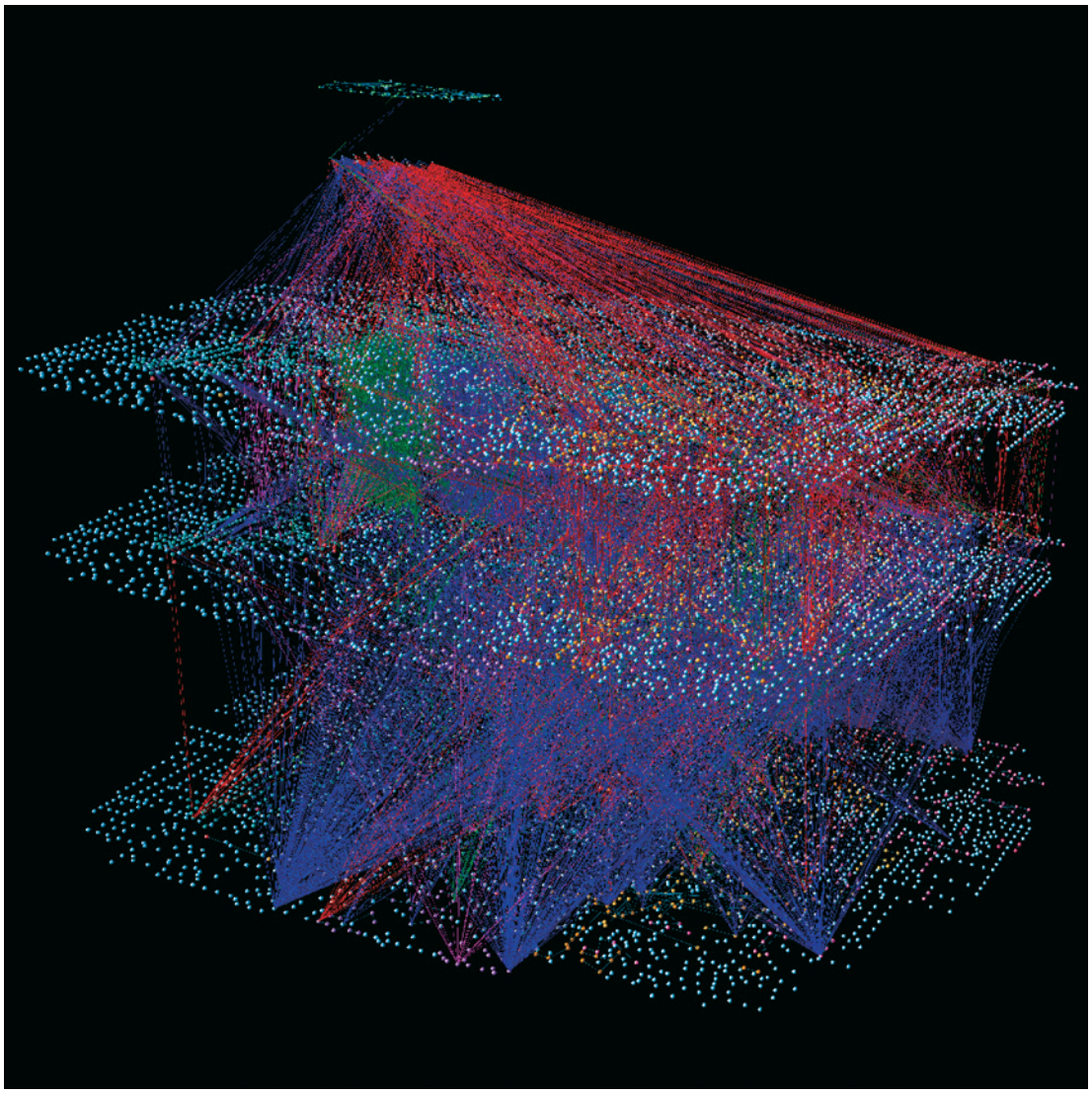
RIKEN IMS Annual Report 2022

RIKEN Center for Integrative Medical Sciences



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Director's Report

Compared to the past several years, 2022 brought a greater sense of normalcy back to research life at IMS. I thank the staff and scientists at the centre for their vigilance as we continue to navigate the changing face of the SARS-CoV-2 virus, and for their hard work in contributing to crucial scientific discoveries that will benefit society for years to come.

The opening of Japan's borders and easing of travel restrictions allowed many IMS researchers to resume international activities, including attend international meetings in person. I was fortunate to take part in several joint meetings between IMS and our collaborators overseas, such as the IMS-Karolinska Institute-SciLifeLab symposium in Stockholm and the IMS-McGill joint meeting in Montreal. While I, like most others, have enjoyed the convenience of online meetings over the past few years, I cannot deny that they often left me feeling slightly dissatisfied. I had missed the in-depth discussions that can arise spontaneously within and outside the formal conference setting—crucial bonding opportunities that I was overjoyed to engage in again when we finally met in person. I truly believe that such interactions help solidify the mutual relationship between our centres.

Prior to the formal IMS-Karolinska Institute-SciLifeLab symposium, 12 young researchers from IMS and the University of Tokyo also participated in a 9-day exchange program with SciLifeLab as part of an ongoing goal in our partnership to promote scientific exchange of young talent between Japan and Sweden. Each participant had the opportunity to experience research life in an assigned host laboratory and learn bioinformatics-related skills they could take home with them to enhance their own projects at IMS. I believe the program is an exceptional experience for young researchers and look forward to continuing the initiative in the future.

The COVID-19 pandemic has put infectious disease outbreaks at the forefront of research and government agendas around the world. At IMS, we have expanded our biosafety level 3 laboratory capabilities to facilitate future research on infectious disease. Thanks to the institute's leading expertise in human immunology research, IMS has been selected to support the government's initiative to boost Japan's preparedness for new infectious disease outbreaks over the next five years. We are proud to contribute to the proposed plan to enhance vaccine development across a variety of infectious diseases, which will be led by The Strategic Center of Biomedical Advanced Vaccine Research and Development for Preparedness and Response (SCARDA).

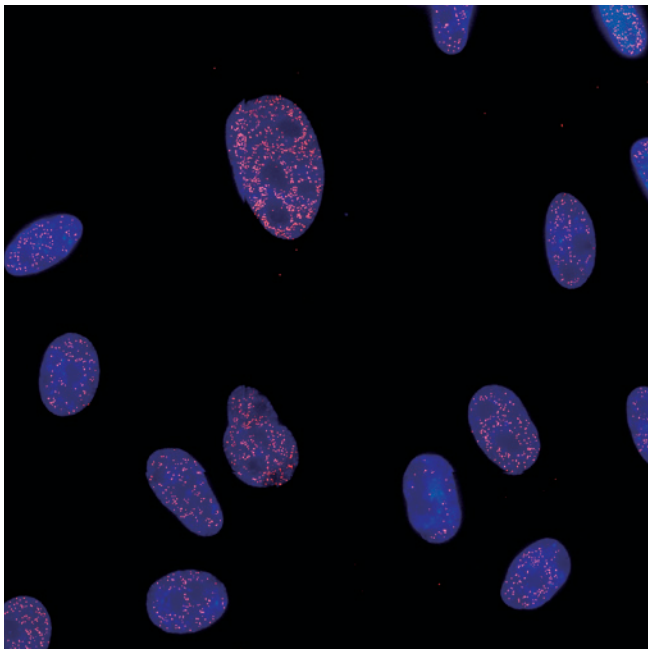
IMS scientists continued to break new ground by producing high impact studies on a variety of topics in 2022. One example is the study by Yukihide Momozawa's team, which showed that BRCA1/2 genes are altered in as many as seven types of cancers—not just the four widely recognized breast, ovarian, prostate and pancreatic cancers. These findings could lead to the development of early-risk markers for patients with these diseases. Another noteworthy example is the ambitious large-scale and detailed analysis of the transcriptome of 27 immune cell types in patients with systemic lupus erythematosus conducted by Kazuyoshi Ishigaki's team in collaboration with the University of Tokyo. The study highlights the importance of examining disease activity and provides publically available data that could evoke novel research questions about SLE.

In 2023, IMS laboratories will take part in the second IMS Advisory Council meeting of this seven-year midterm. All laboratories will be evaluated on their research concept and performance by a distinguished panel of scientists. Although these evaluations are often daunting, I am confident that the panel will recognize each team's achievements and IMS's strong standing in Japanese research and crucial contribution to the evolving needs of society.

Kazuhiko Yamamoto
Director
RIKEN Center for Integrative Medical Sciences

Part 1

Research Highlights



Broadening the relevance of BRCA

Yukihide Momozawa

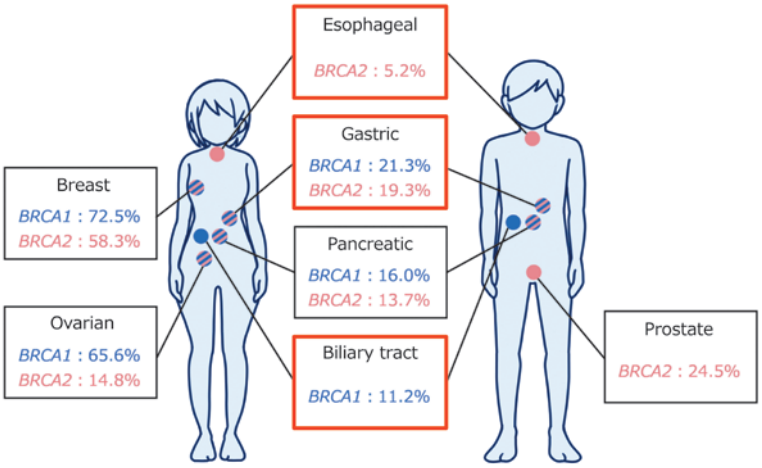


Figure: Expansion of cancer risk profile for BRCA1 and BRCA2 pathogenic variants
A case-control study of 63,828 patients with 14 common cancer types and 37,086 controls revealed that pathogenic variants in BRCA1 were associated with biliary tract cancer, those in BRCA2 with esophageal cancer, and those in BRCA1/2 with gastric cancer. These findings indicate that genetic testing for BRCA1/2 could have broader clinical relevance than previously thought.

IMS researchers link three new cancers to BRCA genes, prompting an update of screening guidelines and treatment indications.

In 2013, Hollywood actress Angelina Jolie stunned the world when she announced that she had "a faulty BRCA1 gene" and had undergone preventive surgery to minimize her risk of developing breast cancer. Her account led to a surge in genetic testing for mutations in BRCA1 and its cousin BRCA2, which in addition to breast and ovarian cancer have since also been linked to prostate and pancreatic cancer.

As a geneticist, Yukihide Momozawa, Team Leader of the Laboratory for Genotyping Development at IMS, found validation in Jolie's story. "It shows that you can use genetics to escape disease," he said.

However, he wondered whether the known variants associated with BRCA genes were applicable to Japanese people. This is because rare genetic variants such as those found in BRCA genes are population-specific.

"Unfortunately, most data has come from European populations," Momozawa said. "We hypothesized that if we examined Japanese data, we may identify Japanese-specific rare variants."

To test this theory, Momozawa and his team collaborated with one of the largest disease-based biobanks in the world, Biobank Japan, to conduct the biggest-of-its-kind study on BRCA genes. The researchers included controls and cases with 14 cancer types whose DNA and clinical information were available in Biobank Japan. Published in JAMA Oncology, the study ultimately examined data from 100,914 individuals.

The team harnessed their experience with large-scale analysis to perform a combination of "wet" and "dry" experiments to sequence and then analyse the abundance of DNA. This led them to identify 315 unique pathogenic variants in BRCA1 and 2 genes.

With help from epidemiologists Keitaro Matsuo of Aichi Cancer Center and Amanda Spurdle of QIMR Berghofer Medical Research Institute, the team then classified the variants and linked them to breast, ovarian, prostate, and pancreatic cancer as well as three additional cancers. They showed that pathogenic variants in BRCA1 were associated with biliary tract cancer, those in BRCA2 with esophageal cancer, and those in BRCA1/2 with gastric cancer.

These findings have important implications for both screening and treatment. According to Momozawa, a representative from the Guidelines for Diagnosis and Treatment of Hereditary Breast and Ovarian Cancer has already informed him that they will be adding biliary tract, esophageal and gastric cancer to their upcoming edition of recommendations. Meanwhile, drugs known as PARP inhibitors currently used to treat the main cancers associated with BRCA could also be useful remedies for the newly identified cancers, although this will need to be confirmed in clinical trials.

The team also examined potential regional differences in BRCA variants across Japan and, to their surprise, found variations across 7 areas. Momozawa notes that this finding has implications for genetics research. "It suggests that it is very important to collect case and control samples from the same region," he said.

Going forward, Momozawa also wants to incorporate environmental factors into their analyses. Including variables such as smoking habit and history of viral and bacterial infections, he believes, could reveal further unknown genetic links to cancer.

Original paper:
Momozawa Y, Sasai R, Usui Y, Shiraishi K, Iwasaki Y, Taniyama Y, Parsons MT, Mizukami K, Sekine Y, Hirata M, Kamatani Y, Endo M, Inai C, Takata S, Ito H, Kohno T, Matsuda K, Nakamura S, Sugano K, Yoshida T, Nakagawa H, Matsuo K, Murakami Y, Spurdle AB, Kubo M. Expansion of Cancer Risk Profile for BRCA1 and BRCA2 Pathogenic Variants. ***JAMA Oncol*** 8, 871-878 (2022)

Revealing the reality of somatic recombination

Piero Carninci

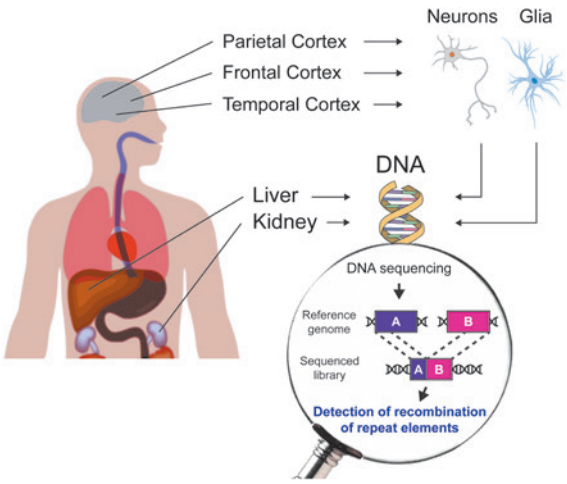


Figure: Detecting recombination–mutations generated by the fusion of repeat elements–in health and disease

A novel bioinformatics pipeline was used to detect recombination events in brain and non-brain (liver and kidney) tissues from healthy individuals and different regions of the brain (parietal, frontal and temporal cortex) in samples from patients with Parkinson's and Alzheimer's disease.

IMS researchers discover that healthy people harbour widespread recombinations–mutations formed from the fusion of repeated DNA sequences–paving the way to understanding the mechanisms that differentiate health from disease.

In comic books and movies, mutations such as DNA recombination are portrayed to confer superpowers, like Mystique's shape-shifting abilities, or used by mad scientists to generate new species, as in the mutant dinosaurs in the Jurassic Park saga. In reality, recombination of the DNA in our genomes is typically linked to disease and, with a few exceptions, has long been considered an extremely rare event.

However, Giovanni Pascarella, a Senior Research Scientist in the Laboratory for Transcriptome Technology at IMS, found himself challenging this dogma while studying sequences of DNA that are present in multiple copies in each cell. These so-called repeat elements are known to participate in recombinations that can change the shape and structure of the DNA, leading to afflictions like cancer. Yet, despite their known connection to disease, Pascarella was struck by the sheer number of repeat elements in the healthy genome.

"I thought, there are more than one million of these sequences in the genome of each cell," he said. "Is it possible that this process of recombination is also happening in normal cells, and does not always result in cancer?"

In their study published in Cell, Pascarella and Team Leader Piero Carninci tackled this question by focusing on a specific type of DNA recombination event that involves the fusion of two repeat elements called Alu and L1. The IMS team collaborated with researchers at the University of Tokyo to develop a bioinformatics pipeline to detect these events in cells and tissues.

They then ran samples from healthy donors through the pipeline. To their surprise, they discovered extraordinarily high numbers of these recombination events—much more than previously thought.

"This particular type of recombination event has never been studied on such a vast scale before," Carninci noted. "These findings show that the genome can actually tolerate a very high number of mutations without turning into anything bad."

To better understand the role of these events in healthy individuals, the team next compared brain and non-brain samples. Just as unexpectedly, they found a different number and distribution of mutations in the different tissues.

Theorising that the mutations may have a developmental origin, the team profiled human stem cells and the neurons they were transformed into in culture. The neurons indeed had different recombination profiles to the stem cells.

The researchers also studied the mutations in disease by examining samples from patients with Parkinson's and Alzheimer's disease—two common ailments that have been linked to DNA damage. They found both disease- and tissue-specific mutation profiles.

The team's findings open the door to a myriad of questions, such as what is controlling these ubiquitous DNA recombinations, what are the consequences for the fitness of the genome, and are the mutations are a cause or consequence of disease? Pascarella plans to start whittling down this list by going back to simple, controlled studies to understand the mechanisms that drive the recombination of repeat elements.

In the meantime, the team have published a technical protocol to allow other scientists to detect and analyse Alu and L1 recombination events. "We hope that with this tool, many more people will be able to look at recombination even in their own data," Pascarella concluded.

Original paper:

Pascarella G, Hon CC, Hashimoto K, Busch A, Luginbühl J, Parr C, Yip WH, Abe K, Kratz A, Bonetti A, Agostini F, Severin J, Murayama S, Suzuki Y, Gustincich S, Frith M, Carninci P*. Recombination of repeat elements generates somatic complexity in human genomes. ***Cell*** 185, 3025-3040.e6 (2022)

Delving deep and wide into SLE

Kazuyoshi Ishigaki

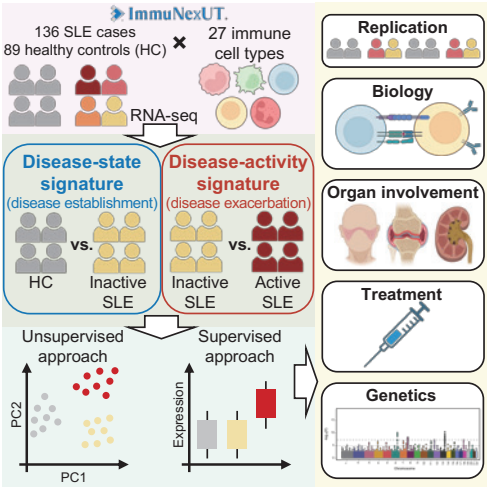


Figure: Examining almost all immune cell types in a large-scale transcriptome study of systemic lupus erythematosus (SLE)
In 27 immune cell types from 136 SLE cases and 89 healthy controls (HC), RNA transcript profiles were compared between HC and patients with inactive SLE and between patients with inactive and active SLE. The respective cell-type-specific disease-state and disease-activity signatures were then subjected to extensive downstream analyses using both unsupervised and supervised approaches. Created with BioRender.com (https://www.biorender.com/)

A large-scale transcriptome study of almost all types of immune cells in the body highlights the importance of examining disease activity to understand and treat systemic lupus erythematosus.

Lupus is a disease that has been around since antiquity, when physicians named it after the Latin word for "wolf" in reference to the wolf-bite-like lesions inflicted on patients' skin. Since then, lupus has been classified as an autoimmune disease and found to take several forms, the most common of which is systemic lupus erythematosus (SLE). Due to its heterogeneous effects—which range from mild to widespread inflammation and organ damage—SLE is notoriously difficult to treat.

Studies aiming to understand the cause and to develop treatments for SLE typically examine whole blood samples from patients. However, this approach could be masking important cell-specific effects, says Kazuyoshi Ishigaki, Team Leader of the Laboratory for Human Immunogenetics at IMS, since blood contains a plethora of immune cells, some of which may be more prevalent in certain individuals than others.

Now, in a first-of-its-kind study published in Cell, Ishigaki's team and their collaborators from the University of Tokyo have attempted to dissect the cell-specific effects of SLE by analysing the transcriptomes of almost all types of immune cells in the body. To do this, the team recruited 136 patients with SLE and 89 healthy volunteers from the Immune Cell Gene Expression Atlas from the University of Tokyo (ImmuNexUT) cohort and undertook the enormous task of purifying 27 immune cell types from each individual's blood and sequencing their transcriptomes.

Next, the researchers compared the cell-specific RNA profiles of healthy volunteers and SLE patients to determine the disease-state signatures. Unconventionally, they also compared the profiles of patients with stable SLE and active SLE to extract the disease-activity signatures.

"Almost all disease-oriented studies ask how cases differ from healthy people," Ishigaki noted. "But most of the time, only patients, not healthy people, visit the hospital. So we think the more important comparison in medical practice is case versus case."

The researchers did a series of in-depth downstream analyses of both signatures, linking the cell-specific data with biological processes such as cytokine and transcription factor pathways, clinical observations such as which organs are affected, and treatment outcomes. These datasets, which are now publically available, could help other scientists identify untapped features of SLE biology for future research and even novel drug targets, Ishigaki said.

Importantly, the team found key discrepancies when they integrated their transcriptome findings with previously published results from genome-wide association studies (GWAS). Specifically, while genetic variants found to be associated with SLE in GWAS mostly overlapped with disease-state signatures, they were largely distinct from disease-activity signatures.

Given that GWAS typically compares patients with healthy individuals, Ishigaki notes that these findings are not necessarily surprising. However, he believes that they highlight a crucial limitation of current GWAS.

"We believe that the disease activity signature is very valuable in clinical settings. That it did not show good consistency with GWAS findings indicates that focusing only on genetic results might lead researchers to miss critical aspects of biology," Ishigaki said, adding that designing GWAS around disease activity could lead to more clinically relevant results.

Original paper:
Nakano M, Ota M, Takeshima Y, Iwasaki Y, Hatano H, Nagafuchi Y, Itamiya T, Maeda J, Yoshida R, Yamada S, Nishiwaki A, Takahashi H, Takahashi H, Akutsu Y, Kusuda T, Suetsugu H, Liu L, Kim K, Yin X, Bang SY, Cui Y, Lee HS, Shoda H, Zhang X, Bae SC, Terao C, Yamamoto K, Okamura T, Ishigaki K, Fujio K. Distinct transcriptome architectures underlying lupus establishment and exacerbation. ***Cell*** 185, 3375-3389.e21. (2022)

The final piece of the artificial embryo puzzle

Haruhiko Koseki

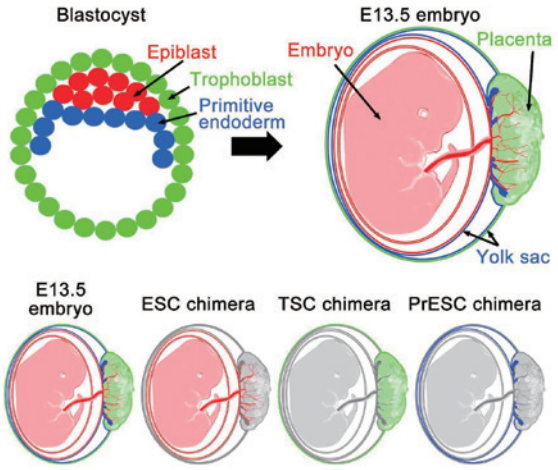


Figure: Primitive endoderm stem cells (PrESCs) have been successfully derived for the first time
The mammalian blastocyst is made up of three distinct cell types: the epiblast, which gives rise to the embryo (red); the trophoblast, which forms the placenta (green); and the primitive endoderm, which develops into the yolk sac (blue). Until now, only stem cells representing the epiblast (ESC) and trophoblast (TSC) had been generated. The newly cultured PrESCs fully recapitulate the function of the primitive endoderm.

For the first time, IMS researchers have successfully cultured stem cells that give rise to the yolk sac, revealing their critical role in implantation.

In the early 1980s, a world of possibilities opened up for biologists when British scientists Martin Evans and Matthew Kaufman successfully isolated and cultured embryonic stem cells (ESCs)—cells that can transform into any tissue in the body. One possibility was the potential to generate artificial embryos, which scientists believe could be a powerful platform for understanding the biological processes needed to create life.

"Usually, the real proof of our understanding comes from the relationship between expectation and results," said Haruhiro Koseki, Team Leader of the Laboratory for Developmental Genetics at IMS. "If we can make artificial embryos, we should have the minimal components to construct and study this complex system."

However, ESCs are only one component needed to create life. An early developmental structure found in mammals called the blastocyst contains three types of precursor cells: those that give rise to the embryo, those that form the placenta, and those that develop into the yolk sac.

In addition to successfully growing ESCs from the first type, scientists have also already cultured trophoblast stem cells (TSCs), which form the placenta, from the second type. Meanwhile, attempts to produce precursors of the yolk sac in culture, known as the primitive endoderm, have so far fallen short.

To achieve the final piece of the puzzle in mice, Koseki and his team set about determining the optimal conditions needed to grow primitive endoderm cells and maintain their developmental capability in culture. In their study published in Science, the researchers, including first author Yasuhide Ohinata, exposed blastocysts to various culture cocktails—painstakingly tweaking countless components, such as compounds that perturb key developmental signalling pathways and small molecules, until they had the conditions just right to produce primitive endoderm stem cells (PrESCs).

They tested the functionality of their PrESCs by injecting them into blastocysts that had been treated to remove their primitive endoderm cells. When transplanted into the uterus of pseudopregnant mice, blastocysts that harboured PrESCs not only implanted into the uterine lining, but also developed into normal offspring. Meanwhile, blastocysts lacking a primitive endoderm could not implant.

To test their long-range goal of creating embryos exclusively from cultured stem cells, the team next created an artificial blastocyst from ESCs, TSCs and PrESCs and injected it into pseudopregnant mice. The artificial blastocyst again successfully implanted, although this time no offspring were produced.

"Implantation did not happen with only ESC and TSC aggregates," Koseki noted. "Our findings suggest the importance of PrESCs and the primitive endoderm for the implantation of embryos into the uterine wall," he said, adding that further understanding of the developmental mechanisms of these cells could one day improve implantation-related infertility problems in humans.

However, such a feat is still a long way away given that blastocyst development in mice differs substantially from that in humans. To take a step closer towards this clinical objective, the team are now attempting to generate the precursor cell types in pigs, which share more comparable developmental mechanisms to humans.

Original paper:
Ohinata Y*, Endo TA, Sugishita H, Watanabe T, Iizuka Y, Kawamoto Y, Saraya A, Kumon M, Koseki Y, Kondo T, Ohara O, Koseki H*. Establishment of mouse stem cells that can recapitulate the developmental potential of primitive endoderm. ***Science*** 375, 574-578 (2022)

Beneficial bacterium breaks down trypsin

Kenya Honda

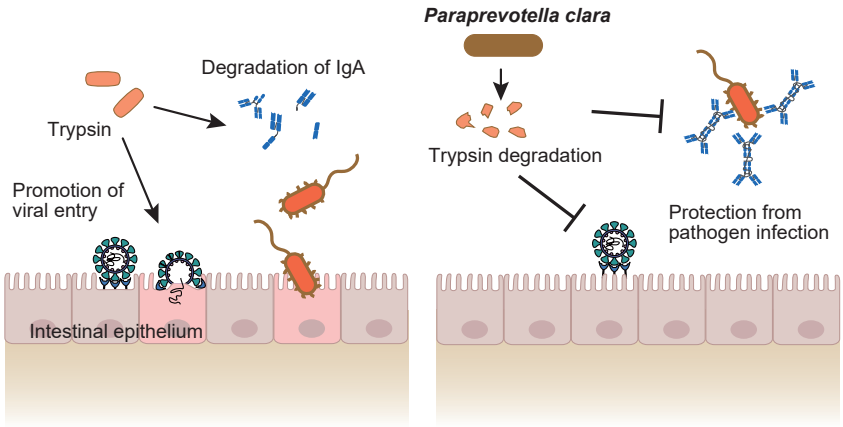


Figure: The little-known bacterium *Paraprevotella clara* degrades trypsin, resulting in a range of beneficial health effects
(Left) High levels of trypsin lead to the degradation of immunoglobulin A (IgA), which can no longer protect the body against pathogens. Trypsin also helps viruses invade healthy cells.
(Right) In the presence of *P. clara*, trypsin levels decline. This leads to higher levels of IgA and corresponding protection against pathogens, and the inhibition of viral entry.

A novel beneficial bacterium that degrades the digestive enzyme trypsin could be an effective medicine for preventing everything from viral infections to irritable bowel syndrome.

There has been a recent explosion in research on the trillions of microorganisms that inhabit our bodies—known collectively as the microbiome. In fact, studies conducted over the last decade have linked the gut microbiome to conditions ranging from inflammatory bowel syndrome to Alzheimer's disease. These findings point to a multitude of critical roles for gut microbes, some of which are just now being unearthed.

Kenya Honda, Team Leader of the Laboratory for Gut Homeostasis at IMS, and his team are some of the researchers studying the inner workings of the gut microbial community. In a recent collaboration, they probed its function using a sensitive proteomics pipeline developed by former IMS Team Leader, Osamu Ohara—allowing them to comprehensively analyse the proteins present in the faeces of conventional mice compared to germ-free mice, which lack all microorganisms.

To their surprise, they found that germ-free mice had elevated levels of trypsin, a digestive enzyme that degrades proteins in the small intestine. "Until now, no one had considered that the microbiota might contribute to the regulation of the digestive enzyme levels in the intestine," Honda said.

Given that high trypsin levels in the large intestine are implicated in complications such as Crohn's disease, ulcerative colitis, and irritable bowel syndrome, Honda conjectured that identifying the bacterial species that degrades trypsin could lead to treatments for patients with a range of afflictions.

In their paper published in Nature, Honda and colleagues tested their theory using a classical top-down approach. First, they attempted to identify trypsin-degrading bacteria by culturing faecal samples from germ-free mice that had received a human faecal transplant, which expectedly lowered the rodent's trypsin levels. The faeces yielded 35 bacterial species, which co-first author Eiichiro Watanabe tirelessly narrowed down to just a single little-known strain called *Paraprevotella clara*.

With the first-known trypsin-degrading bacterium in hand, co-first author Youxian Li next sought to identify its trypsin-degrading machinery. Through a series of painstaking experiments, he demonstrated that *P. clara* uses a surface protein called PROKKA_00502 to bind and break down trypsin.

Finally, the team tested the clinical relevance of their findings in several ways. By disrupting PROKKA_0050-mediated trypsin degradation in mice, they unexpectedly found that it also reduced levels of the critical defence molecule immunoglobulin A (IgA). "This means that *P. clara* could be useful for maintaining overall health," Honda said.

The team additionally tapped into knowledge that trypsin-like enzymes help a variety of viruses invade healthy cells. Experiments in mice infected with a lethal dose of a mouse version of coronavirus showed that *P. clara* improved survival. The bacterium's trypsin-degrading machinery likewise proved beneficial for human patients with COVID-19: those harbouring the human equivalent of PROKKA_00502 presented with milder bouts of diarrhoea.

The team are already harnessing the clear therapeutic potential of *P. clara*. Having patented their findings, they are now working with a pharmaceutical company to develop a freeze-dried version of the bacterial strain, which they hope to test on patients with inflammatory and irritable bowel disease in the future.

Original paper:
Li Y, Watanabe E, Kawashima Y, Plichta DR, Wang Z, Ujike M, Ang QY, Wu R, Furuichi M, Takeshita K, Yoshida K, Nishiyama K, Kearney SM, Suda W, Hattori M, Sasajima S, Matsunaga T, Zhang X, Watanabe K, Fujishiro J, Norman JM, Olle B, Matsuyama S, Namkoong H, Uwamino Y, Ishii M, Fukunaga K, Hasegawa N, Ohara O, Xavier RJ, Atarashi K, Honda K. Identification of trypsin-degrading commensals in the large intestine. ***Nature*** 609, 582-589 (2022)

Predicting treatment response in esophageal cancer

Hidewaki Nakagawa

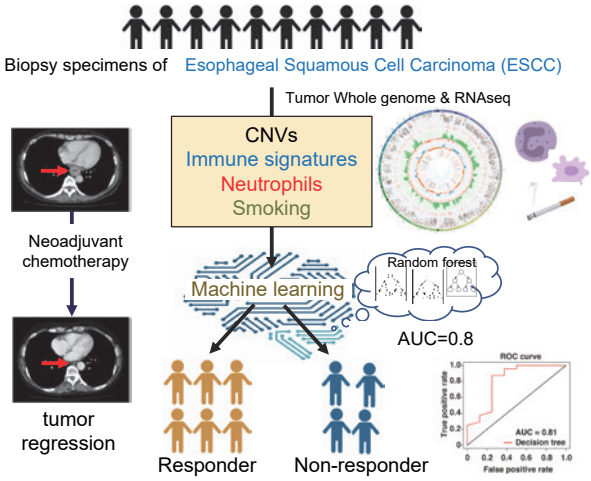


Figure: Predicting chemotherapy response with machine learning

Biopsy specimens were taken from 141 patients with esophageal squamous cell carcinoma (ESCC) prior to treatment with neoadjuvant chemotherapy and subjected to whole-genome and RNA sequencing. Through analysis of the relationship between tumour gene expression and response to chemotherapy, copy-number variations (CNVs) and neutrophils were among the main factors found to be associated with chemotherapy response. Incorporating these factors into a machine learning model enabled high accuracy prediction of patients who would respond well (responder) and poorly (non-responder) to chemotherapy.

A new machine learning model could help clinicians determine whether esophageal cancer patients are likely to respond to chemotherapy or if they would benefit from receiving surgery first.

In the 19th century, esophageal cancer was considered an aggressive and incurable disease, leaving clinicians to focus mainly on relieving patients' pain and swallowing difficulties. Although it remains one of the most aggressive cancers even today, esophageal cancer is now mostly treatable thanks to the development of chemotherapy and surgical techniques.

The course of treatment typically involves chemotherapy first, then surgery. However, not all patients respond to chemotherapy. This holds true even for neoadjuvant chemotherapy (NAC), the gold standard for the dominant type of esophageal cancer found in Japan and other parts of East Asia called esophageal squamous cell carcinoma (ESCC).

"While some patients respond well to chemotherapy, and some even have their tumours completely eliminated, others do not respond at all," noted Hidewaki Nakagawa, Team Leader of the Laboratory for Cancer Genomics at IMS, who witnessed this reality first-hand as a gastrointestinal surgeon in the late 90s.

Nakagawa and his clinician colleagues wondered if they could somehow discriminate responders from non-responders ahead of time. This would allow them to allocate those in the former group to receive chemotherapy only, and those in the latter group to receive surgery first—saving time and money.

To develop a way to predict response, young researcher Shota Sasagawa in Nakagawa's team first sought to identify the contributing genetic and immunological factors. In their paper published in Cell Reports Medicine, which is first-authored by Sasagawa, the researchers performed whole-genome and RNA sequencing analyses of biopsy specimens from 141 ESCC patients from Kindai University Hospital before chemotherapy treatment. They then analysed the relationship between tumour gene expression and response to chemotherapy.

By classifying patients based the estimated abundance of four immune cell types: CD8+ T, CD4+ T, B cells and neutrophils, the team found that NAC response was lower in those with high levels of neutrophils. "This finding was surprising as few studies have reported a relationship between neutrophils and chemotherapy response," Nakagawa said, adding that they plan to further investigate the role of neutrophils in cancer in the future.

The researchers also examined copy number signatures, which their collaborators at the Cancer Research UK Cambridge Institute have linked to chemotherapy response in ovarian cancer. As Nakagawa explains it, the number of copies of a gene is often altered in cancer, and the "signature" provides an overall profile of these copy-number variations. Using an analysis method developed by the UK group, the team demonstrated that copy number signatures were likewise related to NAC response in ESCC patients.

To use these factors to predict response, the team next took the advice and lead of Sasagawa to incorporate the factors into a machine learning model. By testing the model on a small number of newly collected samples, the team confirmed that they could predict patients' chemotherapy response with high accuracy.

Sasagawa and Nakagawa believe that this model and others like it will increasingly be used to stratify patients as part of the precision medicine boom around the world. The team is looking to develop prediction models for other types of cancers going forward.

Original paper:

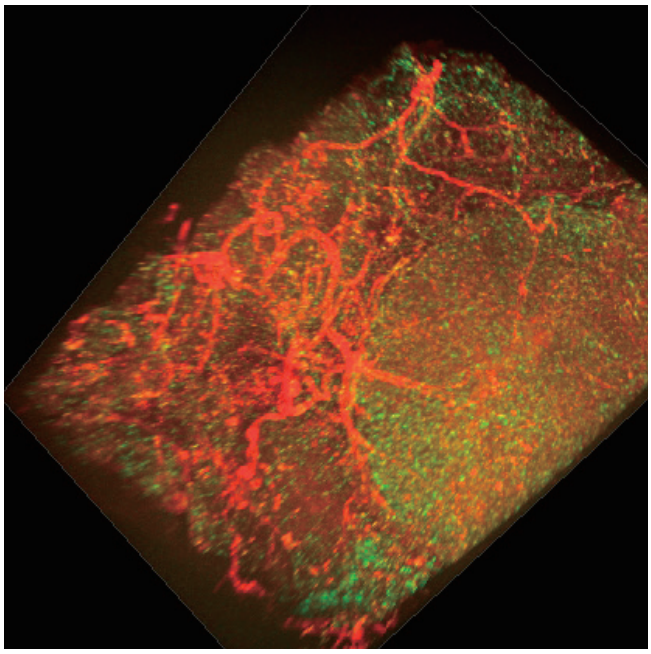
Sasagawa S, Kato H, Nagaoka K, Sun C, Imano M, Sato T, Johnson TA, Fujita M, Maejima K, Okawa Y, Kakimi K, Yasuda T, Nakagawa H. Immuno-genomic profiling of biopsy specimens predicts neoadjuvant chemotherapy response in esophageal squamous cell carcinoma. ***Cell Rep Med*** 3, 100705 (2022)

Award Winners 2022

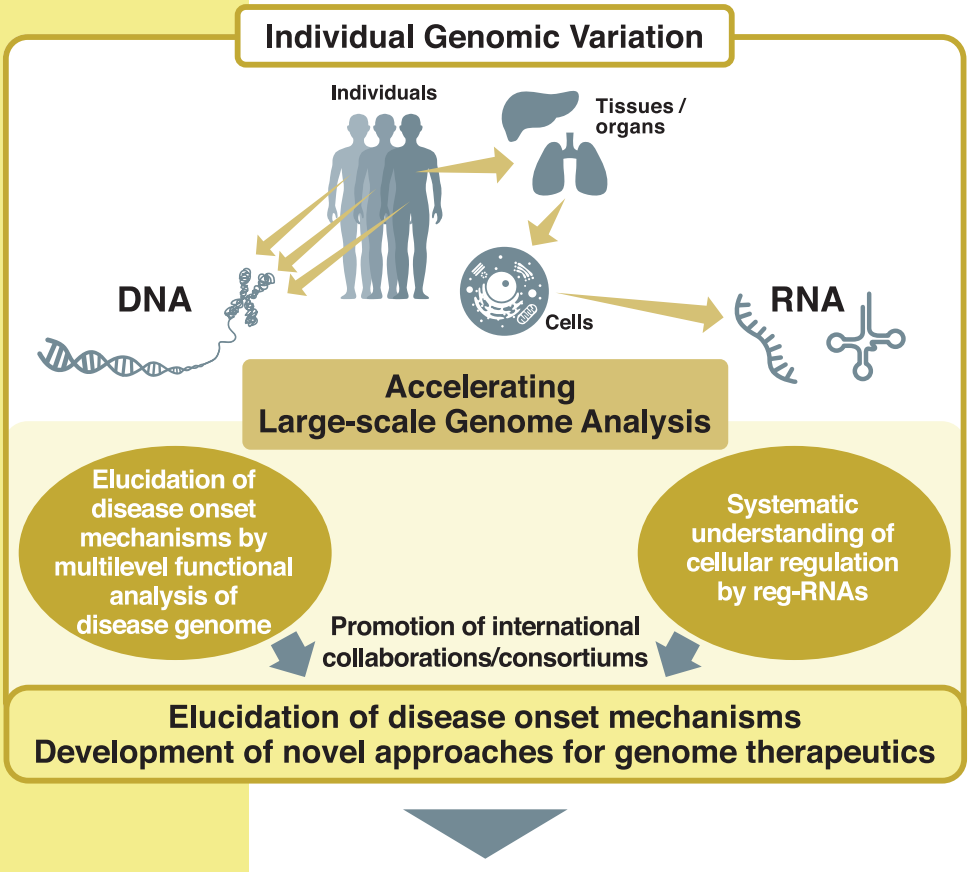
Name of the awardee	Name of the award	Date of the announcement
Hiroshi Ohno, Team Leader, Laboratory for Intestinal Ecosystem	Uehara Award	Dec 2022
Azusa Inoue, Team Leader, Laboratory for Epigenome Inheritance	The Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology, The Young Scientists' Prize	Apr 2022
Hiroshi Ohno, Team Leader, Laboratory for Intestinal Ecosystem	Takamine Memorial Daiichi Sankyo Award	Jul 2022
Yukinori Okada, Team Leader, Laboratory for Systems Genetics	Osaka Science Prize	Nov 2022
Kaoru Ito, Team Leader, Laboratory for Cardiovascular Genomics and Informatics	Circulation journal. Best reviewers award for 2021	Mar 2022
Yukinori Okada, Team Leader, Laboratory for Systems Genetics	Academic Awards, the Japanese Society of Human Genetics	Dec 2022
Momoko Horikoshi, Team Leader, Laboratory for Genomics of Diabetes and Metabolism	Female Scientist Award, The 66th Annual Meeting of Japan Diabetes Society	May 2023
Shiro Ikegawa, Team Leader, Laboratory for Bone and Joint Diseases	Russell A. Hibbs Basic / Translational Award, The 57th Annual Meeting of Scoliosis Research Society	Sep 2022
Masahiro Nakano, Postdoctoral Reseacher, Laboratory for Autoimmune Diseases	The European Alliance of Associations for Rheumatology (EULAR) 2022 Best abstract award (Basic Science)	May 2022
Syunya Hatai, Student Trainee Laboratory for Innate Immune Systems	The best poster award, The 2nd conference Food, microbiota and immunity	Jun 2022
Syunya Hatai, Student Trainee Laboratory for Innate Immune Systems	Encouragement Award, The 50th Japanese Society for Mucosal Immunology	Jun 2022
Kiyokazu Kakugawa, Reseacher, Laboratory for Immune Crosstalk	Melvin Cohn Award of the La Jolla Immunology, Runner up	Oct 2022
Shota Sasagwa, Researcher, Laboratory for Cancer Genomics	Best Young Researcher Poster Award, the 81st Annual meeting of the Japanese Cancer Association (JCA)	Sep 2022
Takashi Kanaya, Deputy Team Leader, Laboratory for Intestinal Ecosystem	Tadamitsu Kishimoto Internationa Travel Award	Apr 2022
Tadashi Takeuchi, Postdoctoral Researcher, Laboratory for Intestinal Ecosystem	ICMI2022 Travel Award, Japanese Society for Mucosal Immunology	Jul 2022
Tadashi Takeuchi, Postdoctoral Researcher, Laboratory for Intestinal Ecosystem	Young Researchers Award, Japanese Society for Mucosal Immunology	Jul 2022
Yuuri Yasuoka, Researcher, Laboratory for Comprehensive Genomic Analysis	The Young Scientist Award of the Zoological Society of Japan	Sep 2022
Kokoro Ozaki, Deputy team leader, Laboratory for Comprehensive Genomic Analysis	The 14th CBIR Young scientist Inspire Symposium, The best presentation award, 2022	Feb 2022
Keiko Hikino, Postdoctoral researcher, Laboratory for Pharmacogenomics	The American Society of Human Genetics 2022 Annual Meeting, Reviewers' Choice Abstract Award	Oct 2022
Keiko Hikino, Postdoctoral researcher, Laboratory for Pharmacogenomics	The 67th Annual Meeting of the Japan Society of Human Genetics, ASHG 2022 Annual Meeting Travel Award	Dec 2022
Kazuo Miyazawa, Researcher, Laboratory for Cardiovascular Genomics and Informatics	The 70th Annual Scientific Session of the Japanese College of Cardiology, The Young Investigator Award	Sep 2022
Yoshihiko Tomofuji, Visisting student, Laboratory for Systems Genetics	Japan Society of Promotion of Science Ikushi Priz	Jan 2023
Kyuto Sonehara, Visisting researcger, Laboratory for Systems Genetics	Best presentation award, the 67th Annual Meeting of the Japanese Society of Human Genetics	Dec 2022
Tatsuhiko Naito, Visisting researcger, Laboratory for Systems Genetics	The University of Tokyo President's Award for Students	Mar 2022

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**

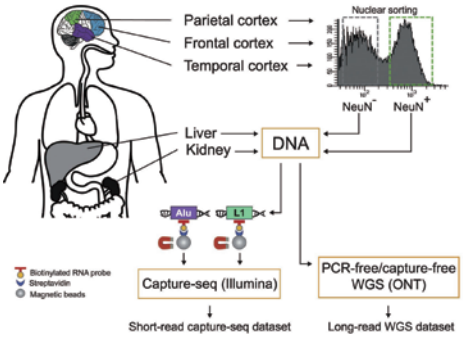


Figure: Experimental approach for the annotation of somatic recombination of Alu and L1
Schematics of the experimental setup.

Technologies for detection and analysis of regulatory regions

We focus on the identification of genome regulatory elements that control transcription, the transcribed functional RNAs and their biological functions.

- We optimized the CAGE technology reducing the amount of required RNA for 96 well assays, all compatible with new sequencer models (Illumina Nextseq and Novaseq). CAGE allows the detection of transcription of all capped RNAs and mapping promoters and enhancers that specifically regulate transcription. We're involved in a single-cell CAGE-like protocol, developing a reliable package of protocol plus computational tools.

- A comprehensive catalog of transcripts still lacks a model for a large number of lncRNAs and unconventional transcripts, including enhancer RNA, promoters and termination-associated RNAs, etc. We've adapted the cap-trapper protocol for full-length RNA sequencing of polyA+ and – RNAs using Oxford Nanopore technology.

FANTOM

The FANTOM6 Project has published a functional screening based on perturbation of the function of RNAs and imaging, identifying function for about ~30% of analyzed lncRNAs. Moving into the FANTOM6 phase II, to broadly decipher function based on the RNA interactome, we are broadly analyzing a set of ~15 biological samples including iPS cells differentiated into neurons and activated monocytes.

We produced and analyzed multiomics data to assign functions to regulatory RNAs, with a focus on identifying RNAs that regulate chromatin activity. We give emphasis to RNA-chromatin interactomes using the RADICL-seq technology, identifying classes of chromatin interacting RNAs and inferring their functions.

RNA Biology

We study the structure-function relationship of lncRNA using the SINEUPs, antisense lncRNA that enhances translation of targeted proteins. We have made substantial progress by (1) producing the first full NMR structure of a functional SINE-derived RNA, (2) part of the protein interactome for the function of SINEUPs (PTBP1 and HNRNPK) and (3) RNA modifications needed, such as pseudouridine.

Aging

We showed that the genome is recombined in somatic human tissues in correspondence to SINE and LINE elements, with cell- and aging-specific patterns, particularly in brains from old donors.

Recent Major Publications

Robbe P, Ridout KE, Vavoulis DV, Dréau H, Kinnersley B, Denny N, Chubb D, Appleby N, Cutts A, Cornish AJ, Lopez-Pascua L, Clifford R, Burns A, Stamatopoulos B, Cabes M, Alsolami R, Antoniou P, Oates M, Cavalieri D; Genomics England Research Consortium; CLL pilot consortium; Gibson J, Prabhu AV, Schwessinger R, Jennings D, James T, Maheswari U, Duran-Ferrer M, Carninci P, Knight SJL, Månsson R, Hughes J, Davies J, Ross M, Bentley D, Strefford JC, Devereux S, Pettitt AR, Hillmen P, Caulfield MJ, Houlston RS, Martín-Subero JI, Schuh A. Whole-genome sequencing of chronic lymphocytic leukemia identifies subgroups with distinct biological and clinical features. ***Nat Genet*** 54, 1675-1689 (2022)

de Hoon M, Bonetti A, Plessy C, Ando Y, Hon CC, Ishizu Y, Itoh M, Kato S, Lin D, Maekawa S, Murata M, Nishiyori H, Shin JW, Stolte J, Suzuki AM, Tagami M, Takahashi H, Thongjuea S, Forrest ARR, Hayashizaki Y, Kere J, Carninci P. Deep sequencing of short capped RNAs reveals novel families of noncoding RNAs. ***Genome Res*** 32, 1727-35 (2022)

Pascarella G, Hon CC, Hashimoto K, Busch A, Luginbühl J, Parr C, Yip WH, Abe K, Kratz A, Bonetti A, Agostini F, Severin J, Murayama S, Suzuki Y, Gustincich S, Frith M, Carninci P*. Recombination of repeat elements generates somatic complexity in human genomes. ***Cell*** 185, 3025-3040.e6 (2022)

Invited presentations

Carninci P. "Conventional and unconventional capped transcripts detected by long reads." The Banbury Center meetings (Cold Spring Harbor Laboratory), (New York, USA) October 2022

Carninci P, "Long non-coding RNAs and genomic regulation" The 10th Keio-Stanford Webinar: Functional Genomics (USA/Online) September 2022

Carninci P. "Transcriptional regulation revealed by high throughput genomics technologies: towards nucleic acids medicine" Seminar at Tor Vergata University of Rome (Rome, Italy) June 2022

Carninci P, "Long non-coding RNAs from interactome to function" SIBBM 2022 Frontiers in Molecular Biology (Rome, Italy) June 2022

Carninci P, "Biological regulation by non-coding RNAs and non-coding genome" TRR 267 Webinar Series (Munich, Germany) June 2022

Laboratory for

Cellular Function Conversion Technology

Team Leader: **Harukazu Suzuki**

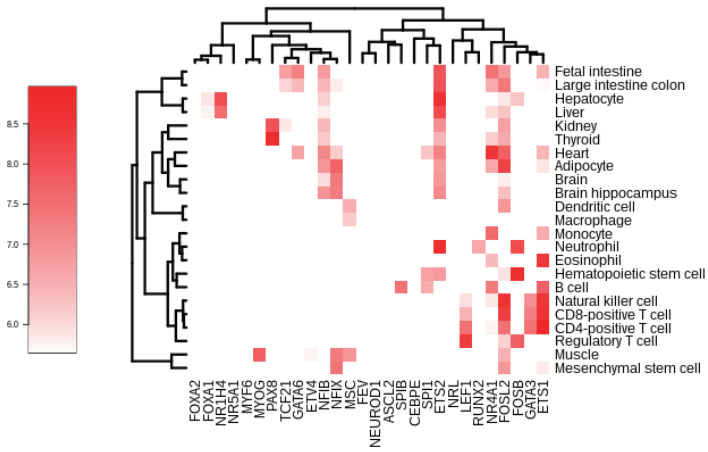


Figure: Gene-expression analysis of the identified TFs with DNA-demethylation-promoting activity

Gene-expression level of the 28 identified TFs in 23 cells or tissues was subjected to cluster analysis and color-coded.

DNA methylation at gene regulatory regions plays an important role in downstream gene expression. Interestingly, a subgroup of transcription factors (TFs) can promote DNA demethylation at their own binding sites. We have computationally predicted approximately 400 TFs that are likely associated with DNA demethylation. Validation of a subset of these candidate TFs revealed that a large number of various TF families are associated with cell-type-specific DNA demethylation during human cellular development. We also explored the precise mechanisms of TF-mediated DNA demethylation during the differentiation of iPS cells into hepatocytes. We found that GATA6 induces DNA demethylation together with chromatin activation in a binding-site-specific manner during endoderm differentiation, uncovering an epigenetic role for transcription factors in early liver development. We are also focusing on application of knowledge about TF-mediated DNA demethylation in medical research. We established model cells for familial platelet disorder with associated myeloid malignancy (FPD). We found that ETS family TF binding motifs are enriched at the hyper-methylated regions. The ETS family TF *FLI1* was significantly down-regulated in the FPD models and its knocked-down showed inefficient megakaryocyte differentiation. Mutations in Ten-Eleven Translocation-2 (TET2), an enzyme involved in TF-mediated DNA demethylation, have been reported in human myeloid malignancies. Using single-cell RNA sequencing, we analyzed progenitors isolated from hematopoietic cell-specific Tet2-deficient mice and identified a novel group of progenitors that could be leukemic progenitors. In addition, we have applied omics technologies to drug-mediated neuronal reprogramming from dedifferentiated fat cells, epithelial-to-mesenchymal transition (EMT) in cellular function modulation, ovarian follicles generated from pluripotent stem cells, *in vitro* cultured testis, and *Mycobacterium tuberculosis* infected macrophages. We will also apply these technologies to studies of the tumor microenvironment of hepatic tumorigenesis and the molecular mechanism of intestinal regeneration.

Recent Major Publications

Suzuki T, Furuhata E, Maeda S, Kishima M, Miyajima Y, Tanaka Y, Lim J, Nishimura H, Nakanishi Y, Shojima A, Suzuki H. GATA6 is predicted to regulate DNA methylation in an *in vitro* model of human hepatocyte differentiation. ***Commun Biol*** 5, 414 (2022)

Miyajima Y, Noguchi S, Tanaka Y, Li JR, Nishimura H, Kishima M, Lim J, Furuhata E, Suzuki T, Kasukawa T, Suzuki H. Prediction of transcription factors associated with DNA demethylation during human cellular development. ***Chromosome Res*** 30, 109-121 (2022)

Yip CW, Hon CC, Yasuzawa K, Sivaraman DM, Ramilowski JA, Shibayama Y, Agrawal S, Prabhu AV, Parr C, Severin J, Lan YJ, Dostie J, Petri A, Nishiyori-Sueki H, Tagami M, Itoh M, López-Redondo F, Kouno T, Chang JC, Luginbühl J, Kato M, Murata M, Yip WH, Shu X, Abugessaisa I, Hasegawa A, Suzuki H, Kauppinen S, Yagi K, Okazaki Y, Kasukawa T, de Hoon M, Carninci P, Shin JW. Antisense-oligonucleotide-mediated perturbation of long non-coding RNA reveals functional features in stem cells and across cell types. ***Cell Rep*** 41, 111893 (2022)

Invited presentations

Qin XY. "Chemoprevention by vitamin A and its derivatives" 22nd IUNS-International Congress of Nutrition, December 2022

Laboratory for

Genome Information Analyses

Team Leader: **Chung-Chau Hon**

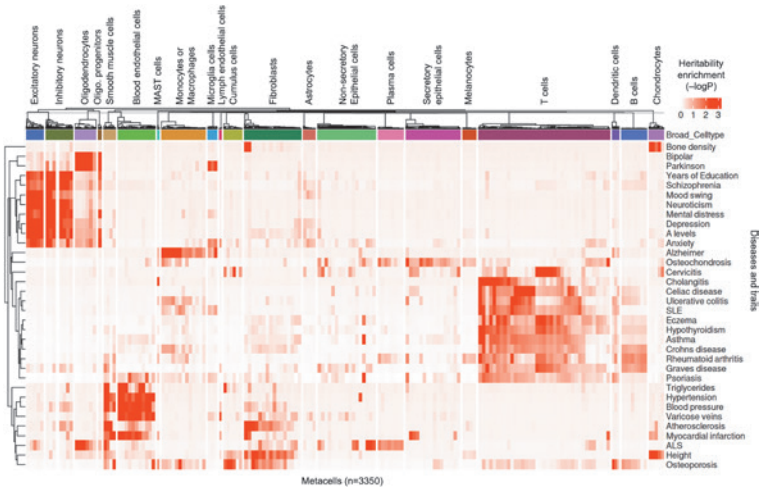


Figure: Enrichment of disease heritability at metacell resolution
We have complied a tCRE atlas comprising >500,000 cells across human tissues. We collapsed this tCRE atlas into 3,350 metacells and devised a novel method, based on tCRE module activities, to estimate the enrichment of disease heritability at each metacell and complied a cell-disease atlas for multiple complex diseases and traits.

Regulation of gene expression is tightly linked to pathogenesis and predisposition to complex diseases. Our team is dedicated to studying the roles of the non-coding genome in gene regulation within disease contexts. To achieve this, we utilize three approaches: 1) performing functional perturbations of non-coding loci, 2) conducting large-scale profiling of regulatory element activities, and 3) using deep learning to decipher the sequence grammar of gene expression. Our work on functional perturbations of non-coding loci involves a collaboration with Takeda Pharma and focuses on Parkinson's disease as an example. Specifically, we performed a CRISPRi screening of non-coding elements in neurons survival upon oxidative stress and identified the non-coding elements at Parkinson's disease risk loci that potentially regulate genes involved in autophagy, apoptosis, and stress responses. In addition, our team developed computational methods to detect authentic transcribed *cis*-regulatory elements (tCREs) at single-cell resolution and generated a single-cell atlas of tCREs across human tissues. We have devised a method that integrates these tCRE data with genome-wide association data, enabling us to evaluate the relevance of cell types, transcription factors, and regulatory elements to complex diseases (Figure). Currently, we are applying these methods to several population scale cohorts, including PBMCs from Asian populations, induced motor neurons from ALS patients, and colon biopsies from Ulcerative Colitis patients. Finally, we aim to integrate these transcriptomic data using deep learning models to derive predictive models of gene expression. These predictive models will enable us to perform *in silico* mutagenesis and assess the effects of non-coding elements on gene expression. With the use of these *in silico* mutagenesis data, we have developed a reliable method to predict the target genes of non-coding elements in a cell-type-specific manner. These methods will enable us to annotate the functional contexts of non-coding elements in a genome-wide and cell-type-specific manner for understanding their roles in gene regulation and diseases.

Recent Major Publications

Moody J, Kouno T, Chang JC, Ando Y, Carninci P, Shin JW, Hon CC*. SCAFE: a software suite for analysis of transcribed *cis*-regulatory elements in single cells. ***Bioinformatics*** 38, 5126-5128 (2022)

Pascarella G, Hon CC, Hashimoto K, Busch A, Luginbühl J, Parr C, Hin Yip W, Abe K, Kratz A, Bonetti A, Agostini F, Severin J, Murayama S, Suzuki Y, Gustincich S, Frith M, Carninci P. Recombination of repeat elements generates somatic complexity in human genomes. ***Cell*** 185, 3025-3040 (2022)

Tanemoto S, Sujino T*, Miyamoto K, Moody J, Yoshimatsu Y, Ando Y, Koya I, Harada Y, Tojo A, Ono K, Hayashi Y, Takabayashi K, Okabayashi K, Teratani T, Mikami Y, Nakamoto N, Hosoe N, Ogata H, Hon CC*, Shin J, Kanai T*. Single-cell transcriptomics of human gut T cells identifies cytotoxic $CD4^+CD8A^+$ T cells related to mouse CD4 cytotoxic T cells. ***Front Immunol*** 13, 977117 (2022)

Invited presentations

Hon CC. "An atlas of transcribed *cis*-regulatory elements in human single cells" The 67th Annual Meeting of the Japan Society of Human Genetics (Yokohama, Japan) December 2022

Hon CC. "An atlas of transcribed *cis*-regulatory elements in human single cells" Human Cell Atlas Asia Meeting (Bangkok, Thailand) November 2022

Hon CC. "An atlas of transcribed *cis*-regulatory elements in human single cells" Graduate course "Introduction to Advanced Medical Research", Yokohama City University (Yokohama, Japan) October 2022

Hon CC. "An atlas of transcribed *cis*-regulatory elements in human single cells" Department Seminar of HERMS, Karolinska Institute (Stockholm, Sweden) October 2022

Hon CC. "An atlas of transcribed *cis*-regulatory elements in human single cells" Department Seminar of IMBS, The University of Hong Kong (Hong Kong, China) August 2022

Laboratory for Applied Computational Genomics

Team Leader: Michiel de Hoon

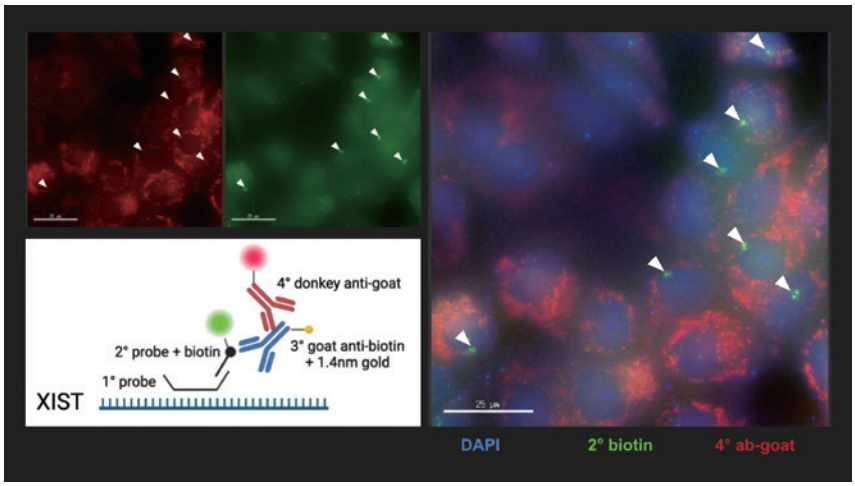


Figure: Labeling of specific transcripts for visualization by electron microscopy
Noncoding RNA *XIST* was labeled with a transcript-specific primary probe, a biotinylated secondary probe carrying a green fluorophore, a tertiary probe consisting of an anti-biotin antibody with a conjugated nanogold bead for observation in EM, and a quaternary probe consisting of an antibody against the tertiary probe carrying a red fluorophore. B. Overlapping signals of the secondary and quaternary probe visible by light microscopy confirm successful labeling of *XIST* by the tertiary probe.

Recent Major Publications

Yip C, Hon C, Yasuzawa K, Sivaraman DM, Ramilowski JA, Shibayama Y, Agrawal S, Prabhu AV, Parr C, Severin J, Lan Y, Dostie J, Petri A, Nishiyori-Sueki H, Tagami M, Itoh M, López-Redondo F, Kouno T, Chang J, Luginbühl J, Kato M, Murata M, Yip W, Shu X, Abugessaisa I, Hasegawa A, Suzuki H, Kauppinen S, Yagi K, Okazaki Y, Kasukawa T, De Hoon M, Carninci P, Shin JW. Antisense oligonucleotide-mediated perturbation of long non-coding RNA reveals functional features in stem cells and across cell types. ***Cell Rep*** 41, 111893 (2022)

De Hoon M, Bonetti A, Plessy C, Ando Y, Hon C, Ishizu Y, Itoh M, Kato S, Lin D, Maekawa S, Murata M, Nishiyori H, Shin JW, Stolte J, Suzuki A, Tagami M, Takahashi H, Thongjuea S, Forrest AR, Hayashizaki Y, Kere J, Carninci P. Deep sequencing of short capped RNAs reveals novel families of noncoding RNAs. ***Genome Res*** 32, 1727-1735 (2022)

Hashimoto M, Saito Y, Nakagawa R, Ogahara I, Takagi S, Takata S, Amitani H, Endo M, Yuki H, Ramilowski JA, Severin J, Manabe R-I, Watanabe T, Ozaki K, Kaneko A, Kajita H, Fujiki S, Sato K, Honma T, Uchida N, Fukami T, Okazaki Y, Ohara O, Shultz LD, Yamada M, Taniguchi S, Vyas P, De Hoon M, Momozawa Y, Ishikawa F. Combined inhibition of XIAP and BCL2 drives maximal therapeutic efficacy in genetically diverse aggressive acute myeloid leukemia. ***Nat Cancer*** 2, 340-356 (2021)

Invited presentations

De Hoon M. "Genomics and transcriptomics at the RIKEN Center for Integrative Medical Sciences" European Union, European Commission, EURAXESS European Researcher Days webinar (Online) December 2021

The Laboratory of Applied Computational Genomics uses bioinformatics methods to understand the molecular basis of cellular functioning in human health and disease. We are particularly interested in discovering and functionally classifying noncoding RNAs by transcriptome and chromatin conformation sequencing data analysis. In FANTOM6, we annotated the function of >10,000 long noncoding RNAs based on the cellular response upon their knockdown, as well as on their physical association with protein-coding genes in chromatin conformation data. The interactive web portal ZENBU-Reports for the visualization, analysis and dissemination of genome-scale bioinformatics analysis results was created by our lab for FANTOM6 and is also being used by other research groups.

In close collaboration with the IMS Laboratory for Human Disease Models, we apply our basic genomics expertise to personalized medicine to understand the regulatory factors involve in acute myeloid leukemia (AML). We analyze the global properties of gene regulatory networks, noncoding RNAs, chromosomal rearrangements, and chromatin conformation in AML patients. In collaboration with multiple IMS laboratories, we study the response of human airway epithelial cells after infection by different strains of SARS-CoV-2 or influenza virus, revealing differential gene expression and promoter usage, and promoter switching.

Complementary to our bioinformatics research, our laboratory develops protocols for electron microscope (EM) imaging of chromatin and specific transcripts in the cell nucleus. Our aim is to open a new field of 3D genomics by integrating EM imaging with sequencing data as an enabling technology to discover the biophysical basis of gene regulation.

Laboratory for

Large-Scale Biomedical Data Technology

Team Leader: Takeya Kasukawa

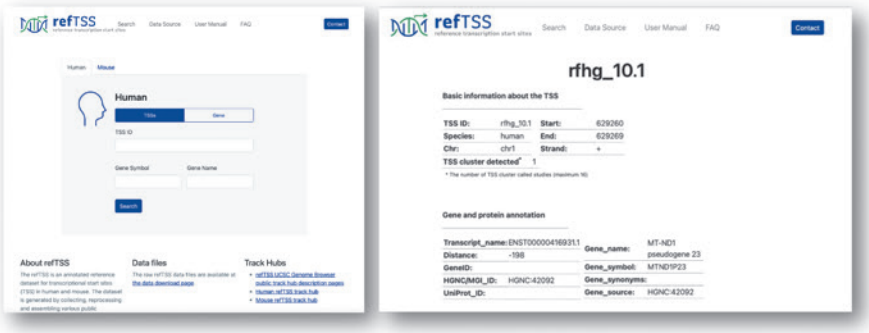


Figure: refTSS web interface (renewed)
(Left) Home page of the refTSS web interface. (Right) Detail page of a TSS.

Recent Major Publications

Yip CW, Hon CC, Yasuzawa K, Sivaraman DM, Ramilowski JA, Shibayama Y, Agrawal S, Prabhu AV, Parr C, Severin J, Lan YJ, Dostie J, Petri A, Nishiyori-Sueki H, Tagami M, Itoh M, López-Redondo F, Kouno T, Chang JC, Luginbühl J, Kato M, Murata M, Yip WH, Shu X, Abugessaisa I, Hasegawa A, Suzuki H, Kauppinen S, Yagi K, Okazaki Y, Kasukawa T, de Hoon M, Carninci P, Shin JW. Antisense-oligonucleotide-mediated perturbation of long non-coding RNA reveals functional features in stem cells and across cell types. ***Cell Rep*** 41, 111893 (2022)

Bono H, Sakamoto T, Kasukawa T, Tabunoki H. Systematic Functional Annotation Workflow for Insects. ***Insects*** 13, 586 (2022)

Abugessaisa I, Hasegawa A, Noguchi S, Cardon M, Watanabe K, Takahashi M, Suzuki H, Katayama S, Kere J, Kasukawa T*. SkewC: Identifying cells with skewed gene body coverage in single-cell RNA sequencing data. ***iScience*** 25, 103777 (2022)

Invited presentations

Kasukawa T, Kawaji H, Masuya H. "Construction of a genome-wide *cis*-regulatory element data resource for understanding the transcriptional regulation" The 45th Annual Meeting of the Molecular Biology Society of Japan (MBSJ2022) (Chiba, Japan) November 2022

Abugessaisa I. "MycEXomics: Development of field-friendly POC diagnostic test for the four most common causative agents of mycetoma" The Mycetoma Update Seminar 2022 (Khartoum, Sudan) November 2022

Kasukawa T. "Construction of an integrative data platform for transcriptional regulations" Togo Symposium (Online) October 2022

Kasukawa T. "Development of *cis*-regulatory element database for data platform of transcriptional regulations" BioPackathon 2022 #9 (Online) September 2022

Morioka MS. "Development of the novel transcription start site information database (refTSS4.0) and its utilization tools for medical research applications" 9th RIKEN-Genome Editing Joint Seminar (Hiroshima, Japan) June 2022

Because of rapid improvements in technologies to measure biomedical phenomena, including sequencing technologies, many types of transcriptomic, genomic and epigenomic data have been generated and made publicly available. Such data resources are potentially useful for the elucidation of biological systems and for the development of medical tools by performing large-scale integrative analyses. Our mission is promoting such data-driven studies in the biomedical field and developing component technologies to efficiently reuse large-scale biomedical data by employing data engineering technologies.

Towards this goal, we now have several ongoing research projects. First, we are developing a database system to support the 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 (SCPortalen, https://single-cell.riken.jp/). We have also developed a new QC method (SkewC) to evaluate whether cells in the single-cell RNA-seq data can be used for the downstream analysis and biological interpretation. 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 (https://reftss.riken.jp/). From FY2022, we started the development of a new database (fanta.bio) of *cis*-regulatory elements in several mammalian genomes and the construction of a new integrated data platform for transcriptional regulation, named INTRARED (https://www.intrared.org/).

Along with the above core research projects, we are working on data coordination for several collaborative large-scale data production projects being done in RIKEN IMS. In addition to these research projects, we are also 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 the computer environments for researchers and support staff and developing and managing web applications for support staff in IMS.

Laboratory for

Advanced Genomics Circuit

Team Leader: **Jay W. Shin**

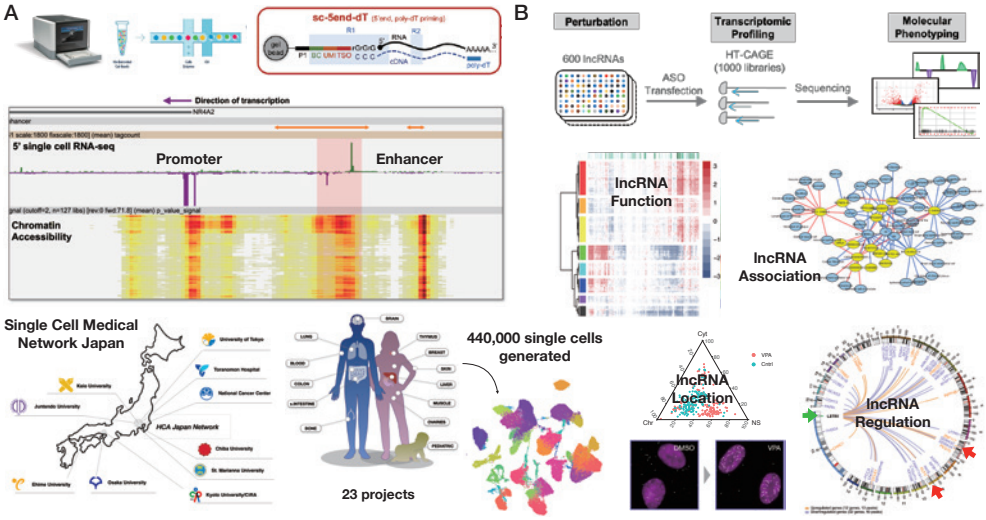


Figure:
A) Single cell 5'RNA-seq reveals promoter and enhancer regulatory elements in the human genome. Using this technology, Single Cell Medical Network (SCMN) consortium was created in Japan to profile over 400,000 single cells across 23 projects – revealing a comprehensive atlas of regulatory elements in the human genome. B) To functionally characterize regulatory elements, such as lncRNA, a systematic knockdown was performed to profile their molecular phenotypes – revealing their function, associations, location and regulation.

Recent Major Publications

Yip CW, Hon CC, Yasuzawa K, Sivaraman DM, Ramilowski JA, Shibayama Y, Agrawal S, Prabhu AV, Parr C, Severin J, Lan YJ, Dostie J, Petri A, Nishiyori-Sueki H, Tagami M, Itoh M, López-Redondo F, Kouno T, Chang JC, Luginbühl J, Kato M, Murata M, Yip WH, Shu X, Abugessaisa I, Hasegawa A, Suzuki H, Kaupinen S, Yagi K, Okazaki Y, Kasukawa T, de Hoon M, Carninci P, Shin JW*. Antisense-oligonucleotide-mediated perturbation of long non-coding RNA reveals functional features in stem cells and across cell types. ***Cell Reports*** 41, 111893 (2022)

Moody J, Kouno T, Chang JC, Ando Y, Carninci P, Shin JW*, Hon CC. SCAFE: a software suite for analysis of transcribed *cis*-regulatory elements in single cells. ***Bioinformatics*** 38, 5126-5128 (2022)

Ducoli L, Agrawal S, Sibler E, Kouno T, Tacconi C, Hon CC, Berger SD, Müllhaupt D, He Y, Kim J, D'Addio M, Dieterich LC, Carninci P, de Hoon MJL, Shin JW*, Detmar M. LETR1 is a lymphatic endothelial-specific lncRNA that governs cell proliferation and migration through KLF4 and SEMA3C. ***Nature Commun*** 12, 925 (2021)

Invited presentations

Shin JW. "The past, present, and prospective of HCA Asia" Human Cell Atlas Asia 2022 Meeting (Bangkok, Thailand) November 2022

Shin JW. "From Discovery to Functional Understanding of Non-Coding Regulatory Elements" IHEC Annual Meeting and Canadian Conference on Epigenetics (Montreal, Canada) October 2022

Shin JW. "Building the Cell Regulatory Network based on sc-5' RNA-seq and Spatial Transcriptomics" Spatial Biology Congress (Hague, Netherlands) September 2022

Shin JW. "Human Cell Atlasing the Transcribed Cis-Regulatory Elements" CZI Single-Cell Biology 2021 Annual Meeting (Paolo Alto, USA/Online) October 2021

Most of the human genome is considered non-coding, yet we and others have found a plethora of regulatory elements – in forms of either RNA or DNA – that regulate gene expression. How they control gene expression across a multitude of cell types and disease states is not well understood. In my lab, we holistically interrogate gene regulation mediated by non-coding regulatory elements through the implementation of single-cell 5' RNA-seq. We actively collaborate with medical institutions in Japan to map single cells using spatial and single cell transcriptomics across human tissues. In collaboration with Dr. Chung Chau Hon's lab (IMS), we developed a computational algorithm to annotate *cis*-regulatory elements, including enhancer RNAs, at single cell resolution. We are using these tools to interrogate *cis*-regulatory elements in association with genetic disorders based on single-cell eQTL, as part of the Human Cell Atlas (HCA) Asia project (CZI funded), and chromatin-chromatin interactions at single cell resolution using long-read DNA sequencers (AMED).

The lab also specializes in gene-targeting tools, including CRISPR-interference and antisense oligonucleotides, to elucidate the functional role of long non-coding RNAs in human stem cells, brain development and cell reprogramming. We are combining gene perturbation methods with single-cell genomics to elucidate non-coding regulatory elements in human brain organoid models in a scalable and cost-effective manner. As part of the FANTOM6, we are analyzing non-coding regulatory elements by their associated molecular pathways and interacting partners, including DNA-DNA, DNA-RNA and RNA-protein interactions, to intervene and modulate gene regulation for potential therapeutic modalities.

Laboratory for
Cellular Epigenomics

Team Leader: **Aki Minoda**

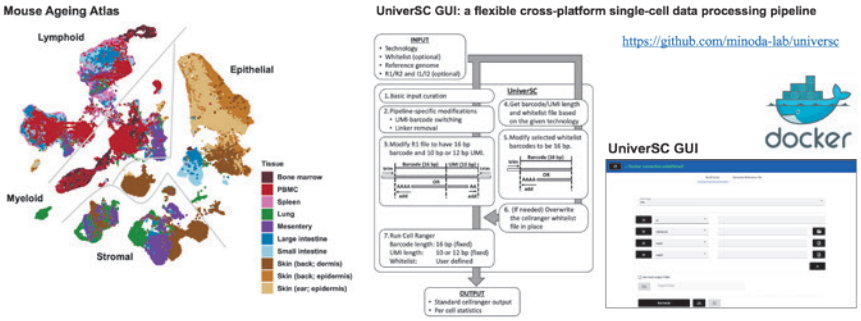


Figure: Construction of a Mouse Ageing Atlas with single-cell genomics and UniverSC: a flexible cross-platform single-cell data processing pipeline
Left: 5' scRNA-seq data from eight mouse tissues obtained from young (2 months) and old (19 months) SPF (specific pathogen-free) or GF (germ-free) mice are combined and displayed.
Right: The pipeline and the GUI for UniverSC.

Recent Major Publications

Hashimoto S, Nagoshi N, Shinozaki M, Nakanishi K, Suematsu Y, Shibata T, Kawai M, Kitagawa T, Ago K, Kamata Y, Yasutake K, Koya I, Ando Y, Minoda A, Shindo T, Shibata S, Matsumoto M, Nakamura M, Okano H. Microenvironmental modulation in tandem with human stem cell transplantation enhances functional recovery after chronic complete spinal cord injury. ***Biomaterials*** 295, 122002 (2023)

Miyao T, Miyauchi M, Kelly ST, Terooatea TW, Ishikawa T, Oh E, Hirai S, Horie K, Takakura Y, Ohki H, Hayama M, Maruyama Y, Seki T, Ishii H, Yabukami H, Yoshida M, Inoue A, Sakaue-Sawano A, Miyawaki A, Muratani M, Minoda A, Akiyama N, Akiyama T. Integrative analysis of scRNA-seq and scATAC-seq revealed transit-amplifying thymic epithelial cells expressing autoimmune regulator. ***Elife*** 11, e73998 (2022)

Kelly ST, Battenberg K, Hetherington NA, Hayashi M, Minoda A*. UniverSC: a flexible cross-platform single-cell data processing pipeline. ***Nature Communications*** 13, 6847 (2022)

Invited presentations

Minoda A. "Activation of type 2 innate immune response with ageing" Molecular Biology Society of Japan (Chiba, Japan/Online) November 2022

Minoda A. "Activation of type 2 innate immune response with ageing" Society for Leukocyte Biology (Kona, Hawaii, USA) October 2022

Minoda A. "Activation of type 2 innate immune response in old age" 17th International Conference on Innate Immunity, (Ioannina, Greece) July 2022

Minoda A. "Mouse Ageing Atlas: effect of the microbiota on ageing" Single Cell Genomics, Gordon Conference (Les Diablerets, Switzerland), May 2022

Minoda A. "Mouse Ageing Promoter Atlas: effect of the microbiota on ageing" RIKEN Next Frontiers in Aging Biology (Online) January 2022

Our lab aims to determine epigenomic and transcriptomic changes in a comprehensive manner in various models by applying the most advanced available technologies, such as single-cell genomics. This information will be utilized to gain mechanistic insights into various biological questions at the molecular level.

Construction of a Mouse Ageing Atlas using single-cell genomics

Inflammation is a major hallmark of ageing. To determine whether the presence of the microbiota is contributing to the increase in inflammation that is observed with age (termed 'inflammaging'), we are generating single-cell genomic (5' scRNA-seq and scATAC-seq) datasets from various tissues in both SPF and germ-free mice at various ages, as well as performing lipidomics (in collaboration with the Arita lab, IMS), metabolomics and microbiome (in collaboration with the Ohno lab, IMS) analyses. Such a rich collection of multi-omics datasets will likely provide us with an unbiased insight at many different levels, including the effect of the microbiome, into the complex biological phenomena of ageing. Our preliminary analysis of the completed datasets from eight different tissues captures increased inflammation signatures with old age at the transcriptomic level, which are in fact reduced in the germ-free mice that completely lack microbes. This indeed suggests that the microbiota contributes to inflammaging.

Development of UniverSC: a flexible cross-platform single-cell data processing pipeline

Single-cell RNA-sequencing analysis to quantify RNA molecules in individual cells has become popular as it can generate a large amount of information from each experiment. We have developed UniverSC (https://github.com/minoda-lab/universc), a universal single-cell RNA-seq data processing tool that supports any UMI-based platform. Our command-line tool enables consistent and comprehensive integration, comparison and evaluation across data generated from a wide range of platforms. In an effort to democratize single-cell analysis, UniverSC is also available through Docker as well as GUI (graphical user interface).

Laboratory for

Comprehensive Genomic Analyses

Team Leader: Yasushi Okazaki

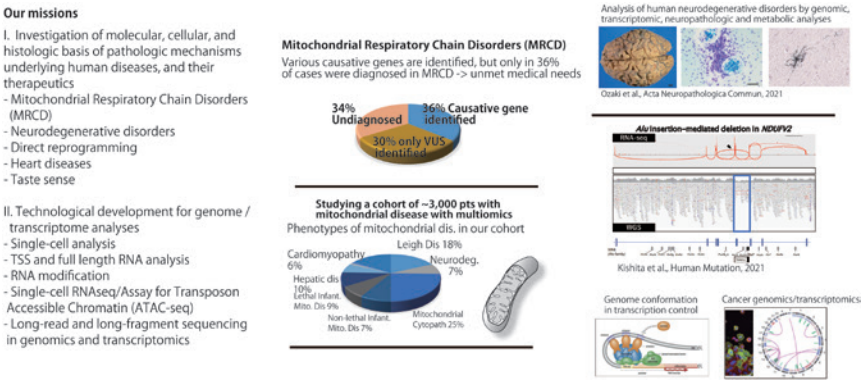


Figure: Missions and projects of Lab. for Comprehensive Genomic Analysis
We are investigating molecular basis of the diseases including mitochondrial respiratory chain disorders (MRCDs), neurological diseases, and others. For mitochondrial diseases, we are analyzing on ~3,000 patients in alliance with Juntendo Univ., Saitama Medical Univ., and Chiba Prefectural Children's hospital. And we also are studying molecular mechanisms underlying direct reprogramming and taste sense. We address these issues by various technologies including short-/long-read sequencing of genome, transcriptome, epigenome, as well as single-cell level transcriptomics and epigenomics. For these missions, we also are developing our proprietary methodologies in wet and dry.

Recent Major Publications

Yasuoka Y. Tissue-specific expression of carbohydrate sulfotransferases drives keratan sulfate biosynthesis in the notochord and otic vesicles of *Xenopus* embryos. ***Front Cell Dev Biol*** 11, 957805 (2023)

Imai-Okazaki A, Nitta KR, Yatsuka Y, Sugiura A, Arao M, Shimura M, Ebihara T, Onuki T, Ichimoto K, Ohtake A, Murayama K, Okazaki Y. Impact of measuring heteroplasmy of a pathogenic mitochondrial DNA variant at the single-cell level in individuals with mitochondrial disease. ***J Inherit Metab Dis*** 45, 1143-1150 (2022)

Yip CW, Hon CC, Yasuzawa K, Sivaraman DM, Ramilowski JA, Shibayama Y, Agrawal S, Prabhu AV, Parr C, Severin J, Lan YJ, Dostie J, Petri A, Nishiyori-Sueki H, Tagami M, Itoh M, López-Redondo F, Kouno T, Chang JC, Luginbühl J, Kato M, Murata M, Yip WH, Shu X, Abugessaisa I, Hasegawa A, Suzuki H, Kauppinen S, Yagi K, Okazaki Y, Kasukawa T, de Hoon M, Carninci P, Shin JW. Antisense-oligonucleotide-mediated perturbation of long non-coding RNA reveals functional features in stem cells and across cell types. ***Cell Rep*** 41, 111893 (2022)

Invited presentations

Yasuoka Y. "Exploring the evolutionary process of vertebrates by developmental genomics" JT Biohistory Research Hall Seminar (Takatsuki, Japan) January 2023

Ozaki K. "Analysis of mitochondrial diseases through multimodal genetic analyses" NGS EXPO 2022 (Osaka, Japan) October 2022

Yasuoka Y. "Evolutionary studies on gene regulatory networks in early animal embryogenesis" The 93rd annual meeting of the Zoological Society of Japan (Tokyo, Japan) September 2022

From FY2016 to FY2017, we provided technical support through next-generation sequencing to researchers in and outside of RIKEN as a facility named Genome Network Analysis Support (GeNAS). In FY 2018, we were reorganized into the Laboratory for Comprehensive Genomic Analysis (CGA) to start our own research activities, while still contributing the support of other researchers, as a part of the "IMS genome platform" activities.

The objectives of our distinct research themes are to elucidate the molecular pathophysiology of human diseases, especially focusing on mitochondrial diseases, neurological diseases and other rare and intractable diseases, and to provide the technological basis for medical therapeutics. We employ a multi-omics approach, with special emphasis on genome and transcriptome analyses. Specifically, we focus on the identification and characterization of novel causative genes for these diseases. We have analyzed clinical cases in which it is difficult to reach a molecular diagnosis, using state-of-the-art sequencing technologies and sometimes developing our own proprietary methodologies. During the last several years, we have identified at least 10 novel pathogenic variants and genes, including two novel repeat expansion diseases.

We also have made major progress in our investigation of the pathogenesis of two neurological diseases (Spinocerebellar ataxia type 34 and Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)). A well-known antihypertensive drug candesartan reversed the molecular pathophysiology in CARASIL, emerging as a candidate for therapeutics.

We are committed to other medically relevant themes as well. We continue to conduct single-cell analyses of mammalian taste receptor systems, as a platform for lifestyle-related diseases. Epigenetic analyses (ChIP/ATAC/Methyl-seq) have clarified molecular mechanisms underlying the direct reprogramming of fibroblasts into another distinctively differentiated cell type, as a prelude to regenerative medicine for intractable diseases. A high-throughput screening system and optical visualization in hearts using zebrafish are under development to discover new potential drug targets for the realization of personalized medicine.

RIKEN-IFOM Joint Laboratory for Cancer Genomics

Team Leader: Yasuhiro Murakawa

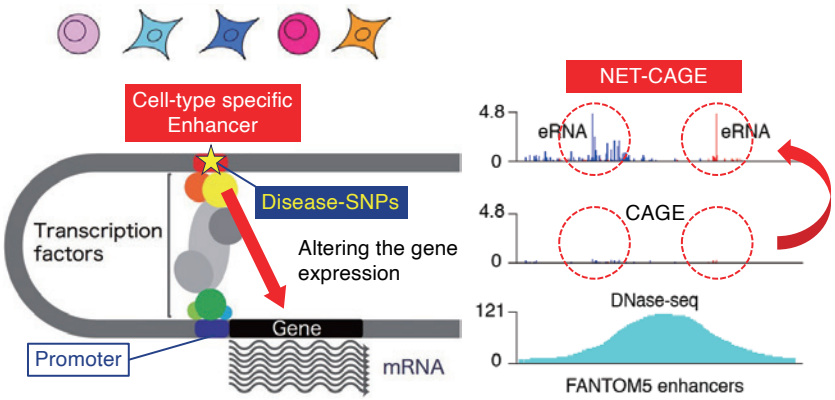


Figure: Building an atlas of transcribed enhancers across human body for decoding human diseases

Enhancers are small segments of DNA *cis*-regulatory elements that significantly enhance the expression of target genes and play key roles in the establishment of cell-type-specific function and identity. Single nucleotide polymorphisms associated with human diseases (GWAS-SNPs) are highly enriched in enhancer regions and are thought to alter disease susceptibility by changing the expression levels of target genes. We have developed original methods such as NET-CAGE to detect enhancer RNAs transcribed from active enhancers with high sensitivity, and are studying the relationship between enhancers and human diseases.

Recent Major Publications

Koido M, Hon CC, Koyama S, Kawaji H, Murakawa Y, Ishigaki K, Ito K, Sese J, Parrish NF, Kamatani Y, Carninci P, Terao C. Predicting cell-type-specific non-coding RNA transcription from genome sequence. ***Nature Biomed Eng*** Online ahead of print (2022)

Sato Y, Oguchi A, Fukushima Y, Masuda K, Toriu N, Taniguchi K, Yoshikawa T, Cui X, Kondo M, Hosoi T, Komidori S, Shimizu Y, Fujita H, Jiang L, Kong Y, Yamanashi T, Seita J, Yamamoto T, Toyokuni S, Hamazaki Y, Hattori M, Yoshikai Y, Boor P, Floege J, Kawamoto H, Murakawa Y, Minato N, Yanagita M. CD153/CD30 signaling promotes age-dependent tertiary lymphoid tissue expansion and kidney injury. ***J Clin Invest*** 132, e146071 (2022)

Guerrini MM, Oguchi A, Suzuki A, Murakawa Y. Cap analysis of gene expression (CAGE) and noncoding regulatory elements. ***Semin Immunopathol*** 44, 127-136 (2022)

Invited presentations

Murakawa Y. "Dynamics and evolution of human *cis*-regulatory elements" 21st Takeda Science Symposium (Osaka, Japan) January 2023

Murakawa Y. "Development of genome analysis technology to elucidate the function of the human genome" LSACJ Annual Meeting 2022 (Kobe, Japan) November 2022

Murakawa Y. "An atlas of transcribed enhancers across helper T cell diversity for decoding human diseases" BIMSB seminar (Berlin, Germany) October 2022

Murakawa Y. "Development of functional genomics technologies towards understandings of human genome" 15th Diabetes Leading-edge Conference (Kyoto, Japan) August 2022

Murakawa Y. "A compendium of human CD4$^+$ T cell enhancers for decoding immune-mediated diseases" CRICK-MSKCC-IFOM meeting (London, UK) May 2022

The body-wide transcriptome is generated by the spatiotemporal orchestration of *cis*-regulatory DNA elements such as promoters and enhancers. In particular, enhancers are distal *cis*-regulatory elements that are crucial for the establishment of cell type-specific function and identity in health and disease. 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 developed a new method, native elongating transcript-cap analysis of gene expression (NET-CAGE), to determine globally the 5' ends (or transcription start sites) of nascent RNAs, which permits sensitive detection of even unstable transcripts including enhancer-derived RNAs. Thus, NET-CAGE enabled ultra-sensitive detection of a number of enhancers at nucleotide resolution as well as the genes that are regulated by them (Hirabayashi *et al.* Nature Genetics, 2019). More recently, we have developed a new 5' single-cell RNA sequencing (5' scRNA-seq) approach to investigate functional enhancers from heterogeneous cell types within a given tissue/cell (Oguchi *et al.*, revised manuscript in preparation). We believe in the importance of developing original disruptive technologies that can solve paradigms that cannot otherwise be solved.

We are applying our new methods such as NET-CAGE and 5' scRNA-seq to describe the active *cis*-regulatory landscape across hundreds to thousands of human samples including various types of tumors and immune cells, to comprehensively catalog cell-type specific enhancers, genes and long non-coding RNAs. Furthermore, by integrating large-scale human disease genomics data with clinical information, we study disease-relevant genetic elements that can be exploited to develop novel molecular therapeutic targets and predictive biomarkers. Our ultimate long-term goal is to revolutionize drug discovery, medicine and healthcare.

Laboratory for Genotyping Development

Team Leader: Yukihide Momozawa

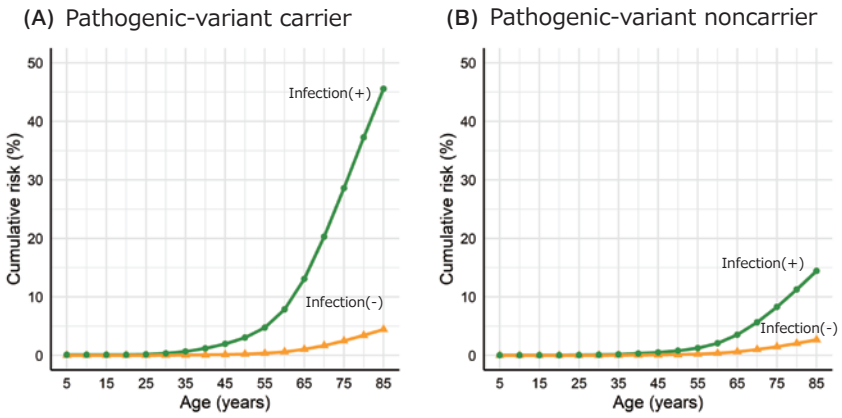


Figure: Cumulative risk of gastric cancer according to *Helicobacter pylori* infection status in (A) pathogenic-variant carrier and (B) pathogenic-variant noncarrier

Individuals with both germline pathogenic variants in homologous recombination genes (*ATM, BRCA1, BRCA2, PALB2*) and *Helicobacter pylori* infection showed an excess risk of gastric cancer compared to individuals with either factor alone. (*N Engl J Med*. 2023; 388:1181-1190)

Recent Major Publications

Usui Y, Taniyama Y, Endo M, Koyanagi Y, Kasugai Y, Oze I, Ito H, Imoto I, Tanaka T, Tajika M, Niwa Y, Iwasaki Y, Aoi T, Hakozaki N, Takata S, Suzuki K, Terao C, Hatakeyama M, Hirata M, Sugano K, Yoshida T, Kamatani Y, Nakagawa H, Matsuda K, Murakami Y, Spurdle A, Matsuo K*, Momozawa Y*. Helicobacter pylori, homologous recombination genes and gastric cancer. ***N Engl J Med*** 388, 1181-1190 (2023)

Momozawa Y, Sasai R, Usui Y, Shiraishi K, Iwasaki Y, Taniyama Y, Parsons MT, Mizukami K, Sekine Y, Hirata M, Kamatani Y, Endo M, Inai C, Takata S, Ito H, Kohno T, Matsuda K, Nakamura S, Sugano K, Yoshida T, Nakagawa H, Matsuo K, Murakami Y, Spurdle AB, Kubo M. Expansion of Cancer Risk Profile for BRCA1 and BRCA2 Pathogenic Variants. ***JAMA Oncol*** 8, 871-878 (2022)

Okawa Y, Iwasaki Y, Johnson TA, Ebata N, Inai C, Endo M, Maejima K, Sasagawa S, Fujita M, Matsuda K, Murakami Y, Nakamura T, Hirano S, Momozawa Y*, Nakagawa H*. Hereditary cancer variants and homologous recombination deficiency in biliary tract cancer. ***J Hepatol*** 78, 333-342 (2022)

Invited presentations

Momozawa Y. "Pan-cancer analysis of 14 cancer types about BRCA1 and BRCA2" Annual Meeting of Japan Society of Clinical Genetics in Obstetrics and Gynecology (Niigata, Japan) October 2022

Momozawa Y. "Application of AI-based genome platforms for cancer care" Annual Meeting of Japan Society of Clinical Oncology (Kobe, Japan) October 2022

Momozawa Y. "A large case-control study of hereditary cancer-predisposing genes" Annual Meeting of the Japanese Cancer Association (Yokohama, Japan) September 2022

Momozawa Y. "Various heterogeneities about BRCA1 and BRCA2" Sapporo International Cancer Symposium (Sapporo, Japan) June 2022

Momozawa Y. "Expectations for personalized medicine based on pan-cancer analysis of 14 cancer types about BRCA1 and BRCA2" Insight #2 (Tokyo, Japan) June 2022

The aims of the Laboratory for Genotyping Development are to produce large-scale genomic data for personalized medicine and to assist with research projects conducted in IMS, other universities and academic institutes, and companies. Our laboratory published 96 papers in 2019-2022.

As our main project, we focused on rare germline pathogenic variants in hereditary cancer genes to broaden personalized medicine. We have analyzed 27 hereditary cancer genes using our previously developed targeted sequencing method in ~84,000 cancer patients with 23 cancer types and in ~38,000 controls from BioBank Japan. In a new study, we analyzed *BRCA1* and *BRCA2* across 14 cancer types in >100,000 samples to identify their pathogenic variants that increase disease risk in new cancer types - biliary tract, esophageal, and gastric cancer. These results suggest that more surveillance of pathogenic variant carriers could be beneficial and the potential efficacy of a PARP inhibitor specific for pathogenic variant carriers (*JAMA Oncol* 2022). We also performed an integrated analysis of pathogenic variants and *Helicobacter pylori* infection in gastric cancer in > 50,000 samples to show that both factors boost disease risk, which suggests that pathogenic variant carriers should receive an evaluation of *Helicobacter pylori* infection status and its eradication if positive (*New Engl J Med* 2023). We will expand this project to provide individual risk estimation based on rare pathogenic variants, common variants, environmental factors, and infections across 23 cancer types.

For supporting other research projects in IMS, we developed a Genome Platform to support library preparation, next-generation sequencing and data analysis. We have conducted 136 projects and performed sequencing runs with MiSeq (N=517), HiSeq2500 (N=326), NextSeq2000 (N=72), NovaSeq6000 (N=467), and Sequel II (N=11). Beginning in 2022, we also joined AMED-BINDS to support research projects in Japan.

We will continue to run our own projects and contribute to other research projects for the implementation of personalized medicine.

Laboratory for

Statistical and Translational Genetics

Team Leader: **Chikashi Terao**

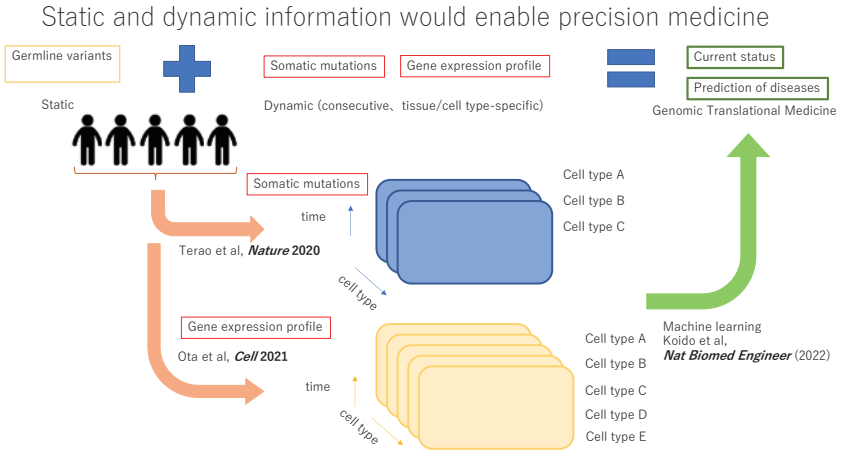


Figure: Combining static and dynamic biological information would lead to precision medicine
It is important to utilize not only static biological information (germline variants) but also dynamic biological information (gene expression profiles and somatic mutations) in order to predict an individual's prognosis and risk of developing diseases. Dynamic biological information should be different for each tissue. Machine learning-based methods can efficiently integrate static and dynamic biological information.

Recent Major Publications

Koido M, Hon CC, Koyama S, Kawaji H, Murakawa Y, Ishigaki K, Ito K, Sese J, Parrish NF, Kamatani Y, Carninci P, Terao C*. Prediction of the cell-type-specific transcription of non-coding RNAs from genome sequences via machine learning. ***Nat Biomed Eng*** Online ahead of print (2022)

Ishigaki K, Sakaue S, Terao C**, Luo Y, Sonehara K, Yamaguchi K, Amariuta T, Too CL, Laufer VA, Scott IC, Viatte S, Takahashi M, Ohmura K, Murasawa A, Hashimoto M, Ito H, Hammoudeh M, Emadi SA, Masri BK, Halabi H, . . ., Huizinga T, Dieudé P, Schneider M, Kerick M, Denny JC; BioBank Japan Project, Matsuda K, Matsuo K, Mimori T, Matsuda F, Fujio K, Tanaka Y, Kumanogoh A, Traylor M, Lewis CM, Eyre S, Xu H, Saxena R, Arayssi T, Kochi Y, Ikari K, Harigai M, Gregersen PK, Yamamoto K, Louis Bridges S Jr, Padyukov L, Martin J, Klareskog L, Okada Y, Raychaudhuri S. Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in rheumatoid arthritis. ***Nat Genet*** 54, 1640-1651 (2022)

Hujoel MLA, Sherman MA, Barton AR, Mukamel RE, Sankaran VG, Terao C, Loh PR.Influences of rare copy-number variation on human complex traits. ***Cell*** 185, 4233-4248. e27 (2022)

* as corresponding author, ** as equal first author

Invited presentations

Terao C. "G-PROB (Genetic Probability tool) - taking advantage of genetic risk scoring" 25th Asia-Pacific League of Associations for Rheumatology Congress (APLAR) (HongKong, China) December 2022

Terao C. "Promising molecules in Large vessel vasculitis" 37th Annual Conference of Indian Rheumatology Association (IRACON) (Indore, India) November 2022

Terao C. "Genomics Unravels the Molecular Basis of Immune Diseases and Traits" The 114th Collagen Disease Research Meeting (Niigata, Japan) November 2022

Terao C. "Aging and somatic mosaicism" The 22nd Scientific Meeting of the Japanese Society of Anti-Aging Medicine (Niseko, Japan) September 2022

Terao C. "International Collaborative Genetic Studies for Complex Traits" US-Japan Conference on Oncology (Washington, USA/Online) June 2022

Genetic associations provide direct evidence for mechanisms of human complex traits. We constructed a Japanese-specific genotype reference panel containing 3,256 Japanese whole-genome sequence (WGS) data. We combined ~260,000 Japanese subjects, the reference panel and statistical fine-mapping and identified 4,423 significant loci across 63 quantitative traits among which 601 were novel and 9,406 putatively causal associations. Novel associations included Japanese-specific coding, splicing and non-coding variants, exemplified by a damaging missense variant with lower heart function and increased risk for heart failure (P=1.4×10^{-15} and OR=4.5 (95%CI:3.1-6.5)). We developed algorithms to detect structural variations (SVs) including copy number variations (CNVs). We developed HI-CNV which can sensitively detect CNVs based on DNA microarray data. We also developed a computational algorithm (MOPline) that sensitively detects SVs using short-read WGS data. Using 3,672 high-coverage WGS datasets, MOPline stably detected ~16,000 SVs per individual, which is over 2-fold higher than previous large-scale projects, while exhibiting a comparable level of statistical quality metrics. We imputed SVs from 181,622 Japanese individuals and found novel associations for diseases and quantitative traits.

Regarding somatic information, we analyzed somatic chromosomal alterations and cell-specific gene regulation mechanisms. We describe population-specific patterns of genomic mutations and clonal selection in hematopoietic cells on the basis of 33,250 autosomal mosaic chromosomal alterations in 179,417 Japanese. In collaboration with the FANTOM consortium, we report the development and utility of a machine-learning model (MENTR) that reliably links genome sequence and ncRNA expression at the cell type level.

Our overall long-term goal is to realize precision medicine/personalized genomic medicine by finding variants, especially population-specific ones, with strong effect sizes, integrating germline information and somatic information including gene expression, understanding the basis of complex traits based on genetic findings, and constructing accurate evaluation models of the current physiological status of the body and prediction models of diseases and outcomes.

Laboratory for Pharmacogenomics

Team Leader: Taisei Mushiroda

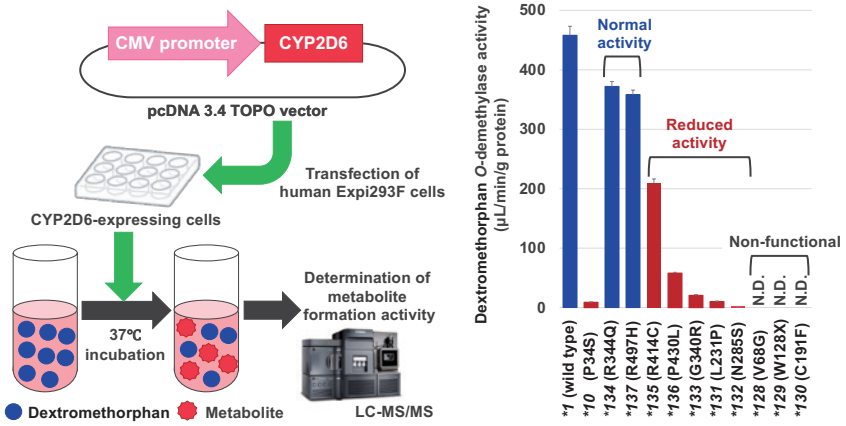


Figure: Functional characterization of variants in genes important for clinical drug therapy using a mammalian suspension cell expression system capable of producing large amounts of recombinant protein

The *in vitro* experimental system was applied to the evaluation of the effects of novel *CYP2D6* variants on metabolic activities for a typical CYP2D6 substrate dextromethorphan.

Recent Major Publications

Hikino K, Tanaka N, Koido M, Tomizuka K, Koike Y, Ito S, Suzuki A, Momozawa Y, Kamatani Y; BioBank Japan Project Consortium; Mushiroda T, Terao C. Genetic Architectures Underlie Onset Age of Atopic Dermatitis. ***J Invest Dermatol*** 142, 3337-3341 (2022)

Diekstra MHM, Swen JJ, van der Zanden LFM, Vermeulen SH, Boven E, Mathijssen RHJ, Fukunaga K, Mushiroda T, Hongo F, Oosterwijk E, Cambon-Thomsen A, Castellano D, Fritsch A, Donas JG, Rodriguez-Antona C, Ruijtenbeek R, Radu MT, Eisen T, Junker K, Roessler M, Jaehde U, Miki T, Böhringer S, Kubo M, Kiemeney LALM, Guchelaar HJ. Genome-Wide Meta-Analysis Identifies Variants in *DSCAM* and *PDLIM3* That Correlate with Efficacy Outcomes in Metastatic Renal Cell Carcinoma Patients Treated with Sunitinib. ***Cancers*** (Basel) 14, 2838 (2022)

Siamoglou S, Koromina M, Hishinuma E, Yamazaki S, Tsermpini EE, Kordou Z, Fukunaga K, Chantratita W, Zhou Y, Lauschke VM, Mushiroda T, Hiratsuka M, Patrinos GP. Identification and functional validation of novel pharmacogenomic variants using a next-generation sequencing-based approach for clinical pharmacogenomics. ***Pharmacol Res*** 176, 106087 (2022)

Invited presentations

Mushiroda T. "Pharmacogenetic testing for prevention of severe cutaneous adverse drug reactions" The 67th Annual Meeting of the Japan Society of Human Genetics (Yokohama, Japan) December 2022

Mushiroda T. "Clinical implementation of pharmacogenetic biomarkers" The 96th Annual Meeting of the Japanese Pharmacological Society (Yokohama, Japan) December 2022

Hikino K. "Pharmacogenomics in Pediatric Patients" The 43rd Annual Scientific Meeting of the Japanese Society of Clinical Pharmacology and Therapeutics (Yokohama, Japan) December 2022

Hikino K. "Pharmacogenomics" The 49th Annual Meeting of the Japan Society of Developmental Pharmacology and Therapeutics (Tokyo, Japan) November 2022

Hikino K. "Personalized medical care for pediatric drug therapy and pharmacogenomics" The 49th Annual Meeting of the Japanese Society of Toxicology (Sapporo, Japan) June 2022

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 the efficacy or risk of ADRs for various drugs. In the USA, information on 310 germline genomic biomarkers is available on US FDA-approved drug labels. However, in Japan, the National Health Insurance system currently covers only three genetic tests, *UGT1A1*, *NUDT15* and *CYP2C9*, to predict drug responses prior to the drug administration. Therefore, we are aiming for clinical implementation of as many germline pharmacogenomic (PGx) biomarkers as possible to realize more appropriate and patient-friendly genotype-based drug therapy.

In collaboration with domestic hospitals, we are conducting genomic analyses for the identification of PGx biomarkers useful for prediction of drug responses. Since it is difficult for individual countries acting alone to collect enough samples for PGx research, we conduct international PGx collaborations, such as the Southeast Asian Pharmacogenomics Research Network (SEAPharm). To achieve our mission, the 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/ADRs, and iii) construction of an integrative database for clinical implementation of PGx testing. To construct the database, we already have PGx variant data for approximately 3,500 individuals in 10 populations, including Japanese, and have constructed a mammalian suspension cell expression system capable of mass-producing recombinant proteins based on the variant information. Using this system, we evaluate functional changes caused by variants in genes important for clinical drug therapy (PGx variant annotation data) and predict drug levels in the blood of carriers of the variants (simulated pharmacokinetic data).

Laboratory for
Bone and Joint Diseases

Team Leader: **Shiro Ikegawa**

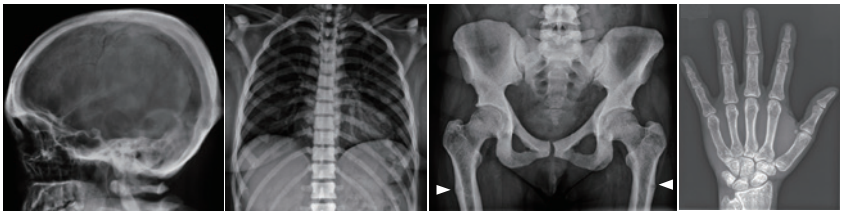


Figure: Clinical features of osteopetrosis, Ikegawa type caused by bi-allelic loss of function mutations in *SLC4A2*
Note generalized increase of bone density including skull. Arrow heads: pseudo-fracture of the femur.

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 pathogenic 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, OPLL, and ANF are in progress and we have succeeded in the identification of many susceptibility genes. Functional studies of the genes *in vitro* and using animal models are underway.

2) Genomic Study of Skeletal Dysplasia

Skeletal dysplasia is a group of heritable (monogenic) disorders affecting the skeleton, More than 450 diseases belong to this category. Skeletal dysplasia is an intractable disease, thus many patients are waiting for an effective treatment. We are engaging in clinical and basic studies of skeletal dysplasia. By large-scale mutation screening, including exome sequencing, we have identified disease-causative genes. As of now, we have identified 32 novel genes including *TMEM53* for craniotubular dysplasia, Ikegawa type and *SLC4A2* for osteopetrosis, Ikegawa type.

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

Recent Major Publications

Xue JY, Ikegawa S, Guo L. SLC4A2, another gene involved in acid-base balancing machinery of osteoclasts, causes osteopetrosis. ***Bone*** 167, 116603 (2023)

Suetsugu H, Kim K , Yamamoto T, Bang SY, Sakamoto Y, Shin JM, Sugano N, Kim JS, Mukai M, Lee YK , Ohmura K, Park DJ , Takahashi D, Ahn GY, Karino K, Kwon YC, Miyamura T, Kim J, Nakamura J, Motomura G, Kuroda T, Niiro H, Miyamoto T, Takeuchi T, Ikari K, ... Seki T, Tanaka Y, Kubo T, Hisada R, Yoshioka T, Yamazaki M, Kabata T, Kajino T, Ohta Y, Okawa T, Naito Y, Kaneuji A, Yasunaga Y, Ohzono K, Tomizuka K, Koido M, Matsuda K, Okada Y, Suzuki A, Kim BJ, Kochi Y, Lee HS, Ikegawa S, Bae SC , Terao C. Novel susceptibility loci for steroid-associated osteonecrosis of the femoral head in systemic lupus erythematosus. ***Hum Mol Genet*** 31, 1082-1095 (2022)

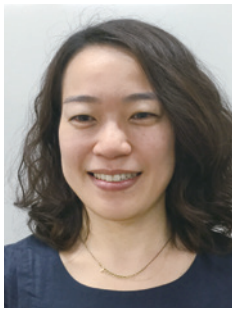
Xue JY, Grigelioniene G, Wang Z, Nishimura G, Iida A, Matsumoto N, Tham E, Miyake N, Ikegawa S, Guo L. SLC4A2 deficiency causes a new type of osteopetrosis. ***J Bone Miner Res*** 37, 226-235 (2022)

Invited presentations

Ikegawa S. "Genetic Testing in Japan for Skeletal Dysplasia and MPS" APAC MPS Summit 2022 (Taipei/Tokyo/Sydney/Seattle/Online) August 2022

Ikegawa S. "Genomic Study of Bone and Joint Diseases" Foreign Expert Seminar, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences (Beijing, China/Online) July 2022

Ikegawa S. "Skeletal Dysplasia from the Basics" The 95th Annual Meeting of the Japanese Orthopedic Society (Kobe, Japan) May 2021



Laboratory for

Genomics of Diabetes and Metabolism

Team Leader: **Momoko Horikoshi**

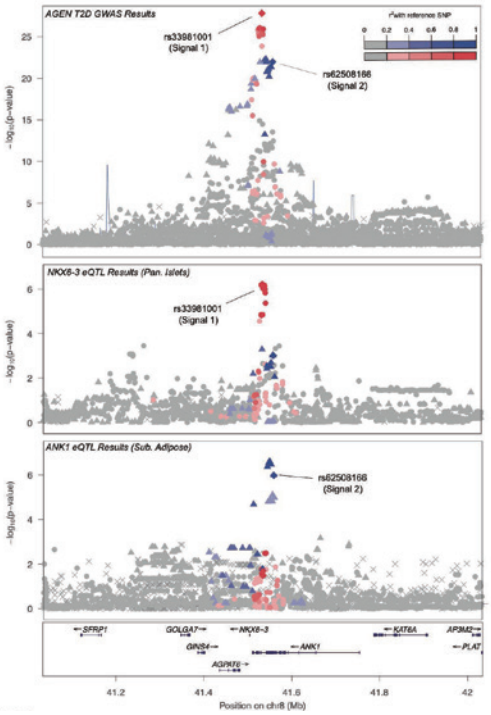


Figure: Two distinct T2D-association signals at the *ANK1-NKX6-3* locus are associated with the expression levels of two transcripts in two tissues

Top, Regional association plot for East Asian sex-combined BMI-unadjusted meta-analysis at the *ANK1-NKX6-3* locus highlighting three distinct T2D-association signals ($P<1x10^{-5}$): signal 1, rs33981001; signal 2, rs62508166; signal 3, rs144239281. Variants are colored red and blue according to the strength of East Asian linkage disequilibrium (LD) with the lead variants of first and second signals, respectively. Middle, Variant rs12549902, which is in high LD (EAS LD r^2=0.80) with signal 1 rs33981001, shows the strongest association with the expression level of *NKX6-3* in pancreatic islets (n=118). Bottom, Variant rs516946, which is in high LD (EAS LD r^2=0.96) with signal 2 rs62508166, shows the strongest association with the expression level of *ANK1* in subcutaneous adipose tissue (n=770).

Our lab is interested in investigating the genetic background of diabetes and related metabolic traits that may help us better understand the underlying disease mechanisms. We have been focusing on the genetic contribution to type 2 diabetes (T2D) susceptibility in the Japanese population by using the rich genetic resources generated by Biobank Japan (BBJ). By using the full BBJ collection, we conducted a single population Genome-wide association study (GWAS) of T2D in 191,764 Japanese. In addition to the then established >150 T2D loci, we identified 28 novel loci. We then joined this effort with our international collaborators in the Asian Genetic Epidemiology Network for T2D (AGEN-T2D) to include 433,540 East Asian individuals in a GWAS meta-analysis. We identified 301 distinct association signals at 183 loci. Previously undescribed associations included signals in or near genes and a microRNA cluster that affects the differentiation of skeletal muscle and adipose tissues, which are essential in the development of T2D. Interestingly, expression quantitative trait loci at two overlapping T2D signals affect two genes in different tissues (Figure). Association studies in diverse populations demonstrated the benefit of identifying additional loci and elucidating disease-associated genes, biology and pathways. These East Asian T2D association data were combined with those from other major ethnicities to conduct a multi-ancestry GWAS meta-analysis of 1,339,889 individuals. The increased sample size and expanded population diversity enhanced the number of associated loci to 237 and improved the fine-mapping ability to localize 54.4% of T2D associations to a single variant with >50% posterior probability. Multi-ancestry genetic risk scores enhanced the transferability of T2D prediction across diverse populations.

Recent Major Publications

Mahajan A, Spracklen CN, Zhang W, Ng MCY, Petty LE, Kitajima H, Yu GZ, Rüeger S, Speidel L, Kim YJ, Horikoshi M, Mercader JM, Taliun D, Moon S, Kwak SH, Robertson NR, Rayner NW, Loh M, Kim BJ, Chiou J, Miguel-Escalada I, Della Briotta Parolo P, Lin K, Bragg F, Preuss MH, Takeuchi F, Nano J, Guo X, Lamri A, Nakatochi M, Scott RA, Lee JJ, Huerta-Chagoya A, Graff M, Chai JF, Parra EJ, Yao J, Bielak LF, Tabara Y, Hai Y, Steinthorsdottir V, Cook JP, Kals M, Grarup N, Schmidt EM, Pan I, Sofer T, Wuttke M, Sarnowski C *et al*. Multi-ancestry genetic study of type 2 diabetes highlights the power of diverse populations for discovery and translation. ***Nat Genet*** 54, 560-572 (2022)

Ruth KS, Day FR, Hussain J, Martínez-Marchal A, Aiken CE, Azad A, Thompson DJ, Knoblochova L, Abe H, Tarry-Adkins JL, Gonzalez JM, Fontanillas P, Claringbould A, Bakker OB, Sulem P, Walters RG, Terao C, Turon S, Horikoshi M, Lin K, Onland-Moret NC, Sankar A, Hertz EPT, Timshel PN, Shukla V, Borup R, Olsen KW, Aguilera P, Ferrer-Roda M, Huang Y, Stankovic S, Timmers PRHJ, Ahearn TU, Alizadeh BZ, Naderi E, Andrulis IL, Arnold AM, Aronson KJ, Augustinsson A, Bandinelli S, Barbieri CM, Beaumont RN, Becher H, Beckmann MW, Benonisdottir S, Bergmann S, Bochud M, Boerwinkle E, Bojesen SE, Bolla MK *et al*. Genetic insights into biological mechanisms governing human ovarian ageing. ***Nature*** 596, 393-397 (2021)

Chen J, Spracklen CN, Marenne G, Varshney A, Corbin LJ, Luan J, Willems SM, Wu Y, Zhang X, Horikoshi M, Boutin TS, Mägi R, Waage J, Li-Gao R, Chan KHK, Yao J, Anasanti MD, Chu AY, Claringbould A, Heikkinen J, Hong J, Hottenga JJ, Huo S, Kaakinen MA, Louie T, März W, Moreno-Macias H, Ndungu A, Nelson SC, Nolte IM, North KE, Raulerson CK, Ray D, Rohde R, Rybin D, Schurmann C, Sim X, Southam L, Stewart ID, Wang CA, Wang Y, Wu P, Zhang W, Ahluwalia TS, Appel EVR, Bielak LF, Brody JA, Burtt NP, Cabrera CP, Cade BE *et al*. The trans-ancestral genomic architecture of glycemic traits. ***Nat Genet*** 53, 840-860 (2021)

Invited presentations

Horikoshi M. "Large-scale genome-wide association study of type 2 diabetes" The 9th Cutting-edge Forum for Diabetes Complication (Chiba, Japan) October 2022

Laboratory for

Cardiovascular Genomics and Informatics

Team Leader: Kaoru Ito

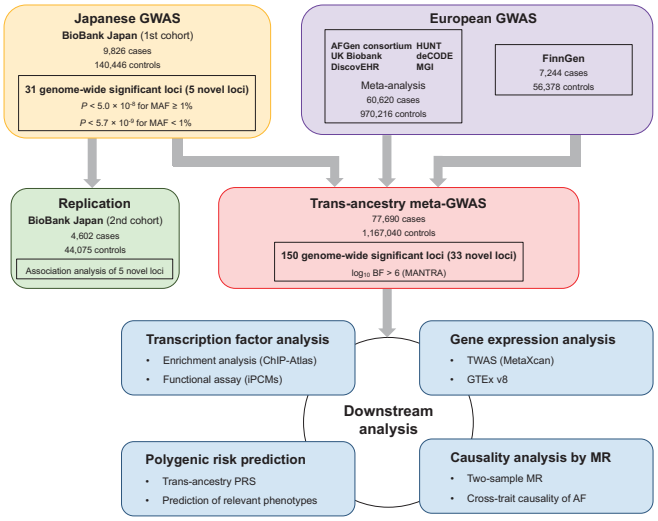


Figure: Comprehensive analysis of Atrial fibrillation
We not only identified new disease susceptibility loci for the disease, but also suggested new key molecules for the pathophysiology and provided evidence for clinical application of the genomic information.

Cardiovascular diseases remain the leading cause of death worldwide. Therefore, understanding their pathogenesis from a basic research perspective and changing clinical practice based on this knowledge, as well as identifying new therapeutic targets, are critical for global health. To this end, we are using state-of-the-art technologies such as whole genome sequencing and artificial intelligence, in addition to conventional statistics, to elucidate the precise mechanisms and to promote better use of medical and genomic information.

Among the cardiovascular diseases, our team mainly targets not only common diseases such as atherosclerotic diseases, arrhythmias and heart failure, but also rare diseases such as Kawasaki disease, chronic thromboembolic pulmonary hypertension and cancer treatment-related cardiac dysfunction. At present, we are: 1) Conducting large-scale studies to understand the genetic underpinnings of ischemic heart disease, the most common atherosclerotic disease, and atrial fibrillation, the most common arrhythmia, as well as identifying the genetic differences between Japanese and Europeans, in collaboration with international consortia. 2) Developing and validating a new genetic analysis method based on a machine learning algorithm that solves the "P greater than N" scenario, where the sample size is small but the number of variants to be analyzed is large. 3) Elucidating of the mechanism of rare cardiovascular diseases using human omics data from multi-center patients in Japan. 4) Performing prospective cohort studies to examine the possibility of clinical application of genomic information. 5) Developing a functional analysis system using massively parallel *in vitro* assays with artificial intelligence. 6) Developing and validating deep learning-based cardiovascular age for clinical applications. We also play an important role in genomic analyses of AMED GRIFIN and AMED intractable disease projects for cardiovascular diseases.

Our goal is to provide useful genomic/omics information and novel medical/biological indicators than can change and improve preventive/diagnostic/management/treatment strategies for cardiovascular diseases.

Recent Major Publications

Miyazawa K, Ito K, Ito M, Zou Z, Kubota M, Nomura S, Matsunaga H, Koyama S,Ieki H, Akiyama M, Koike Y, Kurosawa R, Yoshida H, Ozaki K, Onouchi Y; BioBank Japan Project; Takahashi A, Matsuda K, Murakami Y, Aburatani H, Kubo M, Momozawa Y, Terao C, Oki S, Akazawa H, Kamatani Y, Komuro I. Cross-ancestry genome-wide analysis of atrial fibrillation unveils disease biology and enables cardioembolic risk prediction. ***Nat Genet*** 55, 187-197 (2023)

Ieki H, Ito K, Saji M, Kawakami R, Nagatomo Y, Takada K, Kariyasu T, Machida H, Koyama S, Yoshida H, Kurosawa R, Matsunaga H, Miyazawa K, Ozaki K, Onouchi Y, Katsushika S, Matsuoka R, Shinohara H, Yamaguchi T, Kodera S, Higashikuni Y, Fujiu K, Akazawa H, Iguchi N, Isobe M, Yoshikawa T, Komuro I. Deep learning- based age estimation from chest X-rays indicates cardiovascular prognosis. ***Commun Med (Lond)*** 2, 159 (2022)

Aragam KG, Jiang T, Goel A, Kanoni S, Wolford BN, Atri DS, Weeks EM, ..., Ito K, Jang DK, Kamatani Y, Khera AV, Komuro I, Kullo IJ, Lotta LA, Nelson CP, Roberts R, Thorgeirsson G, Thorsteinsdottir U, Webb TR, Baras A, Bjorkegren JLM, Boerwinkle E, Dedoussis G, Holm H, Hveem K, Melander O, Morrison AC, Orho-Melander M, Rallidis LS, Ruusalepp A, Sabatine MS, Stefansson K, Zalloua P, Ellinor PT, Farrall M, Danesh J, Ruff CT, Finucane HK, Hopewell JC, Clarke R, Gupta RM, Erdmann J, Samani NJ, Schunkert H, Watkins H, Willer CJ, Deloukas P, Kathiresan S, Butterworth AS; CARDIoGRAMplusC4D Consortium. Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants. ***Nat Genet*** 54, 1803-1815 (2022)

Invited presentations

Ito K. "Genetic Underpinnings of Atrial Fibrillation and Prospects for the Clinical Application" The 87th Annual Scientific Meeting of the Japanese Circulation Society (Fukuoka, Japan) March 2023

Ito K. "Frontiers in Genomic Analysis and its Clinical Application for Complex Cardiovascular Diseases" The 4th National Cerebral and Cardiovascular Center Seminar Series (Osaka, Japan/Online) September 2022

Ito K. "Frontiers of Cardiovascular Genomic Analysis Leveraging Large Biobanks" 2022 Annual Meeting of Japan Bioinformatics Society (Osaka, Japan) September 2022

Ito K. "The Development of Cardiovascular Genetic Risk Score and Prospects for the Clinical Implementation" The 54th Annual Scientific Meeting of Japan Atherosclerosis Society (Kurume, Japan), July 2022

Ito K. "Elucidating the genetic background of atrial fibrillation and realizing the precision medicine" The 7th Annual Scientific Meeting of Japan Cardiovascular Association (Online) May 2022

Laboratory for Systems Genetics

Team Leader: Yukinori Okada

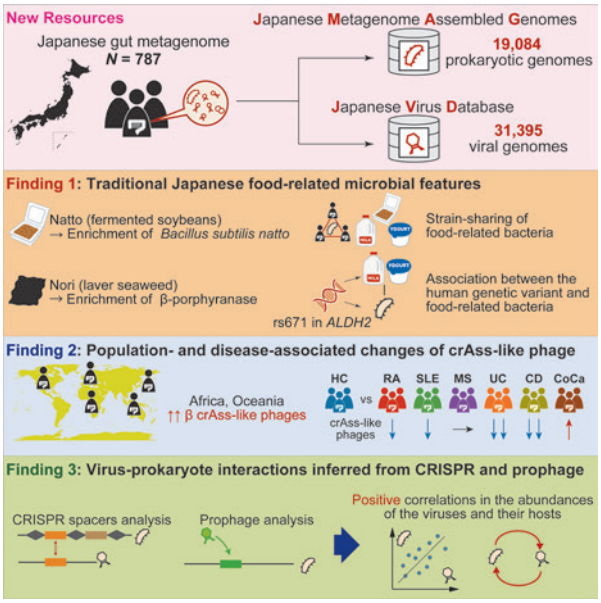


Figure: Construction of gut microbiome catalog of the Japanese population

We constructed a Japanese population-specific microbial genome (MAG) of both metagenome (JMAG) and virome (JVD) by integrating in house 787 gut metagenome shotgun sequence data (Tomofuji Y *et al*. ***Cell Genom*** 2022).

Recent Major Publications

Tomofuji Y, Kishikawa T, Maeda Y, Ogawa K, Otake-Kasamoto Y, Kawabata S, Nii T, Okuno T, Oguro-Igashira E, Kinoshita M, Takagaki M, Oyama N, Todo K, Yamamoto K, Sonehara K, Yagita M, Hosokawa A, Motooka D, Matsumoto Y, Matsuoka H, Yoshimura M, Ohshima S, Shinzaki S, Nakamura S, Iijima H, Inohara H, Kishima H, Takehara T, Mochizuki H, Takeda K, Kumanogoh A, Okada Y*. Prokaryotic and viral genomes recovered from 787 Japanese gut metagenomes revealed microbial features linked to diets, populations, and diseases. ***Cell Genom*** 2, 100219 (2022)

Namkoong H, Edahiro R, Takano T, Nishihara H, Shirai Y, Sonehara K, Tanaka H, Azekawa S, Mikami Y, Lee H, Hasegawa T, Okudela K, Okuzaki D, Motooka D, Kanai M, Naito T, Yamamoto K, Wang QS, Saiki R, Ishihara R, Matsubara Y, Hamamoto J, Hayashi H, Yoshimura Y, Tachikawa N, Yanagita E, Hyugaji T, Shimizu E, Katayama K, ... Biobank Japan Project; Yosuke Omae Y, Nannya Y, Ueno T, Katayama K, Ai M, Fukui Y, Kumanogoh A, Sato T, Hasegawa N, Tokunaga K, Ishii M, Koike R, Kitagawa Y, Kimura A, Imoto S, Miyano S, Ogawa S, Kanai T, Fukunaga K, Okada Y*. DOCK2 is involved in genetics and biology of severe COVID-19. ***Nature*** 609, 754-760 (2022)

Ishigaki K, Sakaue S, Terao C, Luo Y, Sonehara K, Yamaguchi K, Amariuta T, Too CL, Laufer VA, Scott IC, Viatte S, Takahashi M, Ohmura K, Murasawa A, Hashimoto M, Ito H, Hammoudeh M, Emadi SA, Masri BK, Halabi H, Badsha H, Uthman IW, Wu X, Lin L, Li T, ... BioBank Japan Project, Matsuda K, Matsuo K, Mimori T, Matsuda F, Fujio K, Tanaka Y, Kumanogoh A, Traylor M, Lewis CM, Eyre S, Xu H, Saxena R, Arayssi T, Kochi Y, Ikari K, Harigai M, Gregersen PK, Yamamoto K, Louis Bridges S Jr, Padyukov L, Martin J, Klareskog L, Okada Y*, Raychaudhuri S*. Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in rheumatoid arthritis. ***Nat Genet*** 54, 1640-1651 (2022)

Invited presentations

Okada Y. "Methodologies in whole-genome sequence-based association studies" International Common Disease Alliance Meeting (Copenhagen, Denmark) December 2022

Okada Y. "Multi-trait and cross-population genome-wide association studies across autoimmune and allergic diseases identify shared and distinct genetic component" American College of Rheumatology Covergence (Philadelphia, USA) November 2022

Okada Y. "Statistical genetics, disease biology, and drug discovery" Pan-cohort studies, Tohoku Medical Megabank (Sendai, Japan/Online) October 2022

Okada Y. "Statistical genetics, disease biology, and drug discovery" International Conference of Precision Medicine, Taiwan University (Taiwan/Online) October 2022

Okada Y. "Big data analysis of autoimmune diseases" 41st Annual Scientific Meeting of Korean College of Rheumatology 2021 (Seoul, Republic of Korea/Online) October 2021

The genome is the human blueprint. The goal of our team is to decipher the blueprint and elucidate its hidden biology. An individual's genetic background has substantial impact on their risk of a wide range of complex human diseases. Systems Genetics is a research field that evaluates the causality of human genetic variations on human phenotypes, using statistical and bioinformatics approaches. Recent developments in genome sequencing technologies have provided ample resources for genomics research. However, little is known regarding how to develop the methodology to integrate large-scale human genomics data with diverse biological and clinical information. In our team, we focus on large-scale human genome, omics and phenome data, and the underlying high-dimensional network. By developing novel methodologies in statistical genetics and machine learning, we redefine human biology as systems genetics. Our team aims to elucidate disease biology and contribute to novel drug discovery and implementation of genomic personalized medicine.

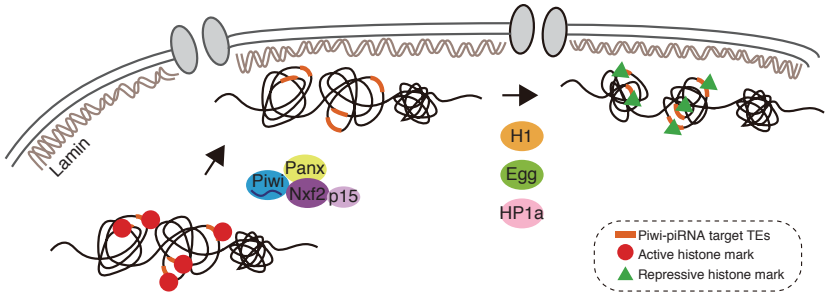
We successfully conducted large-scale, cross-population and biobank-driven genome-wide association studies (GWAS) of hundreds of both common and rare human phenotypes, which identified >10,000 genetically associated loci. Public release of the GWAS results contributed to construction of a global genotype-phenotype catalog. Population genetics analysis of the GWAS resource revealed the evolutionary landscape of the Japanese population. In parallel, we developed novel human omics layers, such as the gut microbiome, by metagenome shotgun sequencing, microRNA expression profiles by short non-coding RNA sequencing and cell type-specific expression profiles by single-cell RNA sequencing. Integrative analysis of trans-layer omics resources with human genetics, represented as a polygenic risk score (PRS), demonstrated its value in implementation of personalized medicine. To accelerate genomics-driven drug development, our team released bioinformatics tools to translate human disease genetics into candidate compounds for drug repositioning. A series of achievements by our team encompasses diverse scientific fields towards a true understanding of the blueprint.

Laboratory for

Functional Non-coding Genomics

Team Leader: **Yuka W. Iwasaki**

Figure: Stepwise Piwi–piRNA-mediated regulation of nuclear architecture and chromatin state
Piwi–piRNA-mediated transcriptional silencing of transposable elements is required to maintain genomic integrity. We found that stepwise heterochromatin-structure formation is found to also involve Piwi–piRNA-mediated nuclear architecture changes at target regions.



Iwasaki et al. *EMBO J* (2021)

Recent Major Publications

Takeuchi C, Yokoshi M, Kondo S, Shibuya A, Saito K, Fukaya T, Siomi H, Iwasaki YW. Mod (mdg4) variants repress telomeric retrotransposon HeT-A by blocking subtelomeric enhancers. ***Nucleic Acids Research*** 50, 11580-11599 (2022)

Hasuwa H, Iwasaki YW, Yeung WKA, Ishino K, Masuda H, Sasaki H, Siomi H. Production of functional oocytes requires maternally expressed PIWI genes and piRNAs in golden hamsters. ***Nature Cell Biology*** 23, 1002-1012 (2021)

Iwasaki YW, Sriswasdi S, Kinugasa Y, Adachi J, Horikoshi Y, Shibuya A, Iwasaki W, Tashiro S, Tomonaga T, Siomi H. Piwi–piRNA complexes induce stepwise changes in nuclear architecture at target loci. ***The EMBO Journal*** 40, e108345 (2021)

Invited presentations

Iwasaki YW. "Co-transcriptional silencing and heterochromatin formation by nuclear PIWI–piRNA complex" Cold Spring Harbor Asia "RNA biology meeting" (Awaji, Japan) December 2022

Iwasaki YW. "Understanding and reconstructing small RNA-mediated heterochromatin formation" The 46th Annual Meeting of the Molecular Biology Society of Japan (Chiba, Japan) December 2022

Iwasaki YW. "Understanding and reconstructing small RNA-mediated heterochromatin formation" The 60th Annual Meeting of the Biophysical Society of Japan (Hakodate, Japan) September 2022

Iwasaki YW. "Understanding and reconstructing small RNA-mediated heterochromatin formation" RIKEN IMS-McGill Symposium (Online) September 2022

Iwasaki YW. "Understanding and reconstructing small RNA-mediated heterochromatin formation" Japan-UK Regulation through Chromatin Conference (Leicester, UK) August 2022

One of the significant achievements of recent transcriptome research is elucidating the importance of "non-coding genomic regions" that do not encode proteins. In diverse eukaryotes, non-coding genomic regions occupy enormous portions of the genome. They include non-coding RNAs, which do not code for proteins but perform various functions as RNAs, and transposable elements that have the property of transposing or jumping around the genome.

Non-coding RNAs (ncRNAs) have been proposed to play critical roles in regulating the flow of genetic information, resulting in their critical impact on cellular processes, organismal development and disease. However, the vast majority of ncRNAs have not yet been functionally characterized and their precise functional mechanisms remain to be elucidated. We have been investigating small non-coding RNA functions using bioinformatics and biochemical approaches. Our recent interest is to elucidate the transcriptional regulatory mechanism of a class of small RNAs called PIWI-interacting RNAs (piRNAs), which are capable of regulating transposable element expression via heterochromatin formation. We aim to further characterize this process and to develop a system to reconstruct and utilize this small RNA-guided heterochromatin formation. In addition, we will perform a functional screening of ncRNAs, which are capable of regulating nuclear events such as heterochromatin formation and chromatin compaction. We are also interested in transposable elements, which may function as long ncRNAs or have potential functions as regulatory DNA elements or domain structures within the genome. We are planning to uncover the uninvestigated molecular functions of transposable elements.

Our overall long-term goal is to understand diseases, including developmental disorders, from new perspectives by clarifying and regulating the functional mechanisms of non-coding genomic regions.

Laboratory for Retrotransposon Dynamics

Team Leader: Tomoichiro Miyoshi

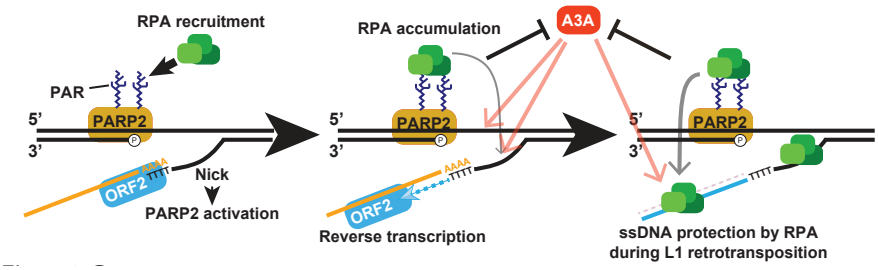


Figure: Current model for L1 retrotransposition facilitated by DNA repair factors
L1 ORF2p EN activity creates a nick in genomic DNA to generate a 5′ phosphate and 3′ hydroxyl group to initiate genomic insertion. The 5′ phosphate group is recognized by PARP2, thereby leading to a local accumulation of PAR (poly[ADP]-ribosylation). PAR can further recruit RPA to the L1 integration site. RPA may then bind to transiently exposed ssDNA regions in retrotransposition to protect ssDNAs from being attacked by the APOBEC3 cytidine deaminase, a potent inhibitor of L1.

Recent Major Publications

Luqman-Fatah A, Watanabe Y, Uno K, Ishikawa F, Moran JV, Miyoshi T. The interferon stimulated gene-encoded protein HELZ2 1 inhibits human LINE-1 retrotransposition and LINE-1 RNA-mediated type I interferon induction. ***Nat Commun*** 14, 203 (2023)

Luqman-Fatah A, Miyoshi T. Human LINE-1 Retrotransposons: Impacts on the Genome and Regulation by Host Factors. ***Genes Genet Syst*** Online ahead of print (2022)

Invited presentations

Miyoshi T. "Mechanisms of retrotransposition of LINE-1, a mobile genetic element" The 192nd Bio Seminar at Nagahama Institute of Bio-Science and Technology (Nagahama, Japan) October 2022

Miyoshi T. "Host defense mechanisms against inhibition of human LINE-1 retrotransposition" The 23rd Symposium of the Graduate School of Biostudies (Kyoto, Japan) July 2022

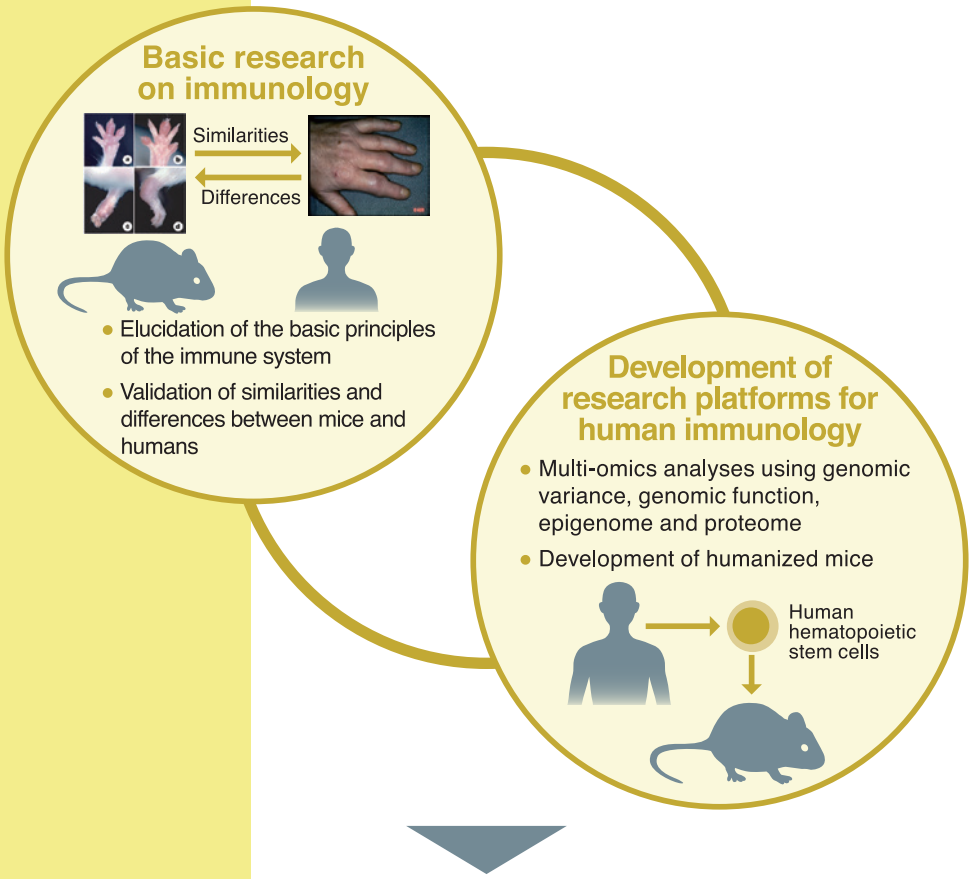
Miyoshi T. "Mechanisms of human LINE-1 retrotransposition" Kyoto University Leading Scientist Seminar (Kyoto, Japan) March 2022

Stable maintenance of genetic information is critical for all living organisms. However, transposable elements (TEs), the most abundant repetitive sequences in mammals, can cause structural variants and disease-causing mutations. TEs mobilize into new genomic locations via a DNA (*i.e.*, DNA transposon) or RNA intermediate (*i.e.*, retrotransposon). Human retrotransposons, Long INterspersed Element-1 (LINE-1s or L1s) and Short INterspersed Elements (SINEs) including Alu, respectively comprise ~17% and ~11% of the genome and still frequently "jump" in the genome. *De novo* L1 and Alu insertion termed retrotransposition have led to sporadic genetic diseases including various types of cancer; however, much remains to be clarified about the mechanisms of action. We posit that a mechanistic understanding of retrotransposition is critical for unraveling the processes that lead to human disease, genetic variation and genome evolution.

We currently focus on i) exploring the mechanisms of L1/Alu retrotransposition and ii) investigating the impact of L1/Alu expression on disease-associated phenotypes such as chronic inflammation. Since L1/Alu have been co-evolving within the host genomes through millions of years, host cellular proteins likely have a dynamic and functional interplay with the L1/Alu retrotransposon-derived RNAs and proteins. However, previous studies of mammalian retrotransposons have lacked a biochemical perspective. Therefore, we have tackled proteomic analyses of the L1 encoded proteins to identify host factors that control L1 retrotransposition. This allowed the identification of a number of L1 regulators, including conserved DNA repair proteins and innate immune response factors. Furthermore, our extensive genetic and biochemical analyses demonstrated that L1s exploit the host DNA repair system to expand their copy number in the genome; however, in response, the host antiviral system may counteract the L1 activities to maintain genome integrity.

Our long-term goal is to elucidate the mechanisms underlying "jumping" of retrotransposons and to develop new methods to suppress L1/Alu activities.

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

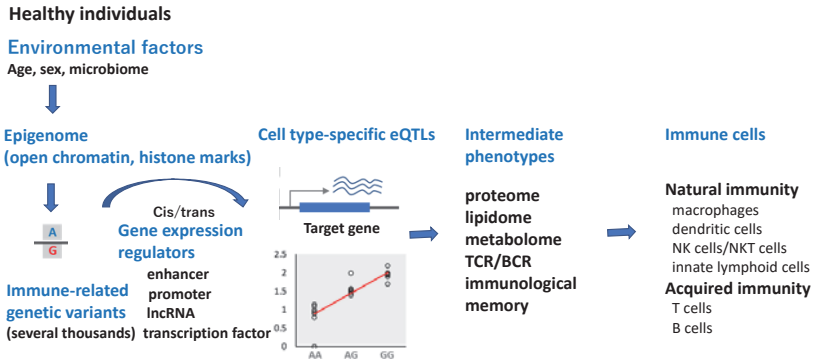


Figure: Advanced multi-omics data sets for the evaluation of human immune function

In collaboration with the Laboratories for Human Immunogenetics, Systems Genetics, Cancer Genomics, Metabolomics,Integrative Genomics, Intestinal Ecosystem, Immunotherapy, Statistical and Translational Genetics, Large-Scale Biomedical Data Technology and YCI unit for proteomics.

Recent Major Publications

Nakano M, Ota M, Takeshima Y, Iwasaki Y, Hatano H, Nagafuchi Y, Itamiya T, Maeda J, Yoshida R, Yamada S, Nishiwaki A, Takahashi H, Takahashi H, Akutsu Y, Kusuda T, Suetsugu H, Liu L, Kim K, Yin X, Bang SY, Cui Y, Lee HS, Shoda H, Zhang X, Bae SC, Terao C, Yamamoto K, Okamura T, Ishigaki K, Fujio K. Distinct transcriptome architectures underlying lupus establishment and exacerbation. ***Cell*** 185, 3375-3389.e21 (2022)

Ishigaki K, Sakaue S, Terao C, Luo Y, Sonehara K, Yamaguchi K, Amariuta T, Too CL, Laufer VA, Scott IC, Viatte S, Takahashi M, Ohmura K, Murasawa A, Hashimoto M, Ito H, Hammoudeh M, Emadi SA, Masri BK, Halabi H, Badsha H, Uthman IW, Wu X, Lin L, Li T, Plant D, Barton A, Orozco G, Verstappen SMM, Bowes J, MacGregor AJ, Honda S, Koido M, Tomizuka K, Kamatani Y, Tanaka H, Tanaka E, Suzuki A, ... Kochi Y, Ikari K, Harigai M, Gregersen PK, Yamamoto K, Louis Bridges S Jr, Padyukov L, Martin J, Klareskog L, Okada Y, Raychaudhuri S. Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in rheumatoid arthritis. ***Nat Genet*** 54, 1640-1651 (2022)

Takeshima Y, Iwasaki Y, Nakano M, Narushima Y, Ota M, Nagafuchi Y, Sumitomo S, Okamura T, Elkon K, Ishigaki K, Suzuki A, Kochi Y, Yamamoto K, Fujio K. Immune cell multiomics analysis reveals contribution of oxidative phosphorylation to B-cell functions and organ damage of lupus. ***Ann Rheum Dis*** 81, 845-853 (2022)

Invited presentations

Yamamoto K. "Immunogenetics of rheumatoid arthritis & way forward" 24th Asia-Pacific League of Associations for Rheumatology (Hong Kong, China) December 2022

Yamamoto K. "Data-driven functional analysis of human lymphocytes" Tsinghua RIKEN Joint workshop (Online) November 2022

Yamamoto K. "Human immune diversity for infection and vaccine development" RIKEN-KI-SciLifeLab Symposium (Stockholm, Sweden) October 2022

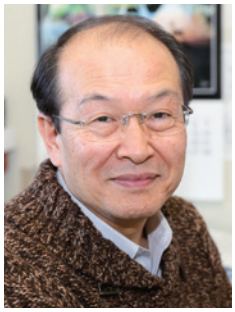
Yamamoto K."Evaluation of human immune function for vaccine development" McGill-RIKEN Symposium (Montreal, Canada) September 2022

Yamamoto K. Ishigaki K. "Trans-ancestry genome-wide association study identifies novel genetic mechanisms in rheumatoid arthritis" International Forum of Rheumatoid Arthritis 2022 (Beijing, China/Online) September 2022

The majority of the disease-susceptibility genetic variants revealed by genome-wide association study (GWAS) function as expression quantitative trait loci (eQTLs) that are involved in gene expression. The effects of eQTL are frequently found in a cell type-specific manner. Such cell specificity is largely due to epigenomic alterations, such as cell type-specific histone modifications and DNA methylation in specific regions of chromosomes. It has been further reported that disease susceptibility variants significantly overlap with the location of histone modifications in promoters and active enhancers of specific immune cell subsets. Therefore, it is possible to obtain causal information about the intermediate phenotypes between genetic information and disease state by qualitatively and quantitatively measuring the functional molecules of immunocompetent cells in various immunological diseases by focusing on disease-susceptibility genetic variants, gene expression (mRNA), epigenome, and proteins.

We are performing functional genomic strategies for integrating GWAS results with the current understanding of specific diseases, mainly focusing on promoters, enhancers, and long non-coding RNAs. We are isolating nearly 30 different lymphocyte subsets from human peripheral blood mononuclear cells of healthy individuals and analyzing genotypes, gene expression and open chromatin regions. Cells from healthy individuals are expected to exhibit the least biased gene expression. Since chromosomes are transmitted to offspring in certain blocks and many neighboring genetic variants behave similarly, it is not easy to determine which among them is the true causal variant. Using several methods including CAGE analysis, we are tracking down the targets.

We are also performing various analyses using recently developed single-cell technologies. By integrating these pieces of information, we can understand the physiological and pathological changes of the whole immune system of an individual and the ways for intervening under unfavorable conditions.



Laboratory for
Cell Signaling

Team Leader: Takashi Saito

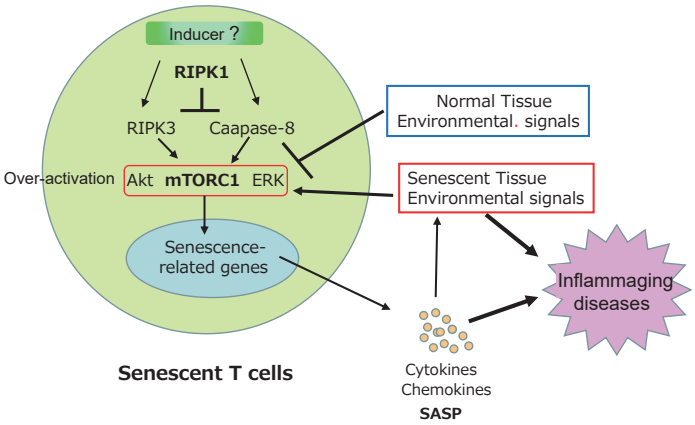


Figure: RIPK1 regulatory mechanism of T cell senescence and consequent inflammation and age-related diseases

RIPK1 inhibits excess activation of mTORC1 by inhibiting RIPK3 and Caspase-8. Overactivation of mTORC1 induces expression of senescence-related genes, promotes T cell senescence, which leads to the production of various cytokines and chemokines, and also promotes the senescence-associated secretory phenotype (SASP), which promotes tissue senescence and induces age-related diseases. Senescent tissue environmental signals enhance mTORC1 activation and exacerbate aging and age-related diseases. On the other hand, normal tissue environmental signals inhibit mTORC1 activation and T cell senescence and inflammaging.

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

During the analyses on the modulation of T cell function by innate-like signals, we found that Receptor-interacting serine/threonine-protein kinase 1 (RIPK1) plays a critical role in T cell function and particularly cellular senescence. RIPK-1 is known to function both in cell death and survival. We generated and analyzed T cell-specific RIPK1-deficient (tKO) mice to analyze its function in metabolism and aging of T cells. RIPK1-tKO mice develop various inflammatory diseases with aging (inflammaging) and early death. T cells in the KO mice show a senescence phenotype from early life through constitutive activation of Caspase-8, RIPK3 and mTORC1. Inhibition of mTORC1 or caspase-8/RIPK3 eliminated the T cell senescence and age-related disease phenotypes. Therefore, RIPK3/caspase-8 induced basal activation of mTORC1 and a senescence program, leading to inflammaging. It has been suggested that senescent cells influence neighboring cells to induce senescence. When senescent T cells were transferred into normal mice, they returned to a normal state, whereas normal T cells become senescent when transferred into RIPK1-KO mice, suggesting critical roles of environmental signals for regulating senescence.

Our finding that TCR-microclusters (MC) initiate T cell activation led us to analyze the dynamics of signaling molecules at the immune synapse. Similar to our previous studies of CTLA4 and PD-1, we have analyzed the dynamic regulation of another inhibitory co-stimulator, LAG3. LAG3 was also colocalized with the TCR-MC upon TCR stimulation to mediate inhibition of T cell activation. Since this association is critical for the inhibitory function, anti-LAG3 Ab induced separation of the LAG3 cluster from the TCR-MC and, consequently, enhancement of T cell activation. Our analyses provide a dynamic view of signal regulation to define the inhibitory mechanism. Furthermore, we have also analyzed negative regulation of T cell activation by autoimmune-related PTPN22. Its deficiency resulted in enhanced activation and an increase in effector/memory T cells. Analysis of the associated proteins revealed that PTPN22 was recruited to the TCR-MC to comprise an "inhibitory complex" with other inhibitory molecules to inhibit activation. A PTPN22 mutant causing susceptibility to autoimmune diseases was defective in recruitment to the TCR-MC. These studies help define the mechanism of autoimmune susceptibility caused by the mutation.

Recent Major Publications

Imanishi T, Unno M, Yoneda N, Motomura Y, Mochizuki M, Sasaki T, Moro K, Pasparakis M, and Saito T. RIPK1 blocks T cell senescent regulated by RIPK3 and caspase-8. ***Science Advances*** 9, eadd6097 (2023)

Takemori T, Sugimoto-Ishige A, Nishitsuji H, Futamura Y, Harada M, Kimura-Someya T, Matsumoto T, Honma T, Tanaka M, Yaguchi M, Isono K, Koseki H, Osada H, Miki D, Saito T, Tanaka T, Fukami T, Goto T, Shirouzu M, Shimotohno K, Chayama K. Establishment of a monoclonal antibody against human NTCP that blocks HBV infection. ***J. Virol*** 96, e0168621 (2022)

Kumagai A, Nara T, Uematsu M, Kakinuma Y, Saito T, and Masuda K. Development and characterization of a unique anti-IgE monoclonal antibody cross-reactive between human and canine IgE. ***Immun. Inflamm. Dis*** 9, 1740-1748 (2021)

Invited presentations

Saito T. "T cell senescence regulated by RIPK1/RIPK3 / caspase-8 induces age-related inflammation diseases" Hokkaido Univ. Seminar (Sapporo, Japan/Online) December 2022

Saito T. "Mechanism of inducing T cell senescence followed by inflammation diseases" OIST conference (Okinawa, Japan) March 2022

Saito T. "Regulation of adhesion and activation of T cells at Immune synapse" The 44th Annual Meeting of Molecular Biology Society of Japan 2021 (Yokohama, Japan/Online) December 2021

Laboratory for

Lymphocyte Differentiation

Team Leader: **Tomohiro Kurosaki**

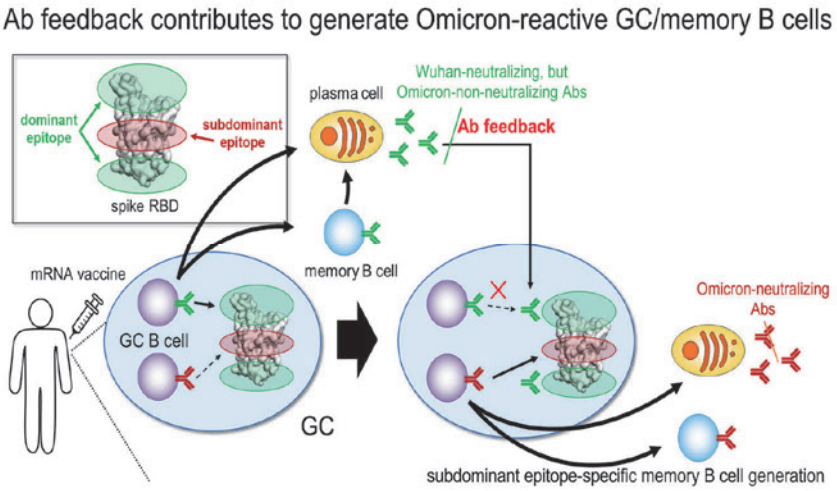


Figure: Antibody feedback takes place with SARS-CoV-2 mRNA vaccination
After initial vaccination, B cells harboring BCRs specific for dominant epitopes (green) are initially activated and differentiate into plasma cells producing antibodies (green antibodies). Then, for example, after a second vaccine dose, the produced antibodies mask their own epitopes, preventing activation of the B cells recognizing the cognate dominant epitope. Instead, B cells targeting a subdominant epitope (red) are activated, thereby producing antibodies (red antibodies). In the case of SARS-CoV-2 vaccination, these red antibodies can also cross-react with and neutralize the Omicron variant viruses.

Recent Major Publications

Inoue T, Shinnakasu R, Kawai C, Yamamoto H, Sakakibara S, Ono C, Itoh Y, Terooatea T, Yamashita K, Okamoto T, Hashii N, Ishii-Watabe A, Butler NS, Matsuura Y, Matsumoto H, Otsuka S, Hiraoka K, Teshima T, Murakami M, Kurosaki T. Antibody feedback contributes to facilitating the development of Omicron-reactive memory B cells in SARS-CoV-2 mRNA vaccinees. ***J Exp Med*** 220, e20221786 (2023)

Koike T, Fujii K, Kometani K, Butler NS, Funakoshi K, Yari S, Kikuta J, Ishii M, Kurosaki T, Ise W. Progressive differentiation toward the long-lived plasma cell compartment in the bone marrow. ***J Exp Med*** 220, e20221717 (2023)

Tanaka S, Ise W, Baba Y, Kurosaki T. Silencing and activating anergic B cells. ***Immunol Rev*** 307, 43-52 (2022)

Invited presentations

Fukuyama H. "Transdermal adjuvant for next-generation vaccines" RIKEN-KI-SciLifeLab Symposium: Preparing for the next pandemic (Solna, Sweden) October 2022

Kurosaki T. "Involvement of BCR signal strength in Germinal center selection" The EMBO workshop on Germinal centers and immune niches (Rehovot, Israel) September 2022

Kurosaki T. "Differentiation to plasma cells and their fates" Dynamics of Immune Repertoires: Exploration and Translation working group "The primary B-cell immune response" (Dresden, Germany) July 2022

Kurosaki T. "Memory B cells; their generation and activation mechanisms" EMBO Workshop Lymphocyte antigen receptor signaling (Siena, Italy) May 2022

Kurosaki T. "B cell fate decisions during germinal center (GC) reactions" UCL Symposium (London, U.K) May 2022

Given that most BCRs of memory B cells and long-lived plasma cells (LLPCs) are extensively somatically hypermutated (SHM), it is important to understand how the germinal center (GC) reaction is taking place, thereby generating memory B cells and LLPCs. From 2019 to 2022, our laboratory has particularly focused on clarifying two fundamental questions. First, do they (memory B cells and LLPCs) act redundantly or does each play a unique role? Second, if such unique roles exist, does each generation mechanism explain these unique roles? From a translational view, we have been establishing platforms for generating single cell BCR (scBCR) repertoire data and analysis of their function by producing recombinant mAb. Then, by employing this technology, we have addressed the question of why a third dose of the original Wuhan SRAS-CoV-2 mRNA vaccine elicits potent neutralizing antibody activity against the Omicron variant (as shown in the Figure).

As mentioned above, we have been studying basic mechanisms to generate memory B cells and LLPCs, but, how these two cellular compartments are maintained has not been well addressed. Particularly, identification of key factors to make differentiation of short-lived plasma cells (SLPCs) into LLPCs is one of the unresolved important questions. Previous studies considered the plasma cells residing in the bone marrow simply as LLPCs. However, given that the bone marrow also contains SLPCs, caution for interpretation of the previous data is required. Thus, to overcome this weak point, we have employed a time-stamping method for plasma cells, thereby allowing us to directly measure the decay time and to distinguish SLPCs and LLPCs.

Laboratory for Transcriptional Regulation

Team Leader: Ichiro Taniuchi

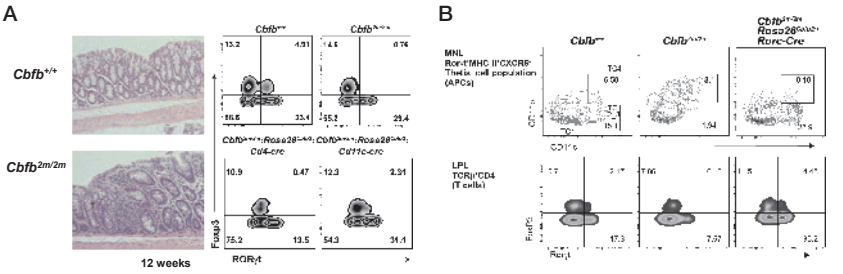


Figure: Runx3/Cbfβ2 dependent development of Thetis antigen-presenting cells imparts Treg-dependent tolerance to gut microbiota
(A) Spontaneous colitis development and specific loss of Roryt^{+} FoxP3^{+} pTreg cells in the gut of Cbfβ2-deficient (*Cbfb*$^{2m/2m}$) mice. (B) Flow cytometry analysis of Thetis cell (TC) subsets in mesenteric lymph nodes. Cbfβ2-deficient mice lack TC2 and TC3 subsets and their development is restored by inducible transgenic expression of Cbfβ2 from the *Rosa26* locus by a *Rorc*-cre transgene, which is accompanied by restoration of Roryt^{+} FoxP3^{+} pTreg development.

Recent Major Publications

Yamashita M, Taniuchi I. Fine-tuning Notch1 by the stage-specific enhancer. ***Nat Immunol.*** 23, 1509-1511 (2022)

Okuyama K, Taniuchi I. Three residues in the BTB domain promote a good partnership between NuRD and Thpok. ***Sci Immunol*** 7, eabq1408 (2022)

Douchi D, Yamamura A, Matsuo J, Lee JW, Nuttonmanit N, Melissa Lim YH, Suda K, Shimura M, Chen S, Pang S, Kohu K, Kaneko M, Kiyonari H, Kaneda A, Yoshida H, Taniuchi I, Osato M, Yang H, Unno M, Bok-Yan So J, Yeoh KG, Huey Chuang LS, Bae SC, Ito Y. A Point Mutation R122C in RUNX3 Promotes the Expansion of Isthmus Stem Cells and Inhibits Their Differentiation in the Stomach. ***Cell Mol Gastroenterol Hepatol.*** 13, 1317-1345 (2022)

Invited presentations

Taniuchi I. "Applying BioID in Mice" 95th Annual Meeting of the Japanese Biochemical Society (Nagoya, Japan) November 2022

Taniuchi I. "Phosphorylation on the terminal tyrosine residue in Runx proteins links environmental cues with cell fate determination" The 23rd international RUNX conference (San Antonio, USA) October 2022

Taniuchi I. "The Roles of Runx family proteins in cancer immunity" 13th annual scientific meeting of SGCC (Singapore, Singapore) July 2022

Taniuchi I. "Phosphorylation of Runx proteins controls thymocyte fate" SEMMinars at IFOM-IEO (Milan, Italy) June 2022

The primary developmental program of T lymphocytes that occurs in the thymus has been shaped to select useful and non-self-reactive immune soldiers to generate pools of lymphocytes with a broad variety of antigen specificities. This selection process requires a sophisticated nuclear program that integrates environmental cues sensed by T cell antigen receptors (TCR). My laboratory has been addressing how TCR signals are sensed and are coupled with cell fate determination programs in the nucleus by using helper versus cytotoxic lineage choice as a model, in which repression of *Zbtb7b* and *Cd4* genes by Runx-dependent silencers at these loci serves as a key regulatory mechanism. Our previous studies showed that the WRPY peptide motif at the C-terminal end of the Runx protein is essential for repression of *Zbtb7b* and *Cd4* genes by recruiting TLE/Groucho corepressor family proteins. Our current genetic study confirmed that the terminal tyrosine (Y) residue is absolutely required for appropriate coupling of MHC restriction with appropriate cell fate. We have confirmed that the terminal Y residue is phosphorylated and that this phosphorylation is essential for the interaction of Runx proteins with TLE proteins. We are investigating how this phosphorylation is regulated.

Our second objective is to understand the functions of Runx/Cbfβ transcription factor complexes during immune system development. In mice lacking Cbfβ2, one of two RNA splice variants of the *Cbfb* gene, peripherally-induced Roryt^{+}Foxp3^{+} pTreg cells are specifically lost and colitis spontaneously develops within 3 months (Fig1. A). Development of pTregs is restored by inducible transgenic expression of Cbfβ2 in antigen-presenting cells. We then examined candidate cells for this APC and found that Thetis cell subsets (TC2 and TC3) were lost in Cbfβ2-deficient mice (Fig. 1B). Thus, our results have resolved a controversial issue of what is the actual APC for pTreg differentiation.

Laboratory for

Immune Cell Systems

Team Leader: **Shigeo Koyasu**

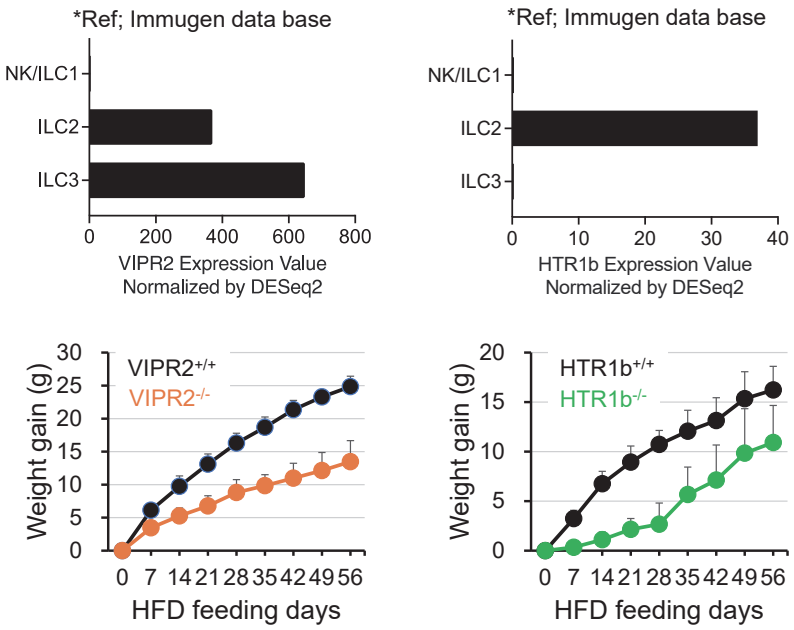


Figure:
(Top panels) Expression levels of VIPR2 (left) and HTR1b (right) on splenic NK/ILC1, SI-ILC2, and SI-ILC3. (Bottom panels) Weight gain of wild type or *Vipr2*$^{-/-}$ mice (left) and wild type or *Htr1b*$^{-/-}$ mice (right) fed a high-fat diet.

Recent Major Publications

*Nomura H, *Wada N, Takahashi H, Kase Y, Yamagami J, Egami S, Iriki H, Mukai M, Kamata A, Itoh H, Fujii H, Ishikura T, Koseki H, Watanabe T, Yamada T, Ohara O, #Koyasu S, #Amagai M. IgM to IgG class-switching is a necessary step for pemphigus phenotype induction in desmoglein 3-specific B cell receptor knock-in mouse. ***J Immunol*** 208, 582-593 (2022)

Misawa T, Wagner M, Koyasu S. ILC2s and adipose tissue homeostasis: Progress to date and the road ahead. ***Front Immunol*** 13, 876029 (2022)

Wagner M, Koyasu S. Cancer immunosurveillance by ILC2s. ***Trends Cancer*** 8, 792-794 (2022)

Invited presentations

Koyasu S. "Role of innate lymphoid cells in diet-induced obesity" Japanese-German Immunology Workshop 2022 (Gosler, Germany) September 2022

Koyasu S. "Group 2 innate lymphoid cells and allergic inflammation" The 50th Annual Meeting of the Japanese Society for Clinical Immunology (Tokyo, Japan) October 2022

Our long-term goal is to elucidate the immune cell network to understand how immune cells induce complex immune reactions in our bodies. Among a variety of immune cells, we have focused on innate lymphoid cells (ILCs) and their role in adipose tissue homeostasis and tumor immunity. We have previously shown that ILC2 and ILC3 in the small intestine but not in the adipose tissue are involved in diet-induced obesity. We also showed that the IL-2/ILC2/3 axis plays an important role in the induction of obesity. Transcriptomic analysis revealed that a serotonin receptor, HTR1b, and a receptor for vasoactive intestinal peptide, VIPR2, were highly expressed on ILC2. *Htr1b*$^{-/-}$ and *Vipr2*$^{-/-}$ mice were generated and both were shown to be resistant to diet-induced obesity, suggesting that intestinal hormones acting on ILCs play a role in the induction of obesity. In addition to obesity, starvation is also known to induce liver steatosis. We have noticed that *Rag2*$^{-/-}$ mice with a larger num-ber of ILCs compared to wild-type mice had more severe steatosis but *Il2rg*$^{-/-}$*Rag2*$^{-/-}$ mice lacking all lymphocytes had less severe steatosis compared to wild type-mice upon starvation. Both ILC2 and ILC3 are involved in this process by regulating lipid uptake in the small intestine. Using the B16 mela-noma model, we have previously shown that the IL-33/ILC2/eosinophil axis suppressed tumor growth. In humans, expression of *IL33* (activation of ILC2) and *SIGLEC8* (recruitment of eosinophils) are associated with better overall survival in melanoma patients, whereas no correlation was observed between the expression levels of *IL33* and *SIGLEC8* and overall survival for some other tumors, such as lung squamous cell carcinoma and pancreatic adenocarcinoma. We have further noticed that ILC2 in the skin plays a role in melanoma-associ-ated lymphangiogenesis and are currently studying its mechanisms.

Laboratory for

Innate Immune Systems

Team Leader: **Kazuyo Moro**

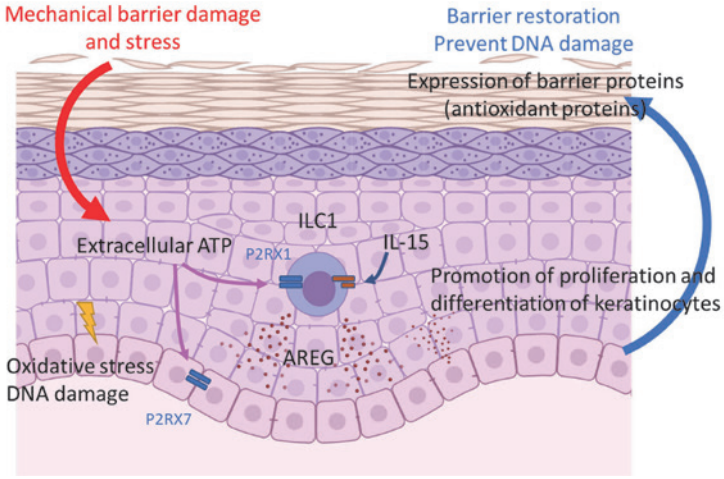


Figure: Schematic representation of ILC1-mediated epithelial barrier response
Mechanical damage induces release of extracellular ATP (eATP) from epithelial cells, which initiates keratinocyte proliferation. eATP simultaneously increases amphiregulin (AREG) production in skin-resident ILC1, which further promotes barrier restoration. The ILC1-meditaed barrier response plays a key role in the protection against mechanical damage-induced oxidative stress and DNA damage.

Recent Major Publications

Kobayashi T, Moro K. Tissue-Specific Diversity of Group 2 Innate Lymphoid Cells in the Skin. ***Front Immunol*** 13, 885642 (2022)

Kobayashi T, Moro K. A hairy situation for ILC2s. ***Immunity*** 55, 1756-1758 (2022)

Kabata H, Motomura Y, Kiniwa T, Kobayashi T, Moro K. ILCs and Allergy. ***Adv Exp Med Biol*** 1365, 75-95 (2022)

Invited presentations

Moro K. "The Scientific Organizing Committee of the 2022 Annual Meeting of the Society for Leukocyte Biology" (Hawaii, USA) October 2022

Moro K. "4th International Conference on Innate Lymphoid Cells" (Hawaii, USA) September 2022

Moro K. "The role of group 2 innate lymphoid cells in pulmonary diseases" 2022 Advanced Immunology Course (FIMSA) (Taiwan/Online) August 2022

Moro K. "The Role of Type 2 innate lymphoid cells in mucosal tissues" Food, Microbiota and Immunity 2022 (Prague, Czech) June 2022

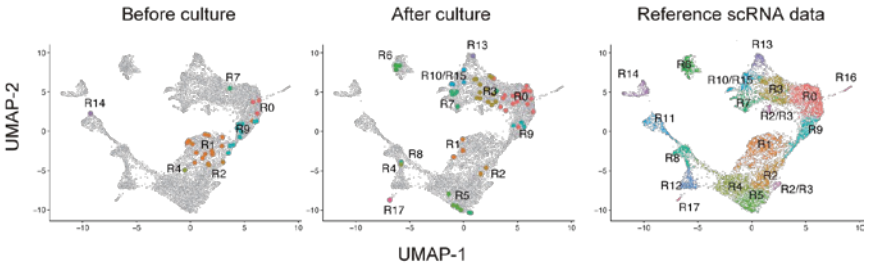
Moro K. "The discovery of group 2 innate lymphoid cells" Global Immunetalks (Online) March 2021

Our team has been investigating group 2 innate lymphoid cells (ILC2s), the innate lymphoid lineage cells identified in 2010. ILC2s are present in various tissues such as fat, lung, intestine, liver, and skin and mediate immune responses to parasite infections via strong type 2 cytokine production, including IL-5, IL-13, IL-9 and GM-CSF. Unlike T and B lymphocytes, ILC2s lack antigen-specific receptors and are activated by stroma cell-derived cytokines such as IL-33. Type 2 cytokines produced by ILC2s play an important role in the pathogenesis of allergic diseases such as asthma and atopic dermatitis; however, most previous studies on allergy have focused on the role of adaptive immune cells (T and B cells) in antigen-dependent allergic responses and the contribution of the innate immune system has been underestimated. Therefore, one of our goals was to investigate the mechanisms by which ILC2 activation is triggered and persistently regulated to establish new therapeutic strategies for allergic diseases. Moreover, we also aim to uncover pleiotropic effector functions of ILC2s. We clarify the roles of ILC2s in homeostatic maintenance of barrier integrity, metabolic regulation and the aging process. Furthermore, as ILC2s are involved not only in allergic diseases but also in a variety of other immune-related diseases, we are also investigating how ILC2s are associated with the pathogenesis of non-allergic diseases such as fibrosis and endometriosis. Our long-term goal is a comprehensive understanding of innate immune systems, particularly ILC2 biology, which plays a key role in human health and diseases.

Laboratory for
Immune Homeostasis

Team Leader: Taishin Akiyama

Figure:
Single cell RNA-seq of isolated TA-TEC candidates and their progeny after the reaggregation thymic organ culture.
Well-based scRNA-seq analysis of TA-TEC and their progeny was performed and the data were integrated with droplet-based scRNA-seq data of TECs for the assignment of cell type.



Recent Major Publications

Miyao T, Miyauchi M, Kelly ST, Terooatea TW, Ishikawa T, Oh E, Hirai S, Horie K, Takakura Y, Ohki H, Hayama M, Maruyama Y, Seki T, Ishii H, Yabukami H, Yoshida M, Inoue A, Sakaue-Sawano A, Miyawaki A, Muratani M, Minoda A, Akiyam N, Akiyama T*. Integrative analysis of scRNA-seq and scATAC-seq revealed transit-amplifying thymic epithelial cells expressing autoimmune regulator. ***Elife*** 11, e73998 (2022)

Katayama Y, Yokota R, Akiyama T, Kobayashi TJ. Machine Learning Approaches to TCR Repertoire Analysis. ***Front Immunol*** 13, 858057 (2022)

Nishijima H, Matsumoto M, Morimoto J, Hosomichi K, Akiyama N, Akiyama T, Oya T, Tsuneyama K, Yoshida H, Matsumoto M. Aire Controls Heterogeneity of Medullary Thymic Epithelial Cells for the Expression of Self-Antigens. ***J Immunol*** 208, 303-320 (2022)

Invited presentations

Akiyama T. "Regulatory mechanisms underlying gene expression in thymic epithelium" The 5th Tsinghua-RIKEN Joint Workshop on Recent Progress in Immunology (Online) November 2022

The thymus plays critical roles in the development of self-tolerant T cells and regulatory T cells, and therefore, thymic dysfunction causes immunodeficiency and autoimmune diseases. The aims of our study are 1) to identify molecular and cellular mechanisms regulating T cell selection and differentiation in the thymus, 2) to elucidate mechanisms underlying the onset of immure-related diseases caused by dysregulation of the thymus and 3) to define the impacts of environmental changes, including aging, on thymic functions and their underlying mechanisms.

Medullary thymic epithelial cells (mTECs) play essential roles in preventing the onset of autoimmune diseases. mTECs ectopically express and present several thousands of tissue-specific antigens (TSAs) and induce apoptosis of TSA-reactive T cells and otherwise converts them into regulatory T cells. The ectopic TSA expression by mTECs is regulated by the transcriptional regulator AIRE and other regulators. AIRE-expressing (AIRE$^+$) mTECs turnover with around a 2-week lifetime, however, mechanisms involved in maintaining mTECs remain elusive. We recently found evidence for the presence of AIRE$^+$ transit amplifying TEC progenitors that differentiate into mature mTECs expressing TSAs (Figure).

Thymoma, a tumor of TECs, is closely associated with the onset of various autoimmune diseases, including myasthenia gravis, which are called thymoma-associated autoimmune diseases. Elucidation of altered gene expression and its regulatory mechanism in thymoma TEC may identify new mechanisms involved in the onset and progression of autoimmune diseases. We performed single-cell RNA-seq analysis of tumor and normal TECs from human thymoma patients and thereby identified specific transcriptional regulators down-regulated in tumor mTECs compared to normal mTECs. Validating the functions of these candidate regulators would be important to find new mechanisms for suppressing the onset of autoimmune diseases.

Laboratory for Immune Crosstalk

Team Leader: Hilde Cheroutre

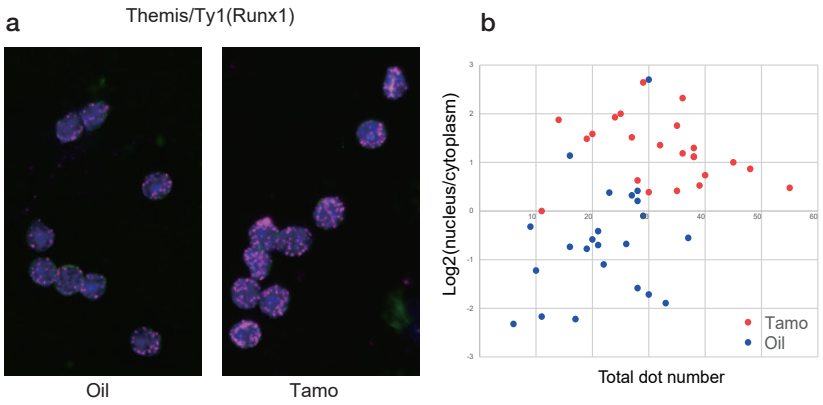


Figure: Proximity between RUNX1 and THEMIS visualized by the PLA assay

a. ERT2-*Themis;Runx1*Ty1 knock-in mice were treated with/without Tamoxifen and thymocytes were examined. Magenta dot indicates proximity between Runx1 and Themis. Nuclei were stained with DAPI.
b. Numbers of dots in the nucleus and cytoplasm were counted. The X axis shows the total number of dots in a single cell and the Y axis shows log2 value of the ratio between nucleus and cytoplasm.

Recent Major Publications

Dicker M, Li Y, Giles DA, Verstichel G, Castelan VC, Ascui-Gac G, Chou TF, Perez-Jeldres T, Cheroutre H, Kronenberg M. CD4^{+}-mediated colitis in mice is independent of the GPR183 and GPR18 pathways. ***Front Immunol*** 28, 1034648 (2022)

Seo GY, Takahashi D, Wang Q, Mikulski Z, Chen A, Chou TF, Marcovecchio P, McArdle S, Sethi A, Shui JW, Takahashi M, Surh CD, Cheroutre H, Kronenberg M. Epithelial HVEM maintains intraepithelial T cell survival and contributes to host protection. ***Sci Immunol*** 7, eabm6931 (2022)

Liu W, Chou TF, Garrett-Thomson SC, Seo GY, Fedorov E, Ramagopal UA, Bonanno JB, Wang Q, Kim K, Garforth SJ, Kakugawa K, Cheroutre H, Kronenberg M, Almo SC. HVEM structures and mutants reveal distinct functions of binding to LIGHT and BTLA/CD160. ***J Exp Med*** 218, e20211112 (2021)

Invited presentations

Kakugawa K. "Dynamic THEMIS subcellular localization is essential for its function" La Jolla Immunology Conference (La Jolla, USA) October 2022

Cheroutre H. Praespero Summit on Autoimmunity and autoimmune diseases (Vancouver, Canada) September 2022

Cheroutre H. "Gastrointestinal Tract XX: Making and Breaking a Gut" FASEB meeting (Steamboat Springs, USA) August 2022

Cheroutre H. "RARa controls FOXP3 T cell fate but not as a nuclear receptor" (North Carolina, USA) April 2022

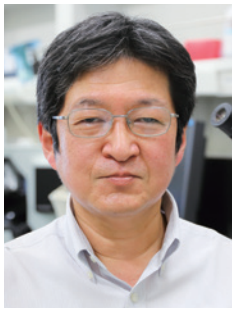
Cheroutre H. Oklahoma seminar "Protective tolerance: a new concept in immunology" (Oklahoma, USA) February 2022

We discovered THEMIS as an essential gene for T cell development. Many GWAS studies revealed that the *Themis* locus associates with T cell-driven autoimmune diseases such as Celiac Disease, Multiple Sclerosis, Rheumatoid Arthritis and Atopic Dermatitis. THEMIS is involved in T cell receptor (TCR) signaling as an adapter molecule able to modulate signal strength. THEMIS-deficiency results in impaired development and selection of conventional mature T cells. However, the mechanisms used by THEMIS to control TCR signaling remain unclear and controversial. Moreover, THEMIS is also present in the nucleus, but its nuclear function has not been addressed.

We aimed to identify THEMIS interacting proteins in the cytoplasm and nucleus with/without TCR stimulation by biotinylating enzyme and Mass spectrometry. We introduced a TurboID-Themis fusion construct into the mouse T cell hybridoma, 2B4 and compared the array of biotinylated proteins after TCR stimulation with those of unstimulated 2B4 and found that, besides cytoplasmic components, several important nuclear proteins were biotinylated. These included histone modification enzymes, transcription factors such as Runx1, components of the nuclear pore complex, and chromatin-remodeling proteins.

We further identified dynamic interactions between RUNX1 and THEMIS using the Proximal Ligation Assay (PLA). When the 2B4 cell line overexpressing ERT2-THEMIS was treated with 4-OH tamoxifen, colocation and direct interaction of these molecules was detected as ERT2-THEMIS entered the nucleus.

Taken together, these findings demonstrate that THEMIS has a dual function in T cells, participating in proximal TCR signaling at the cell surface and translating those signals into the nucleus where, through interaction with nuclear components, THEMIS directs gene expression leading to cell proliferation and differentiation.



Laboratory for
Inflammatory Regulation

Team Leader: Takashi Tanaka

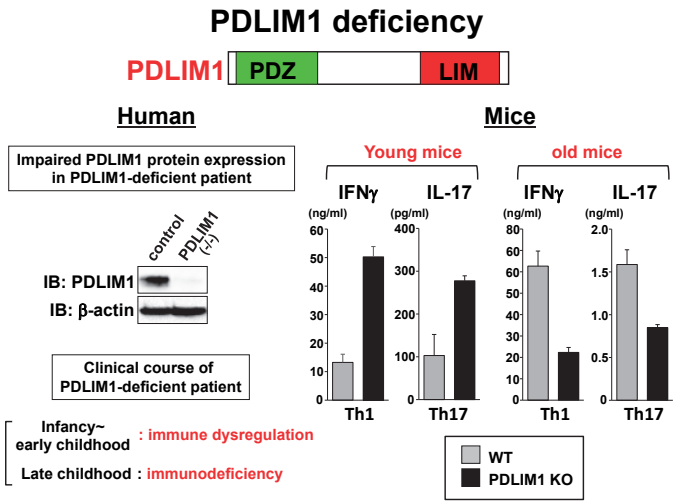


Figure: Loss-of-function mutations in PDLIM1 cause immunodeficiency due to T cell exhaustion in both human and mice

(Upper left) No PDLIM1 protein expression was detected in peripheral blood mononuclear cells from PDLIM1 deficient patient examined by western blot analysis. (Lower left) Clinical course of immunological presentation in PDLIM1 deficient patient. (Right) Age-related change of IFNγ and IL-17 production from Th1 and Th17 cells from PDLIM1 deficient mice examined by ELISA.

Recent Major Publications

Takemori T, Sugimoto-Ishige A, Nishitsuji H, Futamura Y, Harada M, Kimura-Someya T, Matsumoto T, Honma T, Takana M, Yaguchi M, Isono K, Koseki H, Osada H, Miki D, Saito T, Tanaka T, Fukami T, Goto T, Shirouzu M, Shimotohno K, Chayama K. Establishment of a monoclonal antibody against human NTCP that blocks HBV infection. ***J Virol*** 96, e01686-21 (2022)

Saiga H, Ueno M, Tanaka T, Kaisho T, Hoshino K. Transcription factor MafB-mediated inhibition of type I interferon in plasmacytoid dendritic cells. ***Int Immunol*** 34, 159-172 (2021)

Invited presentations

Tanaka T. "Biological function of Nahlsgen to control inflammatory responses in the skin" Special lecture in press conference for the new product "NAHLSNURSE" (Kyoto, Japan) October 2022

The inflammatory response, initiated by dendritic cells, is an important host defense mechanism to eliminate invading microbial pathogens. However, these responses must be terminated at the appropriate time point, otherwise excessive responses may cause massive damage to the host and lead to inflammatory diseases, indicating that negative regulatory systems for inflammation are critical to prevent immunopathology. Our research goal is to identify a series of key negative regulators of inflammation and clarify the molecular mechanisms by which these negative regulators control the homeostasis of the human immune system and prevent the onset of inflammatory diseases.

PDLIM1 (PDZ and LIM domain protein-1) is a negative regulator of NF-κB-mediated inflammatory responses. We previously reported that mice lacking PDLIM1 showed enhanced inflammation, expecting that the lack of PDLIM1 in human may cause inflammatory diseases. Contrary to this prediction, a human patient with a homozygous loss-of-function mutation in PDLIM1 was recently identified and found to develop immunodeficiency. Notably, the patient initially presented with immune dysregulation and enhanced proinflammatory cytokine production in early childhood. However, later in childhood, the patient developed immunodeficiency, suffering from recurrent bacterial infections in the skin and respiratory tract, due to a loss of Th17 cells. Interestingly, PDLIM1-deficient mice showed an immunological phenotype similar to that seen in human PDLIM1 deficiency. The young PDLIM1-deficient mice showed enhanced NF-κB-dependent Th1 and Th17 cell differentiation and this phenotype was completely reversed in elderly PDLIM1-deficient mice with suppressed Th1 and Th17 cell differentiation. FACS analysis of $CD4^+$T cells from both the PDLIM1-deficient patient and the mice showed exaggerated expression of markers associated with T cell activation and exhaustion, suggesting that excessive activation of $CD4^+$T cells in PDLIM1 deficiency may cause T cell exhaustion leading to immunodeficiency.

These data identify PDLIM1 as a novel regulator of Th1 and Th17 differentiation, whose deficiency in human causes a novel type of primary immunodeficiency.

Laboratory for
Cytokine Regulation

Team Leader: **Masato Kubo**

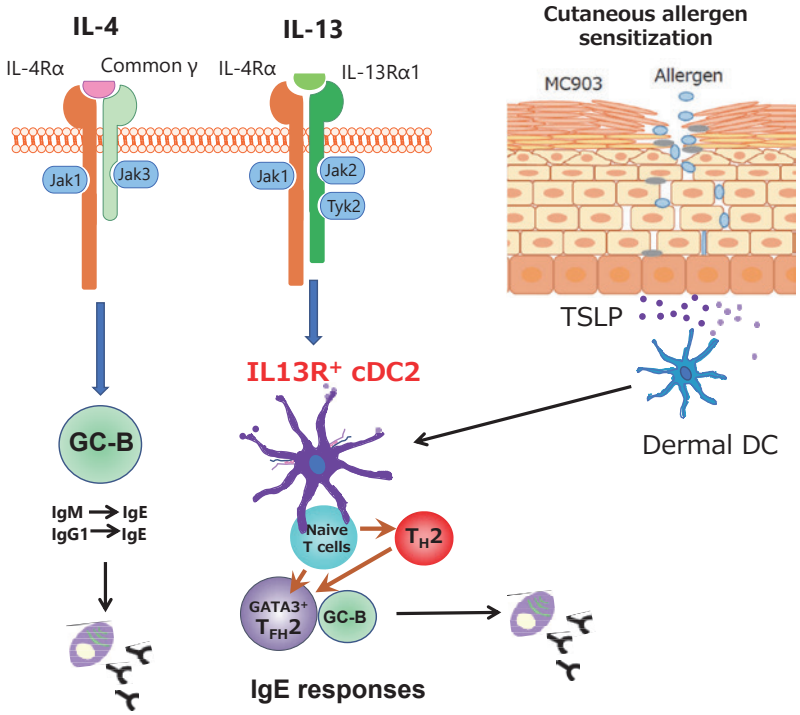


Figure: IL-4 and IL-13 signals independently control IgE-mediated allergic responses
The IL-4 signal directly induces class-switch recombination in B cells. IL-13 controls the development of MHCII^{hi} migratory cDC2s. Cutaneous allergen sensitization promotes IgE-mediated allergic responses by the emergence of IL-13Rα1-expressing cDC2s, which promote T_H2 and GATA3 expressing T_{FH} ($T_{FH}2$).

The adaptive immune system has evolved to mount different types of responses that are matched to the type of invading pathogen. There are two broad divisions of effector CD4$^+$ T cells: T follicular helper (T_{FH}) cells and non-T_{FH} effector cells. T cell-derived cytokines and cytokine signals play a critical role in the effector and regulatory functions of immune responses. We have devoted our efforts to establishing a series of mouse models for allergic diseases (asthma, atopic dermatitis (AD), food allergy, and anaphylaxis).

We established a cutaneous allergen sensitization (CAS) system using a vitamin D3 analog Calcipotriol (MC903), which is known to cause skin inflammation and barrier dysfunction. The CAS model promotes IgE-mediated allergic responses, but the precise mechanisms remain unclear. Single-cell RNA-seq revealed the emergence of IL-13 receptor alpha 1 chain (IL-13Rα1)-expressing type 2 conventional dendritic cells (cDC2s) in CAS. Similar DC populations were identified in allergic rhinitis individuals with IgE antibodies specific to cedar pollen. Lineage-specific disruption of IL-13 signaling resulted in a marked reduction of MHC class II^{hi} (MHCII^{hi}) cDC2s, which control the germinal center entry of T_{FH} cells required for IgE responses. These data reveal a unique role for IL-13 in enhancing the expansion of MHCII^{hi} cDC2s and associated T_{FH} cell responses in the allergy setting. Therefore, IL-13Rα1-expressing cDC2s are the critical cells connecting local and systemic lymphoid organs to facilitate efficient induction of type 2 TFH response in the independent way of IL-4 mediate signaling.

Recent Major Publications

Harada Y, Sasaki T, Wibisana J-N, Okada-Hatakeyama M, Ueno H, Burrows PD, Kubo M. Type 2 helper T cells convert to Interleukin-1 13 expressing follicular helper T cells after antigen repriming. ***Translational and Regulatory Sciences*** 5, 1, (2023)

Liu T-T, Kim S, Desai P, Kim D-H, Huang X, Ferris ST, Wu R, Ou F, Egawa T, Van Dyken SJ, Diamond MS, Johnson PF, Kubo M, Murphy TL, Murphy KM. Ablation of cDC2 development by triple mutations within the Zeb2 enhancer. ***Nature*** 607, 142-148 (2022)

Tomiaki C, Miyauchi K, Ki S, Suzuki Y, Suzuki N, Morimoto H, Mukoyama Y, Kubo, M. Role of FK506-sensitive signal in asthmatic lung inflammation. ***Front Immunol*** 13, 1014462 (2022)

Invited presentations

Kubo M. "Immune Regulation against viral infection and type 2 immunity" Allergy Research Conference Series, Feinberg School of Medicine, Northwestern University (USA/Online) September 2022

Kubo M. "Immune Regulation against viral infection and type 2 immunity" JSICR/MMCB joint symposium (Tokyo, Japan) June 2022

Sasaki T. & Kubo M. "A pathogenic role of IL-13 in anaphylaxis" The 50th Annual Meeting of the Japanese Society for Immunology, Nara Kasugano, International Forum I-RA-KA (Nara, Japan) December 2021

Kubo M. "Different immunodominance of influenza virus between infection and vaccination" The 5th International Immunological Memory and Vaccine Forum (5th IIMVF) (Online) April 2021

Laboratory for

Human Immunogenetics

Team Leader: **Kazuyoshi Ishigaki**

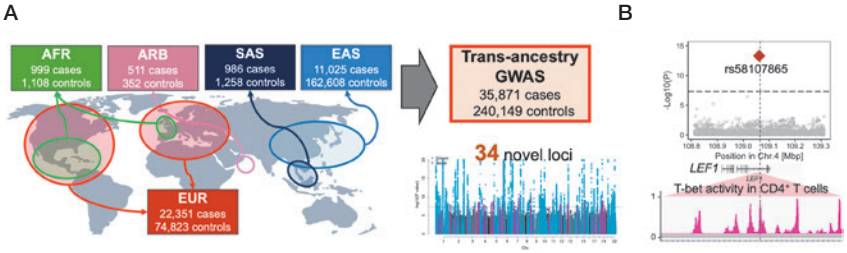


Figure: Overview of our multi-ancestry GWAS
(A) The left panel shows geographical regions and ancestries in this study. The right panel shows the Manhattan plot of our multi-ancestry GWAS. (B) A representative example of the fine-mapped variant at the *LEF1* locus. The bottom figure indicates the gene regulatory activity in $CD4^+$ T cells (T-bet IMACT annotation track; Amariuta and Ishigaki *et al. Nat Genet* 2020).

Our laboratory aims to elucidate the genetic basis of autoimmunity and we have committed to five major research topics. The first is computational and experimental fine-mapping. We conducted the largest-scale multi-ancestry genome-wide association study (GWAS) for rheumatoid arthritis and successfully fine-mapped multiple risk variants (Ishigaki *et al. Nature Genetics* 2022a). In addition, our laboratory has established a genome-editing platform using primary human T cells and experimentally validated the molecular functions of the fine-mapped variants. The second topic is the high-throughput screening of causal cellular states. We have established an experimental system that accurately and efficiently quantifies the chromatin accessibility of the target genomic region. By applying this system to cells with various conditions, we are searching for the causal cellular states where the risk variant exerts their regulatory functions. The third topic is functional genetics using single-cell analysis. We established a novel analytical method to search expression quantitative trait loci (eQTL) from single-cell gene expression data (Nathan *et al. Nature* 2022). We are expanding this method to infer continuous cellular states affecting the eQTL effect magnitude and to evaluate how the polygenic risk score impacts cellular states. The fourth topic is the T cell receptor (TCR). We developed a novel analytical TCR pipeline and have reported that *human leukocyte antigen* (*HLA*) risk alleles affect thymic selection to increase the frequency of autoreactive TCRs (Ishigaki *et al. Nature Genetics* 2022b). We applied the same analytical pipeline to another study and identified TCR features of regulatory T cells (Lagattuta *et al. Nature Immunology* 2022). The last topic is the clinical transcriptome. We analyzed a large-scale transcriptome dataset of systemic lupus erythematosus (SLE) patients and identified two distinct transcriptome signatures: disease state and activity signatures (Nakano *et al. Cell* 2022). All of these research activities contribute to a better understanding of human autoimmunity pathology.

Recent Major Publications

Ishigaki K, Sakaue S, Terao C, Luo Y, Sonehara K, Yamaguchi K, Amariuta T, Too CL, Laufer VA, Scott IC, Viatte S, Takahashi M, Ohmura K, Murasawa A, Hashimoto M, Ito H, Hammoudeh M, Emadi SA, Masri BK, Halabi H, Badsha H, Uthman IW, Wu X, Lin L, Li T, Plant D, ... BioBank Japan Project; Matsuda K, Matsuo K, Mimori T, Matsuda F, Fujio K, Tanaka Y, Kumanogoh A, Traylor M, Lewis CM, Eyre S, Xu H, Saxena R, Arayssi T, Kochi Y, Ikari K, Harigai M, Gregersen PK, Yamamoto K, Louis Bridges S Jr, Padyukov L, Martin J, Klareskog L, Okada Y, Raychaudhuri S. Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in rheumatoid arthritis. ***Nat Genet*** 54, 1640-1651 (2022)

Nakano M, Ota M, Takeshima Y, Iwasaki Y, Hatano H, Nagafuchi Y, Itamiya T, Maeda J, Yoshida R, Yamada S, Nishiwaki A, Takahashi H, Takahashi H, Akutsu Y, Kusuda T, Suetsugu H, Liu L, Kim K, Yin X, Bang SY, Cui Y, Lee HS, Shoda H, Zhang X, Bae SC, Terao C, Yamamoto K, Okamura T, Ishigaki K, Fujio K. Distinct transcriptome architectures underlying lupus establishment and exacerbation. ***Cell*** 185, 3375-3389.e21 (2022)

Ishigaki K, Lagattuta KA, Luo Y, James EA, Buckner JH, Raychaudhuri S. HLA autoimmune risk alleles restrict the hypervariable region of T cell receptors. ***Nat Genet*** 54, 393-402 (2022)

Invited presentations

Ishigaki K. "T cell receptor and immune regulation" The 71st Annual Meeting of The Japanese Society of Allergology (Tokyo, Japan) October 2022

Ishigaki K. "Autoimmunity pathology elucidated by functional genetics and AI" Symposium of the Japan College of Rheumatology, AI and Rheumatology (Tokyo, Japan) June 2022

Ishigaki K. "Trans-ancestry genome-wide association study identifies novel genetic mechanisms in rheumatoid arthritis" The 66th Annual General Assembly and Scientific Meeting of the Japan College of Rheumatology (Yokohama, Japan) April 2022

Laboratory for

Immunological Memory

Team Leader: Shiki Takamura

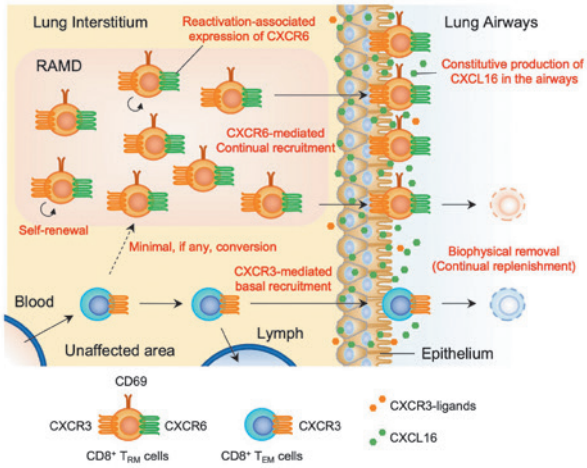


Figure: Schematic model of the maintenance of CD8⁺ T_{RM} and T_{EM} in the lung
In the lung interstitium, CD8⁺ T_{RM} cells (a major population) are predominantly localized in the RAMD while CD8⁺ T_{EM} cells (a minor population) distribute sparsely in unaffected areas. Reactivation of CD8⁺ T_{RM} cells leads to upregulation of CXCR6, which drive continual migration to the airway in response to CXCL16 expressed constitutively in the lung airways. Some CD8⁺ T_{RM} cells in the RAMD undergo homeostatic proliferation to compensate for the continuous loss of cells by intraepithelial migration. Lung interstitium CD8⁺ T_{RM} cells are primarily maintained independently of CD8⁺ T_{EM} cells, although a low level of T_{EM} to T_{RM} conversion may occur. While tissue-circulating CD8⁺ T_{EM} cells in the lung interstitium leave tissues via lymphatics, some cells migrate to the airways in response to CXCR3 ligands. Airway memory CD8⁺ T cells are continuously replenished by new cells recruited from the lung interstitium.

The global pandemic of SARS-CoV-2, with its high mutation rate, has emphasized the urgent need to develop vaccines capable of eliciting long-lasting protective immunity to the original virus as well as its variant strains. Although neutralizing antibody responses are easily evaded by mutation of their cognate epitopes on envelope proteins, antigen-specific CD8⁺ T cells can cross-react with novel variants by targeting highly-conserved internal viral proteins. It is now appreciated that tissue-resident memory CD8⁺ T cells (CD8⁺ T_{RM}) comprise a unique T cell subset that permanently resides in peripheral tissues and plays a predominant role in protective immunity at barrier surfaces. Because of the anatomical and microenvironmental differences in each peripheral tissue, the mechanisms by which CD8⁺ T_{RM} are generated and maintained in each tissue differ significantly. Hence, our laboratory aims to understand factors regulating the formation of CD8⁺ T_{RM} in each tissue with a view to developing novel vaccination and therapeutic strategies.

Using a mouse model of influenza virus infection and experimental approaches, such as intravenous antibody staining and parabiosis, to precisely discriminate memory T cell subsets, we have discovered that CD8⁺ T_{RM} in the lung are generated and maintained in transient niches created at the site of tissue damage and regeneration and that CD8⁺ T_{RM} in these sites are maintained independently of tissue-circulating effector memory T cells (T_{EM}) in the lung. We have termed these sites Repair-Associated Memory Depots (RAMD). At the early stages of infection, we also demonstrated that pulmonary monocytes provide local antigen signaling that drives the subsequent formation of CD8⁺ T_{RM} in the RMAD. Furthermore, CD8⁺ T_{RM} in the RAMD are found to undergo homeostatic proliferation and express the chemokine receptor CXCR6, which promotes the continual migration of T_{RM} from the RAMD to the lung airways, independently of memory in the circulation, thereby sustaining local protective immunity.

T_{RM} also contribute to cancer immunity as high frequencies of T_{RM} in the tumor are associated with an improved response to tumor immunotherapy and favorable clinical outcomes in patients with cancer. In particular cases, however, T_{RM} exacerbate autoimmunity, allergy, and inflammatory disease. Thus, our ultimate research goal is to precisely manipulate the formation of T_{RM} according to the individual situation.

Recent Major Publications

Takamura S. Divergence of tissue-memory T cells: Distribution and function-based classification. ***Cold Spring Harb Perspect Biol*** 12, a037762 (2021)

Hayward SL, Scharer CD, Cartwright EK, Takamura S, Tiger li ZR, Boss JM, Kohlmeier JK. Environmental cues regulate epigenetic reprogramming of airway-resident memory CD8 T cells. ***Nat Immunol*** 21, 309-320 (2020)

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

Invited presentations

Takamura S. "Generation and maintenance of epithelial-tropic CD8⁺ T cells in the peripheral tissues and tumor" The 51st Annual Meeting of the Japanese Society for Immunology (Kumamoto, Japan) December 2022

Infectious Diseases Research Unit

Unit Leader: **Haruhiko Koseki**

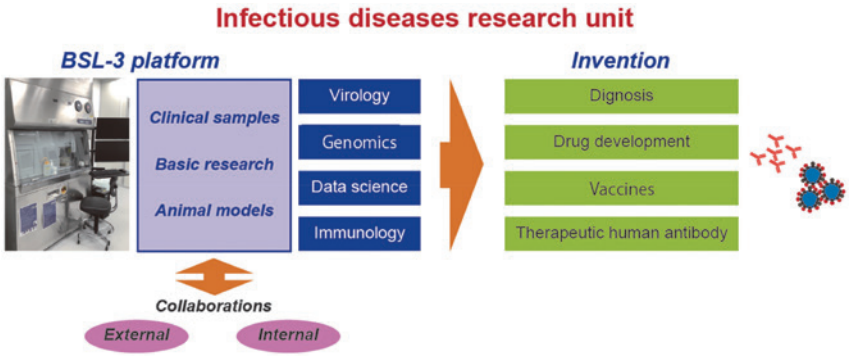


Figure: A schematic view of our research strength and direction
The newly established BSL-3 provided a unique opportunity to perform infectious disease research, leading to inventions.

Recent Major Publications

Takeshita M, Fukuyama H, Kamada K, Matsumoto T, Makino-Okamura C, Uchikubo-Kamo T, Tomabechi Y, Hanada K, Moriyama S, Takahashi Y, Ishigaki H, Nakayama M, Nguyen CT, Kitagawa Y, Itoh Y, Imai M, Maemura T, Furusawa Y, Ueki H, Iwatsuki-Horimoto K, Ito M, Yamayoshi S, Kawaoka Y, Shirouzu M, Ishii M, Saya H, Kondo Y, Kaneko Y, Suzuki K, Fukunaga K, Takeuchi T. SARS-CoV-2 neutralizing antibodies with therapeutic effects in two animal models. ***iScience*** 25, 105596 (2022)

Miyauchi K, Adachi Y, Tonouchi K, Yajima T, Harada Y, Fukuyama H, Deno S, Iwakura Y, Yoshimura A, Hasegawa H, Yugi K, Fujii SI, Ohara O, Takahashi Y, Kubo M. Influenza virus infection expands the breadth of antibody responses through IL-4 signalling in B cells. ***Nat Commun*** 12, 3789 (2021)

Takeuchi T, Miyauchi E, Kanaya T, Kato T, Nakanishi Y, Watanabe T, Kitami T, Taida T, Sasaki T, Negishi H, Shimamoto S, Matsuyama A, Kimura I, Williams IR, Ohara O, Ohno H*. Acetate differentially regulates IgA reactivity to commensal bacteria. ***Nature*** 595, 560-564 (2021)

Invited presentations

Koseki H. "SKP1A links Polycomb-repressed genes with proteasome" Okinawa Institute of Science and Technology (OIST) (Okinawa, Japan) November 2022

Koseki H. "The role for variant PRC1 during transcriptional phase transition" University of Oxford (Oxford, UK) September 2022

Koseki H. "The role for variant PRC1 during transcriptional phase transition" Friedrich Miescher Institute for Biomedical Research (FMI) (Basel, Switzerland) September 2022

Koseki H. "The role for variant PRC1 during transcriptional phase transition" University of Copenhagen (Copenhagen, Denmark) September 2022

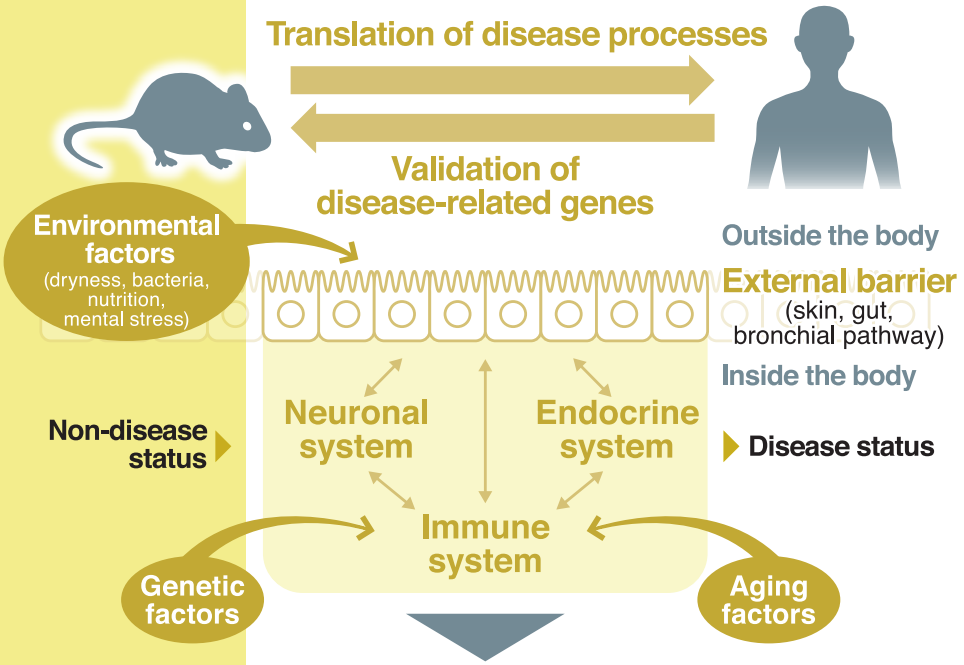
The Infectious Diseases Research Unit was newly established in August 2021 during the COVID-19 pandemic in response to a demand from society and the scientific communities. The unit has built and runs BSL-3 and ABSL-3 laboratories, the only such facilities in the entire RIKEN. Our unit has a two-sided mission: performing our own research and providing a core facility service open to both internal and external research communities.

We aim to provide the basis of therapeutic intervention for infectious diseases and to prepare for the next pandemics. Our own research covers the generation of animal models of infectious diseases, the development of next-generation vaccines, and the understanding of the pathogenesis of various infectious diseases. The following achievements are highlighted: (1) generation of an infectious diseases model animal for COVID-19; (2) discovery of a new transdermal adjuvant for a next-generation vaccine; (3) isolation of therapeutic broadly neutralizing human monoclonal antibodies; (4) delineating the mechanisms of the humoral response following administration of the COVID-19 mRNA vaccine; (5) genome-wide CAGE analysis of CoV-2 infected cells.

Our unit attracts several research groups from RIKEN and elsewhere and one of the fruitful collaborations with them led to success in obtaining a series of human broadly neutralizing antibodies against SARS Coronavirus 2 (CoV-2), leading us to apply for international patents.

We learn from COVID-19 how to prepare for the next pandemic. Our invention of a next-generation vaccine and our understanding of the pathogenesis of infectious diseases will help control the coming pandemics.

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

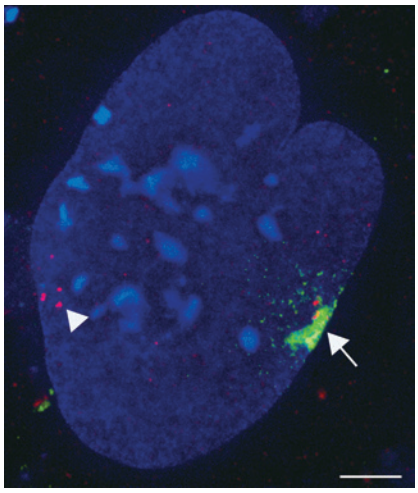


Figure: Image of a trophoblast giant cell (TGC) derived from extra-embryonic tissues of a *Prc1* mutant mouse embryo

Green signals show *Xist* RNA which coats the inactive X chromosome (Xi). Red signals show primary transcripts of an X-linked gene *Rnf12*. Blue signals show DAPI staining that represents nuclear genomic DNA. Arrow; *Rnf12* RNA transcribed from the *Xist*-coated Xi. Arrowhead; *Rnf12* RNA transcribed from the active X chromosome (Xa). *Rnf12* is normally silenced on the Xi in PRC1-intact TGCs. Upon PRC1 deletion, however, *Rnf12* is derepressed and transcribed on the Xi in the ΔPRC1 TGC shown here. Scale bar = 5 micrometers.

Recent Major Publications

Masui O, Corbel C, Nagao K, Endo T, Kezuka F, Diabangouaya P, Nakayama M, Kumon M, Koseki Y, Obuse C, Koseki H*, Heard E*. Polycomb complexes PRC1 and PRC2 are each essential for maintenance of X inactivation in extraembryonic lineages. ***Nature Cell Biol*** 25, 134-144 (2023)

Takano J, Ito S, Dong Y, Sharif J, Nakajima-Takagi Y, Umeyama T, Han Y, Isono K, Kondo T, Iizuka Y, Miyai T, Koseki Y, Ikegaya M, Sakihara M, Bardwell V, Nakayama M, Ohara O, Hasegawa Y, Hashimoto K, Arner E, Klose1 R, Iwama A, Koseki H*, Ikawa T.* PCGF1-PRC1 links chromatin repression with DNA 1 replication during hematopoietic cell lineage commitment. ***Nature Commun*** 13, 7159 (2022)

Ohinata Y*, Endo TA, Sugishita H, Watanabe T, Iizuka Y, Kawamoto Y, Saraya A, Kumon M, Koseki Y, Kondo T, Ohara O, Koseki H*. Establishment of mouse stem cells that can recapitulate the developmental potential of primitive endoderm. ***Science*** 375, 574-578 (2022)

Invited presentations

Koseki H. "SKP1A links Polycomb-repressed genes with proteasome" Okinawa Institute of Science and Technology (OIST) (Okinawa, Japan) November 2022

Koseki H. "The role for variant PRC1 during transcriptional phase transition" University of Oxford (Oxford, UK) September 2022

Koseki H. "The role for variant PRC1 during transcriptional phase transition" Friedrich Miescher Institute for Biomedical Research (FMI) (Basel, Switzerland) September 2022

Koseki H. "The role for variant PRC1 during transcriptional phase transition" University of Copenhagen (Kopenhagen, Danmark) September 2022

The Developmental Genetics Laboratory not only pursues its own research program towards 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 to understand 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 how Polycomb group (PcG) factors function in combination with the ubiquitin-proteasome pathway, DNA replication mechanisms, and DNA damage responses.

A large part of the group is devoted to the maintenance of a high-standard mouse facility in IMS. Through the Animal Core Facility, the group is also responsible for the generation of knock-out and transgenic animals for the various research laboratories at the center, and for the generation of germ-free, gnotobiotic, 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 the generation of iPSC-derived NKT cells for their clinical use in cancer therapy and have initiated 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 for therapeutic intervention. We found that Atopic Dermatitis (AD) is a good model to tackle this issue, 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**

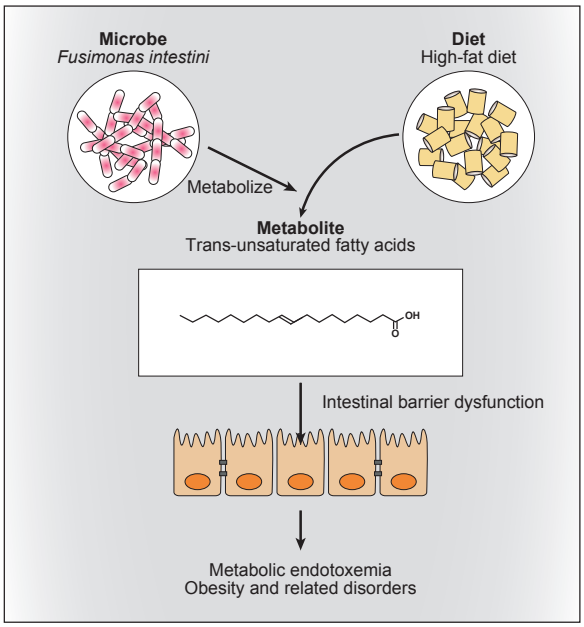


Figure: Schematic representation of the combination of a high fat diet and *Fusimonas intestini* leading to obesity and metabolic disorders
The gut commensal *Fusimonas intestini* metabolizes fatty acids on a high fat diet to produce trans-unsaturated fatty acids such as elaidate, which causes downregulation of tight junction genes and barrier dysfunction, resulting in metabolic endotoxemia and ultimately obesity and related metabolic disorders. (Reproduced from Takeuchi T *et al*. ***Cell Metab*** 35: 361, 2023).

Gut microbiota is the consortium of numerous commensal bacteria residing in our intestines. Our lab has been studying the molecular mechanisms of host-gut microbiota interactions, which deeply impact the host physiology and pathology. We have been applying an integrated omics approach, where exhaustive analyses at different layers of organismal activities are combined, including (meta)genomics, epigenomics, (meta)transcriptomics, and metabolomics.

The host does not freely allow the residence of those microorganisms. The intestinal immune system has developed the ability to sense the bacteria in the gut lumen and tries to contain them. In charge of this process is the M cell, a unique subset of intestinal epithelial cells evolved to recognize and take up luminal bacteria and transfer them to the underlying dendritic cells for initiation of intestinal immune responses. Our lab has been studying the molecular mechanisms of M-cell differentiation and functions. A main end product of intestinal immune responses is immunoglobulin (Ig) A. IgA is a major class of immunoglobulins produced and secreted in the mucosal tissues including the intestine. We have recently shown that the amount and specificity of IgA toward commensal bacteria is regulated by the combination of gut microbial metabolites, microbial components and the intestinal immune system.

Regarding the impact of host-gut microbiota interactions on disease pathogenesis, we have made some progress in the past years. The bacterial composition of the gut lumen and mucosa are distinct and the mucosa-associated bacteria are thought to correlate more closely with host pathophysiology. We have shown that colonic lavage samples from humans can be used to make a good noninvasive estimation of the mucosal microbiota composition. We have also investigated the impact of gut microbiota on autoimmune diseases, namely type 1 diabetes and multiple sclerosis, as well as metabolic disorders including obesity and glucose intolerance.

Recent Major Publications

Takeuchi T, Kameyama K, Miyauchi E, Nakanishi Y, Kanaya T, Fujii T, Kato T, Sasaki T, Tachibana N, Negishi H, Matsui M, Ohno H. Fatty acid overproduction by gut commensal microbiota exacerbates obesity. ***Cell Metab*** 35, 361-375.e9 (2023)

Shi Z, Takeuchi T, Nakanishi Y, Kato T, Beck K, Nagata R, Kageyama T, Ito A, Ohno H. A Japanese Herbal Formula, Daikenchuto, Alleviates Experimental Colitis by Reshaping Microbial Profiles and Enhancing Group 3 Innate Lymphoid Cells. ***Front Immunol*** 13, 903459 (2022)

Nagata N, Takeuchi T, Masuoka H, Aoki R, Ishikane M, Iwamoto N, Sugiyama M, Suda W, Nakanishi Y, Terada-Hirashima J, Kimura M, Nishijima T, Inooka H, Miyoshi-Akiyama T, Kojima Y, Shimokawa C, Hisaeda H, Zhang F, Yeoh YK, Ng SC, Uemura N, Itoi T, Mizokami M, Kawai T, Sugiyama H, Ohmagari N, Ohno H. Human gut microbiota and its metabolites impact immune responses in COVID-19 and its complications. ***Gastroenterology*** 164: 272-288 (2022)

Invited presentations

Ohno H. "Impact of gut microbial metabolites short-chain fatty acids on the host immunity and physiology" Symposium S16 US-Japan Immunology Program Co-organized Session "Microbiota and the host immune system" The 51st Annual Meeting of the Japanese Society for Immunology (Kumamoto, Japan) December 2022

Ohno H. "Impacts of smoking on the gut ecosystem and pathogenesis in inflammatory bowel disease" Strategic International Session ST1 "New frontiers of omics approach in gastroenterology" Japan Digestive Disease Wek 2022 (Fukuoka, Japan) October 2022

Ohno H. "Gut microbial carbohydrate metabolism impacts host insulin resistance" 74th Annual Meeting of the German Society of Hygiene and Microbiology (Berlin, Germany) September 2022

Ohno H. "Gut microbial carbohydrate metabolism impacts host insulin resistance" ImmunoZoom Seminar (Online) July 2022

Ohno H. "Host insulin resistance is attributable to gut microbial monosaccharide productivity" Symposium 5 "Frontiers in the regulation of metabolism by the gut" The 65th Annual Meeting of the Japan Diabetes Society (Kobe, Japan) May 2022

Laboratory for
Integrative Genomics

Team Leader: Jun Seita

Figure:
Figure 1a
The massively parallel single-cell culture system consists of a fully automated microscope, a cell culture robot, a liquid handling robot, and a computer system to control them. This allows reinforcement learning to learn the effects of interventions by observing the state of individual cells, intervening in the environment surrounding the cells and then observing the results of the intervention again over time.
Figure 1b
In the newly built room for mass spectrometers and lab automation, four cutting-edge mass spectrometers, Q Exactive, Orbitrap Exploris 480, Orbitrap Eclipse (not seen), and Sciex TF5600 (right to left) are providing a wide range of proteomics analyses in IMS.

Figure 1a

Figure 1b

Recent Major Publications

Masui O, Corbel C, Nagao K, Endo TA, Kezuka F, Diabangouaya P, Nakayama M, Kumon M, Koseki Y, Obuse C, Koseki H, Heard E. Polycomb repressive complexes 1 and 2 are each essential for maintenance of X inactivation in extra-embryonic lineages. ***Nat Cell Biol*** 25,134-144 (2023)

Tanaka J, Senpuku H, Ogawa M, Yasuhara R, Ohnuma S, Takamatsu K, Watanabe T, Mabuchi Y, Nakamura S, Ishida S, Sadaoka T, Takaki T, Shirota T, Shimane T, Inoue T, Sakai T, Mori M, Tsuji T, Saito I, Mishima K. Human induced pluripotent stem cell-derived salivary gland organoids model SARS-CoV-2 infection and replication. ***Nat Cell Biol*** 24, 1595-1605 (2022)

Ohinata Y, Endo TA, Sugishita H, Watanabe T, Iizuka Y, Kawamoto Y, Saraya A, Kumon M, Koseki Y, Kondo T, Ohara O, Koseki H. Establishment of mouse stem cells that can recapitulate the developmental potential of primitive endoderm. ***Science*** 375, 574-578 (2022)

Invited presentations

Seita J. "The Grand Unification Happening "Now" in Deep Learning and its Impact on Single-cell Analysis" Tokyo Medical & Dental University and SONY Clinical Summit (Online) December 2022

Seita J. "State-of-the-art single cell analysis and Human Cell Atlas project" The 102nd Hokkaido Medical Congress Special Lecture (Sapporo, Japan) October 2022

Seita J. "Big Data to Create Personalized Health Care - Utilization of Cohort-Biobank" Tohoku Medical Megabank Organization (Sendai, Japan) August 2022

Seita J. "Potential of Deep Learning for Medical DX" The 37th Annual Meeting of The Academy of Pharmaceutical Science and Technology, Japan (APSTJ) (Online) May 2022

Seita J. "Reality of Deep Learning in Medicine" The Biometric Society for Japan Annual Meeting, Special Session (Tokyo, Japan) May 2022

We are continuing to evolve the laboratory for integrative genomics toward multi-omics and the AI era. As a part of IMS "Genome Platform", we are implementing methods for single-cell epigenomics and transcriptomics. We also launched the next generation proteomics facility by combining the latest mass spectrometers and deep learning computation to estimate protein structure and protein-protein interactions. In 2022, we launched the "Scientific discovery by AI" project where multi-omics and AI-driven biology are fully merged. We built a system to investigate where reinforcement learning will autonomously discover biological phenomena.

Laboratory for
Mucosal Immunity

Team Leader: Sidonia Fagarasan

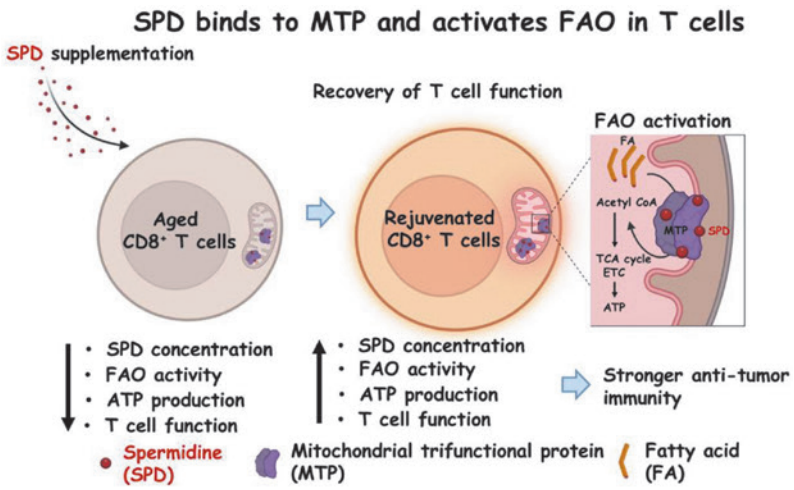


Figure: Spermidine (SPD) boosts mitochondria FAO by directly binding to MTP
A schematic representation of spermidine effect on cytotoxic T cells (adapted from Science report). Decreased SPD levels in aged CD8$^+$ T cells, leads to low FAO activity, less ATP production and less effector functions. SPD supplementation rejuvenates aged CD8$^+$ T cells by activating FAO upon direct binding to mitochondrial trifunctional protein (MTP). Spermidine supplementation enhances the efficacy of PD-1 blockade cancer immunotherapy in aged animals otherwise non-responsive to treatment. Adapted from Al-Habsi M *et al*. ***Science*** 378, eabj3510 (2022).

Immunometabolism and aging: identifying secreted metabolites with immune regulatory function

Immune system function declines with age, with many yet-to-be-discovered factors contributing to such a decline. Cancer incidence increases with age and one of the most powerful cancer treatments, namely checkpoint blockade therapy, is reported to be less effective in aged patients. We found that supplementation with spermidine, a natural polyamine that decreases in abundance with age, improves the effectiveness of anti-PD1 therapy in aged mice. Surprisingly, spermidine supplementation also synergized with anti-PD1 treatment in young mice, significantly reduced tumor growth and prolonged animal survival. These observations raised the question of whether spermidine directly influences immune system function.

We found that addition of spermidine to anti-PD1 therapy increased the number of effector and memory CD8$^+$ T cells in the tumor environment as well as in the draining lymph nodes. The expansion of effector CD8$^+$ T cells was associated with enhanced mitochondrial activity, as evidenced by increased oxidative phosphorylation and spare respiratory capacity of CD8$^+$ T cells. Such mitochondrial activity was unexpectedly observed even at one hour after stimulation and was due to increased mitochondrial fatty acid oxidation (FAO) (summarized in the Figure).

At the molecular level, we found that spermidine directly binds and allosterically activates the hydroxyl coenzyme A dehydrogenase subunits α and β (HADHA and HADHB), which comprise the mitochondrial trifunctional protein (MTP). MTP is the critical enzyme to FAO, and T cell–specific deletion of *Hadha* abolished the antitumor effect of spermidine supplementation in combination with anti-PD-L1. In summary, these findings not only highlight a mechanism by which spermidine deficiency may contribute to poor T cell function in the context of aging but also reveal the therapeutic potential of combining immune checkpoint blockade with spermidine supplementation to enhance antitumor immunity.

Recent Major Publications

Al-Habsi M, Chamoto K, Matsumoto K, Nomura N, Zhang B, Sugiura Y, Sonomura K, Maharani A, Nakajima Y, Wu Y, Nomura Y, Menzies R, Tajima M, Kitaoka K, Haku Y, Delghandi S, Yurimoto K, Matsuda F, Iwata S, Ogura T, Fagarasan S*, Honjo T*. Spermidine activates mitochondrial trifunctional protein and improves antitumor immunity in mice. ***Science*** 378, eabj3510 (2022)
*corresponding authors

Zhang B, Vogelzang A, Fagarasan S. Secreted immune metabolites that mediate immune cell communication and function. ***Trends Immunol*** 43, 990-1005 (2022)

Invited presentations

Fagarasan S. "A novel B cell-derived metabolite inhibiting anti-tumor immunity" 2022 Cell Research Symposium Cancer and Immunity: Mechanism and Therapeutics (Tiantai, China/Online) September 2022

Fagarasan S. "A novel B cell-derived metabolite inhibiting anti-tumor immunity" The 81st Annual Meeting of the Japanese Cancer Association (Yokohama, Japan/Online) September 2022

Fagarasan S. "The biochemical dialog between major physiological systems of the body mediated by immune cells" Clinical Immunology: Kyoto and Osaka University Joint meeting (Osaka, Japan/Online) July 2022

Laboratory for
Gut Homeostasis

Team Leader: **Kenya Honda**

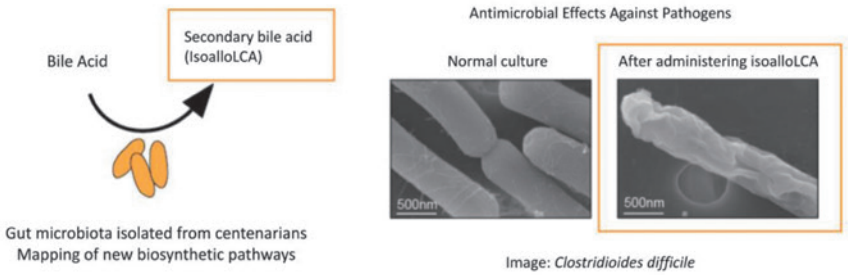


Figure:
Discovery and effects of the biosynthetic pathway that produces isoallo-lithocholic acid (isoalloLCA), a secondary bile acid unique to centenarians.

Recent Major Publications

Li Y, Watanabe E, Kawashima Y, Plichta DR, Wang Z, Ujike M, Ang QY, Wu R, Furuichi M, Takeshita K, Yoshida K, Nishiyama K, Kearney SM, Suda W, Hattori M, Sasajima S, Matsunaga T, Zhang X, Watanabe K, Fujishiro J, Norman JM, Olle B, Matsuyama S, Namkoong H, Uwamino Y, Ishii M, Fukunaga K, Hasegawa N, Ohara O, Xavier RJ, Atarashi K, Honda K. Identification of trypsin-degrading commensals in the large intestine. ***Nature*** 609, 582-589 (2022)

Tuganbaev T, Yoshida K, Honda K. The effects of oral microbiota on health. ***Science*** 376, 934-936 (2022)

Sato Y, Atarashi K, Plichta DR, Arai Y, Sasajima S, Kearney SM, Suda W, Takeshita K, Sasaki T, Okamoto S, Skelly AN, Okamura Y, Vlamakis H, Li Y, Tanoue T, Takei H, Nittono H, Narushima S, Irie J, Itoh H, Moriya K, Sugiura Y, Suematsu M, Moritoki N, Shibata S, Littman DR, Fischbach MA, Uwamino Y, Inoue T, Honda A, Hattori M, Murai T, Xavier RJ, Hirose N, Honda K. Novel bile acid biosynthetic pathways are enriched in the microbiome of centenarians. ***Nature*** 599, 458-464 (2021)

Invited presentations

Honda K. "Mining the gut microbiota to develop rationally designed microbial therapeutics" at NIH, Immunology Online Seminar Series (USA/Online) March 2022

Honda K. "Mining the gut microbiota and identifying effector microbes to combat pathogen infection" The 2022 Gut Microbiota for health summit (USA/Online) March 2022

Honda K. "Identifying effector microbes that causally affect the host physiology to develop defined microbial therapeutics" The 10th Microbiome Interactions in Health and Disease meeting (EU/Online) October 2021

Honda K. "Microbiota and regulation of intestinal immunity" The 2021 Principles of Mucosal Immunology course, Society for mucosal Immunology (USA/Online) July 2021

Honda K. "Mining the microbiota and identifying effector microbes that causally affect the host physiology" KEYSTONE SYMPOSIA Impact of Microbiota Composition, Metabolism and Phage on the Host – Harnessing the Microbiome for Disease Prevention and Therapy (USA/Online) January 2021

Trillions of microorganisms reside in the intestine and maintain gut homeostasis. Our laboratory has been focusing on identifying commensal bacteria that induce specific branches of immune cells in the intestine. We have succeeded in isolating bacterial consortia that stimulate targeted immune responses, including induction of $CD4^{+}Foxp3^{+}$ regulatory T (Treg) cells, TH17 cells, TH1, and CD8 T cells. The 17 Treg cell-inducing consortium is now under evaluation in a Phase 2 study for therapy in patients with ulcerative colitis. The 11 CD8 cell-inducing consortium is now under evaluation in Phase 1/2 studies in the US in combination with anti-PD1 mAb for therapy in patients with checkpoint inhibitor refractory melanoma, gastric cancer and colorectal cancer.

In addition to immune modulatory bacteria, we identified and isolated bile acid-metabolizing bacteria from the feces of centenarians. Centenarians display decreased susceptibility to ageing-associated illness, chronic inflammation and infectious disease. We found that centenarians have a distinct gut microbiome enriched in microbes capable of generating unique secondary bile acids (BAs), including isoallo-lithocholic acid (isoalloLCA). By screening bacterial isolates from a centenarian's fecal microbiota, we identified Odoribacteraceae strains as effective producers of isoalloLCA. Furthermore, we found that isoalloLCA has potent antimicrobial effects against gram-positive (but not gram-negative) multidrug-resistant pathogens, including *Clostridioides difficile* and *Enterococcus faecium*. These findings suggest that specific bile acid metabolism may be involved in reducing the risk of pathobiont infection, thereby potentially contributing to the maintenance of intestinal homeostasis. We have also succeeded in identifying trypsin-degrading gut bacteria and dermatitis-suppressing skin commensal bacteria. We anticipate our findings will assist in designing bacterial consortia that will be able to durably modify the microbiota and the host, resulting in the development of state-of-the-art therapeutics for numerous diseases.

Laboratory for
Skin Homeostasis

Team Leader: Masayuki Amagai

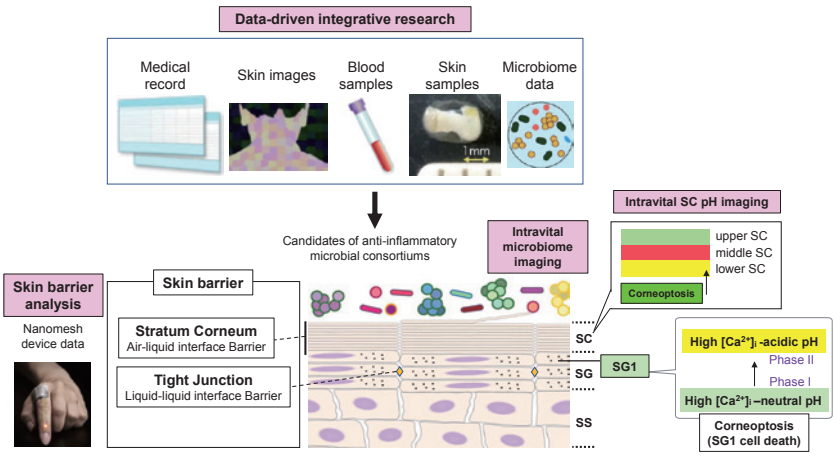


Figure: Comprehensive analysis of skin barrier homeostasis and development of corneotherapy
Our team is trying to clarify the mechanisms of skin barrier homeostasis by focusing on the stratum corneum (SC), tight junction (TJ), and SG1 cells. We established a live imaging system, focusing on a unique SG1 cell death termed 'corneoptosis' and SC-pH distribution. By using an optimized plasmid injection method to study the cornification process in mice, we found that the corneoptosis consists of two phases (I and II). We also study the SC-pH profile and host-microbe interactions on skin. Furthermore, we are conducting data-driven clinical research in order to stratify the diversity of AD pathophysiology and identify beneficial skin microbiota that have the potential to suppress inflammation. For this purpose, we are conducting association analysis with clinical and microbial data as well as integrating data from whole genome analysis and transcriptomic analysis using skin specimens from patients with AD.

The epidermis, the outer layer of the skin, has two sets of protective barriers, the stratum corneum (SC) and tight junctions (TJs). These two barriers prevent the easy penetration of external antigens into the body. The SC is unique, as it can maintain its homeostasis, even though it consists of dead keratinocytes (corneocytes). In addition, the SC is known as a habitat for skin microbiota and alterations in skin microbiota composition, termed dysbiosis, have been associated with chronic inflammatory conditions, such as atopic dermatitis (AD). Our group is trying to clarify (1) how SC homeostasis is maintained under normal conditions and how it is impaired and affects microenvironments of the skin during inflammation, and (2) how skin microbiota interacts with host epidermis to worsen or ameliorate the inflammatory state. Our experimental approaches are comprehensive, combining molecular biology, live imaging, microbiology, and data-driven clinical research.

We recently demonstrated via intravital imaging of mouse skin that a unique type of cell death, termed corneoptosis, of the uppermost stratum granulosum keratinocytes (SG1 cells) requires controlled intercellular acidification to convert SG1 cells into corneocytes and that the SC has three stepwise pH zones. In addition, we identified *Staphylococcus cohnii*, whose colonization is accompanied by activation of host glucocorticoid-related pathways and induction of anti-inflammatory genes in the skin and is therefore effective at suppressing inflammation in multiple dermatitis mouse models. Furthermore, we have succeeded in long-term continuous measurement (30h) of skin electrical resistance using nanomesh electrodes with excellent elasticity, durability, and air permeability. This enables us to measure dynamic change patterns of SC barrier functions of human skin. Combining these tools and techniques, and going back and forth between our basic science findings in mice and those in clinical science in humans, we aim to develop more targeted therapeutic approaches with fewer side effects for patients suffering from inflammatory skin diseases.

Recent Major Publications

Morimoto A, Fukuda K, Ito Y, Tahara U, Sasaki T, Shiohama A, Kawasaki H, Kawakami E, Naganuma T, Arita M, Sasaki H, Koseki H, Matsui T, Amagai M. Microbiota-Independent Spontaneous Dermatitis Associated with Increased Sebaceous Lipid Production in Tmem79-Deficient Mice. ***J Invest Dermatol*** 142, 2864-2872. e2866 (2022)

Miyamoto A, Kawasaki H, Lee S, Yokota T, Amagai M, Someya T. Highly Precise, Continuous, Long-Term Monitoring of Skin Electrical Resistance by Nanomesh Electrodes. ***Adv Healthc Mater*** 11, e2102425 (2022)

Ito Y, Amagai M. Controlling skin microbiome as a new bacteriotherapy for inflammatory skin diseases. ***Inflamm Regen*** 42, 26 (2022)

Invited presentations

Amagai M. "Homeostatic mechanisms of stratum corneum as niche for skin microbiota" The 51st of Annual Meeting of the Japanese Society for Immunology (Kumamoto, Japan) December 2022

Amagai M. "Homeostatic mechanisms of skin barrier and their disruption in skin inflammation" 12th Asian Dermatological Congress (Tokyo, Japan) August 2022

Amagai M. "Corneoptosis, new functional cell death and live imaging" The 121st Annual Meeting of the Japanese Dermatological Association (Kyoto, Japan/Online) June 2022

Laboratory for
Tissue Dynamics

Team Leader: **Takaharu Okada**

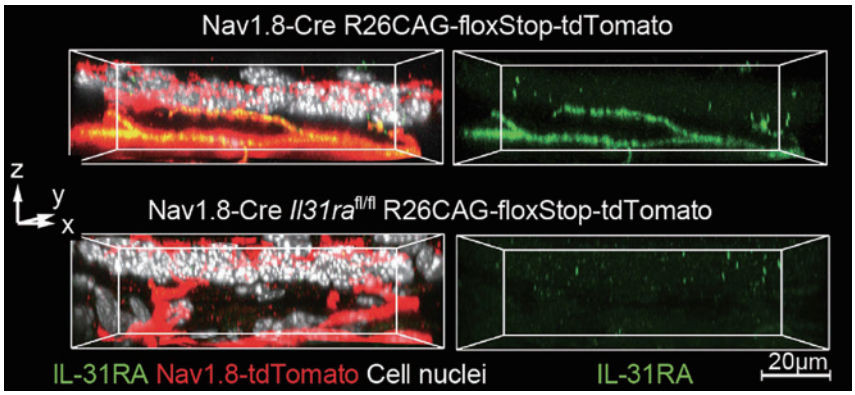


Figure: IL-31 receptor-expressing skin sensory nerves
Whole-mount confocal immunofluorescence images of the ear skin from control (Nav1.8-Cre R26CAG-floxStop-tdTomato) and sensory nerve-specific IL-31RA-deficient (Nav1.8-Cre I31ra$^{fl/fl}$ R26CAG-floxStop-tdTomato) mice. The images show horizontal views.

The goal of the laboratory is to understand the mechanisms that underlie tissue homeostasis and its breakdown during disease development. As a most recent focus, we have been studying the mechanisms by which sensory nerves are activated to induce pathogenic pruritus in inflammatory skin conditions such as atopic dermatitis. The therapeutic strategies for pruritus are currently undergoing a profound transformation and the IL-31 receptor is one of the major new targets. Our work provides direct evidence that the IL-31 receptor on sensory neurons (Figure), but not on keratinocytes, is essential for IL-31-induced itch. Moreover, our study demonstrates that sensory neuronal STAT3 is essential for IL-31-induced itch and further contributes to IL-31-independent itch associated with dermatitis. These are unexpected findings because previous reports suggested that the STAT molecules including STAT3 might play only modulatory roles in itch induced by type 2 cytokines including IL-31.

We have been also continuing our studies to understand the mechanisms of adaptive immune responses. Since 2018 before COVID-19 started, we have been collaborating with expert researchers in the field of drug delivery to investigate the mechanism by which an mRNA vaccine equipped with a novel lipid material elicits efficient $CD8^+$ T cell responses. Our work elucidates the *in vivo* cellular mechanism by which mRNA vaccine antigens are presented for activation of $CD8^+$ T cells.

Recent Major Publications

Yeh CH, Finney J, Okada T, Kurosaki T, Kelsoe G. Primary germinal center-resident T follicular helper cells are a physiologically distinct subset of CXCR5hiPD-1hi T follicular helper cells. ***Immunity*** 55, 272-289.e7 (2022)

Gomi M, Sakurai Y, Okada T, Miura N, Tanaka H, Akita H. Development of Sentinel LN Imaging with a Combination of HAase Based on a Comprehensive Analysis of the Intra-lymphatic Kinetics of LPs. ***Mol Ther*** 29, 225-235 (2021)

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

Invited presentations

Okada T. "The role for sensory neuronal IL-31 receptor and STAT3 in inflammatory itch" The 51st Annual Meeting of the Japanese Society for Immunology, Symposium 14 (Kumamoto, Japan) December 2022

Okada T. "Activation mechanisms of primary sensory neurons transmitting itch" The 30th International Symposium of Itch (Online) November 2021

Okada T. "Imaging analysis of epidermal sensory nerves and keratinocyte tight junctions" The 58th Annual Meeting of the Biophysical Society of Japan, Symposium 2S-7 (Online) September 2020

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

Laboratory for Metabolomics

Team Leader: **Makoto Arita**

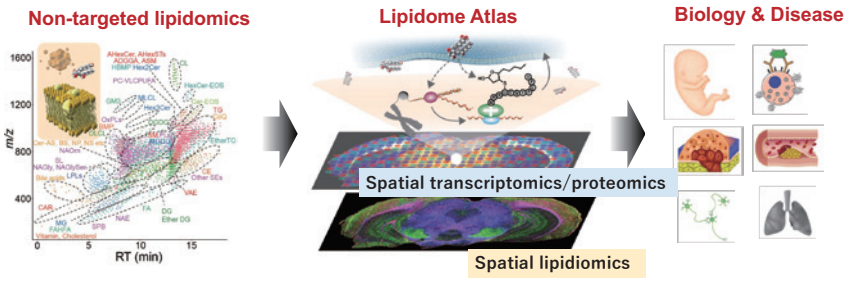


Figure: Innovative lipidomics for creation of the Lipidome Atlas
The Lipidome Atlas will facilitate the discovery of new biological systems shaped by lipid diversity, leading to an integrated understanding of lipid-centric biology.

Recent Major Publications

Iino Y, Naganuma T, Arita M. Dysregulated ceramide metabolism in mouse progressive dermatitis resulting from constitutive activation of Jak1. ***J Lipid Res*** 64, 100329 (2023)

Uchino H, Tsugawa H, Takahashi H, Arita M. Computational mass spectrometry accelerates C=C position-resolved untargeted lipidomics using oxygen attachment dissociation. ***Commun Chem*** 5, 162 (2022) selected in 2022 Editor's Highlights

Yoshida M, Ishihara T, Isobe Y, Arita M. Genetic deletion of Cyp4f18 disrupts the omega-3 epoxidation pathway and results in psoriasis-like dermatitis. ***FASEB J*** 36, e22648 (2022)

Invited presentations

Arita M. "Advanced lipidomics technology reveals the biology of lipid diversity and disease control" 11th International Singapore Lipid Symposium (iSLS11) (Singapore, Singapore) March 2023

Arita M. "Biology of LipoQuality and Lipidome Atlas" The 95th Annual Meeting of the Japanese Biochemical Society (Nagoya, Japan) November 2022

Arita M. "Cutting-edge lipidomics technology reveals the biology of lipid diversity and disease control" 17th International Conference on Bioactive Lipids in Cancer, Inflammation and Related Diseases (New Orleans, USA) November 2022

Arita M. "From LipoQuality to the Lipidome Atlas: Advanced lipidomics to elucidate the biology of lipid diversity and disease control" International Symposium for Lipid-based Multi-Omics (Daegu, South Korea) October 2022

Arita M. "Advanced non-targeted lipidomics to explore lipidome changes associated with aging and commensal microbiota" 62nd International Congress on the Bioscience of Lipids (ICBL2022) (Montreal, Canada) September 2022

Lipids constitute biological membranes and play a variety of other roles as energy sources, signaling molecules, and their precursors. Some lipids are biologically active as single molecules, while others are involved in the formation of membrane domains as molecular assemblies. Since lipids are extremely diverse molecules, the precise determination of different molecular species of lipid – a process we have termed "LipoQuality", is important for understanding their functions in physiology and disease, and for discovering novel bioactive lipids that may have therapeutic benefits. In general, dysregulated lipid metabolism is associated with diseases such as obesity, atherosclerosis, stroke, hypertension, and diabetes, and hence there is great interest in furthering our understanding of how they behave within complex biological systems. We aim to elucidate the mechanisms that create, regulate, and recognize lipid diversity as a spatiotemporal system by constructing a "Lipidome Atlas", as well as to elucidate diseases caused by its disturbance. The discovery of the significance of lipid molecules involved in various life phenomena and their diversity through non-targeted, highly accurate, and in-depth original technologies is expected to have a ripple effect on a wide range of life science fields and contribute to medical science and a healthy and long-lived society based on scientific evidence.

Laboratory for Microbiome Sciences

Team Leader: Hiroshi Ohno

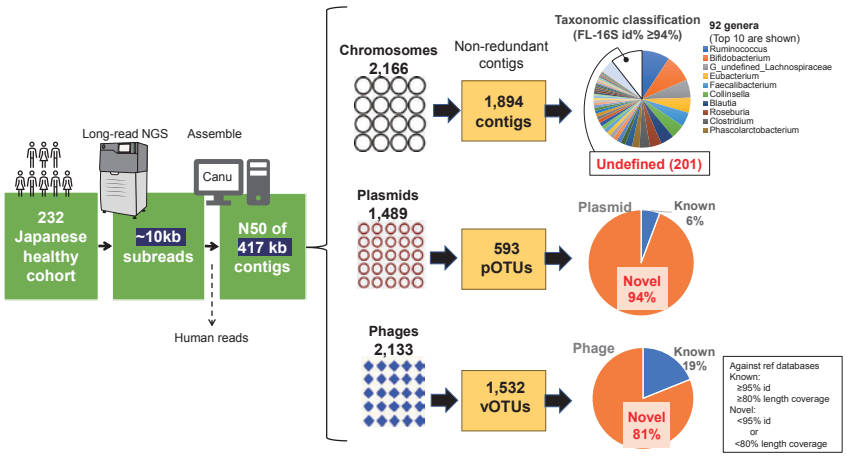


Figure: Reconstructing complete bacterial genomes, plasmids, and viral genomes directly from metagenomic data

Using a long-read sequencing technique, we analyzed 232 fecal metagenomic DNA samples from healthy Japanese individuals. Obtained reads with an average length of ~10 kb were brought for *de novo* assembly and the resulting contigs showed the average N50 of 416.64 kb. From these high-quality contigs, we identified 1,894 non-redundant complete/near-complete bacterial chromosomes (≥1 Mb). Among them, 1,693 (90%) were assigned to known species based on a similarity search with full-length 16S rRNA genes; the remaining 201 (10%) were novel species that are noted as 'undefined' in the current database.
Furthermore, we identified 593 non-redundant plasmids and 1,532 non-redundant bacteriophages (phages). Among them, 559 (94 %) of the plasmids and 1,242 (81 %) of the phages were novel.

Recent Major Publications

Nagata N, Takeuchi T, Masuoka H, Aoki R, Ishikane M, Iwamoto N, Sugiyama M, Suda W, Nakanishi Y, Terada-Hirashima J, Kimura M, Nishijima T, Inooka H, Miyoshi-Akiyama T, Kojima Y, Shimokawa C, Hisaeda H, Zhang F, Yeoh YK *et al*. Human gut Microbiota and its metabolites impact immune responses in COVID-19 and its complications. ***Gastroenterology*** 164, 272-288 (2023)

Li Y, Watanabe E, Kawashima Y, Plichta DR, Wang Z, Ujike M, Ang QY, Wu R, Furuichi M, Takeshita K, Yoshida K, Nishiyama K, Kearney SM, Suda W, Hattori M, Sasajima S, Matsunaga T, Zhang X, Watanabe K *et al*. Identification of trypsin-degrading commensals in the large intestine. ***Nature*** 609, 582-589 (2022)

Furuhashi H, Takayasu L, Isshi K, Hara Y, Ono S, Kato M, Sumiyama K, Suda W. Effect of storage temperature and flash-freezing on salivary microbiota profiles based on 16S rRNA-targeted sequencing. ***Eur J Oral Sci*** 130, e12852 (2022)

Invited presentations

Suda W. "Human × Microbiome" Front Line ~Symbiosis between the human body and micro-organisms, the challenge of the unknown~, LIFE University Human & Being School (Online) October 2022

Suda W. "Metagenomics of human microbiome" The 59th Congress of Japanese Society for Surgical Metabolism and Nutrition (Ibaraki, Japan) July 2022

The Laboratory for Microbiome Sciences has been engaged in the study of the complex interactions between symbiotic microbial ecosystems and their hosts. Through the development of original experimental and informatics-based technologies using state-of-the-art sequencers, we aim to comprehensively understand the whole "picture" of microbiome structures.

We have been working on developing a novel pipeline for high-resolution metagenome analysis using long-read sequencers. These instruments enable us to reconstruct complete bacterial genomes, plasmids, and viral genomes directly from metagenomic data (Figure). High-quality genome catalogs constructed here are also expected to serve as references for future meta-transcriptome and meta-proteome analysis. Furthermore, we optimized protocols for human fecal DNA extraction and developed the original method for recovering microbial DNA from extremely low biomass.

These technology developments have given us insights into the relationship between diseases and microbiome. We reported an alteration in gut microbiome in multiple sclerosis patients according to disease severity and, using a data-driven approach, identified and isolated candidate strains correlated with pathogenesis. We also discovered characteristic alterations of gut microbiomes in COVID-19 patients uniquely found in a Japanese cohort. We further reported that the salivary microbiome could be used for non-invasive diagnosis of Primary sclerosing cholangitis (PSC) and IgA nephropathy.

We also have been focused on the temporal dynamics of gut microbiomes. We analyzed the gut microbiome from birth to death in mice and reported that most of the lifespan-related microbes are "life-core" and are observed at most of the periods throughout life. We are now planning to perform a high-resolution time-series analysis of gut microbiome by developing an automatic sampling device for disease model mice. Understanding the relationship between microbial dynamics and the host could lead to future control of human health based on gut microbiome time-course monitoring.

Laboratory for Integrated Cellular Systems

Team Leader: Katsuyuki Yugi

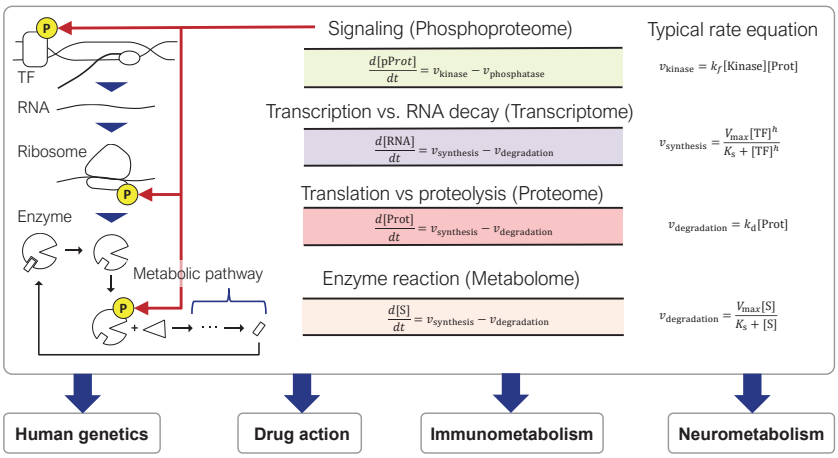


Figure: Differential equation representation of a trans-omic network and its application to related fields

We integrate multiple omic data with postulating a dynamic picture of cellular processes driven by reaction kinetics. Each reaction rate (terms represented by '*v*') is a function of the number of molecules that belong to the same or other omic layers. We apply this methodology to characterize complex metabolic regulatory systems related to drug action, the nervous system, the immune system, human genetics, etc.

Recent Major Publications

†Okamoto L, †Watanabe S, †Deno S, Nie X, Maruyama J, Tomita M, Hatano A, Yugi K. Meta-analysis of transcriptional regulatory networks for lipid metabolism in neural cells from schizophrenia patients based on an open-source intelligence approach. ***Neurosci Res*** 175, 82-97 (2022)

Kokaji T, Eto M, Hatano A, Yugi K, Morita K, Ohno S, Fujii M, Hironaka K, Ito Y, Egami R, Uematsu S, Terakawa A, Pan Y, Maehara H, Li D, Bai Y, Tsuchiya T, Ozaki H, Inoue H, Kubota H, Suzuki Y, Hirayama A, Soga T, Kuroda S. In vivo transomic analyses of glucose-responsive metabolism in skeletal muscle reveal core differences between the healthy and obese states. ***Sci Rep*** 12, 13719 (2022)

Terakawa A, Hu Y, Kokaji T, Yugi K, Morita K, Ohno S, Pan Y, Bai Y, Parkhitko AA, Ni X, Asara JM, Bulyk ML, Perrimon N, Kuroda S. Trans-omics analysis of insulin action reveals a cell growth subnetwork which co-regulates anabolic processes. ***iScience*** 25, 104231 (2022)

Invited presentations

Yugi K. "Integration of multiple omic data on the basis of reaction kinetics and open source intelligence" The 95th Annual Meeting of the Japanese Biochemical Society (Nagoya, Japan) November 2022

Yugi K. "Trans-omic analysis of pharmacological actions" Niigata University (Niigata, Japan) October 2022

Yugi K. "Integration of multiple omic data on the basis of reaction kinetics and open source intelligence" HU-RIKEN-OIST Joint Workshop "Understanding Life and Physical Phenomena using Mathematical Models and Analysis" (Higashi-hiroshima, Japan) June 2022

Metabolism is a biological process involved in various diseases, not only metabolic diseases such as obesity and diabetes, but also autoimmune diseases, psychiatric diseases, and cancer. Biochemical metabolic pathways consist of myriad feedback loops and branch points, thereby defying simple causation analyses frequently performed in linear cascades. Furthermore, metabolism undergoes multiplexed regulation from other omic layers: phosphorylation of enzymes by signal transduction (phosphoproteome), transcriptional regulation (transcriptome), translational regulation (expression proteome), etc. Our research interest is to understand intracellular metabolism and its regulatory mechanisms as a system of biochemical reactions in dynamic, macroscopic, and quantitative contexts. We employ the methodology of 'trans-omics' to reconstruct global metabolic regulatory networks that span multiple omic layers, not as a group of indirect statistical correlations but as chains of direct mechanistic interactions on the basis of reaction kinetics (Yugi *et al.*, *Trends Biotechnol.*, 2016; Yugi and Kuroda, *Cell Syst.*, 2017; Yugi and Kuroda, *Curr. Opin. Syst. Biol.*, 2018; Yugi *et al.*, *Curr. Opin. Syst. Biol.*, 2019; Okamoto *et al.*, *Neurosci. Res.* 2022). Interdisciplinary approaches, such as 'wet' biology experiments and 'dry' data analyses, such as mathematical models and statistical methods, are utilized to characterize the global metabolic regulatory networks. The network reconstruction is performed based on comprehensive measurement data, public databases, and a kinetic picture of the cellular processes (Figure). The comprehensive data of multiple omic layers should be measured under identical conditions preferably in a time-series manner so that one can construct mathematical models of the multi-layered network for subsequent systems biological analyses. We eventually aim to reveal the chain of logic from individual biochemical reactions to omics-scale metabolic regulatory systems.

Laboratory for
Metabolic Networks

Team Leader: **Toshimori Kitami**

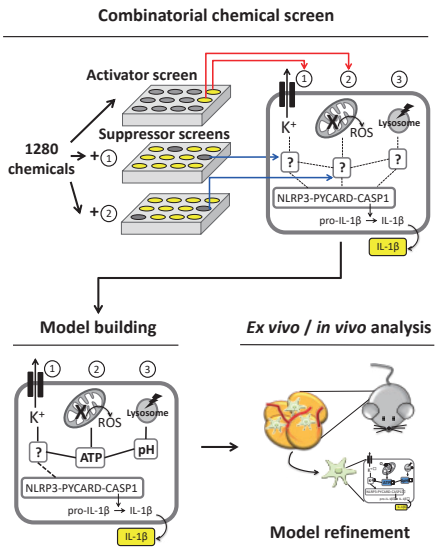


Figure: Schematic of our chemical screening strategy for uncovering the role of mitochondria in NLRP3 inflammasome activation

Recent Major Publications

Kobayashi A, Azuma K, Takeiwa T, Kitami T, Horie K, Ikeda K, Inoue S. FRET-based respirasome assembly screen defines potential therapeutic intervention that improves muscle mitochondrial respiration and exercise performance. ***Nat Commun*** 14, 312 (2023)

Kitami T, Fukuda S, Kato T, Yamaguti K, Nakatomi Y, Yamano E, Kataoka Y, Mizuno K, Tsuboi Y, Kogo Y, Suzuki H, Itoh M, Morioka MS, Kawaji H, Koseki H, Kikuchi J, Hayashizaki Y, Ohno H, Kuratsune H, #Watanabe Y. Deep phenotyping of myalgic encephalomyelitis / chronic fatigue syndrome in Japanese population. ***Sci Rep*** 10, 19933 (2020)

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

Invited presentations

Kitami T. "Dissecting the mitochondrial stress response network using chemical screening and metabolomics" Symposium. Japanese Biochemical Society Annual Meeting (Nagoya, Japan) November 2022

Mitochondria are dynamic organelles central to energy homeostasis, intermediary metabolism, ion homeostasis, and cell death. Inherited defects in mitochondria cause the most common inborn errors of metabolism, but a growing body of evidence also links mitochondria to more complex diseases including type 2 diabetes, cardiovascular disease, and neurodegeneration. Despite our basic understanding of mitochondrial functions, the precise 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 and to develop novel therapeutics centered on mitochondria.

Towards our goal, we initiated chemical screens focusing on the role of mitochondria in inflammation and neuronal cell death, both of which converge to accelerate neurodegenerative processes such as Parkinson's disease. In macrophages, we identified small molecules that specifically block mitochondrial damage-induced activation of the NLRP3 inflammasome pathway. In neuronal cells, we identified small molecules that block neuronal death triggered by mitochondrial inhibitors. We are currently working to test our lead compounds and molecular insights gained from these studies in mouse models of Parkinson's disease and rare mitochondrial diseases. We are also working to establish methods to manipulate cellular metabolism in a cell type-specific manner in mice to dissect and computationally model metabolic cooperativity between cell types in neurodegeneration. These tools will be useful for understanding how mitochondrial damage can be buffered by metabolic adaptation of neighboring cells and how disruptions in these interactions accelerate neurodegenerative processes.

In addition, we are examining the role of mitochondria in other complex disease pathways by taking advantage of large-scale omics datasets generated at RIKEN IMS. We hope that our multi-omics and chemical biology efforts will not only help clarify the role of mitochondria in complex diseases but also point to common therapeutic strategies for a variety of mitochondria-related disorders.

Laboratory for

Epigenome Inheritance

Team Leader: **Azusa Inoue**

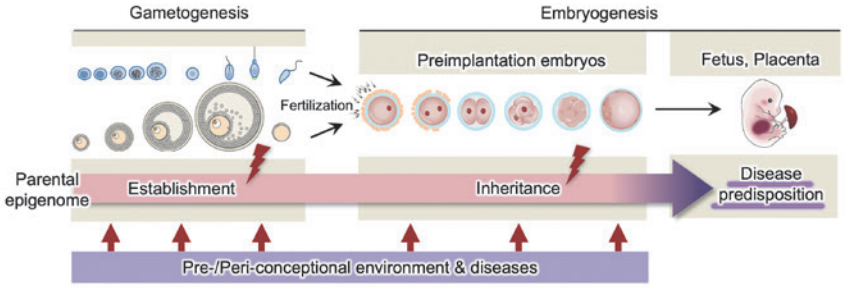


Figure: Parental programming hypothesis
Parental epigenomes are established during gametogenesis, and partially inherited by embryos to regulate gene expression in the fetus and placenta. Our lab investigates the mechanisms and functions of histone modification inheritance and the effects of the pre-/peri-conceptional parental environment on epigenetic inheritance and disease predisposition in the offspring.

Genetic information is passed on to the offspring through oocytes and sperms (gametes) and greatly contributes to their phenotypes and disease susceptibility. Recent studies have revealed that the parental genomes in mammals are accompanied by epigenetic information that is also passed on to the next generation. Defects in epigenetic inheritance lead to various phenotypes in prenatal and postnatal growth in mice. This raises the possibility that epigenetic changes in gametes, possibly induced by the parental environment, might influence disease susceptibility in the offspring via epigenetic inheritance mechanisms across generations.

Our laboratory is studying the mechanisms and functions of transgenerational inheritance of histone post-translational modifications (hPTMs) in mammals. Our specific aims are as follows (Figure): (1) To understand the molecular basis and functions of hPTM establishment and inheritance during gametogenesis and embryogenesis. (2) To link hPTM inheritance to the pre- and peri-conceptional parental environment; (3) To understand how the parental environment might influence disease susceptibility in the offspring. To address these questions, we integrate cutting-edge low-input epigenomic technologies, reproductive engineering techniques, and genome/epigenome-modified mouse models. This study will not only reveal how lifestyle influences epigenetic memory and gene expression in cells but will also call for an evaluation of the contribution of epigenetic mechanisms to hereditary diseases. It will provide a basis for new approaches to preventive and predictive medicine.

Recent Major Publications

Inoue A†. Noncanonical imprinting: intergenerational epigenetic inheritance mediated by Polycomb complexes. ***Curr Opin Genet Dev*** 78,102015, 1-9 (2023)

Matoba S*, Kozuka C*, Miura K, Inoue K, Kumon M, Hayashi R, Ohhata T, Ogura A, Inoue A*†. Noncanonical imprinting sustains embryonic development and restrains placental overgrowth. ***Genes Dev*** 36, 483-494 (2022)

Mei H*, Kozuka C, Hayashi R, Kumon M, Koseki H, Inoue A*†. H2AK119ub1 guides maternal inheritance and zygotic deposition of H3K27me3 in mouse embryos. ***Nat Genet*** 53, 539-550 (2021)

Invited presentations

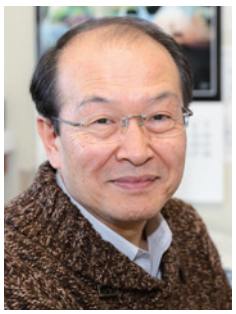
Inoue A. "Genomic imprinting mediated by maternal histone modifications" The 2nd Subhash Mukhopadhyay Symposium (India/Online) January 2023

Inoue A. "Genomic imprinting by maternal Polycomb repressive complexes" The 20th International Symposium on Developmental Biotechnology at the Korean Society of Animal Reproduction and Biotechnology (Korea/Online) October 2022

Inoue A. "Genomic imprinting by Polycomb repressive complexes" University of California at Davis, Microbiology and Molecular Genetics, Invited seminar (USA/Online) May 2022

Inoue A. "Mechanism and functions of non-canonical imprinting" EMBO Workshop 2022, Molecular Mechanisms of Developmental and Regenerative Biology (Kyoto, Japan/Online) April 2022

Inoue A. "Maternal epigenetic inheritance by Polycomb repressive complexes" EMBO meeting CellBio Virtual 2021 (USA/Online) December 2021



Drug Discovery Antibody Platform Unit

Unit Leader: Takashi Saito

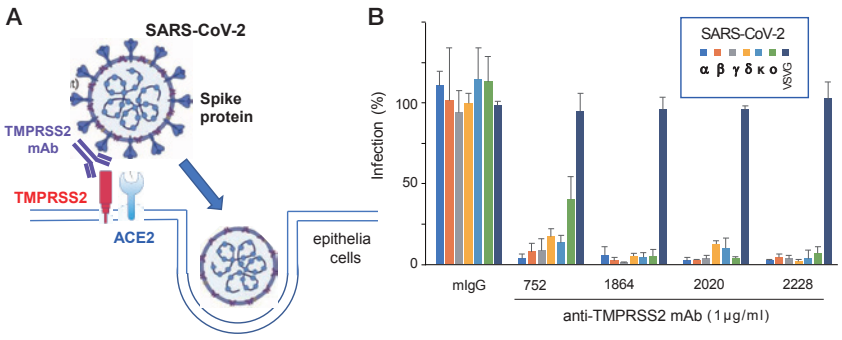


Figure: TMPRSS2 mAbs inhibit infection by multiple variants of SARS-CoV-2

A) Infection of epithelial cells by SARS-CoV2 through binding of the Spike protein to the ACE2 receptor. TMPRSS2-mediated cleavage of Spike is required for ACE2 binding. TMPRSS2 mAbs block the binding and internalization of multiple SARS-CoV-2 Variants of Concern (VOC).
B) Inhibition of infection of epithelial cells (Cal-3) with various SARS-CoV-2 VOC by four representative TMPRSS2 mAbs. Controls for these experiments are mouse IgG (mIgG) and vesicular stomatitis virus G (VSVG), an unrelated virus.

The Drug Discovery Antibody Platform Unit (Ab Platform) is one of nine Drug Discovery Basic Units in the Drug Discovery and Medical Technology Platform (DMP). DMP develops innovative new pharmaceuticals to transfer the findings from basic research performed at the institute to the clinics. The Ab Platform creates new monoclonal Abs (mAb) for therapeutic purposes of preventing/modulating various diseases.

We have recently established mAbs against human TMPRSS2 for the purpose of inhibiting infection with SARS-CoV2. TMPRSS2 is critical for viral entry, and small molecule inhibitors of TMPRSS2 have been shown to inhibit SARS-CoV2 infection, although these compounds also have side effects and are unstable. Therefore, mAbs against TMPRSS2 may have a more specific inhibitory function and better modulate COVID-19. Indeed, some mAbs showed strong inhibition of infection by any of the currently circulating SARS-CoV2 variants *in vitro*. The binding affinity of the mAbs to TMPRSS2 is in the nM range and the binding epitopes were identified using peptide mapping and cryo-EM. The *in vivo* blocking function of the mAb was shown using a Cynomolgus monkey infection model; the mAb inhibited expansion of the virus, particularly in the lung.

We have also developed and analyzed a mAb against a human hepatitis B virus (HBV) receptor, NTCP (sodium-taurocholate co-transporting polypeptide). Since the preS1-domain of HBV binds to NTCP, it could be a key target for the development of HBV-blocking agents. Indeed, the established mAb inhibits the entry of HBV into human liver cells *in vitro* and inhibits *in vivo* infection in human-liver chimeric mice. Since the mAb has the advantage of not blocking bile acid import by NTCP, it becomes an ideal specific inhibitor of HBV infection without side effects. Currently, humanized NTCP mAbs are being developed and a trial to improve the binding affinity is being undertaken for eventual clinical applications.

We additionally established mAbs against CRTAM (Cytotoxic and Regulatory T Cell Molecule). CRTAM is critical for the development/function of $CD4^+$ cytotoxic T cells (CTL), which are thought to be essential for late-phase induction of experimental autoimmune encephalomyelitis (EAE). Indeed, preliminary results showed significant inhibition of the late phase of EAE induction by administration of a CRTAM mAb, suggesting its potential therapeutic use.

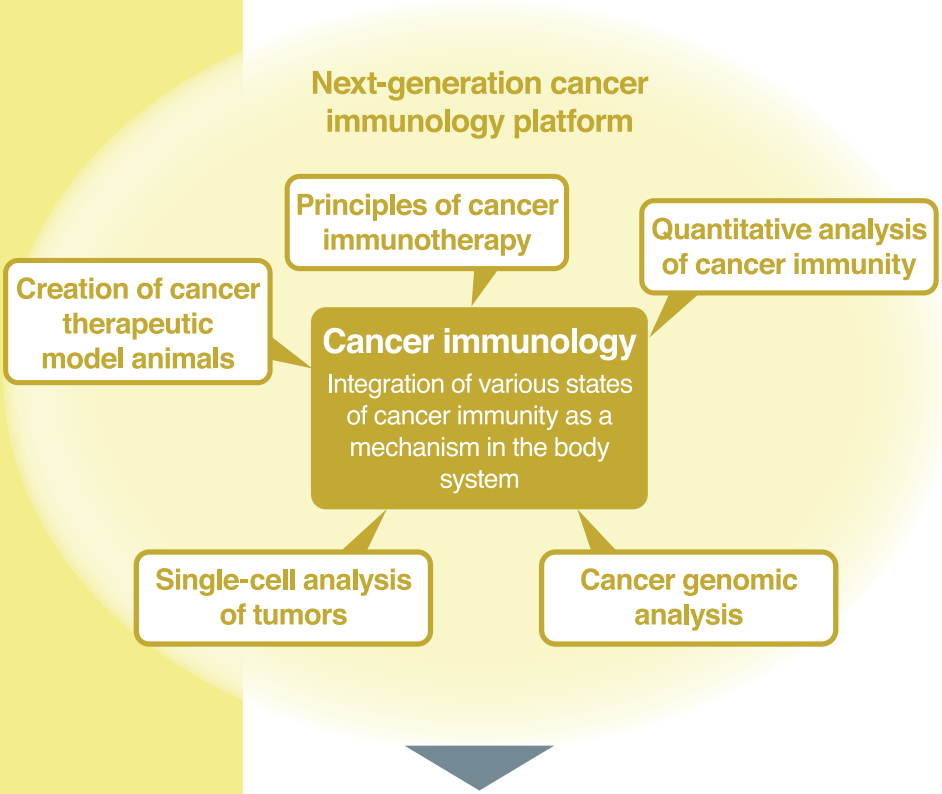
Recent Major Publications

Takemori T, Sugimoto-Ishige A, Nishitsuji H, Futamura Y, Harada M, Kimura-Someya T, Matsumoto T, Honma T, Tanaka M, Yaguchi M, Isono K, Koseki H, Osada H, Miki D, Saito T, Tanaka T, Fukami T, Goto T, Shirouzu M, Shimotohno K, Chayama K. Establishment of a monoclonal antibody against human NTCP that blocks HBV infection. ***J Virol*** 96, e0168621 (2022) doi: 10.1128/JVI.01686-21

Kumagai A, Nara T, Uematsu M, Kakinuma Y, Saito T, Masuda K. Development and characterization of a unique anti-IgE monoclonal antibody cross-reactive between human and canine IgE. ***Immun Inflamm Dis*** 9, 1740-1748 (2021)

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)

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
Medical Science Mathematics

Team Leader: Tatsuhiko Tsunoda

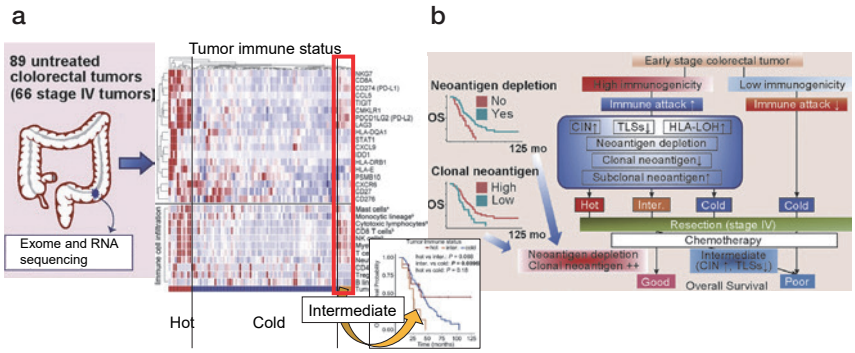


Figure: Results from our analysis of advanced colorectal cancer

(a) Discovery of new subtype of advanced colorectal tumors and (b) neoantigen status vs. survival. (Sugawara T., ..., Tsunoda T. ***iScience*** 25, 103740 (2022).)

Recent Major Publications

Sugawara T, ..., Lysenko A, ..., Boroevich KA, ..., Tsunoda T. Immune subtypes and neoantigen-related immune evasion in advanced colorectal cancer. ***iScience*** 25, 103740 (2022)

Matsuo H, Kamatani T, Hamba Y, Boroevich KA, Tsunoda T. Association between high immune activity and worse prognosis in uveal melanoma and low-grade glioma in TCGA transcriptomic data. ***BMC Genomics*** 23, 351 (2022)

Yamaguchi K, ... Tsunoda T, ..., Kochi Y. Splicing QTL analysis focusing on coding sequences reveals mechanisms for disease susceptibility loci. ***Nat Commun*** 13, 4659 (2022)

In our laboratory, we aim to understand disease dynamics and immunity at the molecular level to conquer diseases such as cancer. Effective utilization of rapidly developing omic profiling technologies and the introduction of personalized/precision/preventive medicine have become major goals of medical research, shifting away from traditional approaches that do not adequately consider the individuality 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 big data such as patient omics, diagnostic images, and clinical data, to discover novel causes/features of diseases. Next, we classify each disease into finer categories using molecular profiles and clarify underlying causal mechanisms with systems-based approaches. Last, we apply mathematical and machine learning techniques to infer optimal therapy for each patient to guide treatment decisions by their hospital or clinic. In this way, we conduct biomedical science research, making full use of state-of-the-art omics profiling technologies, mathematics, and computational science. Our current research projects include (1) tumor microenvironment analysis, (2) contribution to the International Cancer Consortium (ICGC), (3) competitions for cancer multi-omics analyses, (4) an original paradigm for deep learning (DeepInsight suite), (5) prediction models and biomedical analyses with machine/deep learning, (6) prediction of post-translational modifications, (7) WGS/WES analyses, (8) GWAS, and new projects: (9) chromatin structure and lincRNA functionality, and (10) analysis methods for new experimental technologies, e.g. nanopore and spatial omics.

Laboratory for
Cancer Genomics

Team Leader: **Hidewaki Nakagawa**

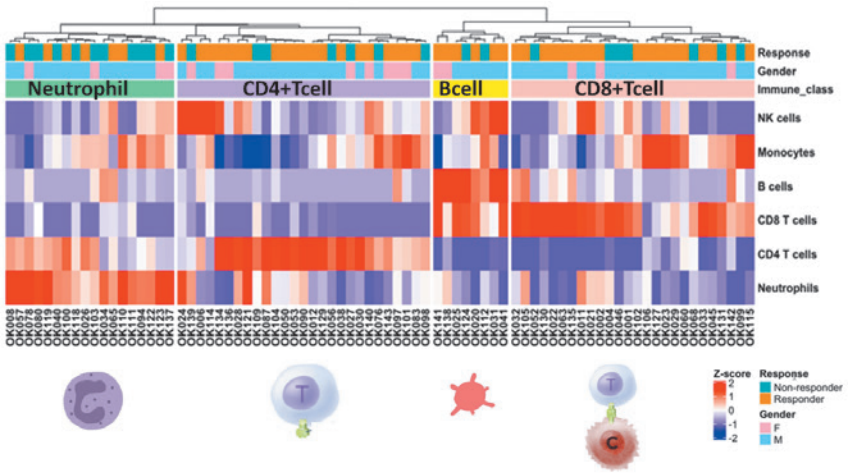


Figure:
Unsupervised clustering of ESCC tissues by six gene expression signatures related to immune cells (NK cells, Monocytes, B cells, $CD8^+$T cells, $CD4^+$T cells, and Neutrophils).

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) and RNA sequencing (RNA-seq). Furthermore, cancer also has been proven to be an "immune disease", with a variety of features 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 human cancer, we have been utilizing WGS and RNA-seq analysis for cancer. These approaches, combined with statistical methods and recent single-cell technologies, can clarify the underlying carcinogenesis and cancer immunology and achieve a molecular sub-classification of cancer, which will facilitate the discovery of biomarkers and personalized cancer medicine.

Recent Major Publications

Okawa Y, Iwasaki Y, Johnson TA, Ebata N, Inai C, Endo M, Maejima K, Sasagawa S, Fujita M, Matsuda K, Murakami Y, Nakamura T, Hirano S, Momozawa Y*, and Nakagawa H*. Hereditary cancer variants and homologous recombination deficiency in biliary tract cancers. ***J Hepatol*** 78, 333-342 (2023)

Fujita M, Chen MM, Siwak DR, Sasagawa S, Arihiro M, Arihiro K, Ono A, Miura R, Osawa-Tatsuguchi A, Maejima K, Aikata H, Ueno M, Hayami S, Yamaue H, Chayama K, Lu Y, Liang H, Nishizuka SS, and Nakagawa H*. Proteogenomic characterization of virus-associated liver cancers reveals potential subtypes and therapeutic targets. ***Nat Commun*** 13, 6481 (2022)

Sasagawa S, Kato H, Nagaoka K, Sun C, Imano M, Sato T, Johnson TA, Fujita M, Maejima K, Okawa Y, Kakimi K, Yasuda T, and Nakagawa H*. Immuno-genomic profiling of biopsy specimens predicts neoadjuvant chemotherapy response in esophageal squamous cell carcinoma. ***Cell Rep Med*** 3, 100705 (2022)

Invited presentations

Nakagawa H. "Cancer genomics and genomic medicine related with tumor immunology" The 26th Annual Meeting of the Japanese Association of Cancer Immunology (Matsue, Japan) July 2022

Nakagawa H. "Proteo-Genomic Characterization of Japanese Primary Liver Cancers Identifies Novel Subtypes and Therapeutic Strategies" The Asian Pacific Association for the Study of the Liver (Tokyo, Japan) June 2022

Okawa Y and Nakagawa H. "Hereditary Cancer Gene Variants and Homologous Recombination Deficiency in Biliary Tract Cancer" The 34th Meeting of Japanese Society of Hepato-Biliary-Pancreatic Surgery (Ehime, Japan) June 2022

Nakagawa H. "Cancer immunogenomics and immune classification of cancer" The 19th Annual Meeting of the Japan Research Association for Immuno-therapeutics (Tokyo, Japan) May 2022

Nakagawa H. "Proteo-Genomic Characterization of Japanese Primary Liver Cancers Identifies Novel Subtypes and Therapeutic Strategies" The 57th Annual Meeting of Liver Cancer Study Group of Japan (Tokyo, Japan) May 2022

Laboratory for
Immunotherapy

Team Leader: **Shin-ichiro Fujii**

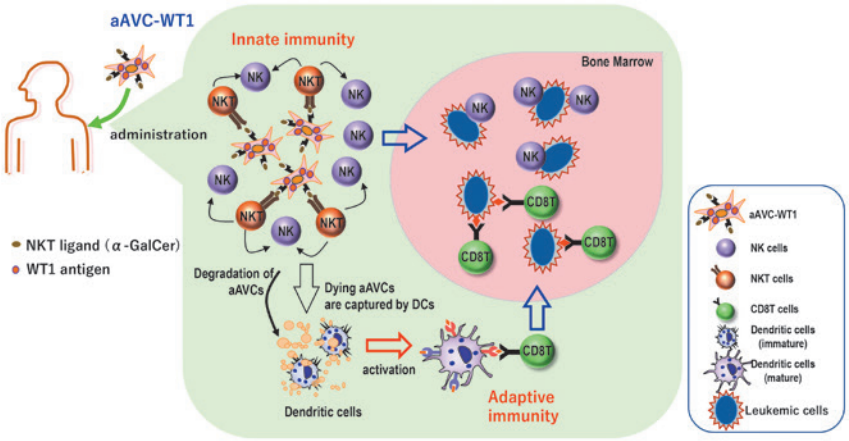


Figure: Development of therapeutic cellular drug "artificial adjuvant vector cells"

Since tumors are often composed of a mixture of HLA class I^- and class I^+ cells, both innate and adaptive immunity are crucial for cancer immune surveillance. However, precise therapeutic strategies to restore such surveillance in cancer patients have yet to be developed. DCs, as "nature's adjuvants", play a pivotal role in determining the character and magnitude of an immune response. Therefore, we have studied the role of DCs *in situ* for anti-tumor immunity by focusing on the link between innate and adaptive immunity. As an *in vivo* DC targeting strategy, we have established artificial adjuvant vector cells (aAVCs) by using $CD1d^+$allogeneic cells loaded with α-GalCer, a ligand for NKT cells, and transfected with tumor antigen-encoding mRNA, thus combining the adjuvant effects of NKT cell activation with delivery of antigen to DCs. This approach can lead to the generation of long-term memory T cells and effective anti-tumor immunity. As a first pipeline of aAVC system, we applied aAVC-WT1 to refractory or relapsed acute myelogenous leukemia in phase I clinical trial.

Recent Major Publications

Iyoda T, Shimizu K, Kawamura M, Shing J, Watanabe T, Fukunaga K, Nushiroda T, Saka H, Kitagawa C, Shimamatsu S, Takenoyama M, Suehiro Y, Imai T, Shingani A, Ito S, Fujii S. Augmenting Granzyme B-Expressing NK Cells by Invariant NKT Ligand-Loaded APCs in Patients with Postoperative Early Stage Non-Small Cell Lung Cancer: Results of a Randomized Phase II Study. ***ImmunoHorizons*** 7, 1-16 (2023)

Fujii S, Kawamata T, Shimizu K, Nakabayashi J, Yamasaki S, Iyoda T, Shinga J, Nakazato H, Sanpei A, Kawamura M, Ueda S, Dörrie J, Mojsov S, Dhodapkar MV, Hidaka M, Nojima M, Nagamura F, Yoshida S, Goto T, Tojo A. Reinvigoration of innate and adaptive immunity via therapeutic cellular vaccine for patients with AML. ***Mol Ther Oncolytics*** 27, 315-332 (2022)

Shimizu K, Ueda S, Kawamura M, Satoh M, Fujii S. A single immunization with cellular vaccine confers dual protection against SARS-CoV-2 and cancer. ***Cancer Sci*** 113, 2536-2547 (2022)

Invited presentations

Fujii S. "The immunotherapy applicable to cancer and infectious diseases, artificial adjuvant vector cells (aAVCs)"The 37th Annual meeting of the Japanese Society for the Study of Xenobiotics (Yokohama, Japan) November 2022

Fujii S. "Vaccine design to stimulate T-cell immunity against infectious diseases" Chemo-Bio Informatic Society Annual Meeting 2022 (Tokyo, Japan) October 2022

Fujii S. "Development of a new type of therapeutic cancer vaccine inducing multifunctional immunity, artificial adjuvant vector cells" 2022 Taiwan-Japan Cancer Immunotherapy Conference (Online) August 2022

Fujii S. "Therapeutic cancer immunotherapy linking innate immunity and adaptive immunity, artificial adjuvant vector cells" The 43rd Annual Meeting of the Japanese Society of Inflammation and Regeneration (Hyogo, Japan) July 2022

Fujii S. "Development of artificial adjuvant vector cells (aAVCs)" The 70rh Drug discovery pharmacology forum (Online) January 2022

The aims of the laboratory are: 1) basic study of cancer immunology and 2) translational research (TR) in immunotherapy. Immunotherapy can stimulate the activities of specific components of the immune system or counteract signals produced by cancer cells that suppress immune responses. Although the successes of current immunotherapy represent a clinical turning point, its efficacy is still limited. We have studied several projects based on innate immunity-driven cancer immunology. First, we invented a new type of immunotherapy, called artificial adjuvant vector cells (aAVC) which is a unique drug delivery platform composed of NKT cell ligand/CD1d complex and a tumor-associated antigen. We have accomplished the first in human, investigator-initiated Phase I clinical trial of aAVC-expressing the Wilms' tumor 1 antigen (WT1) (aAVC-WT1) against relapsed and refractory acute myelogenous leukemia (AML) in collaboration with the Institute of Medical Science, the University of Tokyo (IMSUT). As a proof of concept, we first verified the safety and immune response of aAVC-WT1 in humans. Subsequently, the Phase II study is ongoing for patients with AML. In addition, we have been working on some other TR projects aimed at clinical studies. Second, we are engaged in the multi-omics analysis of the tumor microenvironment, including neoantigen-specific T cell responses. Third, we reported a memory-like long-lived invariant NKT cell subset with strong antitumor effects and have been characterizing these cells in terms of intrinsic and extrinsic factors. In addition to our own projects, we have some collaborative projects; 1) the functional evaluation of the human immune system as the support institute for vaccine development (SCARDA project) and 2) the immunological analysis of the COVID-19 vaccine in cancer patients.

Laboratory for
Human Disease Models

Team Leader: **Fumihiko Ishikawa**

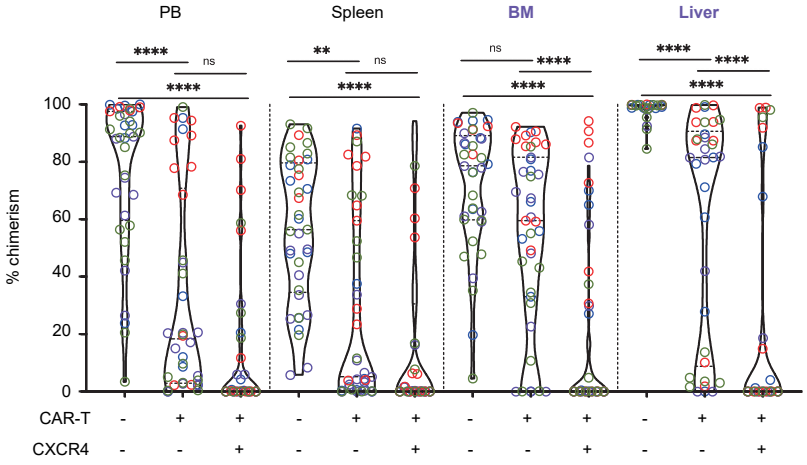


Figure:
Effect of a single injection of CD25-targeting CAR-T cells with and without CXCR4 to % human AML cells in peripheral blood (PB), bone marrow (BM), spleen and liver of AML PDX mice. Following 2.5e6 CD25-targeted CAR-T cell injection, treatment efficacy was variable, with residual AML cells in BM and spleen. With an additional engineering of CXCR4 expression, CAR-T cell efficacy improved, eradicating AML cells in BM and liver as well as PB and spleen (****p<0.0001 and **p<0.01 by two tailed t-test).

Recent Major Publications

Chuprin J, Buettner H, Seedhom MO, Greiner DL, Keck JG, Ishikawa F, Shultz LD, Brehm MA. Humanized mouse models for immuno-oncology research. ***Nat Rev Clin Oncol*** 20, 192-206 (2023)

Hashimoto M, Saito Y, Nakagawa R, Ogahara I, Takagi S, Takata S, Amitani H, Endo M, Yuki H, Ramilowski JA, Severin J, Manabe R, Watanabe T, Ozaki K, Kaneko A, Kajita H, Fujiki S, Sato K, Honma T, Uchida N, Fukami T, Okazaki Y, Ohara O, Shultz LD, Yamada M, Taniguchi S, Vyas R, De Hoon M, Momozawa Y, Ishikawa F*. Combined inhibition of XIAP and BCL2 drives maximal therapeutic efficacy in genetically diverse aggressive Acute Myeloid Leukemia. ***Nat Cancer*** 2, 340-356 (2021)

Saito Y, Shultz LD, Ishikawa F*. Understanding normal and malignant human hematopoiesis using next-generation humanized mice. ***Trends Immunol*** 41, 706-720 (2020)

Invited presentations

Itoh-Nakadai A. Educational Session "Elucidation of the pathogenesis and treatment of AML in animal models" The 84th Annual Meeting of the Japanese Society of Hematology (Online) October 2022

Ishikawa F. "Identification of vulnerabilities in genetically-complex AML" The Annual Conference of European Hematology Association (Online) May 2021

Hashimoto M. Symposium for AML "Integrative transcriptomic and chemical screening identifies patient-specific vulnerabilities in poor-prognosis AML" The 82nd Annual Meeting of the Japanese Society of Hematology (Online) October 2020

Ishikawa F. "Identification of vulnerabilities in genetically-complex AML" Blood Club in Australia (Australia/Online) October 2020

Ishikawa F. "Creating Treatment Strategies for Poor Prognosis Acute Myeloid Leukemia" Summer School at the Jackson Laboratory (USA/Online) August 2020

We have developed *in vivo* models for normal and malignant human hematopoiesis by injecting human stem cells into newborn NOD/SCID/IL2rγKO (NSG) mice. In mice injected with normal human hematopoietic stem cells, we have been able to learn how the immune system develops in organs. On the other hand, the Humanized Mouse model has the caveat of the species barrier between human blood/immune cells and the mouse microenvironment. Though this system may not completely recapitulate the human immune system, it has the unique advantage of understanding *in vivo* kinetics and dynamics of human hematopoiesis and immunity. In the past three years, we have focused on two topics: First, we have performed single-cell transcriptomics for human cells from multiple organs of the Humanized Mice to investigate more dynamic aspects of human blood cell fate. Second, we have analyzed T cell immunity in the Humanized Mice and in patients.

Malignant cells resist and escape kinase inhibition, apoptosis induction, and immune surveillance through mutations and chromosomal abnormalities, leading to poor patient outcomes. For malignant human hematopoiesis, we have focused on understanding of myeloid and lymphocytic leukemia with poor prognostic factors such as complex karyotypes. We already had robust genomic data on human malignancies, but it has yet to be addressed how we can achieve complete remission for the long-term and cure of the diseases. In addition to the information on mutated genes and proteins, it must be crucial to connect function with genomics. Patient-derived NSG xenografts have been one of the gold standards for this specific aim worldwide.

Taking advantage of the strengths at RIKEN IMS, we have been working with non-hematology scientists such as genomics, lipidomics, and iPS researchers. Through such interdisciplinary collaboration, we aim to better understand disease biology, identify vulnerabilities as therapeutic targets, and develop treatment modalities for poor prognosis leukemia.

Laboratory for

Cancer Invasion and Metastasis

Team Leader: **Kohei Miyazono**

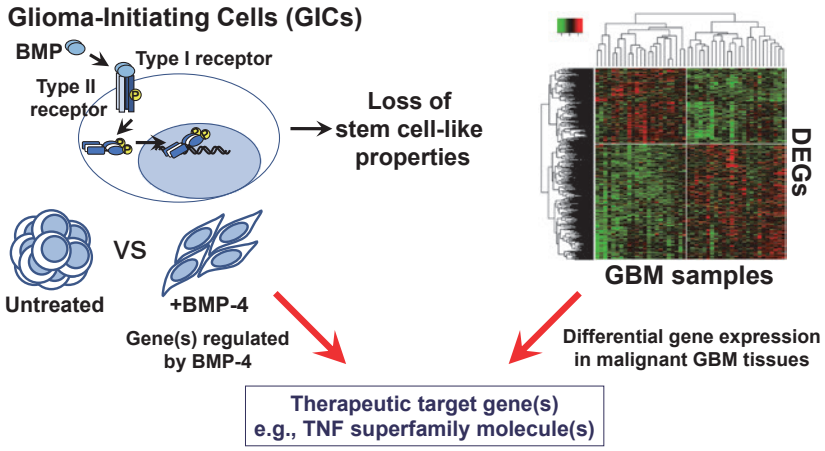


Figure: TNF superfamily protein(s) as molecular targets for the mesenchymal subtype of glioblastoma

Bone morphogenetic proteins (BMPs) induce differentiation of glioma-initiating cells (GICs) As therapeutic molecular targets for the mesenchymal subtype of glioblastoma multiforme (GBM), tumor necrosis factor (TNF) superfamily molecule(s) have been identified.

Recent Major Publications

Ehata S, Miyazono K. Bone Morphogenetic Protein Signaling in Cancer; Some Topics in the Recent 10 Years. ***Front Cell Dev Biol*** 10, 883523 (2022)

Takahashi Kei, Abe K, Kubota SI, Fukatsu N, Morishita Y, Yoshimatsu Y, Hirakawa S, Kubota Y, Watabe T, Ehata S, Ueda HR, Shimamura T, Miyazono K. An analysis modality for vascular structures combining tissue-clearing technology and topological data analysis. ***Nat Commun*** 13, 5239 (2022)

Takahashi Kazuki, Podyma-Inoue KA, Saito M, Sakakitani S, Sugauchi A, Iida K, Iwabuchi S, Koinuma D, Kurioka K, Konishi T, Tanaka S, Kaida A, Miura M, Hashimoto S, Okada M, Uchihashi T, Miyazono K, Watabe T. TGF-β generates a population of cancer cells residing in G1 phase with high motility and metastatic potential via KRTAP2-3. ***Cell Rep*** 40, 111411 (2022)

Invited presentations

Miyazono K. "Mechanisms of the differentiation of glioblastoma-initiating cells by BMPs" 13th International Conference on Bone Morphogenetic Proteins (Dubrovnik, Croatia) October 2022

Miyazono K. "Plasticity of cancer cells and mechanisms of TGF-β-induced cancer metastasis" The 81st Annual Meeting of the Japanese Cancer Association, Symposium: Plasticity and Diversity in Cancer (Yokohama, Japan) September-October 2022

Miyazono K. "Multiple roles of TGF-β signaling in cancer metastasis" FASEB Science Research Conferences 2022 - The TGF-β Superfamily Conference: Signaling in Development and Disease (Dublin, Ireland) July 2022

Miyazono K. "Regulation of blood and lymph-angiogenesis by TGF-β and their visualization" The 46th General Meeting of The Japanese Society of Lymphology (Tokyo, Japan) June 2022

Miyazono K. "TGF-β signaling in progression of cancer" The 10th Sweden-Japan Academic Network Seminar at Royal Academy of Sciences, Sweden (Stockholm, Sweden) April 2022

The Laboratory for Cancer Invasion and Metastasis started in August 2022. Our major research interest is to search for target molecules that may be used for the treatment of intractable cancers. Bone morphogenetic proteins (BMPs), members of the transforming growth factor-β family, induce growth arrest and differentiation of glioma-initiating cells (GICs). Through RNA-sequencing analysis of GICs treated or not with BMP-4, we have found that expression of some tumor necrosis factor receptor superfamily (TNFRSF) protein(s) is suppressed by BMP-4 in certain glioblastoma cells. Glioblastoma is subclassified into four subtypes, i.e., proneural, neural, classical, and mesenchymal subtypes. We have found that one of the TNFRSF proteins is highly expressed in the mesenchymal subtype of human glioblastoma cells and tissues. Silencing of the TNFRSF protein expression resulted in reduced proliferation and neurosphere formation of glioblastoma cells in cell culture and decreased tumorigenic ability and prolonged survival of mice after intracranial injection of the glioblastoma cells.

We have generated a VHH (variable domain of heavy chain of heavy chain antibody) against the TNFRSF related protein. The VHH antibody was humanized, and the Fc portion of human IgG was attached. Pre-clinical studies of the VHH antibody without and with Fc, including pharmacokinetic studies and safety studies, are ongoing.

Special Program for Young Leaders

RIKEN Hakubi Fellows Program

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

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

Young Chief Investigator Program

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

Genome Immunobiology RIKEN Hakubi Research Team

Hakubi Team Leader: **Nicholas Parrish**

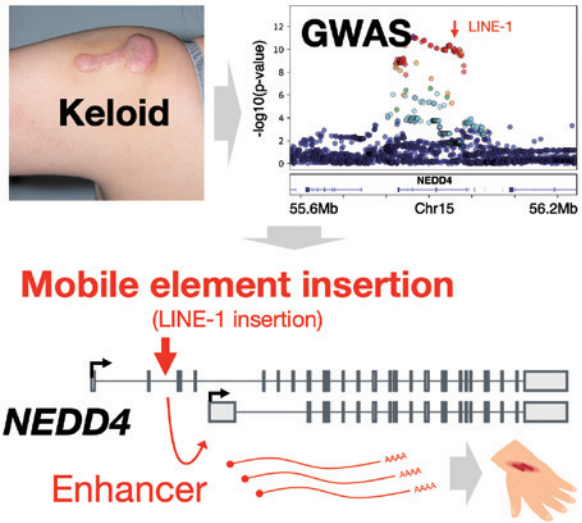


Figure: A LINE-1 insertion in *NEDD4* acts as an isoform-specific enhancer and causes increased keloid risk

Subjects with and without keloid were recruited and genotyped by BioBank Japan, and keloid risk variants were identified by GWAS. Subjects with a LINE-1 insertion in the gene *NEDD4* have higher keloid risk. Using genetic modification of iPSCs and differentiation to fibroblasts, we showed that this LINE-1 insertion acts as an enhancer of a keloid-promoting short isoform of *NEDD4*.

Recent Major Publications

Ito J, Seita Y, Kojima S, Parrish NF, Sasaki K, Sato, K. A hominoid-specific endogenous retrovirus may have rewired the gene regulatory network shared between primordial germ cells and naïve pluripotent cells. ***PLoS Genet*** 18, e1009846 (2022)

Koido M, Hon C, Koyama S, Kawaji H, Murakawa Y, Ishigaki K, Ito K, Sese J, Parrish NF, Kamatani Y, Carninci P, Terao C. Prediction of the cell-type-specific transcription of non-coding RNAs from genome sequences via machine learning. ***Nat Biomed Eng*** Online ahead of print at doi: 10.1038/s41551-022-00961-8 (2022)

Eds. Parrish NF, Iwasaki Y. ***piRNAs: Methods and Protocols. Methods in Molecular Biology***. Springer Nature, New York. Published May, 2022

Invited presentations

Kojima S, Parrish NF. "Polymorphisms of endogenous retroviruses in humans: from detection methods to disease risk" 45th Annual Meeting of the Molecular Biology Society of Japan (Chiba, Japan) November 2022

Hayakawa K, Kojima S, Parrish NF. "Potential involvement of endogenous HHV-6 in lymphangioleiomyomatosis" 45th Annual Meeting of the Molecular Biology Society of Japan (Chiba, Japan) November 2022

Heaton SM, Parrish NF. "Querying the genotype-dependence of stimulus-response phenotypes using single-cell sequencing of genetically diverse human cell libraries" 45th Annual Meeting of the Molecular Biology Society of Japan (Chiba, Japan) November 2022

Kojima S, Parrish NF. "Mobile element variation drives population-specific genome diversification, gene regulation, and disease risk" Cold Spring Harbor Laboratory Meeting: Transposable Elements (Long Island, USA) October 2022

Kojima S, Parrish NF. "Mobile element variation drives population-specific genome diversification, gene regulation, and disease risk" 2022 IMS-McGill Workshop (Montreal, Canada) September 2022

Our research focuses on understanding the biological functions and disease associations of mobile genetic elements (MEs), including transposable elements and endogenous viral elements (EVEs). EVEs are virus-derived sequences that have become integrated into the host genome through past viral invasions.

We previously found that mouse and human EVEs derived from Borna disease virus (BoDV), called endogenous bornavirus-like nucleoprotein elements (EBLNs), are transcribed and processed into PIWI-interacting RNAs (piRNAs). Because piRNAs are known to guide RNA interference against complementary RNA targets, we hypothesized that EBLN-derived piRNAs may target BoDV mRNAs and function as an antiviral mechanism against BoDV. To test the hypothesis, we engineered mutant mice lacking piRNA-generating EBLNs. Additionally, we knocked-in modern Borna disease virus sequences into piRNA-generating loci (piRNA clusters) to simulate the acquisition of a new EBLN-like EVE. Using these genetically modified animals, we are establishing BoDV testis infection models to determine whether EBLN-derived piRNAs are involved in antiviral RNA interference. If so, this could reveal a novel mechanism of germline-encoded innate immune memory in mammals.

Beyond the provocative example provided by EBLNs, we are interested generally in the evolution of novel phenotypes through the activity of MEs, and we have been using biobank-scale human data to uncover new examples. We made tools to detect and genotype germline insertional polymorphisms of human herpesvirus 6 (Liu *et al.*, PLoS Genetics 2020), endogenous retroviruses (Kojima *et al.*, PLoS Genetics 2021) and other MEs (Kojima *et al.*, Nature Genetics 2023). Using statistical genetics and molecular biology, we have found examples in which novel insertions of MEs have generated new human phenotypes, for example, a LINE-1 transposon insertion that causes an increased risk of keloid and fasciitis.

YCI Laboratory for Immunological Transcriptomics

Young Chief Investigator: Hideyuki Yoshida

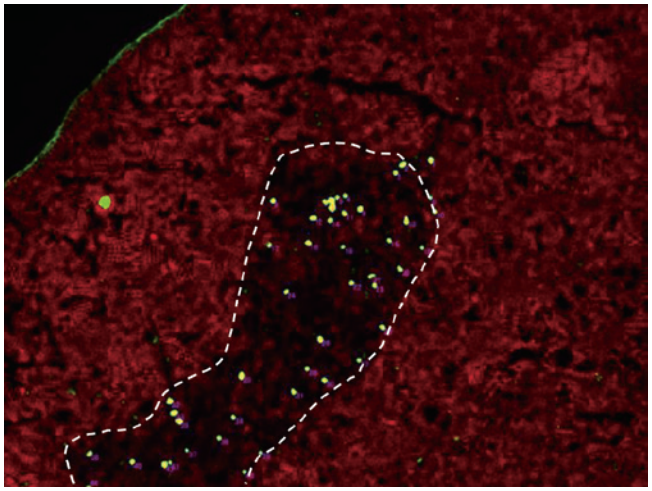


Figure: Immunofluorescence analysis of a mouse thymic tissue section
The green color shows cells that are in the process of dying through apoptosis. This happens because the thymus is sorting out cells that react strongly against the body's own tissues through a process called "negative selection."

Recent Major Publications

Miyazawa R, Nagao JI, Arita-Morioka KI, Matsumoto M, Morimoto J, Yoshida M, Oya T, Tsuneyama K, Yoshida H, Tanaka Y, Matsumoto M. Dispensable Role of Aire in $CD11c^+$ Conventional Dendritic Cells for Antigen Presentation and Shaping the Transcriptome. ***Immunohorizons*** 7, 140-158 (2023)

Nishijima H, Matsumoto M, Morimoto J, Hosomichi K, Akiyama N, Akiyama T, Oya T, Tsuneyama K, Yoshida H, Matsumoto M. Aire Controls Heterogeneity of Medullary Thymic Epithelial Cells for the Expression of Self-Antigens. ***J Immunol*** 208, 303-320 (2022)

Morimoto J, Matsumoto M, Miyazawa R, Yoshida H, Tsuneyama K, Matsumoto M. Aire suppresses CTLA-4 expression from the thymic stroma to control autoimmunity. ***Cell Rep*** 38, 110384 (2022)

Invited presentations

Yoshida H. "mTECs, peripheral tissue-specific antigens, and beyond" The 51st Annual Meeting of the Japanese Society for Immunology (Kumamoto, Japan) December 2022

Yoshida H. "Gene regulations in immunocytes: data-driven approach employing a wide range of immune cells" The 94th Annual Meeting of the Japanese Biochemical Society (Japan/Online) November 2021

Yoshida H. "Data-driven Immunology: large scale multiome analysis revealed comprehensive mechanisms for transcriptional regulation" The 29th Molecular Immunology Forum Tokyo (Japan/Online) March 2021

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

Our research aims to promote the understanding of gene regulation in immune cells and the immune system for better deciphering and treatment of immune disorders. Transcriptomics can be applied to various studies in immunological settings, and we have been engaged in 1) studies of immune tolerance and 2) a project for the systematic analysis of immunocytes.

1) Gene regulation in immune tolerance

The negative selection of the self-reactive T cells occurs in the thymus and is one of the most essential mechanisms to induce immune tolerance. To achieve this, a large number of genes encoding peripheral tissue antigens (PTAs) are expressed in thymic medullary epithelial cells (mTEC), and the developing T cells are eliminated if they respond to these PTAs. Since the disrupted expression of PTAs can result in autoimmune disorders, understanding the mechanisms controlling PTA expression is important to uncover the pathogenesis of autoimmune diseases and to develop new treatments. We are analyzing gene expression in mTEC by employing multiple single-cell profiling methods to reveal detailed gene regulation along with validations employing mouse models.

2) Systematic analysis of the immune system employing a data-driven approach

Bioinformatics has impacted research on gene regulation and is becoming more potent since it began dealing with big data analysis. To promote data-driven studies, we are collaborating with the ImmGen group.

IMS Research and Infrastructure Platforms

IMS Research and Infrastructure Platforms provide all researchers in the Center with access to the most advanced equipment and technologies. The platforms consist of six sections; FACS managed by Dr. Takashi Saito, Imaging and Microscopes managed by Dr. Takaharu Okada, Genome Platform and related activities managed by Dr. Yukihide Momozawa, Animal Facility managed by Dr. Haruhiko Koseki, Metabolomics (Lipidomics) managed by Dr. Makoto Arita, and Information Infrastructure managed by Dr. Takeya Kasukawa.

FACS

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 Aria instruments, including two Aria Fusions and a FACSymphony for multi-color analyses/sorting. In addition to FACS instruments, the lab has a mass spectrometry-based cytometer, HELIOS, which has the potential to analyze more than 40 markers simultaneously with metal-labeled antibodies.

In 2022, still in the difficult period due to the coronavirus pandemic, in total 550 analytical and 927 FACS sorting experiments and 48 analyses with HELIOS were performed.

In the FACS laboratory, a specialized staff member offers various services for users of the equipment (cell analyzers and cell sorters): (1) *Technical support and training*: In 2022, the facility offered 32 technical courses (four for cell sorting and four for cell analysis). The courses were held at three different levels, Canto II (7) and Aria basic (25). An Aria course was also held in English. A total of 56 researchers participated in these courses in 2022. (2) *Cell sorting operation service*: The Laboratory provides a cell sorting operation service, in which researchers can ask an experienced operator to conduct the sorting experiment. In 2022, 128 such services were provided. Advanced cell sorting techniques, such as single-cell sorting, have also been performed. (3) *Management/maintenance of FACS instruments*: FACS machines are available for registered users around the clock and reservations are accepted up to one month in advance through an internal website. In addition to the in-house FACS Laboratory staff, engineers from Becton Dickinson visit once a week to provide maintenance and technical support.

Table: Instruments and their usage in the FACS Laboratory (2022)

Instrument types	Model	# of machines	# of analyses	# of training sessions (# of participants)
FACS cell analyzer	Calibur	3	11	1 (0)
	Canto II	2	550	3 (7)
FACS cell sorter	Aria IIIu/III/ Fusion/Symphony	7	927	3 (25)
Mass cytometer	Helios (CyTOF)	1	48	0 (0)

Imaging and Microscopes

The Microscope Laboratory provides equipment for cell and tissue imaging and coordinates technical support. There are six fluorescence microscopes and one scanning electron microscope available to researchers at IMS.

(1) Inverted Leica SP8 system equipped with hybrid detectors and the LIGHTNING super-resolution image extraction module.
(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. One of the two Ti:Sa lasers is connected to an optical parametric oscillator (OPO) that enables two-photon imaging by long wavelength excitation.
(3) Inverted Leica SP5 system with hybrid detectors.
(4) Inverted Nikon N-SIM/N-STORM super-resolution microscope for dual color imaging.
(5) GE Healthcare DeltaVision Elite system.
(6) Keyence BZ-X700 all-in-one fluorescence microscope.
(7) Hitachi field emission scanning electron microscope (FE-SEM) Regulus8240. The related devices such as a conventional ultramicrotome Leica EM UC7 and an array tomography ultramicrotome ARTOS 3D are also available.

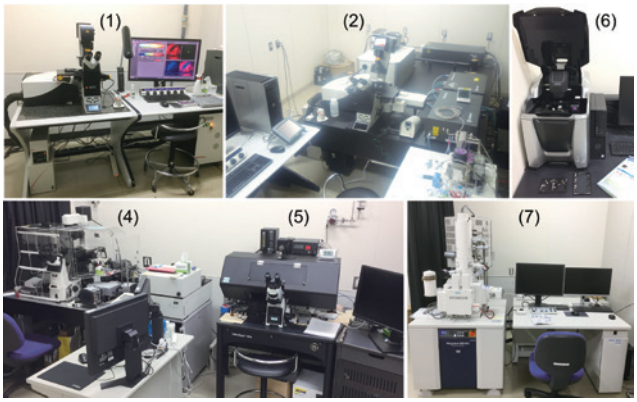


Figure: Leica SP8 confocal microscope (1), Leica SP8 multiphoton microscope (2), Nikon N-SIM/N-STORM super-resolution microscope (4), GE Healthcare DeltaVision Elite system (5), Keyence BZ-X700 microscope (6), and Hitachi Regulus8420 FE-SEM (7)

Genome Platform and related activities

The Genome Platform was launched in September 2020. This platform enables users in IMS to obtain DNA libraries, sequence data and analysis data quickly and at a reasonable cost, thus empowering their research. For library preparation, we support whole-genome sequencing, targeted sequencing, CAGE, single-cell RNA-seq, and bulk RNA-seq. For sequencing, we support NovaSeq6000, NextSeq2000, HiSeq2500, MiSeq, and PacBio Sequel runs. Data analysis is available for whole-genome sequencing, targeted sequencing, CAGE, single-cell RNA-seq, bulk RNA-seq, Chip-Seq, and ATAC-seq. In addition, we also support the registration of data in public databases.

In FY2022, we developed an in-house RamDA-seq analysis method in collaboration with the Nikaido team at RIKEN Center for Biosystems Dynamics Research. We have also transferred NET-CAGE technology in cooperation with the Murakawa team at RIKEN IMS. The genome platform enabled users to receive analysis data online by using the HOKUSAI SS data science platform. In addition, the Illumina DRAGEN Bio-IT platform made routine data analysis fast and easy, and enables data to be provided to users in a short period of time.

This year, we are working on 52 projects. The achievements in library preparation and sequencing are shown in Table 1. In one important project, we conducted whole-genome sequencing analysis of 800 individuals for an Atrial Fibrillation Study in collaboration with the University of Tokyo.

We expect that the intramural interactions fostered by the Genome Platform among the Divisions of Human Immunology, Disease Systems Biology, Cancer Immunology, and Genome Medicine will greatly enhance IMS research activities.

Table1: Central services provided by the Genome Platform in 2022

Library Preparation	# of Samples
whole genome sequence	274
target sequence	42110
bulk RNA-seq	172
SMART-Seq	864
RamDA-seq	1156
NET-CAGE	13
10x 3′GE	19

Table2: Next-generation DNA sequencing

Illumina Sequencer	# of Runs
NovaSeq6000	86
NextSeq2000	27
HiSeq2500	27
MiSeq	183
PacBio Sequel	**# of Runs**
Sequel II	28

Animal Facility

We continue to maintain over 60,000 mice in the SPF area and 1,500 mice in an isolated area. The SPF area also contains 1,000 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". In addition, for COVID-19 research, a new animal biosafety level 3 (ABSL3) room was completed in 2021. The new ABSL3 room has high negative pressure Individually Vented Cage systems (IVCs) (Figure) and has the capacity to breed 150 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 cryo-stocks of genetic resources (frozen embryos and sperm) for 902 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 (96 lines). In addition, we have created 11 lines of germ-free mice. We maintain flexibility so that we can provide space for new experiments in the animal facility, e.g., behavioral testing of germ-free mice.

We have generated genetically modified mice to improve the efficiency of transplantation of human hematopoietic stem cells into NOD.Cg-*Prkdc*^{scid} *Il2rg*^{tm1Wjl}/SzJ (NSG) mice by better "humanizing" the host strain. For this purpose, we have introduced large genomic fragments containing human genes encoding MHC, cytokines, adhesion molecules, virus receptors, and others into the NSG mice. We maintain such transgenic and knock-in mice.

Figure: The new ABSL3 room camera image with Individually Vented Cage systems

Metabolomics (Lipidomics)

Lipids constitute biological membranes and play a variety of roles as energy sources, signaling molecules and their precursors. Some lipids are biologically active as single molecules, while others are involved in the formation of membrane domains as molecular assemblies. In general, the dysregulation of lipid metabolism is associated with human diseases and, hence, the precise determination of lipids is quite important for understanding their functions in physiology and disease, and for discovering novel bioactive lipids that may have therapeutic benefits.

A powerful method for analyzing lipid metabolites is liquid chromatography-tandem mass spectrometry (LC-MS/MS). The Metabolomics Laboratory is equipped with an AQUITY UPLC (Waters) coupled with a TripleTOF 6600, a QTRAP 6500/5500/4500 (Sciex) and a GC-MS TQ8030 (Shimadzu) to cover untargeted and wide-targeted metabolomics. Recently, we introduced timsTOF flex MALDI-2 (Bruker) for MS imaging (spatial lipidomics) analyses. This state-of-the-art lipidomics platform together with our original informatics technologies are powerful tools for elucidating complex lipid structures and visualizing metabolic networks globally and in an unbiased manner. They also provide an opportunity for data-driven hypotheses to make the connection between lipid metabolism and biological phenotypes.

Figure: LC-MS/MS based Advanced Lipidomics Platform

Information Infrastructure

To promote and support large-scale computation for various research activities in IMS, there are several groups that manage the information infrastructure and computational resources. In the West building, we have internal large-scale computation systems (total ~1,000 cores, 2.1PB storage) using RIKEN's internal network and provide them for IMS researchers. In FY2021, RIKEN R-IH launched a new private cloud system named HOKUSAI SS for all RIKEN laboratories. We have utilized HOKUSAI SS to expand the in-house computation systems by providing a seamless environment. In the East building, we also have internal large-scale computation systems (total ~3500 cores, 8PB storage) in a closed network and provide them widely for IMS researchers, not just in the East building; other buildings also have access to these servers, especially for controlled access data, e.g., human-derived data. We are planning to gradually shift the storage system to HOKUSAI SR to securely store human genomics data. Moreover, two remote access terminals have been installed in the East building in order to enable IMS researchers to easily access Tohoku Medical Megabank (ToMMo) data.

Recently, sharing of research data becomes important in the open science era. We have drafted IMS Research Data Guidelines for the treatment of research data obtained in IMS, for discussion in IMS.

Large-scale computation is now essential in biomedical studies and we continue to provide sufficient and the latest computation environment and information infrastructure for IMS researchers.

Figure: The computer servers managed in the West building (left) and in the East building (right)

IMS Bioethics Working Group

IMS aims to clarify the mechanisms underlying the development of human diseases and to use this insight to create new treatments that can improve the well-being of society. More specifically, IMS is engaged in medical research focusing on the elucidation of human immune and genomic functions. Therefore, it is essential to conduct research using human samples and data at various levels, including genome, transcriptome, medical record information, and samples provided by hospitals.

In conducting such research, IMS recognizes the importance of protecting the rights of research participants, ensuring responsible handling of samples and information provided by research participants, complying with research-related regulations, returning research results to society including the participants, and promoting dialogue with the general public. IMS also recognizes that Ethical, Legal, and Social Implications/Issues (ELSI) must be addressed while conducting cutting-edge research.

Therefore, the IMS Office of the Center Director has established a Bioethics Working Group (BWG), which began in earnest in FY2019, to address bioethical challenges facing IMS researchers. Since then, the IMS BWG has focused on providing research ethics support, conducting ELSI-related surveys and feedback, offering research ethics education opportunities, and establishing international collaborations such as the Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard, and the Science Policy Think Tank in U.S.

The BWG has set up a help desk to provide researchers with research ethics consultations, offered ongoing support for some research projects, invited prominent scholars from Japan and overseas to lecture on the latest knowledge and issues, and held forums for exchanging opinions among scholars and researchers.

The IMS BWG also provides support related to ELSI, such as issues of promoting open science while protecting personal information, issues of returning research results, and issues regarding implication of genomic medicine while preventing genetic discrimination.

In addition, in collaboration with other RIKEN departments, the IMS BWG has taken the initiative in improving the systems related to research ethics and conflict of interest. The IMS BWG has been granted the President's Discretionary Fund twice, and over the past three years has made significant progress in improving the environment surrounding and supporting research ethics at IMS.

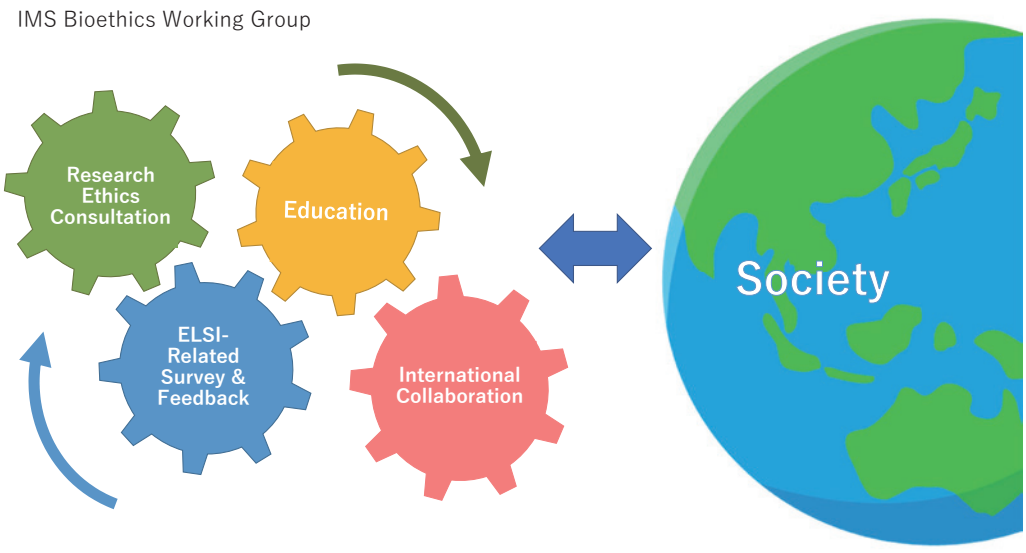


Figure: Four major components of the Bioethics Working Group that interact with society

RIKEN International Program Associate (IPA)

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

The IPA students who studied at IMS in 2022 were

Yan Jun Lan (ETH Zurich, Switzerland) in the Laboratory for Advanced Genomics Circuit

Jingjie Chang (Tokyo Medical and Dental University, Japan) in the Laboratory for Transcriptional Regulation

Yali Xu (Nanjing University, China) in the Laboratory for Cellular Function Conversion Technology

Jan Peter Pack (McGill University, Canada) in the Laboratory for Human Disease Models

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, 30 JRA students studied in IMS.

Haruki Uchino (Laboratory for Metabolomics)
Umi Tahara (Laboratory for Skin Homeostasis)
Hiroto Horikawa (Laboratory for Gut Homeostasis)
Tomo Kakihara (Laboratory for Microbiome Sciences)
Kentarou Kubota (Laboratory for Innate Immune Systems)
Sayoko Kuroha (Laboratory for Metabolomics)
Zhengzheng Shi (Laboratory for Intestinal Ecosystem)
Yuki Tanaka (Laboratory for Cellular Function Conversion Technology)
Susumu Toshima (Laboratory for Tissue Dynamics)
Ryo Nakagawa (Laboratory for Human Disease Models)
Mio Yoshida (Laboratory for Metabolomics)
Nao Tanaka (Laboratory for Statistical and Translational Genetics)
Taichi Akase (Laboratory for Large-Scale Biomedical Data Technology)
Tatsuya Ishikawa (Laboratory for Immune Homeostasis)
Raku Son (RIKEN-IFOM Joint Laboratory for Cancer Genomics)
Yuichiro Tanaka (Laboratory for Intestinal Ecosystem)
Ritsu Nagata (Laboratory for Intestinal Ecosystem)
Naoto Fujioka (Laboratory for Innate Immune Systems)
Satoshi Morozumi (Laboratory for Metabolomics)
Tatsuro Iwasaki (Laboratory for Skin Homeostasis)
Yuki Okawa (Laboratory for Cancer Genomics)
Fumie Ota (Laboratory for Cardiovascular Genomics and Informatics)
Yuta Sakamoto (Laboratory for Cellular Function Conversion Technology)
Xufeng Shu (Laboratory for Transcriptome Technology)
Yu Terauchi (Laboratory for Metabolomics)
Kaiyuan Deng (Laboratory for Metabolomics)
Mio Hayama (Laboratory for Immune Homeostasis)
Tomoya Hirai (RIKEN-IFOM Joint Laboratory for Cancer Genomics)
Rino Maruyama (Laboratory for Cellular Function Conversion Technology)
Soichiro Yoshino (Laboratory for Statistical and Translational Genetics)

RIKEN Special Postdoctoral Researcher (SPDR) Program

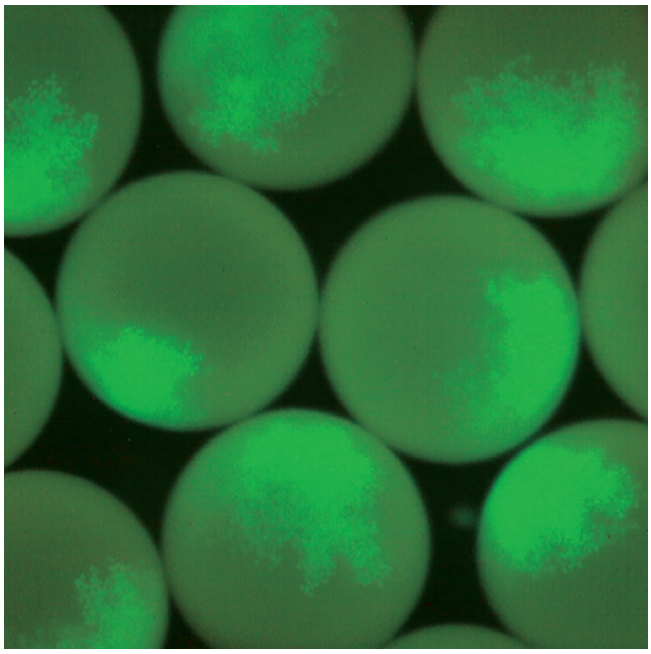
RIKEN's Special Postdoctoral Researcher Program was instituted to provide young and creative scientists the opportunity to be involved in autonomous and independent research in line with RIKEN objectives and research fields. The positions are competitive, but if selected, researchers receive salaries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

This year, 8 postdocs conducted their research at IMS through the SPDR program.

Chisayo Kozuka (Laboratory for Developmental Genetics)
Mari Hashimoto (Laboratory for Human Disease Models)
Baihao Zhang (Laboratory for Mucosal Immunity)
Hideki Terajima (Laboratory for Gut Homeostasis)
Ryota Teramoto (Laboratory for Comprehensive Genomic Analysis)
Steven Matthew Heaton (Genome Immunobiology RIKEN Hakubi Research Team)
Shohei Kojima (Genome Immunobiology RIKEN Hakubi Research Team)
Ayako Matsuyama (Laboratory for Tissue Dynamics)

Part 3

Research Projects



COVID-19 projects in IMS

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 continues. While current COVID-19 vaccines have shown efficacy in many countries, the development of diagnostics and prevention strategies to protect from severe disease is still needed. Here we will introduce several groups in IMS that are currently working on COVID-19 projects. Fukuyama's group, in collaboration with Keio University, have already isolated several human mAbs from COVID-19 patients. They have patented these antibodies, which can neutralize several variants of concern strains of SARS-CoV-2, and started research and development with pharmaceutical companies for formulation of therapeutic neutralizing antibodies. Yamamoto's group has established a system for analyzing the whole picture of peripheral blood mononuclear cells (PBMCs) of those who recovered from COVID-19 and are searching for factors that are involved in infection resistance. They also studied changes in PBMCs and lymphocyte function before and after vaccination by single-cell analysis. Momozawa's group, as a member of the COVID Human Genetic Effort, has been identifying COVID-19 susceptibility genes, genes associated with severe disease and disease resistant genes from clinical information or immunological analysis, and from large-scale whole genome data. Terao's group, as a member of the International Joint Research group, reported COVID-19 patients with mosaic chromosomal alterations (mCAs) have an increased risk of developing severe infections. Honda's group has revealed that intestinal colonization by trypsin-degrading bacteria suppresses mouse hepatitis virus. In addition, they showed that people with a large number of microbiome bacterial genes involved in trypsin degradation had less severe diarrhea symptoms during SARS-CoV-2 infection. Ohno's group searched for gut bacterial markers involved in the severity of COVID-19 and complications in other organs outside the intestine from omics analysis and found that the characteristics of the intestinal flora of patients in Japan are different from those of patients in the United States. Ishikawa's group provided human immune cell data to understand how coronavirus infection affects human immune reactions and differentiation. Several groups are collaborating with the RIKEN Drug Discovery and Medical Platform (DMP). Miyauchi's group previously succeeded in generating high-affinity antibodies that recognize multiple mutant CoV-2 strains by stimulating T follicular helper cells in the germinal center. Saito's group has established neutralizing antibodies that target TMPRSS2, the host enzyme that activates the viral spike protein and are now conducting preclinical studies. Fujii's group has identified an HLA-A24-restricted, cross-reactive QYI peptide for CTL induction using human PBMCs reactive with SARS-CoV-2. Also, since they previously established the concept of the artificial adjuvant vector cell (aAVC) system against cancer, they established a SARS-CoV-2-derived antigen-expressing aAVC (aAVC-CoV-2). In preclinical studies they obtained evidence for anti-viral cytotoxic T cell induction as well as anti-SARS-CoV-2 Ab in vaccinated animals.

Recent advances as IMS projects in the fields of diagnostics, treatment and vaccine development for SARS-CoV-2 infection are summarized in Table.

Table: COVID-19-related research conducted at IMS

Teams	Titles
Hidehiro Fukuyama (Lab. for Lymphocyte Differentiation)	Development of COVID-19 antibody drugs
Kazuhiko Yamamoto (Laboratory for Autoimmune Diseases)	Development of a method for healthy immune cell profiling of individuals recovering from SARS-CoV-2 infection
Yukihide Momozawa (Lab for Genotyping Development)	Genome analysis to identify genes and genome loci associated with individual differences in susceptibility to COVID-19 infection
Kosuke Miyauchi (Lab. for Cytokine Regulation)	Construction of a system to isolate a human monoclonal neutralizing antibodies against SARS-CoV-2 (with DMP)
Kenya Honda (Lab. for Gut Homeostasis)	Understanding host-gut microbiota interactions to develop a therapeutic/preventive strategy for SARS-CoV-2 infection
Hiroshi Ohno (Lab. for Intestinal Ecosystem)	Screening for an intestinal flora marker for COVID-19 in large databases using Omics analysis
Takashi Saito (Lab. for Cell Signaling)	Development of a TMPRSS monoclonal Ab (with DMP)
Chikashi Terao (Laboratory for Statistical and Translational Genetics)	Elucidating the relationship between somatic cell mosaicism and the risk of COVID-19 infection
Fumihiko Ishikawa (Lab. for Human Disease Models)	Mechanism of COVID-19 severity caused by mutant viruses in the post-vaccination period
Shin-Ichiro Fujii (Lab. for Immunotherapy)	Development of aAVC-CoV-2 (with DMP)
Shin-Ichiro Fujii (Lab. for Immunotherapy)	Identification of SARS-CoV-2 epitopes cross-reactive with seasonal coronaviruses

Human Cell Atlas

The Human Cell Atlas (HCA) is an international consortium aiming to create a comprehensive molecular reference map of human cells as a basis for understanding human health and diseases. At RIKEN IMS, led by Dr. Piero Carninci, Dr. Jay Shin, and Dr. Chung-Chau Hon, we contribute to HCA by coordinating HCA activities among Asian institutions (e.g., HCA Asia meetings), developing single-cell experimental and computational methods (e.g., single-cell 5' RNA-Seq analysis methods) and generating single-cell molecular atlases from Asian samples (e.g., Asian Immune Diversity Atlas (AIDA)). Specifically, we devised a method to identify genuine transcribed *cis*-regulatory elements (tCREs) from single-cell 5' RNA-Seq data and used this method to generate a single-cell tCRE atlas from 22 human tissues, comprising >500,000 cells. Using this tCRE atlas, we devised a novel method to estimate the enrichment of disease heritability at single-cell resolution (Figure). This analysis framework was also extended to the AIDA project, which aims to characterize the extent of variation in immune cell types from diverse Asian populations. In the AIDA project, we have profiled the tCREs in >1 million immune cells from 500 individuals collected in Japan, Korea, and Singapore. In the next phase of the project, we will extend our efforts to other Asian countries including Thailand, India, Sri Lanka, Pakistan, and Russia. In summary, these HCA activities leveraged the single-cell transcriptomics and medical genetics expertise in RIKEN IMS to further our understanding of the cellular contexts of human diseases.

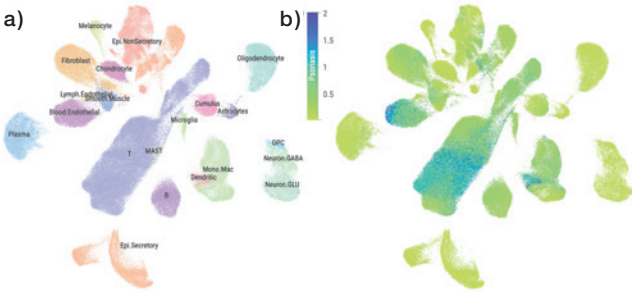


Figure: Enrichment of disease heritability at single-cell resolution
a) UMAP of a single-cell tCRE atlas from 22 human tissues, comprising >500,000 cells, annotated as 21 broad cell types. b) Enrichment of psoriasis heritability across the single-cell tCRE atlas. Heritability enrichment at single-cell resolution is calculated using a novel method based on tCRE module activities. Psoriasis heritability is enriched in subpopulations of T-cells, dendritic cells, fibroblasts, blood vessel endothelial cells, and non-secretary epithelial cells.

Keio-RIKEN IMS HuMED

In 2021, RIKEN IMS embarked on an exciting joint research program with Keio University School of Medicine, "Keio-RIKEN IMS Human Biology and Medicine Program (HuMED)", aiming to maximize the social benefits of medical knowledge derived from genomic studies. The creation of a Keio-RIKEN IMS joint laboratory in the Shinanomachi campus, led by Dr. Jay Shin, Dr. Akiko Minoda and Dr. Chung-Chau Hon, strengthens the already well-established medical research at Keio University with the advanced genomic technologies from RIKEN IMS, through collaborative projects over the next decade. The HuMED project focuses on the applications of single-cell genomics to medical research, in particular large-scale studies of disease cohorts at single-cell resolution. Notable examples include profiling of colon biopsies from ulcerative colitis and Crohn's disease cohorts (n=300), iPSC-induced motor neurons from an ALS cohort (n=150), and salivary gland biopsies from a Sjögren's syndrome cohort (n=30). In addition, the joint program also includes 10^{+} other projects including GVHD of colon transplantation, spatial transcriptomics of brains from Alzheimer's disease and Schizophrenia disease patients, skin biopsies of atopic dermatitis, characterization of human gut T cell populations and *in vitro* differentiation of neural lineages, etc. One of the highlights is the identification of cytotoxic $CD4^{+}CD8A^{+}$ T cells in the human gut and their similarity to mouse CD4 cytotoxic T cells (Figure). The joint research lab is a hub for fruitful collaborations between RIKEN IMS and Keio University, generating highly informative genomic data to transform medicine for a brighter future.

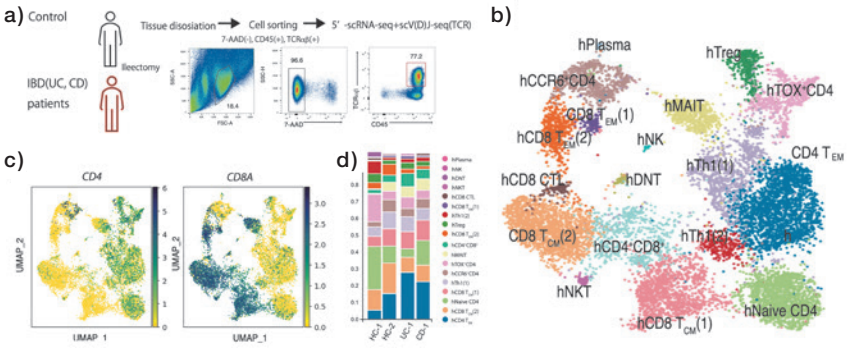


Figure: Identification of cytotoxic $CD4^{+}CD8A^{+}$ T cells in the human gut and their similarity to mouse CD4 cytotoxic T cells
a) Sorting strategy for the human single-cell RNA-seq: Lamina propria lymphocytes (LPLs) collected from digested small intestinal tissues were sorted by identifying $7AAD^{-}CD45^{+}TCRB^{+}$ cells by FACS. b) UMAP of 12,073 cells from healthy controls (n=2) and IBD patients [ulcerative colitis (n=1) and Crohn's disease (n=1)]. Cells were clustered into 18 clusters. The $hCD4^{+}CD8^{+}$, hTreg and hMAIT cluster is considered to be orthologous to mouse CD4 cytotoxic T cells. c) Expression of CD4 and CD8A. d) Proportion of each cluster in controls and patients with ulcerative colitis (UC) and Crohn's disease (CD).

FANTOM Project

Since its start in 2000 in a broad international collaboration, the FANTOM Project aims to elucidate the function of the mammalian genome with a focus on the transcriptome. The goal of the FANTOM6 Project is to systematically elucidate the function of long non-coding RNAs (lncRNAs) in the human genome. FANTOM6 has published an initial functional screening based on perturbation of the function of lncRNAs and imaging, identifying function for about ~30% of analyzed lncRNAs (Ramilowski *et al.*, *Genome Research* 2020; Yip *et al.*, *Cell Reports* 2022).

Moving into the second phase of FANTOM6, we aim to decipher the function of lncRNAs and their regulatory elements by studying their physical interactions with their targets. We are analyzing an initial set of ~15 biological samples and producing multi-omics data using various technologies, including RADICL-seq to detect RNAs interacting with, and likely regulating, chromatin activity. In parallel we characterize in detail the lncRNA sequences and the map of promoters and enhancers. Particular initial focus is dedicated to the interactome along the differentiation from iPS cells to cortical neurons and the differentiation from monocytes to macrophages as a pilot before broadly expanding the biological emphasis.

Given that the majority of RNAs are retained in the nucleus, and there is a broad set of them interacting with chromatin, the produced data from this project will be of great help in elucidating the role of lncRNAs to regulate human genome activity.

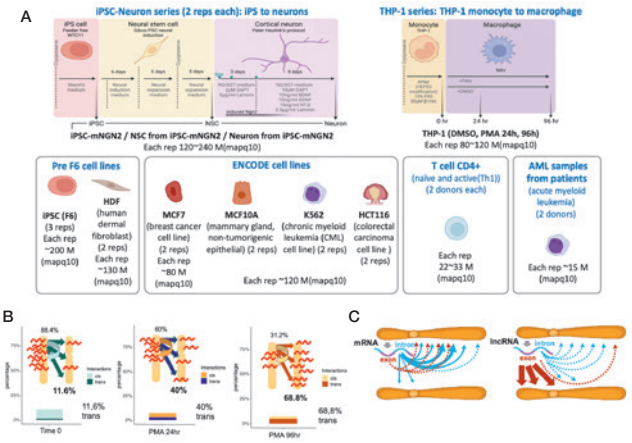


Figure: RNA-chromatin interactome in FANTOM6
A) Cell models and FANTOM6 RADICL-seq libraries B) RNA-chromatin interactions during differentiation from THP-1 monocytes to macrophages: *in trans* interactions, shown as percentages, increase during the differentiation process. Phorbol 12-myristate 13-acetate (PMA), which activates protein kinase C, was used to induce differentiation. C) Different interaction patterns between protein coding RNAs and long non-coding RNAs (lncRNAs): lncRNAs mostly show exon-derived interactome *in trans* or distal *in cis* while protein coding RNAs mostly show intron-derived interactome *in cis* with specific patterns.

Human genome analysis

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

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

A key finding in 2022 is the accumulation of new genomic-based evidence for the pathogenesis of atrial fibrillation (AF) and the application of a genetic risk score (GRS). The integrative analyses suggested that the ERRg transcription factor is involved in the pathogenesis. We also showed the AF-GRS predicted stroke even without AF diagnosis, which expanded its potential for clinical application.

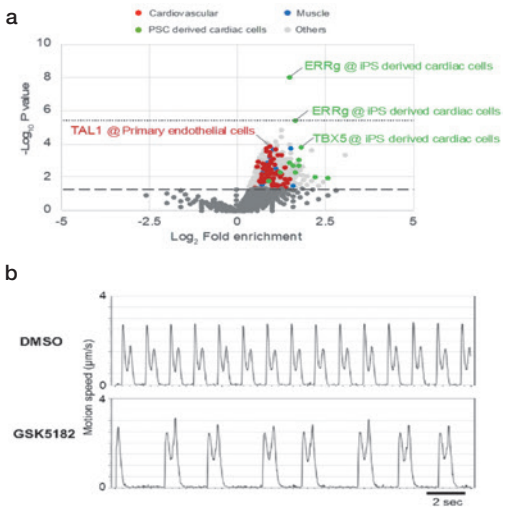


Figure: Integration analysis of genomic data with ChIP-seq data identified a new transcription factor involved in the development of atrial fibrillation
a. Volcano plot analysis utilizing the results of genomic analysis with a ChIP-seq database highlighted the ERRg transcription factor in cardiac cells.
b. Motion analysis of iPS-derived cardiomyocytes (iPSCM) using the SI8000 Cell Motion Imaging System. iPSCMs treated with GSK5182, an inverse agonist of ERRg, showed an arrhythmic phenotype.

SEAPharm for the establishment of stratified medicine in Asia

RIKEN established the Southeast Asian Pharmacogenomics Research Network (SEAPharm) together with five other Asian countries (Korea, Indonesia, Malaysia, Taiwan, and Thailand) in 2012 and membership has been steadily increasing, with Singapore, Vietnam, Nepal, Laos, the Philippines, Brunei, and Myanmar now included. The aims of the collaboration are to identify pharmacogenomic (PGx) biomarkers associated with adverse drug reactions, such as severe cutaneous adverse drug reactions (ADRs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and hepatic injury, to provide technical assistance and training of young researchers from the SEAPharm member countries and to hold international seminars and workshops.

Recently, SEAPharm has started a new project involving targeted next-generation sequencing (NGS) of DNA samples from the 12 member countries to clarify the genetic diversity of 100 pharmacokinetics-related genes in individuals. We reported substantial genetic variations in drug-metabolizing enzymes and drug-transporter genes among Asian populations. Our findings show that NGS-derived data coupled with *in vitro* experimental metabolic validations can provide useful insights towards clinical PGx implementation, which would be the basis for integrating NGS for genetic testing into routine clinical practice.

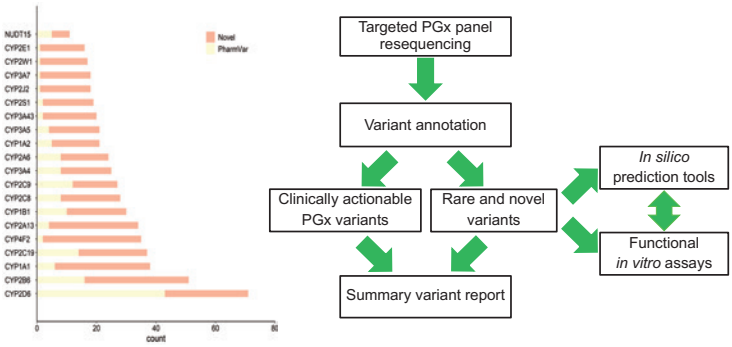


Figure: SEAPharm PGx variation project and proposed clinical workflow for future clinical implementation of PGx testing
We genotyped 1,571 genomic DNA samples using an NGS panel that targets the coding regions of 62 drug-metabolizing enzymes and 37 drug transporter genes. We were able to identify many novel variants in 20 clinically important drug-metabolizing enzyme genes in the SEAPharm populations, which were not registered to The Pharmacogene Variation Consortium (PharmVar, https://www.pharmvar.org/). We wish to propose an approach consisting of NGS coupled with *in vitro* validation assays of the wild type and variant protein activities, resulting in a comprehensive final variant report to support the possible pathogenicity of these variants.

eQTL project: Integration of genetic information into immune functions

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 reported to locate in the non-coding regions on the chromosome and function as an expression-quantitative trait locus (e-QTL), regulating the expression levels of genes. Therefore, by integrating genomic information, qualitative and quantitative analyses of transcriptomes together with cell-specific epigenomes, we will better understand the causal pathogenic components of immune cells in various immune-mediated diseases.

We are now setting up a system to identify various subtypes of leukocytes from peripheral blood mononuclear cells (PBMC) of heathy individuals. We expect to obtain the utmost unbiased relationship between genotypes and gene expression from healthy donors. Cell separation is performed by fluorescence-activated cell sorting into about 30 different subsets. Cells are then analyzed in the steady state or in further stimulated conditions, such as with combinations of cytokines and cell surface receptor agonists to capture the dynamic responses of gene regulation. Firstly, genotyping as well as RNA-seq are performed. With this data, we will obtain eQTL as well as splicing QTL information. Cap analysis of gene expression (CAGE), assay for transposase-accessible chromatin using sequencing (ATAC-seq) and several histone mark analyses for each subset are powerful tools to be used for identifying the causal relationship between genetic variation and gene expression.

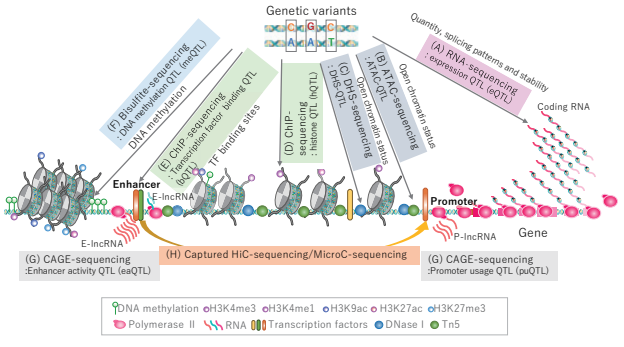


Figure: Integration of genetic information into immune functions: The eQTL project

Identifying gut microbiota-associated biomarkers that aggravate insulin resistance (IR) and insulin sensitivity (IS)

Type 2 diabetes mellitus (T2D) is increasing rapidly and becoming one of the most prevalent diseases worldwide, in association with changes in lifestyle and social environment. It is estimated that about 1 in 5 Japanese suffer from diabetic or prediabetic (medically defined as glucose intolerance) conditions. Thus, prevention of T2D and control of its progression are important and urgent needs - medically, socially, as well as economically. We, therefore, set this issue as one of the center projects to try to identify gut microbial T2D-predictive biomarkers or factors. In collaboration with the University of Tokyo Hospital, we recruited volunteers undergoing a complete medical checkup with the following criteria: 1) no obesity or glucose intolerance (control), 2) obesity (BMI ≥ 25) and 3) glucose intolerance (fasting blood glucose ≥ 110 mg/dl or HbA1c ≥ 6.0%). Clinical examination data from the medical checkup, as well as nutritional and physical activity data (brief self-administered diet history questionnaire (BDHQ) and accelerometry), were done at the University of Tokyo Hospital, while the following were collected in RIKEN: fecal and salivary metagenomic and metabolomic data, plasma metabolomic data, CAGE-based RNAseq, and whole genome sequencing data of peripheral blood mononuclear cells (PBMCs).

We found that IR and metabolic syndrome were significantly associated with fecal monosaccharides and sugar derivatives. We further revealed that these fecal monosaccharides and sugar derivatives were strongly associated with host inflammatory gene expression in PBMCs and with plasma cytokine levels (Figure). We also found that order *Bacteroidales* were negatively correlated with IR and fecal monosaccharides. Order *Bacteroidales* bacteria, especially *Aristipes indistinctus*, consumed a wide variety of carbohydrates in bacterial cultures. We further showed that high-fat diet-induced obesity and IR were ameliorated by *Aristipes* and *Bacteroides*. These results reveal the impact of carbohydrate degradation by microbiota on IR and suggest genus *Aristipes* as a potential therapeutic target for improving IS. This study is now under revision for publication.

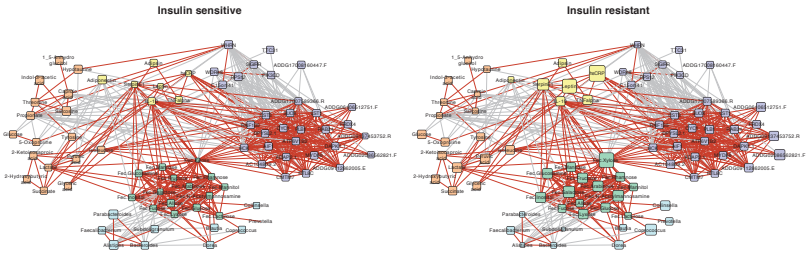


Figure: The networks between fecal carbohydrate metabolites, fecal microbes, plasma hydrophilic metabolites, cytokines, and PBMC genes in IS and IR individuals

Fecal carbohydrate metabolites (green), fecal microbes (sky blue), plasma hydrophilic metabolites (orange), cytokines (yellow), and PBMC genes (purple) are shown. For fecal and plasma metabolites, cytokines and PBMC genes, those significantly associated with both insulin resistance and metabolic syndrome were selected for the analysis. For fecal microbes, those that formed co-abundance groups were selected. To construct the omics network, partial Spearman's correlation corrected by age, sex, body mass index, and fasting blood glucose between all elements was calculated, and the interactions with q values < 0.2 are depicted. Line widths show the absolute values of Spearman's coefficient, and red and grey lines show positive and negative correlations. Disk sizes indicate the overabundance to the median in IS and IR (The abundance of each element in IS or IR was divided by the median of all samples).

Atopic dermatitis

Atopic dermatitis (AD) is a heterogeneous and multifactorial disease. Although it has been suggested that a personalized approach to each patient is important for understanding AD, appropriate methods for this purpose have not yet been established. This study aims to clarify the diverse pathophysiology of human AD by integrating and analyzing the genome, transcriptome and multimodal clinical information of AD patients, and to establish a foundation for personalized predictive medicine according to the pathophysiology of the disease.

We have collected multi-omics and multi-modal clinical data from more than 200 AD patients and 50 healthy controls. By applying machine learning techniques to these data, we have identified immunological signatures that lead to two representative skin phenotypes, as well as the possibility that clinical symptoms and endotypes are closely related longitudinally. These findings suggest that patient stratification focused on endotypes is feasible. In addition, skin tissue transcriptome analysis revealed immune dynamics associated with the therapeutic efficacy of an immunotherapeutic (dupilumab, a mAb that blocks IL4 and IL13), suggesting that metagen-specific marker genes derived from our data analysis may contribute to predicting therapeutic efficacy and disease monitoring.

We have also collected data from mouse models of AD. Through human-mouse data integration, we identified several novel AD drug targets. We are also actively promoting drug discovery projects and have already obtained seed compounds through collaborative research with the University of Tokyo, Keio University School of Medicine, and RIKEN DMP.

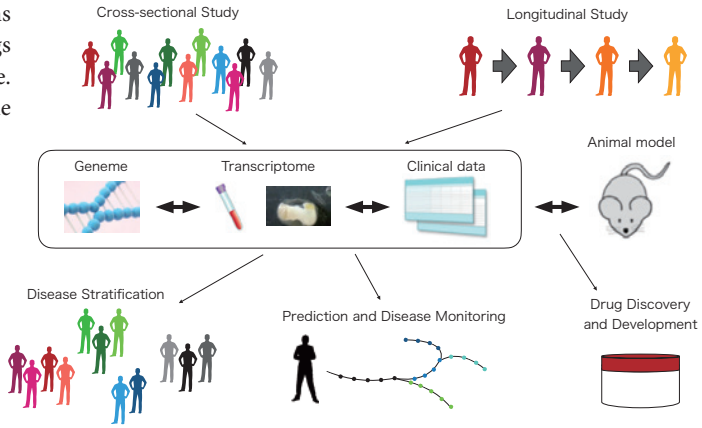


Figure: Study workflow: Data-driven research for Atopic Dermatitis

Combining cross-sectional and longitudinal studies, omics data, mainly genomic and transcriptomic, and clinical multimodal data were collected from cooperative clinical research institutes (in collaboration with Keio University). These will be used for disease stratification and for the development of useful markers for disease monitoring and prediction using machine learning and mathematical techniques. Furthermore, by analyzing these data in combination with animal models, the project also aims to identify new therapeutic targets and develop new therapeutic agents.

iPS Project

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

The facility has operated an IMS Cell Manufacturing Unit to produce iPS-derived human invariant NKT (Vα24⁺iNKT) cells under Good Manufacturing Practice/Good Gene, Cellular, and Tissue-based Products Manufacturing Practice guidelines. The facility has been conducting a clinical trial of iPS-Vα24⁺iNKT cells for head and neck cancer. We have also been planning another clinical trial using a combination therapy with iPS-Vα24⁺iNKT cells and activated dendritic cells for head and neck cancer and it will be started in the next year.

To maximize the efficacy of iPS-Vα24⁺iNKT cells, the facility has focused on introduction of Chimeric Antigen Receptors (CARs) into iPS-Vα24⁺iNKT cells. Among several CARs, the facility chose CD19 and CD25 CARs to treat leukemia. In 2022, we showed a proof of concept. CD19-CAR iPS-Vα24⁺iNKT cells suppressed leukemia in mice. Currently, we are generating GMP grade CD19-CAR iPS cells for a future clinical trial.

The facility also has been developing a protocol with shorter culture times and higher induction efficiency. We have found that iPS-derived early progenitors are multipotential for cell fate determination prior to lymphoid-lineage commitment in our current protocol, which possibly causes low induction efficiency. Thus we are going to improve this with chemical compounds and/or cytokines.

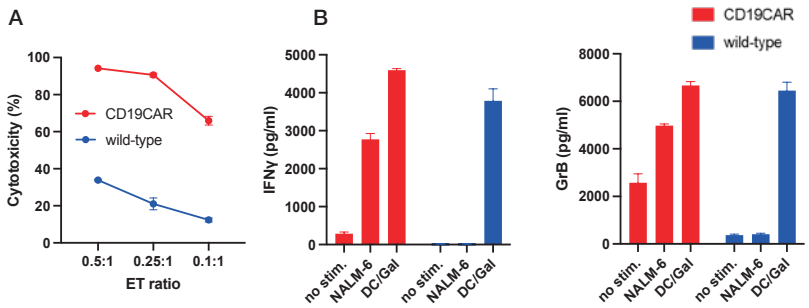


Figure: Anti-tumor effects of CD19CAR iPS-NKT
A) Direct cytotoxicity of CD19CAR iPS-NKT and wild-type iPS-NKT toward the CD19⁺ NALM-6 human leukemia cell line. B) IFN-γ and GrB production by CD19CAR iPS-NKT and wild-type iPS-NKT cocultured with NALM-6 ± α-galactosylceramide-pulsed dendritic cells (DC/Gal).

Humanized Mice

Humanized Mice, a xenograft system reconstituted with normal or malignant human stem cells, have been utilized in wide areas of biological and medical sciences. RIKEN IMS has made an effort to overcome a limitation of the species barrier by inducing the expression of human cytokines or adhesion molecules, which better recapitulates normal human blood and immune systems in the mouse.

For the past decade, the engineering of immune cells and immune checkpoint blockade have emerged as promising treatment modalities to reactivate patient immune cells that have become dysfunctional or exhausted. In the Humanized Mouse model, we aim to elucidate whether the xenograft model can be useful to assess such immune-oncology treatments and to develop new CAR-T cell therapies for poor prognosis leukemia. Using CAR-T cells targeting CD25, CD19 and CD7, we evaluated to what extent the engineered T cells can eradicate patient leukemic cells in multiple organs in patient-derived xenografts for AML, CML and ALL. In particular, the synergistic effect of inhibiting patient-specific vulnerability molecules and of targeting cell surface molecules in the leukemia resulted in robust eradication of patient leukemic cells in multiple organs such as bone marrow, spleen, liver, and peripheral blood (Figure).

Taking advantage of the Humanized Mice, we found how CAR-T cells behaved in organs at distinct time points after infusion. We are now connecting Humanized Mice with single-cell genomics to find out which genes and networks account for potent treatment efficacy of the newly-developed engineered T cells *in vivo*.

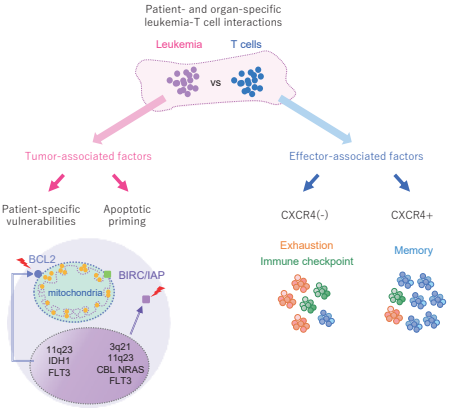


Figure: How to achieve long-term remission for patients suffering from aggressive leukemia
Tumor-associated determinants of leukemia survival include patient-specific critical molecules such as BCL2, MCL1 and IAPs, based on distinct mutations and chromosomal abnormalities (Nature Cancer 2021). By identifying and inhibiting patient-specific vulnerabilities, AML cells become primed for apoptosis and cell death. Pretreatment with inhibitors of patient-specific survival molecules facilitates both immediate and short-term CAR-T cell efficacy and acquisition of immunological memory leading to long-term leukemia suppression. Effector-associated determinants of leukemia eradication include the expression of CXCR4 in CAR-T cells targeting patient-specific cell surface molecules. CXCR4 expression enhances memory CAR-T cell formation and prevents immune checkpoint activation and T cell exhaustion in the context of *in vivo* leukemia-T cell interactions.

Cancer Immunology

The immune system can recognize tumor cells and mediate antigen-specific tumor rejection under certain conditions, however the tumors often evade the immune network. Understanding the tumor immune microenvironment (TIME) will lead to a variety of approaches designed to initiate or enhance antitumor immunity (Figure). The groups in Cancer Immunology are investigating the target molecules and cells and developing a disease stratification system and treatment strategy. Tsunoda's group (Lab for Medical Science Mathematics) reported that the status of the tumor microenvironment and its neoantigen composition will be promising new prognostic biomarkers with potential clinical relevance. Nakagawa's group (Lab for Cancer Genomics) analyzed whole genome, RNAseq and single-cell RNAseq data from the TIME of several cancers. They found that the presence of granulocytes is likely to be associated with response to the treatment. Ishikawa's group (Lab for Human Disease Models) developed a CAR-T cell therapy for myeloid leukemia targeting CD25/IL2RA and also found that engineering the CAR-T cells to express CXCR4 enhances their ability to eradicate leukemic cells. Fujii's group (Lab for Immunotherapy) has made progress with their aAVC projects for cancer. They developed NY-ESO-1-expressing aAVC that showed immunological and anti-tumor effects in a preclinical study. For the aAVC-WT1, they started a Phase II clinical study as multicenter joint research. In addition, Koseki's group (Lab for Developmental Genetics) has started an iPS-NKT cell clinical trial for head and neck cancer. These translational research projects have been supported by an interaction between IMS and the RIKEN Program for Drug Discovery and Medical Technology Platforms.

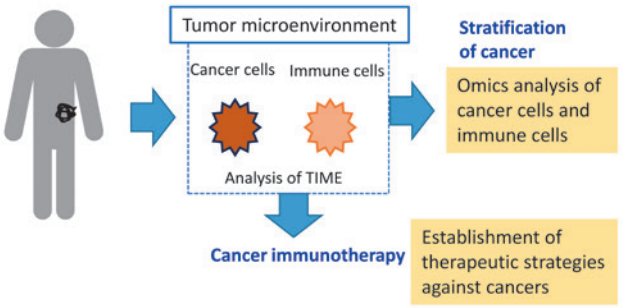


Figure:
Our groups work on two strategies by analyzing the tumor immune microenvironment (TIME). One is for the stratification of tumor tissue through an omics analysis of tumor cells and the TIME, the other one is for the establishment of new cancer immunotherapies.

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

IMS collaborates with DMP to develop innovative new biologics, pharmaceuticals and medical technologies by facilitating the transfer of basic research discoveries within the institute. DMP supports all phases of the development of new therapeutics, from the discovery of promising targets to the identification of potential lead compounds and the acquisition of intellectual property rights to drugs and technologies that can then be brought to the development phase.

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 has contributed to this effort by setting up a facility for the development of antibody drugs, the Drug Discovery Antibody Platform Unit, and the artificial Adjuvant Vector Cell (aAVC) Drug Translational Unit. In 2022, IMS had eight collaborative programs with DMP: Development of aAVC expressing WT1, human papillomavirus (HPV) or SARS-CoV-2 antigen (aAVC-WT1,-HPV and -CoV-2) for cancer and infectious diseases (Shin-ichiro Fujii), iPS-derived NKT cells for cancer (Haruhiko Koseki), Neutralizing mAb for hepatitis B virus infection (Kazuaki Chayama), Development of mAb for multiple sclerosis (Takashi Saito), mAb for TMPRSS to prevent SARS-CoV-2 infection (Takashi Saito), and Development of a drug for atopic dermatitis (Tomohiro Miyai). The investigator-initiated Phase II clinical trial of aAVC-WT1 against AML is ongoing. In addition, an iPS-NKT cell phase I clinical trial for head and neck cancer has started.

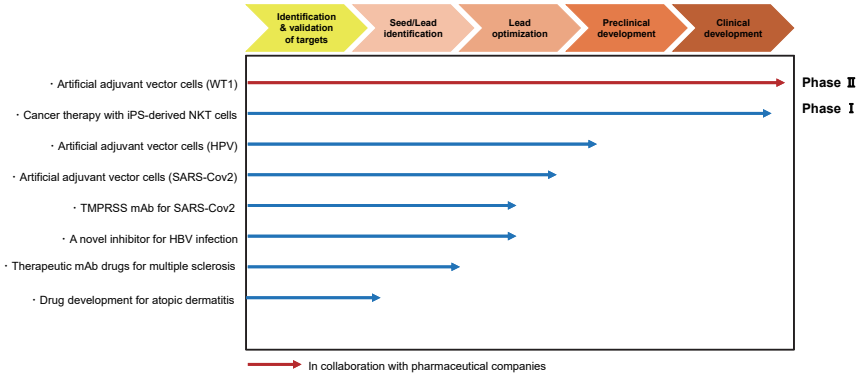
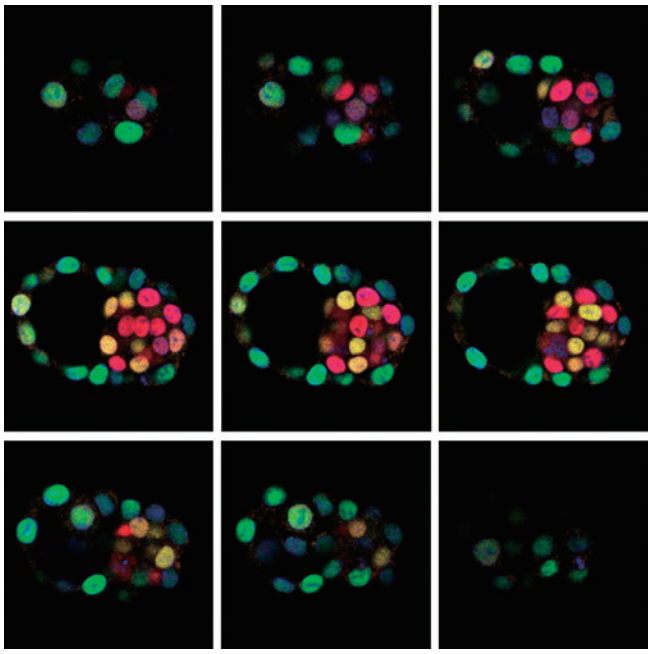


Figure: Collaboration between IMS and DMP for the development of innovative new biologics, pharmaceuticals and medical technologies

Part 4

Events



RIKEN IMS-Stanford ISCBRM Joint Symposium

IMS and Stanford University Institute for Stem Cell Biology and Regenerative Medicine (ISCBRM) have held a series of joint symposiums since 2017. The annual joint symposium has been successfully held in Yokohama and Stanford alternately, and the 6th joint symposium for FY2022 was hosted by RIKEN IMS. Due to COVID-19, it was held online on February 21 and 22, 2023 in Japan time. The symposium was started with the opening remarks by the new director of Stanford ISCBRM, Ravi Majeti, followed by the first session focusing on heart and lung development by Casey Gifford (Stanford), Kaoru Ito (RIKEN), Karen Gonzalez (Stanford), and Maria Martinez (Stanford). The next session was on molecular mechanisms of cell differentiation and disease development by Chengcheng Zou (RIKEN), Sidd Jaiswal (Stanford), and Tetsuro Kobayashi (RIKEN). The third session on day two was about multi-modal and multi-cellular biology by Kazuyoshi Ishigaki (RIKEN), Berfin Azizoglu (Stanford), and Tatsuya Ishikawa (RIKEN). The final session featured human disease biology by Yimiao Qu (Stanford), Hiroshi Ohno (RIKEN), and Ravi Majeti (Stanford). Despite the distance and time-zone difference, we had about 50 participants on both days, and had very active discussions after each talk. The symposium was concluded with IMS Director Kazuhiko Yamamoto's closing remarks hoping to have an in-person meeting for the 7th.

The 5th Tsinghua-RIKEN Joint Workshop

The 5th Tsinghua-RIKEN Joint Workshop, "Recent Progress in Immunology," was held online on November 25, 2022. This joint workshop was originally planned to be held in Beijing in 2020, but it had to be postponed for 2.5 years because of the pandemic. The organizers, Dr. Yun-cai Liu of the Institute of Immunology Tsinghua University (IITU), and Dr. Tomohiro Kurosaki of RIKEN IMS, decided to hold the joint meeting virtually this time. In the opening remarks, Dr. Xiaoyu Hu, the new Director of IITU, and Dr. Kazuhiko Yamamoto, the new Director of RIKEN IMS, applauded resuming joint activities. The meeting gathered 265 participants. The talks covered recent hot topics in immunology such as T-B cell biology by Drs. Hai Qi, Cheng Dong, Kurosaki, and Koseki, innate immunity by Drs. Moro, Coco Chu, and Xiao-Yu Hu, tissue-specific immunology by Drs. Ohno, Xiao-huan Guo, and Wenwen Zeng, translational immunology by Drs. Min Peng, Akiyama, Ishigaki, and Chung-Chau Hon, and finally clinical immunology by Drs. Huji Xu and Yamamoto. After each talk, active questions followed orally, and the discussions continued in the chat. The meeting was closed by Dr. Hai Qi, the dean of School of Medicine in Tsinghua University, and Dr. Tomohiro Kurosaki, sharing their hope for an in-person meeting next time and the mutual visits between the two institutions. RIKEN-Tsinghua International Summer Program is planned to be held in Yokohama in June 2023.

Keio-IMS Joint Symposium

In July 2022, a Keio-IMS joint symposium titled "Single Cell Biology and Clinical Applications" was held in collaboration with Keio University School of Medicine in a hybrid format.

The advances in single-cell profiling technology have opened up new avenues for analyzing molecular signatures in many cells with the single-cell-level resolution, thus providing immense opportunities for the advancement of medicine. RIKEN IMS launched a research collaboration project with Keio University School of Medicine (Keio-RIKEN HuMED) in April 2021 to leverage the knowledge gained from single-cell analysis of human clinical samples for various diseases and maximize the social benefit of human biology and medicine. In order to facilitate this collaboration, the KEIO-RIKEN Joint Research Lab was established on Keio University Shinanomachi campus, fostering innovative collaborations between the advanced genomic profiling technologies of RIKEN IMS and the well-established basic and clinical research at Keio University School of Medicine.

To share the ongoing achievement and stimulate further collaborations, this symposium was held to bring together researchers from RIKEN IMS and Keio University, and featured nine presentations about current collaborations and the latest studies with potential for future collaboration. There were 161 participants that attended onsite or online and enjoyed active discussions on studies utilizing state-of-the-art single-cell technologies. The symposium concluded with a consensus that continued collaboration and interdisciplinary approaches are crucial for driving progress and growth.

RIKEN-McGill Symposiums

Since 2016, 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. The first comprehensive cooperation agreements/MOUs between the two institutes were even earlier, in July 2010. Starting from the first symposium, which was held in May 2017 at McGill University, Montreal, Canada, we had annual symposia either at McGill University, Montreal or Yokohama, Japan. These past symposia encompassed the research areas of genome biology, human genome medicine, immunology and infectious disease, and cancers. However, symposia had been impossible to hold in person since 2020 due to the world-wide pandemic of SARS-CoV-2. Therefore, we kept this partnership by organizing a virtual online symposium in 2021. After the pandemic settled down, we were very pleased to restart on-site symposium in 2022. The 5th symposium was held on September 19 and 20, 2022 at McGill University in hybrid style. We had 10 people from RIKEN IMS visit McGill University and 6 people from Japan present their work online. On the second day, we discussed the topic of biological ethics to further stimulate international collaborations using human-derived materials/information. In total, 115 people attended the symposium in person or online. We enjoyed discussion in person and realized the merit of holding the symposium on site to advance this international activity, and we plan to organize the 6th symposium to be held in Yokohama, Japan in 2023/2024.

RIKEN-KI/SciLifeLab & Student Exchange

The 8th RIKEN-KI-SciLifeLab Symposium with the title *Preparing for the next pandemic* was held October 20, 2022 at the Science for Life Laboratory (SciLifeLab) in Stockholm. The all-day symposium started with welcome notes by the Karolinska Institutet (KI), SciLifeLab, and IMS directors, followed by 16 scientific presentations including the political, organizational, and practical aspects of preparedness for potentially upcoming pandemics, with a focus on Japan and Sweden.

The first RIKEN-KI Doctoral Exchange was conducted in conjunction with the symposium. Twelve doctoral students from RIKEN stayed in KI and SciLifeLab host research groups for two weeks. The exchange students documented their stays on a BLOG website.

https://sites.google.com/view/riken-ki-exchange/home

The day after the symposium, the RIKEN delegation of speakers and doctoral students visited the European Centre for Disease Prevention and Control (ECDC) in Stockholm (left photo).

The Japanese ambassador to Stockholm invited the symposium speakers, doctoral students, and their Swedish host research group leaders to a reception at the ambassador's residence (right photo). (left to right): Stefan Norén (former Ambassador of Sweden to Japan), Dr. Kazuhiko Yamamoto, Masaki Noke (Ambassador of Japan to Sweden), Dr. Olli Kallioniemi (Director of SciLifeLab), Dr. Kazuyuki Kuroda (Director of JSPS Stockholm Office), Dr. Ole Petter Ottersen (Director of KI).

Adjunct Professorship Programs

IMS collaborates with and accepts graduate students from 8 domestic university graduate schools. There are now a total of 33 adjunct professors/associate professors at IMS (Table), and 64 students who had studied at IMS in 2022. On May 21, 2022, 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	Kazuyo Moro (Professor) Takashi Saito (Visiting Professor) Takashi Tanaka (Visiting Professor) Shiro Ikegawa (Visiting Professor)
Graduate School of Medicine, Chiba University	Haruhiko Koseki (Professor) Hiroshi Ohno (Visiting Professor) Ichiro Taniuchi (Visiting Professor) Shin-ichiro Fujii (Visiting Professor) Fumihiko Ishikawa (Visiting Professor)
Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University	Ichiro Taniuchi (Visiting Professor)
Graduate School of Medicine, Yokohama City University	Shiro Ikegawa (Visiting Professor) Hidewaki Nakagawa (Visiting Professor) Taisei Mushiroda (Visiting Professor) Yukihide Momozawa (Visiting Professor) Kaoru Ito (Visiting Professor) Momoko Horikoshi (Visiting Professor)
Graduate School of Medical Life Science, Yokohama City University	Hiroshi Ohno (Visiting Professor) Makoto Arita (Visiting Professor) Takaharu Okada (Visiting Professor) Taishin Akiyama (Visiting Professor) Yukihide Momozawa (Visiting Professor) Takahiro Suzuki (Visiting Associate Professor) Takeya Kasukawa (Visiting Associate Professor) Hazuki Takahashi (Visiting Assistant Professor)
Research Institute of Biological Sciences, Tokyo University of Science	Masato Kubo (Professor) Takashi Saito (Visiting Professor)
Graduate School of Medicine, Keio University	Masayuki Amagai (Professor) Kenya Honda (Professor) Haruhiko Koseki (Visiting Professor) Takaharu Okada (Visiting Professor) Ichiro Taniuchi (Visiting Professor) Sidonia Fagarasan (Visiting Professor)
Graduate School of Science, Tokyo Metropolitan University	Azusa Inoue (Visiting Associate Professor)

Yokohama Campus Open Day 2022

After two years of only being an online event due to COVID-19 restrictions, Yokohama Campus Open Day was a hybrid event this year. There were five events from IMS for Yokohama Campus Open Day.

The teams that contributed to the events this year and their contents:

- Immunosurveillance and immunotherapy against cancer and infectious diseases, from Laboratory for Immunotherapy.
- Let's watch the moment of fertilization, from Laboratory for Epigenome Inheritance.
- Lab tour of the next generation sequencers, from Laboratory for Comprehensive Genomic Analysis.
- Alcohol patch tests to determine whether you have high or low alcohol tolerance, from Laboratory for Human Immunogenetics.
- What is "Ethics on Genomics"? from Laboratory for Genotyping Development and Office of the Center Director.

IMS Social Implementation Seminar Series

This seminar series, launched this year, aims to help young researchers develop a mindset that will enable them to consider entrepreneurship as a future development of their research results. The ultimate goal for this series is to enable young researchers to take action with confidence by providing them with a concrete image of the path to entrepreneurship, the incentives they will receive if they succeed, and examples of successes and failures and their causes.

The seminar series featured regular lectures by invited experts in the field of venture establishment. Each speaker considered content to arouse young researchers' interest in social implementation and to give them hope that their own research could also lead to social implementation.

This year's seminar arrangements are as follows.

Table: IMS Social Implementation Seminar 2022

Date	Spekers
9/30	**Dr. Atsushi Usami** UTEC (The University of Tokyo Edge Capital Partners Co., Ltd.)
12/9	**Dr. Takaaki Nomoto** JST (The Japan Science and Technology Agency) **Dr. Yoji Jokura** Chairman and Exective Director, CoreTissue BioEngineering Inc.

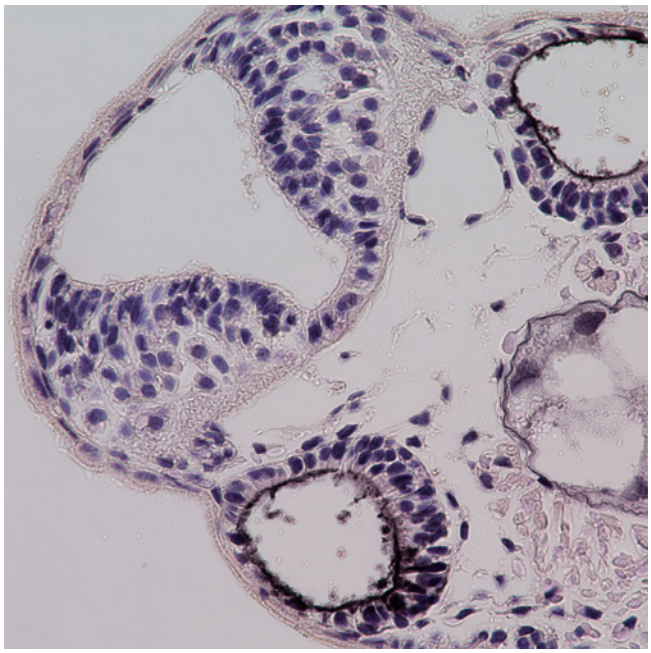
Guest Lectures 2022

Table: Guest Lectures Jan-Dec 2022

Date	Speaker	Affiliation	Country	Title
Jan. 11	Prof. Kaori Muto	Dept. of Public Policy, University of Tokyo Medical Science Research Institute	Japan	Patient Public Involvement (PPI) in basic biomedical research
Jan. 20	Dr. Taro Kitazawa	Transcriptional and Epigenetic Regulation of Craniofacial and Neuronal Development Group, Friedrich Miescher Institute for Biomedical Research	Switzerland	Epigenetic and transcriptional regulation of neuronal activity-response genes
Jan. 26	Prof. Sonia Sharma	La Jolla Institute for Immunology	USA	Mapping and mining the innate immune response for cancer immunotherapeutics
Feb. 22	Dr. Andrea Cerase	Queen Mary University of London	United Kingdom	lncRNAs biology and function: The example of Xist RNA
Jul. 14	Dr. Takuya Yamamoto	National Institutes of Biomedical Innovation, Health and Nutrition	Japan	The study of heterogeneity of age-related immune response by high-dimensional single-cell FACS analysis for vaccine development
Jul. 20	Dr. Hiroshi Kudoh	Center for Ecological Research, Kyoto University	Japan	Phenology of epigenetic regulation: long-term analyses of H3K27me3 and H3K4me3 in a natural plant population
Aug. 17	Dr. Yuka W. Iwasaki	Keio University School of Medicine, Japan	Japan	Understanding and reconstructing small RNA mediated heterochromatin formation
Aug. 29	Dr. Shigeki Nakagome	School of Medicine, Trinity College Dublin	Ireland	A paleogenomic time-travel through agricultural transformation at the edge of Asia
Sep. 27	Dr. Tomoichiro Miyoshi	Graduate School of Biostudies, Kyoto University, Japan	Japan	Mechanisms of human LINE-1 retrotransposition
Sep. 28	Dr. Nabila Bouatia-Naji	Paris-Cardiovascular Research Center, Inserm, Université de Paris	France	The genetic risks of ischemic heart disease in women
Sep. 30	Dr. Atsushi Usami	The University of Tokyo Edge Capital Partners Co., Ltd.	Japan	From social implementation of technologies to creation of new industries
Oct. 26	Dr. Caeul Lim	Cell Host & Microbe, Cell Press	USA	Communicating your Science with Cell Press
Nov. 7	Dr. Paul Wilmes	Systems Ecology, Luxembourg Centre for Systems Biomedicine, University of Luxembourg	Luxemburg	The human expobiome in health and disease
Nov. 9	Prof. David Torrents Arenales	ICREA Research Professor, Computational Genomics Group Leader, Barcelona Supercomputing Centre	Spain	Genomics and Biomedical research at the Barcelona Supercomputing Center
Nov. 29	Prof. Naoto Hirano	University of Toronto/Senior Scientist, Princess Margaret Cancer Centre	Canada	Immunology Meets Bioengineering: Improving the Effectiveness of Adoptive T Cell Therapy
Dec. 5	Dr. Donna L. Farber	Department of Microbiology and Immunology, Columbia University	USA	The changing landscape of human tissue immunity over life
Dec. 9	1. Mr. Nomoto Takaaki 2. Dr. Jokura Yoji	1. Japan Science and Technology Agency (JST) 2. Jokura: CoreTissue BioEngineering Inc.	Japan	1. Start-ups creation and support program conducted by Japan Science and Technology Agency 2. Productization and commercialization of artificial ligament derived from the decellularized animal tissue: a challenge for social implementation as an academia start-up

Part 5

Data and Statistics



IMS PI Seminar

IMS PI Seminar is a monthly seminar aiming to inform all researchers in IMS what projects are undergoing at IMS. Until the end of fiscal year 2021, this seminar series was called IMS CrossTalk, but in the new fiscal year 2022, it was renamed IMS PI Seminar, and the new organizers, Azusa Inoue and Kaoru Ito, started to hold it in a hybrid style (onsite and online). This is expected to facilitate collaboration among IMS. Since RIKEN IMS was formed through the merger of the previous IMS and the Division of Genomic Technologies (DGT), IMS became more comprehensive while centering on genomics and immunology. As such, interactions and collaborations between the researchers have become more relevant to achieve our mission in IMS, which is to elucidate the pathogenesis of human diseases and establish new diagnostic and therapeutic methods, followed by contributing to the development of new medicine for the benefit of society.

"Seminar" is an important venue for publicizing one's own research to an audience, while the feedback from seminar participants can help uncover new collaboration possibilities and gather information from different perspectives.

To achieve this purpose, speakers are expected to introduce their laboratory activities focusing on an emerging topic with a broad introduction and general perspectives. Additionally, a facilitator, who is familiar with the topic and builds a bridge between a presenter and the audience more tightly, is assigned to promote the discussion.

There was a total of 20 talks in 2022 and the IMS Crosstalk/PI Seminar continues to play a significant role to promote the IMS mission.

Table: IMS PI Seminar 2022

From January to March in 2022, it was held as the IMS CrossTalk.

Date	Talk 1		Talk 2		Theme(s)
	Speaker	Facilitator	Speaker	Facilitator	
1/21	Fumihiko Ishikawa	*C.C. Hon*	Hideya Kawaji	*M. de Hoon*	Immunology/Cancer
2/18	Kazuyoshi Ishigaki	*C. Terao*	Jun Seita	*A. Inoue*	–
3/18	Toshimori Kitami	*K. Yugi*	Yukinori Okada	*K. Ishigaki*	–
5/27	Aki Minoda	*S. Fagarasan*	Hiroshi Ohno	*S. Fagarasan*	Epigenetics & Microbiome
6/17	Kaoru Ito	*M. Horikoshi*	Momoko Horikoshi	*K. Ito*	Genetics
7/15	Takashi Tanaka	*I. Taniuchi*	Chikashi Terao	*K. Ishigaki*	Genetics & Immunology
9/16	Fumihiko Ishikawa	*M. de Hoon*	Michiel de Hoon	*F. Ishikawa*	Immunology & RNA
10/28	Jay Shin	*T. Kasukawa*	Haruhiko Koseki	*A. Inoue*	RNA & Hematopoiesis
11/18	Kenya Honda	*S. Fagarasan*	Makoto Arita	*A. Inoue*	Microbiome & Metabolome
12/16	Wataru Suda	*H. Ohno*	Kiyokazu Kakugawa	*I. Taniuchi*	Microbiome & Immunology

IMS Researcher Seminar 2022

The IMS Researcher Seminar series was held once every month with the aim of promoting scientific discussions among young researchers at IMS, introducing research activities conducted in the IMS laboratories, improving presentation skills of young researchers at IMS, and preparing researchers for presenting outside of RIKEN. At the seminars, research scientists, postdocs, research associates, and graduate students presented their work. They received questions from the audience and comments from the chair at the end of their talks, and intriguing ideas were exchanged.

Table: IMS Researcher Seminar 2022

Date	Chair	Speakers	Laboratory	Position
1/21	Yukihide Momozawa	Daiki Takewaki	Laboratory for Microbiome Sciences	Student Trainee
		Haruki Uchino	Laboratory for Metabolomics	Junior Research Associate
2/18	Makoto Arita	Raku Son	RIKEN-IFOM Joint Laboratory for Cancer Genomics	Junior Research Associate
		Yusuke Ogata	Laboratory for Microbiome Sciences	Research Scientist
3/18	Taisei Mushiroda	Saumya Agrawal	Laboratory for Applied Computational Genomics	Research Scientist
		Jonathan Moody	Laboratory for Genome Information Analysis	Research Scientist
4/15	Yukinori Okada	Jessica Severin	Laboratory for Applied Computational Genomics	Technical Scientist
		Imad Abugessaisa	Laboratory for Large-Scale Biomedical Data Technology	Senior Scientist
5/13	Kazuyoshi Ishigaki	Ryoko Yamada	Laboratory for Genotyping Development	Visiting Scientist
		Xiaoxi Liu	Laboratory for Statistical and Translational Genetics	Research Scientist
6/17	Azusa Inoue	Yuuri Yasuoka	Laboratory for Comprehensive Genomic Analysis	Research Scientist
		Junichiro Takano	Laboratory for Developmental Genetics	Postdoctoral Researcher
7/15	Tatsuhiko Tsunoda	Junichi Maruyama	Laboratory for Integrated Cellular Systems	Research Scientist
		Satoshi Morozumi	Laboratory for Metabolomics	Junior Research Associate
9/16	Tomohiro Kurosaki	Aneela Nomura	Laboratory for Transcriptional Regulation	Postdoctoral Researcher
		Ryo Nakagawa	Laboratory for Human Disease Models	Junior Research Associate
10/14	Toshimori Kitami	Yuya Kiguchi	Laboratory for Microbiome Sciences	Visiting Scientist
		Aiko Sekita	Laboratory for Developmental Genetics	Research Scientist
11/18	Yasuhiro Murakawa	Julio Jesus Leon Incio	Laboratory for Advanced Genomics Circuit	Research Scientist
		XianYang Qin	Laboratory for Cellular Function Conversion Technology	Research Scientist
12/16	Kenya Honda	Chisayo Kozuka	Laboratory for Epigenome Inheritance	Special Postdoctoral Researcher
		Takashi Ito	Laboratory for Intestinal Ecosystem	Visiting Researcher

Publications 2022

Table: IMS Publications from January to December, 2022

Journal	Impact Factor (2021)	Number of papers
Nat Rev Immunol	108.6	1
Nat Med	87.2	1
Nature	69.5	7
Cell	66.9	5
Science	63.8	2
Nat Rev Genet	59.9	1
Immunity	43.5	1
Nat Genet	41.4	8
Circulation	39.9	1
Gastroenterology	33.9	2
JAMA Oncol	33.0	1
Annu Rev Immunol	32.5	1
Cell Metab	31.4	1
Nat Immunol	31.3	3
Sci Immunol	30.7	4
JAMA Cardiol	30.2	1
J Hepatol	30.1	1
Nat Biomed Eng	29.2	1
Nat Cell Bio	28.2	1
Ann Rheum Dis	28.0	3
Blood	25.7	3
Nat Hum Behav	24.3	1
Nat Metab	19.9	1
J Clin Invest	19.5	1
Trends Cancer	19.2	1
Nucleic Acids Res	19.2	1
Nat Struct Mol Biol	18.4	1
Genome Biol	18.0	1
Nat Commun	17.7	17
J Exp Med	17.6	4
Hepatology	17.3	1
Cell Rep Med	17.0	2
Arthritis Rheumatol	15.5	2
Sci Adv	15.0	2
J Autoimmun	14.5	1
Ophthalmology	14.3	1
EMBO J	13.8	1
Clin Gastroenterol Hepatol	13.6	1
Genes Dev	12.9	1
J Immunother Cancer	12.5	1
Neurology	12.3	1
Psychiatry Clin Neurosci	12.1	1
Int J Infect Dis	12.1	2
BMC Med	11.8	1
Semin Immunopathol	11.8	1
EBioMedicine	11.2	1
Adv Healthc Mater	11.1	1
Am J Hum Genet	11.0	1
Sci Total Environ	10.8	1
Arterioscler Thromb Vasc Biol	10.5	1
Inflamm Regen	10.4	3
Pharmacol Res	10.3	1
Mol Ther Nucleic Acids	10.2	1
Others		190
Total		**296**

1 Abdelhamid RF, Ogawa K, Beck G, Ikenaka K, Takeuchi E, Yasumizu Y, Jinno J, Kimura Y, Baba K, Nagai Y, Okada Y, Saito Y, Murayama S, Mochizuki H, Nagano S. piRNA/PIWI Protein Complex as a Potential Biomarker in Sporadic Amyotrophic Lateral Sclerosis. ***Mol Neurobiol*** 59, 1693-1705 (2022)

2 Abe K, Kitago M, Kosaki K, Yamada M, Iwasaki E, Kawasaki S, Mizukami K, Momozawa Y, Terao C, Yagi H, Abe Y, Hasegawa Y, Hori S, Tanaka M, Nakano Y, Kitagawa Y. Genomic analysis of familial pancreatic cancers and intraductal papillary mucinous neoplasms: A cross-sectional study. ***Cancer Sci*** 113, 1821-1829 (2022)

3 Adachi Y, Ueda K, Ito K, Nomura S, Takimoto E, Komuro I. Beiging Of Perivascular Adipose Tissue Regulates Its Inflammation And Vascular Remodeling. ***Arteriosclerosis Thrombosis and Vascular Biology*** 42, a354-a354 (2022)

4 Adachi Y, Ueda K, Nomura S, Ito K, Katoh M, Katagiri M, Yamada S, Hashimoto M, Zhai B, Numata G, Otani A, Hinata M, Hiraike Y, Waki H, Takeda N, Morita H, Ushiku T, Yamauchi T, Takimoto E, Komuro I. Beiging of perivascular adipose tissue regulates its inflammation and vascular remodeling. ***Nat Commun*** 13, 5117 (2022)

5 Akamatsu S, Terada N, Takata R, Kinoshita H, Shimatani K, Momozawa Y, Yamamoto M, Tada H, Kawamorita N, Narita S, Kato T, Nitta M, Kandori S, Koike Y, Inazawa J, Kimura T, Kimura H, Kojima T, Terachi T, Sugimoto M, Habuchi T, Arai Y, Yamamoto S, Matsuda T, Obara W, Kamoto T, Inoue T, Nakagawa H, Ogawa O, group ob. Clinical Utility of Germline Genetic Testing in Japanese Men Undergoing Prostate Biopsy. ***JNCI Cancer Spectr*** 6, pkac001 (2022)

6 Akamine Y, Millman JF, Uema T, Okamoto S, Yonamine M, Uehara M, Kozuka C, Kaname T, Shimabukuro M, Kinjo K, Mitsuta M, Watanabe H, Masuzaki H. Fermented brown rice beverage distinctively modulates the gut microbiota in Okinawans with metabolic syndrome: A randomized controlled tria. ***Nutrition Research*** 103, 68-81 (2022)

7 Akita N, Okada R, Mukae K, Sugino RP, Takenobu H, Chikaraishi K, Ochiai H, Yamaguchi Y, Ohira M, Koseki H, Kamijo T. Polycomb group protein BMI1 protects neuroblastoma cells against DNA damage-induced apoptotic cell death. ***Exp Cell Res*** 422, 113412 (2022)

8 Akiyama M, Miyake M, Momozawa Y, Arakawa S, Maruyama-Inoue M, Endo M, Iwasaki Y, Ishigaki K, Matoba N, Okada Y, Yasuda M, Oshima Y, Yoshida S, Nakao S, Morino K, Mori Y, Kido A, Kato A, Yasukawa T, Obata R, Nagai Y, Takahashi K, Fujisawa K, Miki A, Nakamura M, Honda S, Ushida H, Yasuma T, Nishiguchi K, Mori R, Tanaka K, Wakatsuki Y, Yamashiro K, Kadonosono K, Terao C, Chikashi T, Tsujikawa A, Sonoda K, Kubo M, Kamatani Y. GWAS of age-related macular degeneration reveals two new loci implying shared genetic components with central serous chorioretinopathy. ***Ophthalmology*** 130, 361-372 (2022)

9 Al-Jawahiri R, Foroutan A, Kerkhof J, McConkey H, Levy M, Haghshenas S, Rooney K, Turner J, Shears D, Holder M, Lefroy H, Castle B, Reis LM, Semina EV, University of Washington Centre for Mendelian Genomics (UW-CMG); Lachlan K, Chandler K, Wright T, Clayton-Smith J, Hug FP, Pitteloud N, Bartoloni L, Hoffjan S, Park S, Thankamony A, Lees M, Wakeling E, Naik S, Hanker B, Girisha KM, Agolini E, Giuseppe Z, Alban Z, Tessarech M, Keren B, Afenjar A, Zweier C, Reis A, Smol T, Tsurusaki Y, Nobuhiko O, Sekiguchi F, Tsuchida N, Matsumoto N, Kou I, Yonezawa Y, Ikegawa S, Callewaert B, Freeth M, Genomics England Research Consortium; Lotte Kleinendorst L, Donaldson A, Alders M, Paepe AD, Sadikovic B, McNeill A. SOX11 variants cause a neurodevelopmental disorder with infrequent ocular malformations and hypogonadotropic hypogonadism and with distinct DNA methylation profile. ***Genet Med*** 24, 1261-1273 (2022)

10 Andrew TW, Koepke LS, Wang Y, Lopez M, Steininger H, Struck D, Boyko T, Ambrosi TH, Tong X, Sun Y, Gulati GS, Murphy MP, Marecic O, Telvin R, Schallmoser K, Strunk D, Seita J, Goodman SB, Yang F, Longaker MT, Yang GP, Chan CK. Sexually dimorphic estrogen sensing in skeletal stem cells controls skeletal regeneration. ***Nat Commun*** 13, 6491 (2022)

11 Aoki H, Isobe Y, Yoshida M, Kang JX, Maekawa M, Arita M. Enzymatically-epoxidized docosahexaenoic acid, 19,20-EpDPE, suppresses hepatic crown-like structure formation and nonalcoholic steatohepatitis fibrosis through GPR120. ***Biochim Biophys Acta Mol Cell Biol Lipids*** 1868, 159275 (2022)

12 Aragam KG, Jiang T, Goel A, Kanoni S, Wolford BN, Atri DS, Weeks EM, Wang M, Hindy G, Zhou W, Grace C, Roselli C, Marston NA, Kamanu FK, Surakka I, Venegas LM, Sherliker P, Koyama S, Ishigaki K, Åsvold BO, Brown MR, Brumpton B, de Vries PS, Giannakopoulou O, Giardoglou P, Gudbjartsson DF, Güldener U, Haider SM, Helgadottir A, Ibrahim M, Kastrati A, Kessler T, Kyriakou T, Konopka T, Li L, Ma L, Meitinger T, Mucha S, Munz M, Murgia F, Nielsen JB, Nöthen MM, Pang S, Reinberger T, Schnitzler G, Smedley D, Thorleifsson G, von Scheidt M, Ulirsch JC, Arnar DO, Burtt NP, Costanzo MC, Flannick J, Ito K, Jang D, Kamatani Y, Khera AV, Komuro I, Kullo IJ, Lotta LA, Nelson CP, Roberts R, Thorgeirsson G, Thorsteinsdottir U, Webb TR, Baras A, Björkegren JL, Boerwinkle E, Dedoussis G, Holm H, Hveem K, Melander O, Morrison AC, Orho-Melander M, Rallidis LS, Ruusalepp A, Sabatine MS, Stefansson K, Zalloua P, Ellinor PT, Farrall M, Danesh J, Ruff CT, Finucane HK, Hopewell JC, Clarke R, Gupta RM, Erdmann J, Samani NJ, Schunkert H, Watkins H, Willer CJ, Deloukas P, Kathiresan S, Butterworth AS. Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants. ***Nat Genet*** 54, 1803-1815 (2022)

13 Ariyasu Y, Sato Y, Isobe Y, Taniguchi K, Yanagita M, Arita M. Sterol O-Acyltransferase Inhibition Ameliorates High-Fat Diet-Induced Renal Fibrosis and Tertiary Lymphoid Tissue Maturation after Ischemic Reperfusion Injury. ***Int J Mol Sci*** 23, 15465 (2022)

14 Asano F, Tsuboi A, Moriya S, Kato T, Tsuji N, Nakaguma T, Ohno H, Miyamoto H, Kodama H. Amendment of a thermophile-fermented compost to humus improves the growth of female larvae of the Hercules beetle Dynastes hercules (Coleoptera: scarabaeidae). ***J Appl Microbiol*** 134, lxac006 (2022)

15 Baba R, Kabata H, Shirasaki Y, Kamatani T, Yamagishi M, Irie M, Watanabe R, Matsusaka M, Masaki K, Miyata J, Moro K, Uemura S, Fukunaga K. Upregulation of IL-4 receptor signaling pathway in circulating ILC2s from asthma patients. ***J Allergy Clin Immunol Glob*** 1, 299-304 (2022)

16 Baranasic D, Hortenhuber M, Balwierz PJ, Zehnder T, Mukarram AK, Nepal C, Varnai C, Hadzhiev Y, Jimenez-Gonzalez A, Li N, Wragg J, D'Orazio FM, Relic D, Pachkov M, Diaz N, Hernandez-Rodriguez B, Chen Z, Stoiber M, Dong M, Stevens I, Ross SE, Eagle A, Martin R, Obasaju O, Rastegar S, McGarvey AC, Kopp W, Chambers E, Wang D, Kim HR, Acemel RD, Naranjo S, Lapinski M, Chong V, Mathavan S, Peers B, Sauka-Spengler T, Vingron M, Carninci P, Ohler U, Lacadie SA, Burgess SM, Winata C, van Eeden F, Vaquerizas JM, Luis Gomez-Skarmeta J, Onichtchouk D, Brown BJ, Bogdanovic O, van Nimwegen E, Westerfield M, Wardle FC, Daub CO, Lenhard B, Muller F. Multiomic atlas with functional stratification and developmental dynamics of zebrafish *cis*-regulatory elements. ***Nat Genet*** 54, 1037-1050 (2022)

17 Battenberg K, Kelly ST, Ras RA, Hetherington NA, Hayashi M, Minoda A. A flexible cross-platform single-cell data processing pipeline. ***Nat Commun*** 13, 6847 (2022)

18 Bjornsdottir G, Stefansdottir L, Thorleifsson G, Sulem P, Norland K, Ferkingstad E, Oddsson, Zink F, Lund SH, Nawaz MS, Walters G, Skuladottir AT, Gudjonsson SA, Einarsson G, Halldorsson GH, Bjarnadottir V, Sveinbjornsson G, Helgadottir A, Styrkarsdottir U, J Gudmundsson L, Pedersen OB, Hansen TF, Werge, Banasik K, Troelsen A, Skou ST, Thørner LW, Erikstrup C, Nielsen KR, Mikkelsen, D, Bjornsson, Olafsson IH, Ulfarsson E, Blondal, Vikingsson, Brunak S, Ostrowski SR, Ullum H, Thorsteinsdottir U, Stefansson H, Gudbjartsson DF, Thorgeirsson E, Stefansson K, Ikegawa S. Rare SLC13A1 variants associate with intervertebral disc disorder highlighting role of sulfate in disc pathology. ***Nat Commun*** 13, 634-634 (2022)

19 Bo C, Barker CS, Mengle S, Qianbin Z, Rana GK, Wu Y. Multilayered omics reveal sex- and depot-dependent adipose progenitor cell heterogeneity. ***Cell Metab*** 34, 783-799 (2022)

20 Bono H, Sakamoto T, Kasukawa T, Tabunoki H. Systematic Functional Annotation Workflow for Insects. ***Insects*** 13, 586 (2022)

21 Butler-Laporte G, Povysil G, Kosmicki JA, Cirulli ET, Drivas T, Furini S, Saad C, Schmidt A, Olszewski P, Korotko U, Quinodoz M, Çelik E, Kundu K, Walter K, Jung J, Stockwell AD, Sloofman LG, Jordan DM, Thompson RC, Del Valle D, Simons N, Cheng E, Sebra R, Schadt EE, Kim-Schulze S, Gnjatic S, Merad M, Buxbaum JD, Beckmann ND, Charney AW, Przychodzen B, Chang T, Pottinger TD, Shang N, Brand F, Fava F, Mari F, Chwialkowska K, Niemira M, Pula S, Baillie JK, Stuckey A, Salas A, Bello X, Pardo-Seco J, Gómez-Carballa A, Rivero-Calle I, Martinón-Torres F, Ganna A, Karczewski KJ, Veerapen K, Bourgey M, Bourque G, Eveleigh RJ, Forgetta V, Morrison D, Langlais D, Lathrop M, Mooser V, Nakanishi T, Frithiof R, Hultström M, Lipcsey M, Marincevic-Zuniga Y, Nordlund J, Barrett KM, Lee W, Bolze A, White S, Riffle S, Tanudjaja F, Sandoval E, Neveux I, Dabe S, Casadei N, Motameny S, Alaamery M, Massadeh S, Aljawini N, Almutairi MS, Arabi YM, Alqahtani SA, Harthi FS, Almutairi A, Alqubaishi F, Alotaibi S, Binowayn A, Alsolm EA, Bardisy HE, Fawzy M, Cai F, Soranzo N, Butterworth A, Initiative CH, Group DH, Study GM, Center MS, consortium G, Consortium G, Force JC, Center RG, Geschwind DH, Arteaga S, Stephens A, Butte MJ, Boutros PC, Yamaguchi TN, Tao S, Eng S, Sanders T, Tung PJ, Broudy ME, Pan Y, Gonzalez A, Chavan N, Johnson R, Pasaniuc B, Yaspan B, Smieszek S, Rivolta C, Bibert S, Bochud P, Dabrowski M, Zawadzki P, Sypniewski M, Kaja E, Chariyavilaskul P, Nilaratanakul V, Hirankarn N, Shotelersuk V, Pongpanich M, Phokaew C, Chetruengchai W, Tokunaga K, Sugiyama M, Kawai Y, Hasegawa T, Naito T, Namkoong H, Edahiro R, Kimura A, Ogawa S, Kanai T, Fukunaga K, Okada Y, Imoto S, Miyano S, Mangul S, Abedalthagafi MS, Zeberg H, Grzymski JJ, Washington NL, Ossowski S, Ludwig KU, Schulte EC, Riess O, Moniuszko M, Kwasniewski M, Mbarek H, Ismail SI, Verma A, Goldstein DB, Kiryluk K, Renieri A, Ferreira MA, Richards JB. Exome-wide association study to identify rare variants influencing COVID-19 outcomes: Results from the Host Genetics Initiative. ***PLoS Genet*** 18, e1010367 (2022)

22 Cao Y, You Y, Wang Q, Ren X, Li S, Li L, Xia W, Guan X, Yang T, Ikegawa S, Wang Z, Zhao X. Identification of six novel variants from nine Chinese families with hypophosphatemic rickets. ***BMC Med Genomics*** 15, 161 (2022)

23 Casaletto J, Parsons M, Markello C, Iwasaki Y, Momozawa Y, Spurdle A, Cline M. Federated analysis of BRCA1 and BRCA2 variation in a Japanese cohort. ***Cell genomics*** 2, 100109 (2022)

24 Chang S, Toyoda Y, Kawamura Y, Nakamura T, Nakatochi M, Nakayama A, Liao W, Shimizu S, Takada T, Takeuchi K, Wakai K, Shi Y, Shinomiya N, Chen C, Li C, Okada Y, Ichida K, Matsuo H. A meta-analysis of genome-wide association studies using Japanese and Taiwanese has revealed novel loci associated with gout susceptibility. ***Hum Cell*** 35, 767-770 (2022)

25 Chanhom N, Jittikoon J, Wattanapokayakit S, Mahasirimongkol S, Charoenyingwattana A, Udomsinprasert W, Chaikledkaew U, Suvichapanich S, Mushiroda T, Kiertiburanakul S, Rojanawiwat A, Wangsomboonsiri W, Manosuthi W, Kantipong P, Apisarnthanarak A, Sangsirinakakul W, Wongprasit P, Chaiwarith R, Tantisiriwat W, Sungkanuparph S, Chantratita W. The Association of HLA-B*35 and GSTT1 Genotypes and Hepatotoxicity in Thai People Living with HIV. ***J Pers Med*** 12, 940 (2022)

26 Chen S, Guan F, Candotti F, Benlagha K, Camara NO, Herrada AA, James LK, Lei J, Miller H, Kubo M, Ning Q, Liu C. The role of B cells in COVID-19 infection and vaccination. ***Front Immunol*** 13, 988536 (2022)

27 Cheung P, Yang J, Fang R, Borgers A, Krengel K, Stoffel A, Althoff K, Yip C, Siu E, Ng L, Lang K, Cham L, Engel D, Soun C, Cima I, Scheffler B, Striefler J, Sinn M, Bahra M, Pelzer U, Oettle H, Markus P, Smeets E, Aarntzen E, Savvatakis K, Liffers S, Lueong S, Neander C, Bazarna A, Zhang X, Paschen A, Crawford H, Chan A, Cheung S, Siveke J. Progranulin mediates immune evasion of pancreatic adenocarcinoma through regulation of MHCI expression. ***Nat Commun*** 13, 156 (2022)

28 Chiou T, Suda W, Oshima K, Hattori M, Matsuzaki C, Yamamoto K, Takahashi T. Draft Genome Sequence of Lentilactobacillus kosonis NBRC 111893, Isolated from a Japanese Sugar-Vegetable Fermented Beverage called Kôso. ***Microbiol Resour Announc*** 11, e0077522 (2022)

29 Cui G, Shimba A, Jin J, Ogawa T, Muramoto Y, Miyachi H, Abe S, Asahi T, Tani-Ichi S, Dijkstra JM, Iwamoto Y, Kryukov K, Zhu Y, Takami D, Hara T, Kitano S, Xu Y, Morita H, Zhang M, Zreka L, Miyata K, Kanaya T, Okumura S, Ito T, Hatano E, Takahashi Y, Watarai H, Oike Y, Imanishi T, Ohno H, Ohteki T, Minato N, Kubo M, Holländer GA, Ueno H, Noda T, Shiroguchi K, Ikuta K. A circulating subset of iNKT cells mediates antitumor and antiviral immunity. ***Sci Immunol*** 7, eabj8760 (2022)

30 Cuppen E, Elemento O, Rosenquist R, Nikic S, IJzerman M, Zaleski ID, Frederix G, Levin L, Mullighan CG, Buettner R, Pugh TJ, Grimmond S, Caldas C, Andre F, Custers I, Campo E, van Snellenberg H, Schuh A, Nakagawa H, von Kalle C, Haferlach T, Fröhling S, Jobanputra V. Implementation of Whole-Genome and Transcriptome Sequencing Into Clinical Cancer Care. ***JCO Precis Oncol*** 6, e2200245 (2022)

31 De Hoon M, Bonetti A, Plessy C, Ando Y, Hon C, Ishizu Y, Itoh M, Kato S, Lin D, Maekawa S, Murata M, Nishiyori H, Shin JW, Stolte J, Suzuki A, Tagami M, Takahashi H, Thongjuea S, Forrest AR, Hayashizaki Y, Kere J, Carninci P. Deep sequencing of short capped RNAs reveals novel families of noncoding RNAs. ***Genome Res*** 32, 1727-1735 (2022)

32 De Hoon MJ. Atlas of miRNAs and Their Promoters in Human and Mouse. ***Practical Guide to Life Science Databases*** 57-75 (2022)

33 Delobel D, Furutani Y, Nagoshi S, Tsubota A, Miyasaka A, Watashi K, Wakita T, Matsuura T, Usui K. SEB Genotyping: SmartAmp-Eprimer Binary code Genotyping for complex, highly variable targets applied to HBV. ***BMC Infect Dis*** 22, 516 (2022)

34 Diekstra MH, Swen JJ, van der Zanden LF, Vermeulen SH, Boven E, Mathijssen RH, Fukunaga K, Mushiroda T, Hongo F, Oosterwijk E, Cambon-Thomsen A, Castellano D, Fritsch A, Donas JG, Rodriguez-Antona C, Ruijtenbeek R, Radu MT, Eisen T, Junker K, Roessler M, Jaehde U, Miki T, Böhringer S, Kubo M, Kiemeney LA, Guchelaar H. Genome-Wide Meta-Analysis Identifies Variants in DSCAM and PDLIM3 That Correlate with Efficacy Outcomes in Metastatic Renal Cell Carcinoma Patients Treated with Sunitinib. ***Cancers*** 14, 2838 (2022)

35 Dofuku S, Sonehara K, Miyawaki S, Sakaue S, Imai H, Shimizu M, Hongo H, Shinya Y, Ohara K, Teranishi Y, Okano A, Ono H, Nakatomi H, Teraoka A, Yamamoto K, Maeda Y, Nii T, Kishikawa T, Suzuki K, Hirata J, Takahashi M, Matsuda K, Kumanogoh A, Matsuda F, Okada Y, Saito N. Genome-Wide Association Study of Intracranial Artery Stenosis Followed by Phenome-Wide Association Study. ***Transl Stroke Res*** 3, 323 (2022)

36 Doi K, Murata K, Ito S, Suzuki A, Terao C, Ishie S, Umemoto A, Murotani Y, Nishitani K, Yoshitomi H, Fujii T, Watanabe R, Hashimoto M, Murakami K, Tanaka M, Ito H, Park-Min K, Ivashkiv LB, Morinobu A, Matsuda S. Role of Lysine-Specific Demethylase 1 in Metabolically Integrating Osteoclast Differentiation and Inflammatory Bone Resorption Through Hypoxia-Inducible Factor 1α and E2F1. ***Arthritis & Rheumatology*** 74, 948-960 (2022)

37 Dore E, Joly-Beauparlant C, Morozumi S, Mathieu A, Levesque T, Allaeys I, Duchez A, Cloutier N, Leclercq M, Bodein A, Payre C, Martin C, Petit-Paitel A, Gelb MH, Rangachari M, Murakami M, Davidovic L, Flamand N, Arita M, Lambeau G, Droit A, Boilard E. The interaction of secreted phospholipase A (2)-IIA with the microbiota alters its lipidome and promotes inflammation. ***JCI Insight*** 7, e152638 (2022)

38 Fasina OB, Wang J, Mo J, Osada H, Ohno H, Pan W, Xiang L, Qi J. Gastrodin From Gastrodia elata Enhances Cognitive Function and Neuroprotection of AD Mice via the Regulation of Gut Microbiota Composition and Inhibition of Neuron Inflammation. ***Front Pharmacol*** 13, 814271 (2022)

39 Federici S, Kredo-Russo S, Valdés-Mas R, Kviatcovsky D, Weinstock E, Matiuhin Y, Silberberg Y, Atarashi K, Furuichi M, Oka A, Liu B, Fibelman M, Weiner IN, Khabra E, Cullin N, Ben-Yishai N, Inbar D, Ben-David H, Nicenboim J, Kowalsman N, Lieb W, Kario E, Cohen T, Geffen YF, Zelcbuch L, Cohen A, Rappo U, Gahali-Sass I, Golembo M, Lev V, Dori-Bachash M, Shapiro H, Moresi C, Cuevas-Sierra A, Mohapatra G, Kern L, Zheng D, Nobs SP, Suez J, Stettner N, Harmelin A, Zak N, Puttagunta S, Bassan M, Honda K, Sokol H, Bang C, Franke A, Schramm C, Maharshak N, Sartor RB, Sorek R, Elinav E. Targeted suppression of human IBD-associated gut microbiota commensals by phage consortia for treatment of intestinal inflammation. ***Cell*** 185, 2879-2898.e24 (2022)

40 Fujii R, Hishida A, Nakatochi M, Tsuboi Y, Suzuki K, Kondo T, Ikezaki H, Hara M, Okada R, Tamura T, Shimoshikiryo I, Suzuki S, Koyama T, Kuriki K, Takashima N, Arisawa K, Momozawa Y, Kubo M, Takeuchi K, Wakai K. Associations of Genome-Wide Polygenic Risk Score and Risk Factors With Hypertension in a Japanese Population. ***Circ Genom Precis Med*** 15, 334-341 (2022)

41 Fujii S, Shimizu K, Yamasaki S, Iyoda T, Shinga J, Nakazato H, Sanpei A, Kawamura M, Ueda S. Reinvigoration of innate and adaptive immunity via therapeutic cellular vaccine for patients with AML. ***Mol Ther Oncolytics*** 27, 315-332 (2022)

42 Fujii S, Yamasaki S, Hanada K, Ueda S, Kawamura M, Shimizu K. Cancer immunotherapy using artificial adjuvant vector cells to deliver NY-ESO-1 antigen to dendritic cells in situ. ***Cancer Sci*** 113, 864-874 (2022)

43 Fujii S, Yamasaki S, Iyoda T, Shimizu K. Association of cellular immunity with severity of COVID-19 from the perspective of antigen-specific memory T cell responses and cross-reactivity. ***Inflamm Regen*** 42, 50 (2022)

44 Fujimori A, Hirakawa H, Liu C, Akiyama T, Engelward BP, Nickoloff JA, Suzuki M, Wang B, Nenoi M, Sai S. Recombinant cell-detecting RaDR-GFP in mice reveals an association between genomic instability and radiation-induced-thymic lymphoma. ***Am J Cancer Res*** 12, 562-573 (2022)

45 Fujita M, Chen MM, Siwak RD, Sasagawa S, Oosawa A, Arihiro K, Ono A, Miura R, Maejima K, Aikata H, Ueno M, Hayami S, Yamaue H, Chayama K, Lee SJ, Lu Y, Mills GB, Liang H, Nishizuka SS, Nakagawa H. Proteogenomic characterization of virus-associated liver cancers reveals potential subtypes and therapeutic targets. ***Nat Commun*** 13, 6481 (2022)

46 Fujita M, Liu X, Iwasaki Y, Terao C, Mizukami K, Kawakami E, Takata S, Inai C, Aoi T, Mizukoshi M, Maejima K, Hirata M, Murakami Y, Kamatani Y, Kubo M, Akagi K, Matsuda K, Nakagawa H, Momozawa Y. Population-based Screening for Hereditary Colorectal Cancer Variants in Japan. ***Clin Gastroenterol Hepatol*** 20, 2132-2141.e9 (2022)

47 Fukuda K. Networks of $CD8^+$ T Cell Response Activation in Melanoma and Vitiligo. ***Front Immunol*** 13, 866703 (2022)

48 Fukushima T, Chubachi S, Namkoong H, Asakura T, Tanaka H, Lee H, Azekawa S, Okada Y, Koike R, Kimura A, Imoto S, Miyano S, Ogawa S, Kanai T, Fukunaga K, Force TJ. Clinical significance of prediabetes, undiagnosed diabetes and diagnosed diabetes on critical outcomes in COVID-19: Integrative analysis from the Japan COVID-19 task force. ***Diabetes Obes Metab*** 25, 144-155 (2022)

49 Fukushima T, Chubachi S, Namkoong H, Otake S, Nakagawara K, Tanaka H, Lee H, Morita A, Watase M, Kusumoto T, Masaki K, Kamata H, Ishii M, Hasegawa N, Harada N, Ueda T, Ueda S, Ishiguro T, Arimura K, Saito F, Yoshiyama T, Nakano Y, Mutoh Y, Suzuki Y, Murakami K, Okada Y, Koike R, Kitagawa Y, Kimura A, Imoto S, Miyano S, Ogawa S, Kanai T, Fukunaga K, Force tJ. U-shaped association between abnormal serum uric acid levels and COVID-19 severity: reports from the Japan COVID-19 Task Force. ***Int J Infect Dis*** 122, 747-754 (2022)

50 Furuhashi H, Takayasu, Isshi K, Hara Y, Ono S, Kato M, Sumiyama K, Suda W. Effect of storage temperature and flash-freezing on salivary microbiota profiles based on 16S rRNA-targeted sequencing. ***Eur J Oral Sci*** 13, e12852 (2022)

51 Gasperini C, Tuntevski K, Beatini S, Pelizzoli R, Van AL, Mangoni D, Cossu RM, Pascarella G, Bianchini P, Bielefeld P, Scarpato M, Pons-Espinal M, Sanges R, Diaspro A, Fitzsimons CP, Carninci P, Gustincich S, De Pietri Tonelli D. Piwil2 (Mili) sustains neurogenesis and prevents cellular senescence in the postnatal hippocampus. ***EMBO Rep*** 24, e53801 (2022)

52 Giles JB, Steiner HE, Rollin J, Shaffer CM, Momozawa Y, Mushiroda T, Inai C, Selleng K, Thiele T, Pouplard C, Heddle NM, Kubo M, Miller EC, Martinez KL, Phillips EJ, Warkentin TE, Gruel Y, Greinacher A, Roden DM, Karnes JH. Genome-wide association study of platelet factor 4/heparin antibodies in heparin-induced thrombocytopenia. ***Blood Adv*** 6, 4137-4146 (2022)

53 Guignant M, Tedbirt B, Murrell DF, Amagai M, Aoki V, Bauer J, Ciancinni G, Culton D, Daneshpazhooh M, De D, Fairley J, Hall R, Kim S, Korman NJ, Kowalewski C, Mimouni D, Patsatsi A, Hebert V, Saleh MA, Schmidt E, Sprecher E, Uzun S, Venning V, Werth VP, Zillikens D, Joly P. How Do Experts Treat Patients with Bullous Pemphigoid around the World? An International Survey. ***JID Innovations*** 2, 100129 (2022)

54 Gupta S, Tripathi LP, Vundavilli H. An integrative machine learning and bayesian modeling approach highlights the crucial roles of Rho-GDI signaling pathway in the progression of non-small cell lung cancer (NSCLC); implications for drug target discovery. ***IEEE J Biomed Health Inform*** 26, 4785-4793 (2022)

55 Hanyuda A, Goto A, Nakatochi M, Sutoh Y, Narita A, Nakano S, Katagiri R, Wakai K, Takashima N, Koyama T, Arisawa K, Imoto I, Momozawa Y, Tanno K, Shimizu A, Hozawa A, Kinoshita K, Yamaji T, Sawada N, Iwagami M, Yuki K, Tsubota K, Negishi K, Matsuo K, Yamamoto M, Sasaki M, Tsugane S, Iwasaki M. Association Between Glycemic Traits and Primary Open-Angle Glaucoma: A Mendelian Randomization Study in the Japanese Population. ***Am J Ophthalmol*** 245, 193-201 (2022)

56 Hara T, Yamada I, Ohashi T, Tamura M, Hijikata A, Watanabe T, Gao M, Ito K, Kawamata S, Azuma S, Yoshigai E, Sumiyoshi Y, Yasuhiro N, Ohara O, dos Santos HG, Fukada T. Role of Scl39a13/ZIP13 in cardiovascular homeostasis. ***PLoS One*** 17, e0276452 (2022)

57 Harnett D, Ambrozkiewicz MC, Zinnall U, Rusanova A, Borisova E, Drescher AN, Couce-Iglesias M, Villamil G, Dannenberg R, Imami K, Münster-Wandowski A, Fauler B, Mielke T, Selbach M, Landthaler M, Spahn CM, Tarabykin V, Ohler U, Kraushar ML. A critical period of translational control during brain development at codon resolution. ***Nat Struct Mol Biol*** 29, 1277-1290 (2022)

58 Hayashi R, Inoue A. Low-input CUT&RUN for Mouse Oocytes and Preimplantation Embryos. ***Methods Mol Biol*** 2577, 83-92 (2022)

59 Ho W, Tai M, Dennis J, Shu X, Li J, Ho PJ, Millwood IY, Lin K, Jee Y, Lee S, Mavaddat N, Bolla MK, Wang Q, Michailidou K, Long J, Wijaya EA, Hassan T, Rahmat K, Tan VK, Tan BK, Tan SM, Tan EY, Lim SH, Gao Y, Zheng Y, Kang D, Choi J, Han W, Lee H, Kubo M, Okada Y, Namba S, Park SK, Kim S, Shen C, Wu P, Park B, Muir KR, Lophatananon A, Wu AH, Tseng C, Matsuo K, Ito H, Kwong A, Chan TL, John EM, Kurian AW, Iwasaki M, Yamaji T, Kweon S, Aronson KJ, Murphy RA, Koh W, Khor C, Yuan J, Dorajoo R, Walters RG, Chen Z, Li L, Lv J, Jung K, Kraft P, Pharoah PD, Dunning AM, Simard J, Shu X, Yip C, Taib NA, Antoniou AC, Zheng W, Hartman M, Easton DF, Teo SH. Polygenic risk scores for prediction of breast cancer risk in Asian populations. ***Genet Med*** 24, 586-600 (2022)

60 Honda S, Ikari K, Yano K, Terao C, Tanaka E, Harigai M, Kochi Y. Association of Polygenic Risk Scores With Radiographic Progression in Patients With Rheumatoid Arthritis. ***Arthritis Rheumatol*** 74, 791-800 (2022)

61 Horikawa H, Amagai M. T Helper 17/T Helper 22-Skewed Inflammation with Epidermal Barrier Dysfunction in Nonmajor Inherited Ichthyosis Subtypes. ***J Invest Dermatol*** 142, 2303-2305 (2022)

62 Howles SA, Wiberg A, Goldsworthy M, Bayliss AL, Gluck AK, Ng M, Grout E, Tanikawa C, Kamatani Y, Terao C, Takahashi A, Kubo M, Matsuda K, Thakker RV, Turney BW, Furniss D. Author Correction: Genetic variants of calcium and vitamin D metabolism in kidney stone disease. ***Nat Commun*** 13, 3115 (2022)

63 Hu M, Yeh Y, Munakata Y, Abe H, Sakashita A, Maezawa S, Vidal M, Koseki H, Hunter N, Schultz RM, Namekawa SH. PRC1-mediated epigenetic programming is required to generate the ovarian reserve. ***Nat Commun*** 13, 4510 (2022)

64 Hujoel ML, Sherman MA, Barton AR, Mukamel RE, Sankaran VG, Terao C, Loh P. Influences of rare copy-number variation on human complex traits. ***Cell*** 185, 4233-4248.e27 (2022)

65 Ieki H, Ito K, Saji M, Kawakami R, Nagatomo Y, Takada K, Kariyasu T, Machida H, Koyama S, Yoshida H, Kurosawa R, Matsunaga H, Miyazawa K, Ozaki K, Onouchi Y, Katsushika S, Matsuoka R, Shinohara H, Yamaguchi T, Kodera S, Higashikuni Y, Fujiu K, Akazawa H, Iguchi N, Isobe M, Yoshikawa T, Komuro I. Deep learning-based age estimation from chest X-rays indicates cardiovascular prognosis. ***Commun Med (Lond)*** 2, 159 (2022)

66 Ikizawa T, Ikeda K, Arita M, Kitajima S, Soga T, Ichijo H, Naguro I. Mitochondria directly sense osmotic stress to trigger rapid metabolic remodeling via regulation of pyruvate dehydrogenase (PDH) phosphorylation. ***J Biol Chem*** 299, 102837 (2022)

67 Imianowski CJ, Whiteside SK, Lozano T, Evans AC, Benson JD, Courreges CJ, Sadiyah F, Lau CM, Zandhuis ND, Grant FM, Schuijs MJ, Vardaka P, Kuo P, Soilleux EJ, Yang J, Sun JC, Kurosaki T, Okkenhaug K, Halim TY, Roychoudhuri R. BACH2 restricts NK cell maturation and function, limiting immunity to cancer metastasis. ***J Exp Med*** 219, e20211476 (2022)

68 Inabu Y, Taguchi Y, Miyamoto H, Etoh T, Shiotsuka Y, Fujino R, Okada T, Udagawa M, Tsuji N, Matsuura M, Tsuboi A, Kato T, Kodama H, Ohno H, Takahashi H. Development of a novel feeding method for Japanese black calves with thermophile probiotics at postweaning. ***J Appl Microbiol*** 132, 3870-3882 (2022)

69 Inoue A. Noncanonical imprinting: intergenerational epigenetic inheritance mediated by Polycomb complexes. ***Curr Opin Genet Dev*** 78, 102015 (2022)

70 Inoue T, Funatsu Y, Ohnishi M, Isogawa M, Kawashima K, Tanaka M, Moriya K, Kawaratani H, Momoda R, Iio E, Nakagawa H, Suzuki Y, Matsuura K, Fujiwara K, Nakajima A, Yoshiji H, Nakayama J, Tanaka Y. Bile acid dysmetabolism in the gut-microbiota-liver axis under hepatitis C virus infection. ***Liver Int*** 42, 124-134 (2022)

71 Inoue T, Shinnakasu R, Kawai C, Yamamoto H, Sakakibara S, Ono C, Itoh Y, Terooatea T, Yamashita K, Okamoto T, Hashii N, Ishii-Watabe A, Butler NS, Matsuura Y, Matsumoto H, Otsuka S, Hiraoka K, Teshima T, Murakami M, Kurosaki T. Antibody feedback contributes to facilitating the development of Omicron-reactive memory B cells in SARS-CoV-2 mRNA vaccinees. ***J Exp Med*** 220, e20221786 (2022)

72 Ishigaki K, Lagattuta K, Luo Y, James E, Buckner J, Raychaudhuri S. HLA autoimmune risk alleles restrict the hypervariable region of T cell receptors. ***Nat Genet*** 54, 393-402 (2022)

73 Ishigaki K, Sakaue S, Terao C, Luo Y, Sonehara K, Yamaguchi K, Amariuta T, Too CL, Laufer VA, Scott IC, Viatte S, Takahashi M, Ohmura K, Murasawa A, Hashimoto M, Ito H, Hammoudeh M, Emadi SA, Masri BK, Halabi H, Badsha H, Uthman IW, Wu X, Lin L, Li T, Plant D, Barton A, Orozco G, Verstappen SM, Bowes J, MacGregor AJ, Honda S, Koido M, Tomiduka K, Kamatani Y, Tanaka H, Tanaka E, Suzuki A, Maeda Y, Yamamoto K, Miyawaki S, Xie G, Zhang J, Amos CI, Keystone E, Wolbink G, van der Horst-Bruinsma I, Cui J, Liao KP, Carroll RJ, Lee H, Bang S, Siminovitch KA, de Vries N, Alfredsson L, Rantapää-Dahlqvist S, Karlson EW, Bae S, Kimberly RP, Edberg JC, Mariette X, Huizinga T, Dieudé P, Schneider M, Kerick M, Denny JC, Matsuda K, Matsuo K, Mimori T, Matsuda F, Fujio K, Tanaka Y, Kumanogoh A, Traylor M, Lewis CM, Eyre S, Xu H, Saxena R, Arayssi T, Kochi Y, Ikari K, Harigai M, Gregersen PK, Yamamoto K, Louis Bridges S, Padyukov L, Martin J, Klareskog L, Okada Y, Raychaudhuri S. Multi-ancestry genome-wide association analyses identify novel genetic mechanisms in rheumatoid arthritis. ***Nat Genet*** 54, 1640-1651 (2022)

74 Itahashi K, Irie T, Yuda J, Kumagai S, Tanegashima T, Lin Y, Watanabe S, Goto Y, Suzuki J, Aokage K, Tsuboi M, Minami Y, Ishii G, Ohe Y, Ise W, Kurosaki T, Suzuki Y, Koyama S, Nishikawa H. BATF epigenetically and transcriptionally controls the activation program of regulatory T cells in human tumors. ***Sci Immunol*** 7, eabk0957 (2022)

75 Itai T, Wang Z, Nishimura G, Ohashi H, Guo L, Wakano Y, Sugiura T, Hayakawa H, Okada M, Saisu T, Kitta A, Doi H, Kurosawa K, Hotta Y, Hosono K, Sato M, Shimizu K, Takikawa K, Watanabe S, Ikeda N, Suzuki M, Fujita A, Uchiyama Y, Tsuchida N, Miyatake S, Miyake N, Matsumoto N, Ikegawa S. De novo heterozygous variants in KIF5B cause kyphomelic dysplasia. ***Clin Genet*** 102, 3-11 (2022)

76 Ito J, Seita Y, Kojima S, Parrish NF, Sasaki K, Sato K. A hominoid-specific endogenous retrovirus may have rewired the gene regulatory network shared between primordial germ cells and naïve pluripotent cells. ***PLoS Genet*** 18, e1009846 (2022)

77 Ito K, Miyamoto H, Matsuura M, Ishii C, Tsuboi A, Tsuji N, Nakaguma T, Nakanishi Y, Kato T, Suda W, Honda F, Ito T, Moriya S, Shima H, Michibata R, Yamada R, Takahashi Y, Koga H, Kodama H, Watanabe Y, Kikuchi J, Ohno H. Noninvasive fecal metabolic profiling for the evaluation of characteristics of thermostable lactic acid bacteria, Weizmannia coagulans SANK70258, for broiler chickens. ***J Biosci Bioeng*** 134, 105-115 (2022)

78 Ito S, Das ND, Umehara T, Koseki H. Factors and Mechanisms That Influence Chromatin-Mediated Enhancer-Promoter Interactions and Transcriptional Regulation. ***Cancers*** 14, 5404 (2022)

79 Ito Y, Amagai M. Controlling skin microbiome as a new bacteriotherapy for inflammatory skin diseases. ***Inflamm Regen*** 42, 26 (2022)

80 Itotagawa E, Tomofuji Y, Kato Y, Konaka H, Tsujimoto K, Park J, Nagira D, Hirayama T, Jo T, Hirano T, Morita T, Nishide M, Nishida S, Shima Y, Narazaki M, Okada Y, Takamatsu H, Kumanogoh A. SLE stratification based on BAFF and IFN-I bioactivity for biologics and implications of BAFF produced by glomeruli in lupus nephritis. ***Rheumatology*** 62, 1988-1997 (2022)

81 Ivanov II, Tuganbaev T, Skelly AN, Honda K. T Cell Responses to the Microbiota. ***Annu Rev Immunol*** 40, 559-587 (2022)

82 Iwagami M, Goto A, Katagiri R, Sutoh S, Sutoh Y, Nakatochi M, Nakano S, Hanyuda A, Narita A, Shimizu A, Tanno K, Hozawa A, Kinoshita K, Oze I, Ito H, Yamaji T, Sawada N, Nakamura Y, Nakamura S, Kuriki K, Suzuki S, Hishida A, Kasugai Y, Yumiko I, Suzuki M, Momozawa Y, Takeuchi K, Yamamoto M, Sasaki M, Matsuo K, Tsugane S, Wakai K, Iwasaki M. Blood Lipids and the Risk of Colorectal Cancer: Mendelian Randomization Analyses in the Japanese Consortium of Genetic Epidemiology Studies. ***Cancer Prev Res (Phila)*** 15, 827-836 (2022)

83 Iwasaki Y, Takeshima Y, Nakano M, Okubo M, Ota M, Suzuki A, Kochi Y, Okamura T, Endo T, Miki I, Sakurada K, Yamamoto K, Fujio K. Combined plasma metabolomic and transcriptomic analysis identify histidine as a biomarker and potential contributor in SLE pathogenesis. ***Rheumatology*** 62, 905-913 (2022)

84 Jain A, Tripathi LP, Ahmad S. Host-pathogen protein-nucleic acid interactions: A comprehensive review. ***Comput Struct Biotechnol J*** 20, 4415-4436 (2022)

85 Jangid A, Fukuda S, Seki M, Suzuki Y, Taylor TD, Ohno H, Prakash T. Gut microbiota alternation under the intestinal epithelium-specific knockout of mouse Piga gene. ***Sci Rep*** 12, 10812 (2022)

86 Jangid A, Fukuda S, Suzuki Y, Taylor TD, Ohno H, Yadav TP. Shotgun metagenomic sequencing revealed the prebiotic potential of a grain-based diet in mice. ***Sci Rep*** 12, 6748 (2022)

87 Jansen C, Paraiso KD, Zhou JJ, Blitz IL, Fish MB, Charney RM, Cho JS, Yasuoka Y, Sudou N, Bright AR, Wlizla M, Veenstra GJ, Taira M, Zorn AM, Mortazavi A, Cho KW. Uncovering the mesendoderm gene regulatory network through multi-omic data integration. ***Cell Rep*** 38, 10364 (2022)

88 Jaworek T, Xu H, Gaynor BJ, Cole JW, Rannikmae K, Stanne TM, Tomppo L, Abedi V, Amouyel P, Armstrong ND, Attia J, Bell S, Benavente OR, Boncoraglio GB, Butterworth A, Carcel-Marquez J, Chen Z, Chong M, Cruchaga C, Cushman M, Danesh J, Debette S, Duggan DJ, Durda JP, Engstrom G, Enzinger C, Faul JD, Fecteau NS, Fernandez-Cadenas I, Gieger C, Giese A, Grewal RP, Grittner U, Havulinna AS, Heitsch L, Hochberg MC, Holliday E, Hu J, Ilinca A, Irvin MR, Jackson RD, Jacob MA, Rabionet R, Jimenez-Conde J, Johnson JA, Kamatani Y, Kardia SL, Koido M, Kubo M, Lange L, Lee J, Lemmens R, Levi CR, Li J, Li L, Lin K, Lopez H, Luke S, Maguire J, McArdle PF, McDonough CW, Meschia JF, Metso T, Mueller-Nurasyid M, O'Connor TD, O'Donnell M, Peddareddygari LR, Pera J, Perry JA, Peters A, Putaala J, Ray D, Rexrode K, Ribases M, Rosand J, Rothwell PM, Rundek T, Ryan KA, Sacco RL, Salomaa V, Sanchez-Mora C, Schmidt R, Sharma P, Slowik A, Smith JA, Smith NL, Wassertheil-Smoller S, Soderholm M, Stine OC, Strbian D, Sudlow CL, Tatlisumak T, Terao C, Thijs V, Torres-Aguila NP, Tregouet D, Tuladhar AM, Veldink JH, Walters RG, Weir DR, Woo D, Worrall BB, Hong CC, Ross OA, Zand R, de Leeuw F, Lindgren AG, Pare G, Anderson CD, Markus HS, Jern C, Malik R, Dichgans M, Mitchell BD, Kittner SJ. Contribution of Common Genetic Variants to Risk of Early-Onset Ischemic Stroke. ***Neurology*** 99, E1738-E1754 (2022)

89 Jia G, Zhong X, Im HK, Schoettler N, Pividori M, Hogarth DK, Sperling A, White SR, Naureckas ET, Lyttle CS, Terao C, Kamatani Y, Akiyama M, Matsuda K, Kubo M, Cox NJ, Ober C, Rzhetsky A, Solway J. Discerning asthma endotypes through comorbidity mapping. ***Nat Commun*** 13, 6712 (2022)

90 Jikuya R, Murakami K, Nishiyama A, Kato I, Furuya M, Nakabayashi J, Ramilowski JA, Hamanoue H, Maejima K, Fujita M, Mitome T, Ohtake S, Noguchi G, Kawaura S, Okada H, Kawahara T, Komeya M, Shinoki R, Ueno D, Ito H, Ito Y, Muraoka K, Hayashi N, Kondo K, Nakaigawa N, Hatano K, Baba M, Suda T, Kodama T, Fujii S, Makiyama K, Yao M, Shuch BM, Schmidt LS, Linehan W, Nakagawa H, Tamura T, Hasumi H. Single-cell transcriptomes of hereditary kidney cancers underscore genetically defined tumor characteristics and microenvironment. ***iScience*** 25, 104463 (2022)

91 Jin J, Yamamoto R, Takeuchi T, Cui G, Miyauchi E, Hojo N, Ikuta K, Ohno H, Shiroguchi K. High-throughput identification and quantification of single bacterial cells in the microbiota. ***Nat Commun*** 13, 863 (2022)

92 Johnson TA, Maekawa S, Fujita M, An J, Ju Y, Maejima K, Kanazashi Y, Jikuya R, Okawa Y, Sasagawa S, Yagi K, Okazaki Y, Kuroda N, Takata R, Obara W, Nakagawa H. Genomic features of renal cell carcinoma developed during end-stage renal disease and dialysis. ***Hum Mol Genet*** 32, 290-303 (2022)

93 Kabata H, Motomura Y, Kiniwa T, Kobayashi T, Moro K. ILCs and Allergy. ***Adv Exp Med Biol*** 1365, 75-95 (2022)

94 Kageyama Y, Nakamura M, Igari Y, Yamaguchi S, Oguchi A, Murakawa Y, Hattori Y, Sasano Y. Expression of matrix metalloproteinase-3 and -10 is up-regulated in the periodontal tissues of aged mice. ***J Periodontal Res*** 57, 733-741 (2022)

95 Kai Y, Mei H, Kawano H, Nakajima N, Takai A, Kumon M, Inoue A, Yamashita N. Transcriptomic signatures in trophectoderm and inner cell mass of human blastocysts classified according to developmental potential, maternal age and morphology. ***PLoS One*** 17, e0278663 (2022)

96 Kanki Y, Muramatsu M, Miyamura Y, Kikuchi K, Higashijima Y, Nakaki R, Suehiro J, Sasaki Y, Kubota Y, Koseki H, Morioka H, Kodama T, Nakao M, Kurotaki D, Aburatani H, Minami T. Bivalent-histone-marked immediate-early gene regulation is vital for VEGF-responsive angiogenesis. ***Cell Rep*** 38, 110332 (2022)

97 Kanoni S, Graham SE, Wang Y, Surakka I, Ramdas S, Zhu X, Clarke SL, Bhatti KF, Vedantam S, Winkler TW, Locke AE, Marouli E, Zajac GJ, Wu KH, Ntalla I, Hui Q, Klarin D, Hilliard AT, Wang Z, Xue C, Thorleifsson G, Helgadottir A, Gudbjartsson DF, Holm H, Olafsson I, Hwang MY, Han S, Akiyama M, Sakaue S, Terao C, Kanai M, Zhou W, Brumpton BM, Rasheed H, Havulinna AS, Veturi Y, Pacheco JA, Rosenthal EA, Lingren T, Feng Q, Kullo IJ, Narita A, Takayama J, Martin HC, Hunt KA, Trivedi B, Haessler J, Giulianini F, Bradford Y, Miller JE, Campbell A, Lin K, Millwood IY, Rasheed A, Hindy G, Faul JD, Zhao W, Weir DR, Turman C, Huang H, Graff M, Choudhury A, Sengupta D, Mahajan A, Brown MR, Zhang W, Yu K, Schmidt EM, Pandit A, Gustafsson S, Yin X, Luan J, Zhao J, Matsuda F, Jang H, Yoon K, Medina-Gomez C, Pitsillides A, Hottenga JJ, Wood AR, Ji Y, Gao Z, Haworth S, Yousri NA, Mitchell RE, Chai JF, Aadahl M, Bjerregaard AA, Yao J, Manichaikul A, Hwu C, Hung Y, Warren HR, Ramirez J, Bork-Jensen J, Kårhus LL, Goel A, Sabater-Lleal M, Noordam R, Mauro P, Matteo F, McDaid AF, Marques-Vidal P, Wielscher M, Trompet S, Sattar N, Møllehave LT, Munz M, Zeng L, Huang J, Yang B, Poveda A, Kurbasic A, Lamina C, Forer L, Scholz M, Galesloot TE, Bradfield JP, Ruotsalainen SE, Daw E, Zmuda JM, Mitchell JS, Fuchsberger C, Christensen H, Brody JA, Vazquez-Moreno M, Feitosa MF, Wojczynski MK, Wang Z, Preuss MH, Mangino M, Christofidou P, Verweij N, Benjamins JW, Engmann J, Tsao NL, Verma A, Slieker

RC, Lo KS, Zilhao NR, Le P, Kleber ME, Delgado GE, Huo S, Ikeda DD, Iha H, Yang J, Liu J, Demirkan A, Leonard HL, Marten J, Frank M, Schmidt B, Smyth LJ, Cañadas-Garre M, Wang C, Nakatochi M, Wong A, Hutri-Kähönen N, Sim X, Xia R, Huerta-Chagoya A, Fernandez-Lopez JC, Lyssenko V, Nongmaithem SS, Bayyana S, Stringham HM, Irvin MR, Oldmeadow C, Kim H, Ryu S, Timmers PR, Arbeeva L, Dorajoo R, Lange LA, Prasad G, Lorés-Motta L, Pauper M, Long J, Li X, Theusch E, Takeuchi F, Spracklen CN, Loukola A, Bollepalli S, Warner SC, Wang YX, Wei WB, Nutile T, Ruggiero D, Sung YJ, Chen S, Liu F, Yang J, Kentistou KA, Banas B, Nardone GG, Meidtner K, Bielak LF, Smith JA, Hebbar P, Farmaki A, Hofer E, Lin M, Concas MP, Vaccargiu S, van der Most PJ, Pitkänen N, Cade BE, van der Laan SW, Chitrala KN, Weiss S, Bentley AR, Doumatey AP, Adeyemo AA, Lee JY, Petersen ER, Nielsen AA, Choi HS, Nethander M, Freitag-Wolf S, Southam L, Rayner NW, Wang CA, Lin S, Wang J, Couture C, Lyytikäinen L, Nikus K, Cuellar-Partida G, Vestergaard H, Hidalgo B, Giannakopoulou O, Cai Q, Obura MO, van Setten J, Li X, Liang J, Tang H, Terzikhan N, Shin JH, Jackson RD, Reiner AP, Martin LW, Chen Z, Li L, Kawaguchi T, Thiery J, Bis JC, Launer LJ, Li H, Nalls MA, Raitakari OT, Ichihara S, Wild SH, Nelson CP, Campbell H, Jäger S, Nabika T, Al-Mulla F, Niinikoski H, Braund PS, Kolcic I, Kovacs P, Giardoglou T, Katsuya T, de Kleijn D, de Borst GJ, Kim EK, Adams HH, Ikram MA, Zhu X, Asselbergs FW, Kraaijeveld AO, Beulens JW, Shu X, Rallidis LS, Pedersen O, Hansen T, Mitchell P, Hewitt AW, Kähönen M, Pérusse L, Bouchard C, Tõnjes A, Chen YI, Pennell CE, Mori TA, Lieb W, Franke A, Ohlsson C, Mellström D, Cho YS, Lee H, Yuan J, Koh W, Rhee SY, Woo J, Heid IM, Stark KJ, Zimmermann ME, Völzke H, Homuth G, Evans MK, Zonderman AB, Polasek O, Pasterkamp G, Hoefer IE, Redline S, Pahkala K, Oldehinkel AJ, Snieder H, Biino G, Schmidt R, Schmidt H, Bandinelli S, Dedoussis G, Thanaraj TA, Kardia SL, Peyser PA, Kato N, Schulze MB, Girotto G, Böger CA, Jung B, Joshi PK, Bennett DA, De Jager PL, Lu X, Mamakou V, Brown M, Caulfield MJ, Munroe PB, Guo X, Ciullo M, Jonas JB, Samani NJ, Kaprio J, Pajukanta P, Tusié-Luna T, Aguilar-Salinas CA, Adair LS, Bechayda SA, de Silva HJ, Wickremasinghe AR, Krauss RM, Wu J, Zheng W, Hollander AI, Bharadwaj D, Correa A, Wilson JG, Lind L, Heng C, Nelson AE, Golightly YM, Wilson JF, Penninx B, Kim H, Attia J, Scott RJ, Rao DC, Arnett DK, Hunt SC, Walker M, Koistinen HA, Chandak GR, Mercader JM, Costanzo MC, Jang D, Burtt NP, Villalpando CG, Orozco L, Fornage M, Tai E, van Dam RM, Lehtimäki T, Chaturvedi N, Yokota M, Liu J, Reilly DF, McKnight AJ, Kee F, Jöckel K, McCarthy MI, Palmer CN, Vitart V, Hayward C, Simonsick E, van Duijn CM, Jin Z, Qu J, Hishigaki H, Lin X, März W, Gudnason V, Tardif J, Lettre G, Hart LM, Elders PJ, Damrauer SM, Kumari M, Kivimaki M, van der Harst P, Spector TD, Loos RJ, Province MA, Parra EJ, Cruz M, Psaty BM, Brandslund I, Pramstaller PP, Rotimi CN, Christensen K, Ripatti S, Widén E, Hakonarson H, Grant SF, Kiemeney LA, de Graaf J, Loeffler M, Kronenberg F, Gu D, Erdmann J, Schunkert H, Franks PW, Linneberg A, Jukema JW, Khera AV, Männikkö M, Jarvelin M, Kutalik Z, Francesco C, Mook-Kanamori DO, van Dijk KW, Watkins H, Strachan DP, Grarup N, Sever P, Poulter N, Chuang L, Rotter JI, Dantoft TM, Karpe F, Neville MJ, Timpson NJ, Cheng C, Wong T, Khor CC, Li H, Sabanayagam C, Peters A, Gieger C, Hattersley AT, Pedersen NL, Magnusson PK, Boomsma DI, Willemsen AH, Cupples L, van Meurs JB, Ghanbari M, Gordon-Larsen P, Huang W, Kim YJ, Tabara Y, Wareham NJ, Langenberg C, Zeggini E, Kuusisto J, Laakso M, Ingelsson E, Abecasis G, Chambers JC, Kooner JS, de Vries PS, Morrison AC, Hazelhurst S, Ramsay M, North KE, Daviglus M, Kraft P, Martin NG, Whitfield JB, Abbas S, Saleheen D, Walters RG, Holmes MV, Black C, Smith BH, Baras A, Justice AE, Buring JE, Ridker PM, Chasman DI, Kooperberg C, Tamiya G, Yamamoto M, van Heel DA, Trembath RC, Wei W, Jarvik GP, Namjou B, Hayes MG, Ritchie MD, Jousilahti P, Salomaa V, Hveem K, Åsvold BO, Kubo M, Kamatani Y, Okada Y, Murakami Y, Kim B, Thorsteinsdottir U, Stefansson K, Zhang J, Chen Y, Ho Y, Lynch JA, Rader DJ, Tsao PS, Chang K, Cho K, O'Donnell CJ, Gaziano JM, Wilson PW, Frayling TM, Hirschhorn JN, Kathiresan S, Mohlke KL, Sun YV, Morris AP, Boehnke M, Brown CD, Natarajan P, Deloukas P, Willer CJ, Assimes TL, Peloso GM. Implicating genes, pleiotropy, and sexual dimorphism at blood lipid loci through multi-ancestry meta-analysis. ***Genome Biol*** 23, 268 (2022)

98 Karnes JH, Rollin J, Giles JB, Martinez KL, Steiner HE, Shaffer CM, Momozawa Y, Inai C, Bombin A, Shi M, Mosley JD, Stanaway I, Selleng K, Thiele T, Mushiroda T, Pouplard C, Heddle NM, Kubo M, Phillips EJ, Warkentin TE, Gruel Y, Greinacher A, Roden DM. ABO O blood group as a risk factor for platelet reactivity in heparin-induced thrombocytopenia. ***Blood*** 140, 274-284 (2022)

99 Katayama Y, Yokota R, Akiyama T, Kobayashi TJ. Machine Learning Approaches to TCR Repertoire Analysis. ***Front Immunol*** 13, 858057 (2022)

100 Kato D, Mitsuhashi S, Miya F, Saitoh S, Okamoto N, Tsunoda T, Kochi Y. Utility of tissue-specific gene expression scores for gene prioritization in Mendelian diseases. ***J Hum Genet*** 67, 739-742 (2022)

101 Kato T, Kagawa M, Suda W, Tsuboi Y, Inoue-Suzuki S, Kikuchi J, Hattori M, Ohta T, Ohno H. Integrated Multi-Omics Analysis Reveals Differential Effects of Fructo-Oligosaccharides (FOS) Supplementation on the Human Gut Ecosystem. ***Int J Mol Sci*** 23, 11728 (2022)

102 Kausar M, Ain NU, Hayat F, Fatima H, Azim S, Ullah H, Mushtaq M, Khalid S, Hussain S, Naz S, Janjua J, Amjad SB, Baig RM, Makitie O, Qamar R, Ikegawa S, Gen N, Khor CC, Foo JN, Siddiqi S. Biallelic variants in CHST3 cause Spondyloepiphyseal dysplasia with joint dislocations in three Pakistani kindreds. ***BMC Musculoskelet Disord*** 23, 818 (2022)

103 Kawano Y, Edwards M, Huang Y, Bilate AM, Araujo LP, Tanoue T, Atarashi K, Ladinsky MS, Reiner SL, Wang HH, Mucida D, Honda K, Ivanov II. Microbiota imbalance induced by dietary sugar disrupts immune-mediated protection from metabolic syndrome. ***Cell*** 185, 3501-3519.e20 (2022)

104 Kawasaki T, Takeda Y, Edahiro R, Shirai Y, Nogami-Itoh M, Matsuki T, Kida H, Enomoto T, Hara R, Noda Y, Adachi Y, Niitsu T, Amiya S, Yamaguchi Y, Murakami T, Kato Y, Morita T, Yoshimura H, Yamamoto M, Nakatsubo D, Miyake K, Shiroyama T, Hirata H, Adachi J, Okada Y, Kumanogoh A. Next-generation proteomics of serum extracellular vesicles combined with single-cell RNA sequencing identifies MACROH2A1 associated with refractory COVID-19. ***Inflamm Regen*** 42, 53 (2022)

105 Keiji W, Kitamura T, Ogata Y, Shindo C, Suda W. Flavobacterium ammonificans sp. nov. and Flavobacterium ammoniigenes sp. nov., ammonifying bacteria isolated from surface river water. ***Int J Syst Evol Microbiol*** 72 (2022)

106 Kerick M, Acosta-Herrera M, Pilar Simeon-Aznar C, Luis Callejas J, Assassi S, Proudman SM, Nikpour M, Hunzelmann N, Moroncini G, de Vries-Bouwstra JK, Orozco G, Barton A, Herrick AL, Terao C, Allanore Y, Fonseca C, Eugenia Alarcon-Riquelme M, Radstake TR, Beretta L, Denton CP, Mayes MD, Martin J. Complement component C4 structural variation and quantitative traits contribute to sex-biased vulnerability in systemic sclerosis. ***NPJ Genom Med*** 7, 57 (2022)

107 Kikuchi A, Onoda H, Yamaguchi K, Kori S, Matsuzawa S, Chiba Y, Tanimoto S, Yoshimi S, Sato H, Yamagata A, Shirouzu M, Adachi N, Sharif J, Koseki H, Nishiyama A, Nakanishi M, Defossez P, Arita K. Structural basis for activation of DNMT1. ***Nat Commun*** 13, 7130 (2022)

108 Kimura H, Mizuno K, Shiota M, Narita S, Terada N, Fujimoto N, Ogura K, Hatano S, Iwasaki Y, Hakozaki N, Ishitoya S, Sumiyoshi T, Goto T, Kobayashi T, Nakagawa H, Kamoto T, Eto M, Habuchi T, Ogawa O, Momozawa Y, Akamatsu S. Prognostic significance of pathogenic variants in BRCA1, BRCA2, ATM and PALB2 genes in men undergoing hormonal therapy for advanced prostate cancer. ***Br J Cancer*** 127, 1680-1690 (2022)

109 Kırkgöz T, Özkan B, Hazan F, Acar S, Nalbantoğlu Ö, Özkaya B, Kulalı MA, Gürsoy S, Ikegawa S, Guo L. A Null Mutation of TNFRSF11A Causes Dysosteosclerosis, Not Osteopetrosis. ***Front Genet*** 13, 938814 (2022)

110 Kishikawa T, Tomofuji Y, Inohara H, Okada Y. OMARU: a robust and multifaceted pipeline for metagenome-wide association study. ***NAR Genom Bioinform*** 4, Iqac019 (2022)

111 Kiyose H, Nakagawa H, Ono A, Aikata H, Ueno M, Hayami S, Yamaue H, Chayama K, Shimada M, Wong JH, Fujimoto A. Comprehensive analysis of full-length transcripts reveals novel splicing abnormalities and oncogenic transcripts in liver cancer. ***PLoS Genet*** 18, e1010342 (2022)

112 Kobayashi S, Nagafuchi Y, Okubo M, Sugimori Y, Hatano H, Yamada S, Nakano M, Yoshida R, Takeshima Y, Ota M, Tsuchida Y, Iwasaki Y, Setoguchi K, Kubo K, Okamura T, Yamamoto K, Shoda H, Fujio K. Dysregulation of the gene signature of effector regulatory T cells in the early phase of systemic sclerosis. ***Rheumatology (Oxford)*** 61, 4163-4174 (2022)

113 Kobayashi T, Moro K. A hairy situation for ILC2s. ***Immunity*** 55, 1756-1758 (2022)

114 Kobayashi T, Moro K. Tissue-Specific Diversity of Group 2 Innate Lymphoid Cells in the Skin. ***Front Immunol*** 13, 885642 (2022)

115 Koda Y, Sato S, Yamamoto H, Niwa H, Watanabe H, Watanabe C, Sato T, Nakamura K, Tanaka A, Shirouzu M, Honma T, Fukami T, Koyama H, Umehara T. Design and Synthesis of Tranylcypromine-Derived LSD1 Inhibitors with Improved hERG and Microsomal Stability Profiles. ***ACS Med Chem Lett*** 13, 848-854 (2022)

116 Koido M, Hon C, Koyama S, Kawaji H, Murakawa Y, Ishigaki K, Ito K, Sese J, Parrish NF, Kamatani Y, Carninci P, Terao C. Prediction of the cell-type-specific transcription of non-coding RNAs from genome sequences via machine learning. ***Nat Biomed Eng*** in press (2022)

117 Koike T, Fujii K, Kometani K, Butler NS, Funakoshi K, Yari S, Kikuta J, Ishii M, Kurosaki T, Ise W. Progressive differentiation toward the long-lived plasma cell compartment in the bone marrow. ***J Exp Med*** 220, e20221717 (2022)

118 Kokaji T, Eto M, Hatano A, Yugi K, Morita K, Ohno S, Fujii M, Hironaka K, Ito Y, Egami R, Uematsu S, Terakawa A, Pan Y, Maehara H, Li D, Bai Y, Tsuchiya T, Ozaki H, Inoue H, Kubota H, Suzuki Y, Hirayama A, Soga T, Kuroda S. In vivo transomic analyses of glucose-responsive metabolism in skeletal muscle reveal core differences between the healthy and obese states. ***Sci Rep*** 12, 13719 (2022)

119 Kouno T, Carninci P, Shin J. Complete Transcriptome Analysis by 5'-End Single-Cell RNA-Seq with Random Priming. ***Methods Mol Biol*** 2490, 141-156 (2022)

120 Kozuka C, Efthymiou V, Sales VM, Zhou L, Osataphan S, Yuchi Y, Chimene-Weiss J, Mulla C, Isganaitis E, Desmond J, Sanechika S, Kusuyama J, Goodyear L, Shi X, Gerszten RE, Aguayo-Mazzucato C, Carapeto P, Teixeira SS, Sandoval D, Alonso-Curbelo D, Wu L, Qi J, Patti M. Bromodomain inhibition reveals FGF15/19 as a target of epigenetic regulation and metabolic control. ***Diabetes*** 71, 1023-1033 (2022)

121 Kunishima N, Takeda Y, Hirose R, Kume S, Maeda M, Oguchi A, Yanagita M, Shibuya H, Tamura M, Kataoka Y, Murakawa Y, Ito K, Omote K. Compact laboratory-based X-ray microscope enabling non-destructive 3D structure acquisition of mouse nephron with high speed and better user accessibility. ***Microscopy*** 71, 315-323 (2022)

122 Kusuyama J, Makarewicz NS, Albertson BG, Alves-Wagner AB, Conlin RH, Prince NB, Alves CR, Ramachandran K, Kozuka C, Xiudong Y, Xia Y, Hirshman MF, Hatta T, Nagatomi R, Nozik ES, Goodyear LJ. Maternal Exercise-Induced SOD3 Reverses the Deleterious Effects of Maternal High Fat Diet on Offspring Metabolism Through Stabilization of H3K4me3 and Protection Against WDR82 Carbonylation. ***Diabetes*** 71, 1170-1181 (2022)

123 Lagattuta KA, Kang JB, Nathan A, Pauken KE, Jonsson AH, Rao DA, Sharpe AH, Ishigaki K, Raychaudhuri S. Repertoire analyses reveal T cell antigen receptor sequence features that influence T cell fate. ***Nat Immunol*** 23, 446-457 (2022)

124 Langlois AW, El-Boraie A, Fukunaga K, Mushiroda T, Kubo M, Lerman C, Knight J, Scherer SE, Chenoweth MJ, Tyndale RF. Accuracy and applications of sequencing and genotyping approaches for CYP2A6 and homologous genes. ***Pharmacogenet Genomics*** 32, 159-172 (2022)

125 Lee H, Chubachi S, Namkoong H, Asakura T, Tanaka H, Otake S, Nakagawara K, Morita A, Fukushima T, Watase M, Kusumoto T, Masaki K, Kamata H, Ishii M, Hasegawa N, Harada N, Ueda T, Ueda S, Ishiguro T, Arimura K, Saito F, Yoshiyama T, Nakano Y, Mutoh Y, Suzuki Y, Murakami K, Okada Y, Koike R, Kitagawa Y, Kimura A, Imoto S, Miyano S, Ogawa S, Kanai T, Fukunaga K. Characteristics of hospitalized patients with COVID-19 during the first to fifth waves of infection: a report from the Japan COVID-19 Task Force. ***BMC Infect Dis*** 22, 935 (2022)

126 Lee H, Chubachi S, Namkoong H, Tanaka H, Otake S, Nakagawara K, Morita A, Fukushima T, Watase M, Kusumoto T, Masaki K, Kamata H, Ishii M, Hasegawa N, Harada N, Ueda T, Ueda S, Ishiguro T, Arimura K, Saito F, Yoshiyama T, Nakano Y, Mutoh Y, Suzuki Y, Murakami K, Okada Y, Koike R, Kitagawa Y, Kimura A, Imoto S, Miyano S, Ogawa S, Kanai T, Fukunaga K. Effects of mild obesity on outcomes in Japanese patients with COVID-19: a nationwide consortium to investigate COVID-19 host genetics. ***Nutr Diabetes*** 12, 38 (2022)

127 Li Y, Watanabe E, Kawashima Y, Plichta DR, Wang Z, Ujike M, Ang QY, Wu R, Furuichi M, Takeshita K, Yoshida K, Nishiyama K, Kearney SM, Suda W, Hattori M, Sasajima S, Matsunaga T, Zhang X, Watanabe K, Fujishiro J, Norman JM, Olle B, Matsuyama S, Namkoong H, Uwamino Y, Ishii M, Fukunaga K, Hasegawa N, Ohara O, Xavier RJ, Atarashi K, Honda K. Identification of trypsin-degrading commensals in the large intestine. ***Nature*** 609, 582-589 (2022)

128 Lisa BA, Micheal CJ, Masayuki A, Anna BD, Kenji K, Jennifer HD, Ana RB. Type 2 Inflammation Contributes to Skin Barrier Dysfunction in Atopic Dermatitis. ***JID Innovations*** 2, 100131 (2022)

129 Liu T, Kim S, Desai P, Kim D, Huang X, Ferris ST, Wu R, Ou F, Egawa T, Dyken SV, Diamond MS, Johnson PF, Kubo M, Murphy TL, Murphy KM. Ablation of cDC2 development by triple mutations within the Zeb2 enhancer. ***Nature*** 607, 142-148 (2022)

130 Liu Z, Sattabongkot J, White M, Chotirat S, Kumpitak C, Takashima E, Harbers M, Tham W, Healer J, Chitnis CE, Tsuboi T, Mueller I, Longley R. Naturally acquired antibody kinetics against Plasmodium vivax antigens in people from a low malaria transmission region in western Thailand. ***BMC Med*** 20, 89 (2022)

131 Longley RJ, Grigg M, Schoffer K, Obadia, Hyslop S, Piera A, Nekkab N, Mazhari R, Takashima E, Tsuboi T, Harbers M, Tetteh K, Drakeley C, Chitnis C, Healer J, Tham W, Sattabongkot J, White MT, Cooper DJ, Rajahram GS, Barber BE, Timothy W, Anstey NM, Mueller I. Plasmodium vivax malaria serological exposure markers: Assessing the degree and implications of cross-reactivity with P. knowlesi. ***Cell Rep Med*** 3, 100662 (2022)

132 Lopez-Vicario C, Sebastian D, Casulleras M, Duran-Guell M, Flores-Costa R, Aguilar F, Jose Lozano J, Zhang IW, Titos E, Kang JX, Zorzano A, Arita M, Claria J. Essential lipid autacoids rewire mitochondrial energy efficiency in metabolic dysfunction-associated fatty liver disease. ***Hepatology*** 77, 1303-1318 (2022)

133 Luda KM, Da Silva C, Ahmadi F, Mowat AM, Ohno H, Kotarsky K, Agace WW. Identification and characterization of murine glycoprotein 2-expressing intestinal dendritic cells. ***Scand J Immunol*** 96, e13219 (2022)

134 Lv Z, Han J, Li J, Guo H, Fei Y, Sun Z, Dong J, Wang M, Fan C, Li W, Xie Y, Sun W, Chen J, Liu Y, Chen F, Liu Z, Liu A, Wu R, Xu X, Yan W, Jiang Q, Ikegawa S, Chen X, Shi D. Single cell RNA-seq analysis identifies ferroptotic chondrocyte cluster and reveals TRPV1 as an anti-ferroptotic target in osteoarthritis. ***EBioMedicine*** 84, 104258 (2022)

135 Maekawa M, Natsume R, Arita M. Functional significance of ion channels during macropinosome resolution in immune cells. ***Front Physiol*** 13, 1037758 (2022)

136 Mahajan A, Spracklen CN, Zhang W, Ng MC, Petty LE, Kitajima H, Yu GZ, Rüeger S, Speidel L, Kim YJ, Horikoshi M, Mercader JM, Taliun D, Moon S, Kwak S, Robertson NR, Rayner NW, Loh M, Kim B, Chiou J, Miguel-Escalada I, della Briotta Parolo P, Lin K, Bragg F, Preuss MH, Takeuchi F, Nano J, Guo X, Lamri A, Nakatochi M, Scott RA, Lee J, Huerta-Chagoya A, Graff M, Chai J, Parra EJ, Yao J, Bielak LF, Tabara Y, Hai Y, Steinthorsdottir V, Cook JP, Kals M, Grarup N, Schmidt EM, Pan I, Sofer T, Wuttke M, Sarnowski C, Gieger C, Nousome D, Trompet S, Long J, Sun M, Tong L, Chen W, Ahmad M, Noordam R, Lim VJ, Tam CH, Joo YY, Chen C, Raffield LM, Lecoeur C, Prins BP, Nicolas A, Yanek LR, Chen G, Jensen RA, Tajuddin S, Kabagambe EK, An P, Xiang AH, Choi HS, Cade BE, Tan J, Flanagan J, Abaitua F, Adair LS, Adeyemo A, Aguilar-Salinas CA, Akiyama M, Anand SS, Bertoni A, Bian Z, Bork-Jensen J, Brandslund I, Brody JA, Brummett CM, Buchanan TA, Canouil M, Chan JC, Chang L, Chee M, Chen J, Chen S, Chen Y, Chen Z, Chuang L, Cushman M, Das SK, de Silva HJ, Dedoussis G, Dimitrov L, Doumatey AP, Du S, Duan Q, Eckardt K, Emery LS, Evans DS, Evans MK, Fischer K, Floyd JS, Ford I, Fornage M, Franco OH, Frayling TM, Freedman BI, Fuchsberger C, Genter P, Gerstein HC, Giedraitis V, González-Villalpando C, González-Villalpando ME, Goodarzi MO, Gordon-Larsen P, Gorkin D, Gross M, Guo Y, Hackinger S, Han S, Hattersley AT, Herder C, Howard A, Hsueh W, Huang M, Huang W, Hung Y, Hwang MY, Hwu C, Ichihara S, Ikram MA, Ingelsson M, Islam MT, Isono M, Jang H, Jasmine F, Jiang G, Jonas JB, Jørgensen ME, Jørgensen T, Kamatani Y, Kandeel FR, Kasturiratne A, Katsuya T, Kaur V, Kawaguchi T, Keaton JM, Kho AN, Khor C, Kibriya MG, Kim D, Kohara K, Kriebel J, Kronenberg F, Kuusisto J, Läll K, Lange LA, Lee M, Lee NR, Leong A, Li L, Li Y, Li-Gao R, Ligthart S, Lindgren CM, Linneberg A, Liu C, Liu J, Locke AE, Louie T, Luan J, Luk AO, Luo X, Lv J, Lyssenko V, Mamakou V, Mani KR, Meitinger T, Metspalu A, Morris AD, Nadkarni GN, Nadler JL, Nalls MA, Nayak U, Nongmaithem SS, Ntalla I, Okada Y, Orozco L, Patel SR, Pereira MA, Peters A, Pirie FJ, Porneala B, Prasad G, Preissl S, Rasmussen-Torvik LJ, Reiner AP, Roden M, Rohde R, Roll K, Sabanayagam C, Sander M, Sandow K, Sattar N, Schönherr S, Schurmann C, Shahriar M, Shi J, Shin DM, Shriner D, Smith JA, So WY, Stančáková A, Stilp AM, Strauch K, Suzuki K, Takahashi A, Taylor KD, Thorand B, Thorleifsson G, Thorsteinsdottir U, Tomlinson B, Torres JM, Tsai F, Tuomilehto J, Tusie-Luna T, Udler MS, Valladares-Salgado A, van Dam RM, van Klinken JB, Varma R, Vujkovic M, Wacher-Rodarte N, Wheeler E, Whitsel EA, Wickremasinghe AR, van Dijk KW, Witte DR, Yajnik CS, Yamamoto K, Yamauchi T, Yengo L, Yoon K, Yu C, Yuan J, Yusuf S, Zhang L, Zheng W, Raffel LJ, Igase M, Ipp E, Redline S, Cho YS, Lind L, Province MA, Hanis CL, Peyser PA, Ingelsson E, Zonderman AB, Psaty BM, Wang Y, Rotimi CN, Becker DM, Matsuda F, Liu Y, Zeggini E, Yokota M, Rich SS, Kooperberg C, Pankow JS, Engert JC, Chen YI, Froguel P, Wilson JG, Sheu WH, Kardia SL, Wu J, Hayes MG, Ma RC, Wong T, Groop L, Mook-Kanamori DO, Chandak GR, Collins FS, Bharadwaj D, Paré G, Sale MM, Ahsan H, Motala AA, Shu X, Park K, Jukema JW, Cruz M, McKean-Cowdin R, Grallert H, Cheng C, Bottinger EP, Dehghan A, Tai E, Dupuis J, Kato N, Laakso M, Köttgen A, Koh W, Palmer CN, Liu S, Abecasis G, Kooner JS, Loos RJ, North KE, Haiman CA, Florez JC, Saleheen D, Hansen T, Pedersen O, Mägi R, Langenberg C, Wareham NJ, Maeda S, Kadowaki T, Lee J, Millwood IY, Walters RG, Stefansson K, Myers SR, Ferrer J, Gaulton KJ, Meigs JB, Mohlke KL, Gloyn AL, Bowden DW, Below JE, Chambers JC, Sim X, Boehnke M, Rotter JI, McCarthy MI, Morris AP. Multi-ancestry genetic study of type 2 diabetes highlights the power of diverse populations for discovery and translation. ***Nat Genet*** 54, 560-572 (2022)

137 Makishima M, Saiki R, Nannya N, Korotev S, Gurnari C, Takeda J, Momozawa Y, Best S, Krishnamurthy P, Yoshizato T, Atsuta Y, Shiozawa Y, Iijima-Yamashita Y, Yoshida K, Shiraishi Y, Nagata Y, Kakiuchi N, ONIZUKA M, Chiba K, Tanaka H, Kon A, Ochi Y, Nakagawa MM, Okuda O, Mori T, Yoda A, Itonaga H, Miyazaki Y, Sanada M, Ishikawa T, Chiba S, Tsurumi H, Kasahara S, Müller-Tidow C, Takaori-Kondo A, Ohyashiki K, Kiguchi T, Matsuda F, Jansen JH, Polprasert C, Blombery P, Kamatani Y, Miyano S, Malcovati L, Haferlach T, Kubo M, Cazzola M, Kulasekararaj AG, Godley LA, Maciejewski JP, Ogawa S. Germline DDX41 mutations define a unique subtype of myeloid neoplasms. ***Blood*** 141, 534-549 (2022)

138 Manavi F, Sharma A, Sharma R, Tsunoda T, Shatabda S, Dehzangi I. CNN-Pred: Prediction of single-stranded and double-stranded DNA-binding protein using convolutional neural networks. ***Gene*** 853, 147045 (2022)

139 Maquat L, Johnson R, Valadkhan S, Carninci P. Lessons from the functional characterization of lncRNAs: introduction to mammalian genome special issue. ***Mamm Genome*** 33, 245-247 (2022)

140 Mars N, Kerminen S, Feng YA, Kanai M, Läll K, Thomas LF, Skogholt AH, della Briotta Parolo P, Project TB, FinnGen, Neale BM, Smoller JW, Gabrielsen ME, Hveem K, Mägi R, Matsuda K, Okada Y, Pirinen M, Palotie A, Ganna A, Martin AR, Ripatti S. Genome-wide risk prediction of common diseases across ancestries in one million people. ***Cell Genomics*** 2, 100118 (2022)

141 Marston NA, Pirruccello JP, Melloni GE, Koyama S, Kamanu FK, Weng L, Roselli C, Kamatani Y, Komuro I, Aragam KG, Butterworth AS, Ito K, Lubitz SA, Ellinor PT, Sabatine MS, Ruff CT. Predictive Utility of a Coronary Artery Disease Polygenic Risk Score in Primary Prevention. ***JAMA Cardiol*** 8, 130-137 (2022)

142 Masuda T, Tanaka N, Takamatsu K, Hakozaki K, Takahashi R, Anno T, Kufukihara R, Shojo K, Mikami S, Shinojima T, Kakimi K, Tsunoda T, Aimono E, Nishihara H, Mizuno R, Oya M. Unique characteristics of tertiary lymphoid structures in kidney clear cell carcinoma: prognostic outcome and comparison with bladder cancer. ***J Immunother Cancer*** 10, e003883 (2022)

143 Matoba S, Kozuka C, Miura K, Inoue K, Kumon M, Hayashi R, Ohhata T, Ogura A, Inoue A. Noncanonical imprinting sustains embryonic development and restrains placental overgrowth. ***Genes Dev*** 36, 483-494 (2022)

144 Matsuo H, Kamatani T, Hamba Y, Boroevich KA, Tsunoda T. Association between high immune activity and worse prognosis in uveal melanoma and low-grade glioma in TCGA transcriptomic data. ***BMC Genomics*** 23, 351 (2022)

145 McDonald JG, Ejsing CS, Kopczynski D, Holcapek M, Aoki J, Arita M, Arita M, Baker ES, Bertrand-Michel J, Bowden JA, Brugger B, Ellis SR, Fedorova M, Griffiths WJ, Han X, Hartler J, Hoffmann N, Koelmel JP, Kofeler HC, Mitchell TW, O'Donnell VB, Saigusa D, Schwudke D, Shevchenko A, Ulmer CZ, Wenk MR, Witting M, Wolrab D, Xia Y, Ahrends R, Liebisch G, Ekroos K. Introducing the Lipidomics Minimal Reporting Checklist. ***Nat Metab*** 4, 1086-1088 (2022)

146 Mi-ichi F, Tsugawa H, Arita M, Yoshida H. Pleiotropic Roles of Cholesteryl Sulfate during Entamoeba Encystation: Involvement in Cell Rounding and Development of Membrane Impermeability. ***mSphere*** 7, e0029922 (2022)

147 Miki Y, Taketomi Y, Kidoguchi Y, Yamamoto K, Muramatsu K, Nishito Y, Park J, Hosomi K, Mizuguchi K, Kunisawa J, Soga T, Boilard E, Gowda SG, Ikeda K, Arita M, Murakami M. Group IIA secreted phospholipase A (2) controls skin carcinogenesis and psoriasis by shaping the gut microbiota. ***JCI Insight*** 7, e152611 (2022)

148 Misawa T, Wagner M, Koyasu S. ILC2s and adipose tissue homeostasis: Progress to date and the road ahead. ***Front Immunol*** 13, 876029 (2022)

149 Mishra A, Malik R, Hachiya T, Jurgenson T, Namba S, Posner DC, Kamanu FK, Koido M, Le Grand Q, Shi M, He Y, Georgakis MK, Caro I, Krebs K, Liaw Y, Vaura FC, Lin K, Winsvold BS, Srinivasasainagendra V, Parodi L, Bae H, Chauhan G, Chong MR, Tomppo L, Akinyemi R, Roshchupkin GV, Habib N, Jee YH, Thomassen JQ, Abedi V, Carcel-Marquez J, Nygaard M, Leonard HL, Yang C, Yonova-Doing E, Knol MJ, Lewis AJ, Judy RL, Ago T, Amouyel P, Armstrong ND, Bakker MK, Bartz TM, Bennett DA, Bis JC, Bordes C, Borte S, Cain A, Ridker PM, Cho K, Chen Z, Cruchaga C, Cole JW, de Jager PL, de Cid R, Endres M, Ferreira LE, Geerlings MI, Gasca NC, Gudnason V, Hata J, He J, Heath AK, Ho Y, Havulinna AS, Hopewell JC, Hyacinth HI, Inouye M, Jacob MA, Jeon CE, Jern C, Kamouchi M, Keene KL, Kitazono T, Kittner SJ, Konuma T, Kumar A, Lacaze P, Launer LJ, Lee K, Lepik K, Li J, Li L, Manichaikul A, Markus HS, Marston NA, Meitinger T, Mitchell BD, Montellano FA, Morisaki T, Mosley TH, Nalls MA, Nordestgaard BG, O'Donnell MJ, Okada Y, Onland-Moret NC, Ovbiagele B, Peters A, Psaty BM, Rich SS, Rosand J, Sabatine MS, Sacco RL, Saleheen D, Sandset EC, Salomaa V, Sargurupremraj M, Sasaki M, Satizabal CL, Schmidt CO, Shimizu A, Smith NL, Sloane KL, Sutoh Y, Sun YV, Tanno K, Tiedt S, Tatlisumak T, Torres-Aguila NP, Tiwari HK, Tregouet D, Trompet S, Tuladhar AM, Tybjaerg-Hansen A, van Vugt M, Vibo R, Verma SS, Wiggins KL, Wennberg P, Woo D, Wilson PW, Xu H, Yang Q, Yoon K, Bis JC, Bis JC, Lee J, Cheng Y, Meschia JF, Chen WM, Sale MM, Zonderman AB, Evans MK, Wilson JG, Correa A, Traylor M, Lewis CM, Carty CL, Reiner A, Haessler J, Langefeld CD, Gottesman RF, Yaffe K, Liu YM, Kooperberg C, Lange LA, Furie KL, Arnett DK, Benavente OR, Grewal RP, Peddareddygari LR, Kooperberg C, Kooperberg C, Hveem K, Lindstrom S, Wang L, Smith EN, Gordon W, van Hylckama Vlieg A, de Andrade M, Brody JA, Pattee JW, Haessler J, Brumpton BM, Suchon P, Chen M, Frazer KA, Turman C, Germain M, MacDonald J, Braekkan SK, Armasu SM, Pankratz N, Jackson RD, Nielsen JB, Giulianini F, Puurunen MK, Ibrahim M, Heckbert SR, Bammler TK, McCauley BM, Taylor KD, Pankow JS, Reiner AP, Gabrielsen ME, Deleuze J, O'Donnell CJ, Kim J, McKnight B, Kraft P, Hansen J, Rosendaal FR, Heit JA, Tang W, Morange P, Johnson AD, Kabrhel C, van Dijk EJ, van Dijk EJ, Koudstaal PJ, Luijckx G, Nederkoorn PJ, van Oostenbrugge RJ, Visser MC, Wermer MJ, Kappelle LJ, Esko T, Esko T, Metspalu A, Magi R, Nelis M, Irvin MR, Irvin MR, de Leeuw F, Levi CR, Maguire J, Jimenez-Conde J, Sharma P, Sudlow CL, Rannikmae K, Schmidt R, Slowik A, Pera J, Thijs VN, Lindgren AG, Ilinca A, Melander O, Engstrom G, Rexrode KM, Rothwell PM, Stanne TM, Johnson JA, Danesh J, Butterworth AS, Heitsch L, Boncoraglio GB, Kubo M, Pezzini A, Rolfs A, Giese A, Weir D, Jackson RD, Ross OA, Lemmons R, Soderholm M, Cushman M, Jood K, McDonough CW, Bell S, Linkohr B, Lee T, Putaala J, Anderson CD, Anderson CD, Lopez OL, Jian X, Schminke U, Cullell N, Delgado P, Ibanez L, Krupinski J, Lioutas V, Matsuda K, Montaner J, Muino E, Roquer J, Sarnowski C, Sattar N, Sibolt G, Teumer A, Rutten-Jacobs L, Kanai M, Giese A, Gretarsdottir S, Rost NS, Yusuf S, Almgren P, Ay H, Bevan S, Brown RD, Carrera C, Buring JE, Chen W, Cotlarciuc I, de Bakker PI, DeStefano AL, den Hoed M, Duan Q, Engelter ST, Falcone GJ, Gottesman RF, Gustafsson S, Hassan A, Holliday EG, Howard G, Hsu F, Ingelsson E, Harris TB, Kissela BM, Kleindorfer DO, Langenberg C, Lemmens R, Leys D, Lin W, Lorentzen E, Magnusson PK, McArdle PF, Pulit SL, Rice K, Sakaue S, Sapkota BR, Tanislav C, Thorleifsson G, Thorsteinsdottir U, Tzourio C, van Duijn CM, Walters M, Wareham NJ, Amin N, Aparicio HJ, Attia J, Beiser AS, Berr C, Bustamante M, Caso V, Choi SH, Chowhan A, Dartigues J, Delavaran H, Dorr M, Ford I, Gurpreet WS, Hamsten A, Hozawa A, Ingelsson M, Iwasaki M, Kaffashian S, Kalra L, Kjartansson O, Kloss M, Labovitz DL, Laurie CC, Li L, Lind L, Lindgren CM, Makoto H, Minegishi N, Morris AP, Muller-Nurasyid M, Norrving B, Ogishima S, Parati EA, Pedersen NL, Perola M, Jousilahti P, Pileggi S, Rabionet R, Riba-Llena I, Ribases M, Romero JR, Rudd AG, Sarin A, Sarju R, Satoh M, Sawada N, Sigurdsson A, Smith A, Stine OC, Stott DJ, Strauch K, Takai T, Tanaka H, Touze E, Tsugane S, Uitterlinden AG, Valdimarsson EM, van der Lee SJ, Wakai K, Williams SR, Wolfe CD, Wong Q, Yamaji T, Sanghera DK, Stefansson K, Taylor KD, Martinez-Majander N, Sobue K, Soriano-Tarraga C, Volzke H, Akpa O, Akpa O, Sarfo FS, Akpalu A, Obiako R, Wahab K, Osaigbovo G, Owolabi L, Komolafe M, Jenkins C, Arulogun O, Ogbole G, Adeoye AM, Akinyemi J, Agunloye A, Fakunle AG, Uvere E, Olalere A, Adebajo OJ, Chen J, Chen J, Clarke R, Collins R, Guo Y, Wang C, Lv J, Peto R, Chen Y, Fairhurst-Hunter Z, Hill M, Pozarickij A, Schmidt D, Stevens B, Turnbull I, Yu C, Le Grand Q, Le Grand Q, Ferreira LE, Nagai A, Nagai A, Murakami Y, Geerlings MI, Geerlings MI, Gasca NC, Gudnason V, van Vugt M, Gottesman RF, Shiroma EJ, Sigurdsson S, Ghanbari M, Boerwinkle E, Beiser AS, Fongang B, Wang R, Ikram MK, Volker U, de Jager PL, de Cid R, Nordestgaard BG, Sargurupremraj M, Verma SS, de Laat KF, de Laat KF, van Norden AG, de Kort PL, Vermeer SE, Brouwers PJ, Gons RA, Nederkoorn PJ, den Heijer T, van Dijk GW, van Rooij FG, Aamodt AH, Aamodt AH, Skogholt AH, Brumpton BM, Willer CJ, Heuch I, Hagen K, Fritsche LG, Pedersen LM, Gabrielsen ME, Ellekjaer H, Zhou W, Martinsen AE, Kristoffersen ES, Nielsen JB, Hveem K, Thomas LF, Kleinschnitz C, Kleinschnitz C, Frantz S, Ungethum K, Gallego-Fabrega C, Gallego-Fabrega C, Lledos M, Llucia-Carol L, Sobrino T, Campos F, Castillo J, Freijo M, Arenillas JF, Obach V, Alvarez-Sabin J, Molina CA, Ribo M, Munoz-Narbona L, Lopez-Cancio E, Millan M, Diaz-Navarro R, Vives-Bauza C, Serrano-Heras G, Segura T, Delgado P, Dhar R, Delgado-Mederos R, Prats-Sanchez L, Camps-Renom P, Blay N, Sumoy L, Marti-Fabregas J, Schnohr P, Schnohr P, Jensen GB, Benn M, Afzal S, Kamstrup PR, van Setten J, van Setten J, van der Laan SW, Vonk JM, Kim B, Kim B, Curtze S, Curtze S, Tiainen M, Kinnunen J, Menon V, Menon V, Sung YJ, Yang C, Saillour-Glenisson F, Gravel S, Onland-Moret NC, Onland-Moret NC, Heath AK, Millwood IY, Gieger C, Ninomiya T, Grabe HJ, Jukema JW, Rissanen IL, Strbian D, Kim YJ, Chen P, Mayerhofer E, Howson JM, Irvin MR, Adams H, Wassertheil-Smoller S, Christensen K, Ikram MA, Rundek T, Worrall BB, Lathrop GM, Riaz M, Simonsick EM, Korv J, Franca PH, Zand R, Prasad K, Frikke-Schmidt R, de Leeuw F, Liman T, Haeusler KG, Ruigrok YM, Heuschmann PU, Longstreth WT, Jung KJ, Bastarache L, Pare G, Damrauer SM, Chasman DI, Rotter JI, Anderson CD, Zwart J, Niiranen TJ, Fornage M, Liaw Y, Seshadri S, Fernandez-Cadenas I, Walters RG, Ruff CT, Owolabi MO, Huffman JE, Milani L, Kamatani Y, Dichgans M, Debette S. Stroke genetics informs drug discovery and risk prediction across ancestries. ***Nature*** 611, 115-123 (2022)

150 Miyajima Y, Noguchi S, Tanaka Y, Li J, Nishimura H, Kishima M, Lim J, Furuhata E, Suzuki T, Kasukawa T, Suzuki H. Prediction of transcription factors associated with DNA demethylation during human cellular development. ***Chromosome Res*** 30, 109-121 (2022)

151 Miyamoto A, Kawasaki H, Lee S, Yokota T, Amagai M, Someya T. Highly Precise, Continuous, Long-term Monitoring of Skin Electrical Resistance by Nanomesh Electrodes. ***Adv Healthc Mater*** 11, e2102425 (2022)

152 Miyamoto H, Asano F, Ishizawa K, Suda W, Miyamoto H, Tsuji N, Matsuura M, Tsuboi A, Ishii C, Nakaguma T, Shindo C, Kato T, Kurotani A, Shima H, Moriya S, Hattori M, Kodama H, Ohno H, Kikuchi J. A potential network structure of symbiotic bacteria involved in carbon and nitrogen metabolism of wood-utilizing insect larvae. ***Sci Total Environ*** 836, 155520 (2022)

153 Miyamoto H, Kawachi N, Kurotani A, Moriya S, Suda W, Suzuki K, Matsuura M, Tsuji N, Nakaguma T, Ishii C, Tsuboi A, Shindo C, Kato T, Udagawa M, Satoh T, Wada S, Masuya H, Miyamoto H, Ohno H, Kikuchi J. Computational estimation of sediment symbiotic bacterial structures of seagrasses overgrowing downstream of onshore aquaculture. ***Environ Res*** 219, 115130 (2022)

154 Miyao T, Miyauchi M, Kelly ST, Terooatea TW, Ishikawa T, Oh E, Hirai S, Horie K, Takakura Y, Ohki H, Hayama M, Maruyama Y, Seki T, Ishii H, Yabukami H, Yoshida M, Inoue A, Sakaue-Sawano A, Miyawaki A, Muratani M, Minoda A, Akiyama N, Akiyama T. Integrative analysis of scRNA-seq and scATAC-seq revealed transit-amplifying thymic epithelial cells expressing autoimmune regulator. ***Elife*** 11, e73998 (2022)

155 Miyauchi E, Shimokawa C, Steimle A, Desai MS, Ohno H. The impact of the gut microbiome on extra-intestinal autoimmune diseases. ***Nat Rev Immunol*** 23, 9-23 (2022)

156 Momozawa Y, Sasai R, Usui Y, Shiraishi K, Iwasaki Y, Taniyama Y, Parsons MT, Mizukami K, Sekine Y, Hirata M, Kamatani Y, Endo M, Inai C, Takata S, Ito H, Kohno T, Matsuda K, Nakamura S, Sugano K, Yoshida T, Nakagawa H, Matsuo K, Murakami Y, Spurdle AB, Kubo M. Expansion of Cancer Risk Profile for BRCA1 and BRCA2 Pathogenic Variants. ***JAMA Oncol*** 8, 871-878 (2022)

157 Moody J, Kouno T, Chang J, Ando Y, Carninci P, Shin J, Hon C. SCAFE: a software suite for analysis of transcribed cis-regulatory elements in single cells. ***Bioinformatics*** 38, 5126-5128 (2022)

158 Mori K, Kuroha S, Hou J, Jeong H, Ogawa M, Ikeda S, Kang JX, Negishi K, Torii H, Arita M, Kurihara T, Tsubota K. Lipidomic analysis revealed n-3 polyunsaturated fatty acids suppressed choroidal thinning and myopia progression in mice. ***FASEB J*** 36, e22312 (2022)

159 Mori T, Rai A, Tsugawa H, Yamada Y, Saito K. A liquid chromatography-mass spectrometry-based metabolomics strategy to explore plant metabolic diversity. ***Methods Enzymol*** 680, 247-273 (2022)

160 Morimoto A, Fukuda K, Ito Y, Tahara U, Sasaki T, Shiohama A, Kawasaki H, Kawakami E, Naganuma T, Arita M, Sasaki H, Koseki H, Matsui T, Amagai M. Microbiota-Independent Spontaneous Dermatitis Associated with Increased Sebaceous Lipid Production in Tmem79-Deficient Mice. ***J Invest Dermatol*** 142, 2864-2872.e6 (2022)

161 Morozumi S, Ueda M, Okahashi N, Arita M. Structures and functions of the gut microbial lipidome. ***Biochim Biophys Acta Mol Cell Biol Lipids*** 1867, 159110 (2022)

162 Mukai H, Miki N, Yamada H, Goto H, Kawakami T, Suzuki A, Yamamoto K, Nakanishi Y, Takahashi K. Pannexin1 channel-dependent secretome from apoptotic tumor cells shapes immune-escape microenvironment. ***Biochem Biophys Res Commun*** 628, 116-122 (2022)

163 Mukai Y, Horie M, Kojima S, Kawasaki J, Maeda K, Tomonaga K. An endogenous bornavirus-like nucleoprotein in miniopterid bats retains the RNA-binding properties of the original viral protein. ***FEBS Lett*** 596, 323-337 (2022)

164 Mushiroda T. Avoidance of cutaneous adverse drug reactions induced by antiepileptic drugs based on pharmacogenomics. ***J Hum Genet*** 68, 227-230 (2022)

165 Mutai H, Momozawa Y, Kamatani Y, Nakano A, Sakamoto H, Takiguchi T, Nara K, Kubo M, Matsunaga T. Whole exome analysis of patients in Japan with hearing loss reveals high heterogeneity among responsible and novel candidate genes. ***Orphanet J Rare Dis*** 17, 114 (2022)

166 Nagafuchi Y, Ota M, Hatano H, Inoue M, Kobayashi S, Okubo M, Sugimori Y, Nakano M, Yamada S, Yoshida R, Tsuchida Y, Iwasaki Y, Shoda H, Okada Y, Yamamoto K, Ishigaki K, Okamura T, Fujio K. Control of naive and effector CD4 T cell receptor repertoires by rheumatoid-arthritis-risk HLA alleles. ***J Autoimmun*** 133, 102907 (2022)

167 Nagano M, Hu B, Yokobayashi S, Yamamura A, Umemura F, Coradin M, Ohta H, Yabuta Y, Ishikura Y, Okamoto I, Ikeda H, Kawahira N, Nosaka Y, Shimizu S, Kojima Y, Mizuta K, Kasahara T, Imoto Y, Meehan K, Stocsits R, Wutz G, Hiraoka Y, Murakawa Y, Yamamoto T, Tachibana K, Peters J, Mirny LA, Garcia BA, Majewski J, Saitou M. Nucleome programming is required for the foundation of totipotency in mammalian germline development. ***EMBO J*** 41, e110600 (2022)

168 Naganuma T, Fujinami N, Arita M. Polyunsaturated Fatty Acid-Derived Lipid Mediators That Regulate Epithelial Homeostasis. ***Biol Pharm Bull*** 45, 998-1007 (2022)

169 Nagata N, Nishijima S, Kojima Y, Hisada Y, Imbe K, Miyoshi-Akiyama T, Suda W, Kimura M, Aoki R, Sekine K, Ohsugi M, Miki K, Osawa T, Ueki K, Oka S, Mizokami M, Kartal E, Schmidt TS, Molina-Montes E, Estudillo L, Malats N, Trebicka J, Kersting S, Langheinrich M, Bork P, Uemura N, Itoi T, Kawai T. Metagenomic Identification of Microbial Signatures Predicting Pancreatic Cancer From a Multinational Study. ***Gastroenterology*** 163, 222-238 (2022)

170 Nagata N, Takeuchi T, Masuoka H, Aoki R, Ishikane M, Iwamoto N, Sugiyama M, Suda W, Nakanishi Y, Terada-Hirashima J, Kimura M, Nishijima T, Inooka H, Miyoshi-Akiyama T, Kojima Y, Shimokawa C, Hisaeda H, Zhang F, Yeoh YK, Ng SC, Uemura N, Itoi T, Mizokami M, Kawai T, Sugiyama H, Ohmagari N, Ohno H. Human gut microbiota and its metabolites impact immune responses in COVID-19 and its complications. ***Gastroenterology*** 164, 272-288 (2022)

171 Nagata Y, Watanabe R, Eichhorn C, Ohno S, Aiba T, Ishikawa T, Nakano Y, Aizawa Y, Hayashi K, Murakoshi N, Nakajima T, Yagihara N, Mishima H, Sudo T, Higuchi C, Takahashi A, Sekine A, Makiyama T, Tanaka Y, Watanabe A, Tachibana M, Morita H, Yoshiura K, Tsunoda T, Watanabe H, Kurabayashi M, Nogami A, Kihara Y, Horie M, Shimizu W, Makita N, Tanaka T. Targeted deep sequencing analyses of long QT syndrome in a Japanese population. ***PLoS One*** 17, e0277242 (2022)

172 Nagatake T, Kishino S, Urano E, Murakami H, Kitamura N, Konishi K, Ohno H, Tiwari P, Morimoto S, Node E, Adachi J, Abe Y, Isoyama J, Sawane K, Honda T, Inoue A, Uwamizu A, Matsuzaka T, Miyamoto Y, Hirata S, Saika A, Shibata Y, Hosomi K, Matsunaga A, Shimano H, Arita M, Aoki J, Oka M, Matsutani A, Tomonaga T, Kabashima K, Miyachi M, Yasutomi Y, Ogawa J, Kunisawa J. Intestinal microbe-dependent omega 3 lipid metabolite alpha KetoA prevents inflammatory diseases in mice and cynomolgus macaques. ***Mucosal Immunol*** 15, 289-300 (2022)

173 Najnin RA, Al Mahmud MR, Rahman MM, Takeda S, Sasanuma H, Tanaka H, Murakawa Y, Shimizu N, Akter S, Takagi M, Sunada T, Akamatsu S, He G, Itou J, Toi M, Miyaji M, Tsutsui KM, Keeney S, Yamada S. ATM suppresses c-Myc overexpression in the mammary epithelium in response to estrogen. ***Cell Rep*** 42, 111909 (2022)

174 Nakade Y, Iwata Y, Sakai N, Mita M, Nakane M, Hamase K, Suda W, Toyama T, Kitajima S, Hara A, Shimizu M, Ogushi C, Furuichi K, Koshino Y, Morita H, Hattori M, Wada T. Increased levels of oral Streptococcus-derived d-alanine in patients with chronic kidney disease and diabetes mellitus. ***Sci Rep*** 12, 21773 (2022)

175 Nakagawara K, Chubachi S, Namkoong H, Tanaka H, Lee H, Azekawa S, Otake S, Fukushima T, Morita A, Watase M, Sakurai K, Kusumoto T, Asakura T, Masaki K, Kamata H, Ishii M, Hasegawa N, Harada N, Ueda T, Ueda S, Ishiguro T, Arimura K, Saito F, Yoshiyama T, Nakano Y, Mutoh Y, Suzuki Y, Edahiro R, Murakami K, Sato Y, Okada Y, Koike R, Kitagawa Y, Tokunaga K, Kimura A, Imoto S, Miyano S, Ogawa S, Kanai T, Fukunaga K. Impact of upper and lower respiratory symptoms on COVID-19 outcomes: a multicenter retrospective cohort study. ***Respir Res*** 23, 315 (2022)

176 Nakajima T, Yoshifuji H, Yamano Y, Yurugi K, Miura Y, Maekawa T, Yoshida T, Handa H, Ohmura K, Mimori T, Terao C. Co-occurrence of relapsing polychondritis and autoimmune thyroid diseases. ***Orphanet J Rare Dis*** 17, 101 (2022)

177 Nakamori M, Shimizu H, Ogawa K, Hasuike Y, Nakajima T, Sakurai H, Araki T, Okada Y, Kakita A, Mochizuki H. Cell type-specific abnormalities of central nervous system in myotonic dystrophy type 1. ***Brain Commun*** 4, fcac154 (2022)

178 Nakamura Y, Tamura T, Narita A, Shimizu A, Sutoh Y, Takashima N, Matsui K, Miyagawa N, Kadota A, Miura K, Otonari J, Ikezaki H, Hishida A, Nagayoshi M, Okada R, Kubo Y, Tanaka K, Shimanoe C, Ibusuki R, Nishimoto D, Oze I, Ito H, Ozaki E, Matsui D, Mikami H, Kusakabe M, Suzuki S, Watanabe M, Arisawa K, Katsuura-Kamano S, Kuriki K, Nakatochi M, Momozawa Y, Kubo M, Takeuchi K, Wakai K. A genome-wide association study on adherence to low-carbohydrate diets in Japanese. ***Eur J Clin Nutr*** 76, 1103-1110 (2022)

179 Nakano M, Ota M, Takeshima Y, Iwasaki Y, Hatano H, Nagafuchi Y, Itamiya T, Maeda J, Yoshida R, Yamada S, Nishiwaki A, Takahashi H, Takahashi H, Akutsu Y, Kusuda T, Suetsugu H, Liu L, Kim K, Yin X, Bang S, Cui Y, Lee H, Shoda H, Zhang X, Bae S, Terao C, Yamamoto K, Okamura T, Ishigaki K, Fujio K. Distinct transcriptome architectures underlying lupus establishment and exacerbation. ***Cell*** 185, 3375-3389.e21 (2022)

180 Nakayama Y, Kusano M, Kobayashi M, Manabe R, Watanabe M. Catabolic reprogramming of Brassica rapa leaf mesophyll protoplasts during the isolation procedure. ***Plant Growth Regul*** 99, 337-357 (2022)

181 Namba S, Konuma T, Wu K, Zhou W, Initiative GB, Okada Y. A practical guideline of genomics-driven drug discovery in the era of global biobank meta-analysis. ***Cell Genomics*** 2, 100190 (2022)

182 Namkoong H, Edahiro R, Takano T, Nishihara H, Shirai Y, Sonehara K, Tanaka H, Azekawa S, Mikami Y, Lee H, Hasegawa T, Okudela K, Okuzaki D, Motooka D, Kanai M, Naito T, Yamamoto K, Wang QS, Saiki R, Ishihara R, Matsubara Y, Hamamoto J, Hayashi H, Yoshimura Y, Tachikawa N, Yanagita E, Hyugaji T, Shimizu E, Katayama K, Kato Y, Morita T, Takahashi K, Harada N, Naito T, Hiki M, Matsushita Y, Takagi H, Aoki R, Nakamura A, Harada S, Sasano H, Kabata H, Masaki K, Kamata H, Ikemura S, Chubachi S, Okamori S, Terai H, Morita A, Asakura T, Sasaki J, Morisaki H, Uwamino Y, Nanki K, Uchida S, Uno S, Nishimura T, Ishiguro T, Isono T, Shibata S, Matsui Y, Hosoda C, Takano K, Nishida T, Kobayashi Y, Takaku Y, Takayanagi N, Ueda S, Tada A, Miyawaki M, Yamamoto M, Yoshida E, Hayashi R, Nagasaka T, Arai S, Kaneko Y, Sasaki K, Tagaya E, Kawana M, Arimura K, Takahashi K, Anzai T, Ito S, Endo A, Uchimura Y, Miyazaki Y, Honda T, Tateishi T, Tohda S, Ichimura N, Sonobe K, Sassa CT, Nakajima J, Nakano Y, Nakajima Y, Anan R, Arai R, Kurihara Y, Harada Y, Nishio K, Ueda T, Azuma M, Saito R, Sado T, Miyazaki Y, Sato R, Haruta Y, Nagasaki T, Yasui Y, Hasegawa Y, Mutoh Y, Kimura T, Sato T, Takei R, Hagimoto S, Noguchi Y, Yamano Y, Sasano H, Ota S, Nakamori Y, Yoshiya K, Saito F, Yoshihara T, Wada D, Iwamura H, Kanayama S, Maruyama S, Yoshiyama T, Ohta K, Kokuto H, Ogata H, Tanaka Y, Arakawa K, Shimoda M, Osawa T, Tateno H, Hase I, Yoshida S, Suzuki S, Kawada M, Horinouchi H, Saito F, Mitamura K, Hagihara M, Ochi J, Uchida T, Baba R, Arai D, Ogura T, Takahashi H, Hagiwara S, Nagao G, Konishi S, Nakachi I, Murakami K, Yamada M, Sugiura H, Sano H, Matsumoto S, Kimura N, Ono Y, Baba H, Suzuki Y, Nakayama S, Masuzawa K, Namba S, Suzuki K, Naito Y, Liu Y, Takuwa A, Sugihara F, Wing JB, Sakakibara S, Hizawa N, Shiroyama T, Miyawaki S, Kawamura Y, Nakayama A, Matsuo H, Maeda Y, Nii T, Noda Y, Niitsu T, Adachi Y, Enomoto T, Amiya S, Hara R, Yamaguchi Y, Murakami T, Kuge T, Matsumoto K, Yamamoto Y, Yamamoto M, Yoneda M, Kishikawa T, Yamada S, Kawabata S, Kijima N, Takagaki M, Sasa N, Ueno Y, Suzuki M, Takemoto N, Eguchi H, Fukusumi T, Imai T, Fukushima M, Kishima H, Inohara H, Tomono K, Kato K, Takahashi M, Matsuda F, Hirata H, Takeda Y, Koh H, Manabe T, Funatsu Y, Ito F, Fukui T, Shinozuka K, Kohashi S, Miyazaki M, Shoko T, Kojima M, Adachi T, Ishikawa M, Takahashi K, Inoue T, Hirano T, Kobayashi K, Takaoka H, Watanabe K, Miyazawa N, Kimura Y, Sado R, Sugimoto H, Kamiya A, Kuwahara N, Fujiwara A, Matsunaga T, Sato Y, Okada T, Hirai Y, Kawashima H, Narita A, Niwa K, Sekikawa Y, Nishi K, Nishitsuji M, Tani M, Suzuki J, Nakatsumi H, Ogura T, Kitamura H, Hagiwara E, Murohashi K, Okabayashi H, Mochimaru T, Nukaga S, Satomi R, Oyamada Y, Mori N, Baba T, Fukui Y, Odate M, Mashimo S, Makino Y, Yagi K, Hashiguchi M, Kagyo J, Shiomi T, Fuke S, Saito H, Tsuchida T, Fujitani S, Takita M, Morikawa D, Yoshida T, Izumo T, Inomata M, Kuse N, Awano N, Tone M, Ito A, Nakamura Y, Hoshino K, Maruyama J, Ishikura H, Takata T, Odani T, Amishima M, Hattori T, Shichinohe Y, Kagaya T, Kita T, Ohta K, Sakagami S, Koshida K, Hayashi K, Shimizu T, Kozu Y, Hiranuma H, Gon Y, Izumi N, Nagata K, Ueda K, Taki R, Hanada S, Kawamura K, Ichikado K, Nishiyama K, Muranaka H, Nakamura K, Hashimoto N, Wakahara K, Sakamoto K, Omote N, Ando A, Kodama N, Kaneyama Y, Maeda S, Kuraki T, Matsumoto T, Yokote K, Nakada T, Abe R, Oshima T, Shimada T, Harada M, Takahashi T, Ono H, Sakurai T, Shibusawa T, Kimizuka Y, Kawana A, Sano T, Watanabe C, Suematsu R, Sageshima H, Yoshifuji A, Ito K, Takahashi S, Ishioka K, Nakamura M, Masuda M, Wakabayashi A, Watanabe H, Ueda S, Nishikawa M, Chihara Y, Takeuchi M, Onoi K, Shinozuka J, Sueyoshi A, Nagasaki Y, Okamoto M, Ishihara S, Shimo M, Tokunaga Y, Kusaka Y, Ohba T, Isogai S, Ogawa A, Inoue T, Fukuyama S, Eriguchi Y, Yonekawa A, Kan-o K, Matsumoto K, Kanaoka K, Ihara S, Komuta K, Inoue Y, Chiba S, Yamagata K, Hiramatsu Y, Kai H, Asano K, Oguma T, Ito Y, Hashimoto S, Yamasaki M, Kasamatsu Y, Komase Y, Hida N, Tsuburai T, Oyama B, Takada M, Kanda H, Kitagawa Y, Fukuta T, Miyake T, Yoshida S, Ogura S, Abe S, Kono Y, Togashi Y, Takoi H, Kikuchi R, Ogawa S, Ogata T, Ishihara S, Kanehiro A, Ozaki S, Fuchimoto Y, Wada S, Fujimoto N, Nishiyama K, Terashima M, Beppu S, Yoshida K, Narumoto O, Nagai H, Ooshima N, Motegi M, Umeda A, Miyagawa K, Shimada H, Endo M, Ohira Y, Watanabe M, Inoue S, Igarashi A, Sato M, Sagara H, Tanaka A, Ohta S, Kimura T, Shibata Y, Tanino Y, Nikaido T, Minemura H, Sato Y, Yamada Y, Hashino T, Shinoki M, Iwagoe H, Takahashi H, Fujii K, Kishi H, Kanai M, Imamura T, Yamashita T, Yatomi M, Maeno T, Hayashi S, Takahashi M, Kuramochi M, Kamimaki I, Tominaga Y, Ishii T, Utsugi M, Ono A, Tanaka T, Kashiwada T, Fujita K, Saito Y, Seike M, Watanabe H, Matsuse H, Kodaka N, Nakano C, Oshio T, Hirouchi T, Makino S, Egi M, Omae Y, Nannya Y, Ueno T, Katayama K, Ai M, Fukui Y, Kumanogoh A, Sato T, Hasegawa N, Tokunaga K, Ishii M, Koike R, Kitagawa Y, Kimura A, Imoto S, Miyano S, Ogawa S, Kanai T, Fukunaga K, Okada Y. DOCK2 is involved in the host genetics and biology of severe COVID-19. ***Nature*** 609, 754-760 (2022)

183 Nemoto S, Kubota T, Ohno H. Metabolic differences and differentially expressed genes between C57BL/6J and C57BL/6N mice substrains. ***PLoS One*** 17, e0271651 (2022)

184 Neriya Y, Kojima S, Sakiyama A, Kishimoto M, Iketani T, Watanabe T, Abe Y, Shimoda H, Nakagawa K, Koma T, Matsumoto Y. A comprehensive list of the Bunyavirales replication promoters reveals a unique promoter structure in Nairoviridae differing from other virus families. ***Sci Rep*** 12, 13560 (2022)

185 Nomura H, Wada N, Takahashi H, Kase Y, Yamagami J, Egami S, Iriki H, Mukai M, Kamata A, Ito H, Fujii H, Ishikura T, Koseki H, Watanabe T, Yamada T, Ohara O, Koyasu S, Amagai M. IgM to IgG Class Switching Is a Necessary Step for Pemphigus Phenotype Induction in Desmoglein 3-Specific B Cell Receptor Knock-in Mouse. ***J Immunol*** 208, 582-593 (2022)

186 Ogata Y, Watanabe K, Takemine S, Kaida K, Tanokura M, Suda W. Complete Genome Sequence of Aquiluna sp. Strain KACHI24, Isolated from River Surface Water. ***Microbiol Resour Announc*** 11, e00858 (2022)

187 Ogata Y, Watanabe K, Takemine S, Kaida K, Tanokura M, Suda W. Complete Genome Sequences of Rhodoluna sp. Strains KAS3 and KACHI23, Isolated from Lake and River Surface Water. ***Microbiol Resour Announc*** 11, e0112222 (2022)

188 Ogata Y, Watanabe K, Takemine S, Shindo C, Kurokawa R, Suda W. Whole-Genome Sequence of Sediminibacterium sp. Strain TEGAF015, Isolated from a Shallow Eutrophic Freshwater Lake in Japan. ***Microbiol Resour Announc*** 11, e00882-22 (2022)

189 Ohinata Y, Endo TA, Sugishita H, Watanabe T, Iizuka Y, Kawamoto Y, Saraya A, Kumon M, Koseki Y, Kondo T, Ohara O, Koseki H. Establishment of mouse stem cells that can recapitulate the developmental potential of primitive endoderm. ***Science*** 375, 574-578 (2022)

190 Okada M, Shimizu K, Fujii S. Identification of Neoantigens in Cancer Cells as Targets for Immunotherapy. ***Int J Mol Sci*** 23, 2594 (2022)

191 Okada Y, Yamamoto K. Genetics and functional genetics of autoimmune diseases. ***Semin Immunopathol*** 44, 1-2 (2022)

192 Okada Y. An evolving hypothesis in autoimmune disease genetics. ***Nat Rev Genet*** 23, 458-459 (2022)

193 Okawa Y, Iwasaki Y, Johnson TA, Ebata N, Inai C, Endo M, Maejima K, Sasagawa S, Fujita M, Matsuda K, Murakami Y, Nakamura T, Hirano S, Momozawa Y, Nakagawa H. Hereditary cancer variants and homologous recombination deficiency in biliary tract cancer. ***J Hepatol*** 78, 333-342 (2022)

194 Okubo M, Sumitomo S, Tsuchida Y, Nagafuchi Y, Takeshima Y, Yanaoka H, Shirai H, Kobayashi S, Sugimori Y, Maeda J, Hatano H, Iwasaki Y, Shoda H, Okamura T, Yamamoto K, Ota M, Fujio K. Transcriptome analysis of immune cells from Behcet's syndrome patients: the importance of IL-17-producing cells and antigen-presenting cells in the pathogenesis of Behcet's syndrome. ***Arthritis Res Ther*** 24, 186 (2022)

195 Okuyama K, Taniuchi I. Three residues in the BTB domain promote a good partnership between NuRD and Thpok. ***Sci Immunol*** 7, eabq1408 (2022)

196 Oshima K, Kato K, Ito Y, Daiko H, Nozaki I, Nakagawa S, Shibuya Y, Kojima T, Toh Y, Okada M, Hironaka S, Akiyama Y, Komatsu Y, Maejima K, Nakagawa H, Onuki R, Nagai M, Kato M, Kanato K, Kuchiba A, Nakamura K, Kitagawa Y. Prognostic biomarker study in patients with clinical stage I esophageal squamous cell carcinoma: JCOG0502-A1. ***Cancer Sci*** 113, 1018-1027 (2022)

197 Otake S, Chubachi S, Namkoong H, Nakagawara K, Tanaka H, Lee H, Morita A, Fukushima T, Watase M, Kusumoto T, Masaki K, Kamata H, Ishii M, Hasegawa N, Harada N, Ueda T, Ueda S, Ishiguro T, Arimura K, Saito F, Yoshiyama T, Nakano Y, Mutoh Y, Suzuki Y, Murakami K, Okada Y, Koike R, Kitagawa Y, Kimura A, Imoto S, Miyano S, Ogawa S, Kanai T, Fukunaga K. Clinical clustering with prognostic implications in Japanese COVID-19 patients: report from Japan COVID-19 Task Force, a nation-wide consortium to investigate COVID-19 host genetics. ***BMC Infect Dis*** 22, 735 (2022)

198 Otake-Kasamoto Y, Kayama H, Kishikawa T, Shinzaki S, Tashiro T, Amano T, Tani M, Yoshihara T, Li B, Tani H, Liu L, Hayashi A, Okuzaki D, Motooka D, Nakamura S, Okada Y, Iijima H, Takeda K, Takehara T. Lysophosphatidylserines derived from microbiota in Crohn's disease elicit pathological Th1 response. ***J Exp Med*** 219, e20211291 (2022)

199 Parrish N, Iwasaki Y. piRNA: Methods and Protocols. ***Methods in Molecular Biology*** (2022)

200 Parrish NF, Gaston DC. Metagenomics in infectious disease diagnostics: Toward best-use practices to optimize actionable results. ***Transpl Infect Dis*** 25, e13959 (2022)

201 Pascarella G, Hon C, Hashimoto K, Busch A, Luginbühl J, Parr C, Yip W, Abe K, Kratz A, Bonetti A, Agostini F, Severin J, Murayama S, Suzuki Y, Gustincich S, Frith M, Carninci P. Recombination of repeat elements generates somatic complexity in human genomes. ***Cell*** 185, 3025-3040.e6 (2022)

202 Pillon NJ, Smith JA, Alm PS, Chibalin AV, Alhusen J, Arner E, Carninci P, Fritz T, Otten J, Olsson T, de ten Ryen Sv, Deldicque L, Caidahl K, Wallberg-Henriksson H, Krook A, Zierath JR. Distinctive exercise-induced inflammatory response and exerkine induction in skeletal muscle of people with type 2 diabetes. ***Sci Adv*** 8, eabo3192 (2022)

203 Pindzola GM, Razzaghi R, Tavory RN, Nguyen HT, Morris VM, Li M, Agarwal S, Huang B, Okada T, Reinhardt HC, Knittel G, Kashkar H, Young RM, Pittaluga S, Muppidi JR. Aberrant expansion of spontaneous splenic germinal centers induced by hallmark genetic lesions of aggressive lymphoma. ***Blood*** 140, 1119-1131 (2022)

204 Pirruccello JP, Di Achille P, Nauffal V, Nekoui M, Friedman SF, Klarqvist MD, Chaffin MD, Weng L, Cunningham JW, Khurshid S, Roselli C, Lin H, Koyama S, Ito K, Kamatani Y, Komuro I, Jurgens SJ, Benjamin EJ, Batra P, Natarajan P, Ng K, Hoffmann U, Lubitz SA, Ho JE, Lindsay ME, Philippakiss AA, Ellinor PT. Genetic analysis of right heart structure and function in 40,000 people. ***Nat Genet*** 54, 792-803 (2022)

205 Ramdas S, Judd J, Graham SE, Kanoni S, Wang Y, Surakka I, Wenz B, Clarke SL, Chesi A, Wells A, Bhatti KF, Vedantam S, Winkler TW, Locke AE, Marouli E, Zajac GJ, Wu KH, Ntalla I, Hui Q, Klarin D, Hilliard AT, Wang Z, Xue C, Thorleifsson G, Helgadottir A, Gudbjartsson DF, Holm H, Olafsson I, Hwang MY, Han S, Akiyama M, Sakaue S, Terao C, Kanai M, Zhou W, Brumpton BM, Rasheed H, Havulinna AS, Veturi Y, Pacheco JA, Rosenthal EA, Lingren T, Feng Q, Kullo IJ, Narita A, Takayama J, Martin HC, Hunt KA, Trivedi B, Haessler J, Giulianini F, Bradford Y, Miller JE, Campbell A, Lin K, Millwood IY, Rasheed A, Hindy G, Faul JD, Zhao W, Weir DR, Turman C, Huang H, Graff M, Choudhury A, Sengupta D, Mahajan A, Brown MR, Zhang W, Yu K, Schmidt EM, Pandit A, Gustafsson S, Yin X, Luan J, Zhao J, Matsuda F, Jang H, Yoon K, Medina-Gomez C, Pitsillides A, Hottenga JJ, Wood AR, Ji Y, Gao Z, Haworth S, Mitchell RE, Chai JF, Aadahl M, Bjerregaard AA, Yao J, Manichaikul A, Lee W, Hsiung CA, Warren HR, Ramirez J, Bork-Jensen J, Kårhus LL, Goel A, Sabater-Lleal M, Noordam R, Mauro P, Matteo F, McDaid AF, Marques-Vidal P, Wielscher M, Trompet S, Sattar N, Møllehave LT, Munz M, Zeng L, Huang J, Yang B, Poveda A, Kurbasic A, Schönherr S, Forer L, Scholz M, Galesloot TE, Bradfield JP, Ruotsalainen SE, Daw EW, Zmuda JM, Mitchell JS, Fuchsberger C, Christensen H, Brody JA, Le P, Feitosa MF, Wojczynski MK, Hemerich D, Preuss M, Mangino M, Christofidou P, Verweij N, Benjamins JW, Engmann J, Noah TL, Verma A, Slieker RC, Lo KS, Zilhao NR, Kleber ME, Delgado GE, Huo S, Ikeda DD, Iha H, Yang J, Liu J, Demirkan A, Leonard HL, Marten J, Emmel C, Schmidt B, Smyth LJ, Cañadas-Garre M, Wang C, Nakatochi M, Wong A, Hutri-Kähönen N, Sim X, Xia R, Huerta-Chagoya A, Fernandez-Lopez JC, Lyssenko V, Nongmaithem SS, Sankareswaran A, Irvin MR, Oldmeadow C, Kim H, Ryu S, Timmers PR, Arbeeva L, Dorajoo R, Lange LA, Prasad G, Lorés-Motta L, Pauper M, Long J, Li X, Theusch E, Takeuchi F, Spracklen CN, Loukola A, Bollepalli S, Warner SC, Wang YX, Wei WB, Nutile T, Ruggiero D, Sung YJ, Chen S, Liu F, Yang J, Kentistou KA, Banas B, Morgan A, Meidtner K, Bielak LF, Smith JA, Hebbar P, Farmaki A, Hofer E, Lin M, Concas MP, Vaccargiu S, van der Most PJ, Pitkänen N, Cade BE, van der Laan SW, Chitrala KN, Weiss S, Bentley AR, Doumatey AP, Adeyemo AA, Lee JY, Petersen ER, Nielsen AA, Choi HS, Nethander M, Freitag-Wolf S, Southam L, Rayner NW, Wang CA, Lin S, Wang J, Couture C, Lyytikäinen L, Nikus K, Cuellar-Partida G, Vestergaard H, Hidalgo B, Giannakopoulou O, Cai Q, Obura MO, van Setten J, He KY, Tang H, Terzikhan N, Shin JH, Jackson RD, Reiner AP, Martin LW, Chen Z, Li L, Kawaguchi T, Thiery J, Bis JC, Launer LJ, Li H, Nalls MA, Raitakari OT, Ichihara S, Wild SH, Nelson CP, Campbell H, Jäger S, Nabika T, Al-Mulla F, Niinikoski H, Braund PS, Kolcic I, Kovacs P, Giardoglou T, Katsuya T, de Kleijn D, de Borst GJ, Kim EK, Adams HH, Ikram MA, Zhu X, Asselbergs FW, Kraaijeveld AO, Beulens JW, Shu X, Rallidis LS, Pedersen O, Hansen T, Mitchell P, Hewitt AW, Kähönen M, Pérusse L, Bouchard C, Tönjes A, Chen YI, Pennell CE, Mori TA, Lieb W, Franke A, Ohlsson C, Mellström D, Cho YS, Lee H, Yuan J, Koh W, Rhee SY, Woo J, Heid IM, Stark KJ, Zimmermann ME, Völzke H, Homuth G, Evans MK, Zonderman AB, Polasek O, Pasterkamp G, Hoefer IE, Redline S, Pahkala K, Oldehinkel AJ, Snieder H, Biino G, Schmidt R, Schmidt H, Bandinelli S, Dedoussis G, Thanaraj TA, Peyser PA, Kato N, Schulze MB, Girotto G, Böger CA, Jung B, Joshi PK, Bennett DA, De Jager PL, Lu X, Mamakou V, Brown M, Caulfield MJ, Munroe PB, Guo X, Ciullo M, Jonas JB, Samani NJ, Kaprio J, Pajukanta P, Tusié-Luna T, Aguilar-Salinas CA, Adair LS, Bechayda SA, de Silva HJ, Wickremasinghe AR, Krauss RM, Wu J, Zheng W, Hollander AI, Bharadwaj D, Correa A, Wilson JG, Lind L, Heng C, Nelson AE, Golightly YM, Wilson JF, Penninx B, Kim H, Attia J, Scott RJ, Rao D, Arnett DK, Walker M, Scott LJ, Koistinen HA, Chandak GR, Mercader JM, Villalpando CG, Orozco L, Fornage M, Tai ES, van Dam RM, Lehtimäki T, Chaturvedi N, Yokota M, Liu J, Reilly DF, McKnight AJ, Kee F, Jöckel K, McCarthy MI, Palmer CN, Vitart V, Hayward C, Simonsick E, van Duijn CM, Jin Z, Lu F, Hishigaki H, Lin X, März W, Gudnason V, Tardif J, Lettre G, Hart LM, Elders PJ, Rader DJ, Damrauer SM, Kumari M, Kivimaki M, van der Harst P, Spector TD, Loos RJ, Province MA, Parra EJ, Cruz M, Psaty BM, Brandslund I, Pramstaller PP, Rotimi CN, Christensen K, Ripatti S, Widén E, Hakonarson H, Grant SF, Kiemeney L, de Graaf J, Loeffler M, Kronenberg F, Gu D, Erdmann J, Schunkert H, Franks PW, Linneberg A, Jukema JW, Khera AV, Männikkö M, Jarvelin M, Kutalik Z, Francesco C, Mook-Kanamori DO, van Dijk KW, Watkins H, Strachan DP, Grarup N, Sever P, Poulter N, Sheu WH, Rotter JI, Dantoft TM, Karpe F, Neville MJ, Timpson NJ, Cheng C, Wong T, Khor CC, Li H, Sabanayagam C, Peters A, Gieger C, Hattersley AT, Pedersen NL, Magnusson PK, Boomsma DI, de Geus EJ, Cupples LA, van Meurs JB, Ikram A, Ghanbari M, Gordon-Larsen P, Huang W, Kim YJ, Tabara Y, Wareham NJ, Langenberg C, Zeggini E, Tuomilehto J, Kuusisto J, Laakso M, Ingelsson E, Abecasis G, Chambers JC, Kooner JS, de Vries PS, Morrison AC, Hazelhurst S, Ramsay M, North KE, Daviglus M, Kraft P, Martin NG, Whitfield JB, Abbas S, Saleheen D, Walters RG, Holmes MV, Black C, Smith BH, Baras A, Justice AE, Buring JE, Ridker PM, Chasman DI, Kooperberg C, Tamiya, Yamamoto M, van Heel DA, Trembath RC, Wei W, Jarvik GP, Namjou B, Hayes MG, Ritchie MD, Jousilahti P, Salomaa V, Hveem K, Åsvold BO, Kubo M, Kamatani Y, Okada Y, Murakami Y, Kim B, Thorsteinsdottir U, Stefansson K, Zhang J, Chen YE, Ho Y, Lynch JA, Tsao PS, Chang K, Cho K, O'Donnell CJ, Gaziano JM, Wilson P, Mohlke KL, Frayling TM, Hirschhorn JN, Kathiresan S, Boehnke M, Program MV, Consortium GL, Grant S, Natarajan P, Sun YV, Morris AP, Deloukas P, Peloso G, Assimes TL, Willer CJ, Zhu X, Brown CD. A multi-layer functional genomic analysis to understand noncoding genetic variation in lipids. ***Am J Hum Genet*** 109, 1366-1387 (2022)

206 Robbe P, Ridout KE, Vavoulis DV, Dreau H, Kinnersley B, Denny N, Chubb D, Appleby N, Cutts A, Cornish AJ, Lopez-Pascua L, Clifford R, Burns A, Stamatopoulos B, Cabes M, Alsolami R, Antoniou P, Oates M, Cavalieri D, Consortium GE, Consortium CP, Gibson J, Prabhu A, Schwessinger R, Jennings D, James T, Maheswari U, Duran-Ferrer M, Carninci P, Knight SJ, Mansson R, Hughes J, Davies J, Ross M, Bentley D, Strefford JC, Devereux S, Pettitt AR, Hillmen P, Caulfield MJ, Houlston RS, Martin-Subero J, Schuh A. Whole-genome sequencing of chronic lymphocytic leukemia identifies subgroups with distinct biological and clinical features. ***Nat Genet*** 54, 1675-1689 (2022)

207 Ruotsalainen SE, Surakka I, Mars N, Karjalainen J, Kurki M, Kanai M, Krebs K, Graham S, Mishra PP, Mishra BH, Sinisalo J, Palta P, Lehtimaki T, Raitakari O, Milani L, Okada Y, Palotie A, Widen E, Daly MJ, Ripatti S. Inframe insertion and splice site variants in MFGE8 associate with protection against coronary atherosclerosis. ***Commun Biol*** 5, 802 (2022)

208 Sabate-Soler S, Nickels S, Saraiva C, Berger E, Dubonyte U, Barmpa K, Lan Y, Kouno T, Jarazo J, Robertson G, Sharif J, Koseki H, Thome C, Shin J, Cowley S, Schwamborn J. Microglia integration into human midbrain organoids leads to increased neuronal maturation and functionality. ***Glia*** 70, 1267-1288 (2022)

209 Saeki T, Yoshimatsu S, Ishikawa M, Hon C, Koya I, Shibata S, Hosoya M, Saegusa C, Ogawa K, Shin JW, Fujioka M, Okano H. Critical roles of FGF, RA, and WNT signalling in the development of the human otic placode and subsequent lineages in a dish. ***Regen Ther*** 20, 165-186 (2022)

210 Sahoyama Y, Hamazato F, Shiozawa M, Nakagawa T, Suda W, Ogata Y, Hachiya T, Kawakami E, Hattori M. Multiple nutritional and gut microbial factors associated with allergic rhinitis: the Hitachi Health Study. ***Sci Rep*** 12, 3359 (2022)

211 Saita K, Sumitani M, Nishizawa D, Tamura T, Ikeda K, Wakai K, Sudo Y, Abe H, Otonari J, Ikezaki H, Takeuchi K, Hishida A, Tanaka K, Shimanoe C, Takezaki T, Ibusuki R, Oze I, Ito H, Ozaki E, Matsui D, Nakamura Y, Kusakabe M, Suzuki S, Nakagawa-Senda H, Arisawa K, Katsuura-Kamano S, Kuriki K, Kita Y, Nakamura Y, Momozawa Y, Uchida K. Genetic polymorphism of pleiotrophin is associated with pain experience in Japanese adults: Case-control study. ***Medicine (Baltimore)*** 101, e30580 (2022)

212 Saito T, Ikeda M, Terao C, Ashizawa T, Miyata M, Tanaka S, Kanazawa T, Kato T, Kishi T, Iwata N. Differential genetic correlations across major psychiatric disorders between Eastern and Western countries. ***Psychiatry Clin Neurosci*** 77, 118-119 (2022)

213 Sakaue S, Hosomichi K, Hirata J, Nakaoka H, Yamazaki K, Yawata M, Yawata N, Naito T, Umeno J, Kawaguchi T, Matsui T, Motoya S, Suzuki Y, Inoko H, Tajima A, Morisaki T, Matsuda K, Kamatani Y, Yamamoto K, Inoue I, Okada Y. Decoding the diversity of killer immunoglobulin-like receptors by deep sequencing and a high-resolution imputation method. ***Cell Genom*** 2, 100101 (2022)

214 Sano Y, Koyanagi Y, Wong JH, Murakami Y, Fujiwara K, Endo M, Aoi T, Hashimoto K, Nakazawa T, Wada Y, Ueno S, Gao D, Murakami A, Hotta Y, Ikeda Y, Nishiguchi KM, Momozawa Y, Sonoda K, Akiyama M, Fujimoto A. Likely pathogenic structural variants in genetically unsolved patients with retinitis pigmentosa revealed by long-read sequencing. ***J Med Genet*** 59, 1133-1138 (2022)

215 Sasagawa S, Kato H, Nagaoka K, Sun C, Imano M, Sato T, Johnson TA, Fujita M, Maejima K, Okawa Y, Kakimi K, Yasuda T, Nakagawa H. Immuno-genomic profiling of biopsy specimens predicts neoadjuvant chemotherapy response in esophageal squamous cell carcinoma. ***Cell Rep Med*** 3, 100705 (2022)

216 Saunders GR, Wang X, Chen F, Jang S, Liu M, Wang C, Gao S, Jiang Y, Khunsriraksakul C, Otto JM, Addison C, Akiyama M, Albert CM, Aliev F, Alonso A, Arnett DK, Ashley-Koch AE, Ashrani AA, Barnes KC, Barr RG, Bartz TM, Becker DM, Bielak LF, Benjamin EJ, Bis JC, Bjornsdottir G, Blangero J, Bleecker ER, Boardman JD, Boerwinkle E, Boomsma DI, Boorgula MP, Bowden DW, Brody JA, Cade BE, Chasman DI, Chavan S, Chen YI, Chen Z, Cheng I, Cho MH, Choquet H, Cole JW, Cornelis MC, Cucca F, Curran JE, de Andrade M, Dick DM, Docherty AR, Duggirala R, Eaton CB, Ehringer MA, Esko T, Faul JD, Silva LF, Fiorillo E, Fornage M, Freedman BI, Gabrielsen ME, Garrett ME, Gharib SA, Gieger C, Gillespie N, Glahn DC, Gordon SD, Gu CC, Gu D, Gudbjartsson DF, Guo X, Haessler J, Hall ME, Haller T, Harris KM, He J, Herd P, Hewitt JK, Hickie I, Hidalgo B, Hokanson JE, Hopfer C, Hottenga J, Hou L, Huang H, Hung Y, Hunter DJ, Hveem K, Hwang S, Hwu C, Iacono W, Irvin MR, Jee YH, Johnson EO, Joo YY, Jorgenson E, Justice AE, Kamatani Y, Kaplan RC, Kaprio J, Kardia SL, Keller MC, Kelly TN, Kooperberg C, Korhonen T, Kraft P, Krauter K, Kuusisto J, Laakso M, Lasky-Su J, Lee W, Lee JJ, Levy D, Li L, Li K, Li Y, Lin K, Lind PA, Liu C, Lloyd-Jones DM, Lutz SM, Ma J, Mägi R, Manichaikul A, Martin NG, Mathur R, Matoba N, McArdle PF, McGue M, McQueen MB, Medland SE, Metspalu A, Meyers DA, Millwood IY, Mitchell BD, Mohlke KL, Moll M, Montasser ME, Morrison AC, Mulas A, Nielsen JB, North KE, Oelsner EC, Okada Y, Orrù V, Palmer ND, Palviainen T, Pandit A, Park SL, Peters U, Peters A, Peyser PA, Polderman TJ, Rafaels N, Redline S, Reed RM, Reiner AP, Rice JP, Rich SS, Richmond NE, Roan C, Rotter JI, Rueschman MN, Runarsdottir V, Saccone NL, Schwartz DA, Shadyab AH, Shi J, Shringarpure SS, Sicinski K, Skogholt AH, Smith JA, Smith NL, Sotoodehnia N, Stallings MC, Stefansson H, Stefansson K, Stitzel JA, Sun X, Syed M, Tal-Singer R, Taylor AE, Taylor KD, Telen MJ, Thai KK, Tiwari H, Turman C, Tyrfingsson T, Wall TL,

Walters RG, Weir DR, Weiss ST, White WB, Whitfield JB, Wiggins KL, Willemsen G, Willer CJ, Winsvold BS, Xu H, Yanek LR, Yin J, Young KL, Young KA, Yu B, Zhao W, Zhou W, Zöllner S, Zuccolo L, Batini C, Bergen AW, Bierut LJ, David SP, Gagliano Taliun SA, Hancock DB, Jiang B, Munafò MR, Thorgeirsson TE, Liu DJ, Vrieze S. Genetic diversity fuels gene discovery for tobacco and alcohol use. ***Nature*** 612, 720-724 (2022)

217 Sekine Y, Iwasaki Y, Aoi T, Endo M, Hirata M, Kamatani Y, Matsuda K, Sugano K, Yoshida T, Murakami Y, Fukui T, Akamatsu S, Ogawa O, Nakagawa H, Numakura K, Narita S, Habuchi T, Momozawa Y. Different risk genes contribute to clear cell and non-clear cell renal cell carcinoma in 1532 Japanese patients and 5996 controls. ***Hum Mol Genet*** 31, 1962-1969 (2022)

218 Sekine Y, Iwasaki Y, Hakozaki N, Endo M, Kamatani Y, Matsuda K, Murakami Y, Sano T, Akamatsu S, Kobayashi T, Nakagawa H, Numakura K, Narita S, Habuchi T, Momozawa Y. Prevalence and risk estimation of cancer-predisposing genes for upper urinary tract urothelial carcinoma in Japanese. ***Jpn J Clin Oncol*** 52, 1441-1445 (2022)

219 Seo W, Nomura A, Taniuchi I. The Roles of RUNX Proteins in Lymphocyte Function and Anti-Tumor Immunity. ***Cells*** 11, 3116 (2022)

220 Sheehan A, Goldfine A, Bajwa M, Wolfs D, Kozuka C, Piper J, Fowler K, Patti M. Pramlintide for postbariatric hypoglycaemia. ***Diabetes Obes Metab*** 24, 1021-1028 (2022)

221 Shi Z, Takeuchi T, Nakanishi Y, Kato T, Beck K, Nagata R, Kageyama T, Ito A, Ohno H, Satoh-Takayama N. A Japanese Herbal Formula, Daikenchuto, Alleviates Experimental Colitis by Reshaping Microbial Profiles and Enhancing Group 3 Innate Lymphoid Cells. ***Front Immunol*** 13, 903459 (2022)

222 Shimizu K, Ueda S, Kawamura M, Satoh M, Fujii S. A single immunization with cellular vaccine confers dual protection against SARS-CoV-2 and cancer. ***Cancer Sci*** 113, 2536-2547 (2022)

223 Shiraga K, Ogawa Y, Kikuchi S, Amagai M, Matsui T. Increase in the Intracellular Bulk Water Content in the Early Phase of Cell Death of Keratinocytes, Corneoptosis, as Revealed by 65 GHz Near-Field CMOS Dielectric Sensor. ***Molecules*** 27, 2886 (2022)

224 Shirai Y, Nakanishi Y, Suzuki A, Konaka H, Nishikawa R, Sonehara K, Namba S, Tanaka H, Masuda T, Yaga M, Satoh S, Izumi M, Mizuno Y, Jo T, Maeda Y, Nii T, Oguro-Igashira E, The Biobank Japan Project, Morisaki T, Kamatani Y, Nakayamada S, Nishigori C, Tanaka Y, Takeda Y, Yamamoto K, Kumanogoh A, Okada Y. Multi-trait and cross-population genome-wide association studies across autoimmune and allergic diseases identify shared and distinct genetic component. ***Ann Rheum Dis*** 81, 1301-1312 (2022)

225 Shirai Y, Nakayama A, Kawamura Y, Toyoda Y, Nakatochi M, Shimizu S, Shinomiya N, Okada Y, Matsuo H, Consortium JG. Coffee Consumption Reduces Gout Risk Independently of Serum Uric Acid Levels: Mendelian Randomization Analyses Across Ancestry Populations. ***ACR Open Rheumatol*** 4, 534-539 (2022)

226 Siamoglou S, Koromina M, Hishinuma E, Yamazaki S, Tsermpini E, Kordou Z, Fukunaga K, Chantratita W, Zhou Y, Lauschke VM, Mushiroda T, Hiratsuka M, Patrinos GP. Identification and functional validation of novel pharmacogenomic variants using a next-generation sequencing-based approach for clinical pharmacogenomics. ***Pharmacol Res*** 176, 106087 (2022)

227 Singh H, Shipra, Sharma, Sharma, Sharma A, Modeel S, Gupta N, Gupta G, Pandita AK, Butt MF, Sharma R, Pandita S, Singh V, Rai E, Ikegawa S, Sharma S. The first study of epidemiology of adolescent idiopathic scoliosis shows lower prevalence in females of Jammu and Kashmir, India. ***Am J Transl Res*** 14, 1100-1106 (2022)

228 Sonehara K, Kimura Y, Nakano Y, Ozawa T, Takahashi M, Suzuki K, Fujii T, Matsushita Y, Tomiyama A, Kishikawa T, Yamamoto K, Naito T, Suzuki T, Yamaguchi S, Miwa T, Sasaki H, Kitagawa M, Ohe N, Fukai J, Ogiwara H, Kawamura A, Miyawaki S, Matsuda F, Kiyokawa N, Ichimura K, Nishikawa R, Okada Y, Terashima K. A common deletion at BAK1 reduces enhancer activity and confers risk of intracranial germ cell tumors. ***Nat Commun*** 13, 4478 (2022)

229 Suda W, Ogata Y, Shindo C, Watanabe K. Complete Genome Sequences of Two Flavobacterium ammonificans Strains and a Flavobacterium ammoniigenes Strain of Ammonifying Bacterioplankton Isolated from Surface River Water. ***Microbiol Resour Announc*** 11, e0017622 (2022)

230 Sugawara T, Miya F, Ishikawa T, Lysenko A, Nishino J, Kamatani T, Boroevich KA, Kakimi K, Kinugasa Y, Tanabe M, Tsunoda T. Immune subtypes and neoantigen-related immune evasion in advanced colorectal cancer. ***iScience*** 25, 103740 (2022)

231 Sun C, Nagaoka K, Kobayashi Y, Nakagawa H, Nakajima J, Kakimi K. Immunotherapies targeting neoantigens are effective in PD-1 blockade-resistant tumors. ***Int J Cancer*** 152, 1463-1475 (2022)

232 Sun H, Tang C, Chung S, Ye X, Makusheva Y, Han W, Kubo M, Shichino S, Ueha S, Matsushima K, Ikeo K, Asano M, Iwakura Y. Blocking DCIR mitigates colitis and prevents colorectal tumors by enhancing the GM-CSF-STAT5 pathway. ***Cell Rep*** 40, 111158 (2022)

233 Suzuki K, Abe MS, Kumakura D, Nakaoka S, Fujiwara F, Miyamoto H, Nakaguma T, Okada M, Sakurai K, Shimizu S, Iwata H, Masuya H, Nihei N, Ichihashi Y. Chemical-Mediated Microbial Interactions Can Reduce the Effectiveness of Time-Series-Based Inference of Ecological Interaction Networks. ***Int J Environ Res Public Health*** 19, 1228 (2022)

234 Suzuki T, Furuhata E, Maeda S, Kishima M, Miyajima Y, Tanaka Y, Lim J, Nishimura H, Nakanishi Y, shojima A, Suzuki H. GATA6 is predicted to regulate DNA methylation in an *in vitro* model of human hepatocyte differentiation. ***Commun Biol*** 5, 414 (2022)

235 Suzuki T, Hoshina M, Nishijima S, Hoshina N, Chisato K, Tomohiro T, Fukao A, Fujiwara T, Yamamoto T. Regulation of CCR4-NOT complex deadenylase activity and cellular responses by MK2-dependent phosphorylation of CNOT2. ***RNA Biol*** 19, 234-246 (2022)

236 Tachibana N, Chijimatsu R, Okada H, Oichi T, Taniguchi Y, Maenohara Y, Miyahara J, Ishikura H, Iwanaga Y, Arino Y, Nagata K, Nakamoto H, Kato S, Doi T, Matsubayashi Y, Oshima Y, Terashima A, Omata Y, Yano F, Maeda S, Ikegawa S, Seki M, Suzuki Y, Tanaka S, Saito T. RSPO2 defines a distinct undifferentiated progenitor in the tendon/ligament and suppresses ectopic ossification. ***Sci Adv*** 8, eabn2138 (2022)

237 Takano J, Ito S, Dong Y, Sharif J, Nakajima-Takagi Y, Umeyama T, Han Y, Isono K, Kondo T, Iizuka Y, Miyai T, Koseki Y, Ikegaya M, Sakihara M, Nakayama M, Ohara O, Hasegawa Y, Hashimoto K, Arner E, Klose RJ, Iwama A, Koseki H, Ikawa T. PCGF1-PRC1 links chromatin repression with DNA replication during hematopoietic cell lineage commitment. ***Nat Commun*** 13, 7159 (2022)

238 Takeshima Y, Iwasaki Y, Nakano M, Narushima Y, Ota M, Nagafuchi Y, Sumitomo S, Okamura T, Elkon K, Ishigaki K, Suzuki A, Kochi Y, Yamamoto K, Fujio K. Immune cell multiomics analysis reveals contribution of oxidative phosphorylation to B-cell functions and organ damage of lupus. ***Ann Rheum Dis*** 81, 845-853 (2022)

239 Takeuchi C, Moe Y, Shu K, Aoi S, Kuniaki S, Takashi F, Haruhiko, Yuka IW. Mod (mdg4) variants repress telomeric retrotransposon HeT-A by blocking subtelomeric enhancers. ***Nucleic Acids Res*** 50, 11580-11599 (2022)

240 Takeuchi T, Ohno H. Analysis of Peripherally Derived Treg in the Intestine. ***Methods Mol Biol*** 2559, 41-45 (2022)

241 Takeuchi T, Ohno H. IgA in human health and diseases: Potential regulator of commensal microbiota. ***Front Immunol*** 13, 1024330 (2022)

242 Tanaka J, Senpuku H, Ogawa M, Yasuhara R, Ohnuma S, Takamatsu K, Watanabe T, Mabuchi Y, Nakamura S, Ishida S, Sadaoka T, Takaki T, Shirota T, Shimane T, Inoue T, Sakai T, Mori M, Tsuji T, Saito I, Mishima K. Human induced pluripotent stem cell-derived salivary gland organoids model SARS-CoV-2 infection and replication. ***Nat Cell Biol*** 24, 1595-1605 (2022)

243 Tanaskovic N, Dalsass M, Filipuzzi M, Ceccotti G, Verrecchia A, Nicoli P, Doni M, Olivero D, Pasini D, Koseki H, Sabò A, Bisso A, Amati B. Polycomb group ring finger protein 6 suppresses Myc-induced lymphomagenesis. ***Life Sci Alliance*** 5, e202101344 (2022)

244 Tanemoto S, Sujino T, Miyamoto K, Moody J, Yoshimatsu Y, Ando Y, Koya I, Harada Y, Okuzawa Tojo A, Ono K, Hayashi Y, Takabayashi K, Okabayashi K, Teratani T, Mikami Y, Nakamoto N, Hosoe N, Ogata H, Hon C, Shin JW, Kanai T. Single-cell transcriptomics of human gut T cells identifies cytotoxic $CD4^+CD8A^+$ T cells related to mouse CD4 cytotoxic T cells. ***Front Immunol*** 13, 977117 (2022)

245 Tayipto Y, Rosado J, Gamboa D, White MT, Kiniboro B, Healer J, Opi HD, Beeson JG, Takashima E, Takafumi T, Harbers M, Robinson L, Mueller I, Longley R. Assessment of IgG3 as a serological exposure marker for Plasmodium vivax in areas with moderate-high malaria transmission intensity. ***Front Cell Infect Microbiol*** 12, 950909 (2022)

246 Tcheandjieu C, Zhu X, Hilliard AT, Clarke SL, Napolioni V, Ma S, Lee KM, Fang H, Chen F, Lu Y, Tsao NL, Raghavan S, Koyama S, Gorman BR, Vujkovic M, Klarin D, Levin MG, Sinnott-Armstrong N, Wojcik GL, Plomondon ME, Maddox TM, Waldo SW, Bick AG, Pyarajan S, Huang J, Song R, Ho Y, Buyske S, Kooperberg C, Haessler J, Loos RJ, Do R, Verbanck M, Chaudhary K, North KE, Avery CL, Graff M, Haiman CA, Le Marchand L, Wilkens LR, Bis JC, Leonard H, Shen B, Lange LA, Giri A, Dikilitas O, Kullo IJ, Stanaway IB, Jarvik GP, Gordon AS, Hebbring S, Namjou B, Kaufman KM, Ito K, Ishigaki K, Kamatani Y, Verma SS, Ritchie MD, Kember RL, Baras A, Lotta LA, Kathiresan S, Hauser ER, Miller DR, Lee JS, Saleheen D, Reaven PD, Cho K, Gaziano JM, Natarajan P, Huffman JE, Voight BF, Rader DJ, Chang K, Lynch JA, Damrauer SM, Wilson PW, Tang H, Sun Y, Tsao PS, O'Donnell CJ, Assimes TL. Large-scale genome-wide association study of coronary artery disease in genetically diverse populations. ***Nat Med*** 28, 1679-1692 (2022)

247 Terakawa A, Hu Y, Kokaji T, Yugi K, Morita K, Ohno S, Pan Y, Bai Y, Parkhitko AA, Ni X, Asara JM, Bulyk ML, Perrimon N, Kuroda S. Trans-omics analysis of insulin action reveals a cell growth subnetwork which co-regulates anabolic processes. ***iSCIENCE*** 25, 104231 (2022)

248 Teshima T, Kobayashi Y, Kawai T, Kushihara Y, Nagaoka K, Miyakawa J, Akiyama Y, Yamada Y, Sato Y, Yamada D, Tanaka N, Tsunoda T, Kume H, Kakimi K. Principal component analysis of early immune cell dynamics during pembrolizumab treatment of advanced urothelial carcinoma. ***Oncol Lett*** 24, 265 (2022)

249 Thibord F, Klarin D, Brody JA, Chen M, Levin MG, Chasman D, Goode EL, Hveem K, Teder-Laving M, Martinez-Perez A, Aissi D, Daian-Bacq D, Ito K, Natarajan P, Lutsey PL, Nadkarni GN, de Vries PS, Cuellar-Partida G, Wolford BN, Pattee JW, Kooperberg C, Braekkan SK, Li-Gao R, Saut N, Sept C, Germain M, Judy RL, Wiggins KL, Ko D, O'Donnell CJ, Taylor KD, Giulianini F, De Andrade M, Nost TH, Boland A, Empana J, Koyama S, Gilliland T, Do R, Huffman JE, Wang X, Zhou W, Soria JM, Souto JC, Pankratz N, Haessler J, Hindberg K, Rosendaal FR, Turman C, Olaso R, Kember RL, Bartz TM, Lynch JA, Heckbert SR, Armasu SM, Brumpton B, Smadja DM, Jouven X, Komuro I, Clapham KR, Loos RJ, Willer CJ, Sabater-Lleal M, Pankow JS, Reiner AP, Morelli VM, Ridker PM, Vlieg Av, Deleuze J, Kraft P, Rader DJ, Lee KM, Psaty BM, Skogholt AH, Emmerich J, Suchon P, Rich SS, Vy HM, Tang W, Jackson RD, Hansen J, Morange P, Kabrhel C, Tregouet D, Damrauer SM, Johnson AD, Smith NL. Cross-Ancestry Investigation of Venous Thromboembolism Genomic Predictors. ***Circulation*** 146, 1225-1242 (2022)

250 Tomiaki C, Miyauchi K, Ki S, Suzuki Y, Suzuki N, Morimoto H, Mukoyama Y, Kubo M. Role of FK506-sensitive signals in asthmatic lung inflammation. ***Front Immunol*** 13, 1014462 (2022)

251 Tomofuji Y, Kishikawa T, Maeda Y, Ogawa K, Otake-Kasamoto Y, Kawabata S, Nii T, Okuno T, Oguro-Igashira E, Kinoshita M, Takagaki M, Oyama N, Todo K, Yamamoto K, Sonehara K, Yagita M, Hosokawa A, Motooka D, Matsumoto Y, Matsuoka H, Yoshimura M, Ohshima S, Shinzaki S, Nakamura S, Iijima H, Inohara H, Kishima H, Takehara T, Mochizuki H, Takeda K, Kumanogoh A, Okada Y. Prokaryotic and viral genomes recovered from 787 Japanese gut metagenomes revealed microbial features linked to diets, populations, and diseases. ***Cell Genom*** 2, 100219 (2022)

252 Toyofuku E, Takeshita K, Ohnishi H, Kiridoshi Y, Masuoka H, Kadowaki T, Nishikomori R, Nishimura K, Kobayashi C, Ebato T, Shigemura T, Inoue Y, Suda W, Hattori M, Morio T, Honda K, Kanegane H. Dysregulation of the Intestinal Microbiome in Patients With Haploinsufficiency of A20. ***Front Cell Infect Microbiol*** 11, 787667 (2022)

253 Tripathi LP, Arakawa M, Morita E. Flavivirus recruits the valosin-containing protein (VCP)/NPL4 complex to induce stress granule disassembly for efficient viral genome replication. ***J Biol Chem*** 298, 101597 (2022)

254 Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, Bryois J, Chen C, Dennison CA, Hall LS, Lam M, Watanabe K, Frei O, Ge T, Harwood JC, Koopmans F, Magnusson S, Richards AL, Sidorenko J, Wu Y, Zeng J, Grove J, Kim M, Li Z, Voloudakis G, Zhang W, Adams M, Agartz I, Atkinson EG, Agerbo E, Al Eissa M, Albus M, Alexander M, Alizadeh BZ, Alptekin K, Als TD, Amin F, Arolt V, Arrojo M, Athanasiu L, Azevedo MH, Bacanu SA, Bass NJ, Begemann M, Belliveau RA, Bene J, Benyamin B, Bergen SE, Blasi G, Bobes J, Bonassi S, Braun A, Bressan RA, Bromet EJ, Bruggeman R, Buckley PF, Buckner RL, Bybjerg-Grauholm J, Cahn W, Cairns MJ, Calkins ME, Carr VJ, Castle D, Catts SV, Chambert KD, Chan RC, Chaumette B, Cheng W, Cheung EF, Chong SA, Cohen D, Consoli A, Cordeiro Q, Costas J, Curtis C, Davidson M, Davis KL, de Haan L, Degenhardt F, DeLisi LE, Demontis D, Dickerson F, Dikeos D, Dinan T, Djurovic S, Duan J, Ducci G, Dudbridge F, Eriksson JG, Fañanás L, Faraone SV, Fiorentino A, Forstner A, Frank J, Freimer NB, Fromer M, Frustaci A, Gadelha A, Genovese G, Gershon ES, Giannitelli M, Giegling I, Giusti-Rodríguez P, Godard S, Goldstein JI, González Peñas J, González-Pinto A, Gopal S, Gratten J, Green MF, Greenwood TA, Guillin O, Gülöksüz S, Gur RE, Gur RC, Gutiérrez B, Hahn E, Hakonarson H, Haroutunian V, Hartmann AM, Harvey C, Hayward C, Henskens FA, Herms S, Hoffmann P, Howrigan DP, Ikeda M, Iyegbe C, Joa I, Julià A, Kähler AK, Kam-Thong T, Kamatani Y, Karachanak-Yankova S, Kebir O, Keller MC, Kelly BJ, Khrunin A, Kim S, Klovins J, Kondratiev N, Konte B, Kraft J, Kubo M, Kučinskas V, Kučinskiene ZA, Kusumawardhani A, Kuzelova-Ptackova H, Landi S, Lazzeroni LC, Lee PH, Legge SE, Lehrer DS, Lencer R, Lerer B, Li M, Lieberman J, Light GA, Limborska S, Liu C, Lönnqvist J, Loughland CM, Lubinski J, Luykx JJ, Lynham A, Macek M, Mackinnon A, Magnusson PK, Maher BS, Maier W, Malaspina D, Mallet J, Marder SR, Marsal S, Martin AR, Martorell L, Mattheisen M, McCarley RW, McDonald C, McGrath JJ, Medeiros H, Meier S, Melegh B, Melle I, Mesholam-Gately RI, Metspalu A, Michie PT, Milani L, Milanova V, Mitjans M, Molden E, Molina E, Molto MD, Mondelli V, Moreno C, Morley CP, Muntané G, Murphy KC, Myin-Germeys I, Nenadić I, Nestadt G, Nikitina-Zake L, Noto C,

Nuechterlein KH, O'Brien NL, O'Neill FA, Oh S, Olincy A, Ota VK, Pantelis C, Papadimitriou GN, Parellada M, Paunio T, Pellegrino R, Periyasamy S, Perkins DO, Pfuhlmann B, Pietiläinen O, Pimm J, Porteous D, Powell J, Quattrone D, Quested D, Radant AD, Rampino A, Rapaport MH, Rautanen A, Reichenberg A, Roe C, Roffman JL, Roth J, Rothermundt M, Rutten BP, Saker-Delye S, Salomaa V, Sanjuan J, Santoro ML, Savitz A, Schall U, Scott RJ, Seidman LJ, Sharp SI, Shi J, Siever LJ, Sigurdsson E, Sim K, Skarabis N, Slominsky P, So H, Sobell JL, Söderman E, Stain HJ, Steen NE, Steixner-Kumar AA, Stögmann E, Stone WS, Straub RE, Streit F, Strengman E, Stroup TS, Subramaniam M, Sugar CA, Suvisaari J, Svrakic DM, Swerdlow NR, Szatkiewicz JP, Ta TM, Takahashi A, Terao C, Thibaut F, Toncheva D, Tooney PA, Torretta S, Tosato S, Tura GB, Turetsky BI, Üçok A, Vaaler A, van Amelsvoort T, van Winkel R, Veijola J, Waddington J, Walter H, Waterreus A, Webb BT, Weiser M, Williams NM, Witt SH, Wormley BK, Wu JQ, Xu Z, Yolken R, Zai CC, Zhou W, Zhu F, Zimprich F, Atbaşoğlu EC, Ayub M, Benner C, Bertolino A, Black DW, Bray NJ, Breen G, Buccola NG, Byerley WF, Chen WJ, Cloninger CR, Crespo-Facorro B, Donohoe G, Freedman R, Galletly C, Gandal MJ, Gennarelli M, Hougaard DM, Hwu H, Jablensky AV, McCarroll SA, Moran JL, Mors O, Mortensen PB, Müller-Myhsok B, Neil AL, Nordentoft M, Pato MT, Petryshen TL, Pirinen M, Pulver AE, Schulze TG, Silverman JM, Smoller JW, Stahl EA, Tsuang DW, Vilella E, Wang S, Xu S, Adolfsson R, Arango C, Baune BT, Belangero SI, Børglum AD, Braff D, Bramon E, Buxbaum JD, Campion D, Cervilla JA, Cichon S, Collier DA, Corvin A, Curtis D, Forti MD, Domenici E, Ehrenreich H, Escott-Price V, Esko T, Fanous AH, Gareeva A, Gawlik M, Gejman PV, Gill M, Glatt SJ, Golimbet V, Hong KS, Hultman CM, Hyman SE, Iwata N, Jönsson EG, Kahn RS, Kennedy JL, Khusnutdinova E, Kirov G, Knowles JA, Krebs M, Laurent-Levinson C, Lee J, Lencz T, Levinson DF, Li QS, Liu J, Malhotra AK, Malhotra D, McIntosh A, McQuillin A, Menezes PR, Morgan VA, Morris DW, Mowry BJ, Murray RM, Nimgaonkar V, Nöthen MM, Ophoff RA, Paciga SA, Palotie A, Pato CN, Qin S, Rietschel M, Riley BP, Rivera M, Rujescu D, Saka MC, Sanders AR, Schwab SG, Serretti A, Sham PC, Shi Y, St Clair D, Stefánsson H, Stefansson K, Tsuang MT, van Os J, Vawter MP, Weinberger DR, Werge T, Wildenauer DB, Yu X, Yue W, Holmans PA, Pocklington AJ, Roussos P, Vassos E, Verhage M, Visscher PM, Yang J, Posthuma D, Andreassen OA, Kendler KS, Owen MJ, Wray NR, Daly MJ, Huang H, Neale BM, Sullivan PF, Ripke S, Walters JT, O'Donovan MC. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. ***Nature*** 604, 502-508 (2022)

255 Tsuchida Y, Shoda H, Nakano M, Ota M, Okamura T, Yamamoto K, Kurano M, Yatomi Y, Fujio K, Sawada T. Autotaxin is a potential link between genetic risk factors and immunological disturbances of plasmacytoid dendritic cells in systematic lupus erythematosus. ***Lupus*** 31, 1578-1585 (2022)

256 Tsuji K, Shimada W, Kishino S, Ogawa J, Arita M. Comprehensive analysis of fatty acid metabolites produced by gut microbiota using LC-MS/MS-based lipidomics. ***Medical Mass Spectrometry*** 6, 112-125 (2022)

257 Tsumagari K, Sato Y, Shimozawa A, Aoyagi H, Okano H, Kuromitsu J. Co-expression network analysis of human tau-transgenic mice reveals protein modules associated with tau-induced pathologies. ***iSCIENCE*** 25, 104832 (2022)

258 Tsuo K, Zhou W, Wang Y, Kanai M, Namba S, Gupta R, Majara L, Nkambule LL, Morisaki T, Okada Y, Neale BM, Initiative GB, Daly MJ, Martin AR. Multi-ancestry meta-analysis of asthma identifies novel associations and highlights the value of increased power and diversity. ***Cell Genom*** 2, 100212 (2022)

259 Tuganbaev T, Yoshida K, Honda K. The effects of oral microbiota on health. ***Science*** 376, 934-936 (2022)

260 Uchino H, Tsugawa H, Takahashi H, Arita M. Computational mass spectrometry accelerates C = C position-resolved untargeted lipidomics using oxygen attachment dissociation. ***Commun Chem*** 5, 162 (2022)

261 Uchiyama J, Roy R, Wang DO, Morikawa K, Kawahara Y, Iwasaki M, Yoshino C, Mishima Y, Ishihama Y, Imami K. pSNAP: Proteome-wide analysis of elongating nascent polypeptide chains. ***iScience*** 25, 104516 (2022)

262 Udagawa C, Kuah S, Shimoi T, Kato K, Yoshida T, Nakano MH, Shimo A, Kojima Y, Yoshie R, Tsugawa K, Mushiroda T, Tan EY, Zembutsu H. Replication Study for the Association of Five SNPs Identified by GWAS and Trastuzumab-Induced Cardiotoxicity in Japanese and Singaporean Cohorts. ***Biol Pharm Bull*** 45, 1198-1202 (2022)

263 Udagawa C, Nakano MH, Yoshida T, Ohe Y, Kato K, Mushiroda T, Zembutsu H. Association between genetic variants and the risk of nivolumab-induced immune-related adverse events. ***Pharmacogenomics*** 23, 887-901 (2022)

264 Umehara T, Arita H, Miya F, Achiha T, Shofuda T, Yoshioka E, Kanematsu D, Nakagawa T, Kinoshita M, Kagawa N, Fujimoto Y, Hashimoto N, Kiyokawa H, Morii E, Tsunoda T, Kanemura Y, Kishima H. Revisiting the definition of glioma recurrence based on a phylogenetic investigation of primary and re-emerging tumor samples: a case report. ***Brain Tumor Pathol*** 39, 218-224 (2022)

265 Usui Y, Iwasaki Y, Matsuo K, Endo M, Kamatani Y, Hirata M, Sugano K, Yoshida T, Matsuda K, Murakami Y, Maeda Y, Nakagawa H, Momozawa Y. Association between germline pathogenic variants in cancer-predisposing genes and lymphoma risk. ***Cancer Sci*** 113, 3972-3979 (2022)

266 Valentini P, Pierattini B, Zacco E, Mangoni D, Espinoza S, Webster NA, Andrews B, Carninci P, Tartaglia G, Pandolfini L, Gustincich S. Towards SINEUP-based therapeutics: Design of an *in vitro* synthesized SINEUP RNA. ***Mol Ther Nucleic Acids*** 27, 1092-1102 (2022)

267 Vincent SA, Kim J, Pérez-Salamó I, To TK, Torii C, Ishida J, Tanaka M, Endo TA, Bhat P, Devlin PF, Seki M, Devoto A. Jasmonates and Histone deacetylase 6 activate Arabidopsis genome-wide histone acetylation and methylation during the early acute stress response. ***BMC Biol*** 20, 83 (2022)

268 Wagner M, Koyasu S. Cancer immunosurveillance by ILC2s. ***Trends Cancer*** 8, 792-794 (2022)

269 Walker S, Abugessaisa I, Kasukawa T. Single Cell Databases: An Emerging and Essential Tool. ***Practical Guide to Life Science Databases*** (2022)

270 Wang QS, Edahiro R, Namkoong H, Hasegawa T, Shirai Y, Sonehara K, Tanaka H, Lee H, Saiki R, Hyugaji T, Shimizu E, Katayama K, Kanai M, Naito T, Sasa N, Yamamoto K, Kato Y, Morita T, Takahashi K, Harada N, Naito T, Hiki M, Matsushita Y, Takagi H, Ichikawa M, Nakamura A, Harada S, Sandhu Y, Kabata H, Masaki K, Kamata H, Ikemura S, Chubachi S, Okamori S, Terai H, Morita A, Asakura T, Sasaki J, Morisaki H, Uwamino Y, Nanki K, Uchida S, Uno S, Nishimura T, Ishiguro T, Isono T, Shibata S, Matsui Y, Hosoda C, Takano K, Nishida T, Kobayashi Y, Takaku Y, Takayanagi N, Ueda S, Tada A, Miyawaki M, Yamamoto M, Yoshida E, Hayashi R, Nagasaka T, Arai S, Kaneko Y, Sasaki K, Tagaya E, Kawana M, Arimura K, Takahashi K, Anzai T, Ito S, Endo A, Uchimura Y, Miyazaki Y, Honda T, Tateishi T, Tohda S, Ichimura N, Sonobe K, Sassa CT, Nakajima J, Nakano Y, Nakajima Y, Anan R, Arai R, Kurihara Y, Harada Y, Nishio K, Ueda T, Azuma M, Saito R, Sado T, Miyazaki Y, Sato R, Haruta Y, Nagasaki T, Yasui Y, Hasegawa Y, Mutoh Y, Kimura T, Sato T, Takei R, Hagimoto S, Noguchi Y, Yamano Y, Sasano H, Ota S, Nakamori Y, Yoshiya K, Saito F, Yoshihara T, Wada D, Iwamura H, Kanayama S, Maruyama S, Yoshiyama T, Ohta K, Kokuto H, Ogata H, Tanaka Y, Arakawa K, Shimoda M, Osawa T, Tateno H, Hase I, Yoshida S, Suzuki S, Kawada M, Horinouchi H, Saito F, Mitamura K, Hagihara M, Ochi J, Uchida T, Baba R, Arai D, Ogura T, Takahashi H, Hagiwara S, Nagao G, Konishi S, Nakachi I, Murakami K, Yamada M, Sugiura H, Sano H, Matsumoto S, Kimura N, Ono Y, Baba H, Suzuki Y, Nakayama S, Masuzawa K, Namba S, Shiroyama T, Noda Y, Niitsu T, Adachi Y, Enomoto T, Amiya S, Hara R, Yamaguchi Y, Murakami T, Kuge T, Matsumoto K, Yamamoto Y, Yamamoto M, Yoneda M, Tomono K, Kato K, Hirata H, Takeda Y, Koh H, Manabe T, Funatsu Y, Ito F, Fukui T, Shinozuka K, Kohashi S, Miyazaki M, Shoko T, Kojima M, Adachi T, Ishikawa M, Takahashi K, Inoue T, Hirano T, Kobayashi K, Takaoka H, Watanabe K, Miyazawa N, Kimura Y, Sado R, Sugimoto H, Kamiya A, Kuwahara N, Fujiwara A, Matsunaga T, Sato Y, Okada T, Hirai Y, Kawashima H, Narita A, Niwa K, Sekikawa Y, Nishi K, Nishitsuji M, Tani M, Suzuki J, Nakatsumi H, Ogura T, Kitamura H, Hagiwara E, Murohashi K, Okabayashi H, Mochimaru T, Nukaga S, Satomi R, Oyamada Y, Mori N, Baba T, Fukui Y, Odate M, Mashimo S, Makino Y, Yagi K, Hashiguchi M, Kagyo J, Shiomi T, Fuke S, Saito H, Tsuchida T, Fujitani S, Takita M, Morikawa D, Yoshida T, Izumo T, Inomata M, Kuse N, Awano N, Tone M, Ito A, Nakamura Y, Hoshino K, Maruyama J, Ishikura H, Takata T, Odani T, Amishima M, Hattori T, Shichinohe Y, Kagaya T, Kita T, Ohta K, Sakagami S, Koshida K, Hayashi K, Shimizu T, Kozu Y, Hiranuma H, Gon Y, Izumi N, Nagata K, Ueda K, Taki R, Hanada S, Kawamura K, Ichikado K, Nishiyama K, Muranaka H, Nakamura K, Hashimoto N, Wakahara K, Koji S, Omote N, Ando A, Kodama N, Kaneyama Y, Maeda S, Kuraki T, Matsumoto T, Yokote K, Nakada T, Abe R, Oshima T, Shimada T, Harada M, Takahashi T, Ono H, Sakurai T, Shibusawa T, Kimizuka Y, Kawana A, Sano T, Watanabe C, Suematsu R, Sageshima H, Yoshifuji A, Ito K, Takahashi S, Ishioka K, Nakamura M, Masuda M, Wakabayashi A, Watanabe H, Ueda S, Nishikawa M, Chihara Y, Takeuchi M, Onoi K, Shinozuka J, Sueyoshi A, Nagasaki Y, Okamoto M, Ishihara S, Shimo M, Tokunaga Y, Kusaka Y, Ohba T, Isogai S, Ogawa A, Inoue T, Fukuyama S, Eriguchi Y, Yonekawa A, Kan-o K, Matsumoto K, Kanaoka K, Ihara S, Komuta K, Inoue Y, Chiba S, Yamagata K, Hiramatsu Y, Kai H, Asano K, Oguma T, Ito Y, Hashimoto S, Yamasaki M, Kasamatsu Y, Komase Y, Hida N, Tsuburai T, Oyama B, Takada M, Kanda H, Kitagawa Y, Fukuta T, Miyake T, Yoshida S, Ogura S, Abe S, Kono Y, Togashi Y, Takoi H, Kikuchi R, Ogawa S, Ogata T, Ishihara S, Kanehiro A, Ozaki S, Fuchimoto Y, Wada S, Fujimoto N, Nishiyama K, Terashima M, Beppu S, Yoshida K, Narumoto O, Nagai H, Ooshima N, Motegi M, Umeda A, Miyagawa K, Shimada H, Endo M, Ohira Y, Watanabe M, Inoue S, Igarashi A, Sato M, Sagara H, Tanaka A, Ohta S, Kimura T, Shibata Y, Tanino Y, Nikaido T, Minemura H, Sato Y, Yamada Y, Hashino T, Shinoki M, Iwagoe H, Takahashi H, Fujii K, Kishi H, Kanai M, Imamura T, Yamashita T, Yatomi M, Maeno T, Hayashi S, Takahashi M, Kuramochi M, Kamimaki I, Tominaga Y, Ishii T, Utsugi M, Ono A, Tanaka T, Kashiwada T, Fujita K, Saito Y, Seike M, Watanabe H, Matsuse H, Kodaka N, Nakano C, Oshio T, Hirouchi T, Makino S, Egi M, Omae Y, Nannya Y, Ueno T, Takano T, Katayama K, Ai M, Kumanogoh A, Sato T, Hasegawa N, Tokunaga K, Ishii M, Koike R, Kitagawa Y, Kimura A, Imoto S, Miyano S, Ogawa S, Kanai T, Fukunaga K, Okada Y. The whole blood transcriptional regulation landscape in 465 COVID-19 infected samples from Japan COVID-19 Task Force. ***Nat Commun*** 13, 4830 (2022)

271 Wang Z, Xue J, Nishimura, Kometani M, Wilnai Y, Zeitlin L, Kinoshita A, Yoshiura K, Imamura T, Ohashi H, Kawai S, Shiina M, Ogata K, Miyake N, Toguchida J, Superti-Furga A, Matsumoto N, Ikegawa S. Identification of Disease Gene for Camurati-Engelmann Disease, Type II. ***Bone Rep*** 16, 101561 (2022)

272 Watase M, Masaki K, Chubachi S, Namkoong H, Tanaka H, Lee H, Fukushima T, Otake S, Nakagawara K, Kusumoto T, Asakura T, Kamata H, Ishii M, Hasegawa N, Oyamada Y, Harada N, Ueda T, Ueda S, Ishiguro T, Arimura K, Saito F, Yoshiyama T, Nakano Y, Mutoh Y, Suzuki Y, Edahiro R, Sano H, Sato Y, Okada Y, Koike R, Kitagawa Y, Tokunaga K, Kimura A, Imoto S, Miyano S, Ogawa S, Kanai T, Fukunaga K, Force JC. Impact of accumulative smoking exposure and chronic obstructive pulmonary disease on COVID-19 outcomes: Report based on findings from the Japan COVID-19 Task Force. ***Int J Infect Dis*** 128, 121-127 (2022)

273 Weissbrod O, Kanai M, Shi H, Gazal S, Peyrot WJ, Khera AV, Okada Y, Martin AR, Finucane HK, Price AL. Leveraging fine-mapping and multipopulation training data to improve cross-population polygenic risk scores. ***Nat Genet*** 54, 450-458 (2022)

274 Winkler TW, Rasheed H, Teumer A, Gorski M, Rowan BX, Stanzick KJ, Thomas LF, Tin A, Hoppmann A, Chu AY, Tayo B, Thio CH, Cusi D, Chai J, Sieber KB, Horn K, Li M, Scholz M, Cocca M, Wuttke M, van der Most PJ, Yang Q, Ghasemi S, Nutile T, Li Y, Pontali G, Günther F, Dehghan A, Correa A, Parsa A, Feresin A, de Vries AP, Zonderman AB, Smith AV, Oldehinkel AJ, De Grandi A, Rosenkranz AR, Franke A, Teren A, Metspalu A, Hicks AA, Morris AP, Tönjes A, Morgan A, Podgornaia AI, Peters A, Körner A, Mahajan A, Campbell A, Freedman BI, Spedicati B, Ponte B, Schöttker B, Brumpton B, Banas B, Krämer BK, Jung B, Åsvold BO, Smith BH, Ning B, Penninx BW, Vanderwerff BR, Psaty BM, Kammerer CM, Langefeld CD, Hayward C, Spracklen CN, Robinson-Cohen C, Hartman CA, Lindgren CM, Wang C, Sabanayagam C, Heng C, Lanzani C, Khor C, Cheng C, Fuchsberger C, Gieger C, Shaffer CM, Schulz C, Willer CJ, Chasman DI, Gudbjartsson DF, Ruggiero D, Toniolo D, Czamara D, Porteous DJ, Waterworth DM, Mascalzoni D, Mook-Kanamori DO, Reilly DF, Daw EW, Hofer E, Boerwinkle E, Salvi E, Bottinger EP, Tai E, Catamo E, Rizzi F, Guo F, Rivadeneira F, Guilianini F, Sveinbjornsson G, Ehret G, Waeber G, Biino G, Girotto G, Pistis G, Nadkarni GN, Delgado GE, Montgomery GW, Snieder H, Campbell H, White HD, Gao H, Stringham HM, Schmidt H, Li H, Brenner H, Holm H, Kirsten H, Kramer H, Rudan I, Nolte IM, Tzoulaki I, Olafsson I, Martins J, Cook JP, Wilson JF, Halbritter J, Felix JF, Divers J, Kooner JS, Lee JJ, O'Connell J, Rotter JI, Liu J, Xu J, Thiery J, Ärnlöv J, Kuusisto J, Jakobsdottir J, Tremblay J, Chambers JC, Whitfield JB, Gaziano JM, Marten J, Coresh J, Jonas JB, Mychaleckyj JC, Christensen K, Eckardt K, Mohlke KL, Endlich K, Dittrich K, Ryan KA, Rice KM, Taylor KD, Ho K, Nikus K, Matsuda K, Strauch K, Miliku K, Hveem K, Lind L, Wallentin L, Yerges-Armstrong LM, Raffield LM, Phillips LS, Launer LJ, Lyytikäinen L, Lange LA, Citterio L, Klaric L, Ikram MA, Ising M, Kleber ME, Francescatto M, Concas MP, Ciullo M, Piratsu M, Orho-Melander M, Laakso M, Loeffler M, Perola M, de Borst MH, Gögele M, Bianca ML, Lukas MA, Feitosa MF, Biggs ML, Wojczynski MK, Kavousi M, Kanai M, Akiyama M, Yasuda M, Nauck M, Waldenberger M, Chee M, Chee M, Boehnke M, Preuss MH, Stumvoll M, Province MA, Evans MK, O'Donoghue ML, Kubo M, Kähönen M, Kastarinen M, Nalls MA, Kuokkanen M, Ghanbari M, Bochud M, Josyula NS, Martin NG, Tan NY, Palmer ND, Pirastu N, Schupf N, Verweij N, Hutri-Kähönen N, Mononen N, Bansal N, Devuyst O, Melander O, Raitakari OT, Polasek O, Manunta P, Gasparini P, Mishra PP, Sulem P, Magnusson PK, Elliott P, Ridker PM, Hamet P, Svensson PO, Joshi PK, Kovacs P, Pramstaller PP, Rossing P, Vollenweider P, van der Harst P, Dorajoo R, Sim RZ, Burkhardt R, Tao R, Noordam R, Mägi R, Schmidt R, de Mutsert R, Rueedi R, van Dam RM, Carroll RJ, Gansevoort RT, Loos RJ, Felicita SC, Sedaghat S, Padmanabhan S, Freitag-Wolf S, Pendergrass SA, Graham SE, Gordon SD, Hwang S, Kerr SM, Vaccargiu S, Patil SB, Hallan S, Bakker SJ, Lim S, Lucae S, Vogelezang S, Bergmann S, Corre T, Ahluwalia TS, Lehtimäki T, Boutin TS, Meitinger T, Wong T, Bergler T, Rabelink TJ, Esko T, Haller T, Thorsteinsdottir U, Völker U, Foo VH, Salomaa V, Vitart V, Giedraitis V, Gudnason V, Jaddoe VW, Huang W, Zhang W, Wei WB, Kiess W, März W, Koenig W, Lieb W, Gao X, Sim X, Wang YX, Friedlander Y, Tham Y, Kamatani Y, Okada Y, Milaneschi Y, Yu Z, Stark KJ, Stefansson K, Böger CA, Hung AM, Kronenberg F, Köttgen A, Pattaro C, Heid IM. Differential and shared genetic effects on kidney function between diabetic and non-diabetic individuals. ***Commun Biol*** 5, 580 (2022)

275 Xue J, Ikegawa S, Guo L. SLC4A2, another gene involved in acid-base balancing machinery of osteoclasts, causes osteopetrosis. ***Bone*** 167, 116603 (2022)

276 Yaku A, Ishikawa Y, Iwasaki T, Hiwa R, Matsuo K, Saji H, Yurugi K, Miura Y, Furu M, Ito H, Fujii T, Maekawa T, Hashimoto M, Ohmura K, Mimori T, Terao C. Genetic architecture underlying IgG-RF production is distinct from that of IgM-RF. ***Rheumatology (Oxford)*** 62, 2015-2020 (2022)

277 Yakushiji-Kaminatsui N, Kondo T, Ohinata Y, Takano J, Koseki H. Genetic, Genomic, and Imaging Approaches to Dissect the Role of Polycomb Group Epigenetic Regulators in Mice. ***Methods Mol Biol*** 2529, 207-228 (2022)

278 Yamaguchi K, Ishigaki K, Suzuki A, Tsuchida Y, Tsuchiya H, Sumitomo S, Nagafuchi Y, Miya F, Tsunoda T, Shoda H, Fujio K, Yamamoto K, Kochi Y. Splicing QTL analysis focusing on coding sequences reveals mechanisms for disease susceptibility loci. ***Nat Commun*** 13, 4659 (2022)

279 Yamaguchi Y, Kato Y, Edahiro R, Søndergaard JN, Murakami T, Amiya S, Nameki S, Yoshimine Y, Morita T, Takeshima Y, Sakakibara S, Naito Y, Motooka D, Liu Y, Shirai Y, Okita Y, Fujimoto J, Hirata H, Takeda Y, Wing JB, Okuzaki D, Okada Y, Kumanogoh A. Consecutive BNT162b2 mRNA vaccination induces short-term epigenetic memory in innate immune cells. ***JCI Insight*** 7, e163347 (2022)

280 Yamamoto K, Sonehara K, Namba S, Konuma T, Masuko H, Miyawaki S, Kamatani Y, Hizawa N, Ozono K, Yengo L, Okada Y. Genetic footprints of assortative mating in the Japanese population. ***Nat Hum Behav*** 1-9 (2022)

281 Yamashita M, Taniuchi I. Fine-tuning Notch1 by the stage-specific enhancer. ***Nat Immunol*** 23, 1509-1511 (2022)

282 Yamazaki K, Miyauchi E, Kato T, Sato K, Suda W, Tsuzuno T, Yamada-Hara M, Sasaki N, Ohno H, Yamazaki K. Dysbiotic human oral microbiota alters systemic metabolism via modulation of gut microbiota in germ-free mice. ***J Oral Microbiol*** 14, 2110194 (2022)

283 Yan M, Komatsu N, Muro R, Huynh NC, Tomofuji Y, Okada Y, Suzuki HI, Takaba H, Kitazawa R, Kitazawa S, Pluemsakunthai W, Mitsui Y, Satoh T, Okamura T, Nitta T, Im S, Kim CJ, Kollias G, Tanaka S, Okamoto K, Tsukasaki M, Takayanagi H. ETS1 governs pathological tissue-remodeling programs in disease-associated fibroblasts. ***Nat Immunol*** 23, 1330-1341 (2022)

284 Yang S, Ha K, Song W, Fujita M, Kübler K, Polak, Hiyama E, Nakagawa H, Kim H, Lee H. COOBoostR: an extreme gradient boosting-based tool for robust tissue or cell-of-origin prediction of tumors. ***Life*** 13, 71 (2022)

285 Yengo L, Vedantam S, Marouli E, Sidorenko J, Bartell E, Sakaue S, Graff M, Eliasen AU, Jiang Y, Raghavan S, Miao J, Arias JD, Graham SE, Mukamel RE, Spracklen CN, Yin X, Chen S, Ferreira T, Highland HH, Ji Y, Karaderi T, Lin K, Lüll K, Malden DE, Medina-Gomez C, Machado M, Moore A, Rüeger S, Sim X, Vrieze S, Ahluwalia TS, Akiyama M, Allison MA, Alvarez M, Andersen MK, Ani A, Appadurai V, Arbeeva L, Bhaskar S, Bielak LF, Bollepalli S, Bonnycastle LL, Bork-Jensen J, Bradfield JP, Bradford Y, Braund PS, Brody JA, Burgdorf KS, Cade BE, Cai H, Cai Q, Campbell A, Cañadas-Garre M, Catamo E, Chai J, Chai X, Chang L, Chang Y, Chen C, Chesi A, Choi SH, Chung R, Cocca M, Concas MP, Couture C, Cuellar-Partida G, Danning R, Daw EW, Degenhard F, Delgado GE, Delitala A, Demirkan A, Deng X, Devineni P, Dietl A, Dimitriou M, Dimitrov L, Dorajoo R, Ekici AB, Engmann JE, Fairhurst-Hunter Z, Farmaki A, Faul JD, Fernandez-Lopez J, Forer L, Francescatto M, Freitag-Wolf S, Fuchsberger C, Galesloot TE, Gao Y, Gao Z, Geller F, Giannakopoulou O, Giulianini F, Gjesing AP, Goel A, Gordon SD, Gorski M, Grove J, Guo X, Gustafsson S, Haessler J, Hansen TF, Havulinna AS, Haworth SJ, He J, Heard-Costa N, Hebbar P, Hindy G, Ho YA, Hofer E, Holliday E, Horn K, Hornsby WE, Hottenga J, Huang H, Huang J, Huerta-Chagoya A, Huffman JE, Hung Y, Huo S, Hwang MY, Iha H, Ikeda DD, Isono M, Jackson AU, Jäger S, Jansen IE, Johansson I, Jonas JB, Jonsson A, Jørgensen T, Kalafati I, Kanai M, Kanoni S, Kårhus LL, Kasturiratne A, Katsuya T, Kawaguchi T, Kember RL, Kentistou KA, Kim H, Kim YJ, Kleber ME, Knol MJ, Kurbasic A, Lauzon M, Le P, Lea R, Lee J, Leonard HL, Li SA, Li X, Li X, Liang J, Lin H, Lin S, Liu J, Liu X, Lo KS, Long J, Lores-Motta L, Luan J, Lyssenko V, Lyytikäinen L, Mahajan A, Mamakou V, Mangino M, Manichaikul A, Marten J, Mattheisen M, Mavarani L, McDaid AF, Meidtner K, Melendez TL, Mercader JM, Milaneschi Y, Miller JE, Millwood IY, Mishra PP, Mitchell RE, Møllehave LT, Morgan A, Mucha S, Munz M, Nakatochi M, Nelson CP, Nethander M, Nho CW, Nielsen AA, Nolte IM, Nongmaithem SS, Noordam R, Ntalla I, Nutile T, Pandit A, Christofidou P, Pärna K, Pauper M, Petersen ER, Petersen LV, Pitkänen N, Polašek O, Poveda A, Preuss MH, Pyarajan S, Raffield LM, Rakugi H, Ramirez J, Rasheed A, Raven D, Rayner NW, Riveros C, Rohde R, Ruggiero D, Ruotsalainen SE, Ryan KA, Sabater-Lleal M, Saxena R, Scholz M, Sendamarai A, Shen B, Shi J, Shin JH, Sidore C, Sitlani CM, Slieker RC, Smit RA, Smith AV, Smith JA, Smyth LJ, Southam L, Steinthorsdottir V, Sun L, Takeuchi F, Tallapragada DS, Taylor KD, Tayo BO, Tcheandjieu C, Terzikhan N, Tesolin P, Teumer A, Theusch E, Thompson DJ, Thorleifsson G, Timmers PR, Trompet S, Turman C, Vaccargiu S, van der Laan SW, van der Most PJ, van Klinken JB, van Setten J, Verma SS, Verweij N, Veturi Y, Wang CA, Wang C, Wang L, Wang Z, Warren HR, Bin Wei W, Wickremasinghe AR, Wielscher M, Wiggins KL, Winsvold BS, Wong A, Wu Y, Wuttke M, Xia R, Xie T, Yamamoto K, Yang J, Yao J, Young H, Yousri NA, Yu L, Zeng L, Zhang W, Zhang X, Zhao J, Zhao W, Zhou W, Zimmermann ME, Zoledziewska M, Adair LS, Adams HH, Aguilar-Salinas CA, Al-Mulla F, Arnett DK, Asselbergs FW, Åsvold BO, Attia J, Banas B, Bandinelli S, Bennett DA, Bergler T, Bharadwaj D, Biino G, Bisgaard H, Boerwinkle E, Böger CA, Bønnelykke K, Boomsma DI, Børglum AD, Borja JB, Bouchard C, Bowden DW, Brandslund I, Brumpton B, Buring JE, Caulfield MJ, Chambers JC, Chandak GR, Chanock SJ, Chaturvedi N, Chen YI, Chen Z, Cheng C, Christophersen IE, Ciullo M, Cole JW, Collins FS, Cooper RS, Cruz M, Cucca F, Cupples LA, Cutler MJ, Damrauer SM, Dantoft TM, de Borst GJ, de Groot LC, De Jager PL, de Kleijn DP, Janaka de Silva H, Dedoussis GV, den Hollander AI, Du S, Easton DF, Elders PJ, Eliassen AH, Ellinor PT, Elmståhl S, Erdmann J, Evans MK, Fatkin D, Feenstra B, Feitosa MF, Ferrucci L, Ford I, Fornage M, Franke A, Franks PW, Freedman BI, Gasparini P, Gieger C, Girotto G, Goddard ME, Golightly YM, Gonzalez-Villalpando C, Gordon-Larsen P, Grallert H, Grant SF, Grarup N, Griffiths L, Gudnason V, Haiman C, Hakonarson H, Hansen T, Hartman CA, Hattersley AT, Hayward C, Heckbert SR, Heng C, Hengstenberg C, Hewitt AW, Hishigaki H, Hoyng CB, Huang PL, Huang W, Hunt SC, Hveem K, Hyppönen E, Iacono WG, Ichihara S, Ikram MA, Isasi CR, Jackson RD, Jarvelin M, Jin Z, Jöckel K, Joshi PK, Jousilahti P, Jukema JW, Kähönen M, Kamatani Y, Kang KD, Kaprio J, Kardia SL, Karpe F, Kato N, Kee F, Kessler T, Khera AV, Khor CC, Kiemeney LA, Kim B, Kim EK, Kim H, Kirchhof P, Kivimaki M, Koh W, Koistinen HA, Kolovou GD, Kooner JS, Kooperberg C, Köttgen A, Kovacs P, Kraaijeveld A, Kraft P, Krauss RM, Kumari M, Kutalik Z, Laakso M, Lange LA, Langenberg C, Launer LJ, Le Marchand L, Lee H, Lee NR, Lehtimäki T, Li H, Li L, Lieb W, Lin X, Lind L, Linneberg A, Liu C, Liu J, Loeffler M, London B, Lubitz SA, Lye SJ, Mackey DA, Mägi R, Magnusson PK, Marcus GM, Vidal PM, Martin NG, März W, Matsuda F, McGarrah RW, McGue M, McKnight AJ, Medland SE, Mellström D, Metspalu A, Mitchell BD, Mitchell P, Mook-Kanamori DO, Morris AD, Mucci LA, Munroe PB, Nalls MA, Nazarian S, Nelson AE, Neville MJ, Newton-Cheh C, Nielsen CS, Nöthen MM, Ohlsson C, Oldehinkel AJ, Orozco L, Pahkala K, Pajukanta P, Palmer CN, Parra EJ, Pattaro C, Pedersen O, Pennell CE, Penninx BW, Perusse L, Peters A, Peyser PA, Porteous DJ, Posthuma D, Power C, Pramstaller PP, Province MA, Qi Q, Qu J, Rader DJ, Raitakari OT, Ralhan S, Rallidis LS, Rao DC, Redline S, Reilly DF, Reiner AP, Rhee SY, Ridker PM, Rienstra M, Ripatti S, Ritchie MD, Roden DM, Rosendaal FR, Rotter JI, Rudan I, Rutters F, Sabanayagam C, Saleheen D, Salomaa V, Samani NJ, Sanghera DK, Sattar N, Schmidt B, Schmidt H, Schmidt R, Schulze MB, Schunkert H, Scott LJ, Scott RJ, Sever P, Shiroma EJ, Shoemaker MB, Shu X, Simonsick EM, Sims M, Singh JR, Singleton AB, Sinner MF, Smith JG, Snieder H, Spector TD, Stampfer MJ, Stark KJ, Strachan DP, 't Hart LM, Tabara Y, Tang H, Tardif J, Thanaraj TA, Timpson NJ, Tönjes A, Tremblay A, Tuomi T, Tuomilehto J, Tusié-Luna M, Uitterlinden AG, van Dam RM, van der Harst P, Van der Velde N, van Duijn CM, van Schoor NM, Vitart V, Völker U, Vollenweider P, Völzke H, Wacher-Rodarte NH, Walker M, Wang YX, Wareham NJ, Watanabe RM, Watkins H, Weir DR, Werge TM, Widen E, Wilkens LR, Willemsen G, Willett WC, Wilson JF, Wong T, Woo J, Wright AF, Wu J, Xu H, Yajnik CS, Yokota M, Yuan J, Zeggini E, Zemel BS, Zheng W, Zhu X, Zmuda JM, Zonderman AB, Zwart J, Chasman DI, Cho YS, Heid IM, McCarthy MI, Ng MC, O'Donnell CJ, Rivadeneira F, Thorsteinsdottir U, Sun YV, Tai ES, Boehnke M, Deloukas P, Justice AE, Lindgren CM, Loos RJ, Mohlke KL, North KE, Stefansson K, Walters RG, Winkler TW, Young KL, Loh P, Yang J, Esko T, Assimes TL, Auton A, Abecasis GR, Willer CJ, Locke AE, Berndt SI, Lettre G, Frayling TM, Okada Y, Wood AR, Visscher PM, Hirschhorn JN. A saturated map of common genetic variants associated with human height. ***Nature*** 610, 704-712 (2022)

286 Yin X, Kim K, Suetsugu H, Bang S, Wen L, Koido M, Ha E, Liu L, Sakamoto Y, Jo S, Leng R, Otomo N, Kwon Y, Sheng Y, Sugano N, Hwang MY, Li W, Mukai M, Yoon K, Cai M, Ishigaki K, Chung WT, Huang H, Takahashi D, Lee S, Wang M, Karino K, Shim S, Zheng X, Miyamura T, Kang YM, Ye D, Nakamura J, Suh C, Tang Y, Motomura G, Park Y, Ding H, Kuroda T, Choe J, Li C, Niiro H, Park Y, Shen C, Miyamoto T, Ahn G, Fei W, Takeuchi T, Shin J, Li K, Kawaguchi Y, Lee Y, Wang Y, Amano K, Park DJ, Yang W, Tada Y, Lau YL, Yamaji K, Zhu Z, Shimizu M, Atsumi T, Suzuki A, Sumida T, Okada Y, Matsuda K, Matsuo K, Kochi Y, Yamamoto K, Ohmura K, Kim T, Yang S, Yamamoto T, Kim B, Shen N, Ikegawa S, Lee H, Zhang X, Terao C, Cui Y, Bae S. Biological insights into systemic lupus erythematosus through an immune cell-specific transcriptome-wide association study. ***Ann Rheum Dis*** 81, 1273-1280 (2022)

287 Yip C, Hon C, Yasuzawa K, Sivaraman DM, Ramilowski JA, Shibayama Y, Agrawal S, Prabhu AV, Parr C, Severin J, Lan Y, Dostie J, Petri A, Nishiyori-Sueki H, Tagami M, Itoh M, López-Redondo F, Kouno T, Chang J, Luginbühl J, Kato M, Murata M, Yip W, Shu X, Abugessaisa I, Hasegawa A, Suzuki H, Kauppinen S, Yagi K, Okazaki Y, Kasukawa T, de Hoon M, Carninci P, Shin JW. Antisense oligonucleotide-mediated perturbation of long non-coding RNA reveals functional features in stem cells and across cell types. ***Cell Rep*** 41, 111893 (2022)

288 Yonezawa Y, Guo L, Kakinuma H, Otomo N, Yoshino S, Takeda K, Nakajima M, Shiraki T, Ogura Y, Takahashi Y, Koike Y, Minami S, Uno K, Kawakami N, Ito M, Yonezawa I, Watanabe K, Kaito T, Yanagida H, Taneichi H, Harimaya K, Taniguchi Y, Shigematsu H, Iida T, Demura S, Sugawara R, Fujita N, Yagi M, Okada E, Hosogane N, Kono K, Chiba K, Kotani T, Sakuma T, Akazawa T, Suzuki T, Nishida K, Kakutani K, Tsuji T, Sudo H, Iwata A, Sato T, Inami S, Nakamura M, Matsumoto M, Terao C, Watanabe K, Okamoto H, Ikegawa S. Identification of a Functional Susceptibility Variant for Adolescent Idiopathic Scoliosis that Upregulates Early Growth Response 1 (EGR1)-Mediated UNCX Expression. ***J Bone Miner Res*** 38, 144-153 (2022)

289 Yoshida M, Ishihara T, Isobe Y, Arita M. Genetic deletion of Cyp4f18 disrupts the omega-3 epoxidation pathway and results in psoriasis-like dermatitis. ***FASEB J*** 36, e22648 (2022)

290 Yoshioka W, Iida A, Sonehara K, Yamamoto K, Oya Y, Mori-Yoshimura M, Kurashige T, Okubo M, Ogawa M, Matsuda F, Higasa K, Hayashi S, Nakamura H, Sekijima M, Okada Y, Noguchi S, Nishino I. Multidimensional analyses of the pathomechanism caused by the non-catalytic GNE variant, c.620A>T, in patients with GNE myopathy. ***Sci Rep*** 12, 21806 (2022)

291 Yuki S, Akiko O, Fukushima Y, Masuda K, Toriu N, Taniguchi K, Yoshikawa T, Cui X, Kondo M, Hosoi T, Komidori S, Shimizu Y, Fujita H, Jiang L, Kong Y, Yamanashi T, Seita J, Yamamoto T, Toyokuni S, Hamazaki Y, Hattori M, Yoshikai Y, Boor P, Floege J, Kawamoto H, Murakawa Y, Minato N, Yanagita M. CD153/CD30 signaling promotes age-dependent tertiary lymphoid tissue expansion and kidney injury. ***J Clin Invest*** 132, e146071 (2022)

292 Zhang P, Ono A, Fujii Y, Hayes CN, Tamura Y, Miura R, Shirane Y, Nakahara H, Yamauchi M, Uchikawa S, Uchida T, Teraoka Y, Fujino H, Nakahara T, Murakami E, Miki D, Kawaoka T, Okamoto W, Makokha GN, Imamura M, Arihiro K, Kobayashi T, Ohdan H, Fujita M, Nakagawa H, Chayama K, Aikata H. The presence of vessels encapsulating tumor clusters is associated with an immunosuppressive tumor microenvironment in hepatocellular carcinoma. ***Int J Cancer*** 151, 2278-2290 (2022)

293 Zhang Y, Chen F, Fonseca NA, He Y, Fujita M, Nakagawa H, Zhang Z, Brazma A; PCAWG Transcriptome Working Group; PCAWG Structural Variation Working Group; Creighton CJ; PCAWG Consortium. Author Correction: High-coverage whole-genome analysis of 1220 cancers reveals hundreds of genes deregulated by rearrangement-mediated cis-regulatory alterations. ***Nat Commun*** 13, 7572 (2022)

294 Zhang Y, Garcia-Ibanez L, Ulbricht C, Lok LS, Pike JA, Mueller-Winkler J, Dennison TW, Ferdinand JR, Burnett CJ, Yam-Puc JC, Zhang L, Alfaro RM, Takahama Y, Ohigashi I, Brown G, Kurosaki T, Tybulewicz VL, Rot A, Hauser AE, Clatworthy MR, Toellner K. Recycling of memory B cells between germinal center and lymph node subcapsular sinus supports affinity maturation to antigenic drift. ***Nat Commun*** 13, 2460 (2022)

295 Zheng J, Zhang Y, Rasheed H, Walker V, Sugawara Y, Li J, Leng Y, Elsworth B, Wootton RE, Fang S, Yang Q, Burgess S, Haycock PC, Borges MC, Cho Y, Carnegie R, Howell A, Robinson J, Thomas LF, Brumpton BM, Hveem K, Hallan S, Franceschini N, Morris AP, Kottgen A, Pattaro C, Wuttke M, Yamamoto M, Kashihara N, Akiyama M, Kanai M, Matsuda K, Kamatani Y, Okada Y, Walters R, Millwood IY, Chen Z, Smith GD, Barbour S, Yu C, Asvold BO, Zhang H, Gaunt TR. Trans-ethnic Mendelian-randomization study reveals causal relationships between cardiometabolic factors and chronic kidney disease. ***Int J Epidemiol*** 50, 1995-2010 (2022)

296 Zhu Y, Gu H, Yang L, Li N, Chen Q, Kang D, Lin S, Jing Y, Panpan J, Chen Q, Luo L, Liu J, Chang J, Li Z, Wang Y, Dai X, Miller H, Westerberg LS, Park C, Kubo M, Gong Q, Dong L, Liu C. Involvement of MST1/mTORC1/STAT1 activity in the regulation of B-cell receptor signalling by chemokine receptor 2. ***Clin Transl Med*** 12, e887 (2022)

Budget, Personnel and Patents

IMS Budget FY2022

IMS Budget FY2022	JPY Million
Government funding for operations	2,953
External competitive funding	2,111
Total	**5,064**

Patents

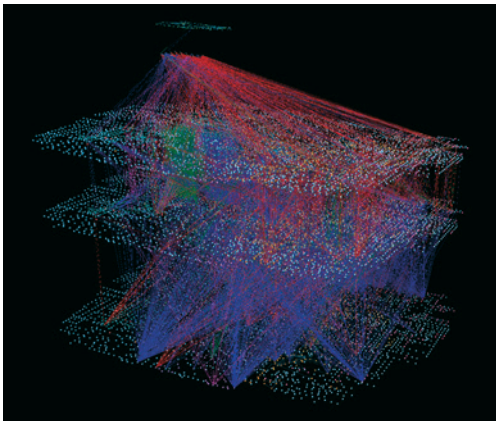
There were 13 patents registered from January to December 2022.

Patents	Total	International patents	Domestic patents (Japan)
2022	13	9	4

Personnel FY2022

Category	Number
Director	1
Deputy Director	3
Senior Advisor	1
Team Leader	40
Coordinator	3
Deputy Team Leader	8
Senior Scientist	15
Senior Research Scientist	4
Research Scientist	53
Postdoctoral Researcher	21
Special Postdoctoral Researcher	8
Research Fellow	8
Research Associate	7
Senior Technical Scientist	4
Technical Scientist	13
Expert Technician	16
Technical Staff I	64
Technical Staff II	45
International Program Associate	3
Junior Research Associate	27
Student Trainee	158
Research Administrator	5
Research Administrative Support Staff	5
Assistant	24
Part-time Staff	49
Senior Visiting Scientist	31
Visiting Scientist	216
Visiting Technicain	13
Visiting Researcher	9
Temporary Staffing	19
Research Consultant	5
Consultant	3
Special Temporary Employee	3
Total	**884**

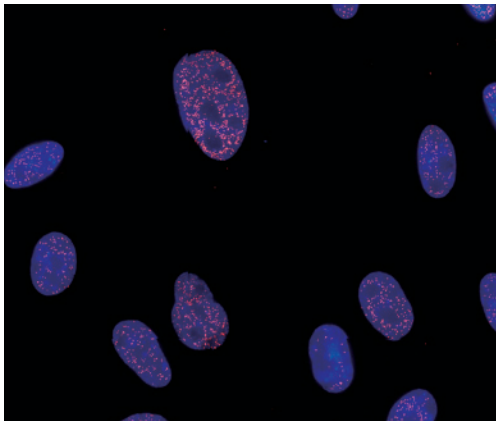
Original Photos of the Cover and Front Pages



Cover

A metabolic regulatory network generated by transomics2cytoscape, our software developed for automatic visualization of molecular networks that spans across multiple omic layers.

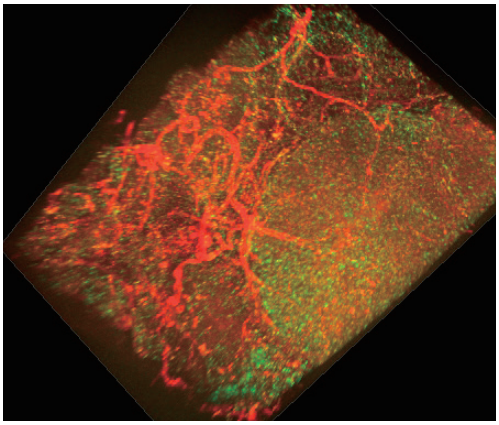
Credit to Mr. Kozo Nishida and Dr. Katsuyuki Yugi
Laboratory for Integrated Cellular Systems



Front page of Part 1

Single molecule fluorescent in-situ hybridization (smFISH) of MEG3 long noncoding RNA in primary human fibroblasts, showing exclusive localization in the nucleus. MEG3 (red); DAPI (blue).

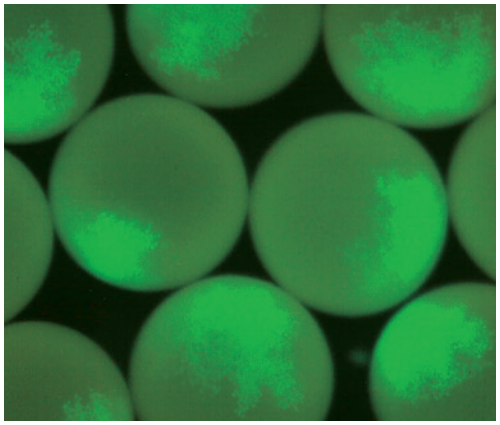
Credit to Dr. Youtaro Shibayama
Laboratory for Advanced Genomics Circuit



Front page of Part 2

Vascular structure of mouse ovary. Endothelial cells of capillary vessels (green) and endothelial cells of large blood vessels (red).

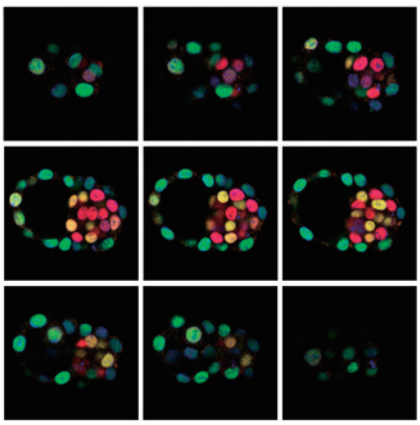
Credit to Drs. Chisayo Kozuka & Masatsugu Ema
Laboratory for Epigenome Inheritance & Shiga University of Medical Science



Front page of Part 3

***Xenopus laevis* (albino) blastula microinjected with mRNA encoding EmGFP localized to mitochondria. Mitochondria of mRNA injected area are labeled with EmGFP as detected under fluorescent microscope.**

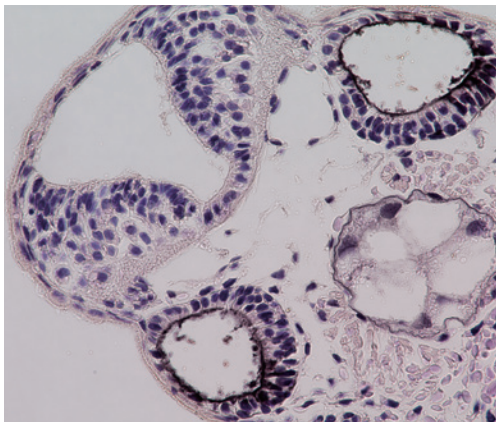
Credit to Dr. Yuuri Yasuoka
Laboratory for Comprehensive Genomic Analysis



Front page of Part 4

Serial imaging of a mouse blastocyst immunostained for Cdx2 (green), Nanog (red), Sox17 (yellow), and DAPI (blue).

Credit to Dr. Chisayo Kozuka
Laboratory for Epigenome Inheritance

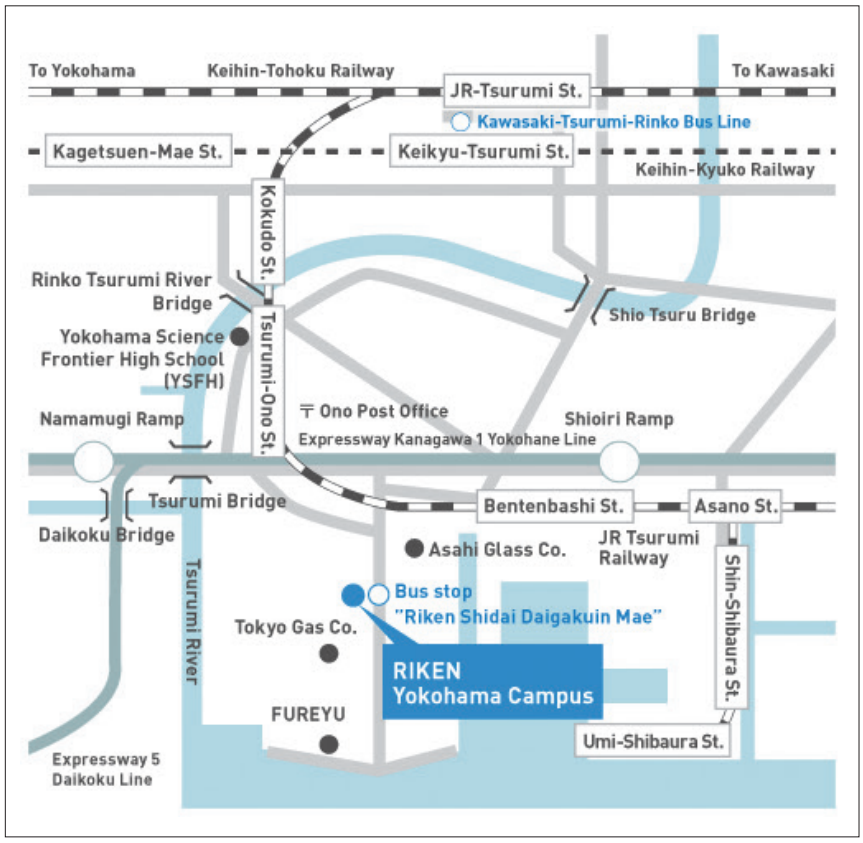


Front page of Part 5

A cross-section of a *Xenopus tropicalis* tadpole immunostained with 5D4 antibody followed by hematoxylin staining. 5D4 antibody detects highly sulfated keratan sulfate (brown) which is enriched inside otic vesicles (top-right and bottom-left) and outside notochord (bottom-right), but not in brain (top-left).

Credit to Dr. Yuuri Yasuoka
Laboratory for Comprehensive Genomic Analysis

Access to RIKEN Yokohama Campus



From the Airport

From Haneda Airport

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

Route 2
Take any train marked with a green (express), red or dark grey kanji sign to Keikyu Kamata Station. Transfer to the Keikyu Main Line and take a local train* toward Yokohama until Keikyu Tsurumi Station* (12 minutes). *Only Airport Express (blue kanji sign) and local trains (dark grey kanji sign) stop at Keikyu Tsurumi Station. Note that Keikyu Tsurumi Station and JR Tsurumi Station are two different railway stations and are separated by a bus rotary (the stations are about 150 meters apart).

From Narita Airport

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

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

Local Access

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

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

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

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

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

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