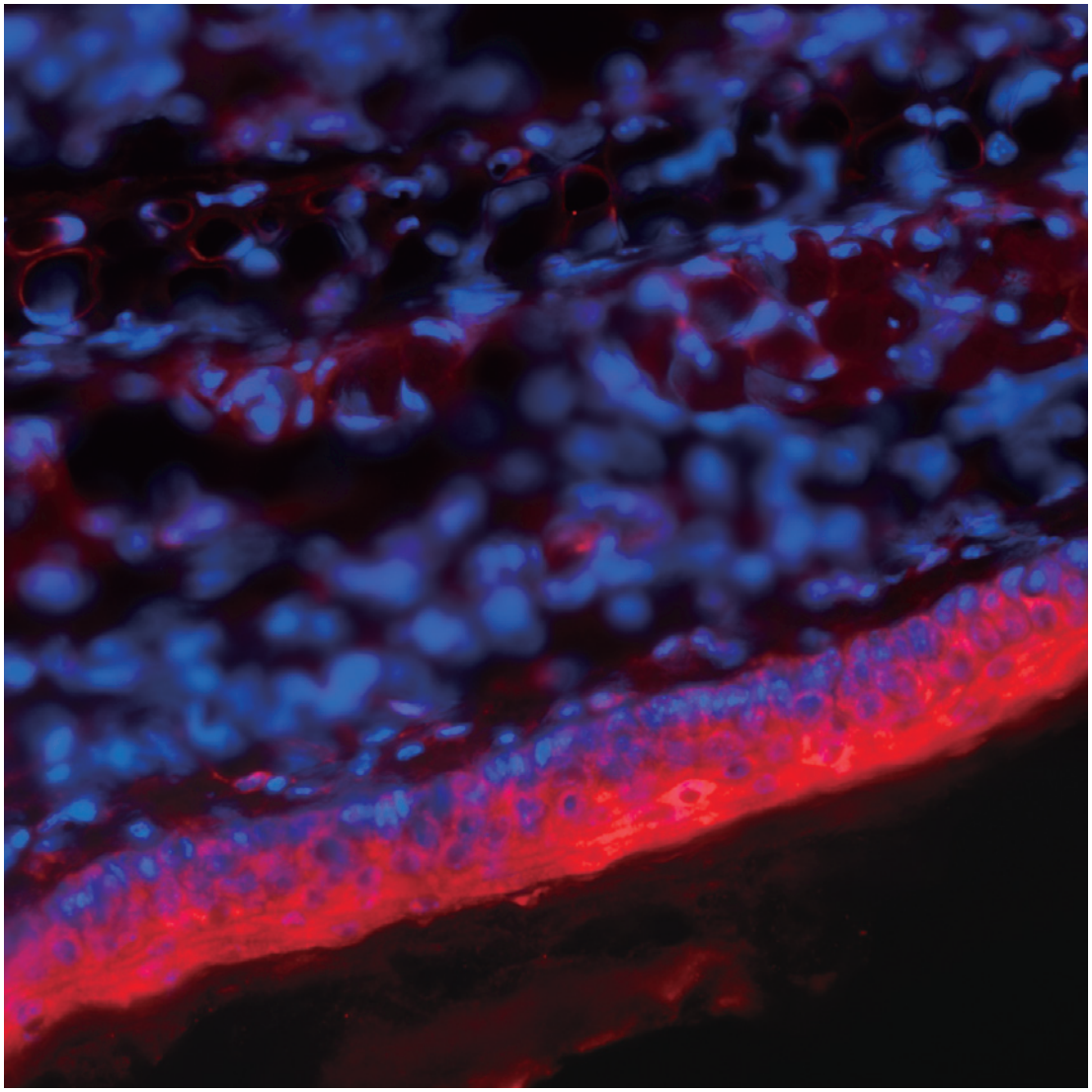
RIKEN IMS Annual Report 2018

RIKEN Center for Integrative Medical Sciences



RIKEN Center for Integrative Medical Sciences Organization Chart

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Kazuhiko Yamamoto

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Laboratory for Cancer Genomics: **Hidewaki Nakagawa**
Laboratory for Immunotherapy: **Shin-ichiro Fujii**
Laboratory for Human Disease Models: **Fumihiko Ishikawa**
Liver Cancer Prevention Research Unit: **Soichi Kojima**

RIKEN Hakubi Research Team

Genome Immunobiology RIKEN Hakubi Research Team: **Nicholas Parrish**

Young Chief Investigator Program

YCI Laboratory for Cellular Bioenergetic Network: **Toshimori Kitami**
YCI Laboratory for Trans-omics: **Katsuyuki Yugi**
YCI Laboratory for Immunological Transcriptomics: **Hideyuki Yoshida**
YCI Laboratory for Next-Generation Proteomics: **Yibo Wu**
YCI Laboratory for Metabolic Epigenetics: **Azusa Inoue**

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Director's report

As the Director of the RIKEN Center for Integrative Medical Sciences (IMS), I am happy and proud to report that 2018 was another exceptional year for our center.

This year saw the official merger of the previous IMS center and the Division of Genomic Technologies from the former RIKEN Center for Life Science Technologies. Under the new center schema, four divisions have been established. The Division of Genomic Medicine, led by Piero Carninci, aims to elucidate disease onset mechanisms originating from the genome. The Division of Human Immunology, led by Kazuhiko Yamamoto, aims to develop research platforms for human immunology and elucidate basic principles of the immune system. The Division of Disease Systems Biology, led by Haruhiko Koseki, aims to understand disease as a dynamic system in the context of environment versus the body. The Division of Cancer Immunology, led by myself, aims to explore novel principles of the immune system, focusing on tumor cells. In addition, we have the RIKEN Hakubi Research Team and five Young Chief Investigator Teams. Together, we are working to create a new research and infrastructure platform that will contribute to the next generation of medical science by providing advanced research facilities and core technologies to researchers both within and outside of IMS. We have several ongoing efforts to incentivize research initiatives within our newly structured center in order to get to know each other and to establish collaborations. Some examples are described later in this report.

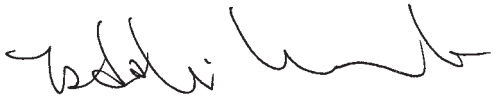
In 2018, our investigators in the new IMS continued to perform outstanding research and published a total of 223 papers, many using interdisciplinary approaches, in significant journals. Ichiro Taniuchi and colleagues reported on Runx-dependent and silencer-independent repression of a maturation enhancer in the *Cd4* gene, which encodes a glycoprotein involved in recognition of antigenic peptides presented by major histocompatibility complex class II molecules (*Nature Communications, 2018*). Tomohiro Kurosaki and colleagues reported on how T follicular helper cell-germinal center B cell interaction strength regulates entry into the plasma cell or recycling GC cell fate (*Immunity, 2018*). The paper 'IgA regulates the composition and metabolic function of gut microbiota by promoting symbiosis between bacteria' by Keiichiro Suzuki, Sidonia Fagarasan, and colleagues was one of the top 10 most-requested articles in 2018 in the *Journal of Experimental Medicine*.

We are driving innovative multidisciplinary science in other ways, including through the work led by Piero Carninci in the field of non-coding RNAs (ncRNAs). Under his leadership, scientists worldwide are constructing ncRNA datasets. His group, working with scientists from the FIRC Institute of Molecular Oncology in Italy, developed a method called Target-Enrichment of small RNAs (TEsR), which enables targeted sequencing of rare small ncRNAs and diverse precursor and mature forms of small ncRNAs (*Nature Protocols, 2018*). In addition, research led by Soichi Kojima demonstrated that acyclic retinoid prevents the recurrence of hepatocellular carcinoma (HCC) through selective targeting of one class of cancer stem cells. A phase 3 clinical trial of acyclic retinoid (or Peretinoin) is currently underway in at least three countries to test the drug's ability to prevent HCC recurrence.

We continue to nurture young researchers, and 2018 was no exception. As part of the recently established RIKEN Hakubi Fellows Program, we welcomed Nicholas Parrish as leader of the Genome Immunobiology RIKEN Hakubi Research Team. As part of the IMS Young Chief Investigator (YCI) program, this year we welcomed Azusa Inoue as leader of the YCI Laboratory for Metabolic Epigenetics.

As part of our international collaborative efforts, several symposiums and workshops were held throughout the year. Collaborative partners include McGill University, Stanford University, the University of Luxembourg, Tubingen University, Tsinghua University, and others (see Part 4 for further details).

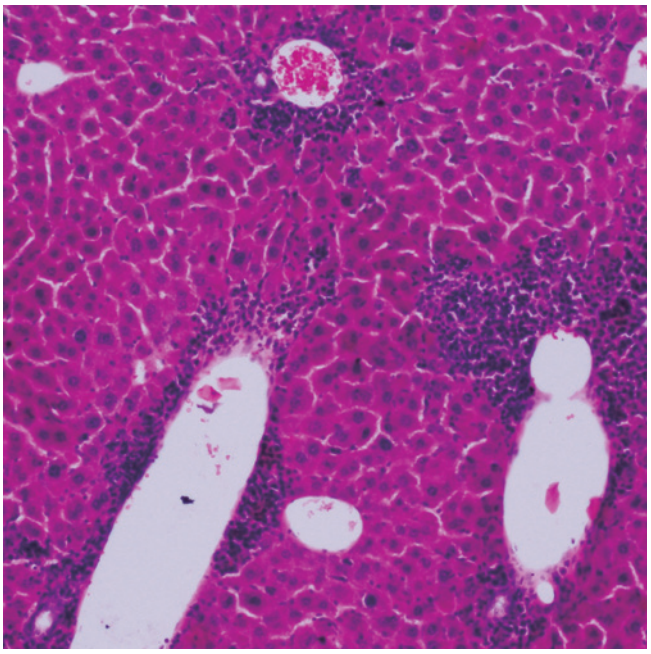
In 2019 and the years ahead, as we continue to develop our research and infrastructure platform aimed toward providing individuals the means for a healthy, long life, I expect we will see an increase in our center's activities both internally and through outside collaborations.



Tadashi Yamamoto
Director
RIKEN Center for Integrative Medical Sciences

Part 1

Research Highlights



Massive genetic analyses link genes, cell types, molecules, and diseases

Figure: By analyzing the DNA of more than 162,000 Japanese, researchers have discovered new connections between genes and diseases in the Japanese population.

Technological advances have enabled biomedical researchers to obtain enormous amounts of genetic and clinical data. However, it is still difficult to perform integrative analysis that link the genome, epigenome, cells, and tissues, and systematically elucidate disease mechanisms. Yoichiro Kamatani of the RIKEN Center for Integrative Medical Sciences and his colleagues are making efforts using genetic studies of human samples, along with various epigenetic data, to illustrate and understand the relationships of genetic traits, regulation of gene expression in cells and tissues, and diseases.

One of their recent achievements was a large genome-wide association study (GWAS) of 160,000 people based on 58 clinical traits, combined with genetic studies of 32 complex diseases (Kanai *et al., Nature Genetics*, 2018). In this large study, they successfully identified 1,407 regions of the genome that affect clinical traits, and 679 of these were completely new to science. The identified genes and loci may be risk factors for specific diseases, and the genetic variants could be used in the future to predict risks of developing a particular disease. To better understand the role of these genes, they cross-referenced their combined dataset with cell-type-specific maps of epigenetic marks that denote which parts of the genome are active and which are silenced. Among their findings, there were links between Treg cells and Graves' disease, an autoimmune disease that results in hyperthyroidism, and between helper T cells and allergic diseases. "Genetic studies of human samples, along with epigenetics data, can depict the relationship between traits and cell types," Kamatani commented.

In November 2018, in collaboration with Yukinori Okada of Osaka University, Kamatani's team also established a novel integrative analytic approach they named "MIGWAS (miRNA-target gene networks enrichment on GWAS)", which links GWAS and microRNA (miRNA) expression (Sakaue *et al., Nucleic Acids Research*, 2018). In this study, they collected 49 GWAS statistics from 500,000 people and combined them with *in silico* analyses of the extensive miRNA expression dataset released by the FANTOM5 consortium. miRNAs are small (~22nt long) noncoding RNAs that bind to mRNAs to negatively regulate gene expression at the posttranscriptional level. Their new approach successfully revealed miRNA/target gene combinations that were associated with genetic traits, such as height and type 2 diabetes. To validate this approach, they used a GWAS of 20,000 rheumatoid arthritis (RA) patients and 60,000 controls, and identified four miRNAs linked to RA. "The analytical power of our approach shows its potential for finding new networks of miRNAs and their target genes linked to traits and diseases in a tissue-specific way," observed Yukinori Okada. "This should make it easier to find new targets that we can focus on for developing new therapeutic strategies for a wide range of diseases."

Original paper:

Kanai M, Akiyama M, Takahashi A, Matoba N, Momozawa Y, Ikeda M, Iwata N, Ikegawa S, Hirata M, Matsuda K, et al. Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. ***Nature Genetics*** 50, 390-400 (2018)

Sakaue S, Hirata J, Maeda Y, Kawakami E, Nii T, Kishikawa T, Ishigaki K, Terao C, Suzuki K, Akiyama M, et al. Integration of genetics and miRNA-target gene network identified disease biology implicated in tissue specificity. ***Nucleic Acids Research*** 46, 11898-11909 (2018)

Transcriptional landscape of *Mycobacterium tuberculosis* infection in macrophages

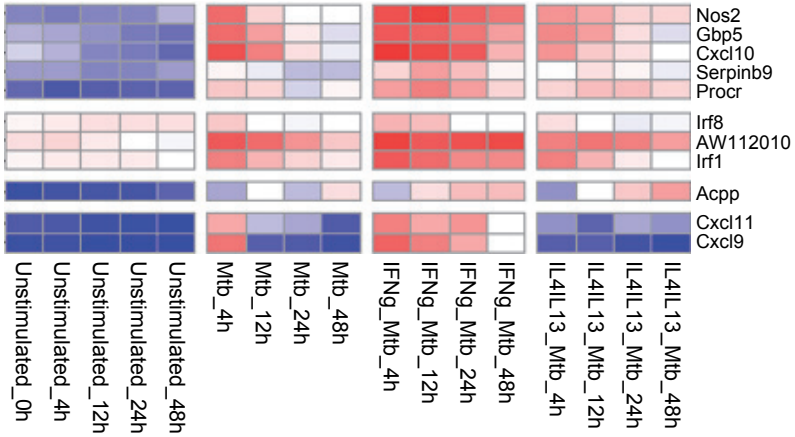


Figure: Augmentation of M1 activation gene expression in Mtb-infected M1 pre-activated macrophages

Gene expression levels are represented from blue (low expression) to red (high expression). Mtb infection induces inflammatory and immune-responsive M1 activation genes, such as *Nos2*, *Cxcl10*, *Cxcl9*, and *Cxcl11*, that are further augmented in Mtb-infected M1 pre-activated macrophages.

Despite the availability of four anti-tubercular drugs and the BCG vaccine for *Mycobacterium tuberculosis* (Mtb), tuberculosis still remains one of the most deadly infectious diseases. Annually 9.6 million people become ill with Mtb and 1.5 million die from the disease worldwide. Macrophages are the primary Mtb target cells, where host-protective inflammatory and immune response genes are induced in Mtb infection. On the other hand, the pathogen exquisitely subverts cellular immune responses by molding the transcriptional landscape of the host macrophages to allow it to hide in these cells. Thus, there are complex and dynamic host-pathogen interactions that can lead to host protection or pathogenesis.

Using a RIKEN-original unique transcriptome technology, Cap Analysis of Gene Expression (CAGE), Harukazu Suzuki and his colleagues at the RIKEN Center for Integrative Medical Sciences, in collaboration with Prof. Frank Brombacher of the International Centre for Genetic Engineering and Biotechnology (ICGEB), Cape Town component, investigated the promoter-based transcriptional landscape of IFNγ (M1) or IL-4/IL-13 (M2) stimulated macrophages during Mtb infection in a time-kinetic manner. Mtb infection widely and dramatically altered macrophage-specific gene expression, an effect that is far larger than that of M1 or M2 activation alone. Gene Ontology enrichment analysis for Mtb-induced differentially expressed genes revealed various terms related to host-protection and inflammation that were enriched among up-regulated genes. On the other hand, terms related to dysregulation of cellular functions were enriched in down-regulated genes. Differential expression analysis revealed known as well as novel transcription factor genes in Mtb infection, many of them significantly down-regulated. Together, the observed transcriptional regulatory dynamics of *Mtb*-infected macrophages might be the result of the cellular war between host immune defense and pathogen evasion responses.

Next, the collaborative research team explored how Mtb infection with IFNγ (M1) or IL-4/IL-13 (M2) pre-stimulation affects gene expression changes in macrophages. IFNγ or IL-4/IL-13 pre-stimulation induced distinct and additional differentially expressed genes in Mtb-infected macrophages. Further, cluster analysis uncovered a significant number of genes displaying prolonged expression changes, demonstrating that Mtb infection of M1 and M2 polarized macrophages results in drastic transcriptional changes, compared to Mtb-infected but otherwise unstimulated macrophages. Importantly, they found that Mtb infection augmented cytokine-mediated M1 and M2 pre-activation, which is considered to be more host-protective in M1 pre-activated macrophages, but more pathogen-evasive in M2 pre-activated macrophages.

"This work was conducted as a satellite project of the Functional Annotation of Mammalian Genome (FANTOM5) project. We have provided a comprehensive in-depth gene expression/regulation profile in Mtb-infected macrophages, an important step forward for a better understanding of host-pathogen interaction dynamics in Mtb infection. Based on this work, we are now planning to explore host-directed drug targeting for tuberculosis," says Suzuki.

Original paper:
Roy S, Schmeier S, Kaczkowski B, Arner E, Alam T, Ozturk M, Tamgue O, Parihar SP, Kawaji H, Itoh M, Lassmann T, Carninci P, Hayashizaki Y, Forrest ARR, Guler R, Bajic VB, Brombacher F, Suzuki H. Transcriptional landscape of *Mycobacterium tuberculosis* infection in macrophages. ***Sci Rep*** 8, 6758 (2018)

Researchers uncover origin of virus-fighting plasma B cells

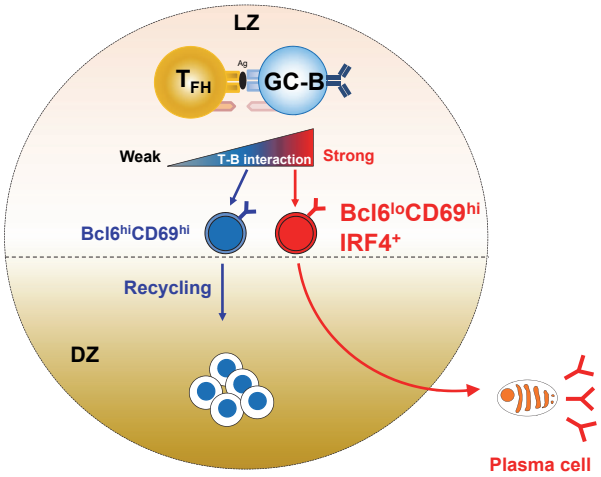


Figure: Key factors in the selection of germinal center B cells to become plasma B cells

In a work published in *Immunity*, a group of researchers from RIKEN and Osaka University have discovered an important mechanism that governs how B cells are chosen to become plasma cells. They found that the key to the commitment to a new state involves the strength of the interaction between the B cells and another type of immune cell, called T follicular helper cells.

It is known that plasma cells express a transcription factor called IRF4, and conversely do not express a transcription factor called Bcl6. The group wondered whether the fate of the cells was already being determined while they were in the germinal centers–groups of cells located in lymph nodes and the spleen where B cells mature. They examined the expression of these two factors in B cells still located in the germinal centers and found that in a subset of cells, Bcl6 was expressed at a low level and IRF4 at a high level. They also found that these cells express a cellular marker called CD69.

To determine whether these cells they had identified were indeed precursors to plasma B cells, they compared them to germinal center-derived plasma B cells, and found that the gene sequences of their B cell receptors, which govern the antibodies they produce, were very similar, indicating that they were from the same cell group. It was also clear that these cells shared the same developmental features with germinal center-derived plasma B cells, suggesting that they were indeed precursors.

Lastly, they decided to examine the relationship between these cells and T follicular helper cells, which are important for the maturation of B cells. Since the T follicular helper cells stimulate B cells via a surface protein called CD40, the team created B cells that express CD40 at low levels, and found that the number of plasma B cells dropped dramatically. Further experiments showed that the strength of the interaction between the plasma B cell precursors and the T follicular helper cells determines whether the B cell precursors are chosen to be plasma B cells or to remain in the germinal center to undergo further mutation before either being selected to perish or to become high-affinity plasma B cells.

Tomohiro Kurosaki of the RIKEN Center for Integrative Medical Science, who led the study, says, "Understanding how the body generates high-affinity plasma B cells, which are important in fighting viral infections such as influenza, which kills around 1,000 people per year in Japan, is important for creating more powerful vaccinations. Our work has given us important insights into how these cells are produced, and we hope it will be useful in this effort."

This article was reproduced from RIKEN Press Release
http://www.riken.jp/en/pr/press/2018/20180418_1/

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

Three transcriptional circuits found between hematopoietic stem cells and B cells

B cells pass through three distinct gene expression networks on their way from stem cells to B cells

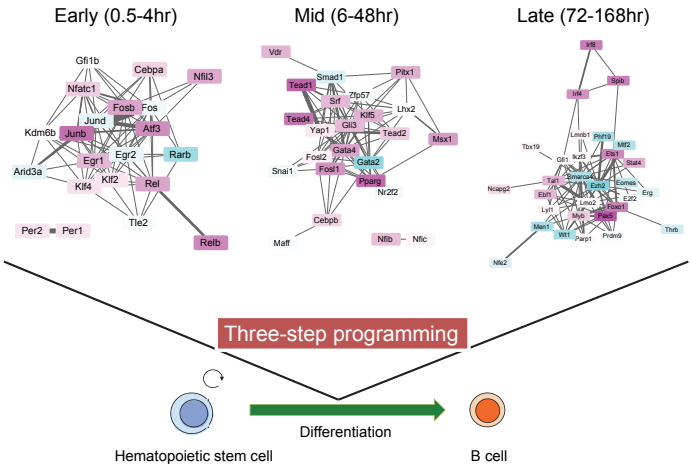


Figure: Three-step transcriptional programming that determines B cell fate

A model of transcriptional networks during B cell commitment is shown. The gene expression profiles and bioinformatic analysis defined the three major transcriptional phases during B cell fate determination.

By analyzing the expression of thousands of genes, RIKEN researchers have shed light on how a stem cell grows up to become a certain type of immune cell. This knowledge will form the basis for future research into B cell leukemia.

B cells are a type of white blood cells, and they help the body fight infections by producing antibodies. They start off life as hematopoietic stem cells (HSCs)—stem cells that go on to become blood cells.

Tomokatsu Ikawa of the RIKEN Center for Integrative Medical Sciences has long been interested in understanding the differentiation process that commits a stem cell to the fate of becoming a B cell. "Key transcription factors have been identified, but the underlying mechanisms remain to be revealed," he notes.

To discover how the expression of genes changes as an HSC becomes a B cell, Ikawa's team used a cell system they had previously developed: the induced leukocyte system. It consists of multipotent progenitor cells—stepping stones between stem cells and mature cells—that can be efficiently differentiated into B cells by triggering the expression of the protein E2A, which is a transcription factor essential for priming HSCs toward the B cell lineage. This cell system allowed Ikawa's team to synchronize the differentiation process and examine the cells' transcriptome at various time points.

When the team analyzed the expression of thousands of genes, they observed distinct waves of expression as cells committed to the B cell lineage. They combined data on the transcription factors that were active in each wave and the genes they regulated with epigenetic data of histone marks. This allowed the researchers to construct three distinct networks: the early network of multipotent progenitor cells, a transitional state, and the network of committed B cells.

While all these data were originally obtained from cells differentiated in a culture dish, the team observed the same expression patterns in B cell progenitors isolated directly from the bone marrow.

"We were surprised to find that the B cell lineage commitment process could be separated into three main stages based on messenger RNA expression profiles," recalls Ikawa.

Ikawa now wants to explore the metabolic pathways and non-coding RNA that underlie the development and function of immune cells; he is particularly interested in the role of long non-coding RNAs in the regulatory process.

Ikawa and his team are focusing on normal B cell development, but he predicts that this approach can also be used to study the mechanism by which B cell leukemia develops. "The more we understand this process, the more likely efficient points of intervention will be found," Ikawa comments.

This article was reproduced from RIKEN Research
http://www.riken.jp/en/research/rikenresearch/highlights/20180427_FY20180001/

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

Genome sequencing analysis reveals genes associated with survival in biliary tract cancers

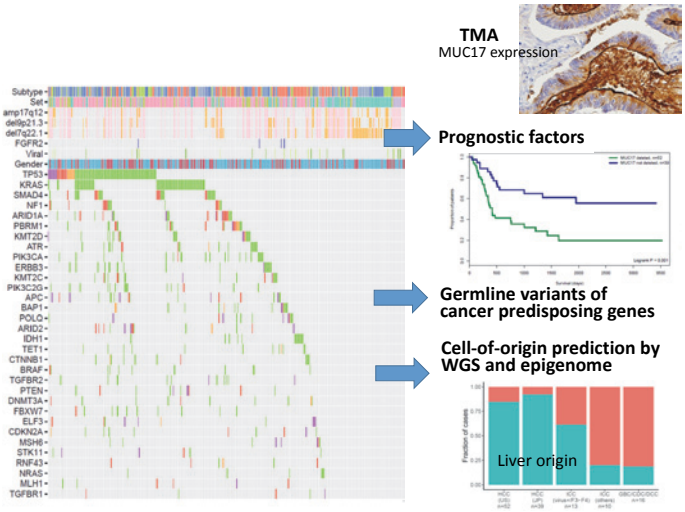


Figure:
Genomic profiles of 412 BTCs
(WGS, WES, target seq, CN analysis)

Although biliary tract cancers (BTCs) are rare worldwide, they frequently occur in Japan. They are highly malignant, invasive, and difficult to resect due to their anatomical location and proximity to the bile ducts. Additionally, the current standard of treatment is chemotherapy regimens involving drugs such as cisplatin and gemcitabine. The results with these drugs are poor at best, resulting in a 5%–10% 5-year survival rate. Thus, targeted treatments against BTCs may help to improve survival. Genetic profiling of BTCs can identify treatments that are likely to be efficacious; however, the genetic characteristics of BTCs remain unknown.

To begin to shed light on the genetic characteristics of BTCs, an international research team led by Hidewaki Nakagawa, Team Leader of the RIKEN Center for Integrative Medical Sciences in Japan, conducted a large-scale genome sequencing analysis of BTC samples in Japanese and Italian populations.

The researchers analyzed a total of 412 BTC samples and found 32 significantly mutated genes, broadly classified as DNA maintenance genes, epigenetic genes, and signaling pathway genes. Sixty-five percent of these samples contained at least one mutation in the list of these 32 genes. The proportion of genes in each of the classifications differed by subtype of BTC; for example, intrahepatic cholangiocarcinoma samples contained more mutations in epigenetic genes, whereas extrahepatic subtypes of BTC contained more mutations in cell cycle genes.

The researchers subsequently performed an SNP array analysis of 95 samples and discovered that 64% of the analyzed samples had a large deletion (100-kb region) in chromosome 7, which was linked to a reduction in disease-free survival (median, 644 days) and overall survival (median, 428 days). Further expression analysis revealed that complete ablation of a gene located in this 100-kb region, MUC17, was responsible for the observed shortening of survival time.

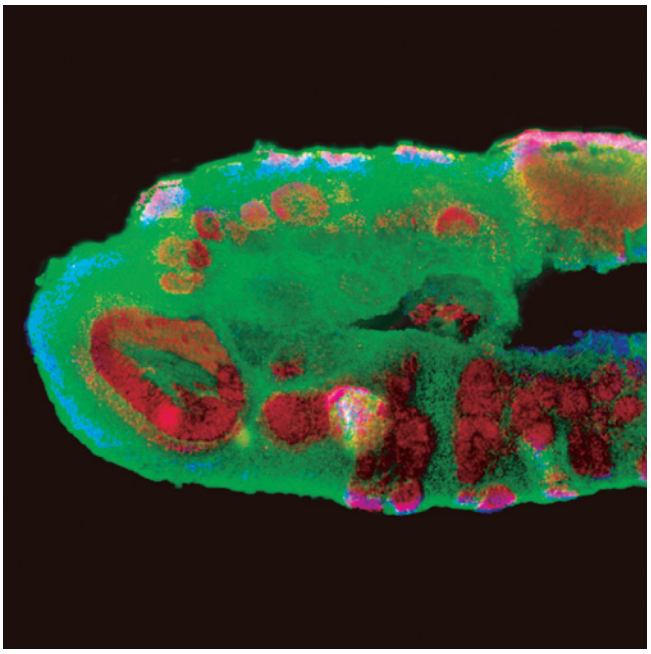
Finally, a cell-of-origin analysis was conducted to help further classify BTC subtypes for treatment. This analysis revealed that BTCs had two major cells of origin: hepatocytes and epithelium. Identifying the cell-of-origin of BTCs could help clinicians find treatments that better target the cancer, as well as aid scientists as they continue the search for novel agents to target BTCs.

The researchers conclude that, based on the genetic profile of BTCs and the identified genes, almost 60% of the lesions have actionable treatment options. Through this study, the authors have opened the doorway to treatments for a previously intractable cancer via genetic profiling. "We found 11% of Japanese BTC cases had deleterious germline mutations in cancer-predisposing genes. Universal tumor screening for these cancer-predisposing genes in general BTC cases might be beneficial to patients with BTC and their family members, enabling assessment of their cancer development risk and of the effectiveness of new anti-cancer drugs," concludes Nakagawa.

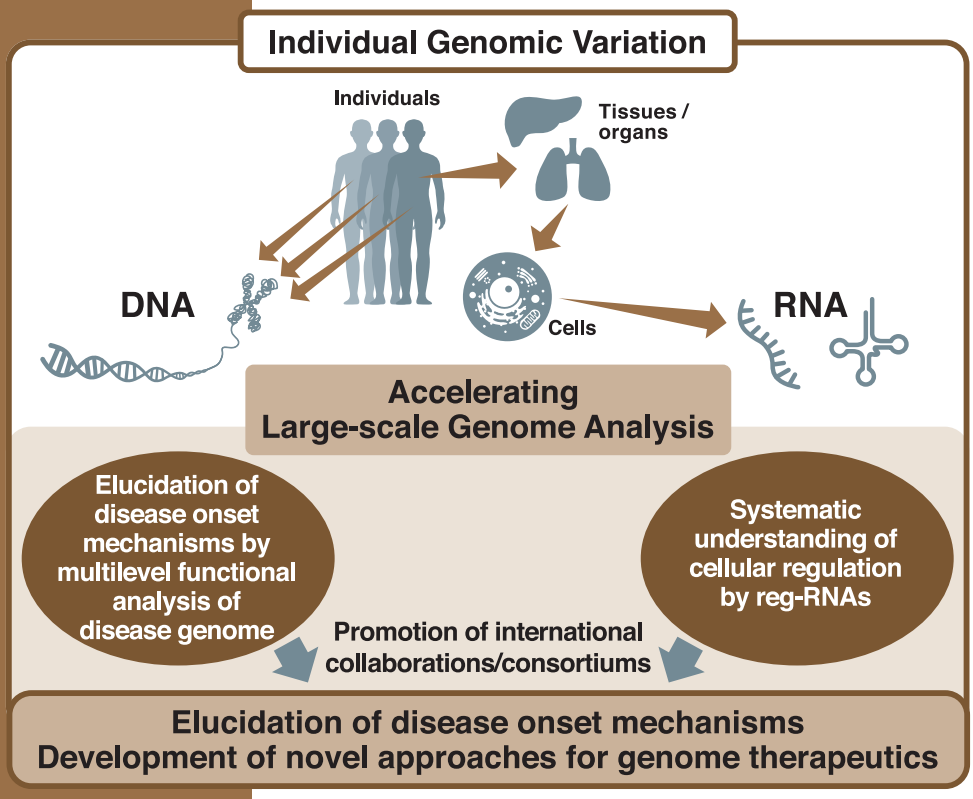
Original paper:
Wardell CP*, Fujita M*, Yamada T, Simbolo M, Fassan M, Karlic R, Polak P, Kim J, Hatanaka Y, Maejima K, Lawlor RT, Nakanishi Y, Mitsuhashi T, Fujimoto A, Furuta M, Ruzzenente A, Conci S, Oosawa A, Sasaki-Oku A, Nakano K, Tanaka H, Yamamoto Y, Michiaki K, Kawakami Y, Aikata H, Ueno M, Hayami S, Gotoh K, Ariizumi SI, Yamamoto M, Yamaue H, Chayama K, Miyano S, Getz G, Scarpa A, Hirano S, Nakamura T, Nakagawa H. (*equally contributed) Genomic Characterization of Biliary Tract Cancers Identifies Driver Genes and Predisposing Mutations. ***J Hepatol*** 68, 959-969 (2018)

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

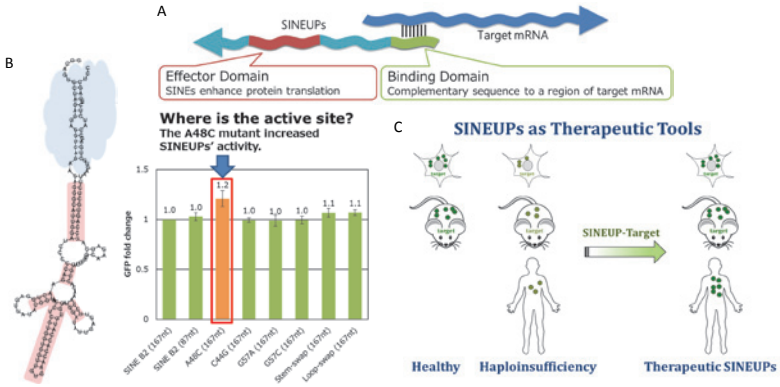


Figure: SINEUPs, antisense lncRNAs that enhance protein translation
(A) Schematic image of a SINEUP and its target mRNA. SINEUPs contain an Effector Domain and a Binding domain. (B) Secondary structure of SINEB2 RNA. Stems marked in red were determined by NMR spectroscopy. The A48C mutant increased protein translation by changing the stem structure. (C) SINEUPs are strong candidates for therapeutic applications, particularly when diseases are caused by decreased levels/lack of proteins, e.g., in haploinsufficiencies.

Recent Major Publications

Takahashi H, Sharma H, Carninci P. Cell Based Assays of SINEUP Non-coding RNAs That Can Specifically Enhance mRNA Translation. ***J Vis Exp*** doi: 10.3791/58627 (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)

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, R Forrest AR, 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)

Invited presentations

Carninci P. "An emerging landscape of transcriptome complexity" The 20th Takeda Science Foundation Symposium on Biosceicne (Osaka, Japan) February, 2019

Carninci P. "Revealing transcription complexity in health and diseases" Takeda Reverse Translation Symposium and Hackathon (Boston, US) October, 2018

Carninci P. "An emerging landscape of transcriptional complexity" Developmental and medical genomics with animal models ZENCODE-ITN Sounio workshop (Attica, Greece) October, 2018

Hashimoto K. "The single cell PBMC transcriptome of supercentenarians" Informatics in Biology, Medicine and Pharmacology (IIBMP2018) (Yamagata Japan) September, 2018

Carninci P. "An atlas of human long non-coding RNAs" European Human Genetics Conference in conjunction with the European Meeting on Psychosocial Aspects of Genetics (Milan, Italy) June, 2018

Our team has traditionally developed technologies, including Cap Analysis of Gene Expression (CAGE), to identify genomic elements and infer their function and regulation. Among the main outputs, we have had a fundamental role in the discovery of long non-coding RNAs (lncRNAs) and the creation of maps of promoters and enhancers in the FANTOM project. The team is currently involved in technology development and exploration of RNA biology, as summarized below.

(1) We are optimizing CAGE for various sequencing platforms to accommodate novel platforms like MGI sequencing, which allows for dramatic cost cutting compared to Illumina sequencing.

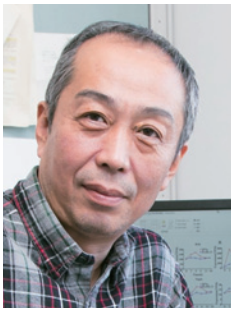
(2) The team is developing RADICL-seq, a novel technology to identify functions of non-coding RNAs, with particular emphasis on those that regulate chromatin activity. The goal is to create global RNA-chromatin interactome maps, with the simultaneous identification of chromatin-regulatory RNAs and their targets. Such global RNA-chromatin bound regions identify a large number of regulatory RNAs and a novel function of RNA as a structural component of the chromatin.

(3) We explore new functions of the genome, in particular related to insertion/recombination of retrotransposon elements in somatic tissues in health and brain diseases. We will identify the degree of somatic mosaicism, a genomics aspect so far underestimated, which may change the way we understand genomic regulation.

(4) We contribute to the RIKEN ageing study by analyzing the transcriptome of supercentenarians, individuals at least 110-years-old, with the objective of identifying the signature of healthy aging as well as the aging signature, both in terms of transcriptome deregulation and changes in cell populations.

(5) We analyze the mechanism of action of SINEUPs, antisense lncRNAs that enhance protein translation. We aim at broadening our knowledge of the role of SINE elements and the definition and characterization of the structural motifs that they form as regulators of translation in mammals.

The team is also involved in the coordination of FANTOM6 to decipher the interactome, the structurome, and the function of a large fraction of the lncRNAs in human cells. Additionally, we are deeply involved in setting up the Human Cell Atlas, being the Asian hub for this project.



Laboratory for Cellular Function Conversion Technology

Team Leader: Harukazu Suzuki

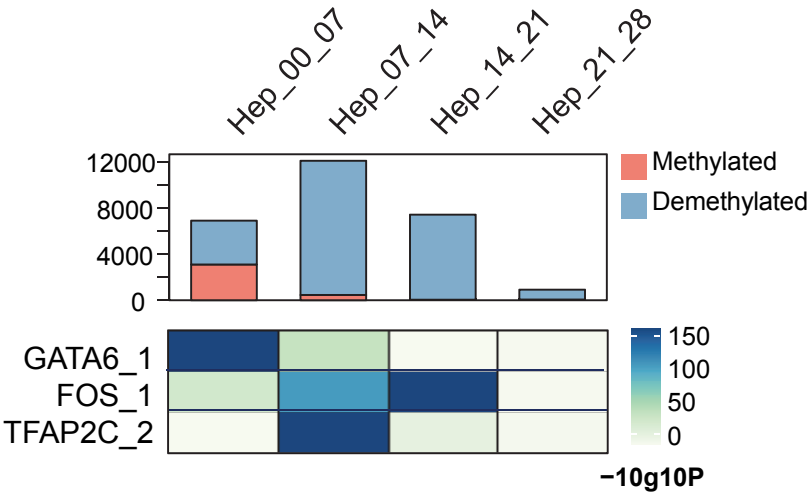


Figure: Methylome analysis during hepatocyte differentiation from iPS cells
The upper panel shows the number of methylated (red) and demethylated (blue) probes in the four stages of the differentiation from day 0-7 (Hep_00_07) to day 21-28 (Hep_21_28). The bottom panel shows representative TF binding motifs, GATA6_1, FOS_1, and TFAP2C_2, that are enriched at demethylated regions in early (Hep_00_07; day 0-7), middle, and late stages of hepatocyte differentiation.

Recent Major Publications

Guler R, Mpotje T, Ozturk M, Nono JK, Parihar SP, Chia JE, Abdel Aziz N, Hlaka L, Kumar S, Roy S, Penn-Nicholson A, Hanekom WA, Zak DE, Scriba TJ, Suzuki H, Brombacher F. Batf2 differentially regulates tissue immunopathology in Type 1 and Type 2 diseases. ***Mucosal Immunol*** 12, 390-402 (2019)

Roy S, Schmeier S, Kaczkowski B, Arner E, Alam T, Ozturk M, Tamgue O, Parihar SP, Kawaji H, Itoh M, Lassmann T, Carninci P, Hayashizaki Y, Forrest ARR, Guler R, Bajic VB, Brombacher F, Suzuki H. Transcriptional landscape of Mycobacterium tuberculosis infection in macrophages. ***Sci Rep*** 8, 6758 (2018)

Invited presentations

Suzuki H. Epigenome regulation mediated by transcription factors. The RIKEN-Luxembourg joint symposium (Luxembourg, Luxembourg) September, 2018

We aim to understand how gene expression is globally regulated in mammals and to apply this knowledge to cellular function conversion. DNA methylation at gene regulatory regions plays an important role in downstream gene expression, and we have discovered that RUNX1 promotes its binding-site-specific DNA demethylation by recruitment of a DNA demethylation enzyme complex. We also demonstrated DNA demethylation by RUNX1 at regulatory regions of the *SPI1/PU.1* gene, another DNA demethylation regulating transcription factor (TF). This finding suggests that a cascade of TF-mediated site-specific DNA demethylations at gene regulatory regions is one mechanism for accurate cellular differentiation. We have begun to explore the precise mechanisms of TF-mediated DNA demethylation during the differentiation of iPS cells into hepatocytes. We have also started to explore the landscape of TF-mediated DNA demethylation using a combination of publicly available International Human Epigenome Consortium (IHEC) whole genome methylome data and our own developed method to identify TFs that induce binding site-directed DNA methylation changes. In the epithelial-to-mesenchymal transition (EMT), we explored mechanisms governing coupling of the dynamics of epithelial genes with those of the mesenchymal genes. Further, we identified the Ovo-like zinc finger (OVOL2) TF as a potent inducer of key epithelial genes during EMT, and demonstrated successful application of OVOL2 to cell reprograming accompanying EMT. We also have begun to address the challenge of drug-induced cell reprogramming, where we have identified a novel compound that promotes neural cell reprogramming from human dedifferentiated fat cells. Finally, exploration of global transcriptional changes in *Mycobacterium tuberculosis*-infected macrophages has been published as a FANTOM5 satellite paper.

Laboratory for Genome Information Analysis

Team Leader: Chung-Chau Hon

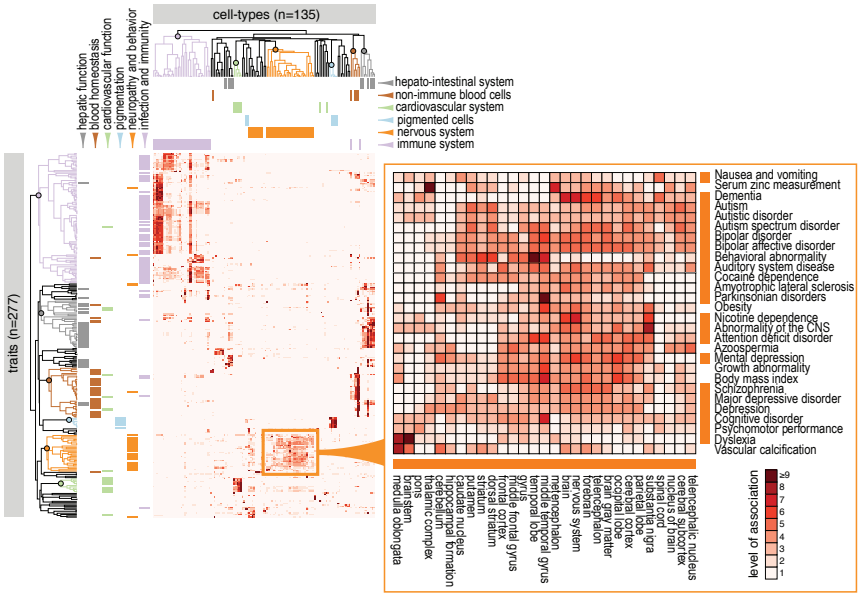


Figure: Association Between Diseases and Cell Types

FANTOM CAGE Associated Transcriptome (CAT) genes were 1) associated with traits based on GWAS data and 2) associated with cell-types based on expression data. We identified pairs of cell types and traits with significant association, and nearly 2000 human long non-coding RNAs were implicated in such associations. ***Hon et al. Nature 543, 199–204 (March 09, 2017)***

Recent Major Publications

Kouno T, Moody J, Kwon AT, Shibayama Y, Kato S, Huang Y, Böttcher M, MotakisE, 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, Deviatiiarov R, Nagai H, Galan L, Arner E, Itoh M, Lassmann T, Kasukawa T, Hasegawa A, Ros MA, Hayashizaki Y, Carninci P, Forrest ARR, Kawaji H, Gusev O, Sheng G. Systematic analysis of transcription start sites in avian development. ***PLoS Biol*** 15, e2002887 (2017)

Hon CC, Ramilowski JA, Harshbarger J, Bertin N, Rackham OJ, Gough J, DenisenkoE, Schmeier S, Poulsen TM, Severin J, Lizio M, Kawaji H, Kasukawa T, Itoh M, Burroughs AM, Noma S, Djebali S, Alam T, Medvedeva YA, Testa AC, Lipovich L, Yip CW, Abugessaisa I, Mendez M, Hasegawa A, Tang D, Lassmann T, Heutink P, Babina M,Wells CA, Kojima S, Nakamura Y, Suzuki H, Daub CO, de Hoon MJ, Arner E, Hayashizaki Y, Carninci P, Forrest AR. An atlas of human long non-coding RNAs with accurate 5′ ends. ***Nature*** 543, 199-204 (2017)

Invited presentations

Hon CC. "Building a better map to navigate through the genetic landscape of diseases" Life of Genomes 2018 (Kazan, Russia) June, 2018

Hon CC. "Building a better map to navigate through the genetic landscape of diseases" Advanced Study Workshop, Genetic Variation, Genome Architecture and the Transcriptome in Development and Disease (Hong Kong, China) June, 2017

Hon CC. "Why do we need a better map for our genomes and how we make one?" The 12th International Workshop on Advanced Genomics (Tokyo, Japan) June, 2017

Hon CC. "An Atlas of Human Long Non-Coding RNA with Accurate 5'Ends" RNA-Seq Summit 2017 (San Francisco, USA) April, 2017

Our mission is to understand the functions of non-coding transcription in the human genome, with a focus on its roles for mis-regulation of gene expression in diseases. Specifically, we have organized our projects towards these three goals: 1) To annotate and classify the origins non-coding transcription events, focusing on long non-coding RNAs, enhancer RNAs and transposable element-derived RNAs; 2) To integrate cell-type specific transcriptomic and epigenomic information for interpretation of non-coding germline and somatic variants associated with diseases; 3) To identify functionally relevant non-coding RNAs by profiling of disease models and genetic perturbations.

Notably, our laboratory participated in the FANTOM5 project, using 5' end-based gene expression data to build an atlas of long non-coding RNAs in the human genome. By integrating this atlas with genetic data, we discovered that over 3000 cell-type specific long non-coding RNAs are potentially relevant to various diseases. To validate these potentially functional non-coding candidate RNAs, we initiated a collaborative project with Takeda Pharmaceutical Company Ltd. to screen for non-coding RNAs relevant to neurodegenerative diseases using large-scale genetic perturbation. We have successfully established an iPS-based *in vitro* model of Parkinson's disease and the perturbation experiments are ongoing. Along the same line, our team also participates in the FANTOM6 project data analyses, to identify long non-coding RNAs using large-scale knockdown.

In addition, our team contributes to the development of single-cell technologies by providing bioinformatics support. These single-cell technologies will be an integral part of Japan's contribution to the international Human Cell Atlas project. This project will eventually lead to a comprehensive atlas of cell-type specific activity of non-coding elements in our genome, which will provide insights into the roles of non-coding variants associated with various diseases.

Laboratory for Applied Computational Genomics

Team Leader: Michiel de Hoon

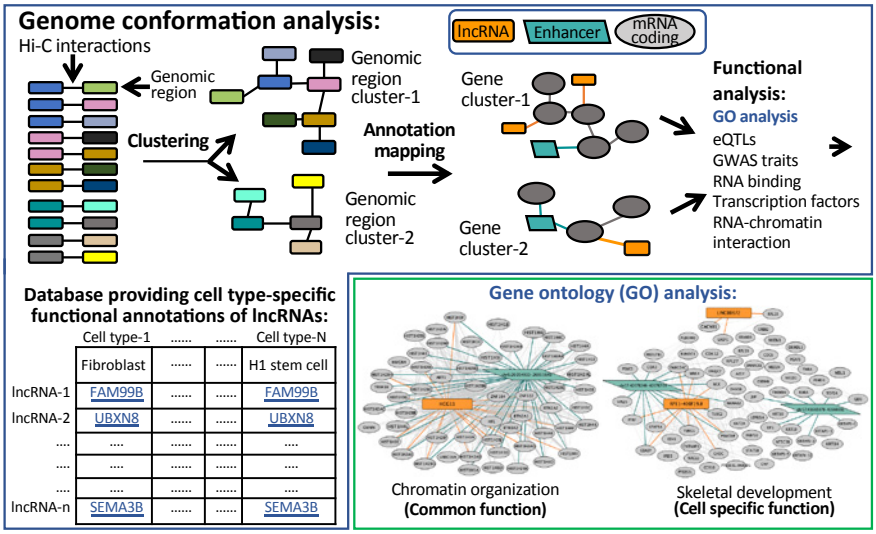


Figure: Functional annotation of long non-coding RNAs using genome conformation data

The majority of transcripts encoded in mammalian genomes are long non-coding RNAs (lncRNAs). The vast majority (97%) of these lncRNAs currently do not have any functional annotation. We use Hi-C chromatin interaction data in different cell types to identify genomic regions that are physically close to each other in 3D space. We then build clusters of interacting genomic regions, and annotate lncRNAs by associating them with genes and other genomic elements in each cluster. We thus provide a comprehensive database of cell type-specific functional annotations of lncRNAs.

Our laboratory applies computational methods to analyze transcriptome and other sequencing datasets to understand cellular regulation in general and long non-coding RNAs (lncRNAs) in particular. We take a leading role in the bioinformatics analysis of data generated by the Functional Annotation of the Mammalian Genome 6 (FANTOM6) project, a pioneering effort to elucidate the function of long non-coding RNA. In particular, we focus on

- The secondary and tertiary structures of lncRNAs, and the structure–function relationship of lncRNAs;
- The 3D structure of the genome as a framework for non-coding RNA-mediated regulatory interactions.

In both aspects, we work together closely with other laboratories in our Center, in particular, by sharing the analysis of the 3D structure of the genome to help understand GWAS SNPs identified in genetic studies performed by colleagues in our Center.

Additionally, we are finalizing projects remaining from FANTOM5 and from the pilot phase of FANTOM6. The FANTOM5 expression atlas of microRNAs was completed and published in 2017. A manuscript summarizing our FANTOM5 analysis of the conservation among vertebrate species of the coding and non-coding transcriptomes in primary cells is planned for submission within FY2018. The FANTOM6 pilot phase paper is currently being written together with Dr. Piero Carninci (Laboratory for Transcriptome Technology, RIKEN IMS) and Dr. Jay Shin (Laboratory for Advanced Genomics Circuit, RIKEN IMS).

Recent Major Publications

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)

De Rie D, Abugessaisa I, Alam T, Arner E, Arner P, Ashoor H, Åström G, Babina M, Bertin N, Burroughs AM, Carlisle AJ, Daub CO, Detmar M, Deviatiiarov R, Fort A, Gebhard C, Goldowitz D, Guhl S, Ha TJ, Harshbarger J, Hasegawa A, Hashimoto K, Herlyn M, Heutink P, Hitchens KJ, Hon CC, Huang E, Ishizu Y, Kai C, Kasukawa T, Klinken P, Lassmann T, Lecellier CH, Lee W, Lizio M, Makeev V, Mathelier A, Medvedeva YA, Mejhert N, Mungall CJ, Noma S, Ohshima M, Okada-Hatakeyama M, Persson H, Rizzu P, Roudnicky F, Sætrom P, Sato H, Severin J, Shin JW, Swoboda RK, Tarui H, Toyoda H, Vitting-Seerup K, Winteringham L, Yamaguchi Y, Yasuzawa K, Yoneda M, Yumoto N, Zabierowski S, Zhang PG, Wells CA, Summers KM, Kawaji H, Sandelin A, Rehli M, The FANTOM Consortium Hayashizaki Y, Carninci P, Forrest ARR, De Hoon MJL. An integrated expression atlas of miRNAs and their promoters in human and mouse. ***Nature Biotechnol*** 35, 872-878 (2017)

Hon CC, Ramilowski JA, Harshbarger J, Bertin N, Rackham OJ, Gough J, Denisenko E, Schmeier S, Poulsen TM, Severin J, Lizio M, Kawaji H, Kasukawa T, Itoh M, Burroughs AM, Noma S, Djebali S, Alam T, Medvedeva YA, Testa AC, Lipovich L, Yip CW, Abugessaisa I, Mendez M, Hasegawa A, Tang D, Lassmann T, Heutink P, Babina M, Wells CA, Kojima S, Nakamura Y, Suzuki H, Daub CO, De Hoon MJL, Arner E, Hayashizaki Y, Carninci P, Forrest ARR. An atlas of human long non-coding RNAs with accurate 5′ ends. ***Nature*** 543, 199-204 (2017)

Invited presentations

De Hoon M. "Functional Annotation of Mammalian Genomes in the FANTOM projects" Annual Meeting of the Brazilian Bioinformatics and Computational Biology Association (X-Meeting) (São Pedro, Brazil) October, 2018

De Hoon M. "The FANTOM5 Integrated Expression Atlas of miRNAs and Their Promoters". The 26th International KOGO Annual Conference: Genomics for the Future Biology and Medicine (Seoul, Korea) September, 2017

Laboratory for
Single Cell Technologies

Team Leader: Piero Carninci

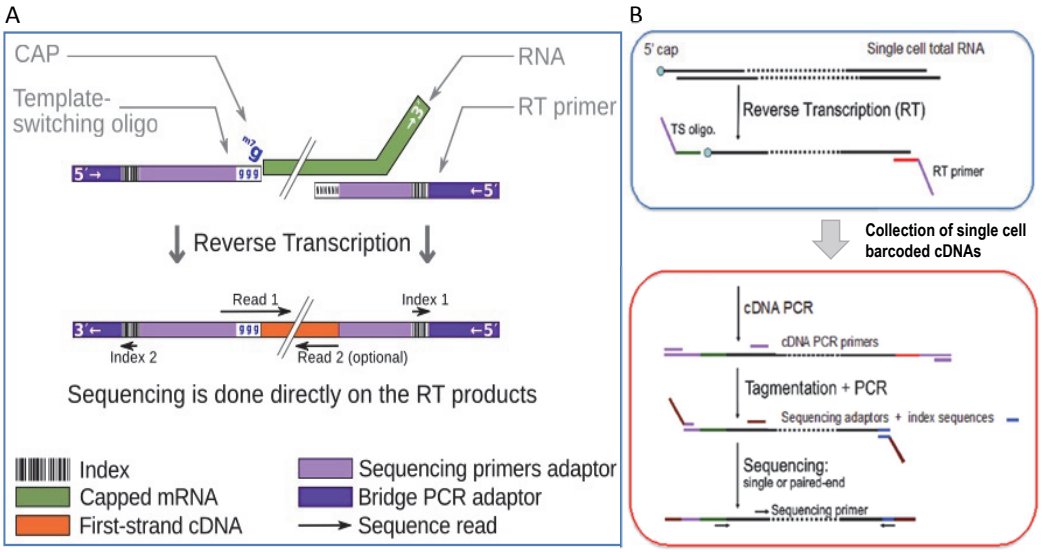


Figure: picoCAGE protocol
A) Sequencing of pooled single-cell cDNAs without PCR amplification. B) Sequencing of pooled single-cell cDNAs after PCR amplification

Recent Major Publications

Danoy M, Bernier ML, Kimura K, Poulain S, Kato S, Mori D, Kido T, Plessy C, Kusuhara H, Miyajima A, Sakai Y, Leclerc E. Optimized protocol for the hepatic differentiation of induced pluripotent stem cells in a fluidic microenvironment. ***Biotechnol Bioeng*** doi: 10.1002/bit.26970. (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)

Bernier ML, Poulain S, Tauran Y, Danoy M, Shinohara M, Kimura K, Segard BD, Kato S, Kido T, Miyajima A, Sakai Y, Plessy C, Leclerc E. Profiling of derived-hepatocyte progenitors from induced pluripotent stem cells using nanoCAGE promoter analysis. ***Biochem Eng J*** 142, 7–17 (2019)

Invited presentations

Poulain S. "Single-molecule transcriptome analysis with the CAGEscan method" AIST-RIKEN Joint Exchange Meeting for Computational Biology (Tokyo, Japan) March, 2018

Our laboratory started with the purpose of developing novel methodologies for single-cell genomics and transcriptomics, providing a high resolution in order to elucidate the regulatory mechanisms of gene expression. Data produced from a single cell show the real condition of the cell in the midst of cellular heterogeneity and give us a richer understanding of health and diseases.

Previously, we developed nanoCAGE/CAGEscan technology, which is a powerful tool to perform whole transcriptome CAGE analysis at single-molecule resolution of biological specimens containing limited amounts of bulk RNA input. The protocol uses template-switching oligonucleotides (TSOs) for capturing the 5'-end of RNA molecules in combination with random priming in the reverse-transcription (RT) reaction. Our goal was to adapt the method to simultaneously analyze the transcriptome of thousands of single cells isolated with a microfluidic device (aka "picoCAGE" method). This technology contributed to the early diagnosis of cervical cancer by transcriptome analysis of single cells isolated from patient biopsies in order to detect Human Papilloma Virus (HPV) transcripts, especially fusion transcripts known to be created by the insertion of HPV16 subtypes within the genome of host cells during carcinogenesis.

The laboratory also has been involved in collaborative efforts to develop the C1-CAGE, which can detect 5'-ends of transcripts at the single-cell level using the C1 microfluidic system (Fluidigm).

Large Scale Data Managing Unit

Unit Leader: Takeya Kasukawa

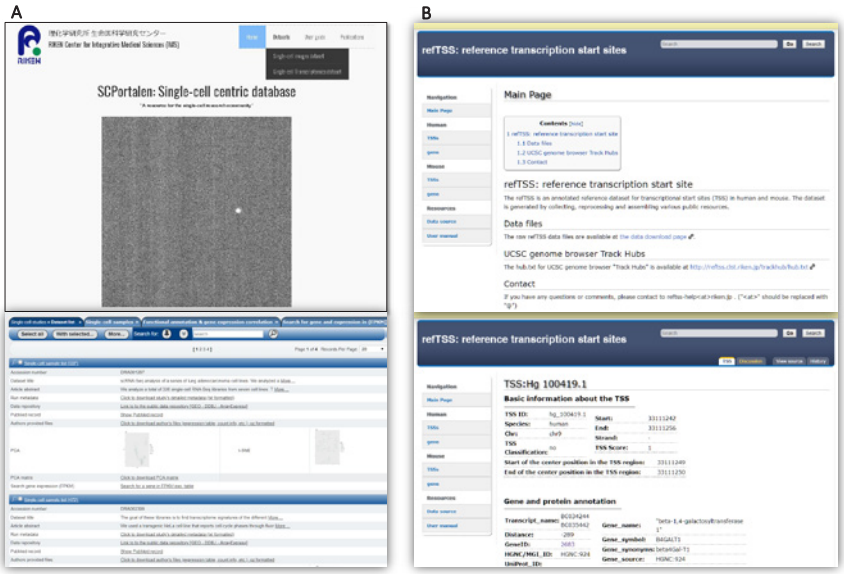


Figure: Web interfaces for single-cell database (SCPortalen) and reference transcription start sites (refTSS)
We have developed and published web interfaces for (A) reprocessed single-cell RNA-seq datasets and (B) a reference dataset of transcriptional start sites. These interfaces are publicly available to all users.

Recent rapid improvements in technologies for the measurement of biological phenomena, including omics profiling, enable researchers to rapidly obtain large-scale biological data. To permit optimal utilization of such data, we are focusing on technology development in bioinformatics analysis and also on engineering for the management of large-scale biomedical data. Towards this goal, we now have several ongoing research projects. First, we are developing a database system to support reuse of published single-cell omics data, especially single-cell RNA-seq data, by the curation and reprocessing of metadata, quality assessment, and development of a web interface (http://single-cell.clst.riken.jp/).

Next, we are constructing a reference dataset of human and mouse transcription start sites that will enable investigators to integrate various information and datasets related to transcriptional regulation (http://reftss.clst.riken.jp/). Third, we are working on data coordination for several collaborative large-scale data production projects being done in RIKEN IMS (and formerly in RIKEN CLST), which include curation of sequence data, metadata collection of samples and sequencing, and development of database systems. We are also comparing software for genome mapping of CAGE (Cap Analysis of Gene Expression) data and developing computational pipelines for sequence data analysis.

Along with the above research projects, we are working to provide and support the information infrastructure for several IMS laboratories. In practice, we have been managing high-performance computation servers and storage platforms for researchers in these laboratories, taking care of computer environments for researchers and support staff, and developing and managing web applications for support staff.

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)

Abugessaisa I, Noguchi S, Böttcher M, Hasegawa A, Kouno T, Kato S, Tada Y, Ura H, Abe K, Shin JW, Plessy C, Carninci P, Kasukawa T. SCPortalen: human and mouse single-cell centric database. ***Nucleic Acids Res*** 46, D781-D787 (2018)

Invited presentations

Noguchi S. "Overview and utilization of the FANTOM web resource" The 41th annual meeting of The Molecular Biology Society of Japan (Yokohama, Japan) November, 2018

Kasukawa T. "Data resource management in the FANTOM projects and SCPortalen single-cell database" ConBio2017 (Kobe, Japan) December, 2017

Kasukawa T. "What is "producing data"? Technologies for data production" The 39th annual meeting of The Molecular Biology Society of Japan (Yokohama, Japan) November, 2016

Abugessaisa I. "Transcriptional Regulation of Coding and Non-coding Genes Enabled by refTSS" The 39th annual meeting of The Molecular Biology Society of Japan (Yokohama, Japan) November, 2016

Laboratory for

Advanced Genomics Circuit

Team Leader: Jay W. Shin

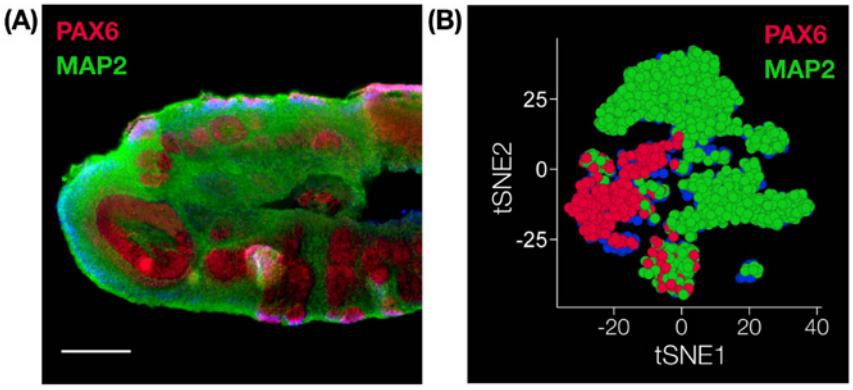


Figure: Spatial and single cell characterization of human iPSC-derived cerebral organoids
(A) Immunofluorescent staining of PAX6$^+$ neuro-progenitor cells (red), MAP2$^+$ neurons (green) and nuclear staining (blue) in day 80 organoid cultures. Scale bar = 0.5 mm. **(B)** Matching single cell 5'-RNA-seq of 80 day cerebral organoids (red = PAX6$^+$ cells, green = MAP2$^+$ cells, blue = PAX6$^-$, MAP2$^-$ cells).

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)

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*** doi: https://doi.org/10.1101/600239 (2019)

Rackham OJ, Firas J, Fang H, Oates ME, Holmes ML, Knaupp AS; FANTOM Consortium, Suzuki H, Nefzger CM, Daub CO, Shin JW, Petretto E, Forrest AR, Hayashizaki Y, Polo JM, Gough J. A predictive computational framework for direct reprogramming between human cell types. ***Nat Genet*** 48, 331-335 (2016)

Invited Presentations

Shin JW. "Functional Elucidation of Long Noncoding RNAs" Keystone Symposia: 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. (Singapore, Singapore) February, 2019

Shin JW. "Functional elucidation of non-coding regulatory elements" IHEC 2018 Annual Meeting & Science Days (Hong Kong, China) October, 2018

Shin JW. "Single Cell CAGE and Single Cell Reprogramming" Single Cell Science Symposium 2018: Single Cell Technologies Toward Human Health (Tokyo, Japan) October, 2018

Shin JW. "More to our Junk DNA than meets the eye" TEDx Kobe (Kobe, Japan) December, 2017

The Laboratory for Advanced Genomics Circuit focuses on the development of single cell RNA-seq at the 5'-end of transcripts in order to profile the transcriptome and epigenome landscape of human cells. In particular, we have been using iPSC-derived cerebral organoids in conjunction with gene-targeting techniques to unravel the gene regulatory processes of neuronal development, reprogramming and degeneration.

The 5'-based single cell RNA-seq method, or single-cell CAGE, reveals functional DNA elements - namely promoters and enhancers - at single-cell resolution. Using this technology, we found that lung cancer cells are concurrently proliferating or differentiating in response to TGF-β. We also report the dynamics of enhancer RNAs, revealing transcriptional bursts arising from either strand in a mutually exclusive manner.

To unravel more complex tissues such as the human brain, we established iPSC-derived cerebral organoids and profiled promoter and enhancer activities at the single cell resolution. We can partially recapitulate the complexity of the human brain through identification of TH+ dopaminergic, vGLUT1+ glutamatergic neurons and GFAP+ astrocytes after 80 days of culture. Based on single cell differential gene analysis, we identified master regulators controlling neuronal subtype specification along with key regulatory enhancers associated with genetic disorders of the brain.

The lab utilizes gene-targeting tools such as CRISPR-interference, full-length overexpression vectors, and antisense oligonucleotides to reconstruct gene regulatory networks. These tools can target transcription factors, long non-coding RNAs and DNA regulatory elements to induce cell fate changes and ultimately cell function. Bridging both experimental and computational techniques, we deciphered the gene regulatory codes to direct cell reprogramming into various neuron subtypes, including dopaminergic and GABAergic neurons.

The lab is also engaging with medical and research communities in Japan to build the Human Cell Atlas (HCA) at single cell- and spatial-resolution. This 'periodic table' of human cells will provide a navigation map to reproducibly study diseases and to accelerate drug discovery, bringing a positive impact to our society.

Genetic Diagnosis Technology Unit
Nucleic Acid Diagnostic System Development Unit

Unit Leader: **Kengo Usui**

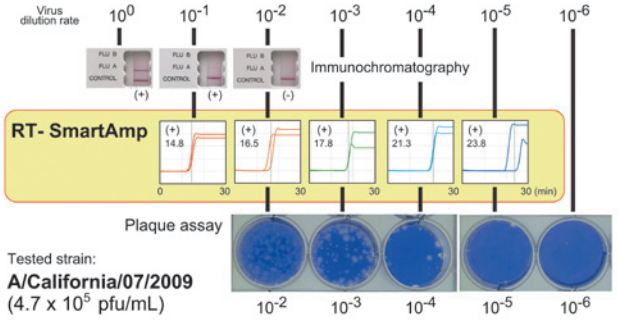


Figure: Detection sensitivity of RT-SmartAmp for influenza

All assays were performed with A/California/07/2009 (H1N1pdm2009), a cultured influenza A virus strain. Immunochromatography was performed using the Alere™ BinaxNow® Influenza A & B Card (Abbott). First, we performed a plaque assay with 10^{-2}–10^{-6} diluted virus and calculated plaque forming units (pfu)/ml of the viral culture fluid. The sample volumes for immunochromatography and RT-SmartAmp were 100 µL and 180 µL, respectively. To compare the sensitivity of each method, the results from the three assays were normalized to viral dilutions from the original viral culture fluid.

We have developed infectious diseases detection primer sets based on our original isothermal amplification method, SmartAmp. These primers target influenza virus, Hepatitis B virus, sexually transmitted disease-related bacteria (*Chlamydia trachomatis* and *Neisseria gonorrhoeae*), and mosquito-borne viruses (Dengue, Zika, Chikungunya, and yellow fever). Additionally, we applied SmartAmp to SNP genotyping of the variant *CPT-2* (carnitine palmitoyltransferase II) gene, which is associated with a high risk of influenza encephalopathy or heat disorder. For detection of cancer-related somatic mutations in several relevant genes, such as *KRAS*, *PIK3CA*, *BRAF*, and *HER2*, we developed a highly-sensitive detection kit using the Eprobe-PCR method and performed a clinical study involving over 400 cancer specimens. Through the study of *KRAS* mutations, we found a significant probability that KRAS G12D and G13D amino acid substitutions promote pulmonary metastasis of colorectal cancer cells. Furthermore, the Eprobe-PCR method allowed for quantitative detection of leukemia-associated fusion RNAs, such as *BCR/ABL1*, with high sensitivity and specificity.

In order to consider actual clinical application of diagnostic tools based on the above studies, development of sample pretreatment technology is very important for easy operation by end-users in medical practice. We successfully developed an influenza virus RNA isolation procedure from nasopharyngeal swab specimens requiring only five minutes of manual handling, and without the need for any special instruments. This pretreatment method has the possibility of being universally applicable for several specimen types, and we are currently evaluating it for urine, blood, and various tissues. Furthermore, we also considered producing the enzymes used for our nucleic acid amplification technologies ourselves in order to reduce the cost and simplify the optimization of the diagnostic tests. We succeeded in purifying one such enzyme, recombinant reverse transcriptase, AMV-RT, from *E. coli*. The amount of purified AMV-RT from a 1 L-culture was sufficient for 10,000 RT-combined SmartAmp reactions, and resulted in a 100-fold price reduction compared to a commercial product.

Currently, we are attempting to realize practical medical applications based on our achievements outlined above. These activities are being performed by our counterpart unit in IMS, "Nucleic Acid Diagnostic System Development Unit", which is supported by the RIKEN Preventive Medicine and Diagnosis Innovation Program (PMI).

Recent Major Publications

Tsuchiya K, Tabe Y, Ai T, Ohkawa T, Usui K, Yuri M, Misawa S, Morishita S, Takaku T, Kakimoto A, Yang H, Matsushita H, Hanami T, Yamanaka Y, Okuzawa A, Horii T, Hayashizaki Y, Ohsaka A. Eprobe-mediated RT-qPCR for the detection of leukemia-associated fusion genes. ***PLoS One*** 13, e0202429 (2018)

Gusev O, Hayashizaki Y, Usui K. Nucleic acid amplification-based diagnostics for pulmonary diseases: What is the current state and perspectives of nucleic acid amplification technologies used in diagnostics associated with pulmonary diseases? In: Kaneko T. (ed), ***Clinical Relevance of Genetic Factors in Pulmonary Diseases***, Singapore: Springer Singapore, Chapter 18, 333-344 (2018)

Takase Y, Usui K, Shimizu K, Kimura Y, Ichihara T, Ohkawa T, Atsumi J, Enokida Y, Nakazawa S, Obayashi K, Ohtaki Y, Nagashima T, Mitani Y, Takeyoshi I. Highly sensitive detection of a *HER2* 12-base pair duplicated insertion mutation in lung cancer using the Eprobe-PCR method. ***PLoS One*** 12, e0171225 (2017)

Invited Presentations

Usui K. "The 15th Annual Meeting of Japanese Society of Hospital General Medicine" (Urayasu, Japan) September 2017

Epigenome Technology Exploration Unit

Unit Leader: Aki Minoda

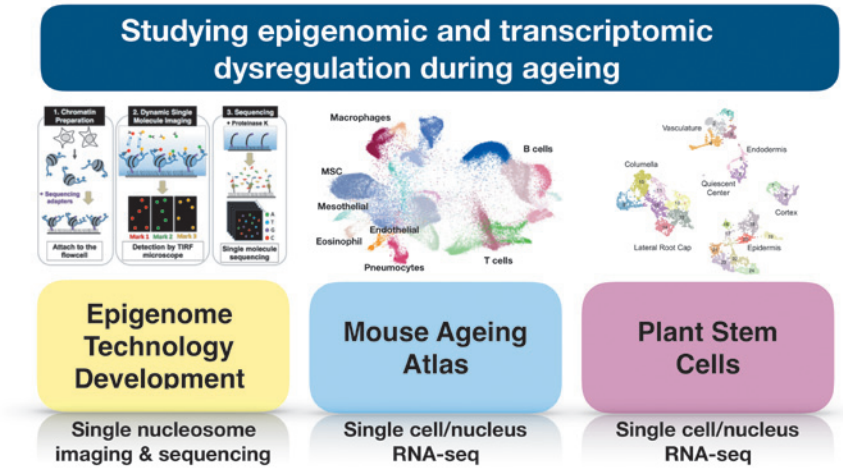


Figure: Ongoing projects in the Unit, towards understanding ageing at the epigenomic and transcriptomic levels in whole tissues.

Recent Major Publications

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)

Koga S, Hozumi K, Hirano KI, Yazawa M, Terooatea T, Minoda A, Nagasawa T, Koyasu S, Moro K. Peripheral PDGFRα^{+}gp38^{+} mesenchymal cells support the differentiation of fetal liver-derived ILC2. ***J Exp Med*** 215, 1609-1626 (2018)

Invited presentations

Minoda A. "Ageing Mouse Atlas" JSI-RIKEN IMS International Symposium on Immunology 2019 (Tokyo, Japan) June, 2019

Minoda A. "Ageing Mouse Atlas" EMBO Workshop on Single Cell Biology (Tokyo, Japan) May, 2019

Minoda A. "Ageing Mouse Atlas" Center for Genomic Regulation (Barcelona, Spain) September, 2018

Minoda A. "Ageing Mouse Atlas" Human Cell Atlas Asia Meeting (Okinawa, Japan) December, 2017

Minoda A. "RIKEN Ageing Resource Project: Of Mice and Super-centenarian Men" 4th RIKEN-Karolinska Institutet-SciLifeLab Joint Symposium (Kobe, Japan) November, 2017

The mission of our lab is to carry out research that contributes to "healthy longevity," towards a society where people can live healthier longer, which is becoming increasingly important as people are living longer. We would like to understand the molecular mechanisms behind functional declines associated with ageing, both at the epigenomic and transcriptomic levels. To accomplish this goal, we apply single-cell genomic technologies to whole tissues, as well as utilize our novel epigenomic technology that enables simultaneous mapping of multiple epigenetic marks at single nucleosome resolution.

Research Projects

a) Mouse Ageing Atlas Project

Due to technical reasons, much of the conventional molecular research in the field of ageing has been carried out with one particular cell type or cell line. However, cells that make up tissues do not function in isolation, often communicating actively with other cells, and thus it is important to understand the process of ageing at the whole tissue level to fully understand how functional decline occurs. To achieve such insight, we are carrying out single-cell/-nucleus RNA-seq of multiple mouse tissues from different ages, along with single-cell ATAC-seq (epigenome) for selected tissues.

b) Novel Epigenome Technology Development

We are developing a novel epigenomic technology to enable simultaneous mapping of multiple histone modifications at the single nucleosome level. This technology combines single-molecule imaging of antibodies on nucleosomes and single-molecule sequencing. Development of such technology will likely reveal how epigenomic regulation is dysregulated during ageing and diseases.

c) Understand plant stem cells [Kakenhi Innovative Research]

We believe it is also important to understand how other organisms, such as plants, manage to live so long, thereby gaining clues regarding the basis of healthy longevity. We are carrying out whole tissue single-cell RNA-seq with various plants as part of the "Plant Stem Cells" group in an attempt to gain insight into the secrets of longevity.

Laboratory for

Comprehensive Genomic Analysis

Team Leader: Yasushi Okazaki

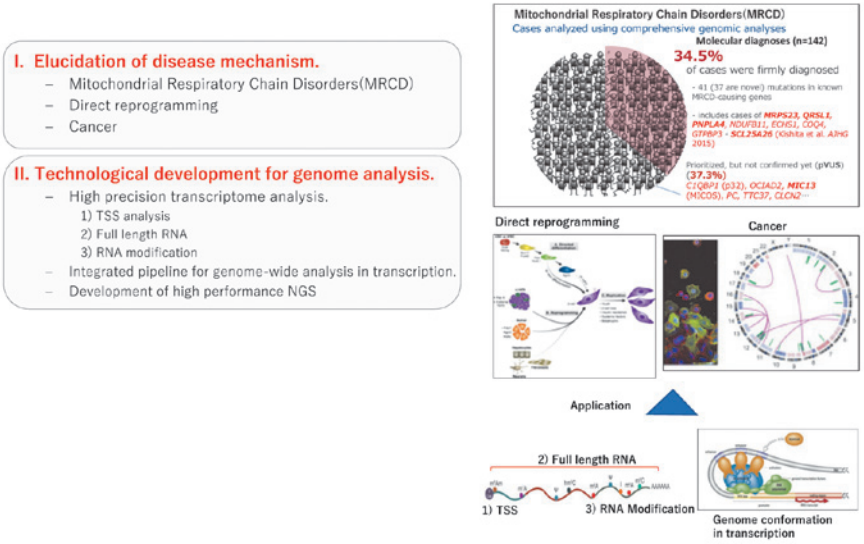


Figure: Future plans
Omics analysis and functional analysis focusing mainly on mitochondrial and neurological diseases, direct reprogramming, and cancer. In the case of technological development for genome analysis, we will focus on target enrichment sequencing and modified RNA analysis using a Nanopore sequencer, and single tube Long Fragment Read (stLFR) long-read sequencing using the MGISEQ-2000 sequencer. The diagnostic rate of mitochondrial respiratory chain disorders using whole exome sequencing analysis is approximately 35%, while approximately 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. Whole genome sequencing, RNA sequencing, and other omics technologies are necessary to solve 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*** (2019)

Noguchi S, et al. FANTOM5 CAGE profiles of human and mouse samples. ***Sci Data*** 4, 170112 (2017)

Kohda M, Tokuzawa Y, Kishita Y (Equally first author), et al, Okazaki Y. A comprehensive genomic analysis reveals the genetic landscape of mitochondrial respiratory chain complex deficiencies. ***PLOS Genet*** 12, e1005679 (2016)

Invited presentations

Okazaki Y. "MGISEQ-2000: the highly versatile platform to satisfy our multiple needs" The 13th International Conference on Genomics (Shenzhen, China) October, 2018

Okazaki Y. "Finding a way to establish Bahrain Genome Projects through the experiences in Japan" Bahrain Genome Symposium (Manama, Kingdom of Bahrain) October, 2018

Okazaki Y. "Genomic solution for ADPKD" The 61st Annual Meeting of the Japanese Society of Nephrology (Niigata, Japan) June, 2018

Okazaki Y. "Mitochondrial cardiomyopathy" Cardiovascular Disease Seminar (Osaka, Japan) May, 2018

Okazaki Y. "Genome medical research aimed at next-generation medical care - Comprehensive genome analysis of mitochondrial respiratory chain disorders" The 4th Nephrology Expert Conference (NEXT) (Tokyo, Japan) July, 2017

From FY2016 to FY2017, we provided research support for researchers inside and outside of RIKEN, such as cross-disciplinary projects within RIKEN and national projects, as a Genome Network Analysis Support facility (GeNAS). Beginning in FY2018, the Laboratory for Comprehensive Genomic Analysis (CGA) was formed and it assumed some of the tasks of research and development from GeNAS.

The CGA laboratory conducts omics analyses to elucidate the pathophysiology of diseases, using functional genomics, and to understand the mechanisms of diseases that disrupt the homeostatic function of various cells and tissues, and to discover new drug targets. More precisely, we will focus our research activities on identifying new disease genes and their functions and finding new drug targets, with the goal of realization of genome medical care. As initial targets, we start with genome and transcriptome analyses of mitochondrial and neurological diseases. In addition, capitalizing on the strengths of the technology developed by our research team, we contribute to ongoing IMS biomedical research. We accomplish this through state-of-the-art genome and transcriptome analysis technology, such as RIKEN's original transcription start site analysis technology, Cap Analysis of Gene Expression (CAGE), and epigenome analysis. As an application using these technologies, we will first focus on single-cell analysis of taste receptor cells and also perform other collaborative studies. Furthermore, we will apply these technologies to define the molecular mechanisms of transcription factors that significantly enhance the direct reprogramming of fibroblasts into pancreatic beta cells.

Laboratory for
Applied Regulatory Genomics Network Analysis

Team Leader: Erik Arner

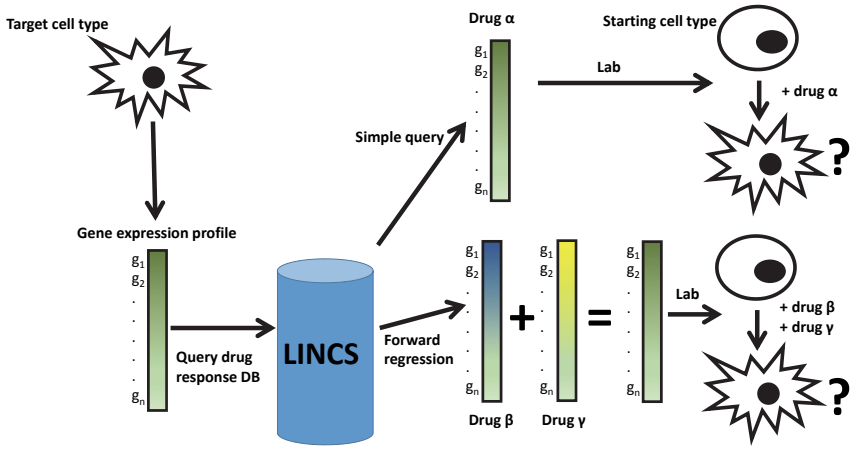


Figure: Identification of small molecules that facilitate cell conversion
Drug response databases such as LINCS, Library of Integrated Network-Based Cellular Signatures, are mined for compounds that, alone or in combination, are likely to facilitate cell conversion to a desired target cell type.

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)

Rapakoulia T, Gao X, Huang Y, de Hoon M, Okada-Hatakeyama M, Suzuki H, Arner E. Genome-scale regression analysis reveals a linear relationship for promoters and enhancers after combinatorial drug treatment. ***Bioinformatics*** 33, 3696-3700 (2017)

Ehrlund A, Mejhert N, Björk C, Andersson R, Kulyté A, Åström G, Itoh M, Kawaji H, Lassmann T, Daub CO, Carninci P, Forrest AR, Hayashizaki Y, Sandelin A, Ingelsson E, FANTOM Consortium, Rydén M, Laurencikiene J, Arner P, Arner E. Transcriptional Dynamics During Human Adipogenesis and Its Link to Adipose Morphology and Distribution. ***Diabetes*** 66, 218-230 (2017)

Invited presentations

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

Arner E. "Novel genome wide technologies at RIKEN IMS" 3rd McGill–RIKEN Symposium (Montreal, Canada) November, 2018

Arner E. "High-resolution characterization of drug-induced cellular response" Human Genome Meeting, (Yokohama, Japan) March, 2018

Arner E. "High-resolution characterization of drug-induced cellular response" Human Cell Atlas Asia Meeting (Okinawa, Japan) November, 2017

Arner E. "Transcriptional response at promoters and enhancers after drug treatment" The 4th RIKEN/ Karolinska Institutet/ SciLifeLab Joint Symposium: Life Science Frontiers in Health, Disease and Aging (Kobe, Japan) November, 2017

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 includes exploration of the transcriptional effects of regulatory molecules at the cellular level and profiling clinical samples in order to identify regulatory networks perturbed in disease states. One interest of the laboratory is to study the effects of drug treatment on the transcriptome at the single-cell level. Here we profile cancer cells (cell lines as well as primary cancer cells derived from patient samples) after treatment with pharmaceuticals that act at the epigenomic level, e.g., histone deacetylase inhibitors and bromodomain inhibitors, using single-cell CAGE technology. Using these approaches, we hope to identify transcriptional signatures at promoters and enhancers that modulate a heterogeneous drug response. We further try to uncover genetic and epigenetic mechanisms underlying diseases by transcriptional profiling of patient cohorts and intersecting these results with data from dynamic cell systems responding to differentiation signals. We are also developing methods for identifying small molecules that, alone or in combination, can facilitate cell conversion. This aspect of our research is achieved through applying data mining and machine learning methods to publicly available drug response transcriptional response data as well as primary cell transcriptome data generated in the FANTOM5 project.

Preventive Medicine and Applied Genomics Unit

Unit Leader: Hideya Kawaji

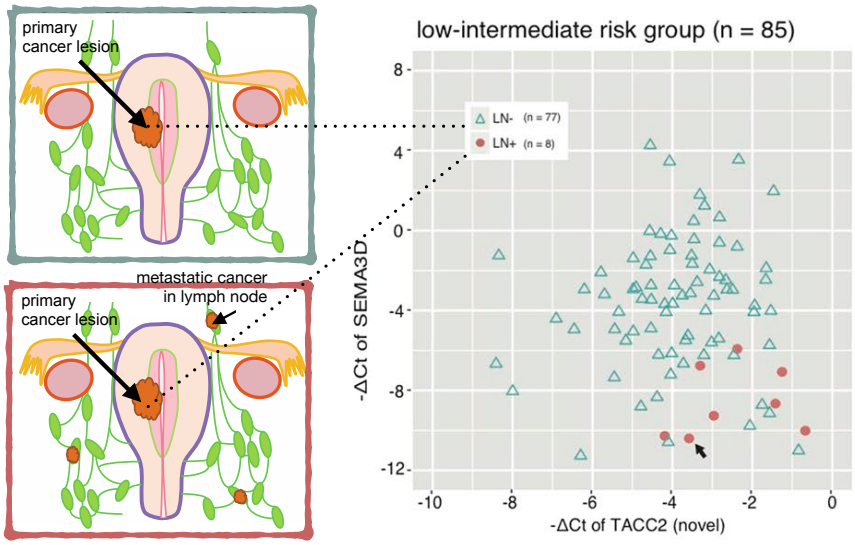


Figure: Newly identified biomarkers for endometrial cancer patients
Expression levels of identified markers [Semaphorin3D (SEMA3D) and Transforming Acidic Coiled-Coil Containing Protein 2 (TACC2)] in the primary lesion of endometrial cancers indicate lymph node metastasis, which could lead to surgery with lower risk by skipping lymphadenectomy in cases of non-metastatic cancers.

Recent Major Publications

Kawaji H, Kasukawa T, Forrest A, Carninci P, Hayashizaki Y. The FANTOM5 collection, a data series underpinning mammalian transcriptome atlases in diverse cell types. ***Sci. Data*** 4, 170113 (2017)

Yoshida E, Terao Y, Hayashi N, Mogushi K, Arakawa A, Tanaka Y, Ito Y, Ohmiya H, Hayashizaki Y, Takeda S, et al. Promoter-level transcriptome in primary lesions of endometrial cancer identified biomarkers associated with lymph node metastasis. ***Sci Rep*** 7, 14160 (2017)

Takamochi K, Ohmiya H, Itoh M, Mogushi K, Saito T, Hara K, Mitani K, Kogo Y, Yamanaka Y, Kawai J, et al. Novel biomarkers that assist in accurate discrimination of squamous cell carcinoma from adenocarcinoma of the lung. ***BMC Cancer*** 16, 760 (2016)

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 to utilize RIKEN technologies to solve clinical problems, and our unit is 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 with RIKEN PMI and these can be roughly classified into three categories: exploration of diagnostic markers useful in patient treatment, identification of cell markers required for regenerative medicine, and our own developments to assist in such translational as well as basic science research.

Our collaborative research led to identification of biomarkers indicating lymph node metastasis for endometrial cancer patients, biomarkers discriminating lung cancer subtypes with higher accuracy than pre-existing markers, and biomarkers discriminating corneal endothelial cells and others, which will be useful in regenerative medicine in addition to diagnosis. We also provided maintenance for the FANTOM5 resource, the largest database of *cis*-regulatory regions based on transcriptome profiles, to assist translational researchers focusing on *cis*-regulatory regions as well as basic scientists. Our collaboration with the University of California, Santa Cruz, made possible rapid access to a widely used genome browser database in Asia. We also successfully contributed to translational research and provided valuable resources in functional genomics.

RIKEN-IFOM Joint Laboratory for Cancer Genomics

Team Leader: Yasuhiro Murakawa

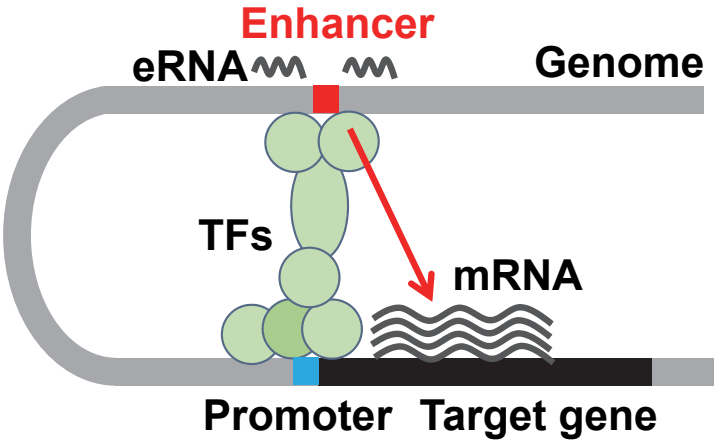


Figure: Enhancer-mediated gene regulation
Enhancers are small segments of distal *cis*-regulatory DNA elements that significantly enhance the expression of target genes and play key roles in the establishment of cell type-specific function and identity.

Recent Major Publications

Yoshihara M, Araki A, Kasama Y, Sunayama M, Abe M, Nishida K, Kawaji H, Hayashizaki Y, *Murakawa Y. Hotspots of de novo point mutations in induced pluripotent stem cells. ***Cell Reports*** 21, 308-315 (2017)

*Murakawa Y. Yoshihara M, Kawaji H, Nishikawa M, Zayed H, Suzuki H, Fantom Consortium, Hayashizaki Y. Enhanced identification of transcriptional enhancers provide mechanistic insights into diseases. ***Trends Genet*** 32, 76-88 (2016)

Hasler D, Lehmann G, Murakawa Y, Klironomos F, Jakob L, Grässer F, Rajewsky N, Landthaler M, Meister G. The Lupus autoantigen La prevents mis-channeling of tRNA fragments into the human microRNA pathway. ***Mol Cell*** 63, 110-124 (2016)

Invited presentations

Murakawa Y, Kume S, Maeda M, Suga M, Tamura M, Kobayashi N. "Seeing the Kidney through Imaging Big Data" The 61st Annual Meeting of the Japanese Society of Nephrology (Niigata, Japan) June, 2018

Murakawa Y. "Analysis of transcriptional network using a novel NET-CAGE method" The 91st Annual Meeting of the Japan Endocrine Society (Miyazaki, Japan) April, 2018

Murakawa Y. "Hotspot of de novo point mutations in iPSCs" The 17th Congress of the Japanese Society for Regenerative Medicine (17JSRM) (Yokohama, Japan) March, 2018

Murakawa Y. "Decoding the Human Genome" LINK-J Symposium (Tokyo, Japan) March, 2017

Murakawa Y. "Genome-wide analysis of the post-transcriptional gene regulation" Life of Genome Symposium (Kazan, Russia) August, 2016

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 (Fig). 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 globally determine the 5'-ends of nascent RNAs, thereby sensitively detecting unstable transcripts including enhancer-derived RNAs. NET-CAGE 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 original 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.

Laboratory for Genotyping Development

Team Leader: Yukihide Momozawa

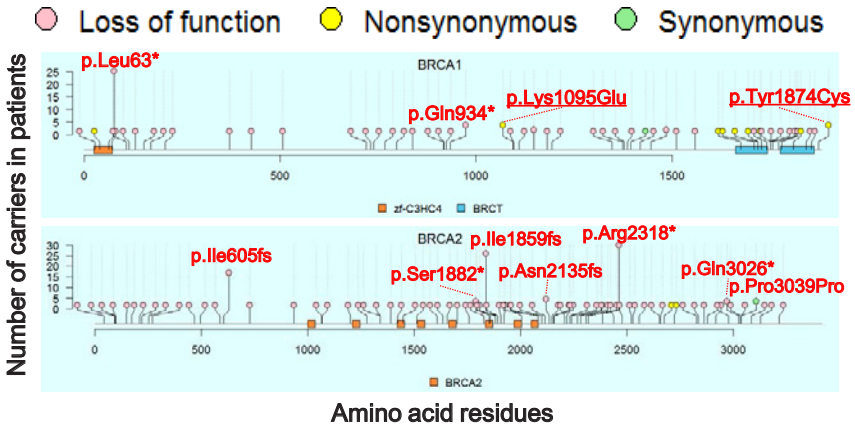


Figure: Location and number of Japanese breast cancer patients with pathogenic genetic variants
The figure illustrates the frequency of the indicated genetic variants in the *BRCA1* gene (top panel) and the *BRCA2* gene (lower panel). The indicated genetic variants can result in loss of protein function (pink, e.g., p.Leu63* or p.Ile605fs), nonsynonymous amino acid substitutions (yellow, e.g., p.Lys1095Glu), or no change in amino acids (synonymous, green, e.g., p.Pro3039Pro). * = translation STOP codon; fs = frame shift. Two variants newly identified as pathogenic variants are underlined.

Recent Major Publications

Momozawa Y, Dmitrieva J, Theatre E, et al: IBD risk loci are enriched in multigenic regulatory modules encompassing putative causative genes. ***Nat Commun*** 9, 2427 (2018)

Momozawa Y, Iwasaki Y, Parsons MT, et al: Germline pathogenic variants of 11 breast cancer genes in 7,051 Japanese patients and 11,241 controls. ***Nat Commun*** 9, 4083 (2018)

Tajima T, Morita H, Ito K, et al. Blood lipid-related low-frequency variants in LDLR and PCSK9 are associated with onset age and risk of myocardial infarction in Japanese. ***Sci Rep*** 8, 8107 (2018)

Invited presentations

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

Momozawa Y. "Complex genetic expression pattern involved in inflammatory bowel disease." Annual Meeting of the Japanese Society of Clinical Immunology (Karuizawa, Japan) November, 2018

Momozawa Y. "Germline pathogenic variants of 11 hereditary breast cancer genes in Japanese" The 77th Annual Meeting of the Japanese Cancer Association (Osaka, Japan) September, 2018

Momozawa Y. "Germline pathogenic variants of 11 hereditary breast cancer genes in 7,051 unselected Japanese breast cancer patients and 11,241 controls" Satellite meeting of Human Genome Meeting (Yokohama, Japan) March, 2018

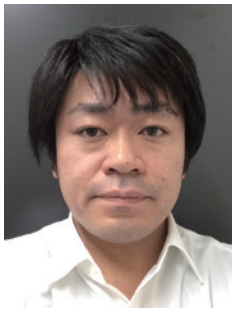
Momozawa Y. "Genomic analysis of disease of companion animals in Europe." The 160th Annual Meeting of the Japanese Society of Veterinary Science (Kagoshima, Japan) September, 2017

The aims of the Laboratory for Genotyping Development are: 1) to produce precise, large-scale genomic data to identify genetic variants associated with disease susceptibility, disease outcomes, and drug responses; and 2) to develop methods and databases useful for personalized medicine.

Our laboratory published 132 papers in 2016-2018. As one main achievement of our laboratory, we estimated disease risk of each gene and revealed demographic and clinical characteristics of pathogenic variants in Japanese hereditary breast cancer patients (*Nat Commun* 9: 4083). This information is already used in hospitals for the interpretation of genetic testing. Currently, we are expanding this effort to 13 other cancer types to provide fundamental information for cancer genetic testing. We also performed fine mapping of disease-associated loci identified by a genome-wide association study to reveal the contribution of rare variants to age-related macular degeneration (*Hum Mol Genet* 25: 5027-5034), inflammatory bowel disease (*Nat Commun* 9: 2427), and myocardial infarction (*Sci Rep* 8: 8107).

Our laboratory has also worked as a research hub for large-scale genomic analysis, collaborating with domestic and international universities, research institutes, and companies. We have contributed to the identification of disease-associated variants and disease biology for various diseases/phenotypes including inflammatory bowel disease (*Nature* 547: 173-178), body mass index (*Nat Genet* 49: 1458-1467), and clinically important quantitative traits (*Nat Genet* 50: 390-400).

We will continue to conduct our own projects and to function as a research hub for large-scale genomic analysis so that we can contribute to the implementation of personalized medicine.



Laboratory for
Statistical Analysis

Team Leader: Yoichiro Kamatani

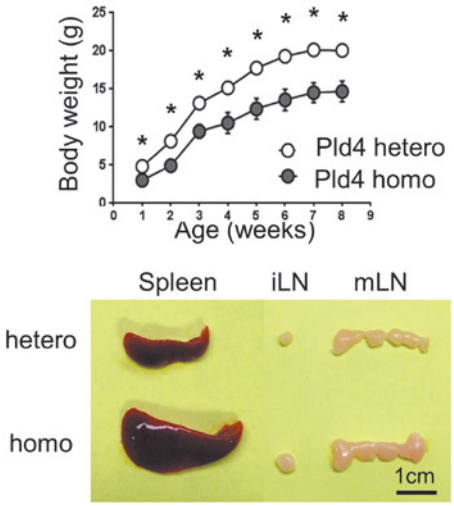


Figure: A mutation in mouse *Pld4*, a novel human SLE susceptibility gene identified by GWAS, results in autoimmune phenotypes in mice.

Homozygous *Pld4* (Phospholipase D4) mutant mice had lower body weight compared to heterozygous mice during the period of observation (Upper panel, *, $p<0.05$). Splenomegaly and lymphadenopathy in *Pld4* mutant mice. Spleen, inguinal lymph node (iLN), and mesenteric lymph nodes (mLN) are compared between -/+ and -/- mice at 15 weeks after birth (Lower panel).

Our laboratory aims to find genetic susceptibility variants associated with complex traits, and to understand their biological roles by using integrative analyses of epigenome and transcriptome data. We have performed dozens of genome-wide association studies (GWAS) and 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, and we freely shared these results after their publication (http://jenger.riken.jp/en/). Our analyses clarified the similarity and differences between populations with regard to genetics of the traits. We performed downstream analyses to understand the biological background underlying these genetic results, and found that trait-relevant cell types can be linked by applying integrative analysis of genetic and epigenetic data. We also support genetic analyses of our collaborators and participate in international meta-analysis consortia, including AFGen, GIANT, and MEGASTROKE, to enhance statistical power to detect genetic signals.

We then moved into two new major research fields. One is to use whole genome sequencing (WGS) analysis to expand our understanding of complex traits. This technique is useful to detect rare variants, which are strong candidates to explain population differences in the genetics of the traits. This study may contribute to 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 set analyses, may lead to the discovery of novel biological principals. This project can proceed more efficiently with further collaborations with other IMS laboratories, and we have begun to discuss the feasibility of such collaborations.

Recent Major Publications

Okazaki S, Morimoto T, Kamatani Y, Kamimura T, Kobayashi H, Harada K, TomitaT, Higashiyama A, Takahashi JC, Nakagawara J, Koga M, Toyoda K, Washida K, Saito S, Takahashi A, Hirata M, Matsuda K, Mochizuki H, Chong M, Paré G, O'Donnell M,Ago T, Hata J, Ninomiya T, Dichgans M, Debette S, Kubo M, Koizumi A, Ihara M. Moyamoya Disease Susceptibility Variant RNF213 p.R4810K Increases the Risk of Ischemic Stroke Attributable to Large-Artery Atherosclerosis. ***Circulation*** 139, 295-8 (2019)

Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK,Bras J, Duncan L, Escott-Price V, Falcone GJ, Gormley P, Malik R, Patsopoulos NA,Ripke S, Wei Z, Yu D, Lee PH, Turley P, Grenier-Boley B, Chouraki V, Kamatani Y, Berr C, Letenneur L, Hannequin D, Amouyel P, Boland A, Deleuze JF, Duron E,Vardarajan BN, Reitz C, Goate AM, et al. Analysis of shared heritability in common disorders of the brain. ***Science*** 360, eaap8757 (2018)

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

Invited Presentations

Kamatani Y. "Comprehensive genetic study for complex diseases." The 83rd Annual Scientific Meeting of the Japanese Circulation Society (Yokohama, Japan) March, 2019

Kamatani Y. "Finding stroke susceptibility genes through genomic analysis of hundreds of thousands of samples." International Seminar of Cerebrovascular Disease (Shinjuku, Japan) February, 2019

Kamatani Y. Genetic analysis of more than 100K Japanese subjects including cardiovascular disorders" The 2nd JCS Council Forum on Basic Cardiovascular Research (Nara, Japan) September, 2018

Kamatani Y. "The Biobank Japan" 23rd workshop of International Stroke Genetics Consortium (Kyoto, Japan) April, 2018

Kamatani Y. "Whole genome analysis and its future in precision medicine" The 22nd Annual Meeting of the Society of Cardiovascular Endocrinology and Metabolism (Miyazaki, Japan) April, 2018

Laboratory for Pharmacogenomics

Team Leader: Taisei Mushiroda

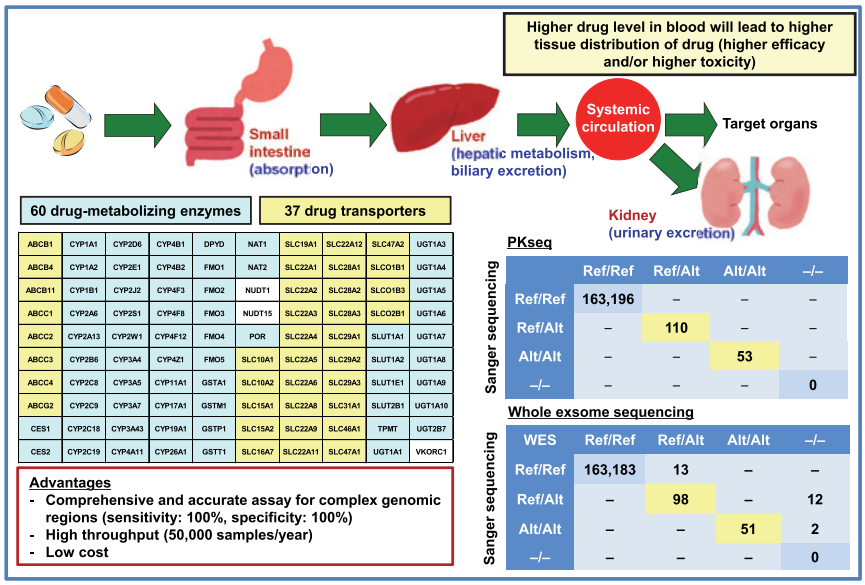


Figure: PKseq, targeted resequencing of a panel of 100 genes related to pharmacokinetics using a combination of multiplex-PCR and next-generation sequencing (NGS)

The newly developed NGS panel, PKseq, can analyze common and rare variants comprehensively and accurately, which is an ideal platform for identification of pharmacogenomics biomarkers useful for predicting drug efficacy and risk of adverse drug reactions. When accuracies of the PKseq and whole-exsome sequencing (WES) were compared in the same Japanese individual (Ref: reference allele, Alt: variant allele), the WES showed some differences from the results of Sanger sequencing, but the PKseq demonstrated the same genotypes as Sanger sequencing, leading to higher sensitivity and specificity compared to the WES.

Individual responses to drugs can 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 polymorphisms have been identified in genes that affect efficacy or risk of ADRs for various drugs. In the USA, information on 161 germline genomic biomarkers is available in US FDA-approved drug labels. However, in Japan, the National Health Insurance System currently covers only two genetic tests, UGT1A1 and BRCA1/2, to predict drug responses prior to the drug administration.

In collaboration with domestic hospitals, we are conducting genomic analyses for the identification of pharmacogenomic (PGx) biomarkers useful for prediction of drug responses. Since it is difficult for individual countries acting alone to collect a sufficient number of samples for PGx research, we conduct international PGx collaborations, such as the Southeast Asian Pharmacogenomics Research Network (SEAPharm). In order to achieve our mission, application of PGx biomarkers to clinical practice, we advance our research according to three primary steps: i) establishment of infrastructure for identification of PGx biomarkers, ii) identification by genomic analyses of PGx biomarkers associated with drug efficacy/adverse drug reactions, and iii) clinical implementation of PGx biomarkers.

Recent Major Publications

Yoshihama T, Fukunaga K, Hirasawa A, Nomura H, Akahane T, Kataoka F, Yamagami W, Aoki D, Mushiroda T. GSTP1 rs1695 is associated with both hematological toxicity and prognosis of ovarian cancer treated with paclitaxel plus carboplatin combination chemotherapy: a comprehensive analysis using targeted resequencing of 100 pharmacogenes. ***Oncotarget*** 9, 29789-29800 (2018)

Mushiroda T, Takahashi Y, Onuma T, Yamamoto Y, Kamei T, Hoshida T, Takeuchi K, Otsuka K, Okazaki M, Watanabe M, Kanemoto K, Oshima T, Watanabe A, Minami S, Saito K, Tanii H, Shimo Y, Hara M, Saitoh S, Kinoshita T, Kato M, Yamada N, Akamatsu N, Fukuchi T, Ishida S, Yasumoto S, Takahashi A, Ozeki T, Furuta T, Saito Y, Izumida N, Kano Y, Shiohara T, Kubo M; GENCAT Study Group. Association of HLA-A*31:01 Screening With the Incidence of Carbamazepine-Induced Cutaneous Adverse Reactions in a Japanese Population. ***JAMA Neurol*** 75, 842-849 (2018)

Ujiie H, Muramatsu K, Mushiroda T, Ozeki T, Miyoshi H, Iwata H, Nakamura A, Nomoto H, Cho KY, Sato N, Nishimura M, Ito T, Izumi K, Nishie W, Shimizu H. HLA-DQB1*03:01 as a Biomarker for Genetic Susceptibility to Bullous Pemphigoid Induced by DPP-4 Inhibitors. ***J Invest Dermatol*** 138, 1201-1204 (2018)

Invited presentations

Mushiroda T. "Adverse effects by anti-tuberculosis drug" Social implications of scientific technology in TB control (Bangkok, Thailand) December, 2018

Mushiroda T. "Pharmacogenomics research in Southeast Asia" The 21st GoldenHelix Pharmacogenomics Day (Singapore, Singapore) August, 2018

Hikino K. "Clinical evidence essential to PGx informed precision medicine in pediatrics" International Symposium on Pediatric Drug Evaluation and Clinical Pharmacology (Tokyo, Japan) June, 2018

Ozeki T. "Genetic analysis for cutaneous adverse drug reactions induced by phenobarbital and phenytoin in Japanese population" The 3rd International Stevens-Johnson Syndrome Symposium (Kyoto, Japan) February, 2018

Laboratory for
Bone and Joint Diseases

Team Leader: Shiro Ikegawa

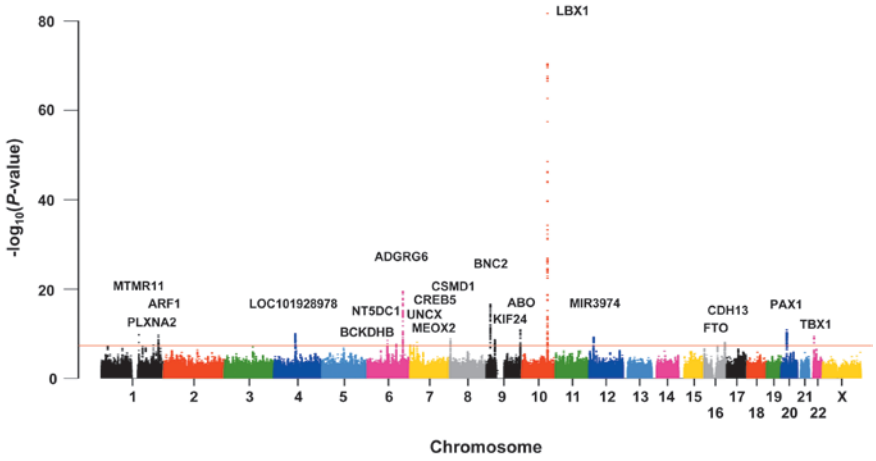


Figure: Manhattan plot for the AIS GWAS
The horizontal red line indicates the genome-wide significance threshold ($P = 5 \times 10^{-8}$). Genetic loci with genome-wide significance are labeled.

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 already succeeded in the identification of several susceptibility genes. Functional studies of the genes *in vitro* and using model animals are underway.

2) Genomic Study of Skeletal Dysplasia

Skeletal dysplasia is a group of heritable (monogenic) disorders affecting the skeleton, and more than 400 diseases belong to this category. Skeletal dysplasia is an intractable disease, so many patients are waiting for an efficacious 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 approach 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 are then performing association studies for common bone and joint diseases corresponding to skeletal dysplasia, the so-called "rare to common" approach.

Recent Major Publications

Kou I, Watanabe K, Takahashi Y, Momozawa Y, Khanshour A, Grauers A, Zhou H, Liu G, Fan YH, Takeda K, Ogura Y, Zhou T, Iwasaki Y, Kubo M, Wu Z, Matsumoto M; Japan Scoliosis Clinical Research Group (JSCRG); Texas Scottish Rite Hospital for Children Clinical Group (TSRHCCG), Einarsdottir E, Kere J, Huang D, Qiu G, Qiu Y, Wise CA, Song YQ, Wu N, Su P, Gerdhem P, Ikegawa S. A multi-ethnic meta-analysis confirms the association of rs6570507 with adolescent idiopathic scoliosis. ***Sci Rep*** 8, 11575 (2018)

Ogura Y, Takeda K, Kou I, Khanshour A, Grauers A, Zhou H, Liu G, Fan YH, Zhou T, Wu Z, Takahashi Y, Matsumoto M; Japan Scoliosis Clinical Research Group (JSCRG); Texas Scottish Rite Hospital for Children Clinical Group (TSRHCCG), Einarsdottir E, Kere J, Huang D, Qiu G, Xu L, Qiu Y, Wise CA, Song YQ, Wu N, Su P, Gerdhem P, Watanabe K, Ikegawa S. An international meta-analysis confirms the association of BNC2 with adolescent idiopathic scoliosis. ***Sci Rep*** 8, 4730 (2018)

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

Invited Presentations

Ikegawa S. "Genetic study of bone and joint diseases" Invited special lecture in Chinese Academy of Medical Sciences (Beijing, China) September, 2018

Ikegawa S. "Genomic study of skeletal dysplasia" Invited special lecture in Marmara University Medical School (Istanbul, Turkey) June, 2018

Ikegawa S. "Extension of genome-wide association study of adolescent idiopathic scoliosis" The International Consortium for Spinal Genetics Development and Disease Conference Meeting in Guangzhou (Guangzhou, China) April, 2018

Ikegawa S. "Natural history and etiology of spine disorders" The International Consortium for Spinal Genetics Development and Disease Conference Meeting in Shenzhen (Shenzhen, China) April, 2018

Ikegawa S. "Genomic study of common spinal diseases" 2018 Annual Meeting of Taiwan Spine Society (Taipei, Taiwan) April, 2018

Laboratory for Endocrinology, Metabolism and Kidney Diseases

Team Leader: Momoko Horikoshi

Recent Major Publications

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)

Horikoshi M*, Day FR, Akiyama M, Hirata M, Kamatani Y, Matsuda K, Ishigaki K, Kanai M, Wright H, Toro CA, Ojeda SR, Lomniczi A, Kubo M, Ong KK, Perry JRB*. Elucidating the genetic architecture of reproductive ageing in the Japanese population. ***Nat Commun*** 9, 1977 (2018).

Beaumont RN, Warrington NM, Cavadino A, Tyrrell J, Nodzenski M, Horikoshi M, Geller F, Myhre R, Richmond RC, Paternoster L, Bradfield JP, Kreiner-Møller E, Huikari V, Metrustry S, Lunetta KL, Painter JN, Hottenga JJ, Allard C, Barton SJ, Espinosa A, Marsh JA, Potter C, Zhang G, Ang W, Berry DJ, Bouchard L, Das S; Early Growth Genetics (EGG) Consortium, Hakonarson H, Heikkinen J, Helgeland Ø, Hocher B, Hofman A, Inskip HM, Jones SE, Kogevinas M, Lind PA, Marullo L, Medland SE, Murray A, Murray JC, Njølstad PR, Nohr EA, Reichetzeder C, Ring SM, Ruth KS, Santa-Marina L, Scholtens DM, Sebert S, Sengpiel V, Tuke MA, Vaudel M, Weedon MN, Willemsen G, Wood AR, Yaghootkar H, Muglia LJ, Bartels M, Relton CL, Pennell CE, Chatzi L, Estivill X, Holloway JW, Boomsma DI, Montgomery GW, Murabito JM, Spector TD, Power C, Järvelin MR, Bisgaard H, Grant SFA, Sørensen TIA, Jaddoe VW, Jacobsson B, Melbye M, McCarthy MI, Hattersley AT, Hayes MG, Frayling TM, Hivert MF, Felix JF, Hyppönen E, Lowe WL Jr, Evans DM, Lawlor DA, Feenstra B, Freathy RM. Genome-wide association study of offspring birth weight in 86 577 women identifies five novel loci and highlights maternal genetic effects that are independent of fetal genetics. ***Hum Mol Genet*** 27, 742-756 (2018)

Invited Presentations

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

Horikoshi M. "Maternal and fetal genetic effects on birth weight and their relevance to cardio-metabolic risk factors" The 8th DOHaD Epidemiological Seminar (Tokyo, Japan) October, 2018

Horikoshi M. "Discovery of genomic loci associated with birth weight and the shared genetic contribution with adult metabolic diseases" RIKEN Summer School 2018 (Tsukuba, Japan) September, 2018

Horikoshi M. "Genetics of Type 2 Diabetes in the Japanese population" The 61st annual meeting of The Japan Diabetes Society (Tokyo, Japan) May, 2018

Horikoshi M. "Genome-wide associations for birth weight and correlations with adult disease" The 3rd meeting for research on metabolism and nutritional mechanism of lifestyle disease and cancer (Tokyo, Japan) March, 2018

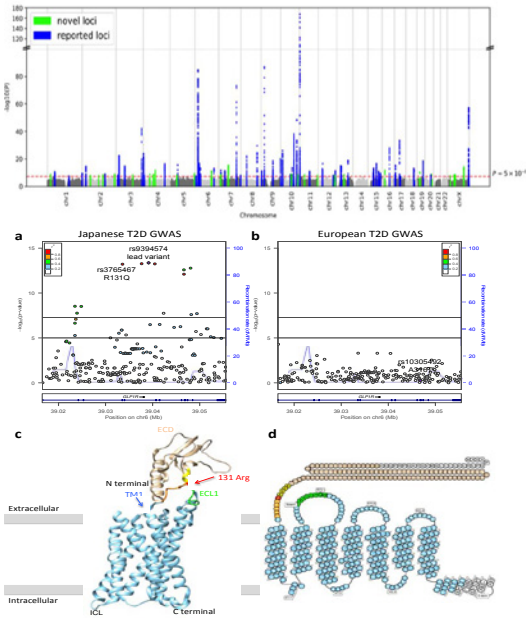


Figure: Manhattan plot of Japanese T2D GWAS and regional association plots of GLP1R with its structure.
Manhattan plot (**top**) summarizes the genome-wide association study of Japanese T2D in 36,614 cases and 155,150 controls. The association *P* value (in −log10*P*) for each of up to 12,557,761 variants (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 extracellular loop (green).

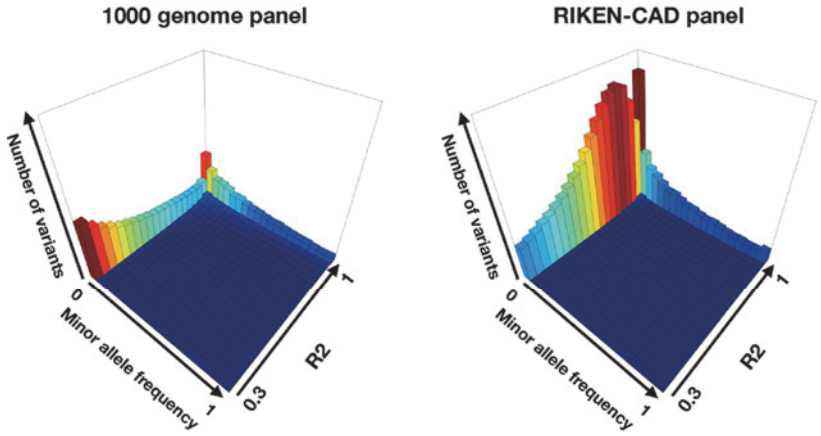
Ever larger scale genome-wide association (GWA) meta-analyses for type 2 diabetes (T2D), in which the included samples now total nearly 1 million, have been extensively conducted, mainly in Europeans. We have been focusing on investigating the genetic contribution to T2D susceptibility in the Japanese population by using the rich genetic resources generated by Biobank Japan (BBJ). By expanding our effort to the full BBJ collection, we conducted a single-population GWA analysis of T2D in 191,764 Japanese. In addition to the >150 T2D loci established as of the end of 2018, we identified 28 novel loci (Figure). We detected several previously unreported T2D-associated missense variants that showed a different spectrum of minor allele frequencies between Japanese and Europeans (Figure). A transethnic comparison of pathway analysis revealed that both groups 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.

We also examined the genetics of reproductive ageing, in collaboration with the REPROgen consortium. Successful genetic studies of reproductive ageing had largely been limited to individuals of European ancestry, but GWA analysis in 67,029 women from the BBJ enabled us to identify 26 loci for puberty timing and age at menopause, representing the first loci for reproductive ageing in any non-European population.

Laboratory for
Cardiovascular Diseases

Team Leader: Kaoru Ito

Figure: Imputation quality in the RIKEN-CAD panel
The 3D plot shows the relationships among minor allele frequency, imputation quality, and the number of variants in imputed samples. In the 1000 genomes project-based imputation, which is the most relevant reference panel in the world, imputation quality of rare variants is low, while numerous rare variants of high quality were observed in the RIKEN-CAD panel.



Recent Major Publications

Nomura S, Satoh M, Fujita T, Higo T, Sumida T, Ko T, Yamaguchi T, Tobita T, Naito AT, Ito M, Fujita K, Harada M, Toko H, Kobayashi Y, Ito K, Takimoto E, Akazawa H, Morita H, Aburatani H, Komuro I. Cardiomyocyte gene programs encoding morphological and functional signatures in cardiac hypertrophy and failure. ***Nat Commun*** 9, 4435 (2018)

Roselli C, Ito K, Kamatani Y, Tanaka T, Ellinor PT, et al. Multi-ethnic genome-wide association study for atrial fibrillation. ***Nat Genet*** 50, 1225-1233 (2018)

Tajima T, Morita H, Ito K, Yamazaki T, Kubo M, Komuro I, Momozawa Y. Blood lipid-related low-frequency variants in LDLR and PCSK9 are associated with onset age and risk of myocardial infarction in Japanese. ***Sci Rep*** 8, 8107 (2018)

Invited Presentations

Ito K. "Cardiovascular Omics Research from the viewpoint of Genomics" The 22nd Annual Scientific Meeting of the Japanese Heart Failure Society (Tokyo, Japan) October, 2018

Ito K. "Introduction to Genomic Research" Statistical Genetics Summer School (Osaka, Japan) August, 2018

Ito K. "Elucidating Genetic Factors for Cardiovascular Diseases" Kickoff Meeting for the Advanced Genomic Research (Tokyo, Japan) July, 2018

Ito K. "Aberrant RNA splicing in Cardiomyopathy" The 4th Japanese Cardiomyopathy Meeting of the Japanese Heart Failure Society (Nara, Japan) June, 2018

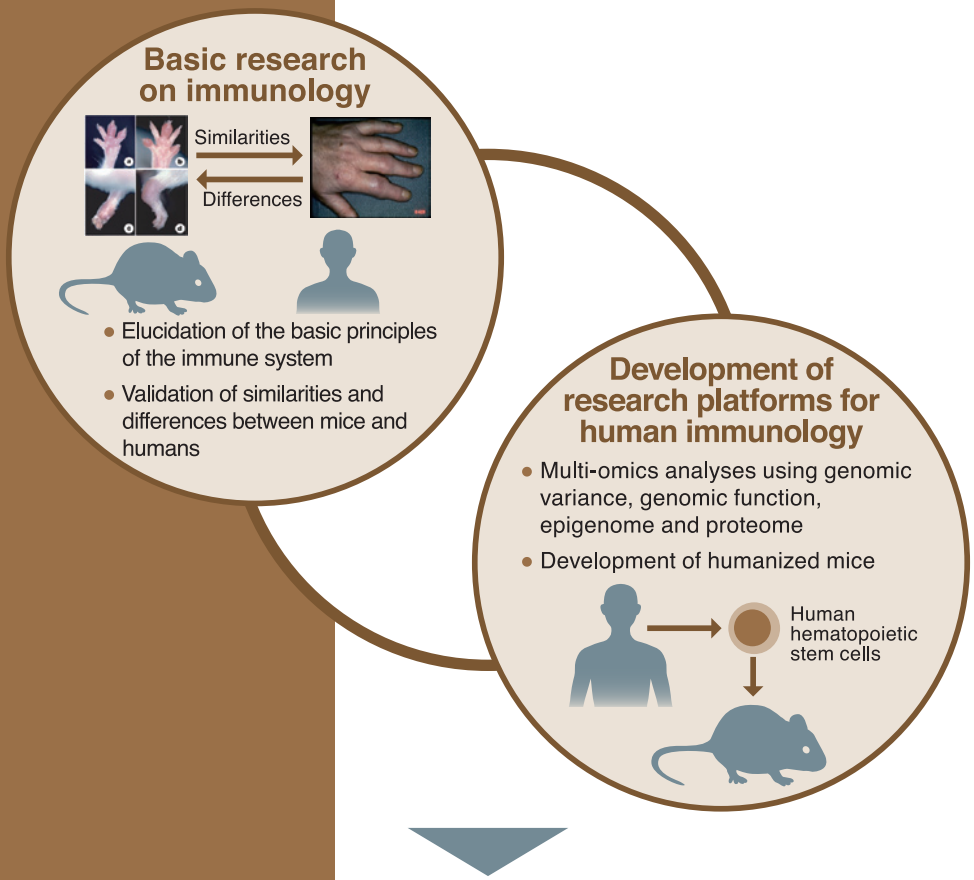
Ito K. "Genomic Research for Onco-cardiology" The 3rd Otemae Seminar (Osaka, Japan) May, 2018

Since cardiovascular diseases cause more than 15% of the deaths in the Japanese population and represent more than 20% of the total medical expenses in Japan, it is important for our society to understand the mechanisms underlying these disorders and to uncover new therapeutic targets for their treatment. To achieve these goals, we 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 diseases of interest to date are coronary artery diseases (CAD), atrial fibrillation (AF), Kawasaki disease (KD), peripheral artery disease (PAD), chronic thromboembolic pulmonary hypertension (CTEPH), and cardiomyopathy (CM). We are currently seeking 1) understand the genetic causes of CAD and the genetic differences between Japanese and European populations, 2) elucidate the mechanism of CTEPH development using human omics data from patients in multiple hospitals, and 3) develop a more sophisticated genetic risk scoring system by machine learning algorithms in the MI and AF projects. Additionally, in the CM project, we developed an *in silico* splicing variant prediction algorithm, a high-throughput cell-based splicing assay, and a downstream *in silico* pipeline to uncover cryptic splice variants, which have been overlooked in the currently established pipelines. Using this pipeline, we are now tackling the TTN (titin) gene, which is expressed in striated muscle and encodes the largest protein in humans, consisting of 34,350 amino acids.

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

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

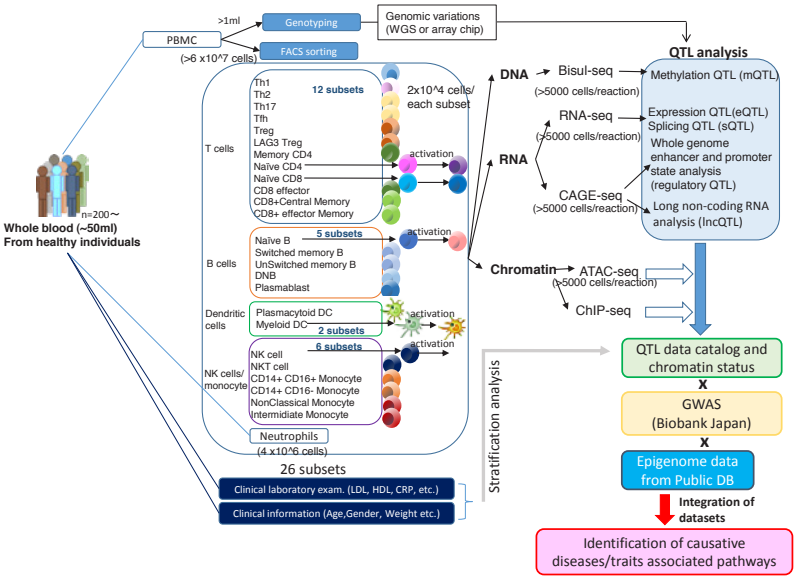


Figure: Integration of genetic variations and multi-omics data

Recent Major Publications

Kochi Y, Kamatani Y, Kondo Y, Suzuki A, Kawakami E, Hiwa R, Momozawa Y, Fujimoto M, Jinnin M, Tanaka Y, Kanda T, Cooper RG, Chinoy H, Rothwell S, Lamb JA, Vencovský J, Mann H, Ohmura K, Myouzen K, Ishigaki K, Nakashima R, Hosono Y, Tsuboi H, Kawasumi H, Iwasaki Y, Kajiyama H, Horita T, Ogawa-Momohara M, Takamura A, Tsunoda S, Shimizu J, Fujio K, Amano H, Mimori A, Kawakami A, Umehara H, Takeuchi T, Sano H, Muro Y, Atsumi T, Mimura T, Kawaguchi Y, Mimori T, Takahashi A, Kubo M, Kohsaka H, Sumida T, Yamamoto K. Splicing variant of WDFY4 augments MDA5 signalling and the risk of clinically amyopathic dermatomyositis. ***Ann Rheum Dis*** 77, 602-611 (2018)

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

Okada Y, Suzuki A, Ikari K, Terao C, Kochi Y, Ohmura K, Higasa K, Akiyama M, Ashikawa K, Kanai M, Hirata J, Suita N, Teo YY, Xu H, Bae SC, Takahashi A, Momozawa Y, Matsuda K, Momohara S, Taniguchi A, Yamada R, Mimori T, Kubo M, Brown MA, Raychaudhuri S, Matsuda F, Yamanaka H, Kamatani Y, Yamamoto K. Contribution of a Non-classical HLA Gene, HLA-DOA, to the Risk of Rheumatoid Arthritis. ***Am J Hum Genet*** 99, 366-74 (2016)

Invited presentations

Yamamoto K. "Genetics and epigenetics of autoimmune diseases" International Congress of Autoimmunity (Lisbon, Portugal) May, 2018

Yamamoto K. "Polygenic burdens on cell-specific pathways" International Forum for RA (IFRA) Karolinska Institute (Stockholm, Sweden) Sept, 2017

Yamamoto K. "Peptidyl arginine deiminase 4 and rheumatoid arthritis" EULAR (European League Against Rheumatism) (Madrid, Spain) June, 2017

Yamamoto K. "Genetics of rheumatoid arthritis" Advanced Target Therapies (Nice, France) March, 2017

Yamamoto K. "Regulation of B cell functions and cellular metabolism in autoimmunity" Cold Spring Harbor Asia Conference (Awaji, Japan) October, 2016

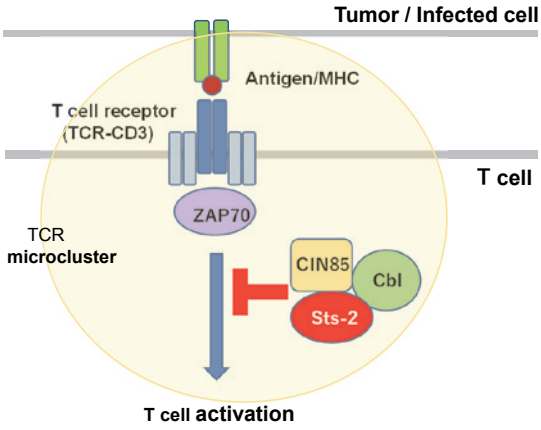
The immune system has mainly been investigated using mouse models. However, there are several distinct and critical differences between mouse and human immune systems. Therefore, human immunology research is indispensable; however, there are several technical limitations in this area. In order to overcome this obstacle, we believe that genetics is invaluable, 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 (eQTL), regulating the expression levels of genes in a cell type-specific manner.

We conducted a cell type-specific eQTL analysis on five immune cell populations ($CD4^+$ T cells, $CD8^+$ T cells, B cells, NK cells, and monocytes) from 105 healthy Japanese volunteers (Ishigaki K et al Nature Genetics 2017). This is one of the largest RNA-seq-based eQTL studies focusing on multiple immune cells. We successfully detected thousands of eQTL variants for each cell population, and deposited the main results of our eQTL analyses into a National Bioscience Database Center (NBDC). We also developed an original method of integrating eQTL data with pathological pathway analyses.

However, immune responses are carried out by the interactions between further differentiated and functionally distinct lymphocyte subsets. Therefore, we are now setting up a system to obtain nearly 20 different lymphocyte subsets from human peripheral blood mononuclear cells (PBMC) of healthy individuals (as the initial project) (Figure) and several different autoimmune diseases (as the second project). The main purpose of these projects is to elucidate the mechanisms of eQTL and underlying epigenetic status, i.e., genetic polymorphisms and gene expression in differentiated lymphocyte subsets under physiological conditions. We hope that insights gained from these studies will provide a way to control pathological processes.

Laboratory for
Cell Signaling

Team Leader: Takashi Saito



Induction of an immune response against tumors and pathogens

Figure: Negative regulation of T cell activation by the CIN85 adaptor protein
The adaptor CIN85 inhibits T cell activation by recruitment of the phosphatase Sts-2 and the ubiquitin ligase Cbl into the TCR microcluster upon TCR stimulation.

The objective of our team is to determine the molecular mechanisms of T cell activation, differentiation, and function. Toward this goal, we have studied basic mechanisms such as antigen recognition, T cell activation and differentiation, and regulation of function from a signaling perspective. Processes of activation at the single cell level by molecular imaging and T cell development/homeostasis within clonal populations are both being investigated.

Our finding that TCR-microclusters (MC) initiate T cell activation led us to analyze the dynamic recruitment/assembly of signaling molecules at the immune synapse. Using approaches similar to those used in our studies of CTLA4 and PD-1, the dynamic regulation of other inhibitory co-stimulation receptors are being analyzed. These inhibitory receptors colocalized with the TCR-MC upon TCR stimulation to mediate inhibition of T cell activation. Our analyses provide a dynamic view of signal regulation and determine their inhibitory mechanism.

We have analyzed several molecules that are highly expressed upon T cell activation as possible targets to modulate T cell activation and function. CRTAM was originally cloned as an adhesion receptor, but is now found to play a critical role in determining the $CD4^+$ CTL lineage. The TCR downstream signaling adaptor CIN85 is now found to mediate negative regulation of T cell activation by recruiting the phosphatase Sts-2. CIN85-Sts-2 is recruited to the TCR-MC and may represent a new inhibitory pathway (Figure 1). The function of the innate-sensor STING in T cells was analyzed since it is highly expressed in T cells. STING activation induced growth inhibition and type I-IFN production in T cells. We showed that STING activation in T cells contributes to anti-tumor immunity.

Our ultimate aim is to elucidate the onset of and to modulate T cell function/activation to prevent immune diseases such as autoimmunity and allergic inflammation. We have analyzed the function of autoimmune-related phosphatases PTPN22 and PTPN2. Their deficiency *per se* did not induce autoimmunity; KO mice showed enhanced activation and an increase in effector/memory T cells. Imaging analysis and MS analysis of PTPN-associated molecules will be used to identify the inhibitory mechanisms that maintain homeostasis.

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)

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

Invited presentations

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

Saito T. "Innate signal regulation in T cell activation" German-Japan Immunology Meeting (Shizuoka, Japan) December, 2017

Saito T, Imanishi T. "Regulation of T cell activation and function by innate signals – STING activation in T cells induce growth arrest and IFN production" FASEB Summer Research conference: Signal Transduction in the Immune System (Colorado, USA) June, 2017

Saito T. "Microsynapse composed of micro-adhesion ring surrounding TCR micro cluster is essential for T cell activation" EMBO conference (Siena, Italy) September, 2016

Laboratory for Lymphocyte Differentiation

Team Leader: Tomohiro Kurosaki

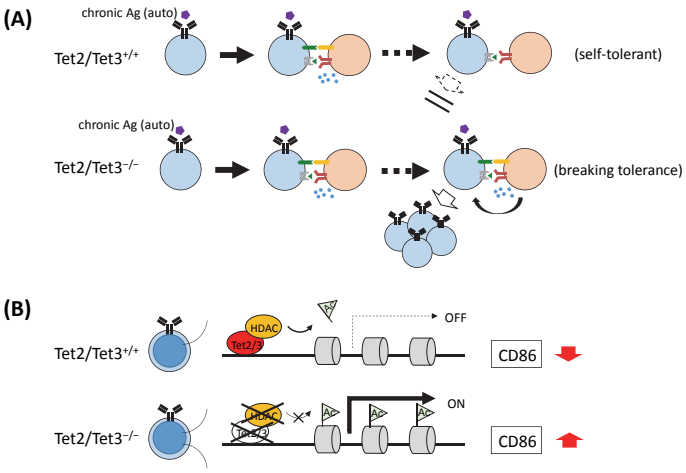


Figure: Tet2 and Tet3 contribute to peripheral B cell tolerance.
(A) CD86 is normally upregulated on activated B cells, but in the case of chronic antigen stimulation, e.g., by autoantigen, CD86 upregulation ceases. Therefore, T cell activation and subsequent B cell proliferation are terminated (self-tolerant state). However, in the absence of Tet2 and Tet3, such chronic antigen stimulation cannot downregulate CD86 expression, thereby changing the B cell fate from peripheral tolerance to proliferation.
(B) Tet2 and Tet3 normally recruit HDAC to the *CD86* locus in the chronic state, thereby dampening transcription of *CD86*.

Recent Major Publications

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

Inoue T, Moran I, Shinnakasu R, Phan TG, Kurosaki T. Generation of memory B cells and their reactivation. ***Immunol Rev*** 283, 138-149 (2018)

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 (2018)

Invited Presentations

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

Kurosaki T. "Fate decision of germinal center B cells" International Symposium on B cells (Shanghai, China) December, 2018

Kurosaki T. "Regulation of B cell tolerance by epigenetic factors" Cluster Science Days 2018 and the 10th international symposium of IFReC (Bonn, Germany) November, 2018

Kurosaki T. "Fate decision of germinal center B cells" Japanese-German Immunology Workshop (Ettal, Germany) September, 2018

Kurosaki T. "Fate decision of germinal center B cells" Keystone Symposia, B Cells: Mechanisms in Immunity and Autoimmunity (Dresden, Germany) June, 2018

As B cell intrinsic tolerance mechanisms, it is known that even modest alterations in B cell signaling thresholds can break tolerance, promoting autoimmunity in the appropriate environmental context. In addition to the B cell signaling components, the contribution of epigenetic factors has been proposed. One of the previously observed epigenetic abnormalities associated with autoimmune diseases is altered DNA methylation, prompting us to examine the roles of Tet proteins in B cell tolerance.

We found that specific deletion of translocation proteins Tet2 and Tet3 in B cells using CD19-Cre resulted in spontaneous hyper T cell activity, autoantibody production, and lupus nephritis. Treatment with anti-CD20 or anti-CD4 depletion antibodies ameliorated aberrant activation of B cells or CD4$^+$ T cells, respectively, suggesting the existence of a positive feed-forward loop between activated B and T cells. Mechanistically, we demonstrated that self-tolerant B cells express low levels of CD86 (B7.2), whereas ablation of Tet2/Tet3 resulted in upregulation of CD86, thereby switching the B cell fate from peripheral tolerance to proliferation through T-B interactions. We also found that Tet2 and Tet3 recruited HDAC2, thereby repressing transcription of CD86 in self-tolerant B cells. Together, our data demonstrate that Tet2/Tet3 contribute to peripheral B cell tolerance by suppressing CD86 expression in a chromatin-modification manner (Figure).

To address the function of Tet2 and Tet3 in normal immune responses, we acutely deleted Tet2/Tet3 in B cells. We found that the initial proliferative response was normal, even in the absence of Tet2 and Tet3, whereas the deficient B cells could not differentiate into germinal center (GC) B cells or plasma cells. Because the transcription factors Bcl6 and IRF4 are known to be critical for GC B cell or plasma cell differentiation, respectively, our data demonstrate the importance of Tet2/Tet3 in the induction of Bcl6 and IRF4 expression. We are now analyzing how Tet2/Tet3 regulates *Bcl6* and *IRF4* transcription.

Laboratory for Transcriptional Regulation

Team Leader: Ichiro Taniuchi

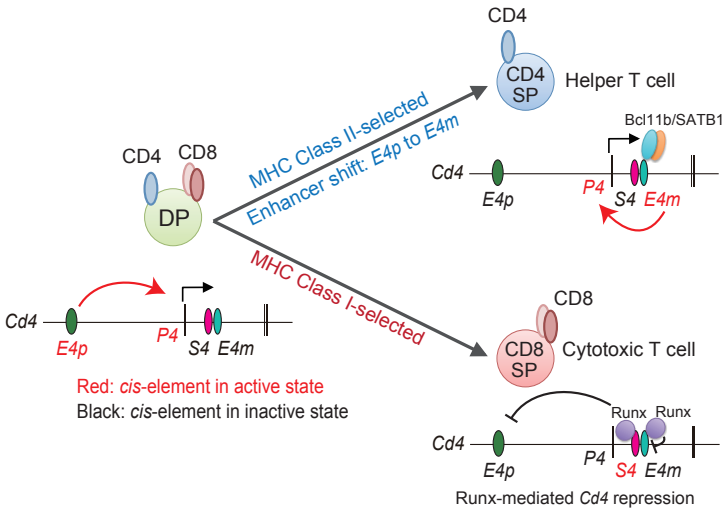


Figure: Model for *Cd4* gene regulation
Activation of the *E4p* enhancer is critical for induction of CD4 expression during transition from the DN to DP stage. During maturation of MHC class II-selected thymocytes, activation of the *E4m* enhancer, at least in part by Bcl11b and SATB1 binding, is essential to establish stable and inheritable CD4 expression. Runx/Cbfβ complexes suppress *E4m* activity in MHC class I-selected thymocytes in both a *Cd4* silencer *(S4)*-dependent and -independent fashion, leading to establishment of a heritable silenced state at the *Cd4* locus.

Recent Major Publications

Miyamoto C, Kojo S, Yamashita M, Moro K, Lacaud G, Taniuchi I, Ebihara T. Runx/Cbfβ complexes protect group 2 innate lymphoid cells from exhaustion during allergic airway inflammation. ***Nat Commun*** 10, 447 (2019)

Kojo S, Yasmin N, Muroi S, Tenno M, Taniuchi I. Runx-dependent and silencer-independent repression of maturation enhancer in the Cd4 gene. ***Nat Commun*** 9, 3593 (2018)

Tenno M, Kojo S, Lawir D-F, Hess I, Shiroguchi K, Ebihara T, Endo T, Muroi S, Satoh R, Kawamoto H, Boehm T, Taniuchi I. Cbfb2 controls differentiation of and confers homing capacity to pre-thymic progenitors. ***J Exp Med*** 215, 595-610 (2018)

Invited presentations

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

Taniuchi I. "Gene Regulation by local and long-range chromatin loops during T cell development" Seminar at National Cancer Institute (Bethesda, USA) November, 2018

Taniuchi I. "Unraveling pathogenesis of human primary immune deficiency by mouse models" The 6th Kyoto Course on Bioinformatics for Genomic Medicine International Symposium on Disease Genomics (Kyoto, Japan) October, 2018

Taniuchi I. "Regulation of dendritic cell development by Runx factors" The 1st International Symposium on NEOSELF (Awaji, Japan) July, 2018

Taniuchi I. "Roles of Runx factors during skin immune cell development" The 67th Annual meeting of Japanese Society of Allergology (Makuhari, Japan) June, 2018

The vertebrate immune system consists of two components, innate and acquired. The acquired 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 coupled with cell fate determination programs in the nucleus by using helper versus cytotoxic lineage choice as a model in which 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 MHC class-I selected thymocytes to become cytotoxic-lineage T cells. We identified Bcl11b and SATB11 as novel *Thpok* silencer binding proteins. Our current results using site-specific chromatin-immune precipitation (ChIP) technology revealed that a cytotoxic-lineage-specific higher-ordered chromatin structure is formed at the *Thpok* locus through mechanisms that depend on the last zinc finger motif in the Bcl11b protein.

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 reveal 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 studies revealed novel roles of Runx/Cbfβ complexes in regulating differentiation of dendritic cell subsets and innate lymphoid cell (ILC) subsets. Our studies also contributed to understanding the roles of two RNA splice variants, Cbfβ1 and Cbfβ2, generated from the *Cbfb* gene, each of which differs only at the C-terminal end.

Laboratory for
Immune Cell Systems

Team Leader: Shigeo Koyasu

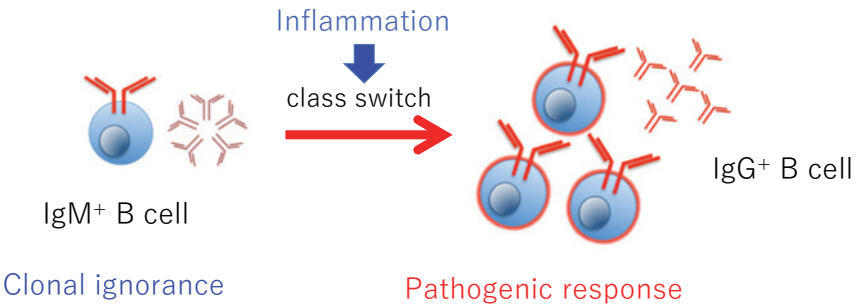


Figure: Tolerance break by immunoglobulin class switch recombination
B cells bearing self-reactive IgM are ignored by self-tolerance mechanisms (left: clonal ignorance). However, strong inflammation induces class switching of IgM to IgG, which binds the keratinocyte cell surface and results in the onset of pemphigus vulgaris (right: pathogenic response)

Recent Major Publications

Kabata H, Moro K, Koyasu S. The group 2 innate lymphoid cell (ILC2) regulatory network and its underlying mechanisms. ***Immunol Rev*** 286, 37-52 (2018)

Vivier E, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, Koyasu S, Locksley RM, McKenzie ANJ, Mebius RE, Powrie F, Spits H. Innate lymphoid cells: ten years on. ***Cell*** 174, 1054-1066 (2018)

Namkoong H, Ishii M, Fujii H, Yagi K, Asami T, Asakura T, Suzuki S, Hegab AE, Kamata H, Tasaka S, Atarashi K, Nakamoto N, Honda K, Kanai T, Hasegawa N, Koyasu S, Betsuyaku, T. Clarithromycin expands CD11b+Gr-1+ cells to ameliorate shock and post-influenza pneumonia. ***PLoS Pathog*** 14, e1006955 (2018)

Invited Presentations

Koyasu S. "Tolerance break by class switch recombination for auto-antibody production" The 7th FIMSA Congress (Bangkok, Thailand) November, 2018

Koyasu S. "Innate lymphoid cells, a new type of lymphocytes without antigen receptors" Interdisciplinary Science Conference (Tainan, Taiwan) May, 2018

The prevention of autoimmunity involves multiple and complex processes to maintain self-tolerance. Mechanisms that break tolerance, leading to autoimmune diseases, are largely unknown. In collaboration with the Department of Dermatology of Keio University School of Medicine, we employed as a model pemphigus vulgaris, an autoantibody-mediated skin blistering disease induced by IgG autoantibodies against desmoglein 3, a desmosomal cell adhesion molecule expressed in the skin and mucous membranes. We generated a knock-in mouse whose B cells express desmoglein 3-reactive immunoglobulin. The naïve knock-in mouse did not develop any disease phenotype, although IgM-bearing B cells were not deleted and migrated into the periphery. IgM autoantibodies were produced in these mice, suggesting that B cells bearing self-reactive IgM are ignored by self-tolerance mechanisms. Immunoglobulin class switching from IgM to IgG induced in the mouse by induction of erosive dermatitis with 1-fluoro-2,4-dinitrobenzene application or by vaccinia virus infection resulted in the development of pemphigus vulgaris with acantholysis, as determined by histology and IgG deposition on the keratinocyte cell surfaces. Based on these results, we propose a novel concept that class switching of self-reactive antibodies is one mechanism for breaking tolerance, a critical step in the development of certain autoantibody-mediated autoimmune diseases.

Laboratory for
Innate Immune Systems

Team Leader: Kazuyo Moro

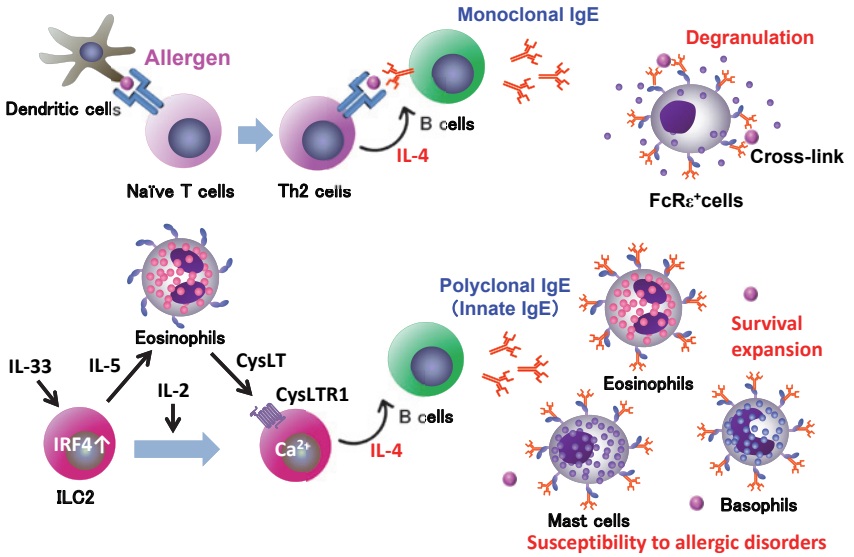


Figure: ILC2-derived IL-4 induces innate IgE production from B1 cells

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.

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 a goal to establish new therapies for allergic disorders by targeting ILC2. While it 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 production of innate IgE induced by IL-4. We previously reported a negative feedback mechanism for 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.

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)

Koga S, Hozumi K, Hirano KI, Yazawa M, Terooatea T, Minoda A, Nagasawa T, Koyasu S, Moro K. Peripheral $PDGFRalpha^{+}gp38^{+}$ mesenchymal cells support the differentiation of fetal liver-derived ILC2. ***J Exp Med*** 215, 1609-1626 (2018)

Morita H, Moro K, Koyasu S. Innate lymphoid cells in allergic and nonallergic inflammation. ***J Allergy Clin Immunol*** 138, 1253-1264 (2016)

Invited presentations

Moro K. "IL-4 Production of Group 2 Innate Lymphoid Cells" VIB Conference series; Type 2 immunity in homeostasis-and-disease (Bruges, Belgium) February, 2019

Moro K. "Role of Group 2 innate lymphoid cells in idiopathic interstitial pneumonias" The 3rd International Conference on Innate Lymphoid Cells (ILC2018) (Tokyo, Japan) November, 2018

Moro K. "Discovery of group 2 innate lymphoid cells" 5th European Congress of Immunology (Amsterdam, Netherlands) September, 2018

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

Moro K. "Suppression mechanism of Group 2 innate lymphoid cells" FASEB Science Research Conferences: IgE and Allergy, 50 Years & Onward (West Palm Beach, USA) September, 2016

Laboratory for
Immune Homeostasis

Team Leader: Taishin Akiyama

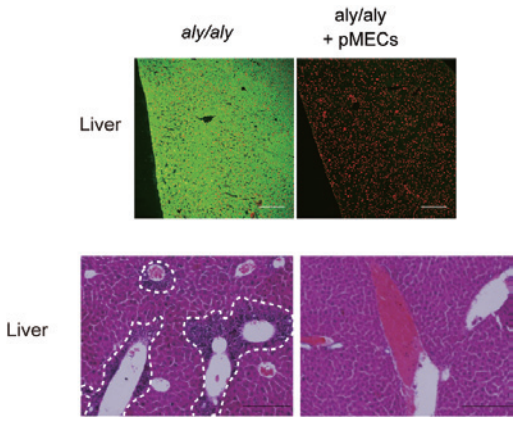


Figure: Introduction of WT pMECs suppressed the onset of autoimmunity provoked by mTEC dysfunction.
Introduction of pMECs into the thymus successfully prevented autoimmunity in aly/aly mice, which have no Aire-expressing mTECs. Upper panels show detection of autoantibody against liver cells. Lower panels show the inflammatory infiltrates into the liver, both of which are eliminated in the mice receiving pMECs.

Recent Major Publications

Horie K, Kudo T, Yoshinaga R, Akiyama N, Sasanuma H, Kobayashi TJ, Shimbo M, Jeon H, Miyao T, Miyauchi M, Shirakawa M, Shiba D, Yoshida N, Muratani M, Takahashi S, Akiyama T. Long-term hindlimb unloading causes a preferential reduction of medullary thymic epithelial cells expressing autoimmune regulator (Aire). ***Biochem Biophys Res Commun*** 501, 745-75 (2018)

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)

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

Invited Presentations

Akiyama T. "Epithelial cells controlling immunological self-tolerance in the thymus" The 2nd RIKEN – McGill Symposium (Yokohama, Japan) February, 2018

Akiyama T. "Differentiation program of thymic epithelial cells essential for preventing onset of autoimmune disease" RIKEN IMS-Stanford Joint Symposium (Yokohama, Japan) May, 2018

Akiyama T. "Dependence of homeostatic maturation of thymic antigen presenting cells on TNF receptor family signaling" The RIKEN IMS-JSI International Symposium on Immunology (Tokyo, Japan) June, 2018

Approximately 5%-10% of the world population is affected by autoimmune diseases. Understanding mechanisms to suppress the onset of autoimmunity is important for developing therapeutic and preventive strategies for autoimmune diseases.

The thymus contributes to suppression of autoimmunity by eliminating self-reactive T cells and generating regulatory T cells. Self-antigen presenting cells (APCs) in the thymic medulla are necessary for this thymic function. We aim to uncover molecular mechanisms regulating development and functions of thymic APCs and to address the significance of these mechanisms in suppressing autoimmune disease onset.

Medullary thymic epithelial cells (mTECs) have the unique property of "promiscuously" expressing different tissue-specific self-antigens (TSAs, e.g., insulin and C-reactive protein), thereby removing TSA-reactive T cells and generating regulatory T cells. The autoimmune regulator (Aire) is expressed in mTECs and controls expression of certain TSAs. Importantly, dysfunctional Aire mutations provoke the human autoimmune disease autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). A recent study further showed involvement of Fez family zinc finger 2 (Fezf2) in TSA expression.

Aire and Fezf2 reportedly control expression of 30%-40% of TSAs in mTECs. Thus, expression of many TSAs is regulated by Aire-independent and Fezf2-independent mechanisms; however, the mechanisms are largely unknown. Moreover, even the underlying mechanisms by which Aire and Fezf2 control "promiscuous" TSA expression still remain elusive. One of our goals is to elucidate molecular and cellular mechanisms regulating the promiscuous TSA expression in mTECs.

mTECs seem to originate from stem/progenitor cells common to thymic cortical TECs. However, the identification of fetal and adult stem/progenitor cells is a controversial area. Moreover, mechanisms for maintaining mTECs in adults remain unclear. We are also attempting to identify molecular and cellular mechanisms regulating mTEC differentiation and mTEC recovery after damage.

Laboratory for
Immune Crosstalk

Team Leader: Hilde Cheroutre

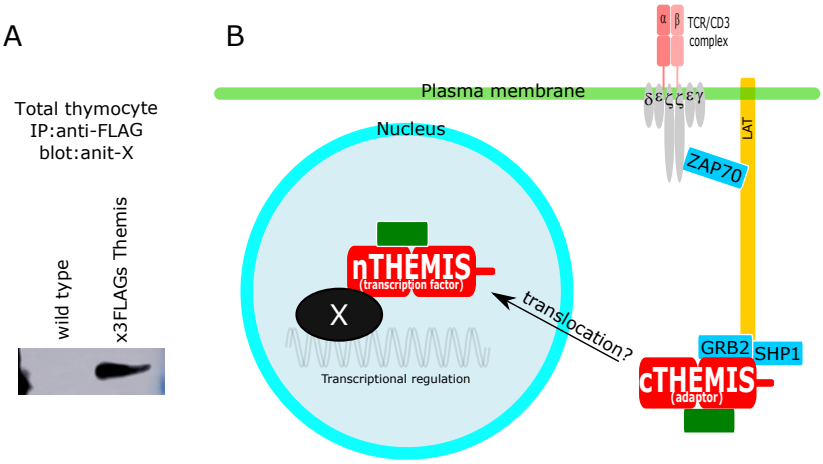


Figure: Dual function of Themis
(A) Themis binds a T cell specific transcriptional factor X. We pulled down Themis protein using FLAG-tag-knock-in Themis thymocytes and anti-FLAG antibody and found that it interacts with T cell specific transcriptional factor X. Wild type thymocytes were used as a negative control. (B) Our model of Themis function. As an adaptor molecule, cytosolic Themis becomes phosphorylated upon TCR stimulation and recruits SHP1, which down-regulates TCR signaling. These activation events also result in the nuclear translocation of Themis. In the nucleus, Themis functions as a transcription factor and, through interaction with other nuclear transcription factors, modulates the transcription profile of the signaled thymocyte or mature T cell.

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)

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

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

Invited presentations

Cheroutre H. "Dietary Antigens Induce the Antipode of Immune Tolerance at the Mucosal Epithelial Barrier of the Intestine." Chiba University-UCSD symposium. (San Diego, USA) February, 2019

Cheroutre H. "A Long (non-coding RNA) Stretch in CD4 plasticity" Genentech, 2018-19 Immunology and Infectious Disease seminar series at Genentech, Inc. (San Francisco, USA) December, 2018

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

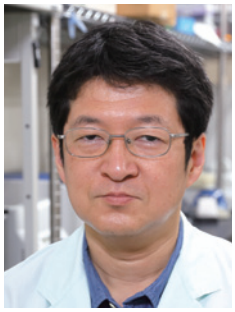
Cheroutre H. "Give-and-Take Relation between TGFbeta and the Gut Environment Drives the CD4 CTL Fate." Keystone Symposia: TGF-β in Immunity, Inflammation and Cancer (Taos, USA) January, 2017

Cheroutre H. "Food for Thought – Mucosal Immune Protection and Regulation Controlled by the Diet" The Korean Association of Immunologists – Academy of Immunology and Microbiology Joint Conference (Seoul, Korea) November, 2016

We identified *Themis* as an essential gene for T cell development and function. Many GWAS analyses of inflammatory diseases, including celiac disease, multiple sclerosis, and atopic dermatitis, have shown an association with the *THEMIS* gene locus. Themis is reported to function as an adaptor and modulate T cell receptor (TCR) signal strength together with Grb2 and SHP1, and Themis-deficiency causes 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 Themis mutant mice that express Themis either exclusively in the cytoplasm or solely in the nucleus, by either deleting the nuclear localization signal (NLS) sequence or by adding the SV40 NLS to Themis, respectively. Surprisingly, in both mutant mice, thymic development is impaired, similar to Themis germ line knock-out mice, suggesting that both cytosolic and nuclear Themis proteins are critical for thymocyte development. Since Themis is also expressed in mature T cells in the periphery, it is likely that it continues to play essential roles for the activation, function, and/or regulation of peripheral T cells. Furthermore, we identified a T cell specific transcription factor as a Themis binding partner in the nucleus, indicating that transcriptional regulation is one Themis function 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.

Besides Themis, additional research interests of the Immune Crosstalk lab are focused on other molecules, including the Pre-TCR and the retinoic acid receptors, which influence the communication between environmental signals and gene transcription programs that ultimately determine the fate of developing and mature T cells in health and disease.



Laboratory for
Inflammatory Regulation

Team Leader: Takashi Tanaka

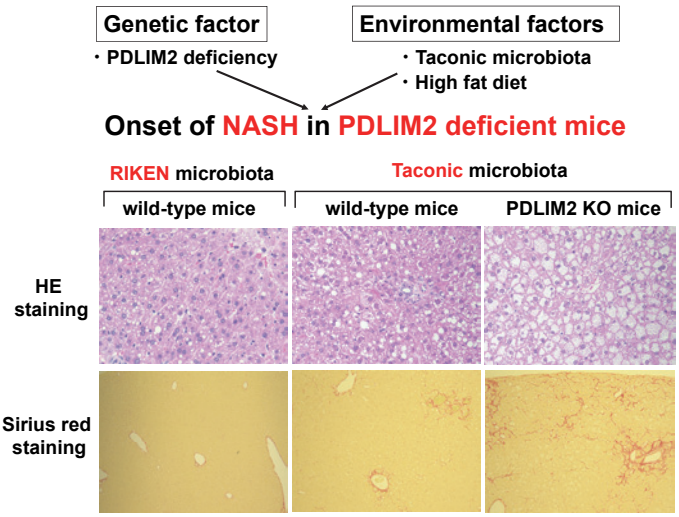


Figure: Microbiota-dependent development of NASH in PDLIM2-deficient mice
Representative Hematoxylin and Eosin (HE) and Sirius Red-stained liver histopathology in wild-type and PDLIM2-deficient mice. Only PDLIM2-deficient mice with a Taconic microbiota develop NASH, characterized by a massive accumulation of lipid droplets in the hepatocytes, infiltration of inflammatory cells, and enhanced fibrosis (detected as red areas by Sirius Red staining).

Recent Major Publications

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

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

Tanaka T. Clarification of the molecular mechanisms that negatively regulate inflammatory responses. In: Miyasaka M, Takatsu K. (eds.), ***Chronic Inflammation, Mechanisms and Regulation***, Tokyo, Japan: Springer Japan, pp.109-118 (2016)

Invited presentations

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

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

Tanaka T. "The roles of LIM protein family in the regulation of inflammatory responses" The 45th Annual Meeting of the Japanese Society for Immunology, S10. Dynamic control of inflammatory signaling by organelle in DC/macrophages (Okinawa, Japan) December, 2016

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

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

Laboratory for
Cytokine Regulation

Team Leader: Masato Kubo

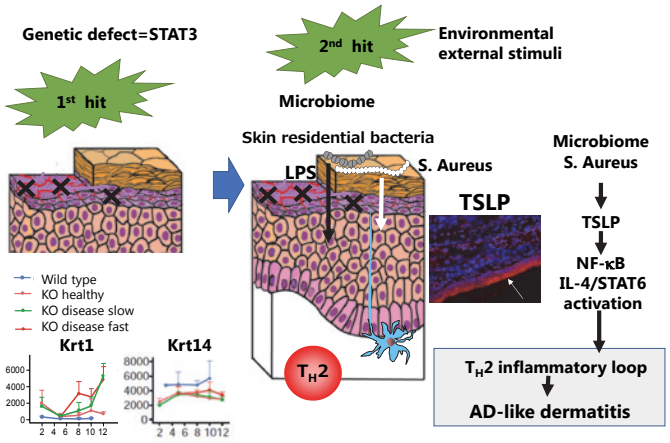


Figure: The combination of a genetic defect and external environmental stimuli are essential for AD disease onset

Recent Major Publications

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

Dominguez-Huttinger E, Christodoulides P, Miyauchi K, Irvine AD, Okada-Hatakeyama M, Kubo M, Tanaka RJ. Mathematical modeling of atopic dermatitis reveals "double-switch" mechanisms underlying 4 common disease phenotypes. ***J Allergy Clin Immunol*** 139, 1861-1872 e7 (2017)

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

Invited presentations

Kubo M. "Th2 cytokines in allergic responses; from Th2 to ILC2" Cytokine 2018 (Boston, USA) October, 2018

Miyauchi K, Kubo M. "Virus replication drive mucosal antibody against heterologous influenza viruses" The 46th Annual Meeting of the Japanese Society for Immunology (JSI) (Sendai, Japan) December, 2017

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

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

Kubo M. "Role of T follicular helper (TFH) in humoral immunity" The 13th International Workshop on Autoantibodies and Autoimmunity (IWAA2016) (Kyoto, Japan) October, 2016

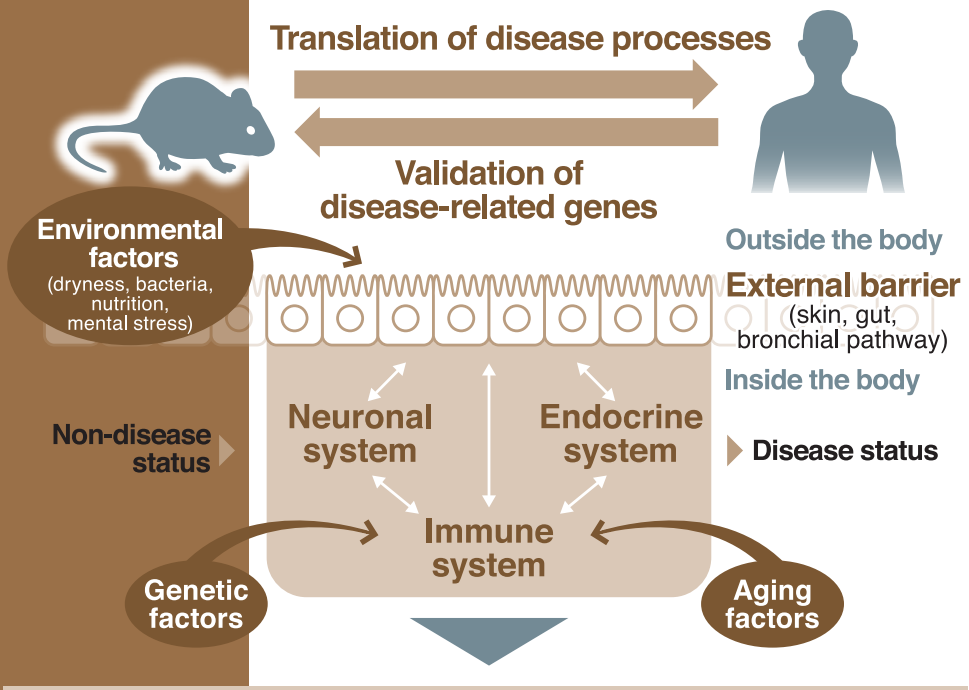
In the last three years, we have focused on the role of T cells in humoral responses to influenza virus and that of cytokine signals in atopic dermatitis.

The adaptive immune system has evolved to mount different types of responses that are matched to the type of invading pathogen. Effector $CD4^+$ T cells are broadly divided into two: T follicular helper (T_{FH}) cells and non-T_{FH} effector cells, including type I helper T (T_H1), T_H2, and T_H17 cells. In the response to Influenza A virus (IAV) in mice, we found that IgG2 antibodies predominated after vaccination with inactivated virus and were responsible for protective immunity to lethal challenge with IAV. Surprisingly, this response emerged even in mice that lacked T_{FH} cells and germinal centers (GC). T_H1 cell-derived interferon-γ (IFN-γ) was essential for the high titers of IgG2 protective antibodies. These results indicated that vaccination with inactivated flu virus is effective for generating neutralizing IgG2 antibodies that protect against the IAV strain used in the vaccine.

In contrast, we found that nasal administration of live virus preferentially induced broadly reactive antibodies. The live-virus vaccine induced high titers of neutralizing IgG antibody that could recognize HA antigens on different viral strains. This response largely depended on T_{FH} cells and GC, and particularly IL-4 derived from T_{FH} cells played an important role in GC formation. Therefore, live-virus vaccination is a useful strategy for producing effective broadly reactive IgG antibody.

Atopic dermatitis (AD) is a common chronic skin disease. We found that *Stat3*$^{flox/flox}$ K5-cre mice were a suitable T_H2-dependent AD-like dermatitis model. Based on multidimensional transcriptome comparisons between asymptomatic and diseased mice, we found that AD onset was dependent on thymic stromal lymphopoietin (TSLP) and IL-4 receptor signaling. *Stat3* deficiency contributed to alterations in the skin barrier structure at an early age and allowed an increase in the threshold of NFkB activation and TSLP induction. Therefore, the STAT3 mouse model has been valuable in identifying TSLP as a prognosis marker for AD onset caused by the T_H2 inflammatory loop.

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

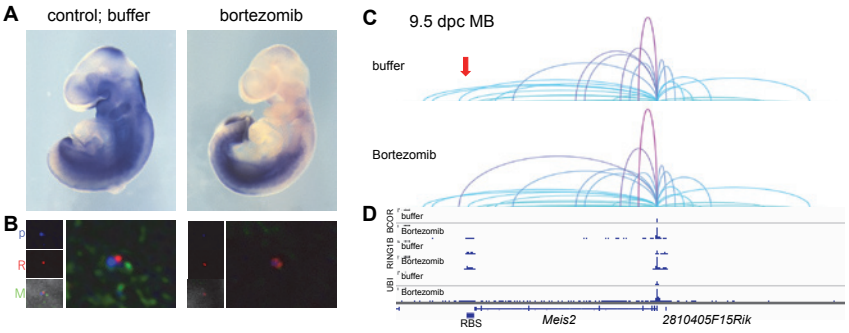


Figure: Effect of a proteasome inhibitor (PI) on Meis2 activation during midbrain development
(A) Meis2 gene expression profiles in mice with or without PI treatment. Meis2 activation failed in mice treated with a PI. (B) Immuno-FISH of Meis2 promoter (blue), RBS (red), and MEIS2 protein (green). The promoter and RBS are separated in the cells with MEIS2 expression, while they stay together in the cells without MEIS2. (C) 4C-seq analysis of mice with or without PI treatment using the Meis2 promoter as bait. Bortezomib-treated midbrain chromatin exhibited strong interaction between the promoter and RBS. (D) ChIP-seq comparison. PI-treated midbrain showed higher accumulation of BCOR, RING1B, and ubiquitylated protein at the promoter and RBS.

Recent Major Publications

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

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

Sharif J, Endo TA, Nakayama M, Karimi MM, Shimada M, Katsuyama K, Goyal P, Brind'Amour J, Sun M-A, Sun Z, Ishikura T, Mizutani-Koseki Y, Ohara O, Shinkai Y, Nakanishi M, Xie H, Lorincz MC, Koseki H. Activation of Endogenous Retroviruses in Dnmt1-/- ESCs Involves Disruption of SETDB1-Mediated Repression by NP95 Binding to Hemimethylated DNA. ***Cell Stem Cell*** 19, 81-94 (2016)

Invited presentations

Koseki H. "Induced activation of Polycomb-repressed genes in mice" The European Molecular Biology Laboratory (EMBL) (Heidelberg, Germany) August, 2018

Koseki H. "Polycomb in development" Cold Spring Harbor Asia (Suzhou, China) April, 2018

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

Koseki H. "Polycomb in transcriptional phase transition of developmental genes" Mini Symposium, Genetic Control of Mouse embryonic Development at Hubrecht Institute (Utrecht, the Netherlands) June, 2016

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

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

In the epigenetics project, we are focusing on understanding how CpG island (CGI) promoters are linked with enhancers and how epigenetic inheritance is maintained after DNA replication. Particular emphasis has been placed on epigenetic regulation mediated by the combinatorial actions of Polycomb group (PcG) and DNA methylation mechanisms.

A large part of our 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 the 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 started a study to apply iPSC technology for human immunology research and therapeutic development. The core facility for iPSC research is engaged in developing efficient protocols to reprogram various lymphocytes and induce differentiation of iPSCs into lymphoid lineage cells. We are particularly engaged in generation of iPSC-derived NKT cells toward their clinical use for cancer therapy and are close to initiating a Phase I clinical study to approve their safety. This research is partly supported by AMED.

No matter what the human disease, it is becoming important to find a way to stratify patients in order to provide the best option of therapeutic intervention. To tackle this issue, we found that atopic dermatitis (AD) is a good model because of its clinical diversity in both symptoms and therapeutic responses. Our approach is to establish mathematical models for AD based on mouse AD models induced by various genetic perturbations and then to extrapolate the model into humans, mainly by using marker genes and protein expression in patients.

Laboratory for
Intestinal Ecosystem

Team Leader: Hiroshi Ohno

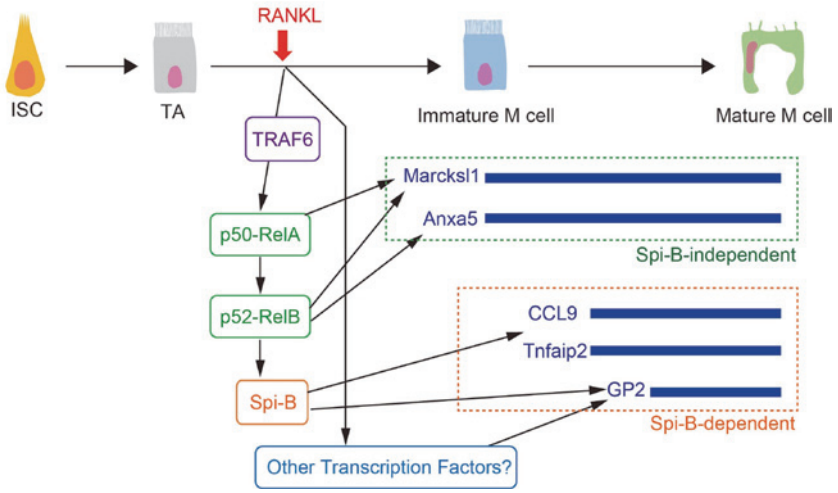


Figure: Updated model of M cell differentiation. RANKL activates canonical NF-κB through TRAF6. The canonical NF-κB transcription factor (p50-RelA) is critical for the activity of the noncanonical NF-κB transcription factor (p52-RelB), which in turn largely contributes to the expression of Marcksl1, one of the Spi-B-independent M cell markers. p52-RelB directly binds the *Spib* promoter and is responsible for Spi-B expression. On the other hand, neither canonical nor noncanonical NF-κB alone is sufficient to induce the final differentiation of M cells with expression of GP2. As yet unidentified transcription factor(s) activated by RANKL are required for the development of mature M cells. ISC: Intestinal stem cell, TA cell: Transit-amplifying cell.

Kanaya *et al.*, **J. Exp. Med** , 2018

Recent Major Publications

Kato T, Yamazaki K, Nakajima M, Date Y, Kikuchi J, Hase K, Ohno H, Yamazaki K. Oral administration of Porphyromonas gingivalis alters the gut microbiome and serum metabolome. ***mSphere*** 3, e00460-18 (2018)

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. "Obesity, Impaired Glucose Tolerance and gut microbiota" 5th International Probiotics and Prebiotics Symposium (Surabaya, Indonesia) December, 2018

Ohno H. "The role of gut microbiota and digestive diseases" Educational Lecture, Japan Digestive Disease Week 2018 (Kobe, Japan) November, 2018

Ohno H. "Host-commensal microbiota interaction" Keynote Lecture, The 25th Anual Meeting of The Japan Society for Portal Hypertension (Osaka, Japan) September, 2018

Ohno H, Miyauchi E, Ohkusa T. "Impact of smoking on the gut microbiota in IBD patients" FALK Sympoium "IBD and Liver: East Meets West" (Kyoto, Japan) September, 2018

Ohno H. "Ruminococcus-induced CD8+ regulatory T cells prevent type 1 diabetes" International Conference on Beneficial Microbes 2018 (Kuching, Malaysia) August, 2018

Enormous numbers of commensal bacteria, collectively called the gut microbiota, reside in our intestines. We do not unconditionally accept those microorganisms. The intestinal immune system somehow senses the kinds and quantity of bacteria in the gut lumen and tries to contain them. Reciprocally, the gut microbiota shape the host immune system. Furthermore, the host-gut microbiota interaction profoundly impacts our physiology and pathology. We are studying this sophisticated and complex host-gut microbiota interaction by applying an integrated omics approach, with different layers of cyclopedic analyses, including (meta)genomics, epigenomics, (meta)transcriptomics, and metabolomics. This approach is applied to understand the molecular basis for the influence on host physiology and pathology by gut microbiota in mice, as well as the impact of gut microbiota on human diseases such as infantile allergic diseases and type 2 diabetes.

To evoke immune responses against gut microbes, they 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 mainly achieved 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. FAE has a unique feature distinct from the surrounding villous epithelium, and we also study how this occurs. We are studying the function and differentiation of M cells at the molecular level. We identified M cell-specific bacterial uptake receptors that could serve as a vaccine delivery target, and we are studying this possibility.

Laboratory for
Integrative Genomics

Team Leader: Osamu Ohara

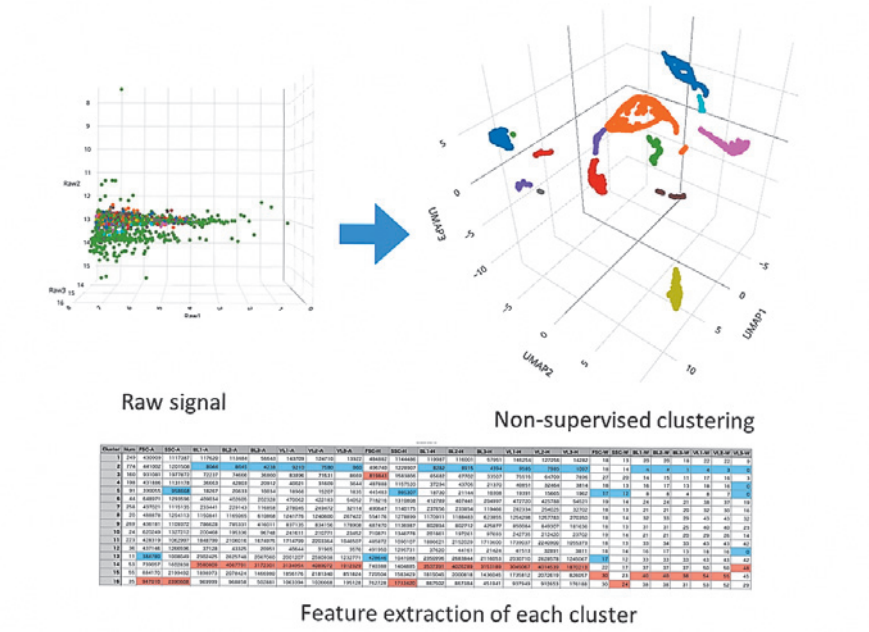


Figure: A decomposition and clustering system of multivariate data
This example shows decomposition and clustering of multi-color flow cytometry data. Several algorithm options (such as tSNE, UMAP, or PCA) are supported. The system can be installed locally and is available at https://github.com/takaho/clusterflowcell/tree/master.

Recent Major Publications

Kawashima Y, Miyata J, Watanabe T, Shioya J, Arita M, Ohara O. Proteogenomic Analyses of Cellular Lysates Using a Phenol-Guanidinium Thiocyanate Reagent. ***J Proteome Res*** 18, 301-308 (2019)

Kawashima Y, Ohara O. Development of a NanoLC-MS/MS System Using a Nonporous Reverse Phase Column for Ultrasensitive Proteome Analysis. ***Anal Chem*** 90, 12334-12338 (2018)

Shirasaki Y, Ohara O. Challenges in Developing Protein Secretion Assays at a Single-Cell Level. ***Methods Mol Biol*** 10808, 1-7 (2018)

Invited presentations

Ohara O. "Omics analyses of immune cell society for a comprehensive understanding of immune disorders" The 46th Annual Meeting of the Japanese Society of Clinical Immunology (Nagano, Japan) November, 2018

Ohara O. "Quality consideration in NGS" The 6th Asian Congress for LSD Screening (Tokyo, Japan) August, 2018

Ohara O. "Technical challenges for newborn screening" The 121st Annual Meeting of the Japan Pediatric Society (Fukuoka, Japan) April, 2018

The mission of our laboratory was originally to serve as a gateway to genomics for immunologists. However, the situation has dramatically changed in the past 10 years. Because genomics has become a popular approach, particularly when we tackle complex problems in biomedical sciences, the actual research activities of our team now are now three-pronged into the following categories: 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. Because of the increasing need for "omics" analyses in various medical science fields, this category has become the biggest research activity of my laboratory in recent years.

However, besides collaborative research and central support, we certainly keep in mind that technology development is another important mission of my laboratory. For this purpose, we consider "Integration" of omics data as a key word, and, thus, our technology development is focused in two directions: one is integration of different omics technologies and the other is linking bulk data with data at single-cell resolution. Along these lines, we developed some new methods for multi-omics analyses and implemented some newly emerging technologies in the center. We have also contributed to enhancement of bioinformatics analysis power in the center because data analyses play a crucial role in multi-omics approaches. For example, we devised a simple bioinformatics analysis tool for dimension reduction of multivariate data on a personal computer in our collaborating laboratories. The Figure shows an example of dimension reduction of multi-color FACS data. As more data become available in terms of volume and types, the more critical will be the setting of the data analysis pipeline in the center. In collaboration with the Medical Sciences Innovation Hub program (MIH, http://www.riken.jp/en/research/labs/mih/), our laboratory is working for this purpose.

Laboratory for
Mucosal Immunity

Team Leader: Sidonia Fagarasan

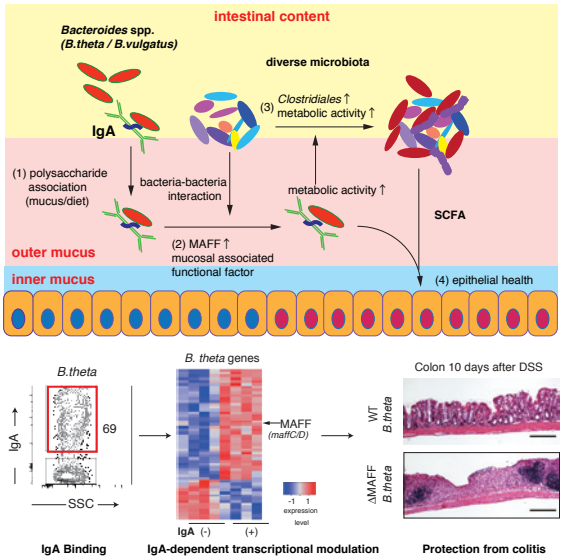


Figure: A schematic representation of how IgA binding to Bacteroides species impacts its localization and metabolic reprogramming contributing to symbiosis with Firmicutes species and fitness of the epithelial barrier

Understanding the role of IgA in shaping gut microbiota

Our group has obtained over the years robust evidence that the adaptive immune system controls the growth and distribution of commensals within the intestinal lumen. We demonstrated that mucosal IgA is required for maintaining diverse and balanced communities of commensal bacteria, and that such IgA production is highly controlled by the expression of T cell signaling receptors (PD-1) and transcription factors (Foxp3, Bcl6) of T cells. However, how exactly IgA functions in symbiotic process is not well understood. Our recent work showed a novel mechanism by which heavily glycosylated IgA efficiently coats bacterial surfaces, especially Bacteroidetes sp., thereby modulating bacterial genes within the mucus environment. We provisionally named the set of genes upregulated in the presence of IgA as Mucus-Associated Functional Factors (MAFF). Importantly, glycosylated IgA and MAFF upregulation by Bacteroidetes sp. promoted symbiotic interactions between different bacterial phyla, like Firmicutes, and regulated the composition and metabolic function of the overall microbial community (Figure). This work was featured by the JEM among the ten best papers published in 2018.

Understanding how activation of the immune system shifts metabolites, leading to neuro-endocrine disorders in mouse

We revealed novel and unexpected effects of immune system activation on systemic metabolic homeostasis with far-reaching effects on major physiological systems of the body. We demonstrated that persistent T cell activation resulted in drastic systemic metabolic changes, including depletion of serum amino acids. Furthermore, we linked the depletion of tyrosine and tryptophan in the periphery to reduced synthesis of brain monoamine neurotransmitters such as dopamine and serotonin. We showed that such biochemical alterations caused abnormal behavior in mice, dominated by anxiety and enhanced fear responses.

Recent Major Publications

1. 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)
2. Miyajima M, Zhang B, Sugiura Y, Sonomura K, Guerrini MM, Tsutsui Y, Maruya M, Vogelzang A, Chamoto K, Honda K, Hikida T, Qin H, Sanuki R, Suzuki K, Furukawa T, Ishihama Y, Matsuda F, Suematsu M, Honjo T, Fagarasan S. Metabolic shift induced by systemic activation of T cells in PD-1 deficient mice perturbs brain monoamines and emotional behavior. ***Nat Immunol*** 18, 1342-1352 (2017)
3. Chamoto K, Chowdhury PS, Kumar A, Sonomura K, Matsuda F, Fagarasan S, Honjo T. Mitochondrial activation chemicals synergize with surface receptor PD-1 blockade for T cell-dependent antitumor activity. ***Proc Natl Acad Sci U S A*** 114, E761-E770 (2017)

Invited presentations

Fagarasan S. "Excessive T cell activation in the absence of PD-1 affects behavior". Cold Spring Asia meeting on inflammation: Basic Mechanisms & Relevant Diseases (Suzhou, China) December, 2017

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

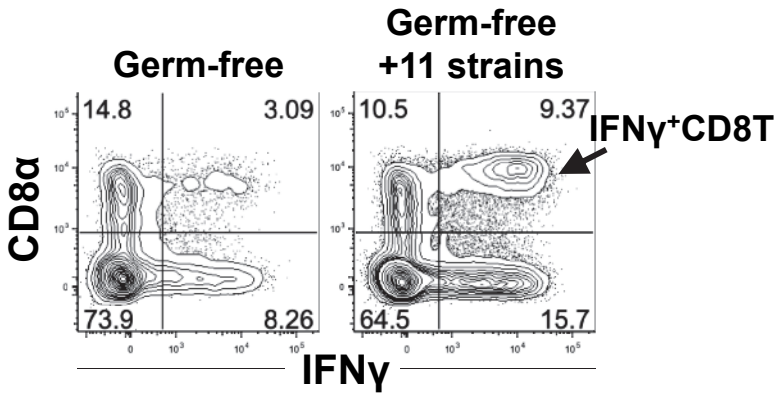
Fagarasan S. "Involvement of PD-1 in antibody diversification and body homeostasis" NHRI/IBMS International conference on inflammation and disease (Taipei, Taiwan) February, 2017

Fagarasan S. "Involvement of T cells in antibody diversification and shaping of the microbial landscape" Immune Profiling in Health and Disease 2016 (The Nature Conference) (Seattle, USA) October, 2016

Fagarasan S. "On germinal centers, IgA synthesis and the intestinal ecosystem" International Congress of Immunology ICI 2016 (Melbourne, Australia) August, 2016

Laboratory for
Gut Homeostasis

Team Leader: Kenya Honda



(gated on CD3ε+ TCRβ+ cells in colon LP)

Figure: Germ-free mice inoculated with human-derived 11 commensal bacterial strains show a large accumulation of IFNγ-producing CD8 T cells in the colonic lamina propria.

There are multiple immune cell subsets residing in the intestine, many of which may be correlated with the diversity of the microbiota. The Laboratory for Gut Homeostasis has been aiming to identify microbial consortia responsible for regulation of specific branches of the host immune system and to understand the underlying mechanisms. Our long-term goal is to establish strategies to treat/prevent pathological conditions such as inflammatory bowel disease (IBD), allergy, cancer, and obesity by manipulation of the microbiota.

Previously, we succeeded in isolating 17 human gut-derived clostridial strains that together are able to induce intestinal CD4+Foxp3+ regulatory T (Treg) cells, in part through production of short chain fatty acids. Oral introduction of these 17 strains in mouse models reduced the disease severity of allergy, colitis, and graft versus host disease (GVHD). In addition to Treg-inducing strains, we isolated and identified *Klebsiella* strains from saliva samples of IBD patients. These *Klebsiella* strains were innocuous in the oral cavity but potently induced TH1 cells when they colonized the intestine. The isolated *Klebsiella* strains were resistant to multiple antibiotics, tended to colonize in dysbiotic microbiota, and elicited a severe gut inflammation in mice genetically prone to colitis, indicating that the oral cavity may serve as a reservoir for potential intestinal pathobionts and exacerbate intestinal disease. In our latest project, we have succeeded in identifying 11 bacterial strains of healthy human donor origin that are capable of robust induction of IFNγ-producing CD8+ T cells in the intestine. Colonization with the 11-strain consortium protected mice from *Listeria monocytogenes* infection and enhanced the therapeutic efficacy of immune checkpoint inhibitors in syngeneic tumour models. We have also succeeded in identifying trypsin-degrading gut bacteria and dermatitis-suppressing skin commensal bacteria. Our findings should ultimately permit the design of bacterial consortia that durably activate or suppress specific adaptive immune programs, resulting in development of state-of-the-art therapeutics for numerous human diseases.

Recent Major Publications

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)

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

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

Invited presentations

Honda K. "Microbial Regulation of Host Immune Responses" KEYSTONE SYMPOSIA Microbiome: Chemical Mechanisms and Biological Consequences (Montreal, Canada) March, 2019

Honda K. "Immune modulation by the gut microbiota" NYC Inflammatory Bowel Disease Research Day (New York, USA) September, 2018

Honda K. "Modulation of the immune system by the gut microbiota" Cell-Weizmann Institute of Science Symposium: Next Gen Immunology (Rehovot, Israel) February, 2018

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

Honda K. "Regulation of T Cells by the Gut Microbiota" Gordon Research Conference (GRC) in Immunochemistry and Immunobiology (Lucca, Italy) June, 2016

Laboratory for
Skin Homeostasis

Team Leader: Masayuki Amagai

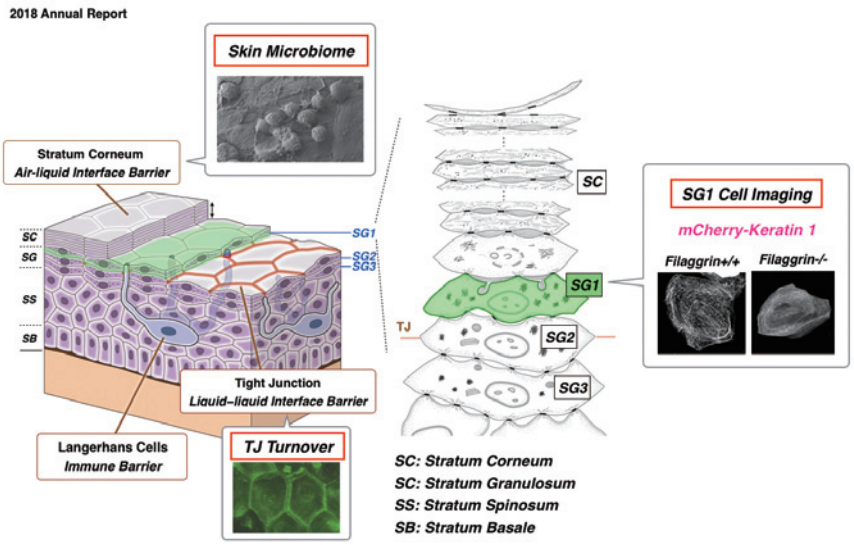


Figure: Comprehensive analysis of skin barrier homeostasis

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

Recent Major Publications

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

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

Invited presentations

Amagai M. "Peripheral tolerance to autoimmune target in pemphigus" The 3rd Inflammatory Skin Disease Summit (Vienna, Austria) December, 2018

Amagai M. "Peripheral tolerance to desmoglein3, pemphigus vulgaris antigen" "Frontiers in Skin Immunity" International Symposium of the CRC156 (Heidelberg, Germany) June, 2018

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

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

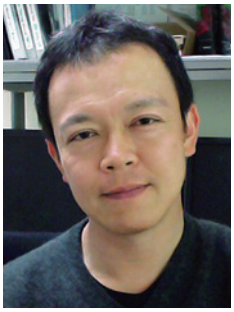
Amagai M. "Skin barrier homeostasis and its failure in atopic dermatitis" Plenary lecture at 25th European Academy of Dermatology and Venereology Congress (Vienna, Austria) September, 2016

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

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. A fundamental biophysical paradox regarding the function of the epidermis is how it can maintain the barrier, yet still constantly replace and shed cells.

Our group is trying clarify how epidermal barrier homeostasis is maintained under normal conditions and how impaired barrier function occurs and affects microenvironments of the skin in various disease conditions. Our experimental approaches are comprehensive, combining molecular biology, biochemistry, ultrastructural anatomy, live imaging, microbiology, and systems biology. For example, we have recently succeeded in characterizing isolated SG1 cells and performing intravital imaging of Ca^{2+}/organelles/pH during cornification.

Another of our strengths is to be 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.



Laboratory for
Tissue Dynamics

Team Leader: Takaharu Okada

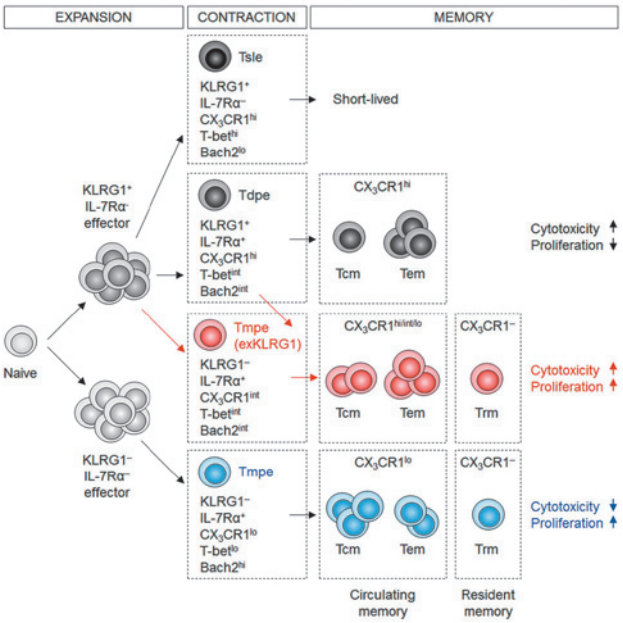


Figure: Differentiation pathways of effector CD8⁺ T cells to memory CD8⁺ T cells

Recent Major Publications

Herndler-Brandstetter D*, Ishigame H*†, Shinnakasu R, Plajer V, Stecher C, Zhao J, Lietzenmayer M, Kroehling L, Takumi A, Kometani K, Inoue T, Kluger Y, Kaech SM, Kurosaki T, Okada T†, Flavell RA†. 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.

Ise W, Fujii K, Shiroguchi K, Ito A, Kometani K, Takeda K, Kawakami E, Yamashita K, Suzuki K, Okada T, Kurosaki T. T Follicular Helper Cell-Germinal Center B Cell Interaction Strength Regulates Entry into Plasma Cell or Recycling Germinal Center Cell Fate. ***Immunity*** 48, 702-715. e4 (2018)

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

Invited presentations

Okada T. "Imaging of epidermal nerve dynamics and activity in normal and pruritic dermatitis conditions" The 47th Annual Meeting of the Japanese Society for Immunology, Joint Symposium 2 "Crosstalk between immune and nervous system at surface" (Fukuoka, Japan) December, 2018

Okada T. "Imaging of skin nerves involved in chronic inflammation" The 39th Annual Meeting of the Japanese Society of Inflammation and Regeneration, Symposium 6 (Tokyo, Japan) July, 2018

Okada T. "Intravital imaging of dendritic cells" The 117th Annual Meeting of the Japanese Dermatological Association, Educational Lecture 32 (Hiroshima, Japan) June, 2018

Okada T. "Dynamic interactions of sensory nerves, keratinocytes, and immune cells in the skin" The Banff International Research Station for Mathematical Innovation and Discovery (BIRS) of Casa Matemática Oaxaca (CMO). "Quantitative Analysis of Immune Cell Migration and Spatial Processes in Health and Disease" (Oaxaca, Mexico) June, 2018

Okada T. "Imaging of epidermal nerve dynamics and activity in normal and pruritic dermatitis conditions" IMS-JSI International Symposium on Immunology 2018 "Checkpoint in Medical Science and Its Technology" (Tokyo, Japan) June, 2018

The goal of the 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, in particular two-photon microscopy, to analyze cellular activities in the tissues. For example, by intravital imaging, we have found that sensory nerve endings in the skin epidermis are constitutively remodeled through interactions with the skin barrier structure, and that impairment of the barrier in mouse models of itchy dermatitis disrupts the nerve remodeling and leads to aberrant activation of the sensory nerves. In addition, in order to address molecular mechanisms of nerve activities observed by the imaging study, we have started internal collaborations at RIKEN to analyze the gene expression of individual sensory neurons with different functional characteristics.

We have also been continuing our studies to understand how the fate of activated immune cells is determined during longitudinal, adaptive immune responses. For this purpose, we develop and utilize fate-mapping tools that enable us to irreversibly label lymphocytes at particular phases of their activation and/or differentiation. By utilizing this technique, in an international collaboration we have recently found that effector cytotoxic T cells receiving intermediate amounts of activating and inflammatory signals become all known types of CD8⁺ memory T cells while retaining high cytotoxic and proliferative capacity. In other collaborations, our fate-mapping technique contributed to elucidation of the mechanisms by which germinal center B cells choose their differentiation pathway to memory B cells or plasma cells.

Laboratory for Metabolomics

Team Leader: Makoto Arita

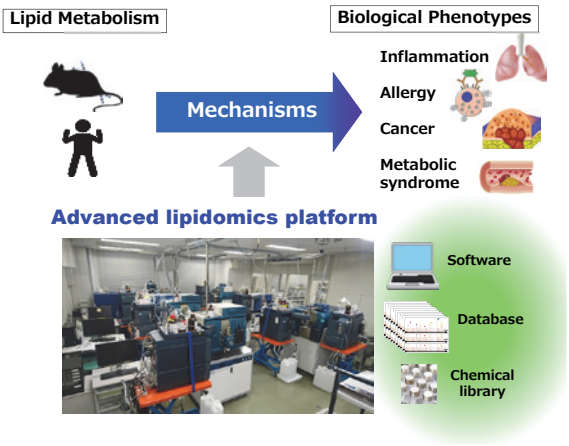


Figure: Advanced lipidomics platform to discover novel links between lipid metabolism and biological phenotypes

Recent Major Publications

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*** 10.1111/all.13726 (2019)

Isobe Y, Itagaki M, Ito Y, Naoe S, Kojima K, Ikeguchi M, Arita M. Comprehensive analysis of the mouse cytochrome P450 family responsible for omega-3 epoxidation of eicosapentaenoic acid. ***Sci Rep*** 8, 7954 (2018)

Isobe Y, Kawashima Y, Ishihara T, Watanabe K, Ohara O, Arita M. Identification of protein targets of 12/15-lipoxygenase-derived lipid electrophiles in mouse peritoneal macrophages using omega-alkynyl fatty acid. ***ACS Chem Biol*** 13, 887-893 (2018)

Invited Presentations

Arita M. "Genetics and lipidomics of omega-3 polyunsaturated fatty acid biology" The 3rd International Symposium on Lipids Science and Health (Qingdao, China) November, 2018

Arita M. "The importance of LipoQuality in biological systems (Keynote Lecture)" 8th Mind-Body Interface International Symposium (Taichung, Taiwan) October, 2018

Arita M. "Genetics and Lipidomics of Omega-3 Polyunsaturated Fatty Acid Biology" Keystone Symposia on Molecular and Cellular Biology, The Resolution of Inflammation in Health and Disease (Dublin, Ireland) March, 2018

Arita M. "The importance of LipoQuality in biological system" 7th International Singapore Lipid Symposium 2018 (iSLS7) (Singapore) March, 2018

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

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 physiology and disease but also to discover novel bioactive lipids that may link lipid metabolism and biological phenotypes. A powerful method for the analysis of lipid metabolites is liquid chromatography tandem mass spectrometry (LC-MS/MS). Our research is aimed at elucidating the structure and function of endogenous lipid metabolites that regulate inflammation and tissue homeostasis.

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

We also developed a new methodology, a non-targeted lipidomics platform, to discover novel links between lipid metabolism and biological phenotypes. By taking advantage of Q-TOF (global lipid screening) and TripleQ (quantitative analyses) mass spectrometry, our new approach has a strong potential to search for lipids of interest globally and to identify unknown lipid species in a non-biased fashion. In particular, we focus on developing an MS/MS library of oxidized phospholipids, skin barrier lipids such as acylceramides, and unique lipid metabolites produced by the commensal microbiota. We also develop software that enable us to more precisely and comprehensively search for lipid structures.

Laboratory for Microbiome Sciences

Team Leader: Masahira Hattori

Recent Major Publications

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

Costea PI, Zeller G, Sunagawa S, Pelletier E, Alberti A, Levenez F, Tramontano M, Driessen M, Hercog R, Jung FE, Kultima JR, Hayward MR, Coelho LP, Allen-Vercoe E, Bertrand L, Blaut M, Brown JRM, Carton T, Cools-Portier S, Daigneault M, Derrien M, Druesne A, de Vos WM, Finlay BB, Flint HJ, Guarner F, Hattori M, Heilig H, Luna RA, van Hylckama Vlieg J, Junick J, Klymiuk I, Langella P, Le Chatelier E, Mai V, Manichanh C, Martin JC, Mery C, Morita H, O'Toole PW, Orvain C, Patil KR, Penders J, Persson S, Pons N, Popova M, Salonen A, Saulnier D, Scott KP, Singh B, Slezak K, Veiga P, Versalovic J, Zhao L, Zoetendal EG, Ehrlich SD, Dore J, Bork P: Towards standards for human fecal sample processing in metagenomic studies. ***Nat Biotechnol*** 35, 1069-1076 (2017)

Takayasu L, Suda W, Takanashi K, Iioka E, Kurokawa R, Shindo C, Hattori Y, Yamashita N, Nishijima S, Oshima K, Hattori M: Circadian oscillations of microbial and functional composition in the human salivary microbiome. ***DNA Res*** 24, 261-270 (2017)

Invited presentations

Hattori M. "Gut extrachromosomal genetic elements uncovered by long-read metagenomics" 69th International Symposium and Annual Meeting, The Korean Society of Food Science and Nutrition (Pusan, Korea) November, 2018

Hattori M. "Elucidation of the ecology and physiology of human microbiomes by metagenomics" The 7th Japan Food Research Laboratories Conference (Tokyo, Japan) October, 2018

Hattori M. "The human microbiome and its association with health and disease" The 61th Annual Meeting and Symposium of the Japan Diabetes Society (Tokyo, Japan) May, 2018

Hattori M. "Strategies and technologies for analysis of the human microbiome" The 48th Annual Meeting of Japanese Association for Anaerobic Infection Research (Hiroshima, Japan) March, 2018

Hattori M. "The Japanese bowels: its relation with gut microbe" Public Symposium in the 71st Annual Meeting of the Anthropological Society of Nippon (Tokyo, Japan) November, 2017

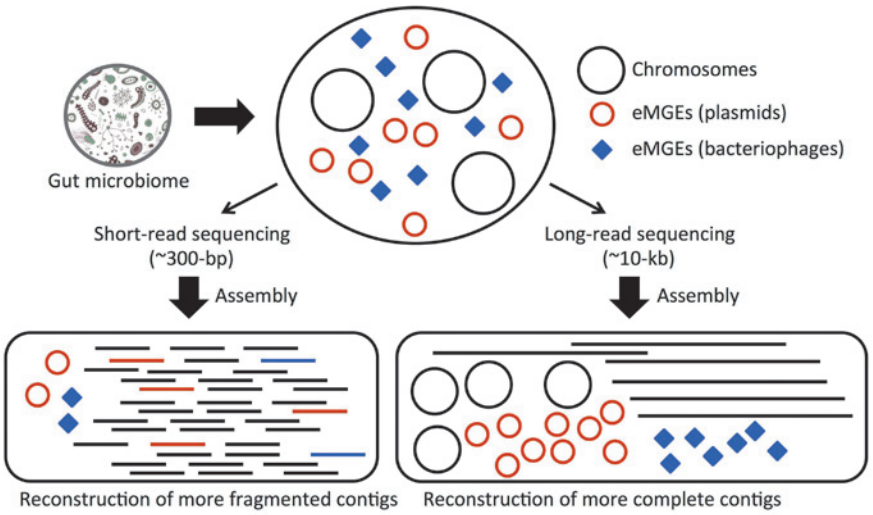


Figure: Long-read metagenomics provides an efficient approach for reconstructing complete chromosomes and extrachromosomal mobile genetic elements (eMGEs)

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 technologies for the analysis of metagenomic and genomic datasets from microbiomes and microbes produced by next-generation sequencers. Currently, we are setting up 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 (Fig). This improvement is accomplished by assembly of metagenomic reads of approximately 10 kb from microbiome samples, consequently providing efficient reconstruction of high-quality chromosomes and bins as well as complete extrachromosomal mobile genetic elements, such as plasmids and bacteriophages, in the community. Thus, metagenomic sequencing using the long-read PacBio Sequel provides a powerful approach to elucidate not only chromosomes/species and their genes but also extrachromosomal plasmids and bacteriophages in the community. In addition, the combined use of the long-read PacBio Sequel and short-read sequencers will allow us to rapidly construct complete and near-complete genomes of individual microbial strains with high accuracy. We have also developed analytical pipelines for PacBio Sequel long reads, which will be useful and helpful to facilitate analysis of microbial communities and individual microbial genomes.

Drug Discovery Antibody Platform Unit

Unit Leader: Toshitada Takemori

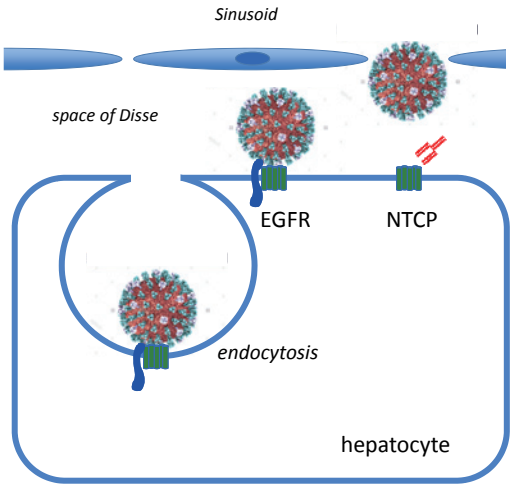


Figure: HBV entry into hepatocytes
HBV particles circulate in the sinusoidal blood and enter the space of Disse through gaps between endothelial cells. After reversible attachment to heparan sulfate proteoglycans on the hepatocyte, HBV particles contact the integral membrane receptor NTCP and form an irreversible complex. NTCP is a sodium-dependent uptake transporter expressed on the blood-side membrane of hepatocytes and is primarily responsible for the uptake of bile acids from the sinusoids. After HBV attachment to the NTCP, the epidermal growth factor receptor (EGFR) mediates HBV–NTCP internalization following fusion of the viral and cellular membranes. Our established mAb inhibits formation of the NTCP-virus complex, but does not impair the normal NTCP-dependent uptake of bile acids.

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)

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

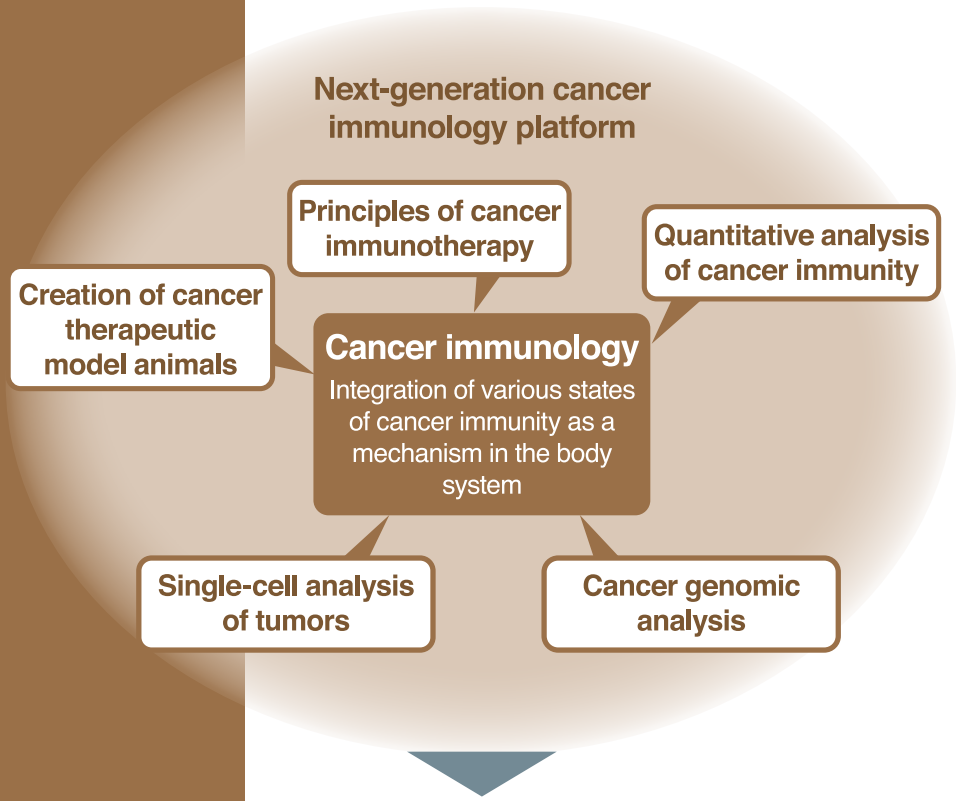
Kaji T, Hijikata A, Ishige A, Kitami T, Watanabe T, Ohara O, Yanaka N, Okada M, Shimoda M, Taniguchi M, Takemori T. CD4 memory T cells develop and acquire functional competence by sequential cognate interactions and stepwise gene regulation. ***Int Immunol*** 28, 267-82 (2016)

In order to conduct research and development of novel drugs and medical technologies, RIKEN established the Drug and Medical Technology Basic Program (DMP) in December 2009. To achieve effective progress in this area, DMP organizes various technological platform units to manage the program through close cooperation with the Drug Discovery Basic Unit established at each research center. In this context, a Drug Discovery Antibody Platform Unit was established in IMS with budgetary support from the DMP. Our aim is to contribute to the identification of new treatments for cancer and other diseases by promoting collaboration inside or outside RIKEN for the development of innovative new pharmaceuticals and medical technologies.

In response to proposals by researchers, this Unit creates new monoclonal antibodies (mAbs) that can be useful as immunotherapeutic drugs to meet medical needs. During this process, we first review the proposal on the basis of clinical usefulness and feasibility, frequently under discussion with clinical experts. In accordance with the nature of the research, we then accumulate information and scientific background on the current state of the field and build up new experimental systems that can critically answer the requests as much as possible.

We have worked on several projects for creating new therapeutics, including targeting human acute myeloid leukemia (AML) stem cells, development of novel entry inhibitors for the treatment of acute and chronic hepatitis B virus infections and for intervention in inflammatory bowel disease. In the process of this activity, we have for the first time established a mAb against an HBV receptor that prevents viral infection *in vitro* (Figure).

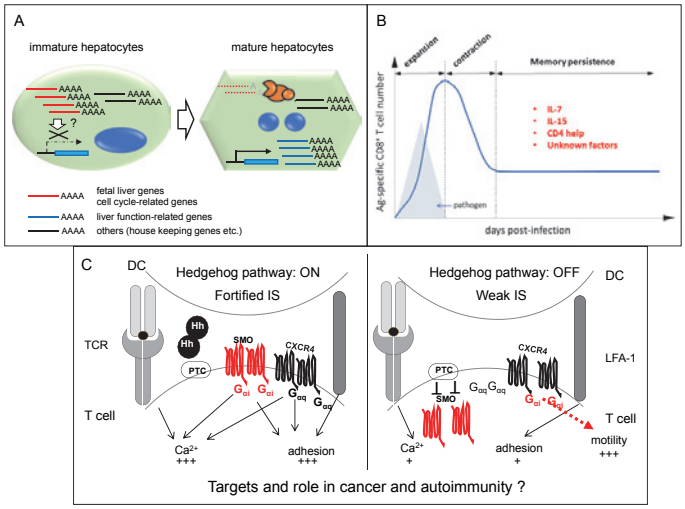
Division of Cancer Immunology



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



Figures: Research projects in the laboratory

A. mRNA decay in liver functional maturation
Cnot complex degrades immature liver-related and cell cycle-related mRNAs during liver maturation. The process influences a transcriptional induction of mature liver mRNAs. (Suzuki et al, *Development* 146, pii: dev168146, 2019)

B. The critical factors for memory CD8 T cell persistence after the contraction of effector CD8 T cells
The kinetics of antigen (Ag)-specific CD8 T cells and pathogen load in acute infection. The mechanisms involved with memory CD8 T cell maintenance still remain elusive.

C. Hedgehog signaling in human naive lymphocytes at the immune synapse (IS) with DC
Upon TCR engagement, Hh ligand is secreted into the immune synapse and initiates the Hh signaling cascade in the T cell. The SMO signal transducer competes for $G_{\alpha i}$ coupling with CXCR4. It depletes a shared pool of available $G_{\alpha i}$ proteins, forcing CXCR4 to switch to a $G_{\alpha 11/q}$ state. This switch abrogates motility of the lymphocyte, consolidates inside-out signaling, and increases the affinity of integrins, thus fortifying immune synapse stability.

Recent Major Publications

Suzuki T, Kikuguchi C, Nishijima S, Nagashima T, Takahashi A, Okada M. Yamamoto T. Postnatal liver functional maturation requires Cnot complex-mediated decay of mRNAs encoding cell cycle and immature liver genes. ***Development*** 146, pii: dev168146 (2019)

Shirai Y, Mizutani A, Nishijima S, Horie M, Kikuguchi C, Elisseeva O, Yamamoto T. CNOT3 targets negative cell cycle regulators in non-small cell lung cancer development. ***Oncogene*** 38, 2580-2594 (2018)

Horie K, Kudo T, Yoshinaga R, Akiyama N, Sasanuma H, Kobayashi TJ, Shimbo M, Jeon H, Miyao T, Miyauchi M, Shirakawa M, Shiba D, Yoshida N, Muratani M, Takahashi S, Akiyama T. Long-term hindlimb unloading causes a preferential reduction of medullary thymic epithelial cells expressing autoimmune regulator (Aire). ***Biochem Biophys Res Commun*** 501, 745-750 (2018)

Invited presentations

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

Yamamoto T. "Advanced Medicine & Bioengineering" STS Forum (Kyoto, Japan) October, 2018

Yamamto T. "Cell death and CCR4-NOT, an mRNA decay machinery" ZPM-RIKEN Symposium (Tubingen, Germany) July, 2018

Yamamoto T. "Biology of mRNA poly(A) tail" 2nd RIKEN IMS-Stanford ISCBRM Joint Symposium (Yokohama, Japan) May, 2018

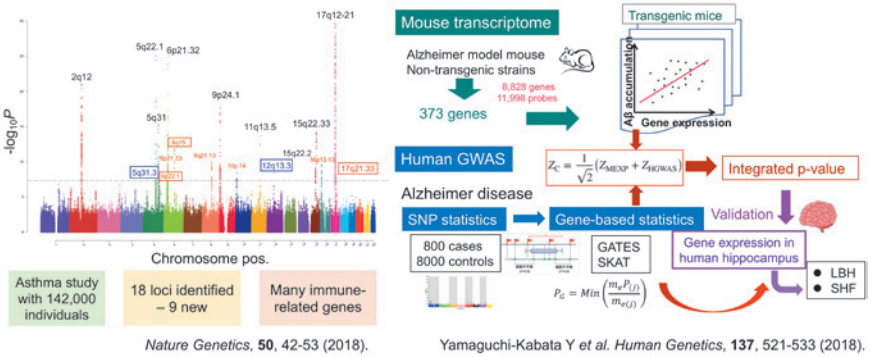
1) One of the essential post-transcriptional mechanisms is regulation of mRNA stability. Suppression of mRNA deadenylase, an enzyme that triggers mRNA degradation by shortening their polyA tails, leads to abnormal tissue development concomitant with loss of the ability to eliminate unnecessary mRNAs. We have been investigating how the deadenylase regulates tissue development and function. Furthermore, clinical studies have identified mutations in mRNA decay-related genes in human diseases. Viruses also affect host mRNA stability by targeting mRNA decay molecules to create a cellular environment optimal for viral amplification, resulting in virus-related diseases. We will understand the relationship of mRNA decay with extracellular stresses and virus infection. Our long-term goal is to develop novel therapeutics for human diseases caused by impaired mRNA decay.

2) Memory CD8 T cells are long-lived antigen (Ag)-specific CD8 T cells that respond quickly, proliferate robustly, and exert effector functions faster than naïve CD8 T cells upon reencounter with their cognate Ag. By such functions, memory CD8 T cells protect our body from infectious agents and tumors. Pools of memory CD8 T cells are maintained at a stable size over a long period of time, but the mechanisms that affect their long-term persistence still remain incompletely understood. One of the objectives of our study is to reveal how memory CD8 T cells are maintained *in vivo*. Results of this research may provide new vaccination strategies for the induction of protective immunity to tumors and chronic infections.

3) Cancer immunotherapy has become an indispensable arm of cancer treatment in recent years. Checkpoint inhibitors like CTLA4 or PD-1 antibodies have revolutionized the field, but had 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 efficiency. Thus, Hedgehog signaling, which is under investigation in the laboratory, could potentially be another target for such a combinational therapy and needs to be evaluated in detail in health and disease.

Laboratory for Medical Science Mathematics

Team Leader: Tatsuhiko Tsunoda



Nature Genetics, **50**, 42-53 (2018). Yamaguchi-Kabata Y *et al. Human Genetics*, **137**, 521-533 (2018).

Figure: An international collaboration revealed nine new asthma-related loci (left), and integrative omic-analysis applied with human GWAS and mouse transcriptome identified new Alzheimer genes (right).

Recent Major Publications

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

Yamaguchi-Kabata Y, Morihara T, Ohara T, Ninomiya T, Takahashi A, Akatsu H, Hashizume Y, Hayashi N, Shigemizu D, Boroevich KA, Ikeda M, Kubo M, Takeda M, Tsunoda T. Integrated analysis of human genetic association study and mouse transcriptome suggests LBH and SHF genes as novel susceptible genes for amyloid-β accumulation in Alzheimer's disease. ***Hum Genet*** 137, 521-533 (2018)

Lysenko A, Sharma A, Boroevich KA, Tsunoda T. An integrative machine learning approach for prediction of toxicity-related drug safety. ***Life Sci Alliance*** 1, e201800098 (2018)

Invited Presentations

Tsunoda T. "Omic Big Data Analysis Drives Precision Medicine" The 8th Annual Translational Bioinformatics Conference/2018 Annual Conference of Korean Society for Bioinformatics (Seoul, Korea) November, 2018

Tsunoda T. "Public Big Data Accelerate Medical Science Research" Symposium - Public database and application for medicine in Japan and Asia, The 63rd Annual Meeting of the Japan Society of Human Genetics (Yokohama, Japan) October, 2018

Lysenko A. "Machine learning-driven analysis of biological networks for predictive modelling of drug toxicity" 14th International Symposium on Integrative Bioinformatics (Harpenden, UK) June, 2018

Effective utilization of rapidly developing omic profiling technologies and, in particular, the introduction of personalized/precision/preventive medicine have recently 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 mathematics 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 such as cancer, common diseases such as coronary artery disease and type 2 diabetes, and neurodegenerative diseases. Next, we classify each disease into finer categories using molecular profiles and 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) International collaborations for genome-wide association studies (GWAS) with imputation, meta-analysis, and eQTL analysis techniques; (2) Development of new methodologies for increasing GWAS statistical power and sample size estimation; (3) Integrating trans-omic analysis with GWAS; (4) Accurate insertion/deletion calling from next-generation sequencing (NGS) data, whole genome sequencing (WGS), and targeted-sequencing analysis; (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) Development of original network/pathway analysis methods for disease-causing genes; (10) Drug toxicity prediction with machine learning; (11) Prediction of post-translational amino-acid modifications and protein structure; (12) Clarifying cancer immunology for therapy; and (13) Utilizing deep neural networks for image and omic data analyses.

Laboratory for
Cancer Genomics

Team Leader: Hidewaki Nakagawa

Recent Major Publications

Furuta M, Tanaka H, Shiraishi Y, Unida T, Imamura M, Fujimoto A, Fujita M, Oku-Sasaki A, Maejima K, Nakano K, Kawakami Y, Arihiro K, Aikata H, Ueno M, Hayami S, Ariizumi S, Yamamoto M, Gotoh K, Ohdan H, Yamaue H, Miyano S, Chayama K*, Nakagawa H*. Characterization of HBV integration patterns and timing in liver cancer and HBV-infected liver. ***Oncotarget*** 9, 25075-25088 (2018)

Boot A, Huang MN, Ng AW, Ho SC, Lim JQ, Kawakami Y, Chayama K, Teh BT, Nakagawa H, Rozen SG. In-depth characterization of the cisplatin mutational signature in human cell lines and in esophageal and liver tumors. ***Genome Res*** 28, 654-665 (2018)

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

Invited presentations

Nakagawa H. "Whole genome sequencing and immuno-genomic analysis for liver cancer" The 49th Princess Takamatsu Cancer Research Fund International Conference (Tokyo, Japan) November, 2018

Nakagawa H, Miyano S. "Pan-cancer Whole Genome Sequencing Project (PCAWG) in ICGC/TCGA" Symposium 10: Overview of cancer genome research and new challenges. The 77th Annual Meeting of Japanese Cancer Association (Osaka, Japan) September, 2018

Nakagawa H. "Cancer Whole Genome Sequencing and Immuno-genomic Analysis for Cancer" The 27th Korean Genome Organization Annual Conference (Seoul, Korea) September, 2018

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

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

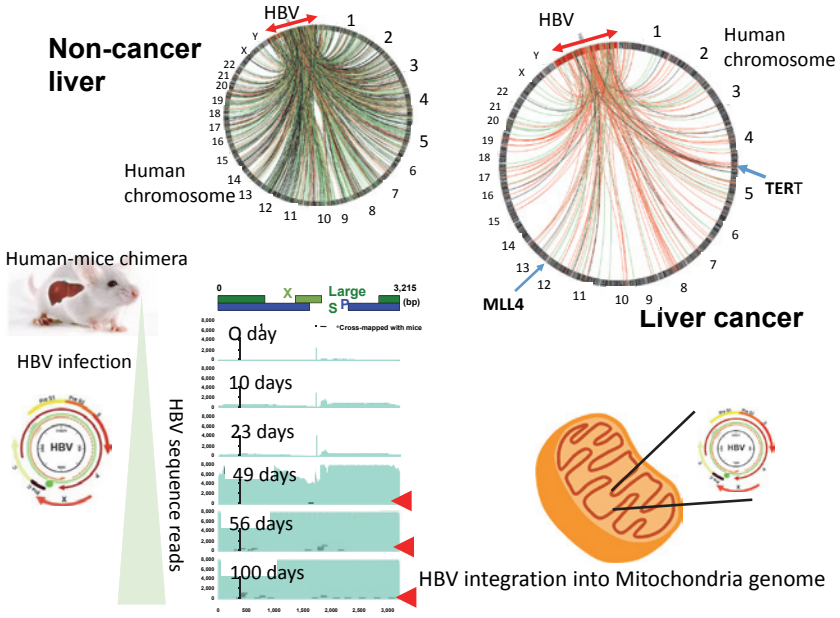


Figure: HBV integration in human liver cancers, non-cancer HBV infected liver tissues and HBV-infected liver tissues in human-mice chimera model

Ultra-deep sequencing targeting HBV sequence identified 1684 HBV integration sites in 113 HBV-infected liver tissues. In liver cancer, TERT and MLL4 genes were preferential regions for HBV integration, and HBV integration sites were significantly enriched in regions annotated as exhibiting open chromatin and early replication timing in non-cancer liver tissues. In the HBV-infected human-mouse chimera model, HBV integration occurred between 24-49 days after HBV infection and was predominant in mitochondrial DNA.

Cancer is essentially a "disease of the genome" that develops and evolves with the accumulation of a variety of mutations in its genetically unstable background. Some somatic mutations of driver genes have been successfully targeted for cancer treatment. Now, genotype-based personalized cancer therapy is in the clinical stage. Understanding of, and attention to the underlying genetic diversity in cancer is, therefore, likely to increase the success of new cancer treatment modalities. Recent explosive advances in next-generation sequencing (NGS) and bioinformatics enable us to perform systematic, genome-wide identification of all somatic abnormalities by whole genome sequencing (WGS), whole exome sequencing, and RNA sequencing (RNA-seq). Furthermore, cancer has been proven to have a feature of "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 been addressing WGS and RNA-seq analyses for cancer. 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

Recent Major Publications

Shimizu K, Iyoda T, Okada M, Yamasaki S, Fujii S*. Immune suppression and reversal of the suppressive tumor microenvironment. ***Int Immunol*** 30, 445-454 (2018)

Yamada D, Iyoda T, Vizcardo R, Shimizu K, Sato Y, Endo TA, Kitahara G, Okoshi M, Kobayashi M, Sakurai M, Ohara O, Taniguchi M, Koseki H, Fujii S*. Efficient regeneration of Human Vα24^{+} invariant NKT cells and their anti-tumor activity in vivo. ***Stem Cells*** 34, 2852-2860 (2016)

Shimizu K, Yamasaki S, Shinga J, Sato Y, Watanabe T, Ohara O, Kuzushima K, Yagita H, Komuro Y, Asakura M, and Fujii S*. Systemic DC activation modulates the tumor microenvironment and shapes the long-lived tumor-specific memory mediated by CD8^{+} T cells. ***Cancer Res*** 76, 3756-66 (2016)

Invited Presentation

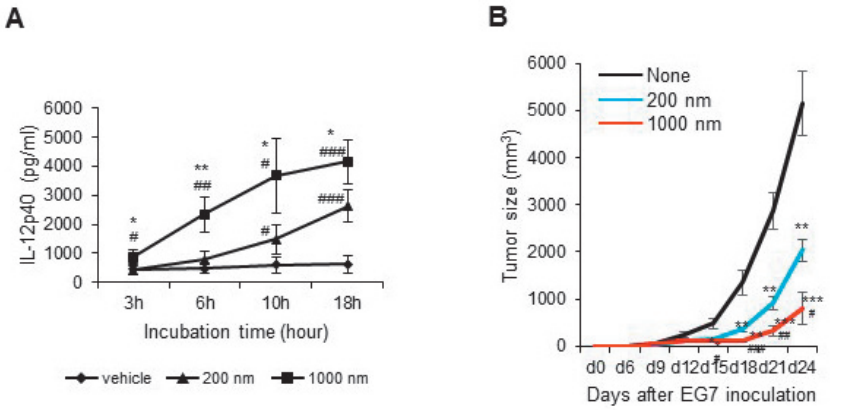
Fujii S. "Immunotherapy utilizing invariant NKT cell-licensed dendritic cells in situ., Korean Association on Immunologists meeting" KAI International Meeting 2018, Sejong University Convention Center (Seoul, Korea) November, 2018

Fujii S. "Novel type of cancer vaccine, artificial adjuvant vector cells with multiple immunopotentiating effects against melanoma" The 77th Annual Meeting of the Japanese Cancer Association, Osaka International Convention Center (Osaka, Japan) September 28, 2018

Fujii S. Multifunctional cancer vaccine "Artificial adjuvant vector cell" The 16th Annual Meeting of Japanese Society of Clinical Oncology (Kobe, Japan) July, 2018

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

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



4) Figure: Engineering nanoparticles for cancer therapy

(A) Cytokine production by DCs after particle capture. OVA antigen-encapsulated liposomes—small (200 nm) and large (1,000 nm)—were fabricated to contain OVA protein. IL-12p40 in culture supernatants from bone marrow-derived DCs cultured with vehicle or each type of liposome was measured by ELISA. DCs that took up liposomes produced IL-12, but the large ones induced higher levels and more rapid cytokine production. (B) Mice that had been inoculated subcutaneously with 2×10^{5} OVA-expressing lymphoma (EG7) cells (day 0) were treated twice i.v. with OVA-containing large liposomes and poly(I:C) (day 6 and 9) and then treated twice i.t. with small or large liposomes and poly(I:C) (day 12 and 15). Tumor size was measured every 3 days. (Significance of difference between vehicle and small or large liposomes: $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$. Significance of difference between small and large liposomes: $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$.)

The laboratory conducts basic research in cancer immunology with a strong translational component in immunotherapy. The recent success of immune checkpoint blockade (ICB) therapy represents a turning point in cancer immunotherapy. We have been studying cancer immunology and have developed an immunostimulatory immunotherapy against cancer. We have three ongoing projects in basic cancer immunology. We have 1) identified KLRG1+ invariant (i)NKT cells as having a memory-like phenotype with strong antitumor activity, and have characterized them in terms of intrinsic and extrinsic factors; 2) developed an immunotherapeutic strategy using tumor-derived neo-antigens; and 3) begun a bioengineering collaboration to develop a drug delivery system using nanoparticles.

We also have 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. We have completed the regulatory science consultation discussing the pharmaceutical quality and the design of a clinical study with the Pharmaceuticals and Medical Devices Agency. This project has also been accepted by the RIKEN translational program and been reviewed by the Institutional Review Board (IRB) of the Institute of Medical Science, the University of Tokyo (IMSUT). In July 2017, we launched a physician-initiated phase I clinical trial for refractory or relapsed acute myelogenous leukemia (AML) at the Department of Hematology/Oncology, the Institute of Medical Science, the University of Tokyo (IMSUT) hospital. In two other TR studies, we are engaged in the analyses of iPS-iNKT cells in preclinical tumor models and also collaborated with the National Hospital Organization (NHO) in a joint clinical phase I/IIa study of NKT cell therapy for early-stage post-operative lung cancer patients.

Laboratory for
Human Disease Models

Group Director: **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. Co-activation of macrophages and T cells contribute to chronic GVHD in human IL-6 transgenic humanised mouse model. ***EBioMedicine*** 41, 584-596 (2019)

Fujimoto H, Saito Y, Ohuchida K, Kawakami E, Fujiki S, Watanabe T, Ono R, Kaneko A, Takagi S, Najima Y, Hijikata A, Cui L, Ueki T, Oda Y, Hori S, Ohara O, Nakamura M, Saito T, Ishikawa F. Deregulated Mucosal Immune Surveillance through Gut-Associated Regulatory T Cells and PD-1^{+} T Cells in Human Colorectal Cancer. ***J Immunol*** 200, 3291-3303 (2018)

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

Invited Presentations

Ishikawa F. "Overcoming genetically-complex leukemia using humanized mouse" Regeneron (Tarrytown, USA) November, 2018

Ishikawa F. "Finding targets and creating therapeutic compounds for genetically-complex human hematological malignancies" JCA Morning Lecture (Osaka, Japan) September, 2018

Ishikawa F. "Linking biological heterogeneity and genetic complexity of human malignancies using the humanized mouse" AACR: Meet-the-Expert session (Chicago, USA) April, 2018

Ishikawa F. "Understanding clonal complexity of human hematologic malignancies by single cell genomics and PDX modeling" AACR: PDX workshop (Chicago, USA) April, 2018

Ishikawa F. "Functional single cell genomics for targeting genetically-complex acute myeloid leukemia" AACR: Single cell workshop (Chicago, USA) April, 2018

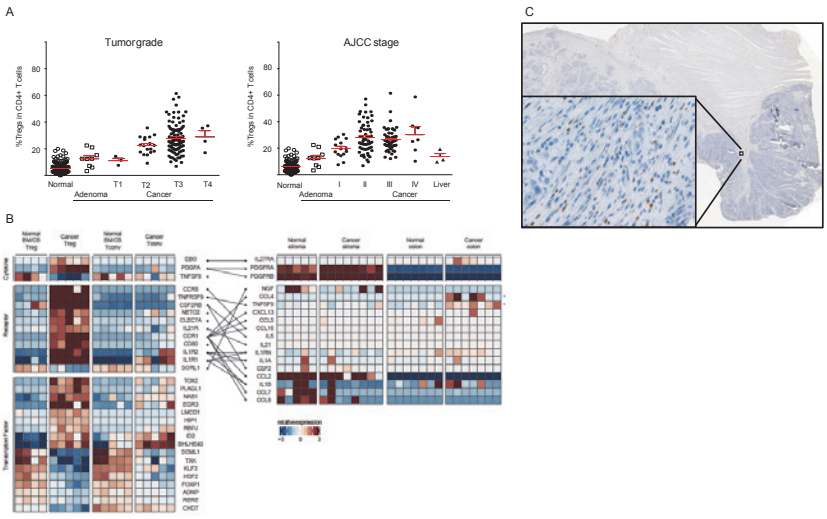


Figure: Involvement of Tregs in human colorectal tumors

(A) The proportions of Tregs among CD4^{+} T cells according to the (Left) TNM T classification and (Right) TNM stage. The proportion of Tregs is significantly higher in benign adenoma compared with normal mucosa, and higher still in adenocarcinoma at each T grade and TNM stage compared with benign adenoma. T3 adenocarcinoma shows significantly increased Treg frequency compared with T2. There is increase in the Treg frequency between adenoma and stage I and between stage I and stage II. (B) (Left) Heat map of genes highly expressed in cancer Tregs compared with normal BM/cord blood (CB) Tregs, Tconvs, and cancer Tconvs. (Right) For cytokine and chemokine receptors, expression levels of their ligands in normal and cancer stromal cells and in epithelial cells are presented as a heat map. (C) Foxp3^{+} Tregs were most abundant in the stroma-rich area of colon adenocarcinoma.

To understand *in vivo* behavior of normal and malignant human hematopoietic/immune cells, we have developed a system called "humanized mice". Although we have successfully achieved high chimerism of human hematopoietic cells in multiple immune organs of the humanized mice, the species barrier between human cells and the mouse tissue microenvironment has been one of the major obstacles. To overcome this caveat of humanized mice, we have been making efforts to create next-generation humanized mice with a humanized microenvironment. In collaboration with Drs. Koseki and Dr. Ohara at RIKEN IMS and Dr. Shultz at the Jackson Laboratory, we have been developing immune-compromised mice expressing human MHCs, cytokines, and adhesion molecules.

We have also applied the humanized mouse system to a study of human hematologic malignancies. To date, we succeeded in recapitulating adult acute myeloid leukemia (AML) and infant acute lymphoblastic leukemia (ALL). Human leukemias are heterogeneous in aggressiveness and genetic abnormalities. The use of humanized mice for leukemia studies has enabled us to understand inter-patient leukemia heterogeneity in terms of both biology and genomics. Further, by combining *in vivo* stem cell biology, immunology, and multi-omics, we are currently attempting to discover therapeutic targets and to develop new and effective treatments against poor prognosis AML and ALL. In addition, we aim to analyze interaction between human immunity and human leukemia by creating HLA-expressing humanized mice. We hope to translate knowledge gained by humanized mouse research into the clinic in the near future.

Liver Cancer Prevention Research Unit

Unit Leader: Soichi Kojima

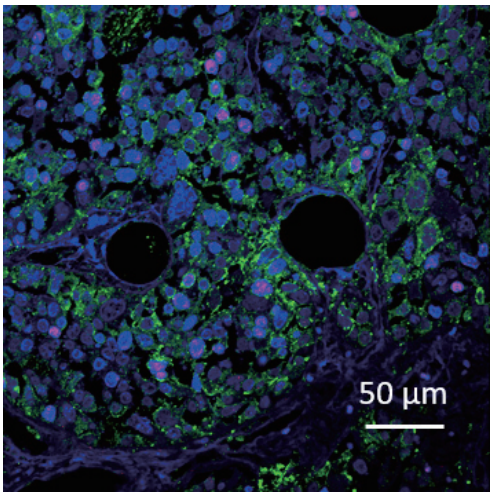


Figure: Immunofluorescence staining of human hepatocellular carcinoma (HCC) tissues.
Pictured is a fluorescent microphotograph of a section of HCC tissue stained for MYCN (red), a cancer stem cell marker, EpCAM (green), and DNA (blue).

Approximately 250 million people worldwide are infected with hepatitis B virus (HBV), which can progress to hepatitis, fibrosis, decompensated cirrhosis, and hepatocellular carcinoma (HCC). In infected hepatocytes, HBV forms covalently closed circular DNA (cccDNA), from which pre-genomic RNAs and mRNAs are transcribed to sustain HBV replication. This process is suppressed by nucleotide analogues (NAs) by inhibiting reverse transcriptase, but the cccDNA is retained in the nucleus of the infected cells. Thus, inhibited cccDNA formation and its degradation are critical for eradication of the virus. Interferon (IFN)-α enhances the expression of the cytidine deaminase APOBEC (apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like) family, leading to cccDNA degradation. Beginning from a structure-activity relationship study of compounds that mimic IFN-α, we found that these compounds had a strong anti-HBV activity that was accompanied by a decrease in cccDNA, and thus renamed them as cccDNA modulators (CDMs). CDMs bound to a novel pocket in the IFN receptor and worked *in vitro* in combination with an NA.

We established a sensitive ELISA to quantify TGF-β latency-associated protein (LAP)-degradation products (DPs) at levels as low as 2 pM. The presence of these DPs reflects plasma kallikrein-dependent TGF-β activation and an increase in activated hepatic stellate cells, which are responsible for liver fibrosis, thereby serving as a novel biomarker for liver fibrogenesis.

HCC is highly lethal, partly because of its high rate of recurrence, which is caused by the presence of liver cancer stem cells (CSCs). Using a selective chemopreventive agent, acyclic retinoid (ACR), as a bioprobe, we identified MYCN as a therapeutic target of ACR in HCC through a selective deletion of MYCN+ liver CSCs. We also demonstrated that the expression of MYCN in HCC served as a prognostic biomarker that positively correlated with the recurrence of HCC after curative treatment. These findings highlight MYCN as a useful biomarker and an important therapeutic target in drug discovery for screening chemopreventive agents against the recurrence of HCC.

Recent Major Publications

Qin X-Y, Suzuki H, Honda M, Okada H, Kaneko S, Inoue I, Ebisui E, Hashimoto K, Carninci P, Kanki K, Tatsukawa H, Ishibashi N, Masaki T, Matsuura T, Kagechika H, Toriguchi K, Hatano E, Shirakami Y, Shiota G, Shimizu M, Moriwaki H, Kojima S. Prevention of hepatocellular carcinoma by targeting MYCN-positive liver cancer stem cells with acyclic retinoid. ***Proc Natl Acad Sci U S A*** 115, 4969-4974 (2018)

Shrestha R, Shrestha R, Qin XY, Kou TF, Oshima Y, Iwatani S, Teraoka R, Fujii K, Hara M, Li M, Takahashi-Nakaguchi A, Chibana H, Lu J, Cai M, Kajiwara S, Kojima S. Fungus-derived hydroxyl radicals kill hepatic cells by enhancing nuclear transglutaminase. ***Sci Rep*** 7, 4746 (2017)

Tatsukawa H, Furutani Y, Hitomi K, Kojima S. Transglutaminase 2 has opposing roles in the regulation of cellular functions as well as cell growth and death. ***Cell Death & Disease*** 7, e2244 (2016)

Invited presentations

Kojima S. "Gut dysbiosis, nuclear transglutaminase and hepatocyte death" The 13th International Symposium on ALPD and Cirrhosis (Kyoto, Japan) September, 2018

Kojima S. "Drug discovery researches at academia on prevention, diagnosis, and treatment of liver diseases" The 18th Meeting of the Kansai Society for Kinetics of Hepatic Blood stream and Imaging of Hepatic functions (Osaka, Japan) July, 2018

Kojima S. "Molecular mechanism by which acyclic retinoid selectively kills MYCN-positive liver cancer stem cells" FASEB the 4th International Conference on Retinoids (Steamboat Springs, USA) June, 2018

Kojima S, Furutani Y. "Combinational treatment of CDM-3008 and entecavir for suppression of HBV reactivation" Taiwan-Japan-Korea Research Symposium on Hepatitis B Virus (Taipei, Taiwan) April, 2018

Kojima S. "Genomic and nongenomic actions of acyclic retinoid on deletion of $MYCN^{+}CD133^{+}$ liver cancer stem cells" Xiamen University AFPS2017-The 104 Sciences 2017 (Xiamen, China) November, 2017

Special Programs for Young Leaders

RIKEN Hakubi Fellows Program

RIKEN offers junior Principal Investigator (PI) positions, the RIKEN Hakubi Fellows, for exceptionally talented researchers for a maximum of 7 years. RIKEN Hakubi Fellows are expected to independently engage 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 the 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 a 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 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

Team Leader: Nicholas Parrish

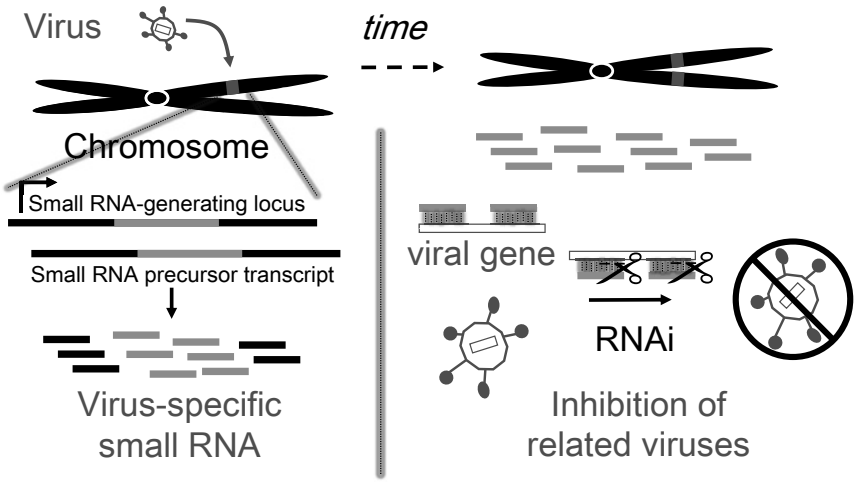


Figure: Central Hypothesis - Integrated Virus Sequences Enable Heritable RNA-based Immunity
We hypothesize that viral sequences are integrated into host genome loci that are transcribed and processed into small RNAs. After integration into the genome, these sequences are stable over time, even over generations if integrated into the germline. Small RNAs produced from these integrated viral sequences can guide RNA-cleaving enzymes to silence the expression of viral proteins, blocking replication and/or pathogenesis. The goal of this laboratory is to test this hypothesis and thereby reject the hypothesis or demonstrate that eukaryotes have a heritable RNA-based immune system analogous to CRISPR/Cas-mediated immunity in prokaryotes.

Recent Major Publications

Parrish NF, Feurer ID, Matsuoka LK, Rega SA, Perri R, Alexopoulos SP. The Changing Face of Liver Transplantation in the United States: The Effect of HCV Antiviral Eras on Transplantation Trends and Outcomes. ***Transplant Direct*** (in press)

Invited presentations

Parrish NF. "Interfering Small RNAs Derived from Ancient Viral Sequences in Mammalian Genomes: a CRISPR/Cas-like Eukaryotic Immune System?" RIKEN Center for Biosystems Dynamics Research, internal seminar (Kobe, Japan) October, 2018

Parrish NF. "Interfering Small RNAs Derived from Ancient Viral Sequences in Mammalian Genomes: a CRISPR/Cas-like Eukaryotic Immune System?" Tokyo University Department of Neurochemistry, internal seminar (Tokyo, Japan) August, 2018

We are testing the hypothesis that viral sequences integrated into eukaryotic genomes can influence antiviral immunity, analogous to CRISPR/Cas-mediated immunity in prokaryotes. We hypothesize that small RNAs transcribed from integrated viral sequences can interfere with viral protein expression and thus block viral replication and/or pathogenesis. In humans and mice, we have shown that a class of non-retroviral endogenous viral elements called endogenous bornavirus-like nucleoprotein elements (EBLNs) often encode small RNAs called Piwi-interacting RNAs (piRNAs). piRNAs can silence retrotransposons, from which piRNAs are also transcribed, but this process has not been shown for infectious viruses.

We are using two complementary model systems to test this hypothesis and are collaborating to test a third model system: 1) knocking out EBLNs present in the mouse genome, and knocking in viral sequences into functionally similar loci, 2) characterizing immunity to human herpesvirus 6 (HHV-6) in ~1% of humans in whom this virus has become endogenous, and 3) introducing arboviral genes into mosquito genomes and testing arboviral vector competence. The three arms of the research program provide a balanced platform to test the high-risk, high-reward concept that eukaryotes have an unrecognized immune system based on virus-to-host gene transfer. If such a system is demonstrated, it would have practical applications for non-human germline and human somatic genome engineering for virus resistance.

YCI Laboratory for

Cellular Bioenergetic Network

Young Chief Investigator: **Toshimori Kitami**

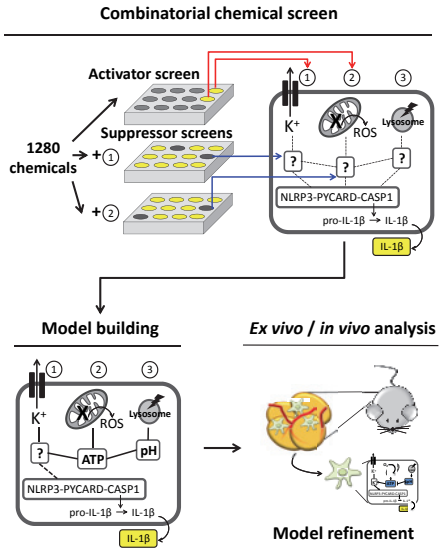


Figure: Schematic of activator-suppressor screens for NLRP3 inflammasome, model building, and validation.

Recent Major Publications

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

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

Invited presentations

Kitami T. "Systematic dissection of mitochondrial functions via chemical genetics approach" Saitama Medical University Research Center for Genomic Medicine (Saitama, Japan) October, 2018

Kitami T. "Systematic dissection of mitochondrial functions via chemical screening approach" Symposia: Renaissance of the 'Mitochondrial World' unveiled by cutting-edge technologies. The 91st Annual Meeting of the Japanese Biochemical Society (Kyoto, Japan) September, 2018

Kitami T. "Mitochondrial chemical compendium version 2: detection of genotype-specific mitochondrial toxicity" The 1st Annual COCKPI-T (Co-Create Knowledge for Pharma Innovation with Takeda) Presentation Day (Kanagawa, Japan) July, 2017

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, and 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 mechanisms by which mitochondria participate in disease pathogenesis remain largely unanswered. 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.

Toward our goal, we initiated a project focused on the role of mitochondria in the NLRP3 inflammasome, which is one of the intracellular pattern recognition receptors 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 also 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 treatment of mitochondria-related disorders.

YCI Laboratory for Trans-Omics

Young Chief Investigator: Katsuyuki Yugi

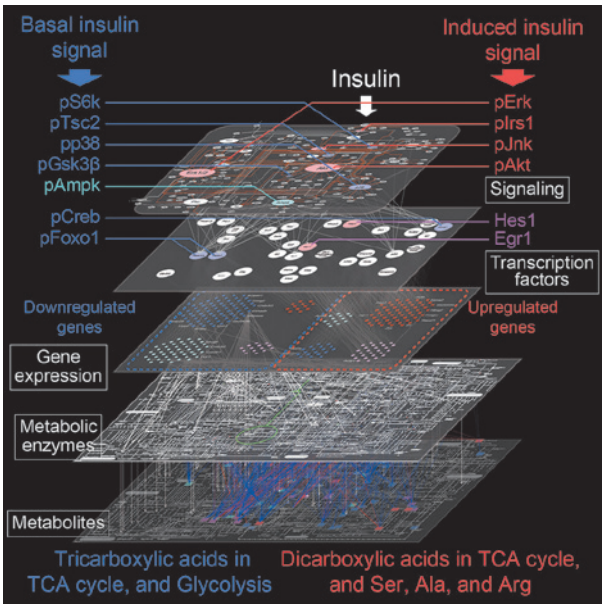


Figure: Selective response of the global metabolic regulatory network to the low-dose (left, blue) and the high-dose insulin signal (right, red)
The downregulated genes and metabolites in glycolysis exhibited high sensitivity to insulin concentration, whereas the upregulated genes and dicarboxylic acids in the TCA cycle exhibited low sensitivity (†Kawata, †Hatano, †Yugi *et al.*, ***iScience***, 2018).

Recent Major Publications

†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)

Yugi K, Kuroda S. Metabolism as a signal generator across trans-omic networks at distinct time scales. ***Curr Opin Syst Biol*** 8, 59-66 (2018)

Invited presentations

Yugi K. "Development of trans-omics technologies that reconstruct molecular networks of psychiatric disorders" Next Generation Brain Project Winter Symposium (Tokyo, Japan) November, 2018

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

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

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

Yugi K, Kubota H, Kuroda S. "Trans-omic reconstruction of insulin signal flow in global phosphorylation and metabolic network" Institut Curie & SBI joint workshop: Modeling and Data Analytics for Cancer Systems Biology (Tokyo, Japan) December, 2016

Trans-omics is a discipline to reconstruct a global molecular network that spans across 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). The network reconstruction is performed based on comprehensive measurement data of multiple omic layers not taken from heterogeneous sources but measured under an identical condition. Our primary research interests are:

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

We have developed methods for integration of metabolome, phosphoproteome, and transcriptome data. The methods have been applied to reveal the 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 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***, 2019).

Our long-term goal is to extend the methodology of trans-omics in two senses: (1) extending the method to incorporate data from other omic layers, such as genomic variants, so that global metabolic regulatory networks behind a broader range of diseases and drug actions can be characterized, and (2) extending availability of trans-omic analysis to non-specialist researchers by development of user-friendly software.

YCI Laboratory for

Immunological Transcriptomics

Young Chief Investigator: Hideyuki Yoshida

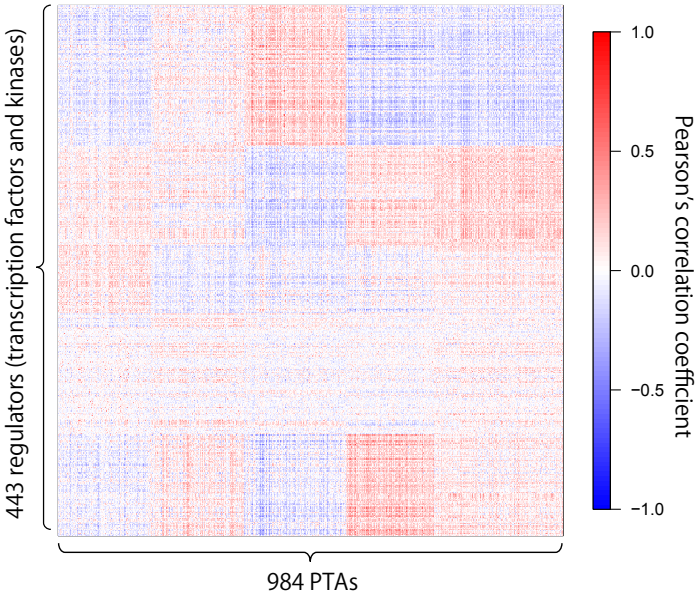


Figure: Correlation of PTAs and their possible regulators in mTECs.
Pearson correlations were computed from RNA profiles from 308 mTECs. Regulators and PTAs that showed significant correlations (q-val <= 0.05) were extracted and clustered by k-means clustering. Color-code indicates Pearson's correlation coefficient.

Recent Major Publications

Hideyuki Y, Caleb L, Ricardo R, Samuel R, Barbara M, Aleksandra W, Fiona D, Aleksey C, Arthur M, Claudia D, Julie T, Edy K, Dan D, Susan S, Tsukasa N, YiLin Q, Bingfei Y, Michelle R, Ki-Wook K, Amy W, Andrew R, Stephen N, Brian B, Sara M, Jason B, Benoist C and the Immunological Genome Project. The cis-Regulatory Atlas of the Mouse Immune System. ***Cell*** 176, 1–16 (2019)

Bansal K, Yoshida H, Benoist C and Mathis D. The transcriptional regulator Aire binds to and activates super-enhancers. ***Nat Immunol.*** 18, 263-273 (2017)

Sara M, Hideyuki Y (Co-first author), Devapregasan M, Hugo L, Katherine R, Towfique R, Chun-Jimmie Y, Nicolas C, Shen-Ying Z, Ting F, Mark L, Jean-Laurent C, James C, Martin H, Jean-Baptiste T, Nir H, Philip J, Aviv R, Diane M, Benoist C and the Immunological Genome Project Consortium. Parsing the interferon transcriptional network and its disease associations. ***Cell*** 164, 564-578 (2016)

Invited presentations

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

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

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

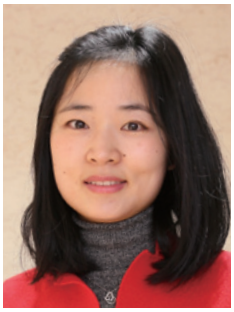
Our research aims to promote our understanding of gene regulation in immune cells and the immune system by utilizing the techniques of cutting-edge transcriptomics for better understanding and treatment of immune disorders. Transcriptomics can be applied to various studies in immunological settings,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

1) Focused subject: Gene regulation in immune tolerance

Negative selection of self-reactive T cells occurs in the thymus and is an essential mechanism for induction of immune tolerance. To achieve this, many peripheral tissue antigens (PTAs) are expressed in thymic medullary epithelial cells (mTECs) and the developing T cells are eliminated if they respond too strongly to these PTAs. Since the disrupted expression of PTAs can lead to autoimmune disorders, understanding the mechanisms controlling their expression is important for understanding the pathogenesis of autoimmune diseases and for developing new treatments. We are analyzing gene expression in mTECs by single-cell RNA-seq to examine gene regulation in detail and to identify the regulators involved. Candidate genes identified by RNA-seq will be validated using mouse models.

2) Data-driven project: Systematic analysis of various immune cell types

Bioinformatics has already impacted research on gene regulation and is becoming even more powerful since we have begun dealing with big data analysis. To promote these data-driven studies, we are collaborating with the ImmGen group (www.immgen.org).



Laboratory for

Next-Generation Proteomics

Young Chief Investigator: **Yibo Wu**

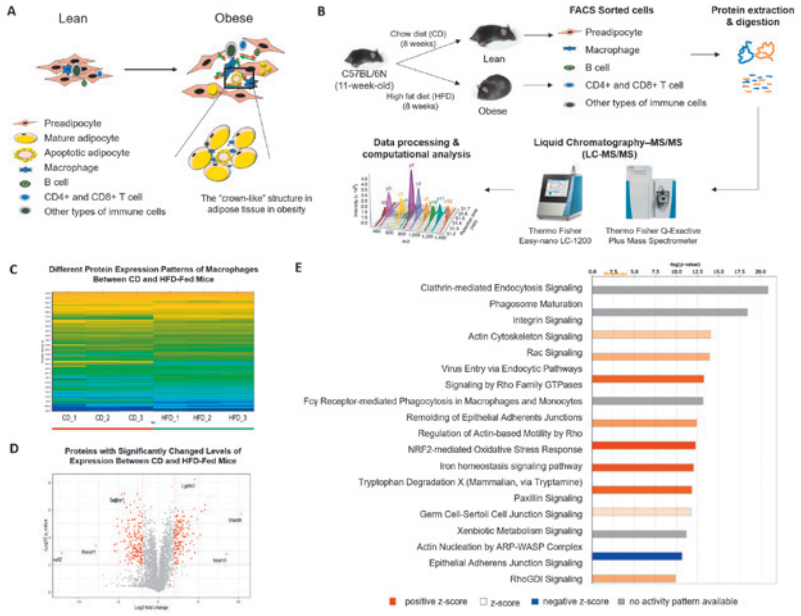


Figure: A mass spectrometry-based proteomics analysis of preadipocytes and immune cell populations in mouse visceral adipose tissue. (A) The composition and activity of immune cells are dramatically different in the lean and obese state. (B) We perform mass spectrometry-based proteomics analysis of preadipocytes and different types of immune cells in mouse visceral adipose tissue. 11-week-old C57BL/6N mice were fed a normal chow diet (CD) or a high-fat diet (HFD) for 8 weeks, and different cell populations were sorted from the visceral adipose tissue by flow cytometry. We extracted and digested the proteins from each sorted cell population and analyzed them by liquid chromatography-mass spectrometry (LC-MS/MS). Then we performed computational analysis for precise protein quantification. (C) Protein expression patterns are clearly different in macrophages from CD or HFD-fed mice. (D) Proteins that significantly change in macrophages from CD and HFD-fed mice. Right: up-regulated in HFD-fed mice. Left: down-regulated in HFD-fed mice. (E) Pathways that are significantly enriched in the macrophage proteome (top 19). Red: up-regulated in HFD-fed mice. Blue: down-regulated in HFD-fed mice.

Recent Major Publications

Terfve C*, Sabidó E*, Wu Y*, Gonçalves E, Choi M, Vaga S, Vitek O, Saez-Rodriguez J, Aebersold R. System-Wide Quantitative Proteomics of the Metabolic Syndrome in Mice: Genotypic and Dietary Effects. ***J Proteome Res*** 16, 831-841 (2017)

Williams EG*, Wu Y*, Wolski W, Kim JY, Lan J, Hasan M, Halter C, Jha P, Ryu D, Auwerx J, Aebersold R. Quantifying and Localizing the Mitochondrial Proteome Across Five Tissues in A Mouse Population. ***Mol Cell Proteomics*** 17, 1766-1777 (2018)

Wu Y*, Williams EG*, Aebersold R. Application of SWATH Proteomics to Mouse Biology. ***Curr Protoc Mouse Biol*** 7, 130-143 (2017) (*co-first author)

Invited presentations

Yibo Wu. "Quantifying and Localizing the Mitochondrial Proteome" The 91st Annual Meeting of the Japanese Biochemical Society (Kyoto, Japan) September, 2018

Yibo Wu. "Quantifying and Localizing the Mitochondrial Proteome" IMS-JSI International Symposium on Immunology (Tokyo, Japan) June, 2018

Yibo Wu. "Quantifying and Localizing the Mitochondrial Proteome" Conference on Mass Spectrometry and Proteomics (Osaka, Japan) May, 2018

Yibo Wu. "Systems proteomics of liver mitochondrial activity" 2nd International Symposium of the Kyoto Biomolecular Mass Spectrometry Society (Kyoto, Japan) February, 2018

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

Proteins are the functional molecules that play an essential role in determining the overall status of a cell or organ. The proteome is extremely multifaceted owing to alternate RNA splicing and posttranslational protein modifications, and this is further amplified by the interconnectivity of proteins into complexes and signaling networks that are highly divergent in time and space. These physical and chemical properties of proteins and protein complexes make them more difficult to analyze than their corresponding genes and transcripts. Proteome analysis relies heavily on mass spectrometry.

Our lab applies state-of-the-art mass spectrometry and computational methods for proteome analysis in complex biological samples. Currently we have two research topics: one focuses on the proteome changes associated with aging-related diseases, another focuses on the protein networks established between adipocytes and immune cell populations during the development of obesity. In the first study, we analyze bulk tissues as well as isolated immune cell populations at 7 to 8 age time points and look for proteins that are significantly changed during aging. We aim to identify the causative factors for age-associated defects in each tissue, e.g., lung and liver. In the second project, we use visceral adipose tissue and isolate the (pre)adipocytes and various types of immune cells, e.g., macrophages, $CD4^+$ and $CD8^+$ T cells, and B cells, from mice under control and high-fat diets and analyze their respective proteomes. It has been reported that chronic inflammation is associated with obesity and that the immune cell populations and their activation status in the adipose tissue change dramatically during development of obesity. However, an omics view of these events is still missing. We expect that our results will help elucidate the underlying mechanisms of the initial events during obesity and provide targets to improve obesity immune therapy.

YCI Laboratory for
Metabolic Epigenetics

Young Chief Investigator: **Azusa Inoue**

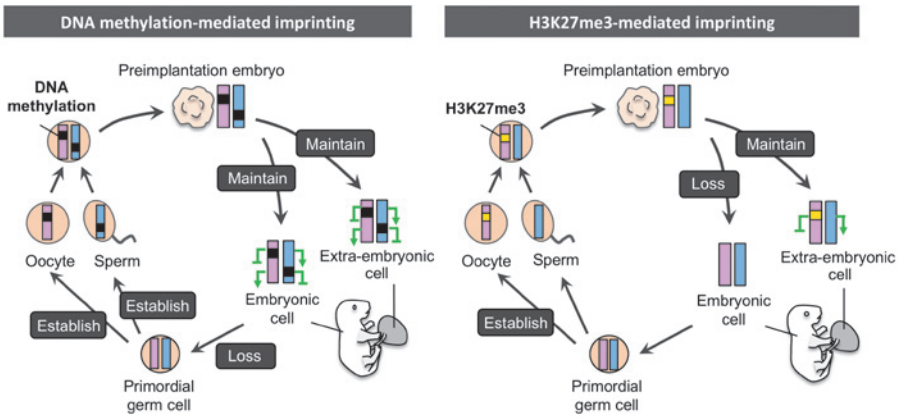


Figure: Developmental dynamics of DNA methylation-mediated imprinting and H3K27me3-mediated imprinting
H3K27me3 imprinting is established when oocytes, but not sperm, are formed. Oocyte-derived H3K27me3 resists epigenetic reprogramming after fertilization and is faithfully maintained during preimplantation development. When genes with maternal allele-specific H3K27me3 are expressed, they are expressed from the paternal allele. At implantation, this imprinting is lost in the embryonic cell lineage but maintained in the extra-embryonic cell lineage that gives rise to the placenta, etc. This dynamics is different from DNA methylation-mediated imprinting, which is lost only in primordial germ cells.

Recent Major Publications

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)

Inoue A, Jiang L, Lu F, Zhang Y. Genomic imprinting of Xist by maternal H3K27me3. ***Genes Dev*** 31, 1927-1932 (2017)

Inoue A, Jiang L, Lu F, Suzuki T, Zhang Y. Maternal H3K27me3 controls DNA methylation-independent imprinting. ***Nature*** 547, 419-424 (2017)

Invited presentations

Inoue A. "Genomic imprinting by maternal histones" The 9th meeting of Japanese Society for Quantitative Biology (Osaka, Japan) January, 2019

Inoue A. "Genomic imprinting by maternal histones" The 36th Annual Meeting of Japan Society of Fertilization and Implantation (Chiba, Japan) July, 2018

Inoue A. "Genomic imprinting by maternal histones" The 16th Stem Cell Research Symposium (Fukuoka, Japan) June, 2018

Inoue A. "Genomic imprinting by maternal histones" The 12th Japanese Epigenetic Symposium (Sapporo, Japan) May, 2018

Inoue A. "The zygote world –Epigenetic reprogramming & Genomic imprinting–" Chinese Academy of Sciences at Beijing (Beijing, China) April, 2018

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

Here we challenge the issue of oocyte-mediated inheritance of maternal metabolic disorders by integrating developmental engineering and low-input epigenome analysis technologies. The key to intergenerational epigenetic inheritance is resistance to epigenetic reprogramming that takes place after fertilization. Namely, while most of epigenetic information in gametes is erased after fertilization, certain genomic loci can resist the reprogramming and carry epigenetic information into the offspring. Our research has recently identified such loci genome-wide and revealed that a repressive histone modification, H3K27me3, inherited from oocytes is critical for the resistance in a DNA methylation-independent manner. Consequently, maternally derived H3K27me3 enables maternal allele-specific gene silencing in preimplantation embryos, and this non-canonical imprinting is maintained in the placenta (Figure, Nature 2017; Genes Dev 2017; Genes Dev 2018). These results highlight an unexpected link between the oocyte epigenome and the placenta, giving rise to the hypothesis that changes in the oocyte epigenome could influence the offspring's metabolic traits via placental dysfunction. We are now trying to test this hypothesis by using a T2D mouse model and a newly developed mouse model in which H3K27me3-mediated placental imprinting is defective. In addition, we are trying to understand the functions, regulatory mechanisms, and evolutional conservation of H3K27me3-mediated imprinting.

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, the Confocal Laboratory, the Genomics/Proteomics Laboratory, and the Animal Facility.

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 CyTOF2, a mass-spectrometry-based cytometer that has the potential to analyze more than 30 markers simultaneously with metal-labeled antibodies.

In 2018, 735 analytical and 1366 sorting experiments 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 2018, 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 50 researchers participated in these courses in 2018. (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 2018, we provided 155 such services. Advanced cell sorting techniques, such as single-cell sorting, have also been performed. (3) *Management and 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	64	2
	Canto II	2	735	16
FACS cell sorter	Aria II/III/Fusion	6	1,366	32
Mass cytometer	CyTOF2	1	49	2

Confocal Laboratory

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

1. Inverted Leica SP5 system with a visible laser for single-photon excitation and a 405 nm violet laser for UV excitation.
2. Inverted Leica SP8 system with two femtosecond Ti:Sa lasers for multiphoton excitation. This system is equipped with two types of scanners (resonant and galvano) and hybrid detectors with high sensitivity and low background noise. One of the two Ti:Sa lasers is connected to an optical parametric oscillator (OPO) that enables two-photon imaging by long wavelength excitation (Photo).
3. 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. Inverted Olympus FV1200 system with a visible laser for single-photon excitation.
5. Inverted Nikon N-SIM/N-STORM super-resolution microscope for dual color imaging (Photo).
6. GE Healthcare DeltaVision Elite system (Photo).
7. Keyence BZ-X700 all-in-one fluorescence microscope (Photo).

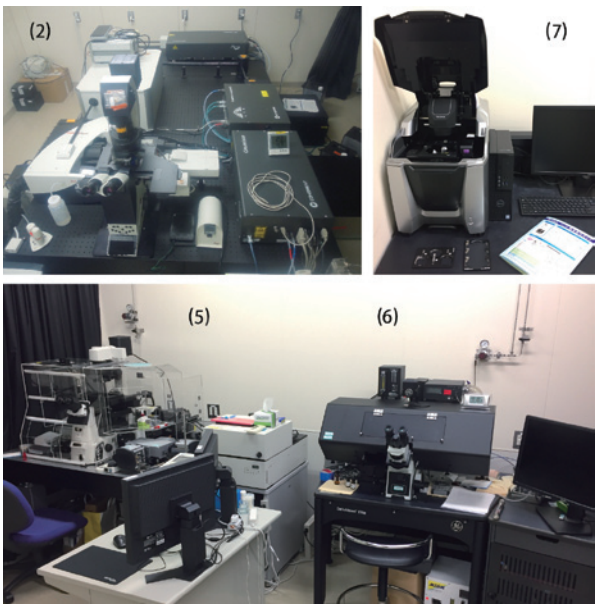


Photo: Leica SP8 multiphoton microscope (2), Nikon N-SIM/N-STORM super-resolution microscope (5), GE Healthcare DeltaVision Elite system (6), and Keyence BZ-X700 microscope (7).

Genomics and related activities

One of the missions of the Laboratory for Integrative Genomics is to serve as a technical support service lab that provides state-of-the-art genome- and proteome-wide analyses for research groups in IMS. We thus offer a variety of services to suit the needs of different labs. These include DNA sequencing, proteomics analysis, multiplex suspension array, cDNA/genomic clone distribution, and primer/labeled probe distribution for qRT-PCR analysis of immune cells (Table). In practice, next-generation DNA sequencing on an Illumina HiSeq2500 (ver4) is supported both by our laboratory and the Laboratory for Genotyping Development. We also perform mass spectrometry-based quantitative proteome analysis using an AB SCIEX TripleTOF 5600. Utilizing this support system, even researchers who are not familiar with such instrumental analyses can easily undertake genomics and proteomics approaches when necessary.

Besides these support activities for conventional genomics and related technologies, it should be noted that IMS strongly encourages collaborations between experts and non-experts in genomics. Because the Division of Genomic Medicine at IMS has many unique technologies and know-how in transcriptomics and genetics (e.g., CAGE technologies, GWAS, and whole genome sequencing), we expect that the intramural interactions among the Divisions of Human Immunology, Disease Systems Biology, Cancer Immunology, and Genome Medicine fostered by these technologies will greatly enhance research activities in IMS. In this respect, the genomics support activity may serve as a gateway to initiate efficient collaboration among the divisions in IMS.

Table: Central services provided by the Genomics Lab in 2018

Next-generation DNA sequencing	**# of samples**	**# of teams**
RNA sequencing	2,438	21
ChIP sequencing	326	4
Others (Exome etc)	1,311	5
Proteomics	**# of samples**	**# of teams**
Mass spectrometry analysis	41	2
Multiplex suspension array	1,304	7
Sanger DNA sequencing	**# of samples**	**# of teams**
36 cm capillary	10,312	13
50 cm capillary	2,304	17
cDNA clone delivery	**# of samples**	**# of teams**
	37	2
Primer/labeled probe delivery	**# of samples**	**# of teams**
	21	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 for "humanized mice". We introduce mouse lines into the SPF area via a combination of *in vitro* fertilization (IVF) and embryo transfer methods, and have also generated cryostocks of genetic resources (frozen embryos and sperms) for 737 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 (54 lines). In addition, we have made KO and KI mice (53 lines) using the CRISPR/Cas system and have created 21 lines of germ-free mice. We provide space for new experiments in the animal facility, e.g., the CRISPR/Cas system using fertilized egg electroporation (Figure), and behavioral testing for germ-free mice.

We have generated genetically modified mice to improve the efficacy 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 begun backcrossing them onto the NSG mouse background using the speed-congenic method.

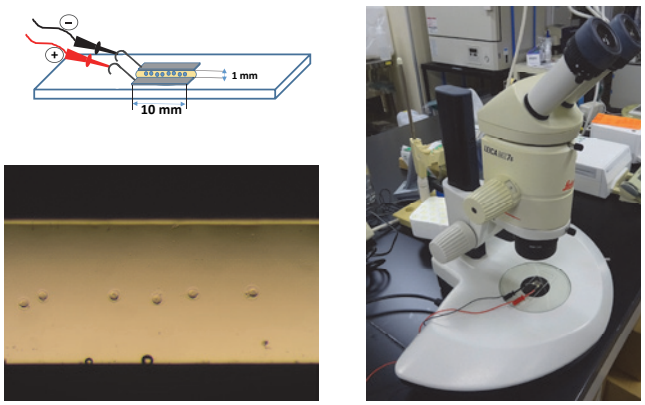


Figure: Application of the CRISPR/Cas system by electroporation of fertilized eggs

RIKEN International Program Associate (IPA)

IMS accepted eight 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 2018 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
Hsing-Fang Lu (Taipei Medical University, Taiwan) in the Laboratory for Bone and Joint Diseases
Jack Thomas Flanagan (The University of Liverpool, UK) in the Laboratory for Endocrinology, Metabolism and Kidney Diseases
Michael Boettcher (Bielefeld University, Germany) in the Laboratory for Transcriptome Technology
Mengqian Li (Tokyo Medical and Dental University, from China) in the Liver Cancer Prevention Research Unit
Daniela Kajihara (University of Sao Paulo, Brazil) in the Laboratory for Transcriptome Technology

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, 24 JRA students studied in IMS.

Yosuke Ito (Preventive Medicine and Applied Genomics Unit)
Junichiro Takano (Laboratory for Developmental Genetics)
Yoshihiro Ito (Laboratory for Skin Homeostasis)
Eiichiro Watanabe (Laboratory for Gut Homeostasis)
Takaaki Kawaguchi (Laboratory for Gut Homeostasis)
Keiko Usui (Laboratory for Skin Homeostasis)
Mamoru Ogawa (Laboratory for Metabolomics)
Hiroki Sugishita (Laboratory for Developmental Genetics)
Hiroe Tetsu (Laboratory for Innate Immune Systems)
Manabu Nagayama (Laboratory for Gut Homeostasis)
Ari Morimoto (Laboratory for Skin 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)
Iori Motoo (Laboratory for Gut Homeostasis)
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 (Laboratory for Transcriptome Technology)
Tomoaki Takahashi (Preventive Medicine and Applied Genomics Unit)
Takahiro Matsunaga (Laboratory for Gut Homeostasis)

RIKEN Special Postdoctoral Researcher (SPDR) Program

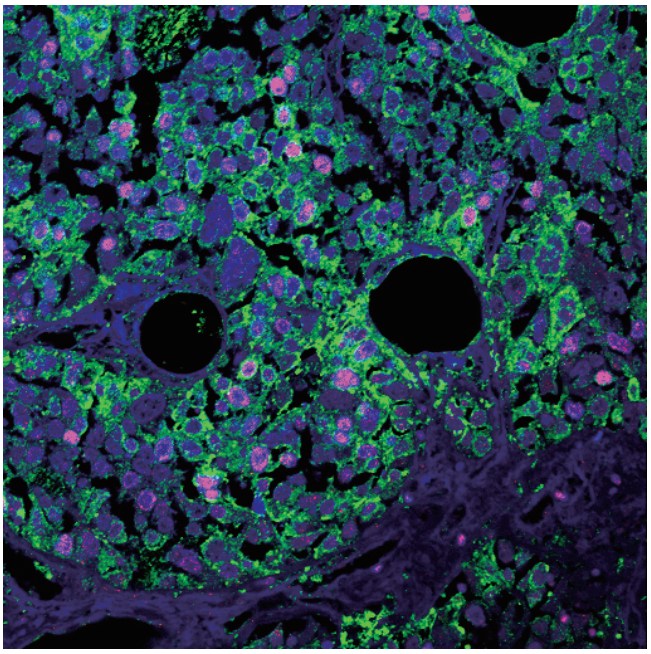
RIKEN's Special Postdoctoral Researcher Program was instituted to provide young and creative scientists the opportunity to be involved in autonomous and independent research in line with RIKEN objectives and research fields. The positions are competitive, but if selected, researchers receive salaries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

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

Eiji Miyauchi (Laboratory for Intestinal Ecosystem)
Alexis Vogelzang (Laboratory for Mucosal Immunity)
Keiichiro Shiraga (Laboratory for Skin Homeostasis)
Xiaoxi Liu (Laboratory for Genotyping Development)
Callum Parr (Laboratory for Advanced Genomics Circuit)
Rei Nakano (Laboratory for Cellular Function Conversion Technology)
Tsuyoshi Kiniwa (Laboratory for Innate Immune Systems)
Divya Mundackal Sivaraman (Laboratory for Advanced Genomics Circuit)

Part 3

Research Projects



The Human Cell Atlas project

Our bodies have 37 trillion cells, and for decades, scientists have been sorting different types of cells, such as neurons, skin cells, liver cells, and tumors, in bulk. With this 'averaged' profiling, it is impossible to know which cells express particular genes, making it challenging to fully understand diseases and develop effective and safe treatments for them. Now, new and powerful DNA sequencing methods have emerged and they are finally allowing us to determine which genes are expressed at single-cell resolution across the entire human body.

To tackle this enormous yet meaningful challenge, an international team called the Human Cell Atlas (HCA) consortium was recently established, coming together to build an open "Google Map of the human body". The goal of the HCA is creating effective diagnostics based on very precise molecular information on all the cells in the body. In the context of tumors, we expect to identify all the key genes and cells and how they are related to each other, providing clinicians with a more precise understanding of the disease and drug response status.

At RIKEN IMS, we are deploying a 5'-based single-cell genomics strategy to uncover gene regulatory mechanisms and biomarkers of both coding and non-coding RNAs. Particularly, the 5'-approach captures enhancer-derived RNAs that guide us to the precise location of disease-associated regulatory elements. Building the Human Cell Atlas in Japan is necessary to provide a more precise map of local genetics and environment. By focusing on the most relevant diseases, this approach will catapult effective healthcare for the Japanese people.

For this effort, RIKEN IMS is engaging with medical institutions across Japan to collect and process human samples to elucidate the mechanisms of health and disease. We envisage that single-cell medical network in Japan will accelerate local research and innovation, and initiate new engagements with industries (both life sciences and technologies) to positively impact the health and economy of Japan.

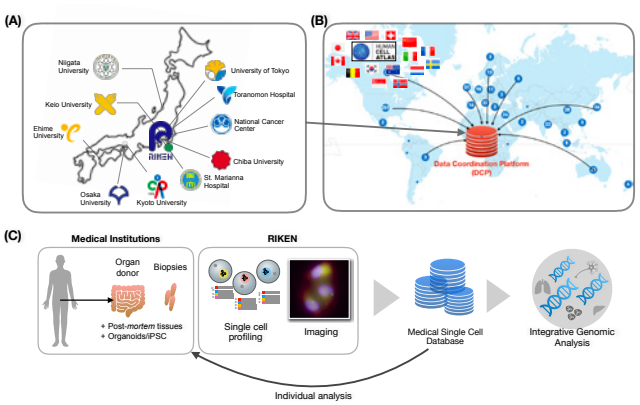


Figure. The Single Cell Medical Network in Japan
(**A**) RIKEN is collaborating with various medical institutions in Japan to collect human samples. (**B**) RIKEN will work with the global Human Cell Atlas to create the reference map. (**C**) Samples from medical institutions will be processed by RIKEN using single-cell profiling techniques. Individual analysis will be processed and returned to sample providers and integrative genomic analysis will be performed to construct a global map of promoters and enhancers at single-cell resolution.

FANTOM

The FANTOM project started in the year 2000 with a meeting, where it was decided to embark on an ambitious mission to annotate the function of mammalian genes by the analysis of full-length cDNA collections. FANTOM has evolved over the years through deciphering genomic regulatory elements and networks that control the function of the genome. During the past 19 years, we (1) constructed comprehensive catalogues of annotated protein coding genes, (2) found that the majority of the output of the genome consists of lncRNAs, (3) comprehensively annotated promoters and enhancers and provided the most comprehensive map of them, and (4) inferred the regulation of regulatory elements, such as promoters, enhancers, and lncRNAs. These achievements were made possible by international collaborative efforts, and the current project, FANTOM6, includes more than 250 researchers from over 60 research organizations.

The lncRNA collection produced by FANTOM5 has accurate 5'-end data, which allowed us to reliably recount the number of lncRNAs in mammalian cells. We estimated that at least 29,000 lncRNAs exist and inferred 19,175 potentially functional human lncRNAs, either by examining conservation of promoters/exons, overlap with GWAS or implication in eQTL databases (Hon *et al, Nature* 2017). Currently, more than 96% of lncRNAs have no reference in PubMed (De Hoon *et al. Mamm. Genome* 2015), discouraging further investigation into their biology. To overcome this limitation, FANTOM6 proposes to broadly screen for the function of lncRNAs. We believe that a substantial fraction of the identified lncRNAs will be revealed to have some sort of function.

Photo: FANTOM6 NATSU Meeting (Aug 31-Sep 1, 2017)

Human genome analysis

In 2015, the Japanese government established priority disease areas for the implementation of genomic information for actual medical practice. Rare (hereditary) diseases, cancer, dementia, infectious diseases, and pharmacogenomics were selected as the first priority areas because they were thought to be very close to being amenable to successful implementation of findings from basic research. Common multifactorial diseases such as diabetes and cardiovascular disease were positioned as the second priority disease areas, because they need further basic genomic research to precisely elucidate the relationships between genetic variants and diseases.

Different laboratories in IMS have analyzed various diseases by genome-wide association study and/or targeted- and whole-genome sequencing-based association studies: cancer (Momozawa & Nakagawa), pharmacogenomics (Mushiroda), bone & joint diseases (Ikegawa), diabetes (Horikoshi), cardiovascular diseases (Ito), autoimmune diseases (Yamamoto K), and integrated analysis of all common diseases (Kamatani). In addition, we integrated our results with knowledge of non-coding regions and single-cell sequencing approaches being done by laboratories for the FANTOM and Human Cell Atlas projects to better understand the disease biology. We also have collaborations with large Japanese cohorts (BioBank Japan, Tohoku Medical Megabank, Japan Multi-Institutional Collaborative Cohort Study, and Japan Public Health Center-based Prospective Study) and various domestic and international universities, academic institutes, hospitals, and companies to implement personalized medicine.

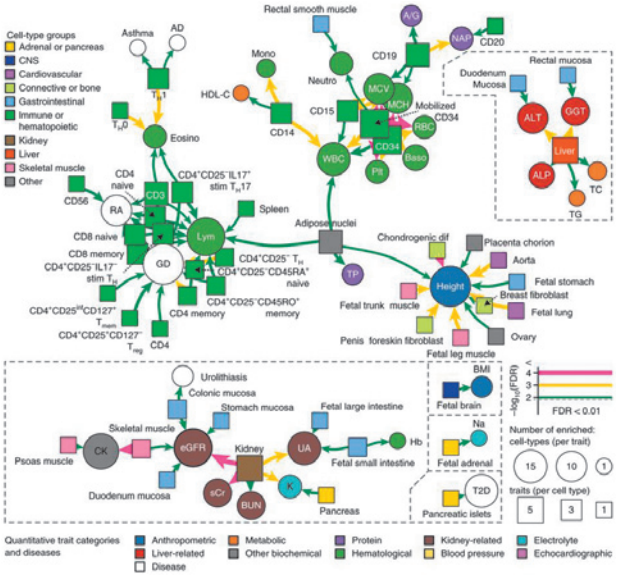


Figure: Genomic analyses reveal cell-type specific networks of complex traits

SEAPharm for 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 considerably high 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 Han Chinese and other Asian populations with a high prevalence of this allele, which is associated with 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, and Nepal, Laos, and the Philippines in 2017. This year, SEAPharm has two newcomers, Brunei and Myanmar, on the team.

The aims of the collaboration are to identify genomic biomarkers associated with ADRs, such as skin rash induced by anti-epileptic drugs and antibiotics and hepatic injury induced by anti-tuberculosis drugs, to provide technical assistance and training of young researchers from the SEAPharm member countries, and to hold international seminars and workshops. Recently, SEAPharm has started a new project involving next-generation sequencing of 1,500 genomic DNA samples from 10 countries to clarify the genetic diversity of drug-metabolizing enzymes and drug transporters in individuals from Southeast Asia, Sothern Asia, Middle East, and Southern Europe. The discoveries from these collaborative efforts will lead to the establishment of stratified medicine based on genotype-guided drug therapies.

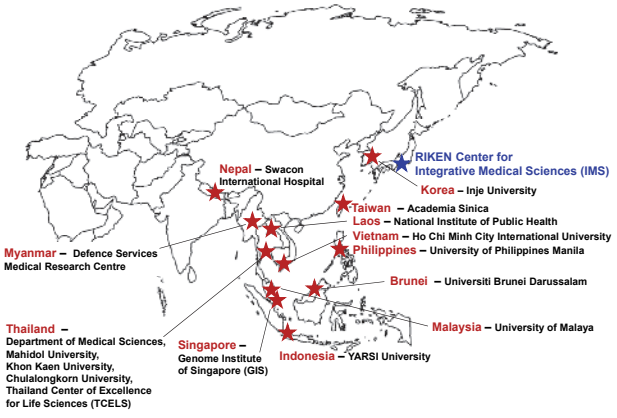


Figure: Members of the South East Asian Pharmacogenomics Research Network (SEAPharm)
Please visit http://www.pharmagtc.org/seapharm/index.php

International Cancer Genome Consortium (ICGC) and PCAWG

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 May 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 the second ICGC initiative, the ICGC launched a "Pan-Cancer" Whole Genome project (PCAWG) in 2014, in which WGS data together with RNA-Seq of 2834 donors were analyzed in uniform pipelines within the same computational environment and cloud computing. RIKEN and IMUT (The Institute of Medical Sciences, The University of Tokyo) are contributing to this project as a member of a technical working group arranging ten cloud data centers and PI/researchers in working groups for driver gene, mutational signature, germline, immuno-genomics, and mitochondrial genomics. RIKEN provided WGS data from 270 liver cancers to the PCAWG (10% of the total), making us the most productive group within the ICGC. In 2018, as a PCAWG-15 working group, RIKEN and IMUT analyzed the immuno-genomic landscape from PCAWG data, including mutations in HLAs and immune suppressor genes, neo-antigen profiles, and immune micro-environmental signatures, and observed that tumors acquired many types of immune escape mechanisms. As a PCAWG-10 working group, RIKEN also analyzed PCAWG WGS data for genome-wide somatic mutations in microsatellite or repeat regions, one of the most difficult regions to analyze by NGS, and defined microsatellite instability (MSI) cancers at a genome-wide level. They also identified highly mutated microsatellites that can be used to detect MSI cancers with high sensitivity.

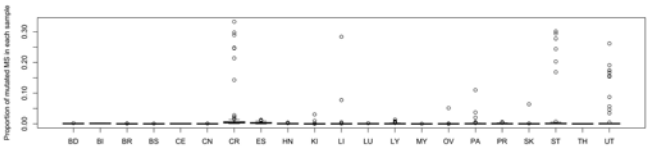


Figure: Mutation rate of 7M microsatellite regions in each type of cancer.
CR (colorectal), ST (stomach), and UT (Uterine) cancers showed a higher mutation rate (>0.3% of 7M) in microsatellite regions, indicating microsatellite instability (MSI).

eQTL project

Integration of genetic information and immune functions

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

We are now using a system to obtain various subtypes of leukocytes from peripheral blood mononuclear cells (PBMCs) from healthy individuals in order to obtain the utmost unbiased relationship between genotypes and gene expression. Cell separation is performed using fluorescence-activated cell sorting into about 20 different subsets. Cells are then analyzed in the steady state or under stimulated conditions, such as with combinations of cytokines and cell surface receptor agonists to capture the dynamic responses of gene regulation. As the first step, genotyping as well as RNA-seq are performed. Subsequently, we also perform epigenetic analyses, specifically focusing on enhancers and promoters, as well as long non-coding RNAs. We believe that cap analysis of gene expression (CAGE), assay for transposase-accessible chromatin using sequencing (ATAC-seq), and analysis of several histone marks for each subset will be powerful tools for identifying the causal relationship between genetic variation and gene expression.

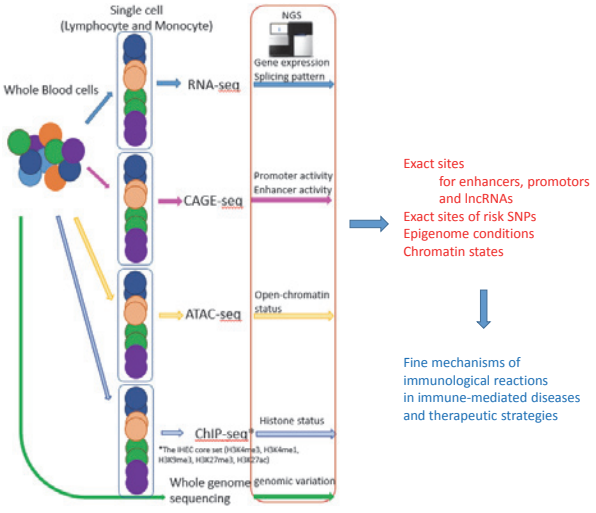


Figure: Integration of genetic information and immune functions: The eQTL project

Search for gut microbiota-associated biomarkers involved in the pathogenesis of T2D

T2D is a highly prevalent metabolic disease worldwide, including in Japan. It has been estimated that approximately 20 million Japanese, as many as 1 out of 5 individuals, suffer from diabetic or prediabetic (medically defined as glucose intolerance) conditions. Therefore, prevention of T2D is an urgent need both socially and economically. To identify T2D-preventive biomarkers or factors involved in the pathogenesis of T2D, individuals with glucose intolerance should be carefully analyzed, instead of already diagnosed and treated T2D patients. To this end, as an IMS center project, we have been collaborating with the University of Tokyo Hospital and recruited three groups (n = 100 each) of volunteers from those undergoing a complete medical checkup: 1) no abnormal examination outcome (control), 2) obesity (BMI ≥ 25), and 3) glucose intolerance (fasting blood glucose ≥ 110 mg/dl and HbA1c ≥ 6.0%) (Fig). 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 are significantly associated with particular sugar derivatives, as are certain bacteria belonging to the family Lachnospiraceae among gut microbes.

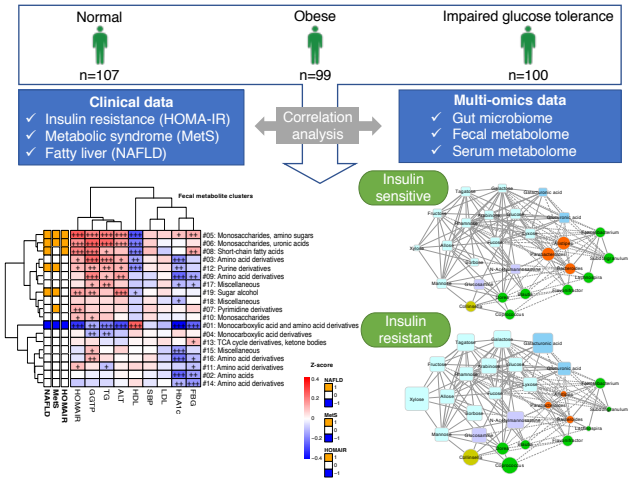


Figure: Correlating clinical and multi-omics data to identify biomarkers involved in the pathogenesis of type 2 diabetes mellitus.
The data in the bottom part of the figure are examples of fecal metabolome analyses.

Medical Sciences Innovation Hub Program (MIH)

We aimed to establish a pipeline for the modeling of pathogenetic processes of human diseases to facilitate discovery of biomarkers and potential targets for therapeutic intervention. Our strategy is to combine the comprehensive study of disease model animals with multimodal data derived from patients. It is therefore necessary to gather, integrate, and analyze clinical data and multimodal data from patient-derived materials. To initiate this process, we have chosen atopic dermatitis (AD) as a model to generate a platform for data collection and integration, and performed a comprehensive study to stratify AD patients based on endophenotypes in collaboration with the RIKEN Medical Innovation Hub (RIKEN-MIH) program and Keio University Hospital. Within this framework, we have so far collected transcriptomic and histological data of skin tissue from approximately 60 AD patients and 25 healthy controls and will ultimately collect 200 and 50 samples from patients and healthy donors, respectively. These data are stored in a fully isolated server installed in RIKEN-MIH and are being integrated to facilitate our mathematical challenge for patient stratification. This collaboration with RIKEN-MIH and external university hospitals will be continued and even expanded to establish a seamless pipeline to collect, analyze, and store patient-derived materials and information in RIKEN.

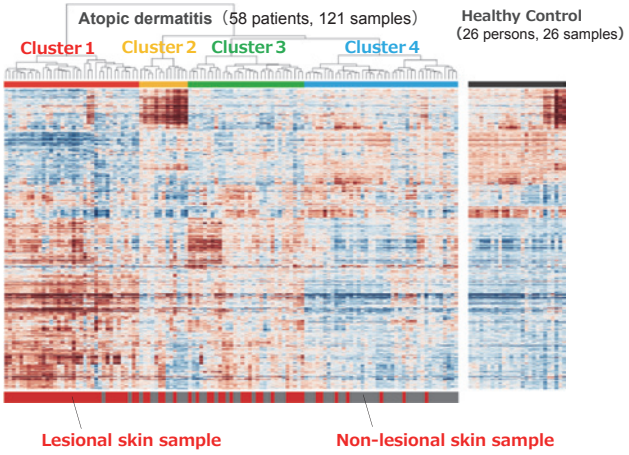


Figure: Unsupervised clustering analysis of skin transcriptomic data identifies four clusters of AD patients.

iPS project

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

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

Differences in human leukocyte antigen class I (HLA-I) genes can cause rejection in an allogeneic transplantation situation. To address this concern, this year, the facility aimed to prepare *Beta-2-Microgloblin* (*B2M*) gene-disrupted human iPS-Vα24$^+$iNKT cells using CRISPR/Cas9 and then they observed a distinct reduction in alloreactive CD8$^+$ T cell-mediated killing (Figure 1). These results suggest that *B2M*-disrupted iPS-Vα24$^+$iNKT cells will be more useful in allogeneic transplantation due to their longer half-life.

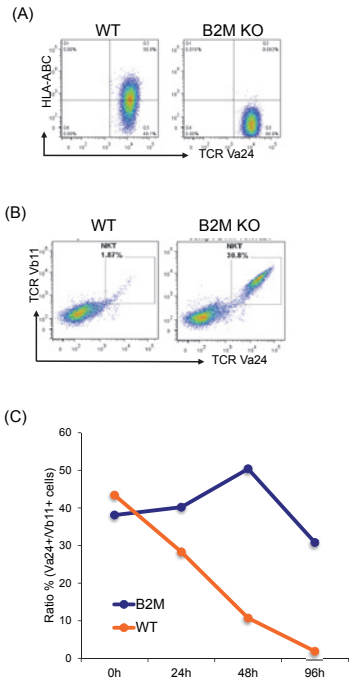


Figure: Minimization of alloreactive CD8$^+$ T cell-mediated killing of HLA class I depleted iPS-Vα24$^+$iNKT cells *in vitro*.
(A) A representative flow cytometry plot of *B2M*-disrupted iPS-Vα24$^+$iNKT cells (B2M KO) showing lack of cell surface expression of MHC class I. Wild type (WT) iPS-Vα24$^+$iNKT cells are shown as a control. (B) A representative flow cytometry plot of a cytotoxic assay of alloreactive CD8$^+$ T cells against B2M KO or WT iPS-Vα24$^+$iNKT cells after 96 hours. The alloreactive CD8$^+$ T cells were prepared from healthy donor-derived PBMC, and they were cultured with B2M KO or WT iPS-Vα24$^+$iNKT cells and analyzed by flow cytometry. (C) Time-course analysis of B2M KO or WT iPS-Vα24$^+$iNKT cells in a cytotoxic assay of alloreactive CD8$^+$ T cells. The frequency of the Vα24$^+$iNKT cell specific TCR (Vα24$^+$ and Vβ11$^+$) cells was calculated at the indicated time points.

Humanized mouse

We have been developing "humanized mice" to study normal human hematopoiesis and immunity as well as human hematologic malignancies. When we transplanted purified human hematopoietic stem/progenitor cells, we could detect multiple human immune subsets in thymus, bone marrow, spleen, and intestinal mucosa. Therefore, the *in vivo* system is valuable to understand how stem/progenitor cells determine their *in vivo* fate and to what extent human immune cells are functional in each organ. Using human immune cells and leukemic cells of humanized mice and those of human individuals, we have been taking a multi-omics approach to measure expression of biologically relevant molecules. By comparing normal and leukemic cells of human origin, we aim to find therapeutic targets that are specifically expressed by leukemic cells. Through multi-faceted analyses, we hope to create therapeutic modalities for poor prognosis leukemia and to find key molecules determining stemness in human hematopoiesis.

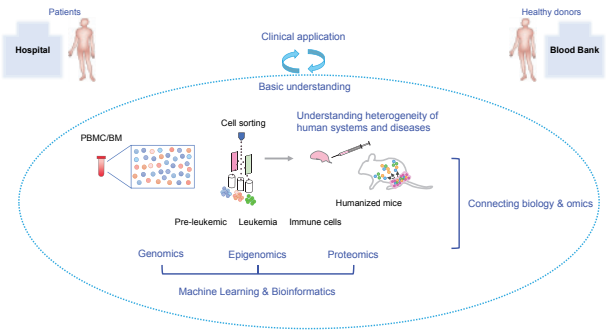


Figure: Connecting human blood/immune cell biology with multi-omics
Peripheral blood mononuclear cells (PBMCs), bone marrow cells, or cord blood are isolated from patients or healthy donors for creating mice recapitulating patient leukemic status or reconstituting normal human blood/immune systems. The generated "humanized mice" have enabled us to study *in vivo* blood/immune cell behavior. Multi-omics approaches and machine leaning also pave the way for a comprehensive analysis of the cellular heterogeneity of human hematopoiesis and drug development for leukemia.

Cancer immunology

We regard cancer immunology as an interdisciplinary branch of immunology, since cancer represents a failure of homeostasis of the immune system, involving many components. The first goal of cancer immunology is to understand the role of immune system immunoediting in the development and progression of cancer. An understanding of this process will lead to the stratification of cancer diseases by identification of the target molecules or antigens for immune recognition of cancer. Several groups initiated the cancer immunology theme. Ishikawa's and Fujii's groups recently demonstrated the important function of T cell subsets and NKT/NK cells, respectively, in the regulation of progression of some cancers. The second goal of the cancer immunology group is to develop a cancer immunotherapy strategy to treat cancer by enhancing the host protective response. We have several translational research projects aiming at application of NKT cell therapy, including iPS-NKT and aAVC therapy. Among them, Koseki's group has almost completed an iPS-NKT cell preclinical trial. Fujii's group has launched a Phase I clinical trial of aAVC-WT1 therapy in acute myeloid leukemia. These projects have been supported partly by the Japan Agency for Medical Research and Development (AMED) as well as the RIKEN Drug Discovery and Medical Technology Platforms (DMP). In addition, as a clinical study, Fujii's group has been collaborating with 15 National Hospital Organization (NHO) hospitals using autologous iNKT cell ligand-loaded DC therapy in a randomized phase IIa trial in early-stage lung cancer patients. In this study, they have been performing immunological analyses of the patients.

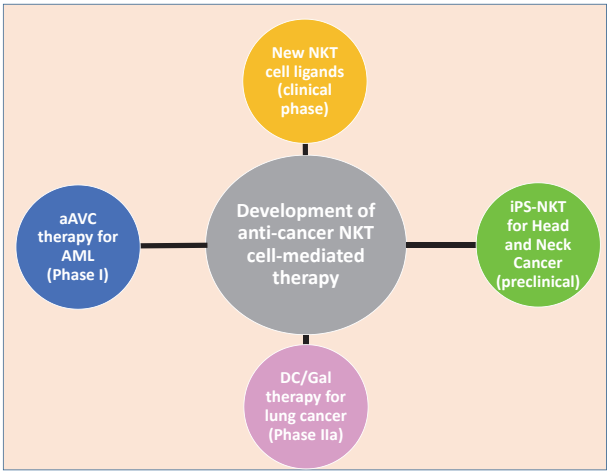


Figure: NKT cell-mediated anti-cancer projects in IMS as translational research

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

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

IMS collaborates with DMP to develop innovative new pharmaceuticals and medical technologies by facilitating the transfer of basic research within the institute. DMP was founded in RIKEN in 2010 in order to support all phases of development of new therapeutics, from the discovery of promising targets to the identification of potential lead compounds, such as small molecules and antibodies, and the acquisition of intellectual property rights to drugs and technologies that can then be brought to the development phase.

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

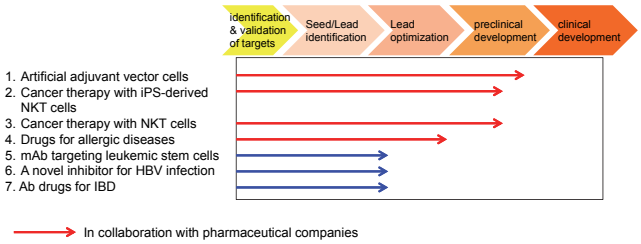


Figure: Collaboration between IMS and DMP for the development of innovative new pharmaceuticals and medical technologies

In memory of Dr. Kimishige Ishizaka
(Dec 3, 1925-Jul 6, 2018)

Photo: Dr. Kimishige Ishizaka
(at the celebration party of his 80th birthday in 2006)

Dr. Kimishige Ishizaka passed away at 7:58 am on July 6th, 2018. Dr. Ishizaka was born on December 3rd, 1925 and he would have turned 93 years old in December of this year. He made many invaluable contributions to the development of our research center, RIKEN Center for Integrative Medical Sciences (IMS). Beginning in 2001, he was the Senior Advisor of our former Center, RIKEN Research Center for Allergy and Immunology, and held that position for twelve years.

Dr. Ishizaka and his wife, Teruko, conducted their research in the US for over 35 years and made several important discoveries during that period, including the discovery of the long-elusive IgE antibody isotype, which elicits allergic reactions. Dr. Ishizaka held positions as Director of the Immunology Department at Johns Hopkins University School of Medicine, President of La Jolla Institute of Allergy and Immunology (LJI), President of the American Association of Immunologists, and Adjunct Professor at the University of California, San Diego. After his return to Japan, his presence at our research center as the Senior Advisor was an inspiration and helped us pull together for the Center's research projects.

LJI and IMS, the two research institutions that Dr. Ishizaka supported during their establishment, continue to collaborate with the goal of overcoming immune-related diseases. The collaborating laboratory, led by Dr. Hilde Cheroutre, has been actively working at IMS to understand the gut mucosal immune system.

Allergy continues to be one of the most important research topics in our Center. From the large-scale ENU mutagenesis project, launched in 2001, we successfully isolated an atopic dermatitis mouse model, named the *Spade* mouse. Using this mouse model, multiple laboratories in the Center and clinical dermatologists at university hospitals collaborate for the elucidation of atopic dermatitis pathogenesis. IMS allergy research has expanded to become a multidisciplinary project involving immunology, genomics, epigenetics, neuroscience, informatics, and clinical medicine. In addition, young researchers are pioneering new concepts for the regulation of asthma and other allergic diseases by the innate immune system.

The scientific discoveries that Dr. Ishizaka left us, and his strict but collaborative attitude toward science, will continue to remain in our hearts and inspire us forever.

Tadashi Yamamoto
Director,
RIKEN Center for Integrative Medical Sciences

Dr. Kimishige Ishizaka was an invaluable mentor for the members of the RIKEN Center for Allergy and Immunology (RCAI), currently restructured as the RIKEN Center for Integrative Medical Sciences (IMS).

Approaching the end of the year in 2000, I received a facsimile message on December 29th. It was announcing that the establishment of a research center for allergy and immunology had been approved in the government budget for 2001, Dr. Ishizaka was appointed as the chairman of the establishment committee, and he asked me to cooperate for the creation of a basic research institution to contribute to allergy and immune regulation fields. Later, the President of RIKEN appointed me as the Director of the Center and Dr. Ishizaka as the Senior Advisor. Thus, Japan's first research institution dedicated to allergy and immunology was founded with the support of 300 million yen from the government. This could not have been realized without Dr. Ishizaka.

In 1966, at the Children's Asthma Research Institute and Hospital in Denver, Colorado, Dr. Ishizaka and his wife, Dr. Teruko Ishizaka, discovered a novel antibody isotype that was associated with allergy (so-called "reagins"). At that time, researchers could not isolate reagins by immunoprecipitation or other biochemical techniques, and the nature of reagins had remained a mystery for 40 years. However, Dr. Ishizaka predicted the existence of extremely low concentrations of reagins in the "IgA fraction" of serum, by demonstrating that reagin activity in the IgA fraction remained the same after IgA neutralization. The only way to prove his hypothesis was to monitor the existence of reagin by intradermal tests.

After moving to the Children's Asthma Research Institute and Hospital in Denver, Dr. Ishizaka and his wife Teruko identified reagins from a truck-load of atopic patients' serum by using an intradermal test on the skin of their own backs to monitor the reagin activity during purification. Further, by using radioisotope-labeled antigens, they finally detected reaginic antibody by agarose-gel immuoelectrophoresis. They named this novel class of immunoglobulin, IgE, which was unique from the already known immunoglobulins, IgG, IgM, IgA and IgD.

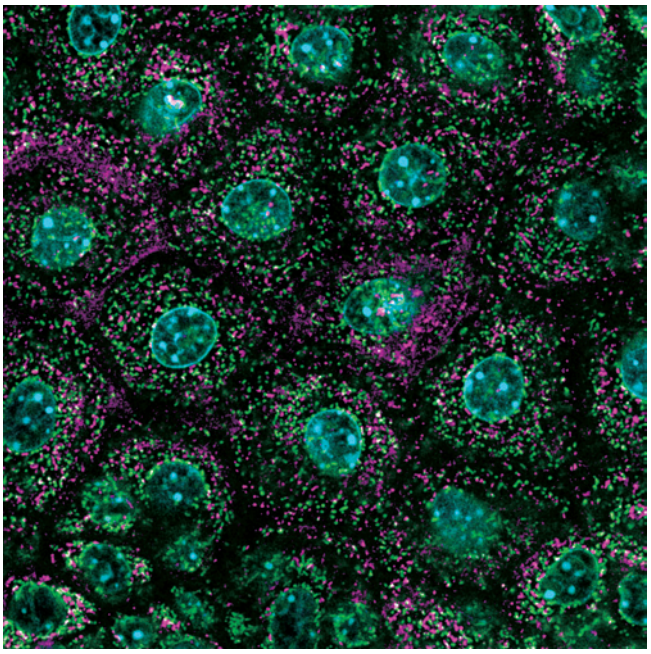
In 1989, Dr. Ishizaka became the Founding Director of the La Jolla Institute for Allergy and Immunology (LJI), where he trained many young investigators. In 1996, the Ishizakas returned to Teruko's hometown in Yamagata, Japan, but Teruko was hospitalized because of her illness. Dr. Ishizaka spent his time with Teruko in her hospital room, but he still managed to attend the Japanese government's research council, monthly meeting of The Japan Academy, research lectures, and Clinical Allergy Strategic Meetings held at the newly established RCAI every month. At RCAI, he participated as an active researcher in the development of an allergy vaccine that suppress IgE production.

I strongly believe that Dr. Ishizaka's research attitude and his research philosophy will be the best model for young scientists and the future leaders in immunology.

Masaru Taniguchi
Senior Visiting Scientist,
Program for Drug Discovery and Medical Technology Platforms,
RIKEN Cluster for Science, Technology and Innovation Hub

Part 4

Events



Human Genome Meeting 2018

The RIKEN Center for Life Science Technologies (CLST) co-hosted the 22nd Human Genome Meeting (HGM) on March 12-15, 2018 at RIKEN's Yokohama campus and the convention center, Pacifico Yokohama. Marking the second time for Japan to host the conference after it was held in Kyoto in 2005, it attracted 460 scientists and other professionals from 39 countries/regions, who presented and discussed a variety of topics related to genome research.

The meeting, once dedicated to the human genome mapping project, is now a major annual scientific conference on human genetics and genomics, genomic medicine, and genome biology and is organized by the Human Genome Organization. Dr. Piero Carninci, former deputy director of CLST and now deputy director of the Center for Integrative Medical Sciences (IMS) chaired the local organizing committee.

The theme of this year's meeting was genome data and health. Topics discussed included genome editing, single-cell biology, and cancer genomics. RIKEN has played a vital role in the international efforts to sequence the human genome, and continues to be a major contributor to developing next-generation genome sequencing technologies, international genome-wide association studies, and the International HapMap Project, a project to develop a haplotype map of the human genome that will describe the common patterns of human genetic variation. RIKEN also leads the FANTOM project to identify the fundamental roles of the non-coding regions of the genome, including non-coding RNAs.

Japan Prize awarded to Dr. Max D. Cooper

On April 18th, 2018, the Japan Prize* was awarded to Dr. Max D. Cooper and Dr. Jacques Miller for their discovery of B and T cell lineages and its impact on understanding normal lymphocyte development and function as well disease pathology and on development of immunotherapeutics.

Dr. Cooper, Professor of Pathology and Laboratory Medicine at Emory University School of Medicine in Atlanta, Georgia, is known for his early work on the recognition of T and B lymphocytes as developmentally separate, functionally intertwined cell lineages. Other research highlights of Dr. Cooper and his collaborators include the identification of B cell precursors and their hematopoietic origin, demonstration that IgM-bearing B cells can switch to produce other classes of antibodies and discovery of an alternative adaptive immune system in jawless fish, such as lampreys and hagfish. Dr. Cooper studies immune system evolution, development and function to gain insight into the pathogenesis of blood cell malignancies, immune deficiencies, and autoimmune diseases.

It was a happy surprise and also a big honor for IMS researchers that Dr. Cooper received the Japan Prize, because he has made significant contributions to RIKEN, specifically to the former Research Center for Allergy and Immunology (RCAI) and then IMS, as Chair of the Advisory Council since 2004. He has visited IMS 10 times since 2004 and interacted with and advised many of the researchers.

On April 23rd, 2018, a commemorative symposium, "Immune system: the discovery of B/T lymphocytes and more," was held at IMS and attended by 110 people. After the opening remarks by IMS Director, Dr. Yamamoto, two IMS researchers gave presentations, "Lymphocytes with innate functions" by Dr. Koyasu and "Excessive T cell activation in the absence of PD-1 affects behavior" by Dr. Fagarasan. After that, Dr. Kuratani from the RIKEN Center for Biosystems Dynamic Research in Kobe introduced his research on morphological evolution "Development of cyclostomes and early evolution of vertebrates," and then Dr. Cooper gave his special lecture on "Evolution of T and B cells." At the closing remarks, Dr. Taniguchi, former RCAI Director, congratulated Dr. Cooper on the award and gave special thanks for his long-time contributions to IMS and RCAI.

Group photo with Dr. Cooper and his wife Rosalie (first row, center)

*Japan Prize: https://www.japanprize.jp/en/index.html

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 second RIKEN IMS-Stanford ISCBRM Joint Symposium, "Bridging Immunology, Stem Cell Biology, and Regenerative Medicine," was held May 23-24, 2018, at the RIKEN Yokohama Campus. The symposium was opened with introductory remarks from RIKEN IMS Director Tadashi Yamamoto and Stanford ISCBRM Director Irv Weissman. Nine participants from Stanford attended the symposium and presented their latest research along with 11 RIKEN IMS scientists. During the two-day symposium, four sessions were held covering the topics of cancer immunology, developmental biology, hematopoietic stem cells, single-cell analysis, and other genomic technologies. Closing remarks were delivered by Drs. Weissman and Yamamoto, including a special address by RIKEN Executive Director Shigeo Koyasu. During the course of the two days, both one-on-one and group discussions were held among the participants to talk about ongoing collaborations and the establishment of new ones. The symposium ended with a closed lunch session at which the members discussed future directions of the collaboration.

The IMS-JSI International Symposium on Immunology 2018

The IMS-JSI International Symposium on Immunology, hosted by the RIKEN Center for Integrative Medical Sciences (IMS) in conjunction with the Japanese Society for Immunology (JSI), was held on June 7-8 at the Ito Hall, Ito International Research Center, the University of Tokyo. The symposium, entitled "Checkpoint in medical science and its technology", included nineteen outstanding speakers presenting their research and attracted more than 350 participants. There were four sessions: (1) Fundamental aspects of immunology, (2) Functional genomics of lymphocytes, (3) Systems biology, and (4) Cancer immunology/Immunotherapy. In addition, we invited several young investigators to present their work in each session. These broad research topics stimulated participants and led to very active and provocative discussions. New technologies such as single-cell gene expression profiling and metabolome analysis added a new research layer to this medical science field. Aided by such technologies, we have begun to understand better and more deeply the integrative nature of the immune system and the networks governing immune responses. Large combined datasets from genetic and epigenetic analyses will help to explain the origins and features of various human diseases. Furthermore, we have begun to explore the important connections between the immune system, environmental factors, and other organs and tissues such as the brain and muscle. To our great honor, we had Professor Tasuku Honjo of Kyoto University speaking in this symposium about cancer immunotherapy by PD-1 blockade. We are truly delighted that half a year later he received the 2018 Nobel Prize in Physiology or Medicine.

ZPM-RIKEN Symposium

RIKEN and ZPM (Center for Personalized Medicine) in UKT (University Hospital Tübingen) have common interests in life and medical sciences and are complementary to each other in several fields. We held the first ZPM-RIKEN symposium on July 16-17th, 2018, at Tübingen University, Germany. The goal of this symposium was to begin to establish international collaborations between these two groups and to exchange information and human resources.

At the opening session, Dr. Malek described the 3M Institute (microbiota-mice-mathematics or malignoma-metablome-microbiome) and large-scale patient registration in University Hospital Tübingen, which can accumulate big health data. There were four sessions that covered 3M concept research of both sides.

(1) Microbiome and regulation of inflammation

Microbiome, lipidome, and IBD models were discussed.

(2) Data integration and systems biology

Ideas were exchanged on systems medicine, as an expansion of systems biology, and the application of machine learning for biomedical data.

(3) Signaling and cancer therapy

Cell-cycle, cell death signaling, immunology, and kinase chemistry for new cancer therapies were discussed.

(4) Imaging and genomic technologies

In vivo imaging for immune cells and lipids, single-cell sequencing, whole genome sequencing, and liquid biopsy sequencing were discussed.

In the breakout session, each subgroup discussed potential collaboration projects for each field and an exchange program for young researchers or students.

(1) Data integration

The vision of joint systems biology approaches for prediction in personalized medicine to develop machine learning-based treatment recommendations was discussed.

(2) Microbiota/Inflammation

Several potential collaboration projects such as gastrointestinal physiology and lipidomics were discussed.

(3) Signaling and Cancer Imaging

How to utilize various mouse models to develop imaging technologies for cancer and immunology were discussed.

(4) Genomics

As the first potential collaboration topic, the group decided to focus on a longitudinal single-cell multi-OMICS study of glioma patients.

In conclusion, this two-day joint symposium was quite productive. We found many topics in common and developed ideas for future collaborations.

RIKEN-KI-SciLifeLab Symposium 2018

This symposium series is organized between RIKEN and the Karolinska Institutet/SciLifeLab in Sweden. The symposium venue alternates between RIKEN and SciLifeLab. The overall main goals of the symposia are a) to identify common scientific interests between RIKEN and SciLifeLab, b) to identify complementary skills and technologies for collaborations, and c) to encourage the exchange of PhD students and postdocs between RIKEN and SciLifeLab/KI.

Several collaborations between groups at SciLifeLab and RIKEN started based on initial contacts during one of these symposia. There are also several examples of PhD students from SciLifeLab visiting RIKEN for a research stay.

The 5th Joint RIKEN-Karolinska Institutet/SciLifeLab Symposium was held on September 20-21, 2018, in Stockholm with the title *Artificial Intelligence Meets Life Science*. Eighteen short scientific presentations were given for 120 participants on the first of two days, covering a range of research topics developing and employing artificial intelligence (AI) at RIKEN, Karolinska Institutet, and SciLifeLab. On the second conference day, around 40 participants discussed their perspectives and the currently perceived

challenges in applying AI methods to life science data, including biomedical data.

The 6th Joint RIKEN-Karolinska Institutet/SciLifeLab Symposium is planned for 2019 in Yokohama.

RIKEN-Luxembourg Joint Symposium and Workshop

On September 25-26, 2018, the second Joint RIKEN-Luxembourg Symposium and Workshop was held at the University of Luxembourg Belval Campus. Members from both RIKEN IMS and the RIKEN Medical Sciences Innovation Hub Program (MIH) participated in the two-day event along with scientists from the University of Luxembourg (UL) Luxembourg Centre for Systems Biomedicine (LCSB) and Life Sciences Research Unit (LSRU), the Luxembourg Institute of Health (LIH), the Integrated BioBank of Luxembourg (IBBL), the National Public Health Laboratory (LNS) and the Luxembourg National Research Fund (FNR). On the first day of the symposium, after a brief welcome by Prof. Dr. Stéphane Pallage, Rector of the University of Luxembourg, a ceremony was held for the main conference room at the Luxembourg Centre for Systems Biomedicine to be named the "RIKEN Conference Room." This was followed by speeches from Ms. Lydia Mutsch, Luxembourg Minister for Health, and Mr. Shigeji Suzuki, the Japanese Ambassador to Luxembourg. Members from Luxembourg then briefly explained their internationalization strategy in healthcare, science, and innovation. Representatives from both countries then presented an overview of current collaborations and plans for future expansion. This was followed by three scientific sessions on the immune system and metabolism in ageing, barrier function along the microbiome-gut-brain axis, and precision systems biomedicine. On the morning of the second day, the RIKEN members

were given tours of several of the Luxembourg institutes (i.e., LIH, LNS, IBBL, and LCSB), and, in the afternoon, a joint workshop was held on establishing a RIKEN Laboratory in Luxembourg together with representatives from the FNR, Luxinnovation, the Luxembourg Ministry for Health, and the Ministry for Higher Education and Research. The two-day event concluded with both parties agreeing to further strengthen their relationship through the expansion of research activities, particularly focusing on the role of gut-brain interactions and barrier function in relation to neuro-inflammatory and neurodegenerative conditions, through the creation of a RIKEN outpost laboratory in Luxembourg that could facilitate research stays for Japanese scientists.

Single Cell Symposium

The RIKEN Center for Integrative Medical Sciences (IMS) organized the Single Cell Science Symposium 2018 on October 9th, 2018 in Jiji Press Hall, located in Ginza, Tokyo. There were over 200 attendees and 11 individuals who presented at the meeting.

Single-cell technologies are becoming increasingly important tools in biological analysis. Complementing average measurements on bulk populations of cells, single- cell measurements provide a finer-grained picture of complex biology and reveal heterogeneity that is present in all tissues.

This one-day symposium, first held in 2017, is a series of meetings that address advanced technologies for single-cell analysis in genomics. This year, the symposium also expanded their topic coverage to include clinically relevant human tissues and computational approaches for analysis of single-cell data. This meeting brought together a broad Japanese community of biologists, clinicians, technologists, physicists, computational scientists, software engineers, and mathematicians who are involved in single-cell biology and also discussed new projects as part of the Human Cell

Atlas Japan initiative. This community of scientists with diverse expertise shares the common goal of creating a comprehensive reference map of all human cells as a basis for understanding human health and diagnosing, monitoring, and treating diseases. Their goal is to meet the needs of medical communities in Japan. Details of the program can be seen at http://www.ims.riken.jp/?p=3539

RIKEN - McGill Symposiums

Since 2016, the RIKEN IMS and the McGill University Faculty of Medicine have established close interactions to pursue research in the areas of genomics, immunology, and cancer across a broad range of diseases, with the first comprehensive cooperation agreements/MOUs between the two institutes beginning as early as July 2010. The first symposium was held in May 2017 at McGill University, Montreal, Canada. In 2018, two symposia were held. The second symposium, "Immunology, Cancer, RNA & Genetics," took place February 19-20 at the RIKEN Yokohama Campus. Opening remarks were delivered by Dr. Ichiro Taniuchi, followed by special greetings from RIKEN Executive Director Shigeo Koyasu and Luci Tremblay, representative from Québec's Delegate General in Japan. During the course of the two days, seven sessions covering the topics of infection and immunity, cancer, RNA biology, and human genomics were held, including one session for young scientists. Eleven researchers from McGill University gave presentations along with an equal number of RIKEN scientists. The symposium ended with both open general and group discussions to exchange opinions, and a closed discussion for setting collaborative projects and future planning. The third symposium, "Joint Initiatives in Genomics, Immunology and Cancer," took place November 12-13 at McGill University. During the first day, nine RIKEN scientists gave presentations in four sessions covering

the topics of genomic approaches and cohort studies for population health, genome biology and technologies, immunology and disease, and other methodologies, and one session with talks from postdoctoral fellows and students. The second day consisted of a closed discussion session where members from both institutes discussed potential funding opportunities and topics for further collaboration, as well as future directions.

RIKEN -Tsinghua Joint Symposium

On November 16, 2018, IMS held the fourth RIKEN-Tsinghua Joint Symposium "Towards the Integration of Basic and Human Immunology". There were 11 participants from the Institute for Immunology, Tsinghua University (IITU) in China and 10 speakers from Japanese institutions, including 4 from Japanese universities and 6 from IMS.

In the first session, Kazuhiko Yamamoto (IMS), Yun-Cai Liu (IITU), and Chung Chau Hon (IMS) discussed how recent genetic and epigenetic studies have impacted contemporary biomedical research. In their talks, they showed examples of genetic and epigenetic regulation of normal immune cell development and differentiation, and their relationships with diseases, as well as the potential involvement of long non-coding RNAs in both processes.

In the following sessions, Toshinori Nakayama (Chiba University) described the newly discovered fibrosis-inducing pathogenic Th2 cells, and he suggested the potential for new treatments of fibrosis-induced allergic disorders based on these findings. Wataru Ise (Osaka University) discussed a new model of germinal center (GC) B cells, in which the stability of contacts between T follicular helper cells and GC B cells is the key for plasma cell-prone GC cell formation. Heiichiro Udono (Okayama University) introduced his recent discovery that metformin, an anti-diabetic drug, activates CD8 T lymphocytes and shows significant tumor growth inhibition *in vivo*. Meng Michelle Xu (IITU) explained her discovery of anti-tumor immunity controlled through an mRNA N6-methyl-

adenosine (m6A) methylation program and a new potential target for anticancer immunotherapy. Finally, Akiharu Kubo (Keio University) introduced his research on skin biology, focusing on the spatiotemporal replacement of tight junctions, a mechanism that maintains skin barrier functions.

The second day was reserved for individual discussions among the researchers. This joint symposium was supported by the JSPS-NSFC bilateral program.

In 2019, the IITU-RIKEN Summer Program will be held at Tsinghua University in Beijing, and the fifth Tsinghua-RIKEN Joint Symposium will be held in 2020. These joint activities will continue to enhance communication between Japan and China in the field of biomedical sciences.

Harvard Summer School 2018

IMS offers a summer internship program for undergraduate students from Harvard University. In this program, students do a research internship in IMS laboratories, have basic biomedical science lectures given by PIs from IMS and other centers, and attend a Japanese language course. They also participate in the RIKEN IMS-JSI International Symposium on Immunology. The participants receive a letter grade from IMS and course credit from Harvard. In 2018, we accepted four students, Gabriela Pelayo, Shivani Aggarwal, Terzah Hill, and Eugene Oh, from Harvard University into the summer program, which was held from June 4th to August 13th.

Ms. Pelayo conducted her research on the theme of "Understanding *in vivo* dynamics of human leukemia and immunity" in the Laboratory for Human Disease Models (Dr. Ishikawa). She learned gene expression profiling and identified several potential therapeutic targets for poor-prognosis acute myeloid leukemia. Ms. Aggarwal studied "Pulmonary localization of ILC2s in asthma" in the Laboratory for Innate Immune Systems (Dr. Moro). By using c-Kit-GFP reporter mice, she visualized that ILC2s localize near the blood vessels with eosinophils under IL-33 stimulation. Ms. Hill worked on "Dissecting roles of Cbfb2 isoform during immune cell development" in the Laboratory for Transcriptional Regulation (Dr. Taniuchi). She learned two techniques for measuring the expression level of a target protein: immunoblot and FACS analysis. Mr. Oh studied "Identification of proliferating thymic epithelial cells essential for preventing onset of autoimmunity" in the Laboratory for Immune Homeostasis (Dr. Akiyama). He found a novel cell subset in thymic epithelial cells essential for preventing autoimmunity. During their internships, the students had numerous discussions with IMS researchers, and at the end of the program, they gave oral presentations describing their research results.

Photo: from the left in the front row, Director Yamamoto, Ms. Hill, Mr. Oh, Ms. Aggarwal, and Ms. Pelayo.

International Conference on Innate Lymphoid Cells

The 3rd International Conference on Innate Lymphoid Cells (ILC2018) was held from November 29 to December 1, 2018, at the Ito International Research Center of the University of Tokyo under the auspices of RIKEN IMS. Since the discovery of multiple subsets of ILCs a decade ago, these cells have established themselves as new and significant players in the field of immunology, contributing to tissue homeostasis as well as defense against pathogens and inflammatory diseases. We set the theme of the conference as "Towards the next generation" and invited up-and-coming independent researchers, while senior researchers in the field were asked to be members of the international program committee and session chairs. We covered several general topics on innate lymphocytes, including NKT, MAIT, and γδT cells. We received over 140 abstracts from 19 countries and welcomed about 300 participants. It was noteworthy that 75% of abstracts and 60% of participants were from abroad, making the conference truly international. Throughout the three-day conference, multiple topics, from developmental pathways of innate lymphocytes to their pathophysiological roles in various diseases, were presented at both oral and poster sessions and discussed with excitement in a warm and friendly atmosphere. As expected, the younger generation certainly showed us their potential to contribute to the future development of the ILC research field. The conference was adjourned after the announcement of the next conference, which will be held in San Francisco in 2020.

http://www2.convention.co.jp/ilc2018/welcome.html

IMS Retreat 2018

The RIKEN IMS retreat is an annual event where members of the center meet and share their scientific knowledge and skills. The IMS retreat 2018, the first such event as a newly reformulated center, featured "Team building" as the main theme, aiming to facilitate new interactions between groups with different backgrounds. Around 230 people including PIs, researchers, technical staff, and students gathered together on December 14 at Yokohama Sambo Hall, about 40 minutes' distance by public transport from the RIKEN Yokohama campus. In team building sessions, 27 teams of 8 members from various positions and with different scientific backgrounds competed against one another in two group projects. The first was to build the tallest tower in 30 minutes using only newspapers. The winning team successfully built a tower over 3 meters high, an achievement that was far beyond the expectations of the organizers. The second group project was a brainstorming exercise to come up with crazy ideas about how to spend 5 quadrillion JPY for happiness and human well-being for a better future. After 50 minutes of discussion, all teams presented many varieties of unique ideas, such as building a Moon-Earth tower, Global education for future happiness, *In vitro* reproduction system, and Inventing a super robot. Finally, the grand prix was awarded to a group who presented, while singing and dancing, a unique plan to save postdoctoral fellows.

In the afternoon poster session, each lab introduced its research and "Seeds and Needs" in science and technology, aiming to explore future research collaborations within the new center. Through their interactions at the retreat, the participants created new personal exchanges and the event was successfully completed.

Adjunct professorship programs

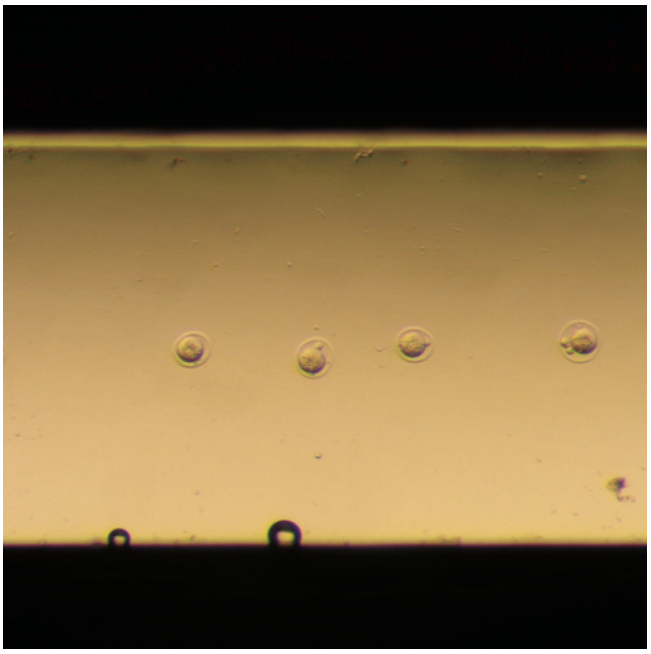
IMS collaborates with and accepts graduate students from 8 domestic university graduate schools. There are now a total of 32 adjunct professors/associate professors in IMS (Table), and 61 students studied at IMS in 2018. On September 1st, 2018, IMS held a briefing session on adjunct graduate school programs to provide an opportunity for students to visit and talk directly with lab leaders and to consider their future directions.

Table: Joint graduate school programs

Graduate Program	Affiliated IMS Investigator
Graduate School of Medicine, Osaka University	Takashi Saito (Visiting Professor), Takashi Tanaka (Visiting Professor), Kazuyo Moro (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 Associate Professor), Kaoru Ito (Visiting Associate Professor), Momoko Horikoshi (Visiting Associate Professor)
Graduate School of Medical Life Science, Yokohama City University	Hiroshi Ohno (Visiting Professor), Makoto Arita (Visiting Professor), Takaharu Okada (Visiting Professor), Kazuyo Moro (Visiting Professor), Piero Carninci (Visiting Professor), Yukihide Momozawa (Visiting Professor), Hideya Kawaji (Visiting Associate Professor), Hidehiro Fukuyama (Visiting Associate Professor)
Research Institute of Biological Sciences, Tokyo University of Science	Masato Kubo (Professor), Takashi Saito (Visiting Professor)
Graduate School of Medicine, Kyoto University	Fumihiko Ishikawa (Visiting Associate Professor)
Graduate School of Medicine, Keio University	Masayuki Amagai (Professor), Kenya Honda (Professor), Shigeo Koyasu (Visiting Professor), Haruhiko Koseki (Visiting Professor)

Part 5

Data and Statistics



Award winners 2018

Name of the awardee	Name of the award	Date of the announcement
Piero Carninci, Team Leader, Laboratory for Transcriptome Technology	The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, Prizes for Science and Technology, Research Category	Apr 2018
Hiroshi Ohno, Team Leader, Laboratory for Intestinal Ecosystem	The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, Prizes for Science and Technology, Research Category	Apr 2018
Haruhiko Koseki, Team Leader, Laboratory for Developmental Genetics	55th ERWIN von BALZ PRIZE	Nov 2018
Hiroshi Ohno, Team Leader, Laboratory for Intestinal Ecosystem	The Hideyo Noguchi Memorial Award for Medical Science	Nov 2018
Kazuyo Moro, Team Leader, Laboratory for Innate Immune Systems	The 8th Nagase Prize	Sep 2018
Masayuki Amagai, Team Leader, Laboratory for Skin Homeostasis	Honorary Member of the Society for Investigative Dermatology (SID)	Nov 2018
Shin-ichiro Fujii, Team Leader, Laboratory for Immunotherapy	RIKEN Eiho Award	Jun 2018
Michiel de Hoon, Team Leader, Laboratory for Applied Computational Genomics	RIKEN Baiho Award (RIKEN Excellent Achievement Award)	Jun 2018
Kenya Honda, Team Leader, Laboratory for Gut Homeostasis	Highly Cited Researchers 2018 by Clarivate Analytics	Nov 2018
Kenya Honda, Team Leader, Laboratory for Gut Homeostasis	The 87th Kitasato Award	Jun 2018
Haruhiko Koseki, Team Leader, Laboratory for Developmental Genetics	RIKEN Industry Partnerships Contribution Award FY2018	Nov 2018
Kaoru Ito, Team Leader, Laboratory for Cardiovascular Diseases	Best Reviewer Award 2017, International Heart Journal	Mar 2018
Kosuke Miyauchi, Deputy Team Leader, Laboratory for Cytokine Regulation	2018 Academic Award, Japanese Society of Interferon & Cytokine Research	Jul 2018
Takashi Kanaya, Senior Scientist, Laboratory for Intestinal Ecosystem	The 13th Japanese Society for Immunology (JSI) Young Investigator Award	Dec 2018
Yuuri Yasuoka, Research Scientist, Laboratory for Comprehensive Genomic Analysis	Young Scientists' Excellent Oral Presentation Award, The 20th Annual Meeting of the Society of Evolutionary Studies, Japan	Aug 2018
Senko Tsukuda, Research Scientist, Liver Cancer Prevention Research Unit	Taisho Toyama Award, Liver Forum Award	Jun 2018
Michio Miyajima, Research Scientist, Laboratory for Mucosal Immunity	RIKEN Research Incentive Award	Mar 2018
Takahiro Suzuki, Senior Scientist, Laboratory for Cellular Function Conversion Technology	RIKEN Research Incentive Award	Mar 2018
Hazuki Takahashi, Special Fixed Term Contract Researcher, Laboratory for Transcriptome Technology	RIKEN Technology Incentive Award	Mar 2018
Marina Lizio, Postdoctoral Researcher, Laboratory for Genome Information Analysis	RIKEN Technology Incentive Award	Mar 2018
Takahiro Suzuki, Senior Scientist, Laboratory for Cellular Function Conversion Technology	RIKEN CLST Researcher Incentive Award	Mar 2018
Marina Lizio, Postdoctoral Researcher, Laboratory for Genome Information Analysis	RIKEN CLST Technician Incentive Award	Mar 2018
Hazuki Takahashi, Special Fixed Term Contract Researcher, Laboratory for Transcriptome Technology	RIKEN CLST Technician Incentive Award	Mar 2018
Yudai Iino, Student Trainee, Laboratory for Metabolomics	Best Presentation Award, 17th Pharma-Bioforum of the Pharmaceutical Society of Japan	Sep 2018
Mio Yoshida, Student Trainee, Laboratory for Metabolomics	Presentation Award, 17th Pharma-Bioforum of the Pharmaceutical Society of Japan	Sep 2018
Joachim Luginbuehl, Research Scientist, Laboratory for Advanced Genomics Circuit	Award for Oral Presentation, The 22nd Human Genome Meeting Trainee Symposium	Mar 2018
Jordan Ramilowski, Research Scientist, Laboratory for Genome Information Analysis	Award for Best Poster Presentation, The 22nd Human Genome Meeting	Mar 2018
Hazuki Takahashi, Special Fixed Term Contract Researcher, Laboratory for Transcriptome Technology	Award for Best Poster Presentation, The 22nd Human Genome Meeting	Mar 2018
Saumya Agrawal, Postdoctoral Researcher, Laboratory for Applied Computational Genomics	Award for Outstanding Poster Presentation, The 22nd Human Genome Meeting	Mar 2018
Tsukasa Kouno, Research Associate, Laboratory for Advanced Genomics Circuit	Award for Outstanding Poster Presentation, The 22nd Human Genome Meeting	Mar 2018
Yasutaka Motomura, Research Scientist, Laboratory for Innate Immune Systems	Poster Award, Medical Science Prize, FY2017 SPDR&FPR Presentation of research results	Jan 2018
Yasutaka Motomura, Research Scientist, Laboratory for Innate Immune Systems	Immunity Poster Award, The 3rd International Conference on Innate Lymphoid Cells (ILC2018)	Dec 2018
Yudai Iino, Student Trainee, Laboratory for Metabolomics	Poster Award, Lipoquality, JSPS Scientific Research on Innovative Area	Jun 2018
Sonoko Takahashi, Student Trainee, Laboratory for Tissue Dynamics	Poster Award, Symposium of the Division of Pharmacology and Drug Therapeutics, Pharmaceutical Society of Japan	Aug 2018
XianYang Qin, Research Scientist, Liver Cancer Prevention Research Unit	Federation of American Societies for Experimental Biology (FASEB), Travel Award	Jun 2018
Tadashi Takeuchi, Student Trainee, Laboratory for Intestinal Ecosystem	Ursula and Fritz Melchers Travel Award, Japanese Society for Immunology	Dec 2018

Guest lectures 2018

Table: Guest Lectures Jan-Dec 2018

Date	Speaker	Affiliation	Country	Title
15-Jan-18	Prof. Bing Zhu	Institute of Biophysics, Chinese Academy of Sciences	China	Establishment and maintenance of epigenetic information
30-Jan-18	Prof. Yi Zhang	Harvard Medical School	USA	Epigenetic and chromatin reprogramming at the beginning of mammalian life
2-Feb-18	Dr. Paola Laurino	Okinawa Institute of Science & Technology	Japan	A journey from an ancient finger print of Rossmann fold enzymes to cofactor engineering
6-Feb-18	Dr. Nicholas F. Parrish	Vanderbilt University Medical Center	USA	Interfering small RNAs derived from endogenous viral elements in mammals: a Eukaryotic CRISPR?
26-Feb-18	Dr. Sho Yamasaki	Research Institute for Microbial Diseases, Osaka University	Japan	Regulation of immune responses via C-type lectin receptors
19-Mar-18	Dr. Tomoki Nakashima	Tokyo Medical and Dental University	Japan	RANKL biology "Key of bone metabolism and immunology"
23-Mar-18	Dr. Prim Singh	Nazarbayev University School of Medicine	Kazakhstan	Epigenetics, heterochromatin and age reprogramming
3-Apr-18	Dr. Tomohiko Okazaki	Graduate School of Pharmaceutical Sciences, The University of Tokyo	Japan	Differential control of interferon and apoptotic responses to viral infection
5-Apr-18	Dr. Catherine Porcher	The MRC Weatherall Institute of Molecular Medicine, University of Oxford	UK	Transcriptional and epigenetic mechanisms of blood cell specification
5-Apr-18	Dr. Paresh Vyas	The MRC Weatherall Institute of Molecular Medicine, University of Oxford	UK	Human hemopoietic hierarchies in normal and leukemic haemopoiesis
9-Apr-18	Prof. Roderic Guigo	Center for Genomic Regulation, University Pompeu Fabra	Spain	Towards a molecular anatomy of the human body
11-Apr-18	Dr. Sungwhan F. Oh	Harvard Medical School and Brigham and Women's Hospital	USA	Dissecting "the holy trinity" of gut microbiome: molecular-level investigation of host-microbiota-diet complex
16-Apr-18	Dr. Lev Becker	The University of Chicago	USA	Obesity and insulin resistance promote atherosclerosis through an IFNg-macrophage pathway
18-Apr-18	Dr. Silvia Zucchelli	University of Eastern Piedmont	Italy	SINEUPs: a versatile tool to increase protein synthesis
19-Apr-18	Prof. Ferenc Krausz Dr. Mihaela Zigman	Max Planck Institute of Quantum Optics	Germany	Molecular fingerprinting and cancer detection with infrared light
24-Apr-18	Dr. Eswar P. R. Iyer	Harvard Medical School, Wyss Institute for Biologically Inspired Engineering	USA	Barcoded oligonucleotides ligated on RNA amplified for multiplex and parallel in-situ analyses
26-Apr-18	Dr. Ryohichi Sugimura	Center for iPS Cell Research and Application	Japan	Hematopoietic stem cells from human pluripotent stem cells.
16-May-18	Dr. Alexej Abyzov	Center for Individualized Medicine, Mayo Clinic	USA	Somatic mosaicism in brain and other tissues
21-May-18	Dr. Ryo Nakaki	Rhelixa, Inc.	Japan	Starting epigenome analysis from scratch
21-May-18	Dr. Davide De Pietri Tonelli	Italian Institute of Technology	Italy	Emerging complexity of small noncoding RNA pathways in mammalian neurogenesis: unconventional functions of miRNA- and piRNA-biogenesis proteins in developing and adult mouse brain
1-Jun-18	Dr. Francesca Buffa	University of Oxford	UK	miRNA aberrant regulation in cancer
4-Jun-18	Dr. Kyogo Kawaguchi	Harvard Medical School	USA	Fate coordination in the epidermal stem cell pool
6-Jun-18	Dr. Yusuke Hirabayashi	Columbia University Medical Center	USA	ER-mitochondria tethering by PDZD8 regulates Ca2+ dynamics in mammalian neurons.
11-Jun-18	Dr. Mahesh Desai	Luxembourg Institute of Health and University of Southern Denmark	Luxembourg	Diet-driven interactions of the gut microbiome with the intestinal mucus barrier
10-Jul-18	Dr. Zheng Chao	SANE ASIA Pte. Ltd.	Singapore	Bioimaging with light-sheet microscopy –ultra gentle imaging of live samples–
12-Jul-18	Dr. Charles Lecellier	The Institute of Molecular Genetics of Montpellier	France	A strict combination of SINE enhancer RNAs is linked to gene expression
21-Jun-18	Dr. Olivier Lantz	Center of Immunotherapy Institut Curie	France	A surprising connection: invariant T cells, vitamins, bacteria and wild mice
21-Jun-18	Dr. Iain Hrynaszkiewicz	Springer Nature	UK	Open research data: the future is now?

Date	Speaker	Affiliation	Country	Title
25-Jul-18	Dr. Takayuki Nojima	University of Oxford	USA	Noncoding transcription and genome maintenance
21-Aug-18	Dr. Patrick Matthias	Friedrich Miescher Institute for Biomedical Research	Switzerland	Acetylation is a novel regulator of stress granules formation and phase separation
13-Sep-18	Dr. Hiroyuki Seimiya	Japanese Foundation for Cancer Research	Japan	Telomere as the starting point of anticancer drug discovery
14-Sep-18	Dr. Masayuki Horie	Institute for Frontier Life and Medical Sciences, Kyoto University	Japan	Co-evolution of eukaryote genomes, retrotransposons and RNA viruses
26-Sep-18	Prof. Zemin Zhang	Beijing Advanced Innovation Center for Genomics, Peking University	China	Single cell RNA sequencing analysis of tumor-infiltrating immune cells
4-Oct-18	Dr. Keisuke Nimura	School of Medicine, Osaka University	Japan	How dysregulation of gene expression results in diseases
5-Oct-18	Dr. Xiaoyang Wu	Cancer Research University of Chicago	USA	Skin engineering with epidermal stem cells.
10-Oct-18	Dr. Ido Amit	Weizmann Institute of Scienc	Israel	The Power of ONE: immunology in the age of single cell genomics
12-Oct-18	Dr. Hirofumi Shintaku	RIKEN Hakubi Fellows Program	Japan	SINC-seq: dissecting nuclear and cytoplasmic RNA expressions in single cells
16-Oct-18	Prof. Frank Brombacher	International Centre for Genetic Engineering and Biotechnology	South Africa	Immunology of tuberculosis: from genes to biomarkers & host directed therapy
16-Oct-18	Dr. Musa Mhlanga	University of Cape Town	South Africa	Immune genes are primed for robust transcription by proximal lncRNAs located in nuclear compartments
17-Oct-18	Dr. Kenneth Baillie	University of Edinburgh, Roslin Institute	UK	Understanding disease pathogenesis through functional genomics
19-Oct-18	Dr. Sjef Verbeek	Leiden University Medical Cente	Netherlands	The role of FxCR and FxCR expressing immune cells in the tumor microenvironment in antibody therapy in cancer
12-Nov-18	Dr. Saulius Klimašauskas	Life Sciences Center, Vilnius University	Lithuania	Catalytic plasticity of DNA methyltransferases: writers, readers and erasers of epigenetic marks.
13-Nov-18	Dr. Jamey D. Young	Vanderbilt University	USA	13C flux analysis in metabolic disease research
27-Nov-18	Dr. Fumiyo Ikeda	Institute of Molecular Biotechnology Austria	Austria	Regulation of inflammatory responses by the ubiquitin system
27-Nov-18	Dr. Stephanie Houston	Journal of Experimental Medicine	USA	Scientific publishing: what, how and why?
6-Dec-18	Dr. Yurina Sekine	Japan Atomic Energy Agency, Materials Sciences Research Center	Japan	Development of wearable sweat devices and their future advancement
7-Dec-18	Dr. Daniel Kaplan	University of Pittsburgh	USA	Nociceptors are sufficient to initiate cutaneous type-17 inflammation
7-Dec-18	Dr. Brian Kim	Washington University School of Medicine	USA	Immune regulation of atopic dermatitis and itch
19-Dec-18	Dr. Takeshi Egawa	Washington University School of Medicine	USA	Tissue and cellular homeostasis during lymphocyte immune responses

Publications 2018

Table: IMS Publications from January to December, 2018

Journal	Impact Factor (2017)	Number of Papers
Chem Rev	52.6	1
Nature	41.6	1
Science	41.1	2
Nat Med	32.6	1
Cell	31.4	4
Nat Genet	27.1	4
Cell Stem Cell	23.3	2
Annu Rev Immunol	22.7	1
Gastroenterology	20.8	3
Immunity	19.7	3
Circulation	18.9	1
Lancet Psychiat	15.2	1
Blood	15.1	3
Mol Cell	14.2	1
Nat Microbiol	14.2	2
Nat Chem Biol	13.8	1
Nat Struct Mol Biol	13.3	1
J Allergy Clin Immun	13.3	3
J Clin Invest	13.3	1
Nat Protoc	12.4	1
Nat Commun	12.4	9
Ann Rheum Dis	12.4	3
Nucleic Acids Res	11.6	2
Jama Neurol	11.5	1
J Exp Med	10.8	6
J Thorac Oncol	10.3	1
Clin Cancer Res	10.2	1
Semin Cancer Biol	10.2	1
Genome Res	10.1	2
Dev Cell	9.6	1
ISME J	9.5	1
Proc Natl Acad Sci U S A	9.5	3
Gene Dev	9.5	2
Immunol Rev	9.2	2
Haematologia	9.1	1
Am J Hum Genet	8.9	1
Cell Rep	8.0	4
Curr Opin Immunol	7.9	2
Arthritis Rheumatol	7.9	1
Elife	7.6	2
J Autoimmun	7.6	1
Mucosal Immunol	7.4	1
Schizophrenia Bull	6.9	1
Oncogene	6.9	3
Clin Pharmacol Ther	6.5	4
J Invest Dermatol	6.4	1
Sci Signal	6.4	1
EBioMedicine	6.2	1
Plos Pathog	6.2	2
Anal Chem	6.0	1
Others		124
Total		**223**

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Budget, personnel and patent

IMS Budget FY2018

IMS Budget FY2018	JPY Million
Government funding for operations	3,064
External competitive funding	2,046
Total	**5,110**

Patents

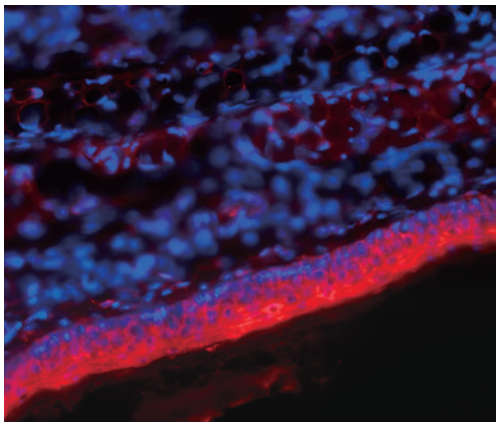
There were 24 patents filed from January to December, 2018.

Patents	Total	International patents (PCT)	Domestic patents (Japan)
2018	24	21	3

Personnel FY2018

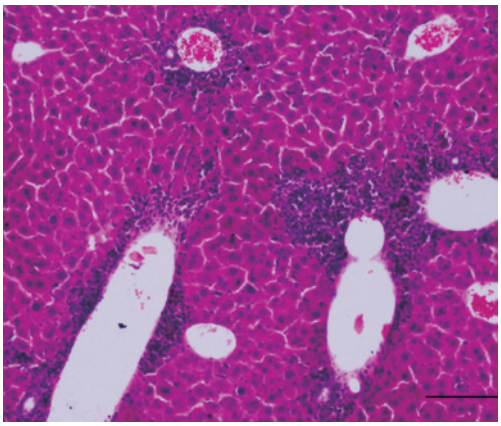
Category	Number
Director	1
Deputy Director	3
Senior Advisor	1
Team Leader	34
Unit Leader	5
Coordinator	5
Deputy Team Leader	9
Senior Scientist	28
Senior Research Scientist	3
Research Scientist	54
Postdoctoral Researcher	24
Special Postdoctoral Researcher	8
Research Fellow	2
Research Associate	15
Senior Technical Scientist	5
Technical Scientist	22
Technical Staff I	74
Technical Staff II	49
International Program Associate	6
Junior Research Associate	24
Intern	2
Student Trainee	110
Research Administrator	4
Research Administrative Support Staff	3
Assistant	31
Part-time Staff	46
Senior Visiting Scientist	23
Visiting Scientist	170
Visiting Technical Scientist	23
Visiting Researcher	3
Temporary Staffing	15
Research Consultant	3
Consultant	1
Temporary Employee	1
Total	**807**

Original photos of the cover and front pages



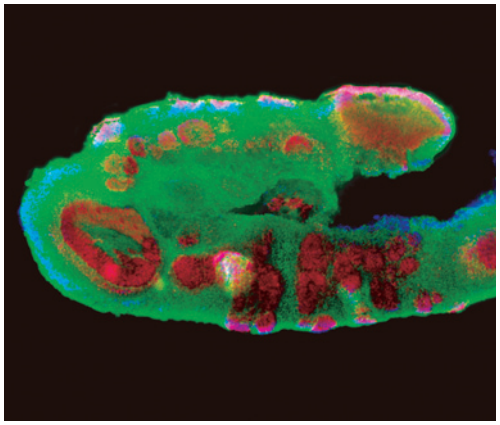
Cover

Credit to Dr. Masato Kubo
Laboratory for Cytokine Regulation



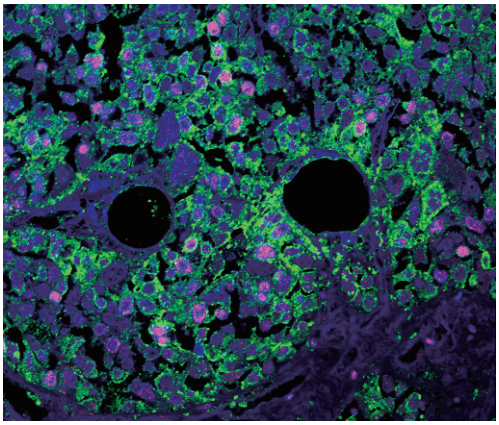
Front page of Part 1

Credit to Dr. Taishin Akiyama
Laboratory for Immune Homeostasis



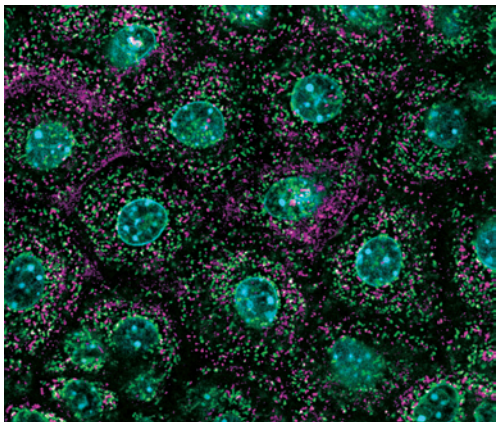
Front page of Part 2

Credit to Dr. Joachim Luginbuehl
Laboratory for Advanced Genomics Circuit



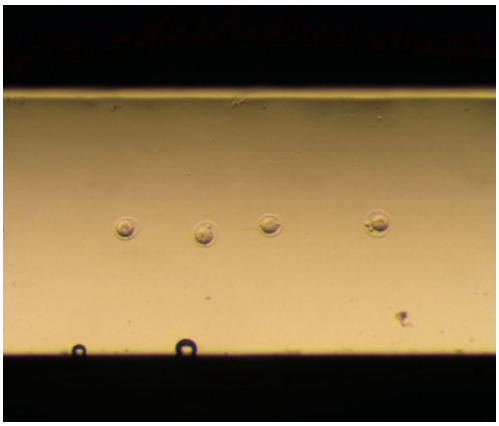
Front page of Part 3

Credit to Dr. Xian-Yang Qin
Liver Cancer Prevention Research Unit



Front page of Part 4

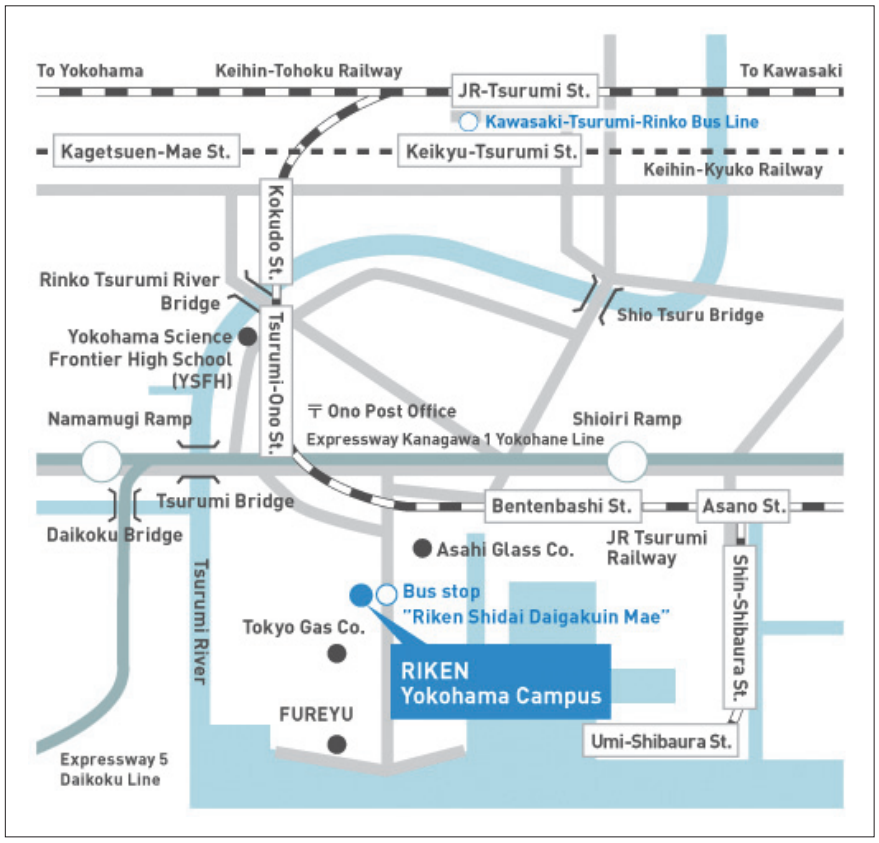
Credit to Dr. Nanako Kadono
Laboratory for Skin Homeostasis



Front page of Part 5

Credit to Animal Facility

Access to RIKEN Yokohama Campus



Local Access

By Bus

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

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

By Train

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

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

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

By Taxi

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

From the Airport

From Haneda Airport

Route 1

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

Route 2

Take any train marked with a green (express), red or dark grey kanji sign to Keikyu Kamata Station. Transfer to the Keikyu Main Line and take a local train* toward Yokohama until Keikyu Tsurumi Station* (12 minutes).
*Only Airport Express (blue kanji sign) and local trains (dark grey kanji sign) stop at Keikyu Tsurumi Station. Note that Keikyu Tsurumi Station and JR Tsurumi Station are two different railway stations and are separated by a bus rotary (the stations are about 150 meters apart).

From Narita Airport

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

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

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

RIKEN Center for Integrative Medical Sciences

http://www.ims.riken.jp/english/

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