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

3:00pm - 3:25pm (EST) 5:00am - 5:25am (JST)	Opening Remarks **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
Lecture Session 1 *(Speaker from Japan)*	***Theme: Neuroscience***
3:25pm – 4:10pm (EST) 5:25am – 6:10am (JST)	Invited Speaker (1) 45 min. including Q & A **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) 6:10am - 6:20am (JST)	Break
Lecture Session 2 *(Speakers from NIH)*	
4:20pm - 5:00pm (EST) 6:20am -7:00am (JST)	Invited Speaker (2) 20 min. including Q & A **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 Invited Speaker (3) 20 min. including Q & A **Dr. Yuta KOUI,** (NIH/NHLBI) [F] Lecture title: NGF-TrkA-PI3K signaling promotes sensory hypersensitivity in diabetes
5:00pm - 5:10pm (EST) 7:00am - 7:10am (JST)	Break
Flash Talk Session	

5:10pm - 5:35pm (EST) 7:10am - 7:35am (JST)	Presentations on Research Plan at NIH by **JSPS-NIH Fellows** (KAITOKU-NIH) Awarded in FY2023 (8 Fellows) 3 mins for each
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-Septemebr 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)

Research Plan at NIH
by JSPS-NIH Fellows Awarded in FY2023

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)

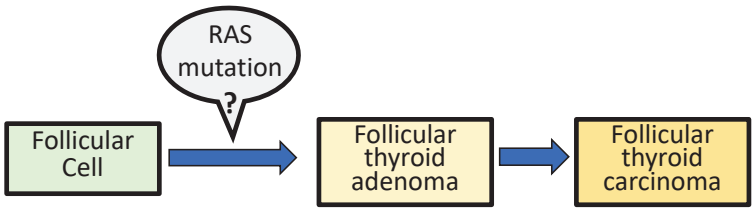
Cancer Innovation Laboratory, Center for Cancer Research, NCI, NIH

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



MODEL MOUSE

Hras^{G12V}*mm;Nkx2-1ff;TPO-cre*
Hras^{G12V}*mm;Nkx2-1ww;TPO-cre*

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

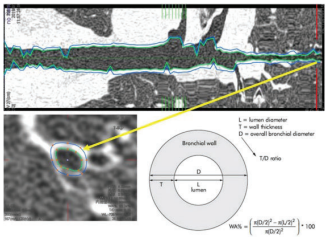
1) To determine the incidence of thyroid tumors between different genotype groups
2) To identify metabolites in serum, specific to thyroid tumors and genotypes in mice – metabolomics analysis
3) To analyze the metabolites of human clinical serum samples

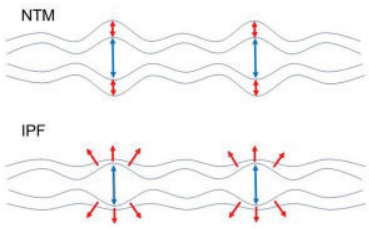
Chiori Tabe

2016 M.D. Hirosaki University

2023 Ph.D. Morphological features of bronchiectasis in patients with non-tuberculous mycobacteriosis and interstitial pneumonia.

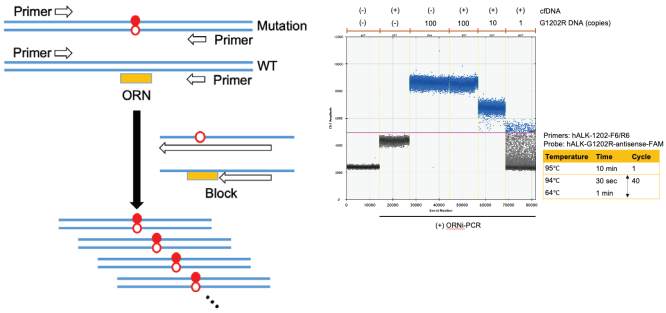
BMC Res Notes. 2022 Jul 26;15(1):263.



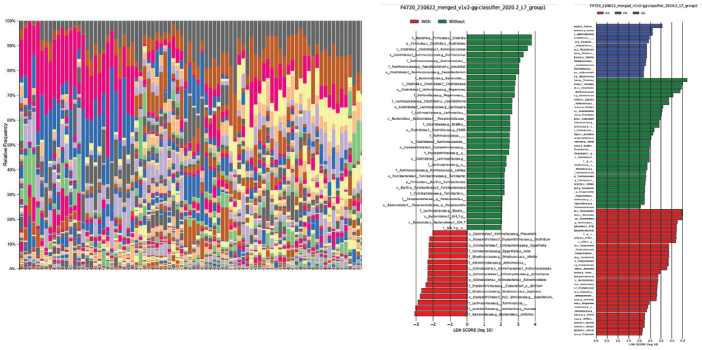


2020.4-

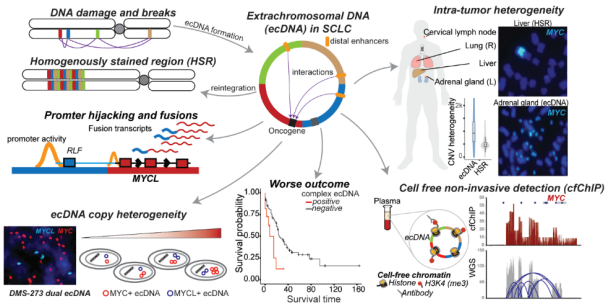
1.The detection of drug-resistant mutation in anaplastic lymphoma kinase (ALK) positive lung cancer patients treated with ALK-TKIs.



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



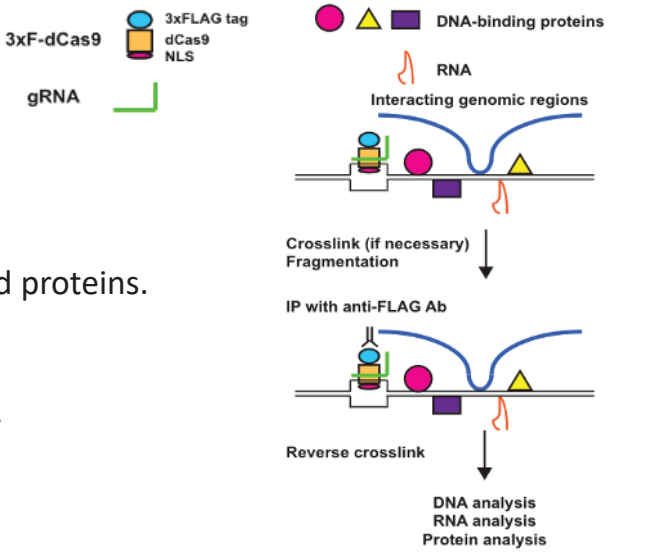
Pongor et al, Cancer Discov. CD-22-0796, 2023.

How are promoter and enhancer activities regulated?

1st year : Identification of associated proteins

enChIP technology

（engineered DNA-binding molecule-mediated chromatin immunoprecipitation）



Biochem Biophys Res Commun 439(1):132-6,2013）

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*)

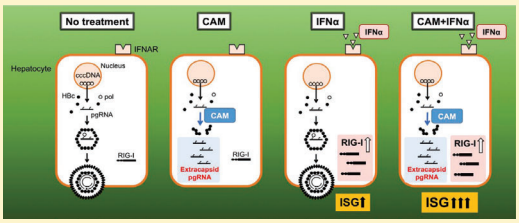
Keisuke Fukutomi

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

- 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



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.

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

Background:

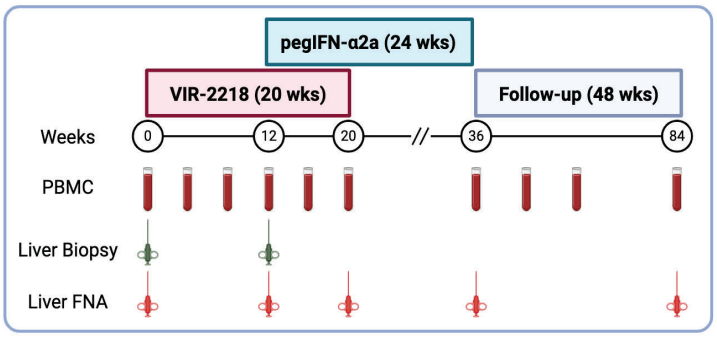
- HBV-specific immune responses are required to recover from acute and chronic HBV infection
- Long-term exposure to HBV antigens results in exhaustion of HBsAg-specific T cells

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

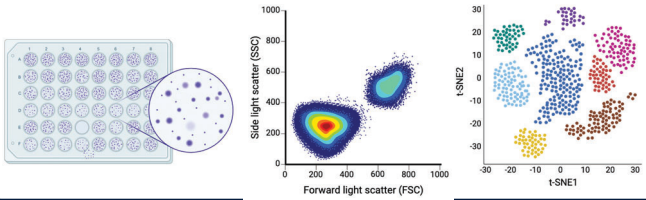
Approach:

- Block HBsAg production with siRNA treatment prior to antiviral treatment



Assess:

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



Leo Yamada, M.D., Ph.D.

公立大学法人 福島県立医科大学 FUKUSHIMA MEDICAL UNIVERSITY

Lab in NIH:
Laboratory of Human Carcinogenesis/NCI

Education & Training

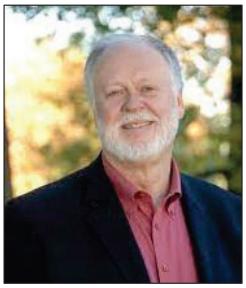
- Surgeon (in Gastroenterology)
- 2012: M.D., Fukushima Medical University
- 2016-2020: Ph.D., Fukushima Medical University

Gastric Cancer (2021) 24:60–71
https://doi.org/10.1007/s10120-020-01094-0

ORIGINAL ARTICLE

Selective sensitivity of EZH2 inhibitors based on synthetic lethality in ARID1A-deficient gastric cancer

Leo Yamada[1] · Motonobu Saito[1] · Aung Kyi Thar Min[1] · Katsuharu Saito[1] · Mai Ashizawa[1] · Koji Kase[1] · Shotaro Nakajima[1,2] · Hisashi Onozawa[1] · Hirokazu Okayama[1] · Hisahito Endo[1] · Shotaro Fujita[1] · Wataru Sakamoto[1] · Zenichiro Saze[1] · Tomoyuki Momma[1] · Kosaku Mimura[1,3] · Shinji Ohki[1] · Koji Kono[1]



PI: Dr. Curtis C. Harris

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.

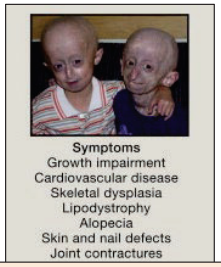
Background

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

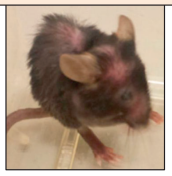
Δ133p53α inhibits premature aging phenotypes and extends lifespan in a progeria mouse model in vivo.



Symptoms
Growth impairment
Cardiovascular disease
Skeletal dysplasia
Lipodystrophy
Alopecia
Skin and nail defects
Joint contractures

Hutchinson-Gilford Progeria Syndrome

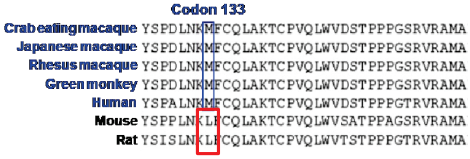
LmnaG609G
(Progeria mouse model)



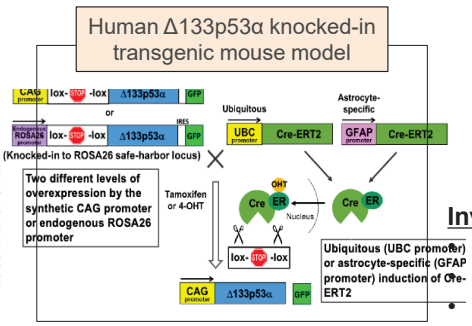
Specific Aim

Investigate the effects of Δ133p53α on aging phenotypes and lifespan in the transgenic mice.

N-terminally truncated p53 protein isoform.



➡ No existence in rodents.



Crossbreeding

Investigate anti-aging effects on

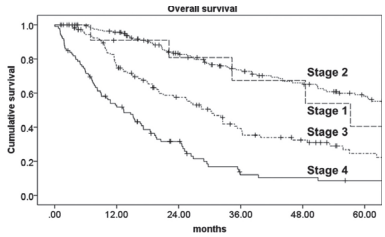
- Lifespan
- Pathological features (cardiovascular disease, skin…etc.)
- Immune exhaustion

Reona Okada, M.D. Ph.D.

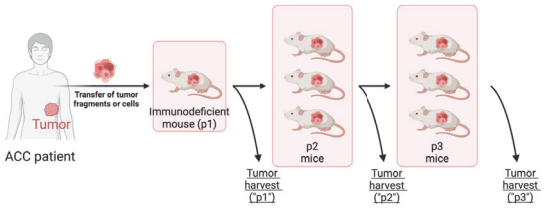
- Pediatric oncologist (2015-2022)
- Ph.D. work in the Seki Lab at Chiba University Graduate School of Medicine (2019-2021): Identification of oncogenes in various cancers using microRNA signatures.
  Dissertation: Regulation of oncogenic targets by miR-99a-3p (passenger strand of miR-99a-duplex) in 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 <u>rare</u> cancer of the adrenal gland without many therapy options for advanced disease



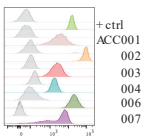
2. We established the largest collection of ACC PDXs (n=6)

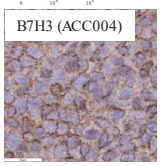


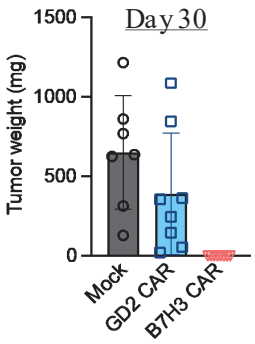
<u>Characterization of the PDXs</u>
- Histology (immunohistochemistry)
- Flow cytometry
- RNA sequencing
- Whole exome sequencing
- Proteomics
- Surface proteomics
- Serum sample analysis

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

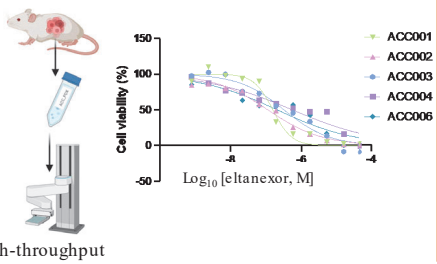
FCM: B7H3 expression







4. ACC PDXs are pan-sensitive to XPO1 inhibition



High-throughput drug screening (NCATS)

- 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)

J Clin Endocrinol Metab (2014) Illustrations created with BioRender.com.

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

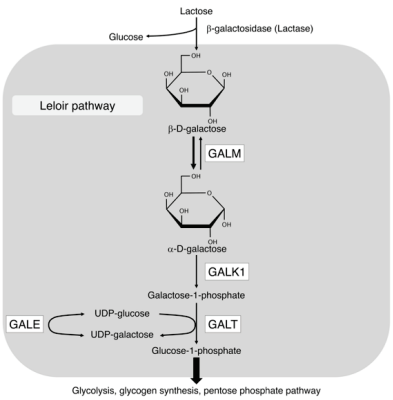
Previous studies

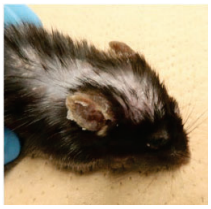
Galactosemia type IV (galactose mutarotase deficiency)
- Identification as a disease entity (MIM#618881) Wada et al, Genet Med 2018
- Prevalence estimation Iwasawa, Kikuchi, Wada, et al., Mol Genet Metab 2019
- Drug repurposing Wada et al, JIMD 2022
- Phenotypic and genetic clarification Mikami-Saito, 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

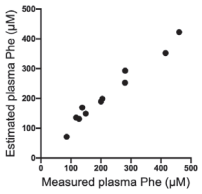
Future direction after NIH-KAITOKU
- Gene therapy development for patients with Inborn Errors of Metabolism

Leloir pathway (metabolic pathway of galactose)





Wada et al, PLOS Genet 2020

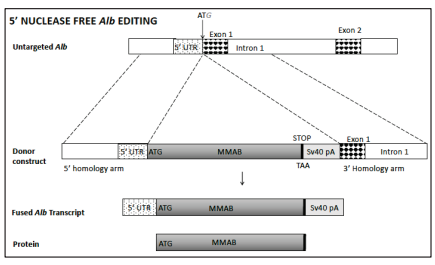


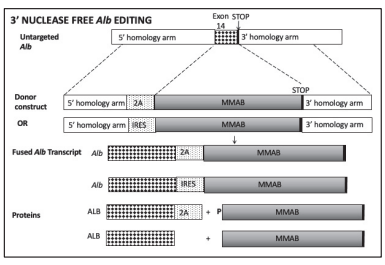
Wada et al, MGM rep 2023

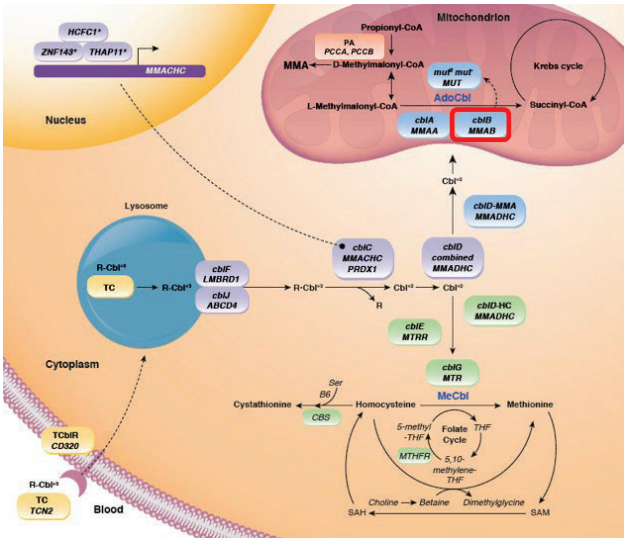
Nuclease free genome editing to treat cobalamin B class methylmalonic acidemia

Cobalamin B class methylmalonic acidemia (cblB)
- caused by biallellic 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

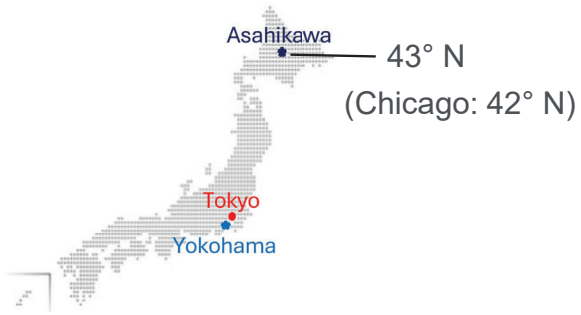






	2024 Q1	2024 Q2	2024 Q3	2024 Q4	2025 Q1	2025 Q2	2025 Q3	2025 Q4
Colony expansion	+	+						
Treatment: short term analysis		+	+					
Treatment: long term analysis			+	+	+	+		
Abstract							+	+
Manuscript								+

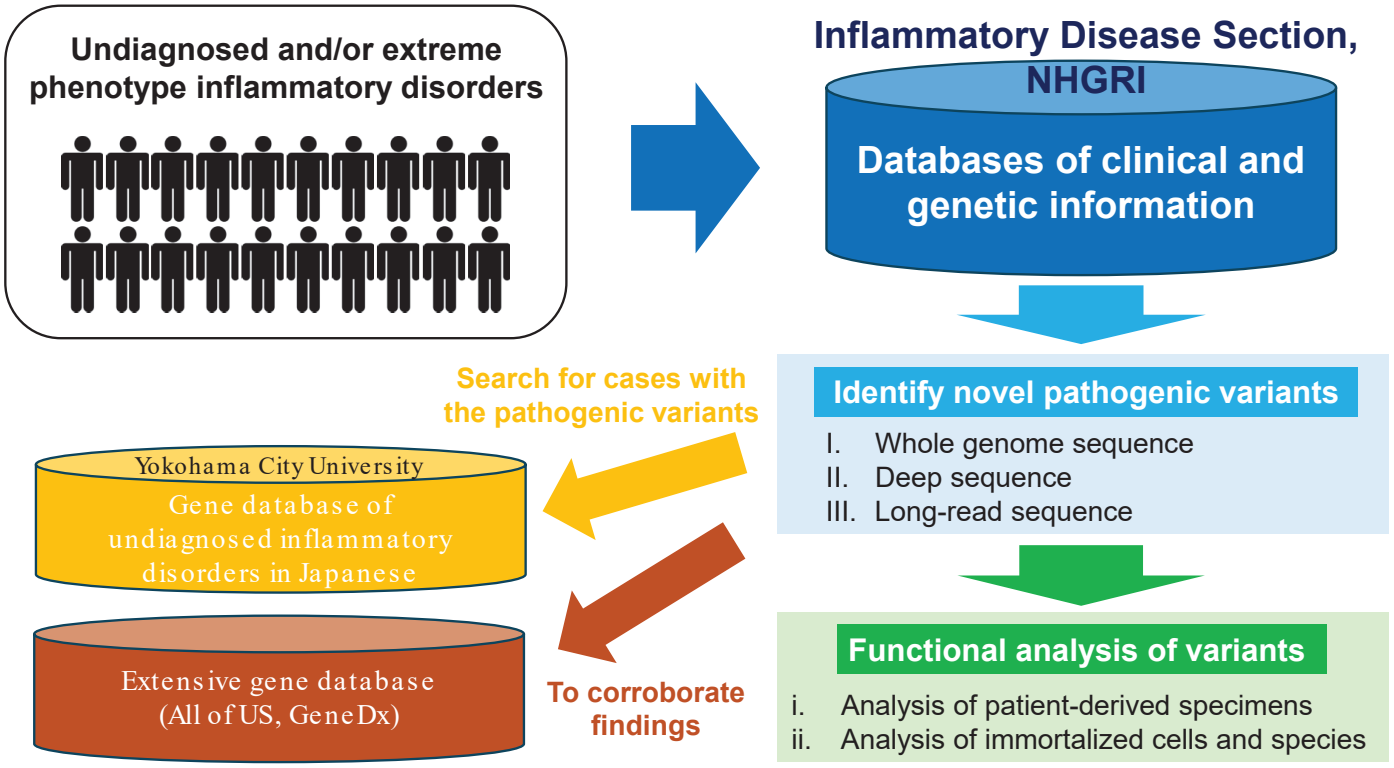
- ✓ My name: Yosuke Kunishita
- ✓ Birth: Asahikawa, Hokkaido, Japan



➢ 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 ~ 2020	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



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.

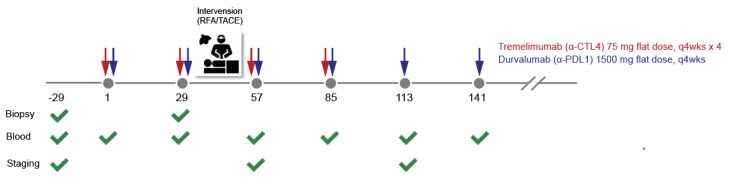
<u>Correlative study of clinical trial of HCC patients treated with immunotherapy</u>

<Material>

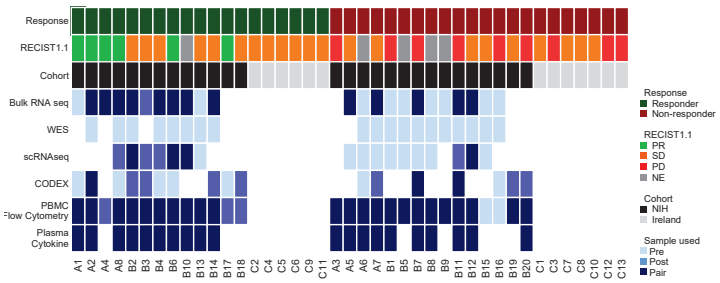
41 patients enrolled the clinical trial

Clinical Data

=> Responders and non-responders / background



Sample availability



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