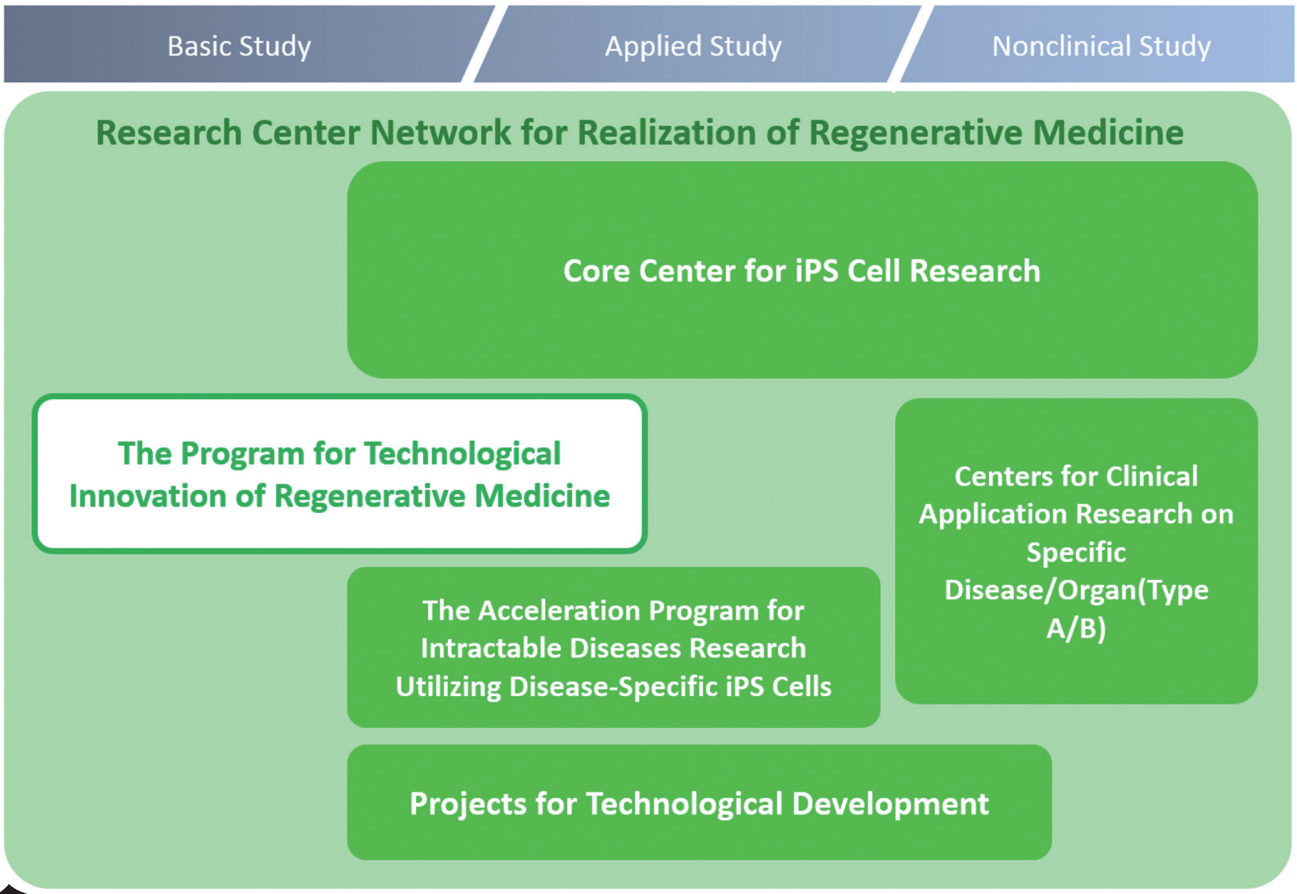
# The Program for Technological Innovation of Regenerative Medicine

The program seeks to support basic research that will contribute to the realization of regenerative medicine and stem cells and their application for drug discovery. It supports basic research to assist in the creation of innovative medical technologies for the treatment of intractable diseases for which no treatment has previously been available. This would enable Japan to lead the world in the field of stem cell/ regenerative medicine in the future.

The program highly regards research based on innovative and unique ideas that have the potential to yield results with significant global impact ranking highly amongst other research in the respective field globally. It also values international/cross-field research in light of the tendency for young Japanese researchers to hesitate to work in a global setting.

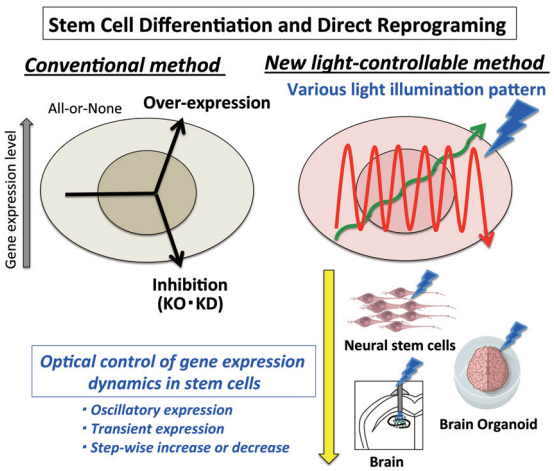


## Development of novel optical methods to regulate differentiation of neural stem cells

Professor, Laboratory of Brain Development and Regeneration,
Graduate School of Biostudies, Kyoto University
**Itaru Imayoshi**

The recent discovery of neural stem cells in the adult central nervous system has raised the possibility of repairing the damaged tissue by recruitment of their latent, endogenous regenerative potentials. Development of innovative methods that can noninvasively manipulate neural stem cells in the brain has been expected for regenerative medicine of the nervous system. We have recently demonstrated the first success of such an approach in artificial manipulation of proliferation and neuronal differentiation of neural stem cells by light. We are currently extending this regenerative approach to various types of neural disease models in mice and primates, such as traumatic injury, neurodegeneration or psychiatric disorder. In this research proposal, by applying the novel light-inducible gene expression system, we will try developing novel methods to selectively and efficiently induce various neural cell types from neural stem cells. More specifically, we will focus on the dynamic expression changes of transcription factors in neural stem cells and manipulate them by the optogenetic approach. We will improve the specificity and efficiency of differentiation of neural stem cells and direct reprograming processes. We will apply these light-mediated control methods to neural stem cells in the brain and iPS cells-derived brain organoids, as well as to cultured neural stem cells.

● URL: https://brainnetworks.jimdofree.com

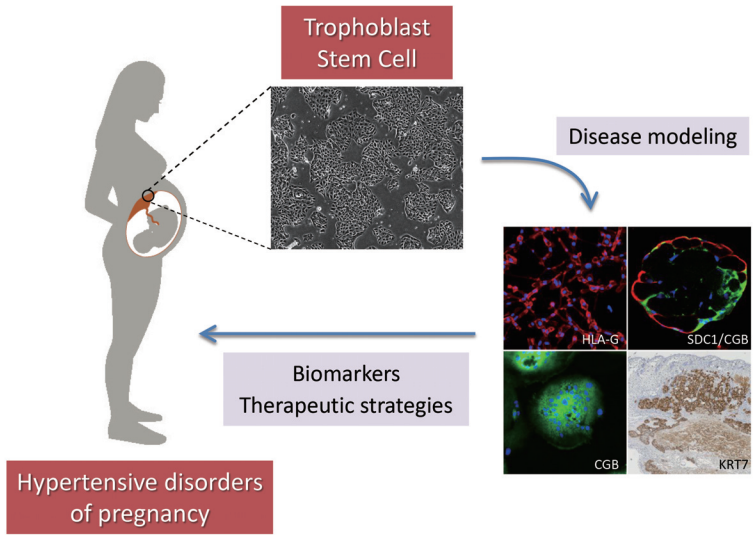



Development of novel optical methods to regulate differentiation of neural stem cells
in neural stem cell cultures, brain organoids, and living brains.

## Characterization of human trophoblast stem cells for medical applications

Associate Professor, Department of Informative Genetics,
Tohoku University Graduate School of Medicine
**Hiroaki Okae**

The placenta is an essential organ that mediates interactions between the mother and the fetus. Placental abnormalities are associated with various human diseases such as miscarriage, preterm birth, hypertensive disorders of pregnancy (HDP) and gestational diabetes. We have recently established a culture system of human trophoblast stem cells (TSCs). TSCs have the capacity to differentiate into all types of trophoblast cells in the placenta and thus provide a useful model to understand placental development and diseases. In this study, we utilize the culture system of human TSCs to understand the pathogenesis of HDP, which is a disease characterized by hypertension after 20 weeks of gestation and remains a major cause of death during the perinatal period. HDP is thought to develop as a result of trophoblast defects, but the underlying mechanisms are poorly understood. The outcome of this study will be beneficial for understanding the pathogenesis of HDP and identifying new biomarkers and therapeutic strategies.

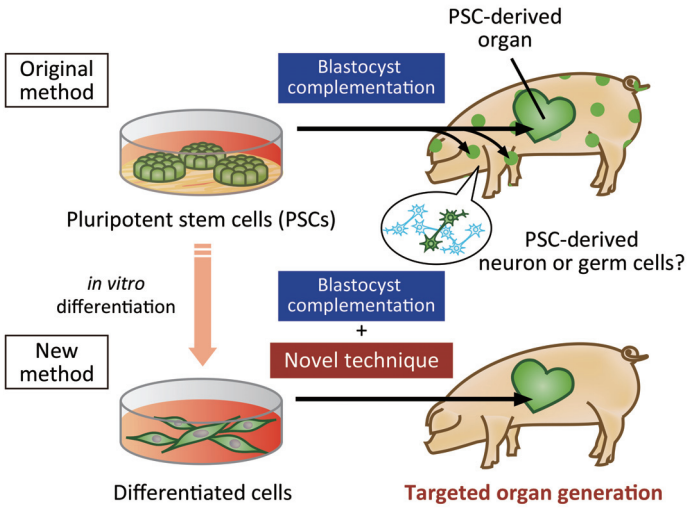


## Development of a novel technique to generate targeted organs from pluripotent stem cells

Assistant professor, Center for Genetic Analysis of Behavior,
National Institute for Physiological Sciences
**Toshihiro Kobayashi**

Generation of human organs from pluripotent stem cells (PSCs) is an ultimate goal of regenerative medicine. While making the organs *in vitro* is challenging due to the complexity of the structure, a capacity of PSCs capable to form chimera *in vivo* allows us to generate functional organs by injection of the PSCs into blastocysts obtained from organ deficient animals. If the method called "blastocyst complementation" is applicable to human PSCs, we might grow human organs in the large animals. However, so far, successful generation of the organs by the blastocyst complementation has been only demonstrated within rodents. In addition, injected donor PSCs not only contribute to the organ but also to all the tissue including neurons and germ cells, which raise ethical concerns when it applies to human and large animals. In this project, by using experimental animals which have unique features in their early development, we attempt to develop a novel technique to minimize the contribution of donor cells in the unwanted tissues in the chimera. Furthermore, by combining the technique with the blastocyst complementation method, we aim to generate a targeted organ from PSC-derived cells.

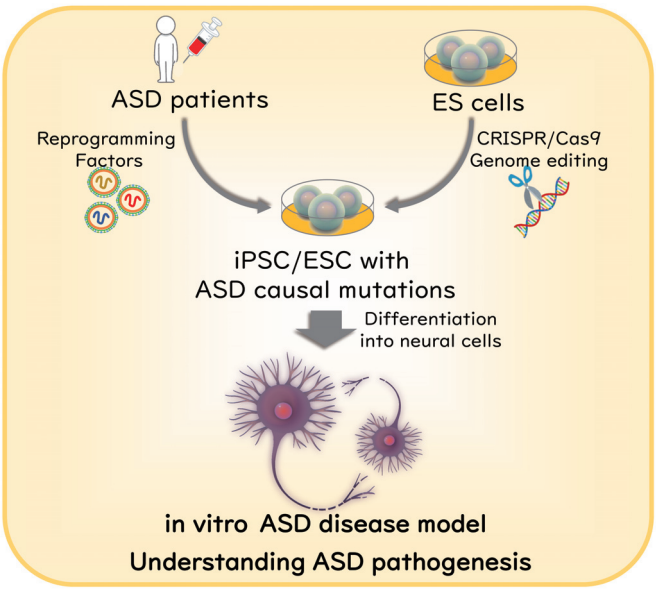
● URL: http://www.nips.ac.jp/mamtg/




## Method for diagnosis of neural and neurodegenerative disorders using iPSC

Senior Researcher, Center for Regenerative Medicine,
National Center for Child Health and Development
**Tohru Sugawara**

It is challenging to understand the relationship between genotypes (genomic information) and phenotypes (diseases and symptoms), even with state of the art technology. Autism spectrum disorder (ASD) is neurodevelopmental disorder characterized by abnormal social interactions and repetitive behaviors. There is no doubt that genetics play a central role in ASD. Unraveling the genetic etiology allows us to understand cellular and molecular mechanisms of ASD and find therapeutic targets. In this study, both ASD patient-derived iPSCs and gene-edited human ESCs will be differentiated into neurons, glial cells and brain organoids to generate *in vitro* ASD disease modeling. Combined with genome-editing technology, this disease model will be applied for experimental validation of ASD causal genes to understand unknown pathological processes and to find markers and potential therapeutic target genes. This disease model can also be used for genetic diagnosis of individuals at risk for ASD at an early stage, resulting in initiation of treatments before disease progression, and in postponement or even prevention of the onset of disease.

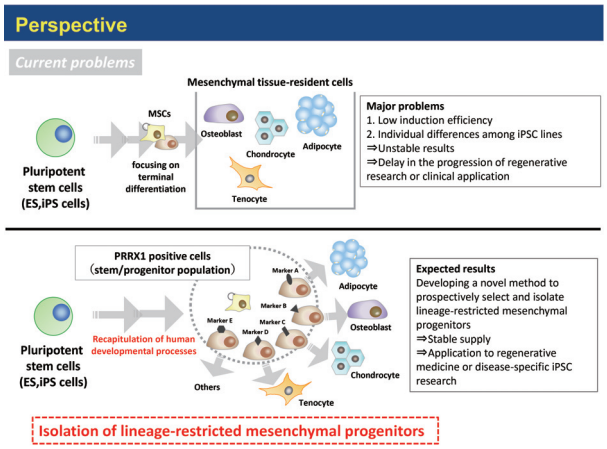


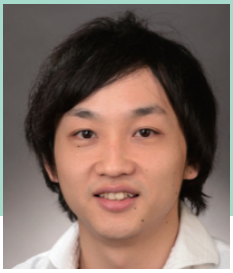
## Development of selection and isolation methods for lineage-restricted mesenchymal progenitors derived from human pluripotent stem cells

Associate Professor, Department of Regenerative Science,
Okayama University
**Takeshi Takarada**

Current methods for inducing mesenchymal cells (e.g., osteoblasts, chondrocytes, adipocytes, skeletal myoblasts, and tendon and ligament cells) from pluripotent stem cells do not account for the quality of the intermediate states (i.e., mesenchymal progenitors) leading to the target cells. This omission leads to interference in the technical development of stable, efficient, and selective induction protocols that target mesenchymal cells. We aimed to develop a novel method to prospectively select and isolate lineage-restricted mesenchymal progenitors following the ontogenetic definition of mouse mesenchymal progenitors based on the molecular signature of gene expression and epigenetic state. PRRX1-positive cells are transiently observed during limb skeletal development in mice. PRRX1-positive cells form heterogeneous populations comprising multiple mesenchymal progenitors with different lineages that are developing into osteoblasts, chondrocytes, dermal fibroblasts, and tendon and ligament cells. We standardized a protocol to selectively induce ontogenetically defined human PRRX1-positive mesenchymal progenitors from human iPS cells based on the molecular signatures of ontogenetically defined mouse mesenchymal progenitors. This technical development can contribute to disease modeling for drug discovery using patient-derived iPSCs by correcting for variance among iPSC lines. The method can also contribute to the development of regenerative medicine by enabling the transplantation of lineage-restricted mesenchymal progenitors.

● URL: https://www.okayama-u.ac.jp/user/syuufuku/



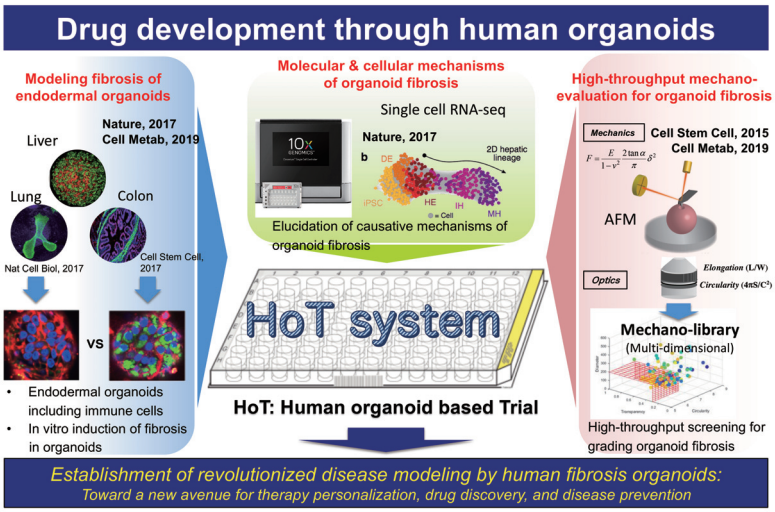



## Induction of fibrosis into endodermal organoids coupled by mechano-screen platform

Professor, Institute of Research,
Tokyo Medical and Dental University
**Takanori Takebe**

Conventional pharmaceutical approaches fai to produce effective therapies for inflammatory and fibrotic diseases such as liver fibrosis, pulmonary fibrosis and inflammatory bowel disease, Herein, together with induced pluripotent stem cells (iPSC) coupled with our unique organoid technology, we propose to develop an *in vitro* organoid model of fibrotic disorders with an implication for drug screening by achieving the following three core-aims: Aim1) to establish a human iPSC derived multicellular endoderm, *i.e.* hepatic, lung and intestinal, organoid capable of modeling fibrosis, Aim2) to determine the causative mechanism of organoid fibrosis by single cell transcriptomics, and Aim3) to devise a high-throughput mechano-evaluation system for grading organoid fibrosis. Through these efforts, we will establish a new and robust assay system using multicellular endodermal organoids with mechanical readouts. Our proposed approaches will revolutionize the disease model approaches and open a new avenue for a number of promising applications including therapy personalization, drug discovery and disease prevention.

● URL: http://takebelab.com/

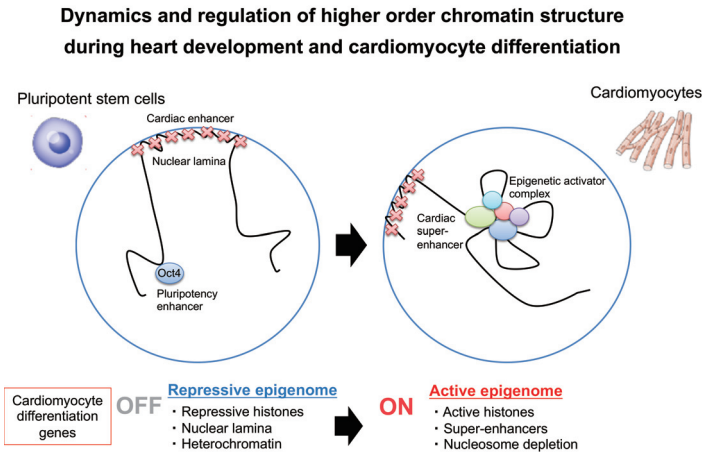


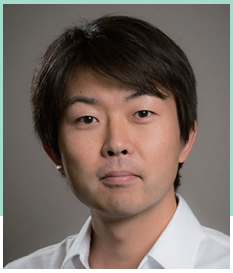
## Dynamics and regulation of higher order chromatin structure during heart development and cardiomyocyte differentiation

Assistant Professor, Department of Cardiovascular Medicine,
The University of Tokyo
**Seitaro Nomura**

Epigenome changes dramatically during cell differentiation and it regulates the acquisition of cell-specific phenotype. The mechanisms how “repressive” epigenetic markers such as heterochromatin or lamina-associated domain (LAD) change and how they regulate cellular differentiation remain elusive. The disruption of lamina caused by genetic mutation of the *LMNA* gene causes laminopathies, which include cardiomyopathy and progeria. Therefore, understanding the regulation system of cardiac differentiation through chromatin conformation and LAD would contribute to the elucidating the disease mechanism of laminopathy. We are collecting the information about the locus of LAD and heterochromatin and analyze chromatin conformation using Hi-C technology from three stages of cardiac differentiation of mouse pluripotent stem cells and ES cells. We are comparing genome-wide data of these repressive epigenetic modification and will identify the loci where specific change occurs. The present study will provide us a new insight on the mechanism of cardiac differentiation and it may serve for the development of a novel method of cardiac induction from pluripotent stem cells and understanding the molecular pathogenesis of cardiomyopathy.

● URL: https://cardiovasc.m.u-tokyo.ac.jp/study/system_cardiology/about



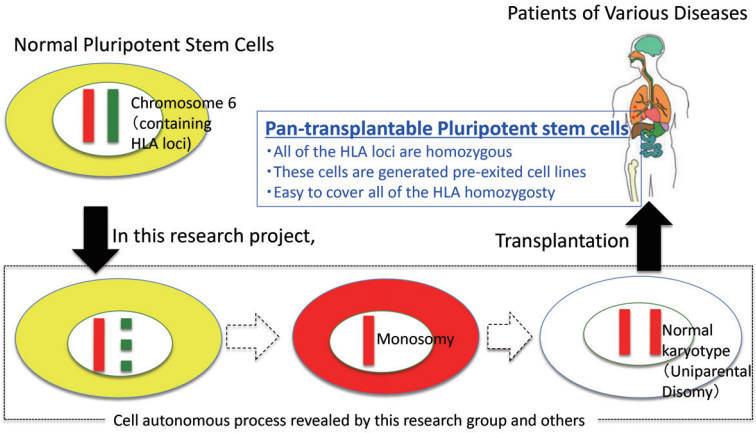



## Development of all HLA homozygous pluripotent stem cells and their evaluation of pan-transplantablity

Team Leader, iPS Cell Advanced Characterization and Development Team,
BioResource Research Center, RIKEN
**Yohei Hayashi**

There are two approaches of the allotransplantation of pluripotent stem cell-derived cells or tissues. First, clinical trials of human embryonic stem cell-derived cells or tissues, which use immunosuppressants in combination, usually do not take into account immunological compatibility. However, it is generally better not use immunosuppressants in considering about safety risks and the quality of recipients' life. Second, induced pluripotent stem cell bank, which are generated from HLA (human leukocyte antigen) homozygous donors, are being established. This bank will serve as the platform to supply transplantable cells and tissues as the recipients' types of HLA. This bank might be hard to cover all of the HLA types. Also, it is unclear that these cells can completely overcome immunorejection. To solve these questions, I aim to generate pan-transplantable human pluripotent stem cells by creating disomy cells of chromosome 6, which have all HLA homozygous loci. Also, I will evaluate that these disomy pluripotent stem cell lines can be used as transplantable cells by examining their whole genome sequence, gene expression, differentiation potentials, their survival rate, therapeutic effectiveness, and safety in transplantation.

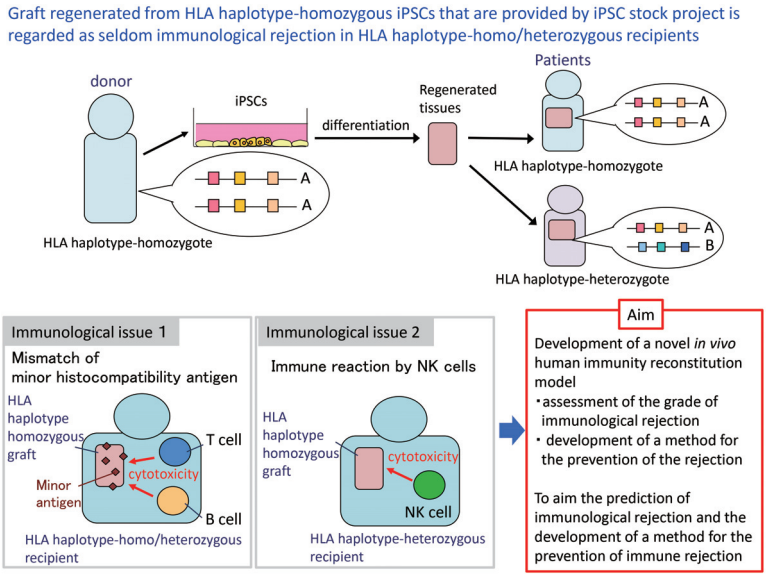
● URL: https://www.riken.jp/en/research/labs/brc/ips_cell_adv_char_dev/

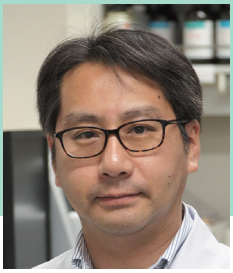


## Development of a method for the prevention of immune rejection against regenerated tissues using a novel *in vivo* human immunity-reconstitution model

Assistant professor, Institute for Frontier Life and Medical Sciences,
Kyoto University
**Kyoko Masuda**

In the regenerative medicine field, the invention of iPSCs allowed us to expect that the required tissue can be regenerated and transplanted in autologous setting. However, it is not a realistic idea that iPSCs are established from each patient because it is costly and time consuming to obtain the qualified iPSCs. Therefore, currently promoted strategy is the allogenic transplantation using regenerated tissues differentiated from HLA haplotype-homozygous iPSCs that are stocked in advance. However, it has not been well studied to what extent the immune reaction take place when regenerated tissues are transplanted in the allogeneic setting. In this study, we aim to develop the *in vivo* system that can assess the grade of the immune reaction for a long period after the tissues regenerated from HLA-haplotype homozygous iPSCs are transplanted. We expect that the system used in this study will provide a powerful tool to develop a novel method for the prevention of graft rejection.



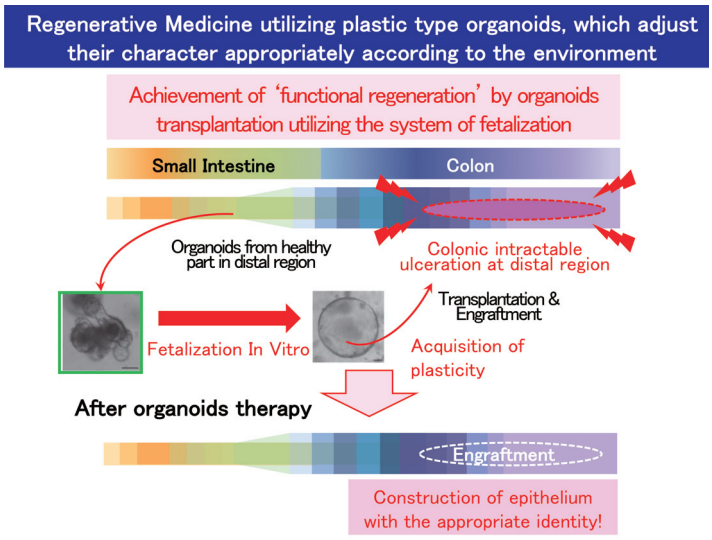



## Development of fetal-like hyper-plastic intestinal organoids derived from maturate adult intestine

Assistant Professor, Center for Stem Cell and Regenerative Medicine,
Tokyo Medical and Dental University
**Shiro Yui**

We, the department of gastroenterology and hepatology and center for stem cell and regenerative medicine, Tokyo Medical and Dental University have been developing the safe regenerative medicine for inflammatory bowel disease such as ulcerative colitis. Our strategy is to utilize healthy tissue stem cells, which are originally equipped in our body.

In our research, we achieved to understand that we have difficulty in the supply of healthy tissue stem cells in severe situation such as pan-colitis. In these cases, strategy to establish organoids from distal part of small intestine and to utilize these organoids for regenerative purpose could be potentially taken, however we already revealed that small intestinal stem cells build intestinal-type epithelium in colon. In this proposed project, we focus on the unique character of TMDU spheres in partial fetal signature. By developing the technology, which can further enhance their fetal signature, we will establish fetal-like hyper-plastic intestinal organoids, which can adjust their character fit into neighboring environment, and aim to establish the effective strategy to regenerate colonic epithelium from intact distal part of small intestine.



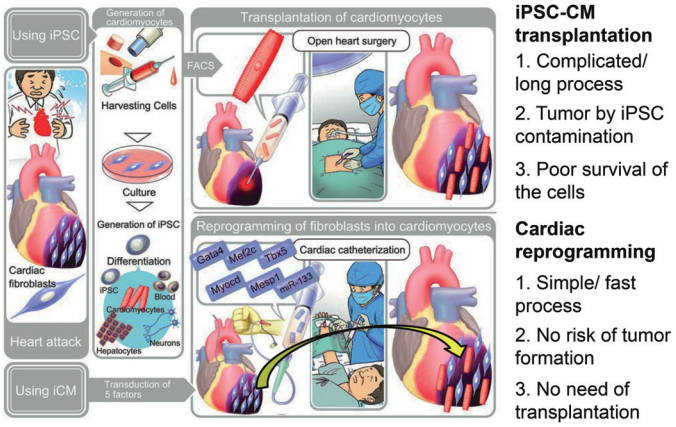
## Direct reprogramming and cardiac regeneration for heart failure

Professor, Faculty of Medicine,
University of Tsukuba
**Masaki Ieda**

Heart failure remains a leading cause of death worldwide. Patients with chronic heart failure show systolic dysfunction and cardiac fibrosis, and the ultimate treatment is heart transplantation. However, due to the limited availability of donor organs, regenerative therapy has received attention as a new treatment for severe heart failure. Transplantation of induced pluripotent stem cell (iPSC)-derived cardiomyocytes in failing hearts may be a potential approach for cardiac regeneration. However, there are several issues to be addressed before clinical application. As an alternative to this conventional cell-based approach, we developed a strategy for cardiac regeneration that may not require cell transplantation. We first discovered that a combination of cardiac-specific transcription factors directly reprogrammed cardiac fibroblasts into induced cardiomyocyte-like cells *in vitro* without reverting to a pluripotent stem cell state. In this study, we will analyze cardiac reprogramming in heart failure in mice and identify small molecules that can improve cardiac reprogramming in fibrotic tissues for cardiovascular reprogramming in failing hearts. Our ultimate goal is to develop a novel cardiac regenerative therapy for heart failure patients.

● URL: http://www.md.tsukuba.ac.jp/clinical-med/cardiology/

Heart Regeneration by Cardiac Reprogramming

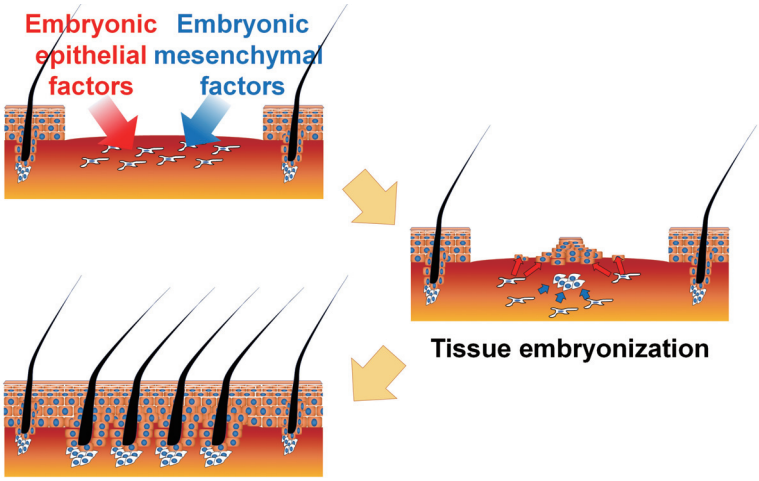



## Development of treatment for cutaneous ulcers by embryonization of tissues

Assistant professor, Department of Plastic, Reconstructive and Aesthetic surgery,
The University of Tokyo Hospital
**Masakazu Kurita**

Cutaneous ulcer is common morbidity resulting from various external and internal causes such as trauma, burns, pressure ulcer and diabetic ulcer. For the compensation of soft tissue deficit, we focused on the potentials of the cells *in situ* to deliver cells harnessing ability to regenerate lost tissues and developed the method to induce *de novo* epithelialization from surface of cutaneous ulcers through direct reprogramming of wound-resident mesenchymal cells to epithelial cells by adeno associated virus (AAV) based gene transduction. In the current research, we aim to expand the technology to regenerate skin with appendages, a complex organ, by reprogramming of wound resident-mesenchymal cells to epithelial embryonic progenitors like cells (Ectodermal origin) and mesenchymal embryonic progenitor like cells (Mesodermal origin), which we call tissue embryonization. The technology of embryonization of tissues *in situ* not only confers radically new therapeutic interventions to clinically intractable cutaneous ulcers, but also represent the way for more broad areas of regenerative medicine.

● URL: http://www.h.u-tokyo.ac.jp/plastic/

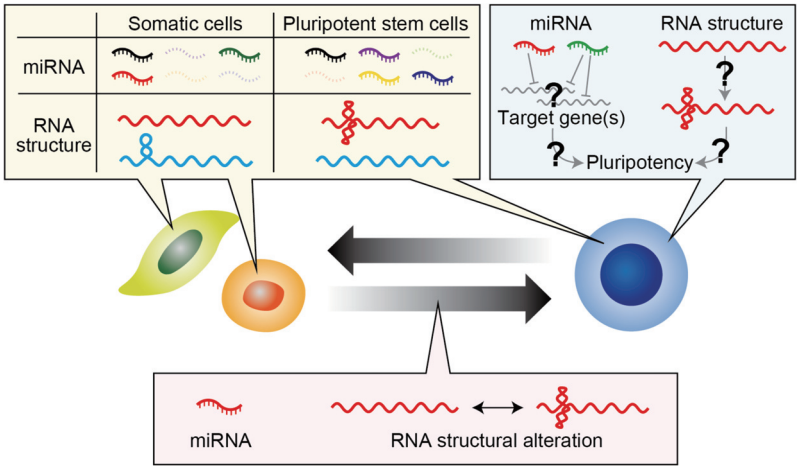


## Elucidation of pluripotent stem cell maintenance mechanism based on regulation of RNA functional structures and cell fate control

Professor, Center for iPS Research and Application,
Kyoto University
**Hirohide Saito**

Technology to control stem cell fate and create desired target cells is important for the next generation of regenerative medicine. However, regenerative medicine using pluripotent stem cells has several challenges. For example, it is necessary to produce pluripotent stem cells safely and efficiently, and to reduce the variation in differentiation induction efficiency caused by the heterogeneity of stem cells. In recent years, the relationship between post-transcriptional regulatory mechanisms and cell-fate regulation by functional RNAs such as microRNAs (miRNAs) has attracted attention. It has become clear that functional RNAs play an important role in maintenance and control of pluripotency. Thus, we aim to identify functional and structural RNA elements that play an important role in human pluripotent stem cells, and elucidate the mechanism by which these RNAs contribute to the cell-fate control. Based on this understanding, we also aim to create cell programming technology that artificial RNA plays an important role from reprogramming to purification of cells, and contribute to regenerative medicine and drug discovery.

● URL: https://sites.google.com/view/hirohidesaitolabjp/home_en

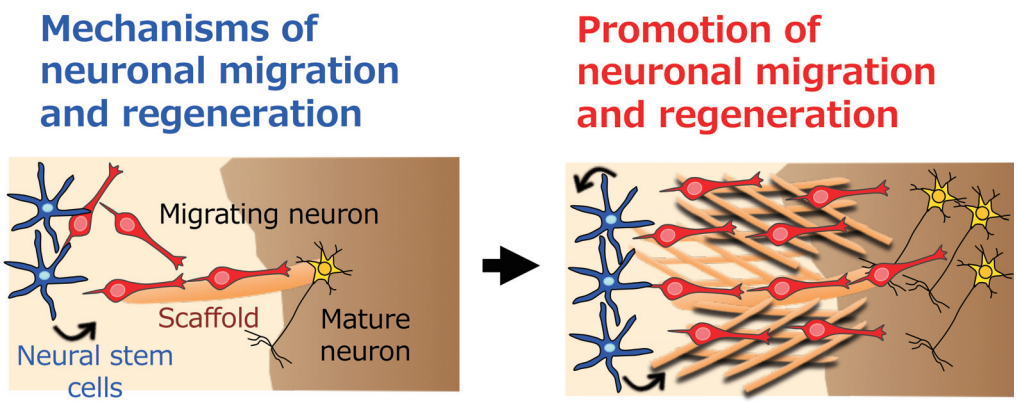


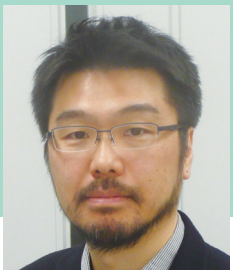

## Strategies for promotion of neuronal migration and regeneration

Professor, Department of Developmental and Regenerative Biology,
Graduate School of Medical Sciences, Nagoya City University
**Kazunobu Sawamoto**

In this project, we will focus on new neurons generated from neural stem cells (NSCs) in the postnatal mouse ventricular-subventricular zone (V-SVZ), and seek to understand the molecular mechanisms for neuronal migration and regeneration in the injured brain. Furthermore, based on these endogenous mechanisms for neuronal regeneration, we will develop novel strategies for treating brain diseases. To understand the spatiotemporal dynamics of migrating new neurons, we will analyze them *in vitro* and *in vivo* using cutting-edge 3D live-imaging techniques. To investigate the molecular machinery responsible for the regenerative processes of neurons in the inured brain, we will perform gene expression analyses including single-cell RNA sequencing. Based on our findings, we will develop methods for promoting the migration and regeneration of new neurons in the injured brain. Since postnatal human brain also contains NSCs in the V-SVZ, this study will provide novel neuronal regeneration strategies using endogenous NSCs for treating brain diseases such as neonatal hypoxia/ischemia.

● URL: http://k-sawamoto.com



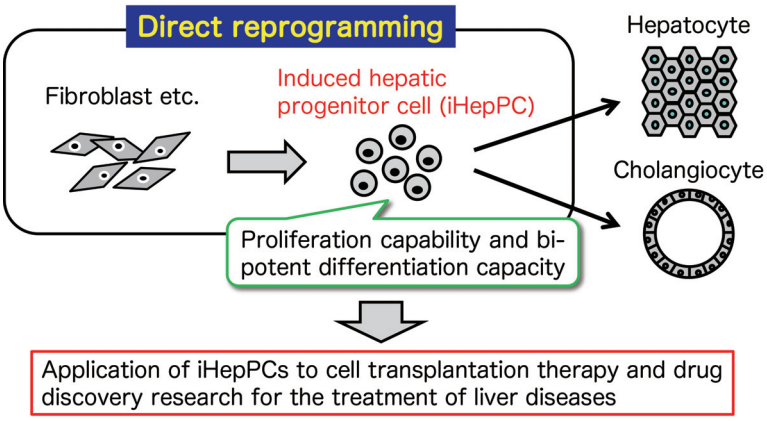


## The study for the development of an innovative regenerative therapy for liver diseases using induced hepatic progenitor cells

Professor, Medical Institute of Bioregulation,
Kyushu University
**Atsushi Suzuki**

Because there is a serious shortage of donor organs for many patients waiting for liver transplantation, it is expected that a liver regeneration therapy based on hepatocyte transplantation will be developed as an alternative approach for treating liver diseases. However, it is still difficult to use hepatocytes in medical applications, because the number of hepatocytes obtained from the liver is limited, and isolated hepatocytes can neither proliferate nor maintain hepatic functions in culture. Thus, another cell source will be required for developing therapeutic strategies for liver diseases. In our previous study, we have identified specific combinations of transcription factors that can directly convert mouse fibroblasts into cells that closely resemble hepatocytes. Based on this finding, we here develop the method for induction of direct reprogramming of human somatic cells into induced hepatic progenitor cells (iHepPCs) that can propagate and continuously produce hepatocytes and cholangiocytes. Moreover, for clinical use of iHepPCs, we also improve the method for generation of iHepPCs and investigate therapeutic effects of iHepPCs *in vivo*. iHepPC-derived hepatocytes will be useful as an alternative to hepatocytes in cell transplantation therapy and drug discovery research for the treatment of liver diseases.

● URL: http://www.bioreg.kyushu-u.ac.jp/labo/orgreg/top.html

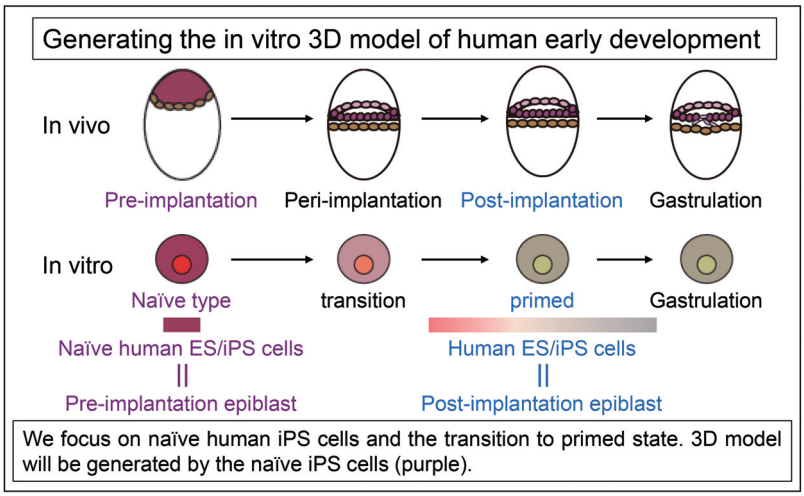


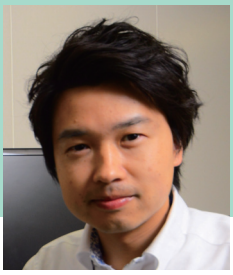

## To clarify the principle of human peri-implantation development using *in vitro* 3D gastruloids

Junior Associated Professor, Center for iPS Research and Application,
Kyoto University
**Yasuhiro Takashima**

Our life starts with one cell called a fertilized egg. The fertilized egg continues to divide and is first divided into cells going to the inner cell mass (ICM) and placenta, and then ICM is destined to cells that make up the fetus (embryonic cells) and non-fetal cells such as yolk sac (extraembryonic cells). An ideal method for differentiation of iPS cells is to differentiate in the same process as human development. However, the human early development during peri-implantation is largely unknown. In this study, naïve human iPS cells which, we previously reported, had a characteristic of pre-implantation epiblasts in the uterus are used to construct human early development *in vitro* and to clarify human development around the implantation stage. Especially, we focus on the transition of epiblast cells from pre-implantation to post-implantation and clarify the molecular mechanisms of human peri-implantation development. To this purpose, we will develop the *in vitro* three-dimensional human model called as gastruloids which mimics the peri-implantation stage using naïve human iPS cells.

● URL: http://www.cira.kyoto-u.ac.jp/j/research/takashima_summary.html



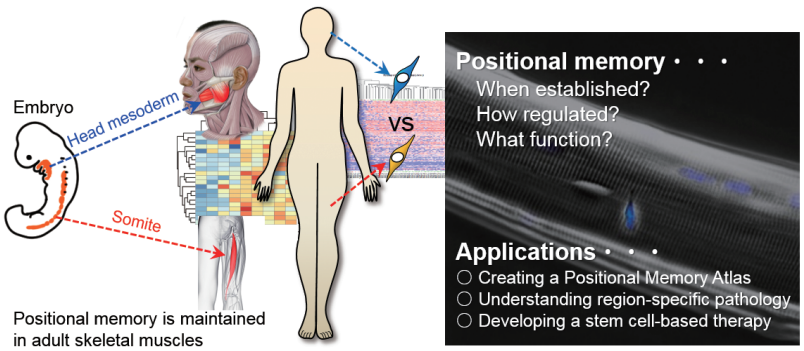


## Development of a positional memory-based therapy for muscle diseases

Associate Professor, Muscle Development and Regeneration,
Institute of Molecular Embryology and Genetics, Kumamoto University
**Yusuke Ono**

Satellite cells are skeletal muscle tissue stem cells located between the basal lamina and sarcolemma of myofibres and play crucial roles in adult muscle repair and regeneration. Satellite cells have a potent regenerative ability, and thus they hold promise in the clinical application for muscle regenerative medicine. In muscle diseases such as muscular dystrophy and age-related sarcopenia, some muscles are particularly affected but not others, e.g. Duchenne muscular dystrophy patients show a severe pathology in limb and trunk muscles but not in head muscle, whereas eye muscles are totally spared. However, the underlying mechanism of the region specific pathology is largely unknown. Recently, we showed that satellite cells retain positional information (positional memory) based on the region and developmental origin in adult skeletal muscle throughout the body in mouse and human. We hypothesized that the individual positional memory influences stemness and regeneration ability in satellite cells. Here, we will attempt to visualize the positional memory based on gene expression profile in satellite cells of different muscles throughout the body, and build a positional memory atlas. Our research will be valuable to better understand the pathophysiology of muscle diseases and to develop a positional memory-based regenerative therapy.

● URL: http://www.imeg.kumamoto-u.ac.jp/bunya_top/muscle_development_and_regeneration/

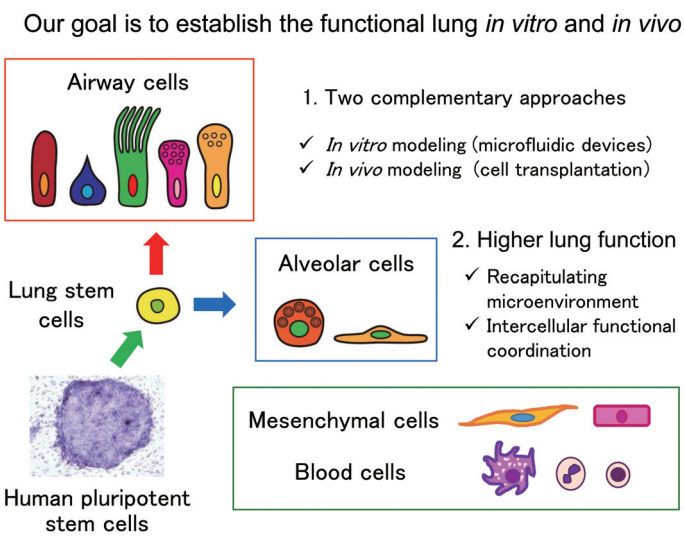


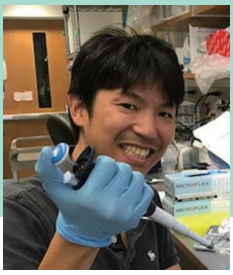

## Generation of lung tissue simulators by human pluripotent stem cells

Associate Professor, Department of Drug Discovery for Lung Diseases,
Kyoto University
**Shimpei Gotoh**

In the era of aging society, refractory lung diseases have increasing impact on each generation and their research has been delayed and regarded as an area of unmet medical needs. Because there has been a gap between animal models and human lung diseases, human-derived cells are expected to provide the research platforms to promote R&D. However, the use of human primary lung cells has been limited technically and ethically. Alternatively, we have established the methods of generating and expanding lung progenitor cells derived from human pluripotent stem cells (hPSCs) and differentiating these progenitor cells into airway and alveolar epithelial cells, overcoming the limitations of the use of human-derived lung cells. However, we are facing a new problem of immaturity of current hPSC-derived models which lack cell-to-cell communications and mechanical stimulations. In this project, we aim at simulating highly organized bona fide lung tissues derived from hPSCs by establishing the platforms of recapitulating cell-to-cell interactions and mechanical stretching by using multi-lineage cells, involving lung epithelial cells, fibroblasts, endothelial cells and/or blood cells.

● URL: http://www.med.kyoto-u.ac.jp/organization-staff/collaboration/#a4





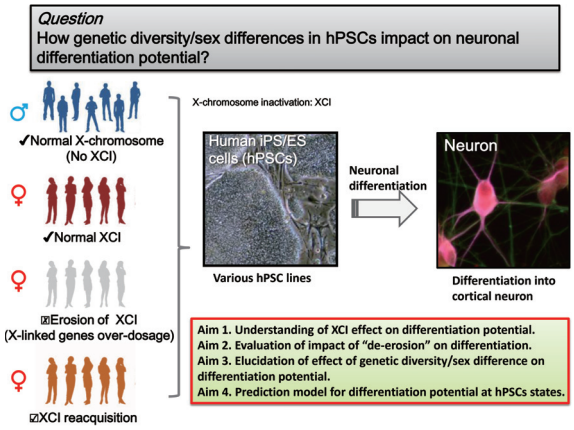
## Understanding and prediction model for neuron development from human pluripotent stem cell based on transcription/epigenetic diversity and sex difference

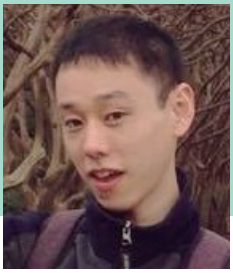
Assistant Professor, Institute of Innovative Science and Technology,
Medical Division, Tokai University
**Atsushi Fukuda**

Human pluripotent stem cells (hPSCs) including embryonic stem cell (ES cell) and induced pluripotent stem cell (iPS cell) have a great promise for drug discovery, regenerative therapy, and disease modeling. Use of human pluripotent stem cells for biomedical researches provides opportunity to investigate how genetic diversity including sex difference affects differentiation potential and disease phenotypes.

In general, one of the two X-chromosomes in female cells is inactivated (X-chromosome inactivation: XCI) to compensate X-linked gene expression dosage between male and female. However, XCI disruption occurs regularly in female hPSCs by long-term culture and results in aberrant X-linked gene reactivation by alteration of epigenetic states. Unfortunately, the erosion of dosage compensation is irreversible phenotype upon differentiation and additional reprogramming. Thus, little is understood about how genetic diversity and sex difference impacts on differentiation potential in hPSC lines.

In our project, using many female hPSC lines with various XCI states, we will understand how XCI states could affect neuronal differentiation potential. Moreover, by comparing of differentiation potential with male hPSC lines and by combination of transcriptome and epigenome analysis, we will try to identify the key genes and/or regulatory regions for controlling the differences for differentiation potential in hPSC lines based on sex difference and genetic diversity. And also, we will try to establish prediction model for differentiation potential at hPSCs states.



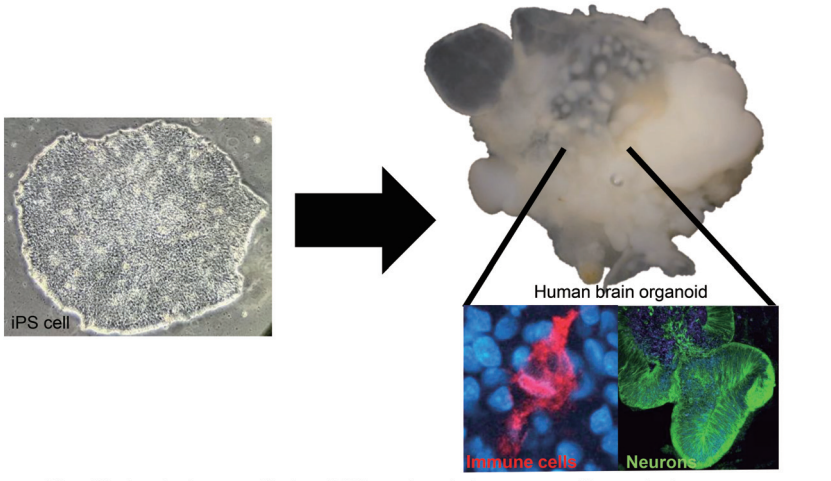



## Development of brain regeneration by the use of vascularized human brain organoid

Assistant Professor, Department of Neurology,
Nara Medical University
**Takeshi Matsui**

Human brains lack the regeneration capacity, and many stroke patients can expect only limited extent of neuronal functional recovery, and they are forced to live a long life with neuronal deficits. It is expected that the method to induce the division of neural stem cells and neuronal differentiation in human brain will contribute to recover neuronal functions of these stroke patients. There is a great difficulty in collecting human brains for the research, and to solve this problem, we will differentiate induced pluripotent stem cells into human brain organoids, which mocks the structure of human brains. Currently, human brain organoids lack the vascular structure, which prevent us from mimicking the brain ischemia, caused by the termination of blood flow. To deal with this issue, we firstly establish vascularized human brain organoids, by which we will further yield new approach to regenerate damaged brain tissue by modulating DNA damage response, mediated by the oxygen concentration.

● URL: http://www.naramed-u.ac.jp/~neu/staff.htm



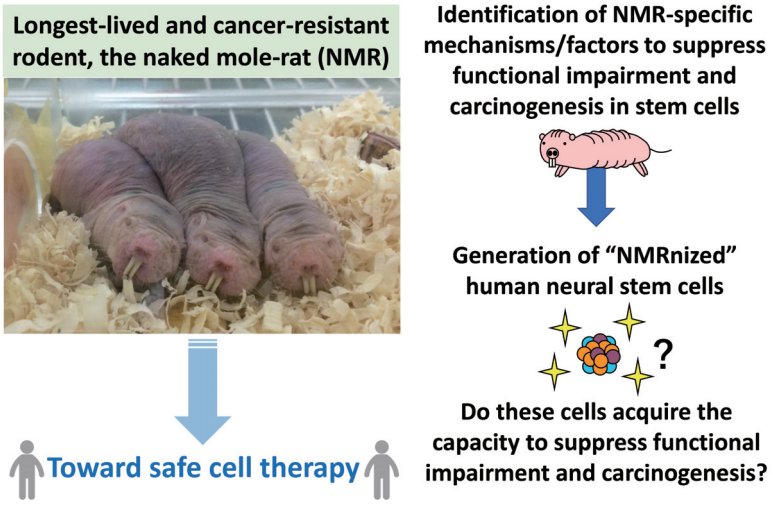

We will induce brain organoids from iPSCs and mock the structure of human brains.
By the use of these brain organoids, investigate the method to regenerate human brains after stroke.

## Development of novel methods to protect stem cells from functional impairment and cancer development using the longest-lived rodent

Associate Professor, Priority Organization for Innovation and Excellence /
Faculty of Life Sciences, Kumamoto University
**Kyoko Miura**

Recently, many researches are energetically performed to realize regenerative medicine using neural stem cells differentiated from induced pluripotent stem (iPS) cells or embryonic stem (ES) cells. To develop novel methods to protect neural stem cells from functional impairment and cancer development, we have focused on the longest-lived and cancer-resistant rodent, the naked mole rat (Heterocephalus glaber). This small, mouse-sized rodent is the longest-lived rodent species with a maximum lifespan of 32 years, exhibiting remarkable cancer-resistance and negligible senescence. Our aim in this project is to elucidate naked mole rat-specific mechanisms/factors to suppress functional impairment and carcinogenesis in stem cells, which would provide useful clues and strategies to suppress functional impairment and carcinogenesis in human neural stem cells. If we can generate "NMRnized" human neural stem cells and succeed to suppress functional impairment and carcinogenesis, it will open the avenue to developing novel methods for improving safety and effectiveness of regenerative therapy.

● URL: https://debalab.org/




## Study of selective survival of gonocytes for the production of qualified Spermatogonial Stem Cell

Associate Professor, Graduate School of Science,
The University of Tokyo
**Soichiro Yamanaka**

Proper self-renewal and differentiation of Spermatogonial Stem Cell (SSC) ensures the lifelong production of sperm, making these cells special among all the cell population in the whole body. So far, most of the works on SSC focus on how they differentiate into sperm. In contrast, under this project, we aim to reveal how SSC is differentiated from its progenitor cell, and how the aging affects the quality of SSC, by harnessing the power of next generation sequencing technique, such as single cell RNA-seq, ATAC-seq, and Hi-C. At present, we found the robust genome wide reprogramming event in embryonic germ cells, which accompanies the relaxation of chromosome 3D structure. Furthermore, we have revealed the high heterogeneity of embryonic germ cells. These results prompt us to elucidate "the molecular mechanism" as well as "the biological significance" of the phenomena above. Eventually, from this analysis, we would like to reveal the molecular determinant which ensures the quality of SSC.

● URL: http://www-siomilab.biochem.s.u-tokyo.ac.jp/index.html