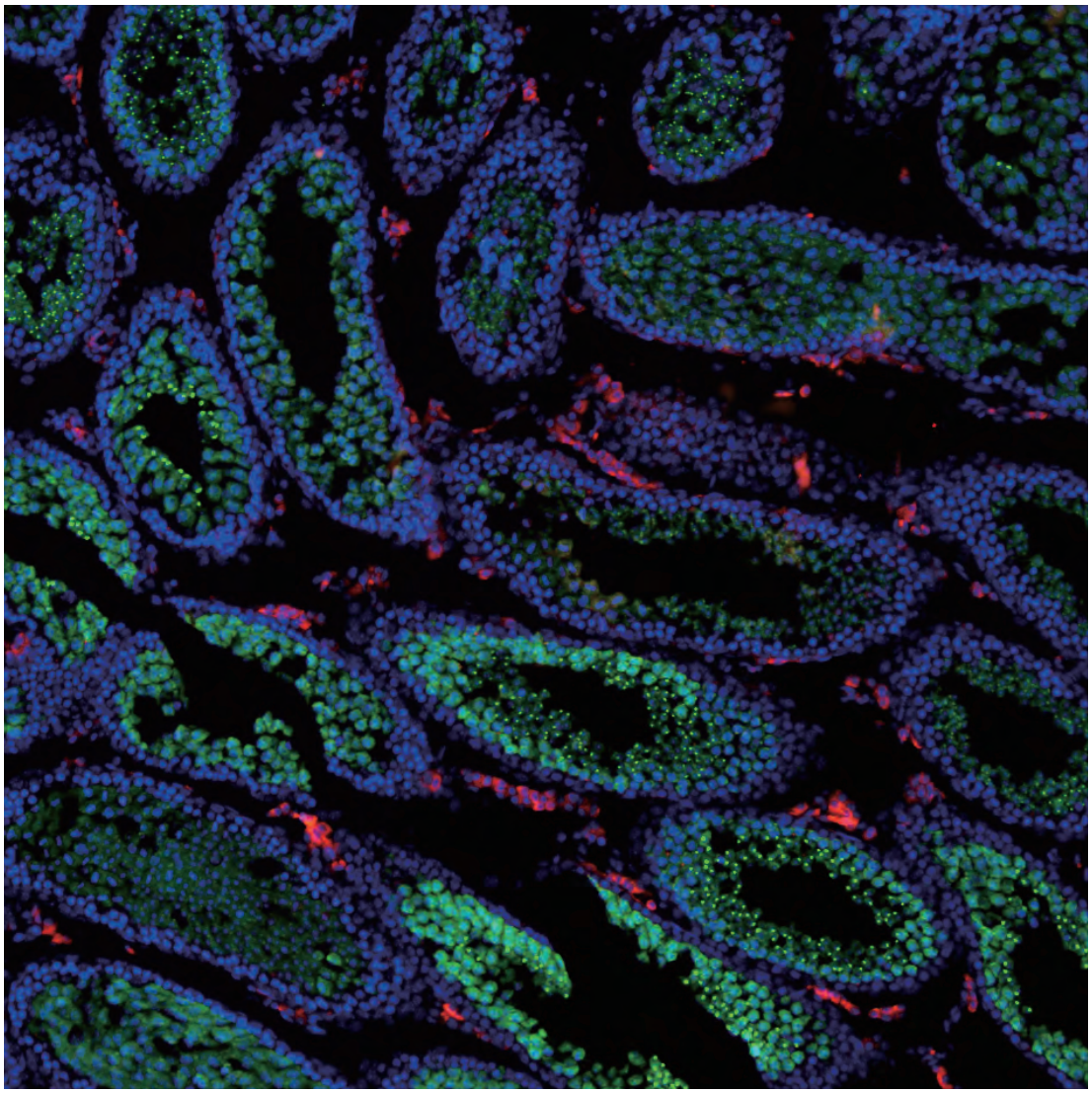
RIKEN IMS Annual Report 2019

RIKEN Center for Integrative Medical Sciences



RIKEN Center for Integrative Medical Sciences Organization Chart

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RIKEN Hakubi Research Team

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YCI Laboratory for Immunological Transcriptomics: **Hideyuki Yoshida**
YCI Laboratory for Next-Generation Proteomics: **Yibo Wu**
YCI Laboratory for Metabolic Epigenetics: **Azusa Inoue**

Contents

Part 1
Research Highlights

Part 2
Lab Activities

Part 3
Research Projects

Part 4
Events

Part 5
Data and Statistics

Director's Report

As the Director of the RIKEN Center for Integrative Medical Sciences (IMS), I am once again proud to look back on 2019 as another exceptional and productive year for our center.

In addition to all of the ongoing research activities and related events, some of which will be described below, IMS held an Advisory Council (AC) Meeting in August, the last being in 2016. An international panel of distinguished scientists reviewed our center's underlying concept and future direction. One of the areas they advised us on and strongly supported was the Research & Infrastructure Platform we recently established. While they agreed that centralizing research techniques and equipment will generally reduce costs, increase efficiency and training of staff, and promote the development of new technologies and international collaborations, it will also lead to some budgetary and personnel issues. For example, because of the New Labor Law on Indefinite Term Employment, most of the assistants and technicians working as part of the platform will become indefinite term employees, leading to further strain on the center's already limited operating budget. Based on the AC's comments, we will continue to integrate the IMS research environment and to work with the RIKEN central administration to ensure that IMS has the necessary budget to continue its groundbreaking research activities.

In response to the recent rapid advances in both informational science and technologies, the Japanese government is promoting new science policies represented by Society 5.0. We are now facing the 4th industrial revolution and are transitioning into a super smart society, in which the fusion of advances in artificial intelligence (AI), robotics, the Internet of Things, 3D printing, genetic engineering, quantum computing, and other technologies is taking place. In the near future, we shall encounter a great societal and technological transition. As we make this transition, what is the role of medical sciences and, in particular, that of IMS in this new society? IMS has been combining immunological and genomic approaches. This strategy shall continue along with incorporation and development of a variety of advanced techniques and technologies for understanding the mechanisms of diseases, in what we term "systems medical sciences". In an effort to bring AI to biology, we recently held a symposium on "Biomedical Data for Artificial Intelligence" in collaboration Sweden's Karolinska Institutet and SciLifeLab. In addition, RIKEN IMS also co-sponsored the International Conference of Systems Biology which was held at the Okinawa Institute of Science and Technology Graduate University.

In 2019, a total of 259 papers from IMS were published, many in high-impact journals, once again demonstrating the diversity and strength of the research being carried out by our investigators. Studies on supercentenarians, who during their lifetimes are relatively immune to illnesses such as infections and cancer, have led to the idea that they may have particularly strong immune systems. Using single-cell RNA analysis, Piero Carninci and colleagues found that these individuals have an excess of a type of immune cell called cytotoxic CD4 T-cells, which are relatively uncommon in most individuals, that could play a protective role in this especially healthy aged group.

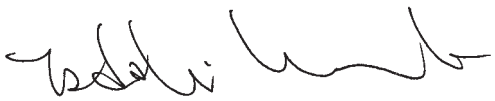
Several prestigious awards were received during the past year by IMS researchers, including a new PI and a young researcher. Chikashi Terao, Team Leader of the Laboratory for Statistical and Translational Genetics, was awarded the Young Scientists' Prize, The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology. And Tetsuro Kobayashi, a Research Scientist in the Laboratory for Innate Immune Systems, won the 2019 LEO Foundation Award in the Asia-Pacific Region. (see Part 4 for further awardees)

Throughout the year IMS held or took part in several international collaborative efforts, including the EMBO Workshop on Single Cell Biology, the Human Cell Atlas-Single Cell Project Symposium, a signing ceremony to establish a joint laboratory between RIKEN and the University of Luxembourg, and others (see Part 4 for further details).

This will be a bittersweet year for me, as I will be relinquishing my role as Center Director at the end of March. However, I am confident that IMS, under the leadership of the next Director, Kazuhiko Yamamoto, will continue its mission to establish a new research field of disease systems medical sciences contributing to the future of medical care.

Finally, I believe that we, together with all human beings on earth, shall overcome the disaster being caused by COVID-19.

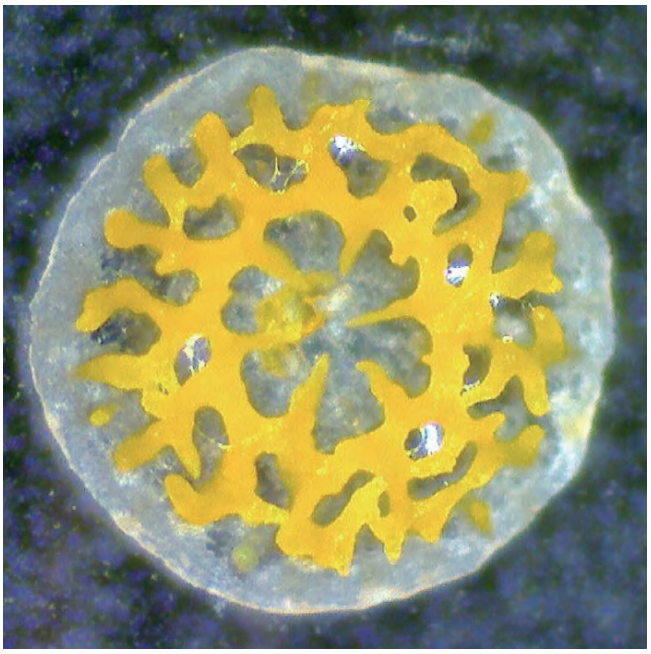
March 31, 2020



Tadashi Yamamoto
Director
RIKEN Center for Integrative Medical Sciences

Part 1

Research Highlights



Rare human gut bacterial strains exhibit potential as broadly effective biotherapeutics

Kenya Honda

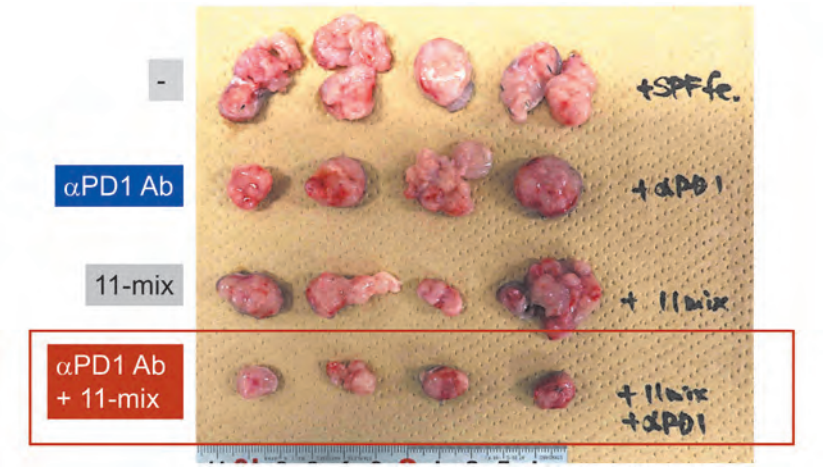


Figure: The combination of αPD1 mAb and 11-mix significantly suppressed tumor growth
SPF mice were subjected to subcutaneous implantation of MC38 cells, followed or not by repetitive oral dosing of the 11 bacterial strain mix (11-mix). PD-1 antibody was injected intraperitoneally three times. Representative photograph of excised MC38 tumours on day 23.

During the analysis of Klebsiella-mediated TH1 cell induction, Kenya Honda of the RIKEN Center for Integrative Medical Sciences and his colleagues recognized that some microbiota members also induce non-CD4 IFNγ-expressing (IFNγ$^+$) T cells, and were intrigued by this phenomena. They determined that the non-CD4 T cells were actually CD8 T cells, indicating that the microbiota can also regulate IFNγ$^+$ CD8 T cells. This was confirmed by analyzing germ-free (GF) and specific pathogen-free (SPF) mice, the latter have many IFNγ$^+$ CD8 T cells in the intestine while the former have very few. Since the lab has always aimed to identify functionally responsible bacterial species that can be translated to the clinic, their goal was to search the human microbiome for bacterial members that could induce IFNγ$^+$ CD8 T cells.

Stool samples were collected from six healthy volunteers and were inoculated into GF mice by oral gavage. After housing the mice in sterile vinyl isolators for 3-4 weeks, they were sacrificed and the intestines were collected and examined for IFNγ$^+$ CD8 T cells. Interestingly, the induction capability of the fecal samples varied substantially in that some samples did not induce IFNγ$^+$ CD8 T cells at all, while other samples showed intermediate or strong induction of IFNγ$^+$ CD8 T cells. For the colonized mouse with the strongest induction capability, the microbiota and cecal content were collected and the cecal content was further inoculated into 4-5 groups of GF mice, each treated with different antibiotics to reduce the microbiota communities. Ampicillin treatment was found to enhance the accumulation of IFNγ$^+$ CD8 T cells, while simultaneously reducing the number of community members. They selected one of the ampicillin-treated mice, then collected and cultured its cecal contents *in vitro* to isolate as many bacterial strains as possible. Twenty-six strains were isolated, cultured individually, and mixed together to make a bacterial cocktail, which, when orally inoculated into GF mice, effectively induced IFNγ$^+$ CD8 T cells. They further narrowed down these strains to a group of 11 that was sufficient for induction of IFNγ$^+$ CD8 T cells.

Next, the group tested whether the 11-strain mix could enhance immune checkpoint blockade therapy against cancer. While it was not their original intention to identify bacteria that could enhance the immune checkpoint blockade, they were encouraged by their colleagues to further pursue this connection because of the IFNγ$^+$ CD8 T cell inducing effect of the 11-strain mix. "To our surprise, the mixture was actually effective in enhancing immune checkpoint blockade therapy," recalled Honda.

The team is now working with both international and domestic partners in clinical trials to test the effectiveness of their 11-strain bacterial cocktail in combination with PD-1 antibody (immune checkpoint blockade) therapy in melanoma patients who previously failed to respond to PD-1 antibody treatment alone. Similar trials will soon be conducted on gastric and colon cancer patients previously shown to be refractory to PD-1 antibody single therapy. It is the teams hope to see cancer patients receive benefit from their 11-strain treatment.

Original paper:
Tanoue T, Morita S, Plichta DR, Skelly AN, Suda W, Sugiura Y, Narushima S, Vlamakis H, Motoo I, Sugita K, Shiota A, Takeshita K, Yasuma-Mitobe K, Riethmacher D, Kaisho T, Norman JM, Mucida D, Suematsu M, Yagu-chi T, Bucci V, Inoue T, Kawakami Y, Olle B, Roberts B, Hattori M, Xavier RJ, Atarashi K, Honda K. A defined commensal consortium elicits CD8 T cells and anti-cancer immunity. ***Nature*** 565, 600-605 (2019)

Systematic analysis of immune cells toward future immunology

Hideyuki Yoshida

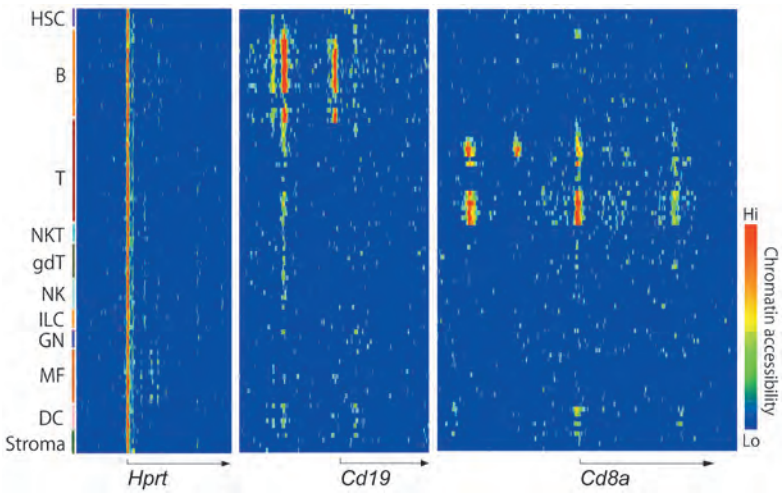


Figure: OCR profiles in 86 immune cell populations

Chromatin accessibility for example loci are shown as indicated by the color strip on the right. Cell populations are grouped by lineage as indicated on the left. OCRs are less variable for the housekeeping *Hprt* locus, but are more lineage-specific for the *Cd19* and *Cd8a* loci, which are representative marker genes for B cells and T cells, respectively.

Our body consists of various types of cells in which different sets of genes are expressed. These cells' identity on the transcriptome level are indispensable to establish their distinct functions, which change during cell differentiation and according to environmental cues. Hence, it has long been studied how gene expression is regulated to understand the mechanisms determining a cell's identity.

The establishment and maintenance of a cell's transcriptional identity is largely driven by the specific activity of cis-regulatory elements: promoters at which initiation complexes are assembled around RNA polymerase II (Pol-II), or distal enhancer elements that facilitate Pol-II loading and/or release from poised configuration (Haberle, 2018). The population- and stimulation-specific expression of a gene results from the combined activity of the several enhancers that control it, each of which may have a different regulatory logic, driven by the combinatorial activity of transcription factors (TFs) and chromatin remodelers. How do changes in the activity of cis-regulatory elements program the differentiation cascade of cell lineages?

The mouse immune system provides an excellent setting to investigate gene regulation during differentiation, as differentiation from common progenitors is well established with discrete cell populations being readily purified and major cell states are well characterized (Hardy and Hayakawa, 2001; Rothenberg, 2014). We used low input epigenomic and transcriptomic profiling methods (ATAC-seq and RNA-seq) to generate chromatin accessibility and gene expression profiles in 86 unique immune cell populations from hematopoietic stem cells in bone marrow to terminally differentiated cells in the periphery that span the entire immune system of the mouse. These profilings enabled us to build a "complete" atlas of 512,595 cis-regulatory OCRs (Open Chromatin Regions), which encompasses the entire span of lineages composing the mouse immune system. Notably, this paired chromatin and transcriptome approach with unprecedented granularity during differentiation empowered us to move beyond merely an epigenomic roadmap, and provided a platform for inferring causal regulatory interactions. First, we connected a number of OCRs to the expression of a nearby gene based on the plausible assumption that such correlations between accessibility of cis-regulatory elements and gene expression signify functional relationships. Second, analysis revealed that while TFs can have either positive or negative consequences on accessibility of an OCR, a majority of TFs had positive effects on accessibility, promoting speculation that chromatin opening is the dominant mode of control for the unfolding of gene expression through immune cell differentiation. Finally, by analyzing the three-way correlations between OCR activity, the TF motifs they contain, and the expression of the TFs, we can predict how groups of TFs orchestrate immunocyte differentiation and function.

These results provide a vast resource of great value for understanding immunological differentiation and function that will be leveraged by the immunological community to guide focused experiments for understanding the regulation of particular genes on immune function or disease. We expect it will serve as an initial scaffold on which to systematically build, through complementary "multi-omics" strategies, additional knowledge toward a complete understanding of genomic regulation in immune cells. Considering that the mouse immune system mirrors human biology remarkably well in many respects, with >90% of the same genes being shared between mice and humans (Waterston, 2002), these insights will be utilized to understand the human immune system.

Original paper:

Yoshida H, Lareau CA, Ramirez RN, Rose SA, Maier B, Wroblewska A, Desland F, Chudnovskiy A, Mortha A, Dominguez C, Tellier J, Kim E, Dwyer D, Shinton S, Nabekura T, Qi Y, Yu B, Robinette M, Kim KW, Wagers A, Rhoads A, Nutt SL, Brown BD, Mostafavi S, Buenrostro JD, Benoist C; Immunological Genome Project. The cis-Regulatory Atlas of the Mouse Immune System. ***Cell*** 176, 897-912.e20 (2019)

New method provides better understanding of how gene "enhancers" work

Yasuhiro Murakawa

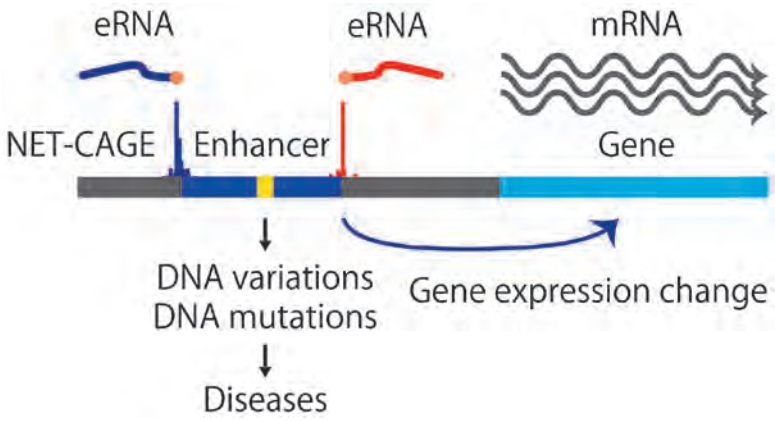


Figure:
We developed a simple and robust NET-CAGE technology to globally determine the 5′-ends of nascent RNAs. Enhancers are distal *cis*-regulatory elements that enhance the expression of target genes in a cell-type specific manner. Interestingly, enhancers produce unstable non-coding enhancer RNAs (eRNAs) bidirectionally from both edges of enhancers regions. NET-CAGE detects eRNAs with high sensitivity at single nucleotide resolution, allowing for ultra-sensitive detection of a number of enhancers encoded in the human genome. Germline DNA variations or somatic mutations within enhancer regions affect the expression of target genes, and thus contribute to the pathogenesis of human diseases.

Scientists from the RIKEN Center for Integrative Medical Science and Istituto FIRC di Oncologia Molecolare (IFOM), along with collaborators from Kyoto University, the Karolinska Institutet, and DNAFORM, have developed a new technique, NET-CAGE, to elucidate the structure of a type of non-coding portion of the genome called enhancers, which function to activate specific genes. These parts of the genome, which were once thought to be unimportant and called "junk DNA," are now known to be associated with a variety of diseases, and understanding their function has become an important goal in genomic research.

Two types of genomic regions, known as promoters and enhancers, work to coordinate the activation of protein-coding genes, essentially by switching them on. While promoters are located right next to the genes they activate, enhancers can be located far away. A variety of techniques have been developed to map enhancers, but they all have certain limitations, such as lack of sensitivity for identification, inability to pinpoint the exact location of the regions, or ill-suitedness for use in frozen cells. To overcome these limitations, the researchers developed a method called NET-CAGE, which is an extension of the CAGE technology developed at RIKEN to identify non-coding regions of the genome, and used it to examine five commonly used types of cancer cell lines.

Using the new method, the researchers made a series of interesting discoveries regarding enhancers. First, they identified nearly 20,000 new enhancers in the human genome. They found that while promoters are activated in a variety of cell types, enhancers tend to function in just one cell type, thus, showing an important difference between the two types of regions. They also uncovered an intriguing relationship between the two types of regions, showing that they are linked topologically according to their cell type specificities. Additionally, they pinpointed the exact locations of active enhancers at high nucleotide resolution within cluster regions known as "super enhancers."

According to Yasuhiro Murakawa of RIKEN IMS, who led the team along with Hideya Kawaji, "We have found that enhancers play an essential role in generating a cell type-specific transcriptome. The new method that was developed in this study can be used to study many aspects of biology. In the long term, the method can be implemented into next-generation genomic medicine. Using this technology, we are making a comprehensive map of enhancer activation in the human body. By integrating this knowledge with data on mutations associated with disease and cancer genomics data, we hope to increase our understanding of disease mechanisms."

Original paper:
Hirabayashi S, Bhagat S, Matsuki Y, Takegami Y, Uehata T, Kanemaru A, Itoh M, Shirakawa K, Takaori-Kondo A, Takeuchi O, Carninci P, Katayama S, Hayashizaki Y, Kere J, Kawaji H, Murakawa Y. NET-CAGE characterizes the dynamics and topology of human transcribed cis-regulatory elements. ***Nat Genet*** 51, 1369-1379 (2019)

Genome-wide genetic analysis of type 2 diabetes in the Japanese population

Momoko Horikoshi

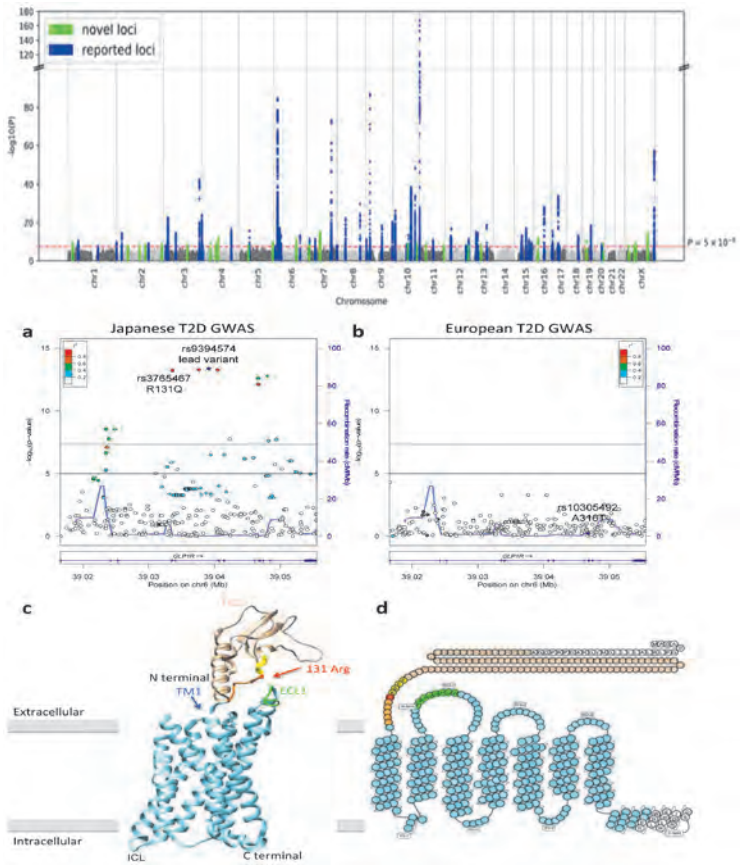


Figure: Manhattan plot of Japanese T2D GWAS and regional association plots of GLP1R with its structure

Manhattan plot (**top**) summarizes the genome-wide association study of Japanese T2D in 36,614 cases and 155,150 controls. The association *P* value (in $-\log_{10}P$) for each of up to 12,557,761 variants (y axis) was plotted against the genomic position (x axis). Association signals that reached genome-wide significance ($P < 5.0 \times 10^{-8}$) are shown in green if novel and in blue if previously reported. Regional association plots of the Glucagon-like Peptide 1 Receptor (*GLP1R*) region in Japanese (**a**) and Europeans (**b**) T2D GWAS highlighting the Japanese-specific T2D association at the *GLP1R* locus. A three-dimensional ribbon model (**c**) and a snake plot (**d**) of GLP1R shows the position of the novel T2D missense variant R131Q (red) at a highly flexible region (yellow and orange) interacting with the extracellular loop (green).

Ever larger scale genome-wide association (GWA) meta-analyses for type 2 diabetes (T2D), in which the included samples now total nearly 1 million, have been conducted extensively, mainly in Europeans. Momoko Horikoshi of the RIKEN Centre for Integrative Medical Sciences and her colleagues and collaborators (now at the University of Tokyo and Osaka University) have been focusing on investigating the genetic contribution to T2D susceptibility in the Japanese population by using the rich genetic resources generated by Biobank Japan (BBJ). By expanding the effort to the full BBJ collection, they conducted a large-scale single population GWA analysis of T2D in 191,764 Japanese. In addition to the >150 T2D loci established as of the end of 2018, they identified 28 novel loci (Fig. top). Among these loci were several previously unreported T2D-associated missense variants that showed a different spectrum of minor allele frequencies between Japanese and Europeans. One such example was detected at the Glucagon-like Peptide 1 Receptor (*GLP1R*) locus (Fig. a-d). The T2D protective genotype, which was associated with increased GLP1-induced insulin secretion, is very common in Japanese (and other East Asians), but rare in Europeans. A transethnic comparison of pathway analysis revealed that Japanese and Europeans had shared and dissimilar impacts of a series of pathways on T2D. "These findings provided a possible explanation for the heterogeneity in response to T2D drugs and clinical features between Japanese and Europeans. 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." says Momoko Horikoshi.

Original paper:

Suzuki K, Akiyama M, Ishigaki K, Kanai M, Hosoe J, Shojima N, Hozawa A, Kadota A, Kuriki K, Naito M, Tanno K, Ishigaki Y, Hirata M, Matsuda K, Iwata N, Ikeda M, Sawada N, Yamaji T, Iwasaki M, Ikegawa S, Maeda S, Murakami Y, Wakai K, Tsugane S, Sasaki M, Yamamoto M, Okada Y, Kubo M, Kamatani Y*, Horikoshi M*, Yamauchi T, Kadowaki T. Identification of 28 new susceptibility loci for type 2 diabetes in the Japanese population. ***Nat Genet*** 51, 379-386 (2019)

*These authors jointly contributed to the work

Genomic and transcriptomic profiling of combined hepatocellular and intrahepatic cholangiocarcinoma reveals distinct molecular subtypes

Hidewaki Nakagawa

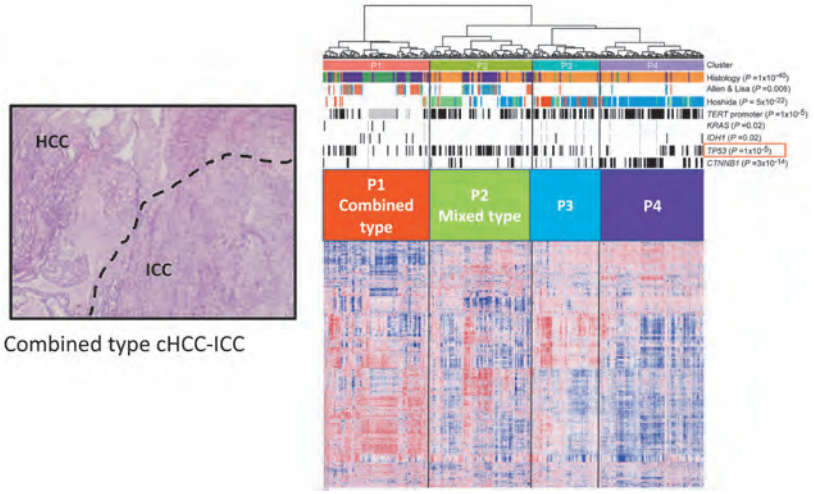


Figure: Unsupervised clustering of gene expression identified four liver cancer clusters
P1, P2, P3, and P4 (right). P1 and P2 include the combined type and the mixed type of cHCC-CC, respectively. The picture of a representative combined type of cHCC-ICC case (left).

Primary liver cancer is basically classified into two types: Hepatocellular carcinoma (HCC) and Intrahepatic cholangiocarcinoma (ICC). Combined hepatocellular and intrahepatic cholangiocarcinoma (cHCC-ICC) is a rare type of liver cancer, showing a mixture of HCC cells and ICC cells, that has the most dismal prognosis. Accurate diagnosis and specialized treatment for cHCC-ICC have yet to meet clinical needs. In addition, whether cHCC-ICC is a unique entity or only a subtype of HCC or ICC remains a long-standing debate.

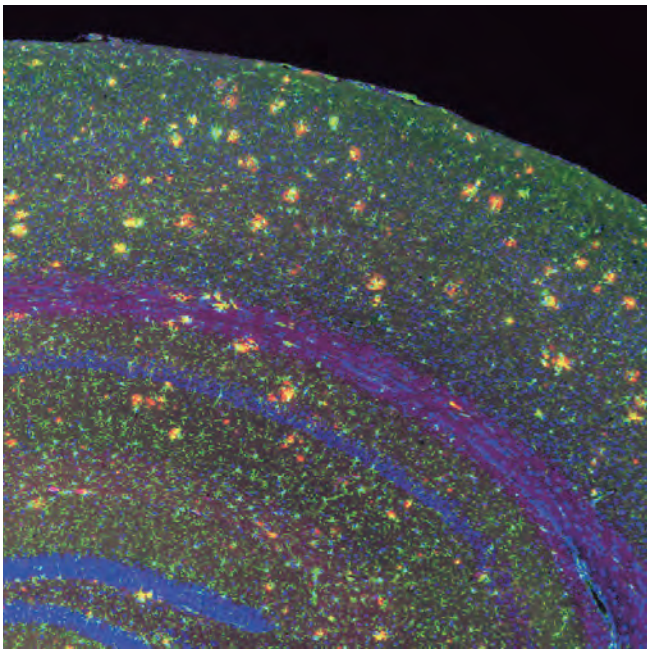
In this collaborative study between Hidewaki Nakagawa and his colleagues at the RIKEN Center for Integrative Medical Sciences and Peking University, China, comprehensive genomic and transcriptomic sequencing analysis was performed on 133 (cHCC-ICC) cases, including separate subtypes, combined subtypes (clear merges between the HCC and ICC portions), and mixed subtypes (unclear merges), resulting in a detailed genomic landscape of cHCC-ICC. By combining these data with HCC/ICC genomic data at RIKEN (totaling more than 300 cases), they performed a comprehensive comparison to the common types of liver cancers (HCCs and ICCs), and classified primary liver cancers into four subtypes based on their differentiation mechanisms: differentiation to cholangiocytes (P1), poor differentiation (P2), differentiation to hepatocytes (P3), and well-differentiated to hepatocytes (P4). The combined type cHCC-ICC showed strong ICC-like features (P1), whereas the mixed type cHCC-ICC showed HCC-like features (P2). The cHCC-ICCs belonging to P1 or P2 showed poorer prognosis and more malignancy. Integrating cancer cell fraction analysis, laser microdissection, and single nucleus sequencing, they revealed both mono- and multi-clonal origins in separate type cHCC-ICCs, whereas the combined and mixed type cHCC-ICCs all had monoclonal origins.

The gene *TP53* was most commonly mutated in cHCC-ICCs (50%), while it was only mutated in 20-35% of HCCs and ICCs, indicating that *TP53* can play some important role in the development and differentiation of cHCC-ICCs. Notably, cHCC-ICC showed significantly higher expression of the stemness marker Nestin, which is regulated by p53. High Nestin expression correlates with poor prognosis, suggesting that Nestin may serve as a new biomarker for diagnosing cHCC-ICC. These findings may direct future therapeutic choices for cHCC-ICC. Most importantly, we identified Nestin expression as a new marker for the diagnosis and prognosis of cHCC-ICC, and therapies targeting Nestin may provide new opportunities for cHCC-ICC treatment.

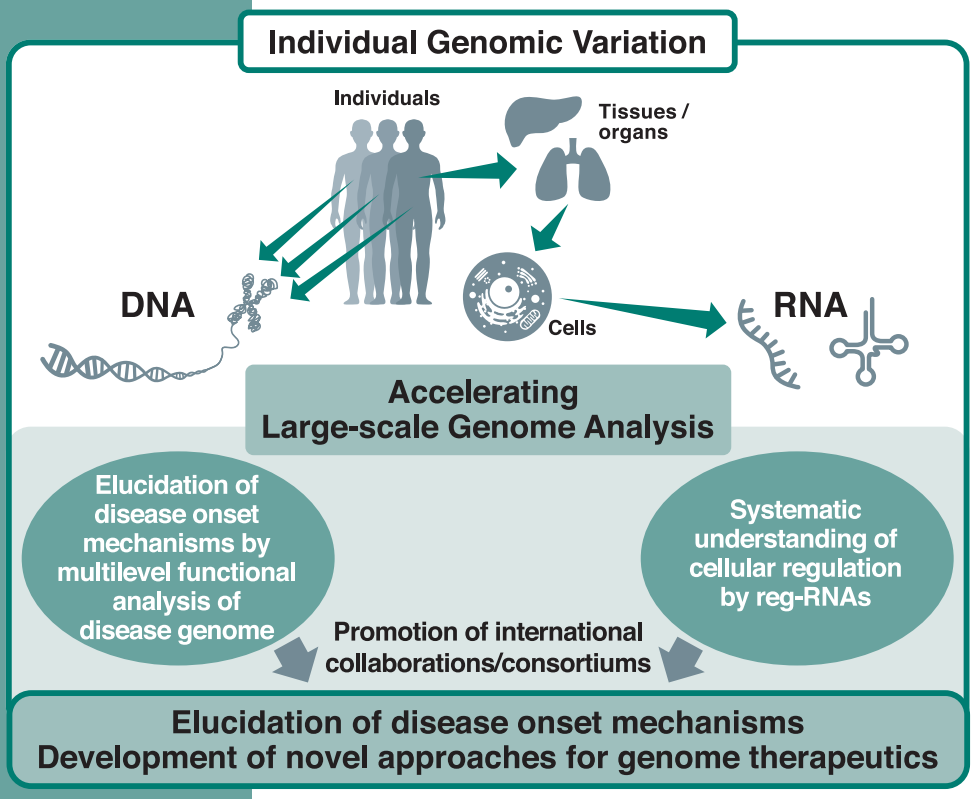
Original paper:
Xue R, Chen L, Zhang C, Fujita M, Li R, Yan SM, Ong CK, Liao X, Gao Q, Sasagawa S, Li Y, Wang J, Guo H, Huang QT, Zhong Q, Tan J, Qi L, Gong W, Hong Z, Li M, Zhao J, Peng T, Lu Y, Lim KHT, Boot A, Ono A, Chayama K, Zhang Z, Rozen SG, Teh BT, Wang XW, Nakagawa H, Zeng MS, Bai F, Zhang N. Genomic and Transcriptomic Profiling of Combined Hepatocellular and Intrahepatic Cholangiocarcinoma Reveals Distinct Molecular Subtypes. ***Cancer Cell*** 35, 932-947.e8 (2019)

Part 2

Lab Activities



Division of Genomic Medicine



Division of Genomic Medicine will develop new methods for genome-based drug discovery and produce supporting evidence for the realization of genomic medicine.

Laboratory for Transcriptome Technology

Team Leader: Piero Carninci

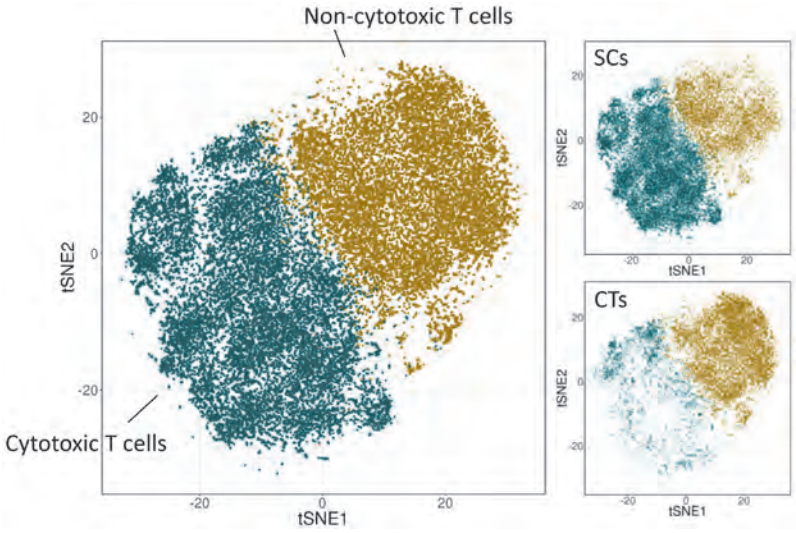


Figure: Expansion of cytotoxic T cells in supercentenarians
Two-dimensional tSNE visualization of total T cells using the Seurat R package. Left: Different colors represent two clusters. Yellow: Non-cytotoxic T cells, Green: Cytotoxic T cells. Right: Top and bottom show supercentenarians (SCs) and controls (CTs), respectively.

Our laboratory focuses on the development of technologies for genomic and transcriptomic sequencing and analysis. We also engage in studies of RNA biology and aging, taking a transcriptomic approach.

Using single-cell transcriptome analysis, in collaboration with Keio University, we recently explored the unique nature of the immune system in Japanese supercentenarians, who have reached the age of 110 or more.

Exceptionally long-lived people tend to have good health throughout their entire lifetime, which implies that their immune systems retain their function in protecting against diseases, such as infection and cancer, and could be a key for a long healthy life.

We performed single-cell transcriptome profiling of 41,208 peripheral blood mononuclear cells (PBMCs) from 7 supercentenarians and 19,994 PBMCs from 5 younger controls and found an expansion of cytotoxic CD4 T cells in the supercentenarians. In order to explore the mechanisms underlying this expansion, we performed single cell T cell receptor sequencing for 2 supercentenarians and identified clonally expanded cytotoxic CD4 T cells.

CD4 T cells are mostly known as helper T cells, which play a role in helping to activate or regulate other immune cells, and not as having cytotoxic features. Previously, some studies have shown that cytotoxic CD4 T cells are present as a small percentage of the total CD4 T cells in healthy PBMCs, but our study showed that 25% of the total T cells, on average, are cytotoxic in the supercentenarians, whereas only 2.8% were cytotoxic in the controls. The role of cytotoxic CD4 T cells is not yet clear, but some studies have shown their cytotoxic activity against tumor cells and viruses, which indicates that the expanded cytotoxic CD4 T cells in supercentenarians might contribute to anti-tumor and antiviral immunity in supercentenarians and this may be one of the secrets of their long healthy life.

Recent Major Publications

Hashimoto K, Kouno T, Ikawa T, Hayatsu N, Miyajima Y, Yabukami H, Terooatea T, Sasaki T, Suzuki T, Valentine M, Pascarella G, Okazaki Y, Suzuki H, Shin JW, Minoda A, Taniuchi I, Okano H, Arai Y, Hirose N, Carninci P. Single-cell transcriptomics reveals expansion of cytotoxic CD4 T cells in supercentenarians. ***Proc Natl Acad Sci U S A*** 116, 24242 (2019)

Valentine MNZ, Hashimoto K, Fukuhara T, Saiki S, Ishikawa KI, Hattori N, Carninci P. Multi-year whole-blood transcriptome data for the study of onset and progression of Parkinson's Disease. ***Sci Data*** 6, 20 (2019)

Nguyen Q, Aguado J, Iannelli F, Suzuki AM, Rossiello F, d'Adda di Fagagna F, Carninci P. Target-enrichment sequencing for detailed characterization of small RNAs. ***Nat Protoc*** 13, 768 (2018)

Invited presentations

Carninci P. "Functional genomics moving into single-cell analysis" The 42nd Annual Meeting of the Molecular Biology Society of Japan (Fukuoka, Japan) December 2019

Carninci P. "Keynote Address: single-cell transcriptomic profiling and cellular response in cancer and immune disorders" Pfizer's Science Day (Cambridge, USA) October 2019

Carninci P. "Single cell transcriptomics in ageing populations" The Human Cell Atlas (HCA) Asia Meeting 2019 (Singapore, Singapore) November 2019

Carninci P. "From discovery to innovation: non-coding RNA for therapies" XXXI General Assembly Italy-Japan Business Group (IJBG) (Tokyo, Japan) November 2019

Carninci P. "Functional Genomics of lncRNAs" Keystone Symposia Conference, Long Noncoding RNAs: From Molecular Mechanism to Functional Genetics (British Columbia, Canada) February 2019

Laboratory for

Cellular Function Conversion Technology

Team Leader: Harukazu Suzuki

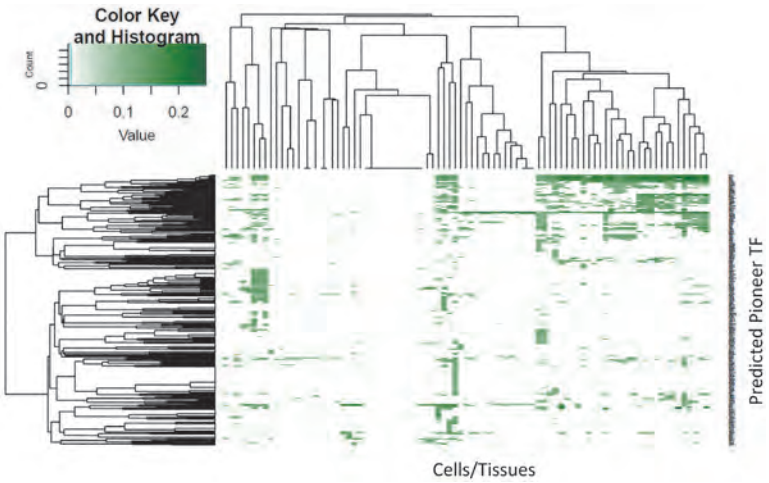


Figure: Prediction of Pioneer TFs
Pioneer TFs were predicted using IHEC methylome data (Centrimo p < 1e-100) and were clustered into a figure (horizontal: cells or tissues, vertical: predicted pioneer TFs). We have succeeded in predicting more than 100 pioneer TFs with DNA demethylation-inducing activity in a cell lineage-specific manner.

DNA methylation is recognized widely as a fundamental epigenetic modification to regulate mammalian gene expression. Recently, a subgroup of transcription factors (TFs), termed pioneer TFs, have been shown to carry out DNA demethylation in a binding site-specific manner. However, only a small number of pioneer TFs with DNA demethylation-inducing activity have been identified to date. We have developed an informatics pipeline to predict pioneer TFs with DNA demethylation inducing activity and applied it to the International Human Epigenome Consortium (IHEC) DNA methylome data set. This allowed us to predict more than 100 pioneer TFs with DNA demethylation-inducing activity in a cell lineage-specific manner, including ones that we previously identified, such as RUNX1 and SPI1/PU.1. We have begun to evaluate the DNA demethylation-inducing activity of the new predicted pioneer TFs using a method that we have recently developed. Further, we have succeeded in creating a RUNX1 mutant without DNA demethylation-inducing activity. This mutation will be knocked-in in iPS cells and its effects on hematopoietic cell development will be explored.

A knowledge tool for TF-mediated DNA demethylation has been applied to understanding disease pathogenesis. Application of our R package to publicly available disease methylome data revealed that several diseases have a DNA methylation abnormality that seems to be linked to TF-mediated DNA demethylation. Further, TET2-deficient mice have been established to explore the role of TF-mediated DNA demethylation in myeloproliferative neoplasms.

In studies of the epithelial-to-mesenchymal transition (EMT) process, we found that EMT-related genes, especially mesenchymal genes, are divergently regulated at a transcriptional level, supporting the divergent EMT phenotypes previously reported in different biological contexts. In drug-induced cell reprogramming studies, we found that the reprogrammed cells derived from human dedifferentiated fat cells not only express neuron-like marker genes and undergo a morphological change, but also develop functional action potentials and responses to several neurotransmitters. We have also been examining spermatogenesis by single-cell RNA-seq analysis of *in vitro* cultured testis, and the results suggest that acute inflammation is a major cause of poor spermatogenesis.

Recent Major Publications

Watanabe K, Panchy N, Noguchi S, Suzuki H, Hong T. Combinatorial perturbation analysis reveals divergent regulations of mesenchymal genes during epithelial-to-mesenchymal transition. ***NPJ Syst Biol Appl*** 5, 21 (2019)

Watanabe K, Liu Y, Noguchi S, Murray M, Chang JC, Kishima M, Nishimura H, Hashimoto K, Minoda A, Suzuki H. OVOL2 induces mesenchymal-to-epithelial transition in fibroblasts and enhances cell-state reprogramming towards epithelial lineages. ***Sci Rep*** 9, 6490 (2019)

Suzuki T. R package for the DNA binding motif enrichment analysis in differentially DNA methylated regions. https://github.com/takahirosuzuki1980/InfiniumDiffMetMotR (2019)

Invited presentations

Harukazu Suzuki *et al*. "Regulation of genomic region-specific DNA methylation states and hope for future psychiatric treatment" JSNP2019 (Fukuoka, Japan) October 2019

Harukazu Suzuki *et al*. "Identification of pioneer transcription factors from DNA methylation profiles" ICGBE Workshop "Epigenetics of infectious and non-communicable diseases" (Cape Town, South Africa) September 2019

Harukazu Suzuki "Regulation of DNA methylation profiles mediated by pioneer transcription factors" Keio University Seminar (Tsuruoka, Japan) July 2019

Laboratory for

Genome Information Analysis

Team Leader: **Chung-Chau Hon**

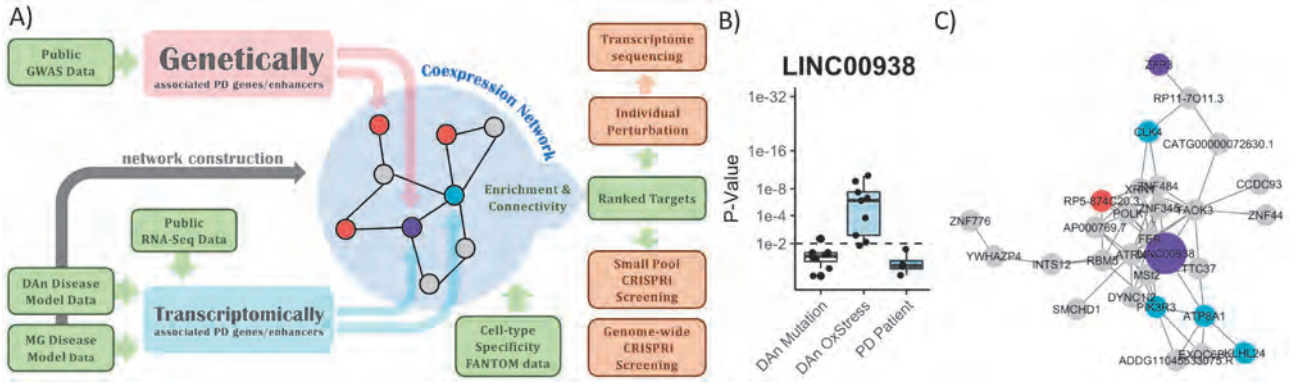


Figure: Prioritization of Genes and Non-Coding Elements relevant to Parkinson's Disease (PD)

A) Overall strategy for prioritization of PD-relevant elements. Transcriptomes of *in vitro* cellular PD models (i.e., dopaminergic neurons and microglia) were profiled and co-expression networks were constructed. Each node within a co-expression module was scored based on the enrichment of genetic (red) and transcriptomic (blue) associations. B) Transcriptomic relevance of an example long non-coding RNA, LINC00938 to PD. *Y*-axis, extent of differential expression (as adjusted *P*-values) in PD disease models (i.e., DAn mutations and DAn oxidative stress) and public PD patient cohorts. C) A meta co-expression network involving LINC00938. An edge corresponds to a co-expression relationship (existing in the same module of at least 3 networks) between nodes. A node could be a coding gene, a long non-coding RNA, or an enhancer. A red, blue or purple node refers to genetic, transcriptomic associations or both, respectively.

Recent Major Publications

Kouno T, Moody J, Kwon AT, Shibayama Y, Kato S, Huang Y, Böttcher M, Motakis E, Mendez M, Severin J, Luginbühl J, Abugessaisa I, Hasegawa A, Takizawa S, Arakawa T, Furuno M, Ramalingam N, West J, Suzuki H, Kasukawa T, Lassmann T, Hon CC, Arner E, Carninci P, Plessy C, Shin JW. C1 CAGE detects transcription start sites and enhancer activity at single-cell resolution. ***Nat Commun*** 10, 360 (2019)

Lizio M, Abugessaisa I, Noguchi S, Kondo A, Hasegawa A, Hon CC, de Hoon M, Severin J, Oki S, Hayashizaki Y, Carninci P, Kasukawa T, Kawaji H. Update of the FANTOM web resource: expansion to provide additional transcriptome atlases. ***Nucleic Acids Res*** 47, D752-D758 (2019)

Hon CC, Shin JW, Carninci P, Stubbington MJT. The Human Cell Atlas: Technical approaches and challenges. ***Brief Funct Genomics.*** 17, 283-294 (2018)

Invited presentations

Hon CC. "Building the Human Cell Atlas For Medicine" The 37th Annual Meeting of JSBMR (Kobe, Japan) October 2019

Hon CC. "Building a better map to navigate through the genetic landscape of diseases" 16th Bone Biology Forum (Chiba, Japan) August 2019

Most common disease-associated genomic variants are located in non-coding regions. Our laboratory focuses on characterizing non-coding genomic elements and their potential roles in complex diseases by the integration of transcriptomic and epigenomic data with genetic data.

Using Parkinson's Disease (PD) as a model, we have established *in vitro* cellular disease models using isogenic mutants (i.e. PARK2 and PINK1 knockouts) iPS cell lines differentiated into dopaminergic neurons (DAn) and microglia (MG) and characterized their transcriptomes and epigenomes. We subjected these *in vitro* disease models to PD-relevant stimulations to mimic neuronal oxidative stress and to mimic activation of neuroinflammation. Transcriptomes of these models were analyzed using CAGE to capture activities of transcribing *cis*-regulatory elements (tCRE). We found that the PD genetic signals are enriched in tCRE active in these models and, in particular, MG-specific and LPS-responding tCRE. To prioritize non-coding elements relevant to PD, we constructed tCRE co-expression networks and examined the enrichment of disease association signals in the networks. The relevance of these prioritized tCREs will be examined in a phenotypic screen using pooled genetic perturbation strategies (Figure).

Our laboratory also exploits the datasets collected from various tissues or primary cells for interpretation of non-coding variants, in particular by using single cell RNA-Seq. We have developed analysis pipelines that to perform genetically multiplexed 5'centric single-cell RNA-Seq in many individuals and to identify the active tCRE at a single cell level. We have applied this method to peripheral blood mononuclear cells from Japanese subjects, in collaboration with Drs. Jay Shin and Yamamoto Kazuhiko, as part of the Asian Immune Diversity Atlas project. We have demonstrated that the cell-type-specific tCRE identified using this method are highly enriched in immunological diseases relevant to a specific immune cell-type. We will further expand these analyses to a larger cohort and perform single cell eQTL analysis.

Laboratory for

Applied Computational Genomics

Team Leader: Michiel de Hoon

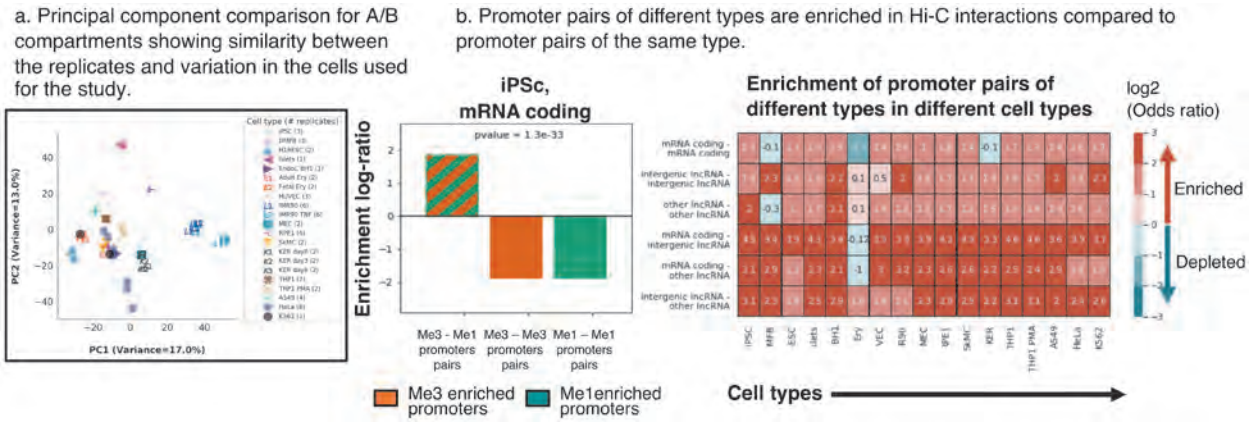


Figure:
Hi-C experiments reveal physical interactions between genomic regions as a framework for the cellular regulatory network involving coding and non-coding RNAs, as well as enhancers. (a) Principal Component Analysis visualizing the broad diversity in cell types included in this study. (b) Bioinformatics analysis of Hi-C data uncovers that interactions between distinct promoter types (classical H3K4me3 promoters and enhancer-like H3K4me1 promoters) as a fundamental principle of regulatory networks, as shown as an example for protein-coding genes in iPS cells in the left panel, and globally as a heatmap across cell types and gene classes in the right panel.

Recent Major Publications

Huang Y, Furuno M, Arakawa T, Takizawa S, De Hoon M, Suzuki H, Arner E. A framework for identification of on- and off-target transcriptional responses to drug treatment. ***Sci Rep*** 9, 17603 (2019)

Guigo, R, De Hoon M. Recent advances in functional genome analysis. ***F1000Res*** 7, F1000 Faculty Rev 1968 (2018)

Sakaue S, Hirata J, Maeda Y, Kawakami E, Nii T, Kishikawa T, Ishigaki K, Terao C, Suzuki K, Akiyama M, Suita N, Masuda T, Ogawa K, Yamamoto K, Saeki Y, Matsushita M, Yoshimura M, Matsuoka H, Ikari K, Taniguchi A, Yamanaka H, Kawaji H, Lassmann T, Itoh M, Yoshitomi H, Ito H, Ohmura K, Forrest ARR, Hayashizaki Y, Carninci P, Kumanogoh A, Kamatani Y, De Hoon M, Yamamoto K, Okada Y. Integration of genetics and miRNA-target gene network identified disease biology implicated in tissue specificity. ***Nucleic Acids Res*** 46, 11898-11909 (2018)

The Laboratory for Applied Computational Genomics uses bioinformatics methods to analyze next-generation sequencing data sets to understand the mammalian transcriptome and its regulation. Our focus is on sequencing data produced as part of the Functional Annotation of the Mammalian Genome (FANTOM) project, organized together with Dr. Piero Carninci (Laboratory for Transcriptome Technology) and Dr. Jay Shin (Laboratory for Advanced Genomics Circuit).

We analyze Hi-C data produced in FANTOM to understand the 3D structure of the mammalian genome in the cell nucleus as a framework for cellular regulation. Hi-C is a technique to identify genomic regions that are physically close to each other in a cell nucleus. Using Hi-C data, we assign functional categories to long non-coding RNAs (lncRNAs) based on their physical association with functionally annotated protein-coding genes.

To understand the structure-function relationships of lncRNAs, we analyze RNA interaction data generated by the RIKEN IMS Laboratory for Transcriptome Technology (led by Dr. Piero Carninci) by cross-linking base-paired RNA in cell lines, followed by deep sequencing. These data allow us to identify secondary structures within each RNA, as well as base-pairing interactions between different RNA molecules.

Using transcriptome data produced in matching primary cell types from multiple vertebrate species, we performed a comparative study to identify the commonalities and differences in the different species. While, surprisingly, many genes were found to be differentially expressed, core parts of the regulatory network involving RNA biology in the cell nucleus tended to be conserved, suggesting that this network plays a key role in establishing cell identity.

This laboratory also maintains and develops ZENBU, a scientific visualization system for genome-wide data. With ZENBU-Reports, we provide a system to create portal websites for sharing supplementary data accompanying scientific publications.

Laboratory for

Large-Scale Biomedical Data Technology

Team Leader: Takeya Kasukawa

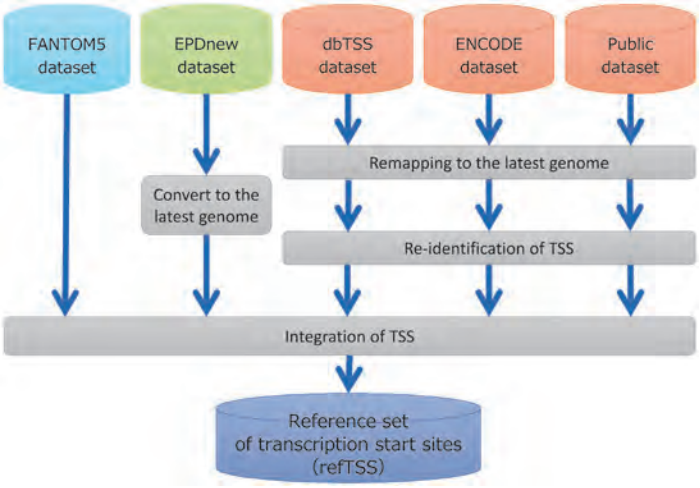


Figure: Flow chart for building a reference set of transcription start sites (refTSS)
The refTSS is built by integrating publicly available 5'-end of transcript datasets and curated TSSs. For some datasets, we remapped and called the TSS peaks or performed "lift-over" of the original coordinates to the latest reference genomes.

Recent Major Publications

Abugessaisa I, Noguchi S, Hasegawa A, Kondo A, Kawaji H, Carninci P, Kasukawa T. refTSS: A reference dataset for human and mouse transcription start sites. ***J Mol Biol*** 431, 2407-2422 (2019)

Kouno T, Moody J, Kwon AT, Shibayama Y, Kato S, Huang Y, Böttcher M, Motakis E, Mendez M, Severin J, Luginbühl J, Abugessaisa I, Hasegawa A, Takizawa S, Arakawa T, Furuno M, Ramalingam N, West J, Suzuki H, Kasukawa T, Lassmann T, Hon CC, Arner E, Carninci P, Plessy C, Shin JW. C1 CAGE detects transcription start sites and enhancer activity at single-cell resolution. ***Nat Commun*** 10, 360 (2019)

Lizio M, Abugessaisa I, Noguchi S, Kondo A, Hasegawa A, Hon C, De Hoon M, Oki S, Hayashizaki Y, Carninci P, Kasukawa T, Kawaji H. Update of the FANTOM web resource: expansion to provide additional transcriptome atlases. ***Nucleic Acids Res*** 47, D752-D758 (2018)

Invited presentations

Abugessaisa I. "Regulation of human aging genes and their association with frailty and clinical phenotypes" Hamad Bin Khalifa University Graduate course (Doha, Qatar) September 2019

Because of rapid improvements in sequencing technologies, many types of transcriptome and epigenome data have been generated and made publicly available. By performing integrative analysis, such datasets are potentially reusable for the elucidation of transcriptional regulatory mechanisms. However, the best way to effectively integrate the genome-wide large-scale transcriptome and epigenome data is still a big issue. To tackle this, we focus on transcription start sites (TSSs) as a reference point to integrate these data. Biological processes of transcriptional regulation, including chromatin state changes, DNA methylation, and transcription factor binding, occur around specific TSSs and control the production of RNA transcripts starting from the TSSs. Therefore, we can associate transcriptional regulation and transcription datasets with TSSs, and we can integrate datasets based on the assigned TSSs.

To implement this strategy, we developed a new reference set of TSSs (refTSS) for human and mouse, since few TSS datasets are available that are adequate for genome-wide integrative analysis. In our development, we consolidated publicly available 5'-end-sequencing results with CAGE and TSS-Seq, and curated TSSs. We then annotated information about gene functions and transcriptional regulation, as well as quality assessments to each TSS. The dataset files and a web interface are publicly available at our web site (http://reftss.clst.riken.jp/).

In addition to the above achievement, we are working on updating our database (scPortalen: http://single-cell.clst.riken.jp/) for reusing public single-cell RNA-seq data for data coordination in the FANTOM6 project, in which we aim to identify functions of lncRNAs (https://fantom.gsc.riken.jp/6/). We are also working on studies targeting several diseases, including the transcriptome analysis of human blood samples from aged patients with frailty phenotype and transcriptome analysis to develop a diagnostic tool for mycetoma, which is an infectious disease on the WHO listing of neglected tropical diseases.

Along with these research projects, we are working to provide and support the information infrastructure for several IMS laboratories. In this fiscal year, we investigated infrastructure and regulations for handling human-derived sequence data in on-premises and cloud environments in a collaboration with the Laboratory for Comprehensive Genomic Analysis.

Laboratory for

Advanced Genomics Circuit

Team Leader: Jay W. Shin

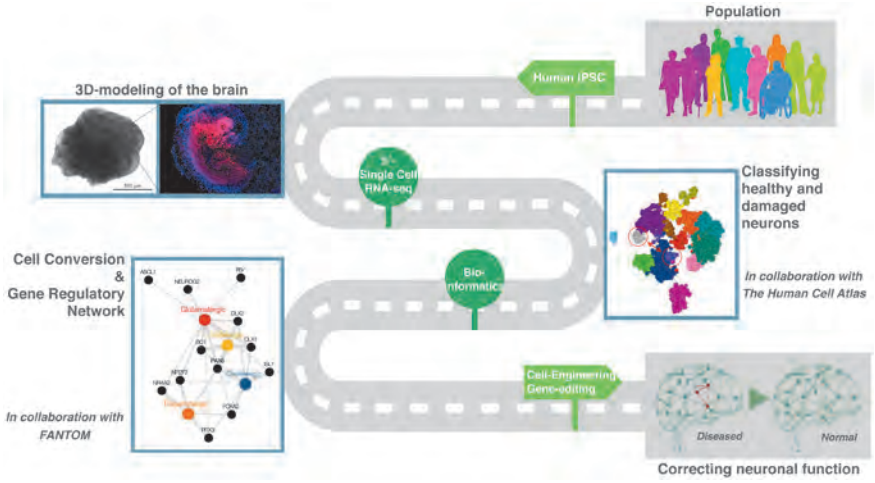


Figure: Unraveling the mystery of human brain development, regeneration, and maturation
Through the implementation of single-cell CAGE and brain organoids, the laboratory aims to characterize the diversity and dynamics of individual cell types, as well as to decode the genetic regulatory networks controlling cellular transitions and specifications.

The human genome is not linear, but rather is a complex entanglement of DNA strands with exquisite coordination of molecules to switch on and off a gene. Understanding how our genome can sense the right cue to activate a cascade of gene expression – especially in a highly dense environment – requires a comprehensive profiling of DNA, RNA, and protein features and their interactions with one another. Unraveling this mystery should shed light on novel ways to manipulate the human genome to correct cellular malfunctions, regenerate cells, and extend the longevity of vital organs.

One of our strategies involves the implementation of single-cell CAGE to profile the coding and non-coding regulatory activities in human cells. We model human brain development through building organoids and investigate *cis*-gene interactions during development at a single cell resolution. The lab also explores gene regulatory elements by analyzing chromatin-chromatin and chromatin-RNA interactions through the FANTOM consortium. We specialize in gene-targeting tools, such as CRISPR-interference, to elucidate the function of *cis*-regulatory interactions involved in human brain development, regeneration, and maturation.

Finally, our lab is spearheading the Human Cell Atlas together with medical and research communities in Japan to build a 'regulatory map' of human cells that will provide a navigation tool to study diseases and to accelerate drug discovery.

Recent Major Publications

Ramilowski J., Yip CW, FANTOM6 Consoritum. De Hoon M., Shin JW, Carninci P. Functional Annotation of Human Long Non-Coding RNAs via Molecular Phenotyping. ***BioRxiv*** [preprint] https://doi.org/10.1101/700864 (2019)

Luginbuehl J, Kouno T, Nakano R, Chater TE, Sivaraman DM, Kishima M, Roudnicky F, Carninci P, Plessy C, Shin JW. Decoding neuronal diversity by single cell convert-seq. ***BioRxiv*** [preprint] https://doi.org/10.1101/600239 (2019)

Kouno T, Moody J, Kwon AT, Shibayama Y, Kato S, Huang Y, Böttcher M, Motakis E, Mendez M, Severin J, Luginbühl J, Abugessaisa I, Hasegawa A, Takizawa S, Arakawa T, Furuno M, Ramalingam N, West J, Suzuki H, Kasukawa T, Lassmann T, Hon CC, Arner E, Carninci P, Plessy C, Shin JW. C1 CAGE detects transcription start sites and enhancer activity at single-cell resolution. ***Nat Commun*** 10, 360 (2019)

Invited presentations

Shin JW. "Single cell genomics to elucidate coding and non-coding regulatory elements in the human body" 3rd Human Cell Atlas Asia Meeting (Biopolis, Singapore) November 2019

Shin JW. "Functional elucidation of long non-coding RNAs based on functional genomics and single cell RNA-seq" Epigenetics of infectious and non-communicable diseases (Cape Town, South Africa) September 2019

Shin JW. 28th "Elucidating non-coding regulatory elements single cell at a time" Korea Genome Organization (KOGO) Conference (Seoul, South Korea) September 2019

Shin JW. "Functional elucidation of lncRNAs" Keystone Symposia Conference | Long Noncoding RNAs: from Molecular Mechanism to Functional Genetics (Whistler, Canada) February 2019

Shin JW. "Decoding neuronal diversity by single cell convert-seq" Cell Symposia. Single Cells: Technology to Biology (Biopolis, Singapore) February 2019

Genetic Diagnosis Technology Unit Nucleic Acid Diagnosis System Developing Unit

Unit Leader: Kengo Usui

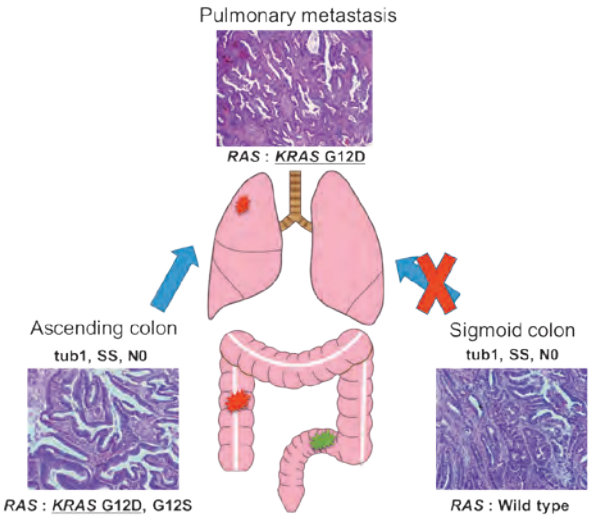


Figure: *RAS* mutation status in double primary cancer and pulmonary metastasis (PM)
This patient had a double primary CRC. One was a primary lesion (ascending colon) with a *RAS* mutation (*KRAS* G12D and G12S) and the other lesion (sigmoid colon) had wild-type *RAS*. The primary lesion with the *RAS* mutation caused the PM, which was homogeneous with a G>A transition mutation (*KRAS* G12D). Ascending colon: Hematoxylin-eosin (HE) staining of the ascending colon cancer with *KRAS* G12D and *KRAS* G12S. Sigmoid colon: HE staining of the sigmoid colon cancer with wild type *KRAS*. PM: HE staining of PM with *KRAS* G12D.

Recent Major Publications

Igarashi T, Shimizu K, Usui K, Yokobori T, Ohtaki Y, Nakazawa S, Obayashi K, Yajima T, Nobusawa S, Ohlawa T, Katoh R, Motegi Y, Ogawa H, Harimoto N, Ichihara T, Mitani Y, Yokoo H, Mogi A and Shirabe K. Significance of *RAS* mutations in pulmonary metastases of patients with colorectal cancer. ***Int J Clin Oncol*** 25, 641-650 (2019)

We have developed an original nucleic acid amplification technology, "SmartAmp", which is an isothermal rapid DNA amplification technology. We focus on infectious disease diagnosis based on SmartAmp, and newly developed or optimized detection kits for influenza virus, Hepatitis B virus (including A-H genotyping primers), sexually transmitted disease (STD)-related bacterium (*Mycoplasma genitalium*, as one of the novel target STD candidates), and mosquito-borne viruses (Dengue, Zika, Chikungunya and yellow fever). Furthermore, to capitalize on the speed of SmartAmp compared to traditional PCR, in this fiscal year we aim to prepare a quantitative RNA kit for detection of a predictive biomarker in uterine cancer. This RNA kit would be used for intraoperative diagnosis (within 30 min) of lymph node metastasis.

Additionally, we also plan to develop other diagnostic tools for cancer-driver mutation detection based on "Eprobe-PCR" technology, which is applicable for highly sensitive detection of low-somatic mutation frequency (<1%). Through the clinical study of cancer-driver somatic mutation detection, we have not only achieved high level detection, but also discovered the following clinically important data: *RAS* mutations in the pulmonary metastasis (PM) of patients with colorectal cancer (CRC) are more common than previously reported. The presence of KRAS mutations in CRC specimens, especially G12D or G13D mutations, seems to promote PM formation (Figure).

Epigenome Technology Exploration Unit

Unit Leader: Aki Minoda

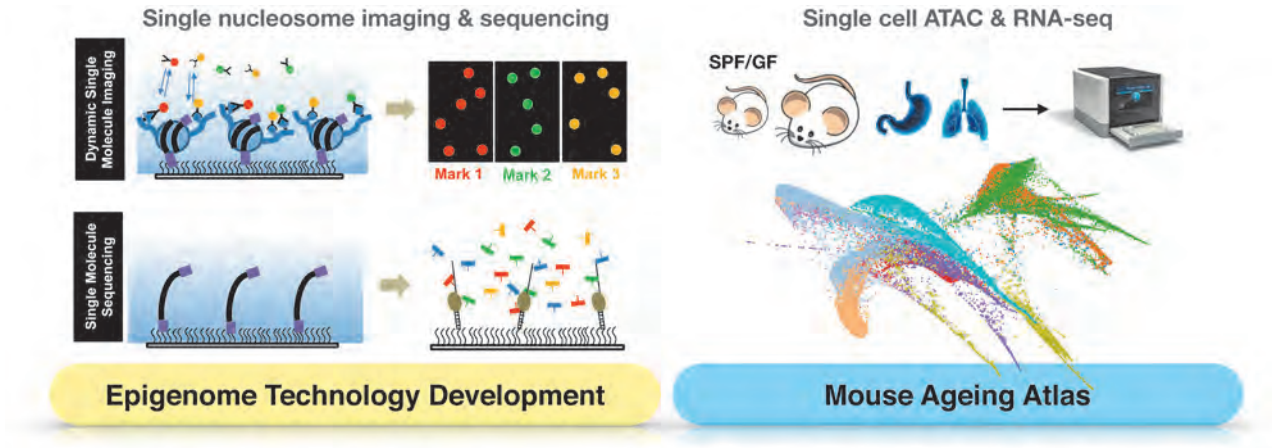


Figure: Summary of research activities
Novel epigenome technology development and application of single cell genomics to construct a Mouse Ageing Atlas.

Recent Major Publications

Watanabe K, Liu Y, Noguchi S, Murray M, Chang JC, Kishima M, Nishimura H, Hashimoto K, Minoda A, Suzuki H. OVOL2 induces mesenchymal-to-epithelial transition in fibroblasts and enhances cell-state reprogramming towards epithelial lineages. ***Sci Rep*** 9, 6490 (2019)

Liu Y, Chang JC, Hon CC, Fukui N, Tanaka N, Zhang Z, Lee MTM*, Minoda.A*. Chromatin accessibility landscape of articular knee cartilage reveals aberrant enhancer regulation in osteoarthritis. ***Sci Rep*** 8, 15499 (2018)

Handoko L, Kaczkowski B, Hon CC, Lizio M, Wakamori M, Matsuda T, Ito T, Jeyamohan P, Sato Y, Sakamoto K, Yokoyama S, Kimura H, Minoda A*, Umehara T*. JQ1 affects BRD2-dependent and independent transcription regulation without disrupting H4-hyperacetylated chromatin states. ***Epigenetics*** 13, 410-431 (2018)

Invited presentations

Minoda A. "Capturing Immunosenescence of the Innate Immune System at the Single Cell Resolution" Human Cell Atlas Asia (Biopolis, Singapore) November 2019

Minoda A. "Capturing Immunosenescence of the Innate Immune System at the Single Cell Resolution" JSI-RIKEN IMS International Symposium on Immunology 2019 (Tokyo, Japan) June 2019

Minoda A. "Strengths of single cell RNA-seq" 68th Japan Allergy Conference (Tokyo, Japan) June 2019

Minoda A "Capturing Immunosenescence of the Innate Immune System at the Single Cell Resolution" EMBO Workshop-Single Cell Biology (Tokyo, Japan) May 2019

Minoda A. "Single cell RNA-seq analysis of meristems" International Symposium: Principles of pluripotent stem cells underlying plant vitality (Sendai, Japan) May 2019

Our lab aims to determine epigenomic and transcriptomic changes in a comprehensive manner in various models by either developing our own technology or applying the most advanced available technologies, such as single cell genomics. Such information will be utilized to gain insights into various biological questions at the molecular level. Our current major focus is aging, which is thought to underlie the pathogenesis of many diseases.

Enabling genomic mapping of multiple histone modifications at single nucleosome resolution

To increase epigenomic resolution, we are developing a method to determine multiple targets (histone modifications) at the single nucleosome level. We first carry out single molecule imaging of fluorophore-labeled antibodies that are specific for different histone markers. Proteins are removed after imaging of the antibodies, so that the genomic DNA that was wrapped around the nucleosomes is left at the same position in the flowcell and can be sequenced (by single molecule sequencing) (Figure). By applying such technology to various models, we believe that we will be able to gain better epigenomic insights into various biological questions.

Construction of a Mouse Ageing Atlas with single cell genomics

We are generating single cell genomics (scATAC-seq and 5' scRNA-seq) datasets of various tissues from both SPF and germ-free mice at various ages, as well as lipidomics (in collaboration with the Arita lab, IMS), metabolomics, and microbiome (in collaboration with the Ohno lab, IMS). Such a rich collection of multi-omics datasets will likely provide us with an unbiased insight at many different levels, including the effect of the microbiome on aging, into the complex biological phenomena of aging.

Understanding the secrets of plant stem cells by applying single cell genomics (RNA- and ATAC-seq) to plant tissues

We are also carrying out scRNA-seq on meristem tissues, which are enriched with stem cells, from various plant models in an attempt to gain insights into the mechanism of plant stem cell maintenance, which is thought to be the foundation for plant longevity and regenerative ability.

Laboratory for

Comprehensive Genomic Analysis

Team Leader: Yasushi Okazaki

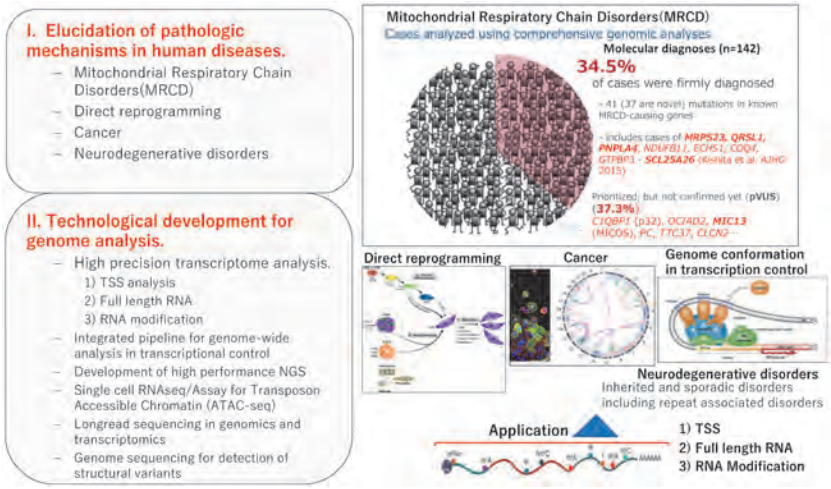


Figure: Future plans

As applicational targets of our technologies, we will conduct omics and functional analyses focusing mainly on mitochondrial and neurological diseases, direct reprogramming, and cancer. In addition, we will continue to be involved in technological development for genomic and transcriptomic analysis. We will be using state-of-the-art technologies such as Nanopore and PacBio long read sequencers, as well as high-quality short read sequencers from Illumina and MGI.
The diagnostic rate of mitochondrial respiratory chain disorders using whole exome sequencing analysis is approximately 35%, while ~37% of cases have variants of uncertain significance. These variants should be evaluated to identify disease causality. Approximately 30% of cases have no candidate genes. We will apply whole genome sequencing, long read sequencing, RNA sequencing, and other omics technologies to these difficult cases.

Recent Major Publications

Borna NN, Kishita Y, Kohda M, Lim SC, Shimura M, Wu Y, Mogushi K, Yatsuka Y, Harashima H, Hisatomi Y, Fushimi T, Ichimoto K, Murayama K, Ohtake A, Okazaki Y. Mitochondrial ribosomal protein PTCD3 mutations cause oxidative phosphorylation defects with Leigh syndrome. ***Neurogenetics*** 20, 9-25 (2019)

Hashimoto K, Kouno T, Ikawa T, Hayatsu N, Miyajima Y, Yabukami H, Terooatea T, Sasaki T, Suzuki T, Valentine M, Pascarella G, Okazaki Y, Suzuki H, Shin Y, Minoda A, Taniuchi I, Okano H, Arai Y, Hirose N, Carninci P. Single-cell transcriptomics reveals expansion of cytotoxic CD4 T cells in supercentenarians. ***Proc Nat Acad Sci*** 116, 24242-24251 (2019)

Ramilowski J, Yip CW, Agrawal S, Chang JC, Ciani Y, Kulakovskiy I, Mendez M, Ooi J, Ouyang J, Parkinson N, Petri A, Roos L, Severin J, Yasuzawa K, Abugessaisa I, Akalin A, Antonov I, Arner E, Bonetti A, Bono H, Borsari B, Brombacher F, Cannistraci C, Cardenas R, Cardon M, Chang H, Ducoli J, Favorov A, Fort A, Garrido D, Gil N, Gimenez J, Guler R, Handoko L, Harshbarger J, Hasegawa A, Hasegawa Y, Hashimoto K, Hayatsu N, Heutink P, Hirose T, Imada E, Itoh M, Kaczkowski B, Kanhere A, Kawabata E, Kawaji H, Kawashima T, Kelly T, Kojima, *et al*. Functional Annotation of Human Long Non-Coding RNAs via Molecular Phenotyping. ***bioRxiv*** 700864 (2019)

Invited presentations

Yasushi Okazaki "Delivering Genomic Medicine in Japan" 11th Annual NGS & Clinical Diagnostics Congress (London England) November 2019

Ken Yagi and Kokoro Ozaki. "Power of DNBSEQ technology: Time is coming to update previous genome analysis technology" The 14th International Conference on Genomics (Shenzhen, China) October 2019

Yasushi Okazaki "Comprehensive Genomic Analysis of Japanese patients with mitochondrial disorders" The 16th Conference of Asian Society for Mitochondrial Research and Medicine [ASMRM] (Fukuoka, Japan) October 2019

From FY2016 to FY2017, we provided research support for RIKEN researchers and researchers outside of RIKEN, such as cross-disciplinary projects within RIKEN and national projects, as a Genome Network Analysis Support facility (GeNAS). Beginning in FY 2018, the Laboratory for Comprehensive Genomic Analysis (CGA) was formed. CGA not only took over some of the tasks of research and development from GeNAS, but also began to develop its own distinct research activities. For this purpose, in FY2019, we strived to enhance our own research activities, as well as collaborative and base-forming activities for other laboratories.

The CGA laboratory conducts omics analyses to elucidate the pathophysiology of human diseases, especially in the field of functional genomics, in order to understand the mechanisms of diseases that disrupt the homeostatic function of various cells and tissues and to discover new drug targets. Specifically, we are focusing our research activities on identifying and characterizing novel causative genes for human hereditary disorders and to discover new potential drug targets for realization of personalized medicine. As our primary targets, we are now working on genome and transcriptome analyses of mitochondrial and neurological diseases. In addition to managing our own research projects, we continue to contribute to research projects led by other teams and outside laboratories in Japan. For example, we provide our special genome and transcriptome analysis technologies, such as Cap Analysis of Gene Expression (CAGE) and bulk, as well as single-cell RNAseq utilizing next generation sequencers. Some of the essential technologies have been developed by us, and we will continuously pursue our goal to create and improve such technologies. In addition, we have introduced long-read sequencers from Oxford Nanopore Technologies, which can read up to hundreds of kilobases per DNA molecule. We not only utilize this technology, but also develop our own technology related to the long read sequencers. We are working with several dozen collaborators utilizing these technologies. For example, we are now analyzing taste receptor cells with single cell technologies. Another example is targeted sequencing of disease-related genomic regions using long read sequencers. Finally, we also are clarifying molecular mechanisms underlying direct reprogramming of fibroblasts into another distinctively differentiated cell type.

Laboratory for

Applied Regulatory Genomics Network Analysis

Team Leader: **Erik Arner**

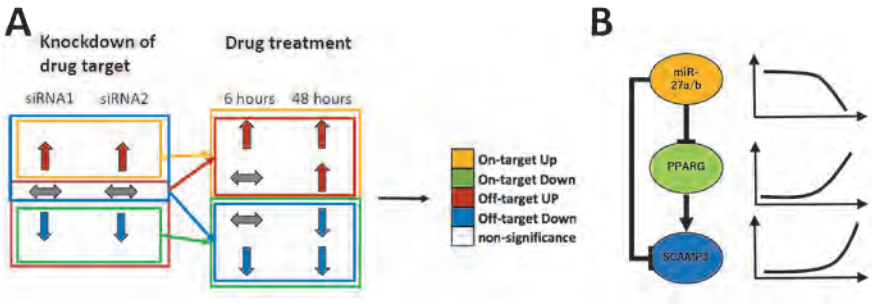


Figure: Recent publications from the lab
(A) Framework for the detection of on- and off-target effects of drug treatment. On-target effects are defined as the transcriptional events that result from inhibiting the main target of the drug under study using siRNAs, while off-target effects are defined as events after drug treatment that differ significantly from the on-target effects.
(B) Identification and validation of a feed-forward loop through which miR-27a/b-3p, PPARG and SCAMP3 cooperatively fine tune the regulation of adipogenesis, with a potential impact on whole body metabolism.

Recent Major Publications

Huang Y, Furuno M, Arakawa T, Takizawa S, de Hoon M, Suzuki H, Arner E. A framework for identification of on- and off-target transcriptional responses to drug treatment. ***Sci Rep*** 9, 17603 (2019)

Kulyté A, Kwok KHM, de Hoon M, Carninci P, Hayashizaki Y, Arner P, Arner E. MicroRNA-27a/b-3p and PPARG regulate SCAMP3 through a feed-forward loop during adipogenesis. ***Sci Rep*** 9, 13891 (2019)

Castillejo-Lopez C, Pjanic M, Pirona AC, Hetty S, Wabitsch M, Wadelius C, Quertermous T, Arner E, Ingelsson E. Detailed Functional Characterization of a Waist-Hip Ratio Locus in 7p15.2 Defines an Enhancer Controlling Adipocyte Differentiation. ***iScience*** 20, 42-59 (2019)

Invited presentations

Arner E. "High-resolution characterization of drug-induced cellular response". Eisai meeting, Data Science Laboratory, hhc Data Creation Center, Eisai Co., Ltd., (Tsukuba, Japan) April 2019

Arner E. "Modeling of the transcriptional response to multidrug treatment for prediction of positive and negative effects of combinatorial drug therapy". The 2nd PSTC Japan Safety Biomarker Conference (Yokohama, Japan) April 2019

Based on genome-wide technologies developed at the Center, with emphasis on recent technological advances such as single cell transcriptome analysis, enhancer expression analysis, and RNA-chromatin interaction profiling, we analyze gene regulation with a focus on clinical and medical applications. This effort includes exploration of the transcriptional effects of regulatory molecules at the cellular level and profiling of clinical samples in order to identify regulatory networks perturbed in disease states. In a recently completed project, we developed a framework for the identification of transcriptional on- and off-target effects of drug treatment by comparing the treatment effects with knock-down of the main drug target. In other work performed together with collaborators at The Karolinska Institute, we identified putative miRNA–TF–target feed forward loops during differentiation and went on to validate one of them in adipogenesis. In another study, we collaborated with investigators at Uppsala University and Stanford University to identify and characterize an enhancer controlling adipocyte differentiation with clinical implications. Ongoing projects include single cell transcriptome analysis of cancer cells after treatment with pharmaceuticals that act at the epigenomic level; developing machine learning and data mining methods for identifying small molecules that, either alone or in combination, can facilitate cell conversion; profiling of enhancer/promoter activity and RNA-chromatin interactions in primary acute myeloid leukemia cells; and establishing platform cell lines useful for the development of novel antibody-drug conjugates.

Preventive Medicine and Applied Genomics Unit

Unit Leader: Hideya Kawaji

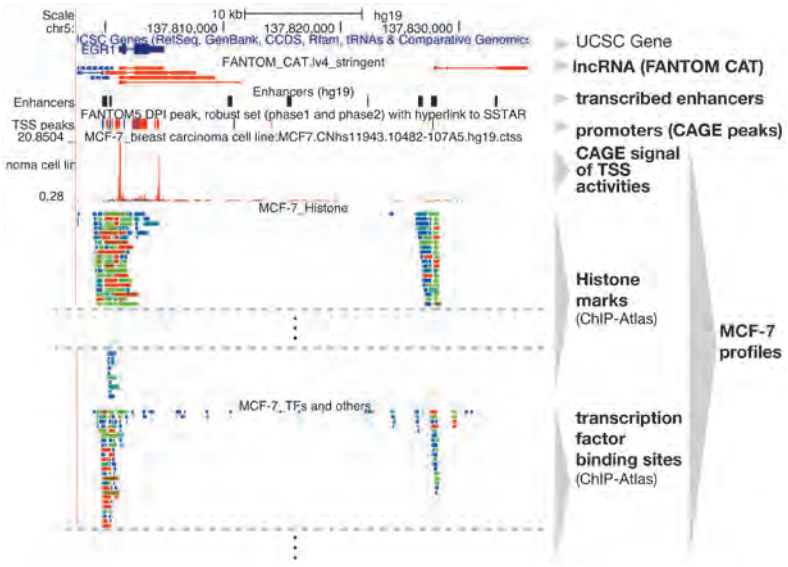


Figure: Integrated view of transcriptome and epigenetic marks provided by the FANTOM5 web resource

Genomic view of the EGR-1 locus with the UCSC Genome browser database, which includes data provided by FANTOM5 and ChIP-Atlas (The figure is from *Nucleic Acids Res*. D752-758, 2019).

Recent Major Publications

Hirabayashi S, Bhagat S, Matsuki Y, Takegami Y, Uehata T, Kanemaru A, Itoh M, Shirakawa K, Takaori-Kondo A, Takeuchi O, Carninci P, Katayama S, Hayashizaki Y, Kere J, Kawaji H, Murakawa Y. NET-CAGE characterizes the dynamics and topology of human transcribed cis-regulatory elements. ***Nat Genet*** 51, 1369-1379 (2019)

Ohashi F, Miyagawa S, Yasuda S, Miura T, Kuroda T, Itoh M, Kawaji H, Ito E, Yoshida S, Saito A, Sameshima T, Kawai J, Sawa Y, Sato Y. CXCL4/PF4 is a predictive biomarker of cardiac differentiation potential of human induced pluripotent stem cells. ***Sci Rep*** 9, 4638 (2019)

Lizio M, Abugessaisa I, Noguchi S, Kondo A, Hasegawa A, Hon CC, de Hoon M, Severin J, Oki S, Hayashizaki Y, Carninci P, Kasukawa T, Kawaji H. Update of the FANTOM web resource: expansion to provide additional transcriptome atlases. ***Nucleic Acids Res*** 47, D752-D758 (2019)

Invited presentations

Kawaji H, "Development of primate genome and RNA database for oligonucleotide therapeutics" the 5th annual meeting of the nucleic acids therapeutics society of Japan (Osaka, Japan) July 2019

Remarkable progress has recently been made in molecular profiling technologies, including genome-wide technologies developed at RIKEN, and their effective use is one of the major interests in life sciences research, in particular to solve medical problems. The RIKEN Preventive Medicine and Diagnosis Innovation Program (RIKEN PMI) is coordinating translational research projects that utilize RIKEN technologies to solve clinical problems, and our unit was established in RIKEN IMS with funding from RIKEN PMI. Hence, our mission is to conduct translational research projects coordinated by RIKEN PMI, in particular from the perspective of information sciences or computational genomics. We currently have more than 50 ongoing projects that can be roughly classified into three categories: identification of cell markers required for regenerative medicine, exploration of diagnostic markers useful in patient treatment, and our own developments to assist in translational, as well as basic science research.

Our collaborative research with RIKEN PMI and the National Institute of Health Sciences (NIHS) led to the identification of biomarkers indicative of the cardiac differentiation efficiency of iPSCs, which can be used in generation of cardiomyocytes as regenerative medicine (Ohashi F et al. *Scientific Reports*, 2019). We also contributed to the field of oligonucleotide therapeutics in an assessment of off-target effects of gapmer antisense oligos (Yoshida et al. *Genes to Cells*, 2019). In collaborations within RIKEN IMS, we integrated epigenetic data into the FANTOM5 resource, the largest database of *cis*-regulatory regions based on transcriptome profiles, to assist translational researchers, as well as basic scientists focusing on *cis*-regulatory regions (Lizio et al. *Nucleic Acids Res*. 2019; Figure). We further succeeded in discovering a substantial number of novel enhancers by development of a method called NET-CAGE, which can capture RNAs, even those subject to rapid degradation, such as enhancer RNAs (Hirabayashi et al. *Nature Genet*. 2019).

RIKEN-IFOM Joint Laboratory for Cancer Genomics

Team Leader: Yasuhiro Murakawa

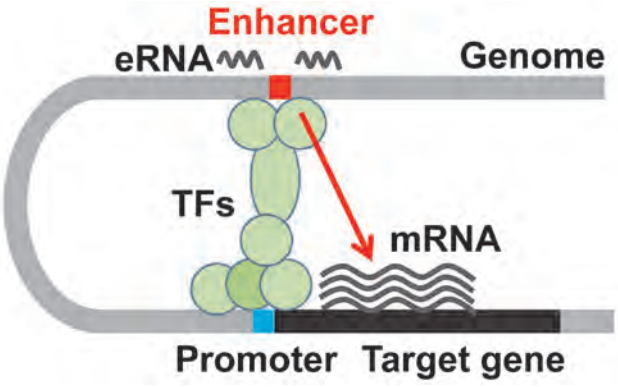


Figure: Enhancer-mediated gene regulation
Enhancers are small segments of distal *cis*-regulatory DNA elements that significantly enhance the expression of target genes and play key roles in the establishment of cell type-specific function and identity.

The body-wide transcriptome is generated by the spatiotemporal orchestration of *cis*-regulatory elements such as promoters and enhancers. In particular, enhancers are distal *cis*-regulatory DNA elements that are crucial for the establishment of cell type-specific function and identity (Figure). We aim to decipher the *cis*-regulatory code that governs the transcriptional landscapes of malignancies, thereby gaining fundamental insight into cancer development and maintenance.

To investigate the *cis*-regulatory code, we have developed a simple and robust technology, NET-CAGE, to determine globally the 5'-ends of nascent RNAs, thereby sensitively detecting unstable transcripts including enhancer-derived RNAs. NET-CAGE has enabled ultra-sensitive detection of a number of enhancers at single nucleotide resolution.

We are applying our original NET-CAGE technology to describe the active *cis*-regulatory landscape across hundreds of diverse tumors, discovering differentially regulated enhancers, genes, and long non-coding RNAs. Furthermore, using our unique atlas of active enhancer regions at single nucleotide resolution, we further aim to develop a series of original technologies to investigate connectivity and functionality of *cis*-regulatory elements at both population and single-cell levels. We believe in the importance of developing novel technologies that can solve paradigms that cannot be otherwise solved.

Lastly, through integrated analysis of (epi) genomic data with clinical information, we explore molecular therapeutic targets and biomarkers.

Recent Major Publications

Hirabayashi S, Bhagat S., Matsuki Y, Takegami Y, Uehata T, Kanemaru A, Itoh M, Shirakawa K, Takaori-Kondo A, Takeuchi O, Carninci P, Katayama S, Hayashizaki Y, Kere J, *Kawaji H, *Murakawa Y. NET-CAGE Characterizes Dynamics and Topology of Human Transcribed *cis*-regulatory Elements. ***Nat Genet*** 51, 1369-1379 (2019)

Hia F, Fan Yang S, Shichino Y, Yoshinaga M, Murakawa Y, Vandenbon A, Fukao A, Fujiwara T, Landthaler M, Natsume T, Adachi S, Iwasaki S, *Takeuchi O. Codon Optimality Confers GC-Rich-Induced Stability to mRNAs in Humans. ***EMBO Rep*** e48220 (2019)

Miyazato P, Matsuo M, Tan BJY, Tokunaga M, Katsuya H, Islam S, Ito J, Murakawa Y, *Satou Y. HTLV-1 contains a high CG dinucleotide content and is susceptible to the host antiviral protein ZAP. ***Retrovirology*** 16, 38 (2019)

Invited presentations

Murakawa Y. "Novel NET-CAGE Technology Reveals the Dynamics and Topology of Human *Cis*-regulatory Elements" Asia Pacific Conference on Human Genetics 2019 (Manila, Philippines) November 2019

Murakawa Y. "Dynamics and topology of human *cis*-regulatory elements" Biomedicum Helsinki seminar (Helsinki, Finland) October 2019

Laboratory for

Genotyping Development

Team Leader: Yukihide Momozawa

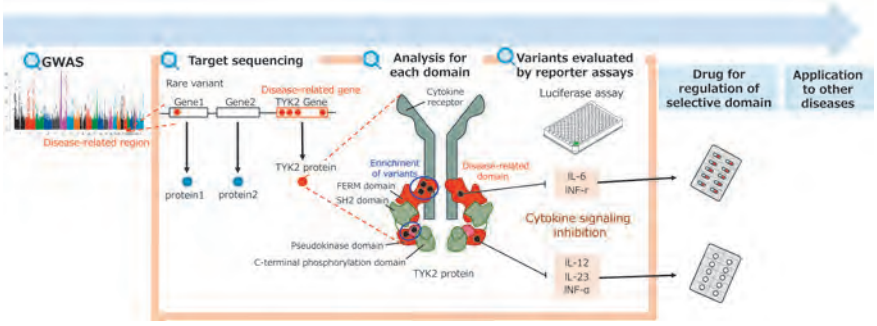


Figure: Targeted sequencing of candidate genes by a genome wide association study identified a potential new target in TYK2 for rheumatoid arthritis

A genome wide association study (GWAS) and subsequent *in silico* analyses previously proposed 98 potential candidate genes for rheumatoid arthritis. In this study, the gene coding regions were sequenced in 2,294 patients and 4,461 controls and we found that rare variants are protective in rheumatoid arthritis. A follow-up functional analysis suggests that rare variants in two different domains work differently. Thus, the selective regulation of cytokine signaling could be a new target for rheumatoid arthritis treatment.

Recent Major Publications

Momozawa Y, Iwasaki Y, Hirata M, Liu X, Kamatani Y, Takahashi A, Sugano K, Yoshida T, Murakami Y, Matsuda K, Nakagawa H, Spurdle AB, Kubo M. Germline pathogenic variants in 7,636 Japanese patients with prostate cancer and 12,366 controls. ***J Natl Cancer Inst*** 112, 369-376 (2020)

Motegi T, Kochi Y, Matsuda K, Kubo M, Yamamoto K, Momozawa Y. Identification of rare coding variants in TYK2 protective for rheumatoid arthritis in the Japanese population and their effects on cytokine signaling. ***Ann Rheum Dis*** 78, 1062-1069 (2019)

Hirata J, Hosomichi K, Sakaue S, Kanai M, Nakaoka H, Ishigaki K, Suzuki K, Akiyama M, Kishikawa T, Ogawa K, Masuda T, Yamamoto K, Hirata M, Matsuda K, Momozawa Y, Inoue I, Kubo M, Kamatani Y, Okada Y. Genetic and phenotypic landscape of the major histocompatibility complex region in the Japanese population. ***Nat Genet*** 51, 470-480 (2019)

Invited presentations

Momozawa Y. "Contribution of dogs as animal model for human diseases". The 64th Annual Meeting of the Japan Society of Human Genetics (Nagasaki, Japan) November 2019

Momozawa Y. "A large-scale genetic analysis for the determination of strategies for cancer prevention" The 78th annual meeting of the Japanese Cancer Association (Kyoto, Japan) September 2019

Momozawa Y. "BioBank Japan and its genetic analysis for personalized medicine" Joint Japan-Lithuania workshop (Vilnius, Lithuania) September 2019

Momozawa Y. "What a large-scale genetic analysis of hereditary cancers have revealed." (Tokyo, Japan) July 2019

Momozawa Y. "Translational science from veterinary medicine to human medicine" Translational and Regulatory Sciences Symposium (Tokyo, Japan) February 2019

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 various laboratories in IMS, and 2) to develop methods and databases useful for personalized medicine. Our laboratory has functioned as a research hub for large-scale genomic analyses, collaborating with domestic and international universities, research institutes, and companies.

Our laboratory published 37 papers in 2019. The main achievements in this year are:

- We sequenced hereditary prostate cancer genes in 7,636 Japanese patients and 12,366 controls using our original target sequencing method to contribute to personalized medicine of prostate cancer with a genetic test. We found that BRCA2 ($P = 1.26 \times 10^{-16}$, OR = 5.65), HOXB13 ($P = 4.57 \times 10^{-11}$, OR = 4.73), and ATM ($P = 1.08 \times 10^{-4}$, OR = 2.86) were significantly associated with prostate cancer risk. Some recurrent pathogenic variants such as p.Gly132Glu of HOXB13 are Japanese-specific. This largest sequencing study provides additional evidence supporting the latest consensus among clinicians (Momozawa Y et. al., *J Nat Cancer Inst*, 112(4): 369-376 (2020)).
- We performed targeted sequencing of 98 positional candidate genes identified by genome wide association studies of rheumatoid arthritis in 2,294 patients and 4,461 controls. Our results suggest that rare variants in TYK2 are protective in rheumatoid arthritis. A follow-up functional study indicates that R231W in the FERM domain especially reduced interleukin (IL)-6 and interferon (IFN)-γ signaling, whereas P1104A in the kinase domain reduced IL-12, IL-23, and IFN-α signaling. These results suggest that the regulation of selective cytokine signaling will be an effective target for rheumatoid arthritis treatment (Motegi T. et. al., *Ann Rheum Dis*, 78 (8), 1062-1069, 2019).

We will continue to work as a research hub for large-scale genomic analyses to contribute to the implementation of personalized medicine.

Laboratory for

Statistical and Translational Genetics

Team Leader: Chikashi Terao

Recent Major Publications

Thompson DJ, Genovese G, Halvardson J, Ulirsch JC, Wright DJ, Terao C, Davidsson OB, Day FR, Sulem P, Jiang Y, Danielsson M, Davies H, Dennis J, Dunlop MG, Easton DF, Fisher VA, Zink F, Houlston RS, Ingelsson M, Kar S, Kerrison ND, Kinnersley B, Kristjansson RP, Law PJ, Li R, Loveday C, Mattisson J, McCarroll SA, Murakami Y, Murray A, Olszewski P, Rychlicka-Buniowska E, Scott RA, Thorsteinsdottir U, Tomlinson I, Moghadam BT, Turnbull C, Wareham NJ, Gudbjartsson DF; International Lung Cancer Consortium (INTEGRAL-ILCCO); Breast Cancer Association Consortium; Consortium of Investigators of Modifiers of BRCA1/2; Endometrial Cancer Association Consortium; Ovarian Cancer Association Consortium; Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL) Consortium; Kidney Cancer GWAS Meta-Analysis Project; eQTLGen Consortium; Biobank-based Integrative Omics Study (BIOS) Consortium; 23andMe Research Team, Kamatani Y, et al. Genetic predisposition to mosaic Y chromosome loss in blood. ***Nature*** 575, 652-657 (2019)

Terao C*, Momozawa Y, Ishigaki K, Kawakami E, Akiyama M, Loh PR, Genovese G, Sugishita H, Ohta T, Hirata M, Perry JRB, Matsuda K, Murakami Y, Kubo M, Kamatani Y. GWAS of mosaic loss of chromosome Y highlights genetic effects on blood cell differentiation. ***Nat Commun*** 10, 4719 (2019)

Ishikawa Y, Ikari K, Hashimoto M, Ohmura K, Tanaka M, Ito H, Taniguchi A, Yamanaka H, Mimori T, Terao C*. Shared epitope defines distinct associations of cigarette smoking with levels of anticitrullinated protein antibody and rheumatoid factor. ***Ann Rheum Dis*** 78, 1480-1487 (2019)

Invited presentations

Terao C. "Updates of genetic studies in rheumatoid arthritis" Educational lecture, Japanese College of Rheumatology (JCR) symposium (Kyoto, Japan) April 2019

Terao C. "Clarification of pathophysiology in Takayasu arteritis through genetic and epidemiological analyses" The 40th Annual Meeting of the Japanese Society of Inflammation and Regeneration (Kobe, Japan) July 2019

Terao C. "Elucidation of Biological Mechanisms in Rare Autoimmune Diseases Through Genetic Approach" The 8th East Asian Group Of Rheumatology 2019 EAGOR (Seoul, Korea) September 2019

Terao C. "Somatic and germ line CNV in the Biobank Japan subjects" SPHN (The Swiss Personalized Health Network) meeting (Tokyo, Japan) September 2019

Terao C. "Development of a new treatment option to Takayasu arteritis based on genetic and epidemiological findings" IRA (Indian Rheumatology Association) Fellows Retreat 2019 (Vellore, India) October 2019

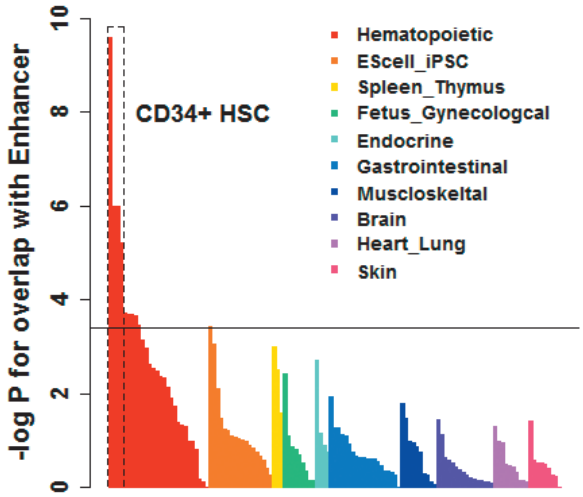


Figure: Significant variants in mosaic loss of chromosome Y showing enriched overlap with enhancer marks in CD34⁺ hematopoietic stem cells

We focus on the identification of genetic susceptibility variants associated with complex traits and on understanding their biological roles by using integrative analyses of epigenome and transcriptome data. We will then deliver these genetic findings to patients as part of our ongoing translational research efforts.

Dozens of genome-wide association studies in our lab have identified thousands of susceptibility loci for multiple complex traits. Most of these accomplishments were viewed in the field as the largest ever human genetic analyses for non-Europeans (available at http://jenger.riken.jp/en/). Our analyses have clarified the similarity and differences between populations with regard to genetics of the traits. We performed downstream analyses to understand the biological background of traits and found that trait-relevant cell-types can be linked by applying integrative analysis of genetic and epigenetic data. In 2019, we successfully identified somatic chromosomal alterations in chromosome Y (mosaic loss of chromosome Y, mLOY) from DNA microarray data that had previously been used only to determine germline variants. We identified 31 novel susceptibility loci that affect the occurrence of mLOY and found that gene expression by hematopoietic stem cells and precursor cells is critical for this somatic alteration. We also collaborated with a UK research group and identified more than 100 new loci to mLOY. The genetic association signals were shared between mLOY and cancer development.

We then moved into two new major research fields. One is to use whole genome sequencing analysis to detect rare variants, which represent strong candidates to explain population differences in the genetics of the traits and to enable the future Genomic Medicine for East Asians. The second is to employ deep learning techniques to predict the biological consequences of trait-relevant variants. Genetic evidence, in conjunction with epigenome, transcriptome, and other cellular multi-omics data, may lead to the discovery of novel biological principles. This project will proceed more efficiently as a result of collaborations with other IMS laboratories.

Laboratory for Pharmacogenomics

Team Leader: Taisei Mushiroda

Recent Major Publications

Tamura K, Imamura CK, Takano T, Saji S, Yamanaka T, Yonemori K, Takahashi M, Tsurutani J, Nishimura R, Sato K, Kitani A, Ueno NT, Mushiroda T, Kubo M, Fujiwara Y, Tanigawara Y. CYP2D6 Genotype-Guided Tamoxifen Dosing in Hormone Receptor-Positive Metastatic Breast Cancer (TARGET-1): A Randomized, Open-Label, Phase II Study. ***J Clin Oncol*** 38, 558-566 (2020)

Hikino K, Ozeki T, Koido M, Terao C, Kamatani Y, Mizukawa Y, Shiohara T, Tohyama M, Azukizawa H, Aihara M, Nihara H, Morita E, Murakami Y, Kubo M, Mushiroda T. HLA-B*51:01 and CYP2C9*3 Are Risk Factors for Phenytoin-Induced Eruption in the Japanese Population: Analysis of Data From the Biobank Japan Project. ***Clin Pharmacol Ther*** 107, 1170-1178 (2020)

Suvichapanich S, Wattanapokayakit S, Mushiroda T, Yanai H, Chuchottawon C, Kantima T, Nedsuwan S, Suwankesawong W, Sonsupap C, Pannarunothai R, Tumpattanakul S, Bamrungram W, Chaiwong A, Mahasirimongkol S, Mameechai S, Panthong W, Klungtes N, Munsoo A, Chauychana U, Maneerat M, Fukunaga K, Omae Y, Tokunaga K. Genome-wide Association Study Confirming the Association of NAT2 with Susceptibility to Antituberculosis Drug-Induced Liver Injury in Thai Patients. ***Antimicrob Agents Chemother*** 63, pii: e02692-18 (2019)

Invited presentations

Hikino K. "Current Status of the Board of Clinical Pharmacology for Physicians Overseas" The 40th Annual Scientific Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics (Tokyo, Japan) December 2019

Fukunaga K. "Development of targeted sequencing panel (PKseq) for pharmacogenomics research and possibility of clinical application" Informatics in Biology, Medicine and Pharmacology (IIBMP) 2019 (Tokyo, Japan) September 2019

Mushiroda T. "Clinical implementation of pharmacogenomic biomarkers for avoidance of severe adverse drug reactions" The 7th China-Japan Joint Meeting of Basic and Clinical Pharmacology (Kunming, China) August 2019

Mushiroda T. "Targeted NGS panel, PKseq as an effective tool to identify pharmacogenomic biomarkers" Genomic Medicine 2019 (Hanoi, Vietnam) June 2019

Ozeki T. "HLA-DQB1*03:01 as a biomarker for genetic susceptibility to bullous pemphigoid induced by DPP-4 Inhibitors" The 4th International Stevens-Johnson Syndrome Symposium (Kyoto, Japan) January 2019

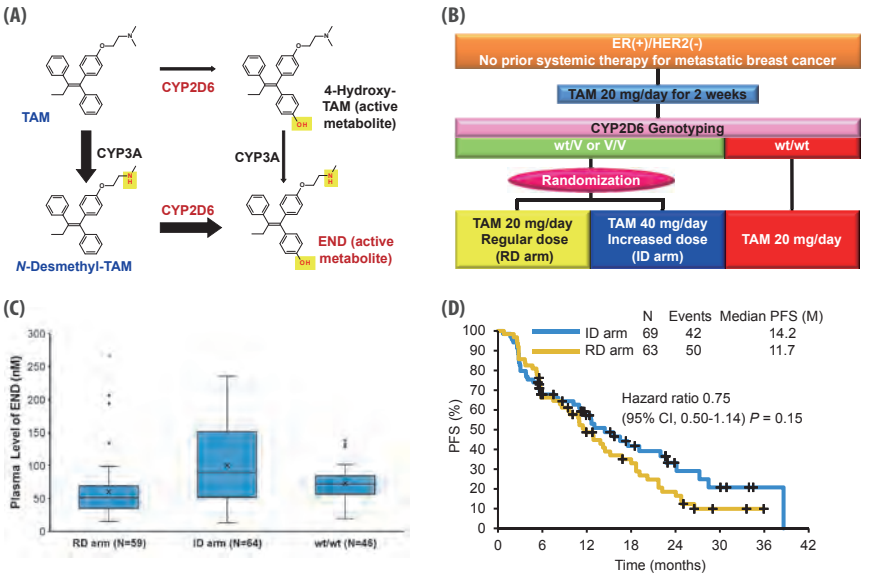


Figure: Genotype-guided tamoxifen dosing in Japanese patients with hormone receptor-positive metastatic breast cancer

(A) TAM metabolic pathways in humans. (B) Design of the TARGET-1 study. (C) Comparison of plasma trough levels of END between wt/V and V/V patients administrated the regular dosage (RD, 20 mg/day) and increased dosage (ID, 40 mg/day) of TAM. The wt/wt patients were administrated TAM at a dosage of 20 mg/day. (D) Kaplan-Meier PFS curves of CYP2D6 wt/V and V/V patients with hormone receptor-positive metastatic breast cancer administrated RD and ID dosages of TAM.

Individual responses to drugs vary widely. Lack of drug efficacy can lead to inadequate disease control and is a waste of resources. Conversely, adverse drug reactions (ADRs) are frequent and often unpredictable. Many germline polymorphisms, which are called pharmacogenomics (PGx) biomarkers, have been identified in genes that affect the efficacy or ADR risk for various drugs. In Japan, the National Health Insurance System currently covers only three germline genetic tests, UGT1A1, NUDT15 and BRCA1/2, to predict drug responses prior to drug administration. We conduct genomic analyses for the identification of PGx biomarkers useful for predicting drug responses.

In order to archive the clinical implementation of probable valid PGx biomarkers that will be useful for genotype-guided drug therapy, we have to perform a prospective clinical trial to demonstrate the clinical utility of genetic testing. To date, we have conducted four such trials for PGx biomarkers. In the TARGET-1 study, a randomized phase II trial was designed to evaluate the effects of increasing tamoxifen (TAM) dosage in patients heterozygous (wt/V) or homozygous (V/V) for CYP2D6 variant alleles on outcomes in hormone-receptor-positive metastatic breast cancer. The trough levels of the key active metabolite endoxifen (END) in the increased dosage (ID) arm were significantly higher than those in the regular dosage RD arm (median: 89.2 nM versus 51.1 nM; $P < 0.0001$), indicating that, in patients carrying the CYP2D6 variant alleles, increasing TAM dosage resulted in higher END levels in plasma. There was no difference in progression free survival (PFS) at 6 months, but there was a trend for longer PFS with TAM at 40 mg/day compared to 20 mg/day, suggesting that the CYP2D6 genotype solely cannot explain individual variability in the efficacy of TAM.

Laboratory for

Bone and Joint Diseases

Team Leader: Shiro Ikegawa

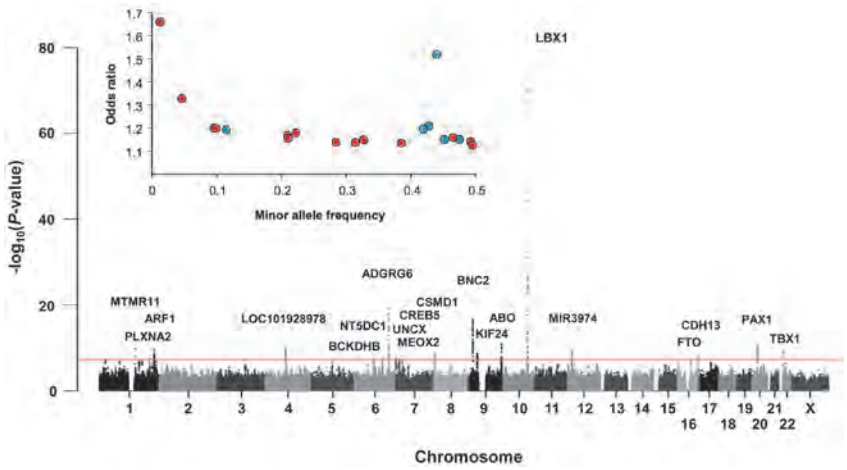


Figure: Manhattan plot for the AIS GWAS
The horizontal red line indicates the genome-wide significance threshold ($P = 5 \times 10^{-8}$). Genetic loci with genome-wide significance are labeled. Inset: Significantly associated SNPs in previous (Nat Genet 2014) and present (Nat Common 2019) studies are in blue and red dots, respectively.

Recent Major Publications

Kou I, Otomo N, Takeda K, Momozawa Y, Lu HF, Kubo M, Kamatani Y, Ogura Y, Takahashi Y, Nakajima M, Minami S, Uno K, Kawakami N, Ito M, Yonezawa I, Watanabe K, Kaito T, Yanagida H, Taneichi H, Harimaya K, Taniguchi Y, Shigematsu H, Iida T, Demura S, Sugawara R, Fujita N, Yagi M, Okada E, Hosogane N, Kono K, Nakamura M, Chiba K, Kotani T, Sakuma T, Akazawa T, Suzuki T, Nishida K, Kakutani K, Tsuji T, Sudo H, Iwata A, Sato T, Inami S, Matsumoto M, Terao C, Watanabe K, Ikegawa S. Genome-wide association study identifies 14 previously unreported susceptibility loci for adolescent idiopathic scoliosis in Japanese. ***Nat Commun*** 10, 3685 (2019)

Matsuda M, Yamanaka Y, Uemura M, Osawa M, Megumu K. Saito MK, Nagahashi A, Nishio M, Guo L, Ikegawa S, Sakurai S, Kihara S, Maurissen TL, Nakamura M, Matsumoto T, Yoshitomi H, Ikeya M, KawakamiN, Yamamoto T, Woltjen K, Ebisuya M, Toguchida J, Alev C. Recapitulating the human segmentation clock with pluripotent stem cells. ***Nature*** 580, 124-129 (2020)

Guo L, Bertola DR, Takanohashi A, Saito A, Segawa Y, Yokota T, Ishibashi S, Nishida Y, Yamamoto GL, Franco JFDS, Honjo RS, Kim CA, Musso CM, Timmons M, Pizzino A, Taft RJ, Lajoie B, Knight MA, Fischbeck KH, Singleton AB, Ferreira CR, Wang Z, Yan L, Garbern JY, Simsek-Kiper PO, Ohashi H, Robey PG, Boyde A, Matsumoto N, Miyake N, Spranger J, Schiffmann R, Vanderver A, Nishimura G, Passos-Bueno MRDS, Simons C, Ishikawa K, Ikegawa S. Bi-allelic CSF1R mutations cause skeletal dysplasia of dysosteosclerosis-pyle disease spectrum and degenerative encephalopathy with brain malformation. ***Am J Hum Genet*** 104, 925-935 (2019)

Invited presentations

Ikegawa S. "Genetic study of skeletal dysplasia" APSS-APPOS 2019 (Incheon, Korea) April 2019

Ikegawa S. "Genomic Study of Bone and Joint Diseases-Study of Genetic Disease in the Genome Sequencing Era" Master program for Clinical Pharmacogenetics and Pharmacoproteomics, Taipei Medical University (Taipei, Taiwan) July 2019

Ikegawa S. "Identification of Novel Disease Genes and Re-classification of Dysosteosclerosis" 14th ISDS meeting (Oslo, Norway) September 2019

Ikegawa S. "Genomic study of skeletal dysplasia in the personal genome sequence era" 4th National Pediatric Genetics Congress (Ankara, Turkey) September 2019

Ikegawa S. "Genomic study of Diseases in the Genome Sequencing Era" Seminar at Chinese Academy of Medical Sciences and Peking Union Medical College (Beijing, China) December 2019

1) Genomic Study of Common Diseases

Common bone and joint diseases are serious worldwide problems for health and the economy, as exemplified by the WHO initiative "Bone and Joint Decade" (2000-2010) and the "Locomotive syndrome 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, avascular necrosis of the femoral head (ANF), scoliosis, and ossification of the posterior longitudinal ligament of the spine (OPLL).

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

2) Genomic Study of Skeletal Dysplasia

Skeletal dysplasia is a group of heritable (monogenic) disorders affecting the skeleton, and more than 450 diseases belong to this category. Skeletal dysplasia is an intractable disease, so many patients are waiting for an effective treatment. We are engaging in clinical and basic studies of these difficult diseases. By large-scale mutation screening, including exome sequencing, we are identifying the disease-causative genes.

Through the analyses of phenotypes and diseases genes, we consider the molecular mechanisms of bone and joint formation and the pathogenesis of common bone and joint diseases, as well as the diagnosis and treatment of rare intractable diseases. Using the disease genes for skeletal dysplasia as candidate genes, we perform association studies for common bone and joint diseases corresponding to skeletal dysplasia, the so-called "rare to common" approach.

Laboratory for Genomics of Diabetes and Metabolism

Team Leader: Momoko Horikoshi

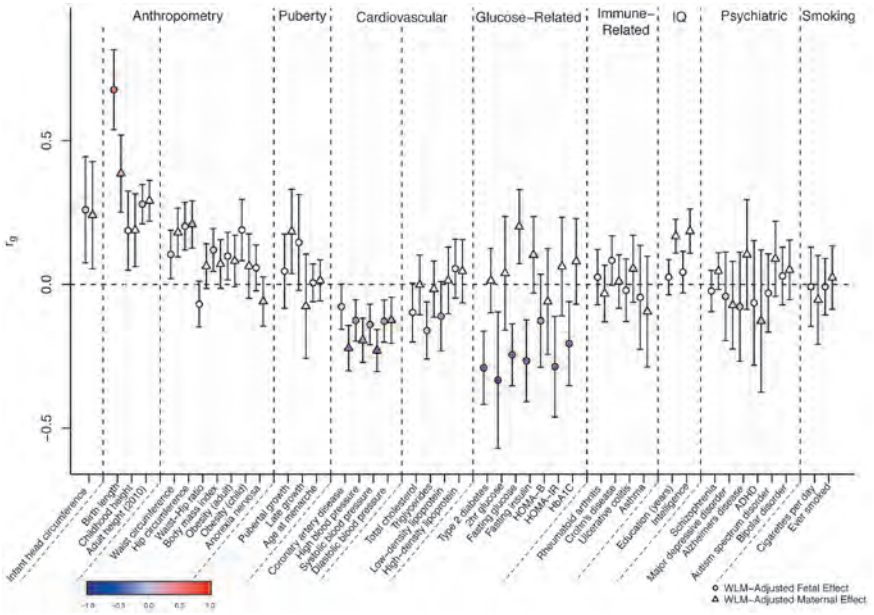


Figure: Genome-wide genetic correlation between birth weight and a range of traits and diseases in later life

Genetic correlation (r_g, x axis) between birth weight and traits (y axis), and corresponding 95% CIs are depicted. The genetic correlation estimates are color coded according to their intensity and direction (red, positive correlation; blue, negative correlation, i.e., lower birth weight correlated with larger trait or disease risk). ADHD, attention deficit hyperactivity disorder; HbA1c, hemoglobin A1c; HOMA-B, homeostasis model assessment of cell function; HOMA-IR HOMA of insulin resistance; T2D, type 2 diabetes.

Recent Major Publications

Warrington NM*, Beaumont RN*, Horikoshi M*, Day FR*, Helgeland Ø*, Laurin C, Bacelis J, Peng S, Hao K, Feenstra B, Wood AR, Mahajan A, Tyrrell J, Robertson NR et al. Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors. ***Nat Genet*** 51, 804-814 (2019)

Inaishi J, Hirakawa Y, Horikoshi M, Akiyama M, Higashioka M, Yoshinari M, Hata J, Mukai N, Kamatani Y, Momozawa Y, Kubo M, Ninomiya T. Association Between Genetic Risk and Development of Type 2 Diabetes in a General Japanese Population: The Hisayama Study. ***J Clin Endocrinol Metab*** 104, 3213-3222 (2019)

Suzuki K, Akiyama M, Ishigaki K, Kanai M, Hosoe J, Shojima N, Hozawa A, Kadota A, Kuriki K, Naito M, Tanno K, Ishigaki Y, Hirata M, Matsuda K, Iwata N, Ikeda M, Sawada N, Yamaji T, Iwasaki M, Ikegawa S, Maeda S, Murakami Y, Wakai K, Tsugane S, Sasaki M, Yamamoto M, Okada Y, Kubo M, Kamatani Y*, Horikoshi M*, Yamauchi T, Kadowaki T. Identification of 28 new susceptibility loci for type 2 diabetes in the Japanese population. ***Nat Genet*** 51, 379-386 (2019)

*These authors jointly contributed to the work

Invited presentations

Horikoshi M. "Recent updates on genome-wide association analysis of type 2 diabetes in Japanese" The 92nd Annual meeting of the Japanese Biochemical Society (Yokohama, Japan) September 2019

Horikoshi M. "Genetic association between birth weight and adult metabolic disease" The 20th Meeting of Japan Endocrinology Society in Kanto-Koshinetsu area (Tokyo, Japan) September 2019

Horikoshi M. "Recent updates on genome-wide association analysis of type 2 diabetes in Japanese" Seminar at Department of Nephrology and Endocrinology, The University of Tokyo hospital (Tokyo, Japan) July 2019

Horikoshi M. "Investigating genetic effect on type 2 diabetes in the Japanese population" Tama Forum (Tokyo, Japan) March 2019

Horikoshi M. "Genetics of Type 2 Diabetes in the Japanese population" Seminar at Kuroda Lab, Department of Biological Sciences, Graduate School of Science, The University of Tokyo (Tokyo, Japan) January 2019

Our lab is interested in investigating the genetic background of diabetes and related metabolic traits that may help us better understand the underlying disease mechanisms.

Birth weight is one of the key indicators of pregnancy outcome and an important predictor of newborn survival. Low birth weight is known to be observationally associated with future risk of adult cardiometabolic diseases, including hypertension and type 2 diabetes. One assumption underlying this observational association is the metabolic adaptation of the fetus that developed in response to an adverse intrauterine environment; a concept called the developmental origin of health and disease (DOHaD). However, this concept is insufficient to explain the complete relationship between lower birth weight and risk of cardiometabolic disease in adulthood. One probable unifying factor is the existence of a shared genetic factor between low birth weight and risk of cardiometabolic disease. Previously, we reported 65 genetic loci associated with birth weight in genome-wide association studies (GWASs), implicating biological pathways that underlie observational associations with adult disease (*Nature* 2016, *Hum. Mol. Genet*. 2018). Since these studies did not distinguish between maternal and fetal genetics, we conducted expanded maternal and fetal GWASs of offspring (n=230,09) and birth weight (n=321,223). We then decomposed the indirect effect of maternal genetics that influence offspring birth weight through the intrauterine environment, and the direct effect of the fetal genetics on birth weight using structural equation modelling. We identified 190 independent association signals and demonstrated the difference in genome-wide genetic correlation between maternal and fetal genetics and various adult cardiometabolic traits (Figure). Mendelian Randomization analyses that illuminate causal pathways showed that fetal, and not maternal, genotype effects explain the negative genetic correlation between birth weight and later development of type 2 diabetes.

Laboratory for

Cardiovascular Genomics and Informatics

Team Leader: Kaoru Ito

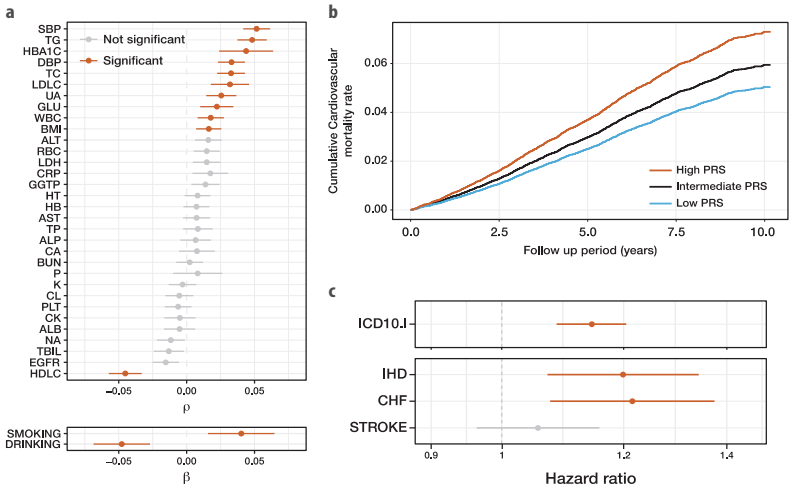


Figure: Correlation between transethnic polygenic risk score for coronary artery disease (CAD-PRS) and clinical indices

a. Upper panel. Each point indicates Spearman's correlation coefficient between CAD-PRS and the clinical indices listed on the left. Error bars indicate 95% confidence intervals. Lower panel. Each point indicates a beta coefficient for 1 SD increase in CAD-PRS estimated by the logistic regression model. Significant correlations or associations are shown in orange ($P < 0.05/34$). b. Adjusted curves for mortality from ICD-10.I diseases estimated by Cox's proportional hazard model are shown. Individuals are stratified into high PRS (top 20 percentile, orange), low PRS (bottom 20 percentile, blue), and intermediate PRS (others, black). c. Each point indicates a hazard ratio of 1 SD increase in CAD-PRS for mortality from ICD10. I subtypes. Error bars represent the 95% confidence interval. PRS, polygenic risk score; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; IHD, ischemic heart disease; CHF, congestive heart failure; SD, standard deviation.

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. Thus, it is important for our society to understand the pathogenesis of these disorders and to uncover new therapeutic targets for their treatment. To achieve these goals, we aim to discover the precise genetic mechanisms underlying those diseases by utilizing leading-edge technologies, such as whole genome sequencing and machine learning. Additionally, we conduct research to push forward the clinical applications of genetic information in the field of cardiovascular medicine.

Our current diseases of interest are coronary artery diseases (CAD), atrial fibrillation (AF), Kawasaki disease (KD), peripheral artery disease (PAD), chronic thromboembolic pulmonary hypertension (CTEPH), and heart failure (HF). We are currently seeking 1) to understand the genetic causes of CAD/AF and the genetic differences between Japanese and European populations; 2) to develop a novel genetic analysis method to solve the "P greater than N" scenario, where the sample size is small, but the number of variants to be analyzed is large; 3) to elucidate the mechanism of CTEPH/cancer therapy-related HF using human omics data from patients in multiple hospitals; 4) to develop a more sophisticated genetic risk scoring system in the MI and AF projects by machine learning algorithms; and 5) to develop a comprehensive system to prioritize variants of unknown significance using massively parallel *in vitro* assays with artificial intelligence.

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 these cardiovascular diseases.

Recent Major Publications

Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, Lunde IG, Wakimoto H, Smith AM, Toepfer CN, Getz K, Gorham J, Patel P, Ito K, Willcox JA, Arany Z, Li J, Owens AT, Govind R, Nuñez B, Mazaika E, Bayes-Genis A, Walsh R, Finkelman B, Lupon J, Whiffin N, Serrano I, Midwinter W, Wilk A, Bardaji A, Ingold N, Buchan R, Tayal U, Pascual-Figal DA, de Marvao A, Ahmad M, Garcia-Pinilla JM, Pantazis A, Dominguez F, John Baksi A, O'Regan DP, Rosen SD, Prasad SK, Lara-Pezzi E, Provencio M, Lyon AR, Alonso-Pulpon L, Cook SA, DePalma SR, Barton PJR, Aplenc R, Seidman JG, Ky B, Ware JS, Seidman CE. Genetic Variants Associated With Cancer Therapy-Induced Cardiomyopathy. ***Circulation*** 140, 31 (2019)

Asanomi Y, Shigemizu D, Miyashita A, Mitsumori R, Mori T, Hara N, Ito K, Niida S, Ikeuchi T, Ozaki K. A rare functional variant of SHARPIN attenuates the inflammatory response and associates with increased risk of late-onset Alzheimer's disease. ***Molecular Medicine*** 25, 20 (2019)

Kim JJ, Yun SW, Yu JJ, Yoon KL, Lee KY, Kil HR, Kim GB, Han MK, Song MS, Lee HD, Ha KS, Sohn S, Ebata R, Hamada H, Suzuki H, Ito K, Onouchi Y, Hong YM, Jang GY, Lee JK, the Korean Kawasaki Disease Genetics Consortium. Identification of SAMD9L as a susceptibility locus for intravenous immunoglobulin resistance in Kawasaki disease by genome-wide association analysis. ***The Pharmacogenomics Journal*** 20, 80 (2020)

Invited Presentations

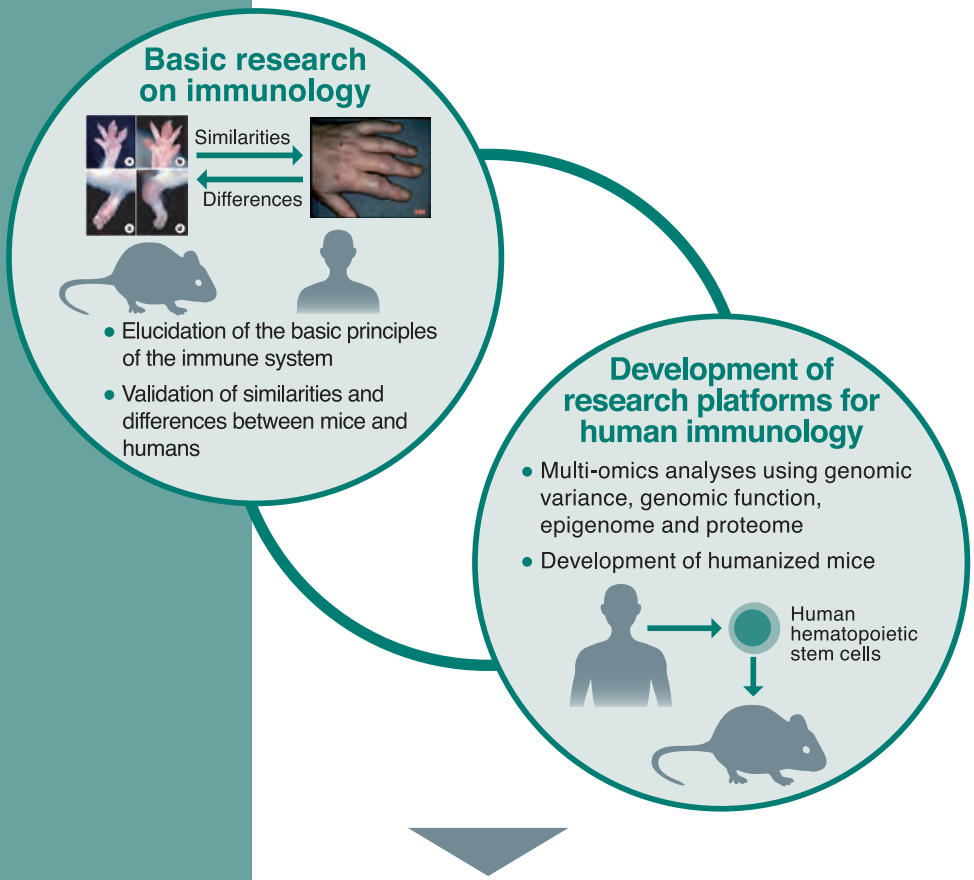
Ito K. "Genetic Basis for Coronary Artery Disease in Japanese and Utility of Transethnic Meta-Analysis for Precision Medicine" The 42nd Annual Meeting of the Molecular Biology Society of Japan (Fukuoka, Japan) December 2019

Ito K. "Cutting Edge of Heart Failure and Cardiomyopathy: Genetic basis of heart failure" Great Wall International Congress of Cardiology 2019 (Beijing, China) October 2019

Ito K. "Heart Failure from the viewpoint of Genomics" The 89rd Tokyo Heart Club (Tokyo, Japan) May 2019

Ito K. "Whole genome sequencing x GWAS Revealed Clinically Important Rare Variants in Coronary Artery Disease" The 83rd Annual Scientific Meeting of the Japanese Circulation Society (Yokohama, Japan) March 2019

Division of Human Immunology



Division of Human Immunology will elucidate the principles of the immune system and develop a research platform for human immunology.

Laboratory for
Autoimmune Diseases

Team Leader: Kazuhiko Yamamoto

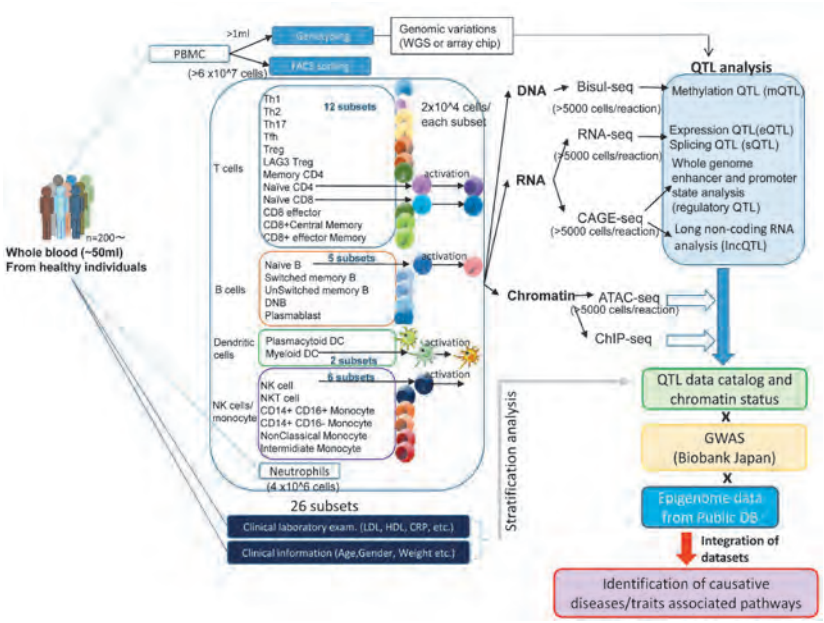


Figure: Integration of genetic variations and multi-omics data

The immune system has been investigated mainly using mouse models. However, there are several distinct and critical differences between mouse and human immune systems. Therefore, human immunology research is indispensable; although technical limitations exist when studying humans. In order to overcome this difficulty, genetics can be helpful because genetic information provides us with evidence of the causal relationship to an observed phenomenon. Recently, many of the disease susceptibility variants identified by genome wide association study (GWAS) have been found to function as expression-quantitative trait loci (e-QTL), regulating the expression levels of genes in a cell type-specific manner. These variants also significantly overlap the histone marks of active promoters or enhancers in specific cells. Further, data obtained using cap analysis of gene expression indicate that long non-coding RNAs (lncRNAs) overlap disease-associated variants in specific cell types. These lncRNAs are also co-expressed with the corresponding mRNAs, suggesting their potential roles in transcriptional regulation. Therefore, integrating these pieces of global genomic information, qualitative and quantitative analyses of transcriptomes together with information about disease susceptibility variants and cell-specific epigenomes will allow us to better understand the causal pathogenic components of immunocompetent cells in various immune-mediated diseases.

Based on the above idea, we are now setting up a system to obtain nearly 30 different lymphocyte subsets from human peripheral blood mononuclear cells of healthy individuals. We expect that the lymphocytes from healthy donors will exhibit the least bias between genotype and gene expression. Genotypes and gene expression are thus analyzed together with the above-mentioned regulatory elements. GWAS variants information can then be integrated into these data. We believe that insights gained from these studies will enable us to understand precise causal pathological processes and develop better strategies to control immune-related diseases.

Recent Major Publications

Negishi H, Endo N, Nakajima Y. Nishiyama N, Tabunoki Y, Nishio J, Koshiba R, Matsuda A, Matsuki K, Okamura T, Negishi-Koga T, Ichinohe T, Takemura S, Ishikawa H, Iemura S, Natsume T, Abe T, Kiyonari H, Doi T, Hangai S, Yanai H, Fujio F, Yamamoto K, Taniguch T. Identification of U1snRNA as an endogenous agonist of TLR-mediated immune pathogenesis. ***Proc Natl Acad Sci USA*** 116, 23653-23661(2019)

Motegi T, Kochi Y, Matsuda K, Kubo M, and Yamamoto K, Momozawa Y, Identification of rare coding variants in TYK2 protective for rheumatoid arthritis in the Japanese population and their effects on cytokine signaling. ***Ann Rheum Dis*** 78, 1062-1069 (2019)

Sakaue S, Hirata J, Maeda Y, Kawakami E, Nii T, Kishikawa T, Ishigaki K, Terao C, Suzuki K, Akiyama M, Suita N, Masuda T, Ogawa K, Yamamoto K, Seki Y, Matsushita M, Yoshimura M, Matsuoka H, Ikari K, Taniguchi A, Yamanaka H, Kawaji H, Lassmann T, Itoh M, Yoshitomi H, Ito H, Ohmura k, Forrest ARR, Hayashizaki Y, Carninci P, Kumanogo A, Kamatani Y, de Hoon M, Yamamoto K, Okada Y. Integration of genetics and miRNA-target gene network identified disease biology implicated in tissue specificity. ***Nucleic Acids Res*** 46, 11898-11909 (2018)

Invited presentations

Yamamoto K. "Integration of Genetic information to immune functions", Advanced Target Therapies. (Palma, Spain) March 2019

Yamamoto K. "Mapping genes to immune cells", EULAR (European League Against Rheumatism) (Madrid, Spain) June 2019

Yamamoto K. "Integration of genetic information to immune functions", 11th International Forum on Rheumatoid Arthritis : Pathogenesis and Emerging Therapeutic Strategies September (Washington DC, USA) September 2019

Yamamoto K. "How do we study the human immune system?", IRACON 2019: 35th Annual Conference of the Indian Rheumatology Association. (Pondicherry, India) December 2019

Laboratory for
Cell Signaling

Team Leader: Takashi Saito

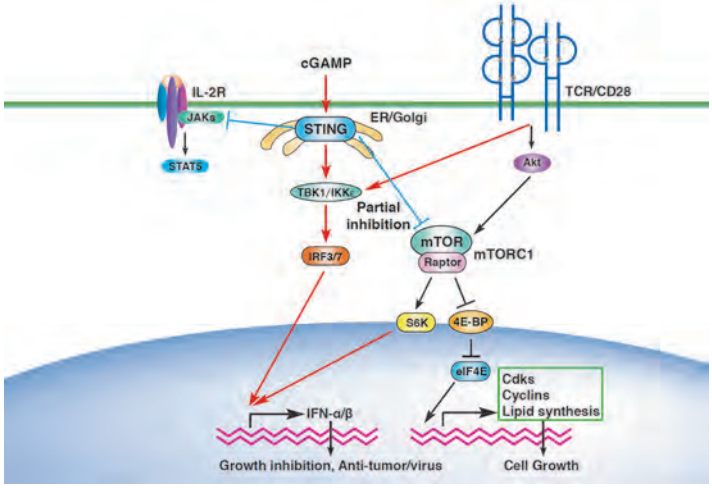


Figure: Molecular mechanism of reciprocal regulation of STING and TCR signaling
Co-stimulation of T cells by STING and TCR activation induces growth arrest by partially inhibiting mTORC1 activation and simultaneously induces IFN-I production though sustained activation of IRF3 and the partial activation of mTORC1. The STING-mediated inhibition of mTORC1 signals is partly dependent on IRF3/IRF7, but not on TBK1/IKKε. cGAMP-induced STING activation also leads to the inhibition of IL-2 signaling pathways.

The objective of our team is to determine the molecular mechanisms of T cell activation, differentiation and function, and ultimately to elucidate the onset of and to modulate T cell function/activation to prevent immune diseases such as autoimmunity and allergic inflammation. Toward this goal, we have analyzed regulation of T cell function from a signaling perspective.

Our finding that TCR-microclusters (MC) initiate T cell activation led us to analyze the dynamics of signaling molecules at the immune synapse. Similar to our previous studies of CTLA4 and PD-1, we are analyzing the dynamic regulation of other inhibitory co-stimulation receptors such as LAG3. These inhibitory receptors co-localize with the TCR-MC to mediate inhibition of T cell activation. Our analyses provide a dynamic view of signal regulation and also define inhibitory mechanisms.

We have also analyzed negative regulation of T cell activation by phosphatases, particularly autoimmune-related PTPN22. Its deficiency resulted in enhanced activation and an increase in effector/memory T cells. Analysis of the associated proteins revealed that PTPN22 was recruited to the TCR-MC as an "inhibitory complex" with other inhibitory molecules to inhibit activation. A PTPN22 mutant causing susceptibility to development of autoimmune diseases was defective in this TCR-MC recruitment. These studies defined the mechanisms of inhibition, as well as the autoimmune susceptibility caused by the mutation.

We have also analyzed the modulation of T cell function by innate signals. T cells are activated by co-stimulation of TCR and TLRs. TLR2, in particular, activates Th1 cells, but not naïve T cells, without TCR stimulation. We found that naïve T cells failed to respond to TLR2 stimulation due to the defective expression of TIRAP. The function of the innate-sensor STING in T cells was also analyzed; STING activation-induced growth inhibition on the one hand and type I-IFN production on the other. Both functions were mediated through mTORC1 activation, and we identified a reciprocal regulation between STING and mTORC1 signals for T cell function (Figure). Furthermore, we showed that STING activation in T cells contributes to anti-tumor immunity.

Recent Major Publications

Kong MS*, Hashimoto-Tane A*, Kawashima Y, Sakuma M, Yokosuka T, Kometani K, Onishi R, Carpino N, Ohara O, Kurosaki T, Phua KK and Saito T. Inhibition of T cell activation and function by the CIN85 adaptor protein. ***Sci Signal*** 12, eaav4373 (2019)

Imanishi T, Unno M, Kobayashi W, Yoneda N, Matsuda S, Ikeda K, Hoshii T, Hirao A, Miyake K, Barber GN, Arita M, Ishii KJ, Akira S, Saito T. Reciprocal regulation of STING and TCR signaling by mTORC1 for T cell activation and function. ***Life Sci Alliance*** 2, e201800282 (2019)

Saito T.: Molecular dynamics of co-signal molecules in T cell activation. ***Adv Exp Med Biol*** 1189, 135-152 (2019)

Invited presentations

Saito T. "T cell activation and its regulation" JSI Summer School (Imabari, Japan), July 2019

Saito T. "Negative regulation of T cell activation by CIN85 adaptor molecule" FASEB conference (Nova Scotia, Canada), June 2019

Saito T. "Dynamic regulation of inhibitory signals on T cell activation" OIST conference, (Okinawa, Japan), March 2019

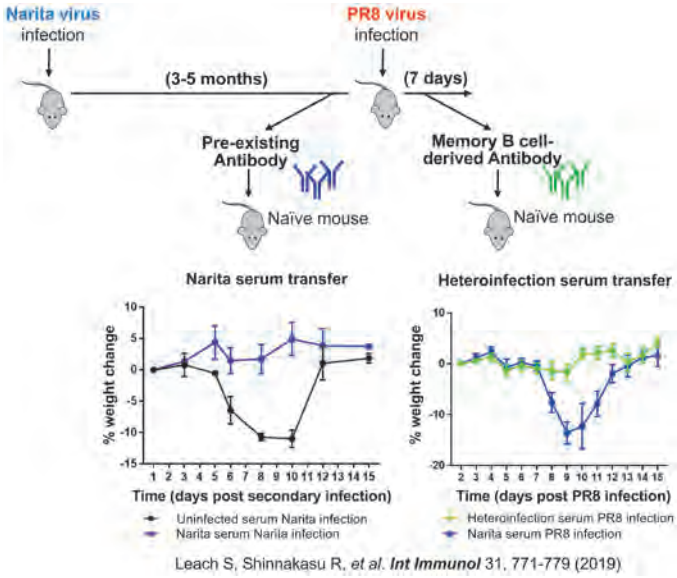
Saito T. "Dynamic regulation of inhibitory signals on T cell activation" EMBO Workshop: Lymphocyte antigen receptor signaling (Siena, Italy), August 2018

Saito T. "Dynamic regulation of T cell co-stimulation at Immune synapse" Merck special seminar (Palo Alto, USA), June 2018

Laboratory for

Lymphocyte Differentiation

Team Leader: **Tomohiro Kurosaki**



Leach S, Shinnakasu R, *et al.* ***Int Immunol*** 31, 771-779 (2019)

Figure: *De novo* generation of HA stem-specific antibodies from memory B cells is required for protection from heterologous infection.
Pre-existing antibodies generated in mice previously infected with Narita virus (3-5 months post infection) provided protection from weight loss in naïve recipient mice infected with Narita virus (Lower left; blue line). By contrast, transfer of serum from Narita-infected mice failed to protect naïve recipient mice infected with the PR8 virus (Lower right; blue line). On the other hand, antibodies generated from memory B cells, which were initially induced after the primary Narita infection, after PR8 heterologous re-infection at day 7 were able to provide protection to naïve recipient mice infected with the PR8 virus (Lower right; green line).

Two humoral memory compartments, long-lived plasma cells (LLPCs) and memory B cells, co-exist in our body. LLPCs constitutively produce antibody (Ab) and neutralize invading pathogens immediately upon re-infection, whereas memory B cells require re-stimulation by cognate antigen for their differentiation into Ab-secreting plasma cells. Since serum Ab titers are known to be correlated with vaccine efficacy, the importance of LLPCs is well-appreciated. In contrast, the importance of memory B cells in conferring protection from re-infection has been controversial.

The majority of, although not all, memory cells and LLPCs are thought to arise from germinal center (GC) reactions. Immunization with NP hapten leads to the introduction of the high-affinity-conferring, W33L VH mutation in a large proportion of LLPC Abs. Thus, the LLPC pool is thought to be primarily composed of specificities possessing the highest affinity for the primary antigen. On the other hand, we and others have recently demonstrated that GC B cells with relatively low affinities are preferentially recruited into the memory B cell compartment. This observation led us to propose that such mechanisms may prevent the memory B cell population from becoming overly committed to the primary antigen, and, instead, allow them to potentially acquire a more diverse repertoire. Therefore, memory B cells might be intrinsically well-suited for recognition of and protection from secondary infection by related, but antigenically variant pathogens.

To rigorously test this proposal, we used a mouse model of drifted viral infection with pandemic H1N1 A/Narita/2009 (Narita) virus first and then re-infection with the H1N1 A/Puerto Rico/8/1934 (PR8) virus. We demonstrate that GC-experienced LLPCs generated during primary infection with Narita virus are not effective in neutralizing the re-infecting PR8 virus. Instead, pre-existing anti-HA stem-specific memory B cells are activated upon PR8 virus re-infection, thereby contributing to host protection (Figure). Furthermore, our results suggest the requirement for maturation of anti-HA stem memory B cells in the GC during primary influenza infection, whereas GC-mediated maturation is not required for protection after secondary re-infection.

Recent Major Publications

Mesin L, Schiepers A, Ersching J, Barbulescu A, Cavazzoni CB, Angelini A, Okada T, Kurosaki T, Victora GD. Restricted Clonality and Limited Germinal Center Reentry Characterize Memory B Cell Reactivation by Boosting. ***Cell*** 180, 92-106 (2020)

Leach S, Shinnakasu R, Adachi Y, Momota M, Makino-Okamura C, Yamamoto T, Ishii KJ, Fukuyama H, Takahashi Y, Kurosaki T. Requirement for memory B cell activation in protection from heterologous influenza virus reinfection. ***Int Immunol*** 31, 771-779 (2019)

Ise W, Kurosaki T. Plasma cell differentiation during the germinal center reaction. ***Immunol Rev*** 288, 64-74 (2019)

Invited Presentations

Kurosaki T. "Function of Tet proteins in B cell tolerance" The International Symposium of Korean Autoimmunity-Synovitis Study Group (Seoul, Korea) December 2019

Kurosaki T. "Immune regulations through B cells and antibodies" The 55th Annual Congress of the Japan Society for Transplantation (Hiroshima, Japan) October 2019

Kurosaki T. "Roles of epigenetic modification in B cell tolerance" TRR 130 Symposium 2019 on B cell responses in immunity and autoimmunity (Freiburg, Germany) October 2019

Kurosaki T. "Generation of humoral memory compartments" The 10th JSH International Symposium 2019 in Ise-Shima (Toba, Japan) May 2019

Kurosaki T. "Selection mechanisms of germinal center cells into the memory B cell compartment" Keystone Symposia: B Cell-T Cell Interactions (Keystone Resort, Colorado, USA) February 2019

Laboratory for

Transcriptional Regulation

Team Leader: **Ichiro Taniuchi**

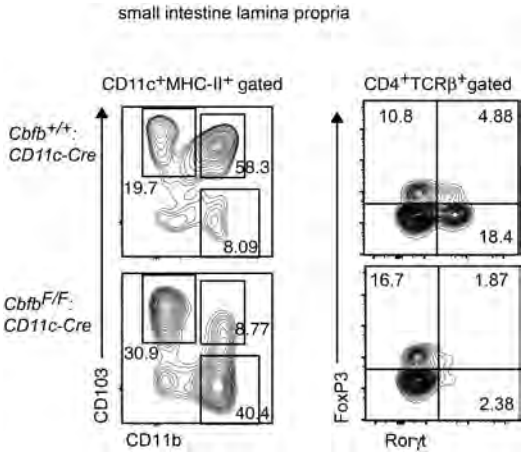


Figure: Runx/Cbfβ regulates development of the cDC2 subset that directs differentiation of Rorγt+ T cells

Dot plots showing CD103 and CD11b expression on gut dendritic cells (DCs) (left) and FoxP3 and Rorγt expression by intestinal lamina propria $CD4^+$ T cells (right). Inactivation of the *Cbfb* gene during DC development (*Cbfb*$^{F/F}$*:CD11c-Cre* mice) results in reduction of the $CD103^+CD11b^+$ cDC2 subset, which is accompanied by loss of both $Ror\gamma t^+$ Th17 cells and $Ror\gamma t^+$ $FoxP3^+$ type 3 T regulatory (Treg) cells.

Recent Major Publications

Seo W, Shimizu K, Kojo S, Okeke A, Kowhi-Shigematsu T, Fujii SI, Taniuchi I. Runx-mediated regulation of CCL5 via antagonizing two enhancers influences immune cell function and anti-tumor immunity. ***Nat Commun*** 11, 1562 (2020)

Kojo S, Ohno-Oishi M, Wada H, Nike S, Seo W, Muroi S, Taniuchi I. Constitutive CD8 expression drives innate $CD8^+$ T cell differentiation via induction of iNKT2 cells. ***Life Sci Alliance*** 3, e202000642 (2020)

Tenno M, Wong AYW, Ikegaya M, Miyauchi E, Seo W, See P, Kato T, Taida T, Ohno-Oishi M, Ohno H, Yoshida H, Ginhoux F, Taniuchi I. Essential functions of Runx/Cbfβ in gut conventional dendritic cells for priming $Ror\gamma t^+$ T cells. ***Life Sci Alliance*** 3, e201900441 (2019)

Invited presentations

Taniuchi I. "Gene regulation by local and long-range chromatin loops during T cell development" The 42nd Annual meeting for MBSJ. (Fukuoka, Japan) December 2019

Taniuchi I. "Roles of Bcl11 proteins During Thymocyte Differentiation" IUIS 2019, 17th International Congress of Immunology. (Beijing, China) October 2019

Taniuchi I. "Roles of Cbfβ in dendritic cells in priming $Ror\gamma t^+$ T cells" RUNX 2019, 22nd International RUNX meeting. (Seoul, Korea) June 2019

Taniuchi I. "Heteromeric interference, a novel pathogenesis for human immunodeficiency" ThymE, T cell and thymus biology. (Rehovot, Israel) May 2019

Taniuchi I. "Gene Regulation by local and long-range chromatin loops during CD4/CD8 lineage choice" Keystone Symposia (Tahoe, USA) February 2019

The vertebrate immune system consists of two components, innate and adaptive. The adaptive immune system appeared later during evolution, minimally by acquisition of a system for generating pools of lymphocytes with a broad variety of antigen-specificities. Thus, the primary developmental program of T lymphocytes that occurs in the thymus has been shaped to select useful and non-self-reactive immune soldiers 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 sensed and are coupled with cell fate determination programs in the nucleus by using the helper- versus cytotoxic-lineage choice as a model, in which the expression of the ThPOK transcription factor serves as a key determinant. Our previous studies identified a transcriptional silencer, referred to as a *Thpok* silencer, in the *Thpok* locus as a switch to turn off *Thpok* expression to direct class-I major histocompatibility complex (MHC) selected thymocytes to become cytotoxic-lineage T cells. In addition to the primary development of T cells in the thymus, differentiation into effector T cell subsets occurs after encountering antigens in the periphery that are presented by antigen presenting cells, such as dendritic cells (DCs). Hence, characterization of DC subsets that direct differentiation into specific T cell subsets is important.

Our second objective is to understand the functions of Runx transcription factor complexes, which consist of a Runx protein and a non-DNA binding Cbfβ protein. Our goal is to identify regulatory mechanisms that modulate the function of Runx complexes, and to provide insights into how Runx complexes regulate immune system development and immune responses. Our recent study revealed a novel role of Runx/Cbfβ complexes in regulating the differentiation of gut DC subsets. We found that the loss of Runx/Cbfβ expression during DC development results in the absence of the $CD103^+CD11b^+$ gut cDC2 subset, which is accompanied by a reduction of both $Ror\gamma t^+$ Th17 cells and type 3 $Ror\gamma t^+$ regulatory T cells in the intestine. Thus, Runx function in cDCs is essential to prime $Ror\gamma t^+$ T cells and enhance type 3 immune responses.

Laboratory for
Immune Cell Systems

Team Leader: Shigeo Koyasu

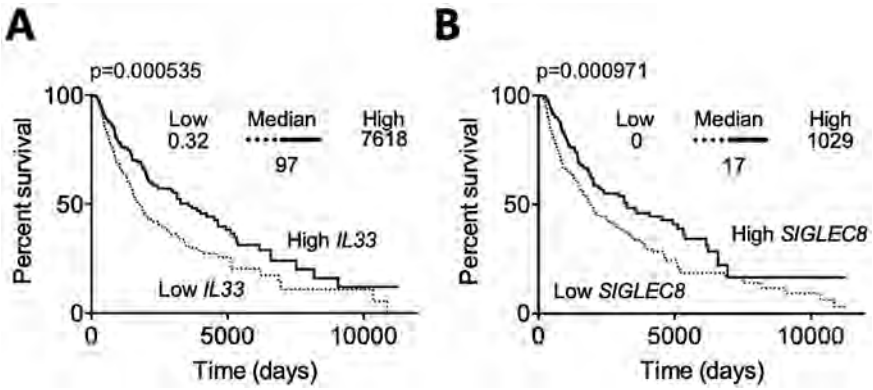


Figure: *IL33 and SIGLEC8* expression positively correlates with better overall survival in human cutaneous melanomas

Overall survival of skin cutaneous melanoma patients (Data generated using the OncoLnc platform). The Cancer Genome Atlas (TCGA) data of 458 melanoma patients were assigned into low or high groups according to the expression level of *IL33* (left) and *SIGLEC8* (right) reported as RNASeq values. Patients with an *IL33* expression level ranging from 0.32 to 97 were considered as low (dotted line) and those having an *IL33* expression level ranging from 97 to 7618 were considered as high (solid line). Patients with a *SIGLEC8* expression level ranging from 0 to 17 were considered as low (dotted line) and those having a *SIGLEC8* expression level ranging from 17 to 1029 were considered as high (solid line).

Recent Major Publications

Bald T, Wagner M, Gao Y, Koyasu S, Smyth MJ. Hide and seek: Plasticity of innate lymphoid cells in cancer. ***Semin Immunol*** 41, 101273 (2019)

Wagner M. Koyasu S. Cancer immunoediting by innate lymphoid cells. ***Trends Immunol*** 40, 415-430 (2019)

Sasaki T, Moro K, Kubota T, Kubota N, Kato T, Ohno H, Nakae S, Saito H, Koyasu S. Innate lymphoid cells in the induction of obesity. ***Cell Rep*** 28, 202-217 (2019)

Invited Presentations

Koyasu S. "Role of innate lymphoid cells in the induction of diet-induced obesity" The 17th International Congress of Immunology (Beijing, China) October 2019

Koyasu S. "Role of innate lymphoid cells in the induction of diet-induced obesity and insulin-resistance" The 30th Anniversary Symposium of RIBS, Tokyo University of Science (Tokyo, Japan) October 2019

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. ILC2s are rare in secondary lymphoid organs relative to other immune cells. Instead, they harbor a unique location within non-lymphoid tissues, especially skin and mucosal barriers (i.e. respiratory and intestinal mucosa), and in fat-associated lymphoid clusters (FALCs) in the visceral adipose tissue. Whereas the importance of NK cells in the antitumor response is firmly established, the role of ILC2s remains ambiguous and poorly understood, partially due to their low abundance in solid tumors. The acquisition of anti-tumorigenic functions appears to depend on the context of tumor specificity and signaling intensity. Recent evidence indicates that metabolic pathways within the tumor microenvironment shape the diversity of infiltrating immune cells. However, the extent to which metabolic deviations from normal set points affects intratumoral ILC2s has not yet been assessed. Using melanoma as a model, we have discovered an immunosuppressive activity imposed on ILC2s by tumor cells through the accumulation of lactic acid in the tumor microenvironment. We show that lactic acid inhibits proliferation and cytokine production, and subsequently decreased survival of ILC2s *in vitro*. Interference with this immunosuppressive axis in B16F10 melanomas by specifically knocking down lactate dehydrogenase A ($LDHA^{low}$) significantly increased the number of intratumoral ILC2s. Importantly, following stimulation with IL-33, expansion of ILC2s within $LDHA^{low}$ B16F10 tumors, accompanied by eosinophils, more effectively controlled melanoma growth compared with control tumors. Of note, an analysis of gene expression data of human cutaneous melanomas revealed that the expression of *LDHA* negatively correlated with markers associated with ILC2s. Moreover, high expression of *IL33* and an eosinophil marker *SIGLEC8* was associated with better overall survival in cutaneous melanoma patients, indicating a role for the IL-33/ILC2/eosinophil axis in anti-melanoma immunity (Figure). Our results identify tumor-derived lactic acid production as a plausible immunosuppressive mechanism that contributes to the paucity of intratumoral ILC2s.

Laboratory for
Innate Immune Systems

Team Leader: Kazuyo Moro

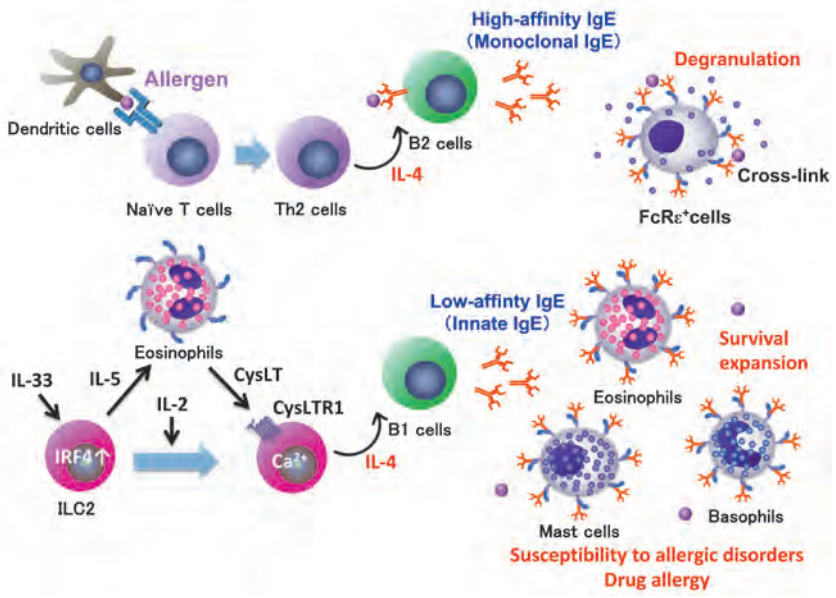


Figure: ILC2-derived IL-4 induces innate IgE production from B1 cells
(Bottom) IL-33 and IL-2 upregulate interferon regulatory factor 4 (IRF4) and Cysteinyl leukotriene receptor 1 (Cysltr1) expression by ILC2, respectively. Eosinophil-derived CysLT initiates IL-4 production by ILC2 through a $Ca2^{+}$ signaling pathway. ILC2-derived IL-4 induces innate IgE production by B1 cells. Innate IgE induces the expansion and survival, but not the degranulation, of $FceRIa^{+}$ cells, resulting in increased susceptibility to allergic responses mediated by allergen-specific IgE (top).

Recent Major Publications

Kobayashi T, Voisin B, Kim DY, Kennedy EA, Jo JH, Shih HY, Truong A, Doebel T, Sakamoto K, Cui CY, Schlessinger D, Moro K, Nakae S, Horiuchi K, Zhu J, Leonard WJ, Kong HH, Nagao K. Homeostatic Control of Sebaceous Glands by Innate Lymphoid Cells Regulates Commensal Bacteria Equilibrium. ***Cell*** 176, 982-997 (2019)

Sasaki T, Moro K, Kubota T, Kubota N, Kato T, Ohno H, Nakae S, Saito H, Koyasu S. Innate Lymphoid Cells in the Induction of Obesity. ***Cell Rep*** 28, 202-217 (2019)

Motomura Y, Kobayashi T, Moro K. The Neuropeptide CGRP Induces Bipolar Syndrome in Group 2 Innate Lymphoid Cells. ***Immunity*** 51, 598-600 (2019)

Invited presentations

Moro K. "The role of ILC2 in idiopathic pulmonary fibrosis" The British Pharmacological Society Annual Meeting (Pharmacology 2019) (Edinburgh, UK) December 2019

Moro K. "ILC2 induce innate IgE secretion by B1 cells via IL-4 and regulate allergic susceptibility" The 17th International Congress of Immunology (IUIS2019) (Beijing, China) October 2019

Moro K. "ILC2 produce IL-4 and regulate susceptibility to allergic inflammation via IgE production by B1 cells" The SCLS-CBIS Joint Life Science Research Workshop on "Frontiers of Basic and Clinical Research on Immune-metabolism and Immunotherapy" (Shanghai, China) September 2019

Moro K. "ILC2 produce IL-4 and regulate susceptibility to allergic inflammation via IgE production by B1 cells" FASEB Science Research Conference: IgE and Allergy (Scottsdale, USA) July 2019

Moro K. "ILC2 induce innate IgE secretion by B1 cells via IL-4 and regulate allergic susceptibility" The 11th International Singapore Symposium of Immunology (Singapore) May 2019

Our team has been focused on group 2 innate lymphoid cells (ILC2), an innate lymphocyte lineage that we identified in 2010. ILC2 localize in a variety of tissues such as fat, lung, intestine, liver, and skin, and mediate immune responses to helminth and fungal infections via strong production of type 2 cytokines including IL-5, IL-13, IL-9, and GM-CSF. Unlike T and B lymphocytes, ILC2 lack antigen-specific receptors and are activated by epithelial cell-derived cytokines such as IL-33. Because ILC2 are also known to produce type 2 cytokines in allergic disorders, including asthma and atopic dermatitis, we wish to identify pathways for regulation of ILC2 function with the goal to establish new therapies for allergic disorders by targeting ILC2. While it is well-known that ILC2 produce IL-4, mechanisms for its production and subsequent function in allergic responses are unknown. We have identified a mechanism by which ILC2 increase susceptibility to allergic disorders through the production of innate IgE induced by IL-4.

We previously reported a negative feedback mechanism for the suppression of tissue-resident ILC2 in ILC2-mediated lung inflammation *in vivo*. Interestingly, we found that mice lacking such suppressive mechanisms in the lung spontaneously develop lung fibrosis in an age-dependent manner. The pathogenesis of the disease in this mouse model is very similar to that of human idiopathic pulmonary fibrosis (IPF). At this time, there is no cure for IPF and the currently established mouse models used for IPF research do not adequately model the human disease. We are now characterizing ILC2 regulation and disease development in these mice and we aim to translate this research to the human disease to develop targeted treatment and prevention strategies.

Along with our colleagues, we are also focused on understanding the cytokine regulation and development of ILC2 and on elucidating the role of ILC2 in a variety of type 2 diseases.

Laboratory for
Immune Homeostasis

Team Leader: Taishin Akiyama

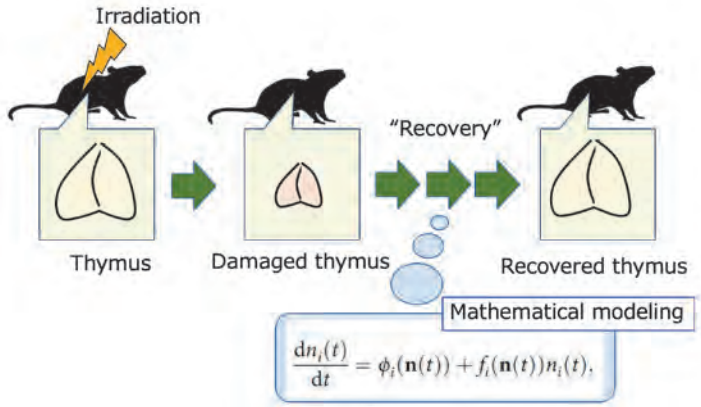


Figure: Mathematical modeling of thymic recovery from irradiation-induced injury
Reciprocal regulation between thymocytes and TECs in the process of thymic recovery were characterized by mathematical modeling using ordinary differential equations.

Recent Major Publications

Horie K, Sasanuma H, Kudo T, Fujita SI, Miyauchi M, Miyao T, Seki T, Akiyama N, Takakura Y, Shimbo M, Jeon H, Shirakawa M, Shiba D, Yoshida N, Muratani M, Takahashi S, and Akiyama T*. Down-regulation of GATA1-dependent Erythrocyte-Related Genes in the Spleens of Mice Exposed to a Space Travel. ***Sci Rep*** 9, 7654 (2019)

Kaneko KB, Tateishi R, Miyao T, Takakura Y, Akiyama N, Yokota R, Akiyama T*, and Kobayashi TJ*. Quantitative analysis reveals reciprocal regulations underlying recovery dynamics of thymocytes and thymic environment in mice. ***Commun Biol*** 2, 44 (2019)

Horie K, Kato T, Kudo T, Sasanuma H, Miyauchi M, Akiyama N, Miyao T, T Seki T, Ishikawa T, Takakura Y, Shirakawa M, Shiba D, Shimbo M, Jeon H, Yoshida N, Inoue J, Muratani M, Takahashi S, Ohno H*, and Akiyama T*. Impact of spaceflight on the murine thymus and mitigation by exposure to artificial gravity during spaceflight. ***Sci Rep*** 9, 19866 (2019)

Invited Presentations

Akiyama T. "Mechanism underlying functions and differentiation required for preventing onset of autoimmunity" Saitama Rheumatoid arthritis Conference 2019 (Kawagoe, Japan) July 2019

Akiyama T. "Mechanism of functions and differentiation essential for preventing onset of autoimmune diseases" The 154th meeting of Medical Society of Toho University (Tokyo, Japan) November 2019

The thymus produces a large number of T cells with properly selected repertoires and is highly sensitive to insults from various stressors (e.g., viral infection, radiation, and psychological stress). Although the thymus can recover from these stressor-induced damages, prolonged recovery from thymic damage can impair T cell-mediated immunity due to reduced generation of a naïve T cell repertoire during the recovery period.

Ionizing radiation is broadly used for hematopoietic transplantation and cancer therapy. Several studies have shown that irradiation reduces cellularity, not only of thymocytes, but also of thymic epithelial cells (TECs). Thymopoiesis is supported by interactions between thymocytes and TECs, thus, understanding thymic recovery requires characterization of the reciprocal regulation between thymocytes and TECs. By combining mathematical models with quantitative data on thymic cell recovery, we have refined the dynamic aspects of thymopoiesis into detailed kinetic information, e.g., rates of proliferation, death, and differentiation. Indeed, *in vivo* recovery dynamics were reproduced by our mathematical model. Furthermore, we demonstrated that the model explained the mechanism of the dynamical change in thymic cell populations. The model predicted, and a subsequent experiment confirmed, that $CD4^+CD8^+$ double positive thymocytes (DPs) temporarily increase their proliferation rate. Moreover, cellularity of the DP subset appears to be negatively regulated by its own population size during the recovery process.

The hostile environments encountered during spaceflight also affect the immune system. Several studies using rodents revealed thymic atrophy after spaceflight. Consistently, a T cell receptor excision circle PCR assay showed that the number of T cells newly generated from the thymus was decreased in the blood of astronauts by spaceflight. Consequently, these studies suggested an impact of spaceflight on thymus homeostasis. However, mechanisms behind spaceflight-inducing thymic dysfunction remain unclear. We aimed to elucidate the impact of spaceflight on the thymus at the molecular level and also tested if exposure to artificial 1x*g* influenced spaceflight-induced changes in the thymus. RNA-seq analysis suggested that the thymic atrophy caused by spaceflight might be ascribed to reduced proliferation of thymic cells. Moreover, the spaceflight-induced atrophy and changes in gene expression in the thymus were significantly rescued by exposure to 1x*g* during spaceflight.

Laboratory for
Immune Crosstalk

Team Leader: Hilde Cheroutre

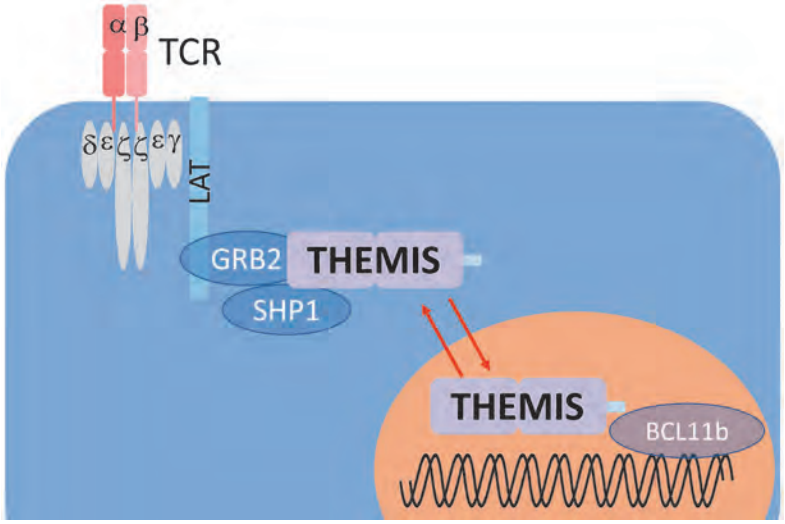


Figure: A model of THEMIS function
As an adaptor molecule, cytosolic THEMIS protein is modified (e.g., by phosphorylation) upon TCR stimulation and recruits the phosphatase SHP1, which down-regulates TCR signaling. These activation events also result in the nuclear translocation of THEMIS. In the nucleus, THEMIS may function as a transcription factor and, through interaction with other nuclear transcription factors including Bcl11b, modulate the transcription profile of the signaled thymocyte or T cell.

We identified THEMIS as an essential gene for T cell development and function. Many GWAS analyses of inflammatory diseases, including Celiac Disease, Multiple Sclerosis, Rheumatoid Arthritis and Atopic Dermatitis, have shown an association with the *THEMIS* gene locus. THEMIS functions as an adapter that modulates T cell receptor (TCR) signal strength together with Grb2 and SHP1, and THEMIS-deficiency causes a reduction of conventional mature T cells in mice. However, the mechanisms used by THEMIS to control TCR signaling remain unclear and controversial. Interestingly, besides its expression in the cytoplasm, THEMIS is also expressed in the nucleus, but its role in the nucleus has not been explored. In order to understand the importance of its cellular localization and possibly diverse functions, we established two mutant mice that express THEMIS either exclusively in the cytoplasm or solely in the nucleus, by either deleting the nuclear localization signal (R-NLS) sequence (*Themis*$^{R\text{-}NLS}$) or by adding the SV40 NLS to *Themis* (*Themis*^{SV40}), respectively. Surprisingly, thymic development is impaired in both mutant mice, similar to *Themis* germ line knock-out mice, suggesting that both cytosolic and nuclear THEMIS proteins are critical for thymocyte development. Furthermore, compound mutant *Themis*$^{SV40/R\text{-}NLS}$, in which THEMIS protein resides in both compartments, but cannot translocate, also showed a similar phenotype, indicating that a dynamic expression of THEMIS in the cytoplasm/nuclear compartments is essential for its function. We also identified a T cell-specific transcription factor BCL11b as a THEMIS binding partner, indicating that transcriptional regulation might be one of its functions in the nucleus.

Our overall goal is to dissect the mechanisms employed by THEMIS to modulate TCR signals and control gene expression and, ultimately, to elucidate the correlation between THEMIS and protective immunity, as well as its role in T cell-specific inflammatory diseases as mentioned above.

Recent Major Publications

Wada H, Yasmin N, Kakugawa K, Ohno-Oishi M, Nieke S, Miyamoto C, Muroi S, Taniuchi I. Requirement for intron structures in activating the Cd8a locus. ***Proc Natl Acad Sci U S A*** 115, 3440-3445 (2018)

Seo GY, Shui JW, Takahashi D, Song C, Wang Q, Kim K, Mikulski Z, Chandra S, Giles DA, Zahner S, Kim PH, Cheroutre H, Colonna M, Kronenberg M. LIGHT-HVEM Signaling in Innate Lymphoid Cell Subsets Protects Against Enteric Bacterial Infection. ***Cell Host Microbe*** 24, 249-260.e4 (2018)

Saadalla AM, Osman A, Gurish MF, Dennis KL, Blatner NR, Pezeshki A, McNagny KM, Cheroutre H, Gounari F, Khazaie K. Mast cells promote small bowel cancer in a tumor stage-specific and cytokine-dependent manner. ***Proc Natl Acad Sci U S A*** 115, 1588-1592 (2018)

Invited presentations

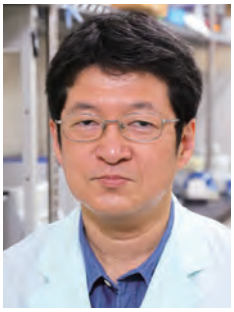
Cheroutre H. "Dietary Antigens induce the antipode of Immune Tolerance" CMAV-UCSD, (San Diego, USA) February 2019

Cheroutre H. "A Long Non-coding RNA in the* Cd8* Locus Controls the Functional Differentiation of CD4 T Cells." The First Inaugural Formosa Immunology Spring School and Symposium (FISS), (Taipei, Taiwan) April 2019

Cheroutre H. "Protective Tolerance not a contradiction but a necessity at the mucosal Barrier", (Los Angeles, USA) May 2019

Cheroutre H. "The Cd8 locus controls CD4 T helper differentiation and plasticity." RIKENIMS-JSI International Symposium, (Tokyo, Japan), June 2019

Cheroutre H. "Autoimmune Diseases: Searching for the Cause is Finding the Cure" Praespero Summit, (Vancouver, Canada), September 2019



Laboratory for
Inflammatory Regulation

Team Leader: Takashi Tanaka

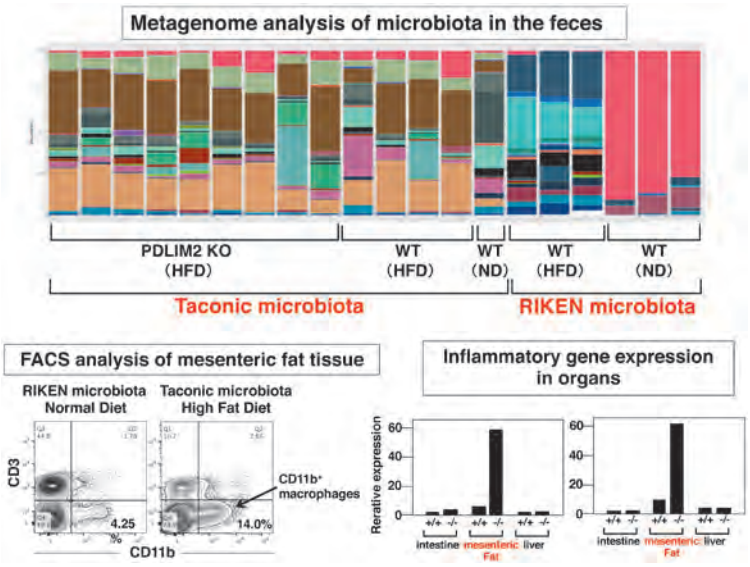


Figure: Analysis of microbiota-dependent development of NASH in PDLIM2-deficient mice
Metagenome analysis of the microbiota composition in wild-type and PDLIM2 deficient mice with RIKEN or Taconic microbiota, fed with normal (ND) or high fat diet (HFD) (upper panel). The accumulation of CD11b$^+$ macrophages in mesenteric fat tissue of mice with Taconic microbiota fed a high fat diet (HFD) (lower left panel). Inflammatory cytokine gene expression in intestine, mesenteric fat tissue, and liver of wild-type and PDLIM2 deficient mice (lower right panel).

Recent Major Publications

Orimo T, Sasaki I, Hemmi H, Ozasa T, Fukuda-Ohta Y, Ohta T, Morinaka M, Kitauchi M, Yamaguchi T, Sato Y, Tanaka T, Hoshino K, Katayama KI, Fukuda S, Miyake K, Yamamoto M, Satoh T, Furukawa K, Kuroda E, Ishii KJ, Takeda K, Kaisho T. Cholera toxin B induces interleukin-1β production from resident peritoneal macrophages through the pyrin inflammasome as well as the NLP3 inflammasome. ***Int Immunol*** 31, 657-668 (2019)

Kimura A, Kitajima M, Nishida K, Serada S, Fujimoto M, Naka T, Fujii-Kuriyama Y, Sakamato S, Ito T, Handa H, Tanaka T, Yoshimura A, Suzuki H.NQO1 inhibita the TLR-dependent production of selective cytokines by promoting IκB-ζ degradation. ***J Exp Med*** 215, 2197-2209 (2018)

Invited Presentation

Tanaka T. "Microbiota-dependent development of non-alcoholic steatohepatitis (NASH) in PDLIM2-deficient mice" ZPR-RIKEN Joint Symposium: Integrative Personalised Medicine -Connecting genomics, microbiomics and metabolomics, (Tubingen, Germany), July 2018

Tanaka T. "Biological function of Nahlsgen® to control inflammatory responses in the skin" The 117th Annual Meeting of the Japanese Society for Dermatology (Hiroshima, Japan), June 2018

Tanaka T. "Biological function of Nahlsgen® to control inflammatory responses in the skin" I.T.O. Users Meeting (Osaka, Japan), August 2018

The inflammatory response is critical for immune cells to fight invading microbial pathogens. However, excessive and prolonged inflammation may cause massive damage to the host, indicating that regulatory mechanisms to promptly terminate inflammatory responses are important to prevent immunopathology. Our research goal is to identify a series of key negative regulators of inflammation and to 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. NASH is clinically important, since 10-20% of NASH case can progress to liver cirrhosis and hepatocellular carcinoma. However, molecular mechanisms underlying the development of NASH remain unclear. Previously, we reported that PDLIM2, a nuclear ubiquitin E3 ligase containing PDZ and LIM domains, functions as a ubiquitin E3 ligase for NF-κB and STAT3/4 transcription factors, thereby negatively regulating inflammatory responses. Recently, we found that PDLIM2-deficient mice spontaneously develop human NASH-like pathology, but only when we colonized them with gut microbiota of mice from Taconic Farms and fed them a higher (15%) fat-containing diet. The colonization of Taconic microbiota and/or the intake of a higher fat diet changes the composition of the gut microbiota and induces the infiltration of CD11b-positive macrophages into mesenteric fat tissue. Notably, the expression of several inflammation-related genes was enhanced in mesenteric fat tissue, but not in the intestine, of PDLIM2-deficient mice compared to wild-type mice. Moreover, the amount of various metabolites in the feces and peripheral blood was significantly different between wild-type and PDLIM2-deficient mice. These data suggest that the Taconic microbiota and a higher fat diet may cause dysbiosis, which allows pathogenic microbiota-derived metabolites to enter the mesenteric vein and induce excessive inflammation, first in the mesenteric fat tissue and then in the liver, leading to the onset of NASH.

Laboratory for
Cytokine Regulation

Team Leader: Masato Kubo

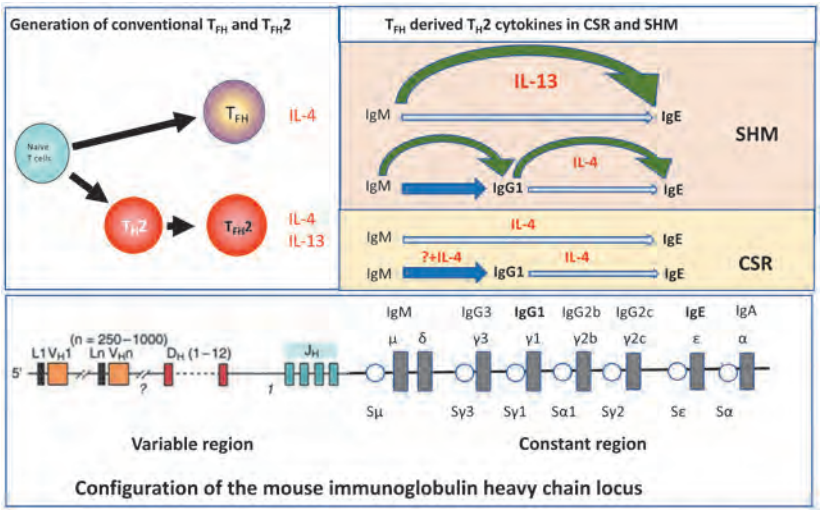


Figure: T_{FH} derived IL-4 and IL-13 independently regulate class switch recombination (CSR) and somatic hypermutation (SHM)
In the mouse immunoglobulin heavy chain locus, T_{FH} derived IL-4 regulates CSR of IgG1 and IgE, but there is no evidence that it controls SHM. Most high affinity IgE-producing cells are generated from high affinity IgG1 cells as a result of sequential class switching. This CSR process is also regulated by IL-4. On the other hand, our studies indicate that $T_{FH}2$-derived IL-13 can regulate SHM of IgE.

Recent Major Publications

Takamura S, Kato S, Motozono C, Shimaoka T, Ueha S, Matsuo K, Miyauchi K, Masumoto T, Katsushima A, Nakayama T, Tomura M, Matsushima K, Kubo M, Miyazawa M. Interstitial-resident memory $CD8^+$ T cells sustain frontline epithelial memory in the lung, ***J Exp Med*** 216, 2736-2747 (2019)

Sasaki T, Yajima T, Shimaoka T, Ogawa S, Saito T, Yamaoka K,Takeuchi T, Kubo M. Synergistic effect of IgG4 antibody and CTLs causes tissue inflammation in IgG4-related disease. ***Int Immunol*** pii: dxz073 (2019)

Sarkander J, Hojyo S, Mursell M, Yamasaki Y, Wu TY, Tumes DJ, Miyauchi K, Tran CL, Zhu J, Löhning M, Hutloff A, Mashreghi MF, Kubo M, Radbruch A, Tokoyoda K. Enhanced cell division is required for the generation of memory CD4 T cells to home to their proper location Journal. ***Front Immunol*** 10, 3113 (2020)

Invited presentations

Kubo M. "Germinal Center and the broadly protective antibody to Influenza" The 3rd Annual Chiba University-UCSD Symposium in conjunction with US-Japan Immunology and International Immunological Memory and Vaccine Forum (San Diego, USA), February 2019

Kubo M. "Amplification device for circulation tumor cells (CTCs) in liver cancer patients" 4th International BioMedical Interface Symposium (Hsinchu, Taiwan), March 2019

Kubo M. "Role of cytokine signal in atopic dermatitis" The 118th Annual Meeting of the Japanese Dermatological Association (Nagoya, Japan), June 2019

Kubo M. "Role of type 2 Follicular Helper T cells in anaphylaxis" The 10th anniversary of the discovery of Bcl6 in Tfh cells (Chun'an, China), July 2019

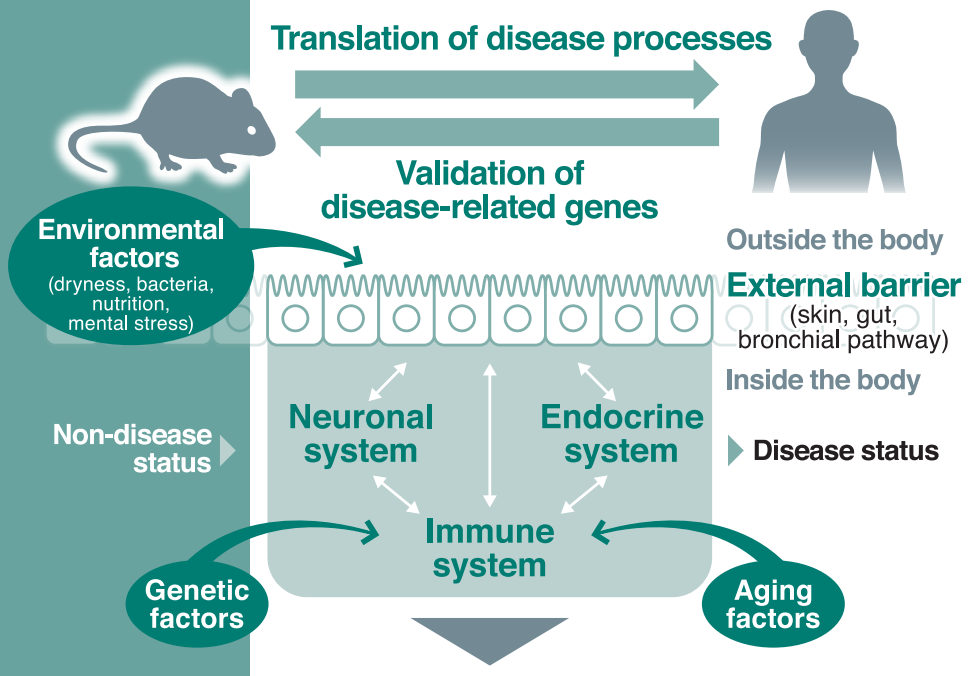
Kubo M. "The Big Crest of a New Wave – Role of T_{FH} and T_H2 cells in anaphylaxis responses" The 30th Anniversary International Symposium of Research Institute for Biomedical Sciences Tokyo University of Science (Tokyo, Japan), October 2019

$CD4^+$ helper T cells consist of T follicular helper (T_{FH}) cells and other effector T cell subsets including T_H1, T_H2, and T_H17 cells, and play central roles in various adaptive immune responses and in inflammatory diseases. My research group has focused mainly on allergic responses, including allergic rhinitis, food allergy and atopic dermatitis.

Anaphylaxis is life-threatening allergic reaction caused by massive degranulation of mast cells through IgE-FcεR crosslinking. Studies of murine anaphylaxis models indicate that the responsible IgE antibodies should bind allergens with high affinity. However, the potential role of T_{FH} for the generation of high affinity IgE remains unclear. We found that IL-13-producing T_{FH} cells, which we designated as $T_{FH}2$ cells, but not conventional T_{FH} cells, caused severe anaphylaxis. The $T_{FH}2$ cells developed from conventional T_H2 cells after antigen sensitization and acquired several overlapping features of both T_{FH} and T_H2 cells. Our studies demonstrated that IL-13 secreted by $T_{FH}2$ cells has a profound effect on the affinity maturation of IgE^+ GC-B cells. The high affinity IgE antibodies arise prior to the emergence of high affinity IgG1 antibodies, and IL-13 deficiency in the $T_{FH}2$ cells selectively impaired affinity maturation of IgE, but not IgG1. Therefore, our studies demonstrate that $T_{FH}2$ cell-derived IL-13 plays an important role to regulate the affinity maturation of IgE, independent of sequential class switching of high affinity IgG1-producing B cells.

Persistent T_H2 sensitization is highly correlated with atopic dermatitis (AD), a skin disease of complex etiology. We found that *Stat3*$^{flox/flox}$ K5-*Cre* mice, which lack STAT3 in keratinocytes, developed T_H2-dependent AD-like eczema. Our time-course RNA-sequencing analysis demonstrated that the STAT3 skin defect resulted in an alteration in the skin environment, leading to an increased susceptibility to *Staphylococcus aureus* colonization and an increase in the threshold of NFκB activation. The *S. aureus* bacteria caused increased expression of skin-derived thymic stromal lymphopoietin (TSLP), leading to the T_H2-mediated skin inflammation.

Division of Disease Systems Biology



Division of Disease Systems Biology will elucidate the regulation of homeostasis and disease onset as a dynamic living system.

Laboratory for
Developmental Genetics

Team Leader: Haruhiko Koseki

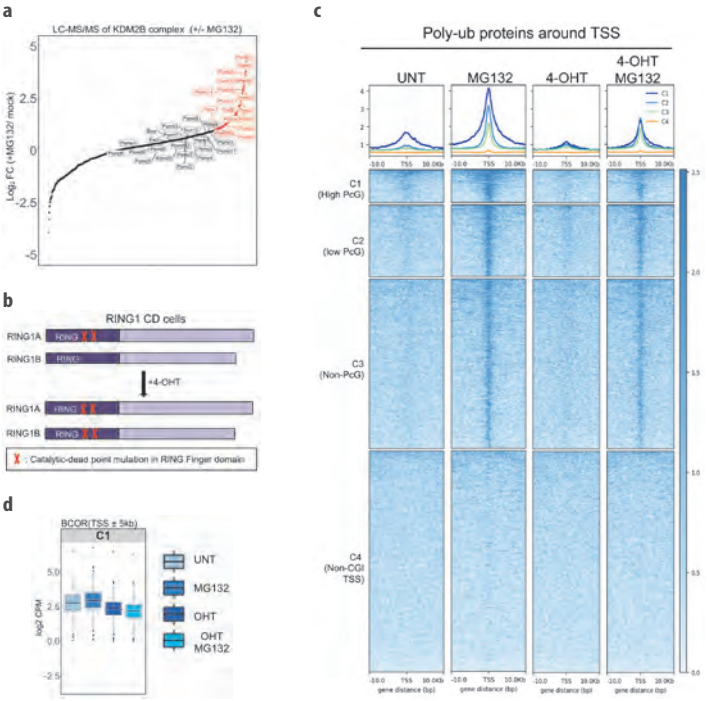


Figure: Self-ubiquitination of PCGF1-PRC1 is coupled to 26S proteasome-mediated degradation

(a) Endogenous IP mass spectrometry of KDM2B complexes shows that 26S proteasome subunits associate with the complex. The label free quantification intensity of the bait (KDM2B) over mock control is plotted with the log ratio between KDM2B purified from proteasome inhibitor (MG132)-treated cells versus non-treated cells. Peptides that are enriched more than two-fold are shown in red font.

(b) Schematic of the PRC1 catalytic dead (CD) cell lines. In RING1 CD cells, RING1A is constitutively mutated (RING1A I50A/D53K) in the RING finger domain and 4-OHT administration causes conversion of RING1B into catalytically inactive form (RING1B I53A/D56K).

(c) Heat map representations of poly-ubiquitinated proteins in wild type and RING1 CD ES cells treated with MG132 and/or 4-OHT for 3 hours. TSS are clustered into 4 groups according to ChIP-seq profiles of RING1B.

(d) A boxplot showing the change in chromatin binding of BCOR upon MG132 and/or 4-OHT treatment in RING1 CD cells.

Recent Major Publications

Healy E, Mucha M, Glancy E, Fitzpatrick DJ, Conway E, Neikes HK, Monger C, Van Mierlo G, Baltissen MP, Koseki Y, Vermeulen M, Koseki H, Bracken AP*. PRC2.1 and PRC2.2 Synergize to Coordinate H3K27 Trimethylation. ***Mol Cell*** 76, 437-452.e6 (2019)

Fursova NA, Blackledge NP, Nakayama M, Ito S, Koseki Y, Farcas AM, King HW, Koseki H, Klose RJ. Synergy between Variant PRC1 Complexes Defines Polycomb-Mediated Gene Repression. ***Mol Cell*** 74, 1-17 (2019)

Matsuda M, Ono R, Iyoda T, Endo T, Iwasaki M, Tomizawa-Murasawa M, Saito Y, Kaneko A, Shimizu K, Yamada D, Ogonuki N, Watanabe T, Nakayama M, Koseki Y, Kezuka-Shiotani F, Hasegawa T, Yabe H, Kato S, Ogura A, Shultz LD, Ohara O, Taniguchi M, Koseki H, Fujii SI, Ishikawa F. Human NK cell development in hIL-7 and hIL-15 knockin NOD/SCID/IL2rgKO mice. ***Life Sci Alliance*** 2, e201800195 (2019)

Invited presentations

Koseki H. "Cancer Immunotherapy by iPSC-derived NKT cells" The 57th Annual Meeting of the Japan Society of Clinical Oncology (Fukuoka, Japan) October 2019

Koseki H. "Variant PRC1 in cellular differentiation" The 91th Annual Meeting of the Genetics Society of Japan (Fukui, Japan) September 2019

Koseki H. "Variant PRC1 in cellular differentiation" Keble College (Oxford, UK) July 2019

Koseki H. "Variant PRC1 in cellular differentiation" Friedrich Miescher Institute for Biomedical Research (Basel, Switzerland) July 2019

Koseki H. "The role for enhancer of polycomb in chromatin replication and epigenetic inheritance" The 3rd RIKEN IMS-Stanford ISCBRM Joint Symposium (Stanford, USA) May 2019

The Developmental Genetics Laboratory not only pursues its own research program towards understanding epigenetic regulation of organ development, but also plays a pivotal role in maintaining core facilities for experimental animals and human induced pluripotent stem cells (iPSCs) and to lead a charged mission towards understanding the pathogenesis of human atopic dermatitis (AD).

In the epigenetics project, we are focused on understanding how CpG island (CGI) promoters are linked with enhancers and how epigenetic inheritance is maintained after DNA replication. In particular, we aim to elucidate the role of the ubiquitin/proteasome pathway to regulate binding of Polycomb Repressive complexes-1 (PRC1) to CGI promoters via their self-ubiquitinating activity. By analyzing mutants for components of PRC1 and Enhancer of Polycomb (EPC), we also aim to understand how epigenetic regulators are converged at replication forks (RFs) and contribute to either maintain or alter chromatin status.

A part of the group is devoted to the maintenance of a high-standard mouse facility in IMS. Through the Animal Core Facility, the group is also responsible for generation of knock-out and transgenic animals for the various research laboratories at the center and for the generation of germ-free, gnotobiote and humanized mice.

We have begun a study to apply iPSC technology for cancer immunotherapy. The core facility for iPSC research is engaged in developing efficient protocols to reprogram various lymphocytes and induce differentiation of iPSCs into T lymphocytes with anti-tumor activity. We are particularly engaged in the generation of iPSC-derived NKT cells towards their clinical use for cancer therapy, and are about to initiate a Phase I clinical study to evaluate their safety. This research is mainly supported by the Agency for Medical Research and Development (AMED).

Laboratory for
Intestinal Ecosystem

Team Leader: Hiroshi Ohno

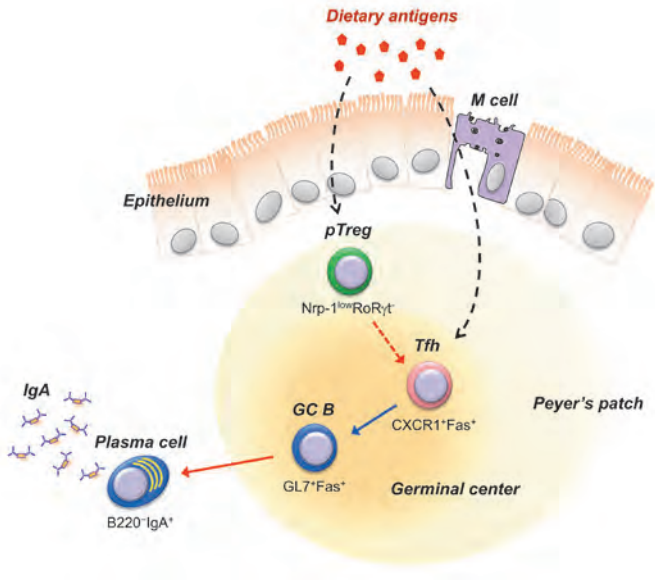


Figure: Dietary antigens are required for efficient Peyer's patch IgA responses
Mice fed with dietary antigen-free elemental diet show reduced numbers of Neuropirin-1^{low}RoRγt^{-} peripherally derived regulatory T cells (pTregs) and CXCR1^{+}Fas^{+} follicular helper T cells (Tfh), as well as GL7^{+}Fas^{+} germinal center B cells (GC B) in Peyer's patches. As a result, there are fewer B220^{-}IgA^{+} plasma cells in the intestinal lamina propria and less fecal IgA. Taken together with the study reporting that Foxp3^{+} T cells convert into Tfh in Peyer's patches, our data suggest that dietary antigens are required for the differentiation of pTreg, which possibly give rise to Tfh (dietary antigens may also be directly involved in Tfh differentiation), in turn promoting the differentiation of GC B cells into IgA-producing plasma cells.

Recent Major Publications

Hara S, Sasaki T, Satoh-Takayama N, Kanaya T, Kato T, Takikawa Y, Takahashi M, Tachibana N, Kim KS, Surh CD, Ohno H. Dietary Antigens Induce Germinal Center Responses in Peyer's Patches and Antigen-Specific IgA Production. ***Front Immunol*** 10, 2432 (2019)

Matsuda C, Kato T, Inoue-Suzuki S, Kikuchi J, Ohta T, Kagawa M, Hattori M, Kobayashi H, Shiba D, Shirakawa M, Mizuno H, Furukawa S, Mukai C, Ohno H*. Dietary intervention of mice using an improved Multiple Artificial-gravity Research System (MARS) under artificial 1*g*. ***NPJ Microgravity*** 5, 16 (2019)

Kanaya T, Sakakibara S, Jinnohara T, Hachisuka M, Tachibana N, Hidano S, Kobayashi T, Kimura S, Iwanaga T, Nakagawa T, Katsuno T, Kato N, Akiyama T, Sato T, Williams IR, Ohno H. Development of intestinal M cells and follicle-associated epithelium is regulated by TRAF6-mediated NF-κB signaling. ***J Exp Med*** 215, 501-519 (2018)

Invited presentations

Ohno H. "Gut microbiota and autoimmune diseases" 17th International Congress of Immunology (IUIS2019) (Beijing, China) October 2019

Ohno H. "Gut microbiota and autoimmune diseases" The Korean Association of Immunologists International Meeting 2019 (Seoul, Korea) October 2019

Satoh-Takayama N. "Group 3 innate lymphoid cells involved in the inflammation and diseases" The Japan Shock Society (Tsu, Japan) July 2019

Ohno H. "Impact of small intestinal bacteria on the pathogenesis of experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis" 13th INTERNATIONAL SCIENTIFIC CONFERENCE ON PROBIOTICS, PREBIOTICS, GUT MICROBIOTA AND HEALTH (Plague, Czech Republic) June 2019

Ohno H. "Impact of small intestinal bacteria on the pathogenesis of experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis" Korean Society for Biochemistry and Molecular Biology (KSBMB) International Conference 2019 (Jeju Island, Korea) June 2019

Enormous numbers of commensal bacteria, collectively called the gut microbiota, reside in our intestines. We do not unconditionally accept those microorganisms. Instead, the intestinal immune system somehow senses the types and quantity of bacteria in the gut lumen and attempts to contain them. On the other hand, the gut microbiota shapes the host immune system. Furthermore, the host-gut microbiota interaction deeply impacts our physiology and pathology. We are studying this sophisticated and complex host-gut microbiota interaction by applying an integrated omics approach, where different layers of cyclopedic analyses are combined, including (meta) genomics, epigenomics, (meta) transcriptomics, and metabolomics.

To evoke immune responses against gut microbes, the responses have to be delivered across the intestinal epithelial barrier to gut-associated lymphoid tissue (GALT) such as Peyer's patches. This delivery is thought to be achieved mainly by a unique subset of epithelial cells, M cells. These cells reside in a limited region of the epithelial layer called the follicle-associated epithelium (FAE), overlaying the GALT lymphoid follicles. The FAE has unique features distinct from the surrounding villous epithelium, and we are investigating its development. We are studying the function and differentiation of M cells at the molecular level and we have identified M cell-specific bacterial uptake receptors and signaling pathways for M-cell differentiation, including key transcription factors, as well as humoral factors regulating the FAE characteristics.

We are also investigating the molecular basis of the impact of the gut microbiota and its metabolites, as well as food antigens, on the gut immune system and host metabolic status. In addition, we are studying the impact of the gut microbiota on diseases such as pediatric allergic diseases, type 2 diabetes, and autoimmune diseases.

Laboratory for

Integrative Genomics

Team Leader: Osamu Ohara

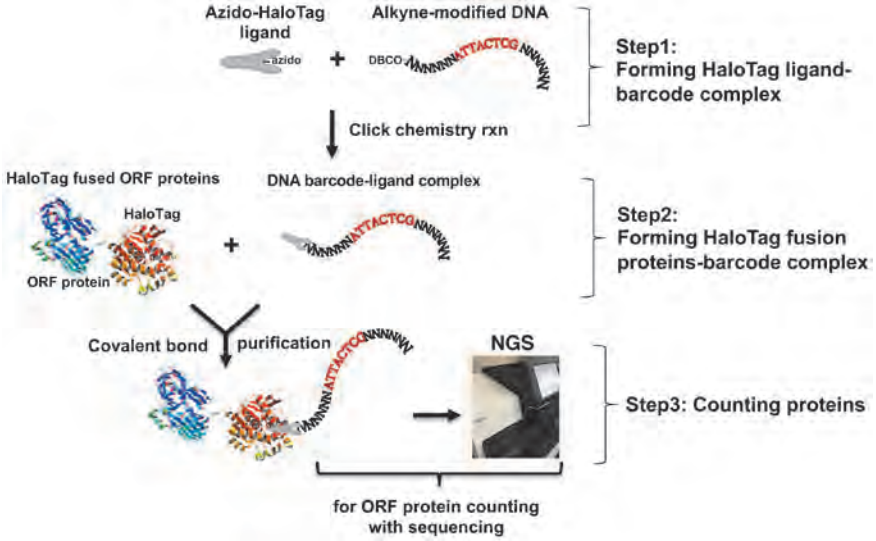


Figure: A Schematic flow of HaloTag protein barcoding labeling
Click chemistry is used for preparation of a HaloTag ligand with DNA barcode sequences. Because the HaloTag protein moiety is simultaneously and covalently labeled with the HaloTag ligand carrying DNA barcodes, the resultant HaloTag fusion proteins with DNA molecular barcode are allowed to interact with binding partners and the number of bound HaloTag fusion proteins is counted by the DNA barcoding method on a next-generation DNA sequencer.

Recent Major Publications

Shimizu K, Sato Y, Kawamura M, Nakazato H, Watanabe T, Ohara O, Fujii SI. Eomes transcription factor is required for the development and differentiation of invariant NKT cells. ***Commun Biol*** 2, 150 (2019)

Kawashima Y, Watanabe E, Umeyama T, Nakajima D, Hattori M, Honda K, Ohara O. Optimization of Data-Independent Acquisition Mass Spectrometry for Deep and Highly Sensitive Proteomic Analysis. ***Int J Mol Sci*** 20, 5932 (2019)

Yazaki J, Kawashima Y, Ogawa T, Kobayashi A, Okoshi M, Watanabe T, Yoshida S, Kii I, Egami S, Amagai M, Hosoya T, Shiroguchi K, Ohara O. HaloTag-based conjugation of proteins to barcoding-oligonucleotides. ***Nucleic Acids Res*** 48, e8 (2020)

Invited presentations

Ohara O. "Challenges to primary immunodeficiencies from genome sciences" The 10th Q-PID Meeting (Fukuoka, Japan) November 2019

Ohara O. "A trend in omics laboratory medicine: Form genome-first to omics-first" The 66th Annual Meeting of Japanese Society of Laboratory Medicine (Okayama, Japan) November 2019

Ohara O. "Regulation of cell society and allergy: An approach from omics measurements" The 56th Annual Meeting of the Japanese Society of Pediatric Allergy and Clinical Immunology (Chiba, Japan) November 2019

As the situation of genomics in biology has changed dramatically over the past decades, and research activities in our laboratory have been modified accordingly, we still maintain our three-pronged approach as follows: Central technical service (non-interactive technical support for researchers in the center), collaborative research programs, and technology development activities. As collaborative research, our laboratory is currently involved in many intramural and extramural collaborations and various strategic projects organized by the center.

However, other than the collaborative research and central support, we certainly keep in mind that technology development is another important mission of my laboratory. For this purpose, in 2019, we focused our efforts on method development for the integration of transcriptomic and proteomic data. In this regard, it should be noted that we recently applied a data-independent acquisition approach to mass spectrometry-based proteomics and successfully obtained high quality quantitative proteome data (*Int. J. Mo .Sci.* 2019 20(23)). In addition, in 2019, we developed a new sensitive and quantitative method to monitor protein-protein interactions (Fig. 1, Nucleic Acids Res. 2020 48(2):e8). This method is based on a molecular barcoding method by next-generation DNA sequencing, which was originally reported by Shiroguchi et al. (*Proc Natl Acad Sci USA*. 2012 109(4):1347-52), and, thereby, enables us to quantify the number of interacting partner molecules with extremely high sensitivity and accuracy. Although current omics analyses are focused only on molecular profiles in terms of their quantities, we believe more functional aspects of biomolecules should become targets in the next-generation omics analyses. Towards this end, this molecular barcoding method to assay for protein-protein interactions will make a major contribution.

Laboratory for
Mucosal Immunity

Team Leader: Sidonia Fagarasan

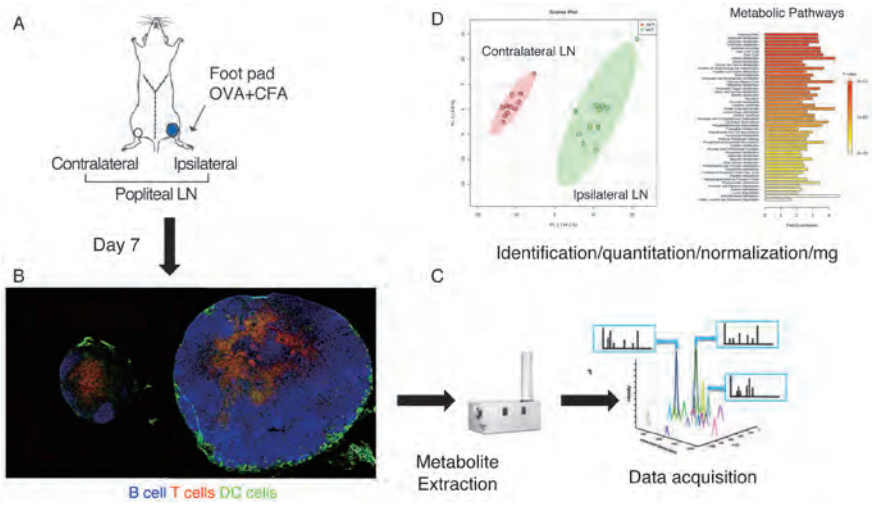


Figure: Experimental design
A. Foot pad immunization and LNs targeted to analyses. B. Immunization-induced enlargement of draining LN with massive expansion of B cells and T cells. C. LC-MS analyses of contralateral LN and ipsilateral LN. D. Metabolome differences between active (ipsilateral) LN and resting (contralateral) LN and enriched metabolic pathways observed. Dots indicate the number of LNs analyzed.

Elucidating the impact of the adaptive immune system in shaping of the intestinal microbiome landscape

We demonstrated that immunoglobulin A (IgA) is a crucial element that establishes an advanced symbiotic relationship with the microbiota (*Fagarasan et al., Science 2002, Suzuki et al., PNAS 2004*), and that not only the quantity but also the quality of IgA is critical for establishing mutualism within the intestinal ecosystem (*Kawamoto et al., Science 2012; Kawamoto et al., Immunity 2014*). Our most recent work revealed a novel mechanism by which glycosylated IgA efficiently coats bacterial surfaces, thereby modulating bacterial genes within the mucus environment (*Nakajima et al., JEM 2018*). We are performing comprehensive analyses of IgAs at transcriptional, translational and post-translational levels. We are inquiring whether IgA glycosylation profiles differ in different mucosal compartments, in immuno-competent versus immuno-deficient mice, or in the absence or presence of inflammation or dysbiosis. The impact of microbial dysbiosis on the host immune system in relation to autoimmunity and checkpoint blockade therapy will be tested in various mouse models.

Immunometabolism: mapping pathways and identifying metabolites with immune regulatory function

Immune cell activation and functional plasticity are closely linked to metabolic reprogramming required to supply the energy and substrates for such dynamic transformations. We hypothesize that many signaling pathways regulating lymphocyte functions are activated by small molecules derived from immune cell metabolism. We are exploring the metabolism of immune cells under resting and activated conditions to identify metabolites with potential regulatory function produced and secreted by B and T lymphocytes (Figure). We aim to uncover metabolic signatures of key immune cells responsible for immune memory and to identify small molecules derived from intracellular metabolism with immune regulatory functions. This knowledge is important, as targeting such metabolites or pathways will allow for selective regulation of immune responses.

Recent Major Publications

Hatae R, Chamoto K, Kim YH, Sonomura K, Taneishi K, Kawaguchi S, Yoshida H, Ozasa H, Sakamori Y, Akrami M, Fagarasan S, Masuda I, Okuno Y, Matsuda F, Hirai T, Honjo H. Combination of host immune metabolic biomarkers for the PD-1 blockade cancer immunotherapy. ***JCI Insight*** 5, e133501 (2020)

Sugiyama E, Guerrini MM, Honda K, Hattori Y, Abe M, Källback P, Andrén PE, Tanaka KF, Setou M, Fagarasan S, Suematsu M, Sugiura Y. Detection of a High-Turnover Serotonin Circuit in the Mouse Brain Using Mass Spectrometry Imaging. ***iScience*** 20, 359-372 (2019)

Nakajima A, Vogelzang A, Maruya M, Miyajima M, Murata M, Son A, Kuwahara T, Tsuruyama T, Yamada S, Matsuura M, Nakase H, Peterson DA, Fagarasan S, Suzuki K. IgA regulates the composition and metabolic function of gut microbiota by promoting symbiosis between bacteria. ***J Exp Med*** 215, 2019-2034 (2018)

Invited presentations

Fagarasan S. "Shaping of microbial landscape and systemic biochemistry by adaptive immune system" The 9th NIF Winter School on Advanced Immunology, (Awaji, Japan) January 2020

Fagarasan S. "Impact of PD-1 deficiency on microbiome and brain" The 20th International Conference in Systems Biology, OIST (Okinawa, Japan) November 2019

Fagarasan S. "Impact of PD-1 deficiency on microbiome and brain" International Union of Immunological Studies (IUIS) 2019 (Beijing, China) October 2019

Fagarasan S. "Excessive T cell activation in the absence of PD-1 affects behavior" NEURO 2019, New Trends in neuro-immunology (Niigata, Japan) July 2019

Laboratory for
Gut Homeostasis

Team Leader: Kenya Honda

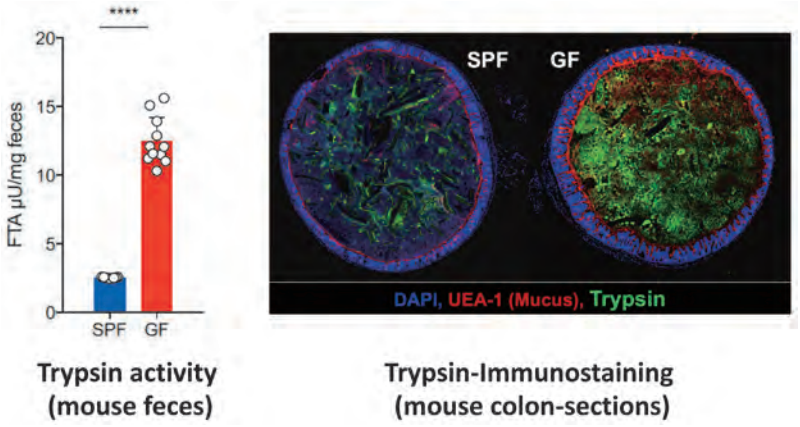


Figure: Fecal trypsin activity in GF and SPF mice
Trypsin is particularly abundant in the feces and colon of germ-free mice, whereas trypsin activity disappears in the SPF mouse colon, suggesting that microbiota play a central role in trypsin degradation.

A vast number of microorganisms reside in the intestine and maintain gut homeostasis. Our laboratory has been focusing on identifying commensal bacteria that induce specific branches of immune cells in the intestine. We have succeeded in isolating bacterial consortia that stimulate targeted immune responses, including induction of $CD4^+Foxp3^+$ regulatory T (Treg) cells, T_H17 cells, and T_H1 cells. We have also identified 11 bacterial strains that induce IFNγ-producing $CD8^+$ T cells in the gut and enhance the therapeutic efficacy of immune checkpoint inhibitors (ICPI) in mouse syngeneic tumour models. Clinical trials using our rationally defined 11 bacterial strains in combination with ICPI have just been initiated for selected types of cancer patients in the United States.

This year, we have identified and isolated trypsin-degrading bacteria from healthy human feces. Although trypsin is indispensable for the host as one of the digestive enzymes, it must be strictly regulated to avoid host injury due to its strong protease activity. Fecal proteome analysis revealed that trypsin is abundant in the colon of germ-free (GF) mice (Figure), but markedly reduced in specific pathogen-free (SPF) mouse colons, suggesting that commensal intestinal bacteria play a role in controlling trypsin. Furthermore, high trypsin activity was observed in fecal samples from both humans with inflammatory bowel disease (IBD) and IL-10-deficient mice with colitis, indicating that if trypsin remains proteolytically active in the large intestine, it is associated with a disturbance of gut homeostasis. Inoculation of a bacterial cocktail consisting of *Paraprevotella clara*, *Parabacteroides merdae*, and *Bacteroide uniformis*, isolated from healthy human feces, degraded trypsin in gnotobiotic mouse colons and protected the host from *Citrobacter rodentium* infection. Our preliminary results suggest that *P. clara* is responsible for trypsin-degradation, apparently by accelerating auto-degradation of trypsin itself.

In our most recent project, we have found that the atopic-like dermatitis that develops in *Tmem79*-deficient mice was significantly suppressed when mice were maintained under GF conditions, indicating that the inflammation is microbiota-dependent. In this dermatitis model, the presence of *Staphylococcus cohnii*, one of the mutualistic commensals in human and murine skin, had a negative correlation with the inflammation. Indeed, two of the isolated *S. cohnii* strains were able to prevent both *S. aureus*-driven dermatitis in *Tmem79*-deficient mice and imiquimod-induced psoriasis-like inflammation.

Recent Major Publications

Kim SG, Becattini S, Moody TU, Shliaha PV, Littmann ER, Seok R, Gjonbalaj M, Eaton V, Fontana E, Amoretti L, Wright R, Caballero S, Wang ZX, Jung HJ, Morjaria SM, Leiner IM, Qin W, Ramos RJJF, Cross JR, Narushima S, Honda K, Peled JU, Hendrickson RC, Taur Y, van den Brink MRM, Pamer EG. Microbiota-derived lantibiotic restores resistance against vancomycin-resistant Enterococcus. ***Nature*** 572, 665-669 (2019)

Ladinsky MS, Araujo LP, Zhang X, Veltri J, Galan-Diez M, Soualhi S, Lee C, Irie K, Pinker EY, Narushima S, Bandyopadhyay S, Nagayama M, Elhenawy W, Coombes BK, Ferraris RP, Honda K, Iliev ID, Gao N, Bjorkman PJ, Ivanov II. Endocytosis of commensal antigens by intestinal epithelial cells regulates mucosal T cell homeostasis. ***Science*** 363, pii: eaat4042 (2019)

Tanoue T, Morita S, Plichta DR, Skelly AN, Suda W, Sugiura Y, Narushima S, Vlamakis H, Motoo I, Sugita K, Shiota A, Takeshita K, Yasuma K, Riethmacher D, Kaisho T, Norman JM, Mucida D, Suematsu M, Yaguchi T, Bucci V, Inoue T, Kawakami Y, Olle B, Roberts B, Hattori M, Xavier RJ, Atarashi K, Honda K. A defined commensal consortium elicites CD8 T cells and anti-cancer immunity. ***Nature*** 565, 600-605 (2019)

Invited presentations

Honda K. "Mining the microbiota for microbial-based therapies" The 17th International Congress of Immunology (IUIS 2019) (Beijing, China) October 2019

Honda K. "Life Sciences - Microbiome and Health" STS forum 2019 - 16th Annual Meeting (Kyoto, Japan) October 2019

Honda K. "Mining the microbiota for microbial-based immunotherapies using gnotobiotes" Tsukuba Conference (Tsukuba, Japan) October 2019

Honda K. "Mining the Microbiota for Microbial-Based Immunotherapies" Kenneth Rainin Foundation 2019 Innovations Symposium (Honolulu, USA) July 2019

Honda K. "Gut microbiota-targeted therapeutic strategy" Cold Spring Harbor Asia conferences: Bacterial Infection & Host Defense (Suzhou, China) April 2019

Laboratory for
Skin Homeostasis

Team Leader: Masayuki Amagai

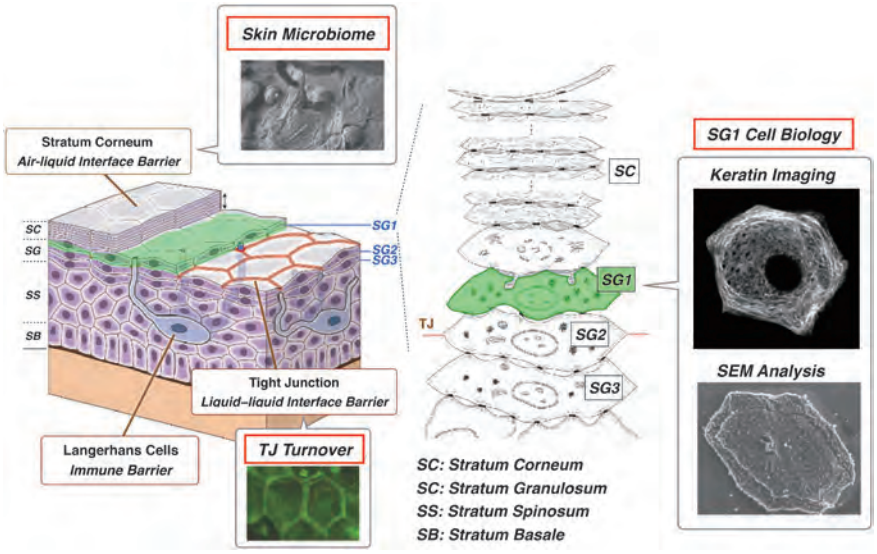


Figure: Comprehensive analysis of skin barrier homeostasis
Our team is trying to clarify the mechanisms of skin barrier homeostasis by focusing on the stratum corneum (SC), tight junctions (TJ), and SG1 cells. We established a live imaging system focusing on keratin and pH and using an optimized plasmid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

Skin is the place where immunity meets external antigens. Cutaneous sensitization is now considered to be the initial key step in many allergic disorders, including 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.

Epidermis, the outermost component of the skin, is composed of keratinized stratified squamous epithelia and consists of the stratum basale, stratum spinosum, stratum granulosum (SG), and stratum corneum (SC), from bottom to top. Our group has been focusing on the SC as an air-liquid barrier and the tight junction (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, yet 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. Our experimental approaches are comprehensive, combining molecular biology, biochemistry, ultrastructural anatomy, live imaging, microbiology, and systems biology. For example, recently, we succeeded in the visualization of keratin filaments in mouse SG cells using a combination of intravital imaging of Ca^{2+}/organelles/pH during cornification.

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

Recent Major Publications

Usui K, Kadono N, Furuichi Y, Shiraga K, Saitou T, Kawasaki H, Toyooka K, Tamura H, Kubo A, Amagai M, Matsui T. 3D *in vivo* imaging of the keratin filament network in the mouse stratum granulosum reveals profilaggrin-dependent regulation of keratin bundling. ***J Dermatol Sci*** 94, 346-349 (2019)

Someya T, Amagai M. Toward a new generation of smart skins. ***Nat Biotech*** 37, 382-388 (2019)

Invited presentations

Amagai M. "Cracking the Codes of Autoimmune and Allergic Skin Diseases." 47th Annual Meeting of the European Society of Dermatological Research (Salzburg, Austria) September 2017

Amagai M. "3D *in vivo* Imaging of Skin Barrier." International Investigative Dermatology 2018 (Florida, USA) May 2018

Amagai M. "Stratum corneum as niche to control skin microbiota." Japan-Singapore International Skin Conference 2019 (Singapore) April 2019

Amagai M. "Important advances in skin barrier function." 24th World Congress of Dermatology (Milan, Italy) June 2019

Amagai M. "Homeostatic mechanisms of skin barrier and their disruption in skin inflammation." Gordon Research Conferences on Epithelial Differentiation & Keratinization, (Maine, USA) July 2019

Laboratory for
Tissue Dynamics

Team Leader: Takaharu Okada

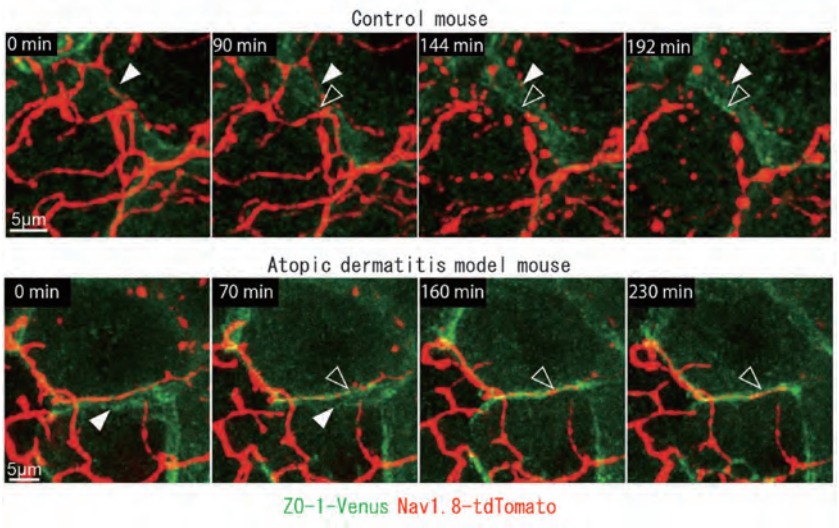


Figure: Epidermal nerve pruning at newly forming tight junctions is disturbed in the mouse model of atopic dermatitis
Time-lapse intravital images of nerve fibers pruned at a newly forming tight junction in the normal mouse epidermis (top) and of a nerve fiber co-localized with a newly forming tight junction without being pruned in the atopic dermatitis model mouse epidermis (bottom). Nav1.8-tdTomato and ZO-1-Venus are the reporters to visualize sensory nerves and tight junctions, respectively. Open and filled arrowheads indicate the new and old TJs, respectively.

Recent Major Publications

Mintz MA, Felce JH, Chou MY, Mayya V, Xu Y, Shui JW, An J, Li Z, Marson A, Okada T, Ware CF, Kronenberg M, Dustin ML, Cyster JG. The HVEM-BTLA axis restrains T cell help to germinal center B cells and functions as a cell-extrinsic suppressor in lymphomagenesis. ***Immunity*** 51, 310-323.e7 (2019)

Takahashi S, Ishida A, Kubo A, Kawasaki H, Ochiai S, Nakayama M, Koseki H, Amagai M, Okada T. Homeostatic pruning and activity of epidermal nerves are dysregulated in barrier-impaired skin during chronic itch development. ***Sci Rep*** 9, 8625 (2019)

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†. KLRG1^{+} effector CD8^{+} T cells lose KLRG1, differentiate into all memory T cell lineages, and convey enhanced protective immunity. ***Immunity*** 48, 716-729.e8 (2018) *equal contribution, †co-corresponding authors

Invited presentations

Okada T. "Dynamic homeostasis of epidermal sensory nerves and its breakdown caused by barrier dysfunction" World Allergy Congress 2019, JSA symposium (Lyon, France) December 2019

Okada T. "Imaging of epidermal nerves in barrier-impaired skin during chronic itch development" The 48th Naito Conference: Integrated Sensory Sciences-Pain, Itch, Smell and Taste (Sapporo, Japan) October 2019

Okada T. "Imaging of epidermal nerve dynamics in normal and inflammatory skin conditions" NEURO2019, Symposium 2S05a (Niigata, Japan) July 2019

The goal of our laboratory is to mechanistically understand the *in vivo* cellular dynamics that underlie tissue homeostasis and their breakdown during disease development. As a most recent focus, we study how barrier tissue function is maintained by interactions between different cell types such as peripheral nerves, epithelial cells, and immune cells. As a strategy for tackling this problem, we use multi-dimensional fluorescent imaging to analyze cellular activities in tissues. For example, our recent intravital imaging study has revealed a previously unknown mechanism by which epidermal sensory nerve endings are kept underneath the skin barrier during turnover of the epidermis. Our data have shown that the mechanism involves nerve pruning at tight junctions that are newly formed between keratinocytes in the granular layer of the epidermis. Furthermore, our imaging results have suggested that during the development of chronic itch caused by epidermal barrier impairment, this nerve pruning process is disturbed, and epidermal nerves are aberrantly activated. Thus, our work provides evidence that the nerve-keratinocyte interaction is important for the maintenance of skin sensory homeostasis. We are currently conducting studies to understand molecular mechanisms of the nerve-keratinocyte interaction, in collaboration with other groups inside and outside RIKEN. We will also investigate how sensory nerve activation and immune cell activation caused by epidermal barrier impairment affect each other.

Laboratory for Metabolomics

Team Leader: Makoto Arita

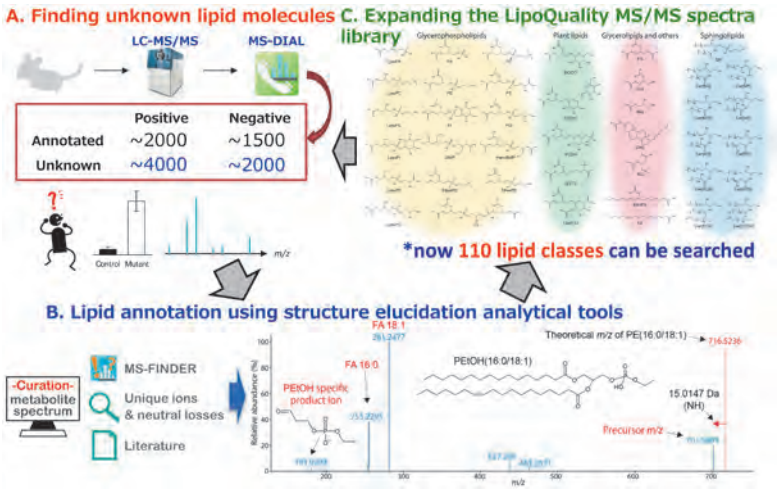


Figure: Advanced non-targeted lipidomics platform
Positive cycles of A-B-C will expand the LipoQuality MS/MS spectra library for better annotation in non-targeted lipidomics.

Lipids are extremely diverse molecules, thus, the precise determination of each molecular species of lipid, termed Lipo-Quality (Quality of Lipids), is a prerequisite not only to understand their biological functions in normal 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 lipid metabolites that regulate inflammation and tissue homeostasis.

Long-chain polyunsaturated fatty acids (LCPUFAs), such as docosahexaenoic acid (DHA, 22:6) and docosapentaenoic acid (DPA, 22:5), are unique lipids that are selectively enriched as membrane phospholipids in certain tissues such as testis, brain, and retina. We questioned how LCPUFAs are selectively enriched in those tissues and what their functional roles are there. We identified acyl-CoA synthetase 6 (ACSL6) as an enzyme that selectively incorporates LCPUFAs into membrane phospholipids in spermatids to support normal spermatogenesis. ACSL6 is highly expressed in differentiating spermatids, and *Acsl6* knockout mice have reduced levels of LCPUFA-containing phospholipids in their spermatids and display severe male infertility due to attenuated sperm number and function. These results clearly demonstrate that LCPUFAs are essential in maintaining normal male fertility.

We have developed a non-targeted lipidomics platform by taking advantage of Q-TOF (global lipid screening) and TripleQ (quantitative analyses) mass spectrometry. Our original system has great potential in the search for lipids of interest globally and for the identification of unknown lipids in a non-biased fashion. We applied this technology to comprehensively monitor the baseline lipid profiles of mouse plasma and tissues, and to monitor changes following dietary intake of different PUFAs, i.e. arachidonic acid, EPA, or DHA. These results offer a comprehensive picture of dietary PUFA metabolism in different tissues. They also provide an opportunity for data-driven hypotheses and biological insights into understanding the molecular mechanisms of how the balance of different PUFAs affects health and disease.

Recent Major Publications

Shishikura K, Kuroha S, Matsueda S, Iseki H, Matsui T, Inoue A, Arita M. Acyl-CoA synthetase 6 regulates long chain polyunsaturated fatty acid composition of membrane phospholipids in spermatids and supports normal spermatogenic processes in mice. ***FASEB J*** 33, 14194-14203 (2019)

Naoe S, Tsugawa H, Takahashi M, Ikeda K, Arita M. Characterization of lipid profiles after dietary intake of polyunsaturated fatty acids using integrated untargeted and targeted lipidomics. ***Metabolites*** 9, 241 (2019)

Miyata J, Fukunaga K, Kawashima Y, Watanabe T, Saitoh A, Hirosaki T, Araki Y, Kikawada T, Betsuyaku T, Ohara O, Arita M. Dysregulated fatty acid metabolism in nasal polyp-derived eosinophils from patients with chronic rhinosinusitis. ***Allergy*** 74, 1113-1124 (2019)

Invited Presentations

Arita M. "Omega-3 fatty acid metabolism that confers anti-inflammation and tissue homeostasis" The 7th International Conference on Food Factors (Kobe, Japan) December 2019

Arita M. "Biology of LipoQuality: Omega-3 fatty acid cascade that controls inflammation and tissue homeostasis" 16th International Conference on Bioactive Lipids in Cancer, Inflammation, and Related Diseases (Florida, USA) October 2019

Arita M. "Omega-3 fatty acid metabolism that controls inflammation and tissue homeostasis" 5th LipidALL International Lipid Symposium (Nanjing, China) October 2019

Arita M. "Polyunsaturated fatty acid metabolism that controls inflammation and tissue homeostasis" 2019 NHRI/IBMS joint International Conference on Inflammation and Disease (Taipei, Taiwan) October 2019

Arita M. "The importance of LipoQuality in biological systems" William Harvey Research Institute Seminar (London, UK) May 2019

Laboratory for
Microbiome Sciences

Team Leader: Masahira Hattori

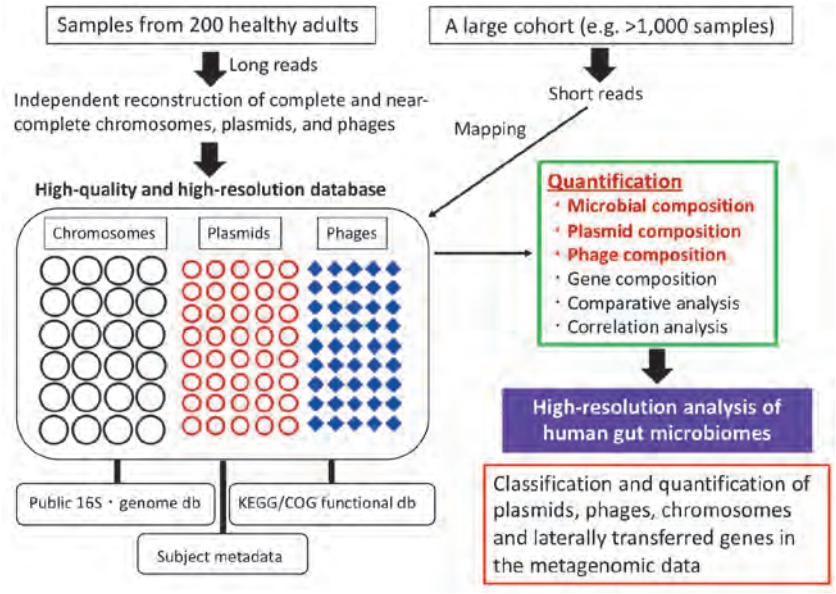


Figure: A new type of database composed of the three independent microbial genetic elements of chromosomes, plasmids, and bacteriophages in the human gut

The figure shows construction of a new type of database composed of the independently complied microbial chromosomes, plasmids, and bacteriophages (phages) from the long-read metagenomic data of approximately 200 individuals, which will be very useful for classification and quantification of the three genetic elements in the short-read metagenomic data of large cohorts.

Recent Major Publications

Suzuki Y, Nishijima S, Furuta Y, Yoshimura J, Suda W, Oshima K, Hattori M, Morishita S. Long-read metagenomic exploration of extrachromosomal mobile genetic elements in the human gut. ***Microbiome*** 7, 119 (2019)

Ohtsu A, Takeuchi Y, Katagiri S, Suda W, Maekawa S, Shiba T, Komazaki R, Udagawa S, Sasaki N, Hattori M, Izumi Y, Influence of Porphyromonas gingivalis in gut microbiota of streptozotocin-induced diabetic mice. ***Oral Dis*** 25, 868-880 (2019)

Nagata N, Tohya M, Fukuda S, Suda W, Nishijima S, Takeuchi F, Ohsugi M, Tsujimoto T, Nakamura T, Shimomura A, Yanagisawa N, Hisada Y, Watanabe K, Imbe K, Akiyama J, Mizokami M, Miyoshi-Akiyama T, Uemura N, Hattori M. Effects of bowel preparation on the human gut microbiome and metabolome. ***Sci Rep*** 9, 4042 (2019)

Invited presentations

Hattori M. "Elucidation of ecological and functional features of human microbiomes by metagenomics" The 156th Japanese Association of Medical Sciences (JAMS) Symposium (Tokyo, Japan) November 2019

Hattori M. "Metagenomics of human microbiomes including gut flora: Detailing the entity of microbial genetic elements linking to host's health and disease" The 28th Gut Flora Symposium (Tokyo, Japan) November 2019

Hattori M. "Metagenomics of the human microbiome" The 26th Annual Meeting of the Japanese Society for Chronobiology (Kanazawa, Japan) October 2019

Hattori M. "Exploration of ecological and functional features of human microbiomes by metagenomics" The 45th 'Chemistry and Biology' Symposium in the 2019 Annual Meeting of The Japan Society for Bioscience, Biotechnology and Agrochemistry (Tokyo, Japan) March 2019

Hattori M. "Overall ecological and functional features of the human gut microbiome" The 12th Annual Meeting of the Japanese Association for Gender-Specific Medicine (Saitama, Japan) January 2019

The Laboratory for Microbiome Sciences engages in intensive research on host-microbial interactions by elucidating the ecological, functional, and medical features of various microbial communities, such as human gut, oral, and skin microbiomes. Our team also develops bioinformatic and statistical tools for the analysis of metagenomic and genomic datasets from microbiomes and microbes produced by next-generation sequencers. Currently, we established a metgenomics platform using a long-read next-generation sequencer, PacBio Sequel, which generates much longer and more accurate contigs than the standard short-read sequencers such as Illumina HiSeq and MiSeq. This improvement is accomplished by assembly of metagenomic reads of ~10 kb from microbiome samples, consequently providing efficient reconstruction of high-quality chromosomes and bins, as well as complete sequences of extrachromosomal mobile genetic elements such as plasmids and bacteriophages. Thus, metagenomic sequencing using long-read PacBio Sequel provides a powerful approach to elucidate not only chromosomes and species, and their genes, but also extrachromosomal elements in the community. In addition, we also established a method for reconstruction of complete and near-complete genomes of individual microbial strains with high accuracy by the combined use of long-read PacBio Sequel and short-read sequencers. We are constructing a database composed of the independently compiled microbial chromosomes, plasmids and bacteriophages in the human gut from data of the long-read metagenomics of fecal samples from approximately 200 individuals. This new type of database, when combined with conventional short-read metagenomic datasets, will be of great use in human gut microbiome research for the classification and quantification of the three independent microbial genetic elements implicated in host health and disease.

Drug Discovery Antibody Platform Unit

Unit Leader: Toshitada Takemori

Table: Overview of HBV entry inhibitors

NTCP is an integral membrane protein that is exclusively expressed on the surface of hepatocytes. Several reagents have been developed to inhibit the HBV entry process, focusing on different classes. However, many of these reagents, except for our N6HB426 mAb and WL4 cyclic peptide, block the absorption of bile acid through NTCP, as defined by *in vitro* assays.

Substance	Molecule	Target	IC_{50}	Bile acid block	Reference
N6HB426*	mAb	NTCP	20-30 nM	>1,000 nM	Patented
WL4	Cyclic peptide	NTCP	660 nM	>5,000 nM	Cell Chem Biol (2018)
NPPD13325	Coumarin derivative	NTCP	12,500 µM	ND	Sci Rep (2018)
Rapamycin	Synthesized	NTCP	14,700 nM	ND	BBRC (2018)
Cyclosporin A	Cyclic peptide	NTCP	1,000 nM	block	Hepatology (2014)
SCYX1454139	Cyclosporin A derived	NTCP	179 nM	blocK	Hepatology (2014)
Myrcludex B	Synthetic N-acylated preS1	NTCP	80 pM	block	Intervirology (2014)
preS1 fragment	7524 BVS7 (21AA)	NTCP	20 nM	block	BMB Reports (2008)
preS1	47 AA	NTCP	8 nM	block	J Virol (2005)

*Estimated activity in an *in vitro* assay.

Recent Major Publications

Tanaka M, Ishige A, Yaguchi M, Matsumoto T, Shirouzu M, Yokoyama S, Ishikawa F, Kitabayashi I, Takemori T, Harada M. Development of a simple new flow cytometric antibody-dependent cellular cytotoxicity (ADCC) assay with excellent sensitivity. ***J Immunol Methods*** 464, 74-86 (2019)

Development of a mAb against human NTCP that inhibits HBV infection

Hepatitis B virus (HBV) is a hepatotropic virus that can establish a persistent infection in humans. Effective and safe vaccines are available and the efficacy against chronic infection with HBV was reported to be 95%. Efficacy against infection falls to 85% with age. Thus, vaccination is the key preventive measure. However, HBV occurrence remains high in South-East Asia and Africa, where HBV vaccination coverage remains suboptimal.

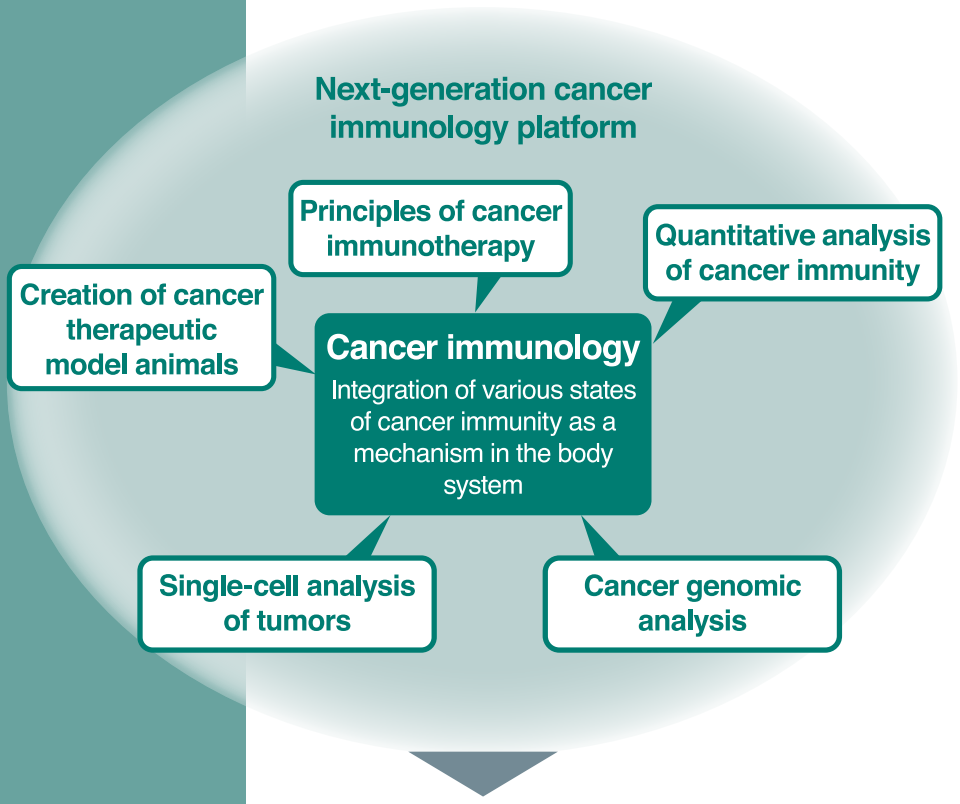
HBV infects 240 million people worldwide. In Japan, it is estimated that 1.3-1.5 million people are chronically infected with HBV. Most adults infected with the virus recover, but ~10% are unable to clear the virus. HBV infection leads to a wide range of liver diseases, such as fulminant hepatic failure, chronic hepatitis, cirrhosis, and hepatocellular carcinoma.

Current therapy includes antiviral agents, such as interferon therapy with peg-IFN alpha, but this rarely results in viral elimination. Antiviral agents for HBV include reverse transcriptase inhibitors, which are nucleoside or nucleotide analogues that can profoundly suppress HBV replication, but require long-term maintenance therapy. In addition, treatment can yield drug-resistant viruses, limiting efficacy, and there are sometimes adverse effects. Thus, there is still a medical need for an efficient HBV cure and immunomodulators.

As HBV binds via the preS1-domain of the viral L protein to the apical sodium-acid dependent bile acid transporter (NTCP), NTCP could be a key target for the development of anti-HBV agents. Accordingly, many HBV entry inhibitors have been developed, however, the majority of these inhibitors block not only the cellular entry of HBV, but also bile acid transport, which leads to significant adverse effects.

To obtain mAbs against human NTCP that are inhibitory for HBV infection, but not for bile acid transport, we immunized NTCP KO mice with NTCP proteins integrated into liposomes and with NTCP-expressing transfected cells. We enriched memory and activated B cells from immunized mice and used them for preparation of hybridomas. After screening of 27,000 hybridomas, we for the first time obtained a mAb that inhibits HBV entry *in vitro* into human liver cells with an IC50=20-30nM but does not inhibit bile acid transport. We will analyze the inhibitory activity of this mAb *in vivo* by utilizing human-liver chimeric mice.

Division of Cancer Immunology



Division of Cancer Immunology will explore novel principles of the immune system, focusing on tumor cells, and promote research for the establishment of novel therapeutics.

Laboratory for
Immunogenetics

Team Leader: Tadashi Yamamoto

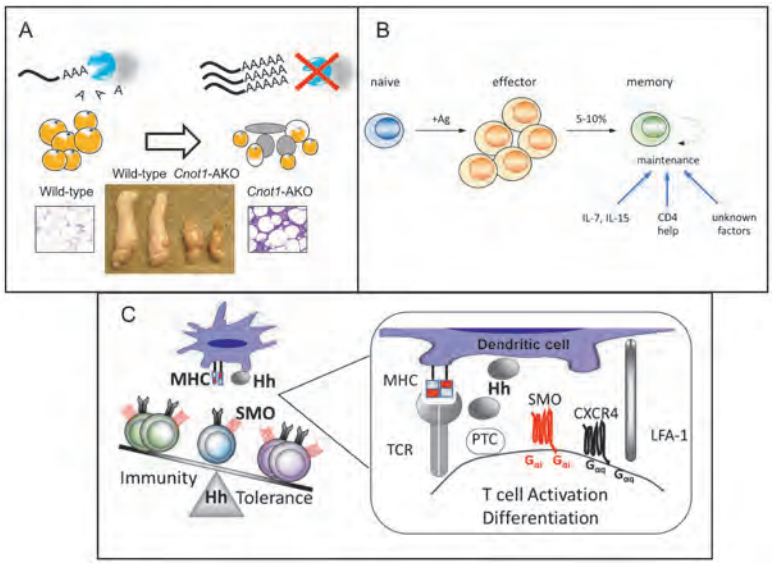


Figure: Research projects in the laboratory

A. A role for mRNA deadenylation in adipocyte identity and function

Loss of the CCR4-NOT complex function in adipocytes leads to lipodystrophy. Representative appearance and HE-stained sections of epididymal white adipose tissue in wild-type and adipose-tissue specific *Cnot1*-knockout (*Cnot1*-AKO) mice are shown (Takahashi et al, *Int J Mol Sci*. 20, pii:E5274, 2019)

B. Critical factors for the maintenance of memory CD8 T cells, which develop from naïve CD8 T cells upon peptide antigen (Ag) – Class I MHC encounter

This simplified diagram illustrates some of the factors involved in memory CD8 T cell maintenance, but our understanding of this process is far from complete.

C. Hedgehog signaling at the immune synapse.

Upon TCR engagement by cognate peptide-MHC on, for example, a dendritic cell, hedgehog ligand (Hh) is secreted into the immune synapse and initiates the patched (PTC)-mediated signaling cascade in the T cell. The smoothened (SMO) signal transducer competes for $G_{\alpha i}$ coupling with the CXCR4 chemokine receptor, thus, fortifying immune synapse stability. LFA-1 is an integrin that also stabilizes the immune synapse. The precise roles of Hedgehog signaling in immunity are not known.

1) Control of mRNA stability is one of the essential post-transcriptional mechanisms to regulate gene expression levels. We found that suppression of mRNA deadenylase, an enzyme that triggers mRNA degradation by shortening the polyA tail, leads to abnormal development and function in various tissues. We have been investigating how the mRNA deadenylase regulates tissue function. Since clinical studies have identified mutations in mRNA decay-related genes in human diseases, we aim to understand the relationship between disruption of mRNA decay and human diseases. Our long-term goal is to develop new therapeutics for human diseases caused by impaired mRNA decay.

2) Memory CD8 T cells are long-lived antigen (Ag)-specific CD8 T cells that protect us from intracellular pathogens and tumors. Pools of memory CD8 T cells are maintained at a stable size over a long period, but the mechanisms that affect their long-term persistence still remain incompletely understood. Our study aims to reveal how memory CD8 T cell numbers and functions are maintained *in vivo*. Results of this research may provide new vaccine strategies for the induction of protective immunity to tumors and chronic infections.

3) In recent years, immunotherapy has become an indispensable arm of cancer treatment, but many questions about the role of the immune system in cancer and its progression are still far from being answered. Monoclonal antibody-based checkpoint inhibitors have revolutionized the field, but have been shown to be more efficient when used in combination with other chemotherapeutic or biological agents, by providing more precision, reducing side effects, and improving efficacy. A better understanding of how different activating and inhibitory signaling cascades regulate effective and persistent immunological responses is needed. We aim to understand how Hedgehog signaling at the immune synapse interacts with other T cell signaling pathways and how they are affected in cancer and autoimmunity.

Recent Major Publications

Mostafa D, Takahashi A, Yanagiya A, Yamaguchi T, Abe T, Kureha T, Kuba K, Kanegae Y, Furuta Y, Yamamoto T, Suzuki T. Essential functions of the CNOT7/8 catalytic subunits of the CCR4-NOT complex in mRNA regulation and cell viability. ***RNA Biology*** 17, 403-416 (2020)

Yazaki J, Kawashima Y, Ogawa T, Kobayashi A, Okoshi M, Watanabe T, Yoshida S, Kii I, Egami S, Amagai M, Hosoya T, Shiroguchi K, Ohara O. HaloTag-based conjugation of proteins to barcoding-oligonucleotides. ***Nucleic Acids Res*** 48, e8 (2020)

Takahashi A, Takaoka S, Kobori S, Yamaguchi T, Ferwati S, Kuba K, Yamamoto T, Suzuki T. The CCR4-NOT deadenylase complex maintains adipocyte identity. ***Int J Mol Sci***. 20, pii:E5274 (2019)

Invited Presentations

Setoguchi R. "Chronic IFN-γ signals impair memory CD8 T cell maintenance" The 28th Molecular Immunology Forum Tokyo (Tokyo, Japan) March 2019

Shiroguchi K. "The combination of live imaging and whole gene expression analysis for single cell studies" Single Cell Surveyor Symposium (Uppsala, Sweden) March 2019

Shiroguchi K. "Linking cell dynamics and gene expression by integration of live imaging and RNA sequencing" LSBM Symposium 2019 (Hakone, Japan) April 2019

Shiroguchi K. "Linking cell dynamics and gene expression:an automated system for combining live cell imaging and single-cell RNA sequencing" The 57th Annual Meeting of The Biophysical Society of Japan (Miyazaki, Japan) September 2019

Shiroguchi K. "Combining live imaging and single-cell whole gene expression analysis by developing an automated cell picking system" The 62nd Symposium of the Japanese Society of Microscopy (Saitama, Japan) November 2019

Laboratory for

Medical Science Mathematics

Team Leader: Tatsuhiko Tsunoda

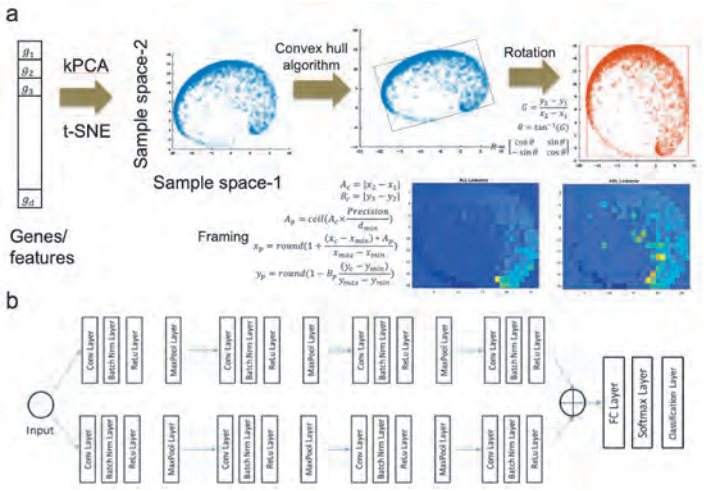


Figure: DeepInsight – deep learning for omic data analysis
(a) Pipeline. Transformation from feature vector to image pixels. (b) Parallel convolutional neural network (CNN) architecture used in DeepInsight.

Recent Major Publications

Choobdar S, Ahsen ME, Crawford J, Tomasoni M, Fang T, Lamparter D, et al. Assessment of network module identification across complex diseases. ***Nat Methods*** 16, 843-852 (2019)

Menden MP, Wang D, Mason MJ, Szalai B, Bulusu KC, Guan Y, et al. Community assessment to advance computational prediction of cancer drug combinations in a pharmacogenomic screen. ***Nat Commun*** 10, 2674 (2019)

Sharma A*, Vans E, Shigemizu D, Boroevich KA, Tsunoda T*. DeepInsight: a methodology to transform a non-image data to an image for convolution neural network architecture. ***Sci Rep*** 9, 11399 (2019)

Invited Presentations

T. Tsunoda. "Data-driven Medical Sciences with Omic Analysis". Moonshot International Symposium (Tokyo, Japan) December 2019

T. Tsunoda. "Exploring etiologies, sub-classification, and risk prediction of diseases based on big-data analysis of clinical and whole omics data in medicine." CREST Joint International Symposium on Big Data (Kanagawa, Japan) December 2019

T. Tsunoda. "Medical Big Data Analysis for Precision Medicine." CREST Joint International Symposium for Big Data (Kyoto, Japan) March 2019

T. Tsunoda. "Cancer heterogeneity and immunology for precision medicine." CREST International Symposium on Big Data Application (Tokyo, Japan) January 2019

T. Tsunoda. " Prediction, treatment and onset of diabetes and related disease by whole genome sequence analysis" AI Medical Application Study Group (Tokyo, Japan) August 2019

Recently, effective utilization of rapidly developing omic profiling technologies and, in particular, the introduction of personalized/precision/preventive medicine have become major goals of medical research. This paradigm shift requires moving away from traditional approaches that do not adequately consider the individual characteristics of each patient. Our laboratory develops strategies to address these challenges by bringing the ideas and methods from mathematical and computational sciences to the medical domain. The first part of our approach is driven by integrative analysis of clinical and omic data and aims to explore the etiologies of intractable diseases. Next, we classify each disease into finer categories, such as types of anti-cancer immune responses, using molecular profiles and, then, clarify underlying causal mechanisms with systems-based approaches. Lastly, we apply mathematical and machine learning techniques to infer optimal therapy for each patient to guide treatment decisions by their hospital or clinic. Similar approaches can be used for disease prevention based on an individual's medical history. Our past and current research projects include: (1) Investigating the relationship between tumor microenvironment, subclonal diversity, drug response and patient prognosis in lung, colorectal and liver cancer; (2) Development and application of novel machine learning methods for cancer immunology multi-omics; (3) Integrative Trans-omics modelling of disease-associated genomic variations; (4) Accurate insertion/deletion calling from next-generation sequencing (NGS) data; (5) Whole exome sequencing (WES) analysis to identify intractable disease-causing genes; (6) Cancer WGS analysis; (7) Development of new clustering methods; (8) Development of cancer classification and prognosis prediction methods based on gene expression data; (9) Prediction of optimal drug combinations for cancer chemotherapy; (10) Drug toxicity prediction with machine learning; (11) Prediction of post-translational amino-acid modifications, protein structure, protein-peptide interactions, molecular recognition features (MoRFs), and protein functions; (12) Discovery of clinically-relevant subtypes for cancer immunotherapy; and (13) Developing AI and deep learning technologies for image and omic data analyses.

Laboratory for
Cancer Genomics

Team Leader: Hidewaki Nakagawa

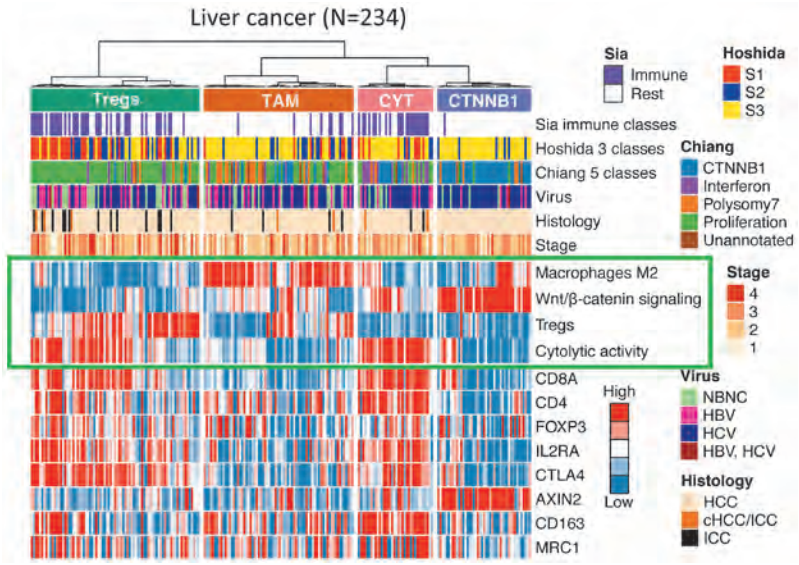


Figure: Classification of liver cancer based on immunosuppression mechanisms
Unsupervised clustering of 234 liver cancers by four gene expression signatures related to immunosuppression mechanisms: macrophages M2 (TAM), Wnt/β-catenin signaling (CTNNB1), regulatory T cells (Treg), and cytolytic activity (CYT). The CYT and Treg subclasses represent inflamed tumors, while the TAM and CTNNB1 subclasses represent non-inflamed tumors.

Recent Major Publications

Fujita M, Yamaguchi R, Hasegawa T, Shimada S, Arihiro K, Hayashi S, Maejima K, Nakano K, Fujimoto A, Ono A, Aikata H, Ueno M, Hayami S, Tanaka H, Miyano S, Yamaue H, Chayama K, Kakimi K, Tanaka S, Imoto S, Nakagawa H*. Classification of primary liver cancer with immunosuppression mechanisms and correlation with genomic alterations. ***EBioMed*** 53, 102659 (2020)

Takata R*, Takahashi A, Fujita M, Momozawa Y, Saunders EJ, Yamada H, Maejima K, Nakano K, Yamaji T, Sawada N, Iwasaki M, Tsugane S, Sasaki M, Shimizu A, Tanno K, Minegishi N, Suzuki K, Matsuda K, Kubo K, Inazawa J, Egawa S, Haiman CA, Ogawa O, Obara W, Kamatani Y, Akamatsu S*, Nakagawa H*. 12 new susceptibility loci for prostate cancer identified by genome-wide association study in Japanese population. ***Nat Commun*** 10, 4422 (2019)

Xue R, Chen L, Zhang C, Fujita M, Li R, Yan SM, Ong CK, Liao X, Gao Q, Sasagawa S, Li Y, Wang J, Guo H, Huang QT, Zhong Q, Tan J, Qi L, Gong W, Hong Z, Li M, Zhao J, Peng T, Lu Y, Lim KHT, Boot A, Ono A, Chayama K, Zhang Z, Rozen SG, Teh BT, Wang XW, Nakagawa H*, Zeng MS*, Bai F*, Zhang N*. Genomic and transcriptomic profiling of combined hepatocellular and intrahepatic cholangiocarcinoma reveals distinct molecular subtypes. ***Cancer Cell*** 35, 932-947 (2019)

Invited Presentations

Nakagawa H. "GEM Japan Updates" GA4GH 7th Plenary National Initiatives Workshop (Boston, USA) October 2019

Nakagawa H. "Whole-Genome mutational landscape and characterization of non-coding and structural mutations in liver cancer" Gordon Research Conference (Hong Kong, China) June 2019

Nakagawa H and Fujita M. "Whole genome and immuno-genomic analysis of liver cancer" the 9th Asan Liver Center Symposium (Seoul, Korea) April 2019

Nakagawa H. "Whole Genome and Immuno-genome Landscape of Liver Cancer" The Asian Pacific Association for the study of the liver (APASL) meeting (Tokyo) April 2019

Nakagawa H, Fujita M, and Momozawa "Germline pathogenic variants of hereditary cancer genes in 12,347 colorectal cancer patients and 27,706 controls in Japanese population" The International Society for Gastrointestinal Hereditary Tumor (InSiGHT) meeting (Auckland, New Zealand) March 2019

Cancer is essentially a "disease of the genome" that develops and evolves through the accumulation of a variety of mutations in its genetically unstable background. Some somatic mutations of driver genes have been targeted successfully for cancer treatment, and germline variants are related to cancer predisposition and risk assessment. Currently, genotype-based personalized cancer therapy is in the clinical stage. Therefore, the understanding of and attention to the underlying genetic diversity in cancer is likely to increase the success of new cancer treatment modalities. Recent explosive advances in next-generation sequencing (NGS) and bioinformatics enable us to perform systematic, genome-wide identification of all somatic abnormalities by whole genome sequencing (WGS), whole exome sequencing (WES), and RNA sequencing (RNA-seq). Furthermore, cancer also has been proven to have features of an immune reaction, and immune therapies targeting immune checkpoints and neo-antigens derived from somatically mutated proteins are also treatment realities. To explore whole genomic and immuno-genomic alterations and their diversity in cancer, we have applied WGS and RNA-seq. These approaches, combined with mathematical analysis and other omics analyses, can clarify the underlying carcinogenesis and cancer immunology and achieve a molecular sub-classification of cancer, which will facilitate discovery of genomic biomarkers and personalized cancer medicine.

Laboratory for Immunotherapy

Team Leader: Shin-ichiro Fujii

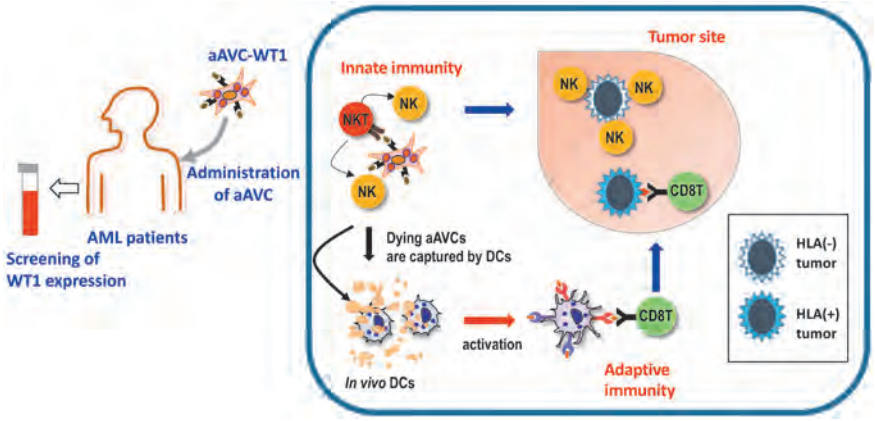


Figure:
After screening AML cells for WT1 expression, positive patients were administered aAVC-WT1 cells intravenously. The aAVC-WT1 activate iNKT cells directly and, soon after, NK cells are activated by IFN-γ from iNKT cells. In turn, activated iNKT/NK cells kill the aAVC-WT1, and then dying aAVC-WT1 are captured by DCs *in situ*. These DCs then undergo maturation by their interaction with activated iNKT cells. Finally, these mature DCs can generate antigen (WT1)-specific $CD8^+$ T cells *in situ*. Antigen-specific CD8 T cells have the potential to kill HLA-Class I positive leukemic cells whereas activated NK cells can kill HLA-Class I negative leukemic cells.

Recent Major Publications

Fujii S, Shimizu K. Immune Networks and Therapeutic Targeting of iNKT Cells in Cancer. ***Trends Immunol*** 40, 984-997 (2019)

Shimizu K, Sato Y, Kawamura.M, Nakazato H, Watanabe T, Ohara O, Fujii S. Eomes transcription factor is required gor the depemopment and differentiation of invariant NKT cells. ***Commun Biol*** 2, 150 (2019)

Iyoda T, Yamasaki S, Kawamura M, Ueda M, Son K, Shimizu K, Fujii S. Optimal therapeutic strategy using antigen-containing liposomes selectively delivered to antigen-presenting cells. ***Cancer Sci*** 110, 875-887 (2019)

Invited Presentations

Fujii S. "Development of anti-cancer therapeutic cellular drug as *in vivo* DC targeting therapy" The 48th Annual Meeting of the Japanese Society for Immunology (Hamamatsu-city, Japan) December 2019

Fujii S. "*In vivo* Dendritic cell-targeting cancer vaccine, "artificial adjuvant vector cells (aAVCs)" The 23rd Annual Meeting of Japanese Association of Cancer Immunology (Kochi City, Japan) August 2019

Fujii S. "Development of therapeutic cancer vaccine utilizing invariant NKT cell-licensed dendritic cells" The 26th International Symposium on Molecular Cell Biology of Macrophage (Tokyo, Japan) June 2019

Fujii S. "Establishment of a new *in vivo* Dendritic cell-targeting cancer vaccine inducing innate and adaptive immunity, "artificial adjuvant vector cells (aAVC)" The 67th Annual Meeting of the Japan Society of Transfusion and Cell Therapy (Kumamoto-city, Japan) May 2019

Fujii S. "Establishment of a new therapeutic cancer vaccine inducing multifunctional immunity, "artificial adjuvant vector cells (aAVC)" The 10th JSH International Symposium (Ise-city, Japan) May 2019

Our main goal is to harness our understanding of the innate and adaptive immune system to develop novel therapies against cancer. To this end, we perform basic immunology, as well as translational studies using tumor models and clinical samples. In particular, we focus on dendritic cells and invariant (i) NKT cells, because the interaction of these cells links innate immunity and adaptive immunity, leading to immunological memory.

We have three ongoing projects in basic cancer immunology research: 1) To develop an immunotherapeutic strategy using tumor-derived neoantigens, 2) To define the cellular and molecular mechanism of generating memory iNKT cells, and 3) To investigate the tumor immune microenvironment and systemic immune cells in murine tumor models undergoing several types of immunotherapies. In the current year, we assessed cytotoxic T lymphocytes (CTL) under immune checkpoint blockade (ICB) therapy in murine colorectal cancer. Using antigen libraries based on immunogenomic data, we identified three H2-K^b-restricted, somatically mutated epitopes as immunogenic neoantigens that enhanced CTL responses. Finally, we demonstrated CTL induction by neoantigen-pulsed DC therapy.

We also have ongoing translational research (TR) projects that are related to iNKT cells and are aimed toward clinical studies. We have established artificial adjuvant vector cells (aAVC) as a new type of drug delivery platform composed of an iNKT cell ligand and tumor-associated antigens. An investigator-initiated phase I clinical trial for refractory or relapsed acute myelogenous leukemia (AML) using aAVC-WT1 has been conducted at the Department of Hematology/Oncology, the Institute of Medical Science, the University of Tokyo in a collaboration that began in 2017. We are engaged in the analyses of treated patient samples to evaluate the anti-tumor immune response. Regarding the aAVC-WT1 technology, RIKEN and Astellas Pharma Inc. entered into a worldwide oncology licensing agreement in September 2019.

Laboratory for
Human Disease Models

Team Leader: Fumihiko Ishikawa

Recent Major Publications

Ono R, Watanabe T, Kawakami E, Iwasaki M, Tomizawa-Murasawa M, Matsuda M, Najima Y, Takagi S, Fujiki S, Sato R, Mochizuki Y, Yoshida H, Sato K, Yabe H, Kato S, Saito Y, Taniguchi S, Shultz LD, Ohara O, Amagai M, Koseki H, Ishikawa F. Humanized Mouse Model for Chronic GVHD Reveals Contribution of reduction of Treg and activated macrophages through IL-6 signaling. ***EbioMedicine*** 41, 584-596 (2019)

Matsuda M, Ono R, Iyoda T, Endo T, Iwasaki M, Tomizawa-Murasawa M, Saito Y, Kaneko A, Shimizu K, Yamada D, Ogonuki N, Watanabe T, Nakayama M, Koseki Y, Kezuka-Shiotani F, Hasegawa T, Yabe H, Kato S, Ogura A, Shultz LD, Ohara O, Taniguchi M, Koseki H, Fujii S, Ishikawa F. Human NK cell development in hIL-7 and hIL-15 knock-in NOD/SCID/IL2rgKO mice. ***Life Sci Alliance*** 2, e201800195 (2019)

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*** eaao1214 (2017)

Invited Presentations

Ishikawa F. "Understanding leukemia biology through interdisciplinary effort" Lecture at National Cancer Center, (Tokyo, Japan) June 2019

Ishikawa F. "Developing therapeutic strategies against genetically-complex AML" The 10th Japan Society of Hematology International Symposium, (Mie, Japan) May 2019

Ishikawa F. "Differentiation capacities of heterogenous human CD34+ cells" US-Japan Symposium on Normal/Malignant Hematopoiesis and Novel Therapies for Hematologic Malignancies, (Maui, USA) February 2019

Ishikawa F. "Understanding human hematopoiesis, immunity, and diseases using humanized mice" Special Lecture at Grant-in-Aid for Scientific Research on Innovative Areas — Platforms for Advanced Technologies and Research Resources (Ohtsu, Japan) January 2019

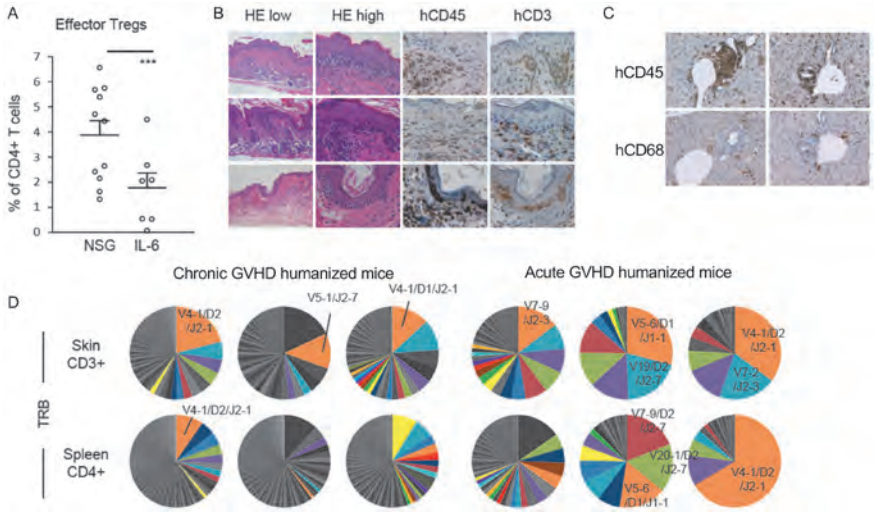


Figure: Creation of humanized mice for acute and chronic GVHD

A. The frequency of effector Tregs in the spleen of hIL-6 TG NSG humanized mice was lower than that in control NSG humanized mice. B. hIL-6 TG humanized mice show abnormal thickening of epidermis (HE staining) and infiltration of T cells in both the dermis and epidermis (IHC). C. Human CD45+ leukocytes including CD68+ macrophages (IHC) are present in the portal triad. D. After injecting human CD34- MNCs, recipient humanized mice develope acute GVHD. T cell repertoire sequencing demonstrates that distinct T cell clones became dominant in both chronic (hIL-6 TG) and acute GVHD humanized mice.

For hematologic malignancies, stem cell transplantation is one of the curative treatment that enables high-dose chemotherapy followed by rescue of normal hematopoiesis and immune reconstitution. Allogeneic donor-derived immune cells play an important role in immune-surveillance against leukemic cells that arise from mutated hematopoietic stem/progenitor cells in patients. On the other hand, as a serious adverse effect, donor-derived immune cells sometimes cause graft-versus-host disease (GVHD) by recognizing patient normal tissues and cells as non-self.

When we created NSG humanized mice that over-express human IL-6, the recipient mice exhibited ruffled fur and skin inflammation at 5-6 months post-transplantation. Histological examination revealed a T cell infiltration in the recipient skin, thickened epidermis, and interface dermatitis, consistent with the pathological finding of chronic GVHD. We also found activated macrophages and T cells in the recipient lung and liver. IL-6 over-expression in the humanized mice resulted in a reduction of effector Tregs, which may cause hyperactivation of human T cells in multiple organs of the recipients. Finally, we identified T cell clones that cause acute GVHD and chronic GVHD in humanized mice. In the future, we hope to translate our finding of beneficial and pathological human T cells into transplantation medicine.

Special Program for Young Leaders

RIKEN Hakubi Fellows Program

RIKEN offers junior PI (Principal Investigator) positions, the RIKEN Hakubi Fellows, to exceptionally talented researchers for a maximum of 7 years. The RIKEN Hakubi Fellows are expected to engage independently in creative and ambitious research in natural and mathematical sciences, including research areas bordering the humanities and social sciences. An important goal of the RIKEN Hakubi Program is to foster stimulating interactions among Fellows with diverse backgrounds and to create an intellectual hub of scientists with different disciplines within and beyond RIKEN.

"Hakubi" is a phrase derived from classical Chinese story about five siblings in ancient China, all gifted, but the most brilliant one had white (haku) eyebrows (bi).

Young Chief Investigator Program

The Young Chief Investigator Program (YCI) aims to provide a career path for young investigators who conduct multidisciplinary research that will bridge immunology with other research fields. In this program, the selected Young Chief Investigator (age below 40) will head an independent research laboratory, but will have an access to mentoring by multiple senior specialists in related research fields. Mentors provide guidance for experimental design, preparation of papers and presentations, promotion of international visibility, and obtaining research funding. The YCI laboratory will also share space, equipment and facilities with a host laboratory in IMS.

Genome Immunobiology RIKEN Hakubi Research Team

Hakubi Team Leader: **Nicholas Parrish**

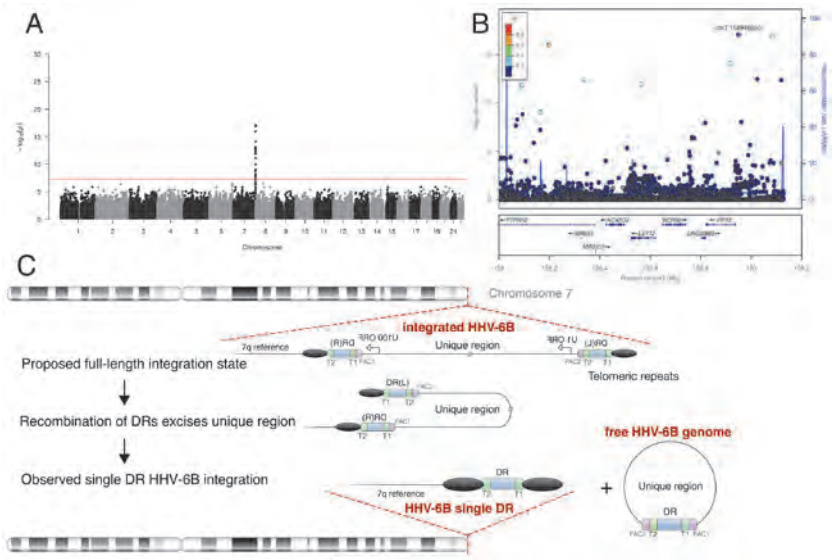


Figure: Recombination and excision of HHV-6B from chromosome 7q

A) Manhattan plot from GWAS of subjects bearing HHV-6B single DR integration (N = 9). The $-\log_{10}$P (Fisher exact test) from variants is plotted according to its physical position on successive chromosomes.
B) Regional association plot of the 7q region. The $-\log_{10}$P (Fisher exact test, y axis) for association in the GWAS of iciHHV-6A are shown. Proxies are indicated with colors determined from their pairwise r^2 from the high-depth BBJ WGS data (red, $r^2 > 0.8$; orange, $r^2 = 0.6$-0.8; green, $r^2 = 0.4$-0.6; light blue $r^2 = 0.2$-0.4; dark blue, $r^2 < 0.2$; or no information available). Recombination rate is plotted on the *x* axis.
C) Model of HHV-6 recombination and excision resulting in the observed integrated single DR. Schematic of the proposed germline recombination event (after Wood and Royle, 2017) leading to excision of the majority of integrated HHV-6B sequence resulting in the integrated single DR form.

Recent Major Publications

Liu X, Kosugi S, Koide R, Kawamura Y, Ito J, Miura H, Matoba N, Matsuzaki M, Fujita M, Kamada AJ, Nakagawa H, Tamiya G, Matsuda K, Murakami Y, Kubo M, Sato K, Momozawa Y, Ohashi J, Terao C, Yoshikawa T, Parrish NF, Kamatani Y. Endogenization and excision of human herpesvirus 6 in human genomes. ***bioRxiv*** doi: https://doi.org/10.1101/2019.12.19.882522 (2019)

Ophinni Y, Palatini U, Hayashi Y, Parrish NF. piRNA-Guided CRISPR-like Immunity in Eukaryotes. ***Trends Immunol*** 40, 998-1010 (2019)

Parrish NF, Tomonaga K. A Viral (Arc) hive for Metazoan Memory. ***Cell*** 11, 1-2 (2018)

Invited Presentations

Parrish NF. "Endogenization and excision of human herpesvirus 6 revealed by genome analysis of Japanese subjects" The 42nd Annual Meeting of the Molecular Biology Society of Japan (Fukuoka, Japan) December 2019

Parrish NF. "Artificial intelligence to discover horizontally-acquired sequences in human genomes" The 6th RIKEN-KI-SciLifeLab Symposium (Yokohama, Japan) November 2019

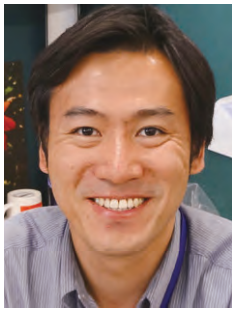
Parrish NF. "Genetic Basis of "Self" Recognition in Immunobiology" The 16th Nikko International Symposium 2019 (Jichi, Japan) October 2019

Parrish NF. "CRISPR-like immunity in eukaryotes via piRNAs transcribed from endogenous viral elements" Kobe University 6th International Course for Health Sciences (Kobe, Japan) September 2019

Parrish NF. "Recurrent endogenization of human herpesvirus 6 on chromosome 22q in East Asians" The 11th International Conference on Human Herpesvirus 6 & 7 (Quebec City, Canada) June 2019

We study endogenous viral elements (EVEs), which are viral sequences that have become integrated into the genomes of their hosts. We are interested in how mammalian EVEs function in antiviral immunity. EVEs are often transcribed and processed into small RNAs called piRNAs, which can guide RNA interference (RNAi) against complementary sequences. We are testing if piRNA-guided RNAi functions as antiviral immunity in eukaryotes, similar to the CRISPR/Cas adaptive immune system in prokaryotes. We previously showed that EVEs present in mouse and human genomes called endogenous bornavirus-like nucleoprotein elements (EBLNs) are transcribed and processed into piRNAs (Parrish NF et al., *RNA*. 2015). While piRNAs are known to guide RNAi against transposons, they have not been shown to function in antiviral immunity against exogenous viruses in mammals. However, recent results suggest that piRNAs are involved in immunity to human herpesvirus 6 (HHV-6) (Liu S et al., *Cell*. 2018). Intriguingly, the HHV-6 genome sequence can be found in the germline genome in about 1% of all humans. Recently, we determined that these sequences are also EVEs, having stably co-evolved with human chromosomes since prehistory.

We are testing for interactions between viruses and their related EVEs in mammalian genomes using two systems: 1) Borna disease virus/EBLNs and 2) human herpesvirus 6/endogenous human herpesvirus 6. We have engineered mutant mice that lack piRNA-generating EBLNs and will soon challenge them with Borna disease virus. We have knocked-in modern Borna disease virus sequences into piRNA-generating loci, to simulate the acquisition of a new EBLN-like EVE, and we hypothesize these mice will show heightened resistance to Borna disease virus. To infer the function of endogenous HHV-6, we are undertaking bioinformatic studies of the distribution and evolutionary patterns of this EVE in diverse humans. We are also analyzing gene expression using cell lines and tissues from subjects who carry endogenous HHV-6.



YCI Laboratory for

Cellular Bioenergetic Network

Young Chief Investigator: **Toshimori Kitami**

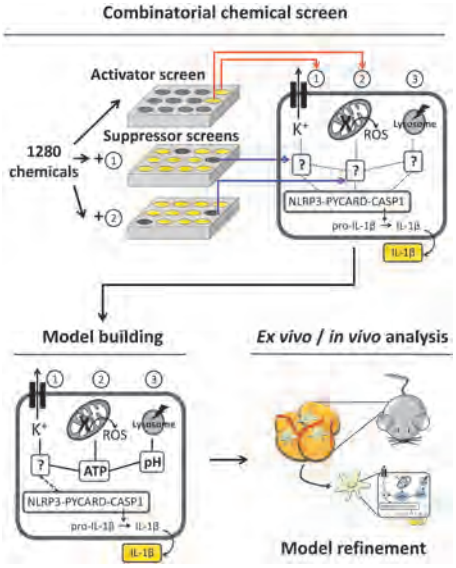


Figure: Schematic of activator-suppressor screens for the NLRP3 inflammasome, model building, and validation

Recent Major Publications

Tran UT, Kitami T. Niclosamide activates the NLRP3 inflammasome by intracellular acidification and mitochondrial inhibition. ***Commun Biol*** 2, 2 (2019)

Invited Presentations

Kitami T. "Dissecting the role of mitochondria in NLRP3 inflammasome activation via chemical genetics approach" Symposia: New horizon of the 'Mitochondria Biochemistry' and disease pathophysiology. The 92nd Annual Meeting of the Japanese Biochemical Society (Yokohama, Japan) September 2019

Kitami T. "Chemical biology of mitochondria". 3rd RIKEN IMS-Stanford ISCBRM Joint Symposium (Stanford, CA, USA) May 2019

Mitochondria are dynamic organelles central to energy homeostasis, intermediary metabolism, ion homeostasis, and cell death. Inherited defects in mitochondria cause the most common inborn errors of metabolism, but a growing body of evidence also links mitochondria to more complex diseases including type 2 diabetes, cardiovascular disease, and neurodegeneration. Despite our basic understanding of mitochondrial functions, the precise mechanism by which mitochondria participate in disease pathogenesis remains largely unknown. The long-term goal of our laboratory is to use our expertise in chemical biology and genomics to critically evaluate the role of mitochondria in disease pathways.

Towards our goal, we initiated a project focused on the role of mitochondria in the NLRP3 inflammasome, which is an intracellular pattern recognition receptor normally involved in the detection of pathogens and cellular damage. However, recent studies also point to its involvement in age-associated diseases. The NLRP3 inflammasome is activated by changes in cellular physiology, including mitochondrial damage, although the molecular players involved have not been fully elucidated. We therefore established a chemical screening platform to dissect the inner wiring of the inflammasome activation pathway. We have successfully identified chemicals that activate or suppress the NLRP3 inflammasome through mitochondria and revealed their mechanisms of action. These chemical tools will be applied to *ex vivo* and *in vivo* disease models to critically evaluate the role of mitochondria in NLRP3 inflammasome activation.

In addition, we are exploring the role of mitochondria in other complex diseases through the use of large-scale datasets generated in our laboratory, as well as in RIKEN IMS. We hope that our genomic and chemical biology efforts will not only help clarify the role of mitochondria in complex diseases, but also point to small-molecule therapies for the treatment of mitochondria-related disorders.

YCI Laboratory for Trans-Omics

Young Chief Investigator: **Katsuyuki Yugi**

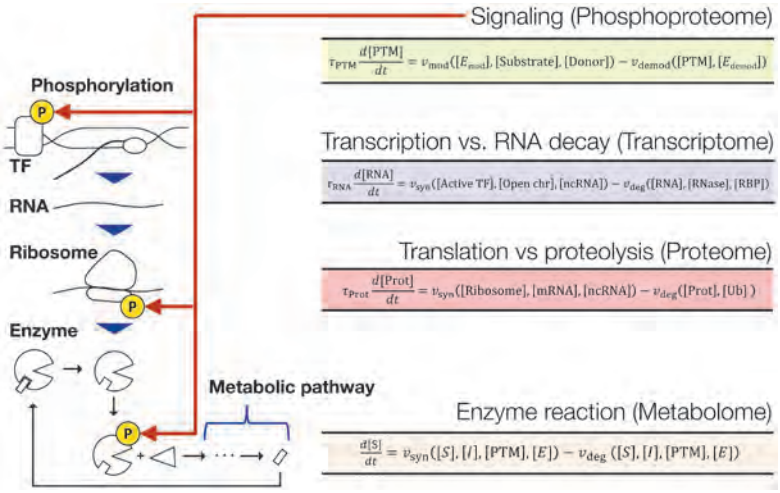


Figure: Differential equation representation of a trans-omic network

We integrate multiple omic data, postulating a dynamic picture of cellular processes driven by reaction kinetics. Each reaction rate (terms represented by '*v*') is a function of the number of molecules that belong to the same or different omic layers. Characteristic time 'τ' emphasizes time scales for each omic layer (PTM, post-translational modification such as phosphorylation of the enzyme; E_{mod}, modification enzyme; Substrate, substrate for the modification reaction; Donor, chemical group donor such as acetyl-CoA for histone acetylation; E_{demod}, demodification enzyme; Active TF, active transcription factor; Open chr, open chromatin; ncRNA, noncoding RNA; RBP, RNA binding proteins; Prot, protein abundance; Ub, ubiquitin; *S*, reactant metabolites; *I*, activators or inhibitors; *E*, enzyme abundance).

Recent Major Publications

Yugi K, Ohno S, Krycer JR, James, DE, Kuroda, S. Rate-oriented trans-omics: integration of multiple omic data on the basis of reaction kinetics. ***Curr Opin Syst Biol*** 15, 109-120 (2019)

†Kawata K, †Yugi K, Hatano A, Kokaji T, Tomizawa Y, Fujii M, Uda S, Kubota H, Matsumoto M, Nakayama KI, Kuroda S. Reconstruction of global regulatory network from signaling to cellular functions using phosphoproteomic data. ***Genes Cells*** 24, 82-93 (2019) († These authors contributed equally)

†Kawata K, †Hatano A, †Yugi K, Kubota H, Sano T, Fujii M, Tomizawa Y, Kokaji T, Tanaka KY, Uda S, Suzuki Y, Matsumoto M, Nakayama KI, Saitoh K, Kato K, Ueno A, Ohishi M, Hirayama A, Soga T, Kuroda S. Trans-omic analysis reveals selective responses to induced and basal insulin across signaling, transcriptional, and metabolic networks. ***iScience*** 7, 212-229 (2018) (Cover Article; † These authors contributed equally)

Invited Presentations

Yugi K. "Integration of phosphoproteome and ^{13}C-metabolome data reveals 'metabolic priming' in the adipocyte" 3rd RIKEN IMS-Stanford ISCBRM Joint Symposium (Stanford, USA) May 2019

Yugi K. "Dose-selective metabolic regulation by insulin across multiple omic layers" The 3rd International Symposium for Trans-Omics (Okinawa, Japan) October 2019

Yugi K. "Trans-omics: integration of multiple omic data on the basis of reaction kinetics" The 6th RIKEN-KI-SciLifeLab Symposium: Biomedical Data for Artificial Intelligence (Yokohama, Japan) November 2019

Yugi K. "Dose-selective metabolic regulation by insulin across multiple omic layers" RIKEN-KU LEUVEN Joint Symposium 2019 (Leuven, Belgium) December 2019

Yugi K. "Trans-omics: integration of multiple omic data on the basis of reaction kinetics" The 412nd Seminar of Chem-Bio Informatics Society (Tokyo, Japan) December 2019

Trans-omics is a discipline that aims to reconstruct a global molecular network spanning multiple omic layers, 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; Yugi and Kuroda, *Curr. Opin. Syst. Biol.*, 2018; Yugi *et al.*, *Curr. Opin. Syst. Biol.*, 2019). The network reconstruction is performed based on comprehensive measurement data, public databases, and a kinetic picture of the cellular processes (Figure). The comprehensive data of multiple omic layers should be measured under identical conditions in a time-series manner so that one can construct mathematical models of the multi-layered network for subsequent analyses. Our primary research interests are:

1. Developing new methods for trans-omics
2. Reconstructing global metabolic regulatory networks in a trans-omic manner

We have developed methods for the integration of metabolome, phosphoproteome, and transcriptome data. These methods have been applied to the following, to understand metabolic regulation by insulin in a global manner: insulin action on adipocytes by integrating phosphoproteome and ^{13}C-labeled metabolome data (Krycer, Yugi *et al.*, *Cell Rep*, 2017), and insulin action on a rat FAO hepatoma cell line by integrating transcriptome, phosphoproteome, and metabolome data (Yugi *et al.*, *Cell Rep*, 2014; Kawata, Hatano, Yugi *et al.*, *iScience*, 2018; Kawata, Yugi *et al.*, *Genes Cells*, 2018).

Our long-term goal is to extend the trans-omics methodology in two senses: (1) extending the method to incorporate data from other omic layers that have not yet been incorporated, such as genomic variants, so that global metabolic regulatory networks underlying a broader range of diseases and drug actions can be characterized, and (2) extending the availability of trans-omic analyses to non-specialist researchers by development of user-friendly software.

YCI Laboratory for

Immunological Transcriptomics

Young Chief Investigator: Hideyuki Yoshida

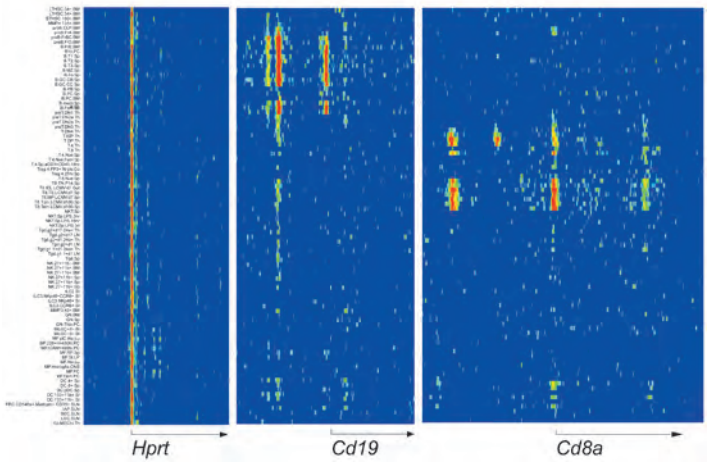


Figure: Cell type-specific structure of chromatin
"Open" and "closed" chromatin in various immune cells was examined by ATAC-seq and is shown by a color gradient (open=red, closed=blue). Since the transcriptional regulatory elements are often found in "open" regions, profiling of open chromatin promotes a clearer understanding of the mechanisms of gene regulation. *Hprt*, housekeeping gene; *Cd19*, B cell-specific gene; *Cd8a*, cytotoxic T cell-specific gene.

Gene regulation is one of the most elemental mechanisms governing cell functions and biological processes, including immune cells and the immune system, and has been studied in many contexts. Recent advances in epigenome and transcriptome profiling, which take advantage of next-generation sequencing (NGS), enable us to investigate gene regulation in an unprecedented manner, and hence the uncharted mechanisms in biology and immunology are now becoming approachable.

Our research aims to promote the understanding of gene regulation in immune cells utilizing the techniques of cutting-edge transcriptomics for better understanding and ultimately treatment of immune disorders. Transcriptomics can be applied to various studies in immunological settings and we have been engaged in 1) a focused subject and 2) a data-driven project for a systematic approach.

1) Focused subject: gene regulation in immune tolerance.

Negative selection of self-reactive T cells occurs in the thymus and is one of the most essential immune tolerance mechanisms. One way to achieve this is via the expression of otherwise peripheral tissue antigens (PTAs) in thymic medullary epithelial cells (TECs). The developing T cells are eliminated by apoptosis if they respond to these PTAs. Since the disrupted expression of PTAs results in severe autoimmune disorders, understanding the mechanisms controlling the expression of PTAs is important to understand the pathogenesis of autoimmune diseases and to develop new treatments. We are analyzing gene expression in TECs by single-cell RNA-seq to examine the gene regulation and the regulators involved in detail, and then validating our findings by employing mouse models.

2) Data-driven project: systematic analysis of various immunocytes.

Bioinformatics has greatly impacted gene regulation research and is becoming more powerful with the advent of big data analysis. To promote these data-driven studies, we are collaborating with the ImmGen group (http://www.immgen.org/).

Recent Major Publications

Tenno M, Wong AYW, Ikegaya M, Miyauchi E, Seo W, See P, Kato T, Taida T, Oishi-Ohno M, Ohno H, Yoshida H, Ginhoux F, Taniuchi I. Essential functions of Runx/Cbfβ in gut conventional dendritic cells for priming Rorγt+ T cells. ***Life Sci Alliance*** 3, e201900441 (2019)

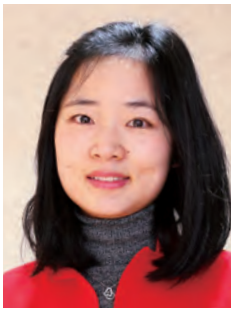
Gal-Oz ST, Maier B, Yoshida H, Seddu K, Elbaz N, Czysz C, Zuk O, Stranger BE, Ner-Gaon H, Shay T. ImmGen report: sexual dimorphism in the immune system transcriptome. ***Nat Commun*** 10, 4295 (2019)

Yoshida H, Lareau CA, Ramirez RN, Rose SA, Maier B, Wroblewska A, Desland F, Chudnovskiy A, Mortha A, Dominguez C, Tellier J, Kim E, Dwyer D, Shinton S, Nabekura T, Qi Y, Yu B, Robinette M, Kim KW, Wagers A, Rhoads A, Nutt SL, Brown BD, Mostafavi S, Buenrostro JD, Benoist C. The cis-Regulatory Atlas of the Mouse Immune System. ***Cell*** 176, 897-912 (2019)

Invited Presentations

Yoshida H. "Cell heterogeneity in a population -What can we investigate by deep sc-RNAseq?" The 6th RIKEN IMS-KI-SciLifeLab Symposium (Yokohama, Japan) November 2019

Yoshida H. "Data-driven immunology: analysis of regulatory mechanisms in immunocytes by comprehensive profiling" The 76th RIKEN evening seminar (Tokyo, Japan) December 2019



Laboratory for

Next-Generation Proteomics

Young Chief Investigator: **Yibo Wu**

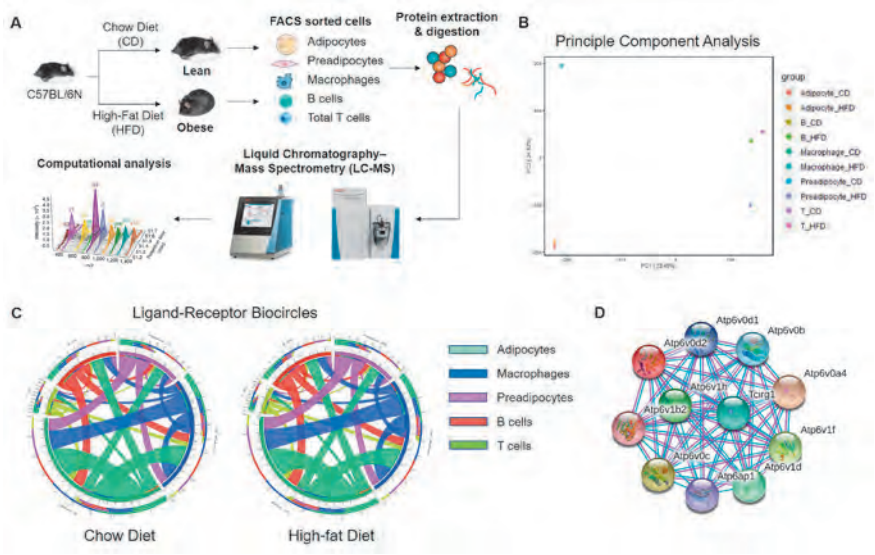


Figure: A mass spectrometry-based strategy for cell type-specific proteomic analysis of mouse white adipose tissue

(A) Mass spectrometry-based proteomics analysis of adipocytes, preadipocytes, and different types of immune cells from mouse visceral adipose tissue. 11-week-old C57BL/6N mice were fed a control diet (CD) or a high-fat diet (HFD) for 8 weeks, and different cell populations were isolated from the visceral adipose tissue by FACS. We extracted and digested the proteins from each cell population and analyzed them by liquid chromatography-mass spectrometry (LC-MS). Then, we performed computational analysis on the acquired data. (B) Different cell types can be clearly distinguished based on protein expression levels. Proteome differences between the dietary conditions can also be observed, but are much smaller than differences among cell types. (C) Intercellular communication network for ligands and their receptors. (D) The v-type ATPases are reported to interact with each other and form a communication network. We observed highly correlated protein expression levels of the v-ATPase family members; some members are not yet reported in this network.

Recent Major Publications

Sendoel A, Subasic D, Ducoli L, Keller M, Michel E, Kohler I, Singh KD, Zheng X, Brümmer A, Imig J, Kishore S, Wu Y, Kanitz A, Kaech A, Mittal N, Matia-González AM, Gerber AP, Zavolan M, Aebersold R, Hall J, Allain FH, Hengartner MO. MINA-1 and WAGO-4 are part of regulatory network coordinating germ cell death and RNAi in C. elegans. ***Cell Death Differ*** 26, 2157-2178 (2019)

Borna NN, Kishita Y, Kohda M, Lim SC, Shimura M, Wu Y, Mogushi K, Yatsuka Y, Harashima H, Hisatomi Y, Fushimi T, Ichimoto K, Murayama K, Ohtake A, Okazaki Y. Mitochondrial ribosomal protein PTCD3 mutations cause oxidative phosphorylation defects with Leigh syndrome. ***Neurogenetics*** 20, 9-25 (2019)

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Invited Presentations

Yibo Wu. "Identification of biomarkers for adipose tissue inflammation by AI" The 6th RIKEN-KI-SciLifeLab Symposium. (Yokohama, Japan) November 2019

Yibo Wu. "Quantifying and Localizing the Mitochondrial Proteome" The KSBMB International Conference 2019 (Jeju Island, Korea) June 2019

Yibo Wu. "Rewiring of Immune Cell Network in Adipose Tissue in Obesity" The 3rd RIKEN IMS-Stanford Joint Symposium (San Francisco, USA) May 2019

Yibo Wu. "Quantifying and Localizing the Mitochondrial Proteome" Visit to University of Texas, southwestern. (Dallas, USA) June 2019

Yibo Wu. "Quantifying and Localizing the Mitochondrial Proteome" Visit to UCSD. (San Diego, USA) May 2019

Our laboratory applies state-of-the-art mass spectrometry and computational methods for proteome analysis in complex metabolic diseases such as obesity. Obesity is one of the pathological outcomes of overnutrition and can increase the risk of serious health conditions, such as cardiovascular diseases, cancer, and type-2 diabetes. Several mechanisms have been linked to the development of obesity. Among them, adipose tissue inflammation can be induced by energy excess and disrupted nutrient metabolism. It is known that multiple types of immune cells are involved in the response to the metabolic overload of obesity. However, it is far from clear how metabolic pathways regulate the intracellular status, as well as the intercellular communication of these cell types. In our study, we use highly precise proteomics data to construct functional networks among adipocyte, preadipocyte, and immune cells in white adipose tissue, and then study how these networks influence energy homeostasis under different metabolic states. We have isolated adipocytes, preadipocytes, and various types of immune cells (macrophages, B cells, and T cells) from visceral adipose tissue of C57BL/6N mice under control and high-fat diets, and performed cell type-specific proteome analysis. We have quantified thousands of proteins at a cell type level of resolution, and they have shown distinct proteome profiles. We have also identified several key pathways that are significantly different in control and high-fat diet fed mice in each cell type. In addition, we have generated an adipose tissue inflammatory map by constructing a ligand-receptor network among different cell types within visceral adipose tissue. We expect that our results will help elucidate the orchestration of these cells types in energy excess and shed new light on the underlying mechanisms of adipose tissue inflammation and obesity.

YCI Laboratory for

Metabolic Epigenetics

Young Chief Investigator: **Azusa Inoue**

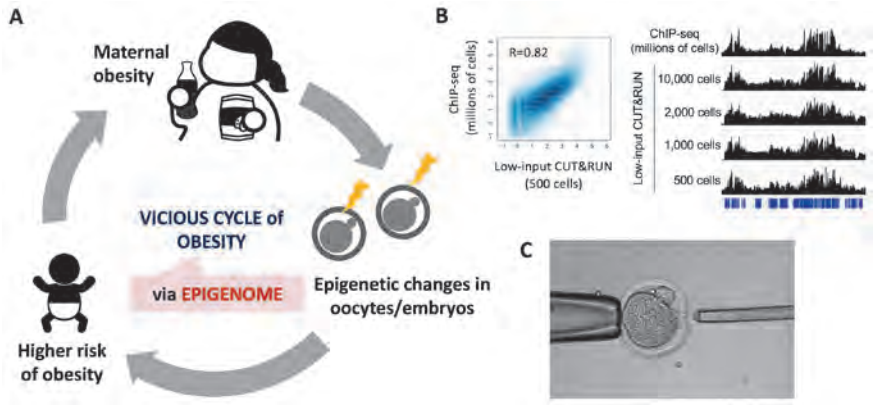


Figure: Aims and research tools of Metabolic Epigenetics YCI Lab
(A) Illustration showing intergenerational inheritance of metabolic disorders via the oocyte epigenome. (B) Data quality of the low-input CUT&RUN analysis using 500 cells for histone H2A mono-ubiquitylation (H2AK119ub1) compared to conventional chromatin immunoprecipitation followed by sequencing (ChIP-seq) using millions of cells. (C) Micromanipulation of mouse zygotes.

Recent Major Publications

Chen Z, Yin Q, Inoue A, Zhang C, Zhang Y. Allelic H3K27me3 to allelic DNA methylation switch maintains noncanonical imprinting in extraembryonic cells. ***Sci Adv*** 5, eaay7246 (2019)

Shishikura K, Kuroha S, Matsueda S, Iseki H, Matsui T, Inoue A, Arita M. Acyl-CoA synthetase 6 regulates long-chain polyunsaturated fatty acid composition of membrane phospholipids in spermatids and supports normal spermatogenic processes in mice. ***FASEB J*** 33, 14194-14203 (2019)

Inoue A, Chen Z, Yin Q, Zhang Y. Maternal *Eed* knockout causes loss of H3K27me3 imprinting and random X inactivation in the extraembryonic cells. ***Genes Dev*** 32, 1525-1536 (2018)

Invited Presentations

Inoue A. "Intergenerational epigenetic inheritance by maternal histones" Research seminar at Tsinghua Univ. (Beijing, China) September 2019

Inoue A. "Epigenetic inheritance by maternal histones" The 91st meeting of Japanese Society of Genetics (Fukui, Japan) September 2019

Inoue A. "Epigenetic inheritance by maternal histones" Institute for Protein Research Seminar (Osaka, Japan) August 2019

Inoue A. "Epigenetic inheritance by maternal histones" National Institute of Genetics workshop for germ cells (Shizuoka, Japan) June 2019

Inoue A. "A new imprinting mechanism independent of DNA methylation" The 6th Ochanomizu Scientific Club (Tokyo, Japan) February 2019

Obesity is a growing social problem in the modern world and the obese population has been increasing globally. Since obesity is associated with an increased risk of various diseases, including cancer, infertility, heart diseases, and type 2 diabetes (T2D), and greatly impacts national healthcare costs, development of preventive therapies for metabolic syndromes has been a long-term effort. Recently, intergenerational heritability of T2D has received much attention. Genetic variants and mutations are estimated to account for <30% of the heritability, suggesting the existence of a non-genetic inheritance mechanism. Studies in animal models have suggested that gametes, at least in part, mediate the inheritance. While significant progress has recently been made to clarify the mechanisms of sperm-mediated paternal inheritance, almost nothing is known about the mechanisms of oocyte-mediated maternal inheritance.

Our lab is studying how maternal metabolic disorders are transmitted into the next generation via epigenetic mechanisms (Figure A). Our specific aims are as follows: (1) To understand the molecular mechanisms underlying intergenerational epigenetic inheritance via oocytes; (2) To understand the functions of the maternally heritable epigenome; and (3) To understand whether and how maternal metabolic disorders can alter the epigenomes of oocytes, early embryos, and offspring. We integrate low-input epigenome analysis technologies (Figure B) and reproductive engineering techniques (Figure C) to address these questions. Our study will not only reveal the mechanisms of intergenerational epigenetic inheritance in mammals, but also provide a foundation for establishing a new venue to prevent unwanted inheritance of metabolic disorders.

Obituary for Dr. Soichi Kojima

December 13, 1961 - August 19, 2019 (aged 57)

Dr. Soichi Kojima, Leader of the Liver Cancer Prevention Unit in RIKEN IMS, passed away on August 19, 2019, at the age of 57. Dr. Kojima dedicated his life to his research on the clarification of pathogenesis and drug discovery for hepatic diseases.

Dr. Kojima was born on December 13, 1961 in Yokohama. He received a Ph.D. from the Tokyo Institute of Technology in 1990, and studied at the New York University School of Medicine from 1990 to 1993 under Professor D.B. Rifkin. After his return to Japan in 1993, he began his career in RIKEN as a Special Postdoctoral Researcher. In 2003, he became a Unit Leader in the RIKEN Discovery Research Institute, and in 2008 he was promoted to Team Leader in the RIKEN Advanced Science Institute. Following a series of reorganizations in RIKEN, his affiliation was moved to the Center for Life Science Technologies and then to IMS. However, he continued to focus his research on pathogenesis and drug discovery for hepatic diseases.

Dr. Kojima served as a leader of the Program for Basic and Clinical Research on Hepatitis, which was financially supported by AMED. Dr. Kojima led one of the biggest projects in the program comprising various research groups from eight universities and institutions all across Japan. The project ranged from basic science to drug development research on the hepatitis B virus (HBV), which Dr. Kojima was very enthusiastic to eradicate. Dr. Kojima identified novel targets for drug discovery against HBV, and conducted high-throughput screening of their regulatory compounds utilizing chemical biology techniques.

Dr. Kojima also developed a novel diagnostic marker to detect the early stages of liver fibrogenesis using antibodies to TGF-β LAP-DP (Latency Associated Protein Degradation Products). He also identified a significantly high expression of the protooncogene MYCN in hepatocellular carcinoma (HCC), and he was planning to explore the possibility of MYCN as a possible prognostic biomarker and therapeutic target for HCC.

Dr. Kojima had Visiting Professor positions in the Tokyo Institute of Technology, Tokyo Medical and Dental University, The Jikei University School of Medicine, and the University of Louis Pasteur in France.

The sudden loss of this distinguished PI in RIKEN shocked and saddened the members of IMS. Only a few days before his passing, Dr. Kojima visited the RIKEN Yokohama Campus, and as usual, he was very active, passionate, and precise in his scientific discussions with other IMS members.

Dr. Kojima had an enormous impact in the science of hepatic diseases. During the course of his career, he mentored many talented researchers and technical staff who are now actively working in various laboratories around the world. He will be sorely missed.

His friend and a collaborator, Professor Tomokazu Matsuura in The Jikei University School of Medicine says “Dr. Kojima had devoted his second life to the difficult research to develop a treatment for hepatitis B virus infection. Now, in the midst of the spread of COVID-19, if he was alive, he would be fiercely fighting SARS-CoV-2. I think his research group will also fight the new enemy. He was a good educator and trained excellent successors.”

Dr. Kojima lived with his beloved wife, Yoko, and their son, Yuta, at their home in Tsukuba.

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, genome research, and disease studies. The Laboratory supports both population and single-cell analysis and has upgraded all FACS Arias, including an Aria Fusion, for multi-color analyses. In addition to FACS instruments, the lab possesses a mass-spectrometry-based cytometer, HELIOS, which has the potential to analyze more than 40 markers simultaneously with metal-labeled antibodies.

In 2019, 800 analytical and 1561 sorting experiments with FACS and 49 analyses with HELIOS were performed in the Laboratory. Two staff members offer various services for users of the FACS equipment (cell analyzers and cell sorters).

(1) *Technical support and training*: In 2019, the facility offered eight technical courses (four for cell sorting and four for cell analysis). The courses were held at three different levels, Calibur basic, Canto II, and Aria basic. A total of 52 researchers participated in these courses in 2019.

(2) *Cell sorting operation service*: The FACS Laboratory provides a cell sorting operation service, in which researchers can ask an experienced operator to conduct the sorting experiment. In 2019, we provided 160 such services. Advanced cell sorting techniques, such as single cell sorting, have also been performed.

(3) *Management/ maintenance of FACS instruments*: FACS machines are available for registered users around the clock and reservations are accepted up to one month in advance through an internal website. In addition to the in-house FACS Laboratory staff, engineers from Becton Dickinson visit once a week to provide maintenance and technical support.

Table: Instruments and their usage in the FACS Laboratory

Instrument types	Model	# of machines	# of users	# of training sessions
FACS cell analyzer	Calibur	4	37	4
	Canto II	2	800	18
FACS cell sorter	Aria II/III/Fusion	7	1,561	30
Mass cytometer	Helios	1	49	2

Confocal Laboratory

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

1. An inverted Leica SP8 system equipped with hybrid detectors and the LIGHTNING super-resolution image extraction module.
2. An 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. One of the two Ti:Sa lasers is connected to an optical parametric oscillator (OPO) that enables two-photon imaging by long wavelength excitation.
3. An 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.
4. An inverted Leica SP5 system with hybrid detectors.
5. An inverted Nikon N-SIM/N-STORM super-resolution microscope for dual color imaging.
6. A GE Healthcare DeltaVision Elite system.
7. A Keyence BZ-X700 all-in-one fluorescence microscope.

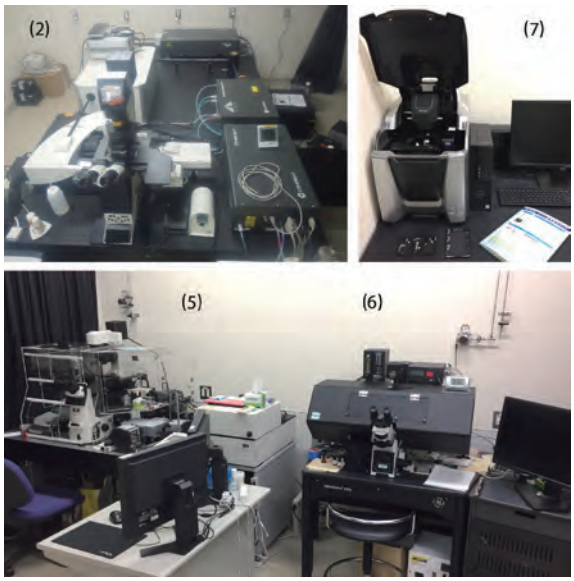


Figure: Leica SP8 multiphoton microscope (2), Nikon N-SIM/N-STORM super-resolution microscope (5), GE Healthcare DeltaVision Elite system (6), and Keyence BZ-X700 microscope (7)

Genomics and Related Activities

As in previous years, the Laboratory for Integrative Genomics serves as a technical support service lab in IMS that provides state-of-the-art genome- and proteome-wide analyses for non-experts in these types of analyses (Table 1). In 2019, a new platform for DNA sequencing was launched to meet increasing needs of large-volume sequencing, such as single-cell RNA sequencing and whole genome sequencing.

The Laboratory for Genotyping Development and the Laboratory for Integrative Genomics jointly developed the Sequencing Platform using HiSeq 2500 (Illumina) and NovaSeq 6000 (Illumina). Users in IMS request sequencing of their libraries through a website. A staff member in the Sequencing Platform receives libraries, performs quality controls, and, then, begins the sequencing run. After confirming that a sequencing run is successful, sequence data are delivered to users. This platform enables users in IMS to obtain sequence data quickly and at a reasonable cost, thus empowering their research. In addition, with time, the Sequencing Platform accumulates various experience and technological expertise, which enhance IMS sequencing abilities. In total, the Sequencing Platform has performed 94 runs (15 TBp) with HiSeq 2500 and 17 runs (8 TBp) with NovaSeq 6000 during the first 9 months. We expect that the intramural interactions among the Divisions of Human Immunology, Disease Systems Biology, Cancer Immunology, and Genome Medicine fostered by the Sequencing Platform will greatly enhance research activities in IMS.

Table: Central services provided by the Genomics Lab in 2019

Next-generation DNA sequencing	**# of samples**	**# of teams**
RNA-sequencing	2,055	15
Chip-sequencing	48	2
Others (Exome Ramda-seq, Quant-sec etc)	1,956	13
Proteomics	**# of samples**	**# of teams**
Mass Spectrometry Analysis	164	3
Multiplex suspension array	728	10
Sanger DNA sequencing	**# of samples**	**# of teams**
36 cm capillary	7,126	16
50 cm capillary	4,102	14
cDNA clone delivery	**# of samples**	**# of teams**
	13	2
Primer/labeled probe delivery	**# of samples**	**# of teams**
	18	1

Animal Facility

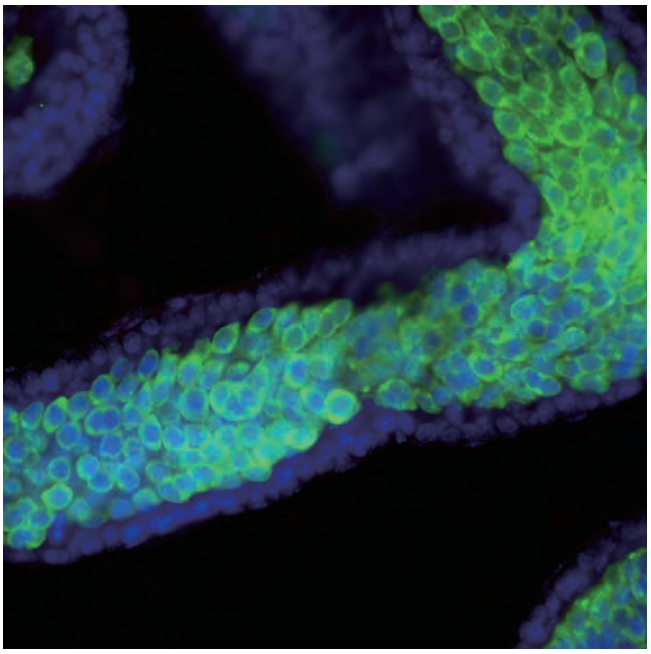
We continue to maintain over 50,000 mice in the SPF area and 1,500 mice in an isolated area. The SPF area also contains 550 germ-free or gnotobiotic mice in vinyl isolator rooms and in vinyl isolation bio-bubble rooms. The former are used by several IMS research groups, in particular, the mucosal immunologists, and the latter are used as "humanized mice". Recently, a new SPF animal facility has been completed and we have begun its management. The new facility has 32 vinyl isolators and 2 Individually Vented Cage systems (IVCs) and has the capacity to breed 1,500 mice (Figure). 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 748 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 (128 lines). In addition, we have created 21 lines of germ-free mice. We maintain flexibility so that we can provide space for new experiments in the animal facility, such as behavioral testing for germ-free mice.

We have generated genetically modified mice to improve the efficiency of transplantation of human hematopoietic stem cells into NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/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 such transgenic and knock-in mice with confirmed expression of human genes on a C57BL/6 background and have backcrossed them onto the NSG mouse background using the speed-congenic method.

Figure: New SPF animal facility

Part 3

Research Projects



The Human Cell Regulatory Atlas

Precise determinations of our health status and risk for disease based on single-cell genomics is a fundamental mission of the Human Cell Regulatory Atlas project in IMS. Our bodies have 37 trillion cells, and emerging single cell genomics technologies are allowing us to determine which genes are expressed and how they are regulated at the single cell resolution. The Human Cell Regulatory Atlas aims to define cell-to-cell connections across various organ systems and delineate the regulatory processes that encompass healthy and disease states of all human cells. Using our 5'-focused single-cell RNA-seq, we profile gene-promoter activities and epigenetic states in the same cell. Based on deep-genomics analyses, we decode cis-regulatory gene networks to evaluate the risks for genetic-associated diseases and to build a cell-to-cell programming atlas as a foundation for cell-based therapeutics. The Human Cell Regulatory Atlas is extensively collaborating with numerous medical and research institutions across Japan, focusing on various human tissues, both healthy and diseased, biobank samples, and organoids models, in conjunction with human genetics. The Human Cell Regulatory Atlas in IMS facilitates discovery of new biological processes, and, at the same time, builds a comprehensive integrative database to power the next generation artificial intelligence to solve health and medical needs we face in our lifetime.

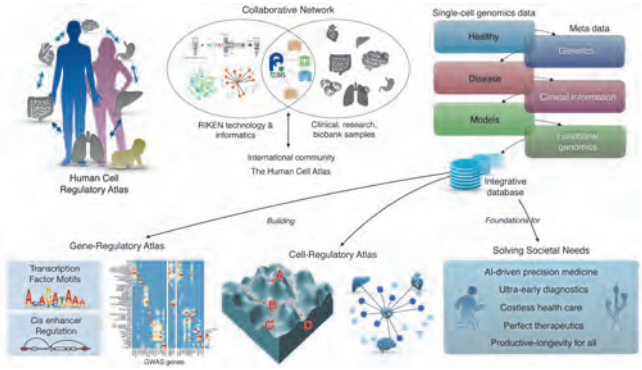


Figure: The Human Cell Regulatory Atlas
The Human Cell Regulatory Atlas relies on an extensive network of collaborators across Japan. It provides valuable samples and meta data to create a highly integrative and comprehensive database, which serves as a foundation to build gene- and cell-regulatory atlases and solving societal needs, including aging and healthcare, in Japan.

FANTOM

FANTOM is an international genome research consortium aiming to understand mammalian genome regulation focusing on transcriptome analysis. The 5th phase of the FANTOM project showed that the vast majority of genes encode long non-coding RNAs (lncRNAs) and created a catalogue of human lncRNAs with precise 5'-end information derived from Cap Analysis of Gene Expression (CAGE) data (Hon *et al. Nature* 2017). Accompanied GWAS and eQTL studies suggested that at least 19,000 lncRNAs are likely to be functional. However, further genome-wide screening is required to identify the distinct roles of each lncRNA.

Currently, the 6th phase of the FANTOM project aims at creating a broad catalogue of experimentally analyzed functional lncRNAs, as a valuable resource for the community.

We have established high-throughput knockdown strategies to assess the function of lncRNAs in human dermal fibroblasts, followed by quantification of cellular growth, morphological changes, and transcriptome profiling using CAGE. The transcriptomic profile recapitulated the observed cellular phenotypes, which provides a powerful approach to explore the distinct function of each lncRNA.

In addition, in order to explore RNA-chromatin interaction, we recently developed a new technology named RNA and DNA Interacting Complexes Ligated and sequenced (RADICL-seq) that precisely maps genome-wide RNA-chromatin interactions in intact nuclei.

We will further explore the changes of the interactome using Chromatin Conformation Capture Sequencing (Hi-C), Psoralen Analysis of RNA Interactions and Structures (PARIS), and RADICL-seq during time courses of cell differentiation. This will identify networks including lncRNAs in their 3D functional conformation.

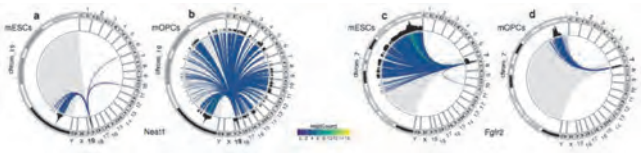


Figure: Circos plots by RADICL-seq depicting RNA-chromatin interactions mediated by Neat1 (a,b) and Fgfr2 (c,d) in mouse embryonic stem cells (mESCs) and oligodendrocyte progenitor cells (mOPCs), respectively

Human genome analysis

In 2015, the Japanese government set rare hereditary diseases, cancer, dementia, infection, and pharmacogenomics as priority disease areas for the implementation of genomic information for actual medical practice. To proceed this, a combination of germline variants with other information including somatic variations, gene expression profiles, and environmental factors would be a key issue.

IMS has analyzed various diseases and phenotypes by genome-wide association studies and/or targeted- and whole-genome sequencing-based association studies, including cancer (Momozawa & Nakagawa), pharmacogenomics (Mushiroda), bone and joint diseases (Ikegawa), diabetes (Horikoshi), cardiovascular diseases (Ito), autoimmune diseases (Yamamoto K), and integrated analysis of all data and phenotypes (Terao). In addition, we began to extract information of somatic variations from DNA microarray data, which had been used only to call germline variants. Further, we integrated our results with knowledge of non-coding regions and single cell sequencing approaches conducted by laboratories for the FANTOM and Human Cell Atlas projects to better understand disease biology. Finally, we have established collaborations with large Japanese cohorts including BioBank Japan, Tohoku Medical Megabank, and domestic and international universities.

A key finding in 2019 was elucidating the genetic background of mosaic loss of chromosome Y (mLOY) and its biological mechanisms. mLOY is reported to share key components in its mechanisms with cancer and aging. We successfully pinpointed cell types and a transcription factor (FLI1) that play critical roles in mLOY and identified hematological markers commonly measured in daily clinical practice, which strongly correlate with degree of mLOY.

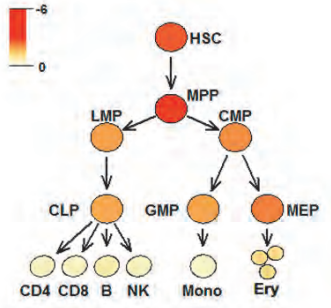


Figure: Genetic signals of mLOY reveal its critical cell types

SEAPharm for the establishment of stratified medicine in Asia

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. In the case of the anti-epileptic drug carbamazepine, the US FDA now recommends preemptive HLA-B*15:02 genetic screening for Asian populations with a high prevalence of this allele, which is associated with the SJS-TEN caused by carbamazepine therapy. 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, Vietnam in 2016, Nepal, Laos, and the Philippines in 2017, and Brunei and Myanmar in 2018.

The aims of the collaboration are to identify genomic biomarkers associated with ADRs, such as skin rash and hepatic injury, to provide technical assistance and training of young researchers from the SEAPharm member countries, and to hold international seminars and workshops. Recently, SEAPharm started a new project involving next-generation sequencing (NGS) of about 2,000 genomic DNA samples from 12 countries to clarify the genetic diversity of drug-metabolizing enzymes and drug transporters in individuals from Southeast Asia, Southern Asia, the Middle East, and Southern Europe. RIKEN is responsible for the targeted sequencing using a PKseq panel and released the sequencing data of 1,571 subjects to the collaborators. Discoveries from the collaborative efforts will lead to the establishment of genotype-guided drug therapies in Asia.

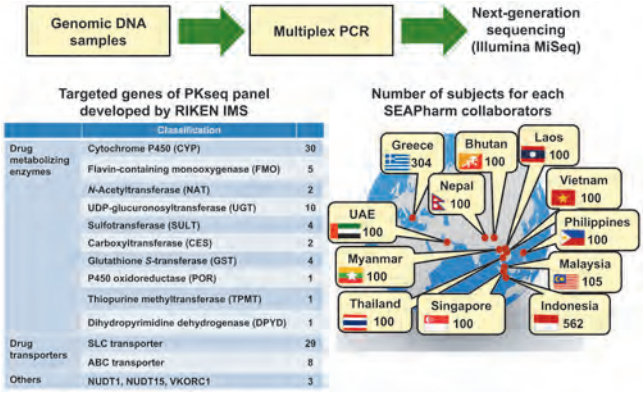


Figure: SEAPharm PKseq Project for the clarification of genetic diversity of drug-metabolizing enzymes and drug transporters in Asian populations

International Cancer Genome Consortium (ICGC) and PCAWG project

Laboratory for Cancer Genomics Laboratory for Medical Science Mathematics

The ICGC was established in 2007, and concluded its mission to define the genomes of 25,000 primary untreated cancers (the 25K Initiative) in 2018. The ICGC solved numerous data governance, ethical, and logistical challenges to make global genomic data sharing for cancer a reality, providing the international community with comprehensive genomic data for many cancer types. As a second initiative, the ICGC launched a "Pan-Cancer" Whole Genome project (PCAWG) in 2014, in which whole genome sequencing (WGS) data together with RNA-seq data from 2834 donors were analyzed in uniform pipelines within the same computational environment and cloud computing. RIKEN and IMUT (Institute of Medical Science, The University of Tokyo) have contributed to this project as a member of a technical working group arranging cloud data centers and PI/researchers in working groups investigating driver genes, mutational signatures, germline, immuno-genomics, and mitochondrial genomics. RIKEN also provided WGS data from 270 liver cancers to the PCAWG (10% of the total), making us the most productive group within the ICGC. In 2019, PCAWG completed most of the main analyses such as non-coding driver genes, mutational signatures, mitochondrial genomics, immunogenomics, and structure variants, thus, completing this project. As a PCAWG-15 working group, RIKEN and IMUT analyzed the immuno-genomic landscape from PCAWG data, including mutations in HLA and immune suppressor genes, neo-antigen profiles, and immune micro-environmental signatures, and observed that tumors acquired many types of immune escape mechanisms.

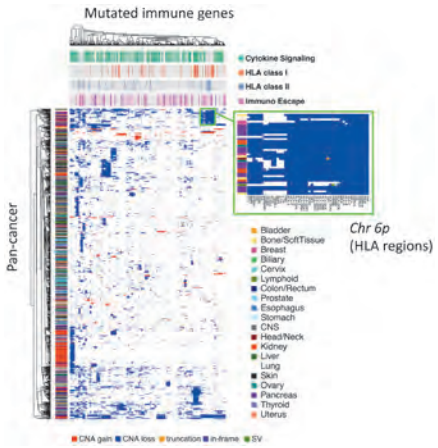


Figure: Mutational landscape of immune-related genes in pan-cancer whole genome

Bidirectional clustering to 537 immune-related gene alterations including SNVs, indels, SVs, and CNVs is shown. Many small clusters were formed, which were composed of genes on the same chromosomes, and the largest gene cluster consisted of genes on chromosome *6p*, which contains HLA genes. Recurrent copy number loss was observed in the cluster, and events involving the loss of HLA regions frequently occurred in pan-creatic cancers.

eQTL project

Integration of genetic information into immune functions

Recently, many disease susceptibility variants have been identified by genome wide association studies (GWAS). Germline genetic variations provide evidence into the causal relationship of an observed phenomenon and its pathogenesis. In this regard, the majority of GWAS risk variants have been reported to function as expression-quantitative trait loci (eQTL), regulating the expression levels of genes. Therefore, integrating genomic information, qualitative and quantitative analyses of transcriptomes, and cell specific epigenomes, we will better understand the causal pathogenic components of immuno-competent cells in various immune-mediated diseases.

We are establishing a system to obtain various subtypes of leukocytes from peripheral blood mononuclear cells (PBMC) of heathy individuals. We expect to obtain an unbiased relationship between genotypes and gene expressions from healthy donors. Cell separation is performed using fluorescence activated cell sorting into about 30 different subsets. Cells are then analyzed in a steady state or in further stimulated conditions, such as in the presence of combinations of cytokines and cell surface receptor agonists, to capture the dynamic responses of gene regulation. First, genotyping as well as RNA-seq are performed. With these data, we will obtain eQTL, as well as splicing QTL information. Subsequently, we perform epigenetic analyses, specifically focusing on enhancers and promotors, as well as long non-coding RNAs. Cap analysis of gene expression (CAGE), assay for transposase-accessible chromatin using sequencing (ATAC-seq), and several histone marker analyses for each subset are powerful tools for identifying the causal relationship between genetic variation and gene expression.

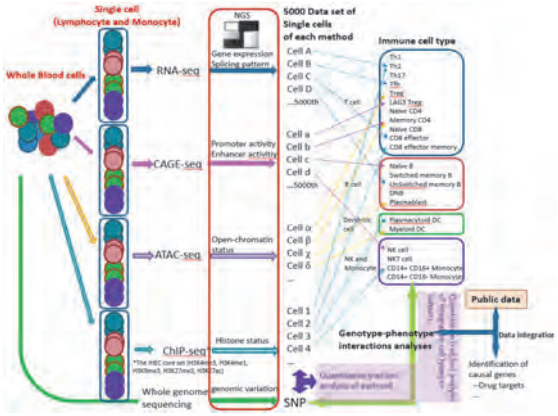


Figure: Integration of genetic information into immune functions: The eQTL project

Search for new biomarkers involved in the pathogenesis of Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2D) is a highly prevalent metabolic disease in Japan and worldwide. Approximately 20 million Japanese, as many as 1 out of 5 individuals, suffer from diabetic or prediabetic (medically defined as glucose intolerance) conditions. Therefore, the prevention of T2D is an urgent need both socially and economically. As a center project, IMS researchers have been committed to identify T2D-preventive biomarkers or factors involved in the pathogenesis of T2D. To this end, individuals with prediabetic glucose intolerance should be analyzed carefully, instead of already diagnosed and treated T2D patients. We are collaborating with the University of Tokyo Hospital and have recruited volunteers using a complete medical checkup into 3 groups (n=100 each): 1) no obesity or glucose intolerance (control), 2) obesity (BMI ≥ 25), and 3) glucose intolerance (fasting blood glucose ≥ 110 mg/dl or HbA1c ≥ 6.0%). In addition to the thorough clinical examination data taken during the medical checkup, the following have been collected in RIKEN: fecal metagenomic and metabolomic data, plasma and urine metabolomic data, CAGE-based RNAseq data of peripheral blood mononuclear cells, and whole genome sequencing data. We are also collecting nutritional and physical activity data using a brief self-administered diet history questionnaire and accelerometry, respectively.

Correlation analysis of clinical data with fecal metabolome and microbiome data has revealed that insulin resistance and metabolic syndrome were significantly associated with monosaccharides and sugar derivatives. We further examined correlation of these fecal monosaccharides and sugar derivatives with plasma metabolites. As a result, these fecal metabolites positively correlate with some plasma metabolites, especially those related to the glycolytic pathways, suggesting that fecal metabolites may impact host sugar metabolism in individuals with insulin resistance and metabolic syndrome.

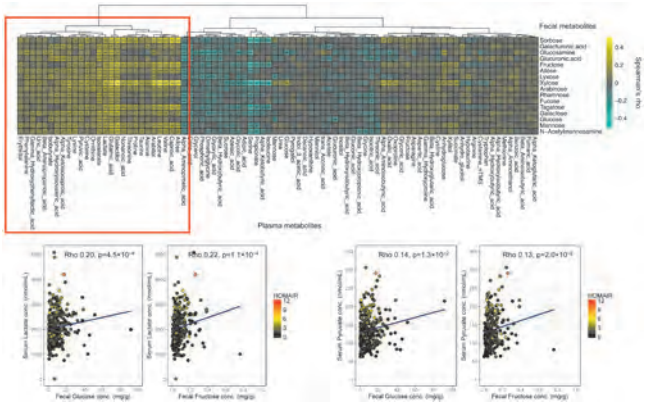


Figure: Correlation of fecal and plasma metabolites in insulin resistance and metabolic syndrome

Top: A schematic view of heatmap showing the Spearman's correlations between fecal sugar derivatives and plasma hydrophilic metabolites. The fecal metabolites that were significantly associated with insulin resistance were included in the analysis.
Bottom: Dot plots with linear regression showing the correlation between fecal glucose and fructose, and plasma lactate and pyruvate which are components of glycolysis.

Medical Sciences Innovation Hub Program (MIH)

Atopic dermatitis (AD) is a heterogeneous and multifactorial disorder. Although it has been suggested that an individual approach to each patient is crucial for the treatment of AD, suitable methods have not been established yet. The purpose of this study, therefore, is to establish a method for disease clustering into sub-groups and to develop a novel predictive treatment algorithm in each sub-group. To achieve this, we will perform an integrated analysis of skin transcriptome data and multimodal clinical information from AD patients.

Consistent with the above approach, we are collecting comprehensive high-quality research samples in collaboration with Keio University Hospital and have established an integrated data analysis and repository infrastructure called Medical Data Integration Assistant (MeDIA). We have acquired more than 880 transcriptome datasets (mRNA-seq of skin tissue) and are performing data analysis using supervised and unsupervised machine learning with other annotating data such as clinical data, PBMC transcriptomes, and serums cytokine profiles. Using this platform, we are identifying potential biomarkers and pathway candidates to help predict disease prognosis. We will verify these biomarkers in appropriate animal models, with a view for future drug development and social contribution. Furthermore, we are preparing whole genome sequencing and association analyses (eQTL analysis) that combine the variant information and the collected transcriptome data to identify genes involved in disease pathology.

Our team is highly focused on the integration of technologies and expertise in various fields. Our approach will not only pave the way for the realization of personalized medicine for AD, but also for the development of new technologies in data-driven medical research, and, therefore, will have a considerable impact on society.

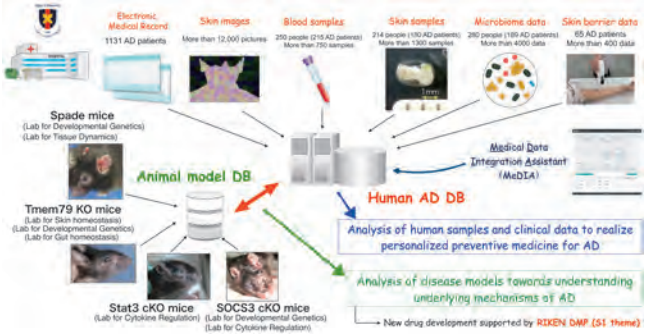


Figure: Study Workflow- Data Driven Research for Atopic Dermatitis

iPS project

Induced pluripotent stem (iPS) cells possess tremendous therapeutic potential in many areas, including regenerative medicine and immune therapy. In collaboration with individual IMS research laboratories, the core facility for iPS research is aiming to put cancer immunotherapy with iPS-derived NKT cells into practical use.

The facility has operated an IMS Cell Manufacturing Unit (CMU) to produce iPS-derived human invariant NKT (Vα24+iNKT) cells under GMP (Good Manufacturing Practice)/ GCTP (Good Gene, Cellular, and Tissue-based Products Manufacturing Practice) guidelines. The safety of these iPS-Vα24+iNKT cells was confirmed by preclinical studies. The facility has been completing PMDA (Pharmaceuticals and Medical Devices Agency) consultation for eventual clinical trials of iPS-Vα24+iNKT cell-mediated head and neck cancer immunotherapy that will start this year.

To assess safety of clinical trials using allogeneic transplantation, the facility also needs to establish a cell tracking system, which enables tracing the transplanted cells in the patient. To achieve this aim, this year, the facility focused on AkaBLI, an all-engineered bioluminescence *in vivo* imaging system, and we generated human iPSCs containing the Akaluc gene using the CRISPR/Cas9 system. Akaluc-expressing human iPS cells were further differentiated to iPS-Vα24+iNKT cells and, then, were injected intravenously into human cytokine knock-in NSG mice. By using the IVIS imaging system, the facility found that strong bioluminescence signals derived from the transplanted cells were clearly observed in the mice (Figure 1). These results suggest that Akaluc-expressing iPS-Vα24+iNKT cells will be more useful to determine residence time of transplanted cells in the patient and future therapeutic planning.

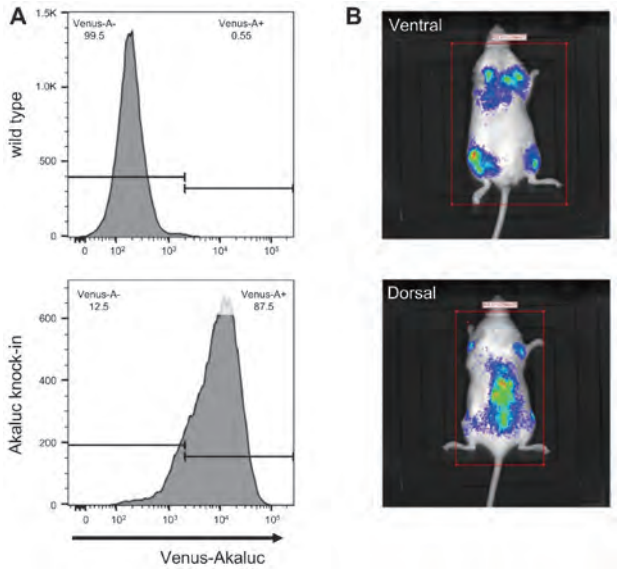


Figure: Analysis of Akaluc-expressing iPS-Vα24+iNKT cells in the mouse
(A) Flow cytometry analysis of Venus-Akaluc expressing cells using wild type iPS-Vα24+iNKT cells and Venus-Akaluc knock-in iPS-Vα24+iNKT cells. (B) Bioluminescence images of mice at 1 month after intravenous injection of Venus-Akaluc expressing iPS-Vα24+iNKT cells. Pictures were kindly provided by Dr. Shin-ichiro Fujii at the Laboratory for Immunotherapy.

Humanized mouse

The heterogeneity and complexity of human hematopoietic and immune systems in normal and diseased states need to be addressed in order to create precision medicine in the future. In addition to direct the examination of human samples, we have developed humanized mice that enable tracing of the *in vivo* fate of human hematopoietic stem/progenitor cells and engraftment kinetics of leukemia-initiating cells.

In 2019, we developed a new humanized mouse model supporting innate immune cells expressing human IL-7 and IL-15. These cytokines help injected human hematopoietic stem cells generate human CD56+ NK cells in bone marrow, spleen, and thymus. With this cytokine support, human NK cells expressed the maturation phenotype CD56+CD94+CD16+. Consistent with the cell surface phenotype, human HSC-derived NK cells produced perforin and granzyme B, and exhibited a gene expression signature similar to that of human PB-derived NK cells. We believe that hIL-7 and hIL-15 KI humanized mice will serve as a preclinical model to examine the function of innate immune cells for cellular therapy.

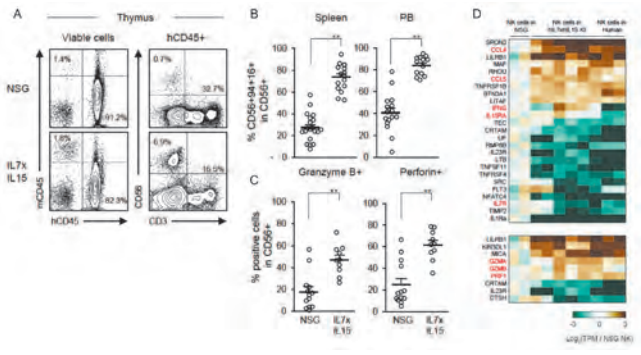


Figure: Human NK cell development in hIL-7xhIL-15 KI Humanized Mice
A. Human T cells and NK cells developed in the thymus of an hIL-7xhIL-15 KI NSG mouse engrafted with human HSPCs. B. In the spleen and blood of an hIL-7xhIL-15 NSG humanized mouse, CD94+CD16+ mature NK cells accounted for the majority of human HSPC-derived NK cells. C. Human NK cells produced granzyme B and perforin in their cytoplasm. D. Humanized mouse NK cells expressed a gene expression signature similar to NK cells in human peripheral blood.

Cancer immunology

We regard cancer immunology as an interdisciplinary branch of immunology, since cancer represents a failure of homeostasis of the immune system and involves many components. The first goal of the cancer immunology group is to understand the carcinogenesis and tumor immune microenvironment (TIME) during the development and progression of cancer by utilizing omic profiling technologies including RNA-seq analysis. In particular, Nakagawa's group has classified four immune subclasses of liver cancer based on immunosuppression mechanisms and is searching for new immuno-target molecules related to immunosuppression of cancer tissues. Tsunoda's group brought the ideas and methods from mathematics and computational sciences and demonstrated the relationship between TIME, subclonal cancer diversity or drug response, and patient prognosis in cancer. In addition, this group has developed novel machine learning methods for cancer immunology multi-omics. The second goal of the cancer immunology group is to develop a cancer immunotherapy strategy to treat cancer by enhancing the host protective response. Ishikawa's group has investigated graft-versus-host disease (GVHD), using allogeneic stem cell transplantation in a humanized mice model with hematological malignancies. They created NSG humanized mice over-expressing human IL-6 (hIL-6 TG) as the GVHD model and observed a reduction of effector Tregs and activation of human macrophages, as well as T cells in multiple organs. Fujii's group, in the current year, assessed cytotoxic T lymphocytes (CTLs) under immune checkpoint blockade (ICB) therapy in murine colorectal cancer. Using antigen libraries based on immunogenomics, they identified three H2-K^{b}-restricted, somatic-mutated epitopes as immunogenic neoantigens in these enhanced CTLs responses. Furthermore, two translational research projects aimed at the application of NKT cell therapy have been ongoing. Koseki's group has almost completed an iPS-NKT cell preclinical trial. Fujii's group has been studying an investigator-initiated Phase I clinical trial of aAVC-WT1 therapy in acute myeloid leukemia. These projects have been supported partly by the RIKEN Drug Discovery and Medical Technology Platforms (DMP).

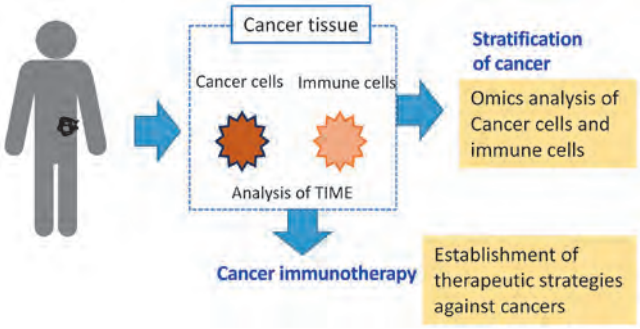


Figure: Current cancer immunology projects in IMS
Cancer immunology groups work though omics analysis of the tumor immune microenvironment (TIME) in the development and progression of cancer. In addition, we attempt to establish cancer immunotherapy to treat cancer by enhancing the host protective response.

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 at 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 setting up a facility for the development of antibody drugs, the Drug Discovery Antibody Platform Unit. As of 2019, IMS has six collaborative programs with DMP, as follows: Artificial adjuvant vector cells (Shin-ichiro Fujii), Cancer therapy with iPS-derived NKT cells (Haruhiko Koseki), Cancer therapy with NKT cells (Hiroshi Ohno, P1), Drugs for allergic diseases (Masato Kubo), 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 Fujii et al. are preparing for an investigator-initiated clinical trial.

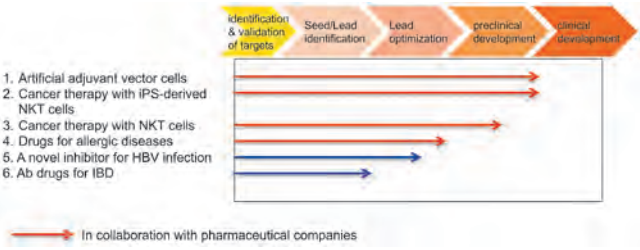


Figure: Collaboration between IMS and DMP for the development of innovative new pharmaceuticals and medical technologies

RIKEN International Program Associate (IPA)

IMS accepted six 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 2019 were
Jiahui Ma (Peking University, China) in the Laboratory for Genome Information Analysis
Yan Jun Lan (ETH Zurich, Switzerland) in the Laboratory for Advanced Genomics Circuit
Shruti Bhagat (Karolinska Institute, Sweden) in the Preventive Medicine and Applied Genomics Unit
Jack Thomas Flanagan (The University of Liverpool, UK) in the Laboratory for Genomics of Diabetes and Metabolisms
Ting Su (Nanjing University, China) in the Liver Cancer Prevention Research Unit
Mao Lin (Peking Union Medical College, China) in the Laboratory for Bone and Joint Diseases

RIKEN Junior Research Associate (JRA) Program

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

This year, 21 JRA students studied in IMS.

Mamoru Ogawa (Laboratory for Metabolomics)
Hiroki Sugishita (Laboratory for Developmental Genetics)
Manabu Nagayama (Laboratory for Gut Homeostasis)
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)
Tsuyoshi Yamane (Laboratory for Metabolomics)
Naoko Toki (Laboratory for Transcriptome Technology)
Makoto Iwasaki (Laboratory for Human Disease Models)
Nao Otomo (Laboratory for Bone and Joint Diseases)
Akiko Oguchi (RIKEN-IFOM Joint Laboratory for Cancer Genomics)
Tomoaki Takahashi (Preventive Medicine and Applied Genomics Unit)
Takahiro Matsunaga (Laboratory for Gut Homeostasis)
Shigeki Hirabayashi (RIKEN-IFOM Joint Laboratory for Cancer Genomics)
Haruki Uchino (Laboratory for Metabolomics)
Zhujun Wang (Laboratory for Gut Homeostasis)
Hiroyuki Suetsugu (Laboratory for Bone and Joint Diseases)
Tahara Umi (Laboratory for Skin Homeostasis)
Hiroto Horikawa (Laboratory for Gut Homeostasis)

RIKEN Special Postdoctoral Researcher (SPDR) Program

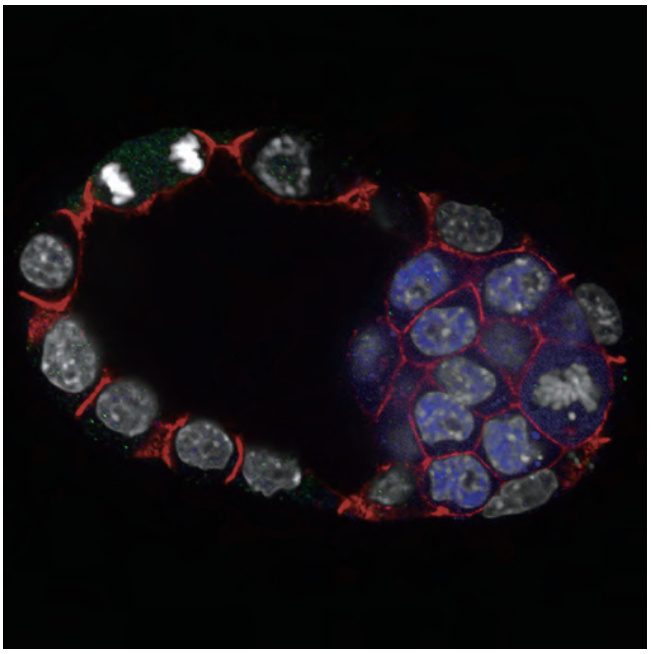
RIKEN's Special Postdoctoral Researcher Program was instituted to provide young and creative scientists the opportunity to be involved in autonomous and independent research in line with RIKEN objectives and research fields. The positions are competitive, but if selected, researchers receive salaries 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.

Alexis Vogelzang (Laboratory for Mucosal Immunity)
Keiichiro Shiraga (Laboratory for Skin Homeostasis)
Xiaoxi Liu (Genome Immunobiology RIKEN Hakubi Research Team)
Callum Parr (Laboratory for Advanced Genomics Circuit)
Rei Nakano (Laboratory for Cellular Function Conversion Technology)
Tsuyoshi Kiniwa (Laboratory for Innate Immune Systems)
Sotaro Ochiai (Laboratory for Tissue Dynamics)

Part 4

Events



RIKEN-KI Joint Doctoral Course 2019

The 2019 RIKEN-Karolinska Institutet Joint Doctoral course "Bioinformatics Analysis of Gene Regulation in Omics Data and its Applications to Medical Problems" was conducted from March 13-27, 2019. The first week of this two-week course with 3.0 European Credit Transfer System (ECTS) consisted of a homework assignment. For the second week, all 30 course participants met at the RIKEN Yokohama west building. Fifteen of the participants came from Karolinska Institutet to Yokohama. The morning sessions consisted of lectures, student presentations, and group discussions. In afternoon sessions, participants worked in groups of six students with hands-on data analysis projects. Each group performed bioinformatics data analysis and produced figures based on one specific paper authored by the supervising teacher of that group. A formal examination with student presentations of the achieved data analyses was conducted on the afternoon of the last course day. The course received very good evaluation scores in the anonymous Karolinska Institutet course evaluation.

RIKEN IMS-Stanford ISCBRM Joint Symposium

RIKEN IMS and the Stanford Institute of Stem Cell Biology and Regenerative Medicine (ISCBRM) began their collaboration in 2017 when the first joint symposium was held at Stanford. The third RIKEN IMS-Stanford ISCBRM Joint Symposium "Bridging Immunology, Stem Cell Biology, and Regenerative Medicine" was held May 20-21, 2019, at Stanford University. Over the course of two full days, sessions covered tissue, stem and progenitor cells; new biology and technologies; how cells and tissues develop; pluripotency; and stem cells, disease and immunology. Representing RIKEN were eight researchers from IMS, and one from the Medical Sciences Innovation Hub Program (MIH), consisting of mostly Young Chief Investigators and other young scientists. Of the 14 Stanford speakers, most were professors, while the audience consisted mostly of students. This continued the format established in the previous year where most of the visiting participants are young up-and-coming scientists who are keen to build their research networks and establish new collaborations. Throughout the two days, this strategy was apparent as researchers from both institutes could been seen breaking away to discuss their research in more detail. The event culminated with a farewell dinner, but the highlight was the catered pizza dinner held the night before at Prof. Irv Weissman's house within walking distance of the university. Both social events allowed for continued discussions in a relaxed environment and included local researchers who were otherwise unable to attend the event. The next symposium will take place in Fall 2020 on the RIKEN Yokohama Campus.

EMBO Workshop on Single Cell Biology

The EMBO workshop "Single Cell Biology" supported by The Company of Biologists was held successfully on May 20 – 22, at Plaza Heiei, Tokyo International Exchange Center, Tokyo, Japan. The workshop covered Single Cell Biology with wide range of topics including immunology, cancer biology, computational biology, aging, developmental biology, cell and gene regulation, spatial imaging, and new technologies.

Single Cell Biology is now bringing about a big impact on the life sciences and healthcare. International research projects on single cell biology, such as Human Cell Atlas and Life Time are being conducted worldwide. Reflecting increasing interest on this field, the workshop was attended by approximately 340 people from academic, hospitals, and industries from 25 countries. During the workshop, 22 leading experts gave outstanding talks that included unpublished data, and oral presenters selected from the submitted abstracts performed inspiring presentations. Besides, 83 researchers and students gave poster presentations and had scientific discussions.

Overall, the quality of the research presented at the workshop was exceptional. Single cell RNA sequencing (scRNA-seq) and single nuclear RNA sequencing (snRNA-seq) techniques have become widely used as the gold standard for single cell biology research. In combination with other innovative technologies, it has been demonstrated that novel immunophenotyping methods and spatial imaging techniques at single cell resolution are being realized. Various projects for building cell atlases were introduced during the workshop, including the Tabula Muris (Mouse Cell Atlas), Mouse Lemur Cell Atlas, Human Tumor Atlas, and Human Developmental Cell Atlas.

Reference website: http://meetings.embo.org/event/19-single-cell-biology

The Human Cell Atlas General Meeting in Tokyo

Hosted by the RIKEN Center for Integrative Medical Sciences and kindly supported by The Kavli Foundation and Chan Zuckerberg Initiative, the Human Cell Atlas (HCA) General Meeting took place from May 23 – 24, 2019 in the Plaza Heisei, Daiba, Tokyo, Japan.

HCA is a scientist-led movement to generate a reference atlas of all cell types in the human body. This effort has grown out of a dedicated and ambitious scientific community that is empowered by rapid advances in the accurate measurement of diverse features of single cells. The vision and scientific leadership for this project coalesced starting in 2016 and, through a series of meetings, workshops, and community organizations. This is the 7th as a global meeting, and the first General meeting in Asia. RIKEN has been leading the organization in Asia.

During the meeting, the scientific vision and direction set by the scientific community, as well as updates of each project were discussed in the sessions. All the discussions and talks were broadcast all over the world. There was also a funding meeting, which discussed how global funders, including government agencies and public and private foundations, can work together in an efficient and coordinated manner to support the scientific vision of the HCA.

Meeting
Thursday May 23rd, 2019, 8:30 AM JST – 18:30 PM JST
Friday, May 24th, 2019, 9:00 AM JST – 13:00 PM JST

Attendees
196 attendees

RIKEN-Tsinghua International Summer Program 2019

The first RIKEN-Tsinghua International Summer Program on Contemporary Immunology was held at the Institute for Immunology, Tsinghua University (IITU) in Beijing on June 8-12, 2019. The program was originally started at RIKEN in 2006 and successfully continued until 2017. In 2017, RIKEN IMS and IITU agreed to take turns hosting this annual international summer program as part of their international cooperative efforts.

Forty-nine selected young scientists from around the world had the opportunity to attend special lectures by prominent researchers, including Drs. Max Cooper, Tak Mak, Alexander Rudensky, Mark Davis, Chen Dong, Tadatsugu Taniguchi, Shigeo Koyasu, Chris Goodnow, Florent Ginhoux, and Hiroshi Ohno. The participants also had opportunities to discuss their own research during the poster presentation session and other informal gatherings. Four junior researchers, Shohei Egami, Sonoko Takahashi, Tommy Terooatea, and Anselmo Jiro Kamada, from IMS took part in the program.

Dr. Chen Dong, Director and Professor of IITU, remarked, "We are very fortunate to host the Tsinghua-RIKEN Summer School for Contemporary Immunology. This program has a long tradition,

and now it is taking turns between Tsinghua and RIKEN. Many young immunologists have experienced this program and made very successful careers. Here you will meet the masters in immunology, interact with future leaders in immunology, and have in-depth discussion on contemporary immunology topics. Also, you will experience different cultures of both China and Japan." A message from the program participants has been uploaded on YouTube (https://www.youtube.com/watch?v=WdUg6Uzq3iA).

The IMS-JSI International Symposium on Immunology 2019

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 24-25 at the Ito Hall, Ito International Research Center, the University of Tokyo. The symposium, entitled "Checkpoint in medical science and its technology", included 19 outstanding speakers presenting their research, and attracted more than 350 participants. There were four sessions: (1) Inflammation, resolution, and repair; (2) Human immunodeficiency; (3) Brain-immunity axis; and (4) Toolbox for biomedical sciences. The program covered a broad range of immunological research fields and was well received among the audience according to our survey. Recent investigations on the nervous and immune systems interconnection provided new insights and show promise in linking the missing pieces between these fields. Elegant studies performed in humans with immuno-deficiencies revealed new diagnostic and therapeutic approaches and emphasized the relevance of solid fundamental research performed in animal models. Current technologies, such as single cell gene expression profiling or live imaging, promise exploration of yet untouched areas and revealing new molecular and cellular players. Especially impressive were the presentations of several young investigators showing great promise for the future of immunological studies. Researchers also had a unique opportunity to directly communicate with a publisher and learn how to best present their results.

Lastly, we sincerely appreciate the support from the Naito Foundation, Japan.

RIKEN Lab Opening in Luxembourg

On July 9, 2019, a ceremony was held in Luxembourg to commemorate the signing of a memorandum of understanding between RIKEN and the University of Luxembourg's Luxembourg Center for System Biomedicine (LCSB) and the Luxembourg Institute of Health (LIH). Based on this agreement, a joint laboratory will be established between RIKEN and the University of Luxembourg. RIKEN's ties with Luxembourg began in 2014 with a joint symposium, which has been held annually since then, along with an agreement signed in that same year between RIKEN and LCSB, as well as an agreement in 2015 between RIKEN and the Luxembourg National Research Fund (NRF). The current agreement built on them by creating a partnership between LCSB and LIH that will create a joint laboratory working in areas including immunology, microbiome, and inflammation research, as well as promoting the training of researchers and students. Luxembourg has been a world leader in the collection and management of data related to clinical specimens, and the joint research will take advantage of this strength, leading to the development of a comprehensive medical data system, incorporation of patient-derived data into disease models, and research into neuroinflammation using human-derived iPS cells. The ceremony, held in the "RIKEN conference room" at the University of Luxembourg, was attended by Jens Kreisel, Vice Rector of the University of Luxembourg; Marc Schiltz, Secretary General of the Luxembourg National Research Fund; Ulf Nehrbass, CEO of the Luxembourg Institute of Health; Jean-Claude Schmit, Director of Health of the Ministry of Health, Luxembourg; and Romain Martin, First Councilor of the Luxembourg Ministry of Higher Education & Research. Attendees from RIKEN included Executive Director Motoko Kotani, IMS Director Tadashi Yamamoto, IMS Deputy Director Haruhiko Koseki, and Medical Sciences Innovation Hub Program (MIH) Deputy Director Kazuhiro Sakurada.

Advisory Council Meeting

The IMS Advisory Council (IMAC) meeting was held August 26-28, 2019, in Tokyo and at the RIKEN Yokohama Institute. This was the first scientific review of IMS to be conducted since its reorganization in April 2018, during which the former IMS center was expanded with the Division of Genomic Technologies from the RIKEN Center for Life Science Technologies. The advisory council (AC) consisted of 18 distinguished science leaders, 13 from overseas and five from Japan, chaired by Dr. Max D. Cooper (Emory University) and co-chaired by Dr. Mark Lathrop (McGill University). The role of the AC is to provide unbiased scientific advice on and evaluation of IMS and to support its Director in all decisions related to research and personnel strategy.

On the first day, after Director Yamamoto welcomed the AC members and they introduced themselves, Executive Director Koyasu gave an overview of RIKEN, Director Yamamoto introduced IMS and the issues to be addressed by the AC, and each of the Deputy Directors briefly introduced their respective Divisions. The second day consisted of reviews of each of the IMS laboratories, which were arranged in six groups by division, overseen by three AC reviewers each. On the morning of the last day, the AC members finished giving their group oral reports to the Director. Finally, after a closed discussion by the AC, they presented their comments and advice in a session attended by the IMS PIs in which Dr. Cooper summarized the overall findings of the IMAC review and the chair of each group provided further details.

In a detailed written report (https://www.ims.riken.jp/english/about/advisory_council.php) subsequently provided by the AC, they stated that, "Overall, the AC was very impressed by the quality of the research being done at IMS. The [continued] promotion of international collaborations with IMS serving as a hub should be encouraged. We urge the RIKEN Central Administration to increase the IMS budget so that the Center's groundbreaking research can continue."

RIKEN-KI-SciLifeLab Symposium 2019

This symposium series is organized between RIKEN in Japan, and the Karolinska Institute (KI) and the Science for Life Laboratory (SciLifeLab) in Sweden. The symposia alternate between RIKEN and SciLifeLab. The 2019 symposium was the sixth symposium and was held at RIKEN in Yokohama. Several collaborations between groups at KI, SciLifeLab, and RIKEN have started based on first contact during one of the symposia.

At the 2019 symposium, two main points were addressed: (a) Production of a White Paper detailing the biomedical/life science areas for which RIKEN, KI, and SciLifeLab see large potential for Artificial Intelligence (AI) contributions to life sciences and (b) Generation of biomedical/life science reference datasets to attract AI researchers and opening of these datasets at the RIKEN and SciLifeLab Data Centers.

Around 80 participants co-created a first draft of the White Paper, which would be structured into a quality-controlled finished paper during 2020. Symposium participants are invited to refine the co-created draft output as co-authors under the supervision of one Swedish and one Japanese co-editor. The White Paper will serve to document the current opportunities and challenges, so that a cross-cultural and cross-discipline perspective is provided. Publishers will be contacted for wide dissemination.

Fourteen AI reference datasets were proposed by the participants working in small groups to refine each of these datasets according to the discussed standards.

Adjunct Professorship Programs

IMS collaborates with and accepts graduate students from 8 domestic university graduate schools. There are now a total of 34 adjunct professors/associate professors in IMS (Table), and 57 students who studied at IMS in 2019. On April 20th and September 21st, IMS held briefing sessions 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	Kazuyo Moro (Professor) Takashi Saito (Visiting Professor) Takashi Tanaka (Visiting Professor) Shiro Ikegawa (Visiting Professor)
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) Soichi Kojima (Visiting Professor)
Graduate School of Medicine, Yokohama City University	Shiro Ikegawa (Visiting Professor) Hidewaki Nakagawa (Visiting Professor) Taisei Mushiroda (Visiting Professor) Yukihide Momozawa (Visiting Professor) Kaoru Ito (Visiting Professor) Momoko Horikoshi (Visiting Professor)
Graduate School of Medical Life Science, Yokohama City University	Hiroshi Ohno (Visiting Professor) Makoto Arita (Visiting Professor) Takaharu Okada (Visiting Professor) Taishin Akiyama (Visiting Professor) Piero Carninci (Visiting Professor) Yukihide Momozawa (Visiting Professor) Hidehiro Fukuyama (Visiting Associate Professor) Takahiro Suzuki (Visiting Associate Professor)
Research Institute of Biological Sciences, Tokyo University of Science	Masato Kubo (Professor) Takashi Saito (Visiting Professor)
Graduate School of Medicine, Keio University	Masayuki Amagai (Professor) Kenya Honda (Professor) Shigeo Koyasu (Visiting Professor) Haruhiko Koseki (Visiting Professor)
Graduate School of Science, Tokyo Metropolitan University	Azusa Inoue (Visiting Associate Professor)
Graduate School of Medicine, Kyoto University	Chikashi Terao (Part-time Lecturer)

Yokohama Campus Open Day

RIKEN's Open Day events are a great opportunity for the public to explore the cutting-edge science being carried out at each RIKEN branch. On September 21st, RIKEN Yokohama Branch held its annual Open Day in collaboration with Yokohama City University. A total of 3151 people visited the branch this year. While enjoying the clear fall weather, people engaged themselves in numerous activities such as lectures, seminars, experiments, quizzes, and poster presentations.

From IMS, 9 hands-on events, one lecture, one facility-site tour, one video presentation, and 18 posters were held, together with a Briefing Session for the IMS Joint Graduate School Program.

There was high interest in lectures by scientists talking about their research. From IMS, Dr. Haruhiko Koseki, from the Laboratory for Developmental Genetics, gave a talk at this Open day seminar series about "Starting of a clinical trial for head and neck cancer with iPS cell-derived NKT cells". More than 100 people came for the seminar and an active FAQ was held after the seminar.

IMS Internship Program

The IMS Internship Program was launched in April 2018 with the aim of hosting young distinguished international scientists to carry out research activities in IMS laboratories. The program benefits both the young researchers, by giving them the chance to experience working in our world-class laboratories, and RIKEN, by promoting IMS activities to up-and-coming young scientists from around the world. The program is open to Master's and Ph.D. students, medical students at a grade equivalent to a Master's student in Japan, and young postdocs who received their Ph.D. within the last three years. Calls for applications occur twice per year for internships (up to three months) that take place in winter and summer. For each application period, 2-3 candidates are selected on a competitive basis, and successful candidates receive financial support that essentially covers all of their travel and living expenses. The program has been viewed as a great success and candidates for the 2020 winter internship period have already been selected.

In 2018* we hosted our first two students, and in 2019 we hosted five students as follows:

Anne de Groot*[A] (University of Groningen, The Netherlands) in the Laboratory for Human disease Models, on "Humanized mouse research for targeting acute lymphocytic leukemia"

Abi Sofyan Ghifari*[B] (The University of Western Australia, Australia) in the Laboratory for Metabolomics, on "Development of lipidome profiler by analyzing lipidomes of various mouse tissues"

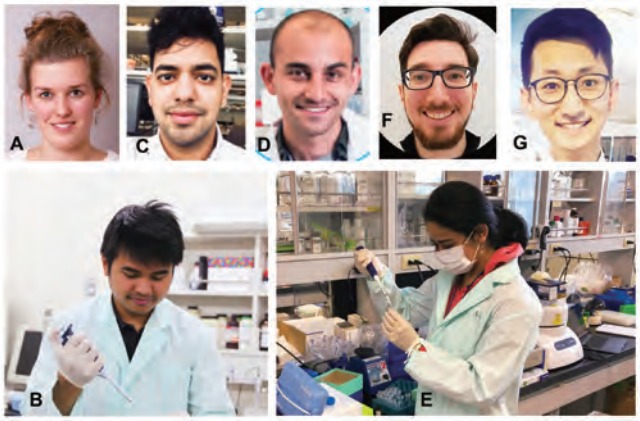
Shubham Gupta[C] (University of Toronto, Canada) in the YCI Laboratory for Next-Generation Proteomics, on "Understanding obesity in mice using high-throughput omics approaches"

Karim Abu Nahia[D] (International Institute of Molecular and Cell Biology Warsaw, Poland) in the Laboratory for Transcriptome Technology, on "Single nuclei RNA-seq analysis of mouse heart during ageing"

Anushka Khasnobish[E] (Okayama University, Japan) in the Laboratory for Microbiome Sciences, on "Training for human microbiome analysis using NGS datasets"

Michel Mertz[F] (Strasbourg University, France) in the Laboratory for Transcriptome Technology, on "Functional analysis of SINE-UPs"

Jenkin Tsui[G] (Yale University, USA) in the Laboratory for Applied Computational Genomics, on "Computational analysis of RNA secondary structure sequencing data in FANTOM6"

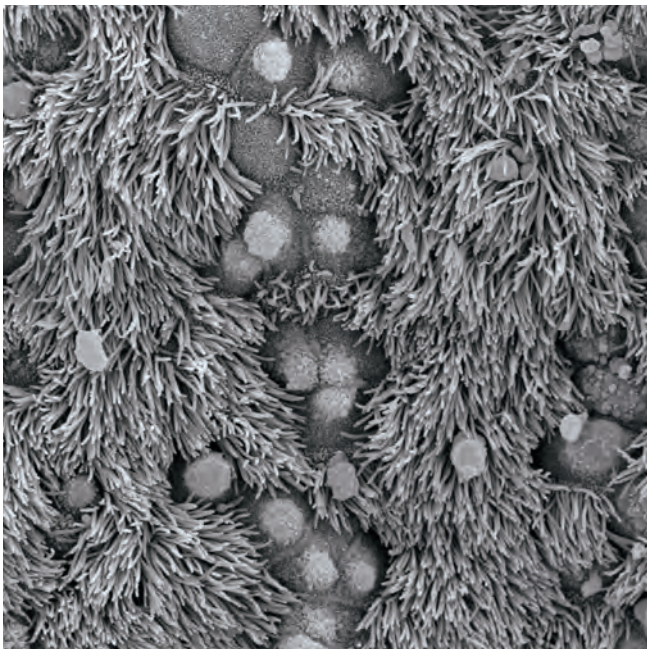


Award Winners 2019

Name of the awardee	Name of the award	Date of the announcement
Chikashi Terao, Team Leader, Laboratory for Statistical and Translational Genetics	The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, The Young Scientists' Prize	Apr 2019
Shiro Ikegawa, Team Leader, Laboratory for Bone and Joint Diseases	Russell A. Dibbs Basic Research Award, The 54th Annual Meeting of Scoliosis Research Society	Sep 2019
Chikashi Terao, Team Leader, Laboratory for Statistical and Translational Genetics	Medical Research Encouragement Prize, The Japan Medical Association	Sep 2019
Tetsuro Kobayashi, Research Scientist, Laboratory for Innate Immune Systems	LEO Foundation Award	Nov 2019
Yukihide Momozawa, Team Leader, Laboratory for Genotyping Development	The RIKEN BAIHO Award (RIKEN Excellent Achievement Award)	Jun 2019
Harumichi Ishigame, Research Scientist, Laboratory for Tissue Dynamics	The RIKEN BAIHO Award (RIKEN Excellent Achievement Award)	May 2019
Haruka Yabukami, Technical Staff I, Laboratory for Cellular Function Conversion Technology	RIKEN Ohbu Technology Incentive Award	Mar 2019
Megumi Hirano, Student Trainee, Laboratory for Metabolomics	Presentation Award, The 18th Pharma-Bioforum of the Pharmaceutical Society of Japan	Sep 2019
Sonoko Takahashi, Postdoctoral Researcher, Laboratory for Tissue Dynamics	The 48th Naito Conference Poster Award for Excellence	Oct 2019
Aiko Sekita, Postdoctoral Researcher, Laboratory for Developmental Genetics	Poster Award (2nd award), European Congress on Clinical and Translational Medicine	Oct 2019
Jen-Chien Chang, Research Scientist, Epigenome Technology Exploration Unit	Human Genome Meeting (HUGO) Poster Award	Apr 2019
Saumya Agrawal, Postdoctoral Researcher, Laboratory for Applied Computational Genomics	Best Poster Award, The 13th International Workshop on Advanced Genomics (13AWG)	Jun 2019
Mio Yoshida, Junior Research Associate, Laboratory for Metabolomics	Ambiotis Resolution Award, The 60th International Conference on the Bioscience of Lipids	Jun 2019
Tom Kelly, Postdoctoral Researcher, Epigenome Technology Exploration Unit	RIKEN-HUGO Scholarship	Apr 2019
Tommy Terooatea, Postdoctoral Researcher, Epigenome Technology Exploration Unit	RIKEN-HUGO Scholarship	Apr 2019

Part 5

Data and Statistics



Guest Lectures 2019

Table: Guest Lectures Jan-Dec 2019

Date	Speaker	Affiliation	Country	Title
Jan. 16	Mr. Vipin Kumar	RIKEN Center for Biosystems Dynamics Research	Japan	Bhi-Cect: a graph based approach to understand the hierarchical structure of the chromosome
Jan. 18	Dr. Takuro Nakamura	The Cancer Institute, Japanese Foundation for Cancer Research	Japan	Modeling leukemia and sarcoma to understand epigenetic modification important for cancer progression
Jan. 23	Dr. Amanda Alvarez	RIKEN Center for Brain Science	Japan	Social media and web for scientific visibility, job search, and more
Jan. 31	Dr. Jonathan Weissman	University of California, San Francisco	USA	Finding and interpreting genetic interactions using Perturb-seq single cell RNA-seq CRISPR screens
Feb. 04	Prof. Klaus Rajewsky	Max Delbrück Center for Molecular Medicine	Germany	Genetic approaches to model and resolve Epstein-Barr-Virus pathologies
Feb. 18	Dr. Natalie van Zuydam	University of Uppsala	Sweden	Zebrafish as a model system to characterise causal genes for LDL cholesterol levels and downstream effects on atherosclerosis and diabetes risk
Feb. 18	Dr. Anubha Mahajan	University of Oxford	UK	Genetics and genomics to biology and translation in type 2 diabetes
Feb. 18	Dr. Andrew P. Morris	University of Liverpool	UK	Trans-ethnic kidney function association study reveals putative causal genes and effects on kidney-specific disease aetiologies
Feb. 21	Dr. Raul Andio	University of California, San Francisco	USA	Immunity and tolerance in insects
Feb. 21	Mr. Simonas Savickas	Technical University of Denmark	Denmark	Hybrid degradomics: interactivity of matrix metalloproteinases and the surrounding degradome at the wound edge
Mar. 05	Dr. Motohiko Kadoki	Harvard Medical School	USA	Inter-organ dialogues during vaccination—lessons from organismal systems immunology—
Mar. 14	Dr. Gong Cheng	Tsinghua University School of Medicine	China	Story of arboviral lifecycle:acquisition mechanism from hosts to mosquitoes
Mar. 12	Dr. M. Teresa Villanueva	Nature Reviews Drug Discovery	UK	The diversifying nature of impact
Mar. 19	Dr. Guillaume Bourque	McGill University and Genome Quebec Innovation Center	Canada	Using comparative epigenomics to better understand non-coding DNA
Mar. 19	Dr. Yoshiki Kawamura	Fujita Health University School of Medicine	Japan	Chromosomally integrated human herpesvirus 6
Mar. 28	Prof. Xing Dai	University of California, Irvine	USA	Skin deep —genetic and genomic approaches to understand the control of skin inflammation and wound healing
Apr. 01	Prof. Adriano Aguzzi	Institute of Neuropathology, University Hospital Zurich	Switzerland	The biology of mammalian prions
Apr. 01	Dr. Hiroshi Haeno	The University of Tokyo	Japan	Mathematical modeling of cancer evolution under immunosurveillance
Apr. 16	Dr. Takashi Fukaya	Institute for Quantitative Biosciences, The University of Tokyo	Japan	Enhancer dynamics in living Drosophila embryos
Apr. 22	Prof. Juha Kere	Karolinska Institutet	Sweden	Fetal HLA-G mediated immune escape and pathogenic immune response in preeclampsia
Apr. 24	Prof. Raffaele Calogero	Molecular Biotechnology Center, University of Turin	Italy	A path to moderate the reproducibility crisis in Bioinformatics
May 14	Dr. Hiroyoshi Nishikawa	National Cancer Center, Exploratory Oncology Research and Clinical Trial Center	Japan	Immune suppressive networks in the tumor microenvironment (TME)
May 10	Dr. Kentaro Senba, Dr. Jun Nakayama	Center for Advanced Biomedical Sciences (TWIns), Waseda University	Japan	Method for identifying carcinogenesis/metastasis regulatory genes
Jun. 03	Dr. Jens Schwamborn	Luxembourg Center for Systems Biomedicine, University of Luxembourg	Luxembourg	Modeling Parkinson's disease in midbrain-like organoids
Jun. 26	Dr. Shingo Iwami	Kyushu University	Japan	Mathematical model-based approach for quantitative data analysis in life sciences
Jul. 03	Dr. Soichiro Yamanaka	The University of Tokyo	Japan	Chromatin reprogramming in mouse gonocyte
Jul. 05	Dr. Kaori Muto	Institute of Medical Science, The University of Tokyo	Japan	Ethical, legal and social implications of scientific/genomic research involving human subjects —points of consideration for ethical handling of human samples and data
Jul. 11	Dr. Luigi Marchionni	Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University	USA	Navigating cancer big data for biomarker discovery and more

Date	Speaker	Affiliation	Country	Title
Jul. 12	Prof. Ferenc Mueller	Institute of Cancer and Genomic Sciences, College of Medical and Dental Sciences, University of Birmingham	UK	Embryonic genome activation elucidated by genome-wide promoter regulation analysis and *in vivo* transcription imaging
Jul. 12	Prof. Boris Lenhard	Institute of Clinical Sciences and MRC London Institute of Medical Sciences, Imperial College London	UK	Deciphering overlapping transcription initiation codes at mammalian promoters using SLIC-CAGE
Jul. 12	Prof. Thomas Mercher	INSERM & Gustave Roussy	France	Pediatric myeloid leukemia: molecular mechanisms & pediatric specificities
Jul. 16	Dr. Koichi Fujimoto	Osaka University	Japan	How mathematical modeling elucidates cooperation and competition of multicellular societies: microbe and epithelium
Jul. 16	Mr. David Bujold	McGill University	Canada	Epigenomic data discovery with the IHEC data portal
Jul. 17	Dr. Rana Herro	La Jolla Institute for Immunology	USA	Shedding LIGHT and TL1A on fibrosis
Jul. 18	Dr. Mashito Sakai	University of California	USA	Decoding environmentally driven gene regulatory networks in hepatic macrophages
Aug. 08	Dr. Luigi Marchionni	Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University	USA	Building resources for genomic data exploration and analysis
Aug. 19	Dr. Pauliina Damdimopoulou	Karolinska University Hospital	Sweden	Characterization of human ovarian tissue cells
Sep. 03	Dr. Isao Naguro	The University of Tokyo	Japan	Molecular entities of cellular osmotic response and their functions in physiology
Sep. 11	Dr. Adam Wilkinson	Stanford University	USA	Long-term *ex vivo* expansion of functional hematopoietic stem cells
Sep. 20	Dr. Takashi Nagano	Institute for Protein Research, Osaka University	Japan	What single-cell Hi-C has shown and will show in future
Sep. 24	Dr. Kenneth M. Murphy	Washington University School of Medicine	USA	Development and function of dendritic cell subsets
Sep. 25	Dr. Masaru Ishii	Osaka University	Japan	Visualization and identification of pathological macrophages in arthritic joints and in other inflammatory tissues.
Oct. 11	Dr. Noriko Saitoh	The Cancer Institute of Japanese Foundation for Cancer Research	Japan	Non-coding RNAs delineate the 3D genome architecture in endocrine–therapy resistant breast cancer
Oct. 23	Dr. Beatrice Bodega	National Institute of Molecular Genetics "Romeo ed Enrica Invernizzi"	Italy	Intronic LINE1 retention mediates the switch to activation in human T lymphocytes
Oct. 24	Prof. Lina Ghibelli	Tor Vergata University of Rome	Italy	Apoptosis of cancer cells as a major goal of antitumor therapies: Yes, but···
Nov. 08	Dr. Sanna Vuoristo	University of Helsinki	Finland	DUX4 regulates early human development
Nov. 14	Dr. Eleonora Leucci	KU Leuven	Netherlands	LncRNAs and beyond: uncoupling cytosolic and mitochondrial translation as an effective anti-melanoma strategy
Nov. 26	Dr. Woong-Yang Park	Samsung Genome Institute, Samsung Medical Center, Sungkyunkwan University	Korea	Tumor immune microenvironment of colorectal cancer
Dec. 06	Dr. Kim Ekroos	Lipidomics Consulting Ltd.	Finland	Lipidomics standards to crack the functional code of individual lipid molecules
Dec. 10	Dr. Branch Moody	Harvard Medical School and Brigham and Women's Hospital	USA	The surprising nature of human T cell responses to CD1
Dec. 19	Dr. Naoki Honda	Research Center for Dynamic Living Systems, Graduate School of Biostudies, Kyoto University	Japan	Forward and inverse problems in biology –mathematical modeling and machine learning–
Dec. 19	Dr. Tetsuo Yasugi	Institute for Frontier Science Initiative, Kanazawa University	Japan	Uniting mathematical modeling with experimental analysis for spatio-temporal neural stem cell differentiation
Dec. 19	Dr. Katsuyuki Yugi	RIKEN Center for Integrative Medical Sciences	Japan	A data-driven and a hypothesis-driven omics integration for systems biology of metabolism
Dec. 25	Dr. Sakie Katsumura	University of Texas, Health Science Center at San Antonio	USA	A hepatic post-transcriptional control of whole body metabolic homeostasis through FGF21 regulation by CCR4-NOT deadenylase

Publications 2019

Table: IMS Publications from January to December, 2019

Journal	Impact Factor (2018)	Number of Papers
Nature	43.1	4
Science	41.1	1
Cell	36.2	2
Nat Methods	28.5	1
J Clin Oncol	28.3	1
Nat Genet	25.5	8
Cancer Cell	23.9	1
Circulation	23.1	3
Gut	17.9	1
Mol Biol Evol	14.8	1
Mol Cell	14.5	2
Ann Rheum Dis	14.3	4
J Allergy Clin Immunol	14.1	1
Genome Biol	14.0	1
ACS Nano	13.9	1
Trends Immunol	13.0	3
Nat Commun	11.9	15
Immunol Rev	11.3	1
Nucleic Acids Res	11.1	2
J Exp Med	10.9	2
Genome Med	10.9	1
Methods Mol Biol	10.7	1
Nat Hum Behav	10.6	1
J Natl Cancer Inst	10.2	1
Genome Res	9.9	1
Am J Hum Genet	9.9	3
Proc Natl Acad Sci U S A	9.6	3
Curr Biol	9.2	1
Dev Cell	9.2	1
Brief Bioinform	9.1	1
Clin Cancer Res	8.9	2
Genet Med	8.7	2
Cell Syst	8.6	1
Mol Ther	8.4	1
Cell Rep	7.8	2
J Natl Compr Canc Netw	7.6	1
Semin Immunol	7.4	1
Neuropsychopharmacology	7.2	2
Allergy	6.8	1
EBioMedicine	6.7	2
Sci Signal	6.6	1
Clin Pharmacol Ther	6.3	1
J Invest Dermatol	6.3	2
Clin J Am Soc Nephrol	6.2	1
Others		170
Total		**259**

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Budget, Personnel and Patents

IMS Budget FY2019

IMS Budget FY2019	JPY Million
Government funding for operations	4,332
External competitive funding	1,927
Total	**6,259**

Patents

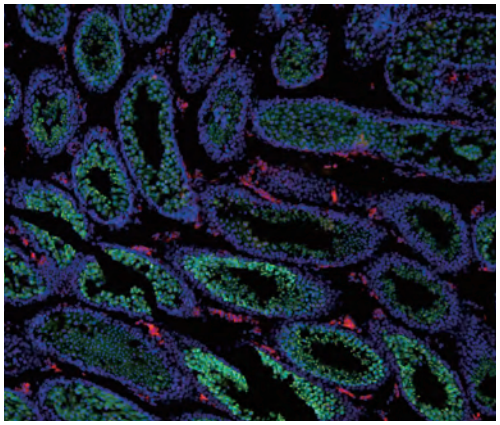
There were 24 patents filed from January to December, 2019.

Patents	Total	International patents (PCT)	Domestic patents (Japan)
2019	12	8	4

Personnel FY2019

Category	Number
Director	1
Deputy Director	3
Senior Advisor	1
Team Leader	35
Unit Leader	5
Coordinator	5
Deputy Team Leader	8
Senior Scientist	28
Senior Research Scientist	4
Research Scientist	55
Postdoctoral Researcher	28
Special Fixed Term Contract Researcher	1
Special Postdoctoral Researcher	7
Research Fellow	7
Research Associate	12
Senior Technical Scientist	3
Technical Scientist	22
Expert Technician	8
Technical Staff I	71
Technical Staff II	54
International Program Associate	6
Junior Research Associate	21
Student Trainee	110
Research Administrator	5
Research Administrative Support Staff	4
Assistant	28
Part-time Staff	44
Senior Visiting Scientist	20
Visiting Scientist	202
Visiting Technical Scientist	19
Visiting Researcher	4
Temporary Staffing	14
Research Consultant	2
Consultant	1
Temporary Employee	2
Total	**840**

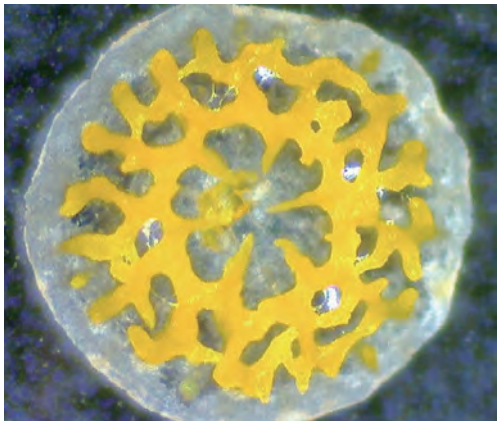
Original Photos of the Cover and Front Pages



Cover

Cross-section of the mouse testis stained for nuclei (blue), Acrosin (green), and Mac-1 (Red).

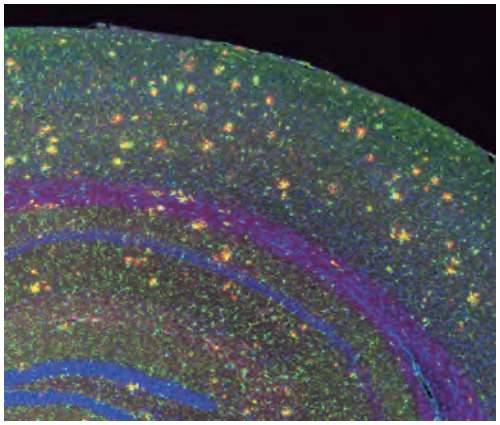
Credit to Dr. Takahiro Suzuki
Laboratory for Cellular Function Conversion Technology



Front page of Part 1

Calcium skeleton of a coral polyp (Acropora tenuis) stained with calcein.

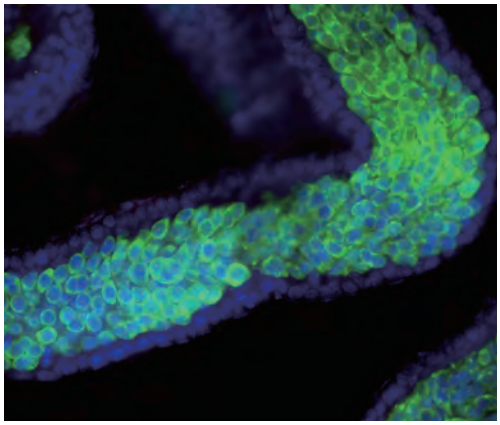
Credit to Dr. Yuuri Yasuoka
Laboratory for Comprehensive Genomic Analysis



Front page of Part 2

Cortex of 6 month old NLGFxCD3eKO mice stained for amyloid beta (red), Iba1 (green, microglia marker) and DAPI (blue, nuclei).

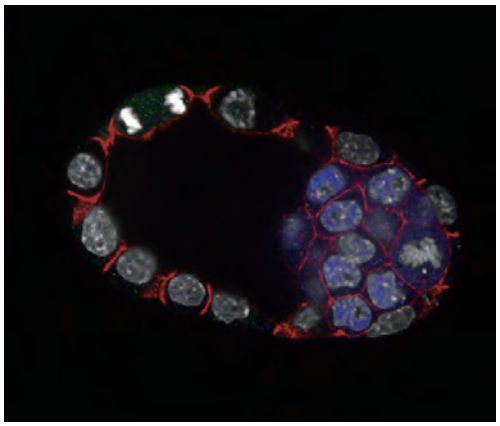
Credit to Dr. Sidonia Fagarasan
Laboratory for Mucosal Immunity



Front page of Part 3

Mouse testicular seminiferous tubules stained for nuclei (blue), and Acrosin (green).

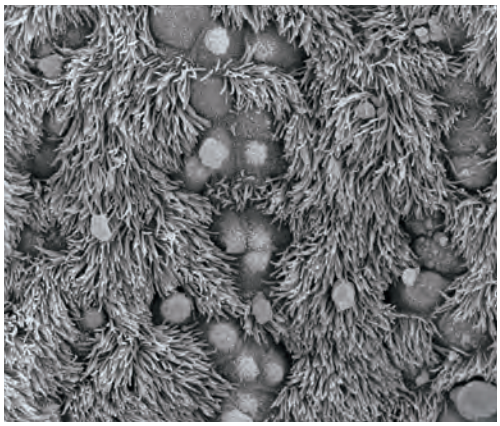
Credit to Dr. Takahiro Suzuki
Laboratory for Cellular Function Conversion Technology



Front page of Part 4

Immunohistochemstry shows that MEIS2 signals (green) are hardly detectable in a 4.0 dpc blastocyst stage embryo co-stained with CDH1 (red), POU5F1 (blue), and white (DAPI).

Credit to Dr. Takashi Kondo
Laboratory for Developmental Genetics

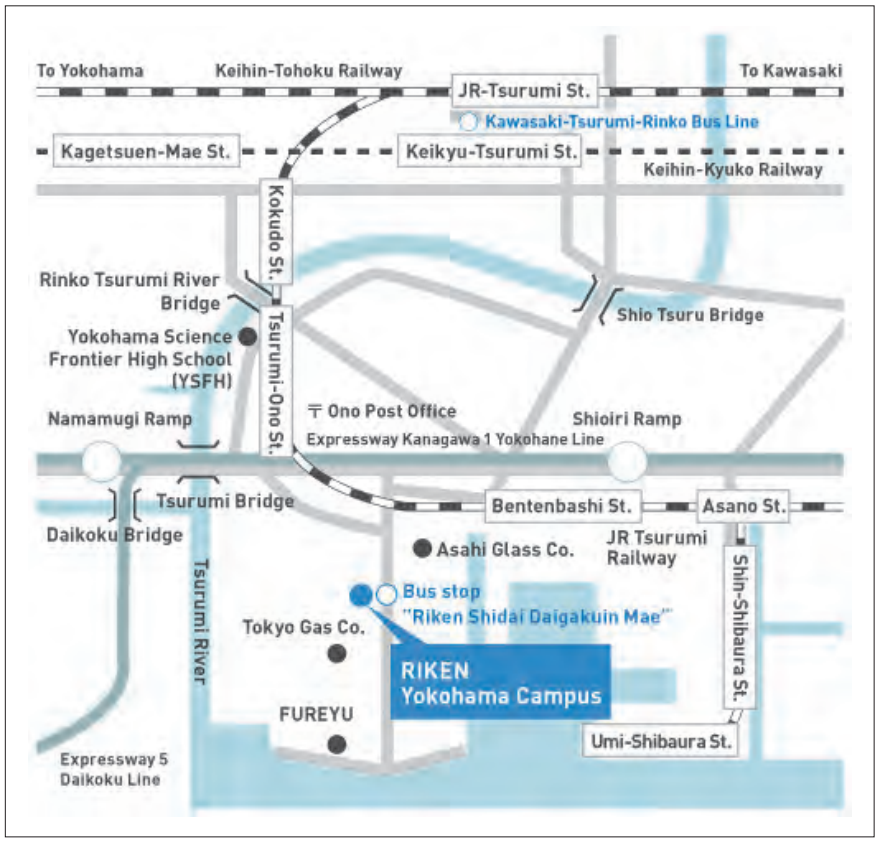


Front page of Part 5

Scanning electron microscopic image of respiratory mucosa in a mouse bronchiolus.

Credit to Dr. Takeshi Matsui
Laboratory for Skin Homeostasis

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 in cash.

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

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

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

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

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RIKEN 2020-044