

The 21st IRCMS Symposium on

# The Dynamics and Development of Normal and Malignant Hematopoietic Stem Cells

Date & Time : 13:00-17:40 (JST), 20<sup>th</sup> February 2024

9:00-12:20 (JST), 21<sup>st</sup> February 2024

Venue : Onsite and Online (IRCMS Lounge, Kumamoto University and Zoom)

**Organized by Goro Sashida**

Supported by Ryunosuke Naito, Yuki Yoshioka, Mai Matsushita, Doi Nazuki and Nanako Watanabe

## **SPEAKERS:**

Yuichiro Arima (Kumamoto University)  
Nariko Arimura (Tohoku University)  
Takayuki Hoshii (Chiba University)  
Atsushi Iwama (University of Tokyo)  
Makoto Makishima (Nihon University)  
Kenichi Miharada (Kumamoto University)  
Satoru Miyagi (Shimane University)  
Goro Sashida (Kumamoto University)  
Yorifumi Sato (Kumamoto University)  
Toshio Suda (Kumamoto University)  
Hitoshi Takizawa (Kumamoto University)  
Takanori Teshima (Hokkaido University)  
Hannah Uckelmann (Goethe University Frankfurt)  
Satoshi Yamazaki (University of Tsukuba)  
Junichiro Yasunaga (Kumamoto University)



**Opening Remarks**      **Goro Sashida (IRCMS, Kumamoto University)**      13:00-13:05

**Session I (13:05-14:30, 20<sup>th</sup> February)**

**Takayuki Hoshii**      The SETD1B catalytic domain regulates H3K4me3 breadth and MYC expression in MLL-rearranged leukemia      13:05-13:30  
Chiba University

**Keynote**

**Hannah Uckelmann**      Targeting epigenetic vulnerabilities in acute myeloid leukemia      13:30-14:30  
Goethe University Frankfurt

Break (14:30-14:55)

**Session II (14:55-16:05 20<sup>th</sup> February)**

**Toshio Suda**      Self-Renew Activity of Aging Hematopoietic Stem Cells      14:55-15:15  
Kumamoto University

**Satoshi Yamazaki**      Establishment of absolute quantitative competitive hematopoietic stem cell function evaluation using X chromosome activation system      15:15-15:40  
University of Tsukuba

**Atsushi Iwama**      Targeting Hippo pathway in bone marrow niche promotes hematopoietic regeneration      15:40-16:05  
University of Tokyo

Break (16:05-16:30)

**Session III (17:00-17:45, 20<sup>th</sup> February)**

**Satoru Miyagi**      Role of CUL4-RING E3 ubiquitin ligase complex in HSC fitness and hematopoiesis      16:30-16:55  
Shimane University

**Goro Sashida**      Trisomy 21 represses expression of PRC2 targets and impairs differentiation program in HSC      16:55-17:15  
Kumamoto University

**Nariko Arimura**      From Marrow to Memory: Tracing Dementia Onset using Down Syndrome Model Mice      17:15-17:40  
Tohoku University

**Session IV (9:00-10:30, 21<sup>st</sup> February)**

**Makoto Makishima**      Regulation of hepatic immune cells by the oxysterol receptors, LXRs      9:00-9:25  
Nihon University

**Kenichi Miharada**      Disruption of maternal bile acid metabolism causes non-fetal-autonomous developmental defect      9:25-9:45  
Kumamoto University

**Yuichiro Arima**      Protective Effects and Therapeutic Applications of Ketone Body Metabolism in Liver      9:45-10:05  
Kumamoto University

Break (10:05-10:25)

**Session V (10:25- 11:05, 21<sup>st</sup> February)**

**Yorifumi Sato**      A human retrovirus inserts ectopic CTCF-binding site and enhancer into the host human genome, thereby inducing aberrant host gene transcription both in cis and in trans      10:25-10:45  
Kumamoto University

**Junichiro Yasunaga**      Coding and non-coding functions of HTLV-1 bZIP factor gene in the oncogenesis of adult T-cell leukemia-lymphoma      10:45-11:05  
Kumamoto University

Break (11:05-11:25)

**Session VI (11:25-12:15, 21<sup>st</sup> February)**

**Hitoshi Takizawa**      Microbial signal-regulated hematopoietic stem cell function      11:05-11:45  
Kumamoto University

**Takanori Teshima**      Alloreactive T-cell targets tissue stem cells and impairs tissue homeostasis in GVHD after allogeneic stem cell transplantation      11:45-12:15  
Hokkaido University

**Closing Remarks**      **Hitoshi Takizawa (IRCMS, Kumamoto University)**      12:15-12:20

# The SETD1B catalytic domain regulates H3K4me3 breadth and MYC expression in MLL-rearranged leukemia

Takayuki Hoshii  
(Chiba University)

## Abstract :

Histone H3 lysine 4 trimethylation (H3K4me3) is abundant in mixed-lineage leukemia-rearranged (MLL-r) acute myeloid leukemia (AML) cells; however, the enzymes responsible for this process and their roles remain unclear. Therefore, this study aimed to identify the H3K4HMT modifier responsible for high H3K4me3 modification in MLL-r leukemia and its downstream targets essential for the cell proliferation. In the present study, we performed a CRISPR-tiling screen against known H3K4 methylation modifiers in an MLL-r AML model. We elucidated the non-redundant roles of H3K4 methyltransferase SETD1B in regulating FLT3-ITD or NrasG12D-expressing AML cell growth that exhibits cytokine-independent growth. Disrupting the SETD1B catalytic SET domain caused cell cycle arrest, apoptosis, cell differentiation, and gene expression downregulation, particularly in the MYC pathway. H3K4me3 and SETD1B are distributed in the gene body of MYC, and SETD1B SET domain loss results in a significant decrease in H3K4me3 breadth. Exogenous MYC expression significantly restored growth defects and transcriptional perturbations in SETD1B SET domain-mutant cells. Disrupting H3K4 demethylase KDM5C enhanced global H3K4me3 levels, promoted AML cell proliferation, and partially rescued the defective cell growth of SETD1B SET domain-mutant cells. These data indicated that SETD1B was required for H3K4me3 breadth and MYC expression to support advanced AML cell proliferation. Thus, a thorough understanding of SETD1B-mediated H3K4me3 breadth is critical for developing markers and therapies for MYC-dependent leukemia subtypes.

## 2-3 major papers:

1. Perlee S, Kikuchi S, Nakadai T, Masuda T, Ohtsuki S, Matsumoto M, Rahmutulla B, Fukuyo M, Cifani P, Kentsis A, Roeder RG, Kaneda A, \*Hoshii T. SETD1A function in leukemia is mediated through interaction with mitotic regulators BuGZ/BUB3. *EMBO Reports* 24(10):e57108. (2023)
1. \*Hoshii T, Perlee S, Kikuchi S, Rahmutulla B, Fukuyo M, Masuda T, Ohtsuki S, Soga T, Nabet B, Kaneda A. SETD1A regulates transcriptional pause release of heme biosynthesis genes in leukemia. *Cell Reports* 41(9):111727 (2022)
1. Hoshii T, Cifani P, Feng Z, Huang CH, Koche R, Chen CW, Delaney CD, Lowe SW, Kentsis A, \*Armstrong SA. A Non-catalytic function of SETD1A regulates Cyclin K and the DNA damage response. *Cell* 172(5):1007-1021 (2018)

## Bio:

Takayuki Hoshii obtained his Ph.D degree from Kumamoto University in 2007. As a postdoctoral researcher, he studied on the roles of PI3K/AKT/mTOR signaling pathway in leukemogenesis. He then joined the laboratory of Dr. Scott Armstrong at MSKCC and Dana-Farber Cancer Institute and found the non-canonical role of SETD1A histone methyltransferase in leukemia. He came back Japan in 2019 and joined the Department of Molecular Oncology in Chiba University. His study goal is to understand the biological roles of histone modification enzymes in leukemia and other pediatric diseases associated with activation or mutation of these enzymes, and to identify therapeutic potential functional domains.

# Targeting epigenetic vulnerabilities in acute myeloid leukemia.

**Hannah Uckelmann**  
**(Goethe University Frankfurt)**

## **Abstract:**

Cytoplasmic NPM1 mutations (NPM1c) in AML were first described almost two decades ago and represent one of the most frequently mutated genes in these leukemias. Much effort has been focused on the cytoplasmic functions of mutant NPM1, however, its mechanistic role in leukemia development remains elusive. Especially, how NPM1c expression in hematopoietic cells leads to its characteristic gene expression pattern including many MLL target genes such as HOXA9 and MEIS1. We have recently shown that NPM1c AMLs are highly sensitive to the disruption of the MLL1 histone methyltransferase complex. Small molecule inhibitors that block the interaction between MLL1 and its adaptor protein Menin have been shown to impair binding of MLL1 to a subset of its target genes and to inhibit leukemia cell proliferation and self renewal. The effectiveness of these molecules in NPM1c AML prompts the question whether NPM1c and the wildtype MLL complex cooperate on chromatin. We now show that a small fraction of mutant NPM1c is localized to the nucleus of leukemia cells where it regulates oncogenic transcription directly on chromatin. We are now investigating the epigenetic complexes that are cooperating with NPM1c to drive leukemogenesis in order to identify novel therapeutic targets.

## **2-3 major papers:**

### **Therapeutic targeting of preleukemia cells in a mouse model of NPM1 mutant acute myeloid leukemia.**

Uckelmann HJ, Kim SM, Wong EM, Hatton C, Giovinazzo H, Gadrey JY, Krivtsov AV, Rücker FG, Döhner K, McGeehan GM, Levine RL, Bullinger L, Vassiliou GS, Armstrong SA.

***Science, 2020.***

### **Mutant NPM1 directly regulates oncogenic transcription in acute myeloid leukemia.**

Uckelmann HJ#, Haarer EL, Takeda R, Wong EM, Perner F, Marinaccio C, Hatton C, Yang L, Brunetti L, Chen CW, Armstrong SA#. #Co-corresponding authors.

***Cancer Discovery, 2023.***

## **Bio:**

Dr. Hannah Uckelmann's research group focuses on studying the epigenetic regulation of self-renewal programs during cancer development and the discovery of new therapeutics. Dr. Uckelmann received her master's degree in Molecular Biosciences from the university of Heidelberg and her PhD with Prof. Andreas Trumpp at the German Cancer Research Center (DKFZ) in Heidelberg. For her postdoctoral training, Dr. Uckelmann joined the group of Prof. Scott Armstrong at the Dana-Farber Cancer Institute in Boston. She was able to show that disrupting the MLL-complex on chromatin using Menin-MLL inhibitors can prevent the development of leukemia in NPM1c-mutant mouse models and treat fully developed human leukemias derived from patient samples. This preclinical work led to the inclusion of NPM1 mutant patients in the ongoing clinical phase II trials for Menin-MLL inhibitors.



# Self-Renew Activity of Aging Hematopoietic Stem Cells

Toshio Suda  
(Kumamoto University)

## Abstract:

It has been previously reported several findings regarding aged hematopoietic HSCs, showing:

- i) a decline in self-renewal capacity (an increase in cells with stem cell markers),
- ii) an increase in oxidative phosphorylation in stem cell mitochondria,
- iii) a reduction in quiescent stem cells.

We have conducted RNAseq and ATACseq analyses of aged hematopoietic stem cells (HSCs). In aging stem cells, gene expression suggests differentiation towards progenitors. and we can also capture aging-related gene changes specific to HSCs. Under the hypothesis that "Aging leads to an enrichment of stem cells with self-renewal advantage genes," we try to identify candidate genes:

It is important to use the common phenotype of HSCs between young and aged HSCs, since some HSC phenotypes are changing by aging. To aim to define HSCs having self-renewal capacity during life span, we have recently provided novel insights into transplantable HSCs during regeneration of hematopoiesis. HSCs highly expressing EPCR (EPCR-high) cells are enriched within the stem cell fraction at the expense of more proliferative EPCR-low HSCs. We have concluded EPCR-high HSCs are initially more primitive than EPCR-low HSCs and enabled stem cell expansion.

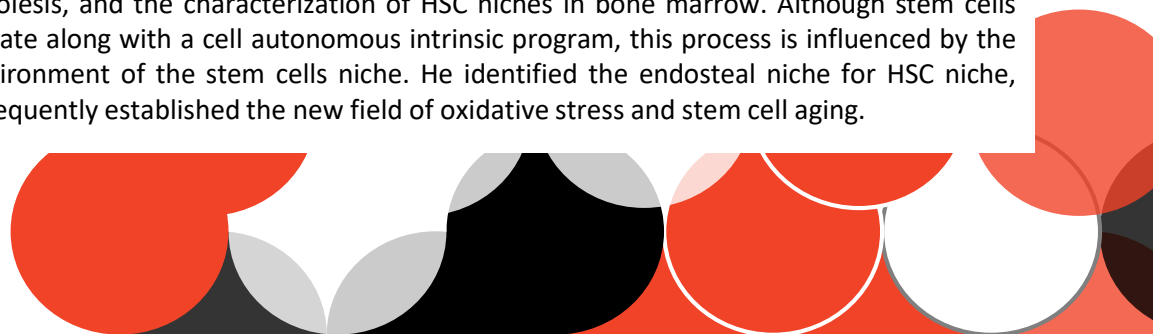
Moreover, we have recently discovered that aging stem cells with a higher quantity of mitochondria (MitoH) persist in the bone marrow. We will clarify how MitoH HSCs can preferentially survive and show the fitness with aged bone marrow.

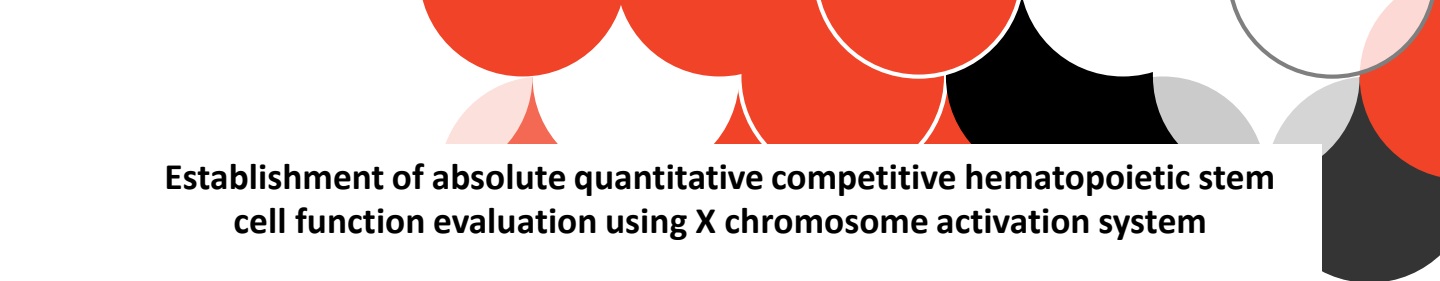
## 2-3 major papers:

1. Umemoto T, Johansson A, Ahmad SAI, Hashimoto M, Kubota S, Odaka H, Kataoka M, Era T, Sashida G, Suda T: The suppression of reductive glutamine metabolism is required to preserve stem cell features in primed hematopoietic stem cells. *EMBO J*. 2022 Apr 19;41(8):e109463. doi: 10.15252/embj.2021109463.
2. Yokomizo T, Ideue, T, Sato T, Takeda N, Kurokawa M, Komatsu N, Araki, K, Osato M, Suda T: Independent origins of fetal liver hematopoietic stem and progenitor cells. *Nature*, Sep;609(7928):779-784. doi: 10.1038/s41586-022-05203-0.
3. Yang C, Yokomori R, Chua LH, Tan SH, Sanda T, Suda T; Mitochondria transfer mediates stress erythropoiesis by altering the bioenergetic profiles of early erythroblasts through CD47. *J Exp Med*, 2022 Dec5;219(12): e20220685. doi: 10.1084/jem.20220685

## Bio:

Toshio Suda has studied hematopoietic stem cells (HSCs) and HSC niches for over forty years. His past work encompasses the purification of HSCs, identification of cytokine signaling in hematopoiesis, and the characterization of HSC niches in bone marrow. Although stem cells differentiate along with a cell autonomous intrinsic program, this process is influenced by the microenvironment of the stem cells niche. He identified the endosteal niche for HSC niche, and subsequently established the new field of oxidative stress and stem cell aging.





# Establishment of absolute quantitative competitive hematopoietic stem cell function evaluation using X chromosome activation system

**Satoshi Yamazaki**  
**(University of Tokyo)**

## **Abstract:**


Hematopoietic stem cells (HSCs) are one of the most well-studied adult stem cell populations and have provided many important concepts in the field of stem cell biology. HSCs are a rare cell population found within the bone marrow (BM) with remarkable functional capabilities of multilineage differentiation and lifelong self-renewal. To date, competitive bone marrow repopulation assays have been used as the gold standard to analyze the molecular mechanisms underlying the functional capacity of HSCs. Generally, competitive bone marrow reconstitution assays involve irradiating the recipient mouse with a lethal dose of radiation, which induces strong inflammation in the body. Analysis of wild-type HSCs in a steady state and essentially competitive hematopoietic stem cells with forced expression or deletion of specific genes due to in vivo inflammatory exposure has not yet been established. In contrast to HSCs, many other adult stem cell populations have successfully verified their steady state stemness through in vivo genetic lineage tracing approaches rather than transplantation assays. Intestinal stem cell analysis using genetic lineage tracing of Lgr5 expression with the Cre/LoxP recombination system has been reported in the most successful cases. In the blood field, experimental systems have been established for the purpose of marking and tracing HSC-specific genes. However, there was no experimental system that competitively compared the wild-type group and the control group without using an experimental system called transplantation. In this Symposium, I will introduce a competitive phenotypic analysis method for HSCs based on the X-chromosome inactivation system that I devised and discuss the absolute quantitative competitive cell comparison method and the interesting aspects of biology that I have learned through this research.

## **2-3 major papers:**

1. Tajima et al., 2017 Scientific Reports

## **Bio :**

Yamazaki is a researcher who aims to make ex vivo expansion of hematopoietic stem cells possible and further uncover the mysteries of stem cells.





# Targeting Hippo pathway in bone marrow niche promotes hematopoietic regeneration

Atsushi Iwama  
(University of Tokyo)

## Abstract:

The distinctive milieu of bone marrow (BM), called a "niche", supports hematopoietic stem cells (HSCs) and serves as the foundation of hematopoietic regeneration. Myeloablative stress disrupts not only hematopoietic cells but also niche components, including endothelial cells (EC) and mesenchymal stromal cells (MSC), which hinders efficient hematopoietic recovery. YAP/TAZ are the two transcriptional coactivators repressed by LATS1/2 kinases downstream of the Hippo pathway essential for regeneration of various organs. However, their role in hematopoietic regeneration remained uncharacterized. Here we show that LATS inhibition promotes remodeling of damaged BM niche, thereby promoting hematopoietic regeneration in mice. We revealed that YAP/TAZ are selectively expressed in ECs and MSCs in BM and are activated by myeloablative genotoxic stresses. Administration of newly developed LATS inhibitors, which efficiently activated YAP/TAZ in niche cells, profoundly accelerated hematopoietic recovery by host cells after myeloablative stresses as well as by donor HSCs in a transplantation model, which was significantly canceled by deletion of *Yap* and *Taz* in BM niche cells. Combination of granulocyte colony-stimulating factor (G-CSF) and LATS inhibitors established significantly earlier recovery of neutrophils than G-CSF alone. These results provide the first evidence of successful manipulation of BM niche cells to boost hematopoietic recovery after myeloablation.

## 2-3 major papers:

1. Itokawa N, Oshima M, Koide S, Takayama N, Kuribayashi W, Nakajima-Takagi Y, Aoyama K, Yamazaki S, Yamaguchi K, Furukawa Y, Eto K, Iwama A. Epigenetic memories inscribed in chromatin accessibility in aged hematopoietic stem cells. **Nat Commun** 13(1): 2691, 2022.
2. Kuribayashi W, Oshima M, Itokawa N, Koide S, Nakajima-Takagi Y, Yamashita M, Yamazaki S, Rahmutulla B, Miura F, Ito T, Kaneda A, and Iwama A. Limited rejuvenation of aged hematopoietic stem cells in young bone marrow niche. **J Exp Med** 218(3):e20192283, 2021.
3. Miyagi S, Sroczynska P, Kato Y, Nakajima-Takagi Y, Oshima M, Rizq O, Takayama N, Saraya A, Mizuno S, Sugiyama F, Takahashi S, Matsuzaki Y, Christensen J, Helin K, and Iwama A. The chromatin binding protein Phf6 restricts the self-renewal of hematopoietic stem cells. **Blood** 133(23):2495-2506, 2019.

## Bio:

Atsushi Iwama is a professor of the Institute of Medical Science, the University of Tokyo. He obtained his M.D. in Niigata University and Ph.D. in Kumamoto University in 1987 and 1996, respectively. He completed an internship and residency at Niigata University Hospital and Jichi Medical School Hospital, respectively. Originally starting his training in clinical hematology, he has specialized in research on hematopoietic stem cells (HSCs) and hematological malignancies. He became independent as a full professor at the Graduate School of Medicine, Chiba University in 2005 and carried out research on the epigenetic regulation of HSCs and the epigenetic dysregulation in hematological malignancies. From March 2018, he has been appointed as a professor at the current institute and is expanding his research field to HSC aging.



# Role of CUL4-RING E3 ubiquitin ligase complex in HSC fitness and hematopoiesis

Satoru Miyagi  
(Shimane University)

## Abstract :

Inactivation of chromatin modifier genes, e.g., *Tet2*, *Dnmt3a*, or *Asx1*, augments the reconstitution activity of hematopoietic stem cells (HSCs) in the transplantation setting. The inactivation of *Tet2* (or *Dnmt3a*) shows divergent effects on HSCs. For instance, the loss of *Tet2* improves the fitness of HSCs in an inflammatory microenvironment in addition to HSC proliferation; therefore, *Tet2* loss confers a competitive advantage on HSCs.

PHF6, which frequently acquires inactivating somatic mutations in various hematological malignancies, is a critical negative regulator of HSCs in stress hematopoiesis. Molecularly, PHF6 regulates gene expression by modifying higher-order chromatin structure. Our previous study demonstrated that PHF6 binds to the downstream effector gene locus of TNF $\alpha$  signaling, including tumor suppressor genes *Nr4a1* and *Junb*, and activates their transcription in a TNF $\alpha$ -dependent manner. Thus, *Phf6*-deficient HSCs show a competitive advantage.

Recently, we found that the PHIP/DCAF14, the substrate receptor subunit of the CUL4-RING E3 ubiquitin ligase complex (CRLc), is a putative binding partner of PHF6 and PHIP overexpression enhances the mono-ubiquitination of PHF6.

The CRLc-mediated mono-ubiquitination takes part in the recruitment of Tet2 on chromatin, and TNF $\alpha$  signaling increases the expression and enzymatic activity of CRLc. In my presentation, I will discuss the role of CRLc in HSC fitness and hematopoiesis.

## 2-3 major papers:

1. Miyagi S, Sroczyńska P, Kato Y, Nakajima-Takagi Y, Oshima M, Rizq O, Takayama N, Saraya A, Mizuno S, Sugiyama F, Takahashi S, Matsuzaki Y, Christensen J, Helin K, Iwama A. The chromatin-binding protein Phf6 restricts the self-renewal of hematopoietic stem cells. **Blood**. 133, 2495-2506, 2019.
2. Miyagi S, Iwama A. Plant homeodomain finger protein 6 in the regulation of normal and malignant hematopoiesis. **Curr Opin Hematol**. 27, 248-253. 2020.
3. Miyagi S\*, Kato Y, Watanabe A, Miyamoto K, Yoshikawa R, Hagiya K, Hirano D, Matsuzaki Y\*. Generation of a BAC transgenic mouse strain that expresses CreERT and a fluorescent protein under the transcriptional control of the *Fzd5* locus. **Inflamm. Regen**. 42, 2022.

## Bio:

I received my Ph.D. from the United Graduate School of Agricultural Sciences, Iwate University (UGAS), Japan, and have expertise in Stem Cell Biology, Molecular Biology, and Biochemistry. After post-doctoral training, I joined Dr. Iwama's lab and have dedicated my academic career to the basic research of hematopoietic stem cells. My research aims to develop new therapeutic strategies to prevent and cure hematological malignancies. My current research focuses on the somatic mutation of the genes that encode chromatin modifiers to elucidate the mechanisms underlying the onset of hematological malignancies. I am setting up my lab at the Faculty of Medicine at Shimane University.

# Trisomy21 represses expression of PRC2 targets and impairs differentiation program in HSC

Goro Sashida  
(Kumamoto University)

## Abstract:

Down syndrome (DS) human show chronic diseases including premature aging phenotypes in blood and brain tissues. Aged hematopoietic stem cells (HSCs) decrease the regenerative capacity and promote myeloid differentiation. Although DS HSC is known to drive aging phenotypes, the molecular mechanisms underlying premature aging is unclear. By using a mouse model TcMAC21, we herein demonstrated that DS mice showed reduced regenerative capacity and myeloid skewing in bone marrow (BM). To determine the intrinsic and extrinsic effects, BM cells from DS/WT mice were transplanted into wild-type recipients, and BM cells from WT mice were transplanted into DS/WT recipients. We found the impaired function of HSC in the DS-BM transplanted WT mice, whereas the WT-BM transplanted DS mice showed mild myeloid skewing but did not impair the HSC function. Transcriptome analysis revealed that the DS-HSC decreased expression levels of stem cell signature genes and polycomb repressive complex 2 (PRC2)-target genes. In addition, level of cytosine DNA methylation was increased in DS mice, accompanied with reduced expression of the Tet2 gene. Since canonical PRC2 targets are shown to gain DNA methylation at their CpG sites in aged cells, our results suggested that DS HSCs accelerated epigenetic aging in the cell-intrinsic manner. Further studies are needed to clarify the mechanisms by which epigenetic alterations affects the age-related diseases in DS HSC.

## 2-3 major papers:

1. Yokomizo-Nakano T, Hamashima A, Kubota S, Bai J, Sorin S, Sun Y, Kikuchi K, Iimori M, Morii M, Kanai A, Iwama A, Huang G, Kurotaki D, Takizawa H, Matsui H, Sashida G\*. Exposure to microbial products followed by loss of Tet2 promotes myelodysplastic syndrome via remodeling HSCs. **J Exp Med** 2023; 220(7): e20220962.
2. Abdallah MG, Niibori-Nambu A, Morii M, Yokomizo T, Yokomizo T, Ideue T, Kubota S, Teoh VSI, Mok MMH, Wang CQ, Omar AA, Tokunaga K, Iwanaga E, Matsuoka M, Asou N, Nakagata N, Araki K, AboElenin M, Madboly SH, Sashida G\*, Osato M\*. RUNX1-ETO (RUNX1-RUNX1T1) induces myeloid leukemia in mice in an age-dependent manner. **Leukemia** 2021. 35(10): 2983-2988.
3. Kubota S, Tokunaga K, Umezue T, Yokomizo-Nakano T, Sun Y, Oshima M, Tan KT, Yang H, Kanai A, Iwanaga E, Asou N, Maeda T, Nakagata N, Iwama A, Ohyashiki K, Osato M\*, Sashida G\*. Lineage-specific RUNX2 super-enhancer activates MYC and promotes the development of blastic plasmacytoid dendritic cell neoplasm. **Nature Commun** 2019; 10(1): 1653.

## Bio:

Goro Sashida received his MD from Tokyo Medical University in 1996. In 2005, he joined Dr. Stephan Nimer's laboratory at Memorial Sloan-Kettering Cancer Center (New York, USA; Dr. Nimer moved to Miami). In 2009, he moved to Dr. Gang Huang's laboratory at Cincinnati Children's Hospital Medical Center (Ohio, USA; Dr. Huang moved to San Antonio). In 2010, he went back to Japan and joined Dr. Atsushi Iwama's laboratory at Chiba University (Chiba, Japan; Dr. Iwama moved to Tokyo). In December 2014, he established his own research group "Laboratory of Transcriptional Regulation of Leukemogenesis" at IRCMS, Kumamoto University, and in 2016 he was promoted to Professor.

# From Marrow to Memory: Tracing Dementia Onset using Down Syndrome Model Mice

Nariko Arimura  
(Tohoku University)

## Abstract:

Dementia refers to the gradual loss of cognitive function due to various factors affecting the brain. Alzheimer's disease is estimated to cause two-thirds of all cases of dementia, but the initial triggers for the onset of the disease are still unknown. Down syndrome is attracting attention as a model for dementia because almost all patients with Down syndrome develop early-onset Alzheimer's disease. People with Down syndrome frequently exhibit immune system dysfunctions, which are increasingly recognized as being linked to neurodegenerative diseases. In light of this, we have initiated a focused investigation into the interplay between dementia and immune cell activity. Behavioral analysis was conducted in wild-type mice transplanted with bone marrow from Down syndrome model mice, and the transplanted mice showed reduced cognition and memory. We have found an increase or decrease in a specific population of neurons based on genetic and immunohistochemical analysis of the hippocampus, the center of memory. These results indicate that bone marrow-derived cells and blood components influence brain function. We are currently investigating how bone marrow-derived components of Down syndrome affect the brain through the blood-brain barrier. In this symposium, we will describe the results of our experiments and discuss new light on the therapeutic use of blood components in treating dementia.

## 2-3 major papers:

1. A Comparative Overview of DSCAM and its Multifunctional Roles in Drosophila and Vertebrates Kento Hizawa, Takuya Sasaki, [Nariko Arimura](#)\* *Neuroscience Research*, in press.
2. Neuronal DSCAM regulates the peri-synaptic localization of GLAST in Bergmann glia for functional synapse formation. Ken-ichi Dewa, [Nariko Arimura](#)\*, Wataru Kakegawa, Masayuki Itoh, Toma Adachi, Satoshi Miyashita, Yukiko U. Inoue, Kento Hizawa, Kei Hori, Natsumi Honjaya, Haruya Yagishita, Shinichiro Taya, Taisuke Miyazaki, Chika Usui, Shoji Tatsumoto, Akiko Tsuzuki, Hiroto Uetake, Kazuhisa Sakai, Kazuhiro Yamakawa, Takuya Sasaki, Jun Nagai, Yoshiya Kawaguchi, Masaki Sone, Takayoshi Inoue, Yasuhiro Go, Noritaka Ichinohe, Kozo Kaibuchi, Masahiko Watanabe, Schuichi Koizumi, Michisuke Yuzaki, Mikio Hoshino\* *Nature Communication*, in press.
3. DSCAM regulates delamination of neurons in the developing midbrain. [Nariko Arimura](#)\*, Mako Okada, Shinichiro Taya, Ken-ichi Dewa, Akiko Tsuzuki, Hiroto Uetake, Satoshi Miyashita, Koichi Hashizume, Kazumi Shimaoka, Saki Egusa, Tomoki Nishioka, Yuchio Yanagawa, Kazuhiro Yamakawa, Yukiko U. Inoue, Takayoshi Inoue, Kozo Kaibuchi, Mikio Hoshino\* *Science Advances*, 6(36) eaba1693-eaba1693, 2020.

## Bio:

I am an Associate Professor specializing in neuroscience at the Graduate School of Pharmaceutical Sciences, Tohoku University. My interest particularly lies in the control systems of cognition and memory and the dynamics of neural circuits. My research has utilized molecular biology, genetics, and cerebral physiology techniques to gain a multidimensional understanding of brain function, aiming to contribute to the elucidation of pathological states. At this symposium, I will discuss the functional control of the brain exerted by Down syndrome marrow and plan to present on the exploration of the molecular mechanisms involved in the onset of dementia.



## Regulation of hepatic immune cells by the oxysterol receptors, LXRs

**Makoto Makishima**  
(Nihon University)

### Abstract:

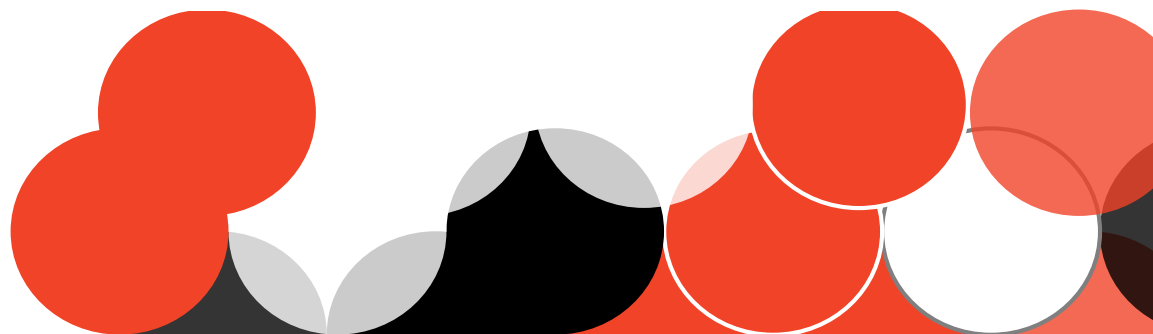
Transcription factors of the nuclear receptor superfamily regulate numerous biological processes including cell growth and differentiation, embryonic development, endocrine regulation, and metabolic homeostasis. The nuclear receptors liver X receptor  $\alpha$  (LXR $\alpha$ ) and LXR $\beta$  are activated by oxysterols and regulate expression of genes involved in lipid metabolism. LXR $\alpha$  is abundantly expressed in liver, intestine, adipose tissues, kidney and macrophages, while LXR $\beta$  is ubiquitously present in the body. LXRs also regulate immune responses in immune cells, such as macrophages, and induction of genes involved in reverse cholesterol transport. In the liver, LXRs are expressed in both hepatocytes and nonparenchymal cells, including leukocytes, hepatic stellate cells, and liver sinusoidal endothelial cells. Since the liver plays important roles in both lipid metabolism and innate immunity as a gateway for dietary compounds, LXRs are suggested to have a gatekeeper function in the liver. We investigated the role of LXRs in hepatic immune cells using LXR $\alpha/\beta$  knockout (KO) mice. LXR $\alpha/\beta$ -KO mice show increased numbers of F4/80<sup>lo</sup>CD11b<sup>+</sup> macrophages in the liver and enhanced inflammatory responses. Hepatic invariant natural killer T cells are nearly absent in the liver of LXR $\alpha/\beta$ -KO mice. Thus, LXRs play an important role in regulation of hepatic macrophages/Kupffer cells and natural killer T cells.

### 2-3 major papers:

1. Endo-Umeda, et al. Liver X receptors regulate natural killer T cell population and antitumor activity in the liver of mice. **Sci Rep** 11: 22595, 2021
2. Endo-Umeda, et al. Liver X receptors regulate hepatic F4/80+CD11b+ Kupffer cells/macrophages and innate immune responses in mice. **Sci Rep** 8: 9281, 2018
3. Endo-Umeda, et al. Dysregulation of Kupffer cells/macrophages and natural killer T cells in steatohepatitis in LXR $\alpha$  knockout male mice. **Endocrinology** 159: 1419, 2018

### Bio:

Dr. Makoto Makishima graduated from National Defense Medical College in 1987. While working as a physician at Ground Self Defense Force and Saitama Comprehensive Mental Health Center, he did research studies at Saitama Cancer Center and received PhD in Medical Science from Jichi Medical University. He joined David Mangelsdorf laboratory at University of Texas Southwestern Medical Center as Associate of Howard Hughes Medical Institute from 1998 to 2002, and reported two papers about bile acid receptors in Science. He worked at Osaka University as Associate Professor from 2002 to 2004. Since 2004, he has been at Nihon University School of Medicine, where he currently is Professor of the Division of Biochemistry, Director of Library and Director of Research Institute of Medical Science. His research team is mainly focused on nuclear receptor regulation of metabolism and immunity.



# Disruption of maternal bile acid metabolism causes non-fetal-autonomous developmental defect

**Kenichi Miharada  
(Kumamoto University)**

## Abstract:

The importance of the maternal environment for fetuses has undoubtedly been described. However, how molecularly maternal metabolism contributes to fetal organ maturation remains unclear. Bile acids are major cholesterol derivatives whose synthesis is enhanced in mothers; however, their role in fetal development has been undiscovered. Here, we demonstrate that the alternative pathway of bile acid synthesis in maternal bodies secures progression of normal fetal organ formation by assuring a translation machinery. Depletion of maternal Cyp27a1 leads to a variety of abnormal pregnancy outcomes. These are caused by accumulating intermediate product, 7 $\alpha$ -hydroxycholesterol (7 $\alpha$ -HC), that destabilized the Fau protein mediating ribosome assembly. Aberrant ribosome biogenesis results in inefficient translation of proteins essential for cellular and organ maturation. Thus, our study indicates that an essential mechanism of securing fetal development by degrading a toxic metabolite in the maternal body.

## 2-3 major papers:

1. Suzuki M, Nakano S, Miharada N, Takei H, Prabhala P, van der Garde M, Müller C, Sigurdsson V, Aerken M, Saito K, Koide S, Westergren-Thorsson G, Magnusson M, Kakiyama G, Nittono H, Miharada M\*. Maternal sterol 27-hydroxylase is crucial for securing fetal development. bioRxiv 2023.11.08.566330.
1. Sigurdsson V, Haga Y, Takei H, Mansell E, Okamatsu-Haga C, Suzuki M, Radulovic V, van der Garde M, Koide S, Soboleva S, Gåfvels M, Nittono H, Ohara A, Miharada K\*. Induction of blood-circulating bile acids supports recovery from myelosuppressive chemotherapy. Blood Adv. 2020 May 12;4(9):1833-1843.
1. Sigurdsson V, Takei H, Soboleva S, Radulovic V, Galeev R, Siva K, Leeb-Lundberg LMF, Iida T, Nittono H, Miharada K\*. Bile acids protect expanding hematopoietic stem cells from unfolded protein stress in fetal liver. Cell Stem Cell 2016 Apr 7;18(4):522-32

## Bio:

Kenichi Miharada, Ph.D, obtained his Ph.D degree from Tsukuba University, Japan, in 2007 for his studies on erythropoiesis. He continued his research at RIKEN as a Special Postdoctoral Researcher and then moved to Lund University, Sweden, in 2009. At Lund Stem Cell Center, he led projects discovering novel HSC regulators. In 2013, he started his research group as a principal investigator (PI) at Lund Stem Cell Center to study the regulation of UPR in HSC. Since 2021, he has become a member of IRCMS as a professor and started a new lab. Dr. Miharada aims to build novel concepts by exploring unexpected connections between various findings.

# Protective Effects and Therapeutic Applications of Ketone Body Metabolism in Liver

Yuichiro Arima  
(Kumamoto University)

## Abstract:

Ketone bodies, consisting of beta-hydroxybutyrate, acetoacetate, and acetone, are metabolic byproducts known as energy substrates during fasting. Recent advancements have shed light on the multifaceted effects of ketone body metabolism, leading to increased interest in therapeutic interventions aimed at elevating ketone body levels. However, excessive elevation of ketone body concentration can lead to ketoacidosis, which may have fatal consequences. Therefore, our main purpose is to decipher the precise role of ketone body metabolism, particularly emphasizing its association with mitochondria and epigenetic modification. Metabolic dysfunction associated fatty liver disease (MAFLD) has been on the increase worldwide due to the increase in the number of patients with obesity and metabolic syndrome. Lifestyle factors such as diabetes and obesity are major causes of the disease, and MAFLD has the risk of progressing to nonalcoholic steatohepatitis (NASH), as well as cirrhosis and hepatocarcinoma. Previously, we have generated the murine model of insufficient ketogenesis by disrupting the rate-limiting enzyme for ketogenesis, HMG-CoA synthase 2 (Hmgcs2) and reported that ketogenesis regulated lipid homeostasis in hepatocytes in neonate. In this presentation, we provide the impact of ketone body metabolism in adult MAFLD models.

## 2-3 major papers:

1. Wenjuan Ma, Yuichiro Arima, Terumasa Umemoto, Tomomasa Yokomizo, Yuqing Xu, Kenichi Miharada, Yosuke Tanaka, Toshio Suda. Metabolic regulation in erythroid differentiation by systemic ketogenesis in fasted mice. **Experimental hematology** 2023 *in press*
2. Yuichiro Arima. The Impact of Ketone Body Metabolism on Mitochondrial Function and Cardiovascular Diseases. **Journal of atherosclerosis and thrombosis** 30(12) 1751-1758 2023 (review)
3. Yuichiro Arima, Yoshiko Nakagawa, Toru Takeo, Toshifumi Ishida, Toshihiro Yamada, Shinjiro Hino, Mitsuyoshi Nakao, Sanshiro Hanada, Terumasa Umemoto, Toshio Suda, Tetsushi Sakuma, Takashi Yamamoto, Takehisa Watanabe, Katsuya Nagaoka, Yasuhito Tanaka, Yumiko K Kawamura, Kazuo Tonami, Hiroki Kurihara, Yoshifumi Sato, Kazuya Yamagata, Taishi Nakamura, Satoshi Araki, Eiichiro Yamamoto, Yasuhiro Izumiya, Kenji Sakamoto, Koichi Kaikita, Kenichi Matsushita, Koichi Nishiyama, Naomi Nakagata, Kenichi Tsujita. Murine neonatal ketogenesis preserves mitochondrial energetics by preventing protein hyperacetylation. **Nature metabolism** 3(2) 196-210 2021

## Bio:

Yuichiro Arima is an associate professor in the developmental cardiology laboratory of the International Research Center for Medical Sciences (IRCMS) at Kumamoto University. He is a physician-scientist and has a keen interest in the relationship between cardiovascular development and pathology, and ketone body metabolism. He is trying to clarify the relationship between cardiovascular development and adult-onset disease through basic research. In addition, in the process of analyzing the neonatal period, he elucidated the significance of ketone body metabolism, by analyzing the knockout (KO) mice for HMG-CoA synthase2 (Hmgcs2), the rate-limiting enzyme in ketone body synthesis. Hmgcs2 KO mice can survive but represent severe hepatostetosis with mitochondrial dysfunction. He has deciphered the underlying mechanism and revealed that ketogenesis itself has a protective function for mitochondria. Multifaceted functions of ketone body metabolism is an important theme for his research.



# A human retrovirus inserts ectopic CTCF-binding site and enhancer into the host human genome, thereby inducing aberrant host gene transcription both *in cis* and *in trans*

Yoshifumi Sato  
(Kumamoto University)

## Abstract:

Human T-cell leukemia virus type 1 (HTLV-1) is a retrovirus that causes adult T-cell leukemia/lymphoma (ATL), a cancer of infected CD4+ T cells. There is both sense and antisense transcription from the integrated provirus. Sense transcription tends to be suppressed, but antisense transcription is constitutively active. Since HTLV-1 integrates and forms proviral DNA in the host genome, there should be some interaction between the proviral DNA and the host genome.

We previously reported that CTCF, a key regulator of chromatin structure and function, binds to the provirus at a sharp border in epigenetic modifications in the pX region of the HTLV-1 provirus (1). CTCF is a zinc-finger protein that binds to an insulator region in genomic DNA and plays a fundamental role in controlling higher order chromatin structure and gene expression in vertebrate cells. We additionally found a previously unidentified viral enhancer in the middle of the HTLV-1 provirus (3). HTLV-1 generates an ectopic enhancer region in addition to the viral CTCF insulator region. These findings indicate that the HTLV-1 enhancer can induce a distinct alteration of the host transcriptome via chromatin looping, and thereby upregulates cancer-related genes near viral integration sites which might contribute to the preferential selection of a specific infected cell for clonal expansion during the early phase of leukemogenesis.

## 2-3 major papers:

1. **Satou Y\***, Miyazato P, Ishihara K, Yaguchi H, Melamed A, Miura M, Fukuda A, Nosaka K, Watanabe T, Rowan A, Nakao M, and Bangham CRM\*. The retrovirus HTLV-1 inserts an ectopic CTCF-binding site into the human genome. *PNAS* 113: 3054-59, 2016.
2. Tan B, Sugata K, Reda O, Matsuo M, Uchiyama K, Miyazato P, Hahaut V, Yamagishi M, Uchimaruk K, Suzuki Y, Ueno T, Suzushima H, Katsuya H, Tokunaga M, Uchiyama Y, Nakamura H, Sueoka E, Utsunomiya A, Ono M\* and **Satou Y\***. HTLV-1 infection promotes excessive T cell activation and transformation into adult T cell leukemia/lymphoma. *JCI*, 131(24):e150472, 2021
3. Matsuo M, Ueno T#, Monde K#, Sugata K#, Miyazato P, Tan B, Rahman A, Islam S, Katsuya H, Nakajima S, Tokunaga M, Nosaka K, Hata H, Utsunomiya A, Fujisawa J, and **Satou Y\***. Identification and characterization of a novel enhancer in the HTLV-1 proviral genome. *Nat Comm* 13(1):2405, 2022.

## Bio:

During my PhD course I carried out studies on novel treatment of ATL (*Leukemia* 2004). As a post doctoral study, I analyze antisense viral gene HBZ about expression and role in HTLV-1 pathogenesis by using clinical samples and transgenic mouse model (*PNAS* 2006, *PLoS Pathogens* 2011). I then performed molecular biology experiment to elucidate the mechanism underlying retroviral latency (*PNAS* 2016). Since I obtained PI position in 2013, I have incorporated high through-put sequencing technology as a tool to understand genetic and epigenetic regulatory mechanism of retroviral latency regarding both HTLV-1 and HIV-1 (*Cell Rep* 2019, *JCI* 2021, *Nat Commun* 2022).





# Coding and non-coding functions of HTLV-1 bZIP factor gene in the oncogenesis of adult T-cell leukemia-lymphoma

Junichiro Yasunaga  
(Kumamoto University)

## Abstract:

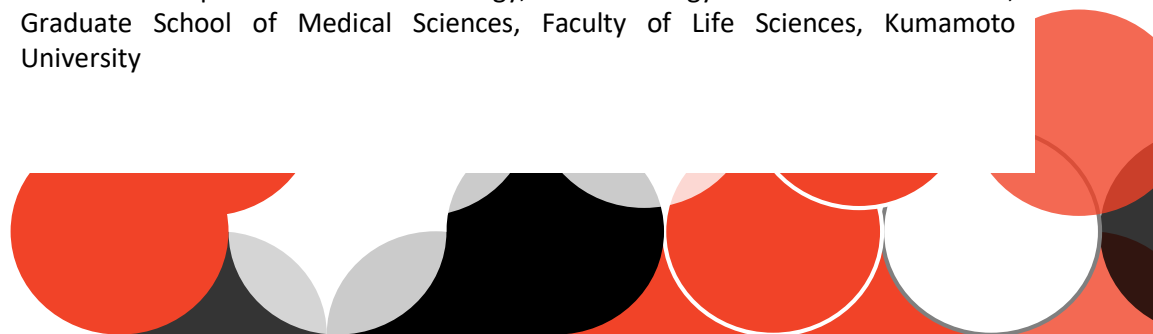
Adult T-cell leukemia-lymphoma (ATL) is a malignancy of mature CD4+ T cells induced by human T-cell leukemia virus type 1 (HTLV-1). HTLV-1 maintains a life-long infection *in vivo* mainly by clonal proliferation of infected cells. Among viral genes encoded in the HTLV-1 provirus, only HTLV-1 bZIP factor (HBZ) is conserved and expressed in all ATL cases. Knock down of HBZ suppresses the proliferation of ATL cell lines, indicating that HBZ is critical for the proliferation and maintenance of ATL. HBZ is a unique gene which transcript not only encodes HBZ protein but also acts like long non-coding RNAs. Recently, we reported that both *HBZ* RNA and HBZ protein upregulate a cellular gene *TAp73* in different manners. Consequently, *TAp73* contributes to both the Warburg effect and epigenetic reprogramming in HTLV-1–infected cells via induction of *MCT1/4* and *EZH2*, respectively. It is also found that nuclear localization of *HBZ* RNA and HBZ protein is associated with their oncogenic properties. The former is regulated by the activation of the 3'LTR, which is a promoter of *HBZ* gene, and the latter is accelerated by the TGF-beta/Smad pathway. These multimodal functions of HBZ are thought to be critical for the leukemogenesis of ATL.

## 2-3 major papers:

1. Toyoda K, [Yasunaga JI](#), Shichijo T, Arima Y, Tsujita K, Tanaka A, Salah T, Zhang W, Hussein O, Sonoda M, Watanabe M, Kurita D, Nakashima K, Yamada K, Miyoshi H, Ohshima K and Matsuoka M. HTLV-1 bZIP factor-induced reprogramming of lactate metabolism and epigenetic status promote leukemic cell expansion. **Blood Cancer Discov**, 2023; 4: 374-393.
2. Ma G, [Yasunaga JI](#), Shimura K, Takemoto K, Watanabe M, Amano M, Nakata H, Liu B, Zuo X, Matsuoka M. Human retroviral antisense mRNAs are retained in the nuclei of infected cells for viral persistence. **Proc Natl Acad Sci USA**, 2021; 118: e2014783118.
3. Higuchi Y, [Yasunaga JI](#), Mitagami Y, Tsukamoto H, Nakashima K, Ohshima K, and Matsuoka M. HTLV-1 induces T-cell malignancy and inflammation by viral antisense factor-mediated modulation of the cytokine signaling. **Proc Natl Acad Sci U S A**, 2020; 117:13740-13749.

## Bio:

2003-2007 Assistant professor at Institute for Virus Research, Kyoto University  
2007-2010 Visiting fellow at National Institute of Allergy and Infectious Diseases, National Institutes of Health, United states  
2010-2019 Lecturer at Institute for Virus Research, Kyoto University  
2019-2023 Associate professor at Departments of Hematology, Rheumatology and Infectious Disease, Graduate School of Medical Sciences, Faculty of Life Sciences, Kumamoto University  
2024- Professor at Departments of Hematology, Rheumatology and Infectious Disease, Graduate School of Medical Sciences, Faculty of Life Sciences, Kumamoto University



# Microbial signal-regulated hematopoietic stem cell function

**Hitoshi Takizawa**  
**(Kumamoto University)**

Hematopoiesis is a continuous blood production that is sustained by hematopoietic stem cells (HSCs), a somatic stem cell that lifelong self-renew and differentiate into all blood and immune cells. When hematopoietic stress such as infection, inflammation, chemotherapy occur, HSC and progenitor function substantially change, i.e., attenuate HSC self-renewal, bias their differentiation potential, etc. We have studied a role of innate immune signaling in HSCs and their offspring in the context of infection, inflammation and leukemogenesis. In this lecture, I would like to show recent findings in the field of stress hematopoiesis and discuss how to extrapolate its role for development and maintenance of hemato-immune system throughout various lifetime events including development, aging and cancer.

## 2-3 major papers:

1. Wang Y, Morishima T, Sezaki M, Sato R, Nakato G, Fukuda S, Kobiyama K, Ishii KJ, Li Y, **Takizawa H**. Akkermansia muciniphila induces slow extramedullary hematopoiesis via cooperative IL-1R/TLR signals. *EMBO Rep.*, 2023 Dec 6;24(12):e57485. doi: 10.15252/embr.202357485. Epub 2023 Oct 23.
2. Sezaki M, Hayashi Y, Nakato G, Wang Y, Nakata S, Biswas S, Morishima T, Fakruddin M, Moon J, Ahn S, Kim P, Miyamoto Y, Baba H, Fukuda S, **Takizawa H**. Hematopoietic stem and progenitor cells integrate microbial signals to promote post-inflammation gut tissue repair. *EMBO J.*, 2022 Oct 18;e110712.
3. **Takizawa H (co-correspondance)**, Fritsch K, Kovtonyuk LV, Saito Y, Yakkala C, Jacobs K, Ahuja AK, Lopes M, Hausmann A, Hardt WD, Gomariz Á, Nombela-Arrieta C and Manz MG. Pathogen-induced TLR4-TRIF innate immune signaling in hematopoietic stem cells promotes proliferation but reduces competitive fitness. *Cell Stem Cell.*, 2017 Aug 3;21(2):225-240. doi: 10.1016/j.stem.2020.06.010.

## Bio (About 100 words is preferred):

I have been specialized in stem cell biology with strong interest and focus on inflammatory stress. Early on, I studied cytokine signalings through c-Kit and c-Mpl for HSC expansion and maintenance (Blood 2006; JCI 2010, Blood 2016). Then, my work was shifted toward understanding of HSC cycling dynamics in a steady state and inflammatory context such as infection, leukemogenesis (JEM 2011, JEM 2014, Cancer Sci 2022). I found that HSCs can sense infection-associated danger signals through toll-like receptor 4 to adapt hematopoiesis into host defense enhancement (Blood 2012, JEM 2011, Cell Stem Cell 2017). More recently, I showed microbiota penetrating through gut upon inflammation or aging affect HSC function (Blood 2022, EMBO J 2022, EMBO Rep 2023). I have also developed a novel animal model with a microenvironment derived from human mesenchymal stem cell (MSC) that are able to maintain HSC dormancy (Annu Rev Immunol., 2013; PNAS 2011; iScience 2019; Stem Cells Dev 2021).

# Alloreactive T-cell targets tissue stem cells and impairs tissue homeostasis in GVHD after allogeneic stem cell transplantation

**Takanori Teshima  
(Hokkaido University)**

## Abstract:

Acute graft-versus-host disease (GVHD), a major complication after allogeneic hematopoietic stem cell transplantation (alloSCT), is an alloreactive T-cell mediated inflammatory disease involving the skin, liver, and gut. Our recent studies on the mechanisms of the target tissue injury have uncovered that tissue stem cells in the GVHD target tissues are targets of GVHD, leading to impaired tissue homeostasis and regeneration. Thus, GVHD can be recognized as a disorder of tissue regeneration and repair. Impairment of intestinal homeostasis disrupts intestinal microbial ecology, which further accelerates GVHD. These novel insights suggest that immunosuppression alone is not sufficient and novel concept of GVHD control should integrate both immunomodulation and tissue modulation. Novel strategies to increase capacity to recover when immune insult is arrested could facilitate tissue repair and restoration of tissue homeostasis.

## 2-3 major papers:

1. Ara T, Hashimoto D, Hayase E, Noizat C, Kikuchi R, Hasegawa Y, Matsuda K, Ono S, Matsuno Y, Ebata K, Ogasawara R, Takahashi S, Ohigashi H, Yokoyama E, Matsuo K, Sugita J, Onozawa M, Okumura R, Takeda K, **Teshima T**: Intestinal goblet cells protect against GVHD after allogeneic stem cell transplantation via Lypd8. **Sci Transl Med.** 2020 Jul 1;12(550):eaaw0720.
2. Peled JU, Gomes ALC, Devlin SM, Littmann ER, Taur Y, Sung AD, Weber D, Hashimoto D, Slingerland AE, Slingerland JB, Maloy M, Clurman AG, Stein-Thoeringer CK, Markey KA, Docampo MD, Burgos da Silva M, Khan N, Gessner A, Messina JA, Romero K, Lew MV, Bush A, Bohannon L, Brereton DG, Fontana E, Amoretti LA, Wright RJ, Armijo GK, Shono Y, Sanchez-Escamilla M, Castillo Flores N, Alarcon Tomas A, Lin RJ, Yáñez San Segundo L, Shah GL, Cho C, Scordo M, Politikos I, Hayasaka K, Hasegawa Y, Gyurkocza B, Ponce DM, Barker JN, Perales MA, Giralt SA, Jenq RR, **Teshima T**, Chao NJ, Holler E, Xavier JB, Pamer EG, van den Brink MRM: Microbiota as Predictor of Mortality in Allogeneic Hematopoietic-Cell Transplantation. **N Engl J Med.** 2020 Feb 27;382(9):822-834.
3. Zeiser R, Polverelli N, Ram R, Hashmi SK, Chakraverty R, Middeke JM, Musso M, Giebel S, Uzay A, Langmuir P, Hollaender N, Gowda M, Stefanelli T, Lee SJ, **Teshima T (equally contributing senior author)**, Locatelli F: Ruxolitinib for Glucocorticoid-Refractory Chronic Graft-versus-Host Disease. **N Engl J Med.** 2021 Jul 15;385(3):228-238.

## Bio:

Dr. Teshima is a distinguished Professor at Hokkaido University. His clinical and research interests are immune therapy such as allogeneic hematopoietic stem cell transplantation (HCT) and CAR-T cell therapy. His major contributions include the discovery of the central role of cytokines in GVHD leading to development of a novel GVHD treatment strategy using cytokine blockade and the discovery of target tissue stem cell involvement with associated intestinal dysbiosis in GVHD leading to a novel concept of GVHD control integrating both immunomodulation and tissue modulation. Dr. Teshima takes the initiative of haploidentical HCT and CAR-T therapy as well as numerous clinical trials of GVHD in Japan.



**\* MEMO \***



# Welcome to Kumamoto!

## Willkommen in Kumamoto!

Kumamoto University is located in Kumamoto city, which is at the center of the Kyushu island (Southwest Japan). Kumamoto is not only a place blessed with natural resources like mountains, rivers, and oceans, but it is also quite rich in history and culture.

Kumamoto Castle is the most symbolic attraction in Kumamoto, which has a history of more than 400 years. Its main feature is its stone walls, known as Musha-gaeshi (武者返し). These walls are warped to prevent enemy invasion. Unfortunately, in the earthquake of 2016, Kumamoto Castle was severely damaged and is going through a 20-years' restoration.

The damage caused by the Kumamoto earthquake extends through several areas of Kumamoto prefecture. The Aso area, which we will visit on this excursion, was one of the most damaged areas. However, we would like you to see not only the great hurt that Kumamoto people has experienced, but also their resilience and the way these people are overcoming such adversities.

Aso is a place where you can feel the magnificence of nature with your whole being. Despite being a place where you can feel the danger of earthquakes and volcanic eruptions, the area is blessed with rich groundwater and hot springs.

In fact, the groundwater which is nurtured by the Aso mountains, is one of the most valuable resources of Kumamoto City. This groundwater provides for well-being of all the 740,000 habitants of Kumamoto City.





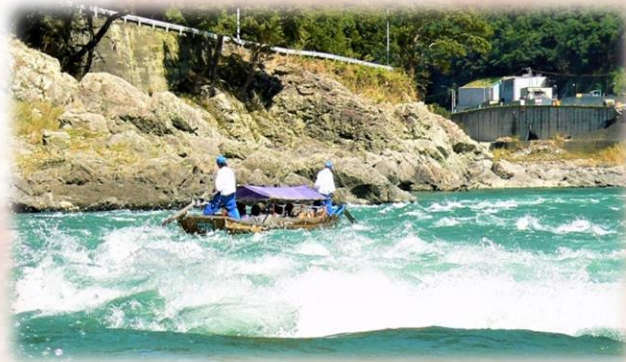
# Welcome to Kumamoto!

## くまもとへようこそ！



The bountiful waters of Kumamoto also nurture delicious food. All the famous foods in Kumamoto can be summarised by the word 'red'. Here is where we produce the most amount of tomatoes and watermelons in Japan. Basashi (馬刺し) is a must-try food for visitors of Kumamoto, it is sashimi prepared with horse meat instead of fish. Kumamoto is also famous for its 'Aka-Ushi' (red cow) wagyu beef. In Kumamoto, horses and cows live in the grasslands of Aso and grow up drinking clean water and breathing pure air, which make their meat delicious.

Kumamoto is proud of its "Sake (清酒/日本酒)" and "Shochu (焼酎)", made from a combination of its nutritious water and locally-produced rice. In fact, Kumamoto is the southernmost area where sake is produced in its natural environment. In the past, it was difficult to produce good sake due to the weather, but people spent years doing research to achieve the current amazing taste. This achievement was only possible because of Kumamoto yeast (No. 9 yeast). Interestingly, Kumamoto yeast is still considered one of the conditions for making good sake, as yeast is an important ingredient in the production of alcohol. A yeast called Kumadai-Yeast was recently discovered at Kumamoto University.



In Hitoyoshi-Kuma area, the most southerly region of Kumamoto Prefecture, spirits alcohol have been produced for more than 500 years. The name Kuma-shochu is an alcoholic beverage for which a specific regional name is used as a brand name, similar to Bordeaux for wine or Cognac for brandy. Kuma-Shochu has a variety of flavours depending on how it is made and how it has aged. Two days is a short time, but please enjoy Kumamoto!





# Our Culture -- Kumadai-Hub!

Operated by Nanako Watanabe, Nazuki Doi and Hanami Sakai (IRCMS Admin)

Kumadai-Hub is an organization of “self-proclaimed” young volunteers researchers at Kumamoto University. It was founded in December 2019 and is keep growing over the last few years. We use the term “self-proclaimed” because the definition of “young” is ambiguous, so our members gather as “people with a fresh mind”. It started as a free small gathering of researchers/research-enthusiasts from different areas, and has grown in size to about 110 members in a two years span.



Currently, Japanese universities’ policies are full of trendy words such as “young people’s development,” “internationalization,” “joint research,” and “fusion research”. As much as these topics are important, nothing compares to “our own mindset and actions”. In this sense, we developed our community with the help of research administrator, emphasizing the fact that researchers need a fixed space that they come and go when they need and discuss their ideas. Similar to what greeks would do in agoras, their public discussion spaces. We have regular quarterly meetings (once every three months) and also hold diverse social events. Recently some collaborations have emerged through our activities. Despite being always on the look for possibilities of “different fields’ collaboration” and “joint research development” that may emerge in the meetings, this is not our primary goal. We just want to make a fun place that let researchers discuss without barriers. This is the Kumadai-Hub’s main mission.





Kumadai-Hub is a group open not only to professional researchers, but also to students, technical staff, administrative staff, and all others involved in university research. Despite Kumamoto University having a large group of researchers spread through its five departments and three campuses. These researchers don't actually know each other very well. We had a poster exhibition in 2022 that provided an opportunity for us to communicate with each other. The most interesting point was that technical and administrative staff, who are usually on the management side, also made and exhibited posters to introduce their own work. Researchers and students tried to avoid using "cryptic jargons" and focused on having more friendly presentations. The most interesting part was that these rules were not something discussed on a gray room, but people came to this conclusion themselves. Studies and sciences are not exclusive and should not be restricted to a small group, so we need to be able to share them with everyone and explain them to anyone. We need more science communicators! This another of Kumadai-Hub's missions.



Lastly, our community values face-to-face, but we also value online connections. Since we are in Japan, most members are more comfortable with Japanese, however we also communicate in English and any other language is welcome. Our greatest value is that we don't have barriers based on whether you are Japanese or non-Japanese, male or female, senior or young, your field of interest, or your job title or position. Kumamoto University has a place where we can discuss freely, flatly, and happily.

# About IRCMS



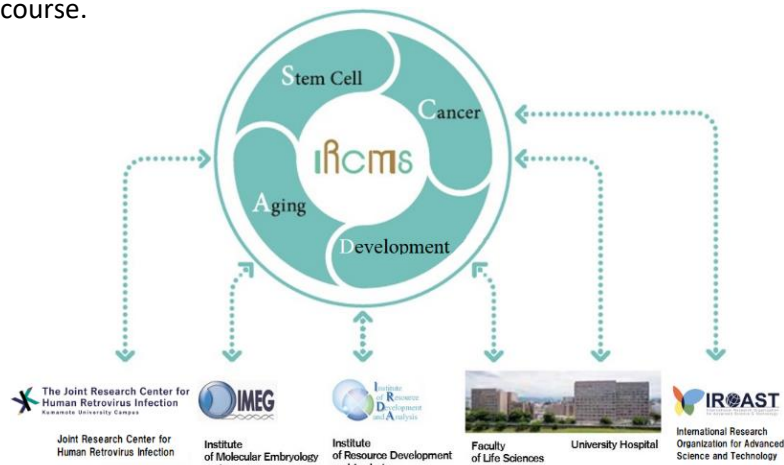
The International Research Center for Medical Sciences (IRCMS) was established in 2015 as the center of excellence in Kumamoto University for world-class research in life sciences through the internationalization of its research environment and the establishment of global collaborations.

The Center features an open lab layout with few walls and partitions between labs to facilitate communication among scientists. A meeting lounge and an open café on the 1st floor support active, informal scientific exchange between researchers. English is the official language for all seminars and lab meetings to promote international scientific discourse.

IRCMS is located in the Honjo-Kuhonji area along with Kumamoto University's School of Medicine, the University Hospital, the Joint Research Center for Human Retrovirus Infection, the Institute of Resource Development and Analysis (IRDA) and the Institute of Molecular Embryology and Genetics (IMEG). Through cooperation with these institutes, IRCMS will create a strong collaborative network in the areas of Stem Cell Research, Aging Research, Development Research and Cancer Research.

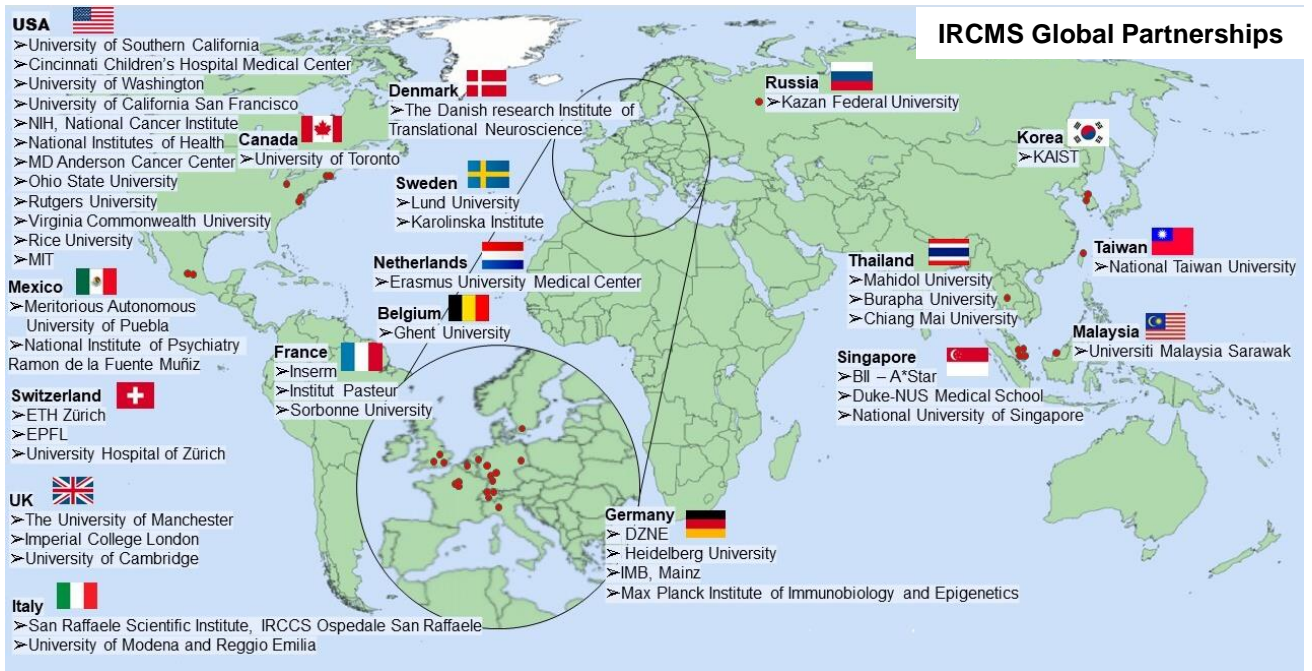
At present, 12 principal investigators (PIs) and their lab members are conducting research at the Center. IRCMS also aims to establish an international research collaboration network with visiting researchers who hold positions in research institutes abroad. Non-Japanese nationals currently account for 40% of the people working at the Center, excluding visiting researchers, and this number is expected to increase to 50% in the future.

The ultimate goal of IRCMS is to become a successful and innovative role model for the internationalization of academic research. IRCMS is now laying new framework that extends beyond the existing research environment to reach this ultimate goal.





# About IRCMS



## Open Lab / Core Facility

IRCMS has adopted an “Open Lab” System to stimulate scientific interaction among the scientists and cultivate inter-laboratory collaboration across multiple disciplines. Scientists share lab space and equipment. All of the laboratories and office are visible through the window from the hallway.

To make research equipment sharing and time management efficient, we have established an online booking system and started technical support for cutting-edge technology such as single cell analysis. There is an open café space on the 1st floor to facilitate discussion and networking.



Open Lab



Core facility



Open space



Experiment in the lab

## Internship

IRCMS has provided research internship opportunities since 2015 for overseas students who have a strong interest toward the advanced medical research, aiming to raise the interest of IRCMS research and recruit the next generation of young researchers internationally.

We have invited more than 35 interns from 19 countries so far, and some of them came back to IRCMS as Ph.D. course students or Postdoc-Researchers.



Conducting experiment



Research instruction

# IRCMS Principal investigator



**TAKIZAWA Hitoshi**  
Ph.D.  
Professor (Director)  
**Research Field**  
Stem Cell Stress



**ARIMA Yuichiro**  
M.D., Ph.D.  
Associate Professor (Vice Director)  
**Research Field**  
Developmental Cardiology



**SUDA Toshio**  
M.D., Ph.D.  
Distinguished Professor  
**Research Field**  
Stem Cell Regulation  
**Double Appointment:**  
National University of Singapore



**Guojun Sheng**  
Ph.D.  
Professor  
**Research Field**  
Developmental Morphogenesis



**SASHIDA Goro**  
M.D., Ph.D.  
Professor  
**Research Field**  
Transcriptional Regulation in  
Leukemogenesis



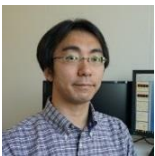
**MIHARADA Kenichi**  
Ph.D.  
Professor  
**Research Field**  
Proteostasis in Stem Cell



**SADA Aiko**  
Ph.D.  
Cross-appointment professor  
**Research Field**  
Skin Regeneration and Aging



**BABA Masaya**  
M.D., Ph.D.  
Associate Professor  
**Research Field**  
Cancer Metabolism



**MIZUNO Hidenobu**  
Ph.D.  
Associate Professor  
**Research Field**  
Multi-dimensional Imaging



**UMEMOTO Terumasa**  
Ph.D.  
Associate Professor  
**Research Field**  
Hematopoietic Stem Cell Engineering



**KUROTAKI Daisuke**  
Ph.D.  
Associate Professor  
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