# 2023 JSPS-NIH Forum

March 17, 2023

Japan Society for the Promotion of Science
Fogarty International Center, National Institutes of Health

# 2023 JSPS-NIH Forum

DATE **2:00 pm – 7:00 pm March 17, 2023 (EDT)**
***[Japan Standard Time 日本時間 ] 3:00 am – 8:00 am March 18, 2023**

VENUE **Hybrid (Building 31, Conference Center, 6th floor, Rooms B & D)**
**In-person Registration (Invitation Only)**
**Online** Registration from **here**

*Time and Format are subject to change based on speakers and regulation on COVID-19

| | |
|---|---|
| 2:00pm - 2:25pm (EDT)<br>3:00am - 3:25am (JST) | Opening Remarks<br>**Dr. Kohji HIRATA**, Director, JSPS Washington Office<br>**Mr. Koji ARIBAYASHI,** Science Counselor, Embassy of Japan in the USA<br>**Dr. Yoh-suke MUKOUYAMA**, Chair of Review Panel / Senior Investigator, NHLBI, NIH<br>**Dr. Michael GOTTESMAN**, Chief, Laboratory of Cell Biology, NCI/CCR, NIH<br>**Dr. Akira IMATANI**, Professor, School of Medicine, Tohoku University (Online) |
| *Lecture Session 1*<br>*(Speaker from Japan)* | ***Theme: Cancer Cell Biology and Microenvironment*** |
| 2:25pm – 3:10pm (EDT)<br>3:25am – 3:10am (JST) | Invited Speaker (1) 45 min. including Q & A<br>**Dr. Junko MURAI**, Associate Professor, Department of Cell Growth and Tumor Regulation Proteo-Science Center, Ehime University<br>Lecture title: Revising the mechanism of the anti-cancer effect of DNA-damaging agents through the functions of Schlafen 11 (SLFN11) |
| 3:10pm - 3:20pm (EDT)<br>4:10am - 4:20am (JST) | Break |
| *Lecture Session 2*<br>*(Speakers from NIH)* | |
| 3:20pm - 4:00pm (EDT)<br>4:20am -5:00am (JST) | Invited Speaker (2) 20 min. including Q & A<br>**Dr. Takanobu TAGAWA**, HIV and AIDS Malignancy Branch, NCI, NIH<br>Lecture title: Exposing stealth strategies: non-coding RNAs during oncogenic herpesvirus infection<br><br>Invited Speaker (3) 20 min. including Q & A<br>**Dr. Ryo SATO**, Laboratory of Stem Cell and Neuro-Vascular Biology, Cell and Developmental Biology Center, NHLBI, NIH<br>Lecture title: Perivascular Neural β-III Tubulin (Tuj1) Expression in Lung Fibrosis: A New Target for Treatment |
| 4:00pm - 4:10pm (EDT)<br>5:00am - 5:10am (JST) | Break |

| *Flash Talk Session* | |
|---|---|
| 4:10pm - 4:35pm (EDT)<br>5:10am - 5:35am (JST) | Presentations on Research Plan at NIH by **JSPS-NIH Fellows** (KAITOKU-NIH) Awarded in FY2022 (8 Fellows)<br>3 mins for each |
| 4:35pm - 4:45pm (EDT)<br>5:35am - 5:45am (JST) | Closing Remarks<br>**Dr. Nina F. SCHOR,** Deputy Director for Intramural Research, NIH<br>**Dr. Christine SIZEMORE,** Director of the Division of International Relations, Fogarty International Center, NIH |
| 4:45pm - 7:00pm (EDT)<br>5:45am - 8:00am(JST) | Networking (only for in-person participants) at **Room B, D & Hallway** |

# 2023 JSPS-NIH Forum

## Cancer Cell Biology and Microenvironment

**Dr. Junko MURAI**
Associate Professor, Ehime University
*"Revising the mechanism of the anti-cancer effect of DNA-damaging agents through the functions of Schlafen 11 (SLFN11)*

**Dr. Takanobu TAGAWA** (NCI/ NIH)
**Dr. Ryo SATO** (NHLBI/ NIH)

*also featuring*

Presentations from current
**JSPS-NIH Fellows (KAITOKU-NIH)**

**Reception** (4:45 - 7:00pm) Invitation Only.
The event is free to attend and will be held in English.

The background-image is a confocal microscopy image of Schlafen 11 protein (green) on chromatin under replication stress condition. The photo was taken by Junko MURAI.

**2:00 - 4:45 PM, Fri. March 17**
Building 31 Conference Center
6th floor Room B&D/ online
**NIH Bethesda Campus (invitation only)**
**Online Registration** by **March 16** at

NIH Fogarty

JSPS

JSPS Washington Office
2001 L St., NW, Suite 1050, Washington, DC 20036
TEL: 202-659-8190 FAX: 202-659-8199
url: jspsusa.org e-mail: was-kaitoku-nih@overseas.jsps.go.jp

JSPS is the premier research funding agency in Japan.
Its Washington Office in cooperation with the Fogarty International Center support the forum.

# JSPS-NIH

## Thank you for joining us

# Forum

JSPS

2:00 – 4:45 PM, Friday, March 17, 2023 (EST)
4:45 – 7:00 PM Reception (In-Person Only)
(Japan Standard Time (Zoom) 3:00 – 5:45 AM, Saturday, March 18, 2023)

NIH Fogarty

## Thank you for joining us

Be sure to mute your microphone whenever you are *not* speaking to avoid background noise and distractions for others.

Download the booklet from our website.
https://jspsusa.org/wp/20230102-2/

# Thank you for joining us

JSPS will take some photographs and video recordings during the forum.

They may be used for the website and other publications by host organizations.

Download the booklet from our website.
https://jspsusa.org/wp/20230102-2/

# Thank you for joining us

Request for Online Audience:

Please do not take pictures or videos.

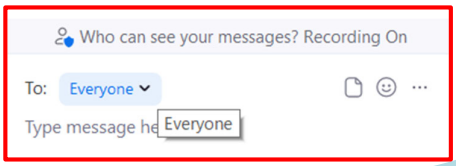
Download the booklet from our website.
https://jspsusa.org/wp/20230102-2/

# Thank you for joining us

## Questions during the lecture session from the online audience can be asked via Zoom Chat.

There will be no Q&A during the flash talk due to the time constraints.

Select Everyone so that moderator and lecturers can review the questions.

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## Opening Remarks

### Dr. Kohji HIRATA
Director, JSPS Washington Office

### Mr. Koji ARIBAYASHI
Science Counselor, Embassy of Japan in the USA

### Dr. Yoh-suke MUKOUYAMA
Chair of Review Panel / Senior Investigator, NHLBI, NIH

### Dr. Michael GOTTESMAN
Chief, Laboratory of Cell Biology, NCI/CCR

### Dr. Akira IMATANI
Professor, School of Medicine, Tohoku University

## Lectures

### Dr. Junko MURAI
Associate Professor, Department of Cell Growth and Tumor Regulation
Proteo-Science Center, Ehime University

### Dr. Takanobu TAGAWA
HIV and AIDS Malignancy Branch, NCI, NIH

### Dr. Ryo SATO
Laboratory of Stem Cell and Neuro-Vascular Biology, Cell and Developmental Biology Center, NHLBI, NIH

## Flash Talks

### JSPS-NIH Fellows (KAITOKU-NIH)

Awarded in FY2022 (8 Fellows)

## Closing Remarks

### Dr. Nina F. SCHOR

Deputy Director for Intramural Research, NIH

### Dr. Christine SIZEMORE

Director of the Division of International Relations, Fogarty International Center, NIH

***Revising the mechanism of the anti-cancer effect of DNA-damaging agents through the functions of Schlafen 11 (SLFN11)***

**Junko MURAI**
Associate Professor
Department of Cell Growth and Tumor Regulation
Proteo-Science Center, Ehime University

## Abstract

The property of unlimited proliferation of cancer cells is a major cause of death by cancer. DNA-damaging anticancer drugs such as platinum derivatives and topoisomerase I inhibitors have been used at the forefront of cancer treatment for nearly half a century. A primary mechanism of action of DNA-damaging agents is to generate replication-dependent lethal DNA damage (i.e., double-strand DNA breaks) in cancer cells. Hence, mutations in DNA repair genes augment the sensitivity to the DNA-damaging agents. In this context, it was a surprise that Schlafen 11 (SLFN11), which is not likely a DNA repair gene, was found in 2012 as its mRNA expression correlates most highly with sensitivity to DNA-damaging agents based on analyses of large cancer cell line databases. Later, the causality has been validated using various models. Although the presence or absence of SLFN11 does not change the amount of DNA damage, when SLFN11 is recruited onto chromatin in response to DNA damage, it causes changes in chromatin structure and irreversible replication arrest, leading to SLFN11-dependent cell death in about 24 hours. On the other hand, SLFN11-negative cells can complete DNA replication despite harboring DNA damage, and the cells in G2 phase can survive for days, allowing time for DNA repair. Therefore, the mechanism of action of DNA-damaging agents can be revised as "leading to cell death by activating SLFN11" rather than "leading to cell death by inducing DNA damage". Since there is still no clinically applicable sensitivity biomarker for platinum derivatives and topoisomerase I inhibitors, SLFN11, which is highly expressed in about half of all cancer tissues, is attracting increasing attention. In the past few years, several clinical reports have revealed a significant correlation between SLFN11 expression and drug response. The history of SLFN11 began in 2012 at Dr. Pommier lab in NCI, NIH. In the talk, I will introduce the basic and clinical frontiers of SLFN11 in cancer therapy.

**Junko MURAI**

## Biography

2000/5-2003/3:
Physician, Osaka University Hospital, Suita, Japan

2008/11-2009/1:
Postdoctoral Fellow, Kyoto University, Sakyo-ku, Japan (Dr. Shunichi Takeda lab.)

2009/2-2010/1:
Postdoctoral Fellow, Dana Farber Cancer Institute, Boston, USA (Dr. Alan D. D'Andrea lab.)

2010/2-2012/9:
Visiting fellow, National Institute of Health, Bethesda, USA (Dr. Yves Pommier lab.)

2012/10-2015/3:
Assistant Professor, Kyoto University, Sakyo-ku, Japan

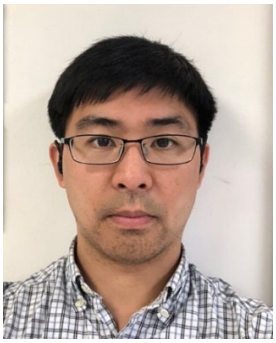
2015/4-2018/9:
Research Fellow, National Institute of Health, Bethesda, USA (Dr. Yves Pommier lab.)

2018/10-present
Project Associate Professor, Institute of Advanced Biosciences, Keio University, Tsuruoka, Japan

2022/3-present
Associate Professor, Department of Cell Growth and Tumor Regulation Proteo-Science Center, Ehime University

***Exposing stealth strategies: non-coding RNAs during oncogenic herpesvirus infection***

**Takanobu TAGAWA**
HIV and AIDS Malignancy Branch, NCI



**Abstract**

Infectious agents are associated with 15~20% of cancers. Oncogenic herpesviruses such as Kaposi sarcoma herpesvirus (KSHV) directly contribute to carcinogenesis. KSHV persists for the life of hosts by maintaining latency, which results in cancers including Kaposi sarcoma and primary effusion lymphoma. Non-coding RNAs (ncRNAs) are critical players during KSHV infection. ncRNAs includes miRNAs, lncRNAs, and an alternative splicing product called circular RNAs (circRNAs), closed-circular single-stranded RNAs. Human circRNAs have emerged as important gene regulators in tumorigenesis, but their roles in oncogenic virus biology is just being realized. We identified 63 human circRNAs that respond to KSHV infection in primary human endothelial cells. One of these, circRELL1(4,5,6), is highly expressed and induced during KSHV, Epstein-Barr virus, and human cytomegalovirus infection. We found that circRELL1(4,5,6) suppresses lytic viral gene expression and virion production. circRELL1(4,5,6) was also shown to promote cell growth and suppress cell death. We identified that circRELL1(4,5,6) interacts with TTI1 mRNA and stabilize the transcript level. TTI1 codes for a component of the mTOR complex. Since mTOR signaling is known to promote cell growth and suppress the KSHV lytic cycle, we propose that circRELL1(4,5,6) to be a novel regulator of the mTOR axis during KSHV infection, resulting in suppression of the lytic cycle and induction of cell growth. In conclusion, we identified a host circRNA induced by multiple herpesviruses that contributes to latency maintenance of an oncogenic virus.

**Takanobu TAGAWA**

## Biography

### EDUCATION

Doctoral degree (Dr. rer. nat, Ph.D. equivalent) in Biology 2011-2016

Ludwig-Maximilians-University, Munich, Germany

Master of Science in Biology

2009-2011

University of Tokyo Graduate School, Tokyo, Japan

Bachelor of Science

2005-2009

University of Tokyo, Department of Biophysics and Biochemistry (Major)

Undergraduate Program for Bioinformatics and Systems Biology (Minor)

### RESEARCH EXPERIENCE

*Postdoctoral fellow,* 2017-present

Laboratory of Joseph Ziegelbauer, Ph.D.

HIV and AIDS Malignancy Branch, National Cancer Institute, USA

*Doctoral Student,* 2011- 2017

Laboratory of Wolfgang Hammerschmidt, Prof. Dr.

Research Unit Gene Vectors, Helmholtz Center Munich, Germany

*Master Student,* 2009 - 2011

Laboratory of Dr. Hideo Iba, Ph.D.

The Institution of Medical Science, University of Tokyo, Japan

### AWARDS AND FELLOWSHIPS

25th International KSHV conference travel award 2022

25th International KSHV conference

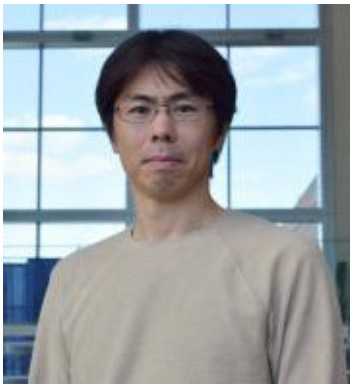
Norman P. Salzman Poster Award in Virology 2019

Foundation for the National Institutes of Health, USA

HIV Think Tank Oral Presentation Travel Award 2018, 2019

Center for Cancer Research, National Cancer Institute, USA

***Perivascular Neural ß-III Tubulin (Tuj1) Expression in Lung Fibrosis: A New Target for Treatment***



**Ryo SATO**
Visiting fellow, M.D., Ph.D.,
Laboratory of Stem Cell and Neuro-Vascular Biology,
Cell and Developmental Biology Center, NHLBI, NIH

## Abstract

Idiopathic pulmonary fibrosis (IPF) is a devastating disease that requires an improved understanding of the pathological mechanisms for the development of novel therapies. Also, IPF shares several pathogenetic similarities with other fibrotic lung diseases, such as COVID-19-induced pulmonary fibrosis and lung cancer. In this study, we identified neuronal ß-III tubulin (Tuj1), a pan-neuronal marker, as a potential biomarker in pulmonary fibrosis, and discovered that Tuj1-expressing pericytes suppressed the severity of lung fibrosis. A series of spatial and temporal imaging and scRNA-seq analysis of bleomycin-induced fibrotic lung revealed the emergence of Tuj1-expressing pericytes in response to lung fibrosis. Our lineage-tracing experiments using the pericyte-specific CreER mice (PDGFRß-CreER or NG2-CreER) and Cre-dependent reporter mice (Rosa-LSL-YFP) supported the observation that Tuj1-expressing cells are derived from pericytes. Importantly, Tuj1-expressing pericytes were also found in human IPF tissues. To investigate the role of Tuj1 (gene name: Tubb3) in lung fibrogenesis, we examined what happens to fibrosis in Tubb3 knockout mice following bleomycin administration. Interestingly, Tubb3 knockout mice exhibited enhanced lung fibrosis without any significant neuronal abnormality, suggesting that Tuj1-expressing pericytes appear to suppress lung fibrosis. Taken together, these studies provide a potential clue for developing a novel therapeutic strategy targeting the Tuj1-expressing pericytes in the fibrotic lung vasculature.

**Ryo SATO**

## Biography

Dr. Sato received his M.D. from Kumamoto University in 2006 and his Ph.D. from Keio University in 2017. He worked as a pulmonologist at Kumamoto University Hospital and started as a visiting fellow at NIH in 2019.

# Research Plan at NIH
# by JSPS-NIH Fellows Awarded in FY2022

# Shinji Ashida

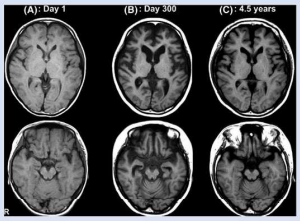
Neuroimmunological Disease Section (NDS)
Laboratory of Clinical Immunology and Microbiology (LCIM), NIAID, NIH

**Kyoto, Japan**
**2009 Graduate of**
**Kyoto Prefectural University of Medicine**

**Trained as Neurologist**

**Turning point**

**Case: 18-year-old**
***Anti- NMDAR Encephalitis***




Ashida et al. *CENI* 2020.

**Research**

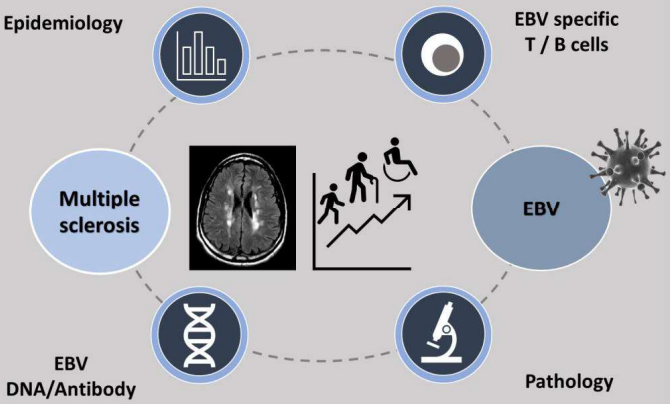
***Myasthenia Gravis and Follicular helper T cells***

Ashida et al. *Neurology N2*. 2020.

***Features of Atypical Multiple sclerosis in Japan***

Ashida et al. *Frontiers Neurology* 2021.
Ashida et al. *Frontiers Neurology* 2022.

## Project at NIAID/NDS lab



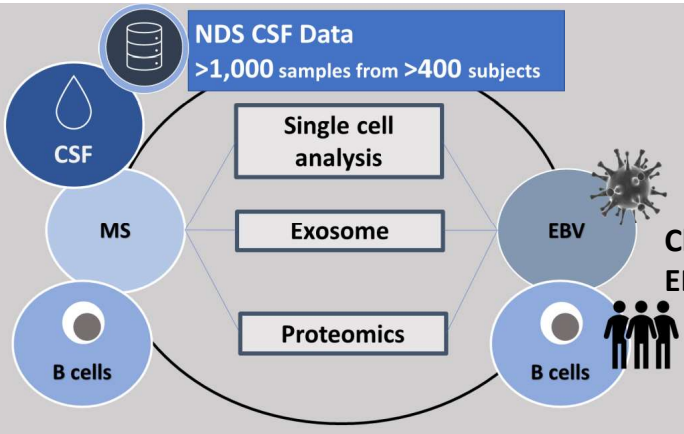

**Association of MS and EBV infection**

**Mechanism which EBV cause MS is unknown.**

**B cells play crucial role in MS mechanism.**

**B cells: 5% of CSF cells**
**2-10 EBV infected / million B cells**

**Elucidation of Multiple sclerosis mechanism underlying EBV infection:**
*Multi omics analysis of Central spinal fluid and EBV-infected B cells*




**Chronic Active EBV Infection**

## Fumiaki Iwane, PhD

2017 – 2021: PhD, Swiss Federal Institute of Technology in Lausanne

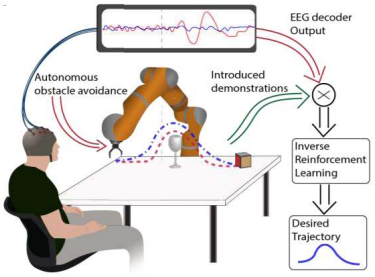
2019 – 2021: Research Fellow, The University of Texas at Austin

Article | Open Access | Published: 16 December 2021

**Customizing skills for assistive robotic manipulators, an inverse reinforcement learning approach with error-related potentials**

Iason Batzianoulis, Fumiaki Iwane, Shupeng Wei, Carolina Gaspar Pinto Ramos Correia, Ricardo Chavarriaga, José del R. Millán & Aude Billard

*Communications Biology* **4**, Article number: 1406 (2021) | Cite this article




2021 – Present: Research Fellow, Human Cortical Physiology and Neurorehabilitation Section (HCPS), NINDS (PI: Dr. Leonardo G. Cohen)

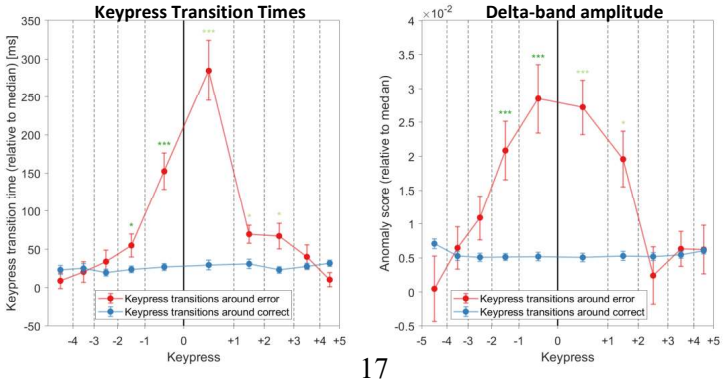
## At HCPS / NINDS

***Goal***: To understand the mechanisms underlying plastic changes in human central nervous system and to develop novel rehabilitation therapies.

## My Project

***Goal***: To predict upcoming erroneous actions during skillful performance.

***Results***: Behavioral slowing and anomalous delta-band MEG amplitude preceded single errors and predicted upcoming errors at the 70%.



# Fuki Kudoh, Ph.D

**Education and Training**

March 2020 Obtained Ph.D in Science from Hokkaido University
Superivsor: Prof. Kazuyasu Sakaguchi
*Laboratory of Biological Chemistry, Dept. of Chemistry*

Protein phosphatase PPM1D, negative regulator of p53 pathway
- Role of PPM1D in myeloid differentiation and inflammation
- Molecular mechanism of PPM1D enzyme

July 2020- Visiting Fellow in Keiko Ozato lab,
Section of Molecular Genetics on Immunity, NICHD

"DNA damage in innate immunity and epigenetic memory"

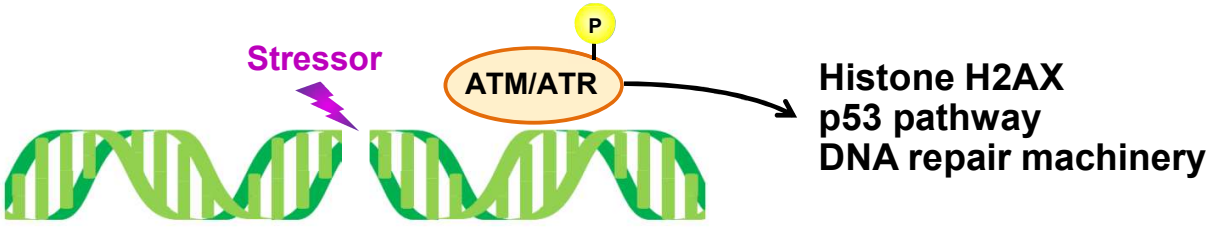
**Plan after fellowship**

Looking for academic career in US and Japan

# My theme of research in NIH

## ❑DNA double strand breaks in innate immunity

**DNA double strand breaks (DBS)**




- Immune cells accumulates DSBs by infection, autoimmune diseases. (Walter D. *et al, Nature* 2015; Mitroulis I. *et al.*, *Cell*, 2018; Manolakou T. *et al.*, *Sci. Ad.*, 2022)

- Dr. Ozato reported histone chaperone KO accumulated DSB in Hematopoietic stem cells. (Chen C. *et al., Cell Rep.,* 2020)

➢ The meaning and mechanism of DBS in the HSC is unknown.

I will focus on
1. The molecular mechanism of DNA damage accumulation by infection
2. DBS as a part of innate immunity, especially in innate immune memory

**Wakako Kuribayashi, Ph.D.**

## Research & Education

**2014** BA of Pharmaceutical Sciences
Tokyo university of Science

**2016** M.S. of Medical Science
Chiba university, Graduate School of Medicine

Internship at National Institute of Infectious Diseases
Research project: Leukemic stem cells in ATL model mice

**2020** Ph.D. of Medical Science
Doctoral Course Students 2 (DC2-JSPS)

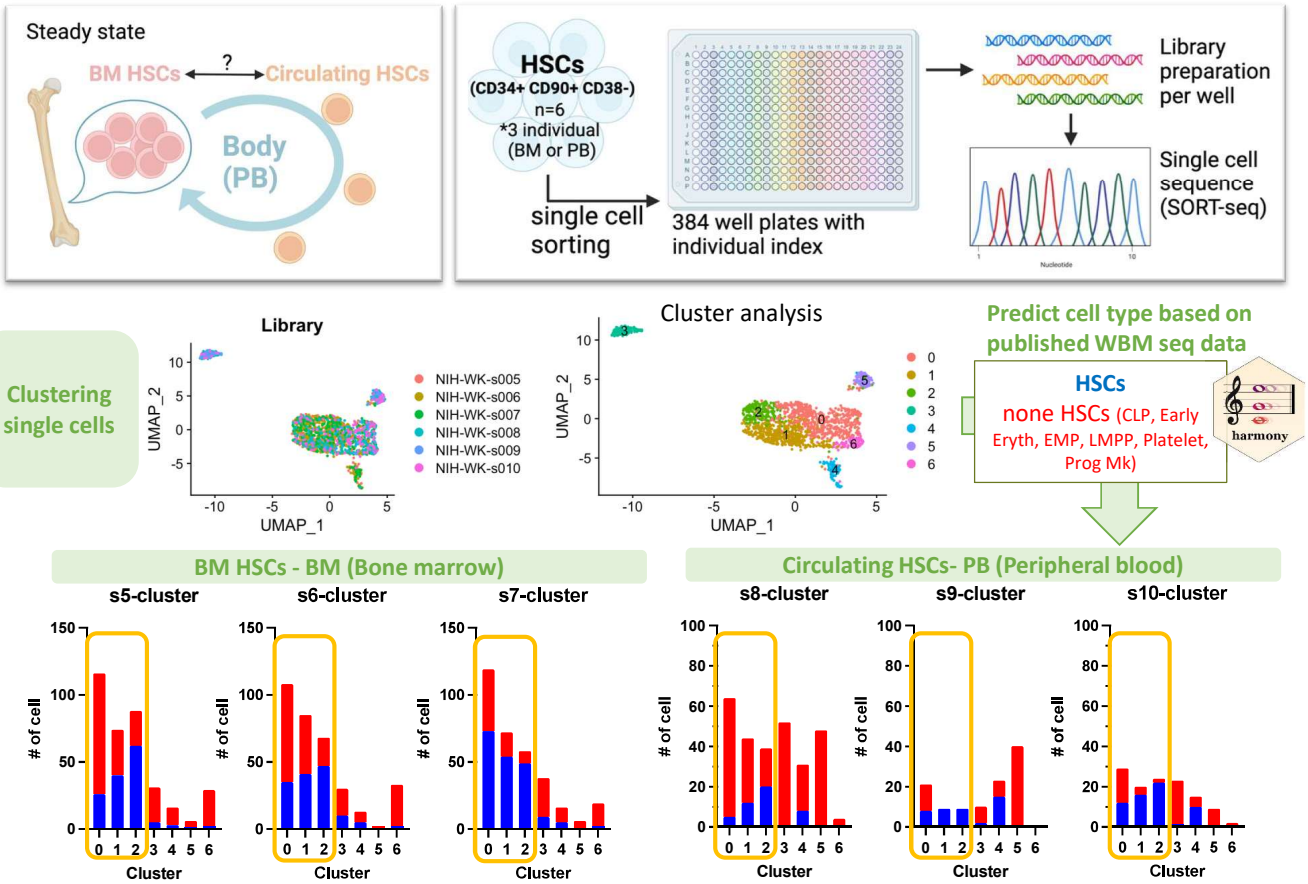
Chiba university, Graduate School of Medicine
Epigenetic and Stem Cell (Dr. Atsushi Iwama)
Research project: Hematopoietic stem cell aging and BM niche

**2020** Specially Appointed Fellow
The Institute of Medical Science, The University of Tokyo
Stem Cell and Molecular Medicine (Dr. Atsushi Iwama)

**2020** Visiting Research Fellow
National Institute on Aging, NIH
Epigenetic Stem Cell Unit (Dr. Isabel Beerman)
Research project: Hematopoietic stem cell aging and epigenetic alteration

After NIH : Exploring

## DNA methylation changes in circulating hematopoietic stem cells (HSCs) during human aging



# Taisuke Sato, M.D., Ph.D.

- OBGYN Specialist (Maternal-Fetal Medicine)
- Clinical Genetic Specialist

**Previous Affiliation in Japan:**

1. Department of Obstetrics and Gynecology, The Jikei University School of Medicine, Tokyo
2. Department of Maternal-Fetal Biology, National Research Institute for Child Health and Development, Tokyo

**Previous Main Work:**

- Develop a new **prenatal diagnosis** using circulating fetal cells and cell-free nucleic acid in maternal peripheral blood

**Current Affiliation (Sep. 2020 - ):**

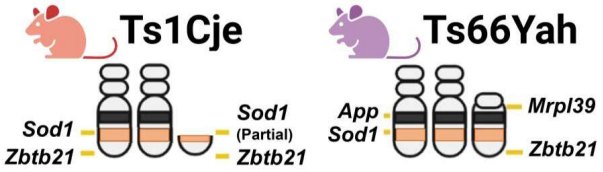
Center for Precision Health Research, Prenatal Genomics and Therapy Research Section, NHGRI (Dr. Bianchi Lab)

**Current Work:** Investigate placental molecular signatures in different models of Down syndrome (DS)

- Little is known about placental development in mouse models of DS
- Placentas should be considered in developing prenatal therapies
- Long-term goal: Develop **prenatal treatments** for DS

**Hypothesis**

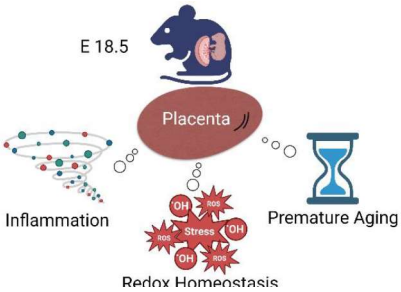
*App* and *Sod1* overexpression induces abnormal oxidative stress, premature aging, and inflammation on DS placenta




## The Roles of Oxidative Stress, Premature Aging, and Inflammation in Preclinical Models of DS

**Preliminary Results**

- Inflammation or redox homeostasis genes & pathways are dysregulated in DS placentas
- Placentas in mouse models show differences in inflammation & redox homeostasis



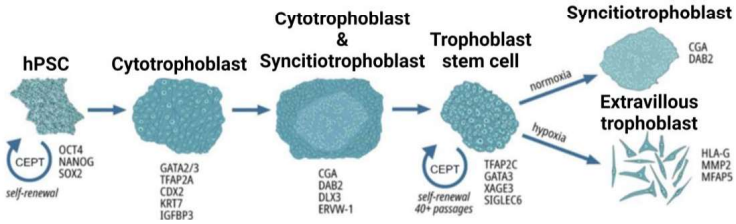


**Research Aim 1:**

Uncover the molecular and cellular mechanisms of abnormal placental development in mouse models of DS

**Research Aim 2:**

Investigate the developmental time course of abnormal placental development using iPSCs derived from individuals with DS



# Kensuke Daida M.D. Ph.D.

Lab in Japan :
Department of Neurology, Juntendo University, Tokyo

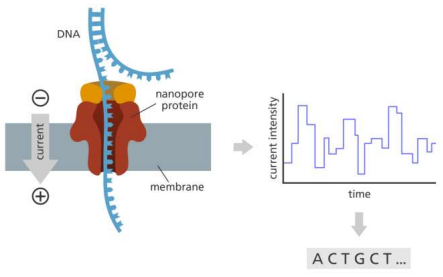
Research focus:
Genetics of Parkinson's disease (PD) and other neurological diseases

Lab in NIH :
Laboratory of Neurogenetics/NIA
Center for Alzheimer's and Related Dementias/NIA

PI : Dr. Cornelis Blauwendraat

After finishing JSPS program: Going back to Japan.

## Research using Long Read Sequencing

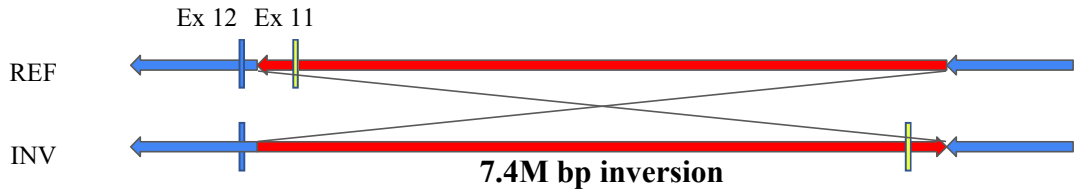



https://doi.org/10.1038/s41592-022-01759-x

Method of the Year 2022: long-read sequencing


- Human brain sample of Alzheimer's, Parkinson's and other ADRD.
- Blood from PD patients
- Familial cases

**Identify structural variants affect to neurological disease combining with expression and methylation data.**



My name: Naoki Hayase

What I have studied in Japan:

- Contribution of extracellular histones and NETs to distant organ injury in ischemia-reperfusion.
- Biomarkers of sepsis-induced organ injuries.

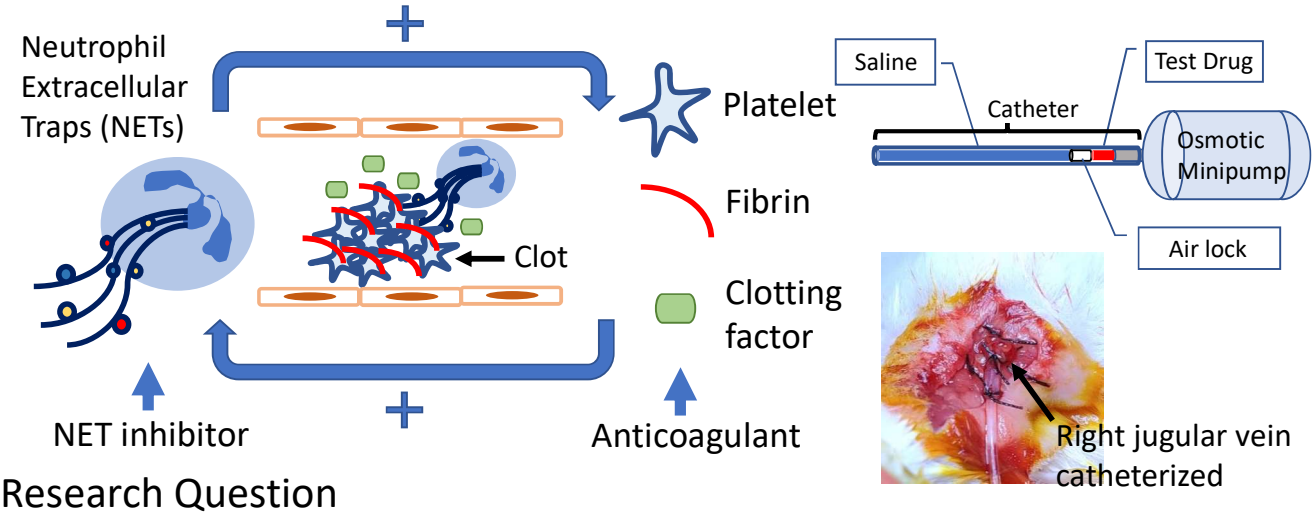
Previous lab: Department of emergency and critical care medicine, the University of Tokyo.

Current lab: Renal Diagnostics and Therapeutics Unit, NIDDK (Host researcher, Dr. Robert A. Star)

My plan after leaving NIH

- A physician scientist to handle basic, clinical, and translational research and educate Ph.D. students.

Sepsis-induced multiple organ dysfunction syndrome
→ immunothrombosis




## Research Question

- Can combination of a NET inhibitor and an anticoagulant treat a clinically relevant sepsis model?

## Methodology

- A fully treated mouse model of sepsis [cecum ligation and puncture (CLP)].
- Continuous infusion of NET inhibitors and/or anticoagulants, or saline via osmotic minipumps with delayed onset starting at 6–12 hours after CLP.

First year: Effect of NET inhibitors and/or anticoagulants on survival.

Second year: Pathophysiology and organ specific effects of NET inhibitors and/or anticoagulants.

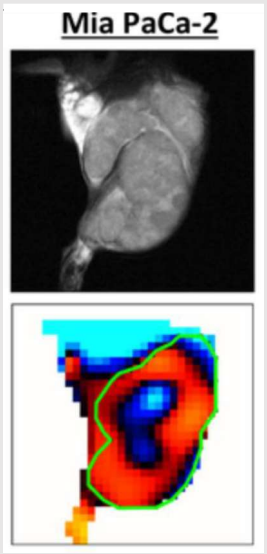
# Kazumasa Horie, M.D., Ph.D.

**2018-2022 Kobe University (iPS cell Applications)**
The impact of valproic acid on patient-derived colorectal cancer organoids

**2022- Radiation Biology Branch / NCI**
Non-invasive Imaging (MRI)

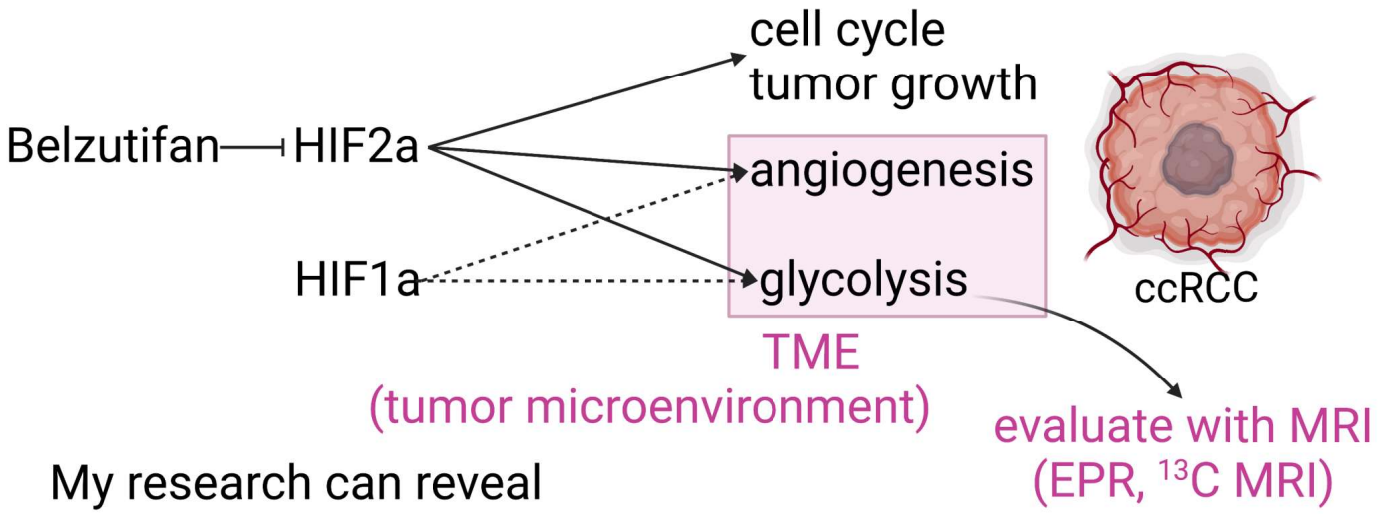
- Electron Paramagnetic Resonance (EPR) $pO_2$ mapping
- Hyperpolarized MRI using $^{13}C$ Metabolic imaging
- Dynamic Contrast-enhanced MRI tissue perfusion / permeability

EPR
($pO_2$ mapping)




**After KAITOKU-NIH**
continue researching about cancer in Japan

## Multimodal molecular imaging detects early responses to novel HIF-2α inhibitor Belzutifan




My research can reveal

1. relation between Belzutifan efficacy and TME change
2. importance of the baseline HIF1a expression

It will be useful for

- optimizing treatment regimens
- predicting treatment efficacy

# NOTE

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# NOTE