RIKEN MIH
Annual Report 2018

RIKEN Medical Sciences Innovation Hub Program

Medical Sciences Innovation Hub Program (MIH)

Program Director
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Deputy Program Director
Kazuhiro Sakurada (Ph.D.)

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Hub for predictive and preventive precision medicine driven by big data

Disease Data Integration Group
Group Director **Tatsuhiko Tsunoda** (Ph.D., Ph.D.)

Disease Biology Group
Group Director **Haruhiko Koseki** (M.D., Ph.D.)

Analytics Platform Development Group
Group Director **Kazuhiro Sakurada** (Ph.D.)

Biomarker Analysis Group
Group Director **Osamu Ohara** (Ph.D.)

Organization Chart

Data Platform Project

Healthcare and Medical Data Multi-level Integration Platform Group

Group Director **Kazuhiro Sakurada** (Ph.D.)

Deputy Group Director **Hideo Yokota** (Ph.D.)

Cancer Immunology Data Multi-level Integration Unit

Unit Leader **Kazuhiro Kakimi** (M.D., Ph.D.)

Developmental Disorder Data Multi-level Integration Unit

Unit Leader **Yukuo Konishi** (M.D., Ph.D.)

Healthcare and Medical Data Driven AI-based Predictive Reasoning Development Unit

Unit Leader **Eiryo Kawakami** (M.D., Ph.D.)

AI-based Healthcare and Medical Data Analysis Standardization Unit

Unit Leader **Jun Seita** (M.D., Ph.D.)

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Preface

The research program at the Medical Innovation Hub (MIH) was originally started in April, 2016 by the Construction Hub Coordination Program of the Japan Science and Technology Agency (JST) and was later established as a RIKEN program within the Cluster for Science, Technology and Innovation Hub (CSTIH) under RIKEN's budget for Data Platform Construction: Health and Medical Data.

This program aims to develop personalized preventive medicine based on precise prediction. To achieve this goal, we acquire patients' data through collaborations with hospitals and analyze these data using AI technologies–including machine learning–which will significantly improve the understanding of diseases. Until now, clinical science has advanced on the basis of a linear scheme of causation (one cause, one disease phenotype). Although a linear scheme of causation is useful for infectious diseases and monogenic diseases, it generates combinatorial explosion when confronted with multifactorial disorders. To overcome the drawbacks of a linear scheme of causation, we are developing an information geometry-based reasoning technology that consists of multidimensional descriptors for multi-omics data and dimensionality reduction technology. These technologies will be applied to the development of personalized prediction algorithms for multifactorial disorders. The technologies we develop will be made available to medical institutions and industry.

We focus on chronic inflammation as a key component of the onset, progression and prognosis of many diseases, including inflammatory diseases, developmental disorders and cancer. We develop new methods and technologies to handle dynamic clinical and experimental data. These include a data-driven mathematical approach and standardization of medical data for AI analysis. In parallel, we perform wet studies for biomarker search and reverse translation based on disease models derived from clinical data analysis, which are pivotal to evaluating our approach. Several RIKEN research groups are working on these studies. It is critical, however, for our program to collaborate with clinicians and researchers at various universities and university hospitals. We are currently collaborating with the University of Tokyo on systemic lupus erythematosus and cancer immunology, Keio University on skin diseases, Osaka University on rheumatoid arthritis and vasculitis, Jikei University on ovarian cancer, and Doshisha University, Kyoto Prefectural University and Tohoku University on developmental disorders. We have also launched several collaborative studies with private companies. We will continue to expand our collaborative effort with other universities, hospitals and companies.

On February 7, 2017, we held a symposium to publicize our program to the broader public: "The 1st International Symposium on Hub for Predictive and Preventive Precision Medicine Driven by Big Data", subtitled "Life Science Paradigm Shift Leading to Innovative Healthcare". In addition to RIKEN program members, prominent scientists in the field including Drs. Rudi Balling of the Luxembourg Center for Systems Biomedicine, Nisar P. Malek of the University Hospital Tübingen, John Aitchison of the Institute for Systems Biology, Kazuyuki Aihara of the University of Tokyo, and Ryozo Nagai of the Jichi Medical School delivered lectures, all of which ignited valuable discussion on approaches to making personalized preventive medicine a reality. In 2018, we continued to publicize our research activities to the general public in multiple venues, listed at the end of this report, and those efforts will continue.

As this annual report highlights, MIH has published many papers in significant journals and conferences. One such major accomplishment is the development of the "energy landscape model" for understanding disease onset and progression in an individual. I hope our ongoing determination to tackle new challenges will yield a flourishing harvest of pioneering works in predictive and preventive precision medicine.

In closing, I hope that readers will find this annual report useful and support our research activities.

Shigeo Koyasu, D.Sc.
Program Director, MIH

Part 1

Concept of Open Systems Biology

Open Systems Science Initiative

Medical Sciences Innovation Hub Program (MIH)

Deputy Program Director **Kazuhiro Sakurada** (Ph.D.)

Personalized Medicine and time development

Personalized medicine is a new paradigm that represents a shift from treating patients as a statistical abstraction toward the view that each patient is unique. This presents a new scientific challenge as well as a new social challenge.

The growth and success of biomedical research has resulted in a large body of mechanistic scientific knowledge that can simplify the view of certain diseases. In biomedical science, a mechanism is a system that approximates a phenomenon of living organisms by means of causality and input/output functions. Mechanisms are directed toward identifying the general principles of organisms. However, these first principles are insufficient to facilitate personalized clinical decision-making.

Solving clinical problems requires an understanding of the unique characteristics of individual patients. For example, non-communicable diseases—including metabolic, cardiovascular, chronic respiratory, immunologic and neurologic diseases, and cancer—which are the predominant health problems in this century, show heterogeneity in development, progression, and complications. While these diseases may appear clinically throughout an individual's lifespan, it has been shown that many diseases originate during development. Abnormal nutrition, infections, or stress during development can lead to functional changes in cells and tissues, predisposing them to diseases that manifest later in life. Developmental Origin of Health and Disease (DOHaD) is the concept that diseases should be described by their development over time. Diseases are not being, but becoming.

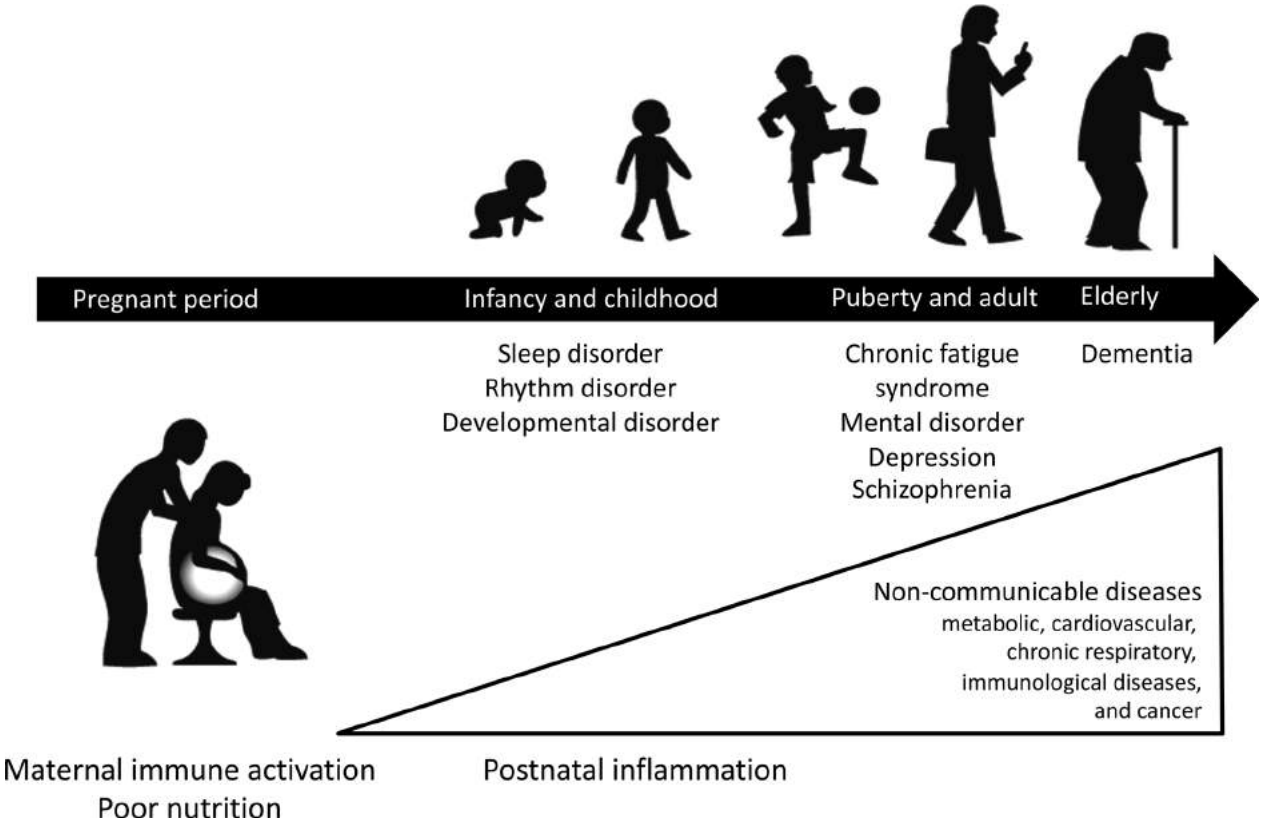

Figure 1: The concept of Developmental Origin of Health and Disease (DOHaD)
Maternal immune activation and poor nutrition are the major environmental risk factors during pregnant period. Postnatal inflammation also contribute to disease progression.

Open Systems Science

The gap between basic biomedical research and clinical practice has been explicitly pointed out by government authorities. Although significant efforts have been made to overcome this problem, no universal solution has been developed.

At present, the biological sciences are systematized by closed systems models. However, complex systems science indicates that an organism is a non-equilibrium open system that cannot be reduced to its constituent elements and explained by linear causation.

Meanwhile, the concept behind today's clinical sciences is Evidence Based Medicine (EBM), which is an approach to medical practice intended to optimize decision-making by using statistical evidence from well-designed studies. However, in clinical practice, Narrative Based Medicine (NBM), an approach that promotes healing, is required.

To overcome the problem of incommensurability between mechanism and organism, between EBM and NBM, biomedical science needs a paradigm shift.

Organisms are open systems that are ever-changing in function and structure; moreover, they are non-linear complex systems. The theory of complex systems provides a new viewpoint of understanding phenomena as time dependent changing systems. Under this theory, complex systems can be expressed as simple non-linear equations. But while such an approach could help us to understand the general properties of complex systems, it cannot be used to solve problems in this real world, such as the case of an individual patient.

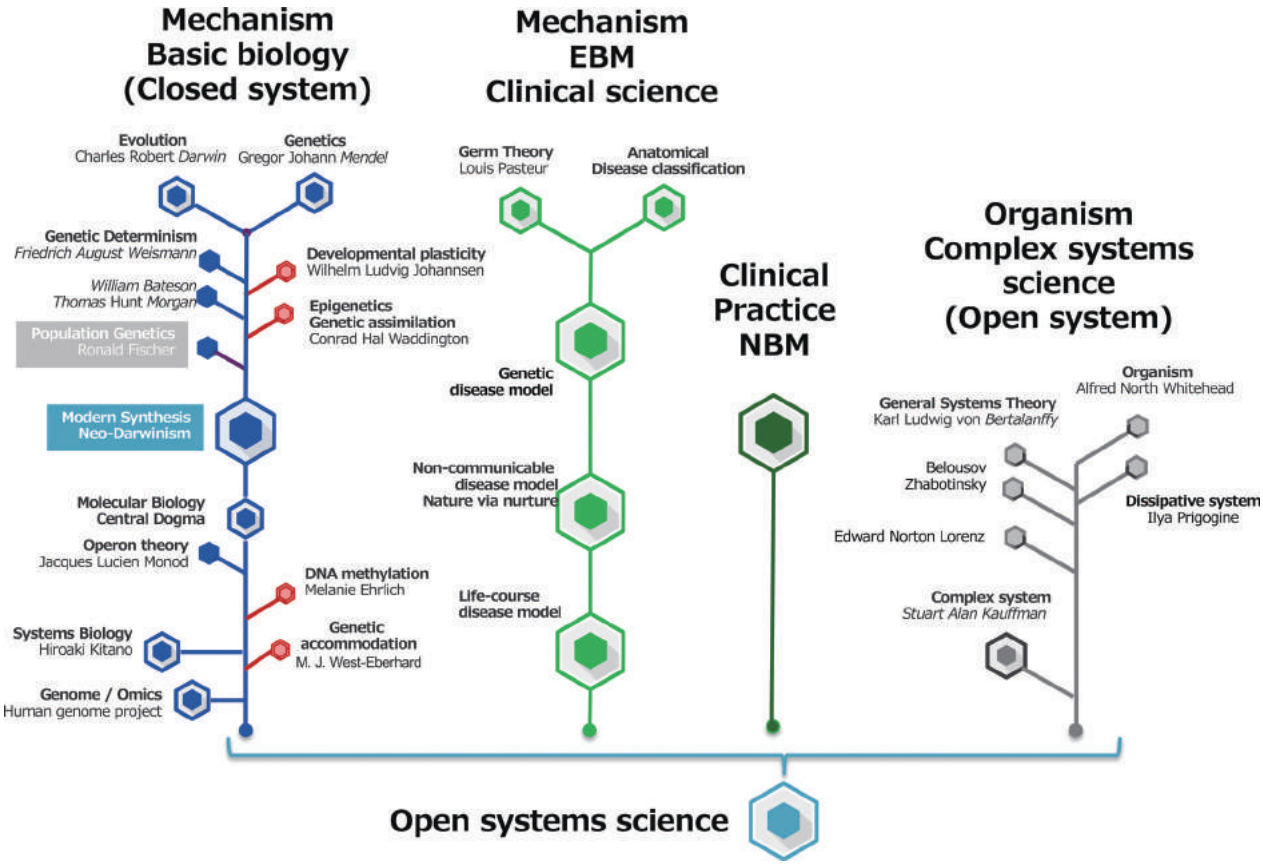

Figure 2: The concept of open systems science
Open systems science initiative is to overcome incommensurability between mechanism based biomedical and clinical practice / complex systems science.

Description of time-dependent changing systems by state allocation

To describe the time development of an organism, a Markov model has been introduced in this study. In this view, time development can be described by a sequence of possible states in which the probability of each state depends only on the previous state. The properties of each state can be approximated by input/

output functions. By discretization of this time series, mechanism and organism can be integrated.

Machine learning is a powerful tool to carry out non-linear stratification of each problem population space based on the concept of state. The number of possible states depends on the number of characteristics and the calculated data granularity. If the organism has eight characteristics and each data field is subdivided into eight areas, the total number of states is 16,777,216. However, the number of possible states in the organism is restricted. The first goal of open systems science is to identify the appropriate reduction of dimensionality and data granularity for stratification. Information geometry is used for this purpose.

Although machine learning is a powerful tool for stratification, it is not the first principle calculation. The accuracy of stratification should be validated from first principles of complex systems and/or solving real world problems.

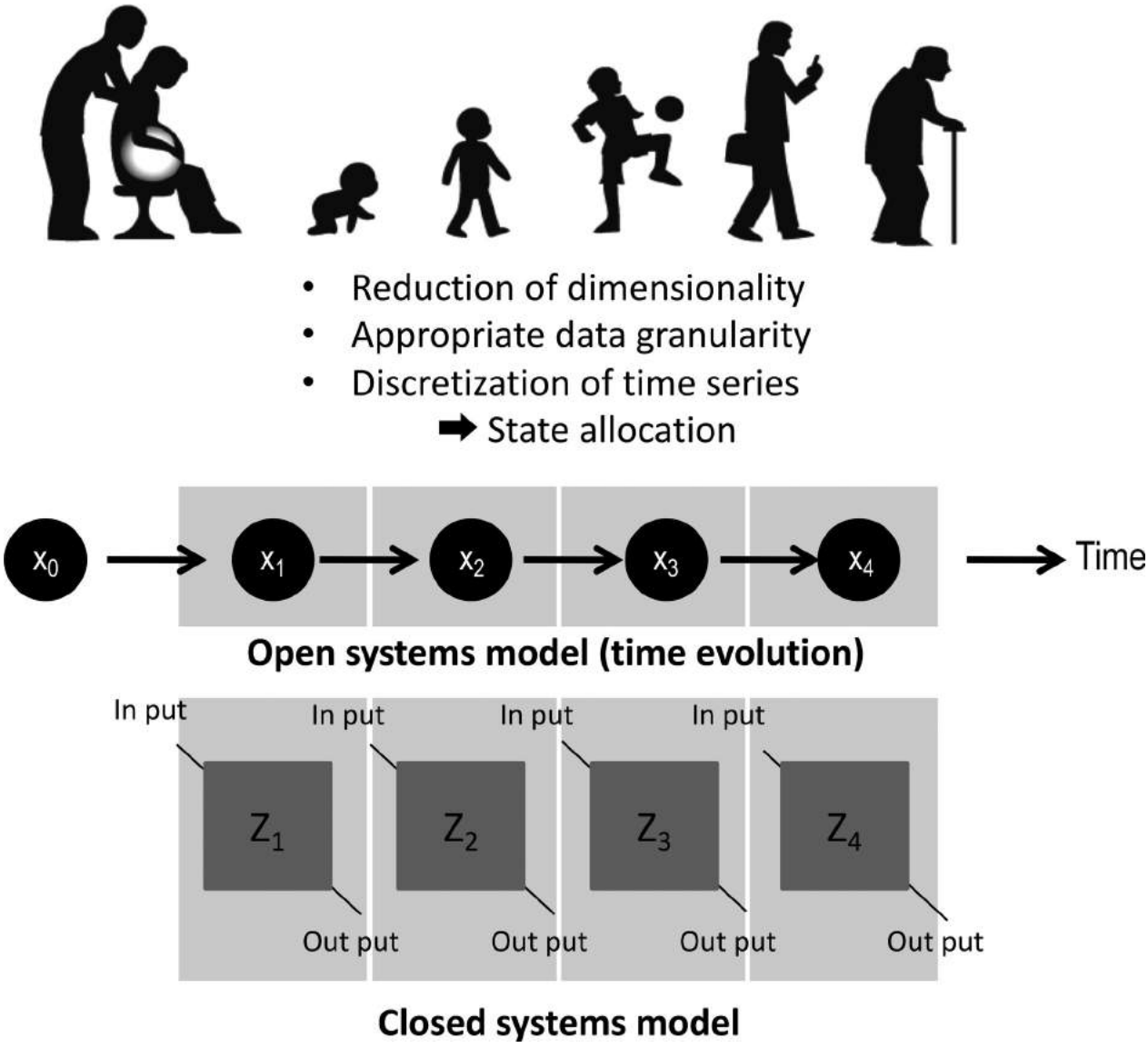

Figure 3: Description of time development by state allocation
By combining, "reduction of dimensionality", "appropriate data granularity" and "discretization of time series", time development of organism can approximate by chain of closed systems.

Constraint of the degrees of freedom and phenotypic style

The second goal of open systems science is to develop a framework to predict future changes in phenotype. For this purpose, I introduced the concept of state transition probability and constraint of the degrees of freedom.

Constraint of the degrees of freedom is the key concept of open systems science. Although the future of a closed system such as a machine is predetermined, the future of an open system remains undetermined. This does not mean that there are infinite probabilities. Each individual organism has its own constraint of the degrees of freedom. This property can be described in a quantitative way by means of a state transition probability matrix.

Classic methodologies of biomedical sciences require reproducibility of phenomena. In this setting, the degrees of freedom are eliminated, leading to a likelihood that deterministic viewpoints such as genetic programming will be generated.

In algorithmic music composition, music is seen as a sequence of symbols. The style of an existing musical corpus is characterized by conditional probabilities. Relationships between music composition and music style correspond to past and future state transition of organisms. In this view, the concept of genetic programming can be substituted for phenotypic style.

Personalized medicine means the capability to stratify each individual by deep clinical phenotyping followed by description of phenotypic style by state transition probability.

Relationships between the states can also described by an action matrix if a sufficient amount of causality information is available. In addition, simulation is possible when critical parameters and equations are obtained.

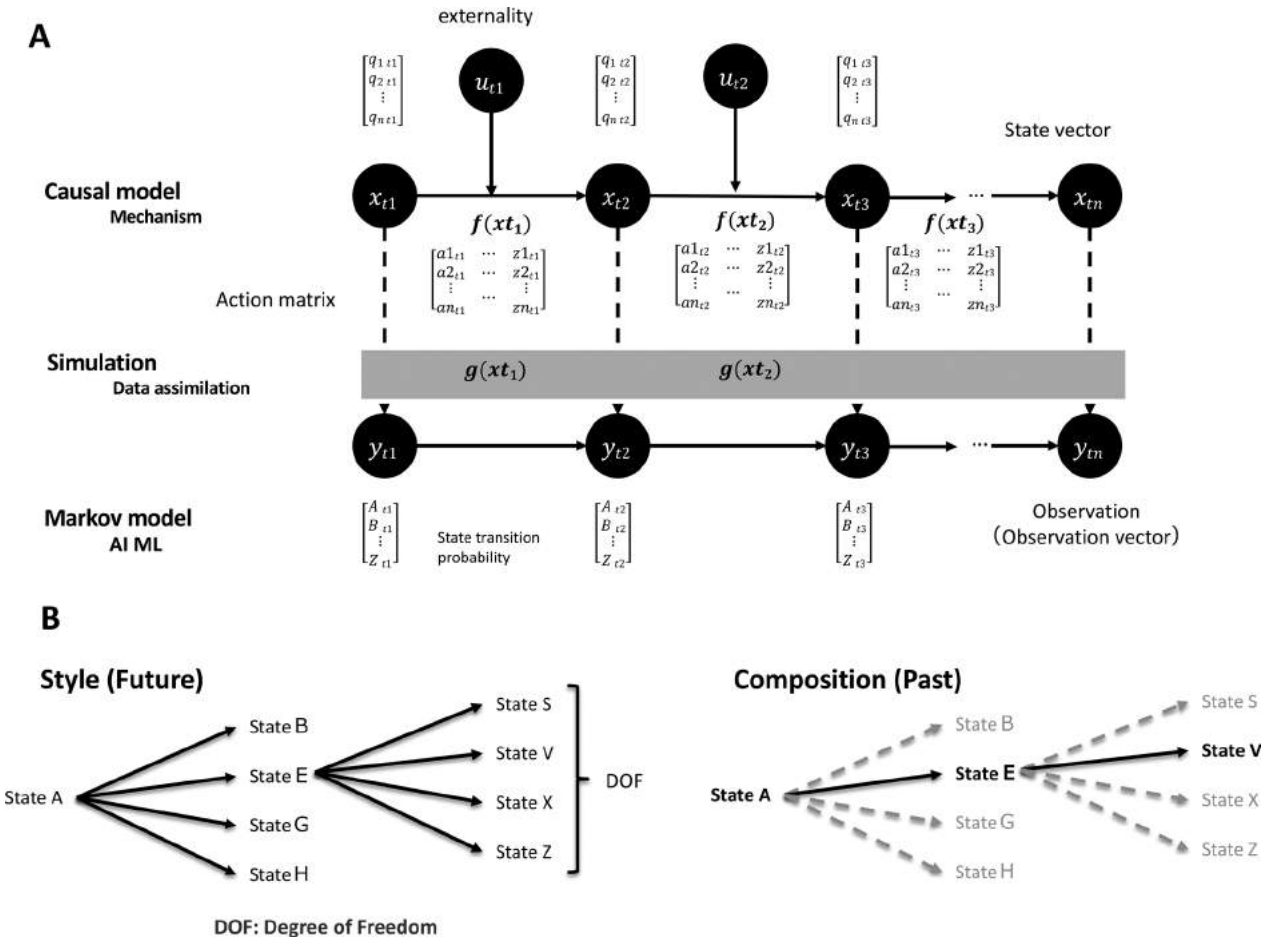

Figure 4: Constraint of the degree of freedom and phenotypic style
Relation between the states can be described by causal model, simulation, and Markov model (A). The concept of state transition probability is the key to represent the future probability. In the reproducible conditions such as experiments and past changes of states are determined. On the other hand, future changes in the real world can be describe by degree of freedom. In other word style.

Synchronization as the driving force of the reduction of the degrees of freedom

Allocation of state and estimation of state transition generate a description of an organism using real world data. To validate the accuracy of this description and identify the intervention operation, it is necessary to explain the phenomena from first principles.

Closed systems are explained by network structure and input/output function. However, network structures of organisms dynamically alter over the life course of the organism through changes in gene expression. An organism is a non-equilibrium open system which has to be described by non-linear oscillators and energy-entropy flow. Non-linear oscillators commonly exhibit synchronization phenomena. Similarly, mutual synchronization is a common phenomenon in organisms. It occurs at different layers of an organism including heartbeat, brain waves, circadian rhythm, and coordinated muscle movement by central pattern generators.

An organism can also be explained as a distributed processing system. Spontaneous activities of each of its subsystems achieve self-organization through synchronization. The reduction of the organism's degrees of freedom can be explained by synchronization of its subsystems.

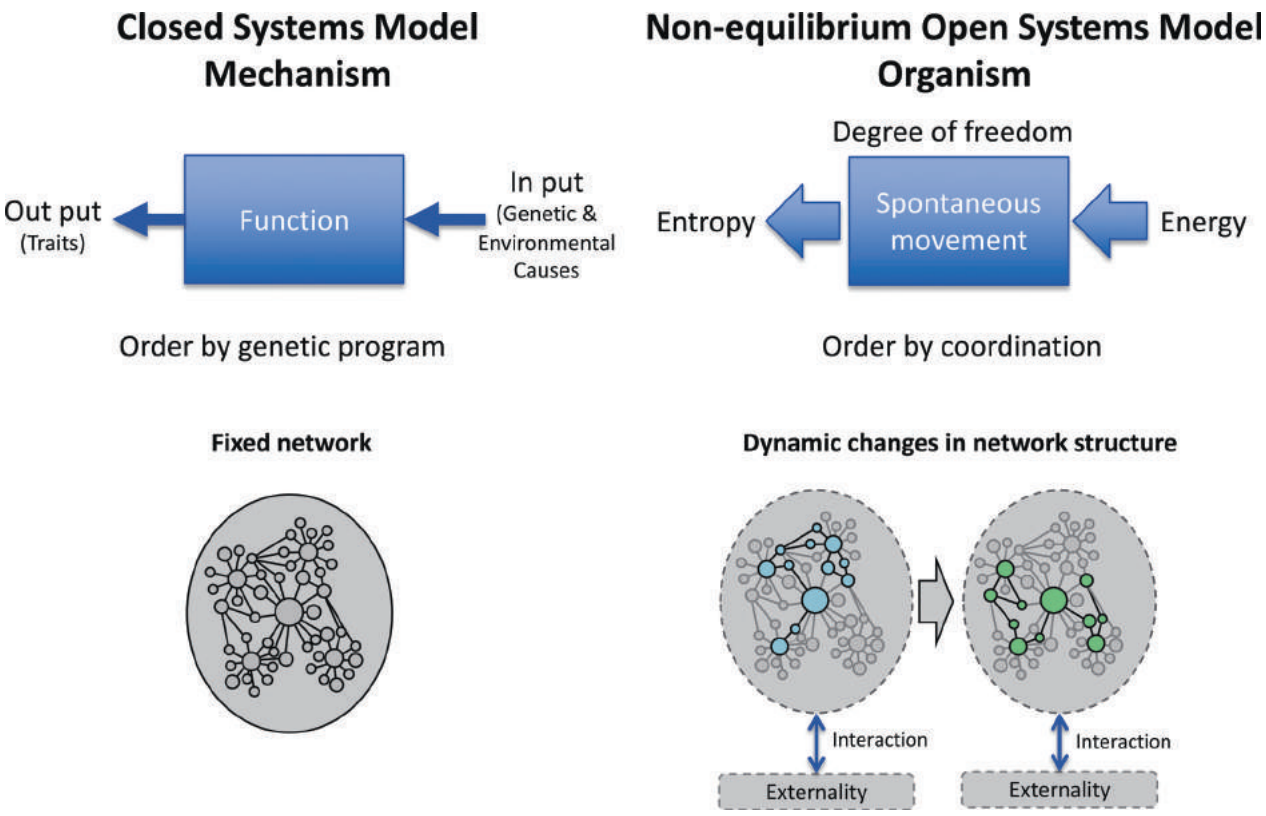

Figure 5: Synchronization as the driving force of order

For long time identification of the relation between genetic or environmental causes and organism's traits has been the goal of biology. In mechanism frame work, organism has been characterized as input output function and the relation between causes and traits are explained by linear causation. Genetic information has been assumed as program in the context of prediction. On the other hand organism is an non-equilibrium open system and generate spontaneous movement and coordination by energy entropy flow. As a result network structure dynamically change. Synchronization is the driving force of open systems to identify biological order.

Hierarchical Hidden Markov Model

The human body is a complex system, which limits measurement of all features. This restriction is likely to generate data bias. Acquired memories, such as epigenetic modifications, are usually unmeasurable. Even if actualized phenotypes are similar, the presence of latent memory will influence future state transition probability. Thus we should consider hidden states generated by unmeasurable epigenetic modifications. This means that identification of the relation between adjacent states is not sufficient. Multidimensional mapping among the states in time series is required to understand the true character of temporal development.

Developmental disorders consist of rhythm disorders, movement disorders, sensory disorders and cognitive diversity. To understand the common principle underlying developmental disorders, the concept of the reduction of degrees of freedom is applied to brain development. For this purpose, studies analyzing the role of the inhibitory-interneuron in rhythm generation and coordination at the neural network level promise to shed new light and lead to development of a new human cognition model.

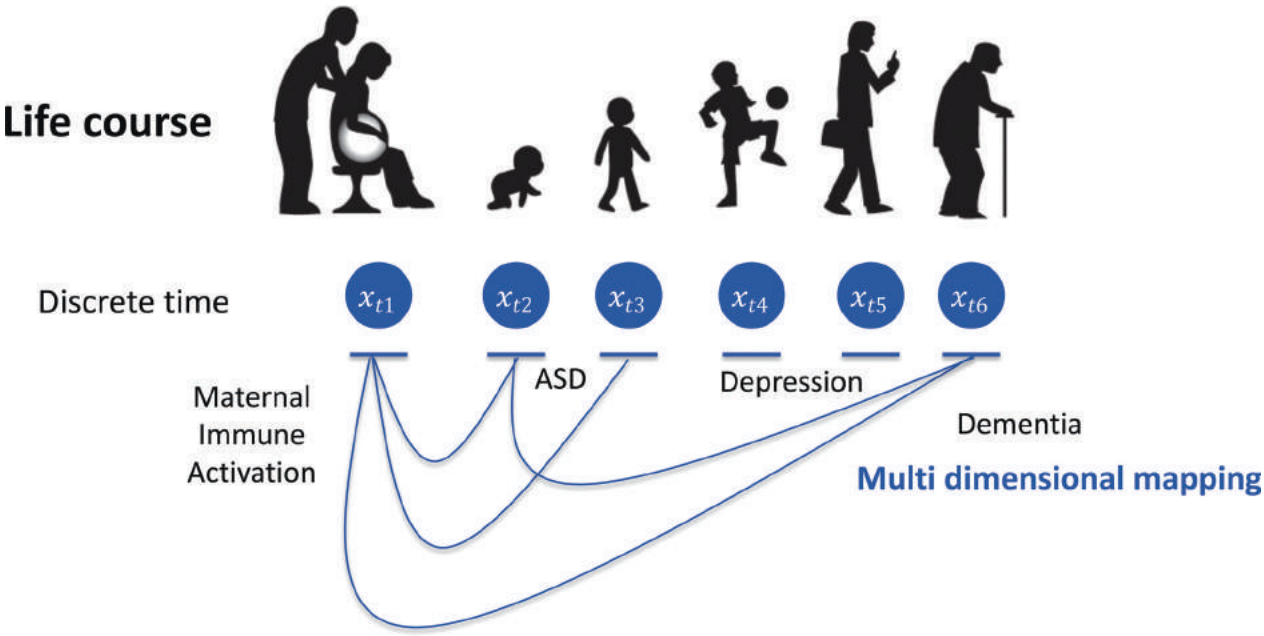

Figure 6: Hierarchical Hidden Markov Model
Simple Markov chain model based on primary mapping is not sufficient to describe the life course appropriately. Since memories of event stored in epigenetic and morphology influence the state transition probability. For example maternal immune activation is the cause of ASD and ASD is the cause of mental disorders and dementia. We have to make multi dimensional mapping. To identify general pattern in mapping, we are investigating human life-course data.

Development of Data Platform

To apply open systems science to personalized healthcare, we need a social system to measure, store, and analyze the life course data of each individual in a safe and accurate manner. For this purpose, we are developing technologies to integrate health and medical data and creating a data utilization platform. Its components include the data collection system, life course database design and life course data analytical methods.

Building a new personalized healthcare ecosystem can be achieved by combining accurate diagnosis and rule-based therapies that incorporate the latest technologies, such as deep learning and medical blockchain technology. For accurate diagnosis, deep clinical phe-

notyping using biomarkers will be required. For rule-based therapies, appropriate disease state allocation methods, including methods of feature extraction and data granularity configuration, will have to be developed. Once these methods are established, well-defined quality data will be utilized in the healthcare ecosystem instead of big data.

These considerations indicate that the structure of a data platform must be different at the search stage and the social implementation stage. RIKEN Medical Innovation Hub Promotion Program has established the search stage data platform system. Now we are collaborating with many different stakeholders to design the data platform for the social implementation stage.

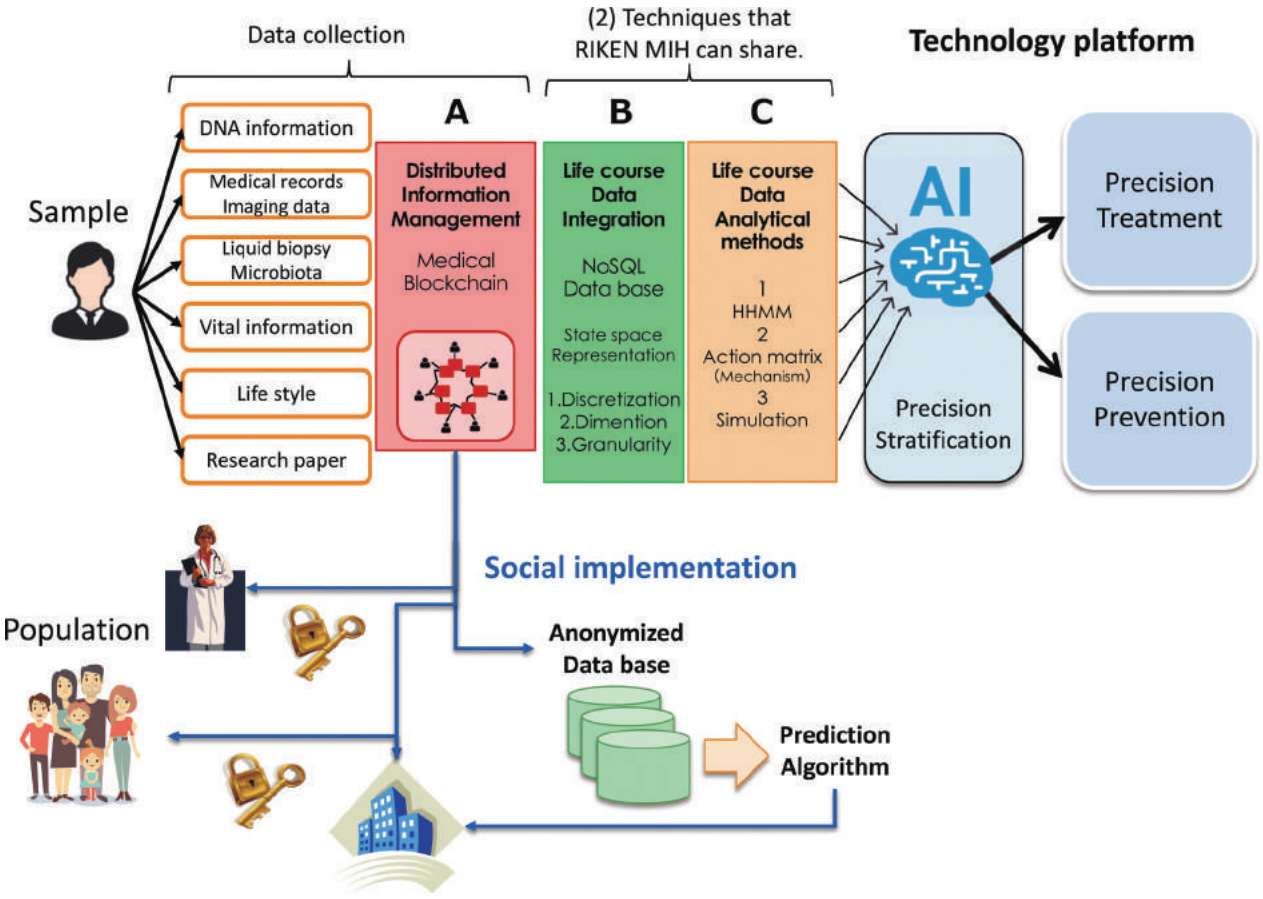

Figure 7: DATA platform
For the social implementation, MIH is developing the data utilization platform. Technology consist from data collection, life course data base design and life course data analytical methods.

A Truly Innovative Organization

Medical Sciences Innovation Hub Program (MIH)

Program Manager **Ichiro Miki** (Ph.D.)

I joined this exciting program in July 2016. Under the excellent vision of program director Dr. Koyasu and deputy director Dr. Sakurada, many talented scientists have joined this program. Our ultimate goal is to bring about personalized medicine and healthcare. Multimodal data collection and novel analysis are required to understand real world evidence. These types of studies are usually carried out in collaboration between medical doctors and data analysts. Ideally, research of this nature will be led by scientists who understand both biology and data science. Such people are rare, but the Medical Sciences Innovation Hub Program (MIH) is fortunate to have Dr. Kawakami and Dr. Seita, both of whom are medical doctors who are also very accomplished in data science. They attract highly motivated students and have a track record of groundbreaking results. Since MIH is a recently established organization, the support system is still under construction. Despite certain difficulties this creates, the members collaborate with and support each other which makes our work in facilitating greater understanding of real world evidence in medicine very enjoyable.

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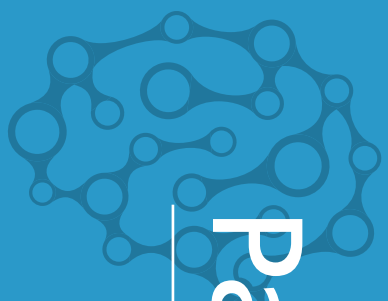


Major Project

Part 2

Chronic Inflammatory Disease Project

Disease Biology Group

Group Director (Principal Investigator) **Haruhiko Koseki** (M.D., Ph.D.)

Today's medical care has been developed based both on the accumulation of knowledge of life principles through fundamental biology research and on human clinical trials and epidemiology. However, while some diseases have seen impressive treatment results, there remain many as-yet unsolved problems in treating chronic inflammatory diseases such as atopic dermatitis (AD), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and ANCA-associated vasculitis. Most medical treatment strategies are designed for the "average patient" with a "one-size-fits-all-approach" that is successful for some patients, such as those suffering from an infectious disease or monogenic disease, but not for others–especially those having chronic inflammatory diseases. Such diseases have been regarded as multifactorial and heterogeneous, in that each genetic component of each patient, along with acquired factors (environment, lifestyle, etc.) are intertwined in a complex fashion to cause onset. These causative factors differ from individual to individual and the pathogenic mechanisms of the disease differ in each patient. We believe that such diseases should be managed with prevention and treatment strategies that take into account people's individual variations in pathogenesis. To achieve this, we conduct data-driven research in clinical and animal models and develop innovative diagnostic technology. We hope to be able to classify patients into subgroups related to pathogenesis by using clinical multimodal data and to better understand their immune status and their pathogenic mechanisms through cooperative analysis with animal models suitable for studying patient condition. Finally, we aim to pursue drug discovery for each patient subgroup and to develop personalized predictive treatment algorithms (Figure 1).

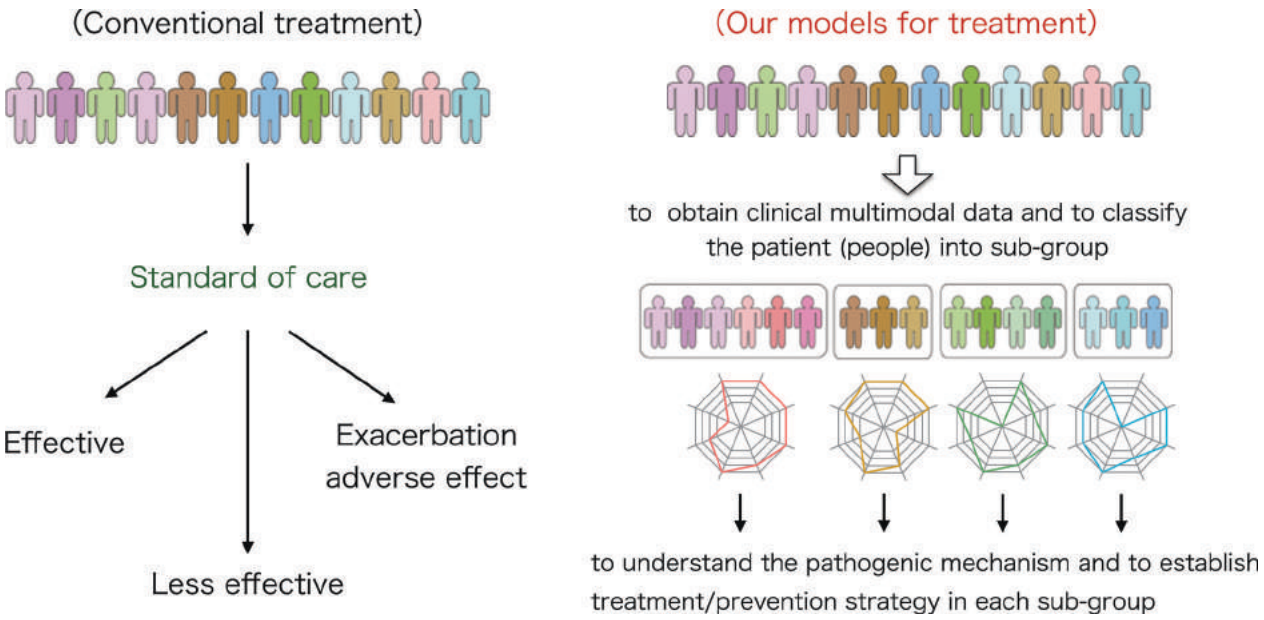


Figure 1

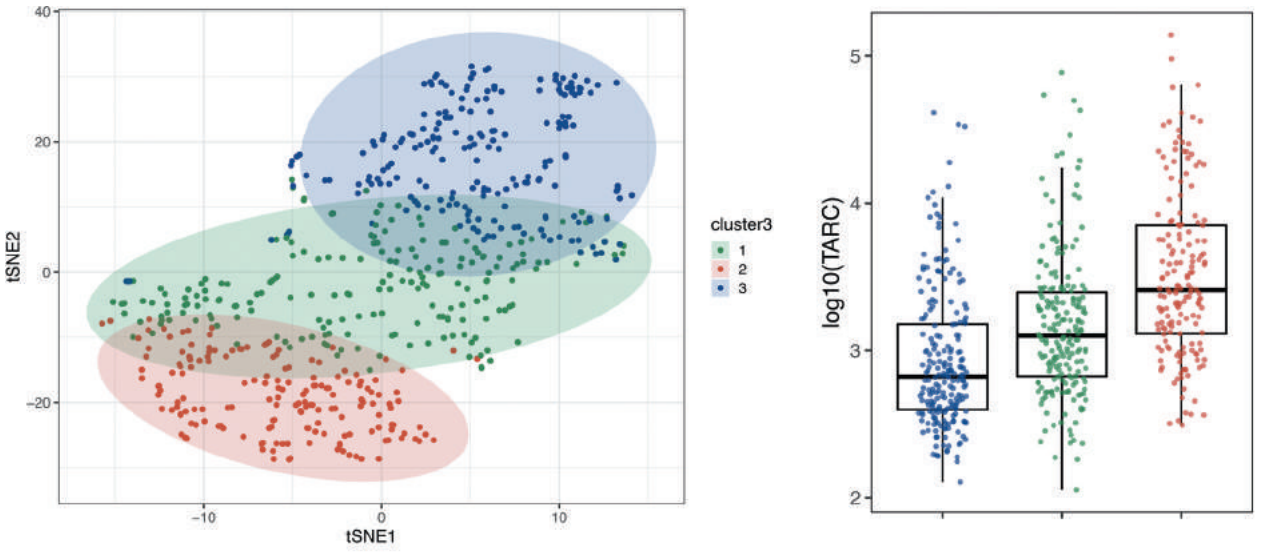
Analysis of human samples and clinical data towards patient stratification in chronic inflammatory diseases

(1) Atopic dermatitis (in collaboration with the Dermatology Department, Keio University School of Medicine)

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by intense itching and recurrent eczematous lesions. AD has a very wide spectrum of clinical phenotype and severity and is now regarded as a multifactorial, heterogeneous disease. It has been suggested that an individualized approach to each patient is crucial for AD. Yet the lack of an evaluation system for personalized disease condition has inhibited research progress so far. The purpose of this study, therefore, is to establish a method to measure and evaluate biomarkers and to build a base for achieving personalized and predictive treatment of AD.

i. Retrospective data analysis

We established a system at Keio University Hospital to perform automatic acquisition of electronic medical records information, in order to quickly and accurately analyze large amounts of medical data. By using this system, we have to this point been able to obtain and analyze a cumulative total of more than 15,000 patients' medical records. So far, various approaches to retrospective data analysis have been performed; for example, we have attempted unsupervised patient clustering based on serum allergen-specific IgE values. Data from 500 adult AD patients, which included allergen-specific IgE values of environmental and food allergens, were subjected to dimensional reduction by non-negative matrix factorization, and then clustered into three groups (Figure 2). We now plan to verify clinical or pathophysiological differences between the groups, by annotating other data such as clinical data, skin/PBMC transcriptome data and serums cytokine data.



Three clusters of AD patients, based on unsupervised clustering analysis using allergen specific IgEs. Statistically significant differences were seen in serum TARC(CCL17), regarded as one of biomarkers, between the clusters.

Figure 2

ii. Longitudinal multimodal data analysis

We obtained longitudinal (monthly over a one-year period) multimodal clinical data and samples from 30 AD patients. The acquired data includes electronic medical records, skin microbiome, cytokines/chemokines in plasma, transcriptome from PBMC, skin barrier function, skin images, etc. These data are subjected to integrated analysis, with the aim of establishing a method to make bias-free evaluations of the present disease condition. In addition, the correlation analysis of each parameter provides us with deep insights into the complex pathophysiological mechanisms of AD and suggests the minimum necessary diagnostic criteria for assessing the disease state.

iii. Exploratory biomarker evaluation study (in collaboration with AMED project))

We have been collecting skin tissue samples and blood samples from AD patients and control individuals such as healthy volunteers as well as patients with other inflammatory skin disorders. For skin tissue samples, we obtained more than 150 transcriptome datasets (mRNA-seq) plus immunohistochemical staining results from 70 individuals. The data obtained are being analyzed for identification of novel tissue-specific biomarkers in skin tissue and for development of classification algorithms in AD patients associated with the pathogenesis. The present transcriptomic analysis suggested the existence of four clusters in AD skin.

For blood samples, we obtained more than 500 plasma samples for ELISA assay and more than 500 PBMC samples for transcriptomic analysis. Analysis of these measurement data is expected to establish predictive markers for treatment response and disease monitoring markers. Once the set of minimum biomarkers useful for treatment selection is determined, we expect it to lead to predictive medicine using small-form factor blood equipment developed by our joint research company.

(2) Rheumatoid arthritis (in collaboration with the Division of Internal Medicine of Clinical Immunology, Osaka University Hospital)

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that can cause joint pain and affect a wide variety of body systems, including the skin, eyes, lungs, heart, and blood vessels. We established a clinical big data analysis system for RA and are developing a system that will apply AI technology to clinical medicine in order to deliver personalized medical care.

i. Construction of database for retrospective clinical data analysis

A database system for clinical assessments of almost all patients with RA was constructed. This database includes names of complications, onset of the disease, symptoms, joint findings, blood or urine laboratory examinations, radiographic (X-ray) findings, patient-oriented outcome (health assessment questionnaire) and treatments. About 900 patients and 15,000 clinical records were registered to the database from 2016 through Aug. 2018.

ii. Medical image diagnosis of joint X-ray

As one of the most important outcomes for treatment of RA is prevention of joint destruction, AI-guided evaluation of joint X-rays would be clinically valuable. When 1,000 X-ray images (extracted from 80 original images by clipping and enhancement) of hands of patients with RA were analyzed by machine learning, promising results for AI assessments of joint X-rays were obtained.

iii. Automatic diagnostic system using natural language processing (NLP)

Clinical charts contain huge volumes of descriptions in for assessing patients. These descriptions, written as natural language, include valuable information for diagnosis or assessing disease conditions. We are now trying to develop an AI-guided diagnostic system using natural language processing (NLP) for patients who manifest joint pain. This system enables earlier and more definite diagnosis of rheumatoid arthritis. We use the genism module for embedding words to corresponding 200–300 dimensional vectors. Thus, words and texts can be analyzed by their mathematical similarity.

iv. Measurements of serum biomarker

To search for useful biomarkers for diagnosing diseases and predicting treatment outcome, bone metabolism-related molecules, inflammatory molecules, and semaphorines are measured by ELISA or western blot by using blood samples. We detected a novel serum marker candidate, Ficolin-1. This complement-related molecule is elevated in patients with rheumatoid arthritis. Therapeutic intervention using the anti-Ficolin-1 monoclonal antibody ameliorated the disease severity in an arthritis mouse model (Katayama et al. ***Int Immunol*** [Epub ahead of print]).

(3) SLE (in collaboration with the Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo)

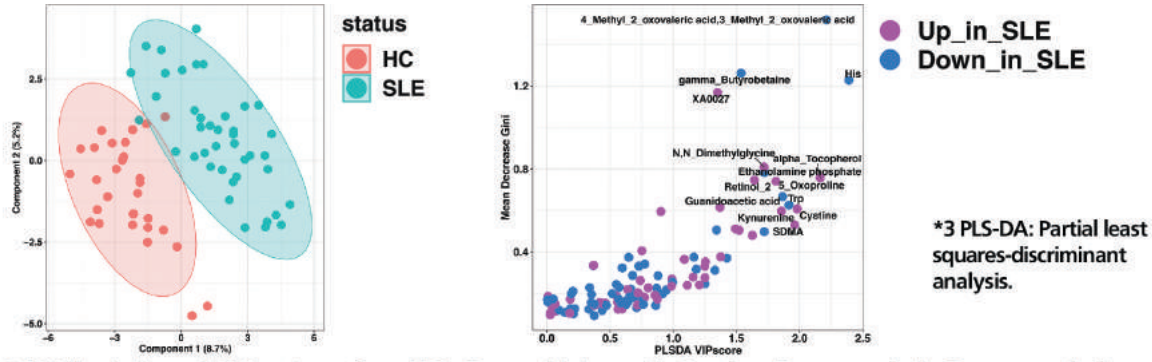
We have collected plasma samples from patients with SLE (n=41) who met the 1997 American College of Rheumatology criteria for SLE and had a history of lupus nephritis. Gender-matched healthy controls (HCs) (n=30) were recruited. For comparison, plasma from 19 rheumatoid arthritis (RA) patients were also collected. Metabolic profiles were analyzed with capillary electrophoresis (CE)- and liquid chromatography (LC)- time-of-flight mass spectrometry (TOFMS) in conjunction

with multivariate statistical analysis. Transcriptome data of SLE patients were obtained from our RNA-sequencing data for each immune cell subset (19 total subsets).

About 180 peaks were detected by CE-TOFMS, including 110 absolutely quantified metabolites, and about 160 peaks were detected by LC-TOFMS. The Random Forest (RF) machine learning algorithm revealed the importance of histidine (His) for distinguishing SLE patients from HCs. Partial least squares discriminant analysis (PLS-DA) also showed the significance of His, whose plasma level was lower in SLE patients. In addition, we divided SLE patients into two groups by using transcriptome data: type I interferon (IFN)-signature high and low. Interestingly, we found some amino acids, such as alanine (Ala) and lysine (Lys), were associated with type I IFN-signature level. In addition, inverse correlation between His level and titer of ds-DNA was detected. His level was also decreased in RA patients compared to HCs and was inversely correlated with DAS28-ESR and CRP in RA. These indicated that lower His level might show some pathophysiological significance in SLE independent of inflammation or type I IFN signal.

Weighted gene co-expression network analysis (WGCNA) revealed that some B cell modules showed negative correlation with His level and positive correlation with disease (SLE). In addition, mitochondria-related genes were significantly enriched in that module. We also investigated the correlations between clinical parameters and metabolites and found some metabolites were correlated with SLEDAI, ANA, and low lymphocytes. The Receiver Operating Characteristic (ROC) curve of combinations of certain amino acids could allow more precise definition of SLE patients.

Plasma metabolic changes in autoimmune diseases might not only reflect the chronic activated immune-status but also be associated with pathogenesis itself. His may be an important factor for SLE pathogenesis, especially in B cells, independently of IFN signals. SLC15A4, a transporter of His on lysosome, is an SLE GWAS SNP that has been reported to play an important role in IFN production in B cells through regulation of TLR7/9 activation. Low plasma level of His could be a useful marker of SLE activity, and maintenance of His homeostasis could become a novel treatment target for SLE. Moreover, there may be a specific amino acids combination that could be a useful marker for diagnosing SLE or distinguishing active SLE patients. More sample collection is required to improve our analytic robustness.



PLS-DA*3 discriminated SLE patients from HCs. By combining with Random Forest analysis, Some metabolites, especially His (histidine), seemed to be important to distinguish SLE.

(4) ANCA-associated vasculitis (in collaboration with Osaka University)

Myeloperoxidase-specific anti-neutrophil cytoplasmic antibodies (MPO-ANCA) are associated with small vessel necrotizing vasculitis and granulomatosis with polyangiitis. In vitro and in vivo studies provide compelling evidence that ANCA play a critical role in the pathogenesis of ANCA-associated vasculitis (AAV). However, it has been reported that polyclonal MPO-ANCA titers do not always correlate well with disease activity, suggesting the co-existence of pathogenic or non-pathogenic MPO-ANCA in AAV patients. We reasoned that the existence of pathogenic B cell or antibody repertoires could be an accurate, reliable biomarker to predict the onset or relapse of AAV.

To identify and characterize MPO-specific B cells in AAV patients, we set up experimental systems to isolate MPO-specific B cells and evaluate the pathogenicity of their B cell receptors (BCRs). By generating recombinant human MPO (hMPO), we were able to detect

hMPO-binding B cells in the spleens of hMPO-immunized mice. Next, we isolated these B cells at the single-cell level, cloned their BCRs, and confirmed that these BCRs indeed bind to hMPO. We plan to isolate MPO-specific B cells from the peripheral blood of AAV patients, clone the BCRs, and analyze their sequences to predict pathogenic repertoires. We will also test the pathogenicity of the predicted pathogenic BCRs in vitro and in vivo.

Analysis of disease models towards understanding underlying mechanisms of inflammatory diseases

In order to clarify causal relationships under specific conditions and to solve clinical problems, analyzing clinical data alone is insufficient; it is indispensable to conduct basic experiments using animal models. A number of animal model studies in AD have been performed to investigate the genetic, physiological, microbial and immune involvement in development of the disease. However, clinical advances and understanding of the exact mechanisms for the progression of AD have remained limited. This is mainly due to the high degree of complexity and diversity of the etiology and pathogenic process underlying AD.

To tackle this challenging complexity, we put together a center-wide project team and conducted a high-resolution integrated analysis, combining experimental and computational approaches, of multimodal data from humans as well as several dermatitis model mice. Our primary goal in this project, and hence the initial milestone, is to investigate the molecular interaction network leading to the onset of AD, its underlying dynamics, and how these play a role in the progression of skin dysfunction in AD. The second milestone is to identify important biomarkers, potential drug targets, and to understand key disease mechanisms in AD. The third milestone will be to develop a system-oriented drug design pipeline for effective treatment of AD.

Model mice for atopic dermatitis (in collaboration with the Skin Homeostasis and Cytokine Regulation team of RIKEN IMS)

In order to describe the complex and heterogeneous pathology of AD, we use several mouse models that have different pathophysiology or manifestations of AD-like skin inflammation. Spade (stepwise, progressive atopic dermatitis) mice, which spontaneously develop pruritic dermatitis, have been found to have a point mutation resulting in hyperactivation of the Jak1 signal transduction molecule as a causative mutation (Yasuda et al. ***J Clin Invest*** 2016). Tmem79 KO is a chronic dermatitis mouse model characterized by bimodal dermatitis. Tmem79 is expressed as a transmembrane protein in cytosol of SG1 (stratum granulosum) cells, and causes altered lamellar granules secretory system and impaired stratum corneum barrier. Mice with keratinocyte specific deletion of Socs3 (Socs3 cKO) exhibit severe skin inflammation and indicate that the IL-6-STAT3-SOCS3 axis has a role in development of dermatitis (Uto-Konomi, Kubo et al. ***PLoS One***, 2012). These mice commonly exhibit phenotypes observed in human AD, such as pruritic dermatitis, impaired skin barrier function, and elevated serum IgE (Figure 3a), but transcriptomic analysis of skin tissues interestingly suggests that the key inflammatory pathway is different between different model mice. Therefore, we are investigating the molecular and cellular network in these mice and approaching the complexity and diversity of human AD by comparing our findings with human data (Figure 3b). In particular, we are attempting to understand the spatio-temporal dynamics of inflammatory reaction and have performed a time-course study of these model mice. Likewise, we are collecting human AD patient samples including lesional/non-lesional or acute/chronic skin on an ongoing basis. A systemic approach to integrated analysis of these data is expected to offer us deep insights into homeostatic and inflammatory control mechanisms.

Exploration of a novel therapeutic target for atopic dermatitis

Recently there has been growing emphasis on the importance of novel biomarkers for accomplishing a more effective and personalized cure for atopic dermatitis (AD). We have already collected a series of transcriptome datasets from AD model mice to highlight the critical regulators for its pathogenesis. Our recent bioinformatics analysis using these datasets revealed multiple effector candidates which contribute to triggering and/or exacerbating the AD pathology. Among them, we identified a candidate factor (gene X) as a bi-directional effector involved both in inflammation and itch sensing. In human samples, striking up-regulation of gene X has been detected exclusively in inflammatory lesions of AD. To confirm its roles, we

are now performing: 1) genetic perturbation of X in the mouse model; 2) biochemical and behavioral assays in the mouse model; and 3) morphological analysis of both mouse and human tissue samples. In addition, we are also exploring the chemical compounds that inhibit X's activity to develop novel molecular-targeted drugs. We believe that the combination of big data-oriented and specific target-oriented approaches should synergistically accelerate innovation in establishing superior therapeutic strategies for AD.

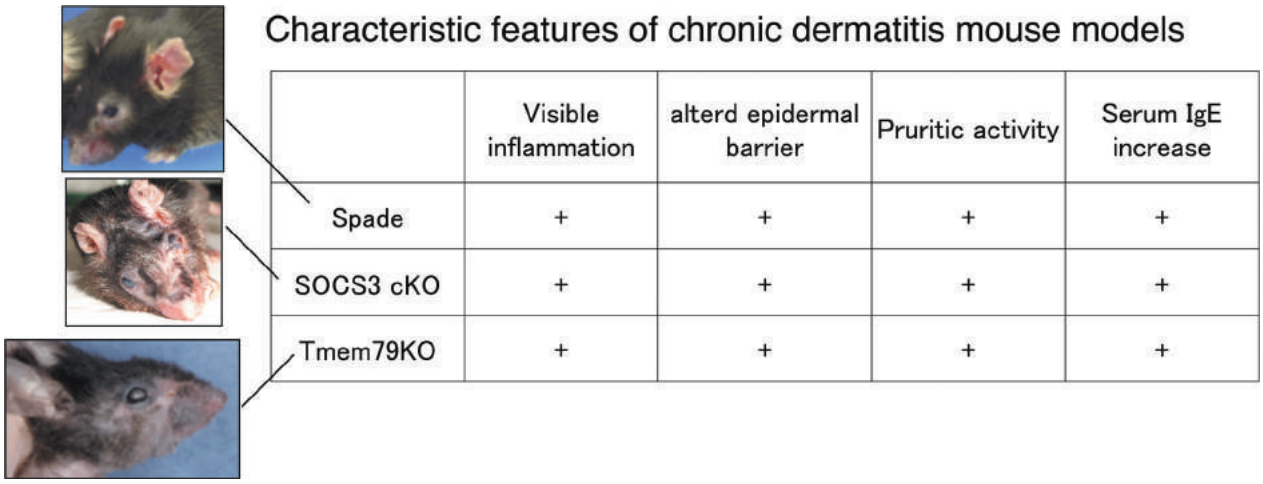


Figure 3a

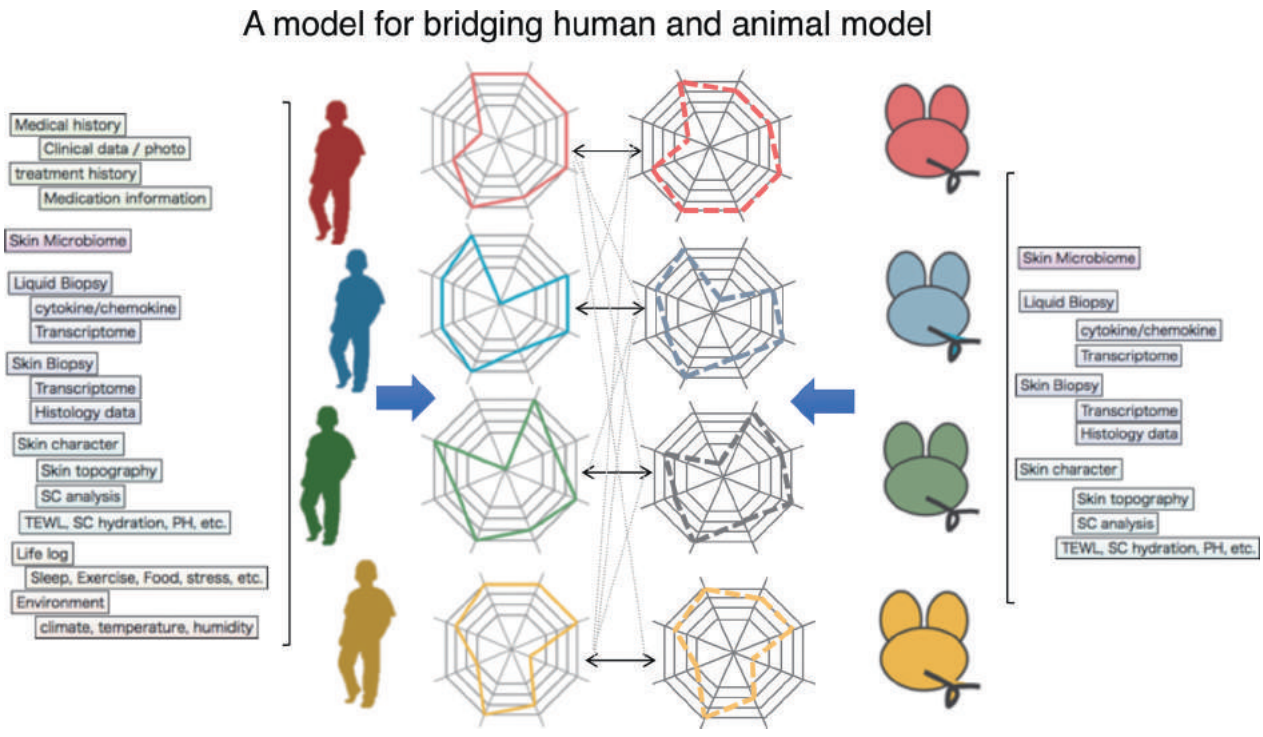


Figure 3b

Evaluation of anti-tumor immune response

Cancer Immunology Data Multi-level Integration Unit

Unit Leader (Principal Investigator) **Kazuhiro Kakimi** (M.D., Ph.D.)

Immunogram

Antibodies targeting PD-1 have been approved for treatment of several malignancies, but in all cases only a minority of patients experiences clinical benefit. It would be extremely useful to be able to predict responsiveness to PD-1 blockade, and several means of doing so are currently under intense investigation. Such methods include assessing the pre-therapy presence of CD8+ tumor-infiltrating lymphocytes (TIL) in the tumor, whether the tumor has a high mutational burden, whether tumor cells express PD-L1 and whether an IFN-γ gene signature is present. Nonetheless, some patients fail to respond despite having these favorable predictive tumor characteristics. A reason for this may be that multiple independent immunosuppressive regulatory systems are active in the tumor microenvironment. Integrating these with other predictive factors calls for comprehensive profiling of clusters of relevant parameters. Moreover, anticancer immunity is a dynamic process which can be annotated as the "Cancer-Immunity Cycle"; different steps in the cycle by which tumors escape immunosurveillance and combinations of those steps are likely to be different patient by patient (Chen et al. ***Immunity*** 39, 1–10 (2013)).

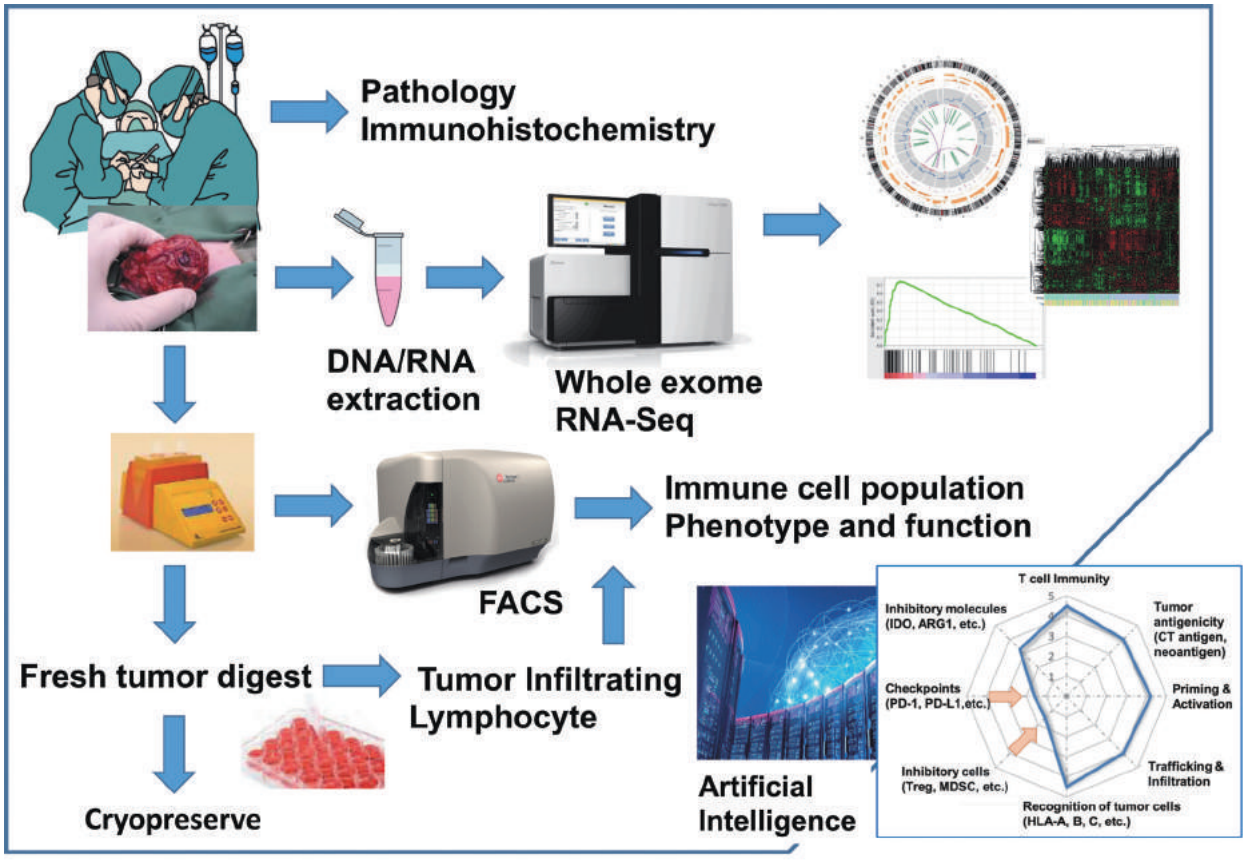
Therefore, a detailed understanding of cancer-immunity interactions is essential for developing and providing effective cancer immunotherapy, which will need to be individualized for each patient (Blank et al. ***Science*** 352, 658–60 (2016)). Recently, we have developed an "Immunogram for the Cancer-Immunity Cycle" as an integrated biomarker that provides us with a clearer view of the cancer-immunity interaction in each patient (Karasaki et al. ***Journal of thoracic oncology*** 12, 791–803 (2017). We constructed this immunogram using next-generation sequencing data to visualize the status of potential antitumor immune responses within the tumor. When this approach is utilized, the conditions of the tumor microenvironment in each patient can be appreciated and any compromised steps of the cancer-immunity cycle can be easily identified.

Immunotherapy is rapidly moving towards a situation in which clinicians, diagnostic laboratories and pharmaceutical companies will be required to input multimodal biomarkers and output an array of treatment options, one of which is likely to be a combination immunotherapy. Although the 8-component immunogram we described in JTO 2017 depicts the cancer-immunity interactions in each patient to some extent, there are still many other factors related to T-cell and other dysfunctionalities, such as abnormal tumor metabolism, T-cell extrinsic components of the tumor immune microenvironment, and so on, which could improve its predictive power if incorporated.

Currently, we are extending our research to include these and other factors and establish a Next-Generation Immunogram for Cancer-Immunity Interactions. To understand the factors responsible for responsiveness or resistance to immunotherapy, it will not be the case that a single biomarker will be maximally informative; rather, a comprehensive understanding of cancer-immunity interactions will be required (Hoshikawa M, et al. ***BBRC*** 495, 2058–2065 (2018), Imai Y, et al. ***Oncol Lett*** 15, 6457–6468 (2018), Karasaki T, et al. ***J Thorac Dis*** 10, 4741–4750 (2018)). Therefore, we will perform integrative immunomonitoring for cancer patients which will include the identification of driver mutations and other somatic mutations predicted to give rise to neoantigens. This will be accomplished by integrating exome-Seq and RNA-Seq data, together with evaluating the tumor microenvironment including metabolic status by means of gene set enrichment analysis (GSEA) and pathway analysis, examining the phenotypes and functions of TILs using flow cytometry, and determining the specificities or reactivities of TILs to tumor antigens and finally antibodies using an array of cancer-germline antigens.

Taking advantage of artificial intelligence, we will reduce the dimensionality of these large-scale

datasets by integrating them into the "Immunogram for Cancer-Immunity Interactions" to evaluate the immunological status of each patient and elucidate factors associating with responsiveness or resistance to immunotherapy. To this end, collecting comprehensive immunological information is crucial. Our goal is to determine which immunological parameters are incorporated into axes of our novel immunogram. Then, we will validate our Next-Generation Immunogram for Cancer-Immunity Interactions as the best tool to understand the tumor immune microenvironment in future studies. It can be continuously improved by incorporating additional related factors, such as general host immune competence by germline genetic factors, microbiome, systemic immunosuppression by pre-treatment, and so on.



Immunogram for Cancer-Immunity Interactions

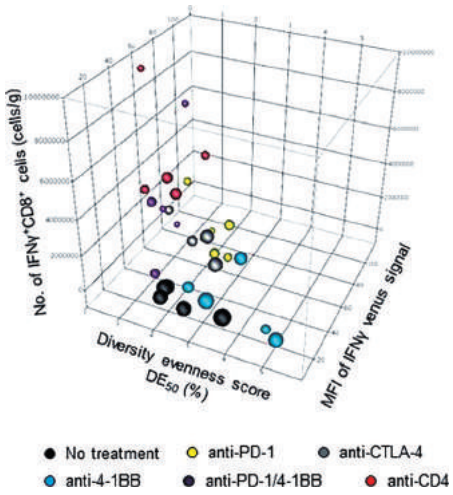
Neoantigens as biomarker of anti-tumor immunity

Cancer cells have genetic alterations which can provide the immune system with targets by which to recognize and eradicate the tumor. Mutated proteins expressed exclusively in cancer cells and recognizable by the immune system are known as neoantigens. The development of next-generation sequencing technology has made it possible to determine the genetic landscape of human cancer and has facilitated the utilization of genomic information to identify such candidate neoantigens in individual cancers. Recently, the tumor mutational burden (TMB) or neoantigen load has come under consideration as a prognostic biomarker in checkpoint blockade therapies. Patients with high mutation rates, such as melanoma, non-small cell lung cancer and MMR-deficient tumors are expected to respond better to checkpoint blockade therapy. Using whole exome and RNA sequencing, we analyzed 97 clear cell renal cell carcinoma patients and demonstrated that neoantigen load with HLA expression in the tumor was a predictive biomarker of overall survival in these patients (Matsushita, et al. ***Cancer Immunol Res*** 4, 463–71(2016)). When we defined the number of neoantigens per missense mutation as "neoantigen frequency", neoantigen frequency in stage I and II ovarian clear cell carcinoma

is an independent prognostic factor for clinical outcome under standard therapy (Matsushita, et al. ***Oncoimmunology*** 6, e1338996 (2017). It is worthwhile to investigate whether the number of neoantigens or neoantigen frequency is informative as a possible biomarker in other types of cancer.

TCR repertoire analysis of tumor infiltrating lymphocytes under immunotherapy

We performed integrated analysis of the intratumoral immune responses induced by various immunotherapies, including anti-PD-1, anti-CTLA-4, anti-4-1BB, anti-CD4 or a combination of anti-PD-1 and 4-1BB antibodies in a B16-tumor bearing mouse model (Hosoi et al. ***Sci Rep*** 18, 1058 (2018)). Activation and expansion of tumor-specific T cells were observed in the tumor to a greater or lesser extent. The absolute number of CD8+ T cells in the tumor or their collective effector function is necessary, but not in itself sufficient for tumor growth suppression. The diversity of the TCR repertoire, reflecting clonal composition, is the crucial factor responsible for tumor growth suppression. We evaluated the diversity of TILs by decomposing them into richness (the number of unique elements in a population) and evenness (the distribution of the frequencies of those elements). The richness was increased by all immunotherapies, irrespective of their anti-tumor activity, whereas evenness of TILs was reduced by the expansion of selected clones in the tumor under effective treatment. We found that the evenness of TCR repertoire diversity in the tumor were found to be closely associated with whether the immunotherapy was successful or not.



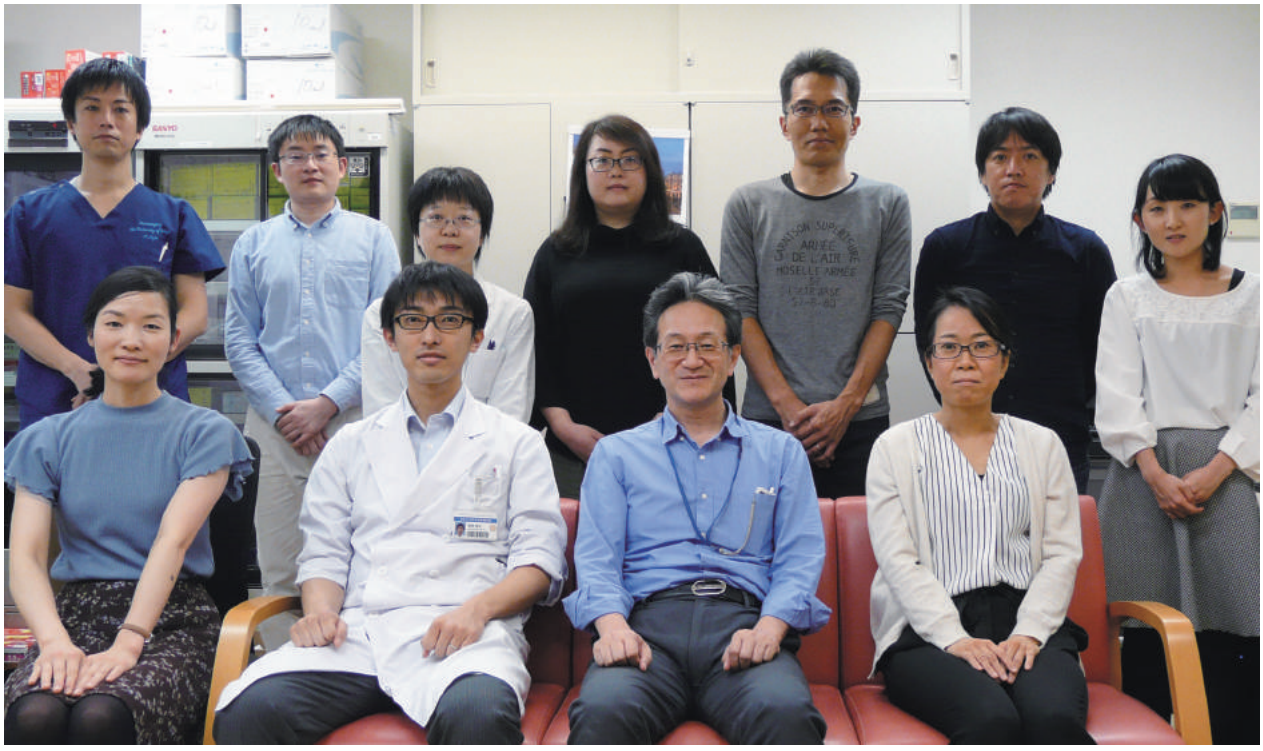
Metabolism does matter in anti-tumor T-cell immunology

We revealed quantitative and qualitative differences in vaccine-primed CD8+ T cells from mice that received either short peptide or dendritic cell (DC) vaccines (Nagaoka K, et al. ***Oncoimmunology*** 7, e1395124 (2017)). Peptide vaccine induced effector memory cells with a partially dysfunctional phenotype and limited proliferative capacity that resulted in less efficient tumor growth suppression. DC vaccine induced active effector and central memory cells with potent proliferative capacity that resulted in the suppression of tumor growth. As expected, these vaccine-primed cells were metabolically distinct from naive cells. They became activated and shifted their metabolism to glycolysis. Importantly, there were notable differences in metabolism between T cells induced by DC vaccine and peptide vaccine. T cells primed by DC vaccine contained subpopulations that shifted metabolic pathways away from glycolysis to mitochondrial oxidative phosphorylation, while such subpopulations were not detected in the peptide vaccine group. We also demonstrated that DC vaccine is superior to peptide vaccine as the strategy of choice for translating combined cancer vaccine and checkpoint blockade therapies.

Translational samples and clinical data collection scheme

Tumor and blood are harvested at the time of surgery and biopsy. The samples obtained at the University of Tokyo Hospital (UTH) are delivered to our laboratory within 30 minutes. Samples from The Cancer Institute Hospital of JFCR, National Center for Global Health and Medicine, Teikyo University Hospital and Tokyo Metropolitan Bokutoh Hospital are transferred to our laboratory in UTH within two hours by hand-carry. Tumors are first fragmented into multiple 5-mm cubes and immersed in RNAlater immediately after resection or biopsy and delivered to our laboratory. There they are cryopreserved, to provide DNA/RNA that will be used for NGS analysis. Other fragments are kept on ice and delivered to our laboratory, where they are enzymatically digested to prepare single cell suspensions that are analyzed by flow cytometry or cryopreserved for the future analysis. The rest of the fragments are put into culture to establish tumor

cell lines and expand TILs. PBMCs and plasma are immediately isolated and cryopreserved in our laboratory. Clinical and pathological data are also provided and collated in our laboratory, under measures that securely protect patients' personal information. Then, the data are transferred to RIKEN–strictly adhering to procedures (including anonymization) for the protection of personal information–for further analysis.



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A new concept for deep clinical phenotyping of autism spectrum disorders

Developmental Disorder Data Multi-level Integration Unit

Unit Leader (Principal Investigator) **Yukuo Konishi** (M.D., Ph.D.)

1. A history of developmental disorders

Until around the 1950s, learning disorders (LD), Autism Spectrum Disorders (ASD) and Minimal Brain Dysfunctions (MBD) were thought of as different diseases caused by different mechanisms. In the 1980s, Attention-deficit Hyperactivity Disorder (ADHD) and Developmental Coordination Disorder were split off from MBD based on phenotype differences. Among developmental disorders, the most muddled concept is ASD. In his landmark 1943 paper, Leo Kanner took the term "autism"–which was previously attributed to the inward, introspective symptoms typical in adult schizophrenia patients–and labeled the children in his study as having "infantile autism" (1). In 1944, Hans Asperger identified a pattern of behavior and abilities that included "a lack of empathy, little ability to form friendships, one-sided conversations, intense absorption in a special interest, and clumsy movements" (2). Developmental disorders have diverged as a result of being diagnosed by phenotypes.

On the other hand, it has been pointed out that ASD, ADHD, LD and Developmental Coordination Disorders (DCD) are associated with each other in the same child, indicating that these disorders have common causes.

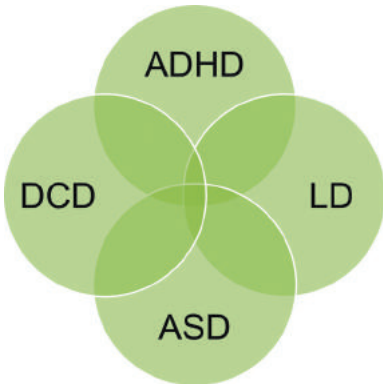

Figure 1: Over lapping different phenotype in a same children
ASD, ADHD, LD and DCD are associate each others in a same children

2. Identification of a common mechanism in ASD

To identify a common mechanism of ASD, we focused on the somatic symptoms of ASD and identified rhythm disorders in several vital functions as follows.

1. Seventy percent of sleep disorders in children are associated with ASD;
2. ASD children have small heartbeat fluctuations (3);
3. One quarter of ASD children with sleep disorders also have rhythm disorder insulin secretion and impaired glucose tolerance;
4. Orthostatic disorder and circadian rhythm disorders are observed in most sleep disorder affected children;
5. Half of ASD children have sleep disorder caused by sensory sensitivity and obtundation;
6. Mothers of these ASD children are likely to have stayed up late during pregnancy.

It is well known that ASD children have difficulty in coordinating behavior and communication with others. These results indicate that rhythm disorders are observed on multiple layers of the human organism (4). In addition, these results show that developmental disorder, motor disorder, sleep disorder, autonomic disbalance, school absenteeism and noncommunicable diseases are mutually related.

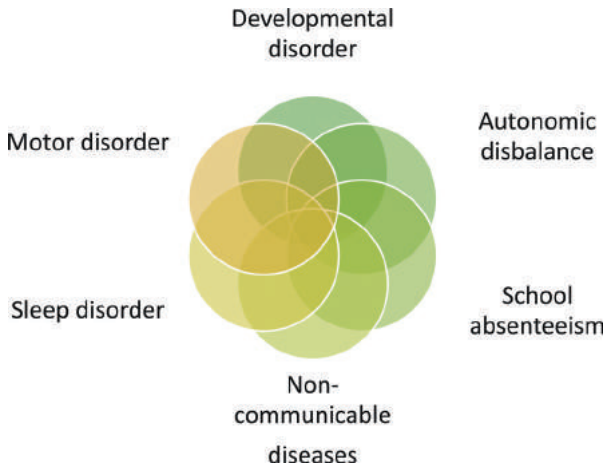

Figure 2: Over lapping different disorders in a same children
Developmental disorder, motor disorder, sleep disorder, autonomic disbalance, school absenteeism and noncommunicable diseases are mutually related.

3. Another key finding to understand the common mechanism of ASD

Another important fact is that the number of ASD and developmental disorder children in 2010 represents a sixfold increase from the early 1990s (5). It has been speculated that two thirds of this increase is caused by environmental factors.

A principal environmental factor after birth is the problem of sleeping habits. A survey of our group in Kizugawa, Kyoto indicated that 30% of children aged 1–6 go to sleep after 10 PM. Our studies using 7,000 kindergarten children indicate that problematic behavior is strongly associated with shortage of sleep and irregular hours.

In addition, lack of sufficient sun exposure cause by overanxiety about the side effects of UV significantly reduces the production of Vitamin D in mother and children (6). Lack of sufficient Vitamin D production in the mother will reduce Vitamin D intake of a breast-fed baby. Vitamin D deficiency (VDD) is likely to induce brain inflammation in children.

VDD during pregnancy will induce sensitivity to maternal immune activation (MIA), which is the principal environmental factor of ASD and developmental disorders (7). It has been shown that IL-17 is transmitted through the placenta and induces inflammation in the fetus (8). When MIA and VDD are associated, brain inflammation occurs in the fetal brain, affecting brain development. In animal models, it has been shown that Vitamin D treatment during pregnancy prevents autism-related phenotypes (9).

Based on these previous findings, we are now analyzing the amount of Vitamin D and inflammatory cytokines in mothers and children.

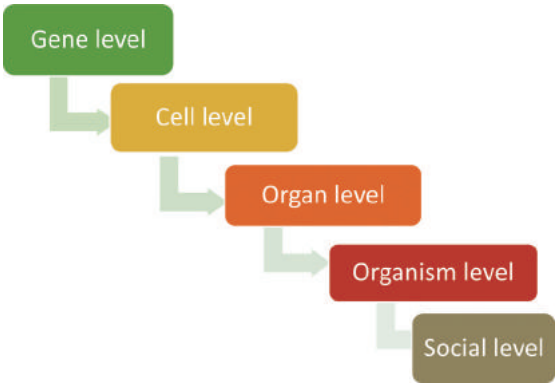

Figure 3: Rhythm disorders are observed in multilayers of human organism
Common genetic and environmental causes in developmental disorders will be able to identify in the view that rhythm disorders in different layers of human organism will reciprocally contribute to developmental disorders

4. Toward predictive, preventive and personalized medicine for developmental disorders

Early detection of developmental disorders will significantly improve the prevention and treatment of developmental disorders. By combining fetal cardiographs, fetal full body movement and eye movement observations, genetic and epigenetic analysis of the placenta, and postnatal sleep pattern measurements, we are developing a new diagnostic system that can detect ASD and developmental disorders at an early stage. For this purpose, we are now studying infants that experienced intrauterine growth retardation.

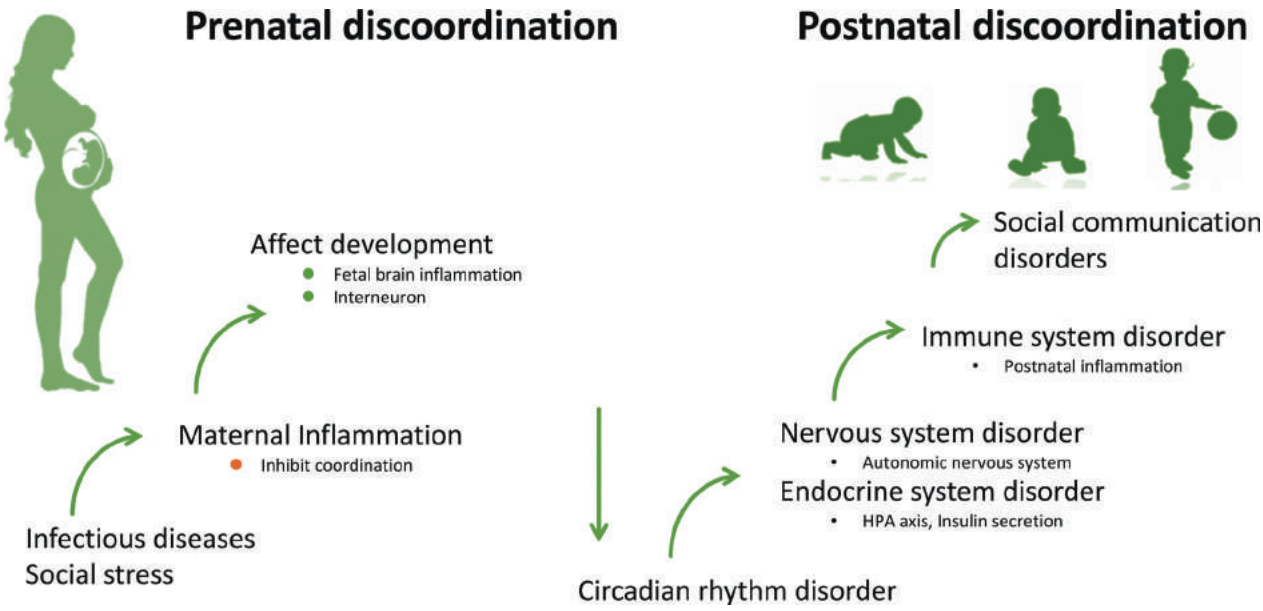

Figure 4: Discoordination model of ASD and developmental disorders
Discoordination of development during pregnancy is the primary cause of developmental disorders and ASD and induce circadian rhythm disorder, nervous, endocrine and immune system discoordination and social communication disorders.

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Data-driven mathematical approaches to reveal dynamic and heterogeneous features of diseases

Healthcare and Medical Data Driven AI based Predictive Reasoning Development Unit

Unit Leader (Principal Investigator) **Eiryo Kawakami** (M.D., Ph.D.)

We conduct research with the goal of establishing a mathematical foundation for understanding and predicting disease and life phenomena based on multimodal clinical data. The life system maintains dynamic homeostasis while always changing its state. It is the theoretical foundation for precision medicine to clarify the rules that hide in the state transition process of the life system. Dynamics and heterogeneity of diseases have rarely been dealt with in traditional medical research, and we have understood diseases as an aggregate of snapshots by using various molecular biological methods. Recently, with the spread of next generation sequencing (NGS) and mass spectrometry, tens of thousands of biomolecules reflecting the patient's condition can be measured relatively easily in clinical samples. Based on these clinical multimodal measurements, attempts to predict disease onset and progression have been made (Zeevi et al. ***Cell*** 2015). However, these studies target diseases whose marker molecules (e.g. blood glucose level) are well known and are based on extensive measurements obtained at planned time points. In many diseases, markers reflecting the disease state are not identified, and sampling often becomes sporadic and irregular due to clinical and experimental constraints. So far, even considering the global picture, mathematical frameworks that deal with such "real world" clinical data have not yet been deployed. We flexibly apply and develop various mathematical approaches suitable for healthcare and medical data based on machine learning, network analysis, and statistics, with the aim of understanding, predicting, and controlling disease and life phenomena in order to progress towards making precision medicine a reality.

We have led several cohort studies in collaboration with medical institutes including Keio University, the Jikei University School of Medicine, Osaka University, Yokohama City University and The University of Tokyo. In collaboration with the Department of Obstetrics and Gynecology of the Jikei University School of Medicine, we developed an ovarian cancer-specific predictive framework for clinical stage, histotype, residual tumor burden, and prognosis using machine learning methods based on multiple biomarkers. We selected 334 patients with EOC and 101 patients with benign ovarian tumors and randomly assigned them to "training" and "test" cohorts for subsequent analysis. Seven supervised machine learning classifiers–Gradient Boosting Machine (GBM), Support Vector Machine (SVM), Random Forest (RF), Conditional Random Forest (CRF), Naïve Bayes (NB), Neural Network (NN), and Elastic Net (EN)–were used to derive diagnostic and prognostic information from 32 parameters commonly available from pretreatment peripheral blood tests and age.

Supervised machine learning techniques were superior to conventional regression-based analyses in predicting multiple clinical parameters pertaining to EOC. Ensemble methods that combine weak decision trees such as GBM, RF, and CRF showed the best performance in EOC prediction. The values for the highest accuracy and area under the receiver operating characteristic curve (AUC) for segregating EOC from benign ovarian tumors with RF were 92.4% and 0.968, respectively. The highest accuracy and AUC for predicting clinical stage with RF were 69.0% and 0.760, respectively. Similarly, serous and mucinous histotypes of EOC could be preoperatively predicted with RF (75.8% accuracy, AUC: 0.785 for serous; 96.0% accuracy, AUC: 0.728 for mucinous). Additionally, an ordinal RF classifier could distinguish complete resection (0 cm) from others with 64.9% accuracy and AUC: 0.697. We have developed a dimension reduction method based on machine learning, which performs dimension compression and unsupervised clustering of high dimensional data by applying a distance measure using the Random Forest method (RF dist, Shi and Horvath 2006).

Many biomedical variables are not normally distributed. There are binary variables such as presence/absence of symptoms and categorical variables such

as histological types of cancer that make it difficult to properly capture the characteristics of data with distances on the assumption of normality and linearity, as in PCA. A method called RF dist calculates the similarity among samples from the frequency of classification of samples into the same leaf in a large (1,000 to 10,000) decision tree constituted by a random forest method. Using RF dist, robust clustering becomes possible regardless of the distribution of variables. In fact, applying RF dist to 32 items of preoperative blood test data yields a stratification of patients who had been uniformly diagnosed with early stage cancer into a "close-to-benign-tumor" type and "close-to-late-stage-cancer" type (Figure 1A). Early stage cancers of the close-to-late-stage tumor type showed a significantly higher risk of recurrence than those of the close-to-benign type (Figure 1B). Therefore, this study was able not only to construct highly accurate predictors of ovarian tumor characteristics, but also to propose an application of AI to revealing difficult-to-recognize clusters of patients from complex combinations of multiple biomarkers. The study indicates the possibility of selecting personalized treatment options by means of pretreatment stratification of patients with EOC using machine learning-based predictive algorithms.

In a collaborative research project with the Dermatology Department of Keio University Hospital, we developed a predictive algorithm to estimate skin barrier function based on skin surface images. Since the identification of Filaggrin as a causative gene of atopic dermatitis, dermatologists have considered skin barrier dysfunction as an important factor of dermatitis. A widely used measurement for estimating the barrier function of the stratum corneum is transepidermal water loss (TEWL). TEWL is the amount of water that evaporates through the stratum corneum to the air; high TEWL suggests skin barrier dysfunction. Since TEWL is sensitive to environmental factors such as humidity and temperature, examinees are required to wait under standardized conditions for about a half hour before measurement. Also, a high-sensitivity humidity sensor is needed to measure TEWL. For these reasons, direct measurement of TEWL is not an easy way to evaluate skin barrier function.

Instead, we tried extracting topological information from each image to use as a descriptor vector, and then applied machine learning techniques on these vectors to generate individualized predictions of TEWL. Topological Data Analysis (TDA) is a collection of methods for finding topological structures in data. Recent advances in computational technology enable us to easily detect topological features of data, such as connected components and loops, making TDA an effective tool to analyze various data in many fields, including material science (Hiraoka et al. 2016), engineering (de Silva and Ghrist 2007), and biology (Chan et al. 2013). Persistent homology is an extension of homology theory which captures not only how many loops, connected components, and cavities there are, but also how robust and how large they are. We exploited this advantage of persistent homology to evaluate uniformity and fineness of skin texture patterns.

Linear regression using features of skin images as explanatory variables showed a remarkable relationship between TEWL and the scale of skin texture. This result indicates that skins with fine and regular texture exercise a strong barrier function. We also performed multiple regression and RF regression and predicted TEWL with good accuracy. The coefficients of determination are 0.51 and 0.63 for multiple regression and RF, respectively. This result shows that feature extraction from skin images using topology is useful for estimation of physiological skin condition.

In addition, as described on page 31, we also introduced an energy landscape model into medical data analysis, which enables us to generate discrete descriptions of a patient's state and its transitions. Through these state-of-art mathematical approaches, we were able to extract for each patient features composed of multiple variables that conventional statistical approaches would find difficult to recognize. These features could serve as a fundamental basis for stratifying patients and making individual predictions. Another advantage of our approach is that it does not require huge amounts of data nor heavy computational costs. In contrast, deep learning, although it has been shown to be very effective in the field of medical image analysis (Greenspan et al. 2016), requires vast numbers of samples (on the order of millions) and consumes a great deal of computational resources. Our approaches based on various mathematical theories will facilitate data-driven knowledge discovery in clinical research, establishing interpretable and convincing models for researchers, clinicians, and patients.

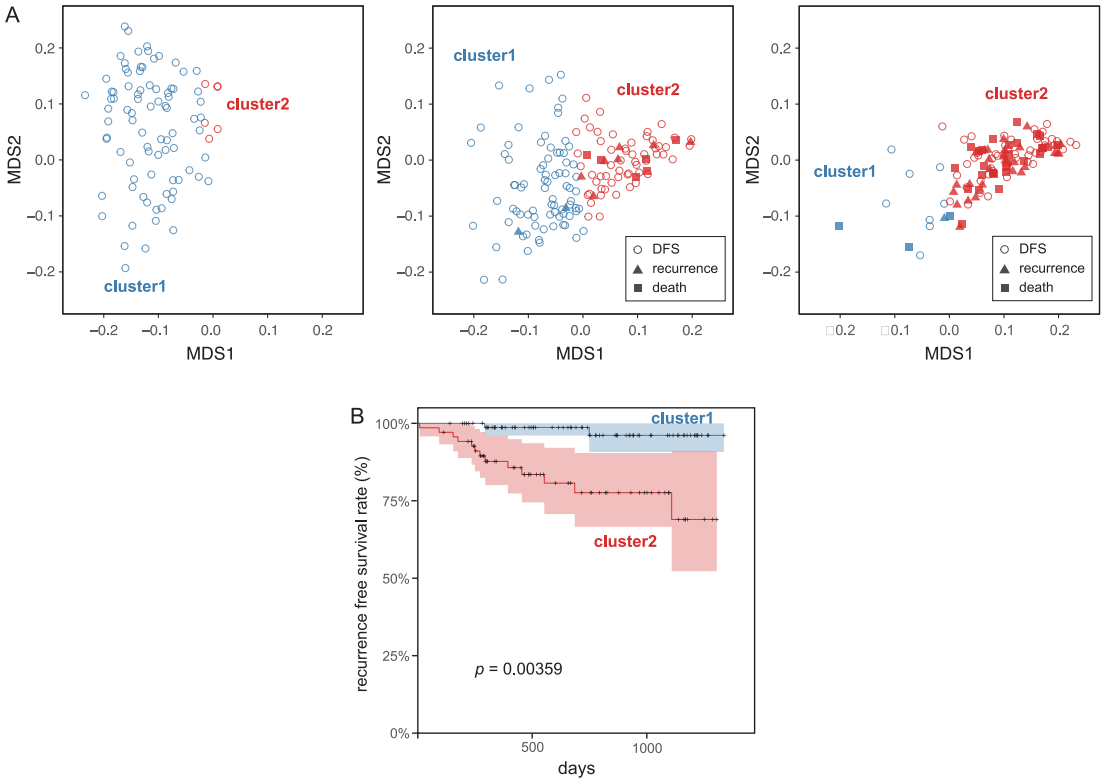

Figure 1: Unsupervised machine learning clustering associated with prognosis.
(A) Multidimensional scaling (MDS) plot based on the RF dissimilarity analysis for all EOC and benign ovarian tumors clustered into two groups using Partitioning Around Medoids (PAM) method. (B) Kaplan–Meier curves indicating recurrence-free survival of each cluster in early-stage EOC patients.

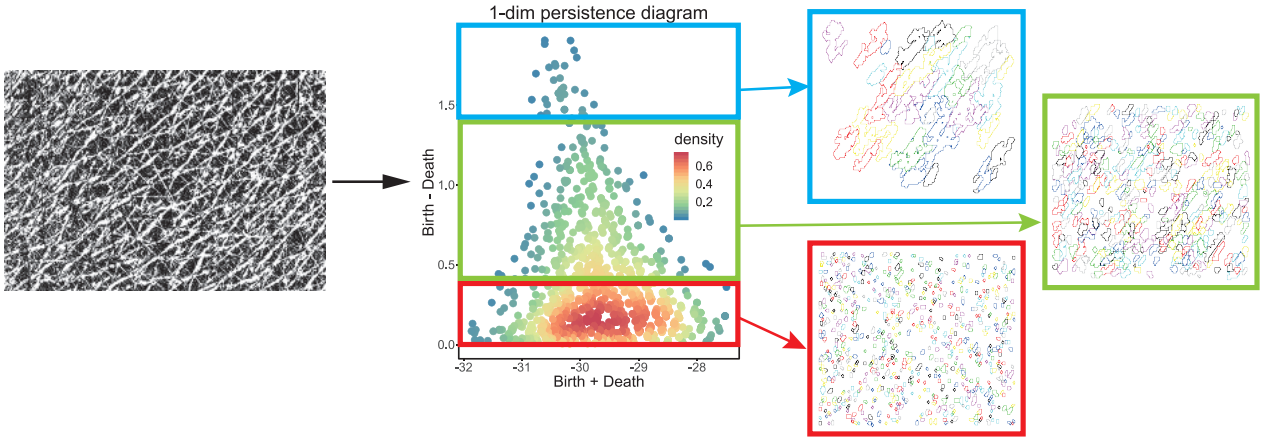

Figure 2: Illustration of feature extraction by persistent homology.
A persistence diagram is generated from processed binary skin images to express the extracted features. We gradually change the threshold of the density of white pixels and record the threshold values at which holes appear and disappear as "birth" and "death". Each area of the plot corresponds to different size of hole.

Let the data flow

AI-based Healthcare and Medical Data Analysis Standardization Unit

Unit Leader (Principal Investigator) **Jun Seita** (M.D., Ph.D.)

Figure 1: Group photo of the lab. As of Dec. 17th, 2018.

Overview and MIH Secure Analysis Platform Management System

The inception of the AI-based Healthcare and Medical Data Analysis Standardization Unit occurred in October 2017, when I joined MIH. During its first twelve months, the unit was fortunate to welcome four talented researchers: Naoki Nonaka, Ph.D.; Tatsuki Koga; Munetomo Takahashi; Arisa Kono; one technical staffer: Kazuko Hirose; and one administrative staffer: Yukari Oikawa (Figure 1). The name of the unit carries a double meaning indicating its missions. The first mission is to standardize healthcare and medical data for the purpose of AI analysis, and the second is to standardize AI analyses for the purpose of handling healthcare and medical data. Among many machine learning methodologies, we decided to focus on deep learning for the latter aim. With respect to both missions, the driving force is the data; thus, in the initial phase our focus has been to "let the data flow" into MIH during the 2018 fiscal year (Figure 2).

Ashizaki and colleagues have developed a Multimodal Clinical Data Acquisition System (reported on page 34), which enables automatic extraction of target patient data from a hospital's data warehouse, as well as uniform anonymization and formatting of data. Data are then transferred to the MIH Secure Analysis Platform (MIHSAP), which is a highly secure data center without any network connection that hosts anonymized medical data derived from many projects. Since it contains private information, RIKEN's ethics panel defines who can access which project's data, and those access privileges are subject to revision at any time. To ensure proper and secure access to the data stored in MIHSAP, we have developed the MIH Secure Analysis Platform Management System. In the system, relationships among researchers, projects, and data are clearly defined, and a simple user interface provides accessibility on MIHSAP only to the information needed for each role (such as regulator, administrator, or individual researcher). Functions to edit information are also defined by role, keeping access privileges secure and updated in a timely manner. Once raw data are analyzed in MIHSAP and statistical values have been obtained, a double check is performed to verify that they contain no remaining private information, and only then are the statistical values allowed to be exported from MIHSAP. The MIH Secure Analysis Platform Management System is also used to record the details of this procedure.

Gene Expression Commons for RNA-seq

Healthcare and medical data contain quite a wide variety of parameters. In order to apply machine learning methodologies to such data, it must be standardized (or normalized) to a comparable form. One typical example is gene expression. Each gene has a different dynamic range of its expression. The biological significance is different between 1,000 FPKM in gene A and in gene B, and a 2-fold change in gene X and in gene Y. Thus, the expression levels of gene A and B must be normalized by dynamic range before comparison. For system-level understanding of gene expression, it is necessary to know the dynamic range of each gene expression.

This issue has been resolved by meta-analysis of a massive amount microarray expression data from around the world, implemented on a web-based open platform named Gene Expression Commons which has been widely used for years. 4,000 scientists from over 60 countries have submitted gene expression data for 3,500 cell types, generated 2,000 working models, and produced over 100 publications. In FY2018, biological projects making use of Gene Expression Commons have been published in PNAS(1), Cell(2), and Nature(3) and others.

Now the time has come to build the same type of platform based on RNA-seq technology. To achieve this, we collected data files for 100k mouse RNA-seq and 50k human RNA-seq from public repositories, then mapped, counted, and statistically analyzed them to obtain gene expression dynamic-ranges (Figure 3). The results are integrated into Gene Expression Commons for RNA-seq, where users' RNA-seq data is mapped onto dynamic-range reference data. We aim to provide the same open platform for RNA-seq via Gene Expression Commons for RNA-seq (https://gexc.riken.jp). The next step for this approach to normalization based on dynamic-range is expanding it to other healthcare and medical data.

Data Augmentation by Deep Learning

Deep learning has significant potential for medical imaging. But in the real world, the incident rate of each disease varies widely, thus the frequency of classes in a medical image dataset is quite imbalanced, leading to poor accuracy for those infrequent classes. One possible solution is data augmentation of infrequent classes using images synthesized by Generative Adversarial Networks (GANs); however, conventional GANs also require a certain quantity of images from which to learn. To overcome this limitation, we have developed General-to-detailed GAN (GDGAN)(4). GDGAN contains two GANs, serially connected: one for general classes and the other for detailed classes. We used GDGAN to produce diverse medical images, and the network–trained with an augmented dataset–outperformed other networks using existing methods in terms of accuracy measured by AUC (Area-Under-Curve) of Receiver Operating Characteristic (ROC) curve.

This approach is also applicable to protecting the privacy of patient data used for machine learning. Whenever we make a data set open to the public as proof of newly published machine learning models trained by patient data, privacy concerns remain. If we could use GAN to generate data sets indistinguishable from actual data to machine learning models, we would be able to separate privacy issues from the data set. We intend to continue exploring the potential of GANs in handling medical data.

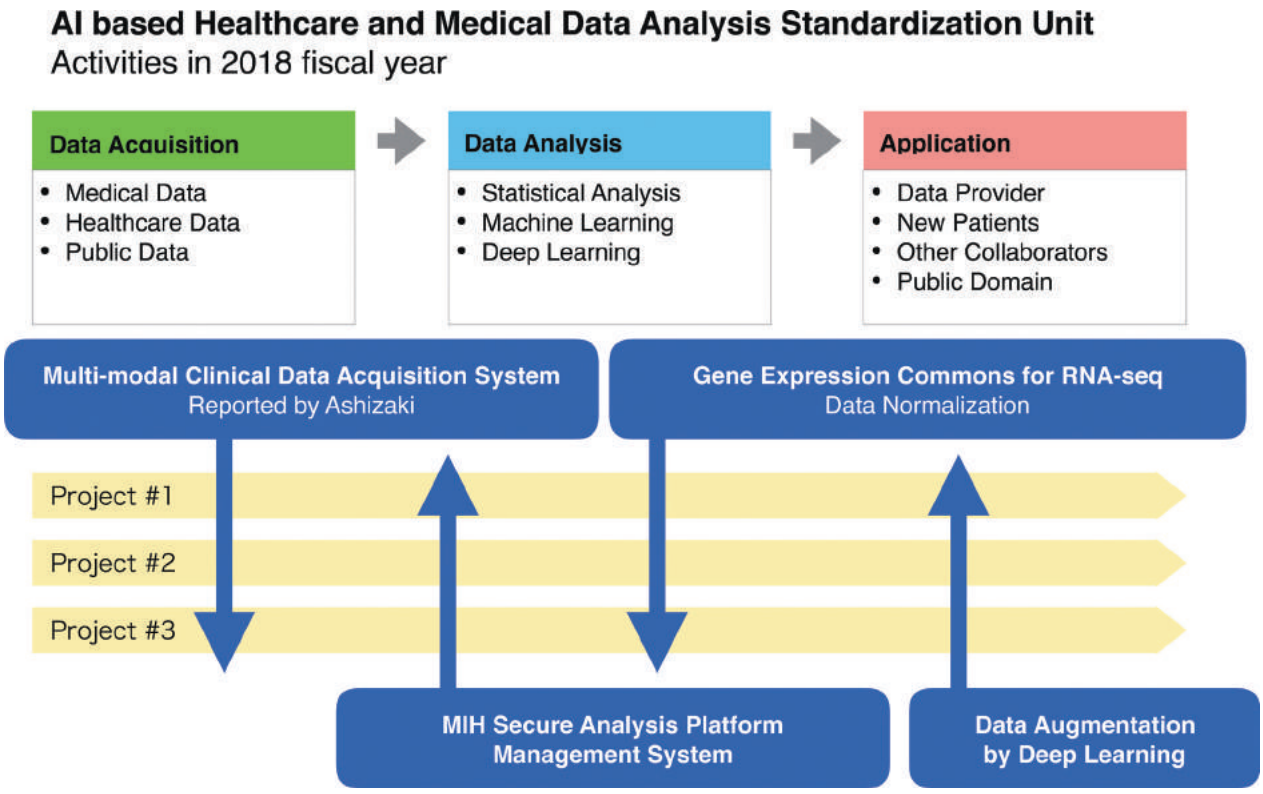

Figure 2: Overview of activities in 2018. Fundamental infrastructures to make medical data flow into machine learning have been studied and developed.

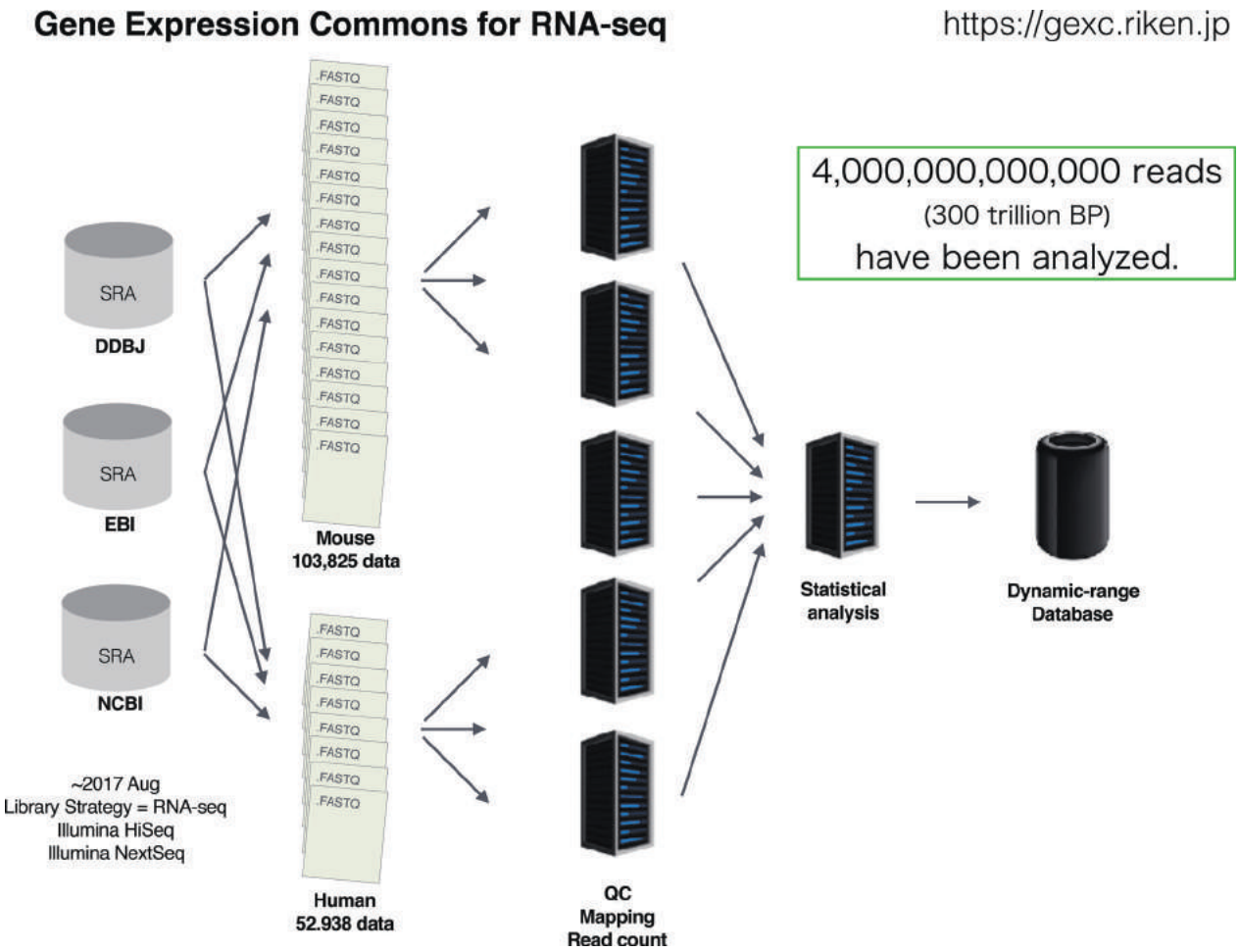

Figure 3: Massive amount RNA-seq data normalization. Publicly available 3 trillion reads have been analyzed to compute gene expression dynamic-range.

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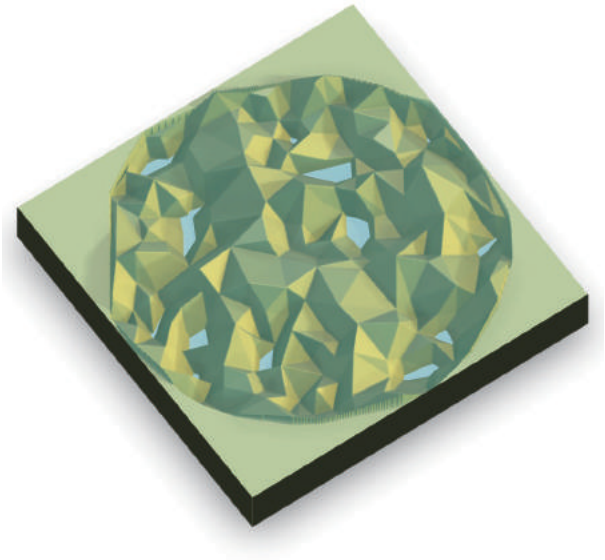
Energy Landscape Analysis of Biomedical Data

Healthcare and Medical Data Driven AI based Predictive Reasoning Development Unit

Research Associate **Tetsuo Ishikawa** (Ph.D.)
Unit Leader (Principal Investigator) **Eiryo Kawakami** (M.D., Ph.D.)

Energy landscape: State visualization of pre-onset diabetes mellitus type 2



Vast amounts of multifaceted healthcare and clinical data are collected at hospitals and on various occasions in people's everyday lives. The health conditions and diseases behind them are diverse, heterogeneous, and often change over time. To demystify this complexity, we developed AI-based, hypothesis-agnostic, and data-driven analytical tools to draw a brand-new health/disease landscape. By applying a method from statistical physics called coarse-graining to multivariate data, we can define discretized states and calculate the energy of each state as a measure of state stability, which is inversely related to the observation frequency of samples in the state. By visualizing not only health/disease states but also the stability of these states, the landscape allows us to interpret the latent state space intuitively and insightfully.

For example, the energy landscape created from the data of over 700 females for prediction of diabetes mellitus type 2 onset is depicted in Figure 1. This data consists of several medical predictor variables, including several biomarkers, somatometric indices, and genetic background factors for diabetes. The topographic map can be constructed from these multilayered data in a purely data-driven manner. Each point on the landscape corresponds to a certain health/disease state; the altitude represents the energy of that point. Lakes and ponds, local minima where water accumulates, represent stable states, whereas hills and mountains represent unstable states. The visualization can be interpreted in terms of the natural tendency driving state transitions toward lower elevation, like a marble rolling downhill.

Remarkably, several lakes and ponds exist in the diabetes landscape. In addition to the prominent lakes pooling the highest and lowest risk profiles for type 2 diabetes, there are also some small ponds: intermediate and presumably presymptomatic states. The five-year onset rate for each stable state supports the validity of the interpretation.

In the future, we plan to apply the energy landscape analysis to more diverse data, from questionnaires to omics (such as single cell RNA-seq). Landscape visualization helps us to understand the diversity and individuality of health/diseases, possibly leading to the discovery of new disease subtypes and presymptomatic conditions. By utilizing these features as a clustering and stratification method, we may gain new insights into appropriate intervention timing, individual variation of drug efficacy, and ultimately how to implement precision medicine. The Royal Geographical Society has a beautiful motto: "Every landscape has a story to tell." We believe this also holds true in the medical sciences.

Towards Standardization of Healthcare and Medical Data

AI-based Healthcare and Medical Data Analysis Standardization Unit

Postdoctoral Researcher **Naoki Nonaka** (Ph.D.)

In order to efficiently obtain knowledge from data using artificial intelligence techniques, including machine learning, it is important that data can be obtained in the same form. Using data collected in different formats imposes the necessity of labor to unify data formats, greatly increasing the cost of analysis. In the realm of medical data, the format of data collected often differs among medical institutions or vendors. Therefore, standardizing healthcare and medical data is important for efficient analysis of these data.

In recent years, several attempts have been made to standardize the format of collected healthcare and medical data. The target data includes electronic health records (EHR), administrative claims, laboratory results and vital records. Standardizing these data lowers the cost of conducting large-scale observational research using multiple data sets and the cost of reproducing published research.

Below, we give an overview of organizations that tackle the standardization of medical data. Specifically, we talk about the OHDSI symposium in which we participated, as well as other organizations which work on medical data standardization.

OHDSI (Observational Health Data Sciences and Informatics)(1) is an organization composed of academia and companies. It is a successor of OMOP, previously established in 2008. OHDSI is an interdisciplinary program consisting of multiple stakeholders–such as physicians, pharmaceutical companies, and government agencies–that is seeking open source solutions through analysis of large-scale medical data. The head office of OHDSI, located at Columbia University in the United States, provides the format of the standard database and associated analysis tools. OHDSI aims to discover medical evidence through extensive observational studies. At the symposium, results were presented that use the OHDSI database and associated tools to reproduce research findings and compare multiple academic research studies. In the poster session, discussions took place about presenting examples of observational research using OHDSI's data format and future expansion. Opinions are exchanged on an OHDSI online forum on a daily basis, and symposia are held throughout the world. A worldwide symposium is held in the United States once a year; regional OHDSI symposia are also held in Europe, South Korea and China.

The CDISC (Clinical Data Interchange Standards Consortium)(2) is a non-profit organization with more than 300 member organizations throughout the medical industry. CDISC was established as a volunteer organization in 1997 and has been operating as a nonprofit organization since 2000. The data collected by each subscribing organization is provided to other subscribing organizations in a vendor-neutral and platform-independent manner. The FDA (USA) and PMDA (Japan) are involved in an effort to designate the CDISC data format as the data format for submitting clinical trial results.

In addition to OHDSI and CDISC, other initiatives related to the standardization of medical data include ISO/TC215(3), PCORnet(4), i2b2(5), and FDA sentinel(6). ISO/TC215 is a technical committee at ISO (International Organization for Standardization) to formulate international standards, targeting standardization of medical information. PCORnet is a common data model of medical data provided by the Patient-Centered Outcomes Research Institute (PCORI). i2b2 is a framework focusing on bridging research developed by the NIH-supported National Center for Biomedical Computing. FDA sentinel is a project to build an information system aimed at monitoring the safety of pharmaceuticals regulated by FDA.

In short, several organizations are active in the standardization of medical data. The object of inter-

est for each organization differs depending on the background of its establishment and the companies and organizations participating in it. In the future, as standardization of medical data progresses, there will be more and more cases where machine learning is applied. As such, we intend to continue to pay close attention to initiatives around the world related to the standardization of medical data.

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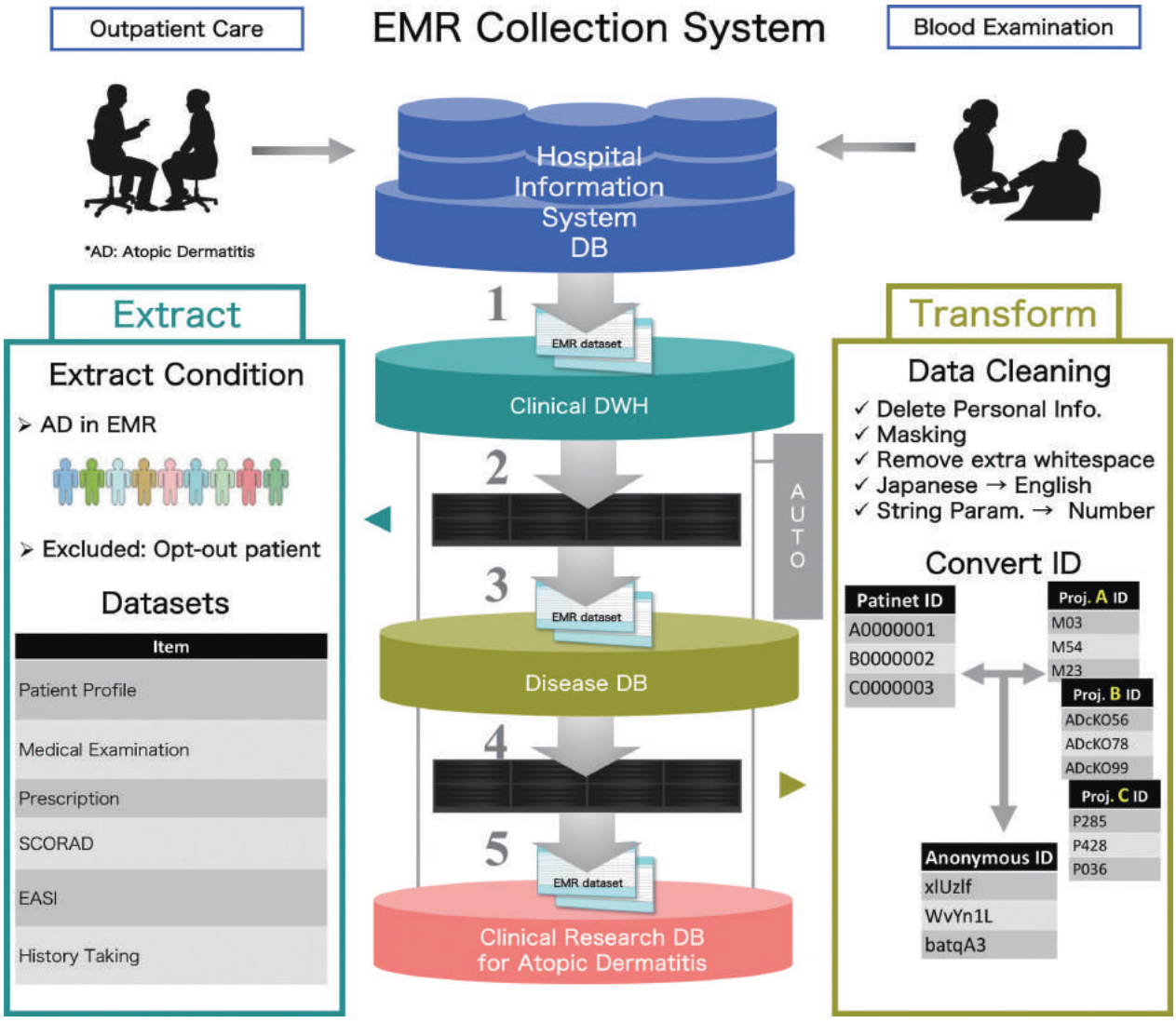
Constructing an automatic collection system for electronic medical records to facilitate data-driven research

Disease Data Integration Group

Group Director (Principal Investigator) **Tatsuhiko Tsunoda** (Ph.D., Ph.D.)
Technical Scientist **Koichi Ashizaki, Yoshiki Mochizuki**
Technical Staff **Takashi Morizono**



We aim to develop a versatile platform to accurately, rapidly, and safely collect and integrate multimodal clinical data with the ultimate objective of implementing precision medicine. In managing various types of clinical data, consideration for the privacy of patients and ensuring reproducibility are both extremely important. Here, we report on a system established at Keio University Hospital that automates the Extract-Transform-Load (ETL) process to collect electronic medical records (EMRs).

In recent years, the amount of clinical data gathered in medical institutions through diagnosis and

examination, which varies among departments, has been increasing. In order to promote data-driven research based on clinical data, it is necessary to efficiently extract and process clinical data while vigilantly protecting personal information. Along with electronic medical records, the use of next-generation sequencers, and of technologies for medical imaging diagnostics has been rapidly spreading in biomedical science.

By analyzing these multimodal clinical data–such as disease condition, clinical inspection, and prescription information–new findings and/or rules can be discovered. Although the quantity of data far exceeds what can be handled manually by medical staff, much manual work still remains in the process of collecting clinical data, and automatic systems for seamless collection of data are not sufficiently developed. Furthermore, manual data collection entails severe problems such as low reproducibility, low quality, and poor security for personal information protection.

In order to solve these problems, we have constructed a system for automatically collecting clinical data of outpatients with atopic dermatitis from the clinical data warehouse (DWH) of Keio University Hospital. Since it is challenging to handle raw data extracted from DWH with adequate safeguards given the insufficient protection of personal information, we first pre-processed the data by using Pandas, a Python library for data analysis, to execute data cleaning and anonymization. We also introduced Docker Engine, an example of virtualization technologies called “containers”, to provide reproducibility and portability.

Consequently, this automated pipeline enabled us to extract and process about 1.1 million clinical records within 4 hours, freeing medical professionals from the tremendous burden of manual extraction while enhancing the reproducibility and quality of data. In addition, we implemented an interface using Plotly to interactively visualize statistics of extracted data. Using this interface, we can continuously monitor the number of patients and records coming in from the Dermatology Department of Keio University Hospital. In the next version, we will extend the range of application of this system to other diseases and other departments to facilitate medical big data research. Further down the road, we aim to integrate clinical data with omics and image data to accelerate medical research and development towards making precision medicine a reality.

Searching for biomarkers reflecting the "state" of complex biological systems in disease

Biomarker Analysis Group

Group Director (Principal Investigator) **Osamu Ohara** (Ph.D.)
Senior Researchers **Junshi Yazaki, Takaho Endo**
Technical Staff **Reiko Kuwahara**

The mission of the Biomarker Analysis Group is to develop and operate pipelines for biomarker exploration that fully exploit the genomic technologies that have been rapidly emerging over the last decade, and which have come to serve as indispensable tools in today's biological sciences. To carry out the mission, we are closely collaborating with the Laboratory of Integrative Genomics at RIKEN IMS, where our group is physically hosted. Another critical reason to closely collaborate with IMS is that studies of genetically engineered disease-model mice that are being carried out there provide us with highly intriguing lines of information regarding the identification of novel biomarkers.

We have thus far been involved in multiple MIH projects, searching for biomarker candidates that are suitable for estimation of pathogenic state in human specimens collected by means of minimally invasive procedures at the RNA and the cytokine levels, mainly by RNA sequencing and multiplex immunoassays, respectively. Over the past two years, we have already carried out RNA sequencing for more than 350 samples of peripheral blood mononuclear cells (PBMCs) and 20 samples of skin punch-outs (with more than 150 PBMC samples and 15 skin punch-out samples currently under preparation), along with multiplex immunoassays (Luminex xMAP® technology) of cytokines for approximately 300 samples of human plasma. In addition to these profiling experiments, when necessary we have also performed genetic analyses based on human exome sequencing for the detection of somatic and germline mutations.

While we have played an active role in data production at MIH, it is also our responsibility to check the quality and the reproducibility of the data. Although we paid close attention to minimizing variability of the data from sample to sample, we nevertheless experienced certain problems with data quality in both RNA and cytokine profiling: sophisticated bioinformatics analyses detected a small number of outliers among the data accumulated over nearly two years. Although some outliers could be eliminated merely by re-measuring the same sample, thus indicating that they originated from technical noise in measurements, other outliers were reproducible and might be attributable to particular incidents during sample preparation; for example, contamination by unexpected human material from an unknown source. The lesson learned from these problems is the necessity of setting a proper data resolution to isolate robust biomarkers that reflect the state of the biological system of interest. Because it is a rare opportunity to accumulate a large set of profiling data at a single site over the course of several years, we are carefully investigating the source of variation in collaboration with MIH research groups. Hopefully this will yield a way to obtain robust biomarkers from variation-containing profiling data. In this respect, it is of great help that some MIH groups have experience in analyzing massive quantities of variation-containing profile data in public databases (***PLoS One.*** 2012;7(7):e40321).

We have so far focused our efforts on using relatively popular technologies for the exploration of biomarkers requested by each MIH project, but at the same time we have always kept in mind what kind of new technologies will be needed to identify brand-new biomarkers for defining the pathological state of biological systems. An obvious direction to move in is tackling the multi-layer structure of the biological system. For example, the RNA/cytokine biomarkers we have been searching for at MIH are regarded as body-scale markers. For these biomarkers, PBMCs and plasma are assumed to be homogeneous entities, and RNA/cytokine profiles of PBMCs/plasma are expected to reflect their respective states. However,

nobody knows whether biomarkers at the body-scale layer provide us with appropriate measurements for estimating the pathogenic state of the whole body. In this context, we might say that the current biomarker exploration is conducted at the body-scale layer simply as a pragmatic initial choice.

On the other hand, technology advances have recently made it possible for us to explore biomarkers at the cell ensemble-scale layer. In this layer, PBMCs are no longer regarded as a homogeneous entity, but a mixture of heterogeneous cells. In other words, the state of PBMCs should be described by the composition of heterogeneous cells on this layer. Our group has been working to develop the new technology of affinity proteomics at single-cell resolution for nearly ten years. We have reported some technologies to monitor protein secretion from single cells in real-time (***Sci Rep.*** 2014 Apr 22;4:4736.; ***Cell Rep.*** 2014 Aug 21;8(4):974–82). However, for identification of biomarkers on this layer, more comprehensive analysis at the single-cell resolution is required; thus we are actively pursuing RNA biomarkers for the purpose of characterization of heterogeneous single cells.

To make this biomarker search possible, we are developing a deep single-cell RNA-seq pipeline based on two different methods: SMART-seq (***Nat Methods.*** 2013 Nov;10(11):1096–8) and RamDA-seq (***Nat Commun.*** 2018 Feb 12;9(1):619.). In particular, the RamDA-seq method was developed by a RIKEN research group (Dr. Itoshi Nikaido, Laboratory for Bioinformatics Research, RIKEN BDR), who kindly provided the group's support to implement this method at RIKEN IMS/MIH. In our hands, RamDA-seq has reproducibly yielded good results and we are already using it for various research applications; however, limitations on the throughput makes it unsuitable for exploration of biomarkers at the single-cell level.

Figure: An overview of the high-throughput single-cell RNA sequencing platform.
Two nanoliter liquid handling robots are shown.

To create a high-throughput single-cell RNA sequencing platform for biomarker search on the cell-ensemble layer, working with Dr. Jun Seita (AI-based Healthcare and Medical Data Analysis Standardization Unit, RIKEN MIH), we set up a pipeline based on the SMART-seq method in collaboration with a Stanford University group. This pipeline takes full advantage of the mosquito® nanoliter liquid handling robot from TTP LabTec. A mosquito can handle liquid volumes as small as 50 nL, which enables us to prepare the RNA-seq library with higher detection efficiency and higher accuracy at lower cost by reducing reagent volume per reaction. The first mosquito (red in the photo) automatically normalizes and merges single cell samples in four 96-well plates into the single 384-well plate, then the other mosquito (blue) with 16-channel pipettes dispenses reagents for library preparation. These robots are applicable to other methodologies of high-density single cell omics protocols. Because the trend in single-cell analysis technologies is obviously towards the capability to analyze proteins and metabolites in addition to RNA, these sophisticated robots will offer us a high-throughput and cost-effective platform for general single-cell omics approaches as well.

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Part 3

Collaboration

Multi-omics analysis reveals prognostic contribution of metabolome and transcriptome in SLE

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Project Assistant Professor **Yasuo Nagafuchi** (M.D., Ph.D.)

Autoimmune disease is a complex common disease that exhibits extensive impact on the patient's prognosis. Identification of immunological parameters associated with prognosis is critically important for precision medicine. We performed multi-omics analysis using a combination of the metabolome, transcriptome and genome of systemic lupus erythematosus (SLE).

We have collected plasma samples from patients with SLE (n=41) who met the 1997 American College of Rheumatology criteria for SLE and had a history of lupus nephritis. Gender-matched healthy controls (HCs) (n=30) were recruited. For comparison, plasma from 19 rheumatoid arthritis (RA) patients were also collected. Metabolic profiles were analyzed with capillary electrophoresis (CE)- and liquid chromatography (LC)- time-of-flight mass spectrometry (TOFMS) in conjunction with multivariate statistical analysis. Transcriptome data of SLE patients were obtained from our RNA-sequencing data for each immune cell subset (19 total subsets).

About 180 peaks were detected by CE-TOFMS, including 110 absolutely quantified metabolites, and about 160 peaks were detected by LC-TOFMS. The Random Forest (RF) machine learning algorithm revealed the importance of histidine (His) for distinguishing SLE patients from HCs. Partial least squares discriminant analysis (PLS-DA) also showed the significance of His, whose plasma level was lower in SLE patients. Notably, plasma concentrations of His exhibited a significant correlation with the SLE damage index, which is one of the most important prognostic measures for SLE.

In addition, we divided SLE patients into two groups by using transcriptome data: type I interferon (IFN)-signature high and low. Interestingly, we found some amino acids, such as alanine (Ala) and lysine (Lys), were associated with type I IFN-signature level. In addition, inverse correlation between His level and titer of ds-DNA was detected. His level was also decreased in RA patients compared to HCs and was inversely correlated with DAS28-ESR and CRP in RA. These findings indicated that lower His level might show some pathophysiological significance in SLE independent of inflammation or type I IFN signal. Weighted gene co-expression network analysis (WGCNA) revealed that some B cell modules showed negative correlation with His level, and positive correlation with disease (SLE). In addition, mitochondria-related genes were significantly enriched in that module.

We also investigated the correlations between clinical parameters and metabolites and found that some metabolites were correlated with SLEDAI, ANA, and low lymphocytes. The Receiver Operating Characteristic (ROC) curve of some combination of amino acids could potentially more precisely define SLE patients.

Plasma metabolic changes in autoimmune diseases might not only reflect the chronic activated immune-status but also associate with their pathogenesis. His may be an important factor for SLE pathogenesis, especially in B cells, independently of IFN signaling. SLC15A4, a transporter of His on lysosome, is one of the SLE GWAS SNPs and has been reported to play an important role in IFN production in B cells through regulation of TLR7/9 activation. Low plasma level of His could be a useful marker of SLE prognosis and maintenance of His homeostasis could become a novel treatment target for SLE. Moreover, a particular combination of amino acids could be a useful marker for diagnosing SLE or distinguishing active SLE patients. More sample collection is required to improve our analytic robustness.

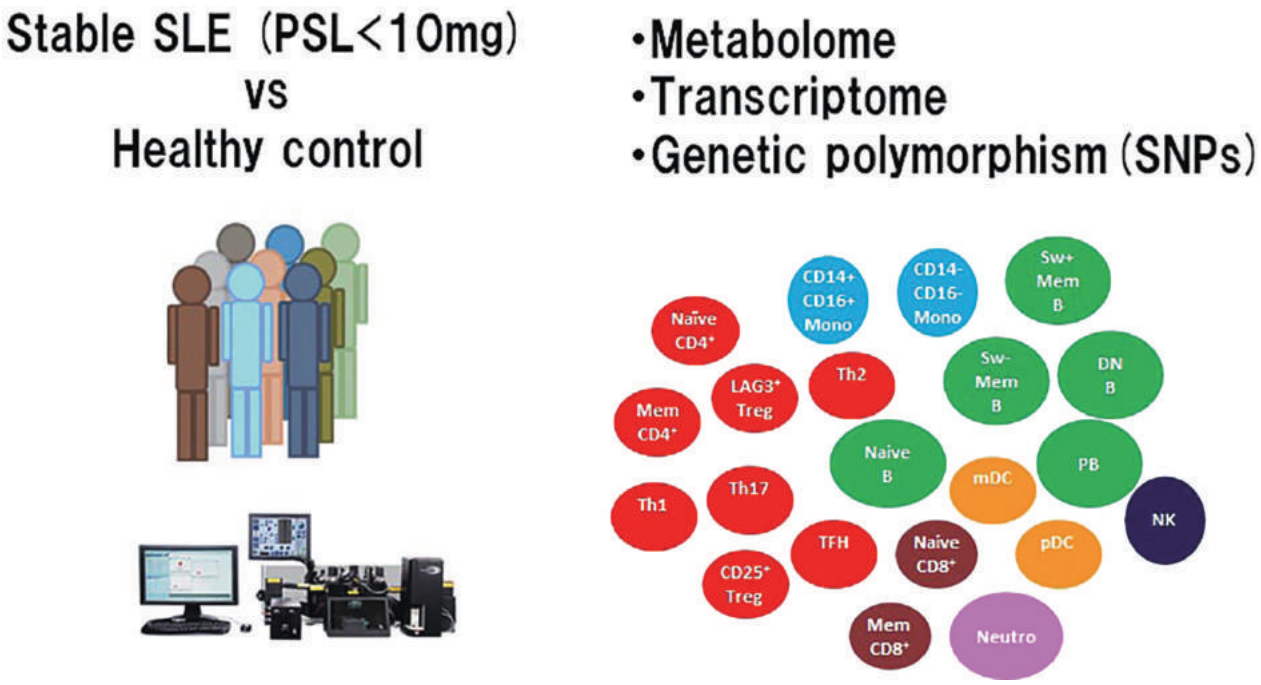
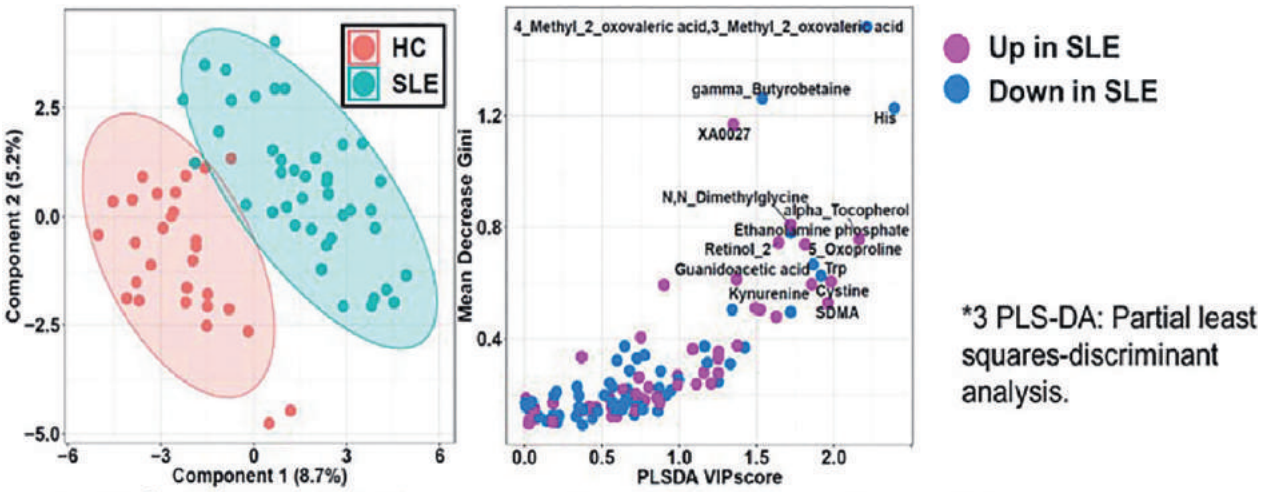


Figure 1: Multi-omics analysis of metabolome and transcriptome



PLS-DA*3 discriminated SLE patients from HCs. By combining with Random Forest analysis, Some metabolites, especially His (histidine), seemed to be important to distinguish SLE.

Figure 2: Histidine discriminates SLE and HC

Construction work for Big Data of clinical assessments for rheumatoid arthritis

Department of Respiratory Medicine and Clinical Immunology, Graduate School of Medicine, Osaka University

Assistant Professor **Toru Hirano** (M.D., Ph.D.)
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Professor **Atsushi Kumanogoh** (M.D., Ph.D.)

Database construction for Big Data of clinical assessments for rheumatoid arthritis

Methods: Database system was constructed for clinical assessments of almost all patients with rheumatoid arthritis at the Division of Internal Medicine of Clinical Immunology, Osaka University Hospital. This database includes names of complications, onset of disease, symptoms, joint findings, blood or urine laboratory examinations, radiographic (X-ray) findings, patient-oriented outcome (health assessment questionnaire) and treatments.

Results: About 900 patients were registered to the database from 2016 to Aug 2018. The number of clinical records totaled 4,990 records in 2016, 6,842 in 2017 and 3,450 in 2018 (through June).

Medical image diagnosis of joint X-rays

Methods: Two thousand and forty-four images of small finger joints were generated from 210 hand X-ray pictures of patients with rheumatoid arthritis by clipping, and these images were analyzed. Pictures were classified and scored according to the degree of joint destruction. The pictures were converted to digital matrix data and analyzed by machine learning. The first step of the machine learning process is detecting the area of joints using the open-cv module; the second step is evaluating the degree of destruction of joints using a convolution neural network (CNN) with the deep-learning module chainer.

Results: Figure 1 shows the result of CNN for hand and foot X-rays. Images of hand or foot X-rays were automatically scored from 0 (normal) to 4 or 5 (severe destruction). This methodology still requires validation in the future. Since one of the most important outcomes for treatment of rheumatoid arthritis is prevention of joint destruction, this AI-guided evaluation is definitely useful for assessing clinical situations.

Automatic diagnostic system using natural language processing (NLP)

Methods: Clinical charts contain huge volumes of descriptions for assessing patients. These descriptions, written as natural language, include valuable information for the diagnosis or assessment of disease conditions. We are now trying to develop an AI-guided diagnostic system for patients who manifest joint pain that uses natural language processing (NLP). This system enables earlier and more definite diagnosis of rheumatoid arthritis. We use the genism module for embedding words into corresponding 200–300 dimensional vectors, thereby allowing words and texts to be analyzed by their mathematical similarity.

Results: About 3,100 words on the website of our institute were processed by the genism module, assigning each word a unique 200-dimensional vector. The same processing was applied to words in texts written by clinicians. Similarities of word-word interaction were calculated, and disease names with similar vectors to the text were automatically ranked. One example is shown in Figure 2. This methodology may be useful not only for differential diagnosis but also assessment of disease conditions.

Measurements of serum biomarker for AI assessments

Method: To diagnose the disease or predict the outcome, laboratory measurements which are not included in conventional clinical assessments are in process. Serum levels of bone metabolism-related molecules (RANKL, sclerostin, osteoprotegerin, DKK-1, etc.), inflammatory molecules (interleukins, TNF, etc.) and semaphoines are measured by ELISA or WB. These results will be assessed by conventional procedures, and additionally will be used for AI assessments in conjunction with huge datasets constructed from the clinical database described above.

Results: We analyzed a portion of datasets and blood samples for developing a clinical marker, and detected a novel serum marker candidate, Ficolin-1. This complement-related molecule is elevated in patients with rheumatoid arthritis, and therapeutic intervention using the anti-Ficolin-1 monoclonal antibody ameliorated disease severity in arthritis mouse models.

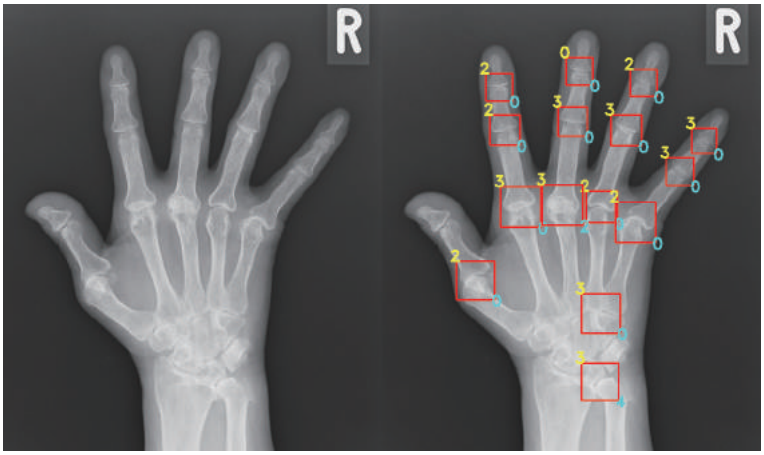

Figure 1

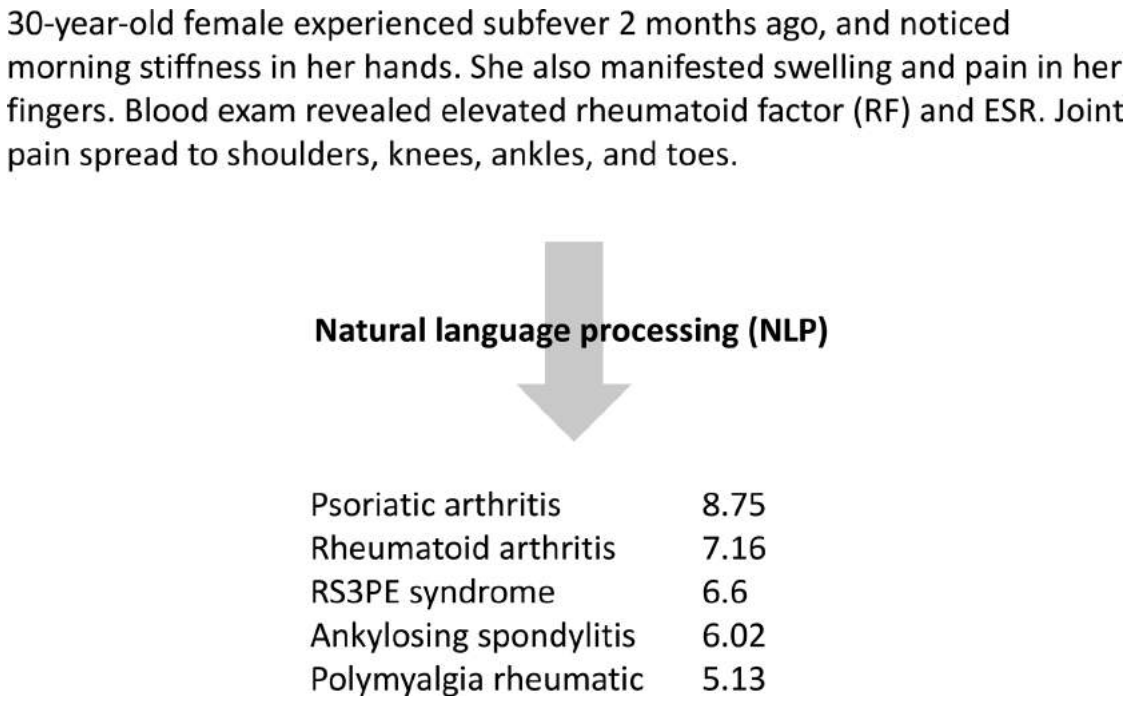

Figure 2

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Application of artificial intelligence for precision medicine in epithelial ovarian cancer

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Research Associate **Junya Tabata** (M.D.)
Research Assistant **Misato Saito** (M.S.)
Research Associate **Ayako Kawabata** (M.D.)
Professor **Aikou Okamoto** (M.D., Ph.D.)

The Department of Obstetrics and Gynecology of the Jikei University School of Medicine conducts retrospective and prospective cohort studies mainly focusing on epithelial ovarian cancer (EOC). Among gynecological tumors, EOC is the disease with the poorest prognosis: of thein gynecologic tumors, with which ~10,000 patients are diagnosed with EOC annually in Japan, and ~4,500 die. EOC is classified into at least five distinct histotypes: high-grade serous carcinoma (HGSC), endometrioid carcinoma (EC), clear cell carcinoma (CCC), mucinous carcinoma (MC), and low-grade serous carcinoma (LGSC). These histotypes exhibit different morphology, etiology, and biological behavior. EOC is surgically and pathologically staged by the International Federation of Gynecology and Obstetrics (FIGO) staging classification. Although there is a need for histotype-specific and/or stage-dependent treatment options, most patients with EOC are still treated with a conventional "one-size-fits-all" approach of surgical intervention and platinum-based combination chemotherapy. To select more effective therapeutic approaches for EOC with complex phenotypes, it is important to identify stratification factors that could accurately define patient characteristics before initial intervention. In the retrospective study, we developed machine learning-based algorithms to perform pretreatment stratification of patients based on 32 parameters commonly available from pretreatment peripheral blood tests, plus age. We have followed that up with a prospective study to acquire more comprehensive measurements that will improve stratification performance and identify novel biomarkers. These measurements include the transcriptomes of tumor tissue and peripheral blood, various cytokine measurements in serum, and somatic mutation analysis of tumors, in addition to general clinical information obtained in clinical practice. In this prospective study, our target is collecting samples for 100 cases; as of August 2018, we had completed sample collection and measurement of 27 cases.

Development of Circadian Clock and Developmental Disorders

Department of Physiology and Systems Bioscience, Kyoto Prefectural University of Medicine

Professor **Kazuhiro Yagita** (M.D., Ph.D.)

Circadian clocks regulate the daily fluctuations of essential biological processes from the molecular to the organismal level to predict and adapt to the cyclic environment of our rotating planet. Cell-autonomous circadian clocks exist in both the SCN and peripheral cells throughout the body, suggesting that circadian clocks may function as an interface connecting cyclic environmental changes and cellular physiology.

The Yagita Lab has committed to understand the "Emergence of Circadian Rhythm", especially the molecular mechanisms of the cell-autonomous emergence of the circadian clock throughout the body. It has been shown that the circadian clock resides in each cell throughout the body and even in cultured fibroblast cells (Yagita et al, ***Science***, 2001). However, interestingly, mammalian zygotes, early embryos, and germline cells do not display circadian molecular rhythms, and the emergence of circadian rhythms occurs gradually during development. In addition, we recently discovered that mESCs and early embryos do not display discernible circadian molecular oscillations, whereas robust circadian molecular oscillation is observed in in vitro-differentiated mESCs (Yagita et a, ***PNAS***, 2010). Moreover, we have shown that circadian oscillations are abolished when differentiated cells are reprogrammed to regain pluripotency through reprogramming factor expression (Oct3/4, Sox2, Klf4, and c-Myc) (Yagita et a, ***PNAS***, 2010), indicating that circadian clock development in mammalian cells is closely correlated with the cellular differentiation process. Supporting this mechanistic link, we also have revealed that perturbation of the cellular differentiation process of mESCs via DNA methyltransferases (Dnmt1, 3a, 3b) deficiency during differentiation results in the abolishment of circadian clock development (Umemura et al, ***PNAS***, 2014). Dysregulation of the cellular differentiation process resulted in disruption of the circadian clock development, suggesting that the appropriate regulation of cellular differentiation is likely to be essential for the emergence of the functionally intact circadian clock. Moreover, we have found the post-transcriptional mechanism controlling CLOCK protein expression that contributes to differentiation-coupled circadian clock development both in ESCs and mouse fetal heart tissue, indicating that strictly controlled mechanisms or programs may create the cellular circadian regulation system (Umemura et al, ***PNAS***, 2017).

Based on these findings we have made, in this collaboration we are using mouse models to investigate the effect of environmental perturbations–for example, the effect of scheduled light-shift or inflammatory conditions–on the development of the mammalian circadian clock. We recently performed a pilot study examining the effect of prolonged circadian misalignment in mice, and it suggested some possibilities such as reduction of longevity (Minami et al, ***Sleep and Biol Rhythm***, 2018). Using these environmental perturbations, the relationship between the circadian clock and developmental disorders will be investigated.

Along with animal models, human physiology is another theme of the Yagita Lab. The aim of this project is to establish a system for evaluating circadian rhythm in patients with developmental disorders. Using combined data on circadian activity rhythm and autonomic activity rhythm, we are trying to understand what constitutes "intact" rhythm and what constitutes "signs of autism" in a non-invasive manner.

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Electrocardiogram measurement before birth (aiming for diagnosis of autism spectrum disorder from fetal stage)

Tohoku University School of Medicine

Professor **Yoshitaka Kimura** (M.D., Ph.D.) | Lecturer **Yoshiyuki Kasahara** (Ph.D.)

The average height of Japanese people has been getting lower since 1970. The main reason for this phenomenon is believed to be an increase in fetal growth restriction babies. Such babies are known to be prone to various diseases such as autism spectrum disorder (ASD). We are the first in the world to succeed in developing a fetal electrocardiograph that can be used clinically starting from the middle trimester of gestation, and that is able to record detailed information about the fetus at the clinical site from about the 20th week of gestation. In addition, using this device, we are developing an inexpensive fetal phonocardiograph that can easily acquire fetal heart sounds by placing simple phonocardiography sensors at the corners of the maternal abdominal wall. Furthermore, in animal experiments we succeeded in continuously measuring the electrocardiogram of a mouse fetus, another world's-first achievement. We have used this technique to elucidate the onset of cerebral palsy in mouse fetuses. Moreover, we found a close relationship between maternal heart rate and fetal heart rate, and we propose that this relationship is disrupted in ASD model mice. In these model mice, autonomic nervous rhythm disorder in the fetal stage has already been reported, and this could be the cause of the disruption in the relationship between the maternal and fetal heart rates. Currently we are investigating safe and effective treatments for ASD starting in the womb.

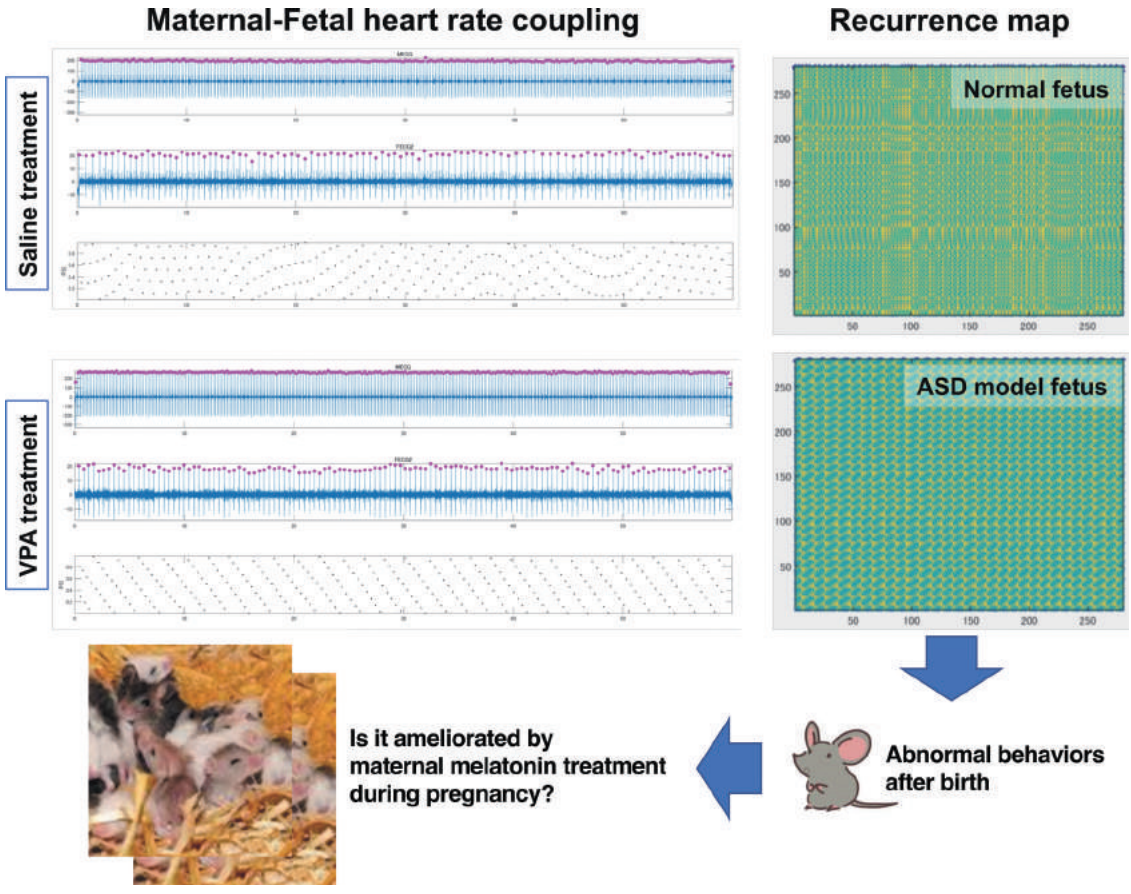

Figure: Analysis of maternal and fetal heart rate couplings in ASD model mouse. Recurrence map shows different coupling patterns between normal fetus and ASD model fetus.

Immune Surveillance and Biomarkers for Immune-checkpoint Therapy in Lung Cancer

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Professor **Mikio Oka** (M.D., Ph.D.)

Lung cancer is the leading cause of cancer deaths worldwide. Most lung cancers, especially non-small-cell lung cancer (NSCLC), are resistant to conventional chemotherapy, resulting in poor prognosis. Recently, immunotherapy using immune-checkpoint inhibitors has prolonged NSCLC patient survival. Programmed death-1 (PD-1) of an immune-checkpoint molecule is expressed on activated CD8 T cells and binds to PD-ligand1 (PD-L1) on tumor cells, resulting in T-cell exhaustion. Therapeutic antibodies (Ab) for PD-1, nivolumab and pembrolizumab, inhibit this binding and reactivate CD8 T cells with cytotoxic function. However, since the response rate of NSCLC to anti-PD-1 therapy is approximately 20% and anti-PD-1 therapy is very costly, response biomarkers have been extensively investigated. Although biomarkers such as tumor PD-L1 expression, tumor mutation burden, and T-cell infiltration are proposed, these markers are not entirely satisfactory and convenient due to issues of reliability, cost, and time requirements.

On the other hand, melanoma antigen-1 (MAGE-A1) of the cancer-testis (CT) antigen was discovered as the first human tumor antigen, and hundreds of CT antigens have since been identified. MAGE-A family members and New York esophageal squamous cell carcinoma-1 (NY-ESO-1) are broadly expressed in various human malignancies. Among CT antigens, MAGE-A1, MAGE-A3, NY-ESO-1, SSX, and XAGE1 elicit spontaneous T-cell and humoral immune responses in cancer patients. NY-ESO-1 has been extensively investigated as a target of cancer vaccines and T-cell therapy because it exhibits the highest immunogenicity among CT antigens. Concerning XAGE1, we have reported that XAGE1 is specifically expressed in approximately 50% of lung adenocarcinoma, and the XAGE1 serum Ab is a good prognostic marker in advanced adenocarcinoma patients (Figure). Thus, NY-ESO-1/XAGE1 may be major immuno-dominant antigens in NSCLC, and spontaneous immune responses against these antigens are considered to play important roles in the immune surveillance of NSCLC.

Next, we hypothesized that NY-ESO-1/XAGE1 Ab have potential as response and monitoring biomarkers in anti-PD-1 therapy for NSCLC, and conducted a prospective multicenter study to verify this hypothesis. Consequently, for the first time we demonstrated that a serum antibody against NY-ESO-1/XAGE1 was independently a robust biomarker for predicting clinical benefits (better response and survival) and monitoring tumor burden in anti-PD-1 therapy for NSCLC (in submission, patent pending). Furthermore, antibody titers in responders transiently increased with spikes and gradually decreased with tumor shrinkage after anti-PD-1 therapy, and were strongly correlated with tumor reduction rates (in submission).

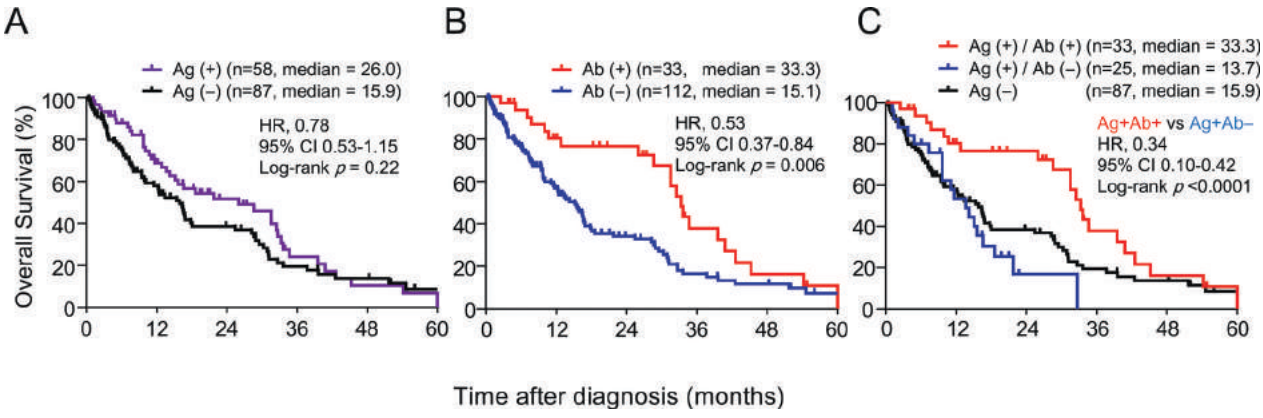

Figure: Overall survival was prolonged in XAGE1 antibody-positive lung adenocarcinoma patients compared with antibody-negative patients.

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Part 4

Cooperation with industry

Skin Diary –an application program for recording the daily treatment of Atopic Dermatitis

Corporate Collaboration: ORSO

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by intensive itching and recurrent eczematous lesions. AD is a multifactorial disease and results from a complex interplay of environmental factors, adverse lifestyle exposures, and genetic predisposition. As many environmental and lifestyle factors can be involved in disease exacerbation, symptoms often deteriorate suddenly at home. With such diseases, it is important to grasp the daily symptomatic and environmental changes and to apply them to therapy. The aim of this project is to develop a mobile application through which the patient records the treatment situation and symptom progression at home, and to evaluate the usefulness of this application for patient guidance and understanding of therapeutic effectiveness. This project is being conducted in collaboration with ORSO and Keio University Hospital.

We developed an app called “Skin Diary” that can be installed on smartphones. It records the daily treatment situation and life log data (Figure). Judging that data exchange via the cloud presented risks from the viewpoint of safety and ethical consideration, this study was carried out without using the cloud, by distributing smartphone terminals with this application pre-installed to patients. 102 AD patients were enrolled in this study and used this application for at least one month. More than 70% of enrolled AD patients used this application on more than 60% of the days. In a questionnaire, a large number of patients reported positive impressions of the app. For example: “The app helps me to communicate with my doctor,” “The app helps to motivate me in daily treatment,” “The app helps me to grasp my daily disease condition and causes of exacerbation,” etc.

For doctors, the app enabled them to understand that in some cases patients did not follow their doctor’s treatment instructions, suggesting that patient guidance be implemented based on this feedback and that there is room for improvement in the quality of medical treatment. We are now analyzing data inputted by patients into the app and verifying the usefulness of the Skin Diary app in research and medical treatment. As a next step, we will revise the app with the aim of implementing it as a cloud-based medical app and/or tool for remote diagnosis. In addition, we are pursuing the establishment of preventive therapy through integrated analysis of clinical information and “real-world” data collected from patients at home such as treatment and life logs.

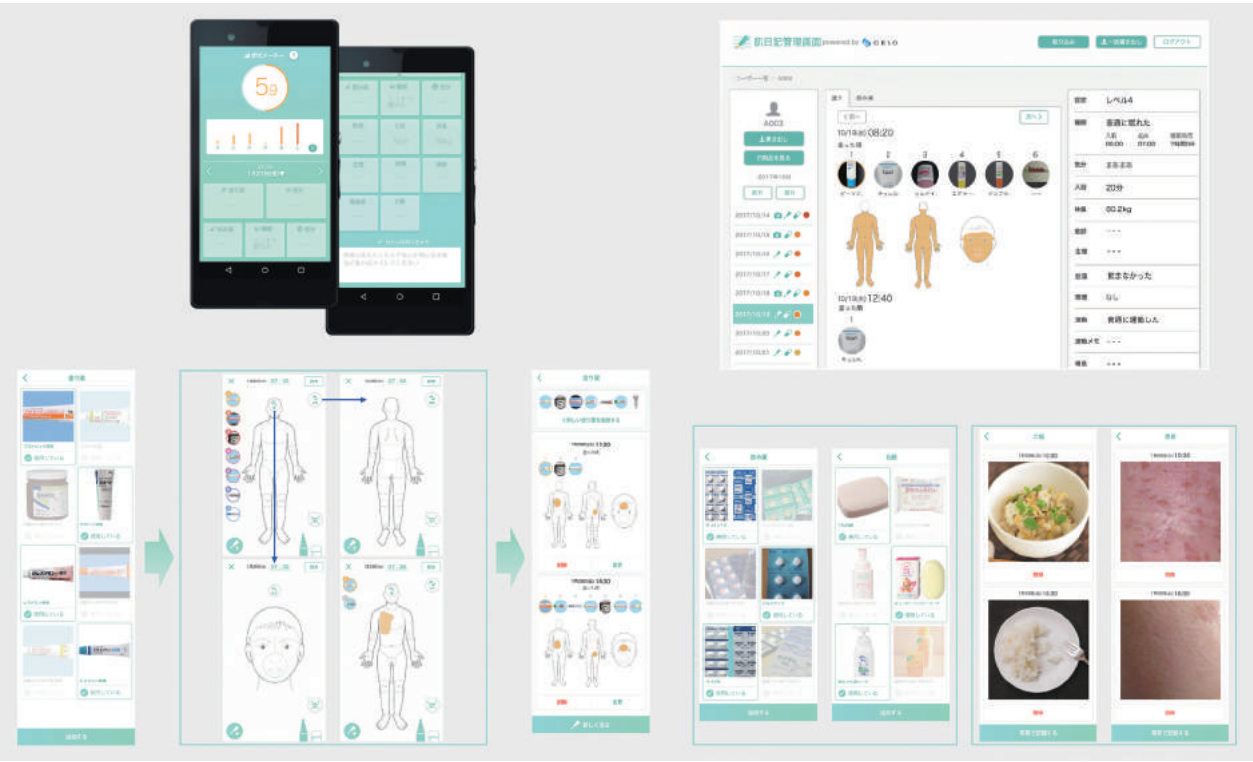
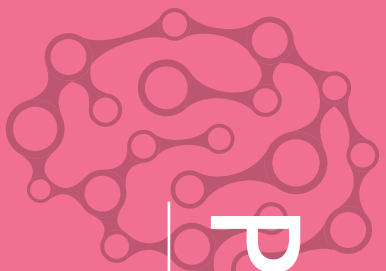


Figure: “Skin Diary”



Part 5

Publications

Original Articles

Title & Author(s)	Announcement Institutions (Participating Institutions only)
Takahide Nejo, Hirokazu Matsushita, Takahiro Karasaki, Masashi Nomura, Kuniaki Saito, Shota Tanaka, Shunsaku Takayanagi, Taijun Hana, Satoshi Takahashi, Yosuke Kitagawa, Tsukasa Koike, Yukari Kobayashi, Genta Nagae, Shogo Yamamoto, Hiroki Ueda, Kenji Tatsuno, Yoshitaka Narita, Motoo Nagane, Keisuke Ueki, Ryo Nishikawa, Hiroyuki Aburatani, Akitake Mukasa, Nobuhito Saito, and Kazuhiro Kakimi. Reduced Neoantigen Expression Revealed by Longitudinal Multiomics as a Possible Immune Evasion Mechanism in Glioma. ***Cancer Immunology Research.*** Published OnlineFirst 2019 May 14. doi: 10.1158/2326-6066.CIR-18-0599.	RIKEN, The University of Tokyo, Kyorin University, National Cancer Center Hospital, Dokkyo Medical University, Saitama Medical University
Eiryo Kawakami, Junya Tabata, Nozomu Yanaihara, Tetsuo Ishikawa, Keita Koseki, Yasushi Iida, Misato Saito, Hiromi Komazaki, Jason S. Shapiro, Chihiro Goto, Yuka Akiyama, Ryosuke Saito, Motoaki Saito, Hirokuni Takano, Kyosuke Yamada, and Aikou Okamoto. Application of artificial intelligence for preoperative diagnostic and prognostic prediction in epithelial ovarian cancer based on blood biomarkers. ***Clinical Cancer Research.*** Published OnlineFirst 2019 Apr 11. doi: 10.1158/1078-0432.CCR-18-3378.	RIKEN, The Jikei University School of Medicine
Rintaro Ono, Takashi Watanabe, Eiryo Kawakami, Makoto Iwasaki, Mariko Tomizawa-Murasawa, Masaya Matsuda, Yuho Najima, Shigeyuki Takagi, Soichiro Fujiki, Rikako Sato, Yusuke Mochizuki, Hiroshi Yoshida, Kohji Sato, Hiromasa Yabe, Shinya Kato, Yoshito Saito, Sakiko Taniguchi, Leonard D. Shultz, Osamu Ohara, Masayuki Amagai, Hirokazu Koseki, Fumitaro Ishikawa. Co-activation of macrophages and T cells contribute to chronic GVHD in human IL-6 transgenic humanised mouse model. ***EBioMedicine.*** 2019 Feb 13. S2352–3964(19)30073-8. doi: 10.1016/j.ebiom.2019.02.001.	RIKEN, Toranomon Hospital, Tokai University, The Jackson Laboratory, Kazusa DNA Research Institute, Keio University
Emily E. Ackerman, Eiryo Kawakami, Manami Katoh, Tokiko Watanabe, Shinji Watanabe, Yuriko Tomita, Tiago J. Lopes, Yukiko Matsuoka, Hiroaki Kitano, Jason E. Shoemaker, Yoshihiro Kawaoka. Network-Guided Discovery of Influenza Virus Replication Host Factors. ***MBio.*** 2018 Dec 18;9(6). pii: e02002-18. doi: 10.1128/mBio.02002-18.	The University of Pittsburgh, The University of Tokyo, Japan Science and Technology Agency, The Systems Biology Institute, The University of Wisconsin-Madison, RIKEN, OIST
Saori Sakaue, Jun Hirata, Yuichi Maeda, Eiryo Kawakami, Takuro Nii, Toshihiro Kishikawa, Kazuyoshi Ishigaki, Chikashi Terao, Ken Suzuki, Masato Akiyama, Naomasa Suita, Tatsuo Masuda, Kotaro Ogawa, Kenichi Yamamoto, Yukihiko Saeki, Masato Matsushita, Maiko Yoshimura, Hidetoshi Matsuoka, Katsunori Ikari, Atsuo Taniguchi, Hisashi Yamanaka, Hideya Kawaji, Timo Lassmann, Masayoshi Itoh, Hiroyuki Yoshitomi, Hiromu Ito, Koichiro Ohmura, Alistair R R Forrest, Yoshihide Hayashizaki, Piero Carninci, Atsushi Kumanogoh, Yoichiro Kamatani, Michiel de Hoon, Kazuhiko Yamamoto, Yukinori Okada. Integration of genetics and miRNA–target gene network identified disease biology implicated in tissue specificity. ***Nucleic Acids Research.*** 2018 Dec 14;46 (22), 11898–11909. doi: 10.1093/nar/gky1066.	Osaka University, RIKEN, The University of Tokyo, Teijin Pharma, Japan Agency for Medical Research and Development, Shizuoka Prefectural General Hospital, Shizuoka University, Kyoto University, Kyushu University, Ono Pharmaceutical Tsukuba Research Institute, National Hospital Organization Osaka Minami Medical Center, Saiseikai Senri Hospital, Tokyo Women's Medical University, Japan Science and Technology Agency, University of Western Australia
Benyamin Rosental, Mark Kowarsky, Jun Seita, Daniel M. Corey, Katherine J. Ishizuka, Karla J. Palmeri, Shih-Yu Chen, Rahul Sinha, Jennifer Okamoto, Gary Mantalas, Lucia Manni, Tal Raveh, D. Nathaniel Clarke, Jonathan M. Tsai, Aaron M. Newman, Norma F. Neff, Garry P. Nolan, Stephen r. Quake, Irving L. Weissman, & Ayelet Voskoboynik. Complex Mammalian-like Hematopoietic System Found in a Colonial Chordate. ***Nature.*** 2018 Dec;564(7736):425–429. doi: 10.1038/s41586-018-0783-x. Epub 2018 Dec 5.	Stanford University, RIKEN, Chan Zuckerberg Biohub, The University of California, University of Padua
Jonathan M. Tsai, Rahul Sinha, Jun Seita, Nathaniel Fernhoff, Simon Christ, Tim Koopmans, Geoffrey W. Krampitz, Kelly M. McKenna, Liujing Xing, Michael Sandholzer, Jennifer Horatia Sales, Maia Shoham, Melissa McCracken, Lydia-Marie Joubert, Sydney R. Gordon, Nicolas Poux, Gerlinde Wernig, Jeffrey A. Norton, Irving L. Weissman, and Yuval Rinkevich. Surgical adhesions in mice are derived from mesothelial cells and can be targeted by antibodies against mesothelial markers. ***Science Translational Medicine.*** 2018 Nov 28;10(469). pii: eaan6735. doi: 10.1126/scitranslmed.aan6735.	Stanford University, RIKEN, German Center for Lung Research
Charles K.F. Chan, Gunsagar S. Gulati, Rahul Sinha, Justin Vincent Tompkins, Michael Lopez, Ava C. Carter, Ryan C. Ransom, Andreas Reinisch, Taylor Wearda, Matthew Murphy, Rachel E. Brewer, Lauren S. Koepke, Owen Marecic, Anoop Manjunath, Eun Young Seo, Tripp Leavitt, Wan-Jin Lu, Allison Nguyen, Stephanie D. Conley, Ankit Salhotra, Thomas H. Ambrosi, Mimi R. Borrelli, Taylor Siebel, Karen Chan, Katharina Schallmoser, Jun Seita, Debashis Sahoo, Henry Goodnough, Julius Bishop, Michael Gardner, Ravindra Majeti, Derrick C. Wan, Stuart Goodman, Irving L. Weissman, Howard Y. Chang, Michael T. Longaker. Identification of the Human Skeletal Stem Cell. ***Cell.*** 2018 Sep 20;175(1):43–56.e21. doi: 10.1016/j.cell.2018.07.029.	Stanford University, University of Graz, RIKEN, The University of California

Title & Author(s)	Announcement Institutions (Participating Institutions only)
Daichi Shigemizu, Fuyuki Miya, Shintaro Akiyama, Shujiro Okuda, Keith A Boroevich, Akihiro Fujimoto, Hidewaki Nakagawa, Kouichi Ozaki, Shumpei Niida, Yonehiro Kanemura, Nobuhiko Okamoto, Shinji Saitoh, Mitsuhiro Kato, Mami Yamasaki, Tatsuo Matsunaga, Hideki Mutai, Kenjiro Kosaki & Tatsuhiko Tsunoda. IMSindel: An accurate intermediate-size indel detection tool incorporating de novo assembly and gapped global-local alignment with split read analysis. ***Scientific Reports.*** 2018 Apr 4;8(1):5608. doi: 10.1038/s41598-018-23978-z. Erratum in: Sci Rep. 2018 Jul 4;8(1):10367.	National Center for Geriatrics and Gerontology, Tokyo Medical and Dental University (TMDU), RIKEN, Niigata University, Kyoto University, Osaka Medical Center, Research Institute for Maternal and Child Health, Nagoya City University, Showa University, Takatsuki General Hospital, National Hospital Organization Tokyo Medical Center, Keio University
Wataru Ise, Kentaro Fujii, Katsuyuki Shiroguchi, Ayako Ito, Kohei Kometani, Kiyoshi Takeda, Eiryo Kawakami, Kazuo Yamashita, Kazuhiro Suzuki, Takaharu Okada, Tomohiro Kurosaki. T Follicular Helper Cell-Germinal Center B Cell Interaction Strength Regulates Entry into Plasma Cell or Recycling Germinal Center Cell Fate. ***Immunity.*** 2018 Apr 17;48(4):702–715.e4. doi: 10.1016/j.immuni.2018.03.027.	Osaka University, RIKEN, Japan Science and Technology Agency, Yokohama City University
Hanae Fujimoto, Yoriko Saito, Kenoki Ohuchida, Eiryo Kawakami, Saera Fujiki, Takashi Watanabe, Rintaro Ono, Akiko Kaneko, Shinsuke Takagi, Yuho Najima, Atsushi Hijikata, Lin Cui, Takashi Ueki, Yoshinao Oda, Shohei Hori, Osamu Ohara, Masafumi Nakamura, Takashi Saito and Fumihiko Ishikawa. Deregulated Mucosal Immune Surveillance through Gut-Associated Regulatory T Cells and PD-1+ T Cells in Human Colorectal Cancer. ***Journal of immunology.*** 2018 May 1;200(9):3291–3303. doi: 10.4049/jimmunol.1701222. Epub 2018 Mar 26.	Chiba University, RIKEN, Kyushu University, The University of Tokyo, Kazusa DNA Research Institute
Tomohiro Miyai, Junichiro Takano, Takaho A. Endo, Eiryo Kawakami, Yasutoshi Agata, Yasutaka Motomura, Masato Kubo, Yukie Kashima, Yutaka Suzuki, Hiroshi Kawamoto and Tomokatsu Ikawa. Three-step transcriptional priming that drives the commitment of multipotent progenitors toward B cells. ***Genes & Development.*** 2018 Jan 15;32(2):112–126. doi: 10.1101/gad.309575.117. Epub 2018 Feb 9.	RIKEN
Yuta Kochi, Yoichiro Kamatani, Yuya Kondo, Akari Suzuki, Eiryo Kawakami, Ryosuke Hiwa, Yukihide Momozawa, Manabu Fujimoto, Masatoshi Jinnin, Yoshiya Tanaka, Takashi Kanda, Robert G Cooper, Hector Chinoy, Simon Rothwell, Janine A Lamb, Jiří Vencovský, Heřman Mann, Koichiro Ohmura, Keiko Myouzen, Kazuyoshi Ishigaki, Ran Nakashima, Yuji Hosono, Hiroto Tsuboi, Hidenaga Kawasumi, Yukiko Iwasaki, Hiroshi Kajiyama, Tetsuya Horita, Mariko Ogawa-Momohara, Akito Takamura, Shinichiro Tsunoda, Jun Shimizu, Keishi Fujio, Hirofumi Amano, Akio Mimori, Atsushi Kawakami, Hisanori Umehara, Tsutomu Takeuchi, Hajime Sano, Yoshinao Muro, Tatsuya Atsumi, Toshihide Mimura, Yasushi Kawaguchi, Tsuneyo Mimori, Atsushi Takahashi, Michiaki Kubo, Hitoshi Kohsaka, Takayuki Sumida, Kazuhiko Yamamoto. Splicing variant of WDFY4 augments MDA5 signalling and the risk of clinically amyopathic dermatomyositis. ***Annals of the Rheumatic Diseases.*** 2018 Apr;77(4):602–611. doi: 10.1136/annrheumdis-2017-212149. Epub 2018 Jan 13.	RIKEN, University of Tsukuba, Kyoto University, Kanazawa University, Kumamoto University, University of Occupational and Environmental Health, Yamaguchi University, University of Liverpool, University of Manchester, Manchester Academic Health Science Centre, Charles University, Prague, Tokyo Women's Medical University, The University of Tokyo, Saitama Medical University, Hokkaido University, Nagoya University, Tokyo Medical and Dental University (TMDU), Hyogo College of Medicine, Juntendo University, National Center for Global Health and Medicine, Nagasaki University, Kanazawa Medical University, Keio University
Eiryo Kawakami, Naruhiko Adachi, Toshiya Senda, Masami Horikoshi. Leading role of TBP in the Establishment of Complexity in Eukaryotic Transcription Initiation Systems. ***Cell Reports.*** 2017 Dec 26;21(13):3941–3956. doi: 10.1016/j.celrep.2017.12.034.	RIKEN, The University of Tokyo, KEK
Mari Tenno, Katsuyuki Shiroguchi, Sawako Muroi, Eiryo Kawakami, Keita Koseki, Kirill Kryukov, Tadashi Imanishi, Florent Ginhoux, Ichiro Taniuchi. Cbfβ2 deficiency preserves Langerhans cell precursors by lack of selective TGFβ receptor signaling. ***Journal of Experimental Medicine.*** 2017 Oct 2;214(10):2933–2946. doi: 10.1084/jem.20170729. Epub 2017 Aug 16.	RIKEN
Norihito Hayatsu, Takahisa Miyao, Masashi Tachibana, Ryuichi Murakami, Akihiko Kimura, Takako Kato, Eiryo Kawakami, Takaho A. Endo, Ruka Setoguchi, Hiroshi Watarai, Takeshi Nishikawa, Takuwa Yasuda, Hisahiro Yoshida, Shohei Hori. Analyses of a Mutant Foxp3 Allele Reveal BATF as a Critical Transcription Factor in the Differentiation and Accumulation of Tissue Regulatory T Cells. ***Immunity.*** 2017 Aug 15;47(2):268–283.e9. doi: 10.1016/j.immuni.2017.07.008. Epub 2017 Aug 1.	RIKEN
Eiryo Kawakami, Shinji Nakaoka, Tazro Ohta, Hiroaki Kitano. Weighted enrichment method for prediction of transcription regulators from transcriptome and global chromatin immunoprecipitation data. ***Nucleic Acids Research.*** 2016 Jun 20;44(11):5010–21. doi: 10.1093/nar/gkw355. Epub 2016 Apr 30.	RIKEN, The University of Tokyo, DBCLS

Review Articles

Title & Author(s)	Announcement Institutions (Participating Institutions only)
Hiroshi Kawasaki, Ayano Fukushima. Metal allergy. ***jinshi kaiho.*** 2019 Mar. 18–26.	RIKEN, Keio University
Kazuhiro Kakimi. Genomic analysis of cancer immunology and immunograms. ***Medical Science Digest.*** 2019 Feb. Vol. 45(2), 91–94.	The University of Tokyo, RIKEN
Hiroshi Kawasaki. The role of skin microbiome in pathophysiology of atopic dermatitis. ***Nihon Rinsho.*** 2019 Jan. Vol. 77(1), 2–7.	The University of Tokyo, RIKEN
Koichi Ashizaki, Hiroshi Kawasaki, Eiryo Kawakami, Daichi Shigemizu, Kazuhiro Sakurada, Tatsuhiko Tsunoda, Tamotsu Ebihara, Masayuki Amagai. Constructing an automatic collection system for electronic medical records to facilitate data-driven research and outcomes of its implementation. ***Joint Conference on Medical Informatics Collected Papers.*** 2018 Nov. 38th edition, 470–473.	RIKEN, Keio University, National Center for Geriatrics and Gerontology
Kazuhiro Sakurada. What is holding back medical research? The complexity of life systems. Drug development in the AI era: problems and solutions. ***Japan Business Press.*** 2018 Oct 26.	RIKEN
Masatoshi Ukezono. Towards relational welfare services. ***Iroenpitsu Mental Health and Wellness Communities (NPO).*** 2018 Aug.	RIKEN
Ayano Fukushima, Hiroshi Kawasaki, Masayuki Amagai. Atopic dermatitis and skin barrier dysfunction. ***Journal of Clinical and Experimental Medicine (IGAKU NO AYUMI).*** 2018 Jun 2. Vol. 265(9), 812–817.	RIKEN, Keio University
Kazuhiro Sakurada. The key to success in healthcare services is personalized medicine! ***Nikkei Digital Health (medical information website).*** 2018 Apr 4.	RIKEN
Hiroshi Kawasaki, Akiharu Kubo. Latest allergy prevention and treatment strategies: the new way of thinking about allergies- atopic dermatitis and filaggrin. ***Japanese Journal of Pediatrics.*** 2017 Nov. Vol. 70(12), 1961–68.	RIKEN, Keio University
Kazuhiro Sakurada. How chemistry can contribute to nonlinear bioscience. ***Chemistry & Chemical Industry.*** 2017 Aug. Vol. 70(8).	RIKEN
Ichiro Miki, Kazuhiro Sakurada. Next-generation medicine will be built on AI: How is the future of healthcare changing? AI plus Big Data equals a medical revolution of optimal prevention and treatment personalized to each individual patient. ***Iryo Hakusho (Medical white paper).*** 2017 Aug. 2017–2018 Part 1, Vol. 3(5), 105–111.	RIKEN
Yusuke Takeshima, Yukiko Iwasaki, Tomohisa Okamura, Keishi Fujio, Kazuhiko Yamamoto. Pathology and systemic lupus erythematosus: possibilities for new clinical applications. ***Immunological Medicine.*** 2017 May. 40(1):40–46 (2017).	The University of Tokyo
Kazuhiro Sakurada. Combining AI and physician expertise makes predictive and preventive personalized medicine possible. ***Saishin Iryo Keiei Phase3.*** 2017 Apr. Vol. 392.	RIKEN
Eiryo Kawakami, Tazro Ohta. Building a gene regulatory network using public high-throughput ChIP data and how to use it. ***Jikken Igaku (Experimental Medicine).*** 2017 Mar. Vol. 35(5)	RIKEN, DBCLS
Hiroshi Kawasaki, Eiryo Kawakami, Masayuki Amagai, Haruhiko Koseki. Tackling the complexity and heterogeneity of life systems: open systems science is a new style of research for making new discoveries; case of reverse translational research on atopic dermatitis. ***Jikken Igaku (Experimental Medicine).*** 2016 Dec 20. 2017, 35(1), 33–39.	RIKEN, Keio University
Kazuhiro Sakurada. Planning how to tackle the complexity and heterogeneity of life systems: open systems science is a new style of research for making new discoveries. ***Jikken Igaku (Experimental Medicine).*** 2016 Dec 20. 2017, 35(1), 2–49.	RIKEN

Part 6

Data and statistics

Invited Presentations

Title & Presenter(s)	Announcement Institutions (Participating Institutions only)
Kazuhiro Sakurada. "How is artificial intelligence different from human intelligence?". Knowledge Management Society of Japan Seminar. Tokyo. 2019 Mar 13.	RIKEN
Mayumi Kusunose. Clinical ethics of decision-making about healthcare at the end-of-life stage. Series 6. Learning clinical ethics: let's try having a clinical ethics consultation/conference with a team incorporating multiple professions! (hosted by Kochi University Hospital). Kochi. 2019 Mar 16.	RIKEN
Kazuhiko Sakurada. "New biomedical sciences in the age of artificial intelligence". Senri Life Science Seminar M5: Big Data and AI Medicine. Osaka. 2019 Feb 13.	RIKEN
Eiryo Kawakami. "Disease stratification and prediction based on machine learning and mathematical science". Senri Life Science Seminar M5: Big Data and AI Medicine. Osaka. 2019 Feb 13.	RIKEN
Kazuhiko Sakurada. "On the future society of the artificial intelligence age". Terashima Strategic Management School. Tokyo. 2019 Feb 4.	RIKEN
Kazuhiko Sakurada. "How is artificial intelligence different from human intelligence?". KEIO WIZARD. Kawasaki. 2019 Feb 3.	RIKEN
Koichi Ashizaki. "A clinical research platform for atopic dermatitis research". Dupixent Atopic Conference. Tokyo. 2019 Jan 25.	RIKEN
Hiroshi Kawasaki. "Efforts toward achieving personalized medicine for atopic dermatitis". Dupixent Atopic Conference. Tokyo. 2019 Jan 25.	RIKEN, Keio University
Eiryo Kawakami. "Data-driven medical records data analysis by machine learning". Institute of Statistical Mathematics 2018 Research Collaboration Key Theme: New developments in statistical machine learning: Research Conference Program. Tokyo. 2019 Jan 17.	RIKEN
Jun Seita. "Deep learning in medicine". Keio Medical AI Center 2nd Seminar. Tokyo. 2019 Jan 17.	RIKEN
Kazuhiro Sakurada. "AI for precision medicine". The 10th International Symposium for Future Technology Creating Better Human Health and Society: Connecting Innovation with Social Issues. Okayama. 2019 Jan 16.	RIKEN
Kazuhiro Sakurada. "The new shape of life sciences and data platforms in the age of IoT/AI". Open Innovation Consortium, The 1st Symposium. Osaka. 2019 Jan 11.	RIKEN
Kazuhiro Sakurada. "How the age of AI will transform medical research and healthcare". Yamaguchi University AISMEC Seminar. Yamaguchi. 2019 Jan 10.	RIKEN
Kazuhiro Sakurada. "AI and onsen". The Forum on Thermalism in Japan, 83rd Monthly Research Forum. Tokyo. 2018 Dec 12.	RIKEN
Kazuhiro Sakurada. "A new paradigm for bioscience in the age of AI: an outlook on life systems that is comfortable with complexity". A conversation with Dr. Kazuhiro Sakurada. Sapporo. 2018 Dec 18.	RIKEN
Kazuhiro Sakurada. "How is human intelligence different from AI?". 45th Spiritual Science Project Forum. Kyoto. 2018 Dec 15.	RIKEN
Kazuhiro Sakurada. "The new shape of healthcare and medicine in the age of AI: Collecting and utilizing life course data". University of Electro-Communications 116th Research Seminar: Advances in AI and comprehensive communications sciences: at the forefront of AI: learning from humans and learning where AI can shine. Tokyo. 2018 Dec 5.	RIKEN
Kazuhiro Sakurada. "From logic machines to cognitive processing". Japan Developmental Neuroscience Society 7th Academic Meeting. Tokyo. 2018 Nov 24.	RIKEN
Kazuhiro Sakurada. "Artificial intelligence in precision medicine". Artificial Intelligence – International Research and Applications: 1st Japanese-German-French DWIH Symposium. Tokyo. 2018 Nov 21.	RIKEN
Kazuhiro Sakurada. "Personalized medicine, UHC (Universal Health Coverage), and gut flora". 24th International Congress of Personalized Medicine. Tokyo. 2018 Nov 18.	RIKEN
Eiryo Kawakami. "Data-driven systems medicine to elucidate and predict heterogeneous disease". South Lake Workshop in Bioinformatics and System Biology, Wuhan University of Technology. China. 2018 Nov 17.	RIKEN

Title & Presenter(s)	Announcement Institutions (Participating Institutions only)
Kazuhiro Kakimi. "Personalized and integrative medicine for cancer immunotherapy". Symposium of the Japan Association for Omics-based Medicine: latest developments in methods in cancer immunotherapy. Tokyo. 2018 Nov 12.	The University of Tokyo, RIKEN
Hiroshi Kawasaki. "Skin condition/characteristics and skin flora". 43rd Educational Seminar of the Japanese Cosmetic Science Society: Keeping Healthy Skin: Aging Care Forefront. Tokyo. 2018 Nov 2.	RIKEN, Keio University
Hiroshi Kawasaki. "How should we think about atopic dermatitis diagnosis in light of the advent of bioformulation?". 4th Shinanomachi Clinical Dermatology Conference. Tokyo. 2018 Oct 25.	RIKEN, Keio University
Kazuhiro Kakimi. "Basic science of cancer immunology". 56th Annual Meeting of Japan Society of Clinical Oncology. Yokohama. 2018 Oct 19.	The University of Tokyo, RIKEN
Kazuhiro Kakimi. "Cancer immunotherapy: what is the next step beyond immune checkpoint blockade therapies?". 36th Kyoto cancer research society. Kyoto. 2018 Oct 12.	The University of Tokyo, RIKEN
Eiryo Kawakami, Tetsuo Ishikawa. "Evaluate Cellular Stability and Transition Based on Single-cell Transcriptome Data". Single Cell Science Symposium 2018: Single Cell Technologies Toward Human Health. Tokyo. 2018 Oct 9.	RIKEN
Kazuhiro Sakurada. "Can AI surpass human intelligence? Rhythm synchronization and intelligence". 82nd Annual Convention of the Japanese Psychological Association. Sendai. 2018 Sep 26.	RIKEN
Eiryo Kawakami. "Approaches based on machine learning and mathematical science towards precision/individualized medicine". Joint RIKEN-Luxembourg Symposium 2018, the University of Luxembourg. Luxembourg. 2018 Sep 25.	RIKEN
Jun Seita. "Objective Gene Expression Profiling by Gene Expression Commons for RNA-seq". Joint RIKEN-Luxembourg Symposium 2018, the University of Luxembourg. Luxembourg. 2018 Sep 25.	RIKEN
Kazuhiro Kakimi. "Cancer immunotherapy using neoantigen biomarkers". 27th Annual Meeting of the Japanese Society for Histocompatibility and Immunogenetics. Nagano. 2018 Sep 21.	The University of Tokyo, RIKEN
Yukuo Konishi. "On vitamin D in pregnant women". Kurume University –RIKEN Joint Laboratory for Pediatric Diseases Opening Commemorative Lecture Meeting. Fukuoka. 2018 Sep 20.	RIKEN, Kurume University, Fukuoka BioValley Project
Kazuhiro Sakurada. "The description of biological phenomena as an open system using machine learning and Markov constraint". The 5th RIKEN-KI/SciLifeLab Joint Symposium Artificial Intelligence Meets Life Sciences. Stockholm. 2018 Sep 20.	RIKEN
Eiryo Kawakami. "A machine learning approach based on preoperative blood makers for diagnostic and prognostic prediction of epithelial ovarian". 60th Conference of the Japan Society of Gynecologic Oncology. Kyoto. 2018 Sep 16.	RIKEN
Kazuhiro Sakurada. "How AI and brain science are changing the future of the healthcare and beauty industries". Beauty & Wellness Summit. Tokyo. 2018 Sep 10.	RIKEN
Kazuhiro Sakurada. "Why AI cannot surpass human intelligence: how the science of thinking about thinking is shaping the values of Society 5.0". The Akiyama Life Science Foundation Special Lecture 2018. Sapporo. 2018 Sep 5.	RIKEN
Mayumi Kusunose. "Clinical ethics for pharmacists : considering medicine that supports sentinel clinical ethics for pharmacists in the era of 100-year lifespans". The Next-Generation Pharmacists Seminar. Kochi. 2018 Sep 2.	RIKEN
Eiryo Kawakami. "Using machine learning and mathematical science to grapple with the heterogeneity and individuality of patients". The 30th Takato Molecular Cell Biology Symposium. Nagano. 2018 Aug 23.	RIKEN
Kazuhiro Sakurada. "The new shape of healthcare and medicine in the age of AI, IQVIA Seminar". Tokyo. 2018 Aug 23.	RIKEN
Kazuhiro Sakurada. "The new shape of life sciences and medicine in the age of AI". 2nd Symposium of AI Systems Medicine Research and Training Center at Yamaguchi University. Yamaguchi. 2018 Aug 4.	RIKEN
Kazuhiro Kakimi. "Immunosurveillance using next-generation sequencers". 22nd Annual Meeting of the Japanese Association of Cancer Immunology. Okayama. 2018 Aug 1.	The University of Tokyo, RIKEN

Title & Presenter(s)	Announcement Institutions (Participating Institutions only)
Eiryo Kawakami. "AI analysis of medical data for predictive, personalized medicine". Chiba University. Chiba. 2018 Jul 31.	RIKEN
Jun Seita. "Objective gene expression profiling by gene expression commons". ZPM-RIKEN Symposium Integrative Personalized Medicine –Connecting genomics, microbiomics and metabolomics. Tubingen. 2018 Jul 16.	RIKEN
Kazuhiro Sakurada. "The description of biological phenomena as an open system: Realization of precision medicine". ZPM-RIKEN Symposium Integrative Personalized Medicine –Connecting genomics, microbiomics and metabolomics, Tubingen. 2018 Jul 16.	RIKEN
Kazuhiro Sakurada. "The new shape of healthcare and preventive medicine in the age of AI: it's all about healing people suffering from diseases". The Graduate School of Project Design. Tokyo. 2018 Jul 12.	RIKEN
Kazuhiro Sakurada. "The new shape of healthcare and preventive medicine in the age of AI: thinking about the meaning of life and humanity". The 4th Gakushuin University Branding Symposium. Tokyo. 2018 Jul 7.	RIKEN
Ichiro Miki. "The AI doctor". 8th Term of Successful Aging Community Minato University, Lecture #4. Tokyo. 2018 Jul 7.	RIKEN
Kazuhiro Sakurada. "How life sciences in the age of AI will usher in Society 5.0". BIO tech 2018. Tokyo. 2018 Jun 28.	RIKEN
Kazuhiro Sakurada. "Life sciences in the age of AI". 417th Kawasaki Medical University Lecture. Okayama. 2018 Jun 20.	RIKEN
Hiroshi Kawasaki. "Skin flora of atopic dermatitis patients and efforts to bring personalized medicine to atopic dermatitis". Sanofi Lecture. Tokyo. 2018 Jun 5.	RIKEN, Keio University
Kazuhiro Sakurada. "Creating new value in the age of Society 5.0". PHC (formerly Panasonic Healthcare) Lecture. Gunma. 2018 May 17.	RIKEN
Kazuhiro Sakurada. "Can AI surpass human intelligence?". Hosei University Workshop. Tokyo. 2018 May 12.	RIKEN
Kazuhiro Sakurada. "Reshaping the life sciences and ushering in Society 5.0". Life Innovation Platform (LIP) Yokohama Network Seminar. Yokohama. 2018 March 29.	RIKEN
Hiroshi Kawasaki. "Skin flora of atopic dermatitis patients". The 28th Skin Immunological Cancer Research Conference. Tokyo. 2018 Mar 22.	RIKEN, Keio University
Mayumi Kusunose. "Suggestions for clinical ethics conferences that address ethical challenges across multiple professions". Learning clinical ethics: let's try having a clinical ethics consultation/ conference with a team incorporating multiple professions! (hosted by Kochi University Hospital). Kochi. 2018 Feb 17.	RIKEN
Kazuhiro Sakurada. "Life sciences in the age of AI". 13th RIKEN Symposium on Digital & Bio Fabrication. Wako. 2018 Mar 9.	RIKEN
Kazuhiro Sakurada. "Life science paradigm shift: from finding principles to solving problems". 73rd Advanced Institute of Wearable Environmental Information Networks Conference/28th Academy of Human Informatics Conference. Tokyo. 2017 Dec 14.	RIKEN
Kazuhiro Sakurada. "The new shape of life sciences in the age of AI: predictive and personalized medicine". 29th Sanwaka Seminar (Japan Society for Bioscience, Biotechnology, and Agrochemistry). Tokyo. 2017 Dec 13.	RIKEN
Eiryo Kawakami. "Data-driven approaches to biomedical research". MEXT Doctoral Program for Data-Related InnoVation Expert (D-DRIVE). Tokyo. 2017 Dec 12.	RIKEN
Kazuhiro Sakurada. "How AI and IoT are changing the future of healthcare : harnessing real-time personal medical information: new challenges and possibilities". Special Seminar on the Elderly and Healthcare. Tokyo. 2017 Dec 6.	RIKEN
Hiroshi Kawasaki. "Microbiomes and atopic dermatitis". 13th TAP (Tokyo scientific forum for Atopic Dermatitis and Psoriasis). Tokyo. 2017 Dec 2.	RIKEN, Keio University
Eiryo Kawakami. "Data-driven approaches to biomedical research". 9th JST Mathematical Design Dojo. Okinawa. 2017 Nov 29.	RIKEN

Title & Presenter(s)	Announcement Institutions (Participating Institutions only)
Kazuhiro Sakurada. "Heterogeneity of human cognition and its origins". 6th Conference of the Japan Developmental Neuroscience Society. Osaka. 2017 Nov 25.	RIKEN
Kazuhiro Sakurada. "How is the future of healthcare changing?". Japan Business Federation Workshop. Tokyo. 2017 Oct 30.	RIKEN
Jun Seita. "What is the role of systems biology in clinical medicine?". 49th Annual Meeting of the Japanese Society for Pediatric Infectious Diseases. Kanazawa. 2017 Oct 22.	RIKEN
Kazuhiro Sakurada. "Biotechnology strategy: creating value with IoT/Big Data: How is the future of healthcare changing?". CEATEC JAPAN 2017 Conference. Chiba. 2017 Oct 5.	RIKEN
Jun Seita. "Objective gene expression profiling by global-scale meta-analysis of expression dynamic-range". Luxembourg FNR-RIKEN Joint Symposium. Yokohama. 2017 Oct 4.	RIKEN
Kazuhiro Sakurada. "Open Systems Science: from understanding principles to solving problems". Luxembourg FNR-RIKEN Joint Symposium. Yokohama. 2017 Oct 4.	RIKEN
Kazuhiro Sakurada. "A new AI-centric framework for data analysis in medicine and pharmacology". 11th Pharma AI Forum. Tokyo. 2017 Sep 28.	RIKEN
Kazuhiro Sakurada. "What is life? Freedom emerging from coordination". The Akiyama Life Science Foundation Special Lecture 2017. Sapporo. 2017 Sep 7.	RIKEN
Kazuhiro Sakurada. "How sensors and AI will create personalized medicine-based healthcare". 78th JSAP Fall Meeting Special Symposium. Fukuoka. 2017 Sep 5.	RIKEN
Kazuhiro Sakurada. "Combining data and simulation to bring about predictive and preventive personalized medicine". K x Data Science Symposium. Tokyo. 2017 Aug 25.	RIKEN
Kazuhiro Sakurada. "The reasons behind poor medical services". Grand Design by Japan. Yokohama. 2017 Aug 6.	RIKEN
Kazuhiro Sakurada. "Predictive and preventive personalized medicine based on open systems science". Institute of Biomedical Research and Innovation Symposium. Kobe. 2017 Jul 24.	RIKEN
Kazuhiro Sakurada. "Developing new reasoning for predictive and preventive personalized medicine". Symposium of MEXT-Supported Program for the Strategic Research Foundation at Private Universities 2017. Tochigi. 2017 Jul 10.	RIKEN
Kazuhiro Sakurada. "Predictive and preventive personalized medicine based on open systems science". Yamaguchi University School of Medicine Symposium. Yamaguchi. 2017 Jul 24.	RIKEN
Eiryo Kawakami. "Data-driven approaches for biomedical research". 3rd Bioinformatics Conference (Institute for Frontier Life and Medical Sciences, Kyoto University). 2017 May 29.	RIKEN
Hiroshi Kawasaki. Making personalized medicine for atopic dermatitis a reality: the paradigm shift to data-centric medicine. 90th Kanagawa Organization of Clinical Dermatologists Academic Conference. 2017 May 13.	RIKEN
Hiroshi Kawasaki. "Heterogeneity of pathology in atopic dermatitis". 33rd Annual Meeting of Japan Organization of Clinical Dermatologists. Kobe. 2017 Apr 23.	RIKEN
Kazuhiro Sakurada. "An endeavor to create new businesses and a 'meta-comfort' and smart society". Keihanna Research Complex Opening Symposium. Kyoto. 2017 Mar 27.	RIKEN
Hiroshi Kawasaki. "Skin barrier function in atopic dermatitis". Protopic Old & New Children Seminar 2017. Tokyo. 2017 Mar 5.	RIKEN
Hiroshi Kawasaki. "Atopic dermatitis and skin barrier". The 80nd Annual Meeting of the Tokyo Division of Japanese Dermatological Association. Yokohama. 2017 Feb 11.	RIKEN
Kazuhiro Sakurada. "Open systems science: The new shape of life sciences in the age of AI". RIKEN Center for Computational Science Seminar. Kobe. 2017 Feb 6.	RIKEN
Kazuhiro Sakurada. "How the humanities can create new health value: information geometry unifies IoT, Big Data and AI". University of Electro-Communications 107th Research Seminar. Tokyo. 2017 Jan 26.	RIKEN
Hiroshi Kawasaki. "Untangling the heterogeneity of atopic dermatitis: towards medicinal care optimized to the individual". Shimizu allergic disease conference. Shizuoka. 2016 Dec 22.	RIKEN

Title & Presenter(s)	Announcement Institutions (Participating Institutions only)
Kazuhiro Sakurada. "About the RIKEN Medical Innovation Hub Promotion Program". Tonomachi Research Complex. Kawasaki. 2016 Dec 7.	RIKEN
Kazuhiro Sakurada. "About the RIKEN Medical Innovation Hub Promotion Program". Life Innovation Platform (LIP) Yokohama Kickoff Symposium. Yokohama. 2016 Dec 1.	RIKEN
Kazuhiro Sakurada. "Aiming for a society where people live long and healthy lives: shifting from regenerative medicine to preventive medicine". The University of Tokyo Graduate School of Frontier Sciences Computational Biology and Medical Sciences. Tokyo. 2016 Oct 28.	RIKEN
Kazuhiro Sakurada. "Harnessing AI to bring about a healthy society". Tsukuba Clinical Research & Development Organization Public Lecture. Ibaraki. 2016 Oct 26.	RIKEN
Kazuhiro Sakurada. "Thinking about aging in terms of the new shape of life sciences: from understanding principles to solving problems". JST CRDS Aging Workshop. Tokyo. 2016 Jul 31.	RIKEN
Kazuhiro Sakurada. "What designing intangible products can teach us about designing tangible products". Terashima Strategic Management School. Tokyo. 2016 Jun 23.	RIKEN
Kazuhiro Sakurada. "Open innovation leading to personalized medicine". Keihanna Research Complex 5th Open Innovation Workshop. Kyoto. 2016 Jun 23.	RIKEN
Kazuhiro Sakurada. "Unifying the information revolution and the biomechanical revolution: predictive and preventive medicine based on IoT and AI". BIO tech 2016. Tokyo. 2016 May 12.	RIKEN

International Conference

Title & Presenter(s)	Announcement Institutions (Participating Institutions only)
Tatsuki Koga, Naoki Nonaka, Jun Sakuma and Jun Seita. "General-to-Detailed GAN for Infrequent Class Medical Images". NIPS (Neural Information Processing System) Annual Meeting. Montreal, Canada. 2018 Dec 8.	RIKEN
Yoko Nakatake, Misa Yamada, Hiroki Furuie, Hiroshi Kuniishi, Masatoshi Ukezono, Kazumi Yoshizawa, Mitsuhiko Yamada. "Chronic social defeat stress induces social avoidance and changes the plasma cytokines levels in mice". A poster presented at The Society for Neurosicence. San Diego, USA. 2018 Nov 3.	RIKEN, National Center of Neurology and Psychiatry
Jun Seita, Hiroki Sugishita, Eiryo Kawakami, Tarzo Ohta. "System-level Gene Expression Profiling by Gene Expression Commons for RNA-seq". 19th International Conference on Systems Biology. Lyon, France. 2018 Oct 28–Nov 1.	RIKEN, NBDC
Yuji Takano, Satoshi Nakashima, Masatoshi Ukezono, Nobuaki Takahashi. "Anterior cingulate cortex lesion changes ultrasonic vocalization in rats". A poster presented at The 11th Federation of European Neuroscience Societies. Berlin, Germany. 2018 Jul 11.	RIKEN, Tohoku University, Hiroshima Shudo University, Bukkyo University
Masatoshi Ukezono, Yuji Takano. "Development of an experimental task for the mirror system in mice". A poster presented at The 11th Federation of European Neuroscience Societies. Berlin, Germany. 2018 Jul 10.	RIKEN, Tohoku University
Fumiyo Yasuda-Sekiguchi, Aiko Shiohama, Hiroshi Kawasaki, Tamotsu Ebihara, Akiharu Kubo, Masayuki Amagai, Takashi Sasaki. "Genetic variants in TLR1, TIRAP and PSAPL1 are enriched in a specific subgroup of adult atopic dermatitis showing persistent skin manifestation on the face and neck area". International Investigative Dermatology 2018. Orlando, USA. 2018 May 19.	RIKEN, Keio University
Horoshi Kawasaki, Eiryo Kawakami, Shoko Obata, Ayano Fukushima, Fumiyo Yasuda-Sekiguchi, Takashi Sasaki, Wataru Suda, Kenya Honda, Tamotsu Ebihara, Masayuki Amagai. "Quantitative skin microbiome analysis enables to understand microbial species associated with atopic dermatitis in higher resolution". International Investigative Dermatology 2018. Orlando, USA. 2018 May 16–19.	RIKEN, Keio University
Eiryo Kawakami, Hiroshi Kawasaki, Shoko Obata, Aki Honda, Naoko Mochimaru, Ayano Fukushima, Fumiyo Yasuda-Sekiguchi, Takashi Sasaki, Wataru Suda, Kenya Honda, Tamotsu Ebihara, Masayuki Amagai. "Dynamic transition of the human skin microbial patterns associated with atopic dermatitis pathology". Cell Symposia Next Gen Immunology. Rehovot, Israel. 2018 Feb 11.	RIKEN

Domestic Conference

Title & Presenter(s)	Announcement Institutions (Participating Institutions only)
Hiromi Oonagi, Junko Uda, Hiroshi Fujita, Takashi Shuto, Takahiro Nakayama, Junichi Fujimoto, Mayumi Kusunose, Yoji Mikami. "Ethics consultation 2: ethical challenges in explaining the condition of advanced cancer to patients and their families". The 7th Annual Conference of the Japan Association for Clinical Ethics. Tokyo. 2019 Mar 30–31.	Yokohama Rosai Hospital, RIKEN
Takahiro Nakayama, Yoko Baba, Mayumi Kusunose, Junko Uda, Hiromi Oonagi, Takashi Shuto, Hiroshi Fujita, Yoji Mikami. "An examination of the contribution and effect of clinical ethics consultation: an approach to education and training for clinical ethics consultation". The 7th Annual Conference of Japan Association for Clinical Ethics. Tokyo. 2019 Mar 30–31.	Yokohama Rosai Hospital, Japan Organization of Occupational Health and Safety, RIKEN
Chiemi Nagai, Shoichi Hishinuma, Mayumi Kusunose, Kazuto Inaba. "The effect of introducing link-staff and ethics team systems on improving clinical case consultation". The 7th Annual Conference of the Japan Association for Clinical Ethics. Tokyo. 2019 Mar 30–31.	Tochigi Cancer Center, RIKEN, Chukyo University
Kayo Takashima, Mayumi Kusunose, Shimon Tashiro, Fumitaka Nagamura, Kaori Muto. "Possibilities and challenges of e-IC (electronic explanation/consent acquisition) in clinical trials of regenerative medicine". The 18th Congress of The Japan Society for Regenerative Medicine. Kobe. 2019 Mar 21–23.	The University of Tokyo, National Cancer Center Japan, RIKEN
Kazuhiro Kakimi. "Immunogram for the Cancer-Immunity Cycle". The 16th Annual Meeting of Japan Research Association for Immunotherapeutics. Tokyo. 2019 Feb 23.	The University of Tokyo, RIKEN
Akihiro Hosoi, Koji Nagaoka, Kazutaka Kitaura, Ryuji Suzuki, Kazuhiro Kakimi. "Detection of tumor-specific T cells using RNA-based T cell receptor (TCR) repertoire analysis". The 16th Annual Meeting of Japan Research Association for Immunotherapeutics. Tokyo. 2019 Feb 23.	The University of Tokyo Hospital, RIKEN, MEDINET Co., Ltd., Repertoire Genesis Inc.
Yasuyoshi Sato, Koichi Yagi, Takamichi Izumi,Shinnocuke Kimura, Fumiya Kobayashi, Nao Fujieda, Yukari Kobayashi, Kazuhiro Kakimi, Yasuyuki Seto. "Combination of chemotherapy with docetaxel/ cisplatin/ fluorouracil (DCF) and autologous gamma/delta T cell transfer therapy for esophageal cancer". The 16th Annual Meeting of Japan Research Association for Immunotherapeutics. Tokyo. 2019 Feb 23.	The University of Tokyo Hospital, RIKEN, MEDINET Co., Ltd.
Yasuyoshi Sato, Koichi Yagi, Takamichi Izumi,Shinnosuke Kimura, Fumiya Kobayashi, Hiromi Otsuka, Nao Fujieda, Yukari Kobayashi, Kazuhiro Kakimi, Yasuyuki Seto. "The efficacy and safety of autologous gamma/delta T cell transfer therapy for esophageal cancer". The 16th Annual Meeting of Japan Research Association for Immunotherapeutics. Tokyo. 2019 Feb 23.	The University of Tokyo Hospital, RIKEN, MEDINET Co., Ltd.
Akihiko Matsumoto, Yusuke Sato, Taketo Kawai, Takamichi Izumi, Shinnosuke Kimura, Fumiya Kobayashi, Nao Fujieda, Yukari Kobayashi, Kazuhiro Kakimi, Haruki Kume. "Safety, efficacy and immunogenicity of autologous tumor lysate-pulsed dendritic cell therapy in patients with advanced renal cell carcinoma". The 16th Annual Meeting of Japan Research Association for Immunotherapeutics. Tokyo. 2019 Feb 23.	The University of Tokyo Hospital, RIKEN, MEDINET Co., Ltd.
Mayumi Kusunose, Kaori Muto. "The current situation and challenges of the EU General Data Protection Regulation (GDPR) in research: UK-US survey report on GDPR". The 4th annual conference on The Dialogue on Research Ethics at Nagoya University Hospital. Aichi. 2019 Feb 9.	RIKEN, The University of Tokyo
Tetsuo Ishikawa, Eiryo Kawakami. "Predicting onset of stage 2 diabetes using energy landscape analysis". 3rd Theoretical Immunology Workshop. Akita. 2019 Jan 25.	RIKEN
Yuki Goshima, Eiryo Kawakami. "Mathematics and the evaluation of collagen disease treatment". 3rd Theoretical Immunology Workshop. Akita. 2019 Jan 25.	RIKEN
Eiryo Kawakami. "Disease stratification and prediction by machine learning". 3rd Theoretical Immunology Workshop. Akita. 2019 Jan 25.	RIKEN
Naoko Mochimaru, Hiroshi Kawasaki, Ayano Fukushima, Shoko Obata, Fumiyo Sekiguchi, Riko Oohashi, Hatsumi Maeo, Masayuki Amagai, Tamotsu Ebihara. "Investigating the effectiveness of Skin Diary, a smartphone application through which atopic dermatitis patients record their treatment situation and skin condition at home". The 82nd Annual Meeting of the Tokyo Division of Japanese Dermatological Association. Tokyo. 2018 Dec 1.	RIKEN, Keio University
Eiryo Kawakami. "Understanding metabolic adaptation through transcriptomic analysis". 41st Annual Meeting of The Molecular Biology Society of Japan. Yokohama. 2018 Nov 30.	RIKEN

Title & Presenter(s)	Announcement Institutions (Participating Institutions only)
Koichi Ashizaki, Hiroshi Kawasaki, Eiryo Kawakami, Daichi Shigemizu, Kazuhiro Sakurada, Tatsuhiko Tsunoda, Tamotsu Ebihara, Masayuki Amagai. "Constructing an automatic collection system for electronic medical records to facilitate data-driven research and outcomes of its implementation". 38th Joint Conference on Medical Informatics/19th Annual Meeting of Japan for Medical Informatics. Fukuoka. 2018 Nov 23.	RIKEN, Keio University, National Center for Geriatrics and Gerontology
Yoko Nakatake, Hiroki Furuie, Misa Yamada, Hiroshi Kuniishi, Masatoshi Ukezono, Kazumi Yoshizawa, Mitsuhiko Yamada. "Mental stress and physical stress have different effects on the behavior and immune systems of mice". 48th Annual Meeting of Japanese Society of Neuropsychopharmacology. Tokyo. 2018 Nov 14.	RIKEN, National Center of Neurology and Psychiatry
Mayumi Kusunose. "The current situation and challenges of the EU General Data Protection Regulation (GDPR) in research: UK-US survey report on GDPR". The second joint conference of RIKEN Safety Centers. Ibaraki. 2018 Nov 2.	RIKEN
Mayumi Kusunose. "The current situation and challenges of the EU General Data Protection Regulation (GDPR) in research: UK-US survey report on GDPR". Regular Study Seminar at Uehiro Research Division for iPS Cell Ethics. Kyoto. 2018 Oct 31.	RIKEN
Mayumi Kusunose. "The current situation and challenges of the EU General Data Protection Regulation (GDPR) in research: UK-US survey report on GDPR". Regular Session of the Research Ethics Study Group. Tokyo. 2018 Oct 19.	RIKEN
Eiryo Kawakami. "Young panel discussion: the present and future of dry analysis in genomics: genetics, GWAS, omics, and AI". 63rd Annual Meeting of the Japan Society of Human Genetics. Yokohama. 2018 Oct 13.	RIKEN
Ayano Fukushima, Hiroshi Kawasaki, Shoko Obata, Fumiyo Sekiguchi, Tamotsu Ebihara, Koichi Ashizaki, Eiryo Kawakami, Masayuki Amagai. "Atopic dermatitis patient clustering based on antigen-specific IgE value patterns". The 82nd Annual Meeting of the Eastern Division of Japanese Dermatological Association. Asahikawa. 2018 Oct 6.	RIKEN, Keio University
Masatoshi Ukezono. "Theoretical re-construction of social facilitation and inhibition: beyond Zajonc's drive theory". 82nd Annual Convention of the Japanese Psychological Association. Sendai. 2018 Sep 27.	RIKEN
Ryunosuke Sudo, Masatoshi Ukezono, Yuji Takano, Satoshi Nakashima. "Influence of thermal environment on moral deicison-making: do cold or heat affect moral judgments?". 82nd Annual Convention of the Japanese Psychological Association. Sendai. 2018 Sep 27.	RIKEN, Kyushu University, Tohoku University, Hiroshima Shudo University
Masatoshi Ukezono. "The future research of social facilitation in the real world rather than in the laboratory". 82nd Annual Convention of the Japanese Psychological Association. Sendai. 2018 Sep 27.	RIKEN
Shunsuke Kidani, Yuji Takano, Kosuke Taniguchi,Yukihisa Minoura, Masatoshi Ukezono. "How children control vocal pitch and sound pressure under noisy conditions". Acoustical Society of Japan 2018 Autum Meeting. Oita. 2018 Sep 13.	RIKEN
Tetsuo Ishikawa, Eiryo Kawakami. "Using machine learning to assess disease state and visualize state transition patterns". 24th Emergent System Symposium, Suwa University of Science. Nagano. 2018 Sep 9.	RIKEN
Yoko Nakatake, Hiroki Furuie, Hiroshi Kuniishi, Masatoshi Ukezono, Misa Yamada, Kazumi Yoshizawa, Mitsuhiko Yamada. "Witnessing the defeat of a conspecific induces social avoidance in mice". A poster presented at The WFSBP Asia Pacific Regional Congress of Biological Psychiatry. Kobe. 2018 Sep 6.	RIKEN, National Center of Neurology and Psychiatry
Mayumi Kusunose. "Academic research & development, and patient & public involvement". Academic Research Organization 6th Annual Meeting. Fukuoka. 2018 Sep 1.	RIKEN, The University of Tokyo
Tetsuo Ishikawa, Eiryo Kawakami. "Using machine learning to assess disease state and visualize state transition patterns". The 30th Takato Molecular Cell Biology Symposium. Nagano. 2018 Aug 23.	RIKEN
Fumiyo Sekiguchi, Aiko Shiohama, Hiroshi Kawasaki, Tamotsu Ebihara, Akiharu kubo, Masayuki Amagai, Takashi Sasaki. "Identifing genomic variation of atopic dermatitis with significant symptoms in head and neck area". 39th Annual Meeting of The Japanese Society of Inflammation and Regeneration. Tokyo. 2018 Jul 11.	RIKEN, Keio University

Title & Presenter(s)	Announcement Institutions (Participating Institutions only)
Hiroshi Kawasaki, Eiryo Kawakami, Shoko Obata, Aki Honda, Naoko Mochimaru, Ayano Fukushima, Fumiyo Sekiguchi, Takashi Sasaki, Wataru Suda, Kenya Honda, Tamotsu Ebihara, Masayuki Amagai. "Skin microbiome analysis with quantitative data is a feasible method in identifing relavant species in atopic dermatitis". 39th Annual Meeting of The Japanese Society of Inflammation and Regeneration. Tokyo. 2018 Jul 11.	RIKEN, Keio University
Hiroshi Kawasaki. "Using systems analysis to understand dysbiosis in atopic dermatitis". 67th Annual Meeting of the Japanese Society of Allergology: Symposium #17: atopic dermatitis: update on pathology and treatment. Chiba. 2018 Jun 24.	RIKEN, Keio University
Hiroshi Kawasaki. "Understanding heterogeneity in atopic dermatitis through skin microbiome research". 67th Annual Meeting of the Japanese Society of Allergology: Symposium #8: the role of microbiomes. Chiba. 2018 Jun 24.	RIKEN, Keio University
Koichi Ashizaki, Hiroshi Kawasaki, Eiryo Kawakami, Kazuhiro Sakurada, Tatsuhiko Tsunoda, Tamotsu Ebihara, Masayuki Amagai. "Advancing data-driven research on atopic dermatitis by constructing a clinical multimodal data collection and management systems". 117th Annual Meeting of the Japanese Dermatological Association. Hiroshima. 2018 May 31-Jun 1.	RIKEN, Keio University
Mayumi Kusunose. "About Medical Sciences Innpvation Hub Program". Public Policy Seminar. Tokyo. 2018 May 6.	RIKEN
Yoko Baba, Junko Uda, Hiromi Oonagi, Yoji Mikami, Kaname Tsukui, Takashi Shuto, Mariko Hida, Takahiro Nakayama, Junichi Fujimoto, Hiroshi Fujita, Mayumi Kusunose. "Ethics consultation 4: On continuation of artificial dialysis". The 6th Annual Conference of the Japan Association for Clinical Ethics. Tokyo. 2018 Mar 17.	RIKEN
Aiko Sekita, Horoshi Kawasaki, Rumi Satoh, Eiryo Kawakami, Haruhiko Koseki. "Deciphering pathogenic mechanisms of atopic dematitis by tissue transcriptomic analysis". 7th NIF Winter Scool on Advanced Immunology. Awaji Island, Japan. 2018 Jan 21.	RIKEN
Eiryo Kawakami. "Using machine learning and mathematical science to grapple with the heterogeneity and individuality of patients". RIKEN Medical Sciences Innovation Hub Program & Tonomachi Research Complex Joint Symposium. Tokyo. 2018 Jan 25.	RIKEN
Hiroshi Kawasaki, Eiryo Kawakami, Shoko Obata, Aki Honda, Naoko Mochimaru, Ayano Fukushima, Fumiyo Yasuda-Sekiguchi, Takashi Sasaki, Wataru Suda, Kenya Honda, Tamotsu Ebihara, Masayuki Amagai. "Longitudinal skin microbiome analysis of atopic dermatitis patients treated by bleach baths". 42nd Annual Meeting of The Japanese Society for Investigative Dermatology. Kochi. 2017 Dec 16.	RIKEN, Keio University
Yukiko Iwasaki, Yusuke Takeshima, Mineto Ota, Yasuo Nagafuchi, Ishigaki Kazuyoshi, Shuji Sumitomo, Akari Suzuki, Yuta Kochi, Tomohisa Okamura, Shigeo Koyasu, Keishi Fujio, and Kazuhiko Yamamoto. "Plasma metabolomic analysis combined with transcriptome data has potential for stratification of SLE patients". Annual Meeting of the Japanese Society for Immunology. Sendai. 2017 Dec 12.	The University of Tokyo, RIKEN
Masatoshi Ukezono, Yuji Takano. "Developing a behavioral experimental task to examine the mirror neuron system in mice". Japan Developmental Neuroscience Society 6th Academic Meeting. Osaka. 2017 Nov 25.	RIKEN
Eiryo Kawakami. "Host transcriptional regulation in viral/bacterial infection". Annual Meeting of Japanese Society for Bacteriology. Sendai. 2017 Mar 21.	RIKEN
Eiryo Kawakami. "Looking at genes en masse: enrichment analysis of gene expression data". 2nd Bioinformatics Conference (Institute for Frontier Life and Medical Sciences, Kyoto University). Kyoto. 2017 Feb 22.	RIKEN
Eiryo Kawakami. "Discovery of combinatorial biomarkers for personalized medicine based on machine learning". 1st International Symposium of the Medical Sciences Innovation Hub Program. Tokyo. 2017 Feb 7.	RIKEN
Kazuhiro Sakurada. "Introducing the RIKEN Medical Innovation Hub Promotion Program". 1st International Symposium of the RIKEN Medical Innovation Hub Promotion Program. Tokyo. 2017 Feb 7.	RIKEN
Eiryo Kawakami. "Network model-based analysis of immune response dynamics". Theoretical Immunology Workshop 2017. Hiroshima. 2017 Jan 19.	RIKEN

Title & Presenter(s)	Announcement Institutions (Participating Institutions only)
Hiroshi Kawasaki, Hiroko Kasai, Takaho A Endo, Koichi Ashizaki, Fumiyo Yasuda, Masayuki Amagai, Tamotsu Ebihara. "The classification of atopic dermatitis patients based on the therapeutic outcome for the proactive treatment using machine learning method". Annual Meeting of The Japanese Society for Investigative Dermatology. Sendai. 2016 Dec 9.	Keio University, RIKEN, Keiyu Hospital
Eiryo Kawakami, Haruhiko Koseki, Shinji Nakaoka. "The regulatory mechanism of stochastic signal transduction mediated by protein complexes". Annual Meeting of the Molecular Biology Society of Japan. Yokohama. 2016 Nov 30.	RIKEN, The University of Tokyo
Eiryo Kawakami. "Reconstruction of transcriptional regulation network and prediction of regulatory transcription factors utilizing public ChIP-seq data". TOGO Day Symposium 2016. Tokyo. 2016 Oct 6.	RIKEN
Eiryo Kawakami. "Exploring latent information in the biological network: comprehensive reconstruction of signal transduction pathway based on protein-protein interaction network". Annual Meeting of the Japanese Biochemical Society. Sendai. 2016 Sep 25.	RIKEN
Eiryo Kawakami. "Understanding life as an information processing system". Summer School (Department of Statistical Genetics, Osaka University). Osaka. 2016 Aug 28.	RIKEN
Eiryo Kawakami. "Predicting transcription factors from gene expression". Tohoku University Researcher Seminar. Miyagi. 2016 Jun 3.	RIKEN

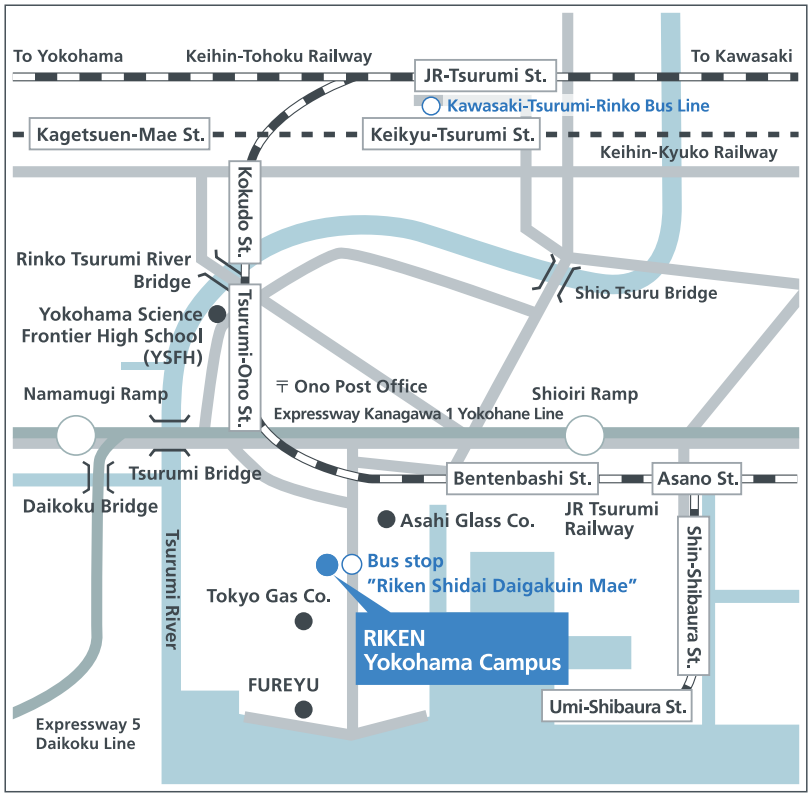
Media

Title & Presenter(s)	Announcement Institutions (Participating Institutions only)
Kazuhiro Sakurada. "Technological progress and artificial intelligence". Future Forecast with Jitsuro Terashima, BS11. Tokyo. 2018 Oct 19.	RIKEN

Patents

Patent name	Application Number	Applicant(s)
State visualization device, state visualization method and state visualization program. Japanese Patent Application No. 2018-221449. Tetsuo Ishikawa, Eiryo Kawakami.	Japanese Patent Application No. 2018-221449	Tetsuo Ishikawa, Eiryo Kawakami
Cells for producing influenza virus and method for producing influenza virus. US Patent App. Yoshihiro Kawaoka, Tokiko Watanabe, Eiryo Kawakami, Shinji Watanabe.	US Patent App. 15/511,988	Yoshihiro Kawaoka, Tokiko Watanabe, Eiryo Kawakami, Shinji Watanabe
Anti-influenza virus agent and screening method for anti-influenza virus agent. US Patent App. 15/511,930. Y Kawaoka, T Watanabe, E Kawakami, S Watanabe.	US Patent App. 15/511,930	Y Kawaoka, T Watanabe, E Kawakami, S Watanabe

Access to RIKEN Yokohama Campus



Local Access

By Bus

Take the #08 bus from Platform 8 at the East Exit of Tsurumi Station (also accessible from the West Exit of Keikyu Tsurumi Station) and get off at the RIKEN Shidai Daigakuin Mae bus stop. The institute is across the street. All buses from this platform are bound for Fureyu.
Buses depart Tsurumi every 5–15 minutes. It takes about 15 minutes to arrive at RIKEN Yokohama.
The fare is 220 yen in cash.

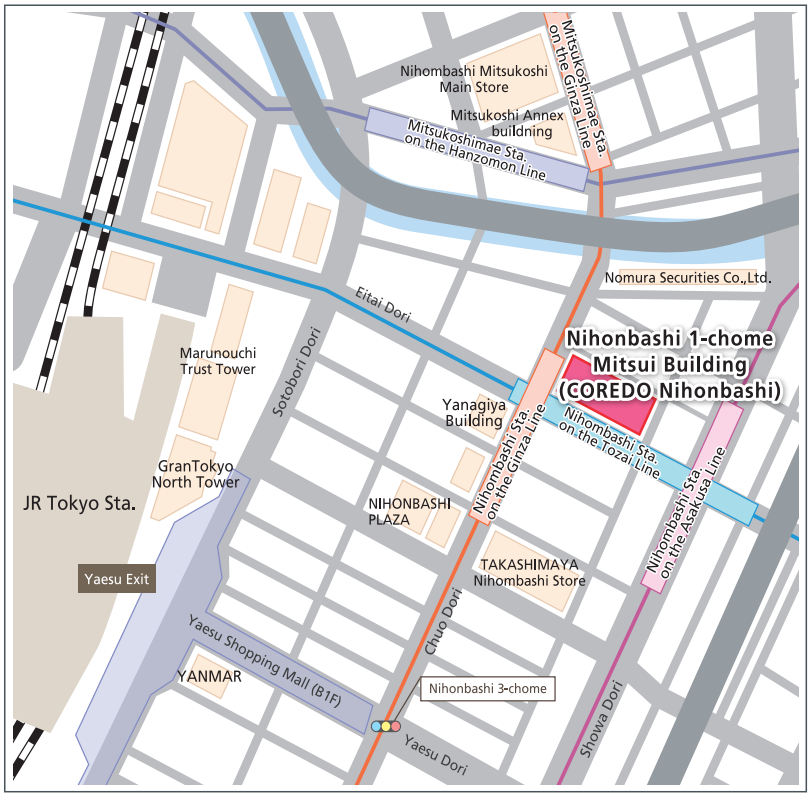
By Train

A 15-minute walk from JR Tsurumi-Ono Station (JR Tsurumi Line), which is directly accessible by transfer from JR Tsurumi Station.
Trains run about every 10 minutes during morning and evening rush hour, but less frequently at other times.
Searchable train timetables in English are available at http://www.hyperdia.com/en/

By Taxi

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

Access to RIKEN Tokyo Liaison Office



Access from the nearest stations

By Train

Nihombashi station :
Directly connected via the B12 and C1 exits from the Tokyo Metro Tozai Line (T10), Ginza Line (G11), Toei Asakusa Line (A13).
Tokyo station :
6 min. walk from the Yaesu Central gate of the JR Line and Tokyo Metro Marunouchi Line.
1 min. walk from the "Subway Nihombashi Station" stop of the Metro Link Nihonbashi bus. (free circular bus)

Access from the nearest stations

By Train (From Narita airport / Haneda airport to Nihombashi station)

Narita Airport Terminal 1 Station / Narita Airport Terminal 2-3 Station to Nihombashi station :
Approximately 60 min. by "Access express" on the Keisei Narita Sky Access Line.
Haneda Airport International Terminal / Haneda Airport Domestic Terminal Station To Nihombashi Station :
Approximately 30min. by Limited Express, and Airport Limited Express on the Keikyu Airport Line.

RIKEN Medical Sciences Innovation Hub Program

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

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