The 27th Science in Japan Forum

# Conquering All Diseases by Metaverse-based Research

**Keynote Speech**

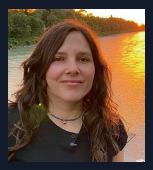
## Kohji Nishida

(Osaka University WPI-PRIMe Director)

**Session 1**

## Takanori Takebe

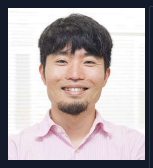
(Cincinnati Children's Hospital/Osaka University WPI-PRIMe)



**Session 2**

## Elisa Domínguez-Hüttinger

(Universidad Nacional Autónoma de México/Osaka University WPI-PRIMe)



**Session 3**

## Takahiro Nemoto

(Osaka University WPI-PRIMe)

**Session 4**

## Nozomu Yachie

(The University of British Colombia/Osaka University WPI-PRIMe)

**Moderator of the Panel Discussion**

## Kazuhiro Sakurada

(Osaka University WPI-PRIMe/Keio University)

# Thursday June 13, 2024

## 1:00pm - 6:00pm (EDT)

**Format: Hybrid (Onsite and Online)**
**Venue: Cosmos Club**
(2121 Massachusetts Ave., NW, Washington, DC)

**On-site participation is by invitation only.**
**Everyone is welcome to participate online.**

JAPAN SOCIETY FOR THE PROMOTION OF SCIENCE 日本学術振興会

AAAS

U.S. DEPARTMENT OF ENERGY | Office of Science

大阪大学 OSAKA UNIVERSITY

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Masashi Yanagisawa

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IIIS
International Institute for Integrative Sleep Medicine
**University of Tsukuba**

Yasuhito Sekine

Earth & Life

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Takashi Yoshimura

Molecules

ITbM
Institute of Transformative Bio-Molecules
**Nagoya University**

Takao K. Hensch

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IRCN
International Research Center for Neurointelligence
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Takeshi Fukuma

Nano Life Science

NanoLSI
Nano Life Science Institute
**Kanazawa University**

Satoshi Maeda

Chemical Reaction Design

ICReDD
Institute for Chemical Reaction Design and Discovery
**Hokkaido University**

Mitinori Saitou

Human Biology

ASHBi
Institute for the Advanced Study of Human Biology
**Kyoto University**

Masashi Hazumi

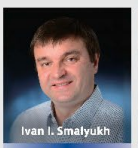
Measurement Science

International Center for Quantum-field Measurement Systems for Studies of the Universe and Particles
**High Energy Accelerator Research Organization (KEK)**

Kohji Nishida

Human Metaverse Medicine

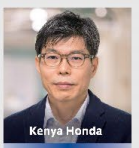
PRIME
Premium Research Institute for Human Metaverse Medicine
**Osaka University**



Ivan I. Smalyukh

Knotted Matter

SKCM²
International Institute for Sustainability with Knotted Chiral Meta Matter
**Hiroshima University**



Kenya Honda

Biology & Quantum

BIO2Q
Human Biology-Microbiome-Quantum Research Center
**Keio University**

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MEXT MINISTRY OF EDUCATION, CULTURE, SPORTS, SCIENCE AND TECHNOLOGY-JAPAN

JSPS JAPAN SOCIETY FOR THE PROMOTION OF SCIENCE 日本学術振興会

## The Twenty-Seventh

# "Science in Japan" Forum

# *Conquering All Diseases by Metaverse-based Research*

Cosmos Club
Washington, DC
June 13, 2024

Sponsored by
Japan Society for the Promotion of Science

Co-sponsored by
AAAS (American Association for the Advancement of Science)
DOE (Department of Energy)
Osaka University
WPI-PRIMe (Premium Research Institute for Human Metaverse Medicine)
US and Canada JSPS Alumni Association
WPI (World Premier International Research Center Initiative)

## Agenda

12:00 pm - Registration

1:00 pm - 1:20 pm

### Opening Remarks

**Tetsuya Mizumoto**, Executive Director, Japan Society for the Promotion of Science
**Kimberly J. Montgomery**, Director of International Affairs and Science Diplomacy, Center for Science Diplomacy, American Association for the Advancement of Science
**Robabeh Rahimi**, Chair of the JSPS Alumni Association Capital Region Chapter

1:20 pm - 2:00 pm

### Keynote Speech: The Human Metaverse Medicine Envisioned by PRIMe

**Kohji Nishida**, Professor, Osaka University WPI-PRIMe Director

2:00 pm – 2:30 pm

### Session 1: Organoid-guided Precision Hepatology: Towards Liver biodigital Twin

**Takanori Takebe**, Director for Commercial Innovation, Center for Stem Cell and Organoid Medicine (CuSTOM) Cincinnati Children's Hospital / Deputy Director, Professor, Osaka University WPI-PRIMe

2:30 pm – 2:50 pm Coffee Break

2:50 pm – 3:20 pm

### Session 2: Towards a bio-digital twin of epithelial function

**Elisa Domínguez Hüttinger**, Universidad Nacional Autónoma de México / Specially Appointed Associate Professor, Osaka University WPI-PRIMe

3:20 pm – 3:50 pm

### Session 3: Developing molecular-state simulators based on disease-modeling human organoids

**Takahiro Nemoto**, Specially Appointed Associate Professor, Osaka University WPI-PRIMe

Time Zone: Eastern Daylight Time

3:50 pm – 4:20 pm

**Session 4: Technologies for "look-back-in-time" biology**

**Nozomu Yachie**, Professor, The University of British Colombia / Specially Appointed Professor, Osaka University WPI-PRIMe

4:20 pm – 4:40 pm Coffee Break

4:40 pm – 5:00 pm

**Introduction for the panel discussion: Deploying Prevention and Precision at Scale by Human Metaverse**

**Kazuhiro Sakurada**, Specially Appointed Professor, Osaka University WPI-PRIMe / Professor, Keio University

5:00 pm – 6:00 pm

**Panel Discussion**

Moderator:

**Kazuhiro Sakurada**

**+ All Speakers**

6:00 pm –

**Closing Remarks**

**Koichi Ai**, Deputy Chief of Mission, Embassy of Japan in the United States of America

**Takanori Takebe**, Deputy Director, Professor, Osaka University WPI-PRIMe

6:20 pm –

**Reception**

Time Zone: Eastern Daylight Time

**<Request for All Participants>**

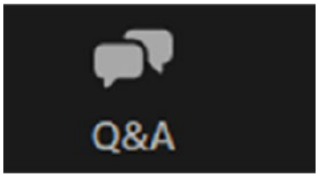
- JSPS will take photographs and videos during the forum. They may be used for the website and other publications by host organizations.
- Please do not take photographs or videos.

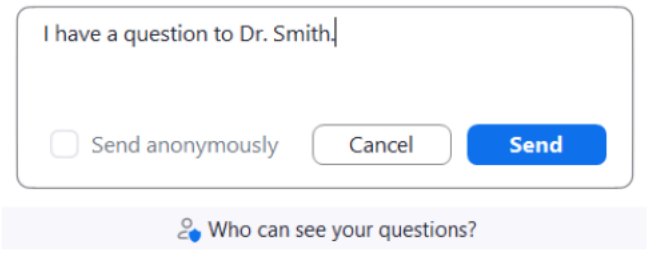
**<Request for In-person Participants>**

- There will be Q&A after each talk. If you have questions, please come to the mic stand.

**<Request for Zoom Participants>**

- Please make sure to mute your microphone and turn off your camera.
- There will be Q&A after each talk.
  Online participants can ask questions via Zoom Q&A function.



# Foreword

The "Science in Japan" forum was started in 1996 by Dr. Masatoshi Koshiba, Director of the Japan Society for the Promotion of Science (JSPS), Washington Office (WO). It aims to promote scientific cooperation between Japan and the United States and is hosted by the JSPS Washington Office every year.

The 27th Forum for 2024 is on "Conquering All Diseases by Metaverse-based Research," which will be obtained by developing the Premium Research Institute for Human Metaverse Medicine (PRIMe). This research institute aims to create a new scientific field, "Human Metaverse Medicine," by which we comprehensively and continuously understand the process of disease development. Then, we develop personalized prevention methods and curative treatments for diseases. The PRIMe was newly established in 2022 at Osaka University.

When I learned about this title last December, I had to study organoid and human metaverse technology. I was very surprised to see the progress being made in developing miniature organs cultured from iPS cells and cutting-edge technology in computer science, which can contribute to medical science. I also hope that through the stimulation of this Forum, good cooperation and competition between Japan and North America will emerge in the near future.

This Forum is co-sponsored by AAAS (American Association for the Advancement of Science), DOE (Department of Energy), Osaka University, PRIMe and US-Canada JSPS AA (Alumni Association), and WPI (World Premier International Research Center Initiative). The JSPS WO and PRIMe staff efficiently prepared this Forum, and I would like to express my gratitude to all of them.

I hope all the participants will find the Forum valuable and enjoyable.

Junji Urakawa
Director, JSPS Washington Office

## Keynote Speech
## The Human Metaverse Medicine Envisioned by PRIMe

Kohji Nishida

Director Premium Research Institute for Human Metaverse Medicine (PRIMe) in World Premier International Research Center Initiative (WPI), Osaka University, Professor and Chairman of Department of Ophthalmology Graduate School of Medicine, Osaka University
PhD in Medical Science

Current treatments are based on evidence-based medicine, which relies on epidemiological data of certain diseases. These treatments are designed for the average patient, meaning they can be highly effective for some, but not for others. To provide personalized healthcare tailored to each individual, genome-based medicine, which focuses on genetic information, has emerged. However, genome-based medicine cannot address chronic diseases caused by the complex interplay of genetic and environmental factors. Therefore, PRIMe aims to overcome all diseases by striving for precision and personalized medicine.

To address chronic diseases heavily influenced by environmental factors, a new medical approach is necessary—one that not only considers genetic information but also observes changes in gene expression and their dynamic impact from cells to tissues and organs across hierarchical and temporal axes.

We are developing a new method to link micro-level information obtained from human organoids with clinical data to predict changes over hierarchical and temporal axes for each patient. Human organoids share the same genomic information as humans and can be subjected to perturbations akin to environmental stress, allowing the observation of dynamic state changes at both micro-level hierarchical and temporal axes. This enables the realization of diversity that animal models could not achieve.

By integrating and modeling life phenomena related to the patient's disease in this manner, we will construct Patient bio-Digital Twins (PbDT). PbDT enables the visualization of desired information, predictions of micro-level information from clinical data, and accurate future forecasts. Human Metaverse Medicine realizes precision and personalized medicine through the construction of PbDT. Lastly, we will report on the latest developments in retinal organoids in the ophthalmology field towards the realization of PbDT.

I have conducted research on eye development and regenerative medicine. I was the first in the world to successfully develop human eye organoids that recreate the entire eye development in a spatiotemporal manner (Nature 2016, Nature Protocol 2017). Using these human eye organoids, I have also succeeded in creating human cornea organoids (Nature 2016), human conjunctiva organoids (Cell Reports 2021), and human lacrimal gland organoids (Nature 2022). Furthermore, for cornea organoids, I conducted a First-in-Human clinical trial for patients with corneal epithelial stem cell deficiency from 2019 to 2022, demonstrating efficacy and safety. Recently, I have been working on the construction of digital twins using organoids.

## Present

Director Premium Research Institute for Human Metaverse Medicine (PRIMe) in World Premier International Research Center Initiative (WPI), Osaka University,
Professor and Chairman of Department of Ophthalmology Graduate School of Medicine, Osaka University
PhD in Medical Science

## Education

1982 - 1988 Osaka University Graduate School of Medicine Medical Science
Obtained M.D.
1993 - 1997 Osaka University Graduate School of Medicine Medical Science
Obtained Ph.D. (Thesis advisor; Prof. Yasuo Tano)

## Academic Career

2013 - 2016 Advisor to the Trustees, Osaka University
2017 - 2019 Vice-Dean, Graduate School of Medicine, Osaka University
2010 - 2015 Director, Data Coordinating Center, Department of Medical Innovation, Osaka University Hospital
2015 - 2017 Director, Medical Center for Translational and Clinical Research, Osaka University Hospital
2017 - 2020 Director, Department of Medical Innovation, Osaka University Hospital
2017 - present Director, Integrated Frontier Research for Medical Science Division, Institute for Open Transdisciplinary Research Initiatives (OTRI), Osaka University
2019 - present Advisor to the Dean, Graduate School of Medicine, Osaka University
2019 - present Director, Artificial Intelligence Center for Medical Research and Application, Osaka University Hospital
2021 - present Vice Dean, Graduate School of Medicine, Osaka University
2021 - present Vice Director, Institute for Open Transdisciplinary Research Initiatives (OTRI), Osaka University
2022 - present Director, Premium Research Institute for Human Metaverse Medicine (PRIMe), Osaka University

## Academic awards

2005 The Alcon Award
2006 The 2nd Pfizer Ophthalmic Award Japan
2009 Minister of Education, Culture, Sports, Science and Technology Award Science and Technology Award Research Division
2015 The Japanese Ophthalmology Society Council Award
2017 The Japanese Society for Regenerative Medicine Award
2021 Asia Cornea Foundation, The 7th Asia Cornea Society Biennial Scientific Meeting
2023 2nd Tai Morishita Memorial Award
2023 Medical Award of The Japan Medical Association

## Organoid-guided Precision Hepatology: Towards Liver biodigital Twin

Takanori Takebe

Deputy Director, Premium Research Institute for Human Metaverse Medicine (PRIMe), Osaka University
Professor of Genome Biology, Graduate School of Medicine, Osaka University
Endowed Chair of Organoid Medicine and Director of Commercial Innovation for Center for Stem Cell and Organoid Medicine (CuSTOM) at Cincinnati Children's Hospital Medical Center

Non-alcoholic fatty liver disease, now known as MASLD, affects billions of people. MASLD was first defined in the USA 35 years ago, yet progress towards a true cure has been incremental and limited to lifestyle modification. MASLD is a complex spectrum of disorders that include excess liver fat, inflammation, fibrosis, and malignant transformation. The dramatic rise in MASLD incidence is driven by multiple, acquired, environmental risk factors, superimposed on common genetic risk factors. However, the significance of risk variants is unresolved, as not all people with genetic susceptibility will develop the disease, which is also influenced by common comorbidities, such as insulin resistance and type 2 diabetes (T2D). For example, pediatric genome-wide association studies (GWAS) identified SNP rs1260326 in the glucokinase regulatory protein (*GCKR*), encoding a loss-of-function protein. rs1260326 is one of the most "pleiotropic" variant affecting glucose and lipid metabolism that promotes NAFLD while protects against T2D. However, the mechanism by which the rs1260326 variant impacts hepatic steatosis in those with insulin insensitive state remains unclear. We propose integrative pre-clinical research, combining patients' datasets and engineered human tissues, using our pioneering steatohepatitis organoids, for a precise mechanistic dissection of the gene variant function on NASH development under insulin resistant conditions. In combination with an population-scale pluripotent stem cell (PSC) organoids, our recent report using this human in-a-dish GWAS system suggest that *GCKR* rs1260326, among the other well-known variants, confer risk for developing steatosis and inflammation under oleic acid-induced conditions with impaired hepatic insulin response; these results are further supported by cohort data from thousands of NASH patients. Our collective research will deliver a fresh view on human liver metabolism through the lens of ***precision hepatology*** to define personalized mechanisms as a fundamental step towards developing evidence-based, rational solutions for mechanism-directed diagnostic and therapeutic investigation.

In this talk, I will summarize our ongoing efforts to construct Patient bio-Digital Twins (PbDT) with a focus on the liver pathobiology. By integrating organoid based disease MASLD modeling, PbDT will pave a new way to realize true precision based preemptive care for MASLD development.

Takebe lab seeks to develop and apply novel approaches and tools to recapitulate, probe and manipulate human liver development and to understand the personalized molecular mechanisms that lead to disease. Towards this goal, he is building experimental organogenesis approaches to engineer hepato-biliary- pancreatic systems using pluripotent stem cells *in vitro* and in animals to construct and deconstruct previously inaccessible phases of human liver health and disease. He is on the board of directors for the International Society for Stem Cell Research and the Japanese Society for Regenerative Medicine.

## Present

Deputy Director, Premium Research Institute for Human Metaverse Medicine (PRIMe) in World Premier International Research Center Initiative (WPI), Osaka University
Professor of Genome Biology, Graduate School of Medicine, Osaka University
Endowed Chair of Organoid Medicine and Director of Commercial Innovation for Center for Stem Cell and Organoid Medicine (CuSTOM) at Cincinnati Children's Hospital Medical Center

## Education

2005 - 2011 Medical Doctor, Yokohama City University School of Medicine
2018 Doctor of Philosophy, Regenerative Medicine Yokohama City University School of Medicine

## Academic Career

2023 - current Professor, Division of Stem Cell and Organoid Medicine, Graduate School of Medicine, Osaka University, Japan
Deputy Director, Premium Research Institute for Human Metaverse Medicine (WPI-PRIMe), Osaka University, Japan
2021 - current Endowed Chair of Organoid Medicine, Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center
2021 - current Associate Professor, Division of Gastroenterology, Hepatology and Nutrition and Division of Developmental Biology, Cincinnati Children's Hospital Medical Center
2016 - 2020 Assistant Professor, Division of Gastroenterology, Hepatology and Nutrition and Division of Developmental Biology, Cincinnati Children's Hospital Medical Center
2017 - current Director of Commercial Innovation, Center for Stem Cell and Organoid Medicine (CuSTOM), Cincinnati Children's Hospital Medical Center, USA
2019 - current Adjunct professor & Founding Director, Communication Design Center, Advanced Medical Research Center, Yokohama City University, Japan
2018 - current Professor, Institute of Research, Tokyo Medical and Dental University, Japan
2013 - 2018 Associate Professor, Department of Regenerative Medicine, Yokohama City University, Japan

## Academic awards

2023 Mochida Memorial Foundation Prize, Tokyo, Japan
2023 ISSCR Outstanding Young Investigator, IL, USA
2022 Inoue Prize for Science, Inoue Foundation for Science, Tokyo, Japan
2022 Falk Transformational Award, IL, USA
2021 Elected member of American Society of Clinical Investigation (ASCI), DC, USA
2020 NIH Director's New Innovator Award, Bethesda, USA

## Towards a bio-digital twin of epithelial function

Elisa Domínguez Hüttinger

Assistant Professor, Department of Molecular Biology and Biotechnology, Institute for Biomedical Research, National Autonomous University of Mexico; Specially Appointed Associate Professor Premium Research Institute for Human Metaverse Medicine (WPI-PRIMe), Osaka University, Japan
PhD in Bioengineering

The epithelium is the main tissue that separates *us* from *the outside*. Examples of such tissues include the epidermis and the lining of the airway and the gut. Healthy epithelial tissues are simultaneously plastic and robust. This is, they dynamically respond to changing environments without large or long-lasting deviations from a homeostatic set point. This fine balance is achieved through exquisitely connected networks of regulatory interactions between biological players such as molecules and cells. What are the feedback control structures maintaining homeostasis? How is epithelial homeostasis lost, giving rise to complex diseases such as mucosal infections and carcinomas? In my talk, I will show how we tackle these questions from a mathematical modelling perspective. We ask how disease emerges from alterations in the regulatory interplay between cellular-level phenotypes and the microenvironment. With this, we can (1) systematically explore the effect of genetic and environmental alterations on homeostasis, (2) identify the mechanisms underlying abrupt pathophysiological transitions, (3) characterise the early warning signals that precedes these catastrophic shifts, and (4) design and optimize therapeutic interventions for disease prevention and reversion. Our mathematical representations of epithelial function in health and disease are the building blocks of the bio-digital twin of epithelial function.

I am a theoretical systems biologist passionate about developing and applying mathematical and computational tools to understand pathogenic mechanisms of complex diseases. My focus is on uncovering mechanisms and early markers of gradual disease transitions. I construct and analyse mathematical models that help to understand and prevent the development of severe forms of disease, and to design and optimize treatment strategies to revert to mild and asymptomatic stages. To achieve these goals, I integrate clinical and experimental data into bottom-up, mechanistic, and quantitative models encoded as coupled non-linear dynamical systems. Typically, my mathematical models encompass different timescales simultaneously, allowing me to reproduce gradual pathogenic transitions as emerging properties of the dynamical coupling between biochemical-level regulatory networks and micro-environmental changes. I have successfully applied this integrative systems biology approach to several epithelial tissue diseases including Atopic dermatitis, tuberculosis, upper airway infection by *Streptococcus pneumoniae*, and carcinomas.

## Present

Associate Professor, Department of Molecular Biology and Biotechnology, Institute for Biomedical Research, National Autonomous University of Mexico; Specially Appointed Associate Professor Premium Research Institute for Human Metaverse Medicine (WPI-PRIMe), Osaka University, Japan.

## Education

2004 - 2008 Undergraduate Student in the Faculty of Sciences, National Autonomous University of Mexico, Obtained B.Sc. in Biology.

2009 - 2015 Graduate Student in the Department of Bioengineering, Imperial College London, Obtained Ph.D. in Bioengineering (Thesis advisor; Dr Reiko J. Tanaka).

## Academic Career

2012 - 2014 Research Technician in Biological Control & Systems, Imperial College London (Dr Reiko J Tanaka's laboratory).

2015 - 2016 Post-Doctoral Fellow at the Department of Bioengineering, Imperial College London (Dr Reiko J Tanaka's laboratory).

2016 - 2018 Post-Doctoral Fellow at the Institute of Ecology, National Autonomous University of Mexico (Dr Elena Álvarez-Buylla's laboratory).

2019 - 2019 Post-Doctoral Fellow at the Institute for Protein Research, Osaka University (Dr Mariko Okada's laboratory).

2018 - 2020 Associate Professor at the Centre for Mathematical Sciences, National Autonomous University of Mexico.

## Academic awards

2014 Santander Mobility Award, Imperial College (London, United Kingdom)

2015 RISP Travel Award, RIKEN Centre for Integrative Medical Sciences (Yokohama, Japan)

2018 Sofía Kovalevskaia award from the Mexican Society for Mathematics (Mexico)

2021 College for Life Sciences Fellowship, Wissenschaftskolleg zu Berlin (Germany)

2022 Level II Member of the National System of Researchers (Mexico)

2023 Scientist-in-Residence Award (Salzburg, Austria)

## Developing molecular-state simulators based on disease-modeling human organoids

Takahiro Nemoto

Specially appointed associated professor, Premium Research Institute for Human Metaverse Medicine (PRIMe), Osaka University
PhD in science

Human organoids, which are stem cell-derived 3D culture systems that mimic human organs, are envisioned as a model system for probing human diseases, complementing traditional animal models. Organoids enable the study of biological processes specific to the human body, with significantly fewer ethical constraints compared to patient-involved clinical studies. Furthermore, they offer flexible testing grounds in quantitatively controlled environments, thus reducing the impact of complex confounding factors. By integrating disease-modeling organoids with omics technologies, we can now observe the dynamic changes in disease-related molecular networks at an in-vitro level. This capability highlights the potential for developing numerical simulators that model these networks under varying environmental and genetic conditions. However, to fully leverage organoids for this purpose, it is crucial to manage and accurately evaluate the statistical uncertainties in organoid generations and omics measurements. In downstream analyses, it is also imperative to understand how high-dimensional molecular omics data can be reduced to low-dimensional features relevant for future predictions. Moreover, provided that molecular-state simulators are created, a long-term goal would be to integrate them with clinical patient information to develop a predictive model of patient health. In this presentation, I will begin by reviewing statistical models used for NGS-based omics measurements. I will then address the key points raised above, based on single-cell RNA sequencing data from pooled liver organoids provided by Prof. Takebe's group, combined with publicly available liver-biopsy transcriptome data.

He received his Ph.D in statistical physics and has since dedicated his research career to mathematical modelling, algorithm development, and data analysis across multidisciplinary fields, such as physics, epidemiology, and bioinformatics. His expertise lies in inference using population MCMC, and his recent work in bioinformatics has involved developing mathematical models to analyze statistical errors in NGS count data obtained in time-series, using a maximum likelihood framework combined with a high-dispersion statistical distribution. Currently, at PRIMe, his team is focusing on creating bioinformatics pipelines for analyzing multi-omics data from human organoids, as well as developing mathematical models that describe the temporal evolution of molecular states in organoids.

## Present

Specially appointed associate professor, Premium Research Institute for Human Metaverse Medicine (PRIMe), Osaka University

## Education

| | |
|---|---|
| 2007 – 2010 | Undergraduate Student in Department of Physics, Tokyo Institute of Technology, Obtained B.Sc. |
| 2010 – 2012 | Graduate Student in the Graduate School of Arts and Sciences, The University of Tokyo, Obtained M.A.Sc. (Thesis advisor; Dr. Shin-ichi Sasa) |
| 2012 – 2015 | Graduate Student in the Graduate School of Science, Kyoto University, Obtained D.Sc. (Thesis advisor; Dr. Shin-ichi Sasa) |

## Academic Career

| | |
|---|---|
| 2015.04 – 2015.10 | Post-Doctoral Fellow at Département de Physique, École Normale Supérieure de Lyon |
| 2015.11 – 2016.10 | Post-Doctoral Fellow at Laboratoire de Probabilités et Modèle Aléatoires, Université Paris VII |
| 2016.11 – 2019.10 | Post-Doctoral Fellow at Philippe Meyer Institute for Theoretical Physics, École Normale Supérieure |
| 2019.11 – 2020.12 | Post-Doctoral Fellow at the laboratory of Mathematical Modeling of Infectious Diseases, Pasteur Institute |
| 2021.01 – 2021.08 | Post-Doctoral Fellow at the Paris Vision Institute |
| 2021.09 – 2023.02 | Assistant professor at the Graduate School of Informatics, Kyoto University |
| 2023.03 – | Specially appointed associate professor at Premium Research Institute for Human Metaverse Medicine (PRIMe), Osaka University |

## Academic awards

2015 Young Scientist Award of the Physical Society of Japan.
2016 Springer Theses award.

## Technologies for "look-back-in-time" biology

Nozomu Yachie

Specially Appointed Professor, Premium Research Institute for Human Metaverse Medicine (PRIMe), Osaka University
Professor, School of Biomedical Engineering, University of British Columbia
PhD in Systems Biology

Cells proliferate from a fertilized egg, pass their genomic information to their offspring, and dynamically change their functions to form diverse tissue structures. Throughout development, intracellular and environmental cues trigger patterns of gene expression that govern cell state transitions and produce additional cellular and environmental cues, leading cells to self-organize into functional clusters within spatially distinct areas. How can these processes be investigated? Our research program is developing technologies using two different approaches: (1) DNA event recording and (2) retrospective clone isolation.

In the idea of DNA event recording, molecular and cellular events of a multicellular organism are progressively stored in synthetic “DNA tapes,” like a molecular ticker tape. Such a system allows for the readout of historical molecular expression profiles of many cells using high-throughput single-cell sequencing.

Another idea to achieve dynamic, high-content observation of progressive systems is retrospective clone isolation. In this concept, cells in a population are first tagged with unique, short DNA barcodes and propagated. A subpopulation is then subjected to a specific assay. After identifying a barcode for a clone of interest, the same clone, or its close relatives, is isolated in a barcode-dependent manner from the initial population or any other subpopulation stored during the experiment. The isolated clone can be subjected to various experiments, including omics measurements and synthetic population reconstitution assays.

## Present

Specially Appointed Professor, Premium Research Institute for Human Metaverse Medicine (PRIMe), Osaka University
Professor, School of Biomedical Engineering, University of British Columbia
PhD in Systems Biology

## Education

| | |
|---|---|
| 2001-2005 | B.A., Faculty of Environmental Information, SFC, Keio University |
| 2005-2007 | M.M.G., Bioinformatics Program, SFC, Keio University |
| 2007-2009 | Ph.D., Systems Biology Program, SFC, Keio University (Thesis advisor; Dr. Masaru Tomita) |

## Academic Career

| | |
|---|---|
| 2020- | Professor (2023.07-Today)<br>Associate Professor (2020.09-2023.06)<br>The University of British Columbia<br>School of Biomedical Engineering<br>Faculty of Applied Science & Faculty of Medicine<br>(July, 2022-Today)<br>Director of Research and Associate Director<br>School of Biomedical Engineering |
| 2023- | Guest Professor (Global)<br>Keio University<br>Graduate School of Media and Governance |
| 2023- | Specially Appointed Professor<br>Osaka University<br>Premium Research Institute for Human Metaverse Medicine (PRIMe) |
| 2020- | Visiting Professor (2023.10-Today)<br>Visiting Associate Professor (2020.09-2023.08)<br>The University of Tokyo<br>Research Center for Advanced Science and Technology (RCAST) |
| 2014-2021 | Adjunct Associate Professor (2015.04-2021.12)<br>Adjunct Assistant Professor (2014.06-2015.03)<br>Keio University<br>Graduate School of Media and Governance, and<br>Institute for Advanced Biosciences |

| | |
|---|---|
| 2014-2020 | Associate Professor<br>The University of Tokyo<br>Research Center for Advanced Science and Technology (RCAST)<br>Director (2018.01-2019.10)<br>Laboratories for Systems Biology and Medicine |
| 2010-2014 | Postdoctoral Fellow (with Dr. Frederick Roth)<br>(April, 2010-November, 2010)<br>Harvard Medical School<br>Department of Biological Chemistry and Molecular Pharmacology<br>(December, 2010-June, 2014)<br>University of Toronto<br>Donnelly Centre for Cellular and Biomolecular Research |
| 2009-2010 | Postdoctoral Fellow (with Dr. Masaru Tomita)<br>Keio University<br>Institute for Advanced Biosciences |

## Academic awards

| | |
|---|---|
| 2023 | JSPS Prize<br>Japan Society for the Promotion of Science |
| 2023 | CIFAR Fellow<br>MacMillan Multiscale Human Program<br>Canadian Institute for Advanced Research |
| 2022 | Allen Distinguished Investigator Award<br>Allen Institute |
| 2020 | Canada Research Chair (Tier 2) in Synthetic Biology<br>Canadian Institute of Health Research (CIHR) |
| 2020 | Minister's Young Scientists Award<br>Ministry of Education, Culture, Sports, Science and Technology, Japan |
| 2012 | Banting Postdoctoral Fellowship<br>National Sciences and Engineering Research Council of Canada |

# NOTES

## Deploying Prevention and Precision at Scale by Human Metaverse

Kazuhiro Sakurada

Professor, Department of Extended Intelligence for Medicine, Keio University School of Medicine & Graduate School of Medicine. Project Leader, Advanced Data Science Project, RIKEN. Specially Appointed Professor, Premium Research Institute for Human Metaverse Medicine (PRIMe), Osaka University. PhD in Science

Transforming medicine from a focus on the symptoms of disease to a focus on the causes of disease is a common goal of many biomedical scientists. Preventive medicine based on highly accurate predictions is essential for sustainable health care. Patients with the same symptoms do not have the same causes of disease. To achieve preventive medicine, technology is needed to predict the onset and progression of disease for each individual based on the underlying cause of the disease. Research combining organoids and clinical data is a new research approach to elucidate the root causes of disease. From this research, the ultimate goal of this project is to identify the many factors involved in the development of disease and to develop new technologies for prevention and treatment. To achieve this goal, it is necessary to combine conventional typing through deep phenotyping and state identification using machine learning with explanatory AI. It is also necessary to integrate causal and data-driven probabilistic models with physics and information theory to predict change. This presentation will summarize the issues that will be discussed in the panel.

Theoretical studies are conducted to explain and predict life phenomena from the principles of physics. While the question of physics is the motion of an object, the question of biology is the change of state of an organism. To bridge this gap, I have developed a method to describe biological change in terms of motion in state space. By introducing Onsager's reciprocal relation theorem into this model, I explored how to describe biological change in terms of the variational principle, leading to the principle of maximum entropy generation. By describing living organisms as systems with the duality of particles and waves, I showed that the maximum entropy generation principle generates coherent order in biological systems, and that changes in topology in real space break this symmetry to generate biological diversity. I am working to apply this fundamental principle to AI for medicine, to elucidate the causes of disease, and to introduce new interpretations of common questions in biology, such as evolution, development, and consciousness.

## Present

Professor, Department of Extended Intelligence for Medicine, Keio University School of Medicine & Graduate School of Medicine.
Project Leader, Advanced Data Science Project, RIKEN.
Specially Appointed Professor, Premium Research Institute for Human Metaverse Medicine (PRIMe), Osaka University.

## Education

1982 - 1986 Undergraduate Student in the Faculty of Science, Osaka University, Obtained B.Sc.
1986 - 1988 Graduate Student in the Department of Genetics, Osaka University, Obtained Ph.D. in 1993 (Thesis advisor; Prof. Hideyuki Ogawa)

## Professional experience

1988 - 2000 Researcher at Kyowa Hakko Tokyo Research Laboratories
1991 - 1992 Visiting researcher at Kyoto University, Graduate School of Medicine
1997 - 1998 Visiting scientist at Salk Institute
2000 - 2004 Principal investigator of Laboratory of Regenerative Medicine at Kyowa Hakko Tokyo Research Laboratories.
2004 - 2006 Head of Research Center and Operating Officer at Nihon Schering (Kobe) and Member of Corporate Research Management Team at Schering AG (Berlin)
2007 - 2007 Head of Research Center and Operating Officer at Bayer Yakuhin (Kobe) and Head of Global Drug Discovery Regenerative Medicine at Bayer Schering Pharma AG (Berlin)
2008 - 2008 Chief Scientific Officer at Izumi Bio Inc. (San Fransisco)
2008 - 2018 Senior Scientist at Sony Computer Science Laboratories Inc.
2016 - 2021 Deputy Program Director at Medical Science Innovation Hub Program, RIKEN
2021 - Present Project Leader at Advanced Data Science Project, RIKEN
2021 - Present Professor at Department of Extended Intelligence for Medicine, Keio University School of Medicine & Graduate School of Medicine.
2023 - Present Specially Appointed Professor, Premium Research Institute for Human Metaverse Medicine (PRIMe), Osaka University.

## Awards and Honors

2011 Chief Distinguished Researcher (Sony, Global)
2011 Technology Development Group Award (Sony, Tokyo)

# NOTES

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