2024 JSPS-NIH Forum

March 1, 2024

Japan Society for the Promotion of Science
Fogarty International Center, National Institutes of Health
# 2024 JSPS-NIH Forum

**DATE**  
3:00 pm – 7:30 pm  March 1, 2024 (EST)  
* [Japan Standard Time 日本時間] 5:00 am – 9:30 am  March 2, 2024

**VENUE** Hybrid (The Lawton Chiles International House (Building 16))  
In-person Registration (Invitation Only)  
Online Registration from [here](#)

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

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| 3:00pm - 3:25pm (EST) | Opening Remarks  
5:00am - 5:25am (JST)  
Dr. Junji URAKAWA, Director, JSPS Washington Office  
Mr. Koji ARIBAYASHI, Science Counselor, Embassy of Japan in the USA  
Dr. Yoh-suke MUKOYAMA, Chair of Review Panel / Senior Investigator, NHLBI, NIH  
Dr. Michael GOTTESMAN, Chief, Laboratory of Cell Biology, NCI/CCR, NIH |
| 3:25pm - 4:10pm (EST) | Invited Speaker (1) 45 min. including Q & A  
5:25am - 6:10am (JST)  
Dr. Motoyuki ITOH, Professor, Graduate School of Pharmaceutical Sciences, Chiba University  
Lecture title: Investigating Age-Induced Alterations in Brain Function and Regeneration Using Zebrafish Model |
| 4:10pm - 4:20pm (EST) | Break  
6:10am - 6:20am (JST) |
| 4:20pm - 5:00pm (EST) | Invited Speaker (2) 20 min. including Q & A  
6:20am - 7:00am (JST)  
Dr. Yuko YASUI, (NIH/NIDA) [E]  
Lecture title: Sigma-1 receptor plays a critical role in cocaine-induced synaptic AMPA receptor plasticity in the VTA dopamine neurons |
| 5:00pm - 5:10pm (EST) | Break  
7:00am - 7:10am (JST) |

**Flash Talk Session**
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<td>5:10pm - 5:35pm (EST) 7:10am - 7:35am (JST)</td>
<td>Presentations on Research Plan at NIH by <strong>JSPS-NIH Fellows</strong> (KAITOKU-NIH) Awarded in FY2023 (8 Fellows) 3 mins for each</td>
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| 5:35pm - 5:45pm (EST) 7:35am - 7:45am (JST) | Closing Remarks  
**Dr. Peter Kilmarx**, Acting Director, Fogarty International Center, NIH  
**Dr. Nina F. SCHOR**, Deputy Director for Intramural Research, NIH |
| 5:45pm - 7:30pm (EST) 7:45am - 9:30am(JST) | Networking (only for in-person participants) |
Investigating Age-Induced Alterations in Brain Function and Regeneration Using Zebrafish Model

Motoyuki ITOH
Professor
Graduate School of Pharmaceutical Sciences
Chiba University

Abstract

Zebrafish, with a lifespan of 3-5 years, share about 70% homology with the mammalian genome and retain over 80% of disease proteins. Our lab uses zebrafish for aging research, comparing their aging processes with mammals. We studied age-related changes in metabolism, learning ability, and the cerebrovascular system. Metabolic aging in zebrafish is evident at 10-14 months, and a decline in learning ability is observed at 15 months. A positive correlation was found between cerebral blood flow and learning ability in 14-month-old zebrafish, similar to aged humans. This suggests that aging symptoms appear in the brain and metabolic rate in zebrafish after 14 months. Unlike mammals, fish, especially zebrafish, have a higher regenerative capacity, including remarkable brain regeneration abilities, considered an anti-aging mechanism. While zebrafish show reduced learning ability with age, the relationship between their regenerative ability and age-related functional decline is unclear. Recent research is focused on elucidating this link, aiming to gain insights into overcoming age-related brain vulnerability in mammals.
Motoyuki ITOH

Biography

Education
1991   Osaka University, Pharmaceutical science, Japan    Bachelor
1993   Osaka University, Pharmaceutical science, Japan    Master
1998   Osaka University, Medical science, Japan    Ph.D

Positions and Employment
1998-1999   Osaka University, Japan    Postdoctoral fellow
1999-2003   LMG/NICHD, USA    Postdoctoral fellow
2003-2012   Nagoya University, Japan    Associate professor
2012-     Chiba University, Japan    Professor
Sigma-1 receptor plays a critical role in cocaine-induced synaptic AMPA receptor plasticity in the VTA dopamine neurons

Yuko YASUI
Staff Scientist
National institute on Drug Abuse
NIH

Abstract

Sigma-1 receptor (Sig1R) is a ligand-operated chaperone that regulates a variety of cellular functions through interaction with proteins including receptors and ion channels. Sig1R has been implicated in cocaine addiction since Sig1R ligands attenuate cocaine-induced behaviors. Cocaine causes neuroadaptation in the mesocorticolimbic dopamine system which is essential for reward and motivational process. This system connects the ventral tegmental area (VTA) to the major projected areas, nucleus accumbens and prefrontal cortex, where alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) play an important role in cocaine-induced synaptic plasticity and long-lasting behavioral effects of cocaine. Single cocaine exposure in vivo induces long-term potentiation in the VTA dopamine neurons at least partly through insertion of GluR2-lacking AMPAR. However, the molecular mechanisms of this process are not fully understood. In this study, we found that a single cocaine injection increased synaptic GluR2-lacking AMPAR in the VTA dopamine neurons of wild-type mice as previously reported, but not in Sig1R knockout mice. Moreover, the expression of GluR2 and GluR3 was decreased on the surface and increased in the endosomes with cocaine treatment in wild-type but not in Sig1R knockout mice. Together, we demonstrate that Sig1R controls cocaine-induced formation of GluR2-lacking AMPAR by altering the intracellular distributions of GluR2 and GluR3. This study suggests Sig1R can be a therapeutic target for cocaine addiction.
Yuko YASUI

Biography

Gifu University, Gifu, Japan
Ph.D., Pharmaceutical Sciences, March 2012

National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), Baltimore, MD
Postdoctoral Research Fellow, October 2012-September 2018

National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), Baltimore, MD
Research fellow, November 2018-August 2020

National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), Baltimore, MD
Staff Scientist, August 2020-present
NGF-TrkA-PI3K signaling promotes sensory hypersensitivity in diabetes

Yuta KOUI
Postdoctoral Fellow
Laboratory of Stem Cell and Neuro-Vascular Biology, Cell and Developmental Biology Center, National Heart, Lung, and Blood Institute National Institutes of Health

Abstract

Diabetic patients often develop small fiber neuropathy in the early stage of diabetes, including obesity and prediabetes. Patients with small fiber neuropathy exhibit dysfunction in skin sensory nerves and blood vessels, leading to severe burning or shooting pain. However, how symptoms are sequentially established and which signaling mechanisms are involved in sensory hypersensitivity remain unclear. Using a novel pain behavior assay and ex vivo live tissue calcium imaging, we demonstrated that diet-induced obesity (DIO) model mice develop painful symptoms and sensory hypersensitivity at 22 weeks-of-age, and exhibit reduced painful symptoms and hypersensitivity at 30 weeks-of-age. Our immunohistochemical analysis revealed sensory axon degeneration in the skin epidermis at 30 weeks-of-age but not at 22 weeks-of-age, indicating that hypersensitivity is established before the onset of axon degeneration. We also observed hyperpermeability in capillary vessels from 22 weeks-of-age onward, suggesting that vascular damage may play a role in the development of sensory dysfunction in the DIO skin. At the mechanistic level, enhanced NGF expression was observed in skin epidermal keratinocytes of the DIO mice at 22 weeks-of-age. Local treatment with anti-NGF neutralized antibody or a small compound inhibitor for PI3K, a downstream component of NGF signaling, suppresses hypersensitivity in the DIO skin. This suggests that keratinocyte-derived NGF induces hypersensitivity in the DIO skin. Collectively, NGF locally regulates sensory activities in diabetes and could be a potential therapeutic target for diabetic small fiber neuropathy.
Yuta KOUI

Biography

Education and position of employment
2014-2019: Master student, Ph.D. Candidate, and Postdoctoral Fellow supervised by Dr. Atsushi Miyajima, Laboratory of Cell Growth and Differentiation. Institute for Quantitative Biosciences, The University of Tokyo, Japan.
2019-present: Postdoctoral Fellow supervised by Dr. Yosuke Mukoyama, Laboratory of Stem Cell and Neuro-Vascular Biology. National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), USA.

Fellowship and Award
2016-2019: Research fellow of Japanese Society of the Promotion of Science (JSPS)
2020-2022: Research Fellowship for Japanese Biomedical and Behavioral Researchers at NIH (JSPS)
2022-2023: Uehara Postdoctoral Fellowship Award (The Uehara Memorial Foundation)
2022-present: Lenfant Fellowship Award (National Heart, Lung, and Blood Institute)
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<td>MYOJIN Yuta</td>
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Atsumi Tamura, M.D., Ph.D.

2009  M.D. Faculty of Medicine, Akita University
Surgical Residency at Tokyo Metropolitan Bokutoh Hospital

2014  Assistant Professor, Department of Surgery, Tokyo Medical University

2018  Ph.D. Department of Surgery, Tokyo Medical University Graduate School

Research Projects:
- Examine tissue thermal damage caused by energy devices used in thyroid surgery
- Observational study with anaplastic thyroid cancer patients
- Clinical research on treatment strategies for thyroid cancer with tracheal invasion

November 2022- Visiting Fellow (Dr. Shioko Kimura Lab)
Cancer Innovation Laboratory, Center for Cancer Research, NCI, NIH

After NIH
Continue research on thyroid carcinogenesis as a surgeon in Japan

Effect of mutated Hras expression and deletion of Nkx2-1 on thyroid carcinogenesis in mice

Background
- **Thyroid cancer**: most common malignancy of endocrine organs
- **Nkx2-1**: homeodomain transcription factor, essential for the genesis, differentiation, and function of thyroid
- **Ras mutations**: Carcinogenesis is insufficient with Hras^{G12V} mutation alone in the thyroid

Aim: To understand whether the loss of Nkx2-1 promotes carcinogenesis expressing mutated Hras in the thyroid of model mouse

1) To determine the incidence of thyroid tumors between different genotype groups
2) To identify metabolites in serum, specific to thyroid tumors and genotypes in mice – metabolomics analysis
3) To analyze the metabolites of human clinical serum samples

RAS mutation ?

Follicular Cell  Follicular thyroid adenoma  Follicular thyroid carcinoma

MODEL MOUSE
Hras^{G12V/mm};Nkx2-1ff;TPO-cre
Hras^{G12V/mm};Nkx2-1ww;TPO-cre
Chiori Tabe

2016 M.D.  Hirosaki University


2020.4-

1. The detection of drug-resistant mutation in anaplastic lymphoma kinase (ALK) positive lung cancer patients treated with ALK-TKIs.

2. The monitoring of the medication-induced changes in the intestinal microbiota in epidermal growth factor receptor (EGFR) positive lung cancer patients treated with EGFR-TKIs.

Identification and characterization of proteins associated with regions of extrachromosomal DNA regulating oncogene expression in small cell lung cancer cells

How are promoter and enhancer activities regulated?

1st year: Identification of associated proteins

- enChIP technology (engineered DNA-binding molecule-mediated chromatin immunoprecipitation)

2nd year: Characterization of the functions of the identified proteins.

Using:
- Knockdown experiments using siRNA / shRNA
- Knockout experiments by genome editing
- Overexpression

Analysis of:
- Cell proliferation (in vitro / in vivo)
- Metastasis (in vitro / in vivo)

### Keisuke Fukutomi

**Mar 2011**
**M.D.**, Osaka University Faculty of Medicine, Osaka, Japan

**Apr 2011-Mar 2017**
Clinical training in Gastroenterology and Hepatology
Osaka National Hospital and Osaka University Hospital, Osaka, Japan

**Apr 2017-Nov 2021**
**Ph.D.**, Osaka University Graduate School of Medicine, Osaka, Japan
- Clinical training in Gastroenterology and Hepatology
  Osaka National Hospital and Osaka University Hospital, Osaka, Japan

**Feb 2022- present**
Postdoctoral Fellow, Immunology Section, Liver Diseases Branch, NIDDK, NIH
  **Section Chief: Dr. Barbara Rehermann**
- Immunopathogenesis of perinatal flares of hepatitis in pregnant women with chronic HBV infection

**Future:** Conduct translational research in immunology.

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**A clinical and immunological pilot study to restore HBV-specific immune responses in chronic hepatitis B virus infection**

**Background:**
- HBV-specific immune responses are required to recover from acute and chronic HBV infection
- Long-term exposure to HBV antigens results in exhaustion of HBsAg-specific T cells

**The problem:**
- HBsAg levels exceed HBV virion levels by a factor of 100,000.
- Conventional anti-HBV drugs block HBV replication but not HBsAg production from cccDNA & integrated DNA

**Approach:**
- Block HBsAg production with **siRNA treatment** prior to **antiviral treatment**

**Assess:**
- Transcriptional change in intrahepatic immune cells
- HBs-specific vs. HBc & pol-specific T cell function
- Response to subsequent pegIFN treatment

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**Fukutomi K et al. *Hepatol Commun* 2022**

- Innate immune response of HBV-infected hepatocytes under treatment with Capsid Assembly Modulator and peg-IFNα
- B cell responses in patients with chronic HBV infection
- Development of an HBsAg-transgenic mouse model to study host immune responses

- Fukutomi K et al. *Hepatol Commun* 2022

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**Future:** Conduct translational research in immunology.
Leo Yamada, M.D., Ph.D.

Education & Training
- Surgeon (in Gastroenterology)
- 2012: M.D., Fukushima Medical University
- 2016-2020: Ph.D., Fukushima Medical University

Previous Affiliation in Japan:
1. Department of Gastrointestinal Tract Surgery, Fukushima Medical University
2. Laboratory of Molecular Carcinogenesis, National Cancer Center Research Institute

After JSPS-NIH
- A physician scientist for translational research.

Investigation of p53 Isoform-Based Therapeutic Strategy for Physiological and Pathological Aging.

Background
Δ133p53α inhibits premature cellular senescence and extends cellular lifespan in progeria cells in vitro.
- Therapeutic potential in CD8+ T cells and brain astrocytes as well.
- Non-oncogenic and non-mutagenic, encouraging clinical translation.

Hypothesis
Δ133p53α inhibits premature aging phenotypes and extends lifespan in a progeria mouse model in vivo.

Specific Aim
Investigate the effects of Δ133p53α on aging phenotypes and lifespan in the transgenic mice.
Reona Okada, M.D. Ph.D.

- Pediatric oncologist (2015-2022)
- Ph.D. work in the Seki Lab at Chiba University Graduate School of Medicine (2019-2021): Identification of oncogenes in various cancers using microRNA signatures.
  
  Dissertation: Regulation of oncogenic targets by miR-99a-3p (passenger strand of miR-99a-duplex) in head and neck squamous cell carcinoma
- Postdoc in the Nguyen Lab in the Pediatric Oncology Branch, NCI (2022-present): Immunotherapy development for various pediatric cancers
  
  GPC2-CAR-T-cells engineered with NFAT-inducible membrane-tethered IL-15/IL-21 exhibit enhanced activity against neuroblastoma (under review)
- Post-fellowship goals: building a translational research program at a university in Japan

Orthotopic patient-derived xenografts (PDXs) of adrenocortical carcinoma (ACC) to accelerate drug discovery

1. ACC is a rare cancer of the adrenal gland without many therapy options for advanced disease

2. We established the largest collection of ACC PDXs (n=6)

3. We identified B7-H3 as a promising CAR T-cell target

4. ACC PDXs are pan-sensitive to XPO1 inhibition

Characterization of the PDXs
- Histology (immunohistochemistry)
- Flow cytometry
- RNA sequencing
- Whole exome sequencing
- Proteomics
- Surface proteomics
- Serum sample analysis

- Cytotoxicity of eltanexor in vivo (ongoing)
- Mechanism studies of eltanexor in ACC (pending proteomic and genetic study)
- Efficacy of combinatorial therapy B7H3-CAR + eltanexor (ongoing)
Yoichi Wada M.D., Ph.D.
Board Certified Pediatrician, Supervisor of Pediatrics (Japan Pediatric Society)
Board Certified Medical Geneticist (Japan Society of Human Genetics)
Specialty: Inborn Errors of Metabolism

2023 – Present  Metabolic Medicine Branch, Organic Acid Research Section, NHGRI
Laboratory of Dr. Charles P. Venditti, Visiting Fellow
2019 – 2023  Tohoku University Hospital, Assistant Professor
2015 – 2019  Tohoku University Graduate School of Medicine
2010 – 2015  Kurashiki Central Hospital, Junior and Senior Resident

Previous studies
Galactosemia type IV (galactose mutarotase deficiency)
- Identification as a disease entity (MIM#618881) Wada et al, Genet Med 2018
- Drug repurposing Wada et al, JIMD 2022
- Phenotypic and genetic clarification Mikami-Saito, Wada et al, under review

Others also based on clinical questions as a pediatrician
- Establishment of mouse model of lanosterol synthase deficiency
- Rapid detection tests for blood Phenylalanine

Future direction after NIH-KAITOKU
- Gene therapy development for patients with Inborn Errors of Metabolism

Nuclease free genome editing to treat cobalamin B class methylmalonic acidemia

Cobalamin B class methylmalonic acidemia (cblB)
- caused by biallelic mutations in MMAB gene
- characterized by metabolic instability, chronic renal disease, and neurological complications
- high mortality and morbidity
- there is no treatment to restore the metabolic condition

We are planning to insert normal MMAB gene into Alb locus without nuclease in model mouse of cblB
My name: Yosuke Kunishita
Birth: Asahikawa, Hokkaido, Japan

Work, education, and research

2011
Doctor of Medicine
Asahikawa Medical University

2013
Rheumatologist
Yokohama City Graduate School of Medicine
Rheumatoid Arthritis, Behçet's disease
(Clinical Research)

2015
Ph.D. of Medical Science
Yokohama City Graduate School of Medicine
Project: Dysfunction of TRIM21 in SLE
(Systemic lupus erythematosus
(Basic Research: mouse, cell-line, human specimen)

Previous
Rheumatologist
Yokohama Minami Kyosai Hospital
Visiting Researcher
Department of Stem Cell and Immune Regulation, Yokohama City University
VEXAS syndrome, RA, SLE
(Translational Research)

Current
Inflammatory Disease Section, NHGRI (Dr. Daniel L. Kastner)

Project: Identification of Pathological Variants in Inflammatory Diseases of Unknown Cause

Undiagnosed and/or extreme phenotype inflammatory disorders

Yokohama City University
Gene database of undiagnosed inflammatory disorders in Japanese

Extensive gene database
(All of US, GeneDx)

Databases of clinical and genetic information

Search for cases with the pathogenic variants

Identify novel pathogenic variants
I. Whole genome sequence
II. Deep sequence
III. Long-read sequence

Functional analysis of variants
i. Analysis of patient-derived specimens
ii. Analysis of immortalized cells and species

To corroborate findings

(43° N) Asahikawa
(Chicago: 42° N)
Yuta Myojin M.D., Ph.D.

-2021.6 Department of Gastroenterology, Osaka University
Research:
1. Cancer associated fibroblast (CAFs) and cancer cell interaction in hepatocellular carcinoma(HCC)
   -Autophagy of CAFs promotes tumor proliferation via several cytokine production.
2. Biomarker research in TKI treatment of HCC
   -The candidate marker discovered in mice screening was validated with clinical samples.

2021.7- NCI / Thoracic and GI Malignancies Branch / Dr. Greten’s lab
Main Research : Correlative study of clinical trial of HCC patients treated with immunotherapy

My plan after leaving NIH
As a physician scientist, I’d like to conduct a clinical trials and translational research in Japan.

Correlative study of clinical trial of HCC patients treated with immunotherapy

(Material)
41 patients enrolled the clinical trial
Clinical Data
=> Responders and non-responders / background

Biopsy samples in pre-post treatment
=>Whole exon sequencing/ Bulk RNA sequencing/ 37-plex immunohistochemistry(CODEX)/single cell RNA sequencing
Blood samples in pre-post treatment
=>PBMC : Spectro-cytometry(2 panel, 42 targets in total)/ Plasma : Multiplex cytokine panel

<Plan>
1. Collect samples of clinical trial and conduct the experiments with multiple modality
2. CODEX data => annotate cells and analyze the cellular neighborhood
3. scRNAseq data => validate the findings above by cell-cell interaction analysis + DEG analysis
4. BulkRNAseq data => validate the data in 1 and 2 by GSEA analysis and immune cell composition analysis
5. WES/Blood data => analyze the change pre and post/ response => combine with results from 1/2/3
6. Mice orthotopic liver tumor model => validate the hypothesis found in the above analysis