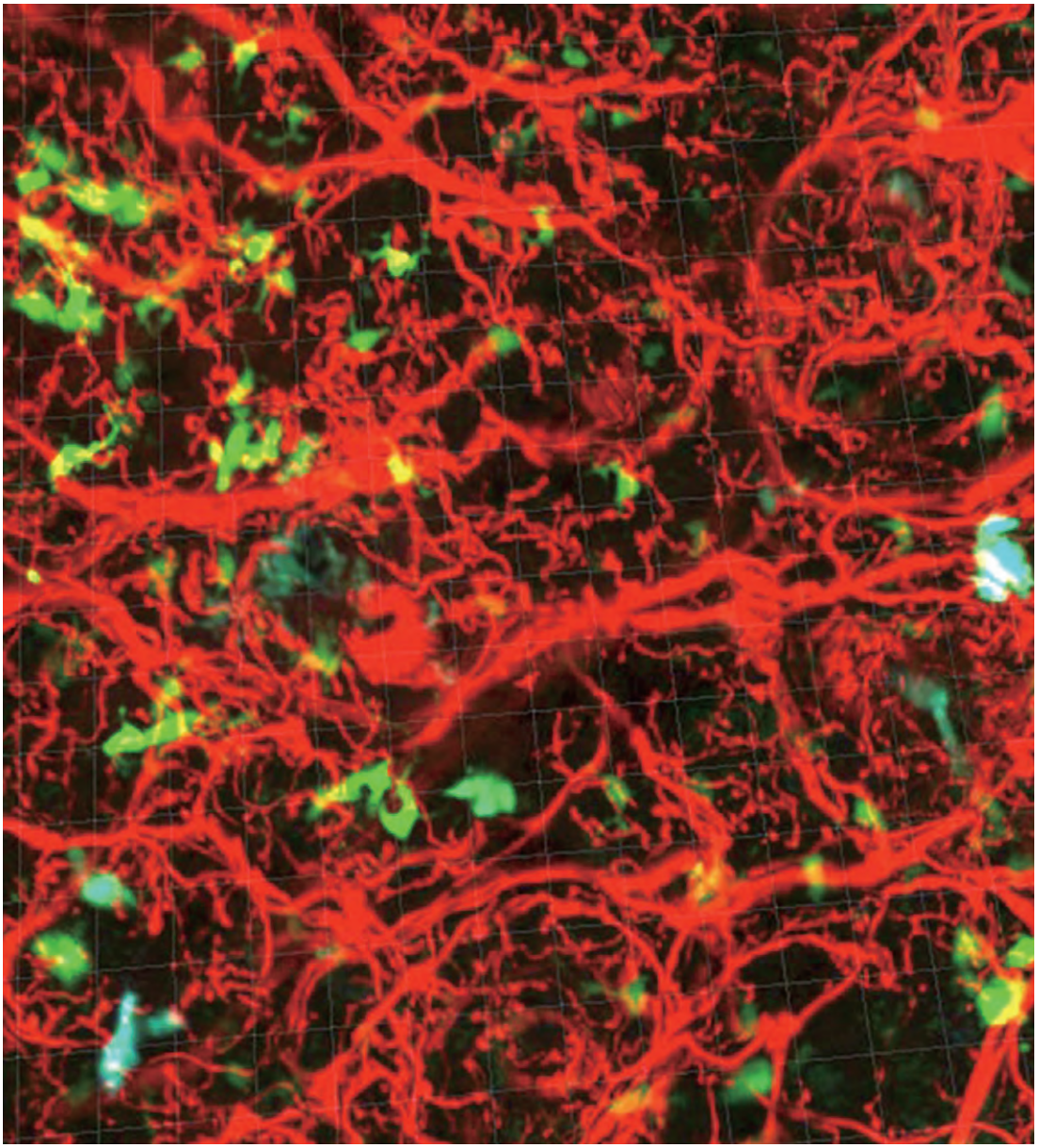
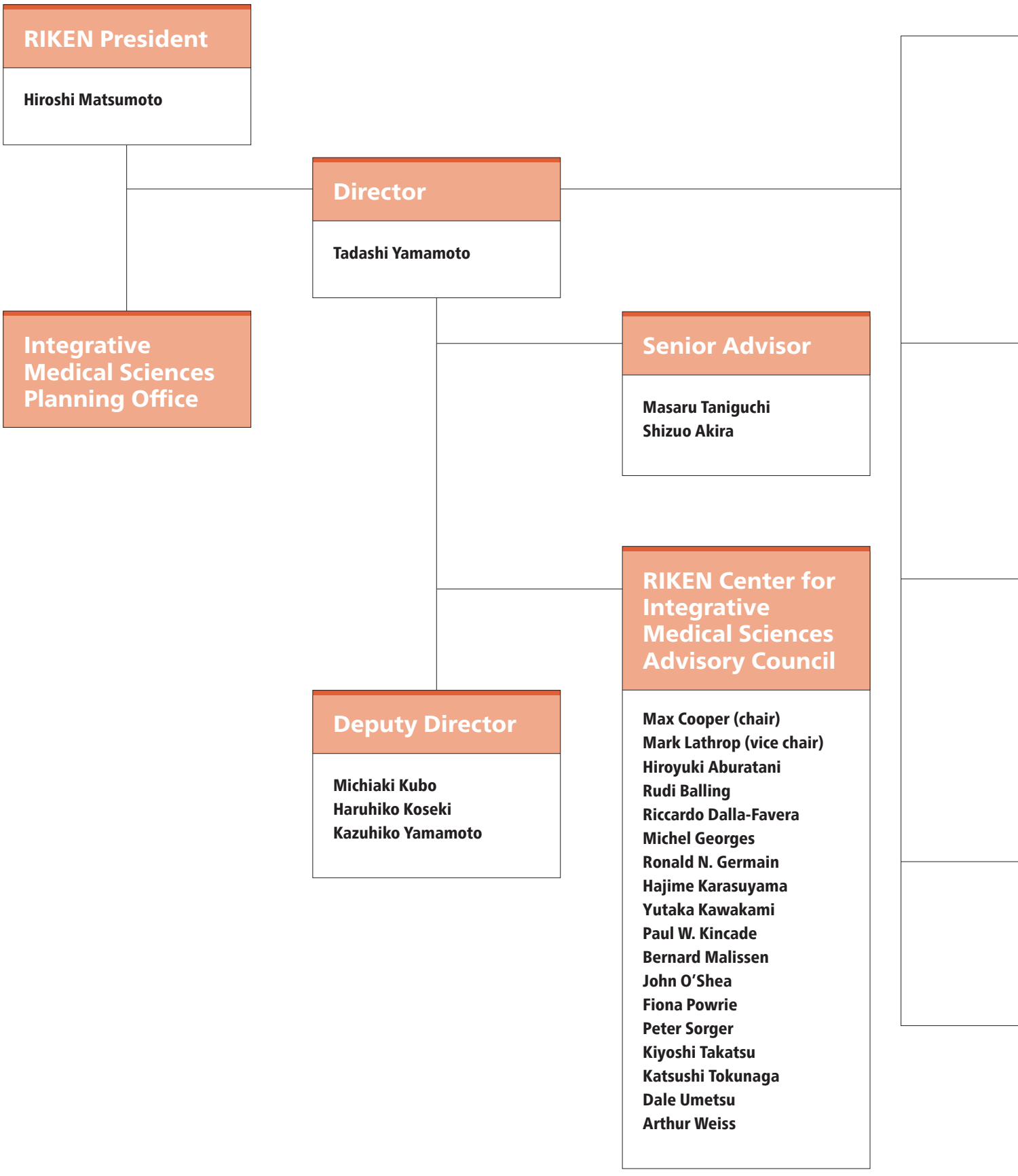


RIKEN IMS
Annual Report 2017

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: **Taishin Akiyama**
- 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**
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- Lab. for Immunogenetics: **Tadashi Yamamoto**
- 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**
- Lab. for Microbiome Sciences: **Masahira Hattori**

Core for Genomic Medicine

- Lab. for Genotyping Development: **Yukihide Momozawa**
- Lab. for Genome Sequencing Analysis: **Hidewaki Nakagawa**
- Lab. for Statistical Analysis: **Yoichiro Kamatani**
- Lab. for Pharmacogenomics: **Taisei Mushiroda**
- Lab. for International Alliance on Genomic Research: **Taisei Mushiroda**
- Lab. for Cardiovascular Diseases: **Kaoru Ito**
- 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: **Momoko Horikoshi**
- Lab. for Respiratory and Allergic Diseases: **Mayumi Tamari**

Program for Medical Innovations

- Lab. for Immune Regulation: **Masaru Taniguchi**
- Lab. for Immunotherapy: **Shin-ichiro Fujii**
- Drug Discovery Antibody Platform Unit: **Toshitada Takemori**

Young Chief Investigator Program

- YCI Laboratory for Immune Regeneration: **Tomokatsu Ikawa**
- YCI Laboratory for Cellular Bioenergetic Network: **Toshimori Kitami**
- YCI Laboratory for Next-Generation Proteomics: **Yibo Wu**
- YCI Laboratory for Trans-omics: **Katsuyuki Yugi**
- YCI Laboratory for Immunological Transcriptomics: **Hideyuki Yoshida**

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Director's Report

Just over two years have passed since I became Director of the RIKEN Center for Integrative Medical Sciences (IMS) in October 2015.

2017 was the last year of our center's five-year mid-term plan. RIKEN IMS was established in 2013 through the merging of two former centers, the Research Center for Allergy and Immunology and the Center for Genomic Medicine. The aim of the new center was to contribute to future medical care through establishment of innovative medical science by clarifying the mechanisms of disease development through a combination of genomic, immunological and omics analysis approaches. Looking back, I believe that we have achieved this aim but it is only the first of many steps to come as we strive towards our long-term goal of contributing to the next generation of medical science leading to a healthy long-lived society.

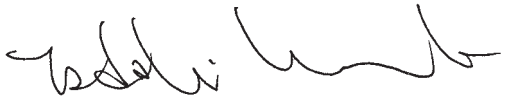
Examples of how IMS researchers are driving innovative multidisciplinary science and laying the foundation for the next IMS mid-term plan include Kazuhiko Yamamoto's work on rheumatoid arthritis, a complex multi-genetic autoimmune disease, and Shin-ichiro Fujii's work on cell therapeutics. By using the results from genome-wide association studies (GWAS), Dr. Yamamoto's team studied how the associated genes in human were involved in disease pathogenesis by combing molecular biology approaches and animal disease models, essentially transforming one type of research (GWAS) to another (mechanistic). Dr. Fujii's laboratory launched a clinical trial study on NKT cell therapy for early stage lung cancer patients in collaboration with the National Hospital Organization. In addition, his group is investigating novel drug delivery systems that have the potential to enhance antitumor immunity, and efforts are currently underway for preclinical studies that could ultimately lead to clinical trials. Such translational research, or application of basic immunology research towards disease therapy, is an area that IMS plans to strengthen in the coming years, especially in the treatment of cancer and development of the field of cancer immunology.

From the feedback we received at the IMS Advisory Council Meeting held in September 2016, and the RIKEN Advisory Council meeting held in December 2016, we began to plan for the second five-year center term that starts in April 2018. While both advisory councils agreed that IMS has made many important scientific contributions in the areas of immunology and genomics, they felt our center could make even more significant advances through the addition of a translational regulation division, specifically the Division of Genomic Technologies (DGT) led by Piero Carninci. We agreed that the inclusion of DGT would have a strong synergistic effect on our center's original goal to establish innovative medical research through multidisciplinary approaches, and I am happy to announce that, as of April 1, 2018, they will become part of the new IMS center. New collaborations and partnerships are already forming, and I look forward to seeing the unfolding of new research fields, platforms and technologies that result from this merger of complimentary expertises.

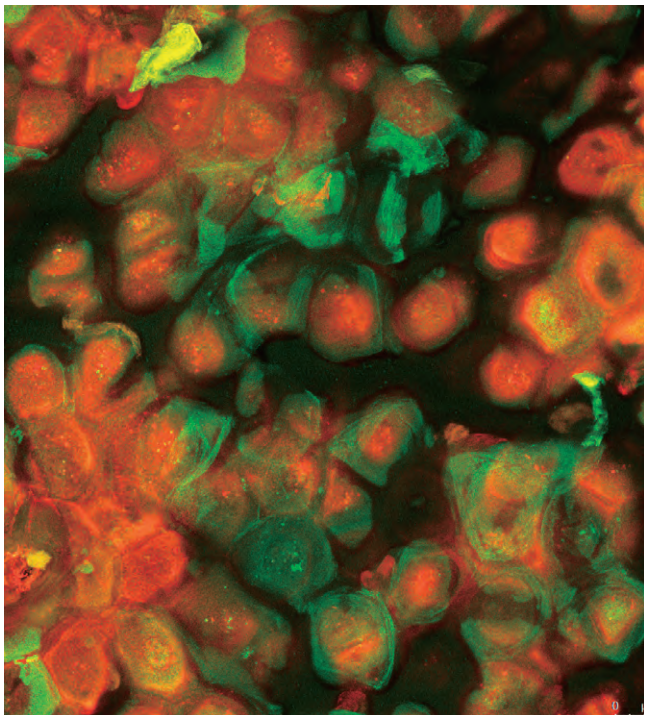
One program I am quite proud of is the IMS Young Chief Investigator (YCI) program. This program was established in 2011 with the hopes of nurturing young scientists who will become future leaders in multidisciplinary research. This year we welcomed two new scientists, Katsuyuki Yugi who heads the YCI Laboratory for Trans-omics, and Yibo Wu who heads the YCI Laboratory for Next-Generation Proteomics. Moreover, as demonstration of this program's success, Tomokatsu Ikawa, former head of the YCI Laboratory for Immune Regeneration, became an Associate Professor in Immunobiology at Tokyo University of Science.

Our researchers continued to perform outstanding research and publish papers in significant journals in 2017. Kenya Honda reported that TH1 cell induction and inflammation is driven by ectopic colonization of oral bacteria in the intestine *(Science, 2017)*. Sidonia Fagarasan reported that brain monoamines and emotional behavior is perturbed in PD-1-deficient mice through metabolic shift induced by systemic activation of T cells *(Nature Immunology, 2017)*. Fumihiko Ishikawa reported that inhibition of critical pathways overcomes mutational complexity in acute myeloid leukemia *(Science Translational Medicine, 2017)*. There were 312 papers published from IMS in 2017.

With the approaching expansion of our center in 2018, I believe that IMS will have an even greater impact on the scientific community in the years ahead.



Tadashi Yamamoto
Director,
RIKEN Center for Integrative Medical Sciences



Part 1

Research Highlights

Alternative pathway for NKT cell development

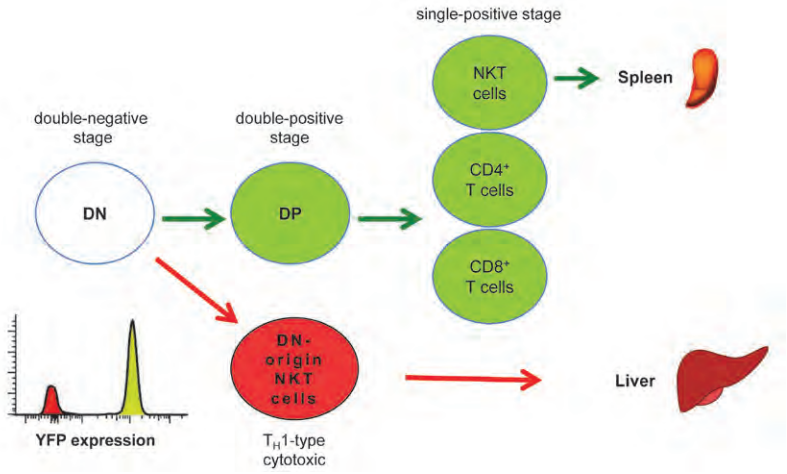


Figure: Novel alternative developmental pathway for NKT cells
In the genetic fate-mapping experiment, yellow fluorescent protein (shown in light green) is turned on starting at the $CD4^+CD8^+$ double-positive (DP) stage, thus making it possible to mark mature T and NKT cells that developed from DP stage thymocyte precursors. However, cells before the DP stage, i.e., at the $CD4^-CD8^-$ double-negative stage as well as mature NKT cells that developed directly from DN stage precursors without passing through the DP stage, would not express the yellow fluorescent protein (shown in red).

The Natural killer T (NKT) cell is called the fourth type of lymphocyte, following the three major types known as T and B lymphocytes as well as natural killer (NK) cells. NKT cells are different from other lymphocytes because they function to activate various types of immune cells in the innate and acquired immune systems, resulting in establishing long-term memory responses against pathogens and tumors.

NKT cells have a single invariant T cell receptor (TCR) recognizing only glycolipid antigens, whereas the TCR repertoire of conventional T cells recognizes an almost unlimited number of peptide antigens. The NKT cell receptor gene is conserved among species by Darwinian-positive selection, thus, NKT cells are thought to be important for protection against pathogens and essential for the species survival. However, the question of how these cells develop remains a puzzle for researchers.

T-lineage cells generally pass through three developmental stages (Figure) as they differentiate in the thymus. The most immature thymic precursor cells, known as the double-negative stage, express neither CD4 nor CD8 surface markers. As these precursors differentiate further, they express both surface markers, called the double-positive stage, before finally maturing into either CD4 or CD8 single-positive T cells.

It has long been believed that NKT cells develop in the thymus through the double-positive stage along with conventional T cells. However as this conventional theory did not provide an explanation for functional differences between NKT and T cells, Nyambayar Dashtsoodol, Masaru Taniguchi and their colleagues in IMS sought to resolve this dilemma by using genetically modified mice that completely lack gene rearrangement at the double-positive stage. If the conventional theory was correct, neither T cells nor NKT cells should exist in this mouse. Surprisingly, they could detect NKT cells, although their number was relatively reduced. "This result suggested the existence of an alternative NKT cell developmental pathway," commented Nyambayar.

To confirm this unexpected finding, they used a technique called genetic fate-mapping. They employed another genetically modified mouse expressing a yellow fluorescent protein (YFP) that turns on during the double-positive stage. While $CD4^+$ and $CD8^+$ T cells from the mice expressed the YFP, some NKT cells did not, indicating that they developed without passing through the double-positive stage. "Our findings demonstrated that some NKT cells can bypass the double-positive stage and differentiate directly from the double-negative stage, which means these cells were differentiated earlier than it was thought" remarked Nyambayar. They also demonstrated that NKT cells generated by this alternative pathway were mainly found in the liver and highly expressed IFN-γ, a cytokine active against pathogens and tumor cells, and perforin and granzyme, proteins that are important for cytotoxic activity.

"NKT cells that develop via this alternative pathway have higher cytotoxic activity and are essential for body defenses. We hope to elucidate their function and contribute to cancer immune therapy in the future," says Masaru Taniguchi.

Original Paper:
Dashtsoodol N, Shigeura T, Aihara M, Ozawa R, Kojo S, Harada M, Endo TA, Watanabe T, Ohara O, Taniguchi M. Alternative pathway for the development of Vα14+ NKT cells directly from $CD4^-CD8^-$ thymocytes that bypasses the $CD4^+CD8^+$ stage. ***Nat Immun*** 18, 274–282 (2017)

Six new genetic loci associated with atrial fibrillation are identified in the Japanese population

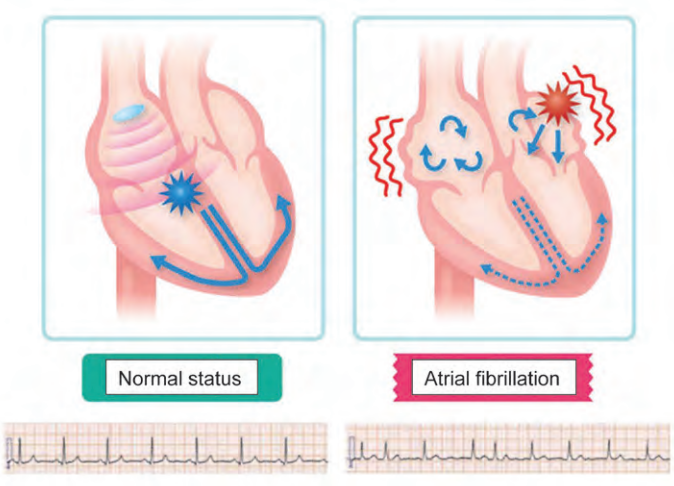


Figure: Atrial fibrillation associated with irregular and rapid heart rate

Atrial fibrillation (A-fib) is the most common cardiac arrhythmia. It is associated with abnormal cardiac rhythm characterized by irregular and often rapid fibrillation of the atria, the upper chambers where blood enters the heart (Figure). Untreated, A-fib increases the risk of stroke, heart failure and other heart-related complications. In Japan and elsewhere, the prevalence of A-fib increases with age, reaching 3.2% among Japanese who are 80 years old. Several studies have indicated a relationship between genetic background and the prevalence of A-fib. For example, individuals who have at least one parent with A-fib have approximately three times greater risk of developing the disease than people without parents with A-fib. In addition, a large-scale cohort study has shown an increased risk of A-fib in populations of European ancestry compared to Africans, Hispanics or Asians. These observations suggested different A-fib pathogenesis and risk factors, especially genetic factors among different ancestry groups. Given the increasing aging population in Japan, the identification of predictive risk markers for A-fib is urgently needed.

To investigate the genetic loci associated with A-fib in the Japanese population, a research team at the RIKEN Center for Integrative Medicine conducted a genome-wide associated study (GWAS) with 8,180 A-fib patients and 28,612 controls, followed by an additional study with 3,120 patients and 125,064 controls from the Japanese population. Combining these two studies into a meta-analysis, the team successfully identified six new loci near the *KCND3*, *PPFIA4*, *SLC1A4-CEP68*, *HAND2*, *NEBL* and *SH3PXD2A* genes. Five of the six newly discovered loci were specific to the Japanese population, suggesting that there might be different genetic factors affecting susceptibility across ancestry groups.

Surprisingly, further expression quantitative trait locus (eQTL) analysis showed that *PPFIA4* and *SH3PXD2A* are involved in neural development processes, especially axon guidance and neural crest cell development. When the investigators analyzed these pathways, they discovered that several genes involved in these neural processes are significantly associated with A-fib. Further study is required to understand the molecular basis of the involvement of axon guidance as well as neural crest cells in A-fib pathogenesis.

The team also evaluated the risk of cumulative effects from a total of 15 associated genetic variants (the newly discovered 6 variants and 9 previously reported variants). In the group of patients who carried the most risk alleles, they predicted an approximately 7.0 times greater risk compared to individuals in the group with the fewest risk alleles. The implementation of a genetic risk score for A-fib could aid in identifying individuals who are at risk for cardiac arrhythmia.

The genotype data of the Japanese population used in this study is publicly available in an anonymous format at the National Bioscience Database Center, Japan Science and Technology Agency (NBDC, JST).

Original paper:
Low SK, Takahashi A, Ebana Y, Ozaki K, Christophersen IE, Ellinor PT, AFGen Consortium, Ogishima S, Yamamoto M, Satoh M, Sasaki M, Yamaji T, Iwasaki M, Tsugane S, Tanaka K, Naito M, Wakai K, Tanaka H, Furukawa T, Kubo M, Ito K, Kamatani Y, Tanaka T. Identification of six new genetic loci associated with atrial fibrillation in the Japanese population. ***Nat Genet*** 49, 953–958 (2017)

Mast cells are crucial for induction of group 2 innate lymphoid cells and clearance of helminth infections

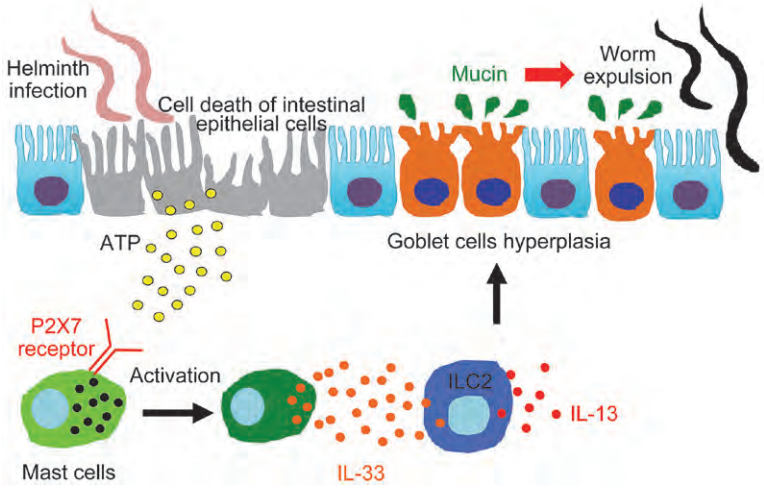


Figure: Mechanism by which mast cells activate ILC2s for worm expulsion
Upon helminth infection, ATP is released from injured/dying epithelial cells (top left) and activates mast cells through the P2X7 receptor (bottom left). Activated mast cells release IL-33 which in turn stimulates ILC2s leading to the production of IL-13 (bottom center). Finally, IL-13 promotes mucin secretion by goblet cells (top right) to expel worms.

The World Health Organization (WHO) reported that more than 1.5 billion people, or 24% of the world's population, suffer from helminth infections and that such infections are widely distributed in tropical and subtropical areas. Infections with intestinal helminths can cause anemia and malnutrition and are major socioeconomic problems in developing countries. There is thus an urgent need to elucidate the mechanism of protective immune responses against helminths.

Our body activates type 1 immune responses against pathogens such as bacteria and viruses, while type 2 immune responses are induced by helminths. A research group led by Hiroshi Ohno of the RIKEN Center for Integrative Medical Sciences demonstrated that mast cells play a critical role for activation of group 2 innate lymphoid cells (ILC2s), which are responsible for parasite expulsion in the early phase of infection.

The researchers examined Spi-B-deficient (*Spib*$^{-/-}$) mice, which exhibit mast cell hyperplasia due to altered myeloid cell differentiation. To analyze the role of Spi-B in intestinal helminth infection, they orally infected *Spib*$^{-/-}$ mice with *Heligmosomoides polygyrus* (Hp), an intestinal helminth, and found that the *Spib*$^{-/-}$ mice were better protected than wild-type (WT) mice. There were far fewer Hp eggs in the feces of *Spib*$^{-/-}$ mice compared to WT mice, and also fewer adult worms. In addition, the number of mucus-producing goblet cells was increased in *Spib*$^{-/-}$ mice. These findings revealed an unexpected resistance of *Spib*$^{-/-}$ mice to Hp infection. Since the depletion of mast cells in *Spib*$^{-/-}$ mice before the infection completely eliminated their Hp resistance, this resistance was dependent on mast cells.

They further found that ILC2s and IL-33, a cytokine that activates ILC2s, were increased in Spib$^{-/-}$ mice after Hp infection. It had been thought that intestinal epithelial cells release IL-33 to activate ILC2s; however, surprisingly, Ohno and colleagues found that mast cells are crucial for IL-33 production and ILC2 activation (Figure). "We found a new function of mast cells in innate immune responses against nematode infection. When the nematode invades the intestinal tissue, adenosine triphosphate (ATP) is released from the injured epithelial cells and stimulates mast cells. Activated mast cells secrete IL-33 and thereby stimulate ILC2s. Then, activated ILC2s produce IL-13, which promotes mucin secretion by goblet cells in the intestinal epithelia, leading to worm expulsion," says Ohno.

Increasing or activating mast cells can be an attractive and effective strategy for controlling helminth infections. However, at the same time, type 2 immune responses, despite the benefit of protection against helminth infections, can be a cause of allergy and inflammatory diseases. "Regulation of mast cell-derived type 2 immune responses could be a new preventive measure and therapy for these diseases," concludes Ohno.

Original paper:
Shimokawa C, Kanaya T, Hachisuka M, Ishiwata K, Hisaeda H, Kurashima Y, Kiyono H, Yoshimoto T, Kaisho T, Ohno H. Mast cells are crucial for induction of group 2 innate lymphoid cells and clearance of helminth infections. ***Immunity*** 46, 863–874 (2017)

Mapping disease genes to immune cells

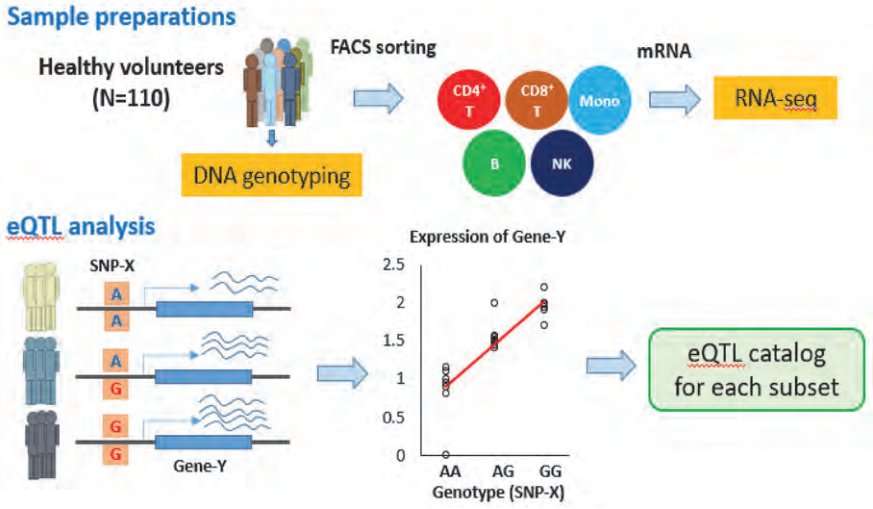


Figure: Researchers demonstrate a new way to identify gene variants associated with complex diseases

Gene variants tied to rheumatoid arthritis and other diseases can now be traced to particular faulty immune cells.

A valuable analytical tool developed by RIKEN researchers could help to reveal when multiple genes are all working through a common pathway in specific immune cells that underpin complex diseases such as diabetes or heart disease.

To demonstrate the tool's effectiveness, the scientists applied it to DNA datasets from rheumatoid arthritis sufferers and confirmed the importance of immune dysregulation through a cell-signaling protein called tumor necrosis factor (TNF). Anti-TNF drugs are some of the best-selling medicines in the world—a fact that Kazuyoshi Ishigaki of the RIKEN Center for Integrative Medical Sciences says confirms the "robustness of our pipeline." As such, he adds, "It's reasonable to expect that our pipeline can be applied to other diseases."

To identify the genes and biological pathways involved in complex immune-related diseases, Ishigaki and his team—led by Kazuhiko Yamamoto and Yuta Kochi, also from the RIKEN Center for Integrative Medical Sciences—first looked for DNA sequences that explained gene activity levels in five kinds of immune cells as well as unfractionated peripheral blood (Figure). They used blood samples from 105 healthy Japanese individuals to build their 'expression quantitative trait loci' (eQTL) database for each of these cell types.

The researchers then cross-referenced their database against a catalogue of published gene-sleuthing studies and showed that even some non-autoimmune diseases, such as Parkinson's disease and schizophrenia, have a large immune component. "By investigating critical immune pathways in these diseases, we might be able to develop novel immunologic treatments for them," Ishigaki says.

The RIKEN investigators next applied their cell-sorting model to genetics datasets from thousands of Japanese individuals with rheumatoid arthritis. They found that the combined action of 176 genes altered TNF signaling in a particular subset of immune cells known as helper T cells, which express a surface protein called CD4, but not in other types of immune cells.

According to Ishigaki, drug developers can use this finding to build a new generation of TNF-targeted drugs that target both TNF and CD4 receptors. This will give the drugs a more anti-inflammatory effect as they will act only in those cells that have gone awry in the autoimmune disease. "Our findings suggest that we can improve the efficiency of current anti-TNF therapy," he says.

Kochi hopes the research community will embrace his team's eQTL database for identifying genes implicated in particular cells in any disease of interest—and since "the prediction models are provided as supplemental data in the article," he says, "anyone can use them."

This article was reproduced from RIKEN Research
http://www.riken.jp/en/research/rikenresearch/highlights/20170017/

Original paper:
Ishigaki K, Kochi Y, Suzuki A, Tsuchida Y, Tsuchiya H, Sumitomo S, Yamaguchi K, Nagafuchi Y, Nakachi S, Kato R, et al. Polygenic burdens on cell-specific pathways underlie the risk of rheumatoid arthritis. ***Nat Genet*** 49, 1120–1125 (2017)

New link between Polycomb and Xist RNA for X chromosome inactivation

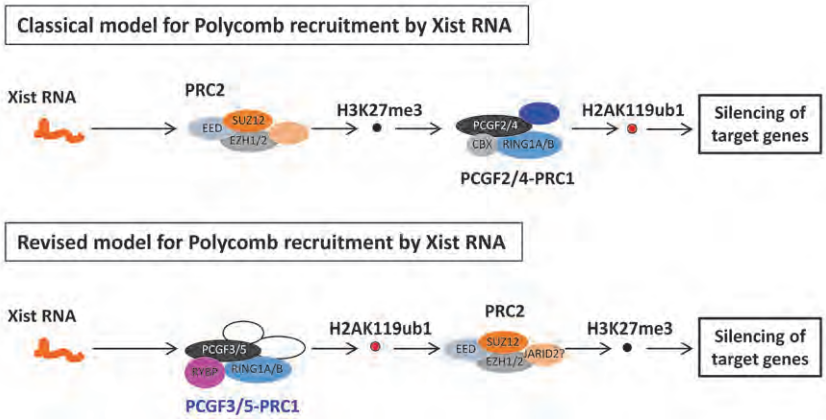


Figure: New model of Polycomb-mediated gene silencing by Xist RNA
The classical model proposed a direct interaction between Xist RNA and PRC2, followed by the recruitment of the PCGF2/4-PRC1 complex through its chromobox-containing CBX protein subunit. Results of the present study have led to a new model in which Xist RNA instead recruits another PRC1 subcomplex, PCGF3/5-PRC1. Subsequent recruitment of PRC2 on the inactive X chromosome is dependent on monoubiquitylation of histone H2A catalyzed by PCGF3/5-PRC1. (Known subunits of the PRC1 and PRC2 complexes are indicated on the figure by their acronyms. Unlabeled subunits are accessory proteins.)

Mammalian females have two X sex chromosomes (XX) but males are XY, so females have twice as many X-linked genes as males. To balance X-linked gene dosage, females randomly silence one of the X chromosomes in individual cells early in development. This epigenetic process, called X chromosome inactivation, involves a noncoding RNA known as Xist and the Polycomb repressive complexes PRC1 and PRC2. Haruhiko Koseki and colleagues of the RIKEN Center for Integrative Medical Sciences, in collaboration with Oxford University and the Kazusa DNA Institute, elucidated a key role of a specific PRC1 complex in initiating Polycomb recruitment by Xist RNA and showed that PRC recruitment is critical for Xist-mediated chromosome silencing and female embryogenesis.

Xist RNA recruits PRC1 and PRC2 to the future inactive X chromosome to deposit suppressive histone modifications, such as the ubiquitination of histone H2A lysine 119 (H2AK119ub1) and the methylation of histone H3 lysine 27 (H3K27me3). These histone modifications are thought to be important for the chromosome-wide gene silencing that occurs with X chromosome inactivation.

Previous studies revealed that Xist RNA directly binds to PRC2 and catalyzes the methylation of H3 Lysine 27. Following this epigenetic modification, the PRC1 complex was proposed to bind to H3K27me3 through its chromobox-containing CBX protein subunit, which has a high affinity for H3K27me3. Although this model is attractive for explaining how Xist RNA establishes Polycomb-mediated suppressive chromatin, experimental evidence to validate it was lacking. In addition, PRC1 was recently shown to exist as four different subcomplexes, making the story less straightforward.

In this study, by using Polycomb group ring finger (*Pcgf3/5*) conditional knockout mice, the collaborative research group showed that one of these four PRC1 subcomplexes, PCGF3/5-PRC1, is necessary for female embryogenesis and for both PRC1-mediated H2AK119 ubiquitylation and PRC2-mediated H3K27 methylation of the inactive X chromosome. Moreover, in this situation the recruitment of PRC2/H3K27me3 was dependent on the initial ubiquitylation of Histone H2A catalyzed by PCGF3/5-PRC1. They also demonstrated that the initiation of Xist-mediated gene silencing is greatly impaired in the absence of PCGF3/5-PRC1, indicating that PCGF3/5-PRC1 initiates Xist-mediated gene silencing by recruiting PRC1 and PRC2. Thus, the authors proposed a new model for the relationship between Xist RNA and Polycomb, in which Xist RNA first recruits PCGF3/5-PRC1 on the future inactive X chromosome to ubiquitylate underlying nucleosomes. PRC2 then binds to this epigenetic histone mark through recognition by the DNA-binding protein JARID2 or by an alternative but currently unknown mechanism (Figure).

"Next, we would like to determine whether other noncoding RNAs use the same mechanism to recruit Polycomb to their target chromatin loci. We hope that future research will reveal the whole picture of X chromosome inactivation" says Koseki.

Original paper:
Almeida M, Pintacuda G, Masui O, Koseki Y, Gdula M, Cerase A, Brown D, Mould A, Innocent C, Nakayama M, Schermelleh L, Nesterova TB, Koseki H, Brockdorff N. PCGF3/5-PRC1 initiates Polycomb recruitment in X chromosome inactivation. ***Science*** 356, 1081–1084 (2017)

BATF is a critical regulator of regulatory T cells in peripheral tissues

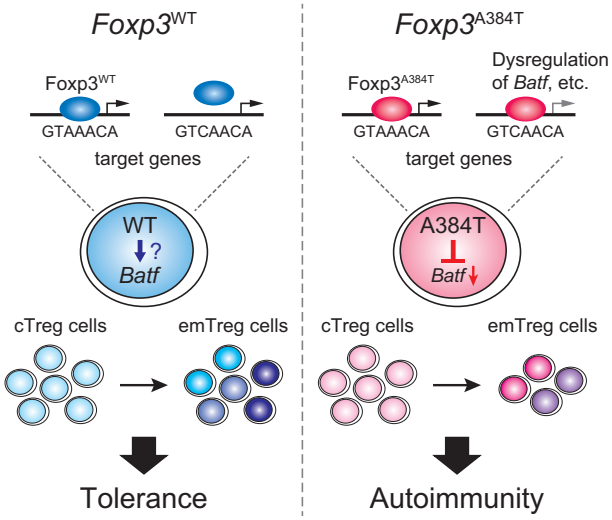


Figure: The A384T mutation impairs effector Treg (eTreg) cell homeostasis by repressing *Batf* expression.

Regulatory T cells (Tregs) establish and maintain immune tolerance by restraining excessive immune responses that lead to autoimmunity, inflammation and allergy, whereas excessive Treg activity suppresses immune responses against pathogens and tumors. Thus, it is important to regulate the delicate balance of Treg activity to maintain immune homeostasis.

Shohei Hori, Team Leader of RIKEN Center for Integrative Medical Sciences (IMS), and Shimon Sakaguchi, Professor of Osaka University, previously reported that the transcription factor Foxp3 acts as a master regulator for the development and immunosuppressive function of Tregs. However, Foxp3 binds to thousands of genomic sites and interacts with hundreds of other proteins. Because of this complex transcriptional network, the molecular mechanisms of Foxp3 function in Tregs remained a mystery.

Mutations in *Foxp3* cause a devastating multi-organ human autoimmune disease called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome. To determine the molecular functions of Foxp3 in Tregs, Shohei Hori and his colleagues established mouse models harboring *Foxp3* mutations (I363V, R397W, and A384T) that had been identified in IPEX patients and predicted to affect Foxp3 DNA binding. Mice harboring either I363V or R397W mutations developed systemic multi-organ inflammation, similar to Foxp3-deficient mice, because of their impaired DNA binding activity. In contrast, A384T mice exhibited an autoimmune phenotype only in certain non-lymphoid tissues, such as skin, lung and colon. Although thymic Treg development was normal, the frequency of Tregs was reduced in those tissues, while inflammatory helper T cells were increased. "A384T mutation does not impair *in vitro* function of Tregs but results in a distinctive autoimmune disease. So, we decided to focus on this mutation," says Hori.

Tregs can be classified into two groups, "central" Treg (cTreg) cells enriched in lymphoid tissues, and "effector" or "memory" Treg (emTreg) cells localized in non-lymphoid tissues. Because cTregs differentiate into emTregs, they thought that the A384T mutation impairs differentiation and expansion of emTregs.

To study how the mutation impairs emTreg differentiation, they analyzed gene expression in A384T Tregs as well as A384T Foxp3 DNA binding. They combined results from these analyses and found that A384T is a gain-of-function mutation that enables Foxp3 binding to the promoter of a transcription factor gene, *Batf*. This binding suppressed BATF expression in Tregs, leading to the impaired differentiation of emTregs (Figure).

To further study the function of BATF, they analyzed Tregs in BATF-deficient mice. Indeed, BATF-deficient and A384T Tregs showed similar functional defects in that both were unable to prevent inflammation *in vivo*. When BATF was retrovirally transduced into A384T Tregs, differentiation to emTregs and their accumulation in peripheral tissues were rescued and immunosuppressive function was recovered.

"BATF has a fundamental function to coordinate the differentiation and accumulation of emTregs. Regulation of BATF expression or function will have a therapeutic possibility as a novel treatment of autoimmunity, inflammation, allergy and cancer," says Hori.

Original paper:
Hayatsu N, Miyao T, Tachibana M, Murakami R, Kimura A, Kato T, Kawakami E, Endo TA, Setoguchi R, Watarai H, Nishikawa T, Yasuda T, Yoshida H, Hori S. Analyses of a mutant *Foxp3* allele reveal BATF as a critical transcription factor in the differentiation and accumulation of tissue regulatory T cells. ***Immunity*** 47, 268–283 (2017)

Genome-wide association study reveals the involvement of B lymphocytes in obesity

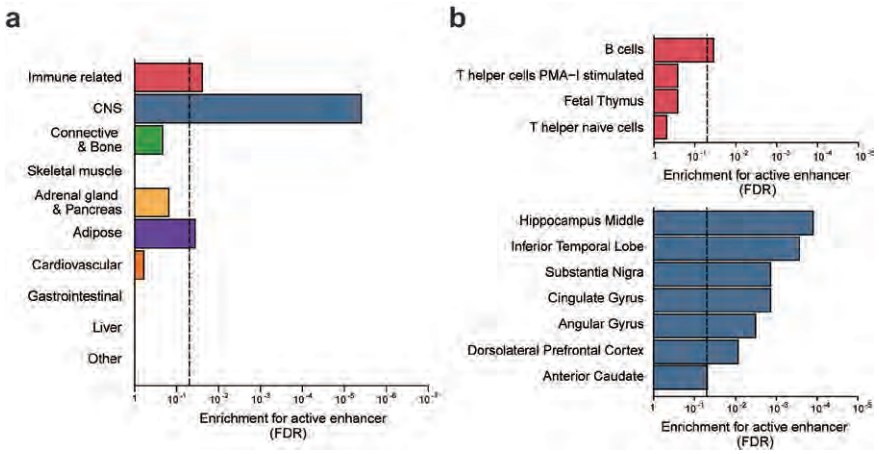


Figure: Enrichment of identified variants in active enhancers
Enrichment of the variants in the active enhancers in 10 cell groups (a) and in immune-related cells (*red*) and the central nervous system (*blue*) (b). PMA-I: phorbol 12-myristate 13-acetate plus ionomycin.

Obesity is a risk factor for a wide variety of health problems. Behavior, environment and genetic factors are thought to interact in causing obesity. However, the mechanisms of body weight regulation and potential differences among individuals remain unknown.

Yoichiro Kamatani and his colleagues at the RIKEN Center for Integrative Medical Sciences (IMS), in collaboration with researchers in the Tohoku Medical Megabank Organization, the Iwate Tohoku Medical Megabank Organization and National Cancer Center Japan, identified 112 new loci associated with obesity. Their findings of the genetic links between body mass index (BMI) and diseases provided surprising evidence that B lymphocytes have a role in the pathogenesis of obesity.

To identify genetic loci associated with obesity, researchers conducted a genome-wide association study (GWAS) of 170 thousand Japanese people using roughly 6 million genetic variants followed by a study of an additional 15 thousand Japanese. By combining these studies, they successfully identified 85 loci including 51 newly discovered loci associated with BMI. They further conducted trans-ethnic meta-analysis using publicly available GWAS data of 350 thousand Europeans. Using a method called MANTRA (Meta-ANalysis of Transethnic Association studies), they identified 61 additional new loci associated with BMI. Thus, a total of 112 new loci were successfully identified in this large-scale GWAS of BMI.

They next investigated biological functions of these newly identified genetic variants. They evaluated enrichment of the identified variants in cell-type-specific epigenetic regulators such as enhancers and promoters. "Unexpectedly, we found significant enrichment of the identified genetic variants in the active enhancers of immune cells, B cells specifically, in addition to cells in the central nervous system and in adipose tissues" said Kamatani. "Significant enrichment was also found in active promoters of B cells, pancreatic islets and brain cells (Figure). Our cell-type-specific analyses suggested a surprising involvement of lymphocytes in the regulation of body weight."

Lastly, they investigated genetic correlations between BMI and other traits. By evaluating the genetic correlations between this study and other previous GWAS studies conducted at RIKEN IMS, they found positive correlations of BMI with type 2 diabetes, cardiovascular diseases, asthma and ossification of posterior longitudinal ligament of the spine (OPLL). Significant negative correlations were observed in adolescent idiopathic scoliosis (AIS), schizophrenia and rheumatoid arthritis (RA). The results indicated that obese people have more risks for type 2 diabetes, cardiovascular diseases, asthma and OPLL, while thin people have more genetic risks for RA, AIS and schizophrenia. "Our findings provide insight into the links between BMI and complex diseases and provide genetic evidence that lymphocytes have a role in the pathogenesis of obesity" noted Kamatani.

Original paper:
Akiyama M, Okada Y, Kanai M, Takahashi A, Momozawa Y, Ikeda M, Iwata N, Ikegawa S, Hirata M, Matsuda K, Iwasaki M, Yamaji T, Sawada N, Hachiya T, Tanno K, Shimizu A, Hozawa A, Minegishi N, Tsugane S, Yamamoto M, Kubo M, Kamatani Y. Genome-wide association study identifies 112 new loci for body mass index in the Japanese population. ***Nat Genet*** 49, 1458–1467 (2017)

Ectopically colonized oral bacteria may induce inflammatory bowel disease.

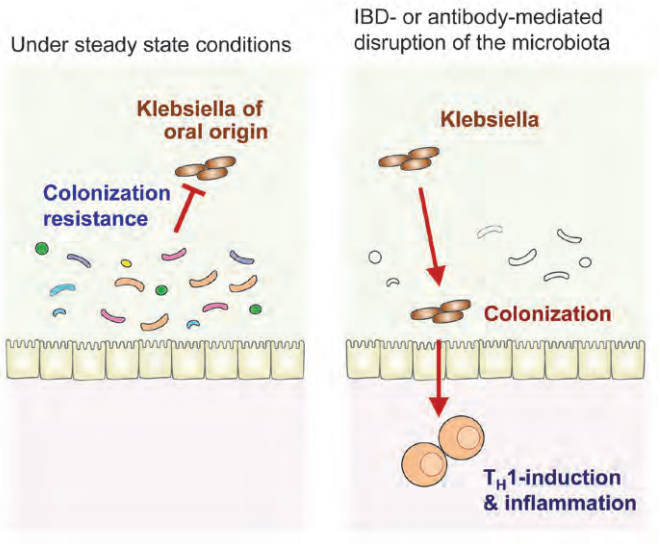


Figure:
The normal gut microbiota suppresses colonization by *Klebsiella* species, but imbalances in the gut microbiota will allow *Klebsiella* species to colonize and proliferate in the gut. This induces the accumulation of TH1 cells and could elicit pathological inflammation in a genetically susceptible host.

A variety of bacteria reside in the gut and oral cavity and they play important roles in maintaining our health by potently affecting our immune system and physiological functions. Intestinal colonization by bacteria of oral origin has been correlated with several negative health outcomes, including inflammatory bowel disease (IBD). However, a causal role of oral bacteria ectopically colonizing the intestine remains unclear. A research group led by Kenya Honda of the RIKEN Center for Integrative Medical Sciences and Keio University, and Masahira Hattori of RIKEN Integrative Medical Sciences and Waseda University showed that oral bacteria called *Klebsiella* species are strong inducers of T helper 1 (TH1) cells when they colonize in the gut. Excessive activation of TH1 cells may contribute to the development of inflammatory bowel diseases, such as Crohn's disease (CD) and ulcerative colitis (UC).

First, these investigators transplanted saliva samples from two patients with CD into germ-free mice. In mice receiving a saliva sample from one of the patients, they noticed a marked accumulation of interferon γ (INF-γ)$^+$ TH1 cells in the intestinal lamina propria. From the feces of these mice they isolated and cultured many oral bacterial strains and inoculated them into other germ-free mice. These experiments identified *Klebsiella pneumoniae* 2H7 (Kp-2H7) as a strong inducer of TH1 cells.

Kp-2H7 was resistant to multiple antibiotics and tended to colonize when the intestinal microbiota was dysbiotic in specific-pathogen-free (SPF) mice. To test the influence of Kp-2H7 colonization on the development and exacerbation of CD, they orally administered Kp-2H7 into both wild-type and colitis-prone *Il10*$^{-/-}$ mice. In the intestine of wild-type hosts, despite induction of TH1 cells, Kp-2H7 colonization did not induce any inflammatory changes, whereas Kp-2H7 colonization in colitis-prone *Il10*$^{-/-}$ mice induced severe gut inflammation. These experiments suggested that Kp-2H7 acts as a gut pathobiont in the context of a genetically susceptible host (Figure).

In addition, they orally administered saliva samples from two healthy donors into germ-free wild-type mice. Unexpectedly, the sample from one healthy donor also induced a substantial increase in TH1 cells, suggesting that *Klebsiella* species with TH1 cell induction capability may exist in the oral cavity of not only IBD patients but also healthy individuals. This result suggests that taking excessive antibiotics over a long period would allow *Klebsiella* species to colonize in the gut of even a healthy person. Furthermore, persistence of *Klebsiella* species is also observed in several other diseases.

"Developing antibiotics to specifically target *Klebsiella* species, or inhibitors of their colonization in the gut could provide a novel therapeutic strategy for IBD. Also, identifying members of the normal gut microbiota that can provide colonization resistance against *Klebsiella* species could lead to new treatments for patients with infections from multi-drug-resistant *Klebsiella* species," says Honda.

Original paper:
Atarashi K, Suda W, Luo C, Kawaguchi, Motoo, Narushima S, Kiguchi Y, Yasuma K, Watanabe E, Tanoue T, Thaiss CA, Sato M, Toyooka K, Said HS, Yamagami H, Rice SA, Gevers D, Johnson RC, Segre JA, Chen K, Kolls JK, Elinav E, Morita H, Xavier RJ, Hattori M, Honda K. Ectopic colonization of oral bacteria in the intestine drives TH1 cell induction and inflammation. ***Science*** 358, 359–365 (2017)

Activation of immune T cells leads to behavioral changes

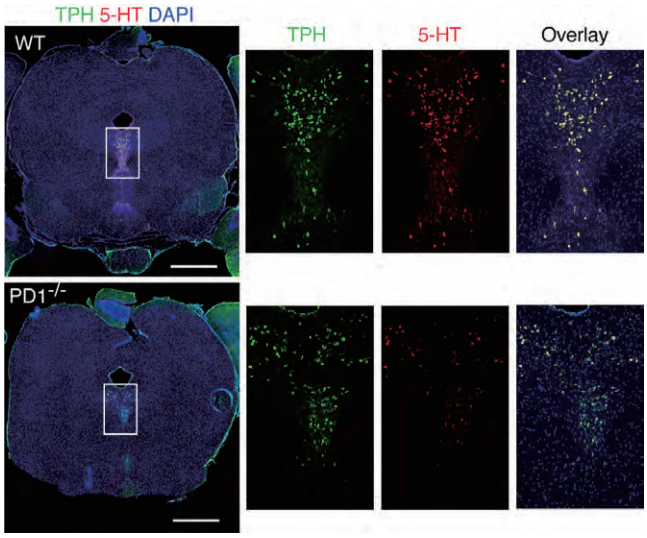


Figure: Reduced levels of monoamine neurotransmitters in the brain of PD-1-deficient mice
Microscopy of coronal brain sections of wild-type and PD-1 deficient mice (left), stained for tryptophan hydroxylase (TPH), serotonin (5-HT) and the DNA-binding dye DAPI; raphe nuclei (white insets) are enlarged in the panels on the right (single-color and overlay images). Scale bars, 1 mm.

Scientists from the RIKEN Center for Integrative Medical Sciences in Japan and collaborators have found that prolonged activation of immune cells changes the body's metabolism, and that this activation actually leads to changes in behavior.

It is currently known that individual T cells change their metabolism to meet their energy needs after being activated, but the systemic metabolic effect of sustained activation of the immune system has remained unexplored. To understand the systemic effects, the group looked at T cell activation in mice designed to lack a surface receptor called PD-1, which is necessary for inhibiting the activity of T cells. T cells remain activated in mice without the receptor, similar to those in the immune systems of people with certain types of autoimmune disease. In these mice, they found that amino acids were depleted in the blood, and that they were increased in T cells themselves, implicating the T cells in the change.

The team tracked and imaged amino acids in many organs, and found that the depletion of amino acids from the blood was taking place due to the accumulation of amino acids in activated T cells in the lymph nodes, showing that strong or long-lasting immune responses can cause metabolic changes elsewhere in the body.

The remaining question was whether this depletion of amino acids was actually having any systemic effect. By analyzing the biochemistry of the brain, they found that the systemic decrease in the amino acids tryptophan and tyrosine in blood led to lower amounts available in the brain, limiting production of the neurotransmitters serotonin and dopamine (Figure). These neurotransmitters affect emotions, motivation and fear—for example, serotonin is often a target of drugs that combat depression. The researchers found that their depletion in mice without PD-1 resulted in behavioral changes dominated by anxiety and exacerbated fear responses, which could be remedied by providing a diet rich in an essential amino acid. "Together these data indicate that excessive activation of T cells causes a systemic metabolomic shift with consequences that extend beyond the immune system," says Michio Miyajima, one of the four first co-authors of this study.

According to Sidonia Fagarasan, the leader of the group, "We were fascinated to see that this happens, as it revealed the power of the immune system to influence many aspects of the body's physiology besides infection and immunity. It will be interesting in the future to investigate whether the trigger of fear and anxiety by T cell activation is merely a side effect of the process, or whether there is an evolutionary benefit of this adaptation. We would also like to further investigate these changes, as the blockade of PD-1 is being investigated as an anti-cancer therapy."

This article was redacted from RIKEN Press Release
http://www.riken.jp/en/pr/press/2017/20171024_1/

Original paper:
Miyajima M, Zhang B, Sugiura Y, Sonomura K, Guerrini MM, Tsutsui Y, Maruya M, Vogelzang A, Chamoto K, Honda K, Hikida K, Ito S, Qin H, Sanuki R, Suzuki K, Furukawa T, Ishihama Y, Matsuda F, Suematsu M, Honjo T, Fagarasan S. Metabolic shift induced by systemic T cell activation in PD-1-deficient mice perturbs brain monoamines and emotional behavior. ***Nat Immunol*** 18, 1342–1352 (2017)

Blocking key pathways is a way to defeat cancer cells

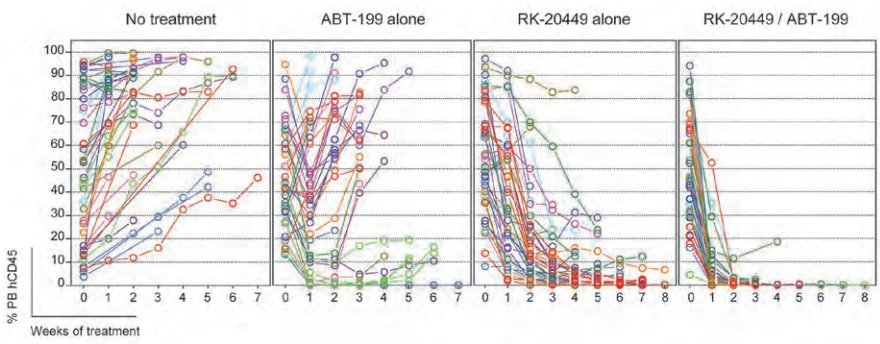


Figure: Eradication of FLT3-ITD+ AML cells in vivo through combined inhibition of a leukemia-initiating mutation and an anti-apoptotic pathway
Mice engrafted with AML derived from 12 patients received four different treatments (no treatment, ABT-199 (BCL-2 inhibitor) alone, RK-20449 alone, and combination). Frequencies of human AML cells in the recipient blood are shown over time.

Scientists from the RIKEN Center for Integrative Medical Sciences and international collaborators have found that in humanized mice, a cocktail of drugs blocking certain key pathways is effective in eliminating acute myeloid leukemia (AML), a disease which is estimated to kill more than 250,000 people a year around the world.

The most difficult problem with AML is disease relapse, which occurs in a majority of patients being treated with chemotherapy. During the last decade or so, it has become recognized that cells called leukemia stem cells (LSCs) can cause relapse because they survive the onslaught of chemotherapy drugs and proliferate.

The group began to investigate compounds that could target these stem cells and in 2013 announced that they had discovered one—now known as RK-20449. This compound targets a certain class of tyrosine kinases—receptors that play an important role in signaling for cells in the bone marrow and blood, such as the ones that cause leukemia.

Now, in research published in Science Translational Medicine, the group has shown that targeting two important pathways simultaneously is a promising route for eliminating cancer.

One of the difficulties of developing targeted therapies against AML and other tumors is that the cancers can be very genetically diverse—cells in different patients and even cells in a single patient may harbor different mutations, making it hard to determine which are truly important for tumor growth or survival. Many of the mutations found in cancerous AML cells, for example, are also found in the cells of people—especially aged people—without leukemia.

To elucidate which mutations are truly relevant, the group took cells from AML patients in various stages of the disease and transplanted them into immune-deficient mice engineered to accept human cells. They then examined how the cells behaved—in either a normal or leukemic way—in organs such as bone marrow or spleen. "What we did," says Fumihiko Ishikawa, the leader of the group, "is to connect the genomic information and biological functions of the cells."

Using this method, they were able to discover that a mutation in a gene coding FLT3, an important tyrosine kinase, is critical for transforming normal bone marrow cells into AML cells and that another gene, BCL2, functions to promote therapeutic resistance in FLT3-mutated AML. This mutation, called FLT3-ITD, is one of the most common mutations found in AML patients. The group showed that by using RK-20449 to block abnormal signaling caused by FLT3-ITD, AML cells with multiple mutations could be effectively eliminated. In addition, by simultaneously targeting BCL-2 with a second drug called venetoclax (ABT-199), they could achieve the complete elimination of AML in the transplanted mice in most of the AML cases tested (Figure).

"This shows," says Fumihiko Ishikawa, "that determining which of the mutations in a diverse landscape are critical in leukemia onset and which of the pathways are critical for therapeutic resistance in leukemia, and simultaneously targeting those pathways is an encouraging way to treat difficult cancers such as AML."

This article was redacted from RIKEN Press Release
http://www.riken.jp/en/pr/press/2017/20171026_1/

Original paper:
Saito Y, Mochizuki Y, Ogahara I, Watanabe T, Hogdal L, Takagi S, Sato K, Kaneko A, Kajita H, Uchida N, Fukami T, Shultz LD, Taniguchi S, Ohara O, Letai AG, Ishikawa F. Overcoming mutational complexity in acute myeloid leukemia by inhibition of critical pathways. ***Sci Transl Med*** 9, eaao1214 (2017)

New asthma risk loci have been identified and found to colocalize with immune cell *cis*-acting regulatory elements

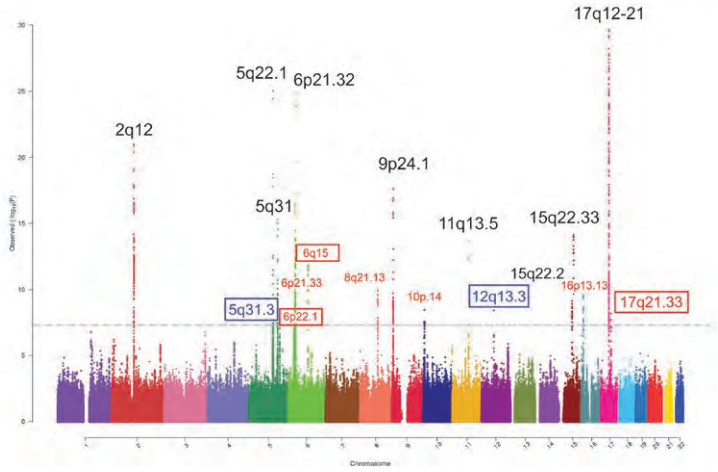


Figure: The results of multi-ancestry GWAS meta-analysis of asthma risk.
The analysis included a total of 23,948 cases and 118,538 controls. Black, previously known loci; red, new loci identified in the European-ancestry meta-analysis; blue, additional new loci identified in the multi-ancestry meta-analysis. The dashed horizontal line denotes $P=5\times10^{-8}$.

An international study by the Trans-National Asthma Genetics Consortium (TAGC) has discovered five new regions of the genome that are associated with an increased risk of asthma. As TAGC members, Tatsuhiko Tsunoda and his colleagues at the RIKEN Center for Integrative Medical Sciences contributed to this effort, the world's largest meta-analysis.

Asthma is a chronic inflammatory disease that affects more than 300 million people worldwide. The prevalence rate of asthma varies from 5–8% in Japan, 3.9% in Mexican Americans and 12.5% in African Americans. The genetic effect on the risk of asthma is estimated to vary from 25–80%. Such high variability reflects the complex nature of the disease, influenced not only by genetics but also by environmental factors such as air pollution and allergens. Moreover, asthma is not a single disease and has heterogeneous symptomatic features. Thus, more than 45 worldwide groups of investigators established TAGC to construct a comprehensive catalog of genetic asthma risk regions that are robust across populations and environmental conditions.

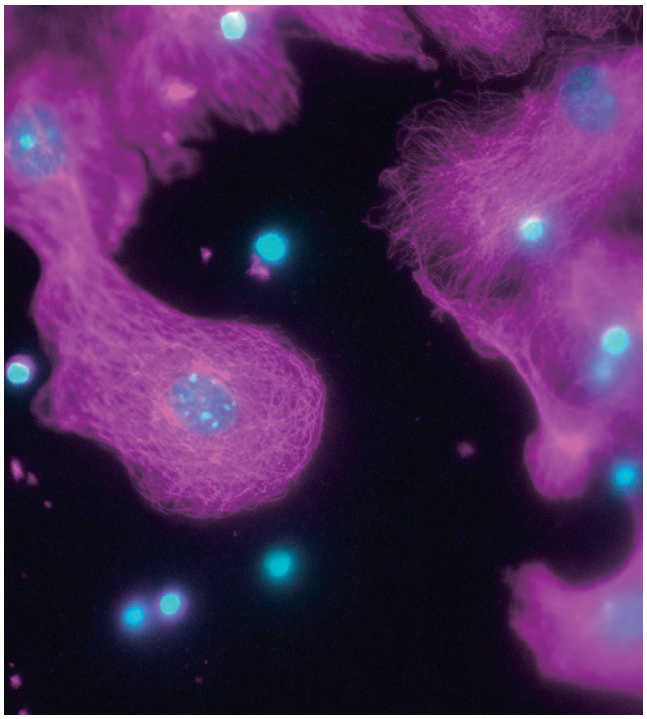
TAGC conducted genome-wide association studies (GWAS) on a total of 142,486 individuals (19,954 asthma cases and 107,715 controls of European ancestry, 2,149 cases and 6,055 controls of African ancestry, 1,239 cases and 3,976 controls of Japanese ancestry, and 606 cases and 792 controls of Latino ancestry.)

As a result, they discovered 18 genetic loci associated with asthma, including five novel loci (Figure). Among them, the strongest correlation with asthma was found in the *BACH2* genomic region, a gene known to be important in the immune response against infections. The second strongest signal was located near the *GNGT2* genomic region, a gene that promotes NF-κB activation. Further study revealed shared overlaps of asthma risk variants with risk alleles for autoimmune diseases and other diseases featuring chronic inflammation, including cardiovascular diseases, cancers, and neuropsychiatric diseases, which strengthens the concept that asthma is a multifactorial disease.

The study also showed that genetic risk variants associated with asthma are often located near epigenetic markers in immune cells of *cis*-acting regulatory elements such as enhancers and promoters. These results suggest a role of asthma risk variants in the epigenetic regulation of immune-related processes.

These discoveries highlight the importance of integrating genomic and epigenomic data to better understand the pathogenesis of complex diseases like asthma and for the development of effective new therapies.

Original paper:
Demenais F, Kubo M, Takahashi A, Tsunoda T, *et al*. Multiancestry association study identifies new asthma risk loci that colocalize with immune-cell enhancer marks. ***Nat Genet*** 50, 42–53 (2018)



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 (T. Akiyama), 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

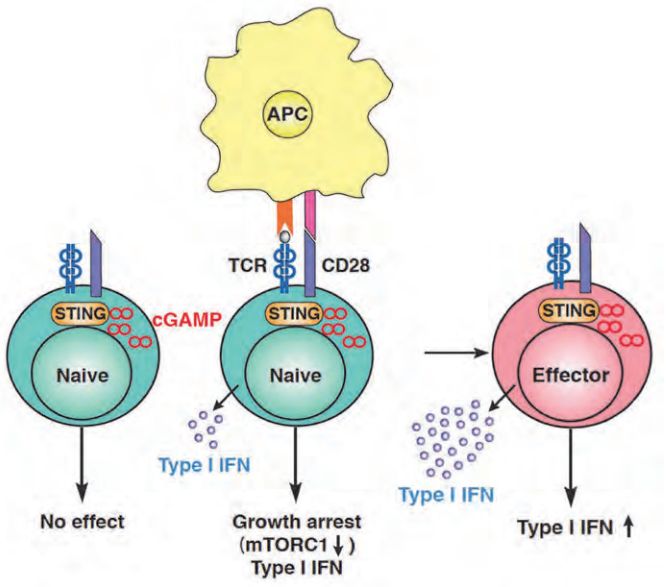


Figure: STING stimulation induces growth arrest and type I-IFN production in T cells.
Stimulation of T cells through TCR (antigen) and STING (STING ligand) induced T cell growth arrest by inhibiting mTORC1 and simultaneously induced production of type-I IFN by T cells. Effector T cells such as Th1 and activated CD8 T cells produce high levels of type-I IFN, which may contribute to anti-tumor immunity and protection from viral infection.

T cells play central roles in immune regulation. They initiate immune responses, and upon activation generate various effector T cells that protect against infection and oncogenesis. Aberrant T cell function results in infectious and autoimmune diseases and cancer. Our group aims to determine the molecular mechanism of T cell activation, differentiation and homeostasis, particularly from a signaling perspective.

T cell activation is induced through TCR-microclusters (MC), the signaling clusters generated by recruiting TCR and proximal signaling molecules. We have analyzed function and dynamics of TCR-MC and downstream signal molecules such as the downstream adaptor molecule CIN85. Analysis of T cell-specific CIN85-deficient mice revealed that CIN85 functions in negatively regulating TCR signals by recruiting several negative regulators such as Sts-2 phosphatase as a feedback regulation of activation.

We also investigated the regulation of T cell activation by innate signals. We have already analyzed the function of TLRs and nucleic acid recognition in T cells. Since STING, a major intracellular DNA sensor in innate cells, is highly expressed in T cells, its function in T cell activation was analyzed. STING activation in T cells induced growth arrest and production of type I-IFN, in an mTORC1 dependent manner. The level of type 1-IFN produced by effector T cells was much higher than by innate cells (Figure). Together with our observation that STING in T cells contributes to anti-tumor immune responses, STING activation in T cells can be utilized for modulating both T cell proliferation and anti-tumor immunity.

The ultimate aim of our diverse approaches is to elucidate the mechanisms of induction of autoimmune diseases through aberrant T cell function in order to be able to modulate them and inhibit/prevent autoimmunity and allergic inflammation. We have analyzed the regulation of T cell function by phosphatases (PTPN22 and PTPN2), whose deficiency is related to the induction of autoimmune diseases. We generated and analyzed mice with a T cell-specific deficiency in these phosphatases and the function of these phosphatases in T cell activation by identifying associated proteins and performing imaging analysis. The onset of autoimmunity will be then analyzed in these mouse models.

Recent Major Publications

Takeuchi A, Saito T. CD4+ CTL, a Cytotoxic Subset of CD4+ T cells, Their Differentiation and Function. ***Front Immunol*** 8, 194 (2017)

Hayashi M, Aoshi T, Haseda Y, Kobiyama K, Wijaya E, Nakatsu N, Igarashi Y, Standley DM, Yamada H, Honda-Okubo Y, Hara H, Saito T, Takai T, Coban C, Petrovsky N, Ishii KJ. Advax, a delta inulin microparticle, potentiates in-built adjuvant property of co-administered vaccines. ***EBioMedicine*** 15, 127–136 (2017)

Hashimoto-Tane A, Sakuma M, Ike H, Yokosuka T, Kimura Y, Ohara O, 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)

Invited Presentations

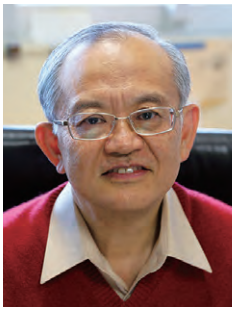
Saito T. "Regulation of T cell activation and function by innate signals" Hokkaido University Seminar (Sapporo, Japan) December, 2017

Saito T. "Regulation of T cell activation and function by innate signals" IFReC Colloquium, August, 2017

Saito T. "STING activation in T cells induces growth arrest and IFN production" FASEB Summer Conference (Snowmass, USA) June, 2017

Saito T. "Dynamic regulation of T cell activation and co-stimulation" MSD special seminar (Boston, USA) June, 2017

Saito T. "Initiation of immune response for protection of our body" RIKEN Wako open campus seminar (Wako, Japan) April, 2017



Laboratory for Lymphocyte Differentiation

Group Director: Tomohiro Kurosaki

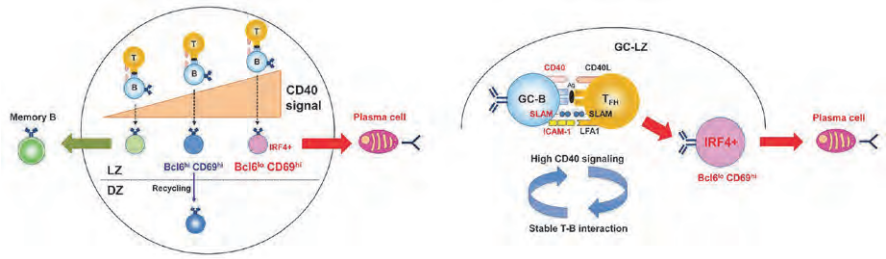


Figure: Development of plasma cell precursors in the germinal center
(Left) A population of Bcl6^{lo}CD69^{hi} light zone (LZ) GC cells with IRF4 and higher affinity BCR favors the plasma cell fate. In contrast, Bcl6^{hi}CD69^{hi} cells with lower affinity BCRs favors GC recycling. CD40 acts as a dose-dependent regulator for plasma cell precursor formation. (Right) CD40 signaling up-regulates adhesion molecules, such as ICAM-1 or SLAM, thereby affording more stable GC B-T$_{FH}$ contacts. The consequence of strong interaction with T$_{FH}$ is the formation of IRF4^{+}Bcl6^{lo} plasma cell-prone GC B cells.

Humoral memory relies on the development of memory B cells and long-lived plasma cells, and the vast majority of these cells are derived from germinal center (GC) B cells. Therefore, our lab has been focusing on characterizing of these three cell types and clarifying how memory B and plasma cells are generated through GC reactions.

For plasma cell differentiation, BCRs in post-GC plasma cells were heavily dominated by somatic mutations that result in high affinity antibodies, even at a time when such mutations were present in only a small fraction of GC cells. Hence, higher-affinity B cells are directed to the plasma cell fate, whereas lower-affinity cells enter into the recycling GC cell pool.

Regarding the selection mechanism, it has been postulated that precursor cells selected towards recycling GC or plasma cell fates already become committed in the GC, thereafter entering the recycling dark zone (DZ) or plasmablast pool, respectively. Indeed, it was already reported that IRF4, a key factor for initiating plasma cell differentiation, is expressed in a small subset of mouse light zone (LZ) GC B cells. However, these IRF4^{+} cells did not express the GC transcription factor Bcl6, therefore the observed IRF4^{+} cells are not GC cells, but early plasmablasts. Thus, this "already committed" GC precursor model still remains speculative.

To rigorously test the GC precursor model, we first identified a small population of Bcl6^{lo}CD69^{hi} LZ GC cells with higher-affinity BCRs and that express IRF4, which favors the plasma cell fate over GC recycling. In contrast, Bcl6^{hi}CD69^{hi} LZ GC cells with lower-affinity BCRs favored GC recycling. The Bcl6^{lo}CD69^{hi} population has begun to down-regulate Bcl6 and S1pr2 and to upregulate EBI2, which likely represent the process of restraining the GC program and of exiting the GC. Mechanistically, the generation of Bcl6^{lo}CD69^{hi} cells relied on CD40 in a dose-dependent manner. Moreover, we found that ICAMI and SLAM levels on LZ GC cells were up-regulated by CD40 stimulation. Consequently, Bcl6^{lo}CD69^{hi} cells expressed higher levels of these adhesion molecules than Bcl6^{hi}CD69^{hi} cells, thereby affording more stable GC B-T$_{FH}$ contacts; attenuating this interaction decreased expression of IRF4. Therefore, we propose a precursor model in which the duration of the T$_{FH}$-GC B interaction is a key decisive factor for formation of plasma cell precursor versus GC recycling precursor cells.

Recent Major Publications

Ise W, Fujii K, Shiroguchi K, Ito A, Kometani K, Takeda K, Kawakami E, Yamashita K, Suzuki K, Okada T, Kurosaki T. T Follicular Helper Cell-Germinal Center B Cell Interaction Strength Regulates Entry into Plasma Cell or Recycling Germinal Center Cell Fate. ***Immunity*** 48, 702–715 (2018)

Inoue T, Shinnakasu R, Ise W, Kawai C, Egawa T, Kurosaki T. The transcription factor Foxo1 controls germinal center B cell proliferation in response to T cell help. ***J Exp Med*** 214, 1181–1198 (2017)

Shinnakasu R, Kurosaki T. Regulation of memory B and plasma cell differentiation. ***Curr Opin Immunol*** 45, 126–131 (2017)

Invited Presentations

Kurosaki T. "Molecular mechanisms of generating human immune memory responses" Consortium of Biological Sciences 2017 (Kobe, Japan) December, 2017

Kurosaki T. "Selection of Germinal Center B Cells into the Memory B Cell or Plasma Cell Compartment" KAI Internationl Meeting 2017 (Seoul, South Korea) November, 2017

Kurosaki T. "Selection mechanism of germinal center cells into plasma fate" The 19th Germinal Centre Conference (Venice, Italy) September, 2017

Kurosaki T. "Molecular mechanisms of generating human immune memory responses" The 19th JSI Immunology Summer School (Hayama, Japan) July, 2017

Kurosaki T. "Selection of germinal-center B cells into memory B cell or plasma cell Compartment" The 6th NIF Winter School on Advanced Immunology (Singapore, Singapore) January, 2017

Laboratory for Transcriptional Regulation

Group Director: Ichiro Taniuchi

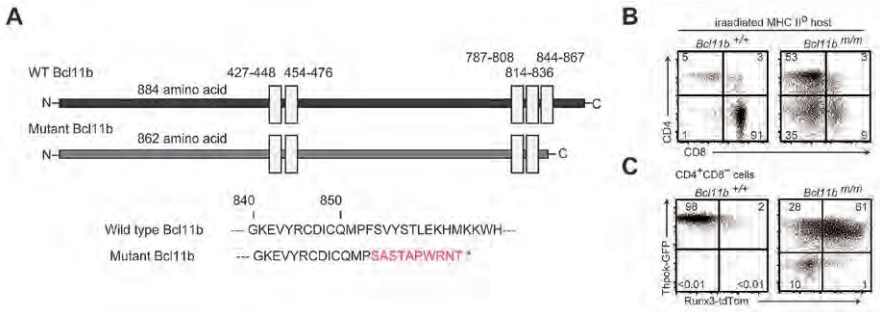


Figure: Lineage scrambling by loss of Bcl11b in helper vs cytotoxic lineage choice.
(A) Predicted structure of wild type and mutant Bcl11b protein lacking the last zinc finger motif at the C-terminal end because of a frameshift mutation. Numbers above the diagrams indicate amino acid positions of the five Bcl11b zinc fingers in the mature protein. Loss of Bcl11b function results in **(B)** redirection of MHC class-I selected cells into $CD4^+CD8^-$ cells and **(C)** emergence of $CD4^+CD8^-$ T cells expressing both ThPOK and Runx3.

Recent Major Publications

Tenno M, Kojo S, Lawir D-F, Hess I, Shiroguchi K, Ebihara T, Endo T, Muroi S, Satoh R, Kawamoto H, Boehm T and Taniuchi I. Cbfβ2 controls differentiation of and confers homing capacity to pre-thymic progenitors. ***J Exp Med*** 215, 595–610 (2018)

Kojo S, Tanaka H, Endo TA, Muroi S, Liu Y, Seo W, Tenno M, Kakugawa K, Naoe Y, Nair K, Moro K, Katsuragi Y, Kanai A, Inaba T, Egawa T, Venkatesh B, Minoda A, Kominami R, Taniuchi I. Priming of lineage-specifying genes by Bcl11b is required for lineage choice in post-selection thymocytes. ***Nat Commun*** 8, 702 (2017)

Kakugawa K, Kojo S, Tanaka H, Seo W, Endo T, Kitagawa Y, Muroi S, Tenno M, Yasmin N, Kohwi Y, Sakaguchi S, Kohwi-Shigematsu, T, Taniuchi I. Essential roles of SATB1 in specifying T lymphocyte subsets. ***Cell Rep*** 19, 1176–1188 (2017)

Invited Presentations

Taniuchi I. "Roles of Runx Transcription Factors in Immune Cell Development" The 46th Annual Meeting of the Japanese Society for Immunology (Sendai, Japan) December, 2017

Taniuchi I. "Unique roles of the C-terminal end sequences in Runx and Cbfb proteins" The 21st International RUNX Conference (Pennsylvania, USA) October, 2017

Taniuchi I. "Roles of Runx Transcription Factors in Immune System Development" IMS-JSI International Symposium on Immunology 2017 - Decoding Immune Complexity from Cell to System - (Tokyo, Japan) June, 2017.

Taniuchi I. "T cell development and Runx transcription factors" Seminar at the University of Massachusetts (Amherst, USA) May, 2017.

Taniuchi I. "Regulation of T cell development in the thymus by transcription factors" Symposium in Honor of Ellen Rothenberg, The Molecular Developmental Biology of Lymphocytes (Los Angeles, USA) April, 2017.

The vertebrate immune system consists of two components, innate and acquired. The acquired immune system, as defined by the acquisition of a system for generating pools of lymphocytes with a broad variety of antigen-specificities, appeared latter during evolution. Thus, a primary developmental program of T lymphocytes that occurs in a primary lymphoid organ, the thymus, has been shaped to select useful and non-self-reactive immune soldiers by using a sophisticated nuclear program that integrates environmental cues sensed by T cell antigen receptors (TCR).

My laboratory has been addressing how TCR signals are integrated into cell fate determination in the cell nucleus by using helper- versus cytotoxic-lineage choice as a model, in which expression of ThPOK transcription factors serves as a key determinant. Our previous studies identified a transcriptional silencer, referred to as the *Thpok* silencer, in the *Thpok* locus as a switch to turn off *Thpok* expression and direct MHC class I-selected thymocytes to become cytotoxic-lineage cells. Our recent studies have identified Bcl11b and Satb1 as novel *Thpok* silencer-binding proteins. Interestingly, both positive and negative regulation of the Thpok gene are impaired by loss of either Bcl1b or Satb1, suggesting that these proteins regulate higher-ordered chromatin structures at the *Thpok* locus. In line with this assumption, a site-specific chromatin-immune precipitation technology revealed that the *Thpok* silencer is assembled in close proximity to enhancer/promoter regions specifically in cytotoxic-lineage T cells. We also found that the last Zn-finger domain in the Bcl11b protein is crucial for regulation of not only *Thpok* but also *Runx3* and *Foxp3*, another lineage-specifying gene essential for cytotoxic and regulatory T cell differentiation, respectively. Thus, dysregulated expression of ThPOK and Runx3 by loss of Bcl11b function led to lineage scrambling, in which a significant proportion of both MHC class I- and class II-selected cells are redirected into the opposite lineage.

Laboratory for Immune Cell Systems

Group Director: Shigeo Koyasu

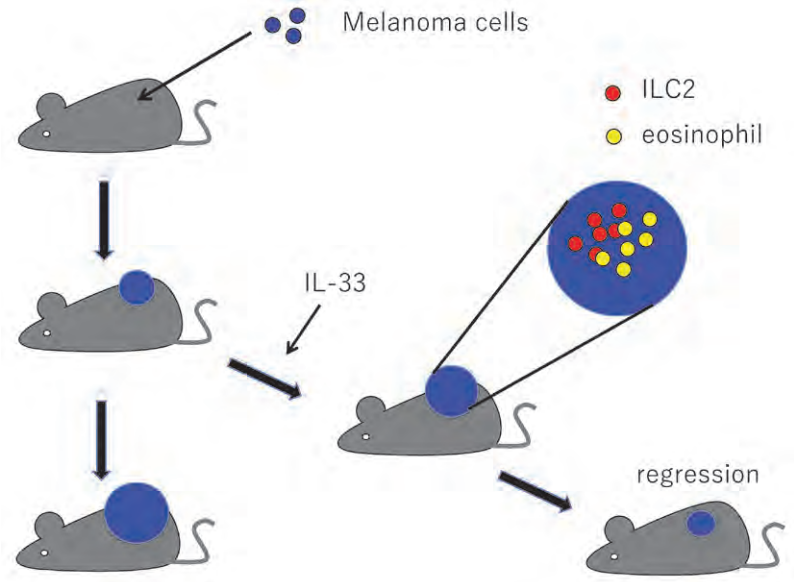


Figure: IL-33-ILC2 axis plays an important role in anti-melanoma immunity.
B16 melanoma cells grow in the recipient mice but intraperitoneal administration of IL-33 significantly suppresses tumor growth. IL-33 administration induces infiltration of ILC2 and eosinophils, which likely have anti-tumor activity, into the tumor tissue.

We have been studying the role of group 2 innate lymphoid cells (ILC2). ILC2 are capable of producing large amounts of type 2 cytokines such as IL-5 and IL-13. We examined the role of the IL-33-ILC2 axis in tumor immunity using the transplantable B16 melanoma model system. We found that intraperitoneal administration of IL-33 significantly reduced melanoma growth in the recipient mice. The protective effect of IL-33 was not observed when we used IL-33 receptor (T1/ST2)-deficient mice as a B16 melanoma cell recipient, indicating that IL-33 signals are critical for the anti-tumor effect. When we examined the tumor tissues, we found an infiltration of ILC2 as well as eosinophils, implying that infiltration and proliferation of eosinophils by ILC2-derived eotaxin and IL-5 plays a role in anti-tumor immunity. We have also found that lactic acid produced by tumor cells suppressed ILC2 expansion in the tumor tissues and that B16 melanoma cells lacking lactate dehydrogenase failed to suppress ILC2 expansion, resulting in a slower melanoma growth rate in the recipient mice compared to mice transplanted with lactate dehydrogenase-sufficient melanoma cells. The effect of IL-33 treatment was stronger against lactate dehydrogenase-deficient melanoma cells compared to lactate dehydrogenase-sufficient melanoma cells. These results suggest that the balance between the IL-33-ILC2 axis and lactate production by tumor cells affects melanoma growth *in vivo*.

Recent Major Publications

Ealey KN, Moro K, Koyasu S. Are ILC2s Jekyll and Hyde in airway inflammation? ***Immunol Rev*** 278, 207–218 (2017)

Wagner M, Moro K, Koyasu S. Plastic heterogeneity of innate lymphoid cells in cancer. ***Trends Cancer*** 5, 326–335 (2017)

Invited Presentations

Koyasu S. "Innate lymphoid cells in helminth infection" The 10th Federation of African Immunological Societies (FAIS) Congress (Hammamet, Tunisia) December, 2017

Laboratory for Human Disease Models

Group Director: Fumihiko Ishikawa

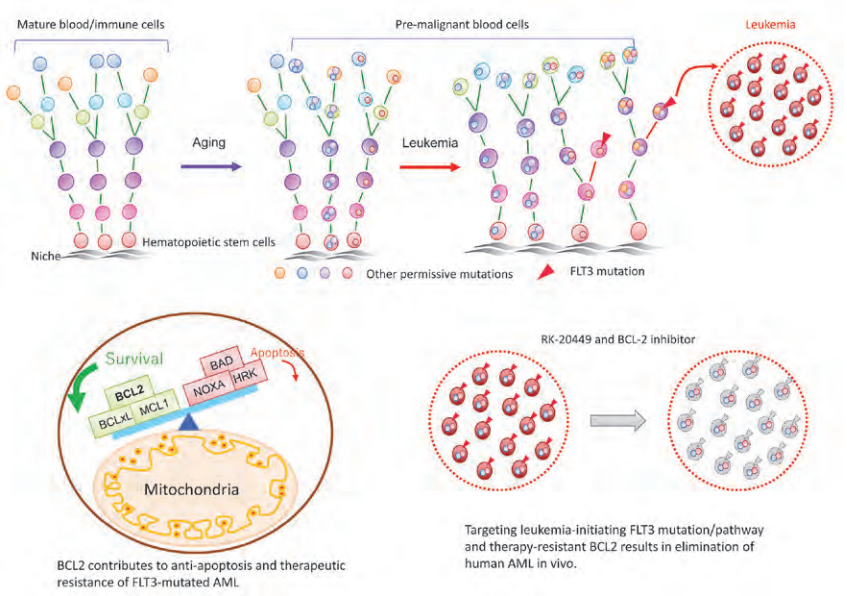


Figure: Creating new therapeutic strategies targeting poor prognosis leukemia through a multifaceted approach
(Upper) Mutations acquired as early as at the hematopoietic stem cell (HSC) level accumulate over time creating clonal, but non-malignant, hematopoiesis. In acute myeloid leukemia (AML) patients, pre-malignant HSCs continue to generate multilineage hematopoietic cells as permissive mutations accumulate. With acquisition of a critical mutation, occurring at various levels of human hematopoietic development, non-malignant clonal hematopoiesis is converted to malignant hematopoiesis. This creates a state in which non-malignant multilineage hematopoiesis and leukemic hematopoiesis co-exist. (Lower left) In FLT3-mutated AML cells, the balance between cell survival and cell death is disturbed by strong BCL2 function (Lower right) By targeting a mutation with high malignant potential and a molecule related to therapeutic resistance, leukemia cells harboring multiple co-existing somatic mutations are eliminated.

Recent Major Publications

Saito Y, Mochizuki Y, Ogahara I, Watanabe T, Hogdal L, Takagi S, Sato K, Kaneko A, Kajita H, Uchida N, Fukami T, Shultz LD, Taniguchi S, Ohara O, Letai AG, Ishikawa F. Overcoming mutational complexity in acute myeloid leukemia by inhibition of critical pathways. ***Sci Trans Med*** 9, eaao1214 (2017)

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)

Invited Presentations

Ishikawa F. "Understanding normal and malignant human hematopoiesis with humanized mice" The 76th Annual Meeting for Japan Cancer Association (Yokohama, Japan) October, 2017

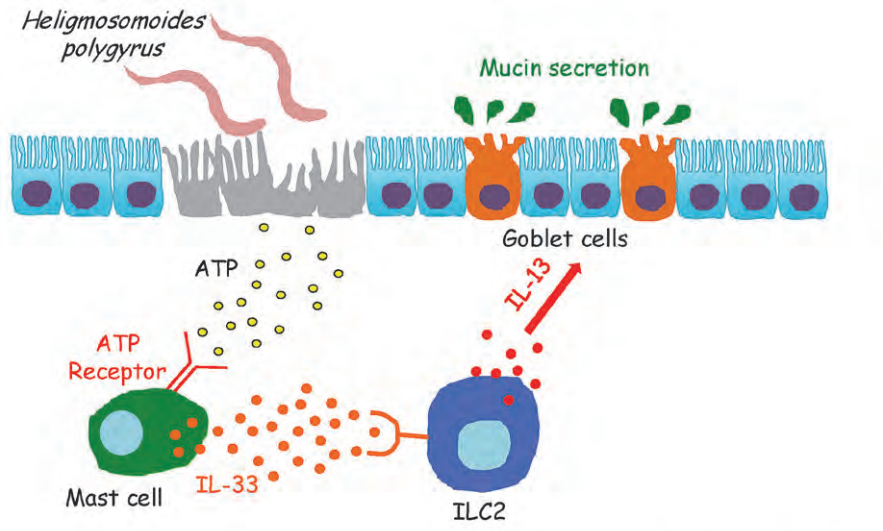
Ishikawa F. "Functional single cell genomics for leukemia" Stanford ISCBRM-RIKEN IMS Joint Symposium (Stanford, USA) May, 2017

The specific aim of our laboratory has been to understand the dynamics of human hematopoiesis, immunity, and diseases, and to apply our research findings to clinical medicine. By transplanting human normal and malignant stem cells into immune-compromised NOD/SCID/Il2rgKO (NSG) newborns, we have succeeded in reconstituting multiple organs of the recipients with human normal or malignant hematopoiesis. We further aim to create next generation humanized mice expressing human proteins, such as cytokines and adhesion molecules, that serve essential roles in mediating signaling in the hematopoietic microenvironment.

In malignant stem cell research, we previously discovered how acute myeloid leukemia (AML) development and relapse occurs using the humanized mouse model. Since whole genome sequencing has revealed the presence of multiple mutations in individual patients' leukemia cells, we have sought to identify critical mutations that need to be targeted to destroy genetically complex human leukemia. To this end, we are currently approaching the disease by integrating single cell genomics and the humanized mouse system.

Laboratory for Intestinal Ecosystem

Group Director: Hiroshi Ohno



Shimokawa *et al.*, **Immunity**, 2017

Figure: Schematic representation of the mechanism for the role of mast cells in activation of ILC2s upon helminth infection
Upon helminth infection, ATP is released from injured epithelial cells (top left) and activates mast cells (bottom left). Activated mast cells release IL-33 which in turn stimulates ILC2s leading to the production of IL-13 (bottom center). Finally, IL-13 promotes mucin secretion by goblet cells (top right) to eradicate helminths.

Enormous numbers of commensal bacteria, called the gut microbiota, reside in our intestines; nevertheless, we do not unconditionally accept those microorganisms. The intestinal immune system somehow senses the type and quantity of bacteria in the gut lumen and tries to contain them. Reciprocally, the gut microbiota shape the host immune system, and the host-gut microbiota interaction profoundly impacts our physiology and pathology.

Gut-associated lymphoid tissue (GALT) such as Peyer's patches is crucial for intestinal immune responses. GALT are covered by a specialized epithelium called follicle-associated epithelium (FAE). The intestinal epithelium is protected from the gut microbiota in several ways, e.g., the epithelial cells secrete antimicrobial proteins such as Reg3γ and are covered by mucus secreted from goblet cells. Fucosylation of the epithelium has also been shown to protect from infection by pathogens such as *Salmonella*. IL-22 signaling induces all these epithelial phenotypes. Interestingly, these features are suppressed in FAE by unknown mechanisms. Recently, we have shown that IL-22BP, an endogenous inhibitor of IL-22 signaling, is strongly expressed only under the FAE and confers the characteristic FAE phenotypes.

We have also reported that mast cells are crucial for induction of group 2 innate lymphoid cells (ILC2s) during the clearance of helminth infection. We found that Spi-B-KO mice, which exhibit mast cell hyperplasia, rapidly expelled the *Heligmosomoides polygyrus* (Hp) nematode. This was accompanied by induction of ILC2s and goblet cell hyperplasia. Upon Hp infection, mast cells were rapidly activated to produce IL-33, a potent ILC2 activator, in response to ATP released from Hp-damaged intestinal epithelium. Inhibition of the ATP receptor on mast cells rendered the Spi-B-KO mice susceptible to Hp, concomitant with elimination of mast-cell activation and ILC2 induction. These results reveal a previously unknown role for mast cells in innate immunity in that activation of mast cells by ATP results in secretion of IL-33 crucial for ILC2 activation (Figure).

Recent Major Publications

Date Y, Ebisawa M, Fukuda S, Shima H, Obata Y, Takahashi D, Kato T, Hanazato M, Nakato G, Williams IR, Hase K, Ohno H. NALT M cells are important for immune induction for the common mucosal immune system. Potential Role of the Formation of Tunneling Nanotubes in HIV-1 Spread in Macrophages. ***Int Immunol*** 29, 471–478 (2017)

Jinnohara T, Kanaya T, Hase K, Sakakibara S, Kato T, Tachibana N, Sasaki T, Hashimoto Y, Sato T, Watarai H, Kunisawa J, Shibata N, Williams IR, Kiyono H, Ohno H. IL-22BP dictates characteristics of Peyer's patch follicle-associated epithelium for antigen uptake. ***J Exp Med*** 214, 1607–1618 (2017)

Shimokawa C, Kanaya T, Hachisuka M, Ishiwata K, Hisaeda H, Kurashima Y, Kiyono H, Yoshimoto T, Kaisho T, Ohno H. Mast Cells Are Crucial for Induction of Group 2 Innate Lymphoid Cells and Clearance of Helminth Infections. ***Immunity*** 46, 863–874 (2017)

Invited Presentations

Ohno H. "Small Intestinal Microbes Accelerate Autoimmune Inflammation in the Central Nerve System" CIMI-PARIS SYMPOSIUM "Microbiota and Medicine" (Paris, France) December, 2017

Ohno H. "Crucial roles of mast cells for induction of group 2 innate lymphoid cells and clearance of helminth infections" 2017 International Conference, Korean Society for Molecular and Cellular Biology (Seoul, Korea) September, 2017

Ohno H. "The function of M cells in host-microbe interaction" Falk Foundation Symposium 207 Gut Microbiome and Mucosal or Systemic Dysfunction: Mechanisms, Clinical Manifestations and Interventions (Brisbane, Australia) May, 2017

Ohno H. "Integrated multi-omics approach for understanding the gut ecosystem" Institut Necker Enfants Malades 2nd International Symposium. Immunology 2017: New Horizons (Paris, France) April, 2017

Ohno H. "The impact of gut microbiome on the pathogenesis of experimental autoimmune encephalomyelitis in mice, a model of multiple sclerosis" The 3rd Microbiome R&D and Business Collaboration Congress: Asia (Hong Kong, China) March, 2017

Laboratory for Mucosal Immunity

Team Leader: Sidonia Fagarasan

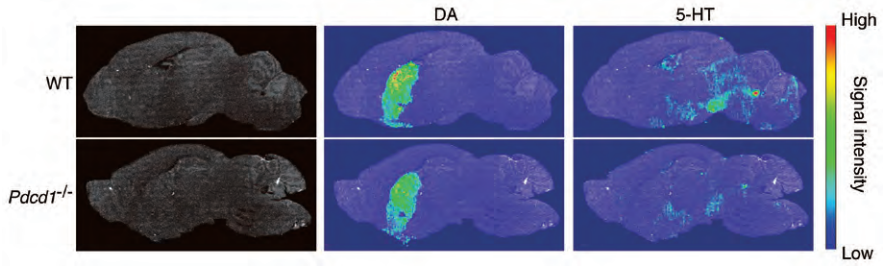


Figure: Reduced levels of monoamine neurotransmitters in the brain of *Pdcd1*$^{-/-}$ mice
Imaging mass spectrometry showing the distribution and relative level of dopamine (DA) and serotonin (5-HT) in sagittal brain sections from WT and *Pdcd1*$^{-/-}$, the gene encoding PD-1, mice.

T cell activation has far-reaching effects on other major physiological systems

We have discovered a novel impact of T cell activation on systemic metabolic homeostasis. We demonstrate that besides boosting immunity, the activation of the immune system has far-reaching effects on other major physiological systems of the body.

We found that persistent T cell activation resulted in drastic systemic metabolic changes, including significant reduction of almost all proteinogenic amino acids (AA) levels from the serum. Remarkably the reduction of aromatic AA like tryptophan, tyrosine and phenylalanine was evident from a relatively young age (two months old) and seems to precede all other aminome changes. Furthermore, we linked the depletion of tyrosine and tryptophan in the periphery to reduced synthesis of brain monoamine neurotransmitters such as dopamine and serotonin. We further demonstrated that such biochemical alterations caused abnormal behavior in mice, dominated by anxiety and enhanced fear responses. Dietary tryptophan supplementation aimed at increasing serotonin in PD-1-deficient mice restored neurotransmitter homeostasis and normal behavior phenotypes.

Mechanistic insights into the T cell-mediated systemic metabolomic shift

We found *in vitro* and *in vivo* that activated T cells increased expression of AA transporters and, as a result, accumulated high concentrations of intracellular AA. Thus, the observed systemic AA depletion is the result of accumulation of AA inside the activated immune cells, particularly effector/memory T cells.

A remarkable and unexpected finding was that the increase of intracellular AA cargo occurred despite the concurrent increase in anabolic activity following activation. This finding illustrates a novel and counterintuitive direct rather than inverse relationship between certain intracellular metabolite concentrations and their downstream catabolism rates. Our results challenge the dogma that increased protein synthesis and catabolism reduce the levels of free AA within cells, a notion strongly held in the field of metabolomics.

Recent Major Publications

Miyajima M, Zhang B, Sugiura Y., Sonomura K., Guerrini MM, Tsutsui Y, Maruya M, Vogelzang A, Chamoto K, Honda K, Hikida T, Qin H, Sanuki R, Suzuki K, Furukawa T, Ishihama Y, Matsuda F, Suematsu M, Honjo T, Fagarasan S. Metabolic shift induced by systemic activation of T cells in PD-1 deficient mice perturbs brain monoamines and emotional behavior. ***Nat Immunol*** 18, 1342–1352 (2017)

Chamoto K, Chowdhury PS, Kumar A, Fagarasan S, Honjo T. Mitochondria activation chemicals synergize with PD-1 checkpoint blockade for T cell-dependent anti-tumor activity. ***Proc Natl Acad Sci U S A*** 114, E761–E770 (2017)

Zhang B, Chikuma S, Hori S, Fagarasan S, Honjo T. Nonoverlapping roles of PD-1 and FoxP3 in maintaining immune tolerance in a novel autoimmune pancreatitis mouse model. ***Proc Natl Acad Sci U S A*** 113, 8490–8495 (2016)

Invited Presentations

Fagarasan S. "Excessive T cell activation in the absence of PD-1 affects behavior" The 1st Cold Spring Harbor Asia conference on inflammation: Basic Mechanisms and Relevant Diseases (Shuzou, China) December, 2017

Fagarasan S. "Involvement of PD-1 in antibody diversification and body homeostasis" 19th International Conference on Lymphatic Tissues and Germinal Centers in Immune Reactions (Venice, Italy) September, 2017 Organizer

Fagarasan S. "Involvement of PD-1 in antibody diversification and systemic homeostasis" 2017 NHRI/IBMS Joint International Conference on inflammation and Disease (Taipei, Taiwan) February, 2017

Laboratory for Gut Homeostasis

Team Leader: Kenya Honda

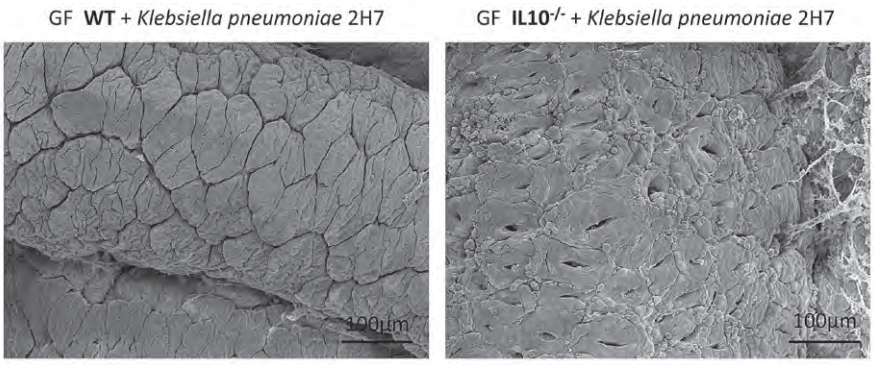


Figure: Th1 cell induction and inflammation by ectopic colonization of oral microbiota
Scanning electron micrograph of the proximal colons of *Klebsiella pneumoniae* strain 2H7 mono-associated wild-type or colitis-prone IL-10 deficient mice. *K. pneumoniae* strain 2H7 induced severe inflammation only in IL-10 deficient mice, suggesting that it acts as a gut pathobiont in the context of a genetically susceptible host.

The Laboratory for Gut Homeostasis has been trying to identify specific members of the gut microbiota that regulate specific branches of the host mucosal immune system. Our long-term goal is to develop new strategies to treat pathological conditions such as inflammatory bowel disease (IBD), allergy, cancer, and obesity by well-informed manipulation of the gut microbiota.

Previously, we succeeded in isolation of 17 human gut-derived clostridial strains that are potent inducers of intestinal CD^4+$Foxp3^+$ regulatory T (Treg) cells. These strains are able to trigger the accumulation of colonic Treg cells with strong suppressive activity for effector T cells. Oral introduction of these 17 strains resulted in reduced GVHD severity and this was mediated through production of short chain fatty acids by the 17 strains. We also isolated 20 strains of TH17-inducing bacteria strains consisting of various genera from an ulcerative colitis patient fecal sample. The 20 strains induce TH17 cells through adhesion to colonic epithelial cells.

This year, we searched for immune stimulatory bacteria in the human saliva microbiota, because it has been reported that intestinal colonization by bacteria of oral origin correlates with several negative health outcomes, such as IBD. Moreover, oral bacteria are often resistant to multiple antibiotics and can cause healthcare-associated intestinal infections. However, the precise influence exerted by ectopically colonized oral bacteria in the gut still remains unclear. To identify immune stimulatory bacteria of human oral origin, saliva samples were obtained from healthy human donors and patients with Crohn's disease (CD) and inoculated into germ-free (GF) mice. A saliva sample from one CD patient induced a marked accumulation of TH1 cells in the colonic lamina propria of the inoculated mice. We cultured cecal contents from the mice inoculated with the CD patient saliva and succeeded in isolation of 8 individual bacterial strains. A significant increase in Th1 cells was observed in GF mice inoculated with a mixture of the isolated 8 strains. Among the 8 strains, a Klebsiella pneumoniae strain was found to be responsible for TH1 cell induction. The isolated Klebsiella strain was resistant to multiple antibiotics, tended to colonize in dysbiotic microbiota and elicited a severe gut inflammation in mice genetically prone to colitis (Fig). These bacteria appeared to produce innate immune ligands, most likely packaged in outer membrane vesicles, to induce TH1 cells. Our work suggests that there is a subtype of IBD in which bacteria of oral origin contribute to the pathogenesis.

Recent Major Publications

Atarashi K, Suda W, Luo C, Kawaguchi, Motoo, Narushima S, Kiguchi Y, Yasuma K, Watanabe E, Tanoue T, Thaiss CA, Sato M, Toyooka K, Said HS, Yamagami H, Rice SA, Gevers D, Johnson RC, Segre JA, Chen K, Kolls JK, Elinav E, Morita H, Xavier RJ, Hattori M, Honda K. Ectopic colonization of oral bacteria in the intestine drives TH1 cell induction and inflammation. ***Science*** 358, 359–365 (2017)

Honda K, Littman DR. The microbiota in adaptive immune homeostasis and disease. ***Nature*** 535, 75–84 (2016)

Tanoue T, Atarashi K, Honda K. Development and maintenance of intestinal regulatory T cells. ***Nat Rev Immunol*** 16, 295–309 (2016)

Invited Presentations

Honda K. "Activation of CD8 T cells by the gut microbiota" CSH ASIA CONFERENCES Microbiota, Metagenomics & Health (Suzhou, China) September, 2017

Honda K. "Intestinal Colonization Resistance Against Oral Resident Bacteria" 18th International Congress of Mucosal Immunology (ICMI 2017) (Washington D.C. USA) July, 2017

Honda K. "Modulation of the immune system by the gut microbiota" CSHL Fundamental Immunology & Its Therapeutic Potential (Cold Spring Harbor, USA) April, 2017

Honda K. "Immune modulation by the gut microbiota" CSH ASIA CONFERENCES Bacterial Infection & Host Defense (Suzhou, China) April, 2017

Honda K. "Regulation of the immune system by the gut microbiota" Alberta-Japan Agency for Medical Research and Development (AMED) Workshop for Medical Innovation (Calgary, Canada) February, 2017

Laboratory for Immune Homeostasis

Team Leader: Taishin Akiyama

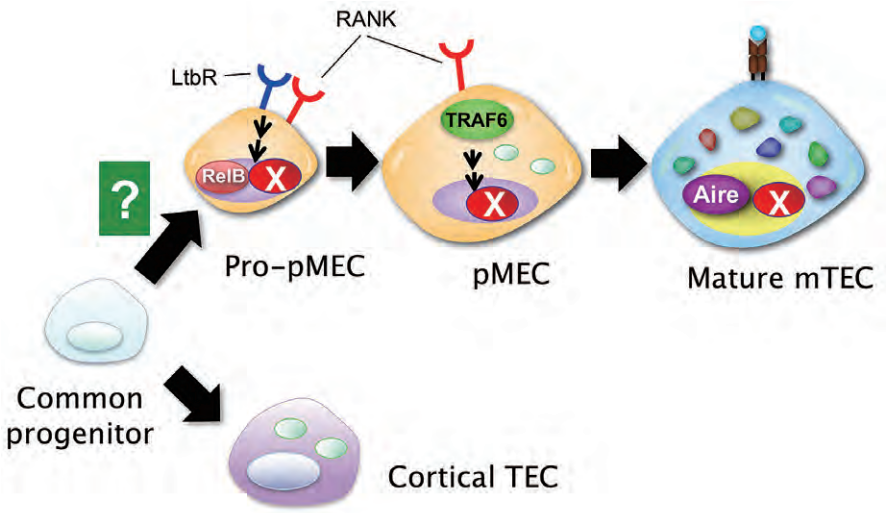


Figure: A hypothetical model of mTEC differentiation
Aire-expressing mature mTECs differentiate from common progenitor cells through pro-pMEC and pMEC stages. Mechanisms underlying commitment to mTEC lineage remain to be determined. We are trying to identify critical regulators for mTEC commitment (referred to as "X").

Recent Major Publications

Inuki S, Aiba T, Kawakami S, Akiyama T, Inoue JI, Fujimoto Y. Chemical Synthesis of d-glycero-d-manno-Heptose 1,7-Bisphosphate and Evaluation of Its Ability to Modulate NF-κB Activation. ***Org Lett*** 19, 3079–3082 (2017)

Kawasaki M, Kawasaki K, Oommen S, Blackburn J, Watanabe M, Nagai T, Kitamura A, Maeda T, Liu B, Schmidt-Ullrich R, Akiyama T, Inoue J, Hammond NL, Sharpe PT, Ohazama A. Regional regulation of Filiform tongue papillae development by Ikkα/Irf6. ***Dev Dyn*** 245, 937–946 (2016)

Akiyama N, Takizawa N, Miyauchi M, Yanai H, Tateishi R, Shinzawa M, Yoshinaga R, Kurihara M, Demizu Y, Yasuda H, Yagi S, Wu G, Matsumoto M, Sakamoto R, Yoshida N, Penninger JM, Kobayashi Y, Inoue J, Akiyama T. Identification of embryonic precursor cells that differentiate into thymic epithelial cells expressing autoimmune regulator. ***J Exp Med*** 213, 1441-1458 (2016)

Medullary thymic epithelial cells (mTECs) play an essential role in self-tolerance induction. mTECs have the unique ability to express many kinds of self-antigens, including proteins that are expressed in a tissue-specific manner (tissue specific antigens; TSAs). TSAs are presented to developing T cells in the thymic medulla either directly by mTECs or indirectly by thymic dendritic cells. As result, developing T cells recognizing TSA peptide-MHC complexes undergo apoptosis or conversion into regulatory T cells, which suppress immune reactions. The transcription factor autoimmune regulator (Aire) promotes expression of some TSAs and controls self-tolerance induction mediated by mTECs.

Several studies showed that mTEC development is dependent on signaling from tumor necrosis factor (TNF) receptor family, receptor activator of NF-κB (RANK), CD40, and lymphotoxin β-receptor (LtβR). It was reported that signaling through these receptors activates the NF-κB transcription factor via two distinct intracellular signaling pathways, classical and non-classical NF-κB pathways. These two modes of NF-κB activation have non-redundant roles in development of Aire-expressing mTECs (Aire$^+$ mTECs). However, it remained to be determined which mTEC differentiation stages are regulated by these signaling pathways.

We recently identified embryonic precursor cells of Aire$^+$ mTECs (pMECs). The pMECs expresses both the mTEC maker UEA-1 ligand and cortical TEC molecules and differentiate into mTECs that are capable of suppressing autoimmune disease onset caused by mTEC dysfunction. Classical NF-κB activation by RANK signaling promotes differentiation of pMEC into Aire$^+$ mTECs. Non-classical NF-κB activation triggered by RANK and LtβR signaling promotes pMEC induction from their progenitors Thus, cytokine-dependent differentiation of embryonic Aire$^+$ mTECs is divided into two stages regulated by distinct intracellular signaling pathways. We are currently investigating gene expression profiles of pMECs and their precursor pro-pMECs to identify molecules critical for commitment to mTEC differentiation.

Laboratory for Skin Homeostasis

Team Leader: Masayuki Amagai

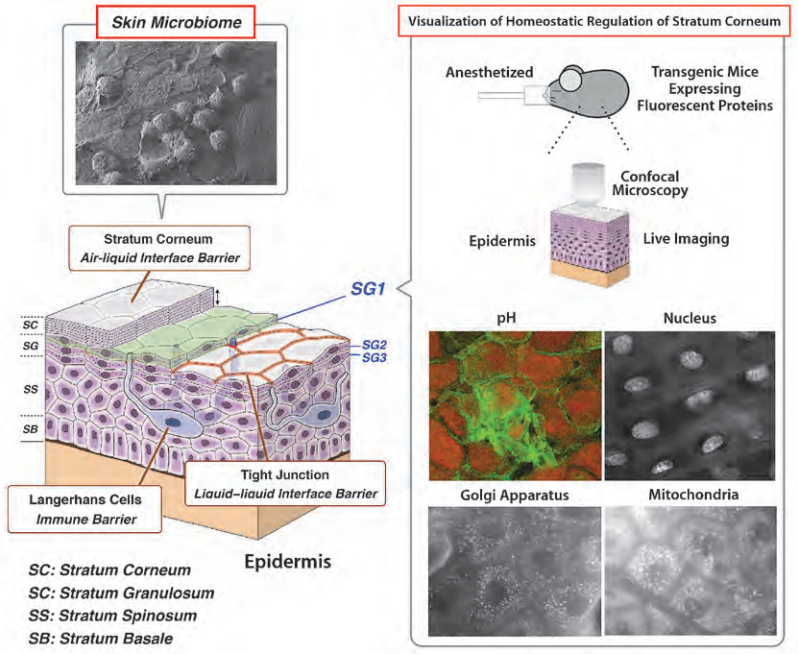


Figure: Comprehensive analysis of skin barrier homeostasis
Our team is trying to clarify the mechanisms of skin barrier homeostasis by focusing on stratum corneum (SC), tight junction (TJ), and SG1 cells. We established a live imaging system to study the cornification process in mice. We also focus on the study of host-microbe interactions on skin.

Skin is the site where immunity meets external antigens. Cutaneous sensitization is now thought to be 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 the SC barrier as an air-liquid barrier, and on tight junctions (TJ) 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 in 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 cell imaging, microbiology, and systems biology. For example, we have recently succeeded in isolating and characterizing SG1 cells and also in visualizing SC-pH in living mice, 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 findings in basic science 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

Miyamoto A, Lee S, Cooray NF, Lee S, Mori M, Matsuhisa N, Jin H, Yoda L, Yokota T, Itoh A, Sekino M, Kawasaki H, Ebihara T, Amagai M, Someya T. Inflammation-free, gas-permeable, lightweight, stretchable on-skin electronics with nanomeshes. ***Nat Nanotechnol*** 12, 907–913 (2017)

Amagai M. Modulating immunity to treat autoimmune disease. ***New Eng J Med*** 375, 1487–1489 (2016)

Yokouchi M, Atsugi T, Logtestijn MV, Tanaka RJ, Kajimura M, Suematsu M, Furuse M, Amagai M, Kubo A. Epidermal cell turnover across tight junctions based on Kelvin's tetrakaidecahedron cell shape. ***eLife*** 5, e19593 (2016)

Invited Presentations

Amagai M. "Stratum corneum as niche to control skin microbiota" The 6th Global Network Forum on Infection and Immunity (Chiba, Japan) October, 2017

Amagai M. "Cracking the codes of autoimmune and allergic skin diseases" Rudi Cormane Lecture at 47th Annual Meeting of the European Society of Dermatological Research (Salzburg, Austria) September, 2017

Matsui T. "Regulation of skin epidermal barrier formation by Ca^{2+} and pH" The Leibniz-AMED Workshop, Chronic Inflammation, Infection and Healthy Aging (Ettal, Germany) September, 2017

Matsui T. "Involvement of endogenous retrovirus in the adaptive evolution of skin" The 2nd Japan-Korea International Symposium for Transposable Elements (Tokyo, Japan) June, 2017

Amagai M. "Skin barrier homeostasis and its failure" 2017 NHRI/IBMS Joint International Conference on Inflammation & Diseases (Taipei, Taiwan) February, 2017

Laboratory for Metabolic Homeostasis

Team Leader: Naoto Kubota

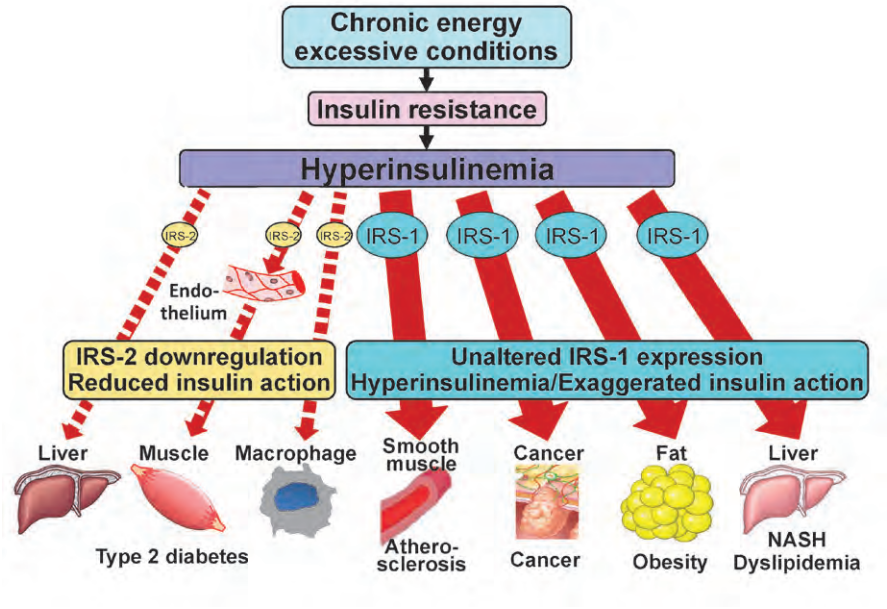


Figure: Pathology arising from failure of insulin homeostasis
In chronic energy excessive conditions, e.g., sustained hyperinsulinemia observed in obesity, there is a consistent reduction in the expression levels of Irs2, but not of Irs1, in endothelial cells, liver cells and macrophages. This results in impaired insulin-induced glucose uptake and suppression of gluconeogenesis. On the other hand, since the expression level of Irs1 is not decreased, excessive insulin activity is observed in liver, smooth muscle cells, cancer cells and adipose tissue, where Irs1 plays pivotal role in insulin signaling. This results in increased hepatic lipogenesis, progression of atherosclerosis, cancer, and obesity under conditions of sustained hyperinsulinemia.

In recent years, there has been a rapid increase in the incidence of type 2 diabetes in both Western and Asian countries. However, the precise molecular mechanisms underlying 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.

1) Molecular mechanism of insulin secretion

Impaired insulin secretion leads to the development of type 2 diabetes. This impaired insulin secretion 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 physiology and pathophysiological role of such genes *in vivo*, we have generated genetically engineered mice (Diabetologia 2014). Specifically, we are investigating common variants in potassium voltage-gated channel subfamily Q member 1 *(KCNQ1)* and ubiquitin-conjugating enzyme E2 E2 *(UBE2E2)*, which confer the largest effect on the risk of type 2 diabetes in Asians.

2) Molecular mechanism of insulin resistance

Obesity-induced insulin resistance plays a crucial role as 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. Until now, we have been studying the role of 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, Nat Commun 2016, Sci Rep 2017, Cell Metab 2017). We will continue to clarify the underlying mechanisms of insulin resistance by studying new aspects of these two molecules.

Recent Major Publications

Sasaki M, Sasako T, Kubota N, Sakurai Y, Takamoto I, Kubota T, Inagi R, Seki G, Goto M, Ueki K, Nangaku M, Jomori T, Kadowaki T. Dual Regulation of Gluconeogenesis by Insulin and Glucose in the Proximal Tubules of the Kidney. ***Diabetes*** 66, 2339–2350 (2017)

Sakurai Y, Kubota N, Takamoto I, Obata A, Iwamoto M, Hayashi T, Aihara M, Kubota T, Nishihara H, Kadowaki T. Role of insulin receptor substrates in the progression of hepatocellular carcinoma. ***Sci Rep*** 7, 5387 (2017)

Kubota T, Kubota N, Kadowaki T. Imbalanced Insulin Actions in Obesity and Type 2 Diabetes: Key Mouse Models of Insulin Signaling Pathway. ***Cell Metab*** 25, 797–810 (2017)

Invited Presentations

Kubota T. "Molecular mechanisms of impairment of M2-type macrophage activation in obesity" 22th Adiposcience Symposium (Osaka, Japan) Aug, 2017

Kubota N, Kubota N, Kadowaki T. "Insulin resistance and atherosclerosis" The 60th Annual Meeting of the Japan Diabetes Society (Nagoya, Japan) May, 2017

Kubota N, Kubota N, Kadowaki T. "New concept of insulin resistance-Metabolic zonation in liver-" The 60th Annual Meeting of the Japan Diabetes Society (Nagoya, Japan) May, 2017

Laboratory for
Immune Crosstalk

Team Leader: **Hilde Cheroutre**

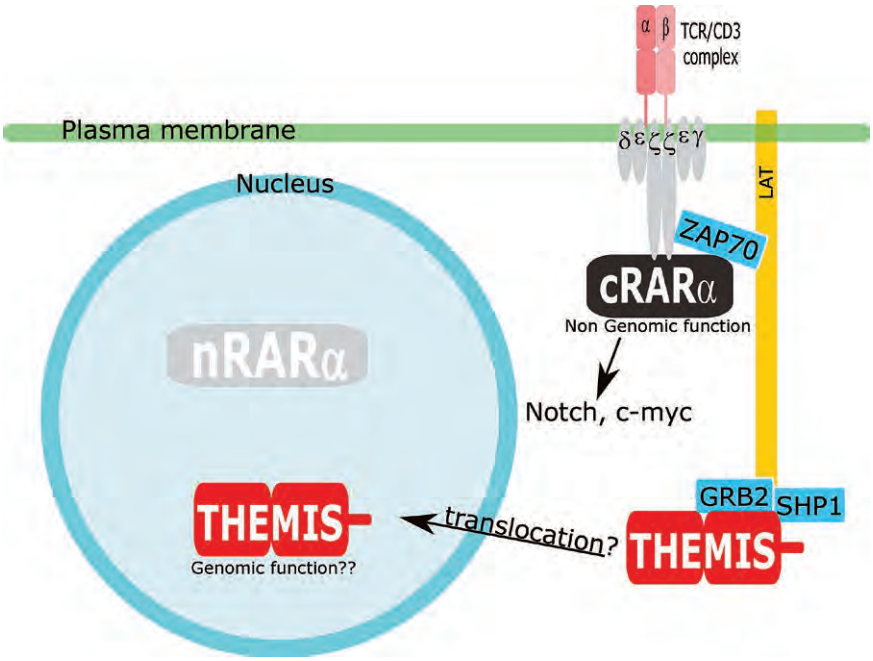


Figure: Our major interest is to understand the link between T cell receptor (TCR) signals at the plasma membrane and nuclear gene expression in developing thymocytes and activated T cells
We identified a novel RARα isoform that localizes preferentially in the cytoplasm (cRARα). This isoform is distinct from the nuclear RARα (nRARα) and is involved in proximal TCR signaling and TCR-induced Notch and c-myc activation, which promote initial T cell proliferation. In another project we examine Themis. Cytoplasmic Themis resides proximal to the TCR and is constitutively associated with Grb2, which binds both LAT and SHP1 and negatively affects TCR signaling. We found that Themis also localizes to the nucleus and that its translocation to the nucleus is critical for its function in developing thymocytes. We are now aiming to elucidate the nuclear function of Themis and evaluate the importance of its genomic function in thymocyte development and T cell activation.

We discovered cytoplasmic retinoic acid receptor alpha (cRARα) as a new member of the TCR signalosome and an interacting partner with ZAP70. We found that cRARα plays a critical non-genomic role in the proximal TCR signaling complex as well as in TCR-induced NOTCH activation and c-Myc expression and early activation-induced proliferation. Furthermore, we characterized cRARα at the molecular level and identified it as an alternative splice form of the nuclear RARα1 and -2, with a shared conserved C-terminal region containing the ligand binding domain (LBD). Cytoplasmic RARα is expressed by mature T cells as well as immature thymocytes, indicating that RARα might also serve non-genomic roles during thymic development and selection. We are now designing various *in vitro* and *in vivo* strategies to fully characterize the non-genomic function of RARα at the molecular and cellular level and under physiological and disease settings. In another study, we newly identified *Themis* as an essential gene for T cell development by phenotype screening of ENU-induced mutant mice. Themis functions by interacting with Grb2 and SHP1, thus down-modulating TCR signal strength and allowing positive selection of thymocytes that further mature to conventional naïve T cells. By generating specific nuclear localization signal deletion 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, we speculate that Themis also plays a role in the nucleus to control TCR-induced gene expression. We are now aiming to elucidate the genomic function of Themis. We generated a Themis-ERT2 fusion protein, which tethers Themis protein in the cytoplasm and induces nuclear translocation upon tamoxifen administration. In addition, we are also generating ChIP-seq data using a newly generated x3FLAG tagged Themis knock-in mouse.

Recent Major Publications

Nieke S, Yasmin N, Kakugawa K, Yokomizo T, Muroi S, Taniuchi I. Unique N-terminal sequences in two Runx1 isoforms are dispensable for Runx1 function. ***BMC Dev Biol*** 17, 14 (2017)

Kakugawa K, Kojo S, Tanaka H, Seo W, Endo TA, Kitagawa Y, Muroi S, Tenno M, Yasmin N, Kohwi Y, Sakaguchi S, Kowhi-Shigematsu T, Taniuchi I. Essential Roles of SATB1 in Specifying T Lymphocyte Subsets. ***Cell Rep*** 19, 1176–1188 (2017)

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

Verstichel G, Vermijlen D, Martens L, Goetgeluk G, Brouwer M, Thiault N, Van Caeneghem Y, De Munter S, Weening K, Bonte S, Leclerq G, Taghon T, Kerre T, Saevs Y, Van Dorpe J, Cheroutre H, Vandekerckhove B. The checkpoint for agonist selection precedes conventional selection in human thymus. ***Sci Immunol*** 2, eaah4232 (2017)

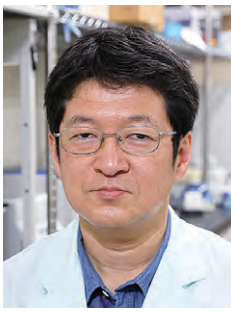
Invited Presentations

Cheroutre H. "Control of the Functional Fate of CD4 T Cells by LncRNA" National Institute of Health MIST meeting (Bethesda, USA) June, 2017

Cheroutre H. "Non-genomic function of RARalpha in T cells" Institute for Research in Biomedicine (Bellinzona, Switzerland) April, 2017

Cheroutre H. "CD4 CTL at the mucosal barrier" The Chiba-UCSD Mucosal Immunology and Vaccine Symposium, UCSD (La Jolla, USA) March, 2017

Cheroutre H. "A Give-and-Take Relation between TGF-beta and the Gut Environment Drives the CD4 CTL Fate." Keystone Symposia: TGF-β in Immunity, Inflammation and Cancer (Taos, USA) January, 2017



Laboratory for Inflammatory Regulation

Team Leader: Takashi Tanaka

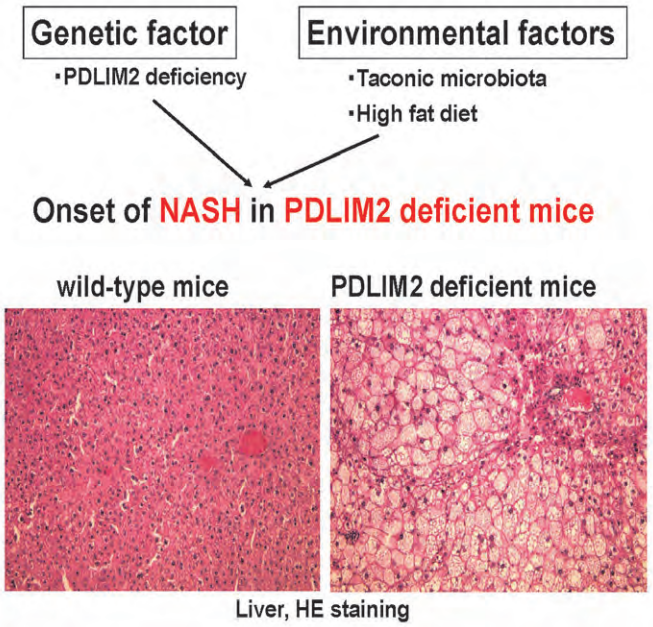


Figure: Microbiota-dependent development of NASH in PDLIM2-deficient mice
Representative Hematoxylin and Eosin (HE)-stained liver histopathology in wild-type and PDLIM2-deficient mice. PDLIM2-deficient liver showed massive accumulation of lipid droplets in the hepatocytes and the infiltration of inflammatory cells.

The inflammatory response is an important host defense mechanism to sense and eliminate invading microbial pathogens. However, these inflammatory responses must be terminated at the appropriate time point, otherwise excessive and uncontrolled responses can damage normal tissue and lead to chronic inflammatory diseases. Our research goal is to identify a series of key negative regulators of inflammation and clarify the complete picture of the molecular mechanisms for regulating inflammatory responses.

Non-alcoholic steatohepatitis (NASH) is a chronic hepatic inflammation associated with immune cell infiltration and fibrosis. In recent years, NASH has become clinically important, since 10–20% of NASH cases may progress to liver cirrhosis and hepatocellular carcinoma. However, the molecular mechanisms underlying the development of NASH remain unclear. PDLIM2 is a nuclear ubiquitin E3 ligase containing PDZ and LIM domains. In our previous study, we demonstrated that PDLIM2 functions as a ubiquitin E3 ligase for NF-κB and STAT3/4 transcription factors, negatively regulating inflammatory responses. We recently found that PDLIM2-deficient mice spontaneously develop NASH-like pathology. Notably, the onset of NASH in these mice completely depends on their environment. PDLIM2-deficient mice develop NASH in the animal facility of Harvard University but not in the RIKEN Yokohama facility. It is well known that systemic inflammation can be modified by gut microbiota. We therefore colonized gut microbiota from Taconic Farms mice into germ-free PDLIM2-deficient mice and found that PDLIM2-deficient mice with Taconic microbiota environment could develop NASH even in the RIKEN facility when fed a higher fat diet. Microarray analysis of PDLIM2-deficient liver showed the upregulation of several inflammation and metabolism-related genes. These data suggest that the Taconic microbiota environment is essential for the development of NASH in combination with PDLIM2-deficiency. We are now trying to identify the specific microbes or microbiota-derived metabolites that contribute to the NASH phenotype.

Recent Major Publications

Shin C, Ito Y, Ichikawa S, Tokunaga M, Sakata-Sogawa K, Tanaka T. MKRN2 is a novel ubiquitin E3 ligase for the p65 subunit of NF-κβ and negatively regulates inflammatory responses. ***Sci Rep*** 7, 46097 (2017)

Tanaka T. Clarification of the molecular mechanisms that negatively regulate inflammatory responses. In: Miyasaka M, Takatsu K. (eds.), ***Chronic Inflammation: Mechanisms and Regulation, 1st edition,*** Tokyo, Japan: Springer Japan KK, pp109–118 (2016)

Invited Presentations

Tanaka T. "Microbiota-dependent development of non-alcoholic steatohepatitis (NASH) in PDLIM2-deficient mice" Luxembourg FNR-RIKEN Joint Symposium, Understanding Inflammatory Diseases beyond Complexity (Yokohama, Japan) October, 2017

Tanaka T. "Molecular mechanism how Nahlsgen controls biological function of the skin" NAHLS Research Symposium (Osaka, Japan) October, 2017

Tanaka T. "Negative regulation of inflammatory responses by LIM proteins" The 1st RIKEN-McGill Symposium, Excellence in Immunology & Genetics (Montreal, Canada) May, 2017

Laboratory for Cytokine Regulation

Team Leader: Masato Kubo

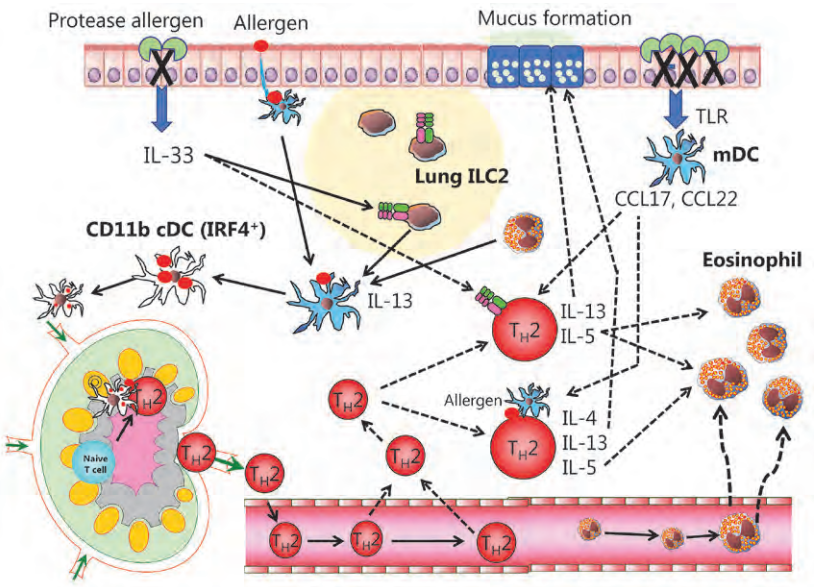


Figure: Innate and adaptive immunity crosstalk during the sensitization and challenge phase of lung inflammation
In the sensitization phase (solid lines), pulmonary epithelial cells can be activated directly by protease allergens. In response, lung epithelial cells release IL-33 that directly or indirectly activates ILC2 to produce IL-13. In some cases, lung eosinophils could be an alternative source of IL-13. IL-13 drives the maturation of CD11b+ cDCs, which depend on the transcription factor IRF4 for their maturation from pre-cDCs. After activation, the CD11b+ cDCs migrate into the draining mediastinal lymph nodes, where naïve T cells differentiate into Th2 cells. During the challenge phase (dashed lines), DCs again have a predominant role in Th2 effector function. A high dose of protease allergen activates monocytic DCs (moDCs) and recruits effector Th2 cells through the production of CCL17 and CCL22. In this case, moDCs need to express pattern-recognition receptors, such as TLRs, to stimulate release of these chemokines. The pulmonary epithelial cell-derived IL-33 directly activates effector Th2 cells to produce IL-5 and IL-13, while the allergen-bearing DCs activate the production of all Th2 cytokines, including IL-4, IL-5, and IL-13, in the response to allergen.

Recent Major Publications

Wang Y, Kuang Z, Yu X, Ruhn KA, Kubo M, Hooper LV. The intestinal microbiota regulates body composition through NFIL3 and the circadian clock. ***Science*** 357, 912–916 (2017)

Kubo M. Innate and adaptive type 2 immunity in lung allergic inflammation. ***Immunol Review***, 278, 162–172 (2017)

Kubo M. T follicular helper and TH2 cells in allergic responses. ***Allergol Int*** 66,377–381 (2017)

Invited Presentations

Kubo M. "Role of T follicular helper (TFH) and TH1 in flu specific humoral immunity" Cytokine 2017 (Kanazawa, Japan) October-November, 2017

Kubo M. "A Role of STAT3 in Barrier Integrity and Microbiota Composition of the Skin" Annual Conference of the Wide River Institute of Immunology International Symposium (Soul, Korea) October, 2017

Kubo M. "Role of cytokine in skin homeostasis and atopic dermatitis" The 4th Japan-Lithuania Natural and Life Sciences Joint Symposium (Tokyo, Japan) October, 2017

Kubo M. "Cytokine signaling in allergic responses" The 3rd Tsinghua-RIKEN Joint Workshop (Beijing, China) September, 2017

Kubo M. "New therapeutic approach for atopic dermatitis (AD) using comprehensive analysis and system biology" International Biomedical Interface Symposium (Taipei, Taiwan) March, 2017

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. IL-4 is a cytokine commonly secreted by TH2 and follicular helper T (TFH) cells after antigenic sensitization. TFH-derived IL-4 is the major contributor to class switch recombination to Immunoglobulin G1 (IgG1) and E (IgE). We have summarized in a review article in ***Allergology International*** (2017) how TH2 and TFH cells contribute to asthma, a pulmonary allergic inflammatory disease, resulting in bronchial hyper reactivity. Atopic asthma is defined by IgE antibody-mediated mast cell degranulation, while in non-atopic asthma there is no allergen specific IgE and more involvement of innate immune cells, such as basophils, group 2 innate lymphoid cells (ILC2), and eosinophils. An innate cell network (IL-33/TSLP - basophil - ILC2 - IL-5/IL-13 axis) can facilitate the sensitization phase of a type 2 inflammatory responses, and this innate network further contributes to the adaptive Th2 cell response in the chronic state. We have discussed the interface and cross-talk between innate and adaptive immune cells in asthma in a review article in ***Immunological Reviews*** (2017).

We have accumulated evidence that NFIL3/E4BP4 is a CLOCK regulating transcription factor that also has a critical role in the pulmonary allergic inflammatory response via controlling development of ILC2s and IL-10 and IL-13 production. Recently, in collaboration with our group, Lora Hooper found a novel role for NFIL-3 as a CLOCK regulator of circadian oscillation-controlled lipid absorption and export in intestinal epithelial cells thorough a DC-ILC3 innate immune cell network (***Science***, 2017).

Laboratory for Innate Immune Systems

Team Leader: Kazuyo Moro

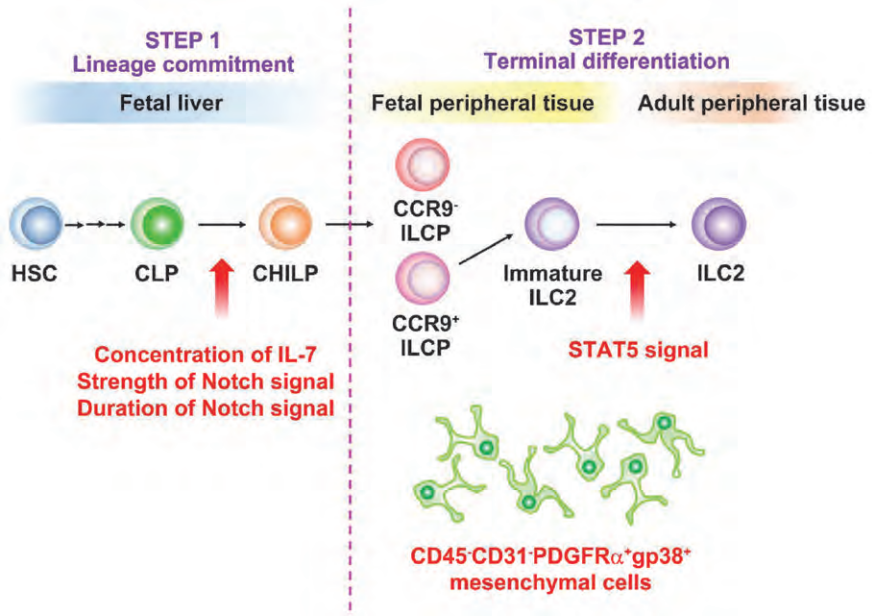


Figure: Development of ILC2 occur in the peripheral tissues.
Step 1 (Lineage commitment): Strength and duration of Notch signals and IL-7 concentrations coordinately regulate the cell fate decision to T cell, B cell, or ILCs from CLP. Step 2 (Terminal differentiation): After commitment to the ILC lineage, CHILP or ILCP migrate to the peripheral tissues during the fetal stage. CCR9⁺ ILC2 committed progenitors (CCR9⁺ ILCP) predominantly differentiate to immature ILC2 *in situ* with the support of CD45-CD31- PDGFRα⁺gp38⁺ mesenchymal cells in the mesentery. STAT5 activators are essential for their maturation after birth.

Our research group focuses on group 2 innate lymphoid cells (ILC2), an innate lymphocyte lineage that we identified in 2010. ILC2 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 by epithelial cells or endothelial cells and activates ILC2, leading to eosinophilia and goblet cell hyperplasia resulting from the activity of IL-5 and IL-13, respectively.

ILC2 are thought to derive from common lymphoid progenitors (CLP) in the bone marrow (BM). The transcription factors essential for ILC2 differentiation have been extensively studied. However, the external factors regulating commitment of CLP to the ILC lineage, as well as the sites and stromal cells that constitute the optimal microenvironment for ILC2-specific differentiation, are not fully defined. To this end, we focused on the development of ILC2 in the peripheral tissues. First, we found that concentration of IL-7, strength and duration of Notch signaling are three key external factors important in the process of CLP to common helper-like ILC progenitor (CHILP) differentiation in the fetal liver. Next, we identified three different stages of ILC2 in the fetal mesentery: ILC progenitors lacking the developmental potential to become T or B cells; CCR9⁺ ILC2 progenitors that differentiate predominantly into ILC2; and KLRG1- immature ILC2 that require STAT5 signals for maturation. We further demonstrated that ILC2 differentiation from ILC progenitors, but not from CLP, is supported by mesenteric PDGFRα⁺gp38⁺ mesenchymal cells. Collectively, our results suggest that early differentiation of ILC2 up until the ILC-committed progenitor stage occurs in the fetal liver via IL-7 and Notch signals, while final differentiation after the CHILP/ILCP stage occurs in the peripheral tissues with the aid of PDGFRα⁺gp38⁺ stromal cells.

Recent Major Publications

Koga S, Hozumi K, Hirano K, Yazawa M, Terooatea T, Minoda A, Koyasu S, Moro K. Peripheral PDGFRα⁺gp38⁺ mesenchymal cells support the differentiation of fetal liver-derived ILC2. ***J. Exp. Med.*** in press

Kamatani T, Fukunaga K, Miyata K, Shirasaki Y, Tanaka J, Baba R, Matsusaka M, Kamatani N, Moro K, Betsuyaku T, Uemura S. Construction of a system using a deep learning algorithm to count cell numbers in nanoliter wells for viable single-cell experiments. ***Sci Rep*** 7, 16831 (2017)

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)

Invited Presentations

Moro K. "Role of fetal liver and peripheral tissues in development and maturation of ILC2" The 46th Annual Meeting of The Japanese Society for Immunology (Sendai, Japan) December, 2017

Moro K. "Current topics in the innate immune system" The 5th Annual Meeting of the International Cytokine and Interferon Society (Kanazawa, Japan) November, 2017

Moro K. "Regulation of lipid metabolite-mediated IL-4 production in group 2 innate lymphoid cells." The 65th Annual Meeting of Japanese Society of Allergology (Tokyo, Japan) June, 2017

Moro K. "Discovery of group 2 innate lymphoid cells" The American Association of Immunologists Annual Meeting (Washington D.C., USA) May, 2017

Moro K. "Group 2 innate lymphoid cell and allergic inflammation" Advances in Targeted Therapies Meeting 2017 (Mandelieu, France) March, 2017

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, we have recently enhanced 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). The laboratory for Medical Science Mathematics is working to fill the gap between humans and mice. 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

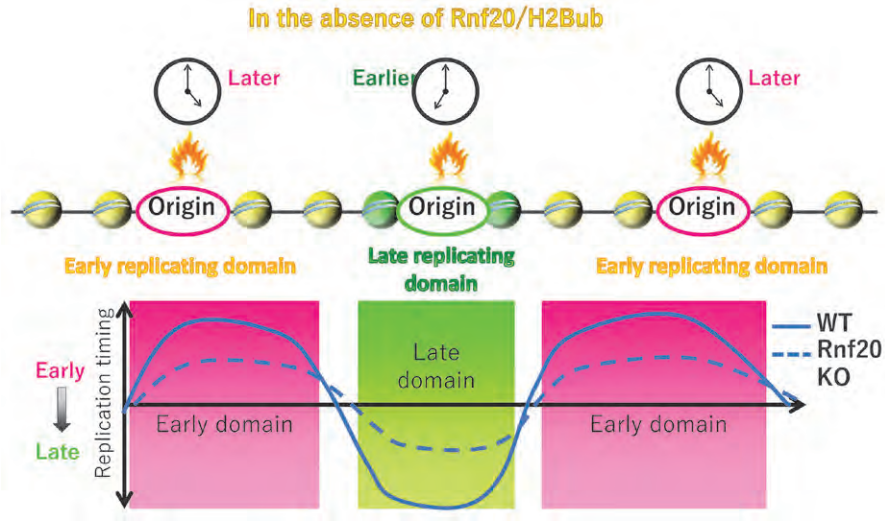


Figure: RNF20-mediated H2BK120ub1 facilitates initiation of early replication
RNF20-mediated H2B monoubiquitination demarcates very early replicating regions and contributes to maintain precise replicating timing.

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) gene products, DNA methylation mechanisms and cell cycle regulation.

DNA replication timing – a term coined to describe the temporal order of DNA segments being replicated in S phase – is recently considered a new epigenetic mark. Like its epigenetic counterparts, DNA replication timing is also cell type-specific and highly correlated with gene transcription status. However, it remains unclear how DNA replication timing is established and whether it is a regulator of gene transcription, or vice versa. To answer these questions, we exploited H2B ubiquitination (H2BK120ub1), a histone modification required for efficient DNA replication and gene transcription, as our study model. By comparing the global distribution of H2BK120ub1 with the DNA replication timing profile, we found that H2BK120ub1 is mostly enriched at the earliest replicating regions. To ask whether H2BK120ub1 was responsible for initiating early replication, we tethered Rnf20, the E3 ubiquitination ligase of H2B ubiquitination, at a particular genomic region and observed earlier replication. Nevertheless, domains according to our genome wide scale analysis, not only the H2BK120ub1 enriched early regions, but also the entire genome rely on this mark, at least partially, to define the replication timing. But interestingly, a shift in DNA replication timing in Rnf20 knockout cells was not accompanied by significant changes in gene expression, suggesting that gene transcription does not depend on DNA replication timing for regulation. By using a series of DNA replication assays, we found that H2B ubiquitination regulates DNA replication timing by modulating the time of replication origin initiation.

Recent Major Publications

Dong Y, Isono KI, Ohbo K, Endo TA, Ohara O, Maekawa M, Toyama Y, Ito C, Toshimori K, Helin K, Ogonuki N, Inoue K, Ogura A, Yamagata K, Kitabayashi I, Koseki H. EPC1/TIP60-mediated histone acetylation facilitates spermiogenesis in mice. ***Mol Cell Biol*** 37, e00082–17 (2017)

Almeida M, Pintacuda G, Masui O, Koseki Y, Gdula M, Cerase A, Brown D, Mould A, Innocent C, Nakayama M, Schermelleh L, Nesterova TB, Koseki H, Brockdorff N. PCGF3/5-PRC1 initiates Polycomb recruitment in X chromosome inactivation. ***Science*** 356, 1081–1084 (2017)

Endoh M, Endo TA, Shinga J, Hayashi K, Farcas A, Ma KW, Ito S, Sharif J, Endoh T, Onaga N, Nakayama M, Ishikura T, Masui O, Kessler BM, Suda T, Ohara O, Okuda A, Klose RJ, Koseki H. PCGF6-PRC1 suppresses premature differentiation of mouse embryonic stem cells by regulating germ cell-related genes. ***Elife*** 6, e21064 (2017)

Invited Presentations

Koseki H. "Activating Polycomb-repressed genes in mammals" France-Japan Epigenetics Workshop (Paris, France) November, 2017

Koseki H. "Development of adoptive immunotherapy for cancer using iPS-derived NKT cells" The 21st Annual Meeting of Japanese Association of Cancer Immunology (Chiba, Japan) June, 2017

Koseki H. "Polycomb-mediated regulation of transition of transcriptional status" The 69th Annual Meeting of the Japan Society for Cell Biology (Sendai, Japan) June, 2017

Koseki H. "Clinical potential of iPS cell-derived invariant NKT cells" Stanford ISCBRM-RIKEN IMS Joint Symposium (Stanford, USA) May, 2017

Koseki H. "Gene regulation by Polycomb variants" RIKEN-McGill Symposium (Montreal, Canada) May, 2017

Laboratory for Integrative Genomics

Group Director: Osamu Ohara

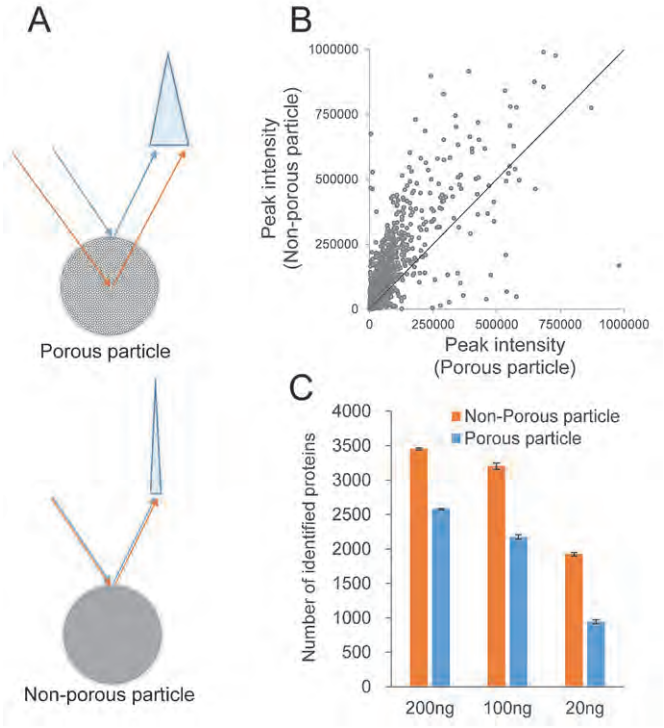


Figure: Comparison of columns packed with non-porous and porous reverse-phase particles for shotgun proteomics
(A) Schematic representations of the flow path in a non-porous and a porous particle. (B) A scatter plot of Peak intensities of common peptides identified in tryptic digests of proteins of HEK293-F cells using columns packed with non-porous and porous reverse-phase particles. (C) Comparison of the number of proteins identified in 200 ng, 100 ng and 20ng of protein digests of HEK293-F cells by chromatographic separation on non-porous and porous reverse-phase particles. We observed that the use of non-porous reverse-phase particles considerably enhances protein identification in a small amount of sample.

Because genomics is now an approach of choice when we tackle complex problems in medical sciences, our laboratory is currently involved in many intramural and extramural collaborations and various strategic projects organized by the center, in addition to providing our colleagues in the center with technical support as a central function. While we spend a considerable amount of time and effort on these activities, a part of effort is also dedicated to continuously updating our approaches with the least delay, but only after new technologies become mature and robust enough for applications in medical sciences.

In addition to this basic mission, we certainly keep it in mind that technology development has had a significant impact on the design of biological experiments and greatly deepens our understanding of biological systems. As we have experienced it first hand by the recent emergence of next-generation DNA sequencing technology, we believe that newly emerging technology frequently changes the experimental approaches in biology. In this context, the most critical issue for our laboratory is to correctly decide on the direction of technology development. We have recently taken advantage of single-cell analysis platforms, but our approaches so far have mainly been based on next-generation DNA sequencing and antibody-assisted imaging technologies. However, we believe that high-sensitivity proteome analysis will play a key role in the very near future. To begin to address this, we recently developed a liquid-chromatography (LC) system to improve the detection sensitivity of mass-spectrometry equipped with LC (Figure). While this is just an example, our laboratory will continue pursuing development of new measurement techniques in genomics for medical science researches at the center.

Recent Major Publications

Kadowaki T, Ohnishi H, Kawamoto N, Hori T, Nishimura K, Kobayashi C, Shigemura T, Ogata S, Inoue Y, Kawai T, Hiejima E, Takagi M, Imai K, Nishikomori R, Ito S, Heike T, Ohara O, Morio T, Fukao T, Kanegane H. Haploinsufficiency of A20 causes autoinflammatory and autoimmune disorders. ***J Allergy Clin Immunol***, 141, 1485–1488 (2018)

Saito Y, Mochizuki Y, Ogahara I, Watanabe T, Hogdal L, Takagi S, Sato K, Kaneko A, Kajita H, Uchida N, Fukami T, Shultz LD, Taniguchi S, Ohara O, Letai AG, Ishikawa F. Overcoming mutational complexity in acute myeloid leukemia by inhibition of critical pathways. ***Sci Transl Med*** 9, eaao1214 (2017)

Fujiki R, Hijikata A, Shirai T, Okada S, Kobayashi M, Ohara O. Molecular mechanism and structural basis of gain-of-function of STAT1 caused by pathogenic R274Q mutation. ***J Biol Chem*** 292, 6240-6254 (2017)

Invited Presentations

Ohara O. "Dissection of the immune cell society by single-cell technologies: Sequencing, production, and characterization of B-cell immunorepertoires retrieved from single cells" Single Cell Science Symposium: TECHNOLOGY MEETS BIOLOGY (Yokohama, Japan) July, 2017

Ohara O. "Applications and future perspectives of advanced genomics for clinical diagnosis" The 27th Annual Meeting of Pediatric Rheumatology Association of Japan (Kyoto, Japan) October, 2017

Laboratory for Disease Systems Modeling

Group Director: Hiroaki Kitano

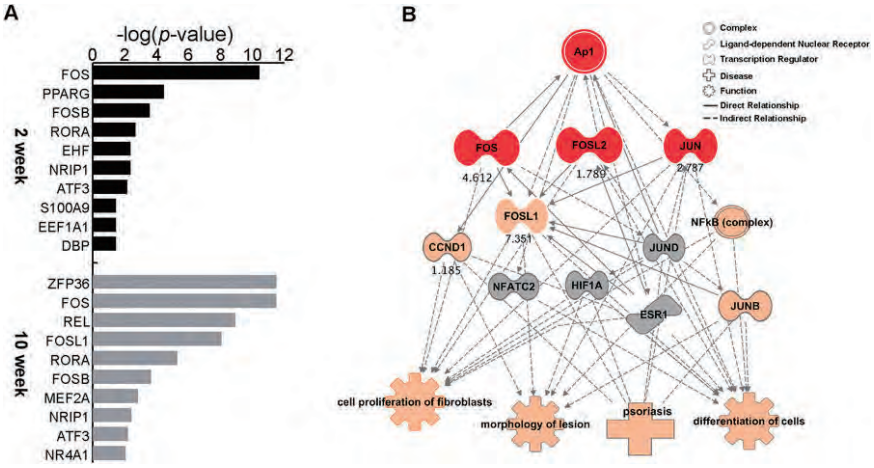


Figure: Transcription regulator network analysis revealed that several regulators of AP-1 are altered in Socs3 cKO.
(A) Upstream analysis was performed using IPA software to identify highly regulated transcription factors at 2 and 10 weeks in Socs3 cKO. Activator protein-1 (AP-1)-related transcription factors were differentially regulated at both time points. (B) Predicted mechanistic network of AP-1 regulation; numbers represent log2(fold change) of AP-1–related genes. Different structures of nodes represent different functional classes of gene products. Red indicates DEGs selected for validation. The nature of the relationship between nodes (direct or indirect) is indicated by a solid or dotted line, respectively.

Recent Major Publications

Bajpai A, Ishii T, Miyauchi K, Gupta V, Nishio-Masaike Y, Shimizu-Yoshida Y, Kubo M, Kitano H. Insights into gene expression profiles induced by Socs3 depletion in keratinocytes. ***Sci Rep*** 7, 15830 (2017)

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)

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 Syst Biol Appl*** 2, 15018 (2016)

Invited Presentations

Kitano H. "Nobel Turing Challenge: The Day AI win The Nobel Prize and Future of Civilization" Luxembourg Centre for Systems Biomedicine seminar (Luxembourg, Luxembourg) May, 2017

Kitano H. "AI-driven Life Science Innovation and Grand Challenge" AI x Life Science Symposium (Tokyo, Japan) May, 2017

Kitano H. "Impacts of Artificial Intelligence for Pharmaceutical Industry: Disruptive Innovations in Scientific Discovery and Biomedical Sciences" The FIP 6th Pharmaceutical Sciences World Congress 2017(PSWC 2017) (Stockholm, Sweden) May, 2017

Kitano H. "Systems Toxicology by artificial intelligence" The 44th Annual Meeting of the Japanese Society of Toxicology (Yokohama, Japan) July, 2017

Kitano H. "Systems Biology: Tools and Integrated Platforms for the 3Rs" The 10th World Congress on Alternatives and Animals in the Life Sciences (Seattle, USA) Aug, 2017

The Laboratory for Disease Systems Modeling (LDSM) is focusing on an in-depth understanding of several biological processes relevant to disease systems, with possible applications to clinical practice. We carried out two major projects, one is to uncover the functions of Socs3 in keratinocytes and the other is study effects of the NAD+ biosynthesis pathway and Sirtuins in aging.

A) Socs3 Project

Specific *in vivo* deletion of suppressor of cytokine signaling 3 (Socs3) in keratinocytes causes severe skin inflammation with infiltration of immune cells. To investigate the role of Socs3 in keratinocytes, we studied global RNA-Seq profiles from Socs3 conditional knockout (cKO) mice at two different ages (2 and 10 weeks). Over 400 genes were differentially expressed at both time points. In samples from 2-week-old mice, there was down-regulation of genes involved in keratin-related functions and up-regulation of genes involved in lipid metabolism. At week 10, multiple chemokine and cytokine genes were up-regulated. Functional annotation revealed that the genes differentially expressed in the 2-week-old mice play roles in keratinization, keratinocyte differentiation, and epidermal cell differentiation. By contrast, differentially expressed genes in the 10-week-old animals are involved in acute immune-related functions. A group of Activator Protein-1–related genes was highly up-regulated in Socs3 cKO mice at both ages. This observation was validated using qRT-PCR in SOCS3-depleted human keratinocyte–derived HaCaT cells. Our results suggest that, in addition to participating in immune-mediated pathways, SOCS3 also plays important roles in skin barrier homeostasis.

B) Aging Project

The effect of SIRT1 (mammalian) and Sir2 (budding yeast), and nicotinamide mononucleotide as a chemical substance to affect these genes via the NAD+ biosynthesis circuit has been investigated. Precision systems biology using budding yeast strengthens our understanding of key biological processes by providing deeper insights into detailed molecular processes with our original gTOW genome-wide assay system. Quantitative analyses using the gTOW assay revealed that a high level of SIR2 expression was permissive in strains with low NAD levels and that SIR2 expression increased NAD levels and growth speed, but SIR2 cannot be highly expressed in strains with normal NAD levels. This implies that SIR2 expression may be precisely regulated with NAD levels.

Laboratory for Medical Science Mathematics

Group Director: Tatsuhiko Tsunoda

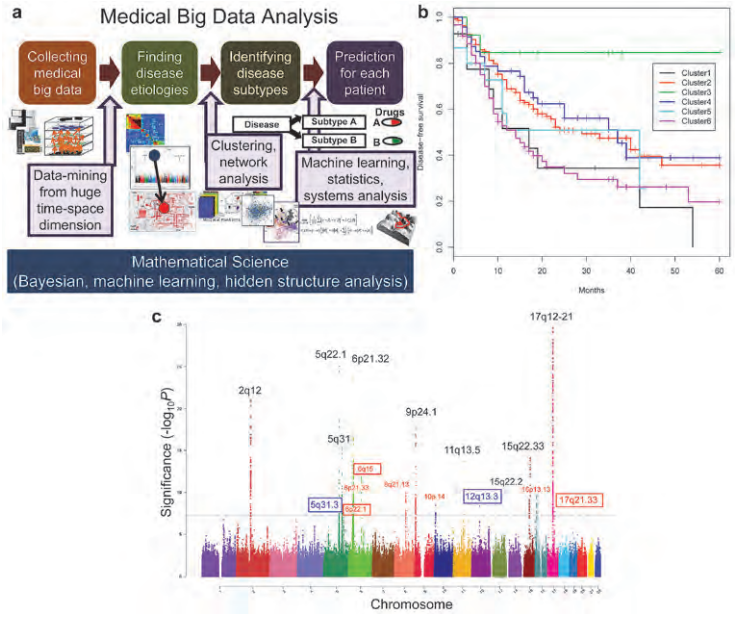


Figure: Medical Big Data Analysis for Precision Medicine
(a) Common analysis steps and methodologies. (b) Application to omics data from 300 hepatocellular carcinoma cases revealed six clusters, which showed significantly different disease-free survival rates (***Nat Genet*** 48, 500–509 (2016)). (c) Multi-ancestry meta-GWAS revealed novel asthma-related loci (***Nat Genet*** 50, 42–53 (2018)). The known asthma loci are in black. The seven novel loci detected in the European-ancestry meta-analysis are in red. The two additional loci detected in the multi-ancestry meta-analysis are in blue.

The application of rapidly progressing omic profiling technologies and, in particular, the promotion of personalized/precision/preventive medicine have recently become major goals of medical research. Traditional therapies do not adequately take into account the individuality of each patient. Our laboratory develops strategies to overcome such medical science limitations 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, driven by need for integrative analysis of clinical and omic data, 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. Last, we apply mathematical methods, e.g., machine learning techniques, to optimize therapy prediction for each patient when she/he visits a hospital or medical institute. We can also apply these methods to disease prevention based on an individual's medical history. Recently, we developed statistical and computational methodologies for analyzing up-to-date omics data, as well as for understanding and predicting cancer progression based on genomic data, with a final aim of establishing precision medicine and applying it to real data [***Nat Genet*** 48, 500–509 (2016); ***Cancer Med*** 6, 1627–1638 (2017); ***IEEE Trans Biomed Eng*** 64, 112–122 (2016); ***J Theor Biol*** 393, 67–74 (2016); ***BMC Bioinformatics*** 17, 319 (2016); ***BMC Med Genomics*** 9 (Suppl 3), 74 (2016)]. On the basis of these methodologies, we succeeded in observing a significant correlation between the molecular clustering of omic data and clinical information, e.g. survival time, based on liver and breast cancer omic analysis, and have recently published these results [***Nat Genet*** 48, 500–509 (2016); ***Cancer Med*** 6, 1627–1638 (2017)]. Another success in medical big data analysis that we have achieved is multi-ancestry GWAS, which revealed five novel asthma-related loci [***Nat Genet*** 50, 42–53 (2018)].

Recent Major Publications

Demenais F, et al. Multiancestry association study identifies new asthma risk loci that colocalize with immune-cell enhancer marks. ***Nat Genet*** 50, 42–53 (2018)

Shigemizu D, Iwase T, Yoshimoto M, Suzuki Y, Miya F, Boroevich KA, Katagiri T, Zembutsu H, Tatsuhiko Tsunoda. The prediction models for postoperative overall survival and disease-free survival in patients with breast cancer. ***Cancer Med*** 6, 1627–1638 (2017).

Fujimoto A^{+}, Furuta M^{+}, Totoki Y^{+}, Tsunoda T^{+}, Kato M^{+} ($^{+}$: co-first), ..., Nakagawa H. Whole genome mutational landscape and characterization of non-coding and structural mutations in liver cancer. ***Nat Genet*** 48, 500–509 (2016)

Invited Presentations

Tsunoda T. "Exploring etiologies, sub-classification, and risk prediction of diseases based on big-data analysis of clinical and whole omics data in medicine" CREST Big Data Fields Joint Meeting (Tokyo, Japan) December, 2017

Tsunoda T. "Trans-omic analysis drives precision medicine" The 1st International Symposium for Trans-Omics (Tokyo, Japan) November, 2017

Tsunoda T. "Multi-omic analysis for precision cancer medicine" DNA sequencing technologies and their application in practice WS (Yerevan, Armenia) October, 2017

Tsunoda T. "Omic analysis drives precision medicine" International Conference for Precision Cancer Medicine (Tokyo, Japan) June, 2017

Tsunoda T. "Multiomics and clinical analysis of cancer" CREST International Symposium on Big Data Application (Tokyo, Japan) January, 2017

Laboratory for Immunogenetics

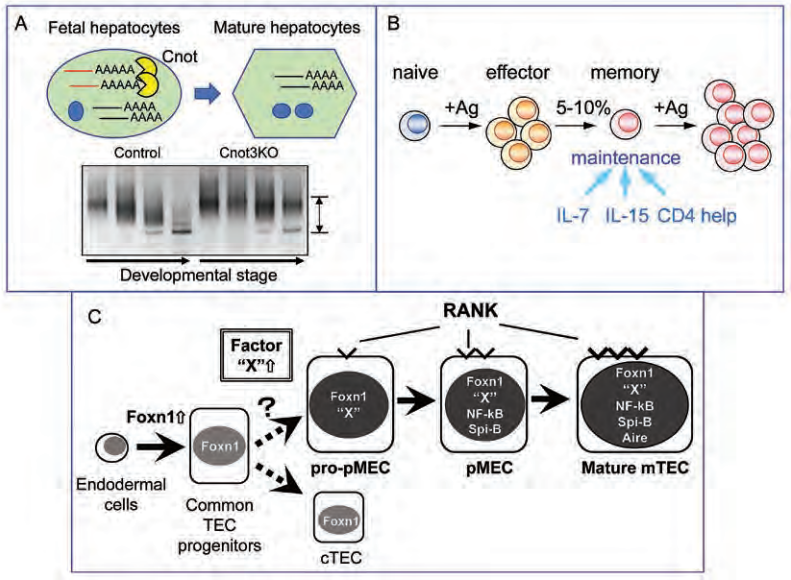
Team Leader: Tadashi Yamamoto

Figures: Research projects in the laboratory

A. mRNA deadenylation in tissue development
Cnot complex-mediated mRNA deadenylation promotes liver development by decreasing undifferentiated cell-specific genes.

B. The responses of Ag-specific CD8 T cells following Ag encounter
IL-7, IL-15, and CD4 help are required for memory CD8 T cell maintenance. Long-lived memory CD8 T cells expand and exert their function quickly when they reencounter Ag.

C. The transcription factor "X" determines the mTEC fate from a common progenitor expressing Foxn1
Cortical thymic epithelial cells (cTECs) and mTECs share a common endodermal origin. We hypothesize that transcription factor "X" determine the development and function from progenitors to mTECs.



Recent Major Publications

Hayatsu N, Miyao T, Tachibana M, Murakami R, Kimura A, Kato T, Kawakami E, Endo TA, Setoguchi R, Watarai H, Nishikawa T, Yasuda T, Yoshida H and Hori S. Analyses of a mutant FoxP3 allele reveal BATF as a critical transcription factor in the differentiation and accumulation of tissue regulatory T cells. ***Immunity*** 47, 268–283 (2017)

Li T, Amari T, Semba K, Yamamoto T and Takeoka S. Construction and evaluation of pH-sensitive immunoliposomes for enhanced delivery of anticancer drug to ErbB2 over-expressing breast cancer cells. ***Nanomedicine*** 13, 1219–1227(2017)

Akiyama N, Takizawa N, Miyauchi M, Yanai H, Tateishi R, Shinzawa M, Yoshinaga R, Kurihara M, Demizu Y, Yasuda H, Yagi S, Wu G, Matsumoto M, Sakamoto R, Yoshida N, Penninger JM, Inoue J and Akiyama T. Identification of embryonic precursor cells that differentiate into thymic epithelial cells. ***J Exp Med*** 213, 1441–1458 (2016)

Invited Presentations

Yamamoto T. "Post-transcriptional regulation by mRNA poly(A) tail" OIST & University of the Ryukyus Joint Symposium 2017 (Naha, Japan) October, 2017

Setoguchi R. "The mechanisms for memory CD8 T cell maintenance" The 7th Awaodori Symposium for Life Science (Tokushima, Japan) August, 2017

Yamamoto T. "Physiology of mRNA poly(A) tail and CCR4-NOT" Department of Biochemistry, McGill University (Montreal, Canada) May, 2017

Yamamoto T. "The CCR4-NOT deadenylase: its role in controlling cells' survival and differentiation in various biological systems" The 6th Symposium of the RIKEN-Max Planck Joint Research Center for Systems Chemical Biology (Naha, Japan) April, 2017

Our team is carrying out three projects to understand the molecular basis of tissue development and function.

1) Tissue development involves dramatic gene expression changes, which are mediated by regulation of mRNA transcription and degradation. Suppression of mRNA deadenylase activity leads to abnormal tissue development concomitant with loss of the ability to eliminate unnecessary mRNAs. We are investigating how the deadenylase regulates tissue development and function in a developmental stage-specific manner and how it is deregulated in diseases.

2) Memory CD8 T cells are long-lived antigen (Ag)-specific cells that proliferate and exert effector functions more robustly than naïve CD8 T cells upon reencounter with their cognate Ag. Memory CD8 T cells are maintained at a stable population over a long period. One of the objectives of our study is to new discover mechanisms by which memory CD8 T cells are maintained *in vivo*. These research findings should lead to innovative vaccination strategies for induction of protective immunity against tumor cells and chronic infections.

3) Medullary thymic epithelial cells (mTECs) expressing autoimmune regulator (Aire) are critical for induction of immune tolerance. However, the differentiation program of Aire-expressing mTECs (Aire$^+$ mTECs) is not fully understood. We have recently identified the precursors of Aire$^+$mTECs (pMECs) by monitoring the expression of RANK, which is required for Aire$^+$ mTEC differentiation. We are now investigating what molecules define cell fates from progenitors to pMECs, and how these molecules regulate the development and functions of mTECs.

Laboratory for Integrated Bioinformatics

Team Leader: Todd D. Taylor

Figure: iCLiKVAL Overview
iCLiKVAL is a web-based tool that uses the power of crowdsourcing to accumulate annotation information for all scientific media found online. Annotations in the form of key-relationship-value tuples are added by users through a variety of methods. Users can create or join common interest groups to work as part of a community. Controlled vocabulary lists can be created, edited and shared. Media can be bookmarked, followed, reviewed and searched. Annotations can be sorted, filtered and edited. The database is completely searchable, without registration, and all of the data are freely available to registered users via our application programming interface.

We are developing an integrated database and sample-tracking system to handle both small- and large-scale datasets of various types of experimental outputs. The system brings together an array of wet-lab experimental types being generated by various labs. Our goal is to develop a flexible system that makes it easy for users to manage, access, analyze, integrate, and visualize their own data as per their requirements.

We also 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. We have constructed a highly-curated genomic-based 16S ribosomal RNA gene database, which is continually being updated as new sequences appear in the public databases. Because metagenomic samples can contain hundreds or thousands of different species and are not easy to visualize or quantify, we developed an alternative visualization method for displaying phylogenic trees that allows users to, at a glance, comprehend the distribution of the species within their samples. Big data in the form of scientific media comes in many languages and formats: journal articles, books, images, videos, etc. While there are many resources for browsing, searching and annotating some of this media, there is no single place to search them all at once, and generalized search engines do not allow for the comprehensive and precise searches researchers require. To address these issues, we have developed a web-based tool that uses the power of crowdsourcing to accumulate annotation information for all scientific media found online. This will allow for richer data searches and discovery of novel connections by integrating all forms of scientific knowledge through a common terminology.

Recent Major Publications

Ong SY, Kho H-P, Riedel SL, Kim S-W, Gan C-Y, Taylor TD, Sudesh K. An integrative study on biologically recovered polyhydroxyalkanoates (PHAs) and simultaneous assessment of gut microbiome in yellow mealworm. ***J Biotechnol*** 265, 31–39 (2018)

Chin KCJ, Taylor TD, Hebrard M, Anbalagan K, Dashti MG, Phua KK. Transcriptomic study of Salmonella enterica subspecies enterica serovar Typhi biofilm. ***BMC Genomics*** 18, 836–844 (2017)

Lye HS, Kato T, Low W-Y, Taylor TD, Prakash T, Lew LC, Ohno H, Liong MT. Lactobacillus fermentum FTDC 8312 combats hypercholesterolemia via alteration of gut microbiota. ***J Biotechnol*** 262, 75–83 (2017)

Invited Presentations

Taylor TD. "Turning big data into small data through crowdsourced curation: integrating all types of medical and scientific knowledge" Malaysia International Genetics Conference (Selangor, Malaysia) September, 2017

Laboratory for Tissue Dynamics

Team Leader: Takaharu Okada

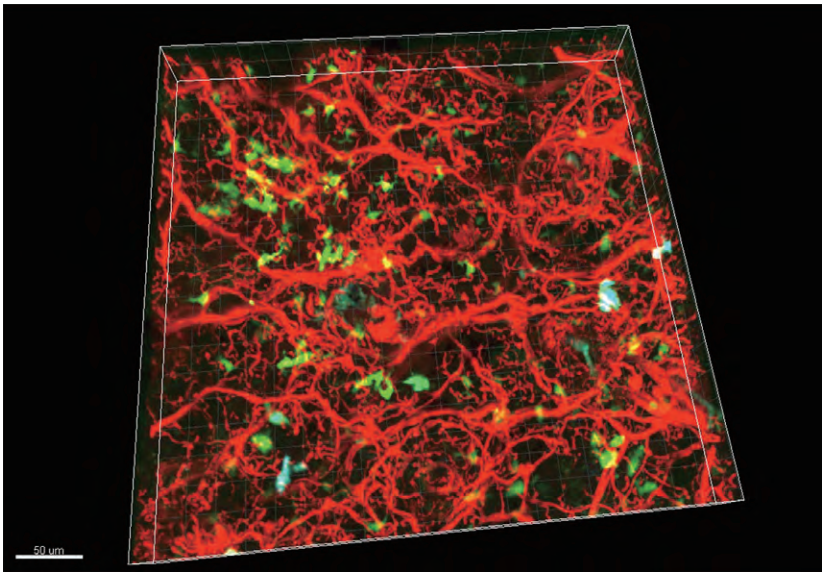


Figure: 3D imaging of skin nerves and dendritic cell subsets
A whole-mount confocal fluorescence image of the ear skin from an Xcr1$^{gfp/+}$ CD11c-YFP mouse. PGP9.5^{+} nerve fibers (red) are visualized together with XCR1^{+} dendritic cells (light blue) and other dendritic cells (green).

The goal of the laboratory is to mechanistically understand the *in vivo* cellular dynamics that shape immune responses and inflammation. For this purpose, we generate and analyze various fate-mapping reporter mice to analyze differentiation plasticity of immune cells and other cells. Using this approach, for example, we have analyzed differentiation of cytotoxic T cells to identify developmental pathways of highly protective memory CD8^{+} T cells. Our new data establish that developmental plasticity of KLRG1^{+} effector CD8^{+} T cells plays a crucial role in promoting functionally versatile memory cells that mount highly protective responses against infections and cancer.

In addition, we are studying the roles for the peripheral nervous system in modulation of inflammation. Through this study, we aim to find strategies to suppress chronic inflammation based on the modulation of neuronal activities. Particularly, we are interested in structural and functional changes in sensory neurons in dermatitis, and their interactions with immune cells and other cells such as keratinocytes. In this study, multi-dimensional fluorescent imaging analysis is very powerful for deciphering the diversity and dynamics of cellular activities. Our imaging data have started to reveal that previously-unknown interactions between sensory neurons and keratinocytes may play an important role in preventing pruritic dermatitis.

Recent Major Publications

Herndler-Brandstetter D, Ishigame H, Shinnakasu R, Plajer V, Stecher C, Zhao J, Lietzenmayer M, Kroehling L, Takumi A, Kometani K, Inoue T, Kluger Y, Kaech SM, Kurosaki T, Okada T, Flavell RA. Developmental Plasticity of KLRG1^{+} Effector CD8^{+} T Cells Promotes Protective Immunity. ***Immunity*** in press

Okada T, Takahashi S, Ishida A, Ishigame H. *In vivo* multiphoton imaging of immune cell dynamics. ***Pflugers Arch*** 468, 1793–1801 (2016)

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)

Invited Presentations

Okada T. "Imaging of peripheral nerves involved in the inflammatory diseases." The 3rd Annual Meeting of Japanese Society of Osteoimmunology (Ishigaki, Japan) June, 2017

Okada T. "Dynamic imaging of immune cells and sensory nerves." RIKEN-McGill Symposium (Montreal, Canada) May, 2017

Laboratory for Integrated Cellular Systems

Team Leader: Mariko Okada

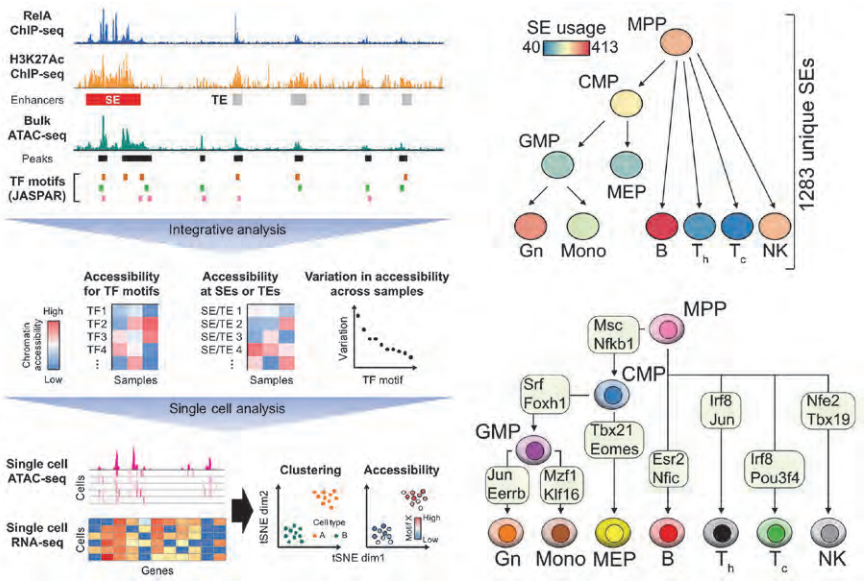


Figure: Super-enhancer(SE)-based analysis of hematopoietic development
Flow chart of the data analysis (left). Specific transcription factors in hematopoietic cells (right).

The aims of the laboratory are to define the general regulatory rules in signal transduction-transcriptional networks in cell determination processes and to apply this knowledge of regulatory principles to the understanding and treatment of human diseases. We are currently pursuing three projects; (1) dynamics of nuclear NF-κB and gene regulation, (2) mathematical modeling of cancer hallmarks and (3) cell adhesion regulated metabolism.

To understand the regulation of NF-κB-mediated gene expression, we are performing integrative transcriptome and epigenetics analyses. Our analyses using H3K27Ac-ChIP, RelA-ChIP and ATAC-seq revealed super-enhancer (SE)-regulated gene expression mechanisms at the single-cell level. The results indicated that a cooperative mechanism for DNA-protein binding mediated by SEs results in threshold responses in mRNA expression in individual B cells. The computational methods are also being applied to understanding hematopoietic development (Figure).

Signaling network is highly complex and exibits dynamic behavior to control cell functions. To understand the complex regulatory mechanism of the cancer cell signaling network, we are attempting to integrate all mathematical models developed in our laboratory that cover 60 % of the pathways in cancer hallmarks. The model parameters can also be integrated with clinical gene expression data and thus can form the basis for personalized simulation analysis.

Cell shapes regulated by cell adhesion are an important visible output of cell systems. We used a mouse model, lacking *Crk* and *Crkl* genes, of which gene products control cell adhesion and performed multi-omics analysis together with quantitative cell shape analysis on mouse embryo fibroblasts (MEF). The MEF obtained from the double-knockout mice were smaller and had a round shape compared with spindle-shaped normal MEFs and this morphology was associated with lower central metabolic activity. This phenotype was rescued by overexpression of an adhesion signaling molecule. Our study reveals a novel mechanism for cell adhesion-dependent activation of metabolism.

Recent Major Publications

Magi S, Iwamoto K, Yumoto N, Hiroshima M, Nagashima T, Ohki R, Garcia-Munoz A, Volinsky N, von Kriegsheim A, Sako Y, Takahashi K, Kimura S, Kholodenko BN. and Okada-Hatakeyama M. Transcriptionally inducible Pleckstrin homology-like domain family A member 1 attenuates ErbB receptor activity by inhibiting receptor oligomerization. ***J Biol Chem*** jbc. M117.778399 (2017)

Magi S, Iwamoto K and Okada-Hatakeyama, M. Current Status of Mathematical Modeling of Cancer – From the Viewpoint of Cancer Hallmarks. ***Curr Opin Syst Biol*** 2, 38–47 (2017)

Inoue K, Shinohara H, Behar M, Yumoto N, Tanaka G, Hoffmann A, Aihara K and Okada-Hatakeyama M. Oscillation dynamics underlies functional switching of NF-κB for B cell activation. ***NPJ Syst Biol Appl*** 2, 16024 (2016)

Invited Presentations

Okada M. "Trans-Omics analysis of NF-κB regulation" CREST & Scientific Research on Innovative Areas Symposium. The 1st International Symposium for Trans-Omics (Tokyo, Japan) November, 2017

Okada M. "Classic yet unique dynamic properties of NF-B gene regulation" OIST-JST Joint Seminar (Okinawa, Japan) November, 2017

Okada M. "Cell shape and metabolism" The 11th Metabolome Symposium (Osaka, Japan) November, 2017

Okada M. "Systems Biology and Database" NBDC Workshop (Tokyo, Japan) November, 2017

Okada M. "Mathematical modeling of cancer signaling network" The Third Trilateral Workshop for Frontier Protein Studies 2017 (Shanghai, China). August–September, 2017

Laboratory for Metabolomics

Team Leader: Makoto Arita

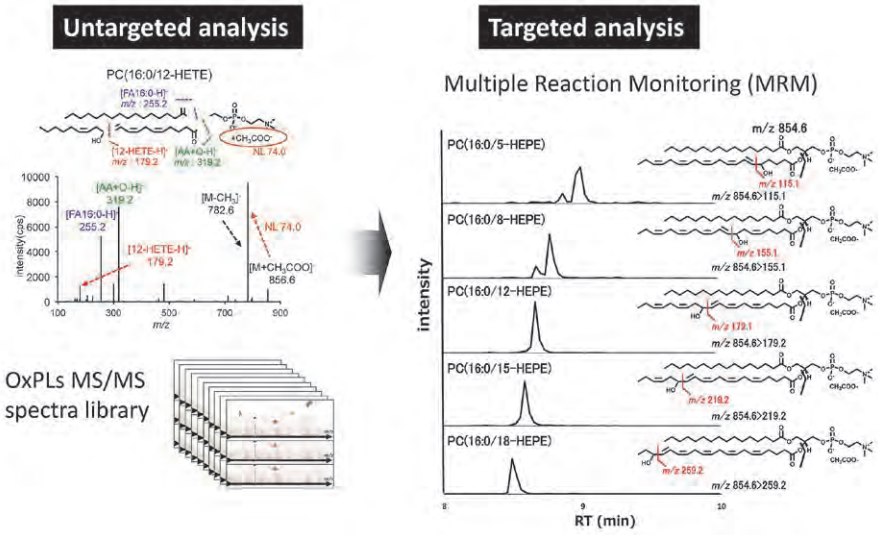


Figure: Comprehensive analysis of oxidized phospholipids (OxPLs) using a measured MS/MS spectra library

Lipids are recognized as extremely diverse molecules. The 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.

Recently we successfully developed a comprehensive analytical method for oxidized phospholipids (OxPLs) (Figure). OxPLs are widely thought to be associated with various diseases such as arteriosclerosis, diabetes and cancer. Biogenic OxPLs were prepared by the addition of specific oxidized fatty acids to cultured cells, where they were incorporated into cellular phospholipids. Untargeted lipidomics by LC-quadrupole/time-of-flight (QTOF) MS was then applied to collect MS/MS spectra for the OxPLs. Based on the measured MS/MS spectra of the biogenic OxPLs, we developed a broad-targeted lipidomics system using triple quadrupole (tripleQ) MS. This advanced method will enable us to elucidate the structure-specific behavior of OxPLs and their physiological relevance *in vivo*.

By taking advantage of Q-TOF (global lipid screening) and TripleQ (quantitative analyses) mass spectrometry, our new approach has a great potential to identify lipids of interest globally and to identify unknown lipid species in a non-biased fashion. Also, we are developing a comprehensive analytical platform with an MS/MS spectra library especially focusing on bioactive lipid mediators and complex structures of lipid metabolites produced by commensal microbiota. We are also developing software that enables us to search for lipid structures more precisely and comprehensively.

Recent Major Publications

Aoyagi R, Ikeda K, Isobe Y, Arita M. Comprehensive analyses of oxidized phospholipids using a measured MS/MS spectra library. ***J Lipid Res*** 58, 2229–2237 (2017)

Tsugawa H, Ikeda K, Arita M. The importance of bioinformatics for connecting data-driven lipidomics and biological insights. ***Biochim Biophys Acta*** 1862, 762–765 (2017)

Tsugawa H, Ikeda K, Tanaka W, Senoo Y, Arita M, Arita M. Comprehensive identification of sphingolipid species by in silico retention time and tandem mass spectral library. ***J Cheminform*** 9, 19 (2017)

Invited Presentations

Arita M. "Omega-3 fatty acid metabolism in controlling inflammation and related diseases" The 7th Mind-Body Interface International Symposium (Taichung, Taiwan) November, 2017

Arita M. "Eosinophil polyunsaturated fatty acid metabolism and its potential control of inflammation and allergy" The 15th International Conference on Bioactive Lipids in Cancer, Inflammation, and Related Diseases (Puerto Vallarta, Mexico) October, 2017

Arita M. "The importance of lipoquality in biological systems" The 1st International Conference on Lipoquality (Tokyo, Japan) September, 2017

Arita M. "Lipidomics and discovery of novel bioactive omega-3 fatty acid metabolites" The 1st International Symposium on Lipid Science and Biotechnology (ISLSB2017) (Guangzou, China) April, 2017

Arita M. "Omega-3 fatty acid metabolism in controlling inflammation and related diseases" The 4th International Forum on Omega-3 and Human Health (Chongqing, China) March, 2017

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

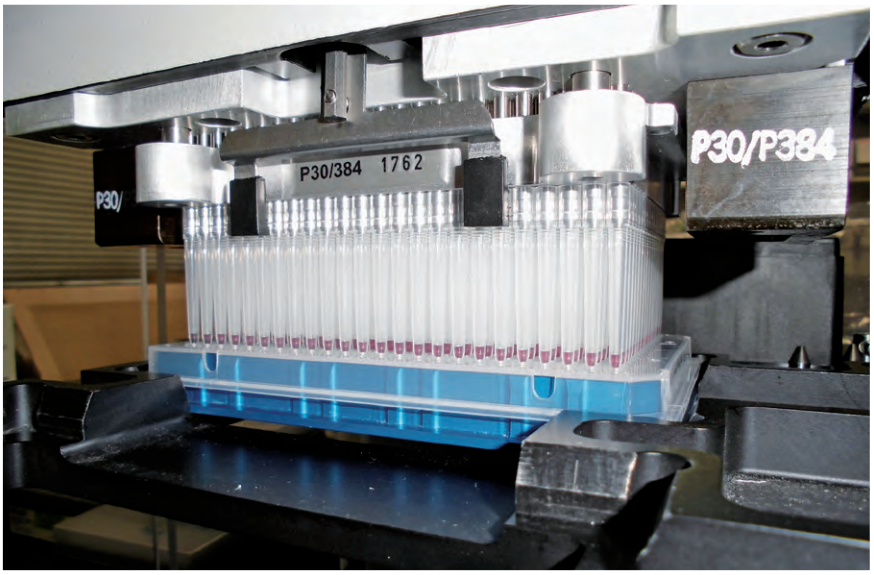


Figure: Our high throughput dispensing system necessary for large scale genomic analyses

The aims of the Laboratory for Genotyping Development are 1) to produce precise and large-scale genomic data to identify genetic variants related to disease susceptibility, outcomes, and drug responses in close collaboration with the Laboratory for Statistical Analysis and 2) to develop methods and databases useful for personalized medicine. Our laboratory has worked as a research hub of large-scale genomic analysis, collaborating with domestic and international universities, research institutes, and companies.

Our laboratory contributed to various projects and published 37 papers in 2017.

- Development of a new *in silico* method from data of genome wide association study into one causative variant with Broad Institute, Sanger Center, and University of Liege (Nature 547, 173–178).
- Identification of 112 new genomic loci for body mass index in Japanese with the Laboratory for Statistical Analysis (Nat Genet 49, 1458–1467).
- Development of Japanese eQTL dataset in six cell types with the Laboratory for Autoimmune Diseases and the Laboratory for Statistical Analysis (Nat Genet 49, 1120–1125)
- Identification of the mechanism of CCDC88B in the pathogenesis of inflammatory bowel disease with McGill University (Nat Commun 8, 932).
- Identification of new protein-altering variants of PTPN2 in childhood-onset Type 1A diabetes with the National Research Institute for Child Health and Development (Diabetic Med, in press)
- Identification of ZNF384-related fusion genes consisting of a distinct subgroup of B-cell precursor acute lymphoblastic leukemia with the National Research Institute for Child Health and Development (Haematologica 102,118–129)

We will continue to work as a research hub for large-scale genomic analysis so that we can contribute to the implementation of personalized medicine.

Recent Major Publications

Akiyama M, Okada Y, Kanai M, Takahashi A, Momozawa Y, Ikeda M, Iwata N, Ikegawa S, Hirata M, Matsuda K, Iwasaki M, Yamaji T, Sawada N, Hachiya T, Tanno K, Shimizu A, Hozawa A, Minegishi N, Tsugane S, Yamamoto M, Kubo M, Kamatani Y. Genome-wide association study identifies 112 new loci for body mass index in the Japanese population. ***Nat Genet*** 49, 1458–1467 (2017)

Huang H, Fang M, Jostins L, Umićević Mirkov M, Boucher G, Anderson CA, Andersen V, Cleynen I, Cortes A, Crins F, D'Amato M, Deffontaine V, Dmitrieva J, Docampo E, Elansary M, Farh KK, Franke A, Gori AS, Goyette P, Halfvarson J, Haritunians T, Knight J, Lawrance IC, Lees CW, Louis E, Mariman R, Meuwissen T, Mni M, Momozawa Y, Parkes M, Spain SL, Théâtre E, Trynka G, Satsangi J, van Sommeren S, Vermeire S, Xavier RJ; International Inflammatory Bowel Disease Genetics Consortium, Weersma RK, Duerr RH, Mathew CG, Rioux JD, McGovern DPB, Cho JH, Georges M, Daly MJ, Barrett JC. Fine-mapping inflammatory bowel disease loci to single-variant resolution. ***Nature*** 547, 173–178 (2017)

Ishigaki K, Kochi Y, Suzuki A, Tsuchida Y, Tsuchiya H, Sumitomo S, Yamaguchi K, Nagafuchi Y, Nakachi S, Kato R, Sakurai K, Shoda H, Ikari K, Taniguchi A, Yamanaka H, Miya F, Tsunoda T, Okada Y, Momozawa Y, Kamatani Y, Yamada R, Kubo M, Fujio K, Yamamoto K. Polygenic burdens on cell-specific pathways underlie the risk of rheumatoid arthritis. ***Nat Genet*** 49, 1120–1125 (2017)

Invited Presentations

Momozawa Y. "Genomic analysis of disease of companion animals in Europe" The 160th meeting of the Japanese Society of Veterinary Science (Kagoshima, Japan) September, 2017

Momozawa Y. "Germline pathogenic variants of 11 hereditary breast cancer genes" Pharmacogenomics Research Network – RIKEN Center for Integrative Medical Sciences (IMS) Strategic Alliance Meeting (San Francisco, USA) September, 2017

Laboratory for Genome Sequencing Analysis

Team Leader: Hidewaki Nakagawa

Recent Major Publications

Wardell CP, Fujita M, Yamada T, Simbolo M, Fassan M, Karlic R, Polak P, Kim J, Hatanaka Y, Maejima K, Lawlor RT, Nakanishi Y, Mitsuhashi T, Fujimoto A, Furuta M, Ruzzenente A, Conci S, Oosawa A, Sasaki-Oku A, Nakano K, Tanaka H, Yamamoto Y, Kubo M, Kawakami Y, Aikata H, Ueno M, Hayami S, Gotoh K, Ariizumi S, Yamamoto M, Yamaue H, Chayama K, Miyano S, Getz G, Scarpa A, Hirano S, Nakamura T, Nakagawa H. Genomic characterization of biliary tract cancers identifies their driver genes and predisposing mutations. ***J Hepatol*** 68, 959–969 (2018)

Fujita M, Matsubara N, Matsuda I, Maejima K, Oosawa A, Yamano T, Fujimoto A, Furuta M, Nakano K, Oku-Sasaki A, Tanaka H, Shiraishi Y, Mateos RN, Nakai K, Miyano S, Tomita N, Hirota S, Ikeuchi H, Nakagawa H. Genomic landscape of colitis-associated cancer indicates the impact of chronic inflammation and its stratification by mutations in RNF43 and Wnt signaling. ***Oncotarget*** 9, 969–981 (2017)

Van Renne M, Roca Suarez A, Duong F, Gondeau C, Calabrese D, Fontaine N, Ababsa A, Bandiera S, Croonenborghs T, Pochet N, De Blasi V, Pessauz P, Piardi T, Sommacale D, Ono A, Chayama K, Fujita M, Nakagawa H, Hoshida Y, Zeisel M, Heim M, Baumert T, Lupberger J. miR-135a-5p-mediated downregulation of protein-tyrosine phosphatase delta is a candidate driver of HCV-associated hepatocarcinogenesis. ***Gut***, gutjnl–2016–312270 (2017)

Invited Presentations

Nakagawa H. "Genomic Landscape of Hepato-Biliary Cancers and Forwarding to Precision Medicine" Molecular Analysis for Personalized therapy (MAP) Conference (Zurich, Switzerland) October, 2017

Nakagawa H. "The Pan-cancer Analysis of Whole Genome (PCAWG) project in the International Cancer Genome Consortium" The 76th Annual Meeting of Japanese Cancer Association (Yokohama, Japan) September, 2017

Fujita M, Nakagawa H. "Precision oncology by genomic profiling for colitic cancer indicate potentials of mutations for cancer diagnosis and treatment" The 76th Annual Meeting of Japanese Cancer Association (Yokohama, Japan) September, 2017

Nakagawa H. "Cancer Whole Genome Sequencing for Precision Oncology and Cancer Immunology" The 2017 Cold Spring Harbor Asia Conference (Suzhou, China) September, 2017

Nakagawa H, Imoto S. "Immuno-genomic landscape of pan-cancer reveals diverse pathways related with immune signature, immune escape, and immuno-editing history" The 13th Scientific Workshop of ICGC (Seoul, Korea) June, 2017

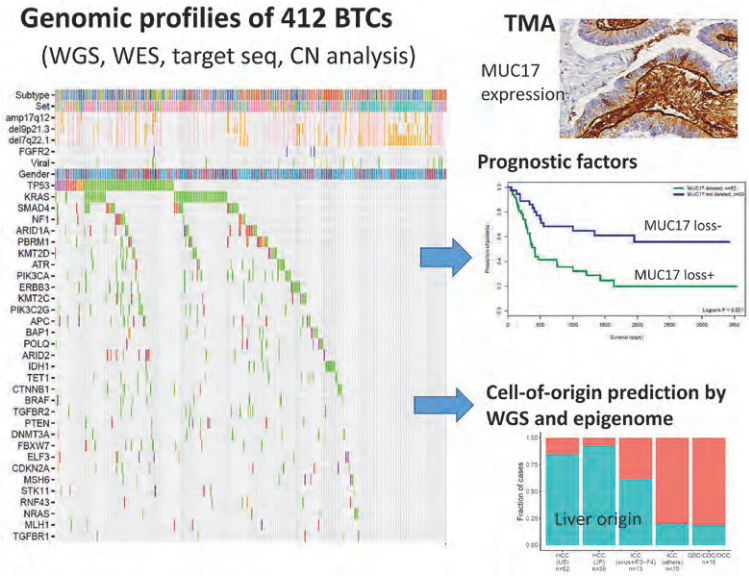


Figure:
We analyzed genomic features of 412 biliary tract cancer (BTC) samples from Japanese and Italian populations by whole genome or exome sequencing. We identified 32 significantly and commonly mutated genes, some of which negatively affected patient prognosis, including a novel deletion of *MUC17* at *7q22.1*, which was also confirmed by tissue microarray analysis (TMA). Cell-of-origin predictions using whole-genome genetic and epigenetic features suggest a hepatocyte-origin of hepatitis-related intrahepatic cholangiocarcinoma. Deleterious germline mutations of cancer-predisposing genes were detected in 11% of BTC patients. BTCs have distinct genetic features including somatic events and germline predisposition.

Cancer is essentially a "disease of the genome" that evolves in the background of germline variants with the accumulation of diverse mutations caused by environmental exposure and intrinsic factors. Germline variants predispose to cancer development and genetic analysis of certain specific genes, such as *BRCA1/2*, is commonly performed for cancer risk, while somatic mutants of driver genes have been targeted for cancer treatment and genotype-based personalized cancer therapy is now a reality. Furthermore, immunology is also an important factor to understand cancer because emerging immune therapies have been shown to be effective in many types of cancers. Now we must understand more about cancer genome-immune interactions and their diversity to develop new and more effective therapies by capitalizing on new technologies. Recent explosive advances in next-generation sequencing (NGS) and bioinformatics/IT enable a systematic, genome-wide identification of all somatic abnormalities and immune activity within cancer tissues by combining whole genome sequencing (WGS), RNA sequencing, and single-cell sequencing. It is important to analyze the likely implications of the huge human genome datasets from NGS and to reach a consensus about how to interpret the biological, immunological and clinical aspects of somatic and germline variants. Our research objectives are to understand cancer genome and microenvironmental activities, including immune activity, by utilizing NGS to identify novel genomic biomarkers and to develop analysis platforms that can be used in clinics for cancer precision medicine.

Laboratory for Statistical Analysis

Team Leader: Yoichiro Kamatani

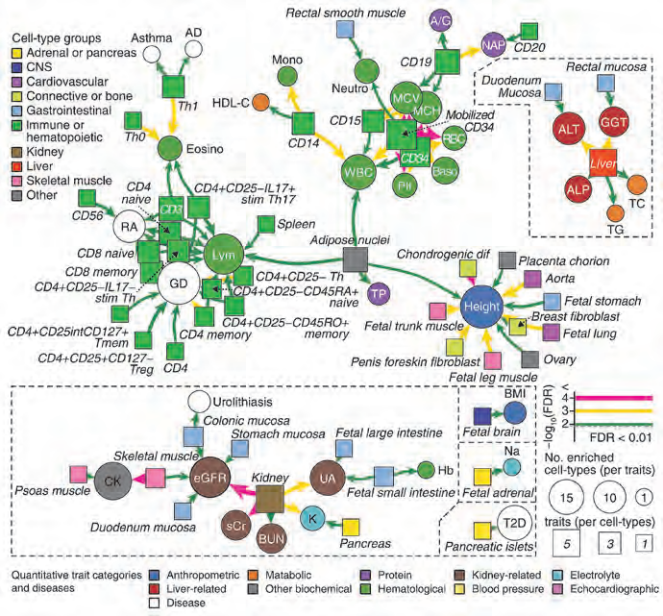


Figure: Human traits and cell type specificity network constructed from GWAS and epigenome data

We performed GWAS of 58 quantitative traits in 162,255 Japanese individuals and found 1,407 trait-associated loci. By incorporating 32 GWAS results from complex diseases and epigenetic data, we investigated the enrichment of the heritability and constructed a cell-type specificity network. The network illustrates where the identified genetic variants may induce functional changes in the human body and thereby affect quantitative trait levels or cause diseases.

Our laboratory aims at identifying susceptibility variants of complex traits by using the genetic association study, as well as then connecting the genetic association findings with biology and medicine using omics data, including epigenome and transcriptome. Until now, we have used genome-wide SNP array data and performed genome wide association studies (GWAS) for dozens of traits. In 2017, we have reported results of GWAS for atrial fibrillation, BMI, and several laboratory tests. These catalogs represent the largest non-European GWAS ever collected for each trait. After their publication, we shared these results, which are freely available at http://jenger.riken.jp/.

We are now moving to address three key issues in this field; missing heritability, functional interpretation of the identified genetic variants, and the genetic architecture of the diseases in question. Firstly, we have finished imputation for the missing rare variants in the SNP results of the ~230,000 subjects described above by using whole genome sequencing (WGS) data of ~1,000 Japanese individuals. The results clearly demonstrated the roles of rare variants and highlight population-specific genetic effects. Secondly, we are now focusing on the interpretation of GWAS signals. Pathway analysis of the GWAS data for atrial fibrillation indicated that the identified genes were enriched for the fetal neural crest development pathway, which provides a novel research clue to elucidate how genetic variants lead to increased risk of developing that disease. We also conducted enrichment of either the lead genetic variants or polygenic effects and found several statistically significant enrichments for cell-type specific regulatory elements. Now we have begun using in-house eQTL data of lymphocyte subtypes generated by the Laboratory for Autoimmune Diseases and long non-coding RNA expression data from several cell types as a collaborative project with the RIKEN Center for Life Science Technologies (CLST). Lastly, we are attempting to use machine-learning techniques to reveal non-additive effects of genomic variants, which have not been investigated well in this field. These novel machine-learning techniques will facilitate detecting such effects.

Recent Major Publications

Kanai M, Akiyama M, Takahashi A, Matoba N, Momozawa Y, Ikeda M, Iwata N, Ikegawa S, Hirata M, Matsuda K, Kubo M, Okada Y, Kamatani Y. Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. ***Nat Genet*** 50, 390–400 (2018)

Akiyama M, Okada Y, Kanai M, Takahashi A, Momozawa Y, Ikeda M, Iwata N, Ikegawa S, Hirata M, Matsuda K, Iwasaki M, Yamaji T, Sawada N, Hachiya T, Tanno K, Shimizu A, Hozawa A, Minegishi N, Tsugane S, Yamamoto M, Kubo M, Kamatani Y. Genome-wide association study identifies 112 new loci for body mass index in the Japanese population. ***Nat Genet*** 49, 1458–1467 (2017)

Low SK, Takahashi A, Ebana Y, Ozaki K, Christophersen IE, Ellinor PT; AFGen Consortium, Ogishima S, Yamamoto M, Satoh M, Sasaki M, Yamaji T, Iwasaki M, Tsugane S, Tanaka K, Naito M, Wakai K, Tanaka H, Furukawa T, Kubo M, Ito K, Kamatani Y, Tanaka T. Identification of six new genetic loci associated with atrial fibrillation in the Japanese population. ***Nat Genet*** 49, 953–958 (2017).

Invited Presentations

Akiyama M, Kamatani Y. "Large-scale genome-wide association study: Past, Present, and Future" Japanese Society of Human Genetics Annual Meeting (Kobe, Japan) November, 2017

Kamatani Y. "GWAS using 200,000 participants of Biobank Japan" Genomic histology of Japonesian (Mishima, Japan) August, 2017

Laboratory for Pharmacogenomics

Group Director: Taisei Mushiroda

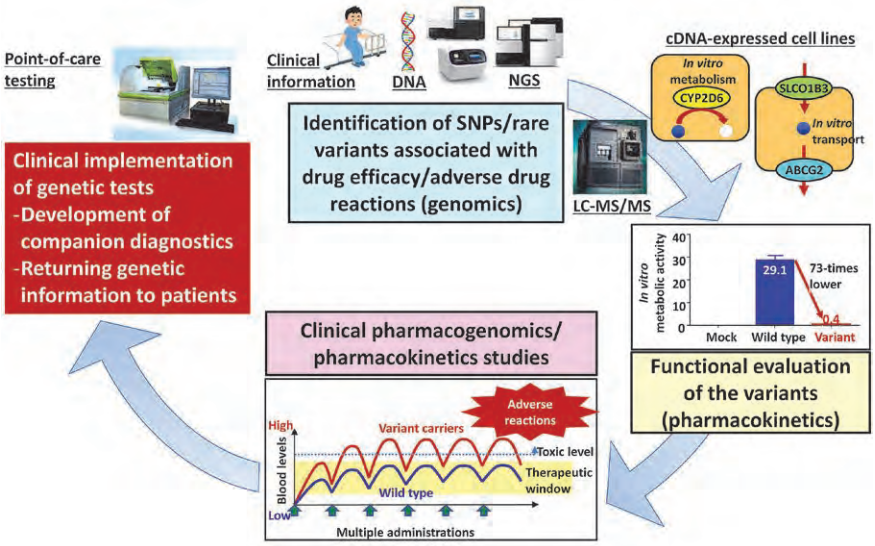


Figure: Road to implementation of PGx biomarkers into clinical practice
GWAS, HLA genotyping, and the 100 "Pharmacogene" panel identify PGx biomarkers. After *in vitro* functional evaluation of SNPs/rare variants associated with drug efficacy or risk of adverse drug reactions, the advantages of PGx biomarkers should be demonstrated by conducting prospective clinical trials that can evaluate the clinical utility of genetic testing for implementation of PGx tests.

Genomic analyses, such as genome-wide association study (GWAS) and HLA genotyping, are efficient for the identification of pharmacogenomics (PGx) biomarkers that can predict efficacy or risk of adverse drug reactions for various drugs. The GWAS presently stands as a standard method in IMS but can explain only a part of the association of genomic variations with drug responses. Pharmacokinetic variabilities are often responsible for inter-individual differences in drug responses. Thus, genetic variations in "Pharmacogenes" encoding proteins involved in pharmacokinetics, drug-metabolizing enzymes and drug transporters, are of increasing importance for identification of PGx biomarkers. However, it has been difficult to examine variations in the pharmacogenes because most of the genes are located within complex genomic regions. We have developed a targeted resequencing panel of 100 pharmacogenes related to pharmacokinetics using a combination of multiplex-PCR and next generation sequencing (NGS), which can analyze rare variants comprehensively and accurately, and thus will be effective for the identification of PGx biomarkers. After identification of the biomarkers, we conduct *in vitro* metabolic and transport experiments in order to evaluate effects of the variants on gene function for understanding of the molecular mechanisms of drug responses.

Since our mission is implementation of PGx testing, we also conduct prospective clinical studies to test the clinical utility of genetic tests using the PGx biomarkers identified by our basic research. If successful, this will lead to use of the PGx biomarkers as *in vitro* diagnostics under the Japan national health insurance system. Recently, we have completed two prospective PGx clinical trials, GENCAT and GENWAT, which showed clinical utility of the genetic tests for patients who needed treatment with the antiepileptic drug carbamazepine or the anticoagulant warfarin.

Recent Major Publications

Mushiroda T, Takahashi Y Onuma T, Yamamoto Y, Kamei T, Hoshida T, Takeuchi K, Otsuka K, Okazaki M, Watanabe M, Kanemoto K, Ohshima T, Watanabe A, Minami S, Saito K, Tanii H, Shimo Y, Hara M, Saitoh S, Kinoshita T, Kato M, Yamada N, Akamatsu N, Fukuchi T, Ishida S, Yasumoto S, Takahashi A, Ozeki T, Furuta T, Saito Y, Izumida N, Kano Y, Shiohara T, Kubo M, on behalf of the GENCAT Study Group. Prospective *HLA-A*31:01* screening and the incidence of carbamazepine-induced cutaneous adverse reactions in the Japanese patients. ***JAMA Neurol*** in press

Ujiie H, Muramatsu K, Mushiroda T, Ozeki T, Miyoshi H, Iwata H, Nakamura A, Nomoto H, Cho KY, Sato N, Nishimura M, Ito T, Izumi K, Nishie W, Shimizu H. *HLA-DQB1*03:01* as a biomarker for genetic susceptibility to bullous pemphigoid induced by DPP-4 inhibitors. ***J Invest Dermatol*** 135, 1201–1204 (2018)

Giacomini KM, Yee SW, Mushiroda T, Weinshilboum RM, Ratain MJ, Kubo M. Genome-wide association studies of drug response and toxicity: an opportunity for genome medicine. ***Nat Rev Drug Discov*** 16, 1 (2017)

Invited Presentations

Mushiroda T. "Clinical utility of *HLA-A*31:01* test for avoidance of carbamazepine-induced skin rash" The 12th Asia-Pacific Conference on Human Genetics (Bangkok, Thailand) November, 2017

Mushiroda T. "Identification of genomic biomarkers associated with cutaneous adverse drug reactions and validation of clinical utility of genetic testing" Genomic Medicine 2017 (Ho Chi Minh, Vietnam) August, 2017

Mushiroda T. "Validation of clinical utility of *HLA-A*31:01* test for avoidance of carbamazepine-induced skin rash" The 2nd International Stevens-Johnson Syndrome Symposium (Kyoto, Japan) January, 2017

Laboratory for Cardiovascular Diseases

Team Leader: Kaoru Ito

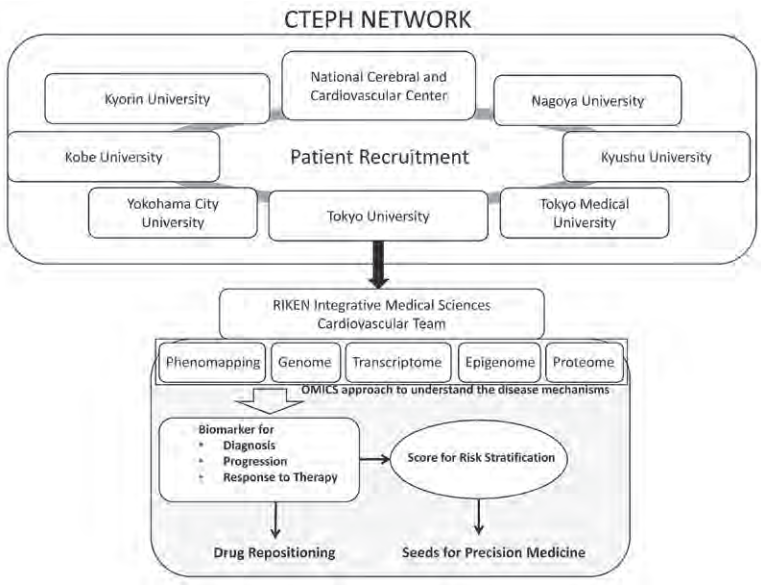


Figure: The Network for Chronic ThromboEmbolic Pulmonary Hypertension (CTEPH) Research
Samples are provided by multiple centers that perform balloon angioplasty for CTEPH. An OMICS approach is taken to elucidate CTPEH disease mechanisms using collected samples.

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 understand the mechanisms underlying these disorders and to uncover new therapeutic targets for their treatment. To achieve these goals, we combine "dry" (NGS technologies, OMICS strategies and computer science) and "wet" (so-called conventional molecular biology) technologies, in an attempt to achieve a comprehensive and precise understanding of these diseases. In other words, there is no border between "dry" and "wet" research in our lab, since we postulate that both will be required to expand the horizons of our knowledge.

Our diseases of interest to date are coronary artery diseases (CAD), atrial fibrillation (AF), Kawasaki disease (KD), peripheral artery disease (PAD), chronic thromboembolic pulmonary hypertension (CTEPH), and cardiomyopathy (CM). We are currently seeking to 1) understand the genetic cause of CAD and highlight the difference between Japanese and European populations, 2) elucidate the mechanism of CTEPH development using human OMICS data from patients in multiple hospitals (see Figure) and 3) develop a more sophisticated genetic risk scoring system by machine learning algorithms in the AF project. Additionally, in the CM project, we developed an *in silico* splicing variant prediction algorithm, a high-throughput cell-based splicing assay and a downstream *in silico* pipeline to uncover cryptic splicing variants, which have been overlooked in the currently established pipeline. Using this pipeline, we are now tackling the *TTN* (titin) gene, which is expressed in striated muscle and encodes the largest protein in humans, consisting of 34,350 amino acids.

We are conducting our research with not only a scientific mind but also a clinical eye, because our ultimate goal is to provide improved diagnostic / management / therapeutic approaches for patients suffering from those diseases.

Recent Major Publications

Ito K, Patel PN, Gorham JM, McDonough B, DePalma SR, Adler EE, Lam L, MacRae CA, Mohiuddin SM, Fatkin D, Seidman CE, Seidman JG. Identification of pathogenic gene mutations in LMNA and MYBPC3 that alter RNA splicing. ***Proc Natl Acad Sci U S A*** 114, 7689–7694 (2017)

Nomura A, Won HH, Khera AV, Takeuchi F, Ito K, McCarthy S, Emdin CA, Klarin D, Natarajan P, Zekavat SM, Gupta N, Peloso GM, Borecki IB, Teslovich TM, Asselta R, Duga S, Merlini PA, Correa A, Kessler T, Wilson JG, Bown MJ, Hall AS, Braund PS, Carey DJ, Murray MF, Kirchner HL, Leader JB, Lavage DR, Manus JN, Hartze DN, Samani NJ, Schunkert H, Marrugat J, Elosua R, McPherson R, Farrall M, Watkins H, Juang JJ, Hsiung CA, Lin SY, Wang JS, Tada H, Kawashiri MA, Inazu A, Yamagishi M, Katsuya T, Nakashima E, Nakatochi M, Yamamoto K, Yokota M, *et al*.
Protein-Truncating Variants at the Cholesteryl Ester Transfer Protein Gene and Risk for Coronary Heart Disease. ***Circ Res*** 121, 81–88 (2017)

Low SK, Takahashi A, Ebana Y, Ozaki K, Christophersen IE, Ellinor PT; AFGen Consortium, Ogishima S, Yamamoto M, Satoh M, Sasaki M, Yamaji T, Iwasaki M, Tsugane S, Tanaka K, Naito M, Wakai K, Tanaka H, Furukawa T, Kubo M, Ito K, Kamatani Y, Tanaka T. Identification of six new genetic loci associated with atrial fibrillation in the Japanese population. ***Nat Genet*** 49, 953–958 (2017)

Invited Presentations

Kaoru I. "Cutting Edge of Genomic Research: GWAS, NGS, and Others" The 10th Asia Pacific Heart Rhythm Society Scientific Session in Conjunction with the Annual Meeting of the Japanese Heart Rhythm Society 2017 (Yokohama, Japan) September, 2017

Kaoru I. "Genomic Analysis for Heart Disease by Bioinformatics and Next-Generation Sequencer." The 3rd Kyoto Cardiovascular Basic Research Seminar (Kyoto, Japan) February, 2017

Laboratory for Autoimmune Diseases

Team Leader: Kazuhiko Yamamoto

Recent Major Publications

Okubo K, Kurosawa M, Kamiya M, Urano Y, Suzuki A, Yamamoto K, Hase K, Homma K, Sasaki J, Miyauchi H, Hoshino T, Hayashi M, Mayadas TN, Hirahashi J. Macrophage extracellular trap formation promoted by platelet activation is a key mediator of rhabdomyolysisinduced acute kidney injury. ***Nat Med*** 24, 232–238 (2018)

Kochi Y, Kamatani Y, Kondo Y, Suzuki A, Kawakami E, Hiwa R, Momozawa Y, Fujimoto M, Jinnin M, Tanaka Y, Kanda T, Cooper RG, Chinoy H, Rothwell S, Lamb JA, Vencovský J, Mann H, Ohmura K, Myouzen K, Ishigaki K, Nakashima R, Hosono Y, Tsuboi H, Kawasumi H, Iwasaki Y, Kajiyama H, Horita T, Ogawa-Momohara M, Takamura A, Tsunoda S, Shimizu J, Fujio K, Amano H, Mimori A, Kawakami A, Umehara H, Takeuchi T, Sano H, Muro Y, Atsumi T, Mimura T, Kawaguchi Y, Mimori T, Takahashi A, Kubo M, Kohsaka H, Sumida T, Yamamoto K. Splicing variant of WDFY4 augments MDA5 signalling and the risk of clinically amyopathic dermatomyositis ***Ann Rheum Dis*** annrheumdis–2017–212149 (2018)

Ishigaki K, Kochi Y, Suzuki A, Tsuchida Y, Tsuchiya H, Sumitomo S, Yamaguchi K, Nagafuchi Y, Nakachi S, Kato R, Sakurai K, Shoda H, Ikari K, Taniguchi A, Yamanaka H, Miya F, Tsunoda T, Okada Y, Momozawa Y, Kamatani Y, Yamada R, Kubo M, Fujio K, Yamamoto K. Polygenic burdens on cell-specific pathways underlie the risk of rheumatoid arthritis. ***Nat Genet*** 49, 1120–1125 (2017)

Invited Presentations

Yamamoto K. "Why should rheumatologists know genetics?" 19th Asia pacific league of Associations for Rheumatology Congress (Dubai, UAE) October, 2017

Yamamoto K. "Polygenic burdens on cell-specific pathways underlie the risk of rheumatoid arthritis" Karolinska University (Stockholm, Sweden) September, 2017

Yamamoto K. "Polygenic burdens on cell-specific pathways underlie the risk of rheumatoid arthritis" Stanford University School of Medicine (Stanford, USA) September, 2017

Yamamoto K. "Peptidyl arginine deiminase 4 and rheumatoid arthritis: from human genetics to murine models" Annual European Congress of Rheumatology (Madrid, Spain) June, 2017

Yamamoto K. "Genetics of rheumatoid arthritis: From genetic information to functional insights" Advances in Targeted Therapies (Cannes, France) March-April, 2017

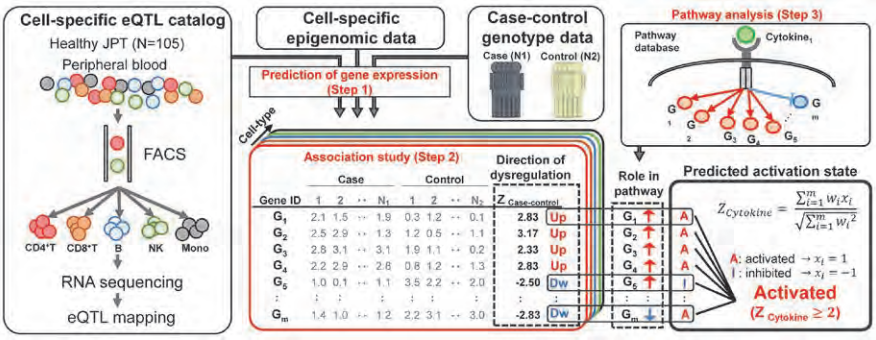


Figure: Strategy to identify the candidate causal pathways of immune-related complex disease

Design of the eQTL study and analytical pipeline. eQTL analysis was conducted on five major subsets of immune cells and unfractionated PB from healthy Japanese individuals using FACS and RNA sequencing. We developed a three-step analytical pipeline. When the direction of change in candidate causal gene expression ($Z_{case\text{-}control}$) was consistent with the activated state of the target cytokine, the gene was judged to be an activating gene. The total effect of each gene on the activity of the target cytokine was summarized, and $Z_{cytokine}$ was calculated.

Our immune system consists of higher-order functions mediated through the interaction of various cell types, molecules and genes. To date, the immune system has mainly been investigated using mouse models, including through inactivation of specific genes (knockout mice). In general, mouse and human immune systems are similar; however, there are distinct and important differences. Therefore, immunological research in humans is vital for understanding the human immune system. In this respect, studies that examine only the phenomena of immune responses may not provide information about causal relationships. Therefore, similar to gene knockout studies in mice, an investigative methodology that clarifies both cause and consequence should be adopted for human immunology research. In this context, the study of disease-susceptible genetic variants is important. With the exception of antigen receptor genes, a patient's genetic information exists before the disease onset and does not change. These genetic findings provide us with evidence into the causal relationship of the observed phenomenon and its pathogenesis. Recently, many of the disease susceptible variants identified by genome wide association study (GWAS) have been found to function as an expression-quantitative trait locus (e-QTL), regulating the expression levels of genes. For example, the SNP risk regions associated with rheumatoid arthritis (RA) significantly overlap the histone mark of an active promoter and enhancer in T cells from patients. Therefore, using global genomic information, qualitative and quantitative analyses of gene expression, together with information about disease susceptible variants, cell-specific epigenomes and proteins, we will better understand the pathogenic components of immunocompetent cells in various immune-related diseases. This research will make it possible to elucidate causal intermediate phenotypes, such as gene expression, epigenome and protein expression patterns, in individual diseases. By obtaining a comprehensive understanding of the human immune system, it could be possible to elucidate the immune status of each individual in more detail, making precision medicine a reality.

Laboratory for Digestive Diseases

Team Leader: Kazuaki Chayama

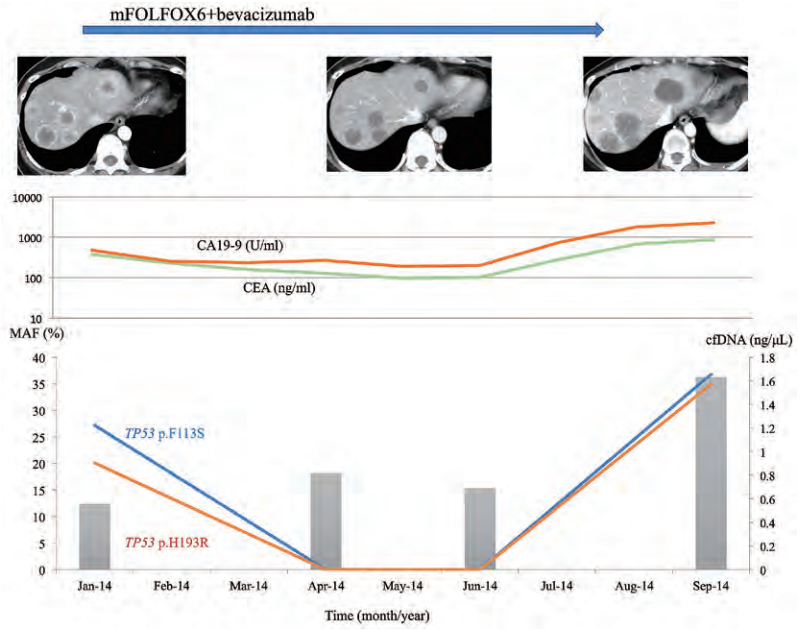


Figure: Changes in the ctDNA levels of two *TP53* mutations over the clinical course
The clinical course of a patient being treated with chemotherapy (mFOLFOX6) and immunotherapy (Bevacizumab, anti-VEGF) was followed by CT scans of liver metastases at baseline, remission and after progression. Changes in two *TP53* ctDNA mutations measured as % mutant allele frequency and in total cell-free DNA (cfDNA, bars) over the clinical course. Changes in the ctDNA levels of two *TP53* mutations are independent of changes in the amount of total cfDNA or tumor markers (CEA and CA19–9).

Although not directly cytopathic, HBV and HCV are responsible for millions of deaths annually, and the aging patient population presents a critical public health challenge. Using a GWAS approach, we have focused on investigating host genetic factors involved in various liver diseases, such as chronic HBV and HCV infection, HCV-induced liver cirrhosis and cancer, and responsiveness to therapy. We have now intensively investigated and verified how to apply such genetic information to clinical practice. We demonstrated that a polymorphism in the interferon lambda-4 (*IFNL4*) gene affects the outcome of simeprevir, peginterferon and ribavirin therapy for older patients with genotype 1 chronic hepatitis C (***Hepatol Res*** 2017). In addition, we found that an inosine triphosphatase (*ITPA*) polymorphism influences the decrease of hemoglobin during the interferon-free regimen of sofosbuvir plus ribavirin for patients with genotype 2 chronic hepatitis C (***J Gastroenterol*** 2017).

We have also participated in whole-genome sequencing (WGS) analysis of liver cancer in collaboration with the Laboratory for Genome Sequencing Analysis (***Nat Genet*** 2016, ***Nat Commun*** 2015). We showed that WGS of multiple liver tumors enabled the accurate diagnosis of multi-centric occurrence versus intrahepatic metastasis prior to selecting a therapeutic strategy for multiple tumors in the liver (***J Hepatol*** 2017). By using WGS data, we analyzed circulating tumor DNA (ctDNA) and found that it reflects tumor progression, microscopic vascular invasion of the portal vein and cancer recurrence (***Cell Mol Gastroenterol Hepatol*** 2015). Recently, we analyzed ctDNA for optimization of anti-VEGF chemotherapy in metastatic colorectal cancer patients. We finally found that changes in ctDNA levels could be useful as predictive biomarkers for survival. Mutations newly detected in ctDNA in the late treatment period might reveal the rise of a minor tumor subclone that may show resistance to the anti-VEGF therapy (***Int J Cancer in press***).

Recent Major Publications

Yamauchi M, Urabe Y, Ono A, Miki D, Ochi H, Chayama K. Serial profiling of circulating tumor DNA for optimization of anti-VEGF chemotherapy in metastatic colorectal cancer patients. ***Int J Cancer*** (in press)

Furuta M, Ueno M, Fujimoto A, Hayami S, Yasukawa S, Kojima F, Arihiro K, Kawakami Y, Wardell CP, Shiraishi Y, Tanaka H, Nakano K, Maejima K, Sasaki-Oku A, Tokunaga N, Boroevich KA, Abe T, Aikata H, Ohdan H, Gotoh K, Kubo M, Tsunoda T, Miyano S, Chayama K, Yamaue H, Nakagawa H. Whole genome sequencing discriminates hepatocellular carcinoma with intrahepatic metastasis from multi-centric tumors. ***J Hepatol*** 66, 363–373 (2017)

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 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 noncoding and structural mutations in liver cancer. ***Nat Genet*** 48, 500–509 (2016)

Invited Presentations

Chayama K. "Baseline RAS Test: Clinical practice" The Liver Week 2017 (Incheon, Korea) June, 2017

Laboratory for Bone and Joint Diseases

Team Leader: Shiro Ikegawa

Recent Major Publications

Sakamoto Y, Yamamoto T, Sugano N, Takahashi D, Watanabe T, Atsumi T, Nakamura J, Hasegawa Y, Akashi K, Narita I, Miyamoto T, Takeuchi T, Ikari K, Amano K, Fujie A, Kubo T, Tada Y, Kaneuji A, Nakamura H, Miyamura T, Kabata T, Yamaji K, Okawa T, Sudo A, Ohzono K, Tanaka Y, Yasunaga Y, Matsuda S, Imai Y; Japanese Research Committee on Idiopathic Osteonecrosis of the Femoral Head, Akiyama M, Kubo M, Kamatani Y, Iwamoto Y, Ikegawa S. Genome-wide Association Study of Idiopathic Osteonecrosis of the Femoral Head. ***Sci Rep*** 7, 15035 (2017)

Akiyama M, Okada Y, Kanai M, Takahashi A, Momozawa Y, Ikeda M, Iwata N, Ikegawa S, Hirata M, Matsuda K, Iwasaki M, Yamaji T, Sawada N, Hachiya T, Tanno K, Shimizu A, Hozawa A, Minegishi N, Tsugane S, Yamamoto M, Kubo M, Kamatani Y. Genome-wide association study identifies 112 new loci for body mass index in the Japanese population. ***Nat Genet*** 49, 1458–1467 (2017)

Ogura Y, Kou I, Takahashi Y, Takeda K, Minami S, Kawakami N, Uno K, Ito M, Yonezawa I, Kaito T, Yanagida H, Watanabe K, Taneichi H, Harimaya K, Taniguchi Y, Kotani T, Tsuji T, Suzuki T, Sudo H, Fujita N, Yagi M, Chiba K, Kubo M, Kamatani Y, Nakamura M, Matsumoto M; Japan Scoliosis Clinical Research Group, Watanabe K, Ikegawa S; Japan Scoliosis Clinical Research Group. A functional variant in MIR4300HG, the host gene of microRNA MIR4300 is associated with progression of adolescent idiopathic scoliosis. ***Hum Mol Genet*** 26, 4086–4092 (2017)

Invited Presentations

Ikegawa S. "Axial spondylometaphyseal dysplasia" 13th International Skeletal Dysplasia Society Meeting (ISDS) (Bruges, Belgium) Sep 2017

Ikegawa S. "Genome study of skeletal dysplasia, rare orthopedic diseases" The 12th ICORD (International Conference on Rare Diseases and Orphan Drugs)/The 6th China Rare Disease Summit (Beijing, China) Sep 2017

Ikegawa S. "Genomic approaches to study idiopathic scoliosis" The combined ICSG and ICVAS meeting (Dallas, Texas, USA) March 2017

Ikegawa S. "Diagnostics of skeletal dysplasias in the next generation" The 4th Nordic skeletal dysplasia workshop (Helsinki, Finland) March 2017

Ikegawa S. "How to study genetic diseases." Taipei Medical University Invited Seminar (Taipei, Taiwan) January 2017

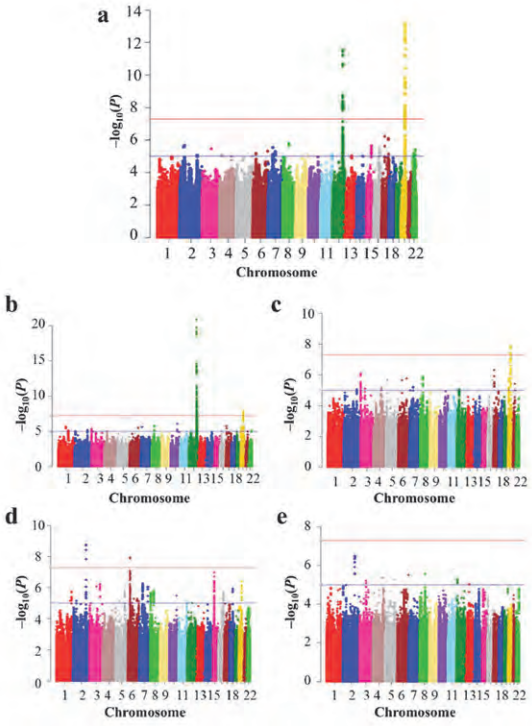


Figure: Manhattan plot of imputed GWAS data for idiopathic osteonecrosis of the femoral head in Japanese (from Sakamoto *et al.* Sci Rep 2017) **(a)** Idiopathic osteonecrosis of the femoral head vs BioBank Japan (BBJ), **(b)** alcohol-associated osteonecrosis of the femoral head (ONFH) vs BBJ, **(c)** alcohol-associated ONFH vs BBJ of heavy drinkers (400 ml/day or more ethanol consumption), **(d)** steroid-associated ONFH vs BBJ, and **(e)** neither-associated ONFH vs BBJ. SNPs with genome-wide significance were identified in **(a)** 12q24.11-12 and 20q12, **(b)** 12q24.11-13 and 20q12, **(c)** 20q12, and **(d)** 2q32 and 6p21. The red and blue lines represented the threshold of genome-wide significance ($P = 5 \times 10^{-8}$) and suggestive association threshold ($P = 1 \times 10^{-5}$), respectively.

a) Genomic Study of Common Diseases

Common bone and joint diseases have become serious concerns for world health and the economy, as exemplified by the WHO initiative "Bone and Joint Decade" (2000–2010) and the "Locomo" campaign in Japan. We are searching for susceptibility genes for common (polygenic) bone and joint diseases including osteoarthritis (OA), lumbar disc disease (LDD)/herniation (LDH), osteoporosis, idiopathic osteonecrosis of the femoral head (ION), 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 then clarify their disease-causing mechanisms at the molecular level. Using the genome information obtained by these studies, we will realize our final goal, "precision medicine" for these diseases. GWASs for OA, LDD/LDH, adolescent idiopathic scoliosis (AIS), OPLL, and ION are in progress and will be followed by functional studies of the genes *in vitro* and using animal models. We have already succeeded in identification of susceptibility genes by GWAS for ION (Figure) and the pathogenic mechanisms of the disease.

b) 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 thus many patients are waiting for treatment. We are engaging in clinical and basic studies of these refractory diseases. By large-scale mutation screening, including exome sequencing, we are identifying the disease-causing genes. So far, we identified new genes for 27 diseases.

Through 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 intractable diseases ('nanbyo'). 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: Momoko Horikoshi

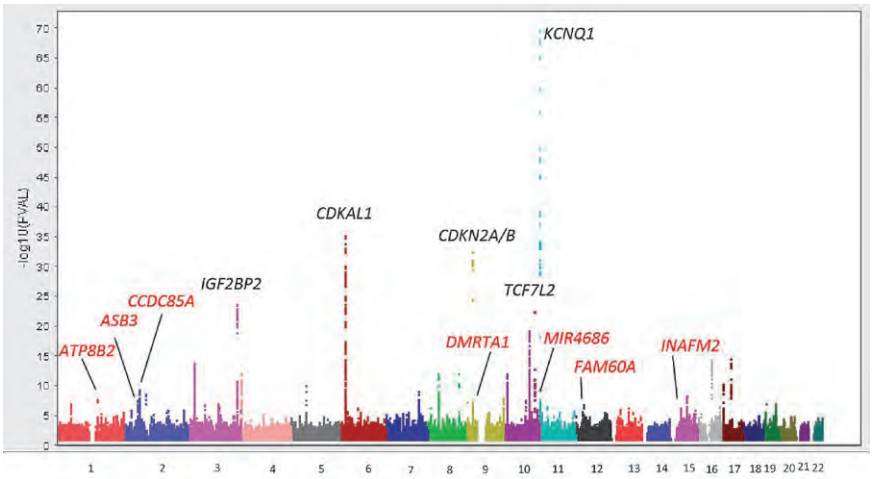


Figure: Results of GWAS meta-analysis for type 2 diabetes in the Japanese population
Names of the previously identified loci are in black and the seven new loci identified in this study are shown in red.

Our primary focus is on establishing the genetic contribution to type 2 diabetes (T2D) susceptibility in the Japanese population. To that end, we are working directly with the state-of-the-art genetic resources generated by Biobank Japan, which includes GWAS data for more than 35,000 T2D subjects. Our recent analyses of a subset of these GWAS data identified seven novel regions of the genome associated with T2D (Fig). Of the more than 90 T2D loci reported as of 2016, we have increased the number of loci reported from the Japanese population to 14 in total. We are currently expanding this effort to the full set of Biobank Japan. We have also investigated genomic regions associated with microvascular complications of T2D, namely, diabetic retinopathy and nephropathy. GWAS for these complications have been performed by several groups, but worldwide efforts to identify susceptibility to these diabetic complications have not met with clear success. We are strengthening our ties with neighboring collaborators by contributing our T2D association data to the Asian Genetic Epidemiology Network (AGEN) Consortium as well as to the world-wide DIAMANTE Consortium.

Recent Major Publications

Mägi R, Horikoshi M, Sofer T, Mahajan A, Kitajima H, Franceschini N, McCarthy MI; COGENT-Kidney Consortium, T2D-GENES Consortium, Morris AP. Trans-ethnic meta-regression of genome-wide association studies accounting for ancestry increases power for discovery and improves fine-mapping resolution. ***Hum Mol Genet*** 26, 3639–3650 (2017)

Horikoshi M, Beaumont RN, Day FR, Warrington NM, Kooijman MN, Fernandez-Tajes J, Feenstra B, van Zuydam NR, Gaulton KJ, Grarup N, Bradfield JP, Strachan DP, Li-Gao R, Ahluwalia TS, Kreiner E, Rueedi R, Lyytikäinen LP, Cousminer DL, Wu Y, Thiering E, Wang CA, Have CT, Hottenga JJ, Vilor-Tejedor N, Joshi PK, Boh ET, Ntalla I, Pitkänen N, Mahajan A, van Leeuwen EM, Joro R, Lagou V, Nodzenski M, Diver LA, Zondervan KT, Bustamante M, Marques-Vidal P, Mercader JM, Bennett AJ, Rahmioglu N, Nyholt DR, Ma RC, Tam CH, Tam WH; CHARGE Consortium Hematology Working Group., Ganesh SK, van Rooij FJ, Jones SE, Loh PR, Ruth KS, Tuke MA, et al. Genome-wide associations for birth weight and correlations with adult disease. ***Nature*** 538, 248–252 (2016)

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 RC, 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 CH, Hirose H, Maegawa H, Ito C, Kaku K, Watada H, Tanaka Y, Tobe K, Kawamori R, Kubo M, Cho YS, Chan JC, et al. Genome-wide association studies in the Japanese population identify seven novel loci for type 2 diabetes. ***Nat Commun*** 7, 10531 (2016)

Invited Presentations

IHorikoshi M. "Genomic loci associated with birth weight identify genetic links between intrauterine growth and adult metabolic disease" CRG Symposium - 7th International Workshop on Genomic Epidemiology (Barcelona, Spain) September, 2017

Horikoshi M. "Genomic loci associated with birth weight identify genetic links between intrauterine growth and adult metabolic disease" The 12th International Workshop on Advanced Genomics (Tokyo, Japan) June, 2017

Horikoshi M. "Linking birth weight and adult diseases through genetics" RCAST Symposium on New Dietetics (Tokyo, Japan) June, 2017

Laboratory for Respiratory and Allergic Diseases

Team Leader: Mayumi Tamari

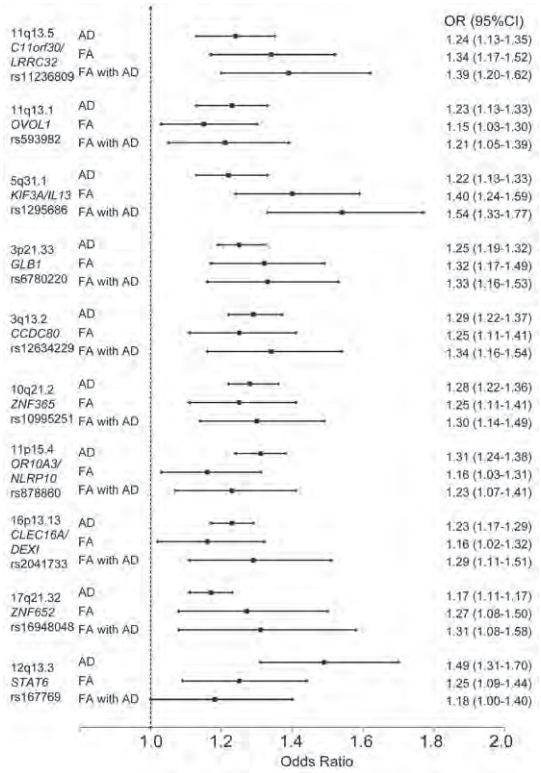


Figure: Effects of the 10 associated loci of childhood FA with AD.
Odds ratios (ORs) and 95% confidence intervals (CIs) observed for AD or EoE in original articles versus those for FA and FA with AD in this study are shown.

The aim of our project is to explore genetic components of respiratory and allergic diseases. Genome-wide association study (GWAS) is a method for comprehensive assessment of genes underlying susceptibility to human disorders. Food allergy (FA) is a problem throughout the world, but the genetic factors affecting FA susceptibility in children remain largely unexplored. We recruited patients with FA who had been diagnosed by pediatric specialists based on positive oral food challenge or a definitive clinical history after food intake. We conducted an association study of childhood FA with GWAS-discovered loci for atopic dermatitis (AD) and eosinophilic esophagitis (EoE). We assessed 19 and seven susceptibility variants previously reported in GWAS for AD and EoE, respectively, and found an association between FA and 14 of these loci. We then stratified the case subjects by AD comorbidity and a total of 10 loci were associated with childhood FA and AD (Figure). We further assessed associations of a total of six filaggrin (*FLG*) null variants with childhood FA, and found a significant association. These findings improve our understanding of the complex heterogeneity of FA.

Wheat-dependent exercise-induced anaphylaxis (WDEIA) is severe food allergy that usually develops after ingestion of wheat products followed by physical exercise. Hydrolysed wheat gluten protein (HWP) is used as an additive for facial soap. In Japan, a total of 2026 cases of immediate wheat allergy and WDEIA due to HWP have been reported. Most patients seemed to be sensitized to HWP (Glupearl 19S®) through the use of the facial soap "Cha-no-shizuku". Glupearl 19S® is a degraded gluten made by the direct resolution of wheat by hydrochloric acid. We conducted GWAS of WDEIA induced by HWP-containing facial soap of 464 cases and 3,099 controls and identified associated SNPs at a region on chromosome 6.

Recent Major Publications

Hirata J, Hirota T, Ozeki T, Kanai M, Sudo T, Tanaka T, Hizawa N, Nakagawa H, Sato S, Mushiroda T, Saeki H, Tamari M, Okada Y. Variants at HLA-A, HLA-C, and HLA-DQB1 confer risk of psoriasis vulgaris in Japanese. ***J Invest Dermatol*** (2017) in press

Hirota T, Nakayama T, Sato S, Yanagida N, Matsui T, Sugiura S, Takaoka Y, Hizawa N, Fujieda S, Miyatake A, Sasaki T, Amagai M, Doi S, Ito K, Ebisawa M, Tamari M. Association study of childhood food allergy with GWAS-discovered loci of atopic dermatitis and eosinophilic esophagitis. ***J Allergy Clin Immunol*** 140, 1713–1716 (2017)

Sunadome H, Matsumoto H, Petrova G, Kanemitsu Y, Tohda Y, Horiguchi T, Kita H, Kuwabara K, Tomii K, Otsuka K, Fujimura M, Ohkura N, Tomita K, Yokoyama A, Ohnishi H, Nakano Y, Oguma T, Hozawa S, Nagasaki T, Ito I, Oguma T, Inoue H, Tajiri T, Iwata T, Izuhara Y, Ono J, Ohta S, Hirota T, Tamari M, Yokoyama T, Niimi A, Izuhara K, Mishima M. IL4Rα and ADAM33 as genetic markers in asthma exacerbations and type-2 inflammatory endotype. ***Clin Exp Allergy*** 47, 998–1006 (2017)

Invited Presentations

Tamari M. "Genetic Factors of Allergic Diseases" The 4th Seminar of Japanese Society of Allergology (Kanagawa, Japan) December, 2017

Tamari M. "Genomics in Atopic Dermatitis and Psoriasis" Seminar in Department of Dermatology, The Jikei University of Medicine (Tokyo, Japan) July, 2017

Tamari M. "Genetic Factors of Allergic Diseases" Symposium, The 66th meeting of Japanese Society of Allergology (Tokyo, Japan) June, 2017

Tamari M. "Genetic Study of Allergic Diseases" Nature Conference (Guangzhou, China) May, 2017

Program for Medical Innovations

Four original projects for clinical applications have been performed: 1) A chemical compound recently developed using the α-galactosylceramide (α-GalCer) analog, RCAI-X. The RCAI-X-loaded autologous cell therapy has been studied preclinically for cancer therapy. 2) 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. 3) 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. 4) 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

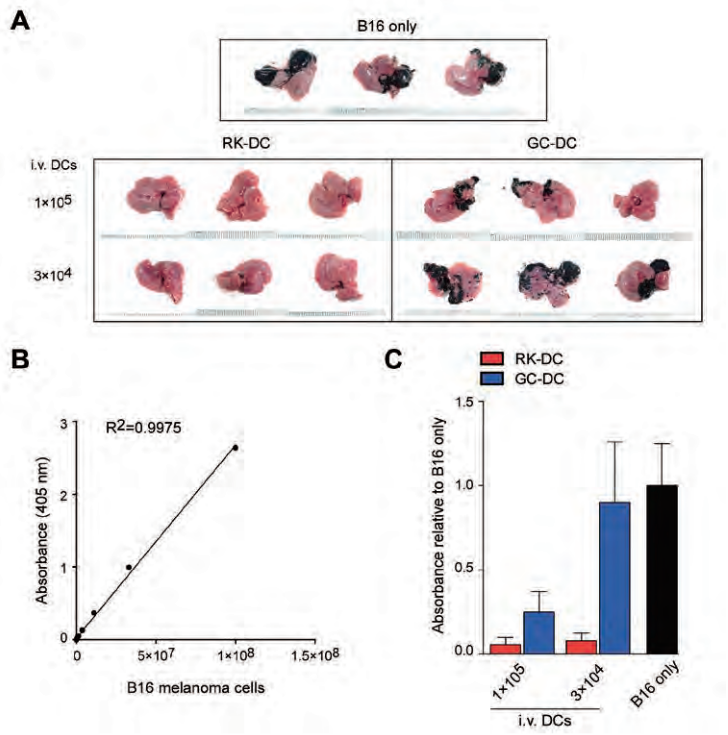


Figure: Superior antitumor activity of dendritic cells (DCs) pulsed with the novel NKT cell-activating ligand RK
(A) Inhibition of B16 melanoma metastasis by specific activation of natural killer T cells with RK-pulsed DCs. The antitumor effect was assessed using the B16 melanoma liver metastasis model. Tumor cells were inoculated into B6 mice on day 0, and the indicated numbers of DCs pulsed with RK or the previous NKT cell ligand α–galactosylceramide (GC) were injected intravenously on day 4. Untreated control mice were inoculated only with the B16 melanoma. Individual liver tissue images obtained from three mice per experimental group on day 14 post-injection are shown. **(B)** Standard curve generated by melanin measurement using visible light spectroscopy at 405 nm obtained from serially diluted B16 melanoma cells. **(C)** Quantitative analysis of B16 melanoma burden in the liver tissues shown in panel (A). Values represent calculated ratios of melanin concentrations assessed by visible light spectroscopy relative to the untreated animals inoculated only with the B16 melanoma (mean ± SEM, $n = 5$ mice per group).

Current tumor therapies, including immunotherapies, focus on passive eradication or at least reduction of the tumor mass. However, cancer patients quite often suffer from tumor relapse or metastasis after such treatments. To overcome these problems, we have developed an NKT cell-targeted immunotherapy focusing on active engagement of the patient's immune system, but not directly targeting the tumor cells themselves. Natural Killer T (NKT) cells express an invariant antigen receptor α chain encoded by *Trav11* (Vα14)–*Traj18* (Jα18) gene segments in mice and *TRAV10* (Vα24)–*TRAJ18* (Jα18) in humans and recognize glycolipid ligand in conjunction with a monomorphic CD1d molecule. The NKT cells play a pivotal role in the orchestration of antitumor immune responses by mediating adjuvant effects that activate various antitumor effector cells of both innate and adaptive immune systems and also aid in establishing a long-term memory response. As a result of our group's long term commitment to translational research supported by AMED, we have recently established an NKT cell-targeted therapy using a newly discovered NKT cell glycolipid ligand, RK, which has a stronger capacity to stimulate both human and mouse NKT cells compared to previously used NKT cell ligands. Moreover, RK mediates strong adjuvant effects in activating various effector cell types and establishes long-term memory responses, resulting in a continuous attack on the tumor that confers long-lasting and potent antitumor effects. Since the NKT cell ligand presented by the monomorphic CD1d can be used for all humans irrespective of HLA types, and also because NKT cell-targeted therapy does not directly target tumor cells, this therapy can potentially be applied to all cancer patients and any type of tumor.

Recent Major Publications

Dashtsoodol N, Shigeura T, Tashiro T, Aihara M, Chikanishi T, Okada H, Hanada K, Sano H, Kurogi A, Taniguchi M. Natural Killer T Cell-Targeted Immunotherapy Mediating Long-term Memory Responses and Strong Antitumor Activity. ***Front Immunol*** 8, 1206 (2017)

Dashtsoodol N, Shigeura T, Aihara M, Ozawa R, Kojo S, Harada M, Endo T, Watanabe T, Ohara O, Taniguchi M. Alternative pathway for the development of Vα14$^+$ NKT cells directly from CD4$^-$CD8$^-$ thymocytes that bypasses the CD4$^+$CD8$^+$ stage. ***Nat Immunol*** 18, 274–282 (2017)

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 Vα14 Natural Killer T Cells with an Undisturbed T Cell Receptor α-Chain Repertoire. ***PLoS One*** 11, e0153347 (2016)

Invited Presentations

Taniguchi M. "NKT cell-targeted anti-cancer therapy" 2017 World Alliance Forum in San Francisco (San Francisco, USA) November, 2017

Taniguchi M. "Alternative pathway for the development of Vα14$^+$ NKT cells directly from CD4$^-$CD8$^-$ thymocytes that bypasses the CD4$^+$CD8$^+$ stage" CD1-MR1 2017 (Napa, USA) November, 2017

Dashtsoodol N. "Revisiting a dogma: Identification of a novel alternative pathway of Vα14$^+$ NKT cell development directly from thymic DN stage bypassing the DP stage" Annual Scientific Conference of the Mongolian National University of Medical Sciences (Ulaanbaatar, Mongolia) April, 2017

Laboratory for Immunotherapy

Team Leader: Shin-ichiro Fujii

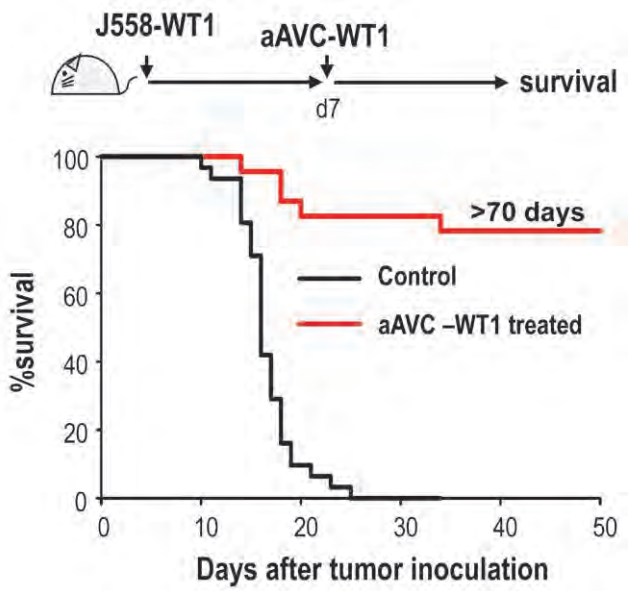


Figure: Preclinical study with aAVC-WT1
Mice were inoculated with a WT1-expressing plasmacytoma cell line (J558-WT1) and then treated with mouse aAVC-WT1 at day 7. In the control untreated group, all of the mice died within 30 days. In contrast, 75% of the aAVC-WT1-treated mice survived for more than 6 months.

The aims of our 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. In this fiscal year, we have started the first-in-human clinical trial using artificial adjuvant vector cells (aAVC), which we first developed in 2009. The aAVC is comprised of allogeneic cells as vector cells, NKT ligand and CD1d complex on the cell surface and cancer-related protein inside of the cells. This aAVC cellular drug therapy activates dendritic cells *in vivo*, resulting in multifunctional immune responses, i.e., not only innate and adaptive immunity, but also memory T cells. Because of this powerful immune response, we observe a strong antitumor therapeutic effect and also a block in tumor metastasis. Since aAVC is a basic platform, we can replace any type of cancer antigen and, therefore, it would possibly be applicable for a variety of diseases. In fact, we have confirmed the activation of multifunctional immune responses by administration of aAVC-OVA, -MART-1, -WT1 and -TRP2 in different tumor-bearing mouse models. In addition, we demonstrated that therapy with aAVC-expressing hemagglutinin (aAVC-HA) should also be useful to combat influenza virus infection. We established a human aAVC product, WT-1 tumor antigen-expressing human aAVC (aAVC-WT1) and finished many pre-clinical studies by consulting with the Japan Pharmaceuticals and Medical Devices Agency (PMDA), similar to the US FDA. As discussed above, we have recently launched an investigator-initiated clinical trial of aAVC-WT1 for relapsed or refractory acute myeloid leukemia patients in collaboration with the group of the Dept. of Hematology and Oncology, The University of Tokyo, The Institute of Medical Science. This clinical study has been supported by the Translation Research center of Tokyo University and RIKEN DMP.

Recent Major Publications

Iyoda T, Yamasaki S, Hidaka M, Kawano F, Abe Y, Suzuki K, Kadowaki N, Shimizu K, Fujii S. Amelioration of NK cell function driven by Vα24$^+$ invariant NKT cell activation in multiple myeloma. ***Clin Immunol*** S1521-6616(17)30503-X (2017)

Harrer DC, Simon B, Fujii S, Shimizu K, Uslu U, Schuler G, Gerer KF, Hoyer S, Dörrie J, Schaft N. RNA-transfection of γ/δ T cells with a chimeric antigen receptor or an α/β T-cell receptor: a safer alternative to genetically engineered α/β T cells for the immunotherapy of melanoma. ***BMC Cancer*** 17, 551 (2017)

Fujii S, Shimizu K. Exploiting antitumor immunotherapeutic novel strategies by deciphering the cross talk between invariant NKT cells and dendritic cells. ***Front Immunol*** 8, 886 (2017)

Invited Presentations

Fujii S. "Development of new cellular vaccine systems with synergistic immunopotentiating effects" The 46th Japanese Society for Immunology (Sendai, Japan) December, 2017

Fujii S. "*in vivo* DC targeting therapy triggered by NKT cell activation" The 21st Annual Meeting of Japanese Association of Cancer Immunology (Tokyo, Japan) June, 2017

Fujii S. "NKT cell-targeted anti-cancer immunotherapy" The 27th Annual Meeting of Japan Cytometry Society (Kobe, Japan) June, 2017

Fujii S, Shimizu K. "Systemic and Potent Dendritic Cell (DC) Activation Modulates the Tumor Microenvironment and Shapes the Long-lived Tumor Specific Memory CD8+T Cells" The 8th JSH International Symposium 2017 (Miyazaki, Japan) May, 2017

Fujii S. "Development of multifunctional anti-cancer vaccine - artificial adjuvant vector cells (aAVC)" The 54th Annual Meeting of Japan Society of Molecular Medicine (Tokyo, Japan) April, 2017

Drug Discovery Antibody Platform Unit

Unit Leader: Toshitada Takemori

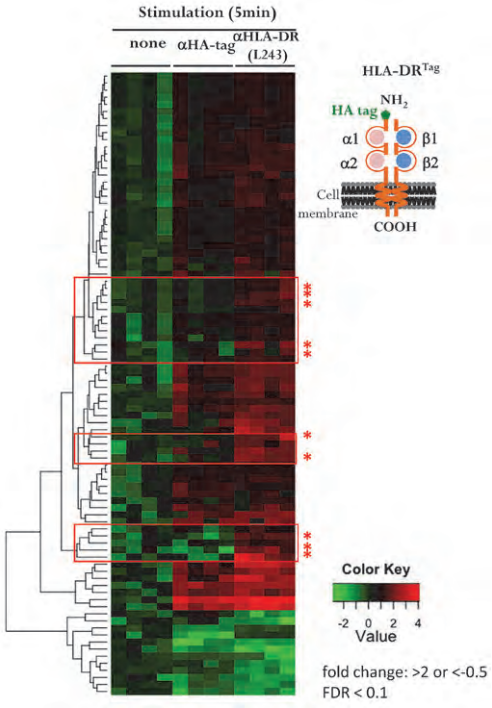


Figure: Induction of phosphorylated proteins by mAb treatment.
A mutant B cell lymphoma cell line lacking HLA-DRα was transfected with HA-tagged HLA-DRα and stimulated with L243 (mIgG2a,κ) or anti-HA (mIgG2a,κ) mAbs. Proteins were extracted from whole cell lysates (nonstimulated (none), stimulated with anti-HA tag mAb or L243 mAb), digested, followed by enrichment of phosphopeptides and finally analyzed by LC-MS/MS. Hierarchical clustering was performed on each protein and the heat map was generated using Java TreeView software (http://jtreeview.sourceforge.net/). The boxed clusters indicate phosphorylated proteins that are only enhanced with L243 stimulation. The color in the map depicts the relative expression value (log2-scale) for each sample.

Non-Hodgkin lymphoma is a heterogeneous group of malignancies, most of which have a B cell phenotype. HLA-DR is highly expressed on hematologic malignancies, and HLA-DR engagement by a pan-HLA-DR mAb recognizing a conformational epitope in the N-terminal α chain of HLA-DR, such as murine L243, directly kill the cells by non-apoptotic cell death. However, the mechanism remains elusive.

HLA-DR molecules do not possess any known signaling motifs in their cytoplasmic domain, but we found that their transmembrane domain is critical to mediate the killing signals, probably via associated molecules including tetraspanin family proteins.

Due to the importance of protein phosphorylation in many aspects of cell signaling, we have focused on the identification of phosphorylated proteins triggering non-apoptotic cell death in B cell lymphoma cell lines. To this end, we prepared 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. The mutant was transfected with HA-tagged HLA-DRα and stimulated with the killing mAb, L243, or an anti-HA mAb that stimulates cell lines but does not induce cell killing. We detected a total of 11 proteins (marked by asterisks in Figure), that were phosphorylated on multiple sites upon stimulation with L243 but not with anti-HA mAbs. These proteins are known as regulators of energy and RNA metabolism, cell cycle and signal transduction. We are now analyzing signaling pathways related to energy metabolism, which could be involved in HLA-DR mediated direct killing by a non-apoptotic pathway in B cell lymphomas.

This work is a collaboration with Drs. Ohara and Kawashima (Laboratory for Integrative Genomics) and Dr. Kawakami (Healthcare and Medical Data Driven AI based Predictive Reasoning Development Unit).

Recent Major Publications

Miyauchi K, Sugimoto-Ishige A, Harada Y, Adachi Y, Usami Y, Kaji T, , Hasegawa H, Watanabe T, Hijikata A, Fukuyama S, Maemura T, Ohara O, Kawaoka Y, Takahashi Y, Takemori T, Kubo M. Protective neutralizing influenza antibody response in the absence of T follicular helper cells. ***Nat Immunol*** 17, 1447–1458 (2016)

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)

Invited Presentations

Harada M, Sugimoto A, Matsuoka S. Takemori T. "CD81 is associated with non-apoptotic cell death in B cell lymphoma cell lines through HLA-DR alpha/beta engagement" The 46th Annual Meeting of Japanese Society for Immunology (Okinawa, Japan) December, 2016

YCI Laboratory for Immune Regeneration

Young Chief Investigator: Tomokatsu Ikawa

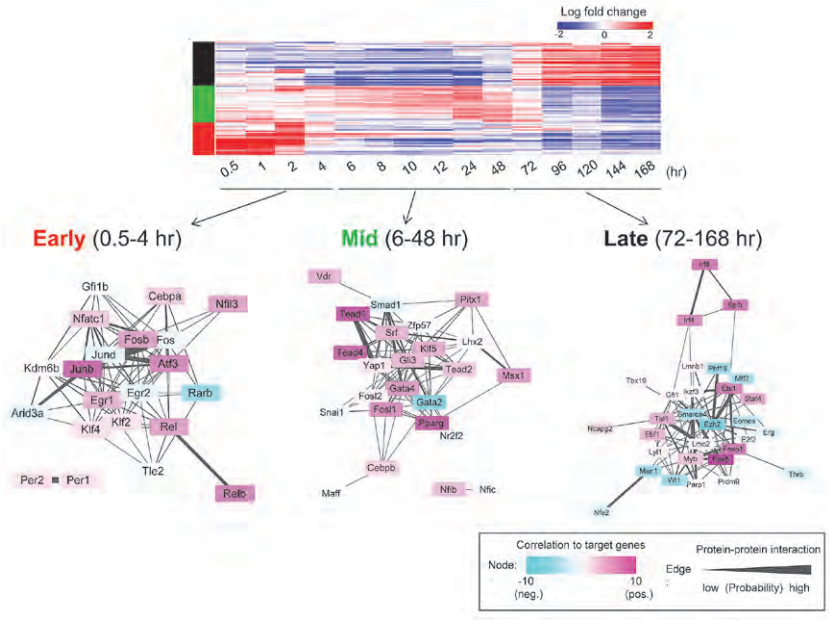


Figure: Transcriptional network during B cell fate determination
The heatmap represents gene expression profiles of highly variable transcription factors. Networks are shown in three time phases (Early, Mid and Late). The color of each node represents the transcriptional activity (activation or suppression of expression of their postulated downstream target genes) at the indicated time phase. Thickness of the edge indicates the probability of protein-protein interaction (experimental score in the STRING database).

B lymphocytes are generated from pluripotent hematopoietic stem cells (HSCs) through a successive series of lineage restriction processes. Although many essential transcription factors (TFs), such as Ikaros, PU.1, E2A, EBF1 and Pax5 have been implicated in regulating cell fate choice in the B cell lineage, molecular mechanisms underlying the generation of these patterns during cell fate determination remain unexplored because of the absence of suitable experimental systems.

We have recently established an ideal system that can be used to examine gene regulatory networks during lymphoid lineage specification from HSCs. We overexpressed Id3 protein fused with ERT2 (Estrogen receptor) protein, whose nuclear translocation is induced by 4-hydroxytamoxifen (4-OHT), in hematopoietic progenitors and cultured them in B cell differentiation conditions. In the presence of 4-OHT, B cell differentiation of Id3-transduced cells was blocked at an early developmental stage but the cells grew enormously and maintained multipotency (Ikawa et al. Stem Cell Reports, 2015). We named these multipotent progenitors as induced leukocyte stem (iLS) cells.

This novel system enabled the analysis of a large set of regulatory molecules that control the generation of T and B lymphocytes. We have recently described the complex transcriptional network operative during B lineage commitment (Figure). This system 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.

Recent Major Publications

Miyai T, Takano J, Endo TA, Kawakami E, Agata Y, Motomura Y, Kubo M, Kashima Y, Suzuki Y, Kawamoto H, Ikawa T. Three-step transcriptional priming that drives the commitment of multipotent progenitors toward B cells. ***Genes Dev*** 32, 112–126 (2018)

Noguchi S, Arakawa T, Fukuda S, Furuno M, Hasegawa A, Hori F, Ishikawa-Kato S, Kaida K, Kaiho A, Kanamori-Katayama M, Kawashima T, Kojima M, Kubosaki A, Manabe RI, Murata M, Nagao-Sato S, Nakazato K, Ninomiya N, Nishiyori-Sueki H, Noma S, Saijyo E, Saka A, Sakai M, Simon C, Suzuki N, Tagami M, Watanabe S, Yoshida S, Arner P, Axton RA, Babina M, Baillie JK, Barnett TC, Beckhouse AG, Blumenthal A, Bodega B, Bonetti A, Briggs J, Brombacher F, Carlisle AJ, Clevers HC, Davis CA, Detmar M, Dohi T, Edge ASB, Edinger M, Ehrlund A, Ekwall K, Endoh M, Enomoto H, *et al*. FANTOM5 CAGE profiles of human and mouse samples. ***Sci Data*** 4, 170112 (2017)

Ikawa T, Masuda K, Endo TA, Endo M, Isono K, Koseki Y, Nakagawa R, Kometani K, Takano J, Agata Y, Katsura Y, Kurosaki T, Vidal M, Koseki H, Kawamoto H. Conversion of T cells to B cells by inactivation of polycomb-mediated epigenetic suppression of the B-lineage program. ***Genes Dev*** 30, 2475–2485 (2016)

Invited Presentations

Ikawa T, Miyai T, Takano J. "Three-step transcriptional priming that drives multipotent progenitors toward B cells." The 46th Annual Meeting of The Japanese Society for Immunology. (Sendai, Japan) December, 2017

Ikawa T. "Epigenetic maintenance of T cell identity by Polycomb-mediated suppression of Pax5." BMB2017. (Kobe, Japan) December, 2017

Ikawa T. "Lymphocyte differentiation and Epigenetics." Biken Seminar, Osaka University (Suita, Japan) November, 2017

Ikawa T, Miyai T, Takano J. "A road map that guides the development of B cells" The 3rd Tsinghua-RIKEN Joint Symposium (Beijing, China) September, 2017

YCI Laboratory for Cellular Bioenergetic Network

Young Chief Investigator: Toshimori Kitami

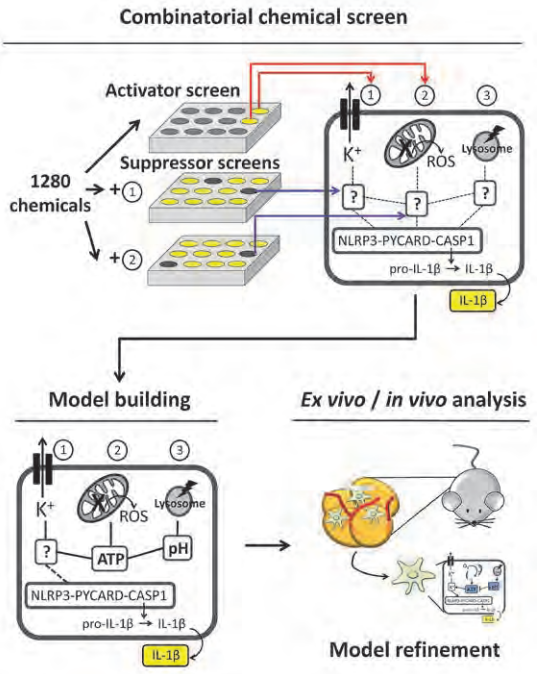


Figure: Searching for chemicals that modulate mitochondrial function using the NLRP3 inflammasome as a disease pathway model
In order to identify chemicals that could activate as well as suppress the NLRP3 inflammasome pathway, we performed multiple layers of screens using IL-1β as a readout of the pathway activity.

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)

Invited Presentations

Kitami T. "Mitochondrial chemical compendium v2: Building a genotype-chemical interaction database for mitochondrial toxicity" The 1st Annual COCKPI-T (Co-create Knowledge for Pharma Innovation with Takeda) (Kanagawa, Japan) July, 2017

The overarching 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 wide variety 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 hope to identify novel pathways that restore or improve mitochondrial function through genetic and chemical screens and 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 age-associated diseases. The NLRP3 inflammasome is activated by cell physiological changes, including mitochondrial damage, although the molecular players involved have not been fully elucidated. To systematically identify key players in this complex pathway, we performed a series of chemical screens and have successfully identified compounds that can activate as well as suppress the NLRP3 inflammasome via mitochondria. Our analysis of these unique chemicals highlighted an important role of mitochondrial energy metabolism in maintaining intracellular ion homeostasis and preventing NLRP3 activation. Moreover, two outputs of the mitochondria, ATP and reactive oxygen species, both compete for activation and suppression of the NLRP3 inflammasome.

In the coming year, we hope to gain a more in-depth quantitative understanding of the interplay between mitochondria and the key interacting molecular players we identified from the screen. In addition, we hope to understand the mechanism by which suppressors of the NLRP3 inflammasome pathway alter or restore the function of mitochondria.

YCI Laboratory for Trans-omics

Young Chief Investigator: Katsuyuki Yugi

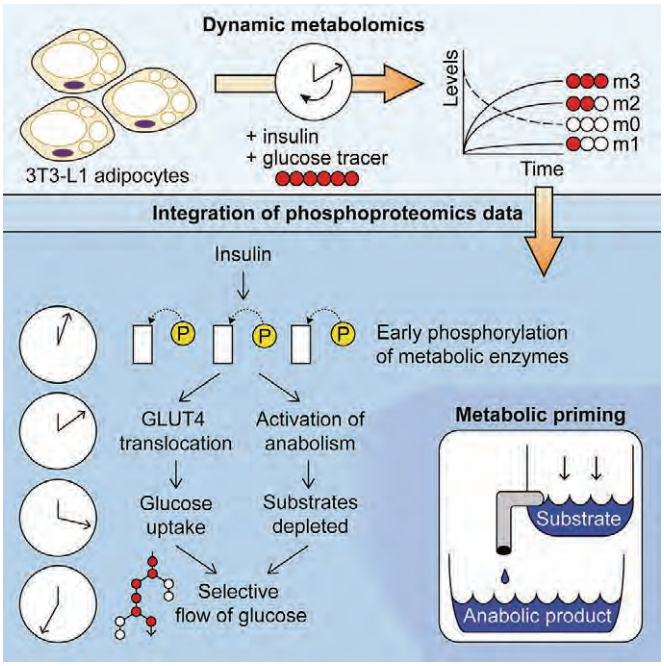


Figure: Metabolic priming in the adipocyte
Integration of time-series phosphoproteome and ^{13}C-labeled metabolome data revealed that insulin-dependent phosphorylation of widespread metabolic enzymes occurs significantly early before the start of glucose transport, which potentially could direct glucose flux towards specific metabolic pathways. (Krycer, Yugi, *et al.*, ***Cell Rep*** 2017)

Trans-omics is a discipline that aims to reconstruct a global and multi-layered molecular network, not as a group of indirect statistical correlations but as chains of direct mechanistic interactions (Yugi *et al.*, ***Trends Biotechnol*** 2016; Yugi and Kuroda, ***Cell Syst*** 2017). The network reconstruction is performed based on comprehensive measurement data of multiple omic layers not taken from heterogeneous sources but measured under an identical condition.

We applied methodologies of trans-omics to reveal how insulin acts on adipocyte metabolism in a global manner by integrating phosphoproteome and ^{13}C-labeled metabolome data (Krycer, Yugi, *et al.*, ***Cell Rep*** 2017). It has been thought that the major role of insulin is to provide anabolic substrates by activating GLUT4 transporter-dependent glucose uptake. However, recent phosphoproteomic analysis showed us that insulin provides widespread phosphorylation changes in the metabolic enzymes of the adipocyte (Humphrey *et al.*, ***Cell Metab*** 2013), and it is unclear how these changes influence the dynamics of glucose metabolism upon insulin exposure. To examine the implications of phosphorylation of these metabolic enzymes, we performed dynamic tracer metabolomics in cultured adipocytes treated with insulin.

By combining phosphoproteome and ^{13}C-labeled metabolome data, we found that insulin-dependent phosphorylation of metabolic enzymes occurs significantly early before glucose transport begins. This allows activation of key anabolic pathways that guide glucose influx into particular pathways where substrate metabolites are needed. We propose that this is a demand-driven system complementing a supply-driven mechanism by substrate accumulation. We named this phenomenon 'metabolic priming', a phenomenon in which insulin signaling kick starts catabolic reactions that generate a thermodynamic driving force that eventually pulls glucose into specific anabolic pathways.

Recent Major Publications

†Krycer JR, †Yugi K(† equal contribution), Hirayama A, Fazakerley DJ, Quek LE, Scalzo R, Ohno S, Hodson MP, Ikeda S, Soji F, Suzuki K, Domanova W, Parker BK, Nelson ME, Humphrey SJ, Turner N, Hoehn KL, Cooney GJ, Soga T, Kuroda S, James DE. Dynamic metabolomics reveals that insulin primes the adipocyte for glucose metabolism. ***Cell Rep*** 21, 3536–3547 (2017)

Yugi K, Kuroda S. Metabolism-centric trans-omics. ***Cell Syst*** 4, 19–20 (2017)

Yugi K, Kubota H, Hatano A, Kuroda, S. Trans-omics: how to reconstruct biochemical networks across multiple 'omic' layers. ***Trends Biotechnol*** 34, 276–290 (2016) (Cover Article)

Invited Presentations

Yugi K. "Trans-omic analysis reveals fed and fasting insulin signal across phosphoproteome, transcriptome, and metabolome" The 1st International Symposium for Trans-Omics (Tokyo, Japan) November. 2017

Yugi K. "A trans-omic reconstruction of insulin-dependent regulatory networks for metabolism" The 4th International Symposium of Gunma University Initiative for Advanced Research (Maebashi, Japan) November, 2017

Yugi K. "Reconstruction of insulin-dependent metabolic regulatory networks from phosphoproteome and metabolome data" RIKEN IMS-Japan Society for Immunology International Symposium on Immunology 2017 (Tokyo, Japan) June, 2017

Yugi K. "A trans-omic analysis of insulin-dependent metabolic regulation based on proteomics, metabolomics, and public databases" The 146th Kanto-area Colloquium, The Mass Spectrometry Society of Japan (Tokyo, Japan) January, 2017

YCI Laboratory for Immunological Transcriptomics

Young Chief Investigator: **Hideyuki Yoshida**

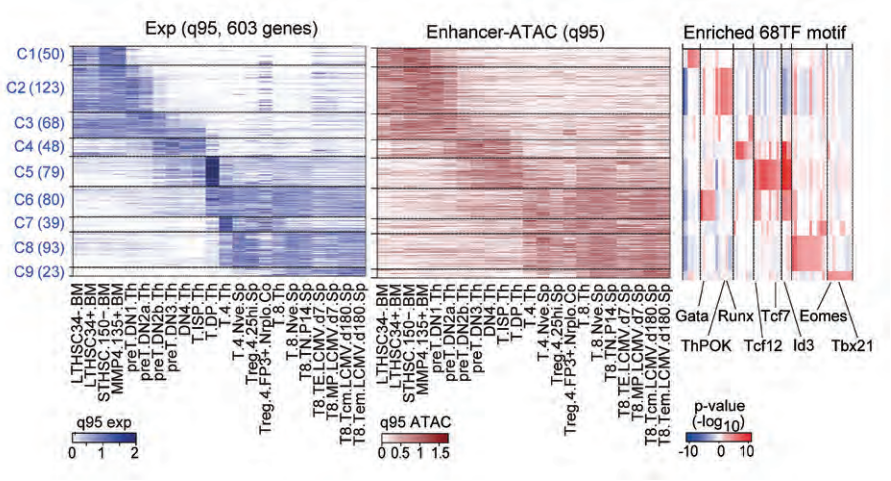


Figure: Open Chromatin Regions (OCRs) associating with altered gene expressions along T cell differentiation pathways
Left: k-means clustering of differentially expressed genes during T cell differentiation. Normalized gene expression is shown. Center: ATAC-seq signals in plausible enhancers for each gene. Right: Enriched TF motifs in corresponding OCRs in each cluster.

Recent Major Publications

Bansal K, Yoshida H, Benoist C and Mathis D. The transcriptional regulator Aire binds to and activates super-enhancers. ***Nat Immunol*** 18, 263–73 (2017)

Moodley D, Yoshida H, Mostafavi S, Asinovski N, Ortiz-Lopez A, Symanowicz P, Telliez JB, Hegen M, Clark JD, Mathis D and Benoist C. Network pharmacology of JAK inhibitors. ***Proc Natl Acad Sci U S A*** 113, 9852–9857 (2016)

Mostafavi S, Yoshida H (Co-first), Moodley D, LeBoite H, Rothamel K, Raj T, Ye CJ, Chevrier N, Zhang S, Feng T, Lee M, Casanova JL, Clark JD, Hegen M, Telliez JB, Hacohen N, DeJager PL, Regev A, Mathis D. Benoist C, Immunological Genome Project Consortium. Parsing the Interferon transcriptional network and its disease associations. ***Cell*** 164, 564–578 (2016)

Invited Presentations

Yoshida H. "ATACseq, cool results, what next?" 2017 Workshop, Immunological Genome Project (Boston, USA) December, 2017

Yoshida H. "IFN response: analysis of transcriptional network by an unbiased approach" The 11th International Symposium of The Institute Network Frontiers in Biomedical Sciences (Tokushima, Japan) January, 2017

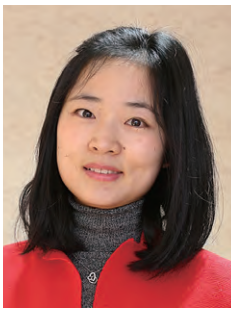
I have been engaging two projects employing transcriptomics, a powerful and effective tool to investigate biological phenomenon.

1) Identifying novel factors involved in thymic negative selection

While some factors including Aire and Fezf2 are known to induce tissue specific antigens (TSAs) in thymic epithelial cells (TECs) and are essential for negative selection, thousands of TSA genes are induced in a manner independent of these factors. By utilizing publicly available databases, I found RNA-binding proteins that lead to mRNA degradation are specifically down-regulated in TECs and can be involved in the regulation of TSA expression. We are assessing the possible functions of these candidates using cell lines and preparing mouse models to investigate their significance *in vivo*. As the concept of TSA regulation by RNA stability is novel, this project can greatly increase our understanding of immune tolerance.

2) Comprehensive analysis of the *cis*-regulatory elements in immunocytes

The establishment and maintenance the unique transcriptional identity of a differentiated cell is largely driven by the combined activity of transcription factors (TFs) and chromatin remodelers at promoters and/or distal enhancer elements. While the existence of enhancers whose activity is restricted to a given cell-type has been recognized in specific context, i.e. specific genes or specific cell populations, their broader integration in related immune cell-types and their cascades along their respective differentiation pathways were not clear. In collaboration with Immunological Genome Project, I have performed paired epigenomic mapping by ATAC-seq and gene expression measurements by RNA-seq to profile 90 immune cell populations and define a *cis*-regulatory atlas of the mouse immune system. This atlas is both comprehensive, likely defining the entirety of the *cis*-regulatory elements in immunocytes, and highly granular, due to scanning of closely related cell-types in differentiation cascades. We are preparing the manuscript for submission.



YCI Laboratory for Next-Generation Proteomics

Young Chief Investigator: **Yibo Wu**

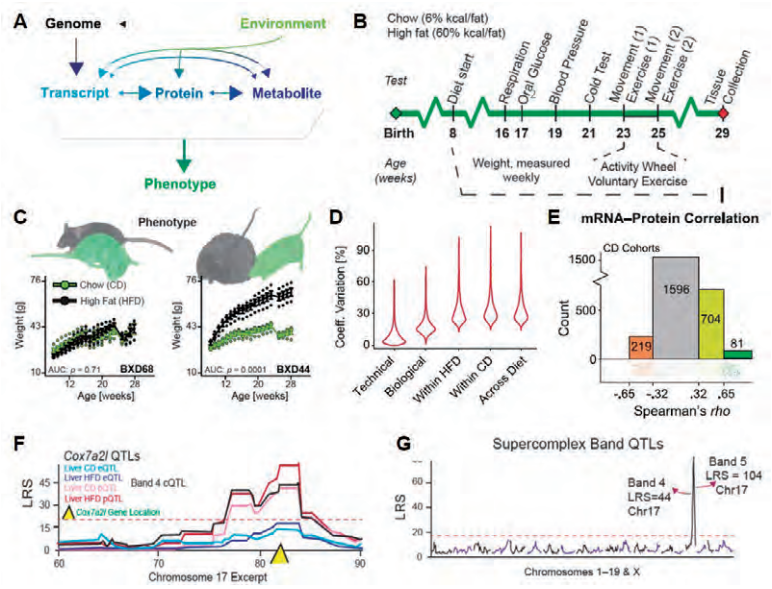


Figure: A multilayered omics study of liver mitochondrial activity
(A) General model of the multilayered omics approach. Arrows indicate causality between metabolic layers. (B) Phenotyping pipeline for all individuals. (C) Body weight in two BXD strains for both diets over the full phenotyping experiment. (D) Error in SWATH-MS measurements due to technical (median CV = 6.5%), biological (CV = 17.0%), across strain within diet (CV = 31.4% in CD, 29.6% in HFD) and across all measurements (CV = 30.8%). (E) Histogram of 2600 transcript-protein pair Spearman correlations in CD. (F) Diet-consistent cis-pQTLs were observed for COX7A2L. No significant cis-eQTLs were observed. (G) Super Complex (SC) bands 4 and 5 mapped significantly as cQTLs to a locus on chromosome 17. This region includes *Cox7a2l* and overlaps with its cis-pQTLs.

Recent Major Publications
Wu Y, Williams EG, Aebersold R. Application of SWATH Proteomics to Mouse Biology. ***Curr Protoc Mouse Biol*** 7, 130–143 (2017)

Williams EG, Wu Y, Jha P, Dubuis S, Blattmann P, Argmann CA, Houten SM, Amariuta T, Wolski W, Zamboni N, Aebersold R, Auwerx J. Systems proteomics of liver mitochondria function. ***Science*** 52, aad0189 (2016) (*Co-first author)

Invited Presentations
Wu Y. "Systems proteomics of liver mitochondrial activity" The 1st International Symposium for Trans-Omics (Tokyo, Japan) November, 2017

Recent improvements in mass spectrometry-based proteomics, including Selected Reaction Monitoring (SRM) and Sequential Window Acquisition of all Theoretical Mass Spectra (SWATH-MS), have been driving the capacity for defining relationships between genetics, molecular pathways and overall phenotypes (Wu and Williams, et al. Cell 2014, Williams and Wu, et al. Science 2016). SWATH-MS has enabled accurate quantification of thousands of proteins across a large number of cohorts (Wu and Williams, et al. Curr Protoc Mouse.Biol 2017).

Here, we have demonstrated the quantification capacity of SWATH-MS by examining mitochondrial function and liver metabolism through the genome, transcriptome, proteome and metabolome in 386 individuals of the BXD mouse genetic reference population. Phenotypic traits, including body weight, vary significantly among these mice due to genetic, environmental and/or gene-by-environment (GxE) factors. SWATH-MS has allowed quantification of 2622 unique proteins with excellent reproducibility. Among these 2622 proteins, we have quantified 2600 transcript-protein pairs and observed only a nominal correlation between mRNA and protein levels, indicating the necessity of proteomic measurement of metabolic pathways to identify unknown molecular mechanisms.

We have identified and validated several links between genetic variants toward transcripts, proteins, metabolites and phenotypes. Among these, sequence variants in *Cox7a2l* alter its protein levels, but not transcript levels. The differences in COX7A2L protein in turn lead to downstream differences in mitochondrial supercomplex formation. These findings indicate that data generated by next-generation proteomics and metabolomics have reached a scope to complement genomics, transcriptomics and phenomics for transomic analyses of complex traits. This integrated omics strategy has provided us a new tool that brings personalized medicine closer.

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 Laboratory provides a range of support for flow cytometry and cell sorting techniques that are essential for nearly all experiments in immunology and disease studies. The FACS Lab has upgraded all FACS Arias including an Aria Fusion for multi-color analyses. In addition to FACS machines, the lab upgraded CyTOF2, a mass-spectrometry-based cytometer that has the potential to analyze more than 40 markers simultaneously with metal-labeled antibodies.

In 2017, 1496 analytical and 3996 sorting experiments were performed in the lab. Two staff members offer various services for users of the FACS machines (cell analyzers and cell sorters): (1) Technical support and training: In 2017, the facility offered 8 technical courses (4 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 31 researchers took the courses in 2017. (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 2017, the lab provided 266 such services. Advanced 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 and the usage in the FACS Lab

Machine types	Machines	# of machines	# of users	# of training sessions
FACS cell analyzer	Calibur Canto II	4 2	58 1438	2 12
FACS cell sorter	Aria II Aria III Aria Fusion	3 2 1	1971 1985 40	17
Mass-cytometer	CyTOF2	1	18	2

Confocal Laboratory

The Confocal Laboratory provides equipment for cell and tissue imaging, and coordinates technical support. There are eight fluorescence microscopes available to researchers at IMS.

1. Inverted Leica SP5 system with visible lasers for single-photon excitation including a 405 violet laser.
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 SP8 system with two femtosecond Ti:Sa lasers for multiphoton 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.
4. Upright Leica SP5 system with two femtosecond Ti:Sa lasers for multiphoton excitation. This system utilizes resonant scanners that enable high-speed acquisition of large z-stacks for live tissue imaging.
5. Inverted Olympus FV1200 system with visible lasers for single-photon excitation.
6. Inverted Nikon N-SIM/N-STORM super-resolution microscope for dual color imaging.
7. GE Healthcare DeltaVision Elite system.
8. Keyence BZ-X700 all-in-one fluorescence microscope.

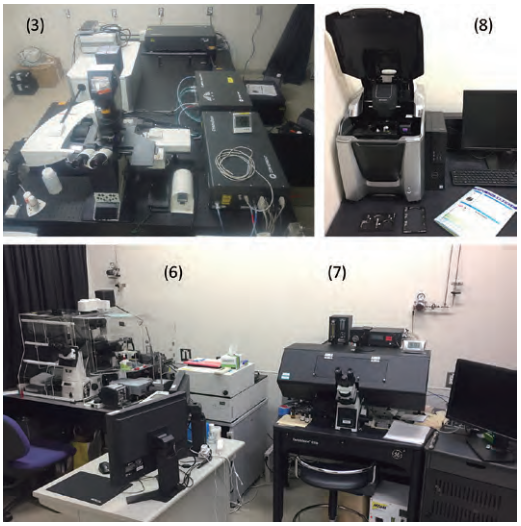


Photo: Leica SP8 multiphoton microscope (3), Nikon N-SIM/N-STORM super-resolution microscope (6), GE Healthcare DeltaVision Elite system (7), and Keyence BZ-X700 microscope (8).

Genomics Laboratory

We are a technical support service lab that provides genome- and proteome-wide analysis for research groups in 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 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 2017

Next-generation DNA sequencing	**# of samples**	**# of teams**
RNA-sequencing	1,756	24
Chip-sequencing	432	5
Others (Exome etc)	49	2
Proteomics	**# of samples**	**# of teams**
Mass Spectrometry Analysis	1	1
Multiplex suspension array	1,219	8
Sanger DNA sequencing	**# of samples**	**# of teams**
36cm capillary	6,856	13
50cm capillary	3,336	15
cDNA clone delivery	**# of samples**	**# of teams**
	43	5
Primer/labeled probe delivery	**# of samples**	**# of teams**
	36	2

Animal Facility

We continue to maintain over 50,000 mice in the SPF area, and 1,500 mice in an isolated area. The SPF area also contains 550 germ-free or gnotobiotic mice 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, and the latter is for "humanized mice". We introduce mouse lines into the SPF area via a combination of *in vitro* fertilization (IVF) and embryo transfer methods, and have also generated cryostocks of genetic resources (frozen embryos and sperm) for 782 lines. We also maintain relatively large colonies of several commonly used strains such as Rag1 KO and Cre deleters, and provide them to users on demand. We have also provided technical assistance to generate knockout and transgenic mice (80 lines). In addition, we made KO and KI mice (73 lines) using the CRISPR/Cas system and have created 17 lines of germ-free mice. We have provided space for new experiments, e.g., behavioral testing for germ-free mice, in the animal facility.

We generated mice to improve the efficacy of transplantation of human hematopoietic stem cells into NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm}/SzJ (NSG) mice by better "humanizing" 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 knock-in mice with confirmed expression of human genes on a C57BL/6 background and have begun backcrossing these mice onto the NSG background using the speed-congenic method.

Photo: Behavioral testing equipment for germ-free mice
Vinyl Isolator in a soundproof room in the SPF area

RIKEN International Program Associate (IPA)

IMS accepted three 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 2017 were
Krutula Nair (Graduate School of Frontier Biosciences, Osaka University) from India studied in the Laboratory for Transcriptional Regulation.
Su Yean Ong (University of Science, Malaysia) in the Laboratory for Integrated Bioinformatics
Yan Yan Hor (University of Science, Malaysia) in the Laboratory for Intestinal Ecosystem.

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 2017, two young researchers studied at IMS as RIKEN FPRs.

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, 26 JRA students studied in IMS.

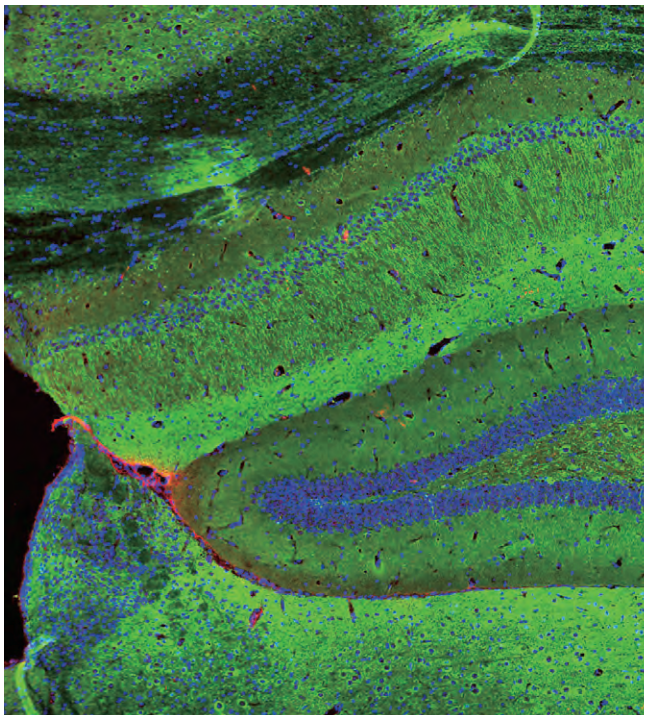
Junichiro Takano (Laboratory for Developmental Genetics)
Yoshihiro Ito (Laboratory for Skin Homeostasis)
Eiichiro Watanabe (Laboratory for Gut Homeostasis)
Satoko Yokoyama (Laboratory for Intestinal Ecosystem)
Yuki Furuichi (Laboratory for Skin Homeostasis)
Tadashi Takeuchi (Laboratory for Intestinal Ecosystem)
Rintaro Ono (Laboratory for Human Disease Models)
Yurina Miyajima (Laboratory for Innate Immune Systems)
Takato Kobayashi (Laboratory for Innate Immune Systems)
Takaaki Kawaguchi (Laboratory for Gut Homeostasis)
Keiko Usui (Laboratory for Skin Homeostasis)
Natsuko Otaki (Laboratory for Innate Immune Systems)
Mamoru Ogawa (Laboratory for Metabolomics)
Hiroki Sugishita (Laboratory for Developmental Genetics)
Hiroe Tetsu (Laboratory for Innate Immune Systems)
Manabu Nagayama (Laboratory for Gut Homeostasis)
Daisuke Hisamatsu (Laboratory for Developmental Genetics)
Ari Morimoto (Laboratory for Skin Homeostasis)
Tomoko Yoshihama (Laboratory for Pharmacogenomics)
Yuki Ariyasu (Laboratory for Metabolomics)
Shohei Egami (Laboratory for Skin Homeostasis)
Shintaro Ono (Laboratory for Integrative Genomics)
Ryota Sato (Laboratory for Lymphocyte Differentiation)
Kyosuke Shishikura (Laboratory for Metabolomics)
Iori Motoo (Laboratory for Gut Homeostasis)
Tsuyoshi Yamane (Laboratory for Metabolomics)

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, seven postdocs conducted their research at IMS through the SPDR program.

Yosuke Isobe (Laboratory for Metabolomics)
Yasutaka Motomura (Laboratory for Innate Immune Systems)
Eiji Miyauchi (Laboratory for Intestinal Ecosystem)
Alexis Vogelzang (Laboratory for Mucosal Immunity)
Keiichiro Shiraga (Laboratory for Skin Homeostasis)
Xiaoxi Liu (Laboratory for Genotyping Development)



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 develop therapeutics. On a collaborative basis with individual RCAI-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 established bioluminescent human iPS-Vα24$^+$iNKT cells for *in vivo* live-cell imaging. We were able to introduce GFPLuc into the human AAVS1 (adeno-associated virus integration site 1) locus in NKT-iPSC using CRISPR/Cas9 and then differentiate the cells into iPS-Vα24$^+$iNKT cells. These iPS-Vα24$^+$iNKT cells showed GFP expression and luciferase activity *in vitro*. Furthermore, the iPS-Vα24$^+$iNKT cells could be monitored by luciferase activity for at least 19 days after inoculation into immunodeficient mice.

The facility has also managed an IMS Cell Manufacturing Unit (CMU) to produce iPS-Vα24$^+$iNKT cells under GMP (Good Manufacturing Practice)/GCTP (Good Gene, Cellular, and Tissue-based Products Manufacturing Practice) guidelines and has started preclinical studies on the safety of these iPS-Vα24$^+$iNKT cells. The facility has also started PMDA (Pharmaceuticals and Medical Devices Agency) consultation for eventual clinical trials of iPS-Vα24$^+$iNKT cell mediated-tumor immunotherapy.

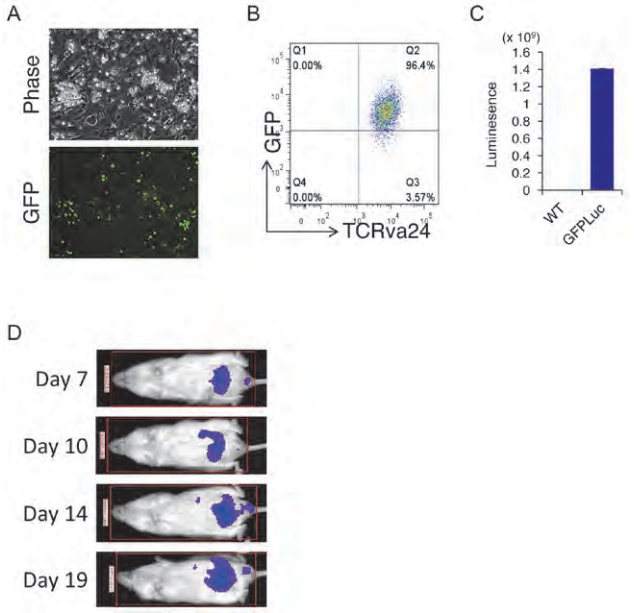


Figure: Live-cell imaging of iPS-Vα24$^+$iNKT cells *in vitro* and *in vivo*.
(A) Representative phase contrast and fluorescence microscope images of human iPS-Vα24$^+$iNKT cells containing introduced GFPLuc. (B) A representative flow cytometry plot of GFPLuc-expressing human iPS-Vα24$^+$iNKT cells. (C) Luciferase activity of GFPLuc-expressing human iPS-Vα24$^+$iNKT cells (GFPLuc). Wild type (WT) human iPS-Vα24$^+$iNKT cells were used as a control. (D) GFPLuc iPS-Vα24$^+$iNKT cells were intraperitoneal injected into human cytokine knock-in NSG mice (kindly provided by the animal facility) and then monitored at the indicated time points for bioluminescence using the IVIS imaging system.

Medical Sciences Innovation Hub Program (MIH)

Ptersonalized medicine is a new paradigm that represents a shift from a statistical abstraction of the patients toward the view that each patient is unique. This is a new scientific challenge as well as a new social challenge. Although linear causations and correlations have been used in the explanation of biological phenomena, biological systems form complex network whose collective behavior cannot be reduced to simple correlations. In addition, explanations usually eliminate information on differences between each individual patient. To overcome this problem, we are developing a new biomedical science based on pure description of diseases by using multiomics data. To describe personal differences, it is necessary to consider the life course trajectory. We have applied a Markov chain model, which is a well-known tool to model temporal properties of many phenomena, to describe life-course changes in individual conditions. The data are being gathered from patients with immune disorders, cancer and developmental disorders. Human studies are then reversed translated in animal studies. We are collaborating with IMS in these studies.

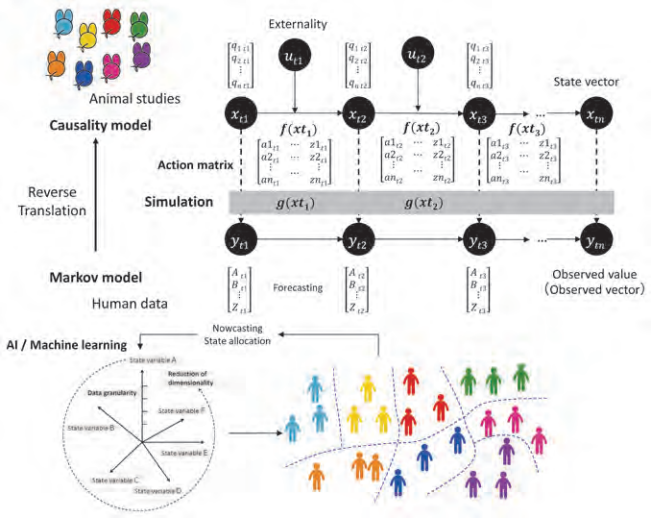


Figure: Description of life course trajectory by Markov chain and reverse translation
The state allocation is done by the reduction of dimensionality and data granularity using machine learning and energy land scale analysis The relation between the present and future state is described by Markov constraints. The causality model is developed by animal studies. Knowledge obtained from human data is applied in developing the animal models.

Integrated omics approach to elucidate the impact of the gut microbiome on the pathogenesis of type 2 diabetes

Recent findings in gut microbiome studies indicate that the loss of microbial diversity, a condition termed dysbiosis, is not the consequence but rather the cause of various diseases including type 2 diabetes (T2D). As an IMS Center project, we are applying a comprehensive integrated omics approach to elucidate the impact of the gut microbiome on the pathogenesis of T2D. This is a collaborative effort with Professors Takashi Kadowaki and Tsutomu Yamazaki from the University of Tokyo Hospital. From RIKEN IMS, the Laboratories for Metabolic Homeostasis, Intestinal Ecosystem, Microbiome Sciences, Metabolomics, Integrative Genomics, and Integrated Bioinformatics are taking the lead on this project. This year, we have started a collaboration with the National Institute of Health and Nutrition to collect data on the nutritional intake and activity of the many participants in this study. Fecal metagenomic, metatranscriptomic and metabolomic data, as well as plasma and urine metabolomic data are 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 and HbA1c ≧ 6.0%). In addition, exomes and SNPs of T2D susceptibility genes are being analyzed. The goal of the project is to identify T2D risk factors, such as certain bacteria and/or their metabolites, by analyzing the metadata from the comprehensive multiple omics analyses, combined with clinical and genetic datasets. We have already finished the recruitment of one hundred volunteers for each group and data acquisition is underway.

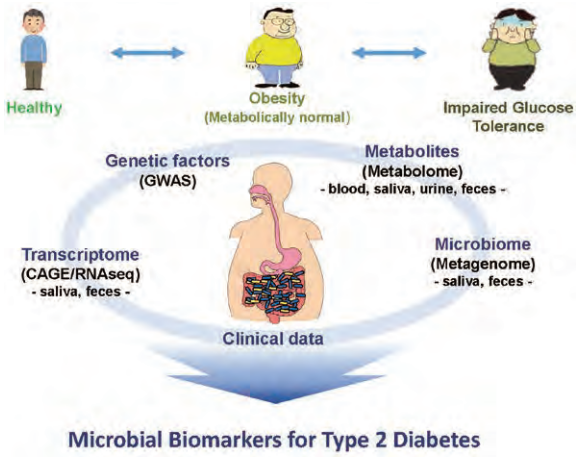


Figure: Analytical scheme to identify microbial biomarkers for type 2 diabetes

Metadata sets shown in the figure are collected from the volunteers (three groups: healthy, obese without metabolic abnormality, and those with impaired glucose tolerance; 100 each) and comprehensively analyzed to identify differential microbial and/or microbial metabolic factors among the groups, which should be candidate biomarkers for the pathogenesis of type 2 diabetes.

NKT cell projects

NKT cells have the capacity to enhance immune responses. The medical innovation groups in IMS have launched projects aimed at application of NKT cell-mediated therapy to cancer as translational research. Here we introduce four NKT cell-related projects aimed at cancer treatment.

In the first project, we have been collaborating with 15 National Hospital Organization (NHO) hospitals on clinical therapeutic studies using the NKT glycolipid, α-GalCer pulsed autologous DCs (DC/Gal) in a randomized phase IIa trial in early stage lung cancer. At present, we have been performing immunological analyses on 53 DC/Gal-treated and control cancer patients. As a second project, IMS was selected to be part of the research center network for realization of regenerative medicine. So far, we have been performing a preclinical study of human iPS-NKT cells for clinical application. Third, as a new type of cancer vaccine, we established artificial adjuvant vector cells (aAVC). In this fiscal year, we launched an investigator-initiated clinical trial of aAVC-WT1 for relapsed or refractory acute myeloid leukemia patients by collaborating with The University of Tokyo, The Institute of Medical Science. This is the First in Man trial. Fourth, we developed several new NKT cell ligand candidates and have been testing their efficacy in preclinical studies for next generation NKT cell ligand cancer immunotherapy. Three of these projects (iPS-NKT therapy, and aAVC therapy and new NKT ligand therapy) have been supported by the Japan Agency for Medical Research and Development (AMED) and are also supported by the RIKEN Drug Discovery and Medical Technology Platforms (DMP).

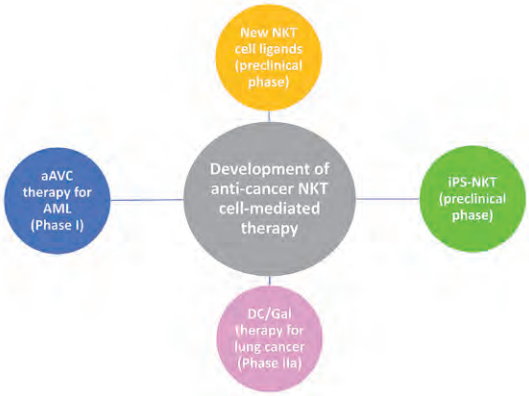


Figure: NKT cell-mediated anti-cancer projects in IMS as translational research

We have four NKT cell-mediated anti-cancer projects underway. Three are cancer therapy translational research projects and the fourth is the analysis of the patients in the Phase II clinical study. All have progressed in this fiscal year.

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. 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.

To achieve effective progress in this area, DMP established nine Drug Discovery Basic Units, in which the types of studies being performed are organized according to the expertise of each PI. IMS contributes to this effort in several ways, including by setting up a facility for the development of antibody drugs, the Drug Discovery Antibody Platform Unit. In addition, IMS now has eight collaborative programs with DMP: Artificial adjuvant vector cells (Shin-ichiro Fujii), Cancer therapy with iPS-derived NKT cells (Haruhiko Koseki), Cancer therapy with NKT cells (Masaru Taniguchi), Drugs for allergic diseases (Yasushi Ishii), Leukemia treatment mAb targeting leukemic stem cells (Fumihiko Ishikawa), mAb therapy for lymphomas (Yasushi Ishii), neutralizing mAb for HBV infection (Daiki Miki) and therapeutic mAb for IBD (Takashi Saito). The preclinical study of the Artificial adjuvant vector cell project for cancer therapy has been completed and, therefore, Fujii et al. are preparing for an investigator initiated-clinical trial.

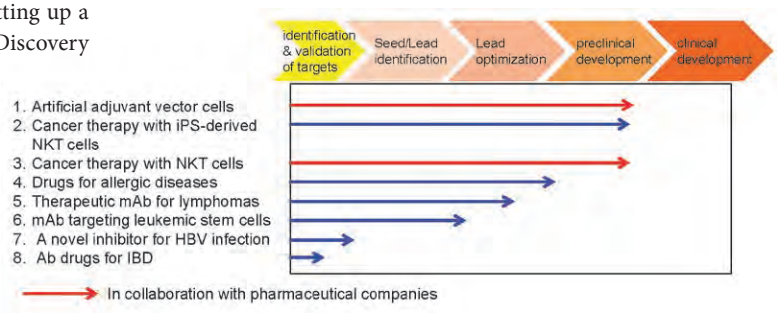


Figure: Collaboration between IMS and DMP for the development of innovative new pharmaceuticals and medical technologies

PGRN-RIKEN IMS Project

The US NIH Pharmacogenomics Research Network (PGRN) is a consortium of research groups funded as individual cooperative agreements with the NIH. PGRN investigators are top researchers from US academic institutions and conduct pharmacogenomics (PGx) studies to identify genes associated with drug responses. We run the PGRN-RIKEN IMS Project under a PGRN-Hub, a resource established to enhance scientific exchange between the PGRN and the scientific community at large, for identification of genetic factors associated with drug efficacy and risk of severe adverse drug reactions.

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 US. RIKEN IMS focuses on high-throughput genome-wide SNP scans and targeted sequencing of selected genes or regions using next generation sequencing (NGS) and also provides technological and methodological expertise to identify genomic biomarkers. Together, the PGRN-RIKEN IMS Project capitalizes on these strengths to advance discoveries in PGx research. To date, we have initiated 48 collaborative projects and have 60 publications through the collaboration, which will lead to development of better and safer medications and realize the dream of global precision medicine. This year, we are going to expand the collaborative activity in the global PGx network involving US, Europe and Japan for implementation of PGx in clinical practice.

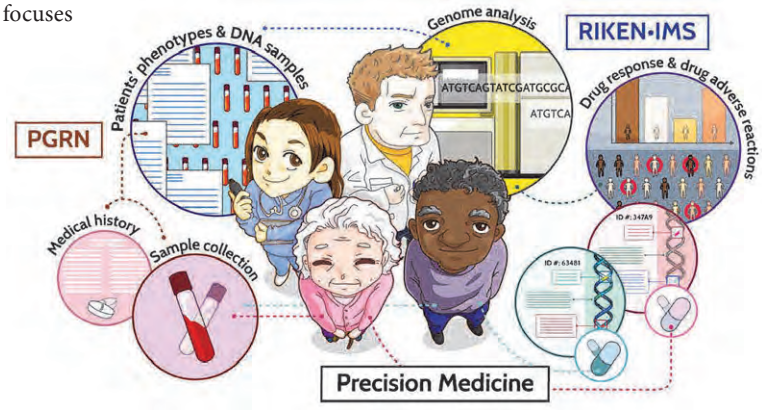


Figure: The Pharmacogenomics Research Network (PGRN)-RIKEN IMS strategic alliance
Please visit http://www.pgrn.org/pgrn-riken.html

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 Asian populations, and several genomic biomarkers 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 prior to the administration of this drug for Han Chinese and other Asian populations with a high prevalence of HLA-B*15:02, due to the risk of SJS-TEN associated with this allele. To tackle this problem regionally, in 2012 we established the South East Asian Pharmacogenomics Research Network (SEAPharm) together with five other Asian countries (Korea, Indonesia, Malaysia, Taiwan, and Thailand). Membership has been steadily increasing, with Singapore joining in 2014, and Vietnam in 2016. This year, SEAPharm has three newcomers, Nepal, Laos and the Philippines, on the team.

The aim of the collaboration is to identify genomic biomarkers associated with ADRs, such as skin rash induced by anti-epileptics and antibiotics, and hepatic injury induced by anti-tuberculosis agents. In addition, we have started a new project involving next generation sequencing of genomic DNA from 1,000 people from 10 countries to clarify the genetic diversity of drug-metabolizing enzymes and drug transporters in Southeast Asian populations. The discoveries from our collaborative efforts will lead to the establishment of "stratified medicine" based on pharmacogenomic-guided drug therapies.

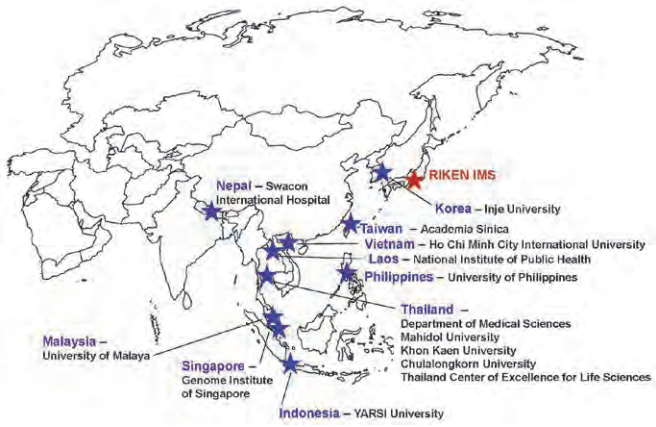


Figure: Members of the South East Asian Pharmacogenomics Research Network (SEAPharm)
Please visit
http://www.pharmagtc.org/seapharm/index.php/seapharm/about-seapharm

International Cancer Genome Consortium (ICGC) and PCAWG

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

The primary goals of the ICGC is to generate comprehensive catalogues of genomic abnormalities in ~25,000 cases of different cancer types and to make the data available to the entire research community with minimal restrictions. At the end of 2017, 78 cancer genome projects across 16 countries and the EU were ongoing, and the ICGC released genomic data from more than 17,000 donors as Release 26 (November, 2017). For this release, the RIKEN group performed whole genome sequencing (WGS) and analysis on 300 liver cancer samples. ICGC launched a "pan-cancer" whole genome project (PCAWG) in 2014, in which WGS data together with RNA-Seq of 2834 donors were analyzed in uniform pipelines within the same computational environment. RIKEN and IMUT are contributing to this project as a member of a technical working group arranging ten cloud data centers and PI/researchers in working groups for driver gene, mutational signature, germline, immuno-genomics, and mitochondrial genomics. We also provided sample data from 270 liver cancers to the PCAWG (10% of the total), making us the most productive group within the ICGC. In 2017, as a PCAWG-15 working group, we analyzed the immuno-genomic landscape from PCAWG data, including mutations in the HLA/antigen presentation complex and immune suppressor genes, neo-antigen profiles from somatic SNVs and indels, GSEA (gene-set enrichment analysis), and immune micro-environmental signatures from RNA-seq data. We observed that tumors acquired many types of immune escape mechanisms through genomic alterations of selective copy number gain of immune genes and failure of the antigen presentation system and immune checkpoint molecules in a tumor-specific manner.

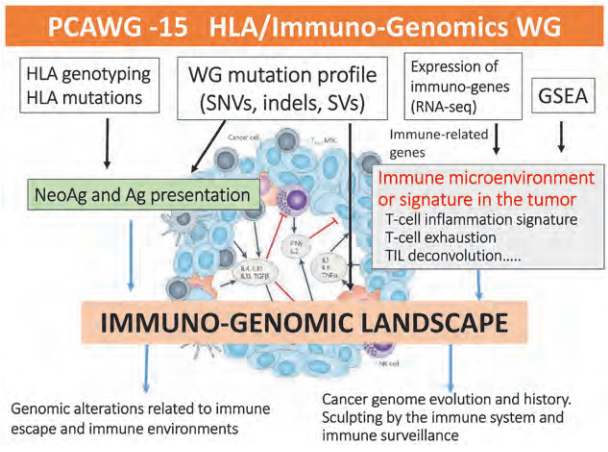


Figure: Immuno-genomic landscape of pan-cancer in PCAWG-15 working group
PCAWG-15 and RIKEN analyzed the immuno-genomic landscape of 2800 WGS pan-cancer data. Neoantigens and neoantigen presentation mechanisms are examined by using information on HLA genotype and somatic mutations (SNVs, indels, and SVs) from the WGS. Immune microenvironment or signatures are analyzed by combined RNA expression profiles of immuno-genes and GSEA. We are exploring immune escape mechanisms and cancer genome evolution and history by analysis of these Immuno-genomic landscapes.

Humanized mouse

One of the obstacles to treating malignant diseases is their biological heterogeneity and genetic complexity. Recent reports have identified pre-malignant stem cells that may foster emergence of malignant stem cells, which can progress to overt disease. To understand the pathophysiology of pre-malignant and malignant cells in human hematopoiesis, we took an approach to link *in vivo* disease biology with genomic profiling by combining a humanized mouse model with single-cell sequencing using human acute myeloid leukemia (AML) samples This integrative approach enabled demarcation of pre-malignant versus malignant cells and the identification of permissive versus disease-initiating mutations among multiple mutations within patient specimens. Inhibition of pathways activated by disease-initiating mutations resulted in efficient eradication of human leukemia cells in AML-engrafted humanized mice. This integrative approach using humanized mice may help our understanding of malignant hematopoiesis in humans and development of new therapeutic strategies for human leukemia.

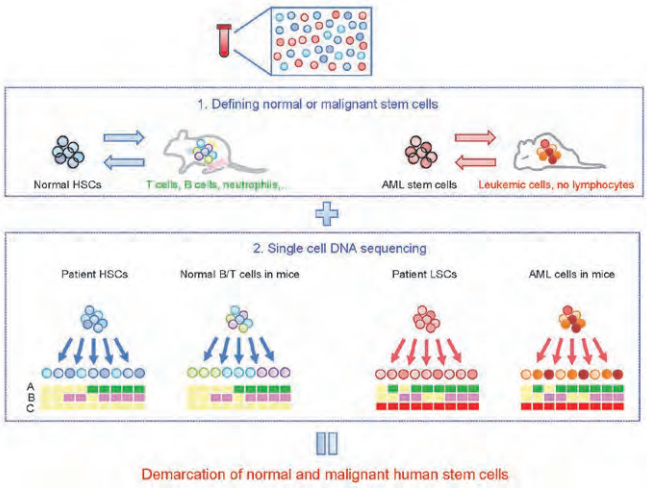
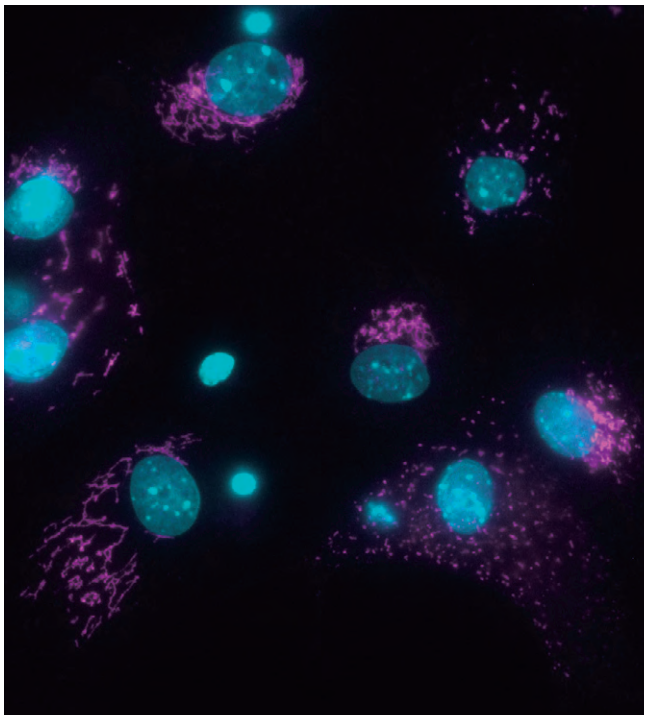


Figure: Heterogenous hematopoietic cells are present in blood or bone marrow of AML patients.
By injecting multiple blood/BM subsets into immune-deficient NOD/SCID/Il2rgKO mice, we identified hematopoietic stem cells and leukemia-initiating stem cells in each patient. With single cell sequencing, we found somatic mutations in functionally-defined normal and leukemic stem cells. The genomic profiling of single human stem cells enabled us to demarcate leukemia-initiating and permissive mutations.

Award winners 2017

Name of the awardee	Name of the award	Date of the announcement
Kazuhiko Yamamoto, Team Leader, Laboratory for Autoimmune Diseases	Medal with Purple Ribbon	Apr, 2017
Fumihiko Ishikawa, Group Director, Laboratory for Human Disease Models	German Innovation Award "Gottfried Wagener Prize 2017"	Jun, 2017
Kazuyo Moro, Team Leader, Laboratory for Innate immune systems	The 13th JSPS PRIZE	Jan, 2017
Kazuyo Moro, Team Leader, Laboratory for Innate immune systems	The13th Japan Academy Medal	Jan, 2017
Yoichiro Kamatani, Team Leader, Laboratory for Statistical Analysis	The Young Scientists' Prize (The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology)	May, 2017
Mariko Okada, Team Leader, Laboratory for Integrated Cellular Systems	Nagase Foundation Award	Apr, 2017
Momoko Horikoshi, Team Leader, Laboratory for Endocrinology, Metabolism and Renal diseases	The 4th Yamato Science Award	Mar, 2017
Tetsuya Kubota, Senior Researcher, Laboratory for Metabolic Homeostasis	The 38th Japan Society for the Study of Obesity (JASSO) Academic Award	Oct, 2017
Yasutaka Motomura, Special Postdoctoral Researcher, Laboratory for Innate immune systems	SMI/MI Journal Poster Award	Jul, 2017
Naoko Satoh, Research Scientist, Laboratory for Intestinal Ecosystem	The 12th JSI Young Investigator Award (The Japanese Society for Immunology)	Nov, 2017
Chikashi Terao, Senior Scientist, Laboratory for Statistical Analysis	Incentive Award (The 62nd Annual Meeting of the Japan Society of Human Genetics)	Nov, 2017
Nyambayar Dashtsoodol, Research Scientist, Laboratory for Immune Regulation	Best Paper Award (Mongolian National University of Medical Sciences)	Feb, 2017
Nyambayar Dashtsoodol, Research Scientist, Laboratory for Immune Regulation	Best Presentation Award (The 45th Annual Meeting of the Japanese Society for Immunology)	Feb, 2017
Hiroe Tetsu, Junior Research Associate, Laboratory for Innate immune systems	Ursula and Fritz Melchers Travel Award (The Japanese Society for Immunology)	Dec, 2017
Takaharu Sasaki, Postdoctoral Researcher, Laboratory for Intestinal Ecosystem	Young Investigator Travel Award (The 18th International Congress of Mucosal Immunology)	Apr, 2017
Takaharu Sasaki, Postdoctoral Researcher, Laboratory for Intestinal Ecosystem	Tadamitsu Kishimoto International Travel Award (The Japanese Society for Immunology)	Apr, 2017
Hirokuni Miyamoto, Senior Visiting Scientist, Laboratory for Intestinal Ecosystem	Technical Award of the Society for Biotechnology, Japan	Sep, 2017



Part 4

Events

RIKEN IMS Summer Program (RISP) 2017

IMS was delighted to once again successfully organize the 11th RISP (RIKEN IMS Summer Program). RISP began as the RCAI International Summer Program (RISP) in 2006 and has been continued by IMS, beginning 4 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 2017 program included topics in genomic studies to understand human health and 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 2017 was co-organized by the Chiba University Leading Graduate School Program.

We were pleased to welcome 42 graduate students and postdoctoral fellows from 11 countries, including 14 participants from Japan, who gathered at Yokohama from June 16 to 23. The scientific sessions consisted of 15 lectures presented by IMS PIs and other invited senior scientists from Japan and abroad. 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.

RISP2017 was again a success; we received excellent feedback comments in the evaluation survey, and many 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. In order to make this successful program even more recognized internationally, IMS is considering a renewal of the RISP and is planning to relaunch the program in a new format in 2019.

The IMS-JSI International Symposium on Immunology 2017

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 June 22–23 at the International Conference Hall, Plaza Heisei, Tokyo International Exchange Center. The symposium, entitled "Decoding Immune Complexity from Cell to System", included 19 outstanding speakers presenting their cutting-edge research and attracted close to 400 participants. There were four sessions: (1) Functional genomics of lymphocytes, (2) Animal model and immunotherapy, (3) Interface between the immune system and environment, and (4) Functional aspects of immunology. In the "Functional genomics of lymphocytes" session, several state-of-the-art research tools and statistical genetics recruiting diverse biological information resources were introduced. The "Animal model and immunotherapy" session expanded our knowledge on how we could apply basic immunology to translational medicine. Control of Treg development by manipulating super-enhancers, epigenetic and transcriptional regulation might open new avenues to prevent autoimmune diseases. Combining conventional electron-microscopic and new two-photon imaging technologies helps to advance our understanding of the pathogenesis of viral infections. The "Interface between the immune system and environment" session updated our view of host-microbe interactions by revealing the importance of innate lymphoid cells, neuro-immune regulation and the adaptive immune system for gut and body homeostasis. In the "Functional aspects of immunology" session, live-imaging technologies revealed new aspects of the dynamics of cell-cell interactions with functional implications for the immune responses. The possibility that a "neo-self" antigen derived from misfolded proteins and its occupation of MHC II might be linked to autoimmune diseases was also discussed. How Aire governs the thymic microenvironment through a unique tissue structure, Hassall's corpuscles, was revealed by elegant studies combining histological studies, molecular biology and immunological approaches. This year we hosted several young investigators to present their work in newly established short talk sessions.

14th/15th PGRN-RIKEN Strategic Alliance Meetings

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 formed 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 the United States, allow for face-to-face discussions about the progress of ongoing projects and future directions for the PGRN-RIKEN collaboration.

In 2017, the 14th and 15th PGRN-RIKEN Strategic Alliance Meetings were held in Yokohama on January 18–19 and in San Francisco on September 8-9, respectively.

The meetings provided a valuable forum for exchanging information on ongoing collaborative activities as well as for presenting interesting topics from both parties.

In addition to these presentations, some 40 participants also explored new research proposals from PGRN members, ultimately deciding to adopt the following themes as additional collaboration projects, and then the meetings concluded successfully.

Projects accepted at the 14th meeting:

1) Genetic biomarkers of thrombotic risk in African American cancer patients (PGRN PI: Minoli Perera, Northwestern University).
2) The relationship of the pharmacogenetics of enzalutamide to its pharmacokinetic disposition/metabolism and clinical pharmacodynamics in advanced prostate cancer patients enrolled in the Alliance A031201 study (PGRN PI: Lionel Lewis, Geisel School of Medicine and The Norris Cotton Cancer Center at Dartmouth).

Projects accepted at the 15th meeting:

1) Deep Sequencing to Identify Genetic Determinants of Heparin-Induced Thrombocytopenia (PGRN PI: Dan Roden, Vanderbilt University School of Medicine).
2) The Genetic Determinates of Metformin Pharmacokinetics (PGRN PI: Kathy M. Giacomini, University of California San Francisco).

RIKEN IMS-Luxembourg FNR Joint Symposium

On October 4, 2017, the Luxembourg Institute of Health (LIH), the Luxembourg Center for Systems Biomedicine (LCSB) in University of Luxembourg, and RIKEN IMS held a joint symposium at IMS in Tsurumi, Yokohama. The symposium began with a special greeting from H. E. Ms. Lydia Mutsch, Luxembourg's Minister of Health, and opening remarks by Professor Marc Schiltz of the National Research Fund, Luxembourg (FNR) and Dr. Shigeo Koyasu, the Executive Director of RIKEN. In her message, the minister expressed her expectations for the further development of research collaborations with RIKEN and research institutions in Luxembourg.

At the Symposium, eight research scientists from LIH and LCSB, and nine Japanese researchers from three RIKEN institutions [RIKEN IMS, RIKEN Center for Lifescience Technologies (CLST), RIKEN Medical Innovation Hub Program (MIH) and Juntendo University] gave presentations and discussed the latest research trends in the fields of immunology and systems biomedicine.

Professor Markus Ollert (LCSB) introduced the financial support for the collaboration by FNR and, in a keynote lecture, Dr. Kenya Honda (IMS) introduced an on-going collaboration between RIKEN and LCSB. The two organizers, Drs. Haruhiko Koseki (IMS) and Markus Ollert (FNR), discussed the expansion of the collaboration and the next joint symposium to be held in Luxembourg in 2019.

Photo: Front row, from left to right: Mr. Jean-Claude Schmit (Chief Medical Officer, Ministry of Health), Ms. Beatrice Kirsch (Ambassador of Luxembourg in Japan), Ms. Mutsch, Dr. Koyasu, Dr. Tadashi Yamamoto (Director, IMS), Mr. Takashi Suzuki (Director, Yokohama Branch)

Tsinghua-RIKEN Joint Symposium on Immunology and Immunotherapy

The third joint workshop between RIKEN IMS and Tsinghua University Institute of Immunology (IITU) was held on September 22nd and 23rd, 2017, at Tsinghua University in Beijing. The first day was a symposium with 14 speakers, six from IMS, four from IITU, and four guest speakers from Harvard Medical School and Amgen Inc.

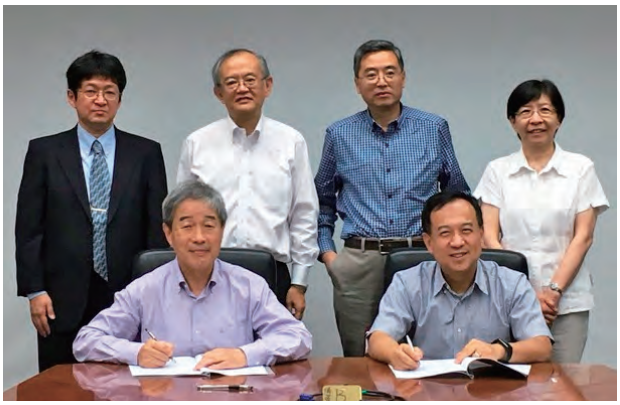
At the opening remarks, Dr. Chen Dong, Director of IITU and Dr. Tadashi Yamamoto, Director of IMS, described a new tie between the two institutions. The research presentations widely covered topics in T cell immunology, immunoregulatory cytokines, antitumor immunity, B cell development, innate lymphoid cells, the neural immune system, and genomics. There were active questions from the audience, especially from the IITU students. In addition to the presentations, an IITU-RIKEN IMS collaboration agreement was signed by the two Directors on the first day.

The second day was reserved for individual discussions among the researchers.

In the morning of the second day, Dr. Yamamoto and the organizers of the symposium, Drs. Tomohiro Kurosaki and Yun-cai Liu, visited Professor Qi-kun Xue, the Deputy President of Tsinghua University, to discuss strengthening the ties between Tsinghua University and RIKEN.

Based on the great success of this third joint workshop, both institutions agreed to cooperate with further collaborations.

Photo: From left: Drs. Tadashi Yamamoto and Chen Dong in the front row and Takashi Tanaka, Tomohiro Kurosaki, Yun-cai Liu and Yan Shi in the back row.



RIKEN IMS-McGill Symposium

RIKEN and McGill made comprehensive cooperation agreements/MOUs beginning in July 2010. In order to strengthen the relationship between RIKEN and McGill University, we organized the first RIKEN IMS - McGill Symposium, entitled "Excellence in Immunology & Genetics", which was held on 8th-9th May, 2017, at McGill University, Montreal, Canada. The goal of the symposium was not only to exchange information about research activity at each organization, but also to begin to establish international collaborative projects between the two organizations. There were eight sessions that covered a broad range of biological research areas including Genetics, Immunology, Inflammation, Tissue Dynamics, Cancer and Technology Development. In the two-day symposium, a total of 30 talks, fifteen from each side, were presented to about 200 participants, including post-docs and students at McGill University. At the close of the meeting, we discussed how we can proceed to set up collaborative projects. Both sides agreed on the importance of having an exchange of young researchers between the participating laboratories, as well as continuing the joint symposium within a short interval. Upon these agreements, the second RIKEN IMS - McGill Symposium will be held on 19th–20th February, 2018 in Yokohama, Japan.

Harvard Summer School 2017

IMS offers a summer internship program for undergraduate students from Harvard University. In this program students do a research internship in IMS laboratories, have basic biomedical sciences lectures given by PIs from IMS and other centers 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 2017, we accepted three students from Harvard University, Gui Zhen Chen, Krystal Katherine Phu, and Lily Xu into the summer program, which was held from June 5 to August 14.

Mr. Chen conducted his research on the theme of "Memory and GC B cell selections" in the Drug Discovery Antibody Platform Unit (Dr. Takemori). He found that selection of high-affinity memory and GC B cells is differentially regulated in the GC reaction. Ms. Phu studied "Analysis of cell and nuclear polarities in epidermis" in the Laboratory for Skin Homeostasis (Dr. Amagai). She found that in differentiated keratinocytes, several polycomb markers were highly localized in pericentric heterochromatin. Ms. Xu worked on "Evaluation of the cytokine response and antitumor effect between NKT cells and iPS-NKT cells" in the Laboratory for Immunotherapy (Dr. Fujii). She studied a synergistic antitumor effect of IL-18 and IL-2 in not only human NKT cells, but also iPS-NKT cells. 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.

Photo: From left: Mr. Chen, Ms. Xu, Ms. Phu and Dr. Tadashi Yamamoto (Dicrector, IMS)

Adjunct Professorship Programs

IMS collaborates with and accepts graduate students from 8 domestic university graduate schools. There are now a total of 28 adjunct professors/associate professors in IMS (Table), and 55 students studied at IMS in 2017. On September 23rd, IMS held a briefing session on adjunct graduate school programs to provide an opportunity for students to visit and talk directly with lab leaders and to consider their future directions.

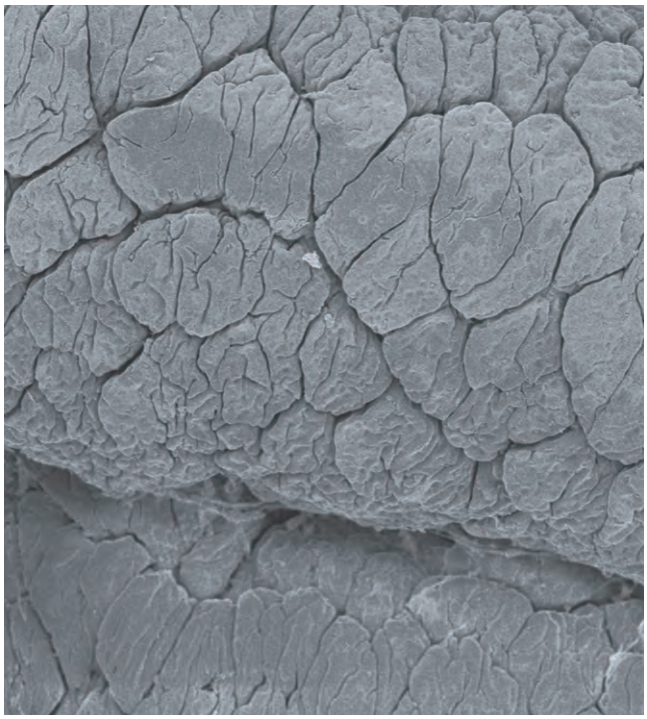
Table: Joint graduate school programs

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 Professor), Fumihiko Ishikawa (Visiting Professor)
Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University	Ichiro Taniuchi (Visiting Professor)
Graduate School of Medicine, Yokohama City University	Michiaki Kubo (Visiting Professor), Shiro Ikegawa (Visiting Professor) Hidewaki Nakagawa (Visiting Professor), Taisei Mushiroda (Visiting Professor), Yukihide Momozawa (Visiting Associate Professor), Kaoru Ito (Visiting Associate Professor), Momoko Horikoshi (Visiting Associate Professor)
Graduate School of Medical Life Science, Yokohama City University	Hiroshi Ohno (Visiting Professor), Makoto Arita (Visiting Professor), Takaharu Okada (Visiting Professor), Kazuyo Moro (Visiting Professor), Hidehiro Fukuyama (Visiting Associate Professor)
Research Institute of Biological Sciences, Tokyo University of Science	Masato Kubo (Professor), Takashi Saito (Visiting 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)

Guest lectures 2017

Table: Guest Lectures Jan–Dec, 2017

Date	Speaker	Affiliation	Country	Title
16–Jan–17	Dr. Masakatsu Yamashita	Ehime University Graduate School of Medicine	Japan	Metabolic and epigenetic regulation of T-cell senescence
25–Jan–17	Dr. Keisuke Chris Nagao	National Cancer Institute, National Institutes of Health (NIH)	USA	Regulation of skin immunity during homeostasis and inflammation
8–Feb–17	Dr. Nisar Malek	University Hospital Tübingen	Germany	Integrating principles of personalized medicine at the university hospital in Tübingen-challenges and opportunities
8–Feb–17	Dr. Rudi Balling	Luxembourg Centre for Systems Biomedicine	Luxembourg	From systems biology to systems medicine – a long road ahead
9–Feb–17	Dr. Yibo Wu	ETH Zurich, Institute of Molecular Systems Biology	Switzerland	Systems proteomics of liver mitochondorial activity
10–Feb–17	Dr. Takashi Satoh	WPI Immunology Frontier Research Center (IFReC), Osaka University	Japan	Functional diversity of various disorder-specific macrophages
16–Feb–17	Dr. Jason E. Shoemaker	University of Pittsburgh	USA	Emergent properties of influenza virus infections
27–Feb–17	Dr. Hiroshi Kurosaka	Graduate School of Dentistry, Osaka University	Japapn	Investigating the etiology of craniofacial abnormalities
9–Mar–17	Dr. Keiji Hirota	Institute for Frontier Life and Medical Sciences, Kyoto University	Japapn	Tissue inflammation mediated by Th17 cells
10–Mar–17	Dr. Florent Ginhoux	Singapore Immunology Network (SIgN), A*STAR	Singapore	Dendritic cell biology: from development to functions
14–Mar–17	Dr. Claus Schneider	Vanderbilt University Medical School	USA	Novel substrates and products in cyclooxygenase catalysis
17–Apr–17	Dr. Masaru Ishii	Graduate School of Medicine, Osaka University	Japan	*In vivo* dynamics and function of osteoclasts, bone-destroying macrophages
23–May–17	Dr. Rahul Sinha	Stanford University School of Medicine	USA	Single-cell RNA-seq: limitations and challenges
7–Jun–17	Dr. Florian Winau	Harvard Medical School	USA	Lipids in immunology: antigens and regulators of immune responses
21–Jun–17	Dr. Azusa Inoue	Harvard Medical School	USA	Discovery of polycomb-mediated genomic imprinting
27–Jun–17	Prof. Koji Hase	Faculty of Pharmaceutical Science, Keio University	Japapn	Microbial fermentation products shape host immune system through epigenetic modifications
18–Jul–17	Prof. Irena Mlinaric-Rascan	Faculty of Pharmacy, University of Ljubljana	Slovenia	Immunoproteasome targeting
26–Jul–17	Dr. Zhuoming Sun	Beckman Research Institute of the City of Hope	USA	Mechanism for RORgammat-regulated Th17 function
4–Aug–17	Dr. Asuka Inoue	Graduate School of Pharmaceutical Sciences, Tohoku University	Japapn	Developing methods to dissect GPCR signaling in health and disease
17–Aug–17	Dr. Kazuki Nagashima	Graduate School of Medicine and Faculty of Medicine, The University of Tokyo	Japapn	Identification of microfold cell-inducer (MCi) cells that promote IgA production and diversify the gut microbiota
22–Aug–17	Dr. Kyle M. Loh	Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine	USA	Understanding how early human tissue progenitors develop by reconstituting them from stem cells
29–Aug–17	Dr. Osamu Takeuchi	Institute for Frontier Life and Medical Sciences, Kyoto University	Japapn	Posttranscriptional control of inflammatory responses
8–Sep–17	Dr. Yuichi Hirata	Columbia University	USA	Identification of specific Treg subset that regulates stem cells
19–Sep–17	Dr. Keiji Kuba	Akita University Graduate School of Medicine	Japapn	mRNA deadenylation-guided regulation of cardiac homeostasis
21–Sep–17	Dr. Charles N. Serhan	Brigham and Women's Hospital and Harvard Medical School	USA	Pro-resolving mediators & mechanisms in infectious inflammation: metabololipidomics in human disease and model organisms
29–Sep–17	Dr. Nada Jabado	McGill University	Canada	Oncohistones in cancer: professional highjackers of the epigenome
16–Oct–17	Prof. Neil Brockdorff	University of Oxford	UK	Advances towards understanding the mechanism of X chromosome inactivation
19–Oct–17	Dr. Ferdinando Cerciello	University Hospital Zurich	Switzerland	Multiplexed biomarkers strategies for the detection of malignant pleural mesothelioma in blood based on targeted proteomics
25–Oct–17	Dr. Toshiro Moroishi	Moores Cancer Center, University of California at San Diego	USA	Hippo pathway in immunity and tissue homeostasis
27–Oct–17	Dr. Ludmila Prokunina-Olsson	National Cancer Institute	USA	From genetics to translational genomics of infection and cancer
30–Oct–17	Dr. Marius Wernig	Stanford University	USA	How to make a neuron
2–Nov–17	Dr. Alejo Chorny	Journal of Experimental Medicine	USA	Scientific publishing: what, how and why
6–Nov–17	Dr. Sara Mostafavi	Centre for Molecular Medicine and Therapeutics, University of British Columbia	Canada	Identifying and interpreting genomic patterns in large population studies.
10–Nov–17	Dr. Heidi H. Kong	National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH	USA	The microbiome in healthy skin and atopic dermatitis
20–Nov–17	Dr. Craig Mak	Cell Systems	USA	How to publish with Cell Systems
21–Nov–17	Dr. Hiroyuki Hosokawa	California Institute of Technology	USA	Dynamic and competitive deployments of transcription factor ensembles mediate T-cell lineage commitment
24–Nov–17	Dr. Yuki Sugiura	Keio University	Japan	Visualization of immune-brain signaling in tissues by mass spectrometry based imaging
24–Nov–17	Dr. Keisuke Kataoka	National Cancer Center Research Institute	Japan	Genetic landscape in adult T-cell leukemia/lymphoma
25–Dec–17	Dr. Toru Hirota	The Cancer Institute Japanese Foundation for Cancer Research	Japan	Molecular grounds underlying chromosomal instability in cancers



Part 5

Data and Statistics

Publications 2017

Table: IMS Publications Jan-Dec, 2017

Journal	IF (2016)	Number of Papers 2017
Nat Rev Drug Discov	57.0	1
Nat Biotechnol	41.7	3
Nature	40.1	3
Nat Rev Immunol	39.9	1
Nat Nanotechnol	39.0	1
Science	37.2	3
Nat Med	29.9	1
Nat Genet	28.0	5
Cell Stem Cell	23.4	1
Immunity	22.8	4
Nat Immunol	21.5	4
Nat Cell Biol	20.1	1
Cancer Discov	20.0	1
Gastroenterology	18.4	1
Cell Metab	18.2	1
Sci Transl Med	16.8	1
Gut	16.7	2
JAMA Oncol	16.6	1
Mol Cell	14.7	1
Circ Res	14.0	1
Mol Psychiatr	13.2	1
J Allergy Clin Immun	13.1	5
Ann Rheum Dis	12.8	1
J Clin Invest	12.8	1
J Hepatol	12.5	1
Nat Commun	12.1	7
J Exp Med	12.0	5
Biol Psychiat	11.4	1
Nat Plants	10.3	1
EMBO J	9.8	1
Proc Natl Acad Sci U S A	9.7	8
Clin Cancer Res	9.6	2
Immunol Rev	9.6	2
Gene Dev	9.4	1
Dev Cell	9.2	1
Am J Hum Genet	9.0	1
Diabetes	8.7	2
Cell Syst	8.4	1
Kidney Int	8.4	1
Curr Opin Immunol	8.4	1
Cancer Immunol Res	8.3	1
Cell Rep	8.3	6
Elife	7.7	1
Haematologica	7.7	1
J Autoimmun	7.6	1
Oncogene	7.5	1
Bioinformatics	7.3	1
Clin Pharmacol Ther	7.3	2
Arthritis Rheumatol	6.9	1
Front Immunol	6.4	3
Breast Cancer Res	6.3	1
J Invest Dermatol	6.3	2
J Infect Dis	6.3	1
PLOS Genet	6.1	1
Lab Chip	6.0	1
Stroke	6.0	1
Others		206
TOTAL		**312**

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Budget, personnel and patents

IMS Budget FY2017

IMS Budget FY2017	JPY Million
Government funding for operations	2,394
Commissioned research	1,036
External competitive funding	839
Total	**4,269**

Patents

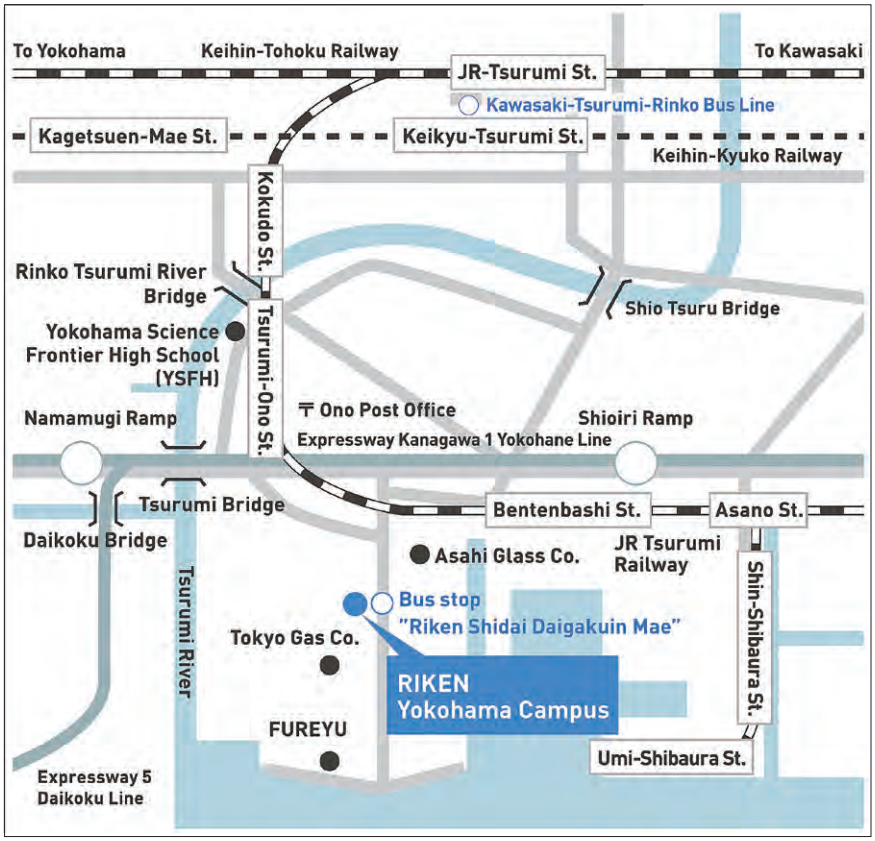
There were 31 patents filed from January to December in 2017.

Patents	Total	International patents (PCT)	Domestic patents (Japan)
2017	31	20	11

Personnel FY2017

Category	Number
Director	1
Deputy Director	3
Senior Advisor	1
Group Director	10
Team Leader	23
Coordinator	2
Partnership-Promotion Coordinator	2
Deputy Team Leader	7
Senior Scientist	22
Senior Research Scientist	1
Research Scientist	38
Postdoctoral Researcher	16
Special Postdoctoral Researcher	6
Foreign Postdoctoral Researcher	2
Research Fellow	5
Research Associate	9
Senior Technical Scientist	3
Technical Scientist	9
Technical Staff I	51
Technical Staff II	62
International Program Associate	1
Junior Research Associate	26
Intern	1
Student Trainee	99
Assistant	26
Part-time Staff	28
Senior Visiting Scientist	11
Visiting Scientist	190
Visiting Technical Scientist	5
Visiting Researcher	1
Temporary Staffing	13
Research Consultant	4
Consultant	1
Total	**679**

Access to RIKEN Yokohama Campus



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/

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.

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

rains 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.

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Integrative Medical Sciences
http://www.ims.riken.jp/english/

RIKEN Yokohama Campus
1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama City,
Kanagawa, 230-0045, Japan

Tel : 045-503-9111
Fax : 045-503-9113
Email: yokohama@riken.jp

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