in Japanese patients. The GENCAT Study is being conducted in order to validate a prediction system for risk of carbamazepine-induced skin rash using a genetic test for HLA-A*31:01. The advanced genetic test for HLA-A*31:01 should significantly reduce the incidence of carbamazepine-induced skin rash in Japanese, indicating its clinical utility.

Responses to drugs vary widely. Lack of drug efficacy can lead to inadequate control of disease and is furthermore a waste of resources. Conversely, adverse drug reactions (ADRs) are frequent and often unpredictable. Many genetic polymorphisms have been identified in genes that affect efficacy or ADR risk for various drugs. In the USA, information on germline genomic biomarkers is available on FDA-approved drug labels. In particular, the US FDA strongly recommends genotyping for polymorphisms in drug-metabolizing enzymes and HLA alleles prior to administration of several drugs, such as eliglustat, nilotinib, pimozide, tetrabenazine, carbamazepine and lapatinib.

By using the samples from Biobank Japan, we are conducting pharmacogenomics (PGx) studies for the identification of genomic biomarkers useful for individualized therapeutics. However, it is difficult for individual countries acting alone to collect a sufficient number of samples for PGx research. Thus, we are conducting two international PGx collaborations, the South East Asian Pharmacogenomics Research Network (SEAPharm) and US NIH PGRN-RIKEN IMS. Since our mission is establishment of PGx-based individualization of drug therapy, the advantages of genomic biomarkers need to be demonstrated with respect to clinical validity, clinical utility and pharmacoeconomics by prospective clinical trials, leading to implementation of pharmacogenomics in clinical practice.

Laboratory for Cardiovascular Diseases

Group Director: Toshihiro Tanaka

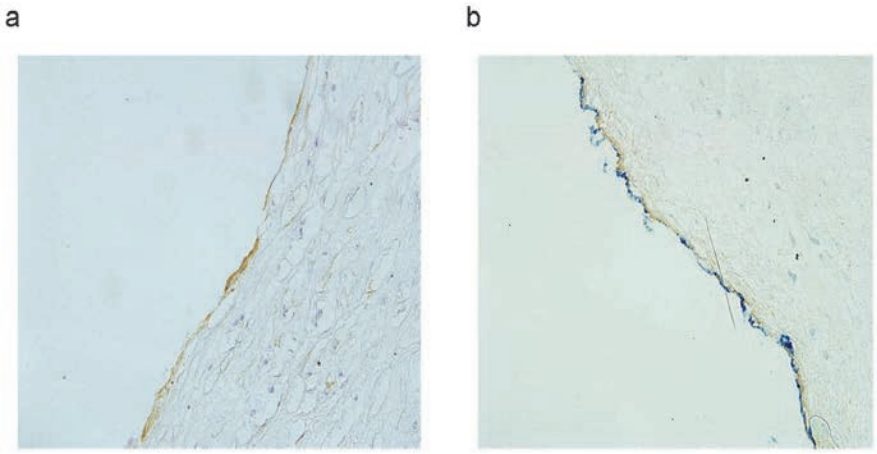


Figure: Immunohistochemistry of a coronary artery.
a: expression of FLT1 in endothelial cells (ECs), single staining, b: Co-localization of FLT1 (brown) and CD31 (blue) in ECs, double staining

Since cardiovascular diseases cause more than 15% of the deaths in the Japanese population and represent more than 20% of the total medical expenses in Japan, it is important for our society to discover the mechanisms underlying these disorders. We have been using comprehensive genetic analyses of the Japanese population followed by functional *in vitro* analyses, and have been among the first researchers to describe genetic background effects in myocardial infarction (MI), atrial fibrillation, Kawasaki disease, and peripheral artery disease. Our ultimate goal is to provide novel diagnostic/therapeutic approaches for such patients. To this end, we are expanding our research area from genetics to molecular biology, including *in vivo* analyses of genetically engineered mice. Also, we are making efforts to develop a new drug for MI that would elute from a coronary stent, which would be a powerful tool for coronary angioplasty.

Recent Major Publications

Onouchi Y, Fukazawa R, Yamamura K, Suzuki H, Kakimoto N, Suenaga T, Takeuchi T, Hamada H, Honda T, Yasukawa K, Terai M, Ebata R, Higashi K, Saji T, Kemmotsu Y, Takatsuki S, Ouchi K, Kishi F, Yoshikawa T, Nagai T, Hamamoto K, Sato Y, Honda A, Kobayashi H, Sato J, Shibuta S, Miyawaki M, Oishi K, Yamaga H, Aoyagi N, Yoshiyama M, Miyashita R, Murata Y, Fujino A, Ozaki K, Kawasaki T, Abe J, Seki M, Kobayashi T, Arakawa H, Ogawa S, Hara T, Hata A, Tanaka T. Variations in ORAI1 gene associated with Kawasaki disease. ***PLoS One*** 11, e0145486 (2016)

Konta A, Ozaki K, Sakata Y, Takahashi A, Morizono T, Suna S, Onouchi Y, Tsunoda T, Kubo M, Komuro I, Eishi Y, Tanaka T. A functional SNP in FLT1 increases risk of coronary artery disease in a Japanese population. ***J of Hum Genet*** 61, 435–41 (2016)

Matsukura M, Ozaki K, Takahashi A, Onouchi Y, Morizono T, Komai H, Shigematsu H, Kudo T, Inoue Y, Kimura H, Hosaka A, Shigematsu K, Miyata T, Watanabe T, Tsunoda T, Kubo M, Tanaka T. Genome-wide Association Study of Peripheral Arterial Disease in a Japanese Population. ***PLoS One*** 10, e0139262, 2015

Invited Presentations

Tanaka T. "Pharmacogenomics in Cardiology" University Seminar at Okayama University (Okayama, Japan) July, 2015

Tanaka T. "Genome Changes Medicine" Forum on Common Diseases and Cognitive Impairment (Kanazawa, Japan) December, 2015

Onouchi Y. "Susceptibility genes for Kawasaki Disease identified by genome-wide studies in Japan" 11th Congress of Asian Society for Pediatric Research (Osaka, Japan) April, 2015

Laboratory for Autoimmune Diseases

Team Leader: Kazuhiko Yamamoto

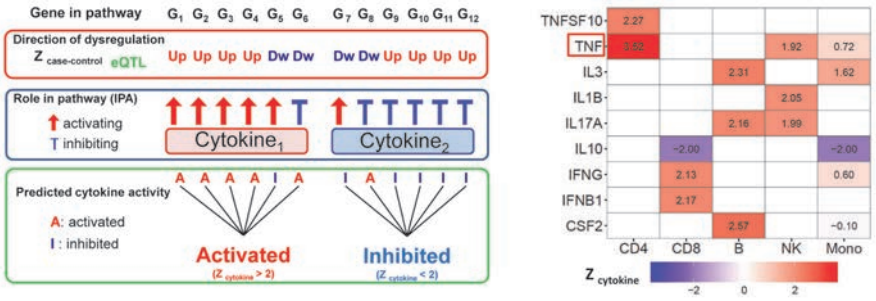


Figure: The strategy to predict cytokine pathway activity based on a cell- specific eQTL database. Left; We utilized upstream regulator analysis provide by Ingenuity Pathway Analysis (IPA). $Z_{case\text{-}control}$ and corresponding gene names were analyzed. When the direction of change in candidate causal genes ($Z_{case\text{-}control}$) is consistent with the activated state of the target cytokine, this gene is identified as an activating gene. The total effect of each gene on the target cytokine activity was summarized and $Z_{cytokine}$ was calculated by IPA. Right; Cell-type specific cytokine activity predicted in rheumatoid arthritis. Positive $Z_{cytokine}$ score indicates that the assessed cytokine is upregulated in RA and a negative score indicates that it is downregulated ($Z_{cytokine} < -2$ or > 2 correspond to p-value < 0.05).

Recent Major Publications

Sun C, Molineros EJ, Looger LL, Zhou X, Kim K, Okada Y, Ma J, Qi Y, Kim-H X, Motghare P, Bhattarai K, Adler A, Bang S-Y, Lee HS, Kim TH, Kang YM, Suh CH, Chung WT, Park YB, Choe JY, Shim SC, Kochi Y, Suzuki A, Kubo M, Sumida T, Yamamoto K, Lee SS, Kim YJ, Han BG, Dozmorov M, Kaufman MK, Wren DJ, Harley BJ, Shen N, Chua KH, Zhang H, Bae SC, Nath KS. High-density genotyping of immune-related loci identifies new SLE risk variants in individuals with Asian ancestry. ***Nat Genet*** 48, 323–330 (2016)

Yamamoto K, Okada Y, Suzuki A, Kochi Y. Genetics of rheumatoid arthritis in Asia—present and future. ***Nat Rev Rheumatol*** 11, 375–379 (2015)

Okada Y, Wu D, Trynka G et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. ***Nature*** 506, 376–381 (2014)

Invited Presentations

Yamamoto K. "Patogeneses and novel treatments of osteoporosis" Bangladesh Rheumatology Society (BRS) Conference-2015 (Dahka, Bangladesh) October, 2015

Yamamoto K. "Genetics and Epigenetics of Rheumatoid Arthritis" The 17th Asia Pacific League of Associations for Rheumatology Congress (Chennai, India) September, 2015

Yamamoto K. "Regulatory T cells in human disease" 11th International Congress on Systemic Lupus Erythematosus (Vienna, Austria) September, 2015

Yamamoto K. "A novel regulatory T cell subset controlling B cell functions: a combination of therapeutic cytokines" 7th International Forum on Rheumatoid Arthritis (IFRA) (Beijing, China) September, 2015

Yamamoto K. "From human immunology to next generation rheumatology" 59th Japan College of Rheumatology (Nagoya, Japan) April 2015

Most autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and Graves' disease, are multifactorial diseases involving both genetic and environmental factors. The aim of our laboratory is to elucidate the etiology of these autoimmune diseases by dissecting their genetic contributions. Furthermore, through functional analyses of disease-associated variants and genes together with epigenetic studies, we also clarify the mechanisms of disease pathogenesis. The majority of disease risk variants of complex traits and diseases are expression quantitative trait loci (eQTLs) and these eQTLs are working mostly in a cell type-specific manner. Therefore, subpopulations of immune related cells, such as T cells, B cells, dendritic cells, macrophages and others should be isolated and investigated. One advantage of research on immune mediated diseases is that we can relatively easily obtain such immune related cells from human subjects. Through genetic as well as informatics analyses on these samples, we are investigating the gene expression and functions of each subset of immune related cells and will dissect their roles in the global immune systems and in several autoimmune diseases.

Laboratory for Digestive Diseases

Team Leader: Kazuaki Chayama

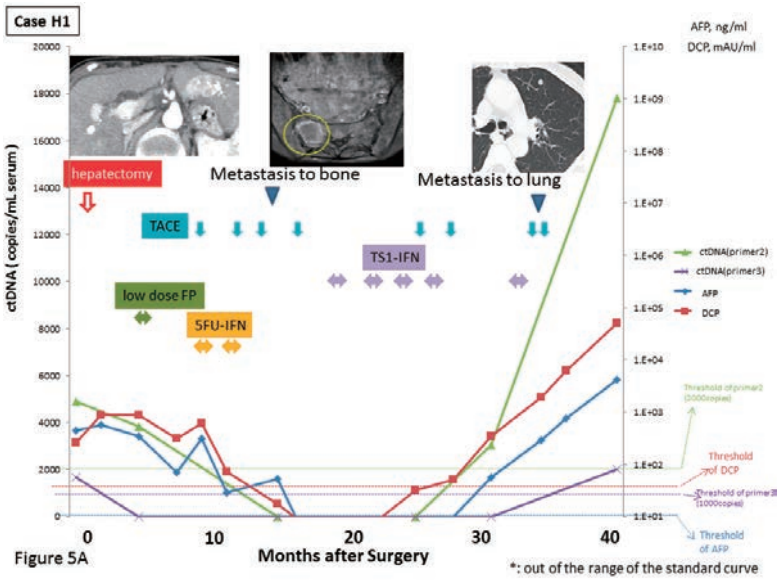


Figure: Monitoring of serial circulating tumor DNA (ctDNA) levels.
The ctDNA was quantified by real-time qPCR in sera serially sampled before and after surgery from a patient with positive ctDNA (case H1). The figure shows the time course of serum levels of ctDNA, alpha-fetoprotein (AFP), and des-gamma carboxy prothrombin (DCP) with clinical events and treatments. Levels of ctDNA are expressed as a ratio relative to levels of those obtained using DNA extracted from tumor tissue.

Figure 5A

Using a GWAS approach, our laboratory has primarily focused on investigating host genetic factors for various liver diseases, such as chronic HBV and HCV infection, HCV-induced liver cirrhosis and cancer, and responsiveness to therapy, including response to interferon therapy and ribavirin-induced anemia.

We have also participated in whole-genome sequencing analyses that have identified several recurrently mutated genes/pathways, HBV integration events, mutations in non-coding regions, and structural variations associated with liver cancer. By using WGS data, we analyzed circulating tumor DNA (ctDNA) to develop a non-invasive liquid biopsy in liver cancer. We found that ctDNA reflects tumor progression and that detection of ctDNA can predict microscopic vascular invasion of the portal vein and cancer recurrence.

We have now intensively investigated and verified how to apply this genetic information to clinical practice. We demonstrated that ribavirin dose reduction during telaprevir/ribavirin/peg-interferon triple therapy for genotype 1 chronic hepatitis C is able to overcome the risk of ribavirin-induced anemia in individuals with the *ITPA* polymorphism. We also found that polymorphism in the *IFNL4* locus predicts the outcome of simeprevir/ribavirin/peg-interferon triple therapy, a more recent treatment for chronic HCV, and that the *ITPA* polymorphism influences the decrease of hemoglobin during treatment.

We have studied not only the human genome but also the genome of the hepatitis C virus to predict and improve treatment response using *in vitro* and *in vivo* infection models. We found that the host *IFNL4* polymorphism was strongly associated with the HCV NS5A-Y93H resistance-associated variant, which confers drug resistance to the NS5A inhibitor class of direct-acting antiviral agents.

In addition, because our GWAS results highlight the importance of the immune system in the etiology of hepatitis B and C infection, we are currently investigating the host immune response to viral infection to elucidate the mechanism of hepatitis and carcinogenesis.

Recent Major Publications

Fujimoto A, Furuta M, Totoki Y, Tsunoda T, Kato M, Shiraishi Y, Tanaka H, Taniguchi H, Kawakami Y, Ueno M, Gotoh K, Ariizumi S, Wardell CP, Hayami S, Nakamura T, Aikata H, Arihiro K, Boroevich KA, Abe T, Nakano N, Maejima K, Sasaki-Oku A, Ohsawa A, Shibuya T, Nakamura H, Hama N, Hosoda F, Arai Y, Ohashi S, Urushidate T, Nagae G, Yamamoto S, Ueda H, Tatsuno K, Ojima H, Hiraoka N, Okusaka T, Kubo M, Marubashi S, Yamada T, Hirano S, Yamamoto M, Ohdan H, Shimada K, Ishikawa O, Yamaue H, Chayama K, Miyano S, Aburatani H, Shibata T, and Nakagawa H (corresponding). Whole genome mutational landscape and characterization of non-coding and structural mutations in liver cancer. ***Nat Genet*** 48, 500–509 (2016)

Fujimoto A, Furuta M, Shiraishi Y, Gotoh K, Kawakami Y, Arihiro K, Nakamura T, Ueno M, Ariizumi S, Nguyen HH, Shigemizu D, Abe T, Boroevich KA, Nakano K, Sasaki A, Kitada R, Maejima K, Yamamoto Y, Tanaka H, Shibuya T, Shibata T, Ojima H, Shimada K, Hayami S, Shigekawa Y, Aikata H, Ohdan H, Marubashi S, Yamada T, Kubo M, Hirano S, Ishikawa O, Yamamoto M, Yamaue H, Chayama K, Miyano S, Tsunoda T, Nakagawa H. Whole-genome mutational landscape of liver cancers displaying biliary phenotype reveals hepatitis impact and molecular diversity. ***Nat Commun*** 6, 6120 (2015)

Akamatsu S, Hayes CN, Ochi H, Uchida T, Kan H, Murakami E, Abe H, Tsuge M, Miki D, Akiyama R, Hiraga N, Imamura M, Aikata H, Kawaoka T, Kawakami Y, Chayama K. Association between variants in the interferon lambda 4 locus and substitutions in the hepatitis C virus non-structural protein 5A. ***J Hepatol*** 63, 554–563 (2015)

Invited Presentations

Chayama K. "HCV Treatment Update-a New Era of All-oral HCV Treatment" The 46th Annual Meeting of GEST and The 25th Annual Meeting of DEST (Taipei, Taiwan) March, 2016

Chayama K. "DAA/PR therapy in Asian HCV patients" Asian Pacific Digestive Week (Taipei, Taiwan) December, 2015

Chayama K. "All Oral Direct Acting Antiviral Therapy for Chronic Hepatitis C" Asia-Pacific Congress of Medical Virology (APCMV) (Taipei, Taiwan) October, 2015

Laboratory for
Bone and Joint Diseases

Team Leader: Shiro Ikegawa

Recent Major Publications

Guo L, Yamashita H, Kou I, Takimoto A, Meguro-Horike M, Horike S, Sakuma T, Miura S, Adachi T, Yamamoto T, Ikegawa S, Hiraki Y, Shukunami C. Functional investigation of a non-coding variant associated with adolescent idiopathic scoliosis in zebrafish: elevated expression of the ladybird homeobox gene causes body axis deformation. ***PLoS Genet*** 12, e1005802 (2016)

Ogura Y, Kou I, Miura S, Takahashi A, Xu L, Takeda K, Takahashi Y, Kono K, Kawakami N, Uno K, Ito M, Minami S, Yonezawa I, Yanagida H, Taneichi H, Zhu Z, Tsuji T, Suzuki T, Sudo H, Kotani T, Watanabe K, Hosogane N, Okada E, Iida A, Nakajima M, Sudo A, Chiba K, Hiraki Y, Toyama Y, Qiu Y, Shukunami C, Kamatani Y, Kubo M, Matsumoto M, Ikegawa S. A functional SNP in BNC2 is associated with adolescent idiopathic scoliosis. ***Am J Hum Genet*** 97, 337–42 (2015)

Sharma S, Londono D, Eckalbar WL, Gao X, Zhang D, Mauldin K, Kou I, Takahashi A, Matsumoto M, Kamiya N, Murphy KK, Cornelia R; TSRHC Scoliosis Clinical Group; Japan Scoliosis Clinical Research Group, Herring JA, Burns D, Ahituv N, Ikegawa S, Gordon D, Wise CA. A PAX1 enhancer locus is associated with susceptibility to idiopathic scoliosis in females. ***Nat Commun*** 6, 6452 (2015)

Invited Presentations

Ikegawa S. "How to identify disease genes in skeletal dysplasias" Third Scandinavian Skeletal Dysplasia Workshop (Oslo, Norway) March, 2016

Ikegawa S. "Genome study of bone and joint diseases" 10th International Congress of Chinese Orthopedic Association (Chongqing, China) November, 2015

Ikegawa S. "Genetic study of common bone and joint disease" 2015 Annual Meeting of Chinese Joint Surgery (Xi'an, China) September, 2015

Ikegawa S. "Combined genetics for rare and common bone and joint diseases" 12th International Skeletal Dysplasia Society Meeting (ISDS) (Istanbul, Turkey) July, 2015

Ikegawa S. "Rare disorders and common problems in the age of deep sequencing" 9th Annual Introductory Course on Skeletal Dysplasias (Lausanne, Switzerland) July, 2015

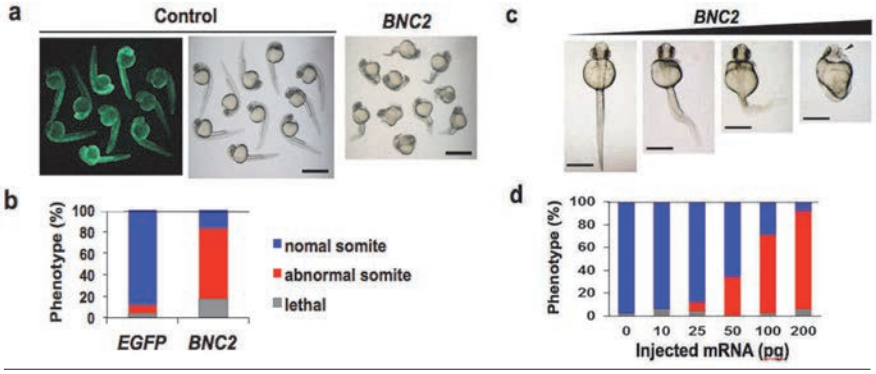


Figure: Over-expression of BNC2 in zebrafish embryos.
a) Embryos (24 hpf) over-expressing *EGFP* (control) and *BNC2* by tol2-mediated transgenesis. Ubiquitous transgene expression was confirmed by green fluorescence (left). The *BNC2* transgenic embryos exhibit severe body curvature and malformation of the somite. Scale bars, 1 mm. b) Quantification of phenotypes of embryos over-expressing *EGFP* (control) or *BNC2*. The percentage of the number of embryos that died by 24 hpf (lethal), that had the deformed somites with body curvature (abnormal somite), and that had no apparent abnormality in the somites (normal somite). c) Zebrafish embryos injected with increasing doses of *BNC2* mRNA. The mRNA injection caused body curvature and severe malformation of the somites in a dose-dependent manner. Arrowhead: delayed pigmentation of the embryo injected with the mRNA at the higher doses (100 and 200 pg). Scale bars, 500 μm. d) Quantification of phenotypes of embryos injected with *BNC2* mRNA

We are working on genetic diseases of bone and joints, both common polygenic and rare monogenic diseases.

1) Genomic Study of Common Diseases

Common bone and joint diseases have become serious concerns for the world health and economy, as exemplified by the WHO initiative "Bone and Joint Decade" (2000–2010). We are searching for susceptibility genes for common (polygenic) bone and joint diseases including osteoarthritis (OA), lumbar disc disease (LDD)/herniation (LDH), osteoporosis, avascular necrosis of the femoral head (ANF), scoliosis, and ossification of the posterior longitudinal ligament of the spine (OPLL).

Through genome-wide association studies (GWASs) and next-generation sequencing approaches, we identify and characterize susceptibility genes, and clarify their disease-causing mechanism at the molecular level. Using the genome information obtained by these studies, we will realize our final goal, "order-made medicine". GWASs for OA, LDD/LDH, adolescent idiopathic scoliosis (AIS), OPLL, and ANF are in progress, and some of them have already succeeded in identification of susceptibility genes. Functional studies of the genes *in vitro* and using animal model are underway.

2) Genomic Study of Skeletal Dysplasia

Skeletal dysplasia is a group of heritable (monogenic) disorders affecting the skeleton, with more than 400 diseases belonging to this category. Skeletal dysplasia is an intractable disease and so many patients are waiting for treatment. We are engaging in the clinical and basic study of these difficult diseases. By large-scale mutation screening, including exome sequencing, we are identifying the disease genes.

Though analysis of their phenotypes and diseases genes, we approach molecular mechanisms of bone and joint formation, pathogenesis of common bone and joint diseases, as well as the diagnosis and treatment of these crippling diseases ('nan-byo'). Using the disease genes for skeletal dysplasia as candidate genes, we are performing association studies for the corresponding common bone and joint diseases.

Laboratory for Endocrinology, Metabolism and Kidney Diseases

Team Leader: **Shiro Maeda**

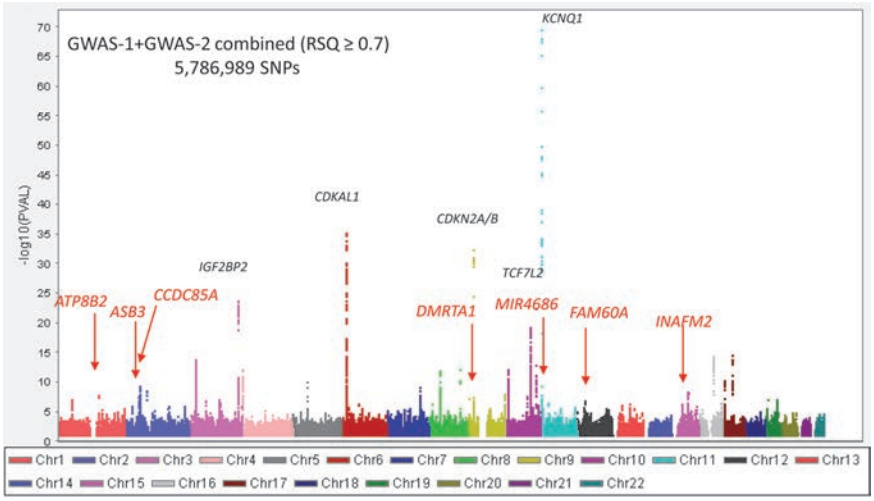


Figure: Results of GWAS meta-analysis for type 2 diabetes in the Japanese population (15,463 patients with type 2 diabetes vs. 26,183 controls). Previously identified loci are in black and the seven novel loci identified in this study are shown in red.

The total number of individuals with diabetes mellitus is estimated to be over 422 million worldwide, and its prevalence continues to increase in many countries, including Japan. The increasing incidence of diabetic microvascular complications such as nephropathy and retinopathy, especially among patients with type 2 diabetes, which accounts for over 90 % of patients with diabetes, is also a serious worldwide concern in terms of both poor prognosis and medical costs. Although the precise mechanisms underlying the development and progression of type 2 diabetes or diabetic microvascular complications have not been elucidated, it is thought that genetic factors play an important role in the pathogenesis. Introduction of genome-wide association studies (GWAS) has brought a significant breakthrough in genetic studies of several common diseases, and over susceptibility 50 loci for type 2 diabetes have been identified as of 2012. However, integration of this genetic information can explain only ~10 % of disease susceptibility, and thus most of the heritability of type 2 diabetes still remains unidentified. GWAS for diabetic nephropathy or retinopathy have also been performed by several groups, including ours, but worldwide efforts to identify susceptibility to these diabetic complications have not met with clear success. Therefore, we have been attempting to expanded GWAS for type 2 diabetes, diabetic nephropathy and diabetic retinopathy to identify additional susceptibility loci.

Autosomal dominant polycystic kidney disease (ADPKD) is a common hereditary kidney disease, and most of its heritability can be explained by mutations in *PKD1* and *PKD2*. The prevalence of ADPKD in patients undergoing chronic renal replacement therapy is between 3.4 and 12.2 %, and the prevalence of clinically diagnosed ADPKD is 1 per 1000~4033. It has been suggested that genetic factors are a powerful indicator of renal prognosis in patients with ADPKD. However, most of the available findings on the molecular basis of ADPKD have been obtained from studies of European and American populations, and there are limited data on ADPKD in East Asian populations, including Japanese. To investigate the genotypic and phenotypic characteristics of ADPKD in Japanese patients, we performed a comprehensive search for *PKD1* and *PKD2* mutations in Japanese ADPKD patients.

Recent Major Publications

Imamura M, Takahashi A, Yamauchi T, Hara K, Yasuda K, Grarup N, Zhao W, Wang X, Huerta-Chagoya A, Hu C, Moon S, Long J, Kwak SH, Rasheed A, Saxena R, Ma RCW, Okada Y, Iwata M, Hosoe J, Shojima N, Iwasaki M, Fujita H, Suzuki K, Danesh J, Jørgensen T, Jørgensen ME, Witte DR, Brandslund I, Christensen C, Hansen T, Mercader JM, Flannick J, Moreno-Macías H, Burtt NP, Zhang R, Kim YJ, Zheng W, Singh JR, Tam CHT, Hirose H, Maegawa H, Ito C, Kaku K, Watada H, Tanaka Y, Tobe K, Kawamori R, Kubo M, Cho YS, Chan JCN, Sanghera D, Frossard P, Park KS, Shu X-O, Kim B-J, Florez JC, Tusié-Luna T, Jia W, Tai ES, Pedersen O, Saleheen D, Maeda S and Kadowaki T. Genome-wide association studies in the Japanese population identify seven novel loci for type 2 diabetes. ***Nat Commun*** 7, 10531 (2016)

Hara K, Fujita H, Johnson TA, Yamauchi T, Yasuda K, Horikoshi M, Peng C, Hu C, Ma RC, Imamura M, Iwata M, Tsunoda T, Morizono T, Shojima N, So WY, Leung TF, Kwan P, Zhang R, Wang J, Yu W, Maegawa H, Hirose H; DIAGRAM consortium, Kaku K, Ito C, Watada H, Tanaka Y, Tobe K, Kashiwagi A, Kawamori R, Jia W, Chan JC, Teo YY, Shyong TE, Kamatani N, Kubo M, Maeda S, Kadowaki T. Genome-Wide Association Study Identifies Three Novel Loci for Type 2 Diabetes. ***Hum Mol Genet*** 23, 239–246 (2014)

Imamura M, Shigemizu D, Tsunoda T, Iwata M, Maegawa H, Watada H, Hirose H, Tanaka Y, Tobe K, Kaku K, Kashiwagi A, Kawamori R and Maeda S. Assessing the clinical utility of a genetic risk score constructed using 49 susceptibility alleles for type 2 diabetes in a Japanese population. ***J Clin Endocrinol Metab*** 98, E1667–1673 (2013)

Invited Presentations

Maeda S. "Genetic Study of type 2 diabetes in Japan" 2016 International Biomedecal Interface Symposium (Taipei, Taiwan) March, 2016

Imamura M. 58th Annual Meeting of Japan Diabetes Society (Shimonoseki, Japan) May, 2015

Laboratory for Respiratory and Allergic Diseases

Team Leader: Mayumi Tamari

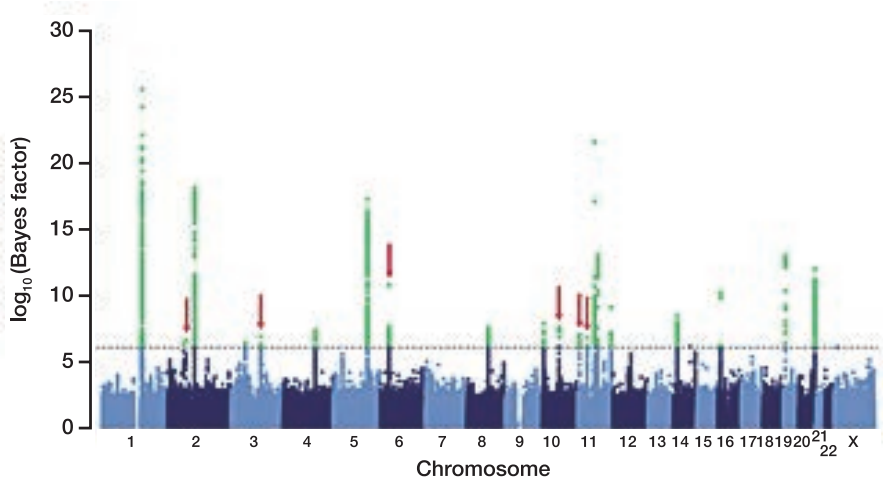


Figure: Manhattan plot of the multi-ancestry MANTRA analysis of atopic dermatitis.
Arrows indicate variants not associated in the European-only analysis. The dotted horizontal line shows the significance threshold for this study, $\log_{10}$ (Bayes factor) = 6.1.

Recent Major Publications

EArly Genetics and Lifecourse Epidemiology (EAGLE) Eczema Consortium. Multi-ancestry genome-wide association study of 21,000 cases and 95,000 controls identifies new risk loci for atopic dermatitis. ***Nat Genet*** 47, 1449–1456 (2015)

Tomita K, Sakashita M, Hirota T, Tanaka S, Masuyama K, Yamada T, Fujieda S, Miyatake A, Hizawa N, Kubo M, Nakamura Y, Tamari M. Variants in the 17q21 asthma susceptibility locus are associated with allergic rhinitis in the Japanese population. ***Allergy*** 68, 92–100 (2013)

Ellinghaus D, Baurecht H, Esparza-Gordillo J, Rodríguez E, Matanovic A, Marenholz I, Hübner N, Schaarschmidt H, Novak N, Michel S, Maintz L, Werfel T, Meyer-Hoffert U, Hotze M, Prokisch H, Heim K, Herder C, Hirota T, Tamari M, Kubo M, Takahashi A, Nakamura Y, Tsoi LC, Stuart P, Elder JT, Sun L, Zuo X, Yang S, Zhang X, Hoffmann P, Nöthen MM, Fölster-Holst R, Winkelmann J, Illig T, Boehm BO, Duerr RH, Büning C, Brand S, Glas J, McAleer MA, Fahy CM, Kabesch M, Brown S, McLean WH, Irvine AD, Schreiber S, Lee YA, Franke A, Weidinger S. High-density genotyping study identifies four new susceptibility loci for atopic dermatitis. ***Nat Genet*** 45, 808–812 (2013)

Invited Presentations

Tamari M. "The Most Important Cause of Asthma in Children" WAC XXIV World Allergy Congress (Seoul, Korea) October, 2015

Tamari M. Genome-Wide Association Study of Allergic Diseases, Plenary Lecture, The Annual Meeting of the 50th Japanese Society of Pediatric Allergy and Clinical Immunology (Kanagawa Japan) October, 2013

Tamari M. "Genomics in Allergic Disease" Symposium 24 World Allergy Forum, Omics in Allergic Disease, European Academy of Allergy and Clinical Immunology & World Allergy Organization World Allergy & Asthma Congress (Milan, Italy) June, 2013

Tamari M. "Genome-Wide Association Study of Allergic Diseases" 8th RCAI-JSI International Symposium on Immunology 2013, Interface between Immune System and Environment (Kanagawa, Japan) June, 2013

Tamari M. "Genetic Study of Allergic Diseases" Taiwan-Japan Joint Symposium on BioBank and Genomic Medicine in Academia Sinica (Taipei, Taiwan) May, 2013

The aim of our project is to explore genetic components of respiratory and allergic diseases. Genome-wide association study (GWAS) is a hypothesis-free method to comprehensively assess genes underlying susceptibility to human diseases. Through GWAS and functional analyses, we have identified several genetic factors for bronchial asthma and atopic dermatitis, and the findings of these studies improve our understanding of the complex heterogeneity of allergic diseases. We participate in the global consortium for meta-analysis of GWASs of atopic dermatitis (AD). In 2015, a multi-ancestry AD GWAS of 21,000 cases and 95,000 controls including our Japanese data set has been reported. The study identified a total of 10 new risk loci for AD in Europeans, and six of the 10 loci (*PPP2R3C, ETS1, C1orf51/MRPS21, MIR5708/ABTB10, IL15RA/IL2RA* and *PUS10*) reached genome-wide significance across studies of all ancestry groups. With these new ones, a total of 31 AD risk loci have been identified. Interestingly, the 3q13.2 (*CCDC80*) and 11p15.4 (*OR10A3/NLRP10*) loci are likely to be Japanese-specific signals. Candidate genes at the new loci suggest roles for regulation of innate host defenses and T cell functions in the pathogenesis of AD. We also participate in the Global Alliance between the U.S. NIH Pharmacogenetics Research Network (PGRN) and RIKEN IMS. In this international collaboration, we have conducted pharmacogenomics GWASs and identified several loci that are associated with treatment responses in subjects with asthma or pulmonary arterial hypertension. To contribute to the development of better treatment and preventive strategies, we will conduct further cross-disciplinary studies combining genetics, immunology and clinical epidemiology for translation of our research into clinical practice.

Program for Medical Innovations

Six original projects for clinical applications have been performed in 2013: 1) A biochemical drug using a PEGylated Cryj-1/2 fusion recombinant protein for Cedar Pollinosis has been developed by the Torii pharmaceutical company and IMS and introduced to the Japanese market. 2) A chemical compound recently developed using the α-galactosylceramide (α-GalCer) analog, RCAI-X, selectively induces apoptosis of IgE but not IgG B cells and preferentially suppresses IgE production. It therefore potentially could be applied to any type of allergic disorder, such as pollinosis, food allergy, as well as allergic asthma. 3) NKT cell-targeted therapy for head and neck tumors has been done in collaboration with Chiba University, and was authorized by the Japanese government as Advanced Medical Treatment B in 2013. 4) The artificial adjuvant vector cell as an anti-tumor vaccine project has been accepted by the translational research network program and developed. This vaccine can be dosed with tumor antigen mRNA together with α-GalCer, so that it activates both innate and acquired protective immunity and also induces long-term memory. 5) The human iPS project for clinical use of *in vitro* generated NKT cells has been accepted as a Center for Clinical Application Research (Type B) in the Research Center Network for Realization of Regenerative Medicine, Japan in 2013. 6) A humanized mouse model for MLL gene-rearranged leukemia was established. Also, certain genes were identified that are differentially expressed between normal stem cells and leukemic stem cells.

Laboratory for Immune Regulation

Group Director: Masaru Taniguchi

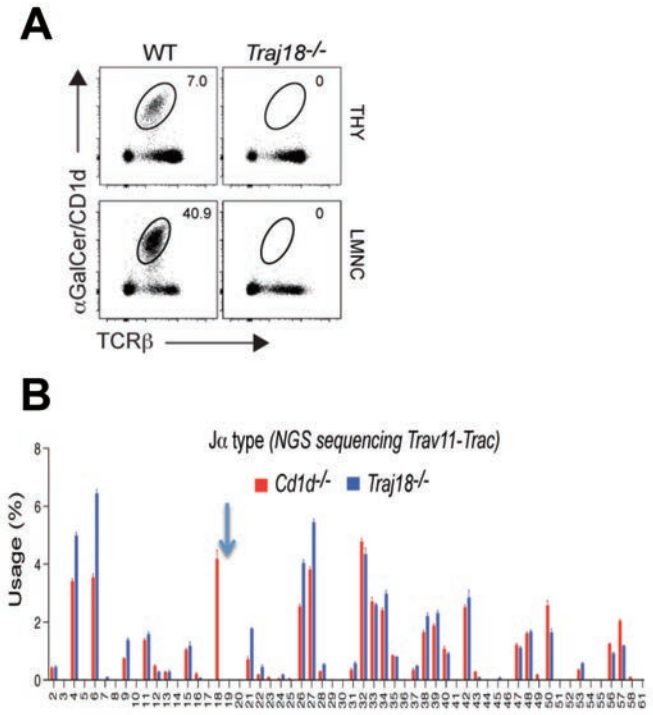


Figure: Generation of novel *Traj18*-deficient mice lacking Vα14 NKT cells with an undisturbed TCRα chain repertoire.
(A) Newly generated *Traj18*-deficient mice lack Vα14 NKT cells by flow cytometry analysis. Numbers indicate percentage of αGC/CD1d dimer$^+$ TCRβ$^+$ NKT cells.
(B) Undisturbed Jα gene usage in newly generated *Traj18*-deficient mice as revealed by next generation sequencing. Bars indicate the percentage of productive *Traj* gene transcripts in *Cd1d*$^{-/-}$ (red bars) and *Traj18*$^{-/-}$ (blue bars) CD4$^+$CD8$^+$ thymocytes. The blue arrow indicates the exclusive absence of *Traj18* gene expression in the *Traj18*$^{-/-}$ mice.

NKT cells are characterized by their expression of an invariant T cell receptor (TCR) α chain encoded by Vα14Jα18 in mouse and Vα24Jα18 in humans, which recognizes glycolipid antigens in association with the non-classical MHC I, CD1d molecule. In order to achieve highly effective immune responses, NKT cell-mediated adjuvant activity is essential. In our laboratory, we had been working to clarify the mechanisms of NKT cell development and function, and also to establish novel NKT cell-targeted immunotherapy for the treatment of any type of cancers.

Based on current models of NKT cell development, NKT cells are derived from DP thymocytes similar to conventional T cells. However, we identified a novel NKT cell developmental pathway originating from late DN stage precursors that bypasses the DP stage, as judged by the following: 1) RORγt, which is essential for maintenance of NKT cells at DP stage, was not necessary for DN NKT cell development. 2) Conditional deletion of the *Rag2* gene controlled by DP-specific E8III-Cre resulted in the loss of Vα14-Jα18 mRNA in DP stage cells but not in DN stage cells, suggesting that NKT cells detected in Rag2-cKO mice are derived from DN stage precursors. 3) Fate-mapping studies using ROSA26-YFP controlled by DP-specific E8III-Cre revealed the presence of YFP-negative NKT cells, suggesting that these NKT cells developed directly from the DN stage bypassing the DP stage. 4) The out-of-frame Vα14-Jα18 sequences were significantly detected in the DN fraction of RAG2-cKO mice.

NKT cells mediate adjuvant activity and can activate both CD8 cytotoxic T cells to kill MHC-class I positive tumor cells and also NK cells to eliminate MHC-negative tumors at the same time. The project on the development of an immunotherapy using a novel NKT ligand was approved in 2015 as a Translational Research Network Program. We generated and selected a novel glycolipid, RK-X, which induces strong NKT-mediated adjuvant activity and tumor rejection in mice.

Recent Major Publications

Dashtsoodol N, Shigeura T, Ozawa R, Harada M, Kojo S, Watanabe T, Koseki H, Nakayama M, Ohara O, Taniguchi M. Generation of Novel Traj18-deficient Mice Lacking V 14 Natural Killer T Cells with an Undisturbed T Cell Receptor -Chain Repertoire. ***Plos One*** 11, e0153347 (2016)

Taniguchi M, Harada M, Dashtsoodol N, Kojo S. Discovery of NKT cells and development of NKT cell-targeted anti-tumor immunotherapy. ***Proc Jpn Acad Ser B Phys Biol Sci*** 91, 292–304 (2015)

Fujii S, Shimizu K, Okamoto Y, Kunii N, Nakayama T, Motohashi S, Taniguchi M. NKT Cells as an Ideal Anti-Tumor Immunotherapeutic. ***Front Immunol*** 4, 409 (2013)

Invited Presentations

Taniguchi M. "Alternative developmental pathway of a Va14+ NKT cell subset bypassing CD4+CD8+ double positive stage" 2015 CD1-MR1 (Lorne, Australia) November, 2015

Taniguchi M. "NKT cell -mediated adjuvant cell therapy on lung cancer and head and neck cancer" FOCIS 2014 (Chicago, USA) June, 2014

Taniguchi M. "Discovery of NKT cells and their clinical application" 12th International Symposium on Sjögren's Syndrome (Kyoto, Japan) October, 2013

Taniguchi M. "Characterization of the cell with NKT cell potential in DN1 thymic fraction" 7th International Symposium on CD1 and NKT Cell (Tours, France) September, 2013

Taniguchi M. "NKT cells as an ideal target for anti-tumor immunotherapy" 15th International Congress of Immunology (Milan, Italy) August, 2013

Laboratory for Immunotherapy

Team Leader: Shin-ichiro Fujii

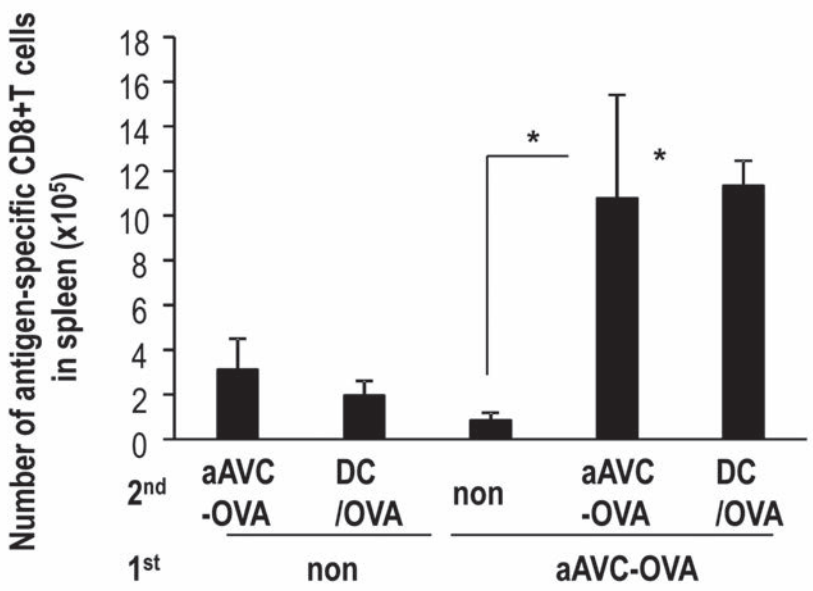


Figure: Secondary response of memory T cells in aAVC vaccinated mice.
C57BL/6 mice were vaccinated with aAVC-OVA (α-GalCer loaded, CD1d-expressing NIH3T3 cells transfected with OVA mRNA)(1st). Antigen-specific CD8+T cells were maintained in aAVC-OVA vaccinated mice 6 month later. Mice were challenged with aAVC-OVA or DC pulsed with OVA peptide (DC/pep) and robust expansion of antigen-specific T cells was observed.

The aims of the laboratory are to extend basic studies for advancing immunotherapy and translational research, from basic studies back and forth to the bedside in the field of cancer and the control of other diseases. For this purpose, we have been focusing on the following 5 projects related to NKT cells. The synthetic glycolipid, α-galactosylceramide (α-GalCer) as an NKT cell ligand is presented by CD1d molecules to invariant NKT lymphocytes. When NKT cells were activated in this way, they showed unique immunostimulatory features for innate immunity. First, as a basic study, we have recently identified memory like KLRG1+NKT cells and have been characterizing them in terms of intrinsic and extrinsic factors (project 1). Additionally, we have been developing translational research projects to establish therapeutic strategies to generate strong antitumor immunity. We previously reported the full maturation of DCs soon after the activation of NKT cells *in vivo*. Based on this observation, we have developed and established artificial adjuvant vector cells (aAVC) as a new type of drug delivery system composed of NKT cell ligand and tumor-associated antigen. We have been elucidating the mechanisms by which aAVC can augment antitumor effects (project 2). Since this project has also been accepted by the RIKEN Translational Program and Translational Research center program at Tokyo University, we are making efforts in translational research toward eventual clinical trials (project 3). As project 4, we work toward the establishment of iPS-NKT cells to develop an iPS-NKT cell transfer strategy, in a collaborative study with the RIKEN iPS-group. In this project, our group plays a role in the preparation of primary NKT cells as starting material for generating NKT cell-derived iPS cells, and analyzing the function of the iPS-derived NKT cells. As a final project (project 5), we have been working on a joint clinical phase I /IIa study of NKT cell therapy for early stage post-operative lung cancer patients with the National Hospital Organization (NHO). In this study, our role is the analyses of immune cells in the trial and also, in collaboration with the RIKEN IMS Genomic Medicine, SNP analysis of responder and poor-responder groups to find suitable biomarkers.

Recent Major Publications

Shimizu K, Yamasaki S, Shinga J, Sato Y, Watanabe T, Ohara O, Kuzushima K, Yagita H, Komuro Y, Asakura M, Fujii S*. Systemic and potent DC activation modulates the tumor microenvironment and shapes the long-lived tumor specific memory CD8+ T cells. ***Cancer Res*** (in press)

Sato Y, Shimizu K, Shinga J, Hidaka M, Kawano F, Kakimi K, Yamasaki S, Asakura M, Fujii S*. Characterization of the myeloid-derived suppressor cell subset regulated by NK cells in malignant lymphoma. ***Oncoimmunol*** 4, e995541 (2014)

Shimizu K, Sato Y, Shinga J, Watanabe T, Endo T, Asakura M, Yamasaki S, Kawahara K, Kinjo Y, Kitamura H, Watarai H, Ishii Y, Tsuji M, Taniguchi M, Ohara O, Fujii S*. KLRG+ invariant natural killer T cells are long-lived effectors. ***Proc Natl Acad Sci U S A*** 111, 12474–12479 (2014)

Invited Presentations

Fujii S. "Development of new type of cancer vaccine for establishment of immune surveillance against cancer" Scientific seminar for RIKEN centennial anniversary of foundation (Tokyo, Japan) November, 2015

Fujii S. "Development of Novel Type of Cancer Vaccine "aAVC" in RIKEN Drug Discovery and Medical Technology Platforms" The 74th Annual Meeting of The Japanese Cancer Association (Nagoya, Japan) October, 2015

Fujii S. "Immunological memory and antitumor immunity elicited by artificial adjuvant vector cells for cancer immunotherapy." The 43rd Annual Meeting of the Japanese Society for Immunology (JSI) (Kyoto, Japan) December, 2014

Fujii S. "Development of new type of tumor immunotherapy utilizing NKT-licensed dendritic cells "artificial adjuvant vector cells. The 6th Society of Immunotherapy for Hematological Disorders (Kyoto, Japan) September, 2014

Fujii S. "Development of a Novel Type of Cancer Vaccine Linking Innate and Adaptive immunity." The 22nd International Symposium on Molecular Cell Biology of Macrophages (MMCB2014) (Kobe, JAPAN) June, 2014

Laboratory for Vaccine Design

Team Leader: Yasuyuki Ishii

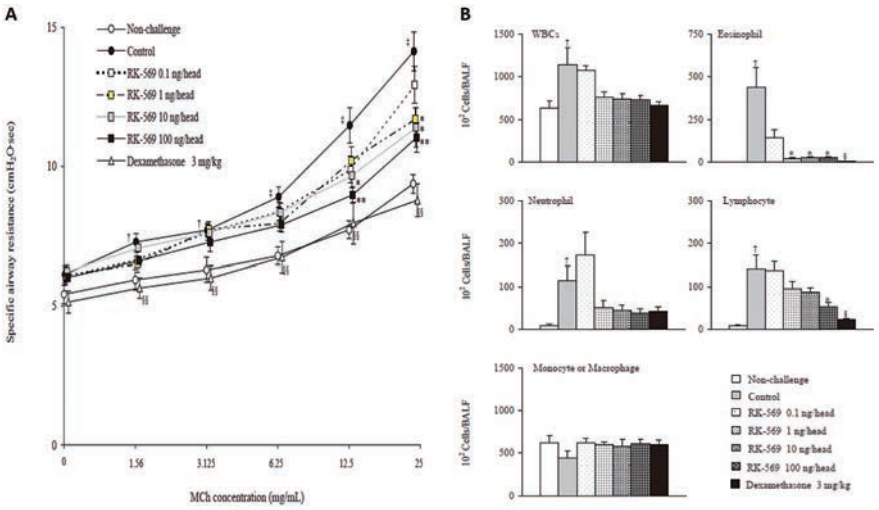


Figure: Effects of liposomal RK-141 (RK-569) and Dexamethasone on airway hyperresponsiveness (AHR) and infiltration of inflammatory cells in bronchoalveolar lavage fluid (BALF) induced by ovalbumin (OVA) inhalation challenge in OVA-sensitized mice.
BALB/c mice were intraperitoneally immunized with OVA/alum three times weekly. The mice were randomized by serum IgE antibody titers at 7 days after the final immunization and then treated with two rounds of intravenous injection of RK-569 at the indicated doses or with Dexamethasone one day before challenge with six consecutive OVA inhalation treatments. AHR and the number of cells in BALF were assessed one day after the last challenge. (A) Airway resistance after methacholine (MCh) inhalation was measured by double chamber plethysmography. Data are the mean±SE of 6 mice. Student's t-test was performed to compare the non-challenge group with the control group ($^{\dagger}p<0.05$, $^{\ddagger}p<0.01$) Dunnett's test was performed to compare the control group with the RK-569 groups ($*p<0.05$, $**p<0.01$) Student's t-test was performed to compare the control group with the dexamethasone group ($^{\parallel}p<0.01$) (B) The total volume of each BALF suspension was adjusted to 1 mL with saline, and cell numbers/μL were calculated. Data are the mean±SE of 5 or 6 mice. Student's/Aspin-Welch's t-test was performed to compare the non-challenge group with the control group ($^{\dagger}p<0.05$) Dunnett's/Steel's test was performed to compare the control group with the RK-569 groups ($*p<0.05$) Student's/Aspin-Welch's t-test was performed to compare the control group with the dexamethasone group ($^{\parallel}p<0.05$)

Natural killer T (NKT) cells play important immunoregulatory roles, such as suppression of IgE responses, as well as having immuno-stimulatory adjuvant effects in host defense. Although the mechanisms of immune activation by NKT cells are fairly well understood, those mediating immune suppression have remained unclear. In our previous studies, we showed that a liposome formulation of α-galactosylceramide (α-GalCer), the prototypical NKT cell ligand, was preferentially delivered to a splenic B220-positive cell subset. As this subset included IgE-expressing B cells, IL-21 derived from NKT cells was involved in the induction of B cell-specific apoptosis and, ultimately, IgE isotype-specific suppression. To develop α-GalCer into an IgE-suppressive drug, we screened analogues and formulations by assessing IL-21 expression by NKT cells from mice injected intravenously with liposomal derivatives. An optimized liposomal α-GalCer analogue designated RK-141 was screened and assessed for *in vivo* efficacy and safety in a mouse experimental asthma model. An intravenous RK-141 injection just one day before a course of antigen-challenge resulted in the suppression of serum chemokines and pro-inflammatory cytokines such as eotaxin, keratinocyte-derived chemokine (KC), IL-5 and IL-13. After the full course of challenge, both airway hyperresponsiveness (AHR) and eosinophil/neutrophil infiltration in bronchoalveolar lavage fluid (BALF) were significantly suppressed (Figure). Surprisingly, after the antigen challenges, the IgE antibody level in BAL fluid, rather than in serum, was significantly suppressed, suggesting that systemic administration of liposomal RK-141 might preferentially suppress regional IgE production in antigen-exposed local organs, a highly beneficial pharmacological outcome. Liposomal RK-141 is now being developed as a project of the RIKEN Program for Drug Discovery and Medical Technology Platforms.

Recent Major Publications

Hirai T, Ishii R, Miyairi S, Ikemiyagi M, Omoto K, Ishii Y, Tanabe K. Clonal Deletion Established via Invariant NKT Cell Activation and Costimulatory Blockade Requires In Vivo Expansion of Regulatory T Cells. ***Am J Transplant*** 16, 426–439 (2016)

Hirai T, Ishii Y, Ikemiyagi M, Fukuda E, Omoto K, Namiki M, Taniguchi M, Tanabe K. A Novel approach inducing transplant tolerance by activated invariant natural killer T cells with costimulatory blockade. ***Am J Transplant*** 14, 554–567 (2014)

Shimizu K, Sato Y, Shinga J, Watanabe T, Endo T, Asakura M, Yamasaki S, Kawahara K, Kinjo Y, Kitamura H, Watarai H, Ishii Y, Tsuji M, Taniguchi M, Ohara O, Fujii S. KLRG+ invariant natural killer T cells are long-lived effectors. ***Proc Natl Acad Sci U S A*** 111,12474–12479 (2014)

Laboratory for Allergic Disease

Team Leader: Toshiaki Kawakami

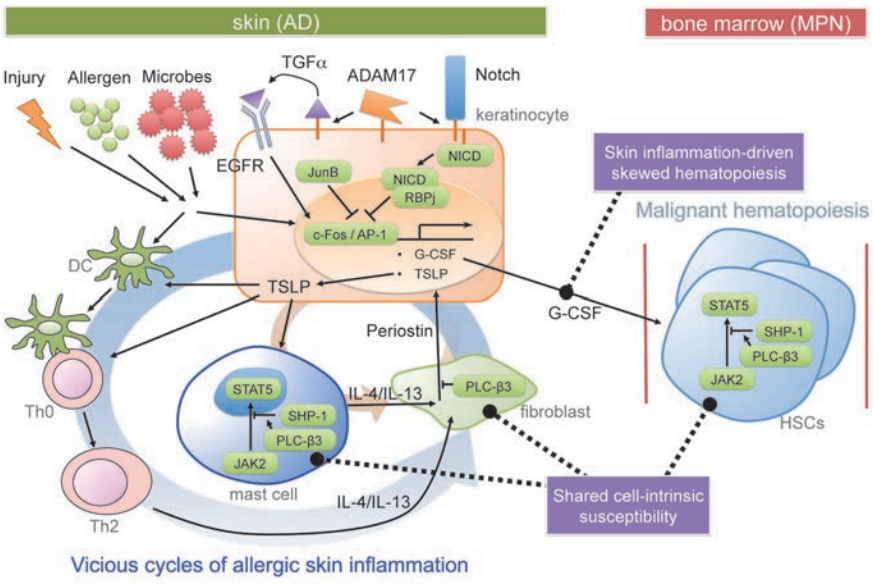


Figure: Pathogenic mechanisms for the hypothetical AD-Myeloproliferative Neoplasm (MPN) Syndrome.
Keratinocyte-derived TSLP together with an impaired skin barrier seem to play a critical role in dendritic cell-dependent Th2 responses to offending allergens or injury. Th2 cytokines predominantly cause an acute inflammation and activation of several types of cells, including dermal fibroblasts. Th2 cytokine-stimulated fibroblasts secrete periostin, an α_v integrin-interacting matricellular protein, which in turn stimulates keratinocytes to secrete TSLP. TSLP also stimulates mast cells to secrete Th2 and other cytokines. Periostin secretion from dermal fibroblasts depends on Th2 cytokines and mast cells, forming at least two positive feedback loops (indicated by thick and thin circular loops). Keratinocyte-derived G-CSF is important for MPN development in certain mutant mice. Expression of genes coding for G-CSF and TSLP is under control of the c-Fos/AP-1 transcription factor, which is positively regulated by EGFR and negatively regulated by Notch signaling and JunB. The proliferative and survival properties of hematopoietic stem cells (HSCs) are positively regulated by Stat5, whose constitutive activation can lead to MPN. PLC-β3 negatively regulates TSLP production in keratinocytes, periostin production in fibroblasts, and Stat5 activity in HSCs, mast cells, and Th2 cells. DC, dendritic cell; NICD, Notch intracellular domain; RBPj, recombination signal binding protein for immunoglobulin kappa region.

Role of histamine-releasing factor (HRF) in allergic diseases

HRF is a cytokine-like protein that can stimulate histamine release and cytokine (IL-4 and IL-13) production/secretion from IgE-sensitized basophils and mast cells. HRF activities are found in bodily fluids during the late phase of allergic reactions. We demonstrated that some, but not all, IgE and IgG molecules interact with HRF with low affinity. By mapping the binding sites on both HRF and IgE/IgG molecules, we developed competitive inhibitors of HRF-IgE (or IgG) interactions. Using these inhibitors, we showed that HRF promotes allergic inflammation in mouse models of anaphylaxis and asthma (Kashiwakura et al., 2012). These findings could be explained by a model where the FcεRI (high-affinity IgE receptor) on mast cells/basophils is cross-linked by receptor-bound IgE and HRF dimers, resulting in release of histamine and other allergic mediators. For the past three years, we have been studying the role of HRF in food allergy. Using an ovalbumin-induced food allergy model, we showed that HRF is involved in the promotion of allergic reactions including diarrhea (unpublished). These and human immunotherapy results support the efficacy of the HRF inhibitors as potential therapeutics for food allergy.

Pathogenic mechanisms of atopic dermatitis (AD)

AD is a chronic pruritic inflammatory skin disease. As part of the AD project, we have been studying its cellular and molecular mechanisms using our previously established in vivo AD induction model and the spontaneously occurring AD-like skin lesions in phospholipase C (PLC)-β3-deficient mice. We showed the importance of PLC-β3-mediated Stat5 regulation in mast cells in causing AD and the crucial role of FcεRI in allergen-induced AD (Ando et al., 2014). Although basophils express the $\alpha\beta\gamma_2$-type FcεRI, similar to mast cells, basophils seem dispensable in allergen-induced AD (Ando et al., unpublished).

Recent Major Publications

Draber P, Halova I, Polakovicova I, Kawakami T. Signal transduction and chemotaxis in mast cells. ***Eur J Pharmacol*** 778, 11–23 (2016)

Carroll-Portillo A, Cannon JL, te Riet J, Holmes A, Kawakami Y, Kawakami T, Cambi A, Lidke DS. Mast cells and dendritic cells form synapses that facilitate antigen transfer for T cell activation. ***J Cell Biol*** 210, 851–864 (2015)

Kawakami T, Ando T, Kawakami Y. Hypothetical atopic dermatitis-myeloproliferative neoplasm syndrome. ***Front Immunol*** 6, 434 (2015)

Invited Presentations

Kawakami T. National Jewish Heath, University of Colorado (Denver, USA) March, 2016

Kawakami T. The 7th EMBRN International Mast Cell and Basophil Meeting, Keynote Speaker (Marseille, France) October, 2015

Kawakami T. SPC-NUS Workshop (Paris, France) October, 2015

Kawakami T. University of Pittsburgh (Pittsburgh, USA) September, 2015

Kawakami T. IMMUNOLOGY 2015, Block Symposium: Mast cell biology (New Orleans, USA) May, 2015

Drug Discovery Antibody Platform Unit

Unit Leader: Toshitada Takemori

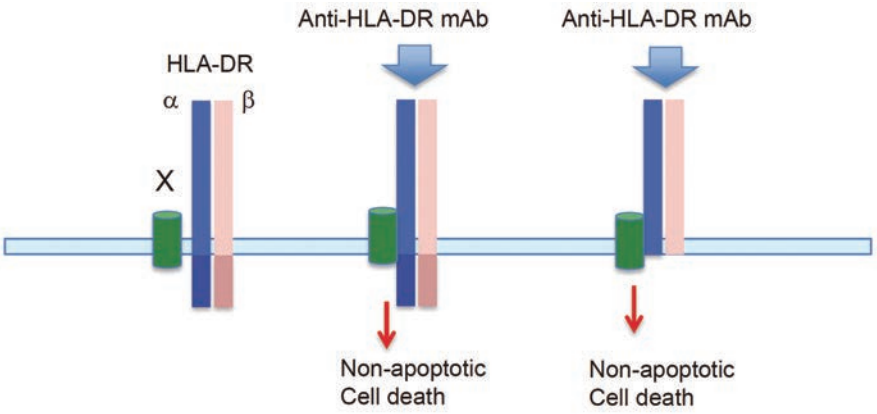


Figure: A possible mechanism of direct killing of B cell lymphomas by HLA-DR engagement.
As a member of the tetraspan family of integral membrane proteins is highly enriched in MHC class II-containing compartment (MIICs), we are analyzing the possibility that a tetraspanin (X) forms a complex with HLA-DR upon stimulation with L243 mAbs and mediates the non-apoptotic killing signal, indepently of the HLA-DR cytoplasmic domains.

This laboratory creates monoclonal antibodies (mAbs) that are candidates for antibody drugs to meet medical needs. In this context, we developed a system that allows for rapid selection of clones secreting antibodies that have high physiological activity from a number of clones during hybridoma cultivation. In this Laboratory, mAbs prepared by hybridoma technology are then generally modified to produce human chimeric or sometimes humanized mAbs. In addition, the Laboratory is now developing new systems to prepare human mAbs directly from target antigen-specific human B cells in peripheral blood or by utilizing the Ribosomal Display System, in collaboration with the Laboratory for Cell-Free Protein Synthesis at the RIKEN Quantitative Biology Center.

We are now trying to establish mAbs that will be candidate drugs for AML and for blocking HBV infection and are analyzing the mechanism of direct killing of a B cell lymphoma cell line by an anti-HLA-DR mAb.

The HLA-DRα/β heterodimer is highly expressed on B cell lymphomas, and the engagement by mAbs, such as L243, directly kills the cells via a non-apoptotic cell death, although HLA-DR molecules do not possesses any known signaling motifs in their cytoplasmic and transmembrane domains. The ability of such anti-HLA-DR mAbs may present a clinical advantage over conventional therapeutic mAbs for leukemia/lymphoma.

To understand the killing mechanism, we have established a mutant B cell lymphoma cell line that is deficient in HLA-DRα expression as a result of genomic manipulation using the CRISPR-Cas9 system. To identify which HLA-DRα region was responsible for mediating the killing activity upon stimulation with the L243 mAb, the HLA-DRα mutant cell line was transfected with chimeric HLA-DRα mutants, followed by L243 stimulation. The results suggest that HLA-DRα is not the element responsible for transducing the killing activity upon L243 stimulation.

Recent Major Publications

Kaji T, Hijikata A, Ishige A, Kitami T, Watanabe T, Ohara O, Yanaka N, Okada M, Shimoda M, Taniguchi M, Takemori T. CD4 memory T cells develop and acquire functional competence by sequential cognate interactions and stepwise gene regulation. ***Int Immunol*** 28, 267–282 (2016)

Takemori T, Kaji T, Takahashi Y, Shimoda M, Rajewsky K. Generation of memory B cells inside and outside germinal centers. ***Eur J Immunol*** 44, 1258–1264 (2014)

Takemori T. Generation of memory B cells. In: Alt F, Honjo T, Radbruch A, Reth M. (eds.), ***Molecular Biology of B cells 2nd edition***, London, UK: Academic Press/ Elsevier, pp. 227–230 (2014)

Invited Presentations

Takemori T. "Antibody Drugs on Cancer" A basic lecture, Sanofi Ltd. (Tokyo, Japan), July (2015)

Takemori T. "CD4 memory T cells develop and acquire functional competence by sequential cognate interactions and stepwise gene regulations." Symposium on the International Leibniz Research Cluster ImmunoMemory (Berlin, Germany) November, (2014)

Takemori T. "CD4 memory T cell development is licensed by Bcl6 and accomplished by expression of a group of genes mediated by cognate B cell interactions." The 36th annual meeting of the Molecular Biology of Japan (Kobe, Japan) November (2013)

YCI Laboratory for
Stem Cell Competency
Young Chief Investigator: Hayato Kaneda

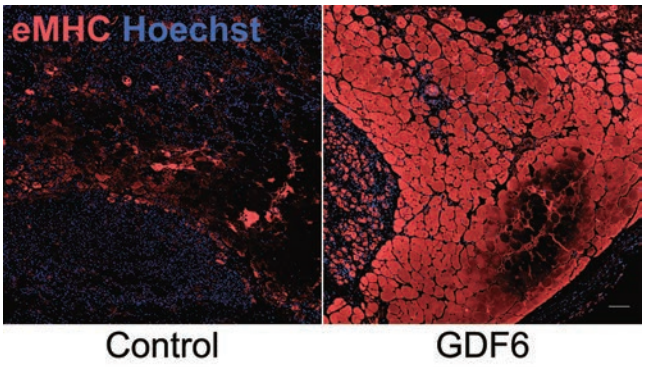
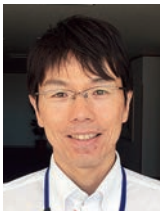


Figure: Restoration of muscle repair capacity by upregulation of GDF6 in old (24 month) mice.
Mesenchymal stem/stromal cells (MSCs) are well known to secrete a variety of homeostatic factors; however no critical factors had been identified yet. We identified GDF6 and investigated its effects on age-related disorders by lentiviral transduction into old mice. We found that GDF6 exerted positive effects *in vivo* on aging-associated pathologies such as reduced lymphopoiesis, insufficient muscle repair, reduced numbers of neural progenitors in the brain, and chronic inflammation.

Adult tissue stem cells (TSCs) become functionally impaired with age. TSC dysfunction and decreased regenerative capacity are involved, at least in part, in age-associated disturbances of tissue homeostasis, e.g., inefficient muscle repair, reduced bone mass, neurodegenerative diseases, and dysregulation of hematopoiesis. Therefore, the restoration of TSC functions is expected to contribute to recovery of tissue homeostasis and improvements in our health.

Previously, we identified the "competence change", which is responsible for the responsiveness of neural stem/progenitor cells (NSPCs) to extrinsic signals (Naka *et al.*, Nat Neurosci, 2008). Moreover, further investigation revealed that competence regulation enabled us to control the neurogenic-to-gliogenic transition and restore neurogenic potential in developmentally-progressed gliogenic NSPCs (Naka-Kaneda *et al.*, Proc Natl Acad Sci USA, 2014). Based on these findings, we have been investigating stem cell aging. Competence regulation is also involved in the aging of other TSCs, such as the decline in differentiation potential in hematopoietic stem cells and mesenchymal stem/stromal cells. We also found that restoration of stem cell functions may improve geriatric disorders (Figure, Hisamatsu et al., Aging, 2016). We aim to elucidate the central molecular machinery of stem cell aging and its influence on tissue homeostasis and, in turn, to develop a method for functional recovery of aged stem cells and restoration/maintenance of tissue homeostasis.



YCI Laboratory for
Immune Regeneration
Young Chief Investigator: Tomokatsu Ikawa

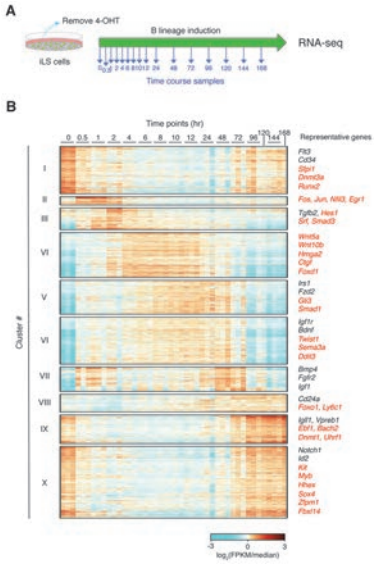
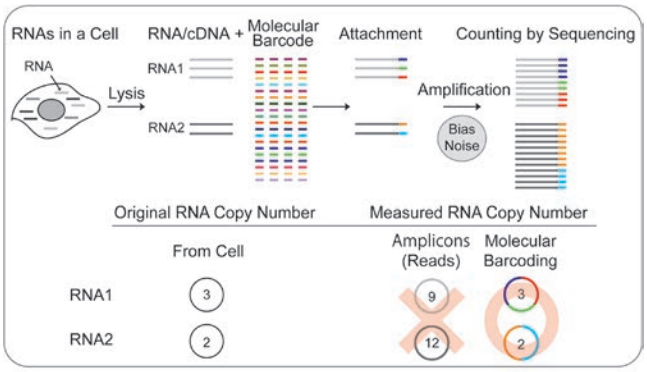


Figure: Genome-wide gene expression profiles during B lineage commitment.
(A) Scheme for sample collection. The induced Leukocyte Stem (iLS) cells were induced to differentiate into B lineage cells by withdrawing 4-OHT. The cells at the indicated time points were harvested, the RNA was purified and RNA-seq analysis was performed. (B) Expression profiles of differentially expressed genes. Gene expression was separated into ten clusters (I-X) based on expression pattern and kinetics. Representative genes are shown in every cluster and transcription factors are highlighted in red.

T, B and NK lymphocytes are generated from pluripotent hematopoietic stem cells (HSCs) through a successive series of lineage restriction process. Transcription factors (TFs) play a key role in regulating lineage-associated gene programs. Although many essential TFs, such as PU.1, Ikaros, GATA3, TCF-1, Bcl11b, E2A, EBF1 and Pax5 have been implicated in regulating the cell fate choice of lymphoid lineages, molecular mechanisms underlying the generation of these patterns during cell fate determination remain unexplored because of the lack of suitable experimental systems.

We have recently established stable multipotent progenitor cells, termed induced Leukocyte Stem (iLS) cells, that can be used to examine gene regulatory networks during lymphoid lineage specification from HSCs (Figure, Ikawa *et al.* Stem Cell Reports, 2015). This novel system enabled the analysis of a large set of regulatory molecules that control the generation of T and B lymphocytes. It can also be applied for *ex vivo* expansion of human hematopoietic stem/progenitors, which will be required for immune cell therapy or transplantation of HSCs. Thus, the aims of our study are 1) from a basic science perspective, to elucidate the mechanisms that orchestrate cell fate specification, commitment and differentiation during lymphocyte development and 2) from a clinical medicine perspective, to establish a novel method to expand human hematopoietic stem/progenitors for the development of HSC transplantation as a clinical strategy.

YCI Laboratory for
Quantitative Omics
Young Chief Investigator: Katsuyuki Shiroguchi



Digital RNA Sequencing (dRNA-Seq)

Figure: Digital RNA Sequencing
(JSI Newsletter vol.24-2, p21)

Quantitative Omics at the Single Cell and Single Molecule Level for Biological and Medical Sciences

In order to understand biological systems and contribute to medical sciences, we have been developing quantitative methods for system-wide genomic analyses. We established a platform for digital RNA sequencing (dRNA-Seq) including cell collection, cDNA library preparation, sequencing, and computational analysis, which provides results of genome-wide gene expression profiling in three days. Using this platform, we established numerous collaborations with researchers inside and outside of IMS, for example, in the analysis of limited numbers of immunologically-related cells. We also have been developing a novel method to measure many cells simultaneously to observe cell-number distributions with single cell resolution. This high throughput and high resolution analysis enables us to identify the state of biological systems based on cell heterogeneity. Using these methods, we are developing applications to contribute to medical sciences as well. I think that understanding cell heterogeneity within a population is important for understanding overall population function. Therefore, the accurate measurement of cell heterogeneity will allow linkage of different biological layers, from cells to tissues to organisms.

YCI Laboratory for
Cellular Bioenergetic Network
Young Chief Investigator: Toshimori Kitami

The central goal of our laboratory is to understand the role of cellular metabolism in the pathogenesis of complex diseases. Research over the past decades has shown that monogenic mutations in metabolic pathways cause a large number of human diseases. However, more recent studies have highlighted the role of cellular metabolism in the development of a wide variety of complex human diseases. Our laboratory in particular has been studying the function of mitochondrial energy metabolism, which is associated with neurodegeneration, cardiovascular disease, type 2 diabetes, and aging. We use genetic and chemical screens to identify novel pathways that restore or improve mitochondrial function and plan to examine their potential therapeutic value using genetically engineered mouse models and unique chemical probes.

Towards our goal, we have begun to explore the role of mitochondria in an innate immune pathway called the NLRP3 inflammasome, which is involved in a variety of complex diseases. The NLRP3 inflammasome is activated by changes in cell physiology, including mitochondrial damage, although the molecular players involved have not been fully elucidated. We hope to leverage our expertise in high-throughput screens to systematically identify genes and pathways involved in NLRP3 inflammasome activation and to place mitochondria in the context of this important disease pathway.

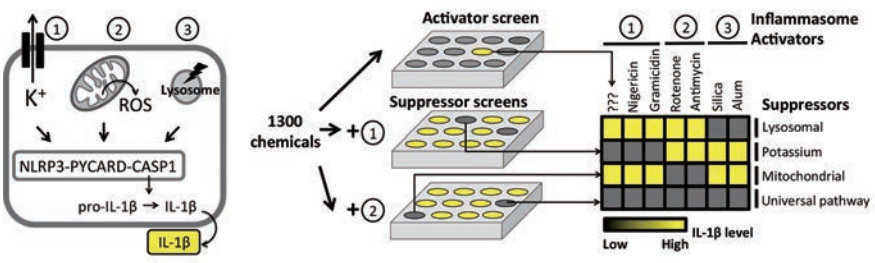


Figure: Chemical dissection of the NLRP3 inflammasome pathway
We have identified a handful of chemicals involved in modifying NLRP3 inflammasome activation. We hope to use these chemical tools to dissect the role of mitochondria in complex disease pathways.

Central Facilities

Central Facilities in IMS provide all researchers in the Center with access to the most advanced equipment and technologies. Central Facilities consist of four sections; the FACS Laboratory managed by Dr. Takashi Saito, the Confocal Laboratory managed by Dr. Takaharu Okada, the Genomics Laboratory managed by Dr. Osamu Ohara, and the Animal Facility managed by Dr. Haruhiko Koseki.

FACS Laboratory

The FACS Lab provides a range of support for flow cytometry and cell sorting, techniques that are essential for nearly all immunological experiments. The FACS Lab has upgraded all FACS Arias and added an Aria Fusion. In addition to FACS machines, the lab installed ImageStreamX, a device that combines flow cytometry with the visual detail of microscopy in a single platform, and upgraded CyTOF2, a mass-spectrometry-based cytometer that has the potential for analyzing more than 30 markers simultaneously with metal-labeled antibodies.

In 2015, 1611 analytical and 1963 sorting experiments were performed in the lab. For the users of the FACS machines (cell analyzers and cell sorters), two staff members offer various services: (1) *Technical support and training*: In 2015, the facility offered 11 technical courses (7 for cell sorting and 4 for cell analysis). Courses were held at 3 different levels, Calibur basic, Canto II and Aria basic. A total of 60 researchers took the courses in 2015. (2) *Cell sorting operation service*: The FACS Lab provides a cell sorting operation service, in which researchers can ask an experienced operator to conduct the sorting experiment. In 2015, the lab provided 205 such operation services. Special cell sorting techniques, such as single cell sorting, have also been performed. (3) *Management/maintenance of FACS machines*: FACS machines are available for registered users 24 hours a day and reservations are accepted up to one month in advance through an internal website. In addition to the in-house FACS Lab staff, engineers from Becton Dickinson visit once a week to provide maintenance and technical support.

Table: Instruments in the FACS Lab.

Machine types	Machines	# of machines
FACS cell analyzer	Calibur Canto II	4 2
FACS cell sorter	Aria II Aria III Aria Fusion	3 2 1
Mass-cytometer	CyTOF2	1
Imaging flow cytometer	ImageStreamX	1

Confocal Laboratory

The Confocal Lab. provides equipment for cell and tissue imaging, and coordinates technical support. There are seven laser-scanning fluorescence microscopes and a super-resolution microscope available to researchers at IMS.

1. IInverted Leica SP2 system with visible lasers for single-photon excitation and a femtosecond Ti:Sa laser for two-photon excitation.
2. Inverted Leica SP2 system with visible lasers for single-photon excitation including a 405 violet laser. This microscope is equipped with a chamber system that controls CO2 concentration, temperature and humidity for live cell imaging.
3. Inverted Leica SP5 system with visible lasers for single-photon excitation including a 405 violet laser.
4. Upright Leica SP2 system with visible and UV lasers for single-photon excitation.
5. Inverted Leica SP8 system with visible lasers for single-photon excitation. SP8 is Leica's newest system with improved optics.
6. Upright Leica SP5 system with two femtosecond Ti:Sa lasers for two-photon excitation. This system utilizes resonant scanners that enable high-speed acquisition of large z-stacks for live tissue imaging.
7. Inverted Leica SP8 system with two femtosecond Ti:Sa lasers for two-photon excitation. This system is equipped with two types of scanners (resonant and galvano) and hybrid detectors with high sensitivity and low background noise. One of the two Ti:-Sa lasers is connected to an optical parametric oscillator (OPO) that enables two-photon imaging by long wavelength excitation.
8. Inverted Nikon N-SIM/N-STORM super-resolution microscope for dual color imaging.

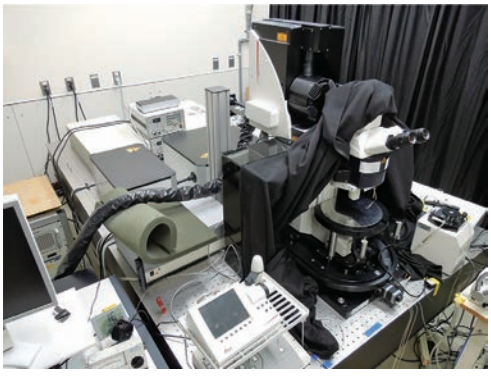


Photo: Upright SP5 two-photon microscope (#6)

Genomics Laboratory

We are a technical support service lab that provides genome- and proteome-wide analysis for research groups in the Center for Integrative Medical Sciences (IMS). We offer a variety of services to suit the needs of different labs. These include DNA sequencing, proteomics analysis, multiplex suspension array, cDNA/Genomic clone distribution, and Primer/labeled probe distribution for qRT-PCR analysis of immune cells (TABLE). Supplying advanced technologies on demand, we provide comprehensive interrogation of the nucleic-acid based information in a cell at single-base resolution with the Illumina HiSeq1500 and as well as proteomic approaches using the AB SCIEX TripleTOF 5600. Using this unbiased sequencing approach, we have interrogated: transcription units, mapping/genome annotation, alternative splice sites, and transcription factor binding sites. Our mass spectrometry system will make it possible to use quantitative proteomic approaches in various immunological studies. These technologies will help to reveal additional hidden features of the dynamic genomic and proteomic landscape that are regulated by both genetic and epigenetic pathways in all organisms.

Table: Central services provided by the Genomics Lab in 2015

Next-generation DNA sequencing	**# of samples**	**# of teams**
RNA-sequencing	1,086	31
Chip-sequencing	277	7
Others (Exome etc)	413	10
Proteomics	**# of samples**	**# of teams**
Mass Spectrometry Analysis	1	1
Multiplex suspension array	2,708	6
Sanger DNA sequencing	**# of samples**	**# of teams**
36cm capillary	5,313	16
50cm capillary	3,602	15
cDNA clone delivery	**# of samples**	**# of teams**
	34	3
Primer/labeled probe delivery	**# of samples**	**# of teams**
	17	1

Animal Facility

We maintain over 50,000 mice in the SPF (specific pathogen free) area and 1,500 mice in the isolated area. In addition, the SPF area contains 550 germ-free or gnotobiotic mice maintained in vinyl isolator rooms, and in vinyl isolator bio-bubble rooms. The former is used by several IMS research groups, in particular the mucosal immunologists; while the latter is used for maintenance of "humanized mice".

We introduce mouse lines into the SPF area by a combination of *in vitro* fertilization (IVF) and embryo transfer techniques. We have also generated cryo(frozen)-stocks of genetic resources for 713 lines. At the same time, we maintain relatively large colonies of several commonly used strains such as NOD/SCID/common γ chain KO (NSG) mice, Rag1 KO mice and Cre delete mice; and provide them to users on demand.

We also provide technical assistance to generate knockout and transgenic mice (57 lines already established). Furthermore, we made 121 KO and KI mouse lines using the CRISPR/Cas technique, and have created 13 lines of germ-free mice.

We have recently launched a new activity to improve the efficacy of transplantation of human hematopoietic stem cells into NSG mice (see above), by enhancing the degree of "humanization" of the host strain. For this purpose, we have introduced large genomic fragments containing human genes encoding MHC, cytokines, adhesion molecules, virus receptors and others, into the NSG mice. We maintain transgenic mice and six knock-in mice with confirmed expression of human genes on a C57BL/6 background; and have started backcrossing these mice into the NSG background, using the speed-congenic method.

Photo: Creation of germ-free mouse

Award winners 2015

Name of the awardee	Name of the award	Date of the announcement
Kazuhiko Yamamoto, Team Leader, Laboratory for Autoimmune Diseases	Carol Nachman Award	May, 2015
Toshitada Takemori, Unit Leader, Drug Discovery Antibody Platform Unit	The Order of the Sacred Treasure, Gold Rays with Rosette	Apr, 2015
Kenya Honda, Team Leader, Laboratory for Gut Homeostasis	The 18th Japanese Society for Immunology (JSI) Award	Nov, 2015
Masayuki Amagai, Team Leader, Laboratory for Skin Homeostasis	Authur Rook Oration from British Association of Dermatologists	Jul, 2015
Masayuki Amagai, Team Leader, Laboratory for Skin Homeostasis	Honorary Membership of the European Society for Dermatological Research	Sep, 2015
Masayuki Amagai, Team Leader, Laboratory for Skin Homeostasis	Honorary Membership of the German Society of Dermatology	Nov, 2015
Naoto Kubota, Team Leader, Laboratory for Metabolic Homeostasis	The Masato Kasuga Award for Outstanding Scientific Achievement, The Asian Association for the Study of Diabetes	Nov, 2015
Naoto Kubota, Team Leader, Laboratory for Metabolic Homeostasis	Outstanding Scientific Achievement Award of the Japan Society of Experimental Diabetes and Obesity	Feb, 2015
Masato Kubo Team Leader, Laboratory for Cytokine Regulation	Tokyo University of Science Outstanding Scientist of the Year 2014	May, 2015
Yuuki Obata, Graduate Student, Laboratory for Intestinal Ecosystem	JSPS (Japan Society for the Promotion of Science) Ikushi Prize	Mar, 2015
Yuuki Obata, Graduate Student, Laboratory for Intestinal Ecosystem	Chiba University President Award for Research Excellence	Mar, 2015
Yuuki Obata, Graduate Student, Laboratory for Intestinal Ecosystem	Chiba University Dean of the Graduate School of Medical and Pharmaceutical Sciences Award for Research Excellence	Mar, 2015
Ikuyo Inaba, Senior Scientist, Laboratory for Bone and Joint Diseases	Young Investigator Award, Japanese Society of Human Genetics	Oct, 2015
Ikuyo Inaba, Senior Scientist, Laboratory for Bone and Joint Diseases	The 6th RIKEN Researcher Incentive Award	Mar, 2015
Takashi Kanaya, Research Scientist, Laboratory for Intestinal Ecosystem	The 6th RIKEN Researcher Incentive Award	Mar, 2015
Tomomitsu Hirota, Research Scientist, Laboratory for Respiratory and Allergic Diseases	Letter of Appreciation from the President of RIKEN	Jan, 2015
Kazuyo Moro, Senior Scientist, Laboratory for Immune Cell System	World Immune Regulation Meeting IX, Best Workshop Presentation Award	Feb, 2015
Akihiro Fujimoto Deputy Team Leader, Laboratory for Genome Sequencing Analysis	Best Paper Award in the Annual Meeting of the Genetics Society of Japan	Nov, 2015
Yoji Ogura, Visiting Scientist and **Shiro Ikegawa,** Team Leader, Laboratory for Bone and Joint Diseases	The John H. Moe Award, Scoliosis Research Society	Oct, 2015
Tomomitsu Hirota, Research Scientist, Laboratory for Respiratory and Allergic Diseases	Travel grant, XXIV World Allergy Congress (WAC2015)	Oct, 2015
Rumiko Ono, Junior Research Associate, Laboratory for Inflammatory Regulation	Ursula and Fritz Melchers Travel Award (Japanese Society of Immunology)	Dec, 2015
Kentaro Inoue, Postdoctoral Researcher, Laboratory for Integrated Cellular Systems	Research Incentive Award (Japanese Society for Bioinformatics 2015)	Oct, 2015
Chikako Shimokawa, Research Scientist, Laboratory for Intestinal Ecosystem	Tadamitsu Kishimoto International Travel Award	Apr, 2015
Takayuki Imanishi, Research Scientist, Laboratory for Cell Signaling	Tadamitsu Kishimoto International Travel Award	Sep, 2015
Miho Tanaka, Technical Staff, Drug Discovery Antibody Platform Unit	DMP Achievement Award	Mar, 2015
Akiko Ishige-Sugimoto, Technical Staff, Drug Discovery Antibody Platform Unit	DMP Achievement Award	Mar, 2015

RIKEN International Program Associate (IPA)

IMS accepted four international students as RIKEN International Program Associates (IPA). Under this IPA program, IMS lab heads host international students from collaborating graduate schools and supervise their Ph.D. program as Joint Supervisors. The students receive a daily living allowance and housing costs for up to a maximum of three years.

The IPA students who studied at IMS in 2015 were
Krutula Nair (Graduate School of Frontier Biosciences, Osaka University) from India studied in the Laboratory for Transcriptional Regulation.
Tsermpini Evangelia (University of Patras, Greece) studied in the Laboratory for International Alliance on Genomic Research.
Kong Mei Suen (University of Science, Malaysia) studied in the Laboratory for Cell Signaling.
Chanyoung Shin (Tokyo Institute of Technology) from Korea studied in the Laboratory for Inflammatory Regulation.

RIKEN Foreign Postdoctoral Researcher (FPR) Program

The RIKEN Foreign Postdoctoral Researcher (FPR) program offers aspiring young foreign researchers with creative ideas and who show promise of becoming internationally active in the future the opportunity to pursue innovative research at RIKEN under the direction of a RIKEN laboratory head. The FPR Program is one of RIKEN's initiatives to open up its facilities and resources to the forefront of global science and technology.

In 2015, three young researchers studied at IMS as RIKEN FPRs.

Wooseok Seo studied in the Laboratory for Transcriptional Regulation.
Michelle Kendle Maslowski studied in the Laboratory for Intestinal Ecosystem.
Ealey Nequan Kafi studied in the Laboratory for Innate Immune Systems.

RIKEN Junior Research Associate (JRA) Program

The Junior Research Associate Program was launched in 1996 to encourage young scientists with fresh ideas and youthful enthusiasm to collaborate with, and learn from, senior scientists with years of experience. This program provides part-time positions at RIKEN for young researchers enrolled in university Ph.D. programs. The JRA program serves the dual purpose of fostering the development of these young scientists while also energizing RIKEN with their innovative thinking.

This year, 21 JRA students studied in IMS.

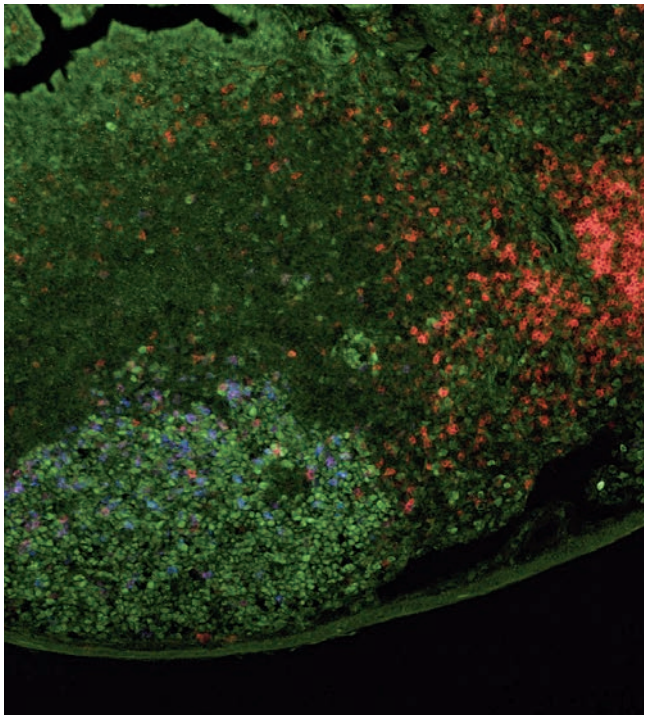
Junichiro Takano (Laboratory for Developmental Genetics)
Yoshihiro Ito (Laboratory for Skin Homeostasis)
Eiichiro Watanabe (Laboratory for Gut Homeostasis)
Satoko Yokoyama (Laboratory for Intestinal Ecosystem)
Ryohei Aoyagi (Laboratory for Metabolomics)
Yuki Furuichi (Laboratory for Skin Homeostasis)
Tadashi Takeuchi (Laboratory for Intestinal Ecosystem)
Rintaro Ono (Laboratory for Human Disease Models)
Rumiko Ono (Laboratory for Inflammatory Regulation)
Takaharu Sasaki (Laboratory for Immune Cell Systems)
Tomohiro Miyai (Laboratory for Immune Cell Systems)
Yujiro Yamamoto (Laboratory for Genotyping Development)
Yurina Miyajima (Laboratory for Innate Immune Systems)
Takato Kobayashi (Laboratory for Innate Immune Systems)
Toshihiro Morita (Laboratory for Gut Homeostasis)
Takaaki Kawaguchi (Laboratory for Gut Homeostasis)
Kensuke Yamaguchi (Laboratory for Autoimmune Diseases)
Keiichi Masaki (Laboratory for Digestive Diseases)
Yuma Sakamoto (Laboratory for Bone and Joint Diseases)
Hirotsugu Oda (Laboratory for Integrative Genomics)
Ye Liu (Laboratory for International Alliance on Genomic Research)

RIKEN Special Postdoctoral Researcher (SPDR) Program

RIKEN's Special Postdoctoral Researcher Program was instituted to provide young and creative scientists the opportunity to be involved in autonomous and independent research in line with RIKEN objectives and research fields. The positions are competitive, but if selected, researchers receive salaries and research budgets (1 million yen) from RIKEN and they are able to conduct their research at one of its laboratories.

This year, five postdocs conducted their research at IMS through the SPDR program.

Guillermo Juan Betancur Medina (Laboratory for Developmental Genetics)
Takeshi Tanoue (Laboratory for Gut Homeostasis)
Jun Miyata (Laboratory for Metabolomics)
Yosuke Isobe (Laboratory for Metabolomics)
Motomura Yasutaka (Laboratory for Innate Immune Systems)



Part 3

Research Projects

iPS project

Induced pluripotent stem (iPS) cells possess tremendous therapeutic potential in many areas, including regenerative medicine and immune therapy. We have begun an activity to apply iPS technology to both mouse and human immunology research and to the development of therapeutics. On a collaborative basis with individual IMS research laboratories, the core facility for iPS research is engaged in developing efficient protocols to reprogram various types of lymphocytes into iPS cells as well as to induce differentiation of iPS cells into a variety of lymphoid lineage cells. This activity is partly supported by the Research Center Network for Realization of Regenerative Medicine from the Japan Agency for Medical Research and Development (AMED) and CREST, Japan Science and Technology Agency.

This year, the facility focused on establishing a robust protocol to prepare functional human Vα24⁺iNKT cells through iPSCs (iPS-Vα24⁺iNKT). Indeed, they confirmed that such iPS-Vα24⁺iNKT cells can be activated by ligand-pulsed dendritic cells (DCs) and can produce a large amount of interferon-γ upon activation, as much as the parental Vα24⁺iNKT cells. Moreover, iPS-Vα24⁺iNKT cells showed much more potent cytotoxic activity against tumor cell lines than that of the parental Vα24⁺iNKT cells. These results are very encouraging for potential clinical application of human iPS-Vα24⁺iNKT cells for tumor immunotherapy. A CPC (Cell Processing Center) has been constructed in IMS (named IMS CMU: Cell Manufacturing Unit). The facility has started the operation of IMS CMU to prepare iPS-Vα24⁺iNKT cells under GMP (Good Manufacturing Practice)/GCTP (Good Gene, Cellular, and Tissue-based Products Manufacturing Practice) guidelines to apply them to preclinical studies.

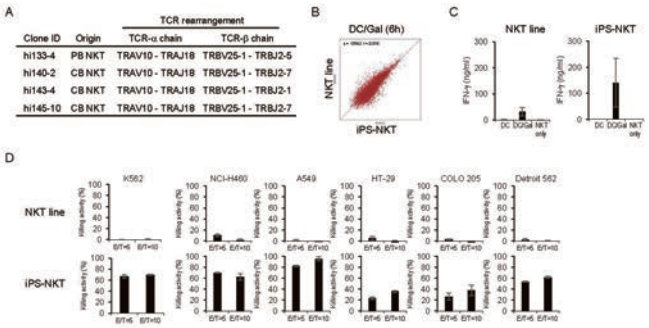


Figure: Preparation of functional human iPS-Vα24⁺iNKT cells.
(A) Identification of rearranged TCRα and TCRβ chain gene segments in established Vα24⁺iNKT-iPSCs. (B) Comparison of global gene expression by RNA-seq analysis of human iPS-Vα24⁺iNKT cells and a Vα24⁺iNKT line upon stimulation with murine DC/Gal for 6h. (C) IFN-γ production by a Vα24⁺iNKT line (left) or iPS-Vα24⁺iNKT cells (right). The cells were co-cultured with murine DC, DC/Gal or nothing for 24 h. IFN-γ production was measured by ELISA. (D) Cytotoxic activity of a Vα24⁺iNKT cell line or iPS-Vα24⁺iNKT cells against a panel of tumor cell lines. Vα24⁺iNKT cells (upper) and iPS-Vα24⁺iNKT cells (lower) were prepared as effector cells. Cells were mixed with the tumor cell lines (K562, NCI-H460, A549, HT-29, COLO 205 and Detroit 562) at ratios of 5:1 or 10:1 and incubated for 6 h, then cytotoxicity was assessed by an LDH assay.

Modeling skin diseases

Human immune-mediated diseases develop and progress through highly complex processes in which various types of immune cells sequentially infiltrate into the sites of inflammation, interact with resident non-immune cells and induce a series of inflammatory mediators, finally causing pathological symptoms and tissue damage. To tackle such complexity, IMS has constructed center-wide projects to clarify the pathogenesis of human diseases, including atopic dermatitis (AD). In each project, multiple research groups work interactively and synergistically to understand the molecular and cellular networks leading to disease development.

In the atopic dermatitis project, we take advantage of AD mouse models, including *Spade*, a mutant mouse line established in RIKEN IMS (J. Clin. Invest. 2016, 126: 2064-2076), and STAT3-deficient mice. Drs. Yoshida and Kubo investigate the RNA-seq-based gene expression profiles of pre-symptomatic events occurring in skin from birth to the onset of dermatitis at ~ 12 weeks. Using their samples, Dr. Ohara's group has conducted transcriptome analysis, and Drs. M. Okada and Kitano's groups have established an integrated feedback model of AD progression. Dr. T. Okada examines the nerve fiber structure in skin by confocal fluorescence microscopy. Drs. Amagai and Tsunoda have been working to connect the findings in mouse and human AD to discover any common mechanisms of disease onset.

Moreover, Dr. Taylor's group has developed an integrated database for various types of experimental data, including flow cytometry data, immunohistochemistry images, blood profiles, RNA-seq data. They are cooperating with the experimental labs led by Drs. Yoshida, Kubo, T. Okada and Amagai, and the computational analysis/modeling labs led by Drs. M. Okada, Kitano, Ohara and Tsunoda.

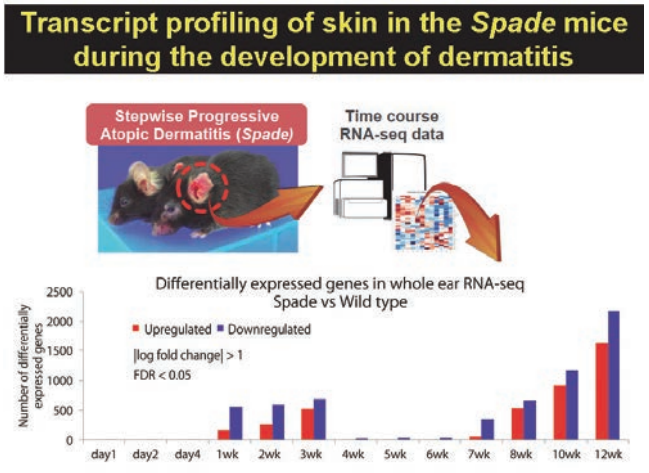


Figure: Pre-symptomatic RNA-seq analysis of skin in the *Spade* AD mouse model
Using novel prediction methods, we elucidate dynamic changes in transcriptional regulation during the development of dermatitis by transcript profiling of the Spade mice at high temporal resolution using RNA-seq. FDR; false discovery rate.

Impact of host-gut microbiome interactions on the pathogenesis of diabetes

Recent studies of the gut microbiome indicate that changes in its composition and the loss of microbial diversity, or dysbiosis, are not the consequence but rather the cause of various diseases (Figure). Type 2 diabetes (T2D) is one such disease. As an IMS Center project, we are using our comprehensive multiple omics approach to determine the impact of host-gut microbiome interactions on the pathogenesis of type 2 diabetes. The project is a collaboration with Professors Takashi Kadowaki and Tsutomu Yamazaki from the University of Tokyo Hospital and Professor Masahira Hattori from Waseda University. From RIKEN IMS, the Laboratories for Metabolic Homeostasis, Intestinal Ecosystem, Metabolomics, Integrative Genomics, and Integrated Bioinformatics are mainly involved in this project. Fecal metagenomic, metatranscriptomic and metabolomic data, as well as plasma and urine metabolomic data will be obtained from three groups of volunteers undergoing a complete medical checkup at the University of Tokyo Hospital (n=100 each): 1) no abnormal examination outcome, 2) obesity (BMI ≧ 25), and 3) glucose intolerance (fasting blood glucose ≥ 110 mg/dl, or blood glucose after a meal ≥ 140 mg/dl, HbA1c ≧ 6.0%). In addition, exomes and SNPs of T2D susceptibility genes will be analyzed. The goal is to identify T2D risk factors, such as certain bacteria and/or their metabolites, by analyzing the meta data from the comprehensive multiple omics analyses, combined with clinical and genetic datasets. 100 volunteers have already been recruited for Group 1, and 50 each have participated so far in the other two groups.

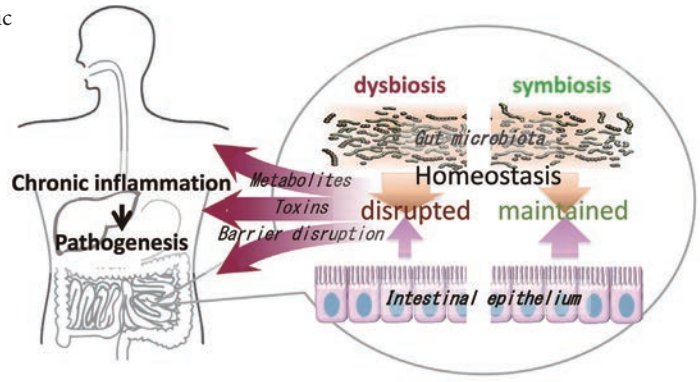


Figure: The contribution of dysbiosis to pathogenesis.
In healthy individuals, the gut microbiota is robust and resistant to perturbations caused by antibiotics and bacterial/viral infections, for example, and can quickly recover and maintain its composition within a normal range to sustain homeostasis, or symbiosis. However, in susceptible individuals, genetic predispositions may make it difficult to maintain homeostasis once the composition of their microbiome is perturbed and the change becomes irreversible. The resultant abnormal microbiota, or dysbiosis, has a causative role in disease by evoking a chronic inflammatory state.

Humanized mouse

To understand the biology of normal and diseased human hematopoiesis and immunity, we have developed a humanized mouse model. To overcome limitations of this model due to species barriers between human cells and the mouse environment, we have been creating immune-compromised mouse strains expressing human cytokines, HLA, and adhesion molecules. In FY2015, we assessed the potential usefulness of HLA-expressing humanized mice in vaccination and gene therapy. In this study, we chose the tumor antigen Wilms tumor protein (WT1) as a model antigen to elicit specific human immune responses *in vivo*. In an experiment testing gene therapy, we transduced WT1-specific T cell receptor genes into human hematopoietic stem cells. By doing transplantation experiments, we found that the transduced human hematopoietic stem cells can generate WT1-specific T cells in the bone marrow and spleen. The WT1-specific T cells were functional in cytokine production and cytotoxicity against WT1-expressing HLA-matched target cells. In the future, we will create next-generation humanized mice with an even more "humanized" environment to better reconstitute human immunity and then use these mice in pre-clinical testing for molecular targeting drugs or immune-targeting therapies.

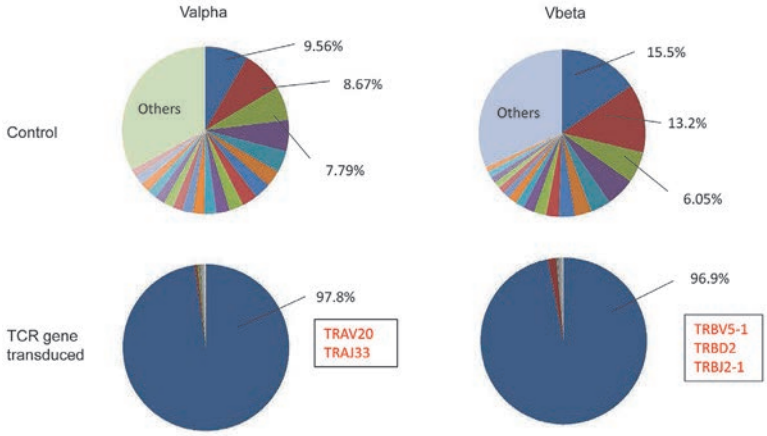


Figure: Skewed TCR repertoire among human CD8⁺ T cells developed in a humanized mouse from WT1 TCR gene transduced HSC.
Human CD8⁺ T cells were purified from a humanized mouse transplanted with WT1-specific TCR transduced human HSCs and from control mice engrafted with non-transduced human HSCs. Pie charts depict the major TCR repertoire greater than 1%.

NKT cell projects

NKT cells have the capacity to either enhance or suppress immune responses. The medical innovation groups in IMS have launched projects aimed at application of NKT cell therapy to cancer and allergic disease as translational research. When an NKT cell ligand is loaded on CD1d$^+$ cells, such as dendritic cells (DCs) or CD1d transfectants, NKT cells can produce IFN-γ. On the other hand, when the ligand is incorporated into a liposomal compound, NKT cells can produce IL-21 and suppress B cell function. Here we introduce five NKT cell-related projects.

First, we have begun a collaboration with 15 National Hospital Organization (NHO) hospitals involving clinical therapeutic studies using the NKT glycolipid, α-galactosylceramide (α-GalCer) pulsed autologous DCs (DC/Gal) in a randomized phase IIa trial in early stage lung cancer (Figure). In our part of this study, we perform immunological analyses of the DC/Gal-treated and control cancer patients. Second, IMS was selected as part of the research center network for realization of regenerative medicine and we have successfully established human iPS-NKT cells. After stimulation with DC/Gal, the iPS-NKT cells produced more IFN-γ than parental NKT cells and had strong antitumor effects *in vivo*. This iPS-NKT cell project has been planned as a clinical application research project. Third, as a new type of cancer vaccine, we established artificial adjuvant vector cells, which contain tumor antigen mRNA and α-GalCer, leading to activation of both innate and adaptive immunity. We have almost completed the preclinical studies through discussions with the Pharmaceuticals and Medical Devices Agency (PMDA). Forth, we developed several new NKT cell ligand candidates and have been investigating the function of one of them. We have been examining its efficacy in preclinical studies for next generation NKT cell ligand cancer immunotherapy. The three preclinical projects have been supported by the Japan Agency for Medical Research and Development (AMED). As a fifth study, we have developed a new chemical liposomal compound that includes a new NKT cell ligand that can be selectively delivered to B cells, resulting in the preferential suppression of IgE production. This drug could be applicable for asthma, pollinosis or food allergy. These four projects (iPS-NKT, new ligand, aAVC therapy and liposomal compound) are also supported by the RIKEN Drug Discovery and Medical Technology Platforms (DMP).

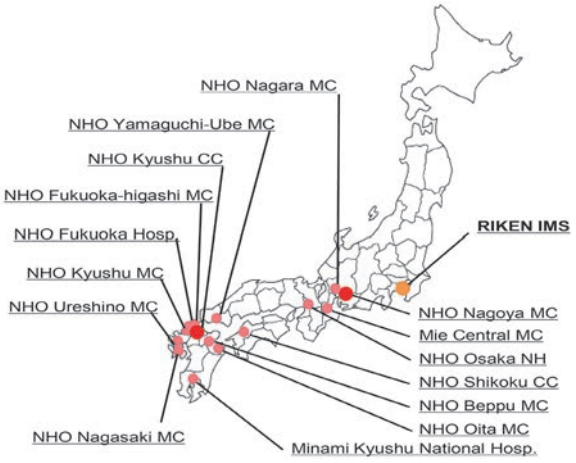


Figure: NKT translational study and clinical projects in IMS.
We have been collaborating with 15 National Hospital Organization (NHO) hospitals for a randomized phase IIa trial of NKT cell therapy in early stage lung cancer patients.

Linkage to RIKEN Program for Drug Discovery and Medical Technology Platforms (DMP)

IMS collaborates with DMP to develop innovative new pharmaceuticals and medical technologies by facilitating the transfer of basic research within the institute.

The DMP was founded in RIKEN in 2010 in order to support all phases of development of new therapeutics, from the discovery of promising targets to the identification of potential lead compounds, such as small molecules and antibodies, and the acquisition of intellectual property rights to drugs and technologies that can then be brought to the development phase. The implementation of drug discovery requires a different technology, thus DMP established several medical technology platforms that promote research and development. IMS contributes to this effort in several ways, including by setting up a facility for development of antibody drugs.

IMS now has five programs in association with DMP, including Artificial adjuvant vector cells (Shin-ichiro Fujii), Leukemia treatment drugs targeting leukemic stem cells (Fumihiko Ishikawa), Cancer treatment with NKT cells (Haruhiko Koseki), Drugs for allergic diseases (Yasushi Ishii), and a monoclonal antibody for HBV prevention (Daiki Miki). The Artificial adjuvant vector cells project for cancer therapy is now at the preclinical stage of drug development.

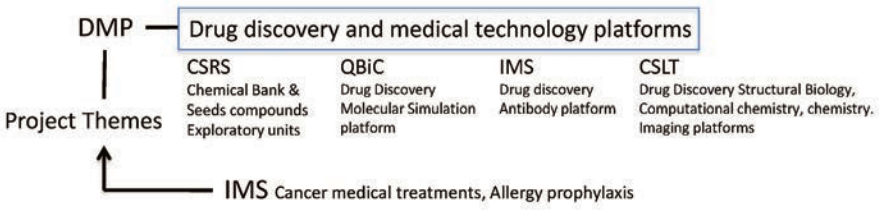


Figure: IMS links to the DMP project

PGRN-RIKEN project

The U.S. NIH Pharmacogenomics Research Network (PGRN) is a consortium of research groups funded as individual cooperative agreements by the NIH. PGRN investigators are top researchers from U.S. academic institutions and conduct studies of variation in human genes relevant to drug metabolism, pharmacokinetics and pharmacodynamics, and the relationship of these genetic variation to drug responses. Principal investigators of the PGRN and RIKEN Center for Genomic Medicine (now RIKEN IMS Core for Genomic Medicine: CGM) held a series of discussions on the need to accelerate discoveries in pharmacogenomics (PGx) and launched the Global Alliance of Pharmacogenetics (GAP) in 2008. Currently, the PGRN-RIKEN Project is conducted under a PGRN-Hub, a newly-formed resource established to enhance scientific exchange between the PGRN and the scientific community at large.

In this international collaboration, the PGRN has been successfully assembling a very large collection of DNA samples from well-phenotyped patients receiving specific drugs and drug combinations in clinical trials conducted in the U.S. The CGM focuses on high-throughput genome-wide SNP scans and targeted sequencing of selected genes or regions using next generation sequencing (NGS). We also provide technological and methodological expertise to identify genetic factors associated with drug responses, risk of severe adverse drug reactions and non-response to medications. Together, the PGRN-RIKEN Project capitalizes on these strengths to advance discoveries in PGx research. To date, we have initiated 41 collaborative projects and have 43 publications and over 55,000 DNA samples genotyped through this collaboration, which will lead to development of better and safer medications and realize the dream of global precision medicine.

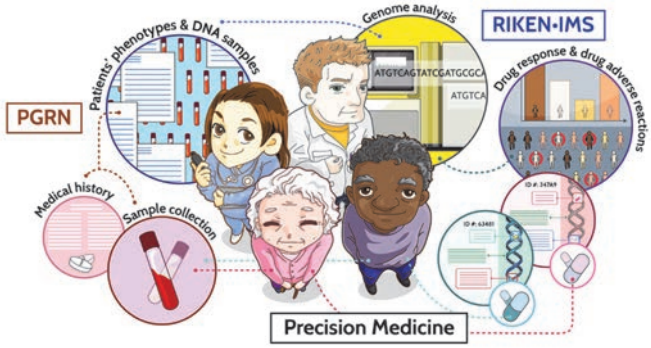


Figure: The Pharmacogenomics Research Network (PGRN)-RIKEN IMS strategic alliance.
Please visit http://www.pgrn.org/

Collaboration with Asian institutes and SEAPharm

It has been noticed that severe cutaneous adverse drug reactions (ADRs), including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), occur at a much higher frequency in East Asian and Southeast Asian populations, and several genetic factors have been reported to be associated with the risk of cutaneous ADRs. In the case of the anti-epileptic drug carbamazepine, the US FDA now recommends HLA-B*15:02 screening for Han Chinese and other Asian populations with a high prevalence of HLA-B*15:02 prior to the administration of carbamazepine, due to the risk of ADR associated with this allele. To tackle this problem regionally, in 2012 we established the South East Asian Pharmacogenomics Research Network (SEAPharm) together with six other Asian countries (Korea, Indonesia, Malaysia, Singapore, Taiwan, and Thailand). The aim of the collaborative efforts is to identify significant ADRs in the region so that we can identify genomic biomarkers associated with their risk, information that could lead to a reduction in severe ADRs. We are now focusing on the identification of genomic biomarkers associated with cutaneous ADRs induced by the anticonvulsant phenytoin and the antibiotic co-trimoxazole, as well as with hepatic injury induced by anti-tuberculosis agents. In addition, we also aim to understand how the identified genomic biomarkers lead to the ADRs by performing functional studies. It is hoped that the discoveries from our collaborative efforts will identify useful biomarkers that can be used to predict the risk of ADRs, leading to the establishment of "stratified medicine" based on pharmacogenomic-guided drug therapeutics.

Figure: South East Asian Pharmacogenomics Research Network (SEAPharm).

Project

International Cancer Genome Consortium (ICGC)

Laboratory for Genome Sequencing Analysis　Laboratory for Medical Science Mathematics　Laboratory for Digestive Diseases

The ICGC has been organized to launch and coordinate a large number of research projects that have the common aim of comprehensively elucidating the genomic changes present in many types of cancers. Its primary goals are to generate comprehensive catalogues of genomic abnormalities in different cancer types and to make the data available to the entire research community with minimal restrictions. At the end of 2015, 78 cancer genome projects across 16 countries and the EU were ongoing, and the ICGC released the genomic data from 14,767 cancer samples as Release 20 (November, 2015). The RIKEN group has been involved with virus-related liver cancer, which is one of the most common and deadly cancers worldwide, especially in Japan and Asia. We performed whole genome sequencing (WGS) and RNA-Seq for 270 liver cancer samples and called their somatic mutations by using our in-house pipeline. We deposited the WGS data from all 270 liver cancers and released them. As an ICGC verification/validation working group, we were involved with benchmark comparison studies, where eleven genome centers analyzed exactly the same raw sequence data or the same DNA by each of their pipelines or platforms to compare their results in somatic mutation identification. Under this pipeline comparison, we released the guidelines for WGS analysis (Nature Communications 2015). ICGC also launched a "pan-cancer" whole genome project (PCAWG) in 2014, where 2834 cancer WGS data +RNA-Seq are analyzed in the uniform pipelines within the same computational environment. Approximately 1000 researchers and technical staff are involved world-wide in 16 theme working groups (Figure). We are contributing to this ambitious project as a member of a technical working group arranging ten "cloud" data centers worldwide, PI and researchers for driver gene analysis, mutational signatures, immunogenomics, and mitochondrial genomics, as well as by providing 270 WGS data to the PCAWG (10% contribution 270/2834), which is the most productive within ICGC/TCGA (Figure). In 2015, we completed the alignment and mutation calls by the Sanger pipeline and we established and validated certain pipelines for immunogenomic profiling from WGS and RNA-Seq, such as HLA genotyping, HLA mutation, and neo-antigen prediction, which was performed in collaboration with the group of The University of Tokyo.

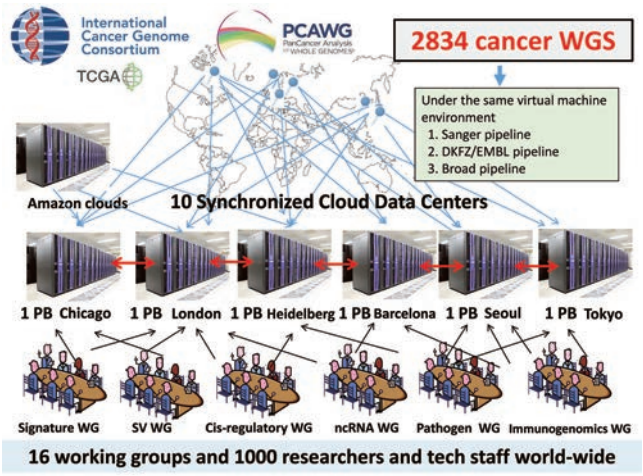


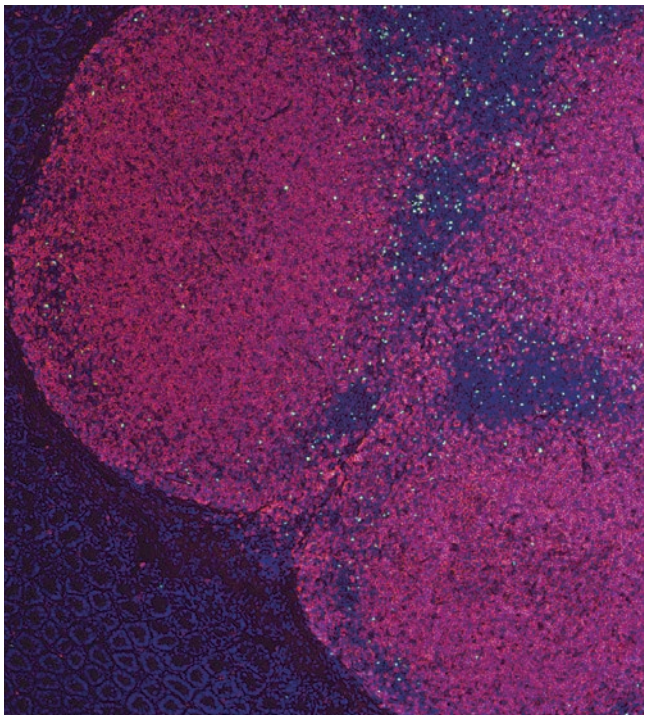
Figure: Overview of the PCAWG2015 ("Pan-CAncer" Whole Genome project) in ICGC/The Cancer Genome Atlas (TCGA).
The ICGC is organizing ten synchronized cloud data centers worldwide, including Amazon clouds, each with 1 petabyte (PB) of storage capacity, where ~3000 WGS pair datasets are analyzed in the same computational environment and by three uniform pipelines (Sanger, Broad, and DKFZ/EMBL pipelines). RIKEN is involved with the Tokyo Data Center, where we performed WGS alignment and mutation calls by Sanger pipeline for 2834 PCAWG donors. There are 16 working groups (WG) including those analyzing signatures, genomic structural variations (SV), *cis*-regulatory elements, non-coding RNA, pathogens, and immunogenomics.

Commissioned Research

The Biobank Japan project

In 2013, the Japanese government started a new initiative for life sciences called Healthcare and Medical Strategy. This initiative consists of nine top priority research fields: 1) Drug development, 2) Development of medical devices, 3) Translational research, 4) Regenerative medicine, 5) Genomic medicine, 6) Cancer, 7) Brain science, 8) Infectious diseases, and 9) Rare diseases. For the genomic medicine research field, in 2015 the government decided to promote rapid and publically visible clinical applications of genomic research findings in parallel with strengthening of the basic infrastructure of human genome research. Based on this concept, the government is planning to establish a network of existing biobanks [Biobank Japan (BBJ), Tohoku Medical Megabank (Tohoku MMB), and National Center Biobank Network (NCBN)]. The government also established priority disease areas in 2015. Rare (hereditary) diseases, cancer, dementia, infectious diseases and pharmacogenomics were selected as the first priority disease areas because these diseases are thought to be very close to implementation of genomic information for actual medical practice Common multifactorial diseases such as diabetes and cardiovascular diseases are positioned as the second priority disease area, which needs further basic genomic research to precisely elucidate the relationships between genetic variations and disease.

The Biobank Japan project was started as a MEXT-commissioned project in 2003, and the final goal of this project is the implementation of personalized medicine. To pursue this aim, the project constructed a large disease biobank, named Biobank Japan, in the Institute of Medical Science, University of Tokyo. This biobank has already collected DNA and clinical information from 230,000 patients suffering from 51 target diseases. The Core for Genomic Medicine has been working as the main infrastructure of genomic research for this project since the beginning. Since the primary area of this project is common multifactorial disease, we are performing large-scale genomic research including GWAS and whole-genome sequencing-based association studies using BBJ samples. We are also collaborating with various international research groups using this important resource.



Part 4

Events

RIKEN IMS Summer Program (RISP) 2015

IMS was delighted to again successfully organize the 10th RISP (RIKEN IMS Summer Program). RISP began as the RCAI International Summer Program (RISP) in 2006 and has been continued by IMS, beginning two years ago. The aim of this activity is to provide networking opportunities on a broad international scale for young scientists, as well as to encourage future collaboration and postdoctoral training experiences in Japan. Due to the broadened research activities of the new IMS, the RISP 2015 program was expanded to include topics in genomic studies to understand human diseases, in addition to its original focus on immunology. The internship program, in which the participants perform research in IMS laboratories, has also been maintained. RISP 2015 was co-organized by the Chiba University Leading Graduate School Program.

Due to financial constraints, IMS was unfortunately unable to cover travel expenses for all RISP students for RISP 2015. However, we were pleased to welcome fifty-four graduate students and postdoctoral fellows from twenty-one countries, together with ten students from Chiba University, who gathered at Yokohama from June 12th to 19th. It is noteworthy that the percentage of students in M.D/Ph.D programs increased this year. RISP began with a tour of IMS research facilities, which include advanced two-photon microscopes, a HILO microscope for single molecule imaging and a CyTOF cell sorting instrument. The scientific sessions included 12 lectures by distinguished senior scientists. RISP students also presented their research in both oral and poster sessions. The RISP program ended with participation in a two day International Symposium on Immunology, co-organized by IMS and the Japanese Society for Immunology.

RISP2015 was again a success; we received very nice feedback comments in the evaluation survey and all students indicated that they would recommend this program to colleagues. From the other perspective, many lecturers commented on how impressed they were with the quality of the RISP students. IMS will again organize RISP in 2016, shifting to include broader topics as necessary to keep pace with recent developments in this rapidly moving life science field.

The IMS-JSI International Symposium on Immunology 2015

The IMS-JSI International Symposium on Immunology, hosted by the RIKEN Center for Integrative Medical Sciences (IMS), in conjunction with the Japanese Society for Immunology (JSI), was held on June 18–19 at the Pacifico Yokohama conference center. The symposium, entitled "Infection and Immunity", included 20 internationally-recognized speakers presenting their cutting-edged research and attracted close to 400 participants. There were four sessions: (1) RNA and immune responses, (2) Infection and inflammation, (3) Vaccine development, and (4) Metabolism and immune regulation. The "RNA and immune responses" session posed the intriguing question of how translational regulation contributes to immune responses. Recent findings about mRNA modifying molecules have revealed the importance of quantitative control of mRNA levels in immune responses. In the "Infection and inflammation" session, besides pathogens infecting the host, the host-pathogen interactions cause dynamic changes in local immune cell integrity, which can often can lead to development of various diseases. Mechanisms controlling this outcome need to be understood. The "Vaccine development" session provided insight into how next-generation vaccines are being designed and developed. Merging structural biology, bioinformatics, and human immunology is a key to this end. In the "Metabolism and immune regulation" session, various metabolites are now being identified using mass spectroscopy and shown to play important roles in the immune system. Using metabolomics, undescribed or as yet unidentified small molecules will give clues to solve many questions in immunology.

Of note, the symposium this year attracted more young researchers, and this added value to the event.

12th PGRN-RIKEN Strategic Alliance Meeting

The Global Alliance for Pharmacogenomics (GAP), a collaborative program between the former RIKEN Center for Genomic Medicine (now RIKEN IMS) and the US National Institute of Health (NIH) Pharmacogenomics Research Network (PGRN), was started in 2008, with the objective of identifying the relationship between genetic variants and individual responses to drugs, including efficacy and side effects. PGRN-RIKEN strategic alliance meetings, held alternately in Japan and United States, allow for face-to-face discussions about the progress of ongoing projects and future directions for the PGRN-RIKEN collaboration.

On September 9–10, 2015, IMS hosted the 12th PGRN-RIKEN Strategic Alliance Meeting at the TKP Garden City Premium of the Landmark Tower Yokohama, in Yokohama, Japan. It started with an introduction to PGRN's structural reform as of July 1, 2015 from Prof. Kathy Giacomini, Program Leader of the PGRN, followed by two presentations by PGRN PIs on the current situation regarding clinical implementation of pharmacogenomics in the US. From the RIKEN side, Dr. Taisei Mushiroda, Group Director of IMS, presented data on the clinical utility of genomic biomarkers for warfarin sensitivity and carbamazepine-induced skin rash.

In addition to these formal presentations, all 35 participants had in-depth discussions about the four ongoing collaborative activities: "Genetic Determinants of Clinical Cardiovascular Events in Patients Receiving Statins", "Genetic Basis of Variability in VEGF Plasma Levels", "African Ancestry Pharmacogenomics" and "Targeted Resequencing of Candidate Genes from CALGB 40101".

Participants also explored three new research proposals from PGRN and finally decided to adopt two of them as additional collaboration projects, then the meeting concluded successfully.

The 2nd IMS Symposium

On May 28, 2015, the RIKEN Center for Integrative Medical Sciences (IMS) held its second public symposium on new medical sciences for the advancement of personalized and preventive medicine at Station Conference Tokyo.

The symposium was attended by 114 participants, including researchers from universities, various research institutes, and pharmaceutical and medical companies.

After the opening greetings by Mr. Hiroshi Tsuboi, Deputy Director-General of the Office of Healthcare Policy in the Cabinet Secretariat and Mr. Yoshiaki Ando, Deputy Director-General, Research Promotion Bureau in the Ministry of Education, Culture, Sports, Science and Technology (MEXT), seven IMS investigators from the center's different research sections spoke about their frontline research activities to advance personalized and preventive medicine in terms of predicting disease in the individual and the development of preventive methods and treatments tailored to the individual.

The keynote lectures were delivered by Dr. Makoto Suematsu, President of the Japan Agency for Medical Research and Development (AMED) and Dr. Masahira Hattori, Professor of the School of Advanced Science and Engineering at Waseda University. Dr. Suematsu spoke about the mission and prospects of AMED, while Dr. Hattori described the present and future of human microbiome research.

Harvard Summer School 2015

IMS offers a summer internship program for undergraduate students from Harvard University. In this program students do a research internship in the IMS laboratories, have basic biomedical sciences lectures by IMS PIs and attend a Japanese language course. They also participate in the RIKEN IMS Summer Program (RISP) and the RIKEN IMS-JSI International Symposium on Immunology. The participants receive a letter grade from IMS and course credit from Harvard. In 2015 from June 1 to August 10, there were three students from Harvard University, Sam Murphy, Larry Zhang, and Lucy Nam.

Mr. Murphy conducted his research project in the Laboratory for Transcriptional Regulation (Dr. Taniuchi), Mr. Zhang in the Laboratory for Medical Science Mathematics (Dr. Tsunoda) and Ms. Nam in the Laboratory for Developmental Genetics (Dr. Koseki). During their internships, the students had numerous discussions with IMS researchers and, at the end of the program, they gave oral presentations describing their research results.

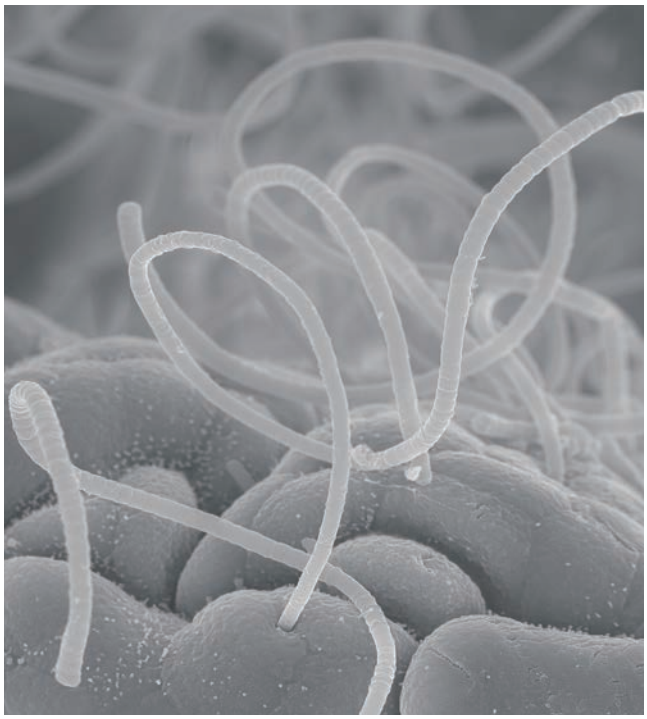
In addition, they visited Yokohama Science Frontier High School and met with students who want to become scientists. On this occasion, they also experienced Japanese culture and learned Sado (tea ceremony) from the local high school students.

Adjunct Professorship Programs

IMS collaborates with and accepts graduate students from 8 domestic university graduate schools. There are now a total of 30 adjunct professors/associate professors in IMS (Table), and 55 students studied at IMS in 2015. On August 29, IMS held a briefing session on adjunct graduate school programs. Thirty students participated from Hokkaido, Miyagi, Tokyo, Kanagawa, Osaka, Tokushima and Fukuoka prefectures. The session provided an opportunity for students to visit and talk directly with lab leaders and to consider their future directions.

Table: Joint graduate school programs

Graduate Program	Affiliated IMS Investigator
Graduate School of Medicine, Osaka University	Takashi Saito (Visiting Professor), Takashi Tanaka (Visiting Professor)
Department of Immunology, Graduate School of Medicine, Chiba University	Takashi Saito (Visiting Professor), Haruhiko Koseki (Visiting Professor), Hiroshi Ohno (Visiting Professor), Ichiro Taniuchi (Visiting Professor), Shin-ichiro Fujii (Visiting Associate Professor), Yasuyuki Ishii (Visiting Associate Professor), Fumihiko Ishikawa (Visiting Associate Professor)
School of Biomedical Science, Tokyo Medical and Dental University	Takashi Saito (Visiting Professor)
Graduate School of Medicine, Yokohama City University	Michiaki Kubo (Visiting Professor), Shiro Ikegawa (Visiting Professor), Mayumi Tamari (Visiting Professor), Tatsuhiko Tsunoda (Visiting Professor), Hidewaki Nakagawa (Visiting Professor), Taisei Mushiroda (Visiting Professor), Yukihide Momozawa (Visiting Associate Professor), Yoichiro Kamatani (Visiting Associate Professor)
Graduate School of Medical Life Science, Yokohama City University	Hiroshi Ohno (Visiting Professor), Makoto Arita (Visiting Professor), Mariko Okada (Visiting Professor), Takaharu Okada (Visiting Associate Professor), Kazuyo Moro (Visiting Associate Professor)
Research Institute of Biological Sciences, Tokyo University of Science	Masato Kubo (Professor), Shohei Hori (Visiting Associate Professor)
Graduate School of Medicine, Kyoto University	Fumihiko Ishikawa (Visiting Associate Professor)
Graduate School of Medicine, Keio University	Masayuki Amagai (Professor), Kenya Honda (Professor), Shigeo Koyasu (Visiting Professor), Haruhiko Koseki (Visiting Professor)



Part 5

Data and Statistics

Publlications 2015

Table: IMS Publlications Jan-Dec, 2015

Journal	IF (2014)	Number of Papers 2015
Nature	41.5	2
Nature Reviews Immunology	35.0	1
Science	33.6	2
Cell	32.2	2
Nature Genetics	29.4	8
Immunity	21.6	2
Nature Immunology	20.0	5
Journal of Clinical Oncology	18.4	1
Cell Metabolism	17.6	1
BMJ-British Medical Journal	17.4	1
Science Translational Medicine	15.8	1
Gut	14.7	1
Genome Research	14.6	1
American Journal of Respiratory and Critical Care Medicine	13.0	1
Journal of Experimental Medicine	12.5	7
Cell Host & Microbe	12.3	1
Journal of Allergy and Clinical Immunology	11.5	3
Nature Communications	11.5	11
Journal of Hepatology	11.3	2
Hepatology	11.1	7
American Journal of Human Genetics	10.9	3
Blood	10.5	3
Leukemia	10.4	1
Trends in Immunology	10.4	1
Annals of the Rheumatic Diseases	10.4	2
Biological Psychiatry	10.3	1
Nature Reviews Rheumatology	9.8	1
Journal of Cell Biology	9.8	1
Proceedings of the National Academy of Sciences of the United States of America	9.7	4
Nature Protocols	9.7	1
Journal of the American Society of Nephrology	9.3	1
eLIFE	9.3	1
Clinical Cancer Research	8.7	1
Oncogene	8.5	1
Cell Reports	8.4	3
Diabetes	8.1	2
BMC Biology	8.0	1
Clinical Pharmacology & Therapeutics	7.9	2
Seminars in Immunopathology	7.7	3
PLoS Pathogens	7.6	1
PLoS Genetics	7.5	1
Current Opinion in Immunology	7.5	2
Mucosal Immunology	7.4	1
Journal of Investigative Dermatology	7.2	2
Journal of Bone and Mineral Research	6.8	1
Diabetologia	6.7	1
Molecular Ecology	6.5	1
Human Molecular Genetics	6.4	4
Science Signaling	6.3	1
Oncoimmunology	6.3	1
Journal of Clinical Endocrinology & Metabolism	6.2	1
Allergy	6.0	2
Arteriosclerosis Thrombosis and Vascular Biology	6.0	1
Others	6.0	166
TOTAL		**279**

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Guest lectures 2015

Table: Guest Lectures Jan–Dec, 2015

Date	Speaker	Affiliation	Country	Title
14-Jan-15	Dr. Matteo Barberis	Synthetic Systems Biology, Swammerdam Institute for Life Sciences, University of Amsterdam	The Netherlands	A systems biology approach to the tuning of cell cycling and chromatin dynamics
23-Jan-15	Dr. Taro Tsujimura	Department of Advanced Nephrology and Regenerative Medicine, University of Tokyo Hospital	Japan	Enhancer allocation and chromatin conformation: topological and regulatory autonomy of the adjacent Tfap2c and Bmp7 genes in mice
23-Jan-15	Dr. Wojciech Makalowski	Institute of Bioinformatics, University of Münster	Germany	Nanopore sequencing for genotyping pathogens of tropical diseases
9-Feb-15	Dr. Hisashi Arase	Laboratory of Immunochemistry, WPI Immunology Frontier Research Center and Department of Immunochemistry, Research Institute for Microbial Diseases, Osaka University	Japan	Cellular misfolded proteins rescued from protein degradation by MHC class II molecules are targets for autoimmune diseases
13-Feb-15	Dr. Daniel K. Nomura	Department of Nutritional Science and Toxicology, University of California Berkeley	USA	Chemoproteomic and metabolomic strategies for drug discovery and toxicology
25-Feb-15	Dr. Gabriel D. Victora	Whitehead Institute for Biomedical Research	USA	Cellular and clonal dynamics in germinal centers
26-Feb-15	Dr. Yeonseok Chung	College of Pharmacy, Seoul National University	Korea	Th17 and Tfh cells at the cross-road of atherosclerosis and autoimmunity
6-Mar-15	Dr. Yibo Wu	Institute of Molecular Systems Biology, ETH Zurich	Switzerland	Multilayered genetic & omics dissection - A new age for biomedical researches
14-May-15	Prof. Susan M. Gasser	Friedrich Miescher Institute for Biomedical Research	Switzerland	Gene and repeat repression during development: a role for histone H3K9 methylation
16-May-15	Dr. Shigeru Kondo	Laboratory of Pattern Formation, Graduate School of Frontier Biosciences Osaka University	Japan	Turing pattern formation without diffusion
22-May-15	Dr. Masashi Watanabe	Experimental Immunology Branch, National Cancer Institute, NIH	USA	The role of tumor suppressor p53 in CD4 T cell function and homeostasis
23-Jul-15	Dr. Richard A. Flavell	Department of Immunobiology, Howard Hughes Medical Institute, Yale School of Medicine	USA	Regulation and resolution of immune response
24-Jul-15	Dr. Melita Vidaković	Department of Molecular Biology, Institute for Biological Research	Serbia	The role of epigenetics mechanisms in diabetes mellitus
28-Jul-15	Dr. Yun-Cai Lui	Division of Cell Biology, La Jolla Institute for Allergy and Immunology	USA	Control of Treg stability and function by O2 sensor
1-Sep-15	Dr. Yasushi Matsumura	Department of Integrated Medicine, Osaka University Graduate School of Medicine	Japan	Toward construction of new clinical research platform
25-Sep-15	Dr. Ichio Aoki	Magnetic Resonance Molecular Imaging Team, National Institute of Radiological Sciences	Japan	Magnetic resonance microimaging and functional "smart" contrast agents
20-Oct-15	Dr. Gregory F. Sonnenberg	Department of Microbiology and Immunology, Weill Cornell Medical College, Cornell University	USA	Immune regulation of intestinal health and disease
21-Oct-15	Dr. Julie Stacey	Chief Editor of EBioMedicine	USA	EBioMedicine: Translating science to improve health
29-Oct-15	Dr. Hajime Karasuyama	Department of Immune Regulation, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University	Japan	Basophils have emerged as a key player in immunity: a neglected minority gains new respect
30-Oct-15	Dr. Yutaka Suzuki	Department of Computational Biology and Medical Sciences, the University of Tokyo	Japan	Single cell analysis of lung cancer cell lines
2-Nov-15	Mr. Tony Z. Jia	Department of Molecular Biology, and Center for Computational and Integrative Biology, Massachusetts General Hospital Department of Chemistry and Chemical Biology, Harvard University	USA	Peptide-assisted nonenzymatic RNA replication
13-Nov-15	Dr. Matthew C. Lorincz	Department of Medical Genetics, University of British Columbia	Canada	Impact of LTR retrotransposons on the methylome, imprintome and transcriptome in mouse oocytes
17-Nov-15	Dr. Mark Shlomchik	Department of Immunology, University of Pittsburgh School of Medicine	USA	How autoimmunity gets started
11-Dec-15	Dr. Yoshihiro Ogawa	Department of Molecular Endocrinology and Metabolism, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University	Japan	Tissue remodeling in metabolic diseases
14-Dec-15	Dr. Yoshiko Takahashi	Department of Zoology, Graduate School of Science, Kyoto University	Japan	The biology of the tail: An organ that is a characteristic feature of the vertebrates but remains poorly understood
25-Dec-15	Dr. Reiko Tanaka	Department of Bioengineering, Imperial College of London	UK	"Double switch" in mathematical models of atopic dermatitis reveals underlying mechanisms of disease progression

Budget, personnel and patents

IMS Budget FY2015

IMS Budget FY2015	JPY Million
Government funding for operations	3,011
Commissioned research	1,266
External competitive funding	977
Total	**5,254**

Patents

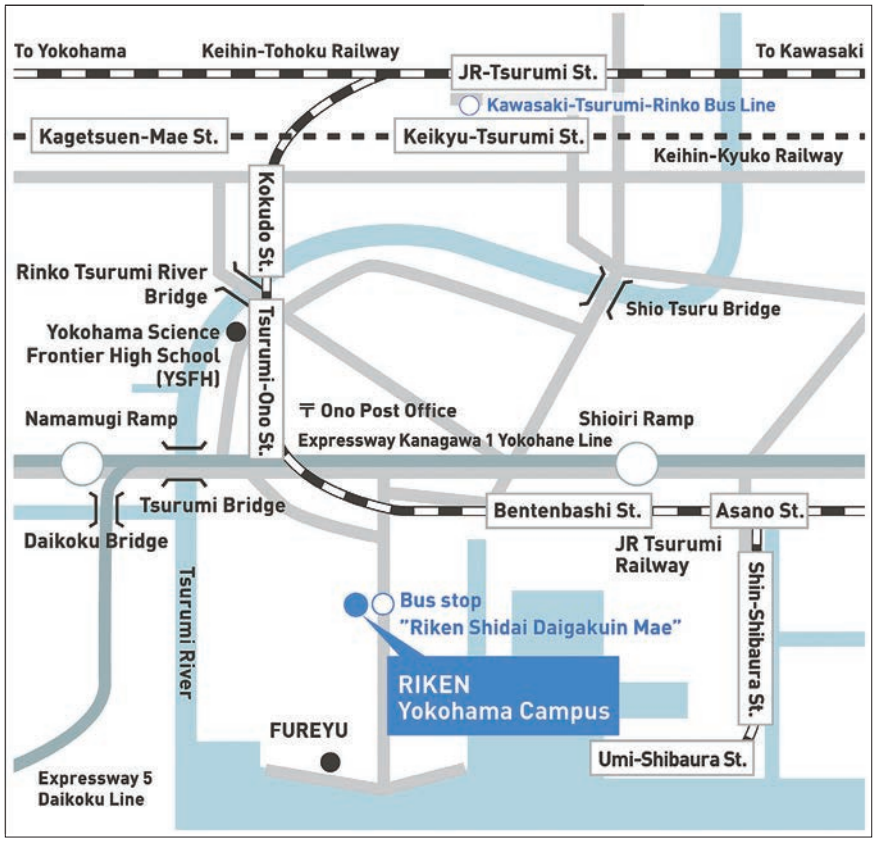
There were 25 patents filed from January to December in 2015.

Patents	Total	International patents (PCT)	Domestic patents (Japan)
2013	32	20	12
2014	32	24	8
2015	25	16	9

Personnel FY2015

Category	Number
Director	1
Senior Advisor	2
Deputy Director	2
Group Director	10
Team Leader	26
Coordinator	2
Partnership-Promotion Coordinator	1
Deputy Team Leader	4
Senior Scientist	20
Research Scientist	40
Postdoctoral Researcher	13
Special Postdoctoral Researcher	5
Foreign Postdoctoral Researcher	3
Research Fellow	7
Senior Technical Scientist	2
Technical Scientist	11
Technical Staff I	55
Technical Staff II	69
International Program Associate	4
Research Associate	7
Junior Research Associate	19
Student Trainee	91
Assistant	29
Part-time Administrative Staff	10
Part-time Research Staff	4
Part-time Technical Staff	17
Research Consultant	2
Consultant	12
Senior Visiting Scientist	8
Visiting Scientist	177
Visiting Technical Scientist	33
Visiting Researcher	3
Temporary Staffing	9
Total	**698**

Access to RIKEN Yokohama Campus



Local Access

By Bus
Take the #08 bus from Platform 8 at the East Exit of Tsurumi Station (also accessible from the West Exit of Keikyu Tsurumi Station) and get off at the RIKEN Shidai Daigakuin Mae bus stop. The institute is across the street. All buses from this platform are bound for Fureyu.

Buses depart Tsurumi every 5–15 minutes. It takes about 15 minutes to arrive at RIKEN Yokohama. The fare is 220 yen in cash.

By Train
A 15-minute walk from JR Tsurumi-Ono Station (JR Tsurumi Line), which is directly accessible by transfer from JR Tsurumi Station.

Trains run about every 10 minutes during morning and evening rush hour, but less frequently at other times.

Searchable train timetables in English are available at http://www.hyperdia.com/en/

By Taxi
Use the taxi stand at the East Exit of JR Tsurumi Station or the West Exit of Keikyu Tsurumi Station. The trip takes about 10 minutes and costs around 1,200 yen.

From the Airport

From Haneda Airport

Route 1
Take the Keikyu Railways Airport Express* (blue kanji sign) for Yokohama and get off at Keikyu Tsurumi Station (27–29 minutes). Airport Express trains run every 10-15 minutes between 9:30 a.m. and 9:30 p.m. Next, follow the Local Access directions above to get to RIKEN Yokohama.

Route 2
Take any train marked with a green (express), red or dark grey kanji sign to Keikyu Kamata Station. Transfer to the Keikyu Main Line and take a local train* toward Yokohama until Keikyu Tsurumi Station* (12 minutes).

*Only Airport Express (blue kanji sign) and local trains (dark grey kanji sign) stop at Keikyu Tsurumi Station. Note that Keikyu Tsurumi Station and JR Tsurumi Station are two different railway stations and are separated by a bus rotary (the stations are about 150 meters apart).

From Narita Airport

From Narita Airport Station take the JR Sobu Line (Rapid Express), Airport Limousine Bus or JR Narita Express* to JR Shinagawa Station. (JR Sobu Line is the most inexpensive option and takes about 1 hour and 15 minutes). From JR Shinagawa Station take the JR Keihin Tohoku Line (Yokohama direction) to JR Tsurumi Station (18 minutes). Next, follow the Local Access directions above to get to RIKEN Yokohama.

* A reserved seat express that requires payment of a surcharge in addition to train fare.

Searchable train timetables in English are available at http://www.hyperdia.com/en/

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