2-B-AC 会長講演

# Elucidation of the principle of operation of living systems to virus infection and the establishment of novel therapeutic strategies

Yumiko Imai

*National Institutes of Biomedical Innovation, Health and Nutrition (NIBIOHN), Infection Medical Information Project*

When an organism is exposed to a viral infection, a variety of pathologies develop over a long period and across multiple organs. This involves factors on the viral side, those on the host side, and social factors. Viral factors are defined by viral genome information, including viral genome mutations. Factors on the host side include epigenomic modifications acquired through aging and environmental factors, in addition to human whole-genome information. Social factors include lifestyle changes, such as exercise, diet, and conversation, due to epidemics of viral infections. In the chronic phase, more than 200 sequelae (e.g., Long COVID) occur, including neurological symptoms (depression, cognitive impairment, and sleep disturbances). By integration of the basic, clinical, and systems biological analyses, we have shown the operating principles of host life systems in response to viral infection with coronaviruses (SARS-CoV and SARS-CoV2) and influenza viruses. In the present time, I would like to talk about the pathogenesis of severe viral infections and sequelae, and the possibility of drug discovery, focusing on our findings.

**1-B-KL** 基調講演

## COVID-19: What we learned

Yoshihiro Kawaoka[1,2]

*[1]NCGM, [2]U of Tokyo*

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for COVID-19, continues to spread around the world and has caused millions of deaths to date. In an effort to develop therapeutics and preventive measures, we are performing numerous research projects with this virus and its variants. In this presentation, I will discuss our findings regarding animal models and their value as tools for evaluating countermeasures against SARS-CoV-2.

1-B-SL01 特別講演01

# Research & Development of New Infectious Disease Drugs to Meet Current Social and Medical Needs and to Prepare for Future Threats

Isao Teshirogi

*Shionogi & Co., Ltd.*

As a leading company in the infectious disease field, SHIONOGI has been pursuing the discovery and development of new drugs for diseases such as HIV, influenza, AMR, and COVID-19.
In my presentation, I‘m going to share our activities in the infectious disease area, as well as what we have learned from the COVID-19 pandemic about preparedness and the ideal partnership between the public and private sectors required to protect society from arising dangers.
First, I would like to talk about SHIONOGI‘s R&D activities and contributions to healthcare in the infectious disease field, an area that many pharmaceutical companies have withdrawn from. In addition, by sharing the difficulties we faced in the development of a COVID-19 drug, I would like to discuss the importance of preparedness for pandemic threats even during normal times, including steps that have been taken in this direction in Japan, such as the establishment of SCARDA and the creation of an emergency approval system.
From here forward, it is expected that Japanese industry, government, and academia will work more closely together to respond to emergencies, with their efforts facilitated by new systems that have been and will be created. In order to meet this expectation, it is required that all sectors share a common perspective regarding the need to improve such capabilities and thereby to prepare effectively. I hope that my presentation can be of some help in achieving the necessary alignment.

1-B-SL02 特別講演02

# Discover, Develop and Deliver Life-Transforming Medicines to Patients across the World

Christophe Weber

*Takeda Pharmaceutical Company Limited*

At Takeda, the patients we serve — and achieving outcomes for them and their health — have been at the heart of everything we do for more than 240 years. We believe our values, making decisions based on Patient – Trust – Reputation – Business, in that order, sets us apart.

Takeda has transformed into a global, science-driven, digital biopharmaceutical company and has accelerated our competitiveness in past several years. Our global footprint, robust financial position, balanced portfolio, and diverse talent gives us the scale needed to bring innovative medicines to patients across the world. Through our R&D transformation, we clarified our focus on well-defined therapeutic areas, diversified our modalities beyond small molecules, and enhanced internal research capabilities and external collaborations which enabled us to make a more meaningful impact on patients and society.

Today, with health care systems increasingly under strain as life expectancies rise, populations age and innovative treatment options expand, our patient-centered and outcomes-focused approach is more relevant than ever. We believe that health care systems need to urgently move toward value-based health care, one that rewards outcome and care quality – the true purpose of any healthcare system. That is why our strategy is centered on the discovery and development of innovative and life-transforming medicines that have the potential to be best-in-class or first-in-class. At the same time, we are building resilience against external risks and making bold investments in data, technology, and AI to upskill our people and drive value creation.

Our culture encourages and appreciates our differences, and we believe the company continues to thrive because of them. We embrace our differences, and these diverse perspectives reflect the perspectives of the patients who rely on the treatments we develop. We ensure that employees, regardless of gender, age, nationality can advance their careers and fully demonstrate their capabilities. At Takeda, we are committed to create an exceptional experience for our people.

**1-B-SL03** 特別講演03

## ACE2-from fly hearts to the heart of a pandemic

*Scientific Director, Helmholtz Centre for Infection Research, Germany*

With particular relevance to the COVID-19 pandemic, Josef Penninger will present how work on ACE2 and its role in lung failure, from the discovery in fly heart development to the first mutant mice and a fundamental understanding of SARS Coronavirus. This data provided the first molecular underpinning why the first SARS-CoV and now SARS-CoV2 causing COVID-19 became "dangerous viruses". ACE2 is the critical receptor for SARS-Cov-2 and has taken center stage in global research and drug and vaccine development. This work has also been translated into ACE2-based drugs as rational and universal prevention and treatment strategies for COVID-19.

1-B-SL04 特別講演04

# Mathematical Understanding of the Complex Control System between Organs and Challenge for Drug Discovery in Preventive and Preemptive Medicine

Kazuyuki Aihara

*IRCN, UTIAS, UTokyo*

In this talk, I introduce mathematical studies for foundation of preventive and preemptive medicine linking Life and Science on the basis of our Moonshot Goal 2 project on Comprehensive Mathematical Understanding of the Complex Control System between Organs and Challenge for Ultra-Early Precision Medicine, supported by the Cabinet Office,Government of Japan and JST. In particular, I explain details of mathematical sensitive detection of signs for deviation from healthy states, the DNB (Dynamical Network Biomarker) theory to detect fluctuations peculiar to pre-disease states before onset of diseases, and treatment of pre-disease states by control theory.

1-B-SL05 特別講演05

# New technology and Information Science for Next Generation Drug Modalities

Kouhei Tsumoto

*Sch Eng and Inst Med Sci, Univ Tokyo*

Antibody as a drug modality contributes to the first runner of biomedicine. Recently, research and development of next generation antibody drugs has remarkable progresses on therapy, e.g. antibody drug conjugate (ADC), bispecific antibody (bsAb), and single domain antibody (VHH, also called nanobody), which has widen the application areas of antibody drugs. These include combination of elemental technologies, and incorporation of information sciences into the drug development. Here I would discuss next generation drug modality, especially focusing on innovation-driven antibody engineering.

1-B-SL06 特別講演06

# Advent of the new era in genome technologies

Yutaka Suzuki

*Dept. of CBMS, Grad. Sch. of Fr. Sci., Univ. of Tokyo.*

In this presentation, I would like to discuss the advent of the new era in genome-related technologies. In fact, a remarkable progress was made in this field in recent years, which may make a substantial effect on the future direction of genome research in Japan. First, I would like to look back at the rapid spread of single-cell analysis. The maturity of the preceding single-cell is further traced back to the dramatic expansion and spread of the sequencing capabilities of next-generation sequencers. Without the ability to analyze the whole human genome on a scale of tens of thousands to hundreds of thousands of people, it would have been impossible to perform genetic analysis on tens of thousands to hundreds of thousands of cells. However, as the single-cell technologies transforms into the gene expression analysis which preserves spatial position information, it is undergoing a major transformation into measurement which does not depend on sequences. The data produced here is mainly image data rather than the sequence data. Inevitably, there will be a major turning point in the way we have used data and databases. As a turning points in the next-generation sequencing era, which has swept the fields of medicine and biology for 10 years, I would like to share with the participants the enthusiasm of the current new era of genomic science. I hope this symposium should provide an opportunity to exchange opinions, rather than just providing information from my perspectives.

**2-B-SL07** 特別講演07

# Understanding of nucleocytoplasmic transport involved in cell functions develops medical science

Yoshihiro Yoneda

*BIKEN*

The nucleus is surrounded by nuclear envelope, a double membrane and about two or three thousand of nuclear pores per one nucleus exist in the nuclear envelope. The nuclear pore complex is a huge structure and consists of about 30 different proteins. A short fiber-like structure extends into the cytoplasm, while a basket-like structure extends into the nucleoplasm. A variety of molecules, such as proteins and RNAs, are transported through the nuclear pores in both directions. The nuclear localization signal (NLS)-containing protein is recognized by importin a in the cytoplasm. Importin b binds to importin a to form a heterotrimeric complex. The trimeric complex translocates through the nuclear pore complex. After translocation of the complex through the nuclear pores, nuclear small GTPase Ran-GTP binds to importin b to trigger the dissociation of the complex. The NLS-substrates become free in the nucleoplasm. Then, importin a and importin b form distinct export complexes in the nucleus together with RanGTP and are recycled back to the cytoplasm by separate pathways. Then importin a and importin b are re-used for next rounds of transport. It has been recently elucidated that the nucleocytoplasmic transport machineries are involved in a variety of cell functions.

**2-B-SL08** 特別講演08

# Signaling pathways regulating cell fate in innate immunity and neural development

Yukiko Gotoh[1,2]

*[1]Graduate School of Pharmaceutical Sciences. The University of Tokyo, [2]International Research Center for Neurointelligence (WPI-IRCN), The University of Tokyo*

A fundamental question in understanding tissue development is how resident stem cells or multipotent progenitors give rise to the various cell types in appropriate numbers and at the right locations to achieve tissue organization. Neural stem/progenitor cells (NPCs) in the mammalian neocortex initially divide symmetrically to increase their pool size (expansion phase). They then start to divide asymmetrically and give rise to neuronal and glial cell types in a region- and developmental stage–dependent manner. In this talk, I will present data regarding the mechanisms underlying the transition from the expansion phase to the neurogenic phase and discuss their potential role in psychiatric diseases such as autism spectrum disorder.
I would also like to present our results regarding signaling pathways involved in innate immunity that regulate cell fate after viral infection.

**2-B-SL09** 特別講演09

# Immunopharmacogenomics

Yusuke Nakamura

*National Institutes of Biomedical Innovation, Health and Nutrition*

With advances in DNA sequencing and various ’ omics ‘ technologies, it has become possible to capture changes in immune cells through the analysis of biologically active substances such as cytokines and chemokines, as well as T- and B- cell receptor sequence analysis in various pathological conditions and drug responses. Furthermore, technological advances in the single cell level have made it possible to understand the dynamic changes in immune cells in detail. In addition, it has been suggested that the immune responses activated through drug and HLA interaction play key roles in drug-induced skin hypersensitivity and hepatotoxicity. HLA class I molecules are associated with drug eruptions such as Stevens-Johnson syndrome, and class II molecules with hepatotoxicity. In cancer treatment, it is becoming clear that the immune environment within cancer tissues and throughout the body is important not only for cancer immunotherapy but also for the responsiveness of other anticancer drugs and radiation therapy. Changes in immune responses during the onset, remission, and progression processes of various diseases have not been completely analyzed until now, but development of immunopharmacogenomics will certainly help to elucidate these changes.

**2-B-SL10** 特別講演10

# Spirit of Drug Discovery

Haruo Naito

*Eisai Co., Ltd.*

“LEQEMBI”, the world's first disease-modifying therapy for Alzheimer's disease (AD), was approved in Japan in September of this year, following the United States, ushering in a new era in dementia treatment. Eisai Co., Ltd. has been engaged in research and development in the field of dementia for more than 40 years, continuing to overcome failures and diversify R&D risks. Although we succeeded in developing the world's first AD drug "ARICEPT" in 1997, we continued to strive for next-generation drug discovery. We have developed a variety of new drug candidates based on the amyloid-$\beta$ (A$\beta$) cascade hypothesis, which is the root cause of AD, but candidates have dropped out one after another. Among them, the anti-A$\beta$ protofibril antibody “LEQEMBI” was developed through careful clinical research, utilizing the results of familial AD research conducted in collaboration with academia. There is no success in drug discovery without failure, and by enduring failure, experience and knowledge are accumulated. This experiential knowledge is the key to success in drug discovery and is the “nautical chart” that guides the ship of new drug development on the right course. The presence of a captain who writes the charts and navigates the sea is also essential. I would like to take this opportunity to touch on “the spirit of drug discovery” that exists based on empathy with AD patients.

2-B-SL11 特別講演11

# Challenges to drug discovery and development based on the genomic analysis of schizophrenia

Kiyofumi Yamada

*Dept. Neuropsychopharmacol. Hosp. Pharmcy, Nagoya Univ. Grad. Sch. Med.*

Schizophrenia is a serious mental disorder that develops from the late teens to the 30s. It is characterized by positive symptoms such as hallucinations and delusions, negative symptoms such as emotional flattening, and cognitive impairment. The etiology remains unknown, but both genetic and environmental factors are involved. Current antipsychotic drugs approved as therapeutic agents for schizophrenia improve positive symptoms, but have little effect on negative symptoms and cognitive impairment, and some individuals are treatment resistant. Serious side effects such as extrapyramidal symptoms are also a problem. Therefore, there is an urgent need to elucidate the disease mechanism and to develop novel therapeutic targets accordingly. We are addressing this issue by promoting translational research based on genome analysis in schizophrenia. Specifically, low-molecular-weight G-protein signaling has been suggested as a relevant pathological pathway. We have identified ARHGAP10 gene variants that are strongly associated with the disease, and have generated Arhgap10 gene-modified mice. In this lecture, I will introduce the antipsychotic-like effects of Rho-kinase inhibitors, along with current findings related to the pathological analysis of Arhgap10 gene-modified mice.

**2-B-SL12** 特別講演12

# Epigenetics, Fate Decision, and Environment

Hiroyuki Sasaki

*Div. Epigenom. Dev., Med. Inst. Bioreg., Kyushu Univ.*

Epigenetics refers to a gene regulatory mechanism that integrates and coordinates genetic programs and environmental cues. It plays a critical role in various biological phenomena, such as cell fate decision, embryonic development, and cellular homeostasis. At the molecular level, epigenetic regulation is achieved by conformational changes in chromatin, depending on chemical modifications of DNA and histone proteins. Random X-chromosome inactivation in mammalian females is a typical epigenetic phenomenon, which for example gives diversity in coat color pattern of calico cats and tortoiseshell cats, but some environmental stresses, especially those imposed on fetuses and young can result in long-lasting epigenetic mis-regulation of genes and adult diseases. Thus, epigenetics can be viewed as an interface between genetics and environment. Normally, epigenetic modifications are reset when genetic information is transmitted to the next generation: however, some epigenetic changes, especially those induced by environmental stresses, can be heritable through the germline. In this talk, I will summarize the basics of epigenetic gene regulation and discuss some recent progress in epigenetics research.

**2-B-SL13** 特別講演13

# Individualized preemptive medicine utilizing artificial intelligence and genomic information

Masatoshi Hagiwara

*Dept. Anat. & Dev. Biol., Grad. Sch. Med.*

Targeted goal of our project is to realize precision medicine of genetic diseases caused by aberrant splicing, induced by deep-intronic VUS. In eukaryotic gene expression system, a precursor mRNA transcribed from genome consists of exonic sequences and intervening intronic sequences, and exonic sequences are connected by RNA splicing reaction, resulting in production of protein-coding sequences. Splicing regulation is regulated by multiple factors, such as chromosomal structure, RNA cis-elements, and trans-acting splicing factors, and due to its complexity, precise prediction of alternative splicing profiles still remains to be achieved today. Recent accumulation of whole genome sequence data facilitated access to deep-intronic sequences, which provides essential information to understand splicing codes. Compared to conventional exome sequencing data, covering approximately 1% of genomic information, whole genome sequencing revealed presence of numerous VUS within the deep-intronic region, which are not accessed by exome studies. Our preliminary observations indicate there are many deep-intronic VUS that affect splicing code to create pseudoexonization of a given intronic region, resulting in pathogenesis by causing frameshifting or insertion, as we recently characterized for NEMO deficiency syndrome (J. Clin. Invest. 2019) and cystic fibrosis (Cell Chem. Biol. 2020). To achieve our goal, we are challenging elucidation of splicing code using artificial intelligence (AI)-driven novel strategy. We will conduct a genome-wide functional annotation for deep-intronic VUS, for more than 10,000 whole genome sequence data available from Tohoku Medical Megabank (ToMMo), The 1,000 Genome Project, and Genome Asia 100k Project. We constructed an original AI and conduct a clinical trial to realize precision medicine of genetic diseases.

**2-B-SL14** 特別講演14

# The impact of clinical big data on the drug development

Shuji Kaneko

*Kyoto Univ.*

To better understand how drugs exert their effects in our human body, we should recognize that only a fraction of the mechanisms has been identified and described in the literature. In fact, affinities for all receptors, enzymes, and channels have not been measured during the development phase, and the safety in humans has been investigated in a limited number of cases within a short time frame. Accordingly, unexpected adverse events have been reported during post-marketing surveillance. Therefore, there will be numerous unknown effects of drugs buried in clinical data, which may contain not only adverse event mechanisms but also unexpected benefits. Then, how can we find out them? In this talk, I will introduce some of our achievements in finding unexpected beneficial effects of drugs from clinical real-world data (RWD).

(1) By statistical analysis of multiple RWD, we found that the anti-arrhythmic drug amiodarone caused interstitial lung injury with chronic inflammation of lung tissue leading to fibrosis, and that the concomitant use of the anti-thrombin drug dabigatran suppressed the incidence of such adverse events. Pharmacological studies revealed that this effect is due to the inhibition of PAR1-PDGFR $\alpha$-MMP12 pathway by dabigatran.

(2) RWD showed that the anti-diabetic DPP4 inhibitors increased the risk of an autoimmune disease, bullous pemphigoid (BP), and that concomitant use of lisinopril, an antihypertensive drug widely used in the US, reduced the risk. Pharmacological studies revealed that lisinopril suppresses the development of BP by inhibiting cutaneous MMP9 expression through suppression of the ACE2-MasR pathway, rather than by acting on immune cell functions.

(3) Short-term administration of the antimicrobial fluoroquinolones increased the risk of tendinopathy after the use. Conventional treatment guidelines suggest that concomitant corticosteroid therapy increases the risk of tendinopathy. However, RWD analysis found a preventive effect of dexamethasone. Interestingly, dexamethasone also decreased the spontaneous incidence of tendinopathy in a aged cohort. From pharmacological studies, we found that fluoroquinolones impair tendon cells by DNA damage with generation of reactive oxygen species, whereas dexamethasone has a beneficial effect on tendon tissue function via increased expression of GPX3, a glutathione peroxidase that contributes as a radical scavenger.

3-B-SL15 特別講演15

# Disease control targeting transporters and drug discovery

Yoshikatsu Kanai

*Dept. Bio-system Pharmacol, Grad. Sch. Med, Osaka Univ.*

Transporters are membrane proteins responsible for the distribution of substances within the body, acting as interfaces between various compartments, thus determining the concentration ratios of substances between these compartments. Consequently, by pharmacologically modulating the function of these transporters, we can shift abnormal compound distributions seen in pathological states, restoring homeostasis and thereby promoting recovery from diseases. For instance, the SGLT2 (SLC5A2) inhibitors, which suppress the reabsorption of glucose in the renal tubules, is an exemplary drug that skews glucose distribution towards the urine, enhancing glucose excretion and rectifying hyperglycemia, establishing its role in diabetes treatment. From another perspective, transporters responsible for nutrient uptake, especially those upregulating in pathogenic cells like cancer cells, become potential drug targets. The amino acid transporter LAT1 (SLC7A5), which is highly expressed with specificity in cancer cells, presents itself as a potential diagnostic and therapeutic target. In this lecture, introducing our research on drug development targeting LAT1 as an example, I would like to discuss the interactions between transporters and compounds as well as the significance of transporters as drug targets.

3-B-SL16 特別講演16

# Brain-AI hybrid

Yuji Ikegaya

*Grad Sch Pharmaceut Sci, UTokyo*

What are modern approaches to improve and augment brain function? In this talk, I will discuss what can be achieved by connecting the brain and artificial intelligence, explaining the research results and background of the ERATO Ikegaya Brain-AI Hybrid Project.

3-B-SL17 特別講演17

# Issues in Japan's healthcare digital transformation seen from examples of medical information use in other countries

Shigeo Kasai

*Information-technology Promotion Agency*

We will explain the outline of the medical DX project promoted by the Japanese government and the technologies involved, and explore issues and solutions in Japan, with reference to secondary use cases such as medical information sharing and analysis in other countries.

3-B-SL18 特別講演18

# Toward elucidation of etiopathogenesis of neurodevelopmental disorders: utilization of genetic and environmental factor models and novel analytical systems

Noriko Osumi

*Tohoku Univ.*

Neurodevelopmental disorders (NDDs) are a complex group of disorders resulting from disturbances of the nervous system that occur early in neurodevelopmental stages and present with complex interrelated symptoms. The number of people affected by NDDs in developed countries continues to increase, yet no curative medicine has yet been developed. To overcome the situation, it is important to establish a model of the disease using rodents, and a variety of models are needed to match the complex symptoms. Genetic analysis has so far identified many responsible/risk genes for NDDs, while environmental factors such as maternal drug exposure, maternal immune activation, and paternal aging are also known to induce NDDs. It is also important to develop analytical systems tailored to the symptoms. In this talk, I would like to introduce these pathological models analyzed in our laboratory and mention a new analysis system that utilizes artificial intelligence and machine learning with big data. Through this talk, I hope to discuss the latest research trends and methodologies for elucidating the etiopathogenesis of NDDs, to better understand the mechanisms, and to contribute to the development of promising therapeutic strategies in future.

3-B-SL19 特別講演19

# Towards Human Systems Biology of Sleep/Wake Cycles: Phosphorylation Hypothesis of Sleep

Hiroki Ueda

*Dept. Systems Pharmacol. Grad. Sch. Med, The Univ. of Tokyo.*

The field of human biology faces three major technological challenges. Firstly, the causation problem is difficult to address in humans compared to model animals. Secondly, the complexity problem arises due to the lack of a comprehensive cell atlas for the human body, despite its cellular composition. Lastly, the heterogeneity problem arises from significant variations in both genetic and environmental factors among individuals. To tackle these challenges, we have developed innovative approaches. These include 1) mammalian next-generation genetics, such as Triple CRISPR for knockout (KO) mice and ES mice for knock-in (KI) mice, which enables causation studies without traditional breeding methods; 2) whole-body/brain cell profiling techniques, such as CUBIC, to unravel the complexity of cellular composition; and 3) accurate and user-friendly technologies for measuring sleep and awake states, exemplified by ACCEL, to facilitate the monitoring of fundamental brain states in real-world settings and thus address heterogeneity in human.

By integrating these three technologies, we have made significant progress in addressing two major scientific challenges in sleep research: 1) understanding sleep regulation (sleep mechanisms) and 2) determining the role of sleep (sleep functions). With regard to sleep mechanisms, we have recently proposed the phosphorylation hypothesis of sleep, which emphasizes the role of the sleep-promoting kinase CaMKII $\alpha$ /CaMKII $\beta$ (Tatsuki et al., 2016; Tone et al., 2022; Ode et al., 2020) and the involvement of calcium signaling pathways (Tatsuki et al., 2016). According to this novel perspective, the dynamics of calcium, representing neural activity during wakefulness, can be integrated and converted into the auto-phosphorylation status of CaMKII $\alpha$ /CaMKII $\beta$, which induces and sustains sleep (Tone et al., 2022). Concerning sleep functions, we conducted computational studies to examine synaptic efficacy dynamics during sleep and wakefulness. Our findings led to the formulation of the Wake-Inhibition-Sleep-Enhancement (WISE) hypothesis, suggesting that wakefulness inhibits synaptic efficacy, while sleep enhances it.

During this talk, we will also present our discoveries regarding the identification of muscarinic acetylcholine receptors (Chrm1 and Chrm3) as essential genes of REM sleep. Furthermore, we will discuss new insights into psychiatric disorders, neurodevelopmental disorders, and neurodegenerative disorders derived from the phosphorylation hypothesis of sleep.