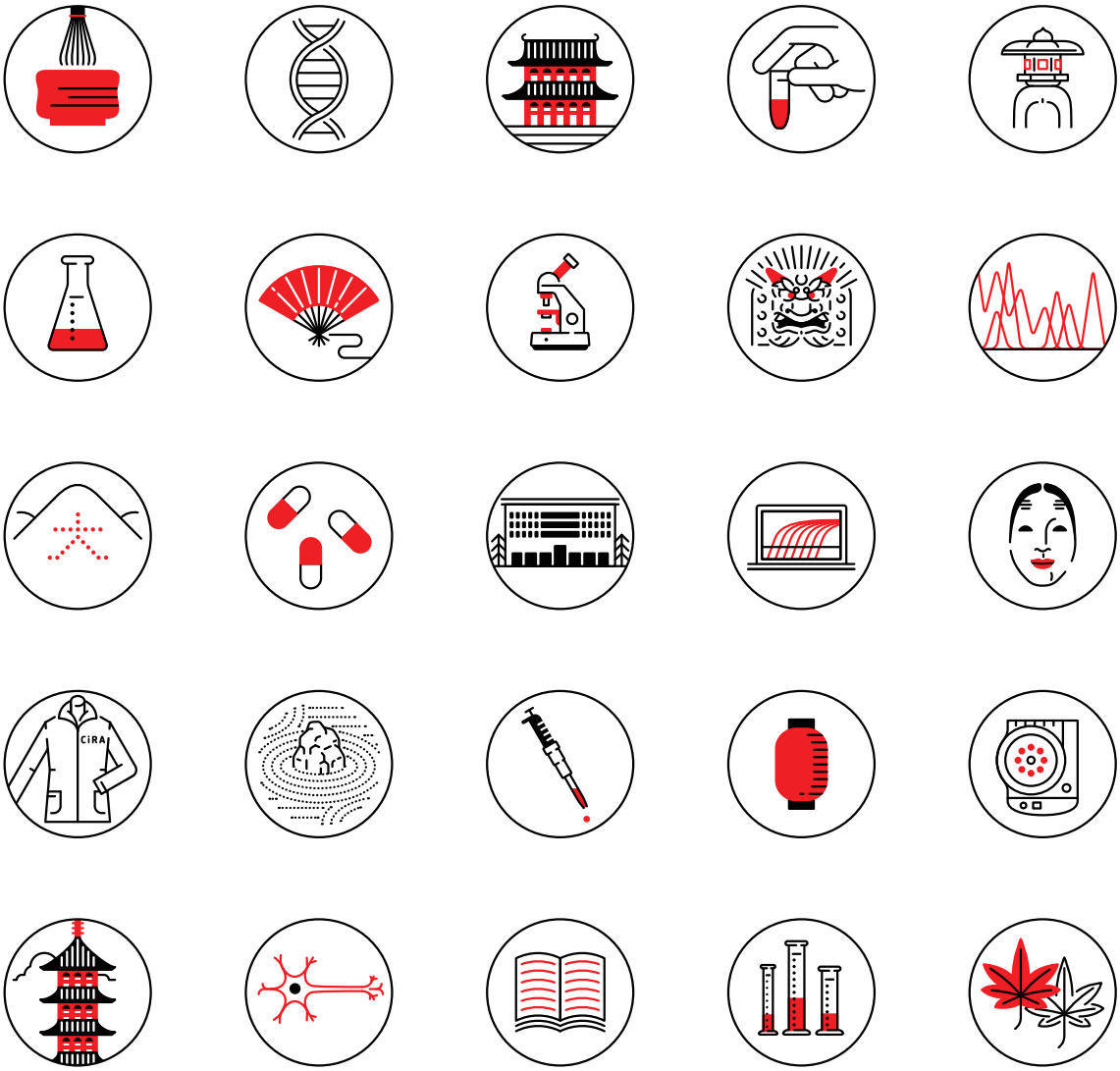
Center for
iPS Cell
Research and
Application,
Kyoto University

Annual Report 2017

CiRA



Contents

*The data in this report reflects activities from April 1, 2017, through March 31, 2018.

Message from the Director

The Director of the Center for
iPS Cell Research and Application (CiRA),
Kyoto University

Shinya Yamanaka

The Center for iPS Cell Research and Application (CiRA), Kyoto University, was founded in 2010 with the purpose of new clinical applications using iPS cells. To support this effort, we completed the construction of our third research building in February 2017. We have CiRA Vision 2030, which states our four primary and long-term goals.

CiRA Vision 2030

1_ Promote the iPS cell stock and iPS cell-based regenerative medicine

2_ Produce new drugs for intractable diseases and personalized medicines using iPS cells

3_ Create new frontiers in the life and medical sciences using iPS cell technology

4_ Provide an outstanding support environment for excellent research and development

One of the most important efforts at CiRA is the iPS Cell Stock for Regenerative Medicine, a project that began in 2013. This stock provides clinical-grade iPS cells to institutions and companies that are developing new medical therapies. We commenced distribution of these cells in August 2015. Cells from this stock were used in a clinical therapy to treat age-related macular degeneration (AMD). The expectation is that cells from the stock will be used to treat many more diseases in the future.

Along with the AMD project, this fiscal year saw a new clinical trial start using iPS cells. CiRA researchers have used patient-derived iPS cells to study fibrodsplasia ossificans progressiva (FOP), which led to a candidate drug. A clinical trial for this drug began in September 2017 at the Kyoto University Hospital. Although separate from the FOP work, T-CiRA, a large-scale collaboration between Takeda Pharmaceutical Co., Ltd. and CiRA, is also expected to bring new drug candidates to clinical trial through iPS cell research.

At the basic science level, using iPS cell reprogramming techniques, this past year CiRA scientists found key factors that lead to the creation of high-quality ES cells, helping clarify how these cells can be used to model development.

It was regrettable that we discovered that one of our scientists had fabricated the data in a scientific paper that was published in February 2017. A thorough investigation by the university identified who was responsible and the depth of the fabrication. As Director, I feel a share of responsibility for the misconduct. To make clear that this behavior is never tolerated, CiRA is implementing new procedures to prevent another occurrence.

Despite this serious setback, we at CiRA remain committed to the new science and medicine that will come from our work on iPS cells, with the ultimate aim of improving patient lives.

March 2018

山中伸弥

Shinya Yamanaka

CiRA Research Departments

Department of Life Science Frontiers

Scientists in this department are exploring new fields of molecular and cellular biology using iPS cells.

Department Head


Shinya Yamanaka
Professor


Yasuhiro Yamada
Professor


Hirohide Saito
Professor


Yoko Hamazaki
Professor


Knut Woltjen
Associate Professor


Makoto Ikeya
Associate Professor


Yoshinori Yoshida
Associate Professor


Yasuhiro Takashima
Junior Associate Professor


Shinji Masui
Junior Associate Professor


Masato Nakagawa
Junior Associate Professor


Keisuke Okita
Junior Associate Professor


Takuya Yamamoto
Junior Associate Professor


Akitsu Hotta
Junior Associate Professor


Akira Watanabe
Assistant Professor


Mitinori Saitou
Professor (Adjunct PI)


Mio Iwasaki
Assistant Professor (Junior PI)

Department of Cell Growth and Differentiation

Cell reprogramming gives access to patient cells for the study of disease etiology and corresponding pathogenic mechanisms. They can also be used for drug discovery.

Department Head


Junya Toguchida
Professor


Noriyuki Tsumaki
Professor


Jun K. Yamashita
Professor


Wataru Fujibuchi
Professor


Haruhisa Inoue
Professor


Kenji Osafune
Professor


Shin Kaneko
Associate Professor

Department of Clinical Application

It is expected that iPS cells will be the basis of new therapies. This department conducts pre-clinical studies on the safety and efficacy of transplanted iPS cell-derived somatic cells.

Department Head


Jun Takahashi
Professor


Koji Eto
Professor


Yoshiya Kawaguchi
Professor


Megumu Saito
Associate Professor


Hidetoshi Sakurai
Associate Professor

Department of Fundamental Cell Technology

With experts in regulation and management of cell manufacturing, this department builds infrastructure and programs that expand the reach of iPS cells.

Department Head


Naoko Takasu
Professor


Isao Asaka
Professor


Naoki Harada
Associate Professor


Kenjiro Konno
Associate Professor

Uehiro Research Division for iPS Cell Ethics

This group studies ethical, legal and social issues related to iPS cells research

Department Head


Misao Fujita
Associate Professor


Yoshimi Yashiro
Associate Professor


Jusaku Minari
Associate Professor

Research Highlight

2017 – 2018

1 Basic Research

Generate high quality ES cells

Derivation of ground-state female ES cells maintaining gamete-derived DNA methylation
Nature

Department of Life Science Frontiers
Yasuhiro Yamada
(Professor)
Takuya Yamamoto
(Junior Associate Professor)

Embryonic stem (ES) cells mimic some of the earliest stage of the embryo. The standard method to produce ES cells is the 2i method. This method blocks the signaling which is necessary for development by inhibiting MEK and Gsk3 protein activity to maintain pluripotency. The quality and stability of the generated ES cells are still to be investigated.

The Yamada and Yamamoto groups examined the DNA methylation status of the imprinting control regions in the mouse ES cell genome, and observed broad DNA demethylation. Moreover, especially in female ES cells, genome imprinting was erased in paternal or maternal genes which plays an important role in development, causing the abnormality in pluripotency. The team improved the method either by attenuating an inhibitor used in the 2i method or by using an alternative inhibitor.

The findings would enable generation and maintenance of high quality pluripotent stem cells, contributing to realizing regenerative medicine as well as to elucidating the early development mechanism of mammals.

Chromosome structure and gene localization characterize pluripotent stem cells

Structural and spatial chromatin features at developmental gene loci in human pluripotent stem cells
Nature Communications

Department of Life Science Frontiers
Takuya Yamamoto
(Junior Associate Professor)

A major factor that determines gene expressions is the chromosome higher-order structure. In pluripotent stem cells, genes which usually shows little expression level can be immediately expressed to respond to differentiation signal.

The Yamamoto group expanded this understanding by comparing chromosome structures of differentiation-related genes and their positions in nuclei between somatic and pluripotent stem cells. They found that the genes with bivalent (i.e. active and inactive) histone modifications tended to co-localize in pluripotent stem cells. These results suggest the chromosome higher-order structure is associated with pluripotency.

The findings are expected to help further understanding of chromosome structure and nuclear localization in cells, which plays an important role in cell reprogramming and differentiation regulation. Moreover, we expect the study would lead to improve the quality of iPS cells and the efficiency of iPS cell generation and their differentiation.

Research Highlight

2017 – 2018

2 Regenerative Medicine

Safety and efficacy of human iPS cell-derived neurons proven in a monkey model

Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model
Nature

MHC matching is efficient for cell engraftment

MHC matching improves engraftment of iPSC-derived neurons in non-human primates
Nature Communications

Department of Clinical Application
Jun Takahashi
(Professor)

Parkinson's disease is caused by the loss of dopaminergic neurons, which results in disabled motor control including tremors and stiffness in the limbs. The Takahashi group has been working on an iPS cell-based therapy to treat the disease by differentiating the cells to dopaminergic neural progenitor cells for transplant. To maximize the number of patients that can benefit from the therapy, they have been preparing for a clinical trial using HLA homozygous iPS cells.

Their follow up in monkey models showed symptom improvement after the transplant of human iPS cell-derived dopaminergic neural progenitor cells. Encouragingly, the cells were engrafted and functioning appropriately and no tumor formation was observed at least in two months after the transplant. Furthermore, the group demonstrated the benefits of using MRI and PET imaging to observe the behavior of the transplanted cells.

To confirm the benefits of using HLA homozygous iPS cells, they compared transplants of MHC (equivalent to HLA for humans) homozygous monkey iPS cell products with transplants of MHC heterozygous iPS cell products. The group found that MHC homozygous-based cell transplants had higher engraftment rate due to the much smaller immune reaction of the host monkey.

Together, the studies are helping finalize the best conditions for the first clinical trial using iPS cells to treat Parkinson's disease.

Research Highlight

2017 – 2018

3 Drug Discovery

New drug for an orphan bone disease

Activin-A enhances mTOR signaling to promote aberrant chondrogenesis in fibrodysplasia ossificans progressiva
The Journal of Clinical Investigation

Department of Cell Growth and Differentiation
Junya Toguchida
(Professor)

Department of Life Science Frontiers
Makoto Ikeya
(Associate Professor)

Fibrodysplasia ossificans progressiva is a disease in which bones are formed in muscle and other soft tissues. When BMP receptors encoded by the mutated ACVR1 gene are stimulated by Activin A, the abnormal BMP signal is transmitted, resulting in heterotopic ossification.

Screening for around 6,800 chemical compounds and conducting animal experiments with patient-derived iPS cells, the Toguchida and Ikeya groups found rapamycin, an immunosuppressant that inhibits mTOR signaling, shows promising preventative effects on the bone formation. Further study elucidated a new molecular mechanism of heterotopic ossification; the Activin A activates the mutated ACVR1, and its encoded ENPP2 protein activates mTOR signaling, causing heterotopic ossification.

To investigate the effectiveness of rapamycin, a clinical trial started at Kyoto University in Sept. 2017.

4 Ethics

Both scientists and general public concern about chimeric brains and gametes

The Japanese generally accept human-animal chimeric embryo research but are concerned about human cells contributing to brain and gametes
STEM CELLS Translational Medicine

Uehiro Research Division for iPS Cell Ethics
Misao Fujita
(Associate Professor)

Some researchers are working on growing human organs in animals by injecting human iPS/ES cells into the animal embryo. Creation of the human-animal chimera for the research have led to concern about the possibility of animals having humanized brains and human-animal hybrids.

The Fujita group conducted a questionnaire survey on the attitude to the chimera research in the Japanese scientific community (n=105) and the public (n=520) in Feb.-Apr. 2016, finding over 80% of scientists and 60% of the public approve chimera generation. However, there is serious concern about the potential contamination of human cells in the chimera brain or gametes. In fact, 45.7% of scientists and 48.5% of the public unconditionally reject the contamination brain and more people (74.3% and 52.1%, respectively) outright reject the contamination in gametes. These results show that efforts must be made to prevent these from happening.

Department of Life Science Frontiers

Creating a new life science with iPS cell technology

Shinya Yamanaka M.D., Ph.D., Professor

Profile

1987 M.D., School of Medicine, Kobe Univ.
1993 Ph.D., Graduate School of Medicine, Osaka City Univ. / Postdoctoral Fellow, Gladstone Institutes
1996 Assistant Professor, Medical School, Osaka City Univ.
1999 Associate Professor, Nara Institute of Science and Technology
2003 Professor, Nara Institute of Science and Technology
2004 Professor, Institute for Frontier Medical Sciences, Kyoto Univ.
2007 Senior Investigator, Gladstone Institutes
2010 Current Position

Publication Highlights

(1) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors
Takahashi K *et al.*
Cell (2006), 126 (4): 663-676

(2) Induction of pluripotent stem cells from adult human fibroblasts by defined factors
Takahashi K *et al.*
Cell (2007), 131 (5): 861-872

(3) Nat1 promotes translation of specific proteins that induce differentiation of mouse embryonic stem cells
Sugiyama H *et al.*
PNAS (2017),
114 (2): 340-345

Summary

iPS cells have the ability to differentiate into almost every cell of the body and to proliferate indefinitely. However, there is still much to learn on how somatic cells are reprogrammed into iPS cells.

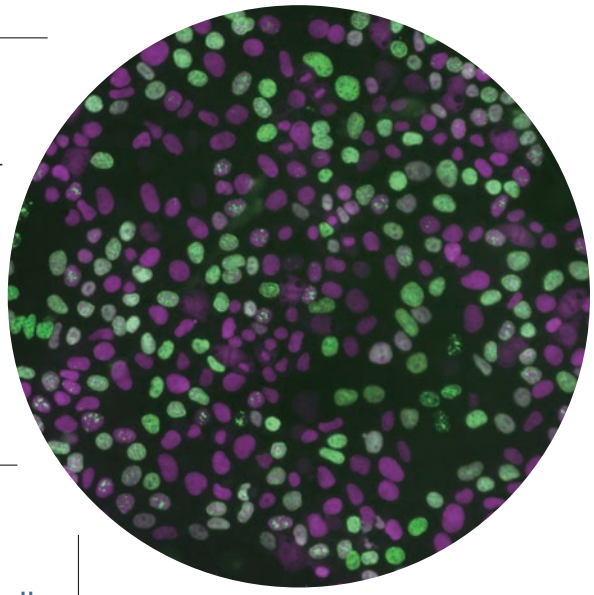
Research Progress

Establishing a global-standard iPS cell culture method

There exists a diverse range of methods to reprogram somatic cells into iPS cells. The diversity includes different source tissues, different cocktails of reprogramming factors and different introduction methods. These differences influence the properties and safety of the iPS cells and the generation efficiency. For drug discovery and regenerative medicine, we are developing safe and effective technology for iPS cell generation along with evaluation methods that can serve as a global standard. So far, we have succeeded in establishing an iPS cell culture method without animal-derived substances.

Members

- Hiroto Hirayama (Assistant Professor)
- Mio Iwasaki (Assistant Professor)
- Yoji Kojima (Assistant Professor)
- Shihori Yokobayashi (Assistant Professor)
- Hayami Sugiyama
- Tsuyoshi Tabata



Immunostaining of human iPS cells
Red: OCT3/4 (indicator of undifferentiated cells),
Green: BrdU (indicator of proliferation), Yellow:merge

Toward a new life science and new medicine

Meanwhile, there are still many puzzles in the reprogramming mechanism to be solved. To maximize clinical application, further research is required to elucidate how pluripotency is maintained. In 2017, we elucidated how the Nat1 gene, which Professor Yamanaka identified in 1997 as a gene essential to the pluripotency of ES cells, is involved.

As a separate project, in January 2018, we welcomed Professor Mitinori Saitou as an adjunct principal investigator, thus establishing a basis for research into the mechanism of human germ cell development using iPS cells.

Together, these projects will contribute to basic research of cell differentiation and reprogramming and the clinical application of iPS cells.

Using iPS cell technology to understand cancer

Yasuhiro Yamada M.D., Ph.D., Professor

Summary

Genes mutations are believed to be a primary determinant of cancer. However, these same mutations do not cause all cells to become cancerous. We are using reprogramming technology to study the causal factors. Our findings have shown that differences in the epigenome are also a major determinant in whether a mutation associated with cancer leads to cancer. In addition, we found the epigenome is also a determinant in the quality of ES cells.

Research Progress

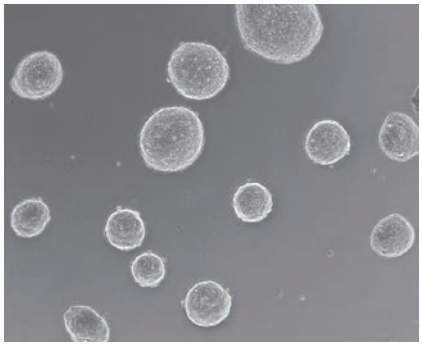
Establishment of iPS cell-like reprogrammed cells

Familial adenomatous polyposis is a cancer caused by mutations in the Apc gene. Using a mouse model of the disease, we generated iPS cell-like reprogrammed cells from colon tumors. By redifferentiating these reprogrammed colon tumor-derived cells (RTCs) into various types of cells, we studied the effect of the mutations. We discovered that the effect varied greatly according to the differentiated cell type. Specifically, we found that secondary tumors were formed only in the intestinal tract of chimeric mice into which RTCs are transplanted.

These findings showed that epigenetic regulation, which determines the cell type, has a great impact on the behavior of oncogenes. They also suggest that the epigenome may be a worthwhile target for cancer prevention.

Stability of epigenetic regulation

We also studied the importance of epigenetic regulation on the generation of mouse ES cells. We discovered that the generation method determines abnormalities in genomic imprinting and that these abnormalities functionally impair the resulting ES cells. We discovered methods that produce high-quality ES cells with few epigenetic abnormalities. These findings should contribute not only to basic research that use mouse ES cells, but also to the realization of effective regenerative medicine.



Mouse ES cells

Members

- Michitada Hirano
- Kenji Ito
- Norihide Jo
- Misato Okada
- Megumi Sakakura
- Hirofumi Shibata
- Yui Shimada
- Yuko Sogabe
- Jumpei Taguchi
- Yukinori Terada
- Tomoyo Ukai
- Masaki Yagi
- Yosuke Yamada

Profile

1997 M.D., School of Medicine, Gifu Univ.
1999 Assistant Professor, Medical School, Gifu Univ.
2002 Ph.D., Graduate School of Medicine, Gifu Univ.
2003 Postdoctoral Fellow, Whitehead Institute for Biomedical Research
2005 Lecturer, Graduate School of Medicine, Gifu Univ.
2008 Associate Professor, Graduate School of Medicine, Gifu Univ.
2010 Professor, CiRA, Kyoto Univ.
2017 Professor, The Institute of Medical Science, The Univ. of Tokyo

Publication Highlights

(1) Derivation of ground-state female ES cells maintaining gamete-derived DNA methylation
Yagi M *et al.*
Nature (2017), 548 (7666): 224-227

(2) Cellular context-dependent consequences of Apc mutations on gene regulation and cellular behavior
Hashimoto K *et al.*
PNAS (2017), 114 (4): 758-763

(3) Premature termination of reprogramming in vivo leads to cancer development through altered epigenetic regulation
Ohnishi K *et al.*
Cell (2014), 156 (4): 663-677

Department of Life Science Frontiers

Visualizing cell types and altering their fate

Hirohide Saito Ph.D., Professor

Profile

1997 Graduated from Faculty of Engineering, The Univ. of Tokyo
2002 Ph.D., Graduate School of Engineering, The Univ. of Tokyo
2005 Assistant Professor, Graduate School of Biostudies, Kyoto Univ.
2010 Associate Professor, The HAKUBI Project, Kyoto Univ.
2011 Associate Professor, CiRA, Kyoto Univ.
2014 Current Position

Publication Highlights

(1) Protein-driven RNA nanostructured devices that function in vitro and control mammalian cell fate
Shibata T *et al.*
Nature Communications (2017), 8 (1): 540

(2) Cell-type-specific genome editing with a microRNA-responsive CRISPR-Cas9 switch
Hirosawa M *et al.*
Nucleic Acids Research (2017), 45 (13): e118

(3) Monitoring and visualizing microRNA dynamics during live cell differentiation using microRNA-responsive non-viral reporter vectors
Nakanishi H *et al.*
Biomaterials (2017), 128: 121-135

Summary

To use iPS-derived cells in the clinic, it is essential to establish purification techniques. Noticing the potential of microRNA and protein, whose expression varies with cell type, we developed a system that regulates gene expressions using these biomolecules.

Research Progress

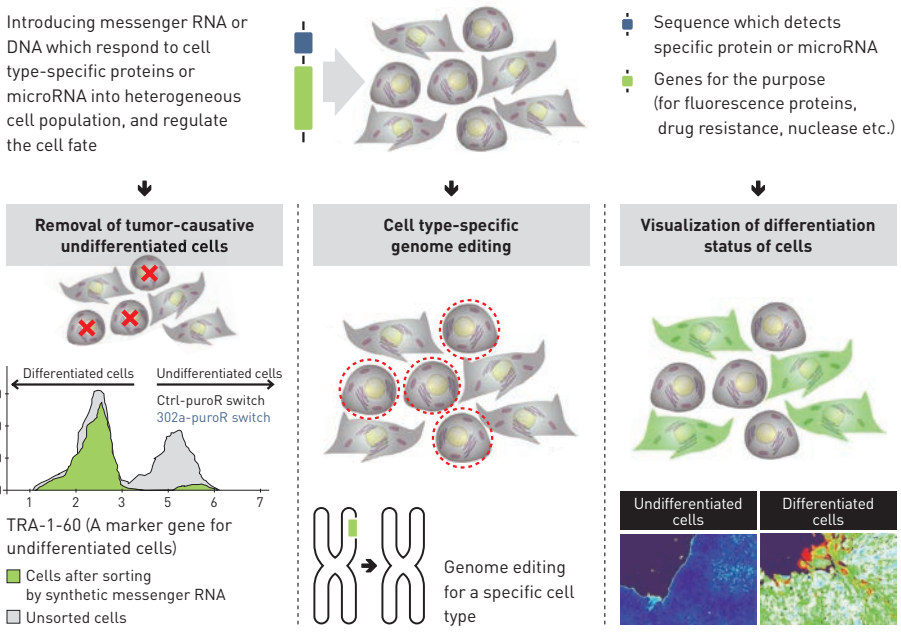
Technology for cell fate regulation

To distinguish target cells from other cell populations, we have developed a system that detects differences in microRNA expressions. This system enables to manipulate the expression of fluorescent proteins according to the differentiation stage. We have also developed messenger RNA that can alter their expression pattern in response to specific proteins. In addition, we have developed RNA / protein complexes that induce cell death in the presence of specific proteins. By detecting the intracellular environment with our RNA technology, it will become possible to visualize the differentiation process and to edit the genome of selected cells in a wide population.

Members

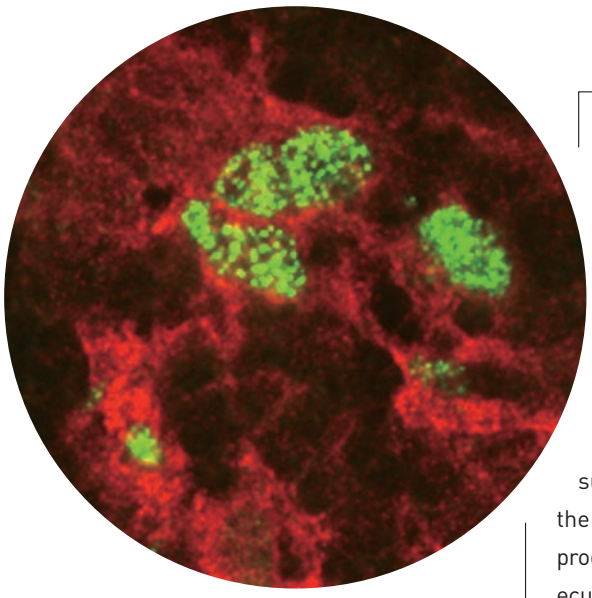
- Yoshihiko Fujita (Assistant Professor)
- Sae Akamine
- Kazuma Fukuya
- Karin Hayashi
- Moe Hirosawa
- Shunsuke Kawasaki
- Kaoru Richard Komatsu
- Sora Matsumoto
- Satoshi Matsuura
- Megumi Mochizuki
- Ruriko Nagashima
- Hideyuki Nakanishi
- Miho Nishimura
- Hirohisa Ohno
- Hiroki Ono
- Shunsuke Wada
- Kuang Yi
- Moe Yokoshi

Using biomolecules to regulate cell fate



Controlling and rebuilding the immune system

Yoko Hamazaki Ph.D., Professor



"Teacher" cells in the thymic medulla function to prevent T cells from an autoimmune response.
Red: Claudin (expressed in teacher cells)
Green: Aire gene

Summary

T cells directly attack infected cells, tumor cells, and foreign cells, as well as stimulate B cells to produce antibodies. Importantly, T cells do not attack our own cells, because supporting cells (Teacher cells) educate T cells to do so during their development in the thymus. We have identified the stem cells that generate these supporting cells in the thymus and found that their activity begins to decline in advance of the age-related thymic atrophy. Based on these findings, we study the mechanisms of thymic involution and T cell aging and try to develop novel strategies to reconstitute thymic function using iPS cell technologies.

Research Progress

The mechanisms to educate and control immune cells

We characterized thymic supporting cells that prevent autoimmune reactions caused by T cells[(1)(2)(3)]. We have also found that supporting cells in bone marrow have the function to regulate and control the production of B cells in response to molecules that stimulate erythrocyte production [Ito *et al., Cell Structure and Function* (2018)]. We wish to clarify how the production and function of immune cells are ensured and disrupted.

Intervention in immunosenescence and age-related diseases

Despite the importance of thymus in immunity, its activity declines rapidly after adolescence (thymic involution), which is supposed to play a significant role in immunosenescence and subsequent age-related diseases. We discovered that, in advance of thymus involution, stem cell activities of thymic supporting cells rapidly declines soon after birth[(1)(2)]. By investigating the mechanisms of this process, we aim to develop methods that prevent thymic involution and immunosenescence, thereby boosting immune functions in elderly clinical settings.

Members

- Chiyomi Inoue
- Takeshi Ito
- Aiko Kato
- Miho Sekai
- Yuko Tanba
- Jianwei Wang

Profile

1995 Graduated from Faculty of Applied Biological Sciences, Hiroshima Univ.
1997 M.S., Graduate School of Medicine, Univ. of Tsukuba
1997 Clinical Development Dept., KIRIN Brewery Co., Ltd.
2003 Ph.D., Graduate School of Medicine, Kyoto Univ.
2010 Associate Professor, Graduate School of Medicine, Kyoto Univ.
2017 Current Position / Professor, Graduate School of Medicine, Kyoto Univ.

Publication Highlights

(1) Medullary thymic epithelial stem cells: Role in thymic epithelial cell maintenance and thymic involution
Hamazaki Y *et al.*
Immunological Reviews (2016), 271(1): 38-55

(2) Medullary thymic epithelial stem cells maintain a functional thymus to ensure lifelong central T cell tolerance
Sekai M *et al.*
Immunity (2014), 41(5): 753-761

(3) Medullary thymic epithelial cells expressing Aire represent a unique lineage derived from cells expressing claudin
Hamazaki Y *et al.*
Nature Immunology (2007), 8 (3): 304-311

Department of Life Science Frontiers

Engineering genomes and cell functions

Knut Woltjen Ph.D., Associate Professor

Profile

1998 Graduated from Univ. of Alberta
2001 Researcher, School of Medicine, Kyushu Univ.
2006 Ph.D., Dept. of Biochemistry and Molecular Biology, Univ. of Calgary / Postdoctoral Research Fellow, Mount Sinai Hospital, Samuel Lunenfeld Research Institute
2009 Facility Manager, The Hospital for Sick Children, Ontario Human iPS Cell Facility
2010 Assistant Professor, CiRA, Kyoto Univ.
2013 Associate Professor, The HAKUBI Project, Kyoto Univ. / Current position

Publication Highlights

(1) Microhomology-assisted scarless genome editing in human iPSCs
Kim S-I, Matsumoto T *et al.*
Nature Communications (2018), 1–14

(2) Engineering the AAVS1 locus for consistent and scalable transgene expression in human iPSCs and their differentiated derivatives
Oceguera-Yanez F, Kim S-I *et al.*
Methods (2016), 101: 43–55

(3) KLF4 N-terminal variance modulates induced reprogramming to pluripotency
Kim S-I *et al.*
Stem Cell Reports (2015), 4: 727–743

Summary

Pioneering genome engineering technologies in human iPS cells for nearly a decade, the Woltjen Laboratory develops cell engineering strategies for disease modelling and improved stem cell therapies. Employing molecular biology tools such as DNA transposons, programmable nucleases, and site-specific recombinases, we purposefully edit the human genome. Our methods have been applied to enhance reprogramming, muscle and neural differentiation, as well as correct mutations causing metabolic diseases such as diabetes.

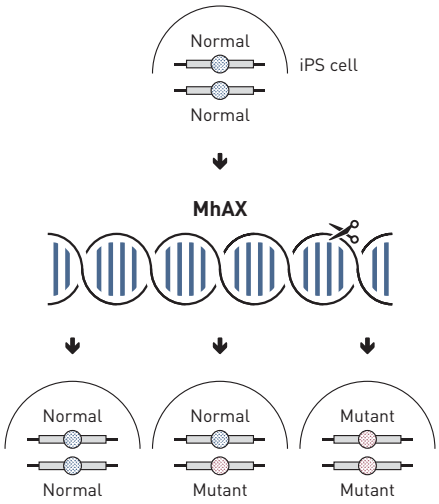
Research Progress

Tools for precise genome editing and understanding cellular reprogramming

Single nucleotide polymorphisms (SNPs) are common variations in the human genome. In order to address the role of SNPs in disease, we developed new technology for "scarless" single-base gene editing in iPS cells. Our new method attains high efficiency gene editing via antibiotic enrichment, with the ability to scarlessly remove antibiotic markers from the genome through engineered microhomology and endogenous microhomology-mediated end joining (MMEJ) repair. Additionally, our method can simultaneously generate all possible allelic combinations at the target locus, simplifying any homozygous gene editing steps required to correct or study recessive diseases.

Our research into somatic cell reprogramming mechanisms uses *piggyBac* transposon technology. Our studies revealed a fundamental difference in cloned Klf4 that affects protein stoichiometry, influencing both the initiation and stabilization of true iPS cells. Using this system, we have recently identified transcriptional regulators which suppress the growth of partially reprogrammed cells and streamline the establishment of induced pluripotency.

Simultaneously derive an isogenic iPS cell panel



Members

- Mitchell Braam
- Janin Grajcarek
- Ryoko Hirohata
- Mayumi Ikeda
- Harunobu Kagawa
- Shin-Il Kim (Specially-Appointed Assistant Professor)
- Yanjun Lan
- Tomoko Matsumoto
- Thomas Luc Maurissen
- Michiko Nakamura
- Jose Fabian Oceguera Yanez
- Anika Reinhardt

Using disease-specific iPS cells to reveal the cause of bone and cartilage diseases

Makoto Ikeya Ph.D., Associate Professor

Summary

We are researching new therapies for diseases related to bone and cartilage using patient-derived iPS cells.

Research Progress

Bone and cartilage diseases lacking radical therapeutic options

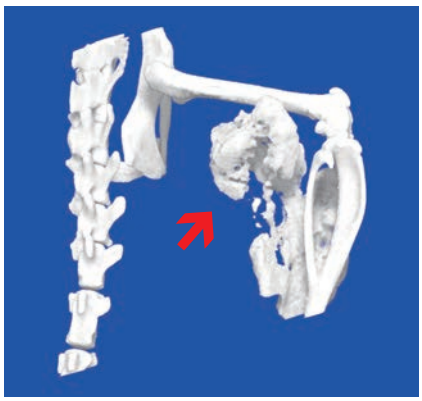
Among intractable bone diseases, fibrodysplasia ossificans progressiva (FOP) is a progressive form of heterotopic ossification in which bones are gradually formed in the fibrous connective tissue such as the muscles, the fascia, the tendons, and the ligaments. Patients lose mobility in the spine, the chest, the limb joints, and elsewhere, severely impairing daily activities. The disease affects around one in two million people, and has no radical therapy at present.

Start of a clinical trial to test the efficacy of rapamycin

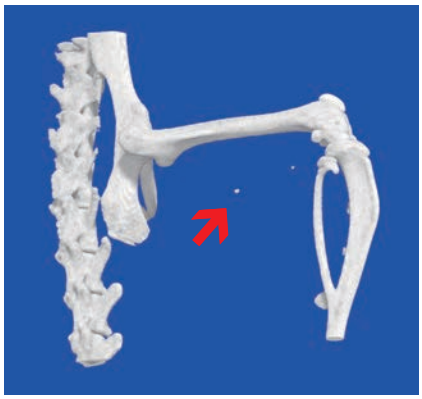
We found rapamycin (Sirolimus) prevents the abnormal bone growth in a FOP-patient iPS cell model, suggesting it could inhibit disease progression. Rapamycin is a drug already marketed as an immunosuppressant. Our findings led to a clinical trial conducted under the chief guidance of Professor Toguchida.

Elsewhere, we are working on modeling the pathology of diseases caused by abnormalities in neural crest cells and developing differentiation methods for cells difficult to induce. By deploying these experimental assays, we aim to overcome disease from the standpoint of basic research.

Control group



Rapamycin administrated group



Upper figure, FOP mouse model with heterotopic bone formation induced by FOP-iPS cells. Lower figure, Administration of rapamycin suppresses the heterotopic bone formation.

Members

- Yayoi Toyooka (Assistant Professor)
- Nicholas James Boyd-Gibbins
- Daisuke Kamiya (Specially-Appointed Assistant Professor)
- Yukiko Nakagawa
- Taiki Nakajima
- Toshiko Sato
- Mitsuaki Shibata
- Mika Suga
- Mai Tanaka
- Mei Terashima
- Naoki Yamada
- Chengzhu Zhao

Profile

1996 Graduated from Faculty of Science, Kyoto Univ.
2001 Ph.D., Graduate School of Science, Kyoto Univ. / Researcher, RIKEN
2007 Research Fellow of Basic Science, RIKEN
2009 Associate Professor, Institute of Molecular Embryology and Genetics, Kumamoto Univ.
2010 Researcher, Institute for Frontier Medical Science, Kyoto Univ.
2011 Current Position

Publication Highlights

(1) Activin-A enhances mTOR signaling to promote aberrant chondrogenesis in fibrodysplasia ossificans progressiva
Hino K *et al.*
Journal of Clinical Investigation (2017), 127 (9): 3339-3352

(2) Neofunction of ACVR1 in fibrodysplasia ossificans progressiva
Hino K *et al.*
PNAS (2015), 112 (50): 15438-15443

(3) Derivation of mesenchymal stromal cells from pluripotent stem cells through a neural c rest lineage using small molecule compounds with defined media
Fukuta M *et al.*
PLOS ONE (2014), 9 (12): e112291

Department of Life Science Frontiers

Using heart and blood cells for regenerative medicine and drug discovery research

Yoshinori Yoshida M.D., Ph.D., Associate Professor

Profile

1997 M.D., Faculty of Medicine, Kyoto Univ.
1999 Dept. of Cardiovascular disease, Social Insurance Kokura Kinen Hospital
2006 Assistant Professor, Dept. of Cardiovascular Disease, Kyoto University Hospital
2007 Ph.D., Graduate School of Medicine, Kyoto Univ.
2008 Research Fellow, Dept. of Stem Cell Biology, Institute for Frontier Medical Sciences, Kyoto Univ.
2009 Assistant Professor / Lecturer, iCeMS, Kyoto Univ.
2010 Junior Associate Professor, CiRA, Kyoto Univ.
2016 Current Position

Publication Highlights

(1) Induced pluripotent stem cells 10 years later: For cardiac applications
Yoshida Y, Yamanaka S
Circulation Research (2017), 120 (12): 1958-1968

(2) Epigenetic variation between human induced pluripotent stem cell lines is an indicator of differentiation capacity
Nishizawa M *et al.*
Cell Stem Cell (2016), 19 (3): 341-354

(3) Efficient detection and purification of cell populations using synthetic microRNA switches
Miki K *et al.*
Cell Stem Cell (2015), 16 (6): 699-711

Summary

We have shown that optimizing the maturity of ES / iPS cell-derived cardiomyocytes improves the engraftment rate and survival after engraftment. We are also generating models and screening drugs for diseases of the heart and blood.

Research Progress

Regenerative medicine with iPS cell-derived cardiomyocytes

We reported that optimizing the maturity of human iPS cell-derived cardiomyocytes contribute to their efficient engraftment in mice with myocardial infarction in vivo. We also conducted screenings to find compounds that improve the engraftment rate.

Disease models using disease-specific iPS cells

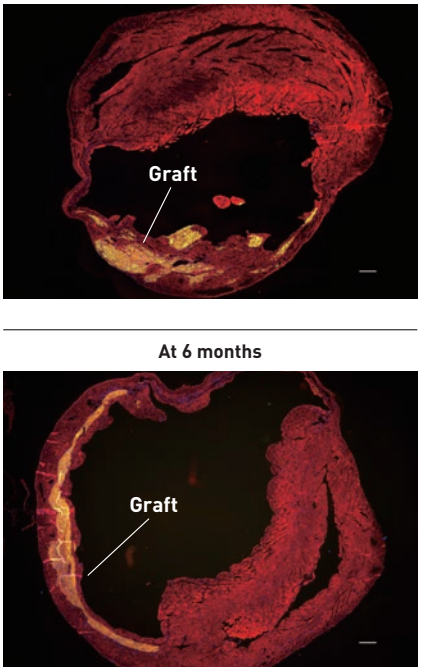
Using gene editing technology, we established a model of hypertrophic cardiomyopathy from iPS cells. We also made use of cardiomyocytes derived from long QT syndrome Type 1-specific iPS cells to construct an arrhythmogenic detection assay that is applicable for high-throughput screening using a membrane-potential-sensitive dye. Other disease models include myelodysplastic syndrome and heritable sideroblastic anemia.

Inducing maturation of differentiated cells

Cardiomyocytes differentiated from iPS cells are immature, which compromises their use in research. We are developing methods to control the cell maturation.

Members

- Kenji Miki (Assistant Professor)
- Kazuhisa Chonabayashi
- Takeshi Ego
- Rie Fujii
- Takeshi Hatani
- Azusa Inagaki
- Julia Junghof
- Manabu Kasamoto
- Misato Koakutsu
- Antonio Lucena-Cacace
- Ai Mieda
- Yuki Morimoto
- Megumi Narita
- Misato Nishikawa
- Aya Ogura
- Chikako Okubo
- Masako Sasaki
- Ikue Sasozaki
- Kazuma Shinno
- Kazuma Suda
- Tadashi Takaki
- Tetsuya Takada
- Ming-Heng Tsai
- Yoko Uematsu
- Masayuki Umeda
- Hidaka Yokota
- Masatoshi Yoshimoto



Engraftment of transplanted iPS cell-derived cardiomyocytes in heart tissue of a mouse with myocardial infarction [immunostained by antibodies against luciferase (yellow)]

Early development and regenerative medicine using naïve human iPS cells

Yasuhiro Takashima M.D., Ph.D., Junior Associate Professor

Summary

The pluripotency of pluripotent stem cells (PSCs) has two states: naïve, which resembles the fertilized egg state, and primed, which resembles a more advanced developmental stage. It is thought that naïve PSCs can differentiate into a wider range of cells with a higher differentiation efficiency. We successfully reset human iPS cells into the naïve state and are now visualizing the early stages of development in vitro using these cells.

Research Progress

Human naïve iPS cells and regenerative medicine

Of the two states, mouse PSCs show naïve properties, and human PSCs show primed properties. We have reported a system that can reset human PSCs to the naïve state. Naïve PSCs are expected to have higher pluripotency and differentiation efficiency. Our aim is to realize regenerative medicine using human naïve iPS cells.

Human naïve iPS cells and early development

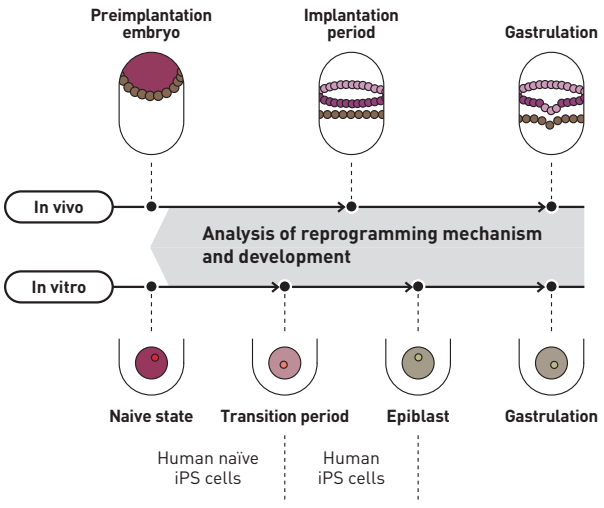
Human life begins with a fertilized egg. As the fertilized egg continues to divide, the cells destined to become the placenta are the first to have their specific fate determined, followed by the cells that make up the fetus (embryonic cells) and non-fetal cells such as the amnion and the yolk sac (extra-embryonic cells).

The ideal differentiation methods from iPS cells will mimic the differentiation process during normal development. We are visualizing the early developmental process in vitro using reset human iPS cells. At the same time, we are also studying naïve iPS cells of marmoset, which resembles the developmental pattern of humans.

Members

- Mayumi Ikeda
- Shingo Io
- Belinda Yunita Kaswandy
- Shungo Mochizuki
- Takumi Okubo
- Katsunori Semi
- Akiko Shimada
- Rika Takashima
- Mai Ueda

Research scheme using next-generation human iPS cells



- Recapitulate human early development in vitro to analyze the reprogramming mechanism.
- Develop differentiation methods to realize regenerative medicine.

Profile

1998 M.D., School of Medicine, Kobe Univ. / Dept. of Internal Medicine, Kobe University Hospital
1999 Dept. of Internal Medicine, Nishiwaki City General Hospital
2007 Ph.D., Graduate School of Medicine, Kobe Univ. / Research Associate, Center for Developmental Biology, RIKEN / Researcher, Wellcome Trust-MRC Stem Cell Institute, Univ. of Cambridge
2015 Current Position

Publication Highlights

(1) Resetting transcription factor control circuitry towards ground state pluripotency in human
Takashima Y *et al.*
Cell (2014), 158 (6): 1254-1269

(2) Discrimination of stem cell status after subjecting cynomolgus monkey pluripotent stem cells to naïve conversion
Honda A *et al.*
Scientific Reports (2017), 7: 45285

(3) Surface markers guide the journey towards Naïve pluripotency
Karagiannis P, Takashima Y
Cell Stem Cell (2017), 20 (6): 237-238

Department of Life Science Frontiers

The impact of transcription factors on cell reprogramming

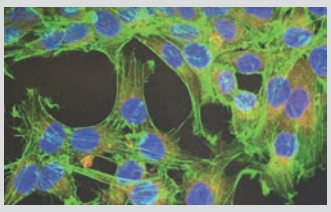
Shinji Masui Ph.D., Junior Associate Professor

Profile

1996 Graduated from School of Science, Hokkaido Univ.
2001 Ph.D., Graduate School of Science, The Univ.of Tokyo / Researcher, RIKEN
2006 Section Chief, Dept. of Regenerative Medicine, Research Institute National Center for Global Health and Medicine
2011 Junior Associate Professor, CiRA, Kyoto Univ.
2018 Associate Professor, Graduate School of Medical Science, Kyoto Prefectural Univ. of Medicine

Publication Highlights

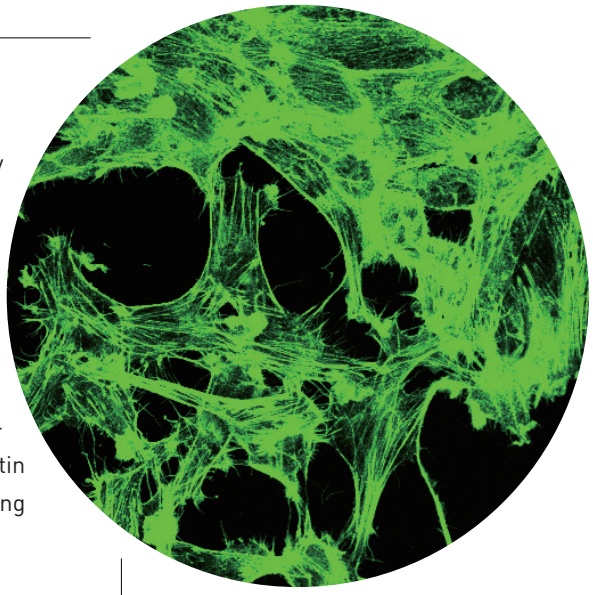
(1) Srf destabilizes cellular identity by suppressing cell-type-specific gene expression programs
Ikeda T *et al.*, *Nature Communications* (2018) ,9 (1) : 1387
(2) OVOL2 maintains the transcriptional program of human corneal epithelium by suppressing epithelial-to-mesenchymal transition
Kitazawa K *et al.*, *Cell Reports* (2016), 15 (6): 1359-1368
(3) Transcription factors interfering with dedifferentiation induce cell type-specific transcriptional profiles
Hikichi T *et al.*
PNAS (2013), 110 (16): 6412-6417



F-actin (green), G-actin (red), and nuclei (blue) in mouse hepatoblasts

Summary

When cells differentiate, they acquire a specific nature (cell identity). From the perspective of cell reprogramming, the genes that determine cell identity can be seen as hindrances to cell reprogramming. Following a comprehensive search, we found the β-actin gene inhibits the reprogramming of multiple cell types.



Fibrous actin (F-actin) in mouse neural progenitor cells

Research Progress

Cell type-specific genes inhibit cell reprogramming

A set of master transcription factors (Yamanaka factors) have been shown to promote cell reprogramming. Similarly, different sets of master transcription factors maintain the identity of different cell types to inhibit reprogramming. Using this logic, we sought genes that inhibit reprogramming.

Suppression of cell identity as a requirement for reprogramming

We identified Actb (β-actin gene) as reprogramming inhibitory gene that is common to many cell types. When β-actin is suppressed, the downstream transcription factor Srf is activated, resulting in the suppression of many cell type-specific genes and making the cell vulnerable to reprogramming. Srf is expressed endogenously in all cell types and is activated by various signals from the extracellular environment. Our findings suggest that great changes in the extracellular environment can activate Srf to destabilize cell identity. These findings give us a clearer understanding on the molecular events that act as roadblocks to cell reprogramming. Our future challenge is to investigate whether this Srf effect can be used to enhance cell reprogramming efficiencies.

Members

- Ryouji Mabuchi
- Tatsuyuki Matsudaira
- Rei Murakami
- Takumi Nakano
- Katsura Noda
- Yoshiki Okita
- Chihiro Yagiu

Unlocking the somatic cell reprogramming mechanism by uncovering protein functions

Masato Nakagawa Ph.D., Junior Associate Professor

Summary

We are investigating the activity of the Yamanaka factors to study the reprogramming mechanism. Also, to improve the reprogramming efficiency, we have developed a new method for introducing the factors into cells and are working on feeder-free cultures.

Research Progress

Understanding the somatic cell reprogramming mechanism

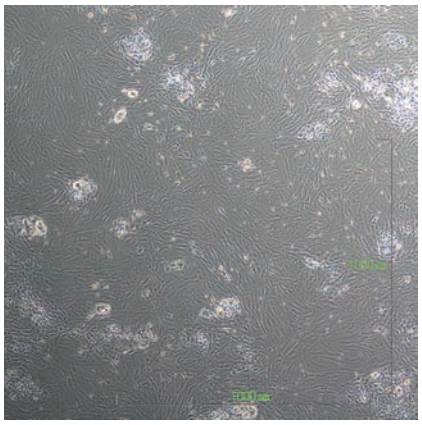
The MYC gene family was identified as an oncogene family and there is growing attention on its multiple functions. c-Myc is one of the Yamanaka factors (Sox2, Oct3/4, Klf4, and c-Myc). However, we found that in human cells, MYCL, another MYC gene, has a greater ability to efficiently generate iPS cells than c-Myc, but the reason is unclear.

In this FY, we showed reprogramming with Sendai virus and RNA improves the reprogramming efficiency to >10% compared to 0.1% with standard episomal vectors. This higher efficiency will help us uncover the molecular functions of MYC and other reprogramming factors.

Efficient culture method for human iPS cells

Conventionally, animal-derived feeder cells were used to culture iPS cells. For clinical-grade cells like those in the iPS Cell Stock, using the animal-derived feeder cells should be avoided.

In this FY, we developed a feeder-free system that matches the cell survival rate and marker expression with systems using animal-derived feeder cells. In the feeder-free culture method, laminin is used as a coating to promote iPS cell adhesion. We are investigating the mechanism through which laminin contributes to the maintenance of pluripotency.



Human fibroblasts undergoing reprogramming. Colonies are thought to contain cells that will later become iPS cells.

Members

- Chiaki Akifuji
- Yu-Shen Cheng
- Rie Fujii
- Yuka Kawahara
- Jun Mukougawa
- Miyuki Ono
- Chiho Sakurai
- Yoko Uematsu

Profile

1997 Graduated from Faculty of Science and Technology, Sophia Univ.
2002 Ph.D., Division of Signal Transduction, Nara Institute of Science and Technology (NAIST) / Research Fellow, Graduate School of Medicine, Nagoya Univ.
2004 Research Associate, Research and Education Center for Genetic Information, NAIST
2005 Assistant, Institute for Frontier Medical Sciences, Kyoto Univ.
2008 Assistant Professor, iCeMS, Kyoto Univ.
2009 Junior Associate Professor, iCeMS, Kyoto Univ.
2010 Current Position

Publication Highlights

(1) Function of MYC in iPS cell induction (in Japanese)
Nakagawa M
Experimental Medicine (2018), 36: 534–538

(2) Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model
Kikuchi T *et al.*
Nature (2017), 548: 592–596

(3) Nat1 promotes translation of specific proteins that induce differentiation of mouse embryonic stem cells
Sugiyama H *et al.*
PNAS (2017), 114: 340-345

Department of Life Science Frontiers

Elucidate the reprogramming mechanism and contribute to the medical applications of iPS cells

Keisuke Okita Ph.D., Junior Associate Professor

Profile

2000 Graduated from Faculty of Veterinary Medicine, Hokkaido Univ.
2004 Ph.D., Graduate School of Medical Sciences, Kumamoto Univ. / Research Fellow, CREST, Japan Science and Technology Agency
2008 Assistant Professor, iCeMS, Kyoto Univ.
2010 Current Position

Publication Highlights

(1) Srf destabilizes cellular identity by suppressing cell-type-specific gene expression programs
Ikeda T *et al.*
Nature Communications (2018), 9: 1387

(2) Screening of human cDNA library reveals two differentiation-related genes, HHEX and HLX, as promoters of early phase reprogramming toward pluripotency
Yamakawa T *et al.*
Stem Cells (2016), 34 (11): 2661-2669

(3) Generation and characterization of induced pluripotent stem cells from aid-deficient mice
Shimamoto R *et al.*
PLOS ONE (2014), 9 (4): e94735

Summary

Understanding the reprogramming mechanism is crucial for the medical application of iPS cells. We have identified genes that affect the reprogramming efficiency. Collaborating with the Masui lab, we are researching ways that destabilize cell identity for better reprogramming.

Research Progress

Analysis of reprogramming mechanism

Elucidating the reprogramming mechanism is essential for generating higher-quality iPS cells. We are tackling this task using gene-based approaches. So far, we have investigated over 2,000 genes and found that two genes, HLX and HHEX, improve the reprogramming efficiency significantly.

In this FY, we continued with the gene screening and identified 14 genes that improve the reprogramming efficiency, but also 63 genes that lower it. By analyzing these genes, we aim to illuminate key aspects of the reprogramming mechanism.

Collaborating with the Masui lab, we also researched the mechanism by which differentiated cells maintain their stability. When the transcription factor Srf is forcibly expressed, differentiated cells are destabilized and the reprogramming efficiency improves. Additionally, we are investigating each culture step to understand the effect on iPS cell quality.

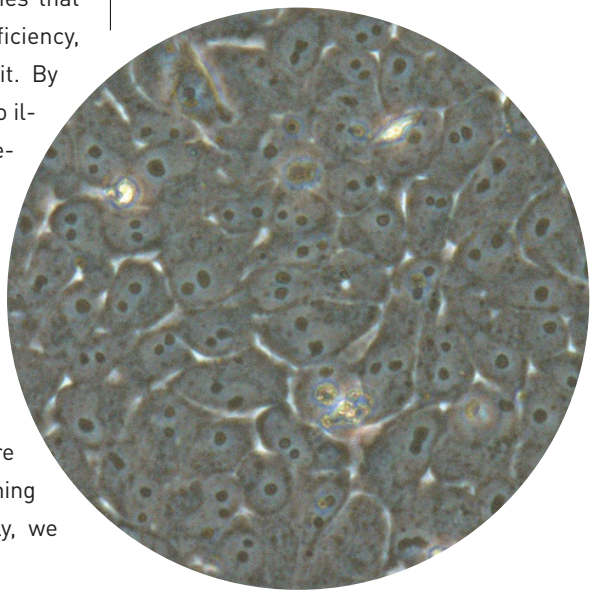
Application to endangered species

Globally, due to uncontrolled hunting, the northern white rhinoceros has only two living individuals. Using iPS cell technology, it may be possible to save the species and others endangered. Zoos and other facilities worldwide have frozen stocks of cells from endangered and extinct animal species. It is expected that populations could be recovered by generating iPS cells from these cells and applying reproduction technology. We are currently in preparation with related research.

Members

- Tomomi Eto
- Rie Fujii
- Mari Hamao
- Takashi Ikeda
- Yasuko Matsumura
- Mizuki Minata
- Yoko Uematsu
- Tatsuya Yamakawa

iPS cells derived from cynomolgus monkeys



Comprehensive analysis of changes accompanying the somatic cell reprogramming process

Takuya Yamamoto Ph.D., Junior Associate Professor

Summary

Our laboratory conducts comprehensive analysis, combining computer science and molecular biology, to elucidate the reprogramming mechanism.

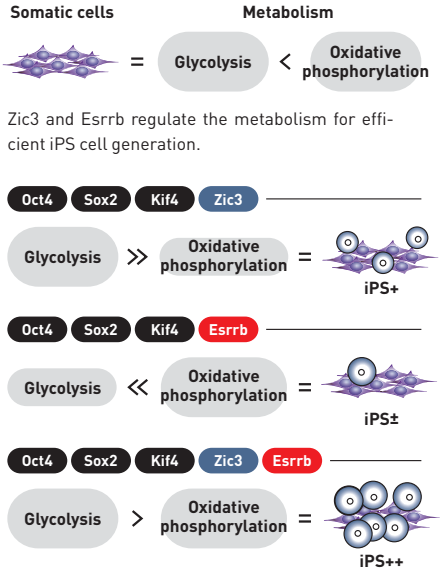
Research Progress

Improving the reprogramming efficiency of mouse cells

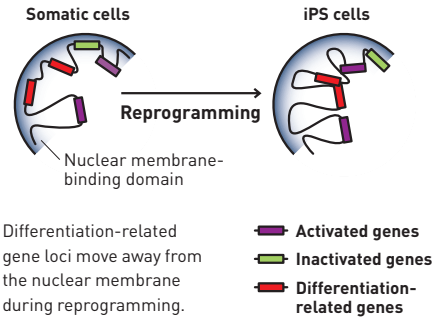
We previously demonstrated that two transcription factors, Zic3 and Esrrb, acting together with Oct4, Sox2, and Klf4, dramatically increase the efficiency of mouse cell reprogramming. Zic3 and Esrrb synergistically enhance glycolysis, but antagonistically regulate oxidative phosphorylation (upper figure). These findings demonstrated that the transcription network acts in concert with the metabolic network to alter cell fate(1).

Meanwhile, analysis of the higher order chromosome structure revealed that differentiation-related gene loci situated in the nuclear membrane move to the nuclear interior with reprogramming and tend to colocalize in pluripotent stem cells. Epigenetic-related factors were found to play an important role (lower figure)(2).

The balance of somatic cell reprogramming and metabolism



Alteration of chromosome positioning in reprogramming



Successful generation of ES cells with high efficiency

With the Yamada lab, we demonstrated that ES cells established in 2i/L culture medium lose genomic imprinting, reducing the quality of the cells. By lowering the concentration of MEK1/2 inhibitor in 2i/L culture medium or replacing it with Src inhibitor, we could maintain the genomic imprinting(3).

Members

- Junya Asahira
- Hiroki Ikeda
- Mayumi Ikeda
- Mio Kabata
- Eri Kawaguchi
- Joonseong Lee
- Satoko Sakurai
- Masamitsu Sone

Profile

2001 Graduated from Faculty of Science, Kyoto Univ.
2006 Ph.D., Graduate School of Biostudies, Kyoto Univ. / Postdoctoral Fellow, Graduate School of Biostudies, Kyoto Univ.
2009 Assistant Professor, iCeMS, Kyoto Univ.
2010 Current Position

Publication Highlights

(1) Hybrid cellular metabolism coordinated by Zic3 and Esrrb synergistically enhances induction of naïve pluripotency
Sone M *et al.*
Cell Metabolism (2017), 25 (5): 1103-1117

(2) Structural and spatial chromatin features at developmental gene loci in human pluripotent stem cells
Ikeda H *et al.*
Nature Communications (2017), 8: 1616

(3) Derivation of ground-state female ES cells maintaining gamete-derived DNA methylation
Yagi M *et al.*
Nature (2017), 548: 224-227

Department of Life Science Frontiers

Combining iPS cell and genome editing technologies to combat intractable genetic diseases

Akitsu Hotta Ph.D., Junior Associate Professor

Profile

2001 Graduated from School of Engineering, Nagoya Univ.
2006 Ph.D., Graduate School of Engineering, Nagoya Univ. / Postdoctoral Research Fellow, Developmental and Stem Cell Biology, Hospital for Sick Children
2008 Research Fellow, Ontario Human iPS Cell Facility
2010 Assistant Professor, iCeMS, Kyoto Univ. / Assistant Professor, CiRA, Kyoto Univ.
2016 Current Position

Publication Highlights

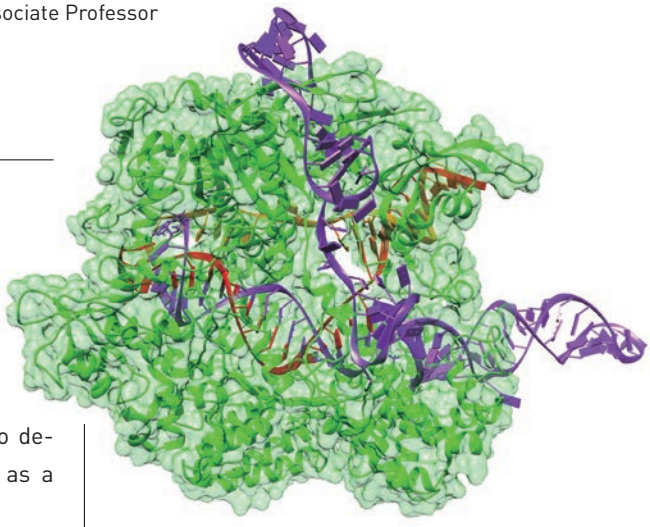
(1) Site-specific randomization of the endogenous genome by a regulatable CRISPR-Cas9 piggyBac system in human cells
Ishida K *et al.*
Scientific Reports (2018), 8 (1): 310

(2) Concordant but varied phenotypes among Duchenne muscular dystrophy patient-specific myoblasts derived using a human iPSC-based model
Choi IY *et al.*
Cell Reports (2016), 15 (10): 2301-2312

(3) Efficient genomic correction methods in human iPS cells using CRISPR-Cas9 system
Li HL *et al.*
Methods (2016), 101: 27-35

Summary

Orphan diseases are rare conditions with no effective treatment available. More than half of these diseases are said to involve gene abnormalities. Our goal is to develop genome editing technology as a therapy for orphan diseases.



Three-dimensional structure of CRISPR-Cas9. The Cas9 protein (green) enfolds the guide RNA (purple) and binds to the target DNA (red) to cleave (created from PDB ID 5F9R).

Research Progress

Developing a method to freely rewrite the genome sequence of iPS cells

CRISPR-Cas9 is a genome editing technology used to cleave targeted sites on the genome, thus inducing base deletions and sequence recombination.[3] However, targeting just one base in the genome and altering it accurately has an extremely low success rate (< 1%).

The efficiency can be raised with efficient delivery of CRISPR-Cas9/gRNA and single-stranded template DNA into the cells. Our laboratory is experimenting with the *piggyBac* transposon vector as the delivery system. If Cas9 functions continuously, it will cause a string of unintended defects. Therefore, we developed a drug-based method, CRONUS (CRISPR Regulated by transcriptional turn-ON and Nuclear Shuttling), to control Cas9 activity and succeeded in triggering the activation of Cas9 only when genome editing is desired. CRONUS makes it possible to induce substitutions of a single base at an unprecedented high rate (> 30%). To make the most use of the CRONUS system, we modified the assay to create different genome-edited cell lines at once by using a mixture of single-stranded DNA templates of various base sequences[1].

The system allows us to generate disease-specific cells and gene-corrected cells simultaneously. Furthermore, it enables us to induce *in vitro* evolution by introducing a random mutation in a gene, or to insert molecular barcodes into the cells. Thus, the system is expected to accelerate gene function analysis and disease research with iPS cells.

Members

- Peter David
- Masataka Ifuku
- Takahiro Iguchi
- Kentaro Ishida
- Naoko Ishihara
- Kumiko Iwabuchi
- Akihiro Kagita
- Mandy Siu Yu Lung
- Yukiko Nakagawa
- Yuya Okuzaki
- Noriko Sasakawa
- Masami Tanaka
- Huaigeng Xu
- Yulia Zhitnyuk

Capturing biological phenomena with ultra-high resolution

Akira Watanabe Ph.D., Assistant Professor

Summary

iPS cells undergo a number of stages when they are differentiated to a final cell state. Each stage is believed to depend on different factors. Identifying these factors has been difficult, however. We have developed single cell analysis tools for the identification. Using the same tools, we could detect the beginnings of cancer-like properties in cells.

Research Progress

Achievements in FY 2017

Our major activities this year can be summarized as follows. ① We conducted single-cell gene expression analysis to elucidate the mechanism of cell fate determination. ② We elucidated the onset mechanism of childhood cancer caused by cell differentiation abnormalities. ③ We developed a method to evaluate the genome of different cell types.

Using single-cell analysis, we recapitulated the process of organ development and identified the transcription networks and signal-regulatory factors specific to particular differentiation stages. We found which factors could increase the differentiation efficiency.

By comparing the epigenome patterns of normal cells at varying differentiation stages with those of cancer cells, we successfully identified the cell of origin in the cancer, thus clarifying the molecular mechanism at the earliest stage of the carcinogenesis.

Evaluating genomic DNA accurately without killing cells

Currently, the evaluation of the genome involves sampling and destroying a portion of the cell colony. In response, we developed a technique to evaluate genomic DNA accurately without destroying any cells. This technique can be used with all cultured cells.

Continuing the direction of this research, we are now using novel genome technology to clarify the behaviour of individual cells towards regenerative medicine.

Members

- Hiroko Endo
- Akiko Hasegawa
- Hiroshi Hayashi
- Erik Martin Johansson
- Ryotaro Kabai
- Unyanee Kato
- Marina Kishida
- Yoko Kitagawa
- Yuki Kubo
- Saki Matsushima
- Masahiro Nakamura
- Katsura Noda
- Mayuko Ochi
- Chihiro Okada
- Satoko Sakamoto
- Midori Sakiyama

Understanding cell fate by multi-omics analysis including genomics

Profile

1998 Graduated from Faculty of Engineering, Tokyo Univ. of Science
2003 Ph.D., Graduate School of Engineering, The Univ. of Tokyo / Postdoctoral Fellow, Center for Advanced Science and Technology, The Univ. of Tokyo
2009 Assistant Professor, iCeMS, Kyoto Univ.
2010 Current Position

Publication Highlights

(1) Autologous induced stem-cell-derived retinal cells for macular degeneration
Mandai M, Watanabe A *et al.*
New England Journal of Medicine (2017),
376 (11): 1038-1046

(2) Developmental and stem cell biology with single cell analysis
Watanabe A
Experimental Medicine special issue A Protocol for Single Cell Analysis (2017), 26–32

(3) Paradigm shift for new life science with single cell technologies
Watanabe A
Experimental Medicine (2015),
33 (1): 2-6

Recapitulating the developmental processes of germ cells

Mitinori Saitou M.D., Ph.D., Professor

Profile

1995 M.D., Faculty of Medicine, Kyoto Univ.
1999 Ph.D., Graduate School of Medicine, Kyoto Univ. / Travelling Research Fellow / Senior Research Associate, Gurdon Institute
2003 Team leader, Center for Developmental Biology, RIKEN
2009 Professor, Graduate School of Medicine, Kyoto Univ.
2018 Current Position

Publication Highlights

(1) Clonal variation of human induced pluripotent stem cells for induction into the germ cell fate
Yokobayashi S *et al., Biology of Reproduction* (2017), 96 (1): 1154-1166

(2) Evolutionarily distinctive transcriptional and signaling programs drive human germ cell lineage specification from pluripotent stem cells
Kojima Y *et al.,Cell Stem Cell* (2017), 21 (4): 517-532

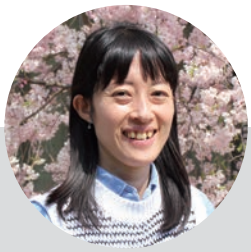
Research Progress

Recapitulating the germ cell development process in vitro

Germ cells are the cells that differentiate into sperms or eggs. Elucidating the mechanism of germ cell development will help clarify the mechanisms of genetic information transmission, epigenetic regulation, and infertility, as well as genetic disorders. We succeeded in differentiating mouse ES/iPS cells into primordial germ cell (PGC)-like cells in vitro, which could contribute to creating sperms, eggs and healthy offspring. We also succeeded in inducing human PGC-like cells from human iPS cells. Furthermore, we identified a developmental coordinate of the pluripotency spectrum in mice, monkeys, and humans, and identified the origin of primate germ cells as the early-stage amnion. In this FY, we elucidated differences in the germ cell differentiation efficiency among human iPS cell clones and their causative factors(1), and identified factors unique to human germ cell development(2).

Members

- Kazuki Kurimoto (Associate Professor)
- Ikuhiro Okamoto (Junior Associate Professor)
- Hiroshi Ohta (Assistant Professor)
- Tomonori Nakamura (Assistant Professor)
- Yoji Kojima (Assistant Professor)
- Shihori Yokobayashi (Assistant Professor)
- Yukiko Ishikura
- Marie Kawasaki
- Sakura Kuzuoka
- Tadahiro Mitani
- Hidetaka Miyauchi
- Yusuke Murase
- Yumiko Nagai
- Sou Nagaoka
- Kaoru Niwa
- Yuko Sakaguchi
- Yoshitake Sakai
- Hiromichi Sasada
- Kotaro Sasaki
- Kotaro Taga
- Marino Takemura
- Shinya Tokunaga
- Yukihiro Yabuta
- Chika Yamagi
- Aki Yamanaka
- Tomohiro Yamanaka



Elucidating the mechanism that determines protein quantity

Mio Iwasaki Ph.D., Assistant Professor

Profile

2008 Graduated from Faculty of Environment and Information Studies, Keio Univ.
2013 Ph.D., Graduate School of Pharmaceutical Sciences, Kyoto Univ. / Postdoctoral Fellow, CiRA, Kyoto Univ.
2017 Current Position

Publication Highlight

(1) Rapid and deep profiling of human induced pluripotent stem cell proteome by one-shot NanoLCMS/MS analysis with meter-scale monolithic silica columns
Yamana R *et al., Journal of Proteome Research* (2013), 12(1): 214-221

Research Progress

Application of high sensitive protein quantification method for analyzing stem cells

It is still difficult to comprehensively and quantitatively measure protein copy numbers in a cell. To elucidate the characteristic of various cell types, mRNA has been analyzed as cellular gene expression profiles. It is known, however, that mRNA and protein quantities do not correlate well. Recently, we developed a highly accurate quantification method for proteins. We have applied this method for stem cells to investigate differences between mRNA and protein quantities during differentiation. Recently, we have identified a group of genes showing a marked divergence between their mRNA and protein quantities appear to influence the survival of stem cells. We would like to uncover the importance of the post-transcriptional regulatory mechanism on cell fate decision including cell reprogramming and cell differentiation.

Members

- Yuka Kawahara
- Tsuyoshi Tabata

Understanding skeletal system diseases to develop innovative therapies

Junya Toguchida M.D., Ph.D., Professor

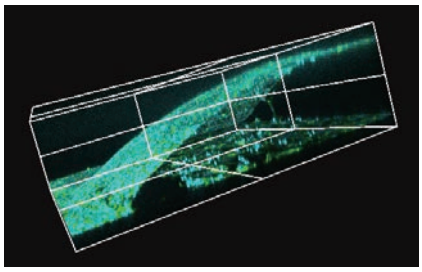
Summary

The skeletal system is made up of bone, cartilage, ligament, tendons, and other tissues. Diseases of the skeletal system can be caused by genetics, trauma, or other causes, and many have no effective therapy. Using iPS cell technology, we aim to not only clarify the pathology of skeletal system diseases, but also develop therapies.

Research Progress

Drug discovery for FOP and initiation of a physician-initiated clinical trial

Our greatest achievement in FY 2017 was to identify a therapeutic drug candidate for fibrodysplasia ossificans progressiva (FOP) using patient iPS cells and to begin a physician-initiated clinical trial using this candidate. FOP—a disease in which heterotopic bone forms in the soft tissues of the whole body—is caused by mutations in the ACVR1/ALK2 gene. We had previously identified activin A as the factor causing heterotopic ossification in FOP. Further study of the related molecular mechanism revealed that mTOR inhibitors suppress the heterotopic ossification caused by activin A.



Visualizing the bone formation process using fluorescence-labeled iPS cells

Start of a clinical trial using Sirolimus

Based on the above findings, we planned a clinical trial using Sirolimus, an mTOR inhibitor, already used in the clinic. Another achievement from this research was a method which allows us to efficiently differentiate iPS cells into bone cells in just 10 days. We are now using this method to visualize the bone formation process in vitro. We have also applied it to drug discovery for the genetic disease osteogenesis imperfecta, and successfully identified therapeutic drug candidates.

In addition to these achievements, we launched a 6-year project in FY 2017 for drug discovery for 6 different skeletal system diseases.

Members

- Hiroyuki Yoshitomi (Associate Professor)
- Cantas Alev (Assistant Professor)
- Yonghui Jin (Assistant Professor)
- Lin Amagase
- Noriko Deguchi
- Masataka Hada
- Kyosuke Hino
- Yu Isobe
- Takeshi Kamakura
- Shunsuke Kawai
- Jin Sol Kim
- Yuko Koyama
- Hirotsugu Maekawa
- Sanae Nagata
- Megumi Nishio
- Nao Okumura
- Mitsuru Soen
- Takeshi Takarada
- Tomoyuki Takeya
- Sakura Tamaki
- Maya Uemura
- Makoto Wanatabe
- Rie Yamamoto
- Yoshihiro Yamanaka
- Hisayo Yasuda
- Marie Yoshino
- Aya Yukawa

Profile

1981 M.D., Faculty of Medicine, Kyoto Univ.
1989 Ph.D., Graduate School of Medicine, Kyoto Univ. / Research Fellow, Massachusetts Eye and Ear Infirmary, Harvard Medical School
1995 Associate Professor, Research Institute for Biomedical Engineering, Kyoto Univ.
2003 Professor, Institute for Frontier Medical Sciences, Kyoto Univ.
2010 Current Position

Publication Highlights

(1) Enhanced mTOR signaling triggered by Activin-A in chondrogenesis of fibrodysplasia ossificans progressiva (FOP)
Hino K *et al., Journal of Clinical Investigation* (2017), 127 (9): 3339-3352

(2) Neofunction of ACVR1 in fibrodysplasia ossificance progressiva
Hino K *et al., PNAS* (2015), 112 (50): 15438-15443

(3) New protocol to optimize iPS cells for genome analysis of fibrodysplasia ossificans progressiva
Matsumoto Y *et al., Stem Cells* (2015), 33 (6): 1730-1742

Administration of Sirolimus suppresses heterotopic bone formation.

Department of Cell Growth and Differentiation

Understanding the mechanism of cartilage cell differentiation to develop cartilage disease therapies

Noriyuki Tsumaki M.D., Ph.D., Professor

Profile

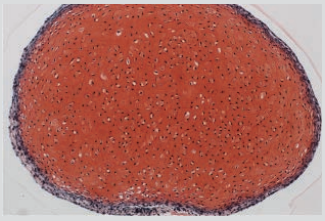
1989 M.D., Faculty of Medicine, Osaka Univ.
1996 Ph.D., Graduate School of Medicine, Osaka Univ. / Visiting Fellow, National Institute of Health
2002 Assistant, Graduate School of Medicine, Osaka Univ.
2007 Associate Professor, Graduate School of Medicine, Osaka Univ.
2011 Current Position

Publication Highlights

(1) Statin treatment rescues FGFR3 skeletal dysplasia phenotypes
Yamashita A *et al., Nature* (2014), 513 (7519): 507-511

(2) Pterosin B prevents chondrocyte hypertrophy and osteoarthritis in mice by inhibiting Sik3
Yahara Y *et al., Nature Communications* (2016), 7: 10959

(3) A-674563 increases chondrocyte marker expression in cultured chondrocytes by inhibiting Sox9 degradation
Kobayashi T *et al. Biochemical and Biophysical Research Communications* (2018), 495: 1468-1475



Human iPS cell-derived cartilage tissue

Summary

Cartilage disease and damage give rise to a range of impairments. To develop therapies, we are researching the molecular mechanism of cartilage cell (chondrocyte) differentiation and examining drug candidates using patient-derived iPS cells. Further, we established a protocol to produce iPS cell-derived cartilage for use in regenerative medicine.

Research Progress

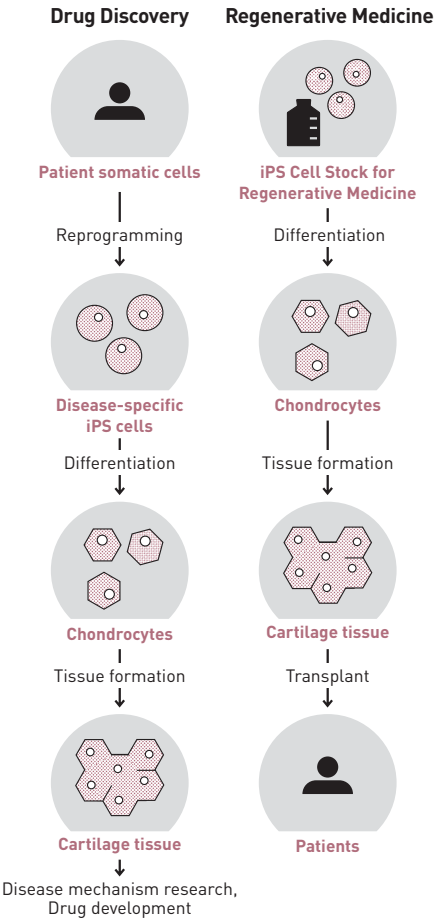
Elucidating the mechanism of chondrocyte differentiation

There are two types of cartilage, growth cartilage and articular cartilage. Impairment in growth cartilage causes skeletal dysplasia, while defects in articular cartilage compromise mobility. In FY 2017, we found candidates that maintain the quality of chondrocytes during culture as part of a cell therapy strategy.

Repairing articular cartilage

Our aim is to realize a regenerative therapy for articular cartilage damage by transplanting iPS cell-derived cartilage. In this FY, we prepared clinical-grade iPS cells and established a method to validate the quality of iPS cell-derived chondrocytes. Going forward, we intend to carry out further validation of the safety and efficacy towards clinical research.

Cartilage disease research with iPS cells



Members

- Akihiro Yamashita (Assistant Professor)
- Xike Chen
- Kaori Fujita
- Asami Harumatsu
- Yuki Iimori
- Tomoko Ikari
- Takashi Kamatani
- Tsubasa Kita
- Kazumi Koba
- Tomohito Kobayashi
- Kanako Konishi
- Azuma Kosai
- Saeko Koyamatsu
- Yuki Makita
- Kenichi Masuda
- Ryoko Matsuda
- Makiko Matsuoka
- Miho Morioka
- Hiromi Nishino
- Yuki Okutani
- Tomonori Ozaki
- Masumi Sanada
- Haruka Sato
- Toshika Senba
- Nobuyuki Shima
- Haruka Shirosawa
- Yoshiaki Takei
- Hiromi Takemoto
- Yoshihiro Tamamura
- Nobuyuki Yajima

Opening new horizons in cardiac regenerative therapy with iPS cells

Jun K. Yamashita M.D., Ph.D., Professor

Summary

We are conducting wide-ranging research to ultimately generate heart cells and tissues from iPS cells. Based on the technology for efficiently generating cardiomyocytes and vascular cells, we are trying to develop new cardiac regenerative therapies and disease models using iPS cell-derived 3D cardiac tissues.

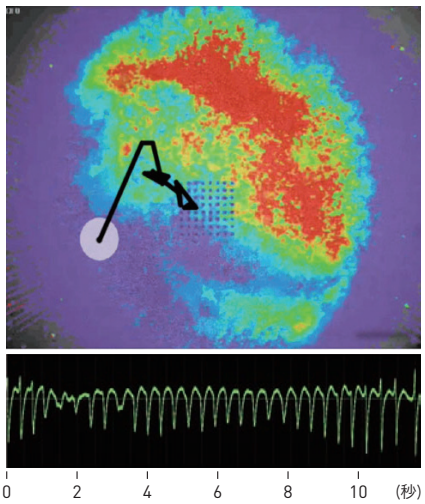
Research Progress

Regeneration of the heart and blood vessels

Our research ranges from basic to application. As an example, we showed that CD82-positive cells are fated to become cardiomyocytes and autonomously differentiate to the cell type with a high rate following transplantation to animals[1]. We also developed an efficient method to differentiate human iPS cells into vascular endothelial cells[3] and commercialized it as an iPS cell-derived endothelial cell product. Furthermore, we generated cardiac tissue-like structures (HiCT) that include the myocardiam, blood vessels, and interstitial tissue from iPS cells. We aim to apply HiCT to regenerative therapy within the next few years.

New model of lethal arrhythmia

By creating a 3D structure of cardiomyocytes and interstitial cells, we succeeded in replicating the pathology of lethal arrhythmia under culture conditions[2]. This is expected to contribute to pharmaceutical safety evaluation, and development of therapies.



Replication of arrhythmia in 3D cardiac tissue. After exposing cardiac tissue to the arrhythmia-inducing agent E-4031, arrhythmia-type extracellular potential waveforms (bottom) with spiraling were observed.
Scale bar:1 mm. White circle:The center of the spiral wave at the start of the measurement. Black line:The trajectory of center.

Members

- Kohei Yamamizu (Assistant Professor)
- Yuji Agawa
- Kiho Araki
- Tengaku Cho
- Daiki Fujita
- Hiroyuki Fukushima
- Hisao Harada
- Daisuke Heima
- Yuka Hirata
- Takuhiro Hoshino
- Tsugumitsu Kandou
- Masahide Kawatou
- Yuu Kinoshita
- Kazuki Kobayashi
- Yajing Liu
- Victor Lopez Davila
- Hidetoshi Masumoto
- Tomohiro Minakawa
- Mami Miyoshi
- Gaku Morinaga
- Chisato Murayama
- Takeichiro Nakane
- Toshikazu Nishie
- Hiroaki Osada
- Mizuho Shino
- Chinatsu Suzuki
- Masaya Suzuki
- Ayano Tabata
- Masafumi Takeda
- Shinya Takimoto
- Yasuhiro Tosaka
- Kazuki Yamano
- Zhennan Yang
- Miki Yoshioka

Profile

1990 M.D., Faculty of Medicine, Kyoto Univ.
1998 Ph.D., Graduate School of Medicine, Kyoto Univ.
2002 Assistant Professor, Graduate School of Medicine, Kyoto Univ.
2003 Assistant Professor, Institute for Frontier Medical Sciences, Kyoto Univ.
2008 Associate Professor, iCeMS, Kyoto Univ.
2010 Associate Professor, CiRA, Kyoto Univ.
2012 Current Position

Publication Highlights

(1) Identification of cardiomyocyte-fated progenitors from human-induced pluripotent stem cells marked with CD82
Takeda M *et al.*
Cell Reports (2018), 22: 546-556

(2) Modelling Torsade de Pointes arrhythmias in vitro in 3D human iPS cell-engineered heart tissue
Kawatou M *et al.*
Nature Communications (2017), 8 (1): 1078

(3) Efficient and robust differentiation of endothelial cells from human induced pluripotent stem cells via lineage control with VEGF and cyclic AMP
Ikuno T *et al.*
PLOS ONE (2017), 12: e0173271

Department of Cell Growth and Differentiation

Designing high-quality cells through theoretical study of cell states

Wataru Fujibuchi Ph.D., Professor

Profile

1991 Graduated from School of Science, Hiroshima Univ.
1995 Research Associate, Institute for Chemical Research, Kyoto Univ.
1999 Visiting Fellow, National Center for Biotechnology Information (NCBI), National Institutes of Health (NIH)
2002 Staff Scientist, NCBI, NIH
2003 Research Scientist, Computational Biology Research Center (CBRC), National Institute of Advanced Industrial Science and Technology (AIST)
2007 Team Leader, CBRC, AIST
2012 Current Position

Publication Highlights

(1) Stem cell-based methods to predict developmental chemical toxicity
Takahashi H *et al.*
Computational Toxicology: Methods and Protocols, in press

(2) Japanese patent application No. 2017-250042

(3) A standard nomenclature for referencing and authentication of pluripotent stem cells
Kurtz A *et al.*
Stem Cell Reports (2018), 10 (1): 1-6

Summary

We are engaged in theoretical cell analysis. To date, with the aim of constructing an artificial intelligence-based system to predict the toxicity of a substance by the reaction in ES cells, we have set up a consortium made up of companies and researchers in related fields. We have also proposed international standards for describing cell information in stem cell banks.

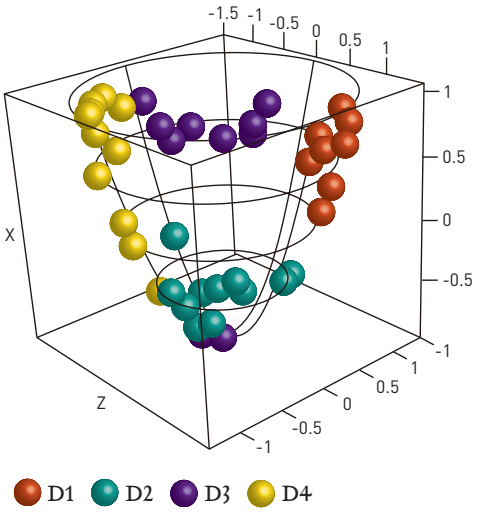
Research Progress

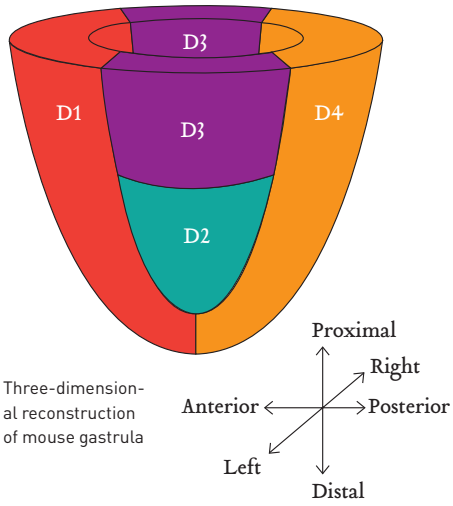
Towards the launch of a stem cell-based toxicity testing system

Using artificial intelligence technology, we reported the construction of a highly accurate compound toxicity prediction system using human ES cells and gene network data(1). We established a consortium consisting of companies and researchers in various fields with the view to developing a stem cell-based toxicity testing system that is fast, cheap, and accurate.

Our laboratory is distinguished by the fact that it has an experimental group, which is unusual for an informatics laboratory. The experimental group provides a wide range of omics data, which we integrate to calculate intercellular distances with the aim of creating computer-based three-dimensional tissue.

Meanwhile, we proposed MIACARM, a guideline for stem cell data which is intended as a basic platform to promote the sharing of data from the world's 20 or more stem cell banks.





Three-dimensional reconstruction of mouse gastrula

Members

- Ying Chen
- Chihiro Iwasa
- Kazunori Jikihara
- Tsuneo Kido
- Yuji Kozakura
- Tomoya Mori
- Kayo Obata
- Souichi Ogata
- Kunie Sakurai
- Anna Elizabeth Sappington
- Hiroki Takahashi
- Yasuhiro Tanaka
- Nobuko Taniyama
- Takanori Tano
- Junko Yamane
- Midori Yuji

Human pluripotent stem cells in neurological drug discovery

Haruhisa Inoue M.D., Ph.D., Professor

Summary

Amyotrophic lateral sclerosis (ALS) and Alzheimer's disease are intractable diseases caused by the degeneration and loss of central nervous system cells. By generating patient-derived iPS cells and differentiating them into in vitro models of motor neurons and cortical neurons, we aim to understand these diseases and develop therapeutic drugs. Using this approach, we have identified effective compounds or cocktails against several diseases.

Research Progress

Elucidating the pathology of intractable neurological diseases

Using iPS cells, we have been developing a drug discovery platform, transplantation therapy, and high-precision medical treatments for neurodegenerative diseases. Going forward, our ambition is to use iPS cell technology to understand the human central nervous system, elucidate pathologies, and ultimately feed this knowledge into clinical practice. Our research can be described as going "from bedside to dish" and "from dish to bedside."

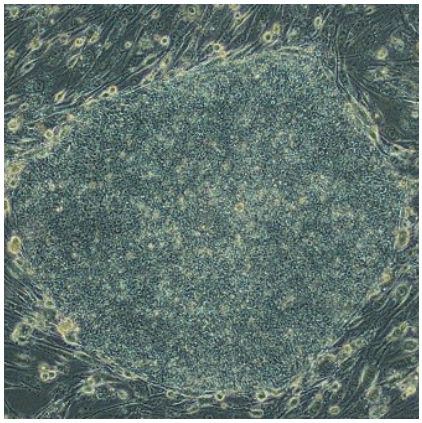
ALS is a disease caused by the degeneration of motor neurons, and patients develop muscular atrophy and muscle weakness. In FY 2017, collaborating with research groups in Japan and overseas, we carried out drug screening for therapeutic drug candidates using motor neurons differentiated from ALS patient-derived iPS cells and identified a molecular pathway as a target of ALS treatment and an existing drug that suppresses cell death in ALS motor neurons(2).

We also work on Alzheimer's disease. This disease results partly from an accumulation of amyloid β in the cerebral cortex. We conducted drug screening using highly purified cerebral cortex neurons generated from Alzheimer's disease patient-derived iPS cells, and discovered a cocktail of existing drugs capable of decreasing the production of amyloid β(1).

Members

- Takayuki Kondo (Assistant Professor)
- Keiko Imamura (Assistant Professor)
- Haruhiko Banno
- Takako Enami
- Noriko Endo
- Misato Funayama
- Kengo Honma
- Mikie Iijima
- Sachiyo Kadomura
- Michiyo Miyake
- Takeshi Niki
- Hiroe Ohnishi
- Yuko Ohno
- Yukako Sagara
- Ran Shibukawa
- Ruri Taniguchi
- Kayoko Tsukita
- Tan Ghee Wan
- Toshifumi Watanabe
- Yuichiro Yada
- Makiko Yasui

ALS patient-derived iPS cells



Profile

1992 M.D., Faculty of Medicine, Kyoto Univ.
1997 Research Resident, National Institute of Neuroscience / Research Fellow, Medical School, Univ. of Pecs
1999 Staff Scientist, RIKEN
2004 Postdoctoral Fellow, Harvard Medical School
2005 Assistant Professor, Graduate School of Medicine, Kyoto Univ.
2009 Associate Professor, iCeMS, Kyoto Univ.
2010 Associate Professor, CiRA, Kyoto Univ.
2014 Current Position

Publication Highlights

(1) iPSC-based compound screening and in vitro trials identify a synergistic anti-amyloid β combination for Alzheimer's disease
Kondo T *et al.*
Cell Reports (2017), 21 (8): 2304-2312

(2) The Src/c-Abl pathway is a potential therapeutic target in amyotrophic lateral sclerosis
Imamura K *et al.*
Science Translational Medicine (2017), 9 (391): eaaf3962

(3) Induced pluripotent stem cell technology: a decade of progress
Shi Y *et al.*
Nature Reviews Drug Discovery (2017), 16 (2): 115-130

Department of Cell Growth and Differentiation

Novel regenerative medicine for the kidney, pancreas, and liver

Kenji Osafune M.D., Ph.D., Professor

Profile

1996 M.D., Faculty of Medicine, Kyoto Univ.
2003 Ph.D., Graduate School of Science, The Univ. of Tokyo
2005 Postdoctoral Fellow, Harvard Stem Cell Institute, Harvard Univ.
2008 Lecturer, iCeMS, Kyoto Univ.
2009 Associate Professor, iCeMS, Kyoto Univ.
2010 Associate Professor, CiRA, Kyoto Univ.
2014 Current Position

Publication Highlights

(1) Human pluripotent stem cell-derived erythropoietin-producing cells ameliorate renal anemia in mice
Hitomi H *et al.*
Science Translational Medicine (2017), 9 (409): eaaj2300

(2) Rho-associated kinases and non-muscle myosin IIs inhibit the differentiation of human iPSCs to pancreatic endoderm cells
Toyoda T *et al.*
Stem Cell Reports (2017), 9 (2): 419-428

(3) Generation of branching ureteric bud tissues from human pluripotent stem cells
Mae SI *et al.*
Biochemical and Biophysical Research Communications (2018), 495 (1): 954-961

Summary

A number of chronic diseases afflict the kidney, pancreas, and liver. By developing an efficient method of differentiating iPS cells into the target cell type, we aim to create disease models, to discover and develop therapeutic drugs and to establish cell transplant therapies.

Research Progress

Kidney regeneration

We have developed a differentiation method from human iPS cells for ureteric bud, a type of fetal-stage renal progenitor cells.

Pancreas regeneration

We have discovered that inhibitors of Rho kinase (ROCK) and myosin promote the differentiation of human iPS cells into pancreatic progenitors. We also found the low-molecular compound AT7867 promotes the proliferation of human iPS cell-derived pancreatic progenitors, and sodium cromoglicate stimulates the differentiation of pancreatic progenitors into pancreatic endocrine cells (figure).

Liver regeneration

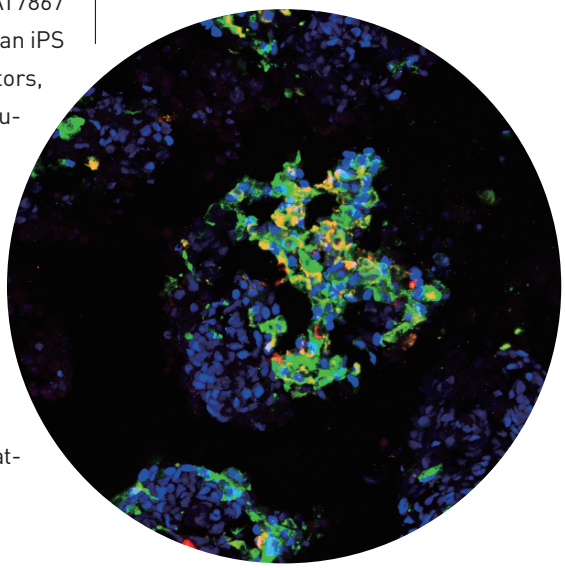
We elucidated a new mechanism in which an adrenalin α1 receptor agonist promotes the differentiation of iPS cells into hepatocytes.

We improved the protocol for differentiating human iPS cells into hepatocytes and succeeded in preparing erythropoietin (EPO)-producing cells. Upon transplantation, these cells improved the symptoms of a renal anaemia mouse model.

Members

- Taro Toyoda (Junior Associate Professor)
- Shin-Ichi Mae (Assistant Professor)
- Toshikazu Araoka
- Mitchell Braam
- Hirofumi Hitomi
- Azusa Hoshina
- Maiko Igami
- Ryo Ito
- Tomoko Kasahara
- Naoko Katagiri
- Timothy J. Kieffer
- Azuma Kimura
- Shuhei Konagaya
- Yasushi Kondo
- Maki Kotaka
- Kyoko Matsuse
- Atsushi Mima
- Erika Moriguchi
- Makoto Nasu
- Miyuki Ochiai
- Natsumi Okamoto
- Shiori Okumura
- Makoto Ryosaka
- Aya Shibasaki
- Fumihiko Shiota
- Tomomi Sudo
- Shinichi Sueta
- Hiromi Tanaka
- Hiraku Tsujimoto
- Saori Uno
- Katsutaro Yasuda

Immunostaining of islet cells differentiated from human iPS cells. Greem C-peptide, Red Glucagon



Clinical application of rejuvenated T cells

Shin Kaneko M.D., Ph.D., Associate Professor

Summary

Cytotoxic T lymphocytes (CTL) recognize and destroy viruses, cancer cells, and other foreign bodies. By using iPS cells, it is possible to create a high-volume supply of CTLs. We are establishing new therapies against cancer and viral infectious diseases using this method.

Research Progress

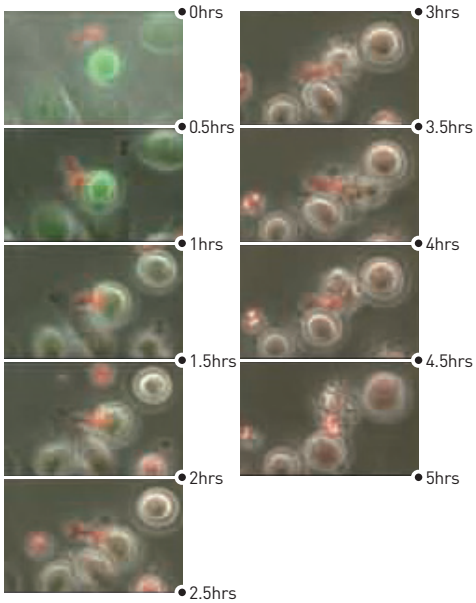
Therapies based on rejuvenated CTLs

We use both iPS cell technology and T cell differentiation technology to regenerate the CTLs of patients with cancer or chronic infectious disease. By improving the quantity and quality of the CTLs, we aim to develop new therapies.

In 2017, the United States approved an immunotherapy that uses patient CTLs, but at a cost of more than 50 million yen (USD 500,000). We seek to lower this cost by sharing our rejuvenated T cell technology with CiRA's iPS Cell Stock and with pharmaceutical companies.

In addition, we are engaged in research commissioned by the Japan Agency for Medical Research and Development (AMED) (Research projects: Pre-clinical study of iPSC-derived CAR expressing T cells; Research for development of new immunotherapy for HIV cure with iPS cell-derived T cells) and establishing a stable production of rejuvenated T cells.

Rejuvenated T lymphocytes attack and destroy cancer cells



Red cells: rejuvenated T lymphocytes
Green cells: cancer cells

Members

- Maika Akizuki
- Wang Bo
- Sayaka Chuganji
- Ken Fukumoto
- Yoichi Higuchi
- Eri Imai
- Shoichi Iriguchi
- Yoshitaka Ishiguro
- Takeshi Ito
- Yoshihiro Iwamoto
- Sanae Kamibayashi
- Yoshiaki Kassai
- Yohei Kawai
- Shuichi Kitayama
- Ayako Kumagai
- Akira Maruyama
- Atsutaka Minagawa
- Yuta Mishima
- Yasuyuki Miyake
- Tadayo Miyasaka
- Kengo Nakagoshi
- Yoshitsugu Nakajima
- Katsura Noda
- Kohei Ohara
- Reiko Saikawa
- Katsunori Sasaki
- Eri Sato
- Hitomi Takakubo
- Shinichiro Takayanagi
- Masahiro Tanaka
- Tomoaki Tanaka
- Tatsuki Ueda
- Masazumi Waseda
- Kana Yamaguchi
- Nariaki Yanagawa
- Hisashi Yano
- Yukata Yasui

Profile

1995 M.D., School of Medicine, Univ. of Tsukuba
2002 Ph.D., Graduate School of Medicine, Univ. of Tsukuba
2003 Lecturer, Graduate school of Medicine, Univ. of Tsukuba
2005 Postdoctoral Fellow, San Raffaele Scientific Institute
2008 Assistant Professor, Graduate School of Medicine, The Univ. of Tokyo
2012 Current Position

Publication Highlights

(1) Cellular adjuvant properties, direct cytotoxicity of re-differentiated Vα24 invariant NKT-like cells from human induced pluripotent stem cells
Kitayama S *et al.*
Stem Cell Reports (2016), 6 (2): 213-227

(2) Generation of rejuvenated antigen-specific T cells by reprogramming to pluripotency and redifferentiation
Nishimura T *et al.*
Cell Stem Cell (2013), 12 (1): 114-126

Department of Clinical Application

"Building a Brain" manipulating cells to cure intractable neurological diseases

Jun Takahashi M.D., Ph.D., Professor

Profile

1986 Mt.D., Faculty of Medicine, Kyoto Univ.
1993 Ph.D., Graduate School of Medicine, Kyoto Univ. / Assistant Professor, Graduate School of Medicine, Kyoto Univ.
1995 Postdoctoral fellow, Salk Institute for Biological Studies
1997 Assistant Professor, Graduate School of Medicine, Kyoto Univ.
2003 Lecturer, Graduate School of Medicine, Kyoto Univ.
2007 Associate Professor, Institute for Frontier Medical Sciences, Kyoto Univ. Graduate School of Medicine, Kyoto Univ.
2008 Associate Professor, CiRA, Kyoto Univ.
2012 Current Position

Publication Highlights

(1) MHC matching improves engraftment of iPSC-derived neurons in non-human primates
Morizane A *et al.*
Nature Communications (2017), 8: 385

(2) Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease model
Kikuchi T *et al.*
Nature (2017), 548: 592-596

(3) Enhanced axonal extension of subcortical projection neurons isolated from murine embryonic cortex using neuropilin-1
Sano N *et al.*
Frontiers in Cellular Neuroscience (2017), 11: 123

Summary

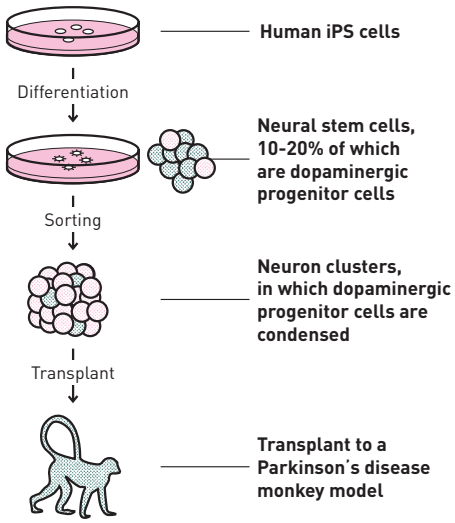
Parkinson's disease is an intractable neurological disease characterized by gradual loss of dopaminergic neurons and the impairment of motor functions. We have carried out experimental transplants with iPS cell-derived cells in animal models as a radical therapy.

Research Progress

Efficacy and safety of iPS cell-derived dopaminergic progenitor cells

We administered dopaminergic progenitor cells differentiated from human iPS cells into the brain of a Parkinson's disease monkey model. The number of cells administered (approximately 5 million), the administration sites (bilateral putamen), the observation period (2 years) and other parameters were almost the same as those of a planned clinical trial. Evaluation by video recordings, positron CT, and histological analysis suggested our approach was efficacious and safe[2].

Efficacy and safety investigation with a monkey model of Parkinson's disease



Long-term observation after the transplant
- Movement evaluation (scoring, video)
- Imaging evaluation (MRI, PET)
- Histological evaluation

Alleviation of immune reaction against transplant

We are planning to conduct a clinical trial with allogeneic transplants, but an associated issue is immune rejection. We carried out MHC-matched transplants and non-matched transplants in the monkey model. Following 4 months' observation without immunosuppression, the immune reaction was significantly less in the matching transplant and the cell engraftment rate was higher[1].

Members

- Daisuke Doi (Assistant Professor)
- Asuka Morizane (Assistant Professor)
- Tomoka Ashida
- Yudai Fujita
- Luc Brice Grinand
- Yulius Hermanto
- Satoe Hiramatsu
- Yuko Ishii
- Markus Karlsson
- Yuki Katano
- Tetsuhiro Kikuchi
- Takahiro Kitahara
- Kei Kubota
- Hiroaki Magotani
- Yoshifumi Miyawaki
- Yukiko Morita
- Hitomi Nakamura
- Takanori Ogura
- Yuki Ozaki
- Hideya Sakaguchi
- Bumpei Samata
- Rena Shiga
- Takafumi Shimogawa
- Yusuke Sugao
- Tadashi Sunohara
- Hideaki Takahashi
- Rika Takaichi
- Yoshie Tanikawa
- Sadaharu Torikoshi
- Emi Yamasaki
- Kenji Yoshida

Cherish the delusion and realize clinical innovation

Koji Eto M.D., Ph.D., Professor

Summary

Patients with severe anemia and thrombocytopenia require blood transfusion. However, platelets can only be stored 4 days after collection, making stable supplies difficult. In response, we have been using iPS cells to create platelet products. We have developed a compound to replace thrombopoietin (TPO), which is involved in platelet production and been investigating a wide range of other physical and chemical conditions as we progress toward commercialization.

Research Progress

Development of a safe and low-cost culture method

TPO regulates platelet production. However, recombinant TPO is not only costly, in some cases but also it causes adverse reactions when administered to patients. To resolve this issue, we developed TA-316, which has equal or superior effectiveness to TPO. TA-316 should greatly contribute to commercialization.

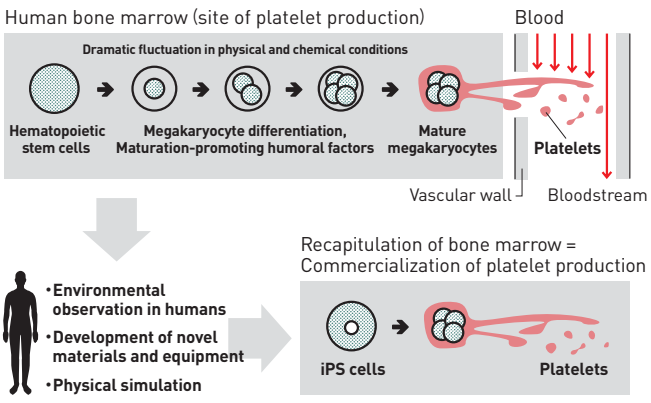
Interdisciplinary approach to platelet generation

Although we can produce platelets from iPS cells, the efficiency rate is quite low. We analyzed platelet release into the blood in bone marrow from the viewpoint of fluid dynamics and discovered that the force exerted by the blood flow is an important factor. Based on this finding, we are currently engaged in the development of a new culture apparatus.

Members

- Naoshi Sugimoto (Assistant Professor)
- Marina Akasaka
- Si Jing Chen
- Shima Date
- Hiroshi Endo
- Kosuke Fujio
- Harumi Ginya
- Kazuya Hashimoto
- Natsumi Higashi
- Akira Ishii
- Yukitaka Ito
- Maki Kawato
- Maya Kimura
- Yuki Kurahashi
- Toshie Kusunoki
- Iori Maeba
- Keiko Manda
- Sumie Matsuguchi
- Takuya Matsumoto
- Noriko Matsunaga
- Sachiyo Misumi
- Miyuki Morizumi
- Itsuro Motegi
- Sou Nakamura (Specially-Appointed Assistant Professor)
- Katsuyuki Nishi
- Hiroyuki Okunaga
- Yoshiko Onozawa
- Hideya Seo
- Akiko Shigemasa
- Shin Shimizu
- Ieva Stirblyte
- Katsumi Suezawa
- Daisuke Suzuki
- Yasuhiko Tosa
- Yuichiro Tsuda
- Michiko Ueda
- Rajneesh Verma
- Sanae Yoshikawa
- Akinori Yuzuriha

Research for commercialization of iPS cell-derived platelet production



Profile

1990 M.D., Faculty of Medicine, Yamanashi Medical Univ.
1996 Assistant Professor, Faculty of Medicine, Teikyo Univ.
1999 Postdoctoral Fellow, The Scripps Research Institute
2003 Associate Fellow, The Scripps Research Institute / Assistant Professor, The Institute of Medical Science, The University of Tokyo
2008 Assistant Professor, Center for Stem Cell Biology and Regenerative Medicine, The Univ. of Tokyo
2009 Associate Professor, Center for Stem Cell Biology and Regenerative Medicine, The Univ. of Tokyo
2011 Current Position

Publication Highlights

(1) Novel TPO receptor agonist TA-316 contributes to platelet biogenesis from human iPS cells
Aihara A *et al.*
Blood Advances (2017), 1 (7): 468-476

(2) Platelet production from induced pluripotent stem cells
Sugimoto N, Eto K
Journal of Thrombosis and Haemostatis (2017), 15 (9): 1717-1727

(3) Expandable megakaryocyte cell lines enable clinically-applicable generation of platelets from human induced pluripotent stem cells
Nakamura S *et al.*
Cell Stem Cell (2014), 14 (4): 535-548

Department of Clinical Application

Using iPS cells as a tool for research into developmental science

Yoshiya Kawaguchi M.D., Ph.D., Professor

Profile

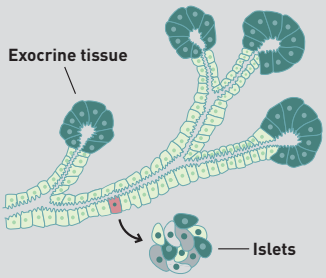
1988 M.D., Faculty of Medicine, Kyoto Univ.
1997 Ph.D., Graduate School of Medicine, Kyoto Univ.
1999 Postdoctoral Fellow, Dept. of Cell Biology, Vanderbilt Univ.
2002 Assistant / Assistant Professor, Graduate School of Medicine, Kyoto Univ.
2009 Lecturer, Graduate School of Medicine, Kyoto Univ.
2011 Current Position

Publication Highlights

(1) Diabetes caused by elastase-cre-mediated Pdx1 inactivation in mice
Kodama S *et al., Scientific Reports* (2016), 6: 21211

(2) Sox9 and reprogramming of liver and pancreatic progenitors
Kawaguchi Y, *Journal of Clinical Investigation* (2013), 123 (5): 1881-1886

(3) Continuous cell supply from a Sox9-expressing progenitor zone in adult liver, exocrine pancreas and intestine
Furuyama K *et al., Nature Genetics* (2011), 43 (1): 34-41



Factors from exocrine tissue are needed to differentiate islets.

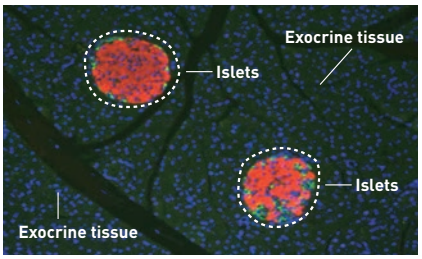
Summary

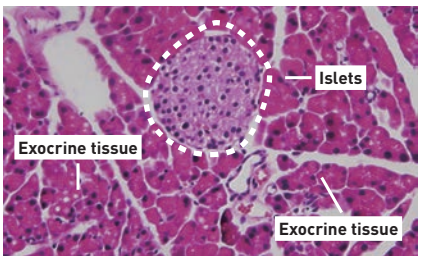
The pancreas contains both exocrine tissue, which secretes digestive enzymes, and endocrine tissue, which secretes hormones. Aiming to generate three-dimensional pancreatic tissue from human iPS cells, we are investigating pancreas development and maturation. We are also studying development of the digestive tract.

Research Progress

Pancreas formation —— exocrine tissue-derived factors that regulate functional maturation

The pancreas is a unique organ that acts both as a digestive organ and an endocrine organ. Its two corresponding tissue types, exocrine tissue and pancreatic islets, are formed almost simultaneously and coexist throughout the lifetime. However, the interrelationship between the two is unclear. We created a mouse model in which the amount of exocrine tissue was extremely small and found that these mice develop diabetes mellitus. In other words, the development of functional pancreatic islets is subject to the regulation of exocrine tissue-derived factors. In FY 2017, we identified several specific exocrine tissue-derived factors and investigated the molecular mechanism.





Exocrine tissue
Secretes digestive enzymes.
Accounts for 95% of the pancreas.

Islets
Regulates blood sugar level.
Accounts for 5% of the pancreas.

The pancreas is a unique organ in which tissues with two different functions coexist. The process of pancreas formation is subject to regulation by exocrine tissue-derived factors.

Research into the development of the digestive tract

The digestive tract can be described as the most basic structure among endoderm organs. In FY 2017, we made new insights into the formation mechanism for the junction between the esophagus and the stomach, and the maturation mechanism for the small intestine stem cell niche.

Members

- Yoshiki Aoyama
- Kaho Fujii
- Masanobu Habu
- Koji Hirata
- Masashi Horiguchi
- Toshihiko Masui
- Sakiko Minemura
- Chihiro Mori
- Yuki Nakanishi
- Kenzo Nakano
- Morito Sakikubo
- Akiko Sankoda
- Nao Sankoda
- Ben Sasaki
- Asahi Sato
- Kunihiko Tsuboi
- Masahiro Yoshida

Studying intractable pediatric diseases with disease-specific iPS cells

Megumu Saito M.D., Ph.D., Associate Professor

Summary

Using patient-derived iPS cells to recapitulate the phenotype, we aim to elucidate the disease mechanism and to establish therapies of intractable pediatric diseases. Focusing on diseases which appear during the neonate or infancy stage, we are investigating causes at the molecular and genetic levels.

Research Progress

Elucidating the causes of congenital immune diseases

In Blau syndrome, a range of lesions appear throughout the body. To understand why, we differentiated patient-derived iPS cells into monocyte and macrophage lineages, and investigated their function. We found that IFN-γ caused an inflammatory response. In contrast, this phenomenon did not occur in normal cells. Moreover, the same phenomenon was observed in patient blood-derived cells, suggesting IFN-γ is an important inflammation trigger.

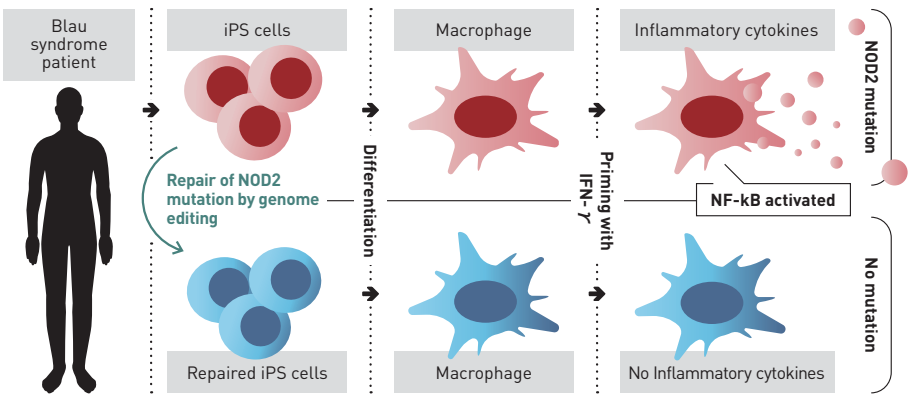
Understanding pathology with disease models

Reticular dysgenesis is the most severe form of severe combined immunodeficiency. Using patient-derived iPS cells, we recapitulated the disease pathology. Our investigation found that the volume and distribution of adenosine triphosphate (ATP) was abnormal.

Members

- Akira Niwa (Assistant Professor)
- Mitsujiro Osawa (Assistant Professor)
- Seiko Benno
- Shi Cho
- Lin Chuang-Yu
- Takeshi Fujimoto
- Jose Ichishima
- Koichi Igura
- Ryunosuke Ikeda
- Akihiro Ikenaka
- Takehiro Iki
- Yuri Kawasaki
- Kosuke Kirino
- Yoko Kitagawa
- Hiroyuki Matsubara
- Shiori Matsuo
- Misa Miyakawa
- Ayako Nagahashi
- Emiri Nakamura
- Chizu Nishida
- Sayaka Nishimura
- Yoko Nishinaka
- Ryo Ohta
- Hiroaki Ono
- Monika Ohno
- Norikazu Saiki
- Madoka Terashima
- Hiromitsu Toshikawa
- Jingxin Wang
- Harumi Watanabe
- Masami Yamashita

Disease modeling with Blau symdrome-specific iPS cells



Profile

1997 M.D., Faculty of Medicine, Kyoto Univ.
2003 Deputy chief doctor, Dept. of Infection Immunity and Allergy, Shizuoka Children's Hospital
2008 Ph.D., Graduate School of Medicine, Kyoto Univ.
2009 Assistant Professor, iCeMS, Kyoto Univ.
2011 Junior Associate Professor, CiRA, Kyoto Univ.
2012 Current Position

Publication Highlights

(1) Identification of a high-frequency somatic NLRC4 mutation as a cause of autoinflammation by pluripotent cell-based phenotype dissection
Kawasaki Y *et al.*
Arthritis & Rheumatology (2017), 69 (2): 447-459

(2) Human AK2 links intracellular bioenergetic redistribution to the fate of hematopoietic progenitors
Oshima K *et al.*
Biochemistry and Biophysical Research Communications (2018), 497 (2): 719-725

(3) Pluripotent stem cell models of Blau syndrome reveal an IFN-γ-dependent inflammatory response in macrophages
Takada S *et al.*
Journal of Allergy and Clinical Immunology (2018), 141(1): 339-349

Department of Clinical Application

Novel therapies for intractable muscular diseases

Hidetoshi Sakurai M.D., Ph.D., Associate Professor

Profile

1998 M.D., School of Medicine, Nagoya Univ. / Dept. of Nephrology, Nagoya Ekisaikai Hospital
2005 Ph.D., Graduate School of Medicine, Nagoya Univ. / Research Resident, Graduate School of Medicine, Nagoya Univ.
2008 Researcher, iCeMS, Kyoto Univ.
2009 Lecturer, iCeMS, Kyoto Univ.
2010 Junior Associate Professor, CiRA, Kyoto Univ.
2015 Current Position

Publication Highlights

(1) A human iPS cell myogenic differentiation system permitting high-throughput drug screening
Uchimura T *et al.*
Stem Cell Research (2017), 25: 98-106

(2) A skeletal muscle model of infantile-onset Pompe disease with patient-specific iPS cells
Yoshida T *et al.*
Scientific Reports (2017), 7 (1): 13473

(3) Efficient and reproducible myogenic differentiation from human iPS cells: prospects for modeling Miyoshi Myopathy in vitro
Tanaka A *et al.*
PLOS ONE (2013), 8 (4): e61540

Summary

We are studying the pathogenesis and new therapies for intractable muscular diseases. The research involves two strategies. One strategy is producing disease models and drug screenings using patient-derived iPS cell, and another strategy is regenerative medicine by transplanting skeletal muscle stem cells differentiated from clinical-grade iPS cells.

Research Progress

iPS cell-based disease modeling and drug discovery

Pompe disease is a systemic condition with serious cardiomyopathy and muscular atrophy. We generated iPS cell-derived skeletal muscle cells from patients with infantile Pompe disease, which follows a particularly severe clinical course, and succeeded in recapitulating the disease phenotypes, namely glycogen accumulation in the lysosome and enlarged lysosome. Moreover, as a secondary pathology, we identified low mTORC1 signaling. Going forward, we are constructing a screening assay for compounds that enhance the function of the lysosome (figure).

Skeletal muscle stem cells for regenerative medicine

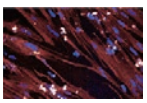
We have succeeded in differentiating human iPS cells into skeletal muscle stem cells with high regenerative ability. In this FY, we investigated the efficacy and safety of transplanting these cells into animal models.

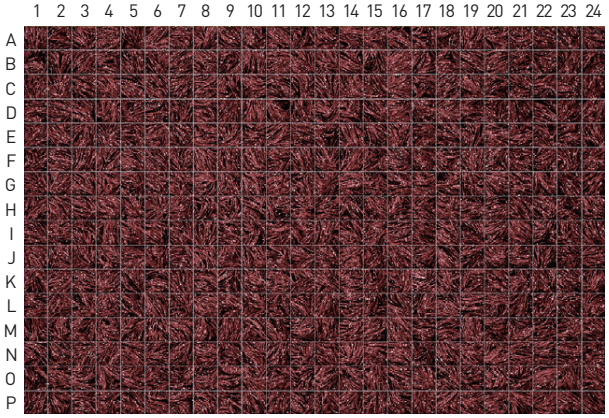
Members

- Meni Arai
- Kei Fujiwara
- Megumi Goto
- Aya Harada
- Mitsuru Honda
- Rukia Ikeda
- Tatsuya Jonouchi
- Machiko Kaneshiro
- Hiroki Kato
- Jin Sol Kim
- Yuko Kokubu
- Yasutomo Miura
- Miki Nagai
- Yukiko Nakagawa
- Harutiun Minas Nalbandian
- Airi Ota
- Jun Otomo
- William Roman
- Chinami Saka
- Masae Sato
- Nana Takenaka
- Midori Tanaka
- Atsutoshi Tazumi
- Tomoya Uchimura
- Takeshi Yoshida
- Mingming Zhao

Uniformly differentiated skeletal myocytes on a 384-well plate for drug screening
Red: Myocytes differentiated from patient-derived iPS cells

IF: MHC+DAPI





Contributing to transplantation medicine through development of an iPS cell stock

Naoko Takasu M.S., Professor

Summary

CiRA has set up the Facility for iPS Cell Therapy (FiT) for the purpose of preparing an iPS cell stock that can be used for regenerative medicine. Collaborating with organizations from various sectors, we are building a manufacturing management system that will provide a stable supply of clinical-grade iPS cells. Additionally, we are researching ways to generate safe and high-quality iPS cells.

Research Progress

Building an iPS cell stock

FiT prepares iPS cells from the blood of healthy volunteers. These iPS cells serve as the raw material for cell therapy. This year, we began supplying two new cell lines from this iPS cell stock. The new lines mean the iPS cells at FiT can cover approximately 24% of the Japanese population. Our preliminary goal is to prepare 10 lines that will cover around half of the Japanese population.

Strengthening the management system for the iPS cell stock

In joint research with Takara Bio Inc., which has expertise in cell production, we installed a production management system to strengthen the governance of FiT. At the same time, we are standardizing iPS cell quality evaluation. These initiatives are designed to ensure a stable supply of the iPS cell stock.

Toward a higher-quality iPS cell stock

Using next-generation methods such as RNA reprogramming, we are developing high-quality human iPS cells with a consistently high level of pluripotency.

Members

- Ryoko Hirohata
- Akira Kunitomi

Stock Production Group

- Yoshiko Sato (GL)
- Norihito Hirai (SGL)
- Yukiko Kobayashi (SGL)
- Naoko Hayakawa
- Yuji Henmi
- Akiko Kadotani
- Yoshihito Kajimura
- Mitsuyo Kawada
- Sayaka Maezori
- Yuki Matsubayashi
- Sonoka Matsuda
- Shun Minobe
- Miyuki Mouri
- Kasumi Nakao
- Eri Nishikawa
- Atsushi Nishizawa
- Wataru Takashiba
- Erina Watanabe
- Maho Yokoi
- Eri Yoneima

Quality Evaluation Group

- Masafumi Umekage (GL)
- Haruna Fujiyama
- Sho Hasegawa
- Satoko Hinatsu
- Akiko Matsumoto
- Mika Nishimura
- Keiko Ono
- Ito Teramoto
- Anna Ueda

Genome Analysis Group

- Naoki Amano (GL)
- Fumiyo Kitaoka (GL)
- Ichiro Fukuoka
- Koichi Kaneko
- Tomoaki Kato
- Kazuhiko Kitajima
- Yuko Kitano
- Junko Kuwahara
- Noriko Mori
- Chika Nakashima
- Masaki Nomura
- Kazuhide Ohnishi
- Mayumi Sakagami
- Tomoko Takahashi

Karyotypic Analysis Group

- Tokiko Ohkame (GL)
- Hitomi Araki
- Masako Kudo
- Yusuke Ohkame

Technology Development Group

- Mitsujiro Osawa (Assistant Professor)
- Ayako Nagahashi (SGL)
- Koichi Igura
- Akira Kunitomi
- Shoko Matsuo
- Misa Miyagawa
- Emiri Nakamura
- Chizu Nishida
- Sayaka Nishimura
- Monica Ohno
- Miho Saito
- Tomomi Yamaguchi
- Masami Yamashita

Profile

1987 M.S., Graduate School of Biosphere Science, Hiroshima Univ. / Sumitomo Pharma Co., Ltd.
1991 Intellectual Property Division, Sumitomo Pharma Co., Ltd.
2008 Head of the Intellectual Property Office, CiRA, Kyoto Univ.
2011 Head of Legal Affairs & IP Office, CiRA, Kyoto Univ.
2012 Concurrently Head of Legal Affairs & IP Office and Head of iPS Cell Therapy Promotion Office, CiRA, Kyoto Univ.
2013 Head of the Medical Applications Promoting Office, CiRA, Kyoto Univ.
2015 Current Position

Publication Highlight

(1) H1foo has a pivotal role in qualifying induced pluripotent stem cells
Kunitomi A *et al.*
Stem Cell Reports (2016), 6 (6): 825-833

GL=Group Leader SGL=Sub Group Leader

Department of Fundamental Cell Technology

Standardize and spread iPS cell technology

Isao Asaka Ph.D., Professor

Profile

1984 Graduated from School of Pharmacy, Kitasato Univ.
1986 M.S., Graduate School of Pharmacy, Kitasato Univ. / Senior Lecturer, Tokyo College of Medico-Pharmaco Technology
1989 AGC Techno Glass Co., Ltd. / Research Associate, School of Pharmacy, Kitasato Univ.
1994 Ph.D., Graduate School of Pharmacy, Kitasato Univ.
2007 Visiting Researcher, The Institute of Medical Science, The Univ. of Tokyo
2008 Junior Associate Professor, iCeMS, Kyoto Univ.
2010 Associate Professor, CiRA, Kyoto Univ.
2015 Current Position

Publication Highlights

(1) Pluripotent stem cell models of Blau syndrome reveal an IFN-γ-dependent inflammatory response in macrophages
Takada S *et al.*
Journal of Allergy and Clinical Immunology (2018), 141 (1): 339-349

(2) Proposal for "Fundamental principles of cell culture"
Kanda Y *et al.*
Tissue Culture Research Communications (2017), 36 (2): 13-19

(3) BMP-SMAD-ID promotes reprogramming to pluripotency by inhibiting p16/INK4A-dependent senescence
Hayashi Y *et al.*
PNAS (2016), 113 (46): 13057-13062

Summary

To expand the medical application of human iPS cells, we offer training programs to internal and external researchers on the establishment of iPS cell lines, cell maintenance and culture, quality evaluation methods, etc.

Research Progress

Activities to promote the wide adoption of iPS cell technology

We disseminate a range of technologies, including methods for the establishment of human iPS cells, culture techniques, and cell quality tools, to scientists and institutions researching human iPS cells towards medical application and drug discovery. To this end, we have been working on the formulation of technology guidelines based on the Good Cell Culture Practice (GCCP) and developing teaching materials for iPS cell education.

In FY 2017, we took part in a working group of the "Research for quality variability and good cell culture practice of hiPSCs" as part of the "Research Project for Practical Applications of Regenerative Medicine" founded by Japan Agency for Medical Research and Development. With an aim of sharing the basic concepts for cell culture by researchers, we drew a draft guidance, "Fundamental principles of cell culture." The document was published in Tissue Culture Research Communications. We also drew a draft guidance, "Fundamental principles of microscopic observation of cultured cells." Meanwhile, to assist beginners establishing feeder-free iPS cell lines from peripheral blood mononuclear cells, we prepared video teaching material that summarizes the experimental techniques.

Fundamental principles of cell culture

Principle 1
Be sufficiently aware that the cultured cell is derived from part of a living organism

Principle 2
Confirm the reliability of the material source and the validity of the usage

Principle 3
Protect the cultured cells from any contamination

Principle 4
Keep accurate records of the management and handling of the cultured cells

Principle 5
Consider the health and safety for cell culture personnels and for environment around

Handling of cell culture

Member

・Hiroko Endo

Supporting iPS cell research through appropriate management and maintenance of common equipment

Naoki Harada Ph.D., Associate Professor

Summary

iPS cell research requires the deployment of various equipment. The Common Equipment Management Office was set up to support research activity by taking charge of the management, maintenance, updating, etc., of the equipment. Among the cardinal items of common equipment are fluorescence-activated cell sorters (FACS), microscopes and other cell imaging machinery, and high-throughput sequencers for genome analysis.

Research Progress

Management of the Common Equipment Management Office

CiRA's Common Equipment Management Office was reorganized in April 2017 and now supports the institute's researchers based on a three-group structure: FACS Group, Imaging Group, and Genome Analysis Group (figure). The Office continues with the management and maintenance of common equipment and additionally provides support to each of its three groups.

The FACS Group possesses several flow cytometers adapted to multi-colored analysis. The Imaging Group is equipped with confocal microscopes and the latest multiphoton microscopes. The Genome Analysis Group possesses high-throughput sequencers to support omics analysis.

We additionally possess a large number of real-time PCR machines, capillary sequencers, and other equipment. The equipment requires systemically planned management and maintenance. As the director of the Common Equipment Management Office, I support our institute's research by budgeting appropriately and ensuring accurate and effective operation.

Organization of CiRA Common Equipment Management Office

- Common Equipment Management Office
  - Managing common equipment, its maintenance and budget. Supporting each group operation.
- FACS Group
  - Cell analysis and separation of target cells.
- Imaging Group
  - Imaging analysis for the cells of interest.
- Genome Analysis Group
  - Genome, epigenome and transcriptome analysis.

DNA sequencer

Member

・Hiroko Endo

Profile

1987 Graduated from Kyushu Medical Engineering College / Kyushu Medical Sciences, Inc.
2004 Ph.D., Graduate School of Medicine, Nagasaki Univ.
2007 Part-time Lecturer, School of Medicine, Nagasaki Univ.
2009 Mitsubishi Chemical Medicine Corporation
2014 Current Position
2015 Project Staff, Pharmaceuticals and Medical Devices Agency / Visiting Professor, Graduate School of Humanities and Sciences, Ochanomizu Univ. / Part-time Lecturer, Graduate School of Biomedical Sciences, Nagasaki Univ.

Publication Highlights

(1) Assessment of genomic stability of induced pluripotent stem (iPS) cells for regenerative medicine
Harada N
Igakunoayumi (2014), 250: 420-424

(2) A clinical study of patients with pericentromeric deletion and duplication within 16p12.2-p11.2.
Okamoto N *et al.*
American Journal of Medicine Genetics Part A (2014), 164A (1): 213-219

(3) Haploinsufficiency of NSD1 causes Sotos syndrome.
Kurotaki N *et al.*
Nature Genetics (2002), 30: 365-366

Department of Fundamental Cell Technology

Preclinical research — linking basic science to clinical application

Kenjiro Konno Ph.D., Associate Professor

Profile

1995 Graduated from Dept. of Veterinary Medicine, Nihon Univ.
1999 Ph.D., Graduate School of Veterinary Medicine, Hokkaido Univ.
2000 Assistant Professor, Institute of Experimental Animal Research, School of Medicine, Gunma Univ.
2006 Lecturer, Center for Molecular Medicine, Jichi Medical Univ.
2009 Assistant Professor, The Univ. of Tokyo Hospital
2010 Assistant Professor, Faculty of Life Sciences, Kyoto Sangyo Univ.
2015 Associate Professor, CiRA, Kyoto Univ.
2018 Head of Academic Collaboration Office, Fukushima Medical Device Development Support Centre

Publication Highlights

(1) Visible, safe and certain endotracheal intubation using endoscope system and inhalation anesthesia for rats
Konno K *et al.*, *Journal of Veterinary Medical Science* (2014), 76 (10): 1375-1381

(2) New visible endotracheal intubation method using the endoscope system for mice inhalational anesthesia
Konno K *et al.*, *Journal of Veterinary Medical Science* (2014), 76 (6): 863-868

(3) Experimental model of lacunar infarction in the gyrencephalic brain of the miniature pig: neurological assessment and histological, immunohistochemical, and physiological evaluation of dynamic corticospinal tract deformation
Tanaka Y *et al.*, *Stroke* (2008), 39 (1): 205-212

Summary

Preclinical research of drug candidates uses animals to test for the pharmaceutical action and efficacy, in vivo pharmacokinetics, safety, and other aspects. The animals must be treated ethically, taking special care with the test methods, breeding facilities, and other aspects so as to prevent animal suffering as much as possible.

Research Progress

Establishment of CiRA's second Animal Research Facility

In July 2017, CiRA opened its second in-house animal research facility, thus establishing a system that will enhance iPS cell-based research and the development of therapeutic treatments.

Aiming for animal welfare-conscious experimentation

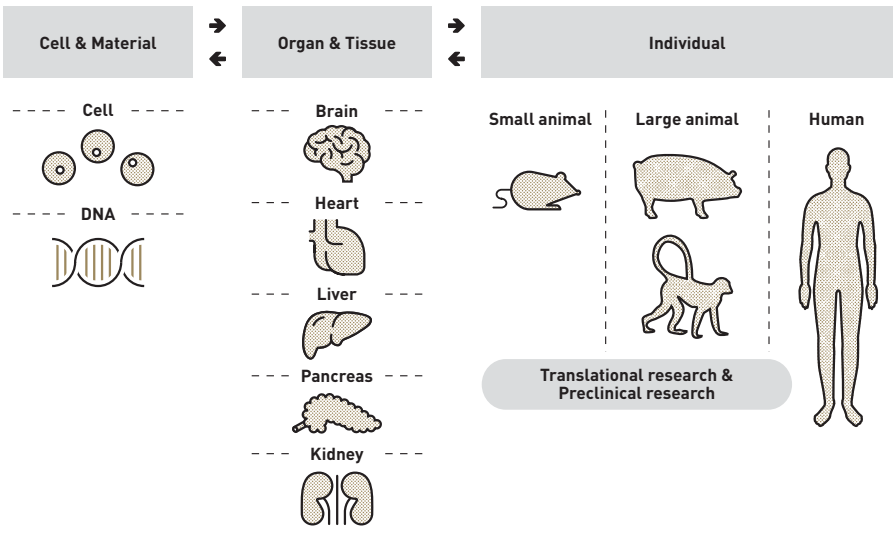
Before research results can be applied to humans, animal experimentation is unfortunately unavoidable, but experiments must be conducted so as to avoid unnecessary suffering onto the animals. One of the most important tools for achieving this is anesthesia.

Accordingly, we are researching anesthetic techniques for mice and rats. To ensure a stable effect, particularly when anesthetic treatment is required for an extended period, we have developed a technique for inhalation anesthesia in small animals, which is performed as in humans via an artificial ventilator with endoscope-guided intubation.

Members

- Yasuhiro Yamada (Professor, Ex-Head of Animal Research Facility)
- Yoriko Indo
- Daisuke Seki
- Akito Tanaka

Research object of life science



Data-based discussion of ethical issues of iPS cell technology

Misao Fujita Ph.D., Associate Professor

Summary

The clinical application of iPS cell technology will be difficult without public understanding and agreement. Accordingly, ethical, legal, and social issues need to be addressed. As a concrete example, we addressed the issue of research using human-animal chimeric embryos.

Research Progress

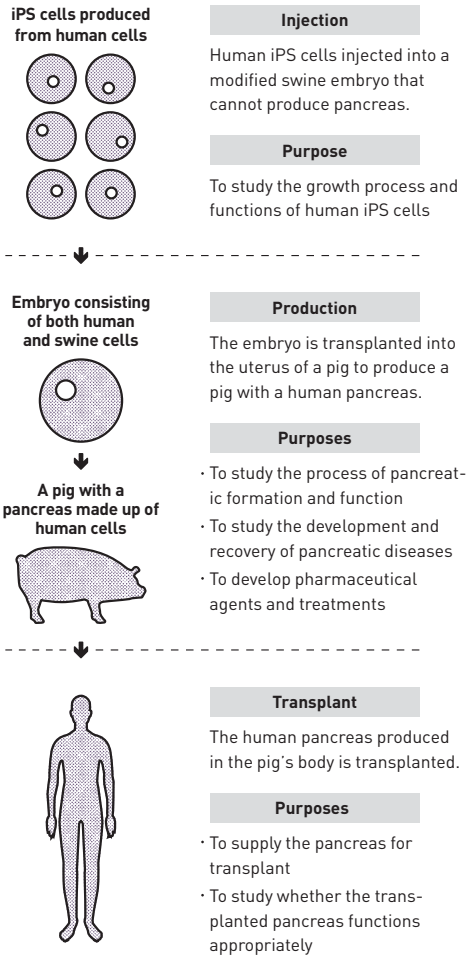
Questionnaire survey of attitudes to human-animal chimeric embryo research

Research using human-animal chimeric embryos involves injecting human iPS cells into animal embryos with the aim of creating human organs (figure). This research holds promise in organ transplant treatment, but it also has serious ethical concerns. According to our questionnaire survey among citizens and researchers, both groups displayed strong resistance to the inclusion of human cells in animal brain, sperm, or eggs, but not in animal heart, liver, blood, or skin. The findings were referred to in discussions on the relaxation of regulations in Japan.

Members

- Jusaku Minari (Associate Professor)
- Yoshimi Yashiro (Associate Professor)
- Taichi Hatta
- Yuko Kuyama
- Chigusa Nakagawa
- Tsutomu Sawai
- Mika Suzuki
- Miki Tanigawa

Examples of research using animal-human chimeric embryos



Publication addressing ethical issues in iPS cell research

We published a Japanese-language book entitled "Where scientific knowledge meets knowledge of humanty-Considering the ethical issues in iPS cell research." Covering the potentially wide impact of iPS cell research, the book aims to transcend barriers between sciences and humanities and inform the public about relevant issues.

Profile

1992 Graduated from Faculty of Human Sciences, Univ. of Tsukuba
2006 Ph.D., Graduate School of Medicine, Kyoto Univ.
2008 Research Assistant Professor, Graduate School of Medicine, The Univ. of Tokyo
2009 Assistant Professor, Graduate School of Medicine, The Univ. of Tokyo
2013 Current Position

Publication Highlights

(1) The Japanese generally accept human-animal chimeric embryo research but are concerned about human cells contributing to brain and gametes
Sawai T *et al.*,*Stem Cells Translational Medicine* (2017), 6 (8): 1749-1750

(2) Public attitudes in Japan towards human-animal chimeric embryo research using human iPS cells
Sawai T *et al, Regenerative Medicine* (2017), 12 (3): 233-248

(3) 科学知と人文知の接点―iPS細胞研究の倫理的課題を考える―
(Where scientific knowledge meets knowledge of humanity-Considering the ethical issues in iPS cell research (Japanese only))
Supervised by Yamanaka S, Edited by Uehiro Research Division for iPS Cell Research (2017), Koubundou Publishers Inc.

Uehiro Research Division for iPS Cell Ethics

Working with society to create a new vision of life in the age of regenerative medicine

Yoshimi Yashiro Ph.D., Associate Professor

Profile

2003 Graduated from Faculty of Pharmacy, Meijo Univ.
2009 Ph.D., Graduate School of Medicine, The Univ. of Tokyo / Assistant Professor, School of Medicine, Keio Univ.
2011 Senior Lecturer, Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical Univ.
2012 Associate Professor, School of Medicine, Keio Univ.
2013 Associate Professor, CiRA, Kyoto Univ.
2018 Professor, Health Innovation School Installation Preparation, Kanagawa Univ. of Human Services

Publication Highlights

(1) 再生医療報道を考える 手術日の即日報道は必要か? ヒトiPS細胞臨床試験と報道 (Clinical trial and news reports about human iPS cells (Japanese only))
Kaori Muto, Yoshimi Yashiro
Journalism (2017), 326: 86-91

(2) A comparative analysis of attitudes on communication toward stem cell research and regenerative medicine between the public and the scientific community
Shineha R *et al.*
Stem Cells Translational Medicine (2018), (2): 251-257

(3) Science communication in regenerative medicine: Implications for the role of academic society and science policy
Shineha R *et al.*
Regenerative Therapy (2017), 7: 89-97

Summary

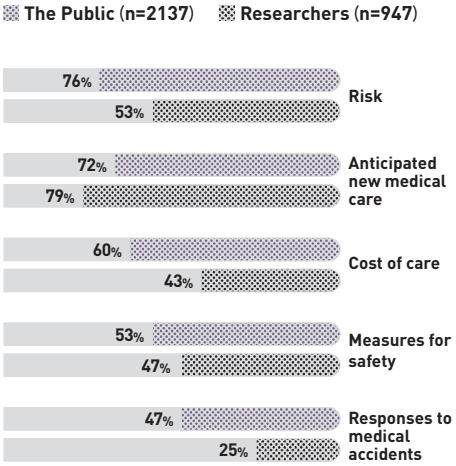
Regenerative medicine attracts a very high level of public interest and the media. We are conducting media analysis and questionnaire surveys to identify differences in the thinking of the general public and researchers. In parallel, we are creating opportunities for non-specialists to deepen their understanding of regenerative medicine.

Research Progress

For regenerative medicine to progress, an understanding of science is needed

Regenerative medicine is the focus of great public hope, but its application is still in its infancy. Our laboratory surveys the current state of reporting by analyzing regenerative medicine-related coverage in newspapers and other media(1), conducting questionnaire surveys to investigate differences in perceptions between non-specialists and researchers(2)(3), and using subcultural contexts such as science fiction, manga comics, and anime to research the relationship between society and regenerative medicine.

Differences in the response between the public and researchers to "What do you want to know?" (for the public) and "What do you want to convey?" (for researchers) (Abstracted and modified from (2))



To establish "responsible research and innovation"

As part of the Program for Developing Risk Communication Models launched by the Japanese Ministry of Education, Culture, Sports, Science and Technology, we are organizing public lectures to raise the level of public awareness about regenerative medicine.

Meanwhile, in FY 2016, we began research into the costs of regenerative medicine as a contribution to ensuring that its benefits can be enjoyed by a broad section of the population. In this research, we explore the optimal price structure of regenerative medicine products and the role that researchers can play in ensuring its soonest possible application. We also study other financial aspects, beginning from the initial stage of the technology's development.

Members

・Chigusa Nakagawa ・Miki Tanigawa

Increasing the public credit in cutting-edge life science research

Jusaku Minari Ph.D., Associate Professor

Summary

We study communication between researchers and the public, the rules and guidelines that govern research, and reactions to the social effects of scientific results, with an emphasis on iPS cell research.

Research Progress

Society and life science research

A key to iPS cell research is public trust. To understand how trust is made and preserved, we are engaged in the "ISLE (Innovation for Science, Life and Ethics) project" adopted by the Japan Science and Technology Agency (JST).

Initiatives under the ISLE project

Under the ISLE project, we are following two lines of research.

First, we are studying potential regulatory frameworks for the promotion of cutting-edge life science research. Here, with reference mainly to government-formulated guidelines, we are investigating guideline formulations, associated issues, and responses to the guidelines. In this examination, we focus mainly on the handling of blood and other samples provided by research participants and the genome data obtained from these samples. In stem cell research, we are working to build a picture of the regulatory environment surrounding clinical applications and biobank operations, especially in Japan and the U.K., which are leading countries in this field.

The other line of research concerns how to communicate with the public. Here, we are engaged in deepening discussions with specialists from a wide range of fields in Japan and overseas on the optimal structure of questionnaire surveys and workshops to extract perceptions and attitudes of the general public. In particular, we are using art and design to engage people with no great interest in life science research.

Members

・Chigusa Nakagawa ・Miki Tanigawa

Researchers discussing government-formulated guidelines

Profile

2005 Graduated from Faculty of Environmental Engineering, The Univ. of Kitakyushu
2010 Ph.D., Graduate School of Environmental Engineering, The Univ. of Kitakyushu / Postdoctoral Fellow, Institute for Research in Humanities, Kyoto Univ.
2013 Assistant Professor, Graduate School of Medicine, Osaka Univ.
2015 Deputy Director, Dept. of Research Infrastructure, Japan Agency for Medical Research and Development (AMED)
2016 Assistant Professor, Graduate School of Medicine, Osaka Univ.
2017 Current Position

Publication Highlights

(1) Including all voices in international data-sharing governance
Kaye *J et al.*
Human Genomics (2018), 12: 13

(2) Island lessons: inheritance, solidarity, creativity (Considerations of islands, science and technologies and art) (in Japanese)
Minari J
Islands (2018), 253: 56-59

(3) Ethics policy and public engagement in biomedical research on genomic information (in Japanese)
Minari J and Yoshizawa G
Journal of Medicine, Life and Ethics, Society (2017), 14: 52-60

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Honors and Awards (2017.4-2018.3)

Reseaech Promotion Awards, Honorary Doctorates, etc.

Month	Name of the Award	Awardee	Lab
2017.6	Kao Science Award	Yoko Hamazaki	Hamazaki Lab.
2017.7	Toshihiko Tokizane Memorial Award for Excellent Graduate Study in Neuroscience	Hideya Sakaguchi	Takahashi Lab.
2017.9	JCA-Mauvernay Award	Yasuhiro Yamada	Yamada Lab.
2018.2	Murao Scholarship Association Academic Encouragement Prize	Makoto Ikeya	Ikeya Lab.
2018.3	Future Foundation Award	Naoko Takasu	Takasu Lab.
2018.3	The 69th NHK Broadcast Cultural Award	Shinya Yamanaka	Yamanaka Lab.
2018.3	Japanese Society for Regenerative Medicine Award	Jun Takahashi Makoto Ikeya	Takahashi Lab. Ikeya Lab.

Young Investigator Awards, Poster Awards, etc.

Month	Name of the Award	Awardee	Lab
2017.5	The 60th Japanese Society of Nephrology Excellent Presentation Award	Tomoko Kasahara, Shinichi Sueta, Natsumi Okamoto, Kenji Osafune	Osafune Lab.
2017.6	The 43rd Naito Conference Excellent Poster Award, The Naito Foundation Research Grant	Kaoru Richard Komatsu	Saito H Lab.
2017.6	Excellent Presentation Award (HISF 20th Anniversary International Symposium)	Kaoru Richard Komatsu	Saito H Lab.
2017.8	Best Presentation Award (Amgen Scholars Japan Symposium 2017)	Anna Elizabeth Sappington	Fujibuchi Lab.
2017.9	The 8th Molecular Pancrea Forum Excellent Presentation Award	Tomoko Kasahara, Shinichi Sueta, Natsumi Okamoto, Kenji Osafune	Osafune Lab.
2017.10	Japanese Society of Hematology Encouragement Prize	Yoko Nishinaka	Saito M Lab.
2017.11	ASH Abstract Achievement Award	Yuki Morimoto	Yoshida Lab.
2018.2	ISN Frontiers Meeting 2018 (ISN: International Society of Nephrology) The Highest Abstract Award	Hirofumi Hitomi, Akira Nishiyama, Kenji Osafune	Osafune Lab.
2018.1	The 1st JCS Council Forum on Basic Cardiovascular Research (BCVR), Poster Award	Masafumi Takeda	Yamashita Lab.
2018.3	FY2017 Tokyo Medical Association Medical Research Encouragement Prize	Akira Kunitomi	Takasu Lab.

Internal Award

Month	Name of the Award	Awardee	Lab
2018.1	The 5th CiRA Prize	Junya Toguchida Makoto Ikeya	Toguchida Lab. Ikeya Lab.

Publications (2017.4-2018.3)

2017

May

01 – Yamamoto Y, Makiyama T, Harita T, Sasaki K, Wuriyanghai Y, Hayano M, Nishiuchi S, Kohjitani H, Hirose S, Chen J, Yokoi F, Ishikawa T, Ohno S, Chonabayashi K, Motomura H, Yoshida Y, Horie M, Makita N, Kimura T
Allele-specific ablation rescues electrophysiological abnormalities in a human iPS cell model of long-QT syndrome with a CALM2 mutation
Human Molecular Genetics, 26(9):1670-1677

02 – Sano N, Shimogawa T, Sakaguchi H, Ioroi Y, Miyawaki Y, Morizane A, Miyamoto S, Takahashi J
Enhanced axonal extension of subcortical projection neurons isolated from murine embryonic cortex using neuropilin-1
Frontiers in Cellular Neuroscience, 11:123

03 – Sone M, Morone N, Nakamura T, Tanaka A, Okita K, Woltjen K, Nakagawa M, Heuser JE, Yamada Y, Yamanaka S, Yamamoto T
Hybrid cellular metabolism coordinated by Zic3 and Esrrb synergistically enhances induction of naive pluripotency
Cell Metabolism, 25(5):1103-1117

04 – Kanki Y, Nakaki R, Shimamura T, Matsunaga T, Yamamizu K, Katayama S, Suehiro J, Osawa T, Aburatani H, Kodama T, Wada Y, Yamashita JK, Minami T
Dynamically and epigenetically coordinated GATA/ETS/SOX transcription factor expression is indispensable for endothelial cell differentiation
Nucleic Acids Research, 45(8):4344-435

05 – Yoshitoshi-Uebayashi EY, Toyoda T, Yasuda K, Kotaka M, Nomoto K, Okita K, Yasuchika K, Okamoto S, Takubo N, Nishikubo T, Soga T, Uemoto S, Osafune K
Modelling urea-cycle disorder citrullinemia type 1 with disease-specific iPSCs Biochemical and biophysical research
Biochemical and Biophysical Research Communications, 486(3):613-619

06 – Liang YJ, Wang CY, Wang IA, Chen YW, Li LT, Lin CY, Ho MY, Chou TL, Wang YH, Chiou SP, Lin YJ, Yu J
Interaction of glycosphingolipids GD3 and GD2 with growth factor receptors maintains breast cancer stem cell phenotype
Oncotarget, 88(29):47454-47473

07 – Chijimatsu R, Ikeya M, Yasui Y, Ikeda Y, Ebina K, Moriguchi Y, Shimamura K, Hart DA, Yoshikawa H, Nakamura N
Characterization of mesenchymal stem cell-like cells derived from human iPSCs via neural crest development and their application for osteochondral repair
Stem Cells International, 2017:1960965

08 – Ohigashi I, Ohte Y, Setoh K, Nakase H, Maekawa A, Kiyonari H, Hamazaki Y, Sekai M, Sudo T, Tabara Y, Sawai H, Omae Y, Yuliwulandari R, Tanaka Y, Mizokami M, Inoue H, Kasahara M, Minato N, Tokunaga K, Tanaka K, Matsuda F, Murata S, Takahama Y
A human PSMB11 variant affects thymoproteasome processing and CD8+ T cell production
JCI Insight, 22(10):e93664

09 – Gee P, Xu H, Hotta A
Cellular reprogramming, genome editing, and alternative CRISPR Cas9 technologies for precise gene therapy of Duchenne muscular dystrophy
Stem Cells International, 2017:8765154

10 – Hirosawa M, Fujita Y, Parr CJC, Hayashi K, Kashida S, Hotta A, Woltjen K, Saito H
Cell-type-specific genome editing with a microRNA-responsive CRISPR–Cas9 switch
Nucleic Acids Research, 45(13):e118

11 – Kawasaki S, Fujita Y, Nagaike T, Tomita K, Saito H
Synthetic mRNA devices that detect endogenous proteins and distinguish mammalian cells
Nucleic Acids Research, 45(12):e117

12 – Kondo Y, Toyoda T, Ito R, Funato M, Hosokawa Y, Matsui S, Sudo T, Nakamura M, Okada C, Zhuang X, Watanabe A, Ohta A, Inagaki N, Osafune K
Identification of a small molecule that facilitates the differentiation of human iPSCs/ESCs and mouse embryonic pancreatic explants into pancreatic endocrine cells
Diabetologia, 60(8):1454-1466

13 – Imamura K, Izumi Y, Watanabe A, Tsukita K, Woltjen K, Yamamoto T, Hotta A, Kondo T, Kitaoka S, Ohta A, Tanaka A, Watanabe D, Morita M, Takuma H, Tamaoka A, Kunath T, Wray S, Furuya H, Era T, Makioka K, Okamoto K, Fujisawa T, Nishitoh H, Homma K, Ichijo H, Julien JP, Obata N, Hosokawa M, Akiyama H, Kaneko S, Ayaki T, Ito H, Kaji R, Takahashi R Yamanaka S, Inoue H
The Src/c-Abl pathway is a potential therapeutic target in amyotrophic lateral sclerosis
Science Translational Medicine, 9(391):eaaf3962

2017

June

14 – Yokobayashi S, Okita K, Nakagawa M, Nakamura T, Yabuta Y, Yamamoto T, Saitou M
Clonal variation of human induced pluripotent stem cells for induction into the germ cell fate
Biology of Reproduction, 96(6):1154-1166

15 – Karagiannis P, Takashima Y
Surface markers guide the journey toward naive pluripotency
Cell Stem Cell, 20(6):737-738

16 – Takada S, Kambe N, Kawasaki Y, Niwa A, Honda-Ozaki F, Kobayashi K, Osawa M, Nagahashi A, Semi K, Hotta A, Asaka I, Yamada Y, Nishikomori R, Heike T, Matsue H, Nakahata T, Saito MK
Pluripotent stem cell models of Blau syndrome reveal an IFN-γ-dependent inflammatory response in macrophages
Journal of Allergy and Clinical Immunology, 141(1):339-349

17 – Kato I, Nishinaka Y, Nakamura M, Akarca AU, Niwa A, Ozawa H, Yoshida K, Mori M, Wang D, Morita M, Ueno H, Shiozawa Y, Shiraishi Y, Miyano S, Gupta R, Umeda K, Watanabe K, Koh K, Adachi S, Heike T, Saito MK, Sanada M, et al.
Hypoxic adaptation of leukemic cells infiltrating the CNS affords a therapeutic strategy targeting VEGFA
Blood, 129(23):3126-3129

18 – Chen Z, Chang WY, Etheridge A, Strickfaden H, Jin Z, Palidwor G, Cho JH, Wang K, Kwon SY, Doré C, Raymond A, Hotta A, Ellis J, Kandel RA, Dilworth FJ, Perkins TJ, Hendzel MJ, Galas DJ, Stanford WL
Reprogramming progeria fibroblasts re-establishes a normal epigenetic landscape
Aging Cell, 16(4):870-887

19 – Hsu K, Lee TY, Periasamy A, Kao FJ, Li LT, Lin CY, Lin HJ, Lin M
Adaptable interaction between aquaporin-1 and band 3 reveals a potential role of water channel in blood CO2 transport
The FASEB Journal, 31(10):4256-4264

20 – Yoshida Y, Yamanaka S
Induced pluripotent stem cells 10 years later: for cardiac applications
Circulation Research, 120(12):1958-1968

21 – Kondo Y, Toyoda T, Inagaki N and Osafune K
iPSC technology-based regenerative therapy for diabetes
Journal of Diabetes Investigation, 9:234-243

22 – Hayano M, Makiyama T, Kamakura T, Watanabe H, Sasaki K, Funakoshi S, Wuriyanghai Y, Nishiuchi S, Harita T, Yamamoto Y, Kohjitani H, Hirose S, Yokoi F, Chen J, Baba O, Horie T, Chonabayashi K, Ohno S, Toyoda F, Yoshida Y, Ono K, Horie M, Kimura T
Development of a patient-derived induced pluripotent stem cell model for the investigation of SCN5A-D1275N-related cardiac sodium channelopathy
Circulation Journal, 81(12):1783-1791

23 – Kuang Y, Miki K, Parr CJ, Hayashi K, Takei I, Li J, Iwasaki M, Nakagawa M, Yoshida Y, Saito H
Efficient, selective removal of human pluripotent stem cells via ecto-alkaline phosphatase-mediated aggregation of synthetic peptides
Cell Chemical Biology, 24(6):685-694

24 – Parr CJ, Yamanaka S, and Saito H
An update on stem cell biology and engineering for brain development
Molecular Psychiatry, 22:808-819

25 – Ito K, Yamada Y
Cellular reprogramming technology for dissecting cancer epigenome in vivo
Epigenomics, 9(7):997-1011

26 – Iki T, Tanaka M, Kitajiri SI, Kita T, Kawasaki Y, Mizukoshi A, Fujibuchi W, Nakagawa T, Nakahata T, Ito J, Omori K, Saito MK
Microarray analyses of otospheres derived from the cochlea in the inner ear identify putative transcription factors that regulate the characteristics of otospheres
PLOS ONE, 12(6):e0179901

27 – Nakanishi H, Miki K, Komatsu KR, Umeda M, Mochizuki M, Inagaki A, Yoshida Y, Saito H
Monitoring and visualizing microRNA dynamics during live cell differentiation using microRNA-responsive non-viral reporter vectors
Biomaterials, 128:121-135

July

28 – Sato K, Kato A, Sekai M, Hamazaki Y, Minato N
Physiologic thymic involution underlies age-dependent accumulation of senescence-associated CD4+ T cells
Journal of Immunology, 199(1):138-148

29 – Sawai T, Hatta T, Fujita M
The japanese generally accept human-animal chimeric embryo research but are concerned about human cells contributing to brain and gametes
Stem Cells Translational Medicine, 6(8):1749-1750

30 – Ohta H, Kurimoto K, Okamoto I, Nakamura T, Yabuta Y, Miyauchi H, Yamamoto T, Okuno Y, Hagiwara M, Shirane K, Sasaki H, Saitou M
In vitro expansion of mouse primordial germ cell-like cells recapitulates an epigenetic blank slate
The EMBO Journal, 36(13):1888-1907

31 – Imajo M, Kondoh K, Yamamoto T, Nakayama K, Nakajima-Koyama M, Nishida E

2017

Antagonistic interactions between extracellular signal regulated kinase mitogen activated protein kinase and retinoic acid receptor signaling in colorectal cancer cells
Molecular and Cellular Biology, 37(15):e00012-17

32 – Yagi M, Kishigami S, Tanaka A, Semi K, Mizutani E, Wakayama S, Wakayama T, Yamamoto T, Yamada Y
Derivation of ground-state female ES cells maintaining gamete-derived DNA methylation
Nature, 548(7666):224-227

33 – Tan G W, Kondo T, Murakami N, Imamura K, Enami T, Tsukita K, Shibukawa R, Funayama M, Matsumoto R, Ikeda A, Takahashi R, Inoue H
Induced pluripotent stem cells derived from an autosomal dominant lateral temporal epilepsy(ADLTE) patient carrying S473L mutation in leucine-rich glioma inactivated 1(LGI1)
Stem Cell Research, 24:12-15

34 – Murakamia N, Ishikawa T, Kondo T, Imamura K, Tsukita K, Enami T, Funayama M, Shibukawa R, Matsumoto S, Izumi Y, Ohta E, Obata F, Kaji R, Inoue H
Establishment of DYT5 patient-specific induced pluripotent stem cells with a GCH1 mutation
Stem Cell Research, 24:36-39

35 – Sekine S, Kondo T, Murakami N, Imamura K, Enami T, Shibukawa R, Tsukita K, Funayama M, Inden M, Kurita H, Hozumi I, Inoue H
Induced pluripotent stem cells derived from a patient with familial idiopathic basal ganglia calcification(IBGC)caused by a mutation in SLC20A2 gene
Stem Cell Research, 24:40-43

August

36 – Chen B, Teng J, Liu H, Pan X, Zhou Y, Huang S, Lai M, Bian G, Mao B, Sun W, Zhou Q, Yang S, Nakahata T, Ma F
Inducible overexpression of RUNX1b/c in human embryonic stem cells blocks early hematopoiesis from mesoderm
Journal of Molecular Cell Biology, 9(4):262-273

37 – Taguchi J, Yamada Y
In vivo reprogramming for tissue regeneration and organismal rejuvenation
Current Opinion in Genetics & Development, 46:132-140

38 – Ikeda T, Uchiyama I, Iwasaki M, Sasaki T, Nakagawa M, Okita K, Masui S
Artificial acceleration of mammalian cell reprogramming by bacterial proteins
Genes to Cells, 22(10):918-928

39 – Toyoda T, Kimura A, Tanaka H, Ameku T, Mima A, Hirose Y, Nakamura M, Watanabe A, and Osafune K
Rho-associated kinases and non-muscle myosin IIs inhibit the differentiation of human iPSCs to pancreatic endoderm
Stem Cell Reports, 9(2):419-428

40 – Hosokawa Y, Toyoda T, Fukui K, Baden MY, Funato M, Kondo Y, Sudo T, Iwahashi H, Kishida M, Okada C, Watanabe A, Asaka I, Osafune K, Imagawa A, Shimomura I
Insulin-producing cells derived from 'induced pluripotent stem cells' of patients with fulminant type 1 diabetes: Vulnerability to cytokine insults and increased expression of apoptosis-related genes
Journal of Diabetes Investigation, 9(3):481-493

41 – Kimura A, Toyoda T, Nishi Y, Nasu M, Ohta A, Osafune K.
Small molecule AT7867 proliferates PDX1-expressing pancreatic progenitor cells derived from human pluripotent stem cells
Stem Cell Research, 24:61-68

42 – Kawamura M, Miyagawa S, Fukushima S, Saito A, Miki K, Funakoshi S, Yoshida Y, Yamanaka S, Shimizu T, Okano T, Daimon T, Toda T, Sawa Y
Enhanced therapeutic effects of human iPS cell derived-cardiomyocyte by combined cell-sheets with omental flap technique in porcine ischemic cardiomyopathy model
Scientific Reports, 7:8824

43 – Morizane A, Kikuchi T, Hayashi T, Mizuma H, Takara S, Doi H, Mawatari A, Glasser MF, Shiina T, Ishigaki H, Itoh Y, Okita K, Yamasaki E, Doi D, Onoe H, Ogasawara K, Yamanaka S, Takahashi J
MHC matching improves engraftment of iPSC-derived neurons in non-human primates
Nature Communications, 8:385

44 – Kikuchi T, Morizane A, Doi D, Magotani H, Onoe H, Hayashi T, Mizuma H, Takara S, Takahashi R, Inoue H, Morita S, Yamamoto M, Okita K, Nakagawa M, Parmar M, Takahashi J
Human iPS cell-derived dopaminergic neurons function in a primate Parkinson's disease mode
Nature, 548(7669):592-596

45 – Watanabe N, Nogawa M, Ishiguro M, Maruyama H, Shiba M, Satake M, Eto K, Handa M
Refined methods to evaluate the in vivo hemostatic function and viability of transfused human platelets in rabbit models
Transfusion, 57(8):2035-2044

September

46 – Hino K, Horigome K, Nishio M, Komura S, Nagata S, Zhao C, Jin Y, Kawakami K, Yamada Y, Ohta A, Toguchida J, Ikeya M
Activin-A enhances mTOR signaling to promote aberrant chondrogenesis in fibrodysplasia ossificans progressiva
Journal of Clinical Investigation, 127(9):3339-3352

47 – Kitani-Morii F, Imamura K, Kondo T, Ohara R, Enami T, Shibukawa R, Yamamoto T, Sekiguchi K, Toguchida J, Mizuno T, Nakagawa M, Inoue H

2017

Analysis of neural crest cells from Charcot-Marie-Tooth disease patients demonstrates disease-relevant molecular signature
NeuroReport, 28(13):814-821

48 – Matsuzono K, Imamura K, Murakami N,Tsukita K, Yamamoto T, Izumi Y, Kaji R, Ohta Y, Yamashita T, Abe K, Inoue H
Antisense oligonucleotides reduce RNA foci in spinocerebellar ataxia 36 patient iPSCs
Molecular Therapy-Nucleic Acids, 8:211-219

49 – Nakano-Kobayashi A, Awaya T, Kii I, Sumida Y, Okuno Y, Yoshida S, Sumida T, Inoue H, Hosoya T, Hagiwara M
Prenatal neurogenesis induction therapy normalizes brain structure and function in Down syndrome mice
PNAS, 114(38):10268-10273

50 – Miyauchi H, Ohta H, Nagaoka S, Nakaki F, Sasaki K, Hayashi K, Yabuta Y, Nakamura T, Yamamoto T, Saitou M
Bone morphogenetic protein and retinoic acid synergistically specify female germ-cell fate in mice
The EMBO Journal, 36(21):3100-3119

51 – Shibata T, Fujita Y, Ohno H, Suzuki Y, Hayashi K, Komatsu KR, Kawasaki S, Hidaka K, Yonehara S, Sugiyama H, Endo M, Saito H
Protein-driven RNA nanostructured devices that function in vitro and control mammalian cell fate
Nature Communications, 8:540

52 – Katayama H, Tamai K, Shibuya R, Nakamura M, Mochizuki M, Yamaguchi K, Kawamura S, Tochigi T, Sato I, Okanishi T, Sakurai K, Fujibuchi W, Arai Y, Satoh K
Long non-coding RNA HOTAIR promotes cell migration by upregulating insulin growth factor-binding protein 2 in renal cell carcinoma
Scientific Reports, 7:12016

53 – Hitomi H, Kasahara T, Katagiri N, Hoshina A, Mae SI, Kotaka M, Toyohara T, Rahman A, Nakano D, Niwa A, Saito MK, Nakahata T, Nishiyama A, Osafune K
Human pluripotent stem cell derived erythropoietin-producing cells ameliorate renal anemia in mice
Science Translational Medicine, 9(409):eaaj2300

54 – Sugimoto N, Eto K
Platelet production from induced pluripotent stem cells
Journal of Thrombosis and Haemostatis, 15(9):1717-1727

October

55 – Ikeda T, Uchiyama I, Iwasaki M, Sasaki T, Nakagawa M, Okita K, Masui S
Artificial acceleration of mammalian cell reprogramming by bacterial proteins
Genes to Cells, 22(10):918-928

56 – Kojima Y, Sasaki K, Yokobayashi S, Sakai Y, Nakamura T, Yabuta Y, Nakaki F, Nagaoka S, Woltjen K, Hotta A, Yamamoto T, Saitou M
Evolutionarily distinctive transcriptional and signaling programs drive human germ cell lineage specification from pluripotent stem cells
Cell Stem Cell, 21(4):517-532

57 – Kieffer TJ, Woltjen K, Osafune K, Yabe D, Inagaki N
Beta-cell replacement strategies for diabetes
Journal of Diabetes Investigation, 9(3):457-463

58 – Kawatou M, Masumoto H, Fukushima H, Morinaga G, Sakata R, Ashihara T, Yamashita JK
Modelling Torsade de Pointes arrhythmias in vitro in 3D human iPS cell-engineered heart tissue
Nature Communications, 8:1078

59 – Kim JH, Kurtz A, Yuan BZ, Zeng F, Lomax G, Loring JF, Crook J, Ju JH, Clarke L, Inamdar MS, Pera M, Firpo MT, Sheldon M, Rahman N, O'Shea O, Pranke P, Zhou Q, Isasi R, Rungsiwiwut R, Kawamata S, Oh S, Ludwig T, Masui T, Novak TJ, Takahashi T, Fujibuchi W, Koo SK, Stacey GN
Report of the international stem cell banking initiative workshop activity: Current hurdles and progress in seed-stock banking of human pluripotent stem cells
Stem Cells Translational Medicine, 6(11):1956-1962

60 – Sugimoto N, Eto K
Development of iPS cell-derived blood products and production guidelines
Rinsho Ketsueki, 58(10):2150-2159

61 – Yagi M, Yamanaka S, Yamada Y
Epigenetic foundations of pluripotent stem cells that recapitulate in vivo pluripotency
Laboratory Investigation, 97(10):1133-1141

November

62 – Barker RA, Parmar M, Studer L, Takahashi J
Human trials of stem cell-derived dopamine neurons for Parkinson's disease: Dawn of a new era
Cell Stem Cell, 21(5):569-573

63 – Hermanto Y, Sunohara T, Faried A, Takagi Y, Takahashi J, Maki T, Miyamoto S
Transplantation of feeder-free human induced pluripotent stem cell-derived cortical neuron progenitors in adult male Wistar rats with focal brain ischemia
Journal of Neuroscience Research, 96(5):863-874

64 – Matsuo K, Sone M, Honda-Kohmo K, Toyohara T, Sonoyama T, Taura D, Kojima K, Fukuda Y, Ohno Y, Inoue M, Ohta A, Osafune K, Nakao K, Inagaki N
Significance of dopamine D1 receptor signalling for steroidogenic differentiation of human induced pluripotent stem cells

2017 - 2018

Scientific Reports, 7(1):15120

65 – Kondo T, Imamura K, Funayama M, Tsukita K, Miyake M, Ohta A, Woltjen K, Nakagawa M, Asada T, Arai T, Kawakatsu S, Izumi Y, Kaji R, Iwata N, Inoue H
iPSC-Based compound screening and in vitro trials identify a synergistic anti-amyloidβ combination for Alzheimer's disease
Cell Reports, 21(8):2304-2312

66 – Ikeda H, Sone M, Yamanaka S, Yamamoto T
Structural and spatial chromatin features at developmental gene loci in human pluripotent stem cells
Nature Communications, 8:1616

67 – Hayano M, Makiyama T, Kamakura T, Watanabe H, Sasaki K, Funakoshi S, Wuriyanghai Y, Nishiuchi S, Harita T, Yamamoto Y, Kohjitani H, Hirose S, Yokoi F, Chen J, Baba O, Horie T, Chonabayashi K, Ohno S, Toyoda F, Yoshida Y, Ono K, Horie M, Kimura T
Development of a patient-derived induced pluripotent stem cell model for the investigation of SCN5A-D1275N-related cardiac sodium channelopathy
Circulation Journal, 81(12):1783-1791

68 – Morita K, Noura M, Tokushige C, Maeda S, Kiyose H, Kashiwazaki G, Taniguchi J, Bando T, Yoshida K, Ozaki T, Matsuo H, Ogawa S, Liu PP, Nakahata T, Sugiyama H, Adachi S, Kamikubo Y
Autonomous feedback loop of RUNX1-p53-CBFB in acute myeloid leukemia cells
Scientific Reports, 7:16604

December

69 – Shirotani K, Matsuo K, Ohtsuki S, Masuda T, Asai M, Kutoku Y, Ohsawa Y, Sunada Y, Kondo T, Inoue H, Iwata N
A simplified and sensitive method to identify Alzheimer's disease biomarker candidates using patient-derived induced pluripotent stem cells(iPSCs)
The Journal of Biochemistry, 162(6):391-394

70 – Mitani T, Yabuta Y, Ohta H, Nakamura T, Yamashiro C, Yamamoto T, Saitou M, Kurimoto K
Principles for the regulation of multiple developmental pathways by a versatile transcriptional factor, BLIMP1
Nucleic Acids Research, 45(21):12152-12169

71 – Shineha R, Inoue Y, Ikka T, Kishimoto A, Yashiro Y
Science communication in regenerative medicine: Implications for the role of academic society and science policy
Regenerative Therapy, 7:89-97

72 – Kotaka M, Toyoda T, Yasuda K, Kitano Y, Okada C, Ohta A, Watanabe A, Uesugi M, Osafune K
Adrenergic receptor agonists induce the differentiation of pluripotent stem cell-derived hepatoblasts into hepatocyte-like cells
Scientific Reports, 7:16734

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The sexual dimorphism of dietary restriction responsiveness in Caenorhabditis elegans
Cell Reports, 21(13):3646-3652

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A prospective study of intensity-modified radiation therapy in comparison with conventional 3D-RT for BR pancreatic cancer patients with arterial involvement
Anticancer Research, 37(12):7023-7030

January

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Overexpressed wild-type superoxide dismutase 1 exhibits amyotrophic lateral sclerosis-related misfolded conformation in induced pluripotent stem cell-derived spinal motor neurons
NeuroReport, 29(1):25-29

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A-674563 increases chondrocyte marker expression in cultured chondrocytes by inhibiting Sox9 degradation
Biochemical and Biophysical Research Communications, 495(1):1468-1475

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Generation of branching ureteric bud tissues from human pluripotent stem cells
Biochemical and Biophysical Research Communications, 495(1):954-961

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Identification of cardiomyocyte-fated progenitors from human-induced pluripotent stem cells marked with CD82
Cell Reports, 22(2):546-556

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A standard nomenclature for referencing and authentication of pluripotent stem cells
Stem Cell Reports, 10(1):1-6

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A comparative analysis of

attitudes on communication toward stem cell research and regenerative medicine between the public and the scientific community
Stem Cells Translational Medicine, 7(2):251-257

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Pluripotent stem cell models of Blau syndrome reveal an IFN-γ-dependent inflammatory response in macrophages
Journal of Allergy and Clinical Immunology, 141(1):339-349

February

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MEIS1 regulates hemogenic endothelial generation, megakaryopoiesis, and thrombopoiesis in human pluripotent stem cells by targeting TAL1 and FLI1
Stem Cell Reports, 10(2):447-460

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Hematopoiesis by iPSC-derived hematopoietic stem cells of aplastic anemia that escape cytotoxic T-cell attack
Blood Advances, 2(4):390-400

84 – Masui T, Sato A, Nakano K, Uchida Y, Yogo A, Anazawa T, Nagai K, Kawaguchi Y, Takaori K, Uemoto S
Comparison of recurrence between pancreatic and duodenal neuroendocrine neoplasms after curative resection: A single-institution analysis
Annals of Surgical Oncology, 25(2):528-534

March

85 – Oshima K, Saiki N, Tanaka M, Imamura H, Niwa A, Tanimura A, Nagahashi A, Hirayama A, Okita K, Hotta A, Kitayama S, Osawa M, Kaneko S, Watanabe A, Asaka I, Fujibuchi W, Imai K, Yabe H, Kamachi Y, Hara J, Kojima S, Tomita M, Soga T, Noma T, Nonoyama S, Nakahata T, Saito MK
Human AK2 links intracellular bioenergetic redistribution to the fate of hematopoietic progenitors
Biochemical and Biophysical Research Communications, 497(2):719-725

86 – Kim SI, Matsumoto T, Kagawa H, Nakamura M, Hirohata R, Ueno A, Ohishi M, Sakuma T, Soga T, Yamamoto T, Woltjen K
Microhomology-assisted scarless genome editing in human iPSCs
Nature Communications, 9:939

87 – Kaye J, Terry SF, Juengst E, Coy S, Harris JR, Chalmers D, Dove ES, Budin-Ljøsne I, Adebamowo C, Ogbe E, Bezuidenhout L, Morrison M, Minion JT, Murtagh MJ, Minari J, Teare H, Isasi R, Kato K, Rial-Sebbag E, Marshall P, Koenig B, Cambon-Thomsen A
Including all voices in international data-sharing governance
Human Genomics, 12(13)

Kyoto University announced on January 22, 2018, that a committee investigating research misconduct at the university had found a Specially-Appointed Assistant Professor at CiRA conducted research fraud. As a result, the following paper, for which he was the first and corresponding author, was retracted on February 13 and the following award was also retracted. The researcher was punitively dismissed in March.

We deeply apologize to those who have supported our activities for this dereliction. CiRA has reinforced its measures to prevent research fraud from happening again.

Publication

In vitro modeling of blood-brain barrier with human iPSC-derived endothelial cells, pericytes, neurons, and astrocytes via notch signaling
Stem Cell Reports, Mar. 14, 2017; 8(3):634-647

Award

Japan Circulation Society 34th Young Investigator's Award (First Place)

CiRA Buildings

Main Building

Completion……February 2010
Total floor space……11,942.9㎡
(Five stories above ground and one below)
Total cost……About 4.5 billion yen
Facilities……Open laboratories, Cell culture rooms, Offices, Auditorium, Meeting rooms, Gallery, Facility for iPS Cell Therapy, Animal Research Facility

The Second Building

Completion……March 2015
Total floor space……5,478.5㎡
(Five stories above ground and two below)
Total cost……About 2.2 billion yen
Facilities……Open laboratories, Cell culture rooms, Offices, Meeting rooms

The Third Building

Completion……February 2017
Total floor space……7,673.5㎡
(Five stories above ground and two below)
Total cost……About 3.5 billion yen
Facilities……Open laboratories, Cell culture rooms, Offices, Facility for iPS Cell Therapy, Animal Research Facility

Ancillary Facilities

Animal Research Facility

Small-sized animal room

X-ray room

This facility conducts imaging of animals and assures experiments satisfy the ethical requirements of research at Kyoto Univ.

- **Head:** Shinya Yamanaka (Professor)
- **Deputy Head:** Noriyuki Tsumaki (Professor)
- **Ex-Head:** Yasuhiro Yamada (Professor)
- Kenjiro Konno (Associate Professor)
- Kaho Fujii
- Daisuke Seki
- Yoriko Indo
- Akito Tanaka

Facility for iPS Cell Therapy (FiT)

This facility prepares and distributes clinical-grade iPS cells to organizations working on regenerative medicine.

Central monitoring room

Cell preservation tank

- **Head:** Shinya Yamanaka (Professor)
- **Deputy Head:** Naoko Takasu (Professor)
- **Advisor for Facility and Training:** Iori Kuranaga

Manufacturing Department

- **Supervisor:** Masayoshi Tsukahara (Specially Appointed Professor)
- Soichiro Kagei
- Ayumi Matsunaga
- Yuko Obara
- Akiko Okada
- Yoko Ohtagaki
- Aki Sasaki
- Yoshichika Yagyu

1st unit for manufacture

Manufactures clinical-grade iPS cells.

- Naoko Hayakawa
- Norihito Hirai
- Yoshifumi Kajimura
- Mitsuyo Kawada
- Yukiko Kobayashi
- Sayaka Maezori
- Yuki Matsubayashi
- Sonoka Matsuda
- Shun Minobe
- Akiko Montani
- Miyuki Mouri
- Kasumi Nakao
- Eri Nishikawa
- Takuo Nishimura
- Atsushi Nishizawa
- Yukiko Sasaki
- Yoshiko Sato
- Erina Watabe
- Maho Yokoi
- Eri Yoneima

2nd unit for manufacture

Manufactures cells differentiated from clinical-grade iPS cells.

- Tomoko Ichisaka
- Taichi Takenawa
- Kumiko Kan

Quality Department

- **Manager and Supervisor:** Shuhei Deguchi (Specially Appointed Professor)

1st unit for quality management

Evaluates iPS cells by genome analysis, karyotype analysis and microbial infection.

2nd unit for quality management

Conducts collaborative research and analysis with external partners.

- Haruna Fujiyama
- Ichiro Fukuoka
- Sho Hasegawa
- Takaaki Hikichi
- Satoko Hinatsu
- Koichi Kaneko
- Tomoaki Kato
- Kazuhiko Kitajima
- Yuko Kitano
- Fumiyo Kitaoka
- Masako Kudo
- Junko Kuwabara
- Ito Miyashita
- Noriko Mori
- Chika Nakajima
- Mika Nishimura
- Masaki Nomura
- Yuki Nouguchi
- Tokiko Ohkame
- Yusuke Ohkame
- Kazuhide Ohnishi
- Keiko Oono
- Mayumi Sakagami
- Tomoko Takahashi
- Saki Tomita
- Anna Ueda
- Masafumi Umekage
- Mie Yamamoto

Quality certification unit

Conducts quality assurance and inspection of cell production.

- Naoki Amano
- Miho Nagatomi
- Yasuko Nakai
- Yohei Osako
- Ryosaku Tomioka
- Shinsuke Yoshida

Experiment Support

Drug Discovery Technology Development Office

This unit provides tools for drug screening including candidate compounds, reagents and equipments. It also provides support for the application of iPS cell technology to drug screening.

- **Head:** Tatsutoshi Nakahata (Professor)
- Akira Ohta (Specially-Appointed Professor)
- Hiromitsu Fuse
- Hideki Hiyama
- Tatsuya Kawamoto
- Yohei Nishi
- Harumi Watanabe
- Yukiko Yamagishi

Common Equipment Management Office

Flow cytometer

This unit is responsible for management and operation of common equipments at CiRA.

- **Head:** Naoki Harada (Associate Professor)
- Tomoko Furubayashi
- Chiaki Kodani
- Yurina Takahashi

FACS Group

Supports the analysis of cell properties by flow cytometers.

- Kanae Mitsunaga (Assistant Professor)

Imaging Group

Supports live imaging of cells and tissues using confocal microscopes and multiphoton microscopes.

- Keiko Imamura (Assistant Professor)
- Shunsuke Kihara

Genome Analysis Group

Analyzes genome and epigenome with next generation sequencers and evaluates iPS cells.

- Takuya Yamamoto (Junior Associate Professor)
- Junya Asahira

Information Security Office

This unit is responsible for management and operation of IT networks at CiRA.

- **Head:** Hirohide Saito (Professor)
- Michihiro Tanaka (Assistant Professor)
- Shinsuke Dokan
- Toyokazu Fujita
- Ryosuke Kawato
- Aoi Kuginuki
- Jun Nishikawa
- Shinya Nishikawa
- Hiromi Nose
- Kenichi Otsuka
- Noriko Saiwaki
- Kotaro Shiraishi
- Risa Tanaka
- Rina Tsuro

Research Support Division

Director's Office

Conducts a variety of activities involving the Director including the promotion of research activities, recruitment, and fundraising.

- **Head:** Toru Kawamura (Specially-Appointed Associate Professor)
- **Assistant Directors:** Fusao Koyama, Shinsuke Morisawa

Academic Research Support Group

- Toru Kawamura (GL)
- Miho Saito
- Sayaka Takeshima

Human Resource Group

- Toru Kawamura (GL)
- Kumi Higashi

Secretary Group

- Rie Kato (GL)
- Fumitaka Watanabe (Acting GL)
- Hitomi Imagawa
- Keiko Kamegawa
- Yoko Miyake
- Takako Nakata
- Sayaka Takeshima

Fundraising Group

- Fumitaka Watanabe (GL)
- Junya Hirasada
- Fusao Koyama
- Yui Okada
- Junko Tokuda
- Aiko Tokunaga
- Rieko Uehara
- Mika Yamagishi

Common Secretary Group

- Fusao Koyama (GL)
- Rie Fujii
- Mayumi Ikeda
- Yukiko Nakagawa
- Katsura Noda
- Yoko Uematsu
- Harumi Watanabe

2017–2018

Research Support

Administration Division

Medical Applications Promoting Office

Supports promotion for regenerative medicine and drug discovery with iPS cells (prepares all agreements with partner organizations).

- **Head:** Naoko Takasu (Professor)
- **Deputy Head:** Tadaaki Hanatani (Associate Professor)

Regenerative Medicine Support Group

- Hiromi Dohi (GL)
- Ayumi Matsunaga (SGL)
- Hiroko Endo
- Tadaaki Hanatani
- Hisae Takenakajima

Ethics and Inspection Group

- Keiichi Tabuchi (GL, Associate Professor)
- Shoko Matsui
- Ayumi Matsunaga
- Miya Nishida
- Keiko Ukita

Contract and Drug Discovery Group

- Atsushi Onodera (GL)
- Hisae Takenakajima (SGL)
- Keiko Aburano
- Suga Hasegawa
- Eri Minamitani
- Kumiko Noguchi
- Yoko Taniguchi

Intellectual Property Group

- Nobuko Tachikawa (GL)
- Mina Asano (Specially-Appointed Professor, Former IP Office Head)
- Hiroko Endo
- Chie Saneyoshi
- Ayumi Suzuki
- Mika Uchiyama

Planning and Coordination Office

Manages research funds and coordinates laboratory and office space.

- **Head:** Ryuya Konishi
- Yuka Ijiri
- Asami Takeuchi
- Megumi Yamauchi

International Public Communications Office

Manages media relations and public events and other science communication activities.

- **Head:** Akemi Nakamura
- Peter Karagiannis (Specially-Appointed Junior Associate Professor)
- Yoko Miyake
- Ayaka Nakauchi
- Misaki Ouchida
- Ayaka Sasaki
- Hiroko Sata
- Masaya Todani
- Hiroyuki Wadahama

CiRA Administrative Office

Provides clerical support for affairs regarding personnel, finance, facilities, contracts, and other operations.

- **Head:** Katsumi Sakamoto

General Affairs

- Hina Furuya (Manager)
- Yuko Kitano (Assistant Manager)
- Natsuko Mimoto (Assistant Manager)
- Mayumi Ikeda
- Kana Ikeshita
- Kohta Katsukawa
- Sumie Minakuchi
- Mayu Mochi
- Akiko Nakagawa
- Yukiko Nakagawa
- Katsura Noda
- Rie Oyagi
- Sakiko Tsubota
- Yoko Uematsu

Personnel Affairs

- Shinya Tomita (Manager)

Financial Affairs

- Motoko Oneda (Assistant Head, Manager)
- Mitsunaga Koide
- Hana Mageshi
- Hajime Seki
- Kana Yamagami
- Gakushi Yamamoto

Outside Faculty Members

Scientific Advisers

- Tomohisa Kato
- Seishi Ogawa
- Yoshiki Sawa
- Masayo Takahashi
- Hidenori Tanaka

Management Adviser

- Hiromichi Mizuno

Communication Adviser

- Motoaki Nishiwaki

GL=Group Leader SGL=Sub Group Leader

2017–2018

Research Activities

1 CiRA Seminars

Date	Lecture Title	Speaker	Affiliation
2017.4.20	Reversal of Alzheimer dementia in older dogs: Proof of concept with patient-specific cell therapy	Michael Valenzuela	Brain and Mind Centre and Sydney Medical School, University of Sydney
2017.5.1	The development of radical therapeutics of Alzheimer's disease based on oligomer hypothesis	Kenjiro Ono	School of Medicine, Showa University
2017.5.1	Optical control of cellular function using carbon and gold nanomaterials	Tatsuya Murakami	Department of Pharmaceutical Engineering, Toyama Prefectural University
2017.5.2	Heparan sulfate proteoglycans in the stem cell niche: Lessons from drosophila	Hiroshi Nakato	Department of Genetics, Cell Biology and Development, University of Minnesota
2017.5.19	Impulse, release and receptor-trafficking in a differentiated neuron	Kazuhiko Yamaguchi	Brain Science Institute, RIKEN
2017.6.5	CiRA-CDB exchange seminar: synthetic developmental biology	Miki Ebisuya	Quantitative Biology Center, RIKEN
2017.7.6	Activities and genome-wide specificities of engineered CRISPR nucleases	Benjamin Kleinstiver	Department of Pathology, Harvard Medical School Division of Anatomic and Molecular Pathology, Massachusetts General Hospital
2017.7.7	Remudy: A patient registry for neuromuscular diseases	En Kimura	Department of Clinical Research Support, Translational Medical Center, National Center of Neurology and Psychiatry
2017.7.24	Moving cells with light	Mark White	BERKELEY LIGHTS
2017.8.4	Modeling host restriction of HIV using iPSC-derived macrophages	Mark A. Wallet	Department of Pathology, Immunology and Laboratory Medicine, University of Florida
2017.9.1	Single cell analysis systems for therapeutics discovery & diagnostic application	Frank Gesellchen, Sara Abalde-Cela	Sphere Fluidics Co., Ltd. The Health Unit, International Iberian Nanotechnology Laboratory
2017.9.6	A transparent ALS model for interrogating TDP-43 toxicity in the spinal motor neuron	Kazuhide Asakawa	Division of Molecular and Developmental Biology, National Institute of Genetics
2017.9.11	Elucidation of immune reaction that NK cells can cause against HLA homozygous iPS cell-derived regenerated cells and development of its prevention	Hiroshi Kawamoto	Institute for Frontier Life and Medical Sciences, Kyoto University
2017.10.11	Mechanism to position nuclei at the periphery of skeletal muscle cells	William Roman	Instituto de Medician Molecular, Faculty of Medicine, University of Lisbon
2017.10.19	The genomics and clinical significance of Alzheimer's disease as a complex disease	Takeshi Ikeuchi	Center for Bioresource-based Researches, Brain Research Institute, Niigata University
2017.10.25	Pluripotent stem cells for research, screening and therapy	Jürgen Hescheler	Institute of Neurophysiology, the University of Cologne

2017-2018

Research Activities

Date	Lecture Title	Speaker	Affiliation
2017.12.5	SMARTer advancement in single cell and other next genome sequencing applications	Suvarna Gandlur	TaKaRa Clontech
2017.12.15	Cell fate decisions on the epigenetic landscape: First principles, formalism and fate prediction	Sui Huang	Institute for Systems Biology
2017.12.15	Toward understanding the mechanism of complex phenotype with big and heterogeneous data	Jun Sese	Artificial Intelligence Research Center, National Institute of Advanced Industrial Science and Technology
2017.12.15	Nobel turing challenge: Grand challenge of AI and systems biology	Hiroaki Kitano	The Systems Biology Institute
2017.12.15	Cancer clinical sequencing enhanced with artificial intelligence	Seiya Imoto	Health Intelligence Center, The Institute of Medical Science, The University of Tokyo
2017.12.25	Genetically encoded tools for stem cell derived cardiomyocyte phenotyping	Matthew J Daniels	Radcliffe Department of Medicine, Oxford University / The Institute of Scientific and Industrial Research, Osaka University
2018.1.19	A blueprint for primate preimplantation development	Thorsten Edwin Boroviak	Wellcome Trust – Medical Research Council Stem Cell Institute, University of Cambridge
2018.1.23	CiRA-CDB exchange seminar: A quantitative and systems approach to vertebrate forebrain and heart morphogenesis	Yoshihiro Morishita	Quantitative Biology Center, RIKEN
2018.1.25	FDA drug repurposing for lethal developmental diseases using human iPS cell models	Masayuki Yazawa	College of Physician and Surgeon, Columbia University
2018.1.30	The role of microglia in neuropathic pain and drug creation: Challenge to green pharma	Kazuhide Inoue	Kyushu University
2018.2.9	Human development and disease through the lens of pluripotent stem cells	Danwei Huangfu	Developmental Biology Program, Memorial Sloan Kettering Cancer Center / Cell and Developmental Biology Program, Weil Cornell Medicine
2018.2.19	Recent progress of clinical application of iPSC in South Korea: "Based on patients' four hands, which a rheumatologist meets at his clinic"	Ju Hyeon Ju	Department of Internal Medicine, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea
2018.2.26	Perspectives on the therapeutic strategy for Alzheimer's disease	Hidekazu Tomimoto	Graduate School of Medicine, Mie University
2018.3.15	Proliferation of the measles virus and molecular basis for its pathofenicity	Makoto Takeda	Department of Virology III, National Institute of Infectious Deseases
2018.3.15	Measles virus vectors	Maino Tahara	Department of Virology III, National Institute of Infectious Deseases
2018.3.19	HIV-specific CAR-T cell generation and their functional and phenotypic analysis	Junichi Nunoya	School of Medicine, Dokkyo Medical University

Research Activities

2 CiRA Research Internship Program

CiRA set up the research internship program, which welcomes undergraduate and graduate students to conduct research in CiRA labs. 16 students from 6 countries (Canada, China, Switzerland, Turkey, U.S. and Japan) joined in 2017. Participants presented their research results at the end of the program.

3 CiRA Progress Seminar

Each week, CiRA researchers gather to attend the CiRA progress seminar, at which 3-4 CiRA researchers present their latest reserach. The seminar provides an opportunity to discuss unpublished work with colleagues and practice to young researchers at presenting their research to a scientific audience.

4 CiRA Retreat

The CiRA Retreat, November 9-10, was held near Lake Biwa. All CiRA participants presented posters or were invited to give an oral presentation about their research. The retreat also invited 11 external speakers to attend.

Speakers

Hans Clevers (Hubrecht Institute) /
Austin Smith (University of Cambridge) /
Allan Bradley (Sanger Institute) /
Juan Carlos Izpisua Belmonte (Salk Institute) /
Fredric Lanner (Karolinska Institutet) /
Thomas Fellner (Lonza) /
Kevin Eggan (Harvard Stem Cell Institute) /
Glyn Stacey (International Stem Cell Banking Initiative) / Yuji Shiba (Shinshu University) /
Mitinori Saitou (Kyoto University) /
Kazutoshi Takahashi (Gladstone Institutes)

(1)

(2)

Best Oral Presentation Award

1st : Masaki Yagi (Yamada Lab.)
2nd: Kaoru Richard Komatsu (Saito H Lab.)
3rd: Mingming Zhao (Sakurai Lab.)

Outstanding Poster Award

Kenji Ito, Megumi Sakakura (Yamada Lab.) /
Moe Hirosawa, Sora Matsumoto (Saito H Lab.) /
Janin Grajcarek (Woltjen Lab.) / Hiroki Ikeda (Yamamoto Lab.) / Huaigeng Xu (Hotta Lab.) /
Shunsuke Kawai (Toguchida Lab.) / Masafumi Takeda (Yamashita Lab.) / Jun Otomo, William Roman, Nana Takenaka (Sakurai Lab.) / Akira Kunitomi (Takasu Lab.)

(1)
A lecture at CiRA Retreat

(2)
Commemorative photo at CiRA Retreat

2017-2018

Research Activities

5 CiRA International Symposium

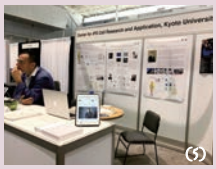
CiRA held its 6th international symposium "A decade of human iPSCs - From bench to bedside" in Kyoto from 6th to 8th November 2017. 481 people attended, including 140 from overseas. The symposium invited 21 global leaders in stem cell research to speak about their work. There was also a Meet the Experts Lunch, which allowed students to talk directly to the speakers about their research projects.

Speakers

Deepak Srivastava, Kazutoshi Takahashi (Gladstone Institutes) / Kevin Eggan, Konrad Hochedlinger (Harvard Stem Cell Institute) / Hans Clevers (Hubrecht Institute) / Glyn Stacey (International Stem Cell Banking Initiative) / Fredrik Lanner (Karolinska Institutet) / Mitinori Saitou (Kyoto University) / Thomas Fellner (Lonza) / Takashi Tsuji (Riken CDB) / Juan Carlos Izpisua Belmonte (Salk Institute) / Allan Bradley (Sanger Institute) / Yuji Shiba (Shinshu University) / Austin Smith (University of Cambridge) / Shinya Yamanaka, Yasuhiro Yamada, Hirohide Saito, Yasuhiro Takashima, Junya Toguchida, Noriyuki Tsumaki, Shin Kaneko (CiRA)

6 Booth Exhibit

CiRA opened booths at several academic meetings to share information about its research and recruit new researchers.



June 14-17, 2017

ISSCR2017 (Boston)
Approx. 3,900 people visited the annual meeting.

October 11-13, 2017

Bio Japan 2017 (Yokohama)
15,711 people visited the fair.

(3)
A lecture at CiRA International Symposium

(4)
Professor Yamanaka at CiRA International Symposium

(5)
CiRA booth at ISSCR2017

(6)
CiRA booth at Bio Japan 2017

2017-2018

Public Outreach

1 CiRA Symposium

CiRA holds symposia for the general public each year. This fiscal year it organized four.

April 8, 2017

Present and Future of iPS Cells
This event was a joint symposium with Hamamatsu Rosai Hospital, Hamamatsu, Shizuoka.
Approx. 1,000 people joined.
[Speakers]
Shigeki Arii (Hamamatsu Rosai Hospital)
Shin Kaneko, Shinya Yamanaka (CiRA)

May 22, 2017

Regenerative Medicine Using iPS Cells
This event was a celebration of the 10th anniversary of human iPS cells and the opening of CiRA's third research building. The event was held at Clock Tower, Kyoto University.
Approx. 400 people participated.
[Speakers]
Koji Nishida (Osaka University) / Naoko Takasu, Jun Takahashi, Shinya Yamanaka (CiRA)

October 2, 2017

iPS Cells in Research, Ethics and Society
This event was part of the 30th anniversary of the Uehiro Foundation on Ethics and Education and joint symposium with the foundation.
This event was held at the Clock Tower, Kyoto University. Approx. 400 people joined.

[Speakers]
Misao Fujita, Yoshimi Yashiro, Mika Suzuki, Shinya Yamanaka (CiRA)
[Panel Discussion]
Satoshi Kodama (Graduate School of Letters, Kyoto University)
Mitinori Saitou (Graduate School of Medicine, Kyoto University)
Toshihiko Hoshino (Cabinet Office, Government of Japan)
Tsutomu Sawai, Taichi Hatta (CiRA)

March 2, 2018

iPS Cells in Drug Discovery
This event was held at the CiRA auditorium.
Approx. 60 people took part.
[Speakers]
Haruhisa Inoue, Akira Ohta, Kenji Osafune, Megumu Saito and Yoshinori Yoshida (CiRA)

2 Ceremony to Celebrate Completion

On May 22, CiRA officially opened its Third Research Building. About 100 people attended the opening ceremony, including government officials and donors to the iPS Cell Research Fund.

3 CiRA Tour

CiRA offers tours of the facilities to the general public. Tours include an introductory lecture on iPS cell research followed by a tour of CiRA facilities not normally open to the public. This FY, six tours on three were held.

(1)
The venue of the symposium "Present and Future of iPS Cells"

(2)
Professor Nishida at the symposium "Regenerative Medicine using iPS Cells"

(3)
Panel discussion at the symposium "iPS Cells in Research, Ethics and Society"

(4)
Professor Inoue at the symposium "iPS Cells in Drug Discovery"

(5)
Ribbon-cutting ceremony to celebrate completion of CiRA third building

2017-2018

Public Outreach

4 CiRA Café

The CiRA Café is an event at which CiRA researchers talk about iPS cell research to the public. This year science café events were held in Osaka and Kanazawa.

May 27, 2017

Life begins from a cell
This event discussed cell's commonality and diversity among species. The event was held at Knowledge Capital in Osaka.
[Speakers]
Mari Toyama (Research Institute for Humanity and Nature)
Etsu Noguchi (Osaka University)
Masahiro Kawakami (Nara Institute of Science and Technology)
Ayaka Nakauchi (CiRA)

July 9, 2017

Listen to and discuss iPS cells
This event discussed the use of iPS cells in regenerative medicine for the kidneys, liver, and pancreas.The event was held at Kanazawa Student Community Civic Center in Kanazawa.
[Speaker]
Kenji Osafune (CiRA)

Jan. 22, Feb. 7, March. 7 and 14, 2018

Drug discovery with iPS cells
This event discussed the use of iPS cells in drug discovery for various diseases. In total, four talks about iPS cell research for disease mechanism elucidation and drug development were given over three months. The event was held at Knowledge Capital in Osaka.
[Speakers]
Junya Toguchida, Hidetoshi Sakurai, Megumu Saito, Mitsujiro Osawa (CiRA)




5 Booth Exhibit

CiRA exhibited booths at events to share our science with the public. Visitors observed iPS cells and had fun with stem cell card games. Most of visitors had never seen real iPS cells although they had heard news of iPS cells. Booth exhibits were good opportunities to let them see and know about iPS cells.

October 21 and 22, 2017

NHK Science Stadium (Tokyo)
Collaborated with science TV program "Science ZERO" by NHK. 1,851 people visited.

November 11 and 12, 2017

Snow Bank Pay It Forward 2017
"Tokyo Snow Festival" (Tokyo)
The event was to promote blood donation and resistration for marrow donor program.
Approx. 250 people visited.


(6)
Talk session at CiRA Café, "iPS Nights"

(7)
A lecture at CiRA Café in Kanazawa

(8)
Professor Toguchida at CiRA Café in Osaka

(9)
Assistant Professor Osawa at CiRA Café in Osaka

(10)
Participants played with stem cell card games at NHK Science Stadium

(11)
CiRA booth at Tokyo Snow Festival

2017-2018

Public Outreach

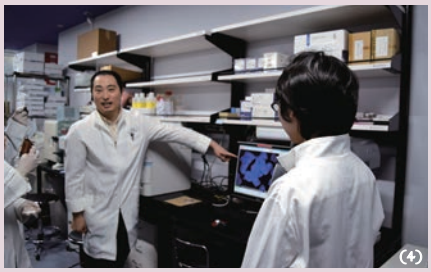
6 Festival for the 10th Anniversary of Human iPS Cells

CiRA celebrated the 10th anniversary of human iPS cells by hosting a full day of events at the institute for the general public. Attendees were welcomed to join a workshop on science illustration, a game workshop, a tour of the institute, conduct simple iPS cell experiments, and attend a science café / bar on iPS cells. 81 people took part in total.


(1)


(2)


(3)


(4)

(1)
iPS bar

(2)
Science illustration workshop

(3)
CiRA Café

(4)
iPS cell experiment

(5)
Science seminar on August 1

(6)
Workshop "iPS Cells: Play and Learn!"

(7)
Researcher Sato talked with participants

(8)
Participants played with a stem cell game

7 Programs for children


(5)


(6)

As a part of "Nurturing the Scientist of the Future Project" run by the Kyoto City Board of Education and "IF class" by the Otsu City Science Museum, CiRA held a science seminar for 35 junior high school students on August 1st. (Lecturer: Makoto Ikeya)

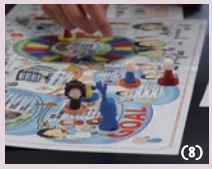
On August 3 and 4, CiRA held a workshop, "iPS Cells: Play and Learn!" in Roppongi, Tokyo, as a part of "Mirai Summer Camp." 90 elementary school students attended the workshop, where they enjoyed making and playing a game and learned about iPS cells.

8 CiRA Classroom

CiRA travelled to Fukui prefecture to give a "CiRA classroom". The program was split into two days (Sept. 30 and Oct. 1), with the first designed for high school teachers and the second for high school students. In total, 56 people participated.

[Lecturer]
Yoshiko Sato (Takasu Lab.)
[Moderator]
Masahiro Kawakami
(Nara Institute of Science and Technology)


(7)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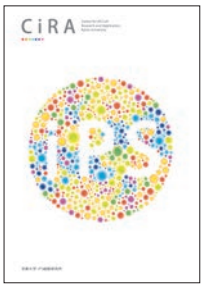
2017–2018

Resources




CiRA Publications

01_CiRA Pamphlet
(Summary of the institute in English and Japanese)
02_CiRA Newsletter
(Newsletter in Japanese, quarterly)
03_CiRA Reporter
(Newsletter in English, quarterly)
04_Stem Cell Handbook (in Japanese)

The publications can be downloaded at the CiRA website.

CiRA Website

www.cira.kyoto-u.ac.jp/e/


CiRA SNS

Facebook
[English and Japanese]
Center for iPS Cell Research and Application (CiRA), Kyoto University

Twitter
[English]
CiRA(@CiRA_KU_E)
[Japanese]
iPS細胞研究所(@CiRA_KU_J)

CiRA Gallery

CiRA gallery is open from 8:30 am to 5:15 pm on weekdays.

2017-2018

iPS Cell Research Fund

The success of CiRA in the FY 2017 has resulted in the most successful year yet for the iPS Cell Research Fund, as the fund collected nearly 3.8 billion yen from over 20,000 donations. In addition, the fund received many recurring gifts and bequests.

As of March 31, 2018, the iPS Cell Research Fund had a balance of over 10 billion yen. This money is being used to convert iPS cell research novel and innovative treatments. It is also being used to hire talented people. While most of CiRA members remain on fixed-term contracts, CiRA has decided that some of them can be employed on indefinite-term contracts by taking advantage of the fund.

The iPS Cell Research Fund is critical to keep talented staff at CiRA and to continue our progress in iPS cell research. Your support is a key to our goal of bringing iPS cell technology to the bedside.

iPS Cell Research Fund
TEL: +81 75 366 7152
FAX: +81 75 366 7185
E-mail: ips-kikin@cira.kyoto-u.ac.jp

FY 2017 Financial Report (April 1, 2017-March 31, 2018)

Revenue	Number of Donations	Amount (yen)
Individual	19,032	3,112,089,322
Corporation / Organization	1,056	655,045,567
Total	20,088	3,767,134,889

Expenditures	Amount (yen)
Personnel	269,331,953
Research projects	50,306,402
Intellectual property	57,862,940
Other operating expenses (*portion to Kyoto University)	156,739,435 (88,200,747)
Total	534,240,730

	Amount (yen)
FY 2017 Balance	10,295,489,002

*This portion contributes to overall operating costs at Kyoto University, including those that support CiRA.

2017-2018

Intellectual Property

Kyoto University has been acquiring patents with the aim of promoting the use of iPS cell technology internationally. The Intellectual Property (IP) Office at CiRA is responsible for IP management of various inventions such as methods for establishing and inducing the differentiation of iPS cells.

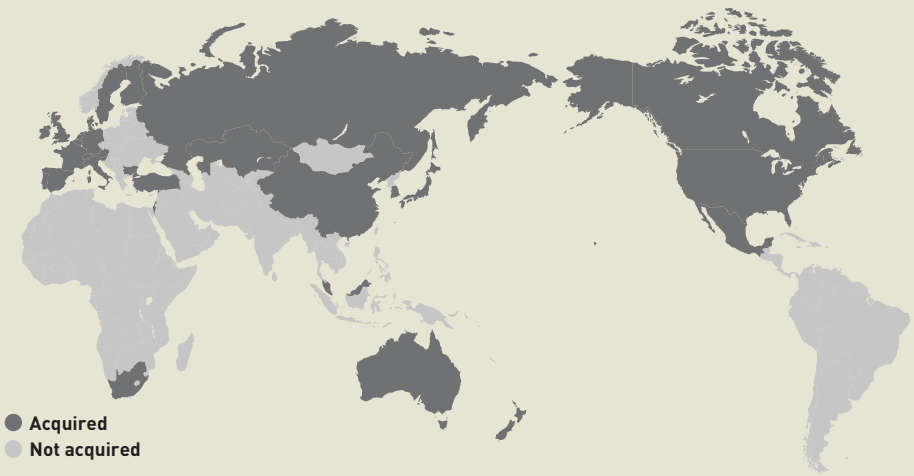
In FY 2017, patents related to basic technology for iPS cells was granted in Mexico and Malaysia. Including these countries, patents owned by CiRA have been granted in 31 countries and 1 region (see figure below) since the end of March 2018. Other patents include IP for the production of iPS cells and for the differentiation of iPS cells to various cells. iPS Academia Japan Inc. is mainly responsible for licensing iPS cell-related patents owned by Kyoto University.

1 **Acquired basic and related patents on iPS cell technology (as of March 31, 2018)**

Nations and Regions	Number of Patents
Japan	37
U.S.A.	28
China	14
European Union *1	16
Singapore	7
Australia	6
Canada	7
Hong Kong *2	4
Eurasia *3	2
U.K. *4	2
Korea	9
Mexico	3
New Zealand	2
South Africa	2
Israel	4
Malaysia	1
Total	144

*1: Indicates countries selected form EPC Parties. *2: Claims rights based on patents established in China or the U.K.
*3: Indicates countries selected from Parties to the Eurasian Patent Convention. *4: Patents applied directly to the United Kingdom Patent Office.

2 **Countries and regions where basic patents were acquired (as of March 31, 2018)**



2017-2018

Major Research Projects

1 Research Center Network for Realization of Regenerative Medicine

Sponsored by the Japan Agency for Medical Research and Development (AMED), the Regenerative Medicine Network Program It consists of five research projects: Core Center for iPS Cell Research, Centers for Clinical Application Research on Specific Diseases / Organs, Projects for Technological Development, Highway Program for Realization of Regenerative Medicine, and the Program for Intractable Disease Research. The program contributes to research on the development of an iPS cell stock for use in regenerative medicine and the establishment of disease-specific iPS cell lines for the creation of a cell bank.

2 Strategic Basic Research Program

Some CiRA researchers are active participants in the Japan Agency for Medical Research and Development (AMED)-Canadian Institutes of Health Research (CIHR) Joint Research Project, "The Epigenetics of Stem Cells," which runs from FY 2013 to FY 2017. The purpose of the project is to control cellular identity for the development of progenitor cell therapies.

3 T-CiRA

T-CiRA (Takeda-CiRA Joint Program for iPS Cell Applications) is a joint research program by CiRA and Takeda Pharmaceutical Co., Ltd. that started in FY 2015. It is based at Takeda Shonan Research Center (currently Shonan Health Innovation Park) in Fujisawa, Kanagawa Prefecture. T-CiRA is a minimum 10-year commitment and is under the direction of CiRA. It aims to innovate medical applications of iPS cells.

In this fiscal year, the project saw progress in research in areas such as neurological disorders, intractable muscle diseases, cancer, heart failure and diabetes. These projects were led by CiRA's Prof. Haruhisa Inoue, Associate Profs. Hidetoshi Sakurai, Shin Kaneko, Yoshinori Yoshida, Makoto Ikeya, Junior Associate Profs. Akitsu Hotta and Taro Toyoda.

Prof. Takanori Takebe of Yokohama City University, and Team Leader Tadashi Suzuki of RIKEN are working on producing miniature livers from human iPS cells for drug discovery, and drug development for NGLY1 deficiency, a complex neurological syndrome, respectively.

(1)

(2)

(1)
Global Head of Regenerative Medicine Unit of Takeda Seigo Izumo (Left) and CiRA Director Shinya Yamanaka (Right) (Photography: Takeda Pharmaceutical Co., Ltd.)

(2)
T-CiRA logo

2017-2018

Major Research Projects

4 iPS Cell Stock for Regenerative Medicine

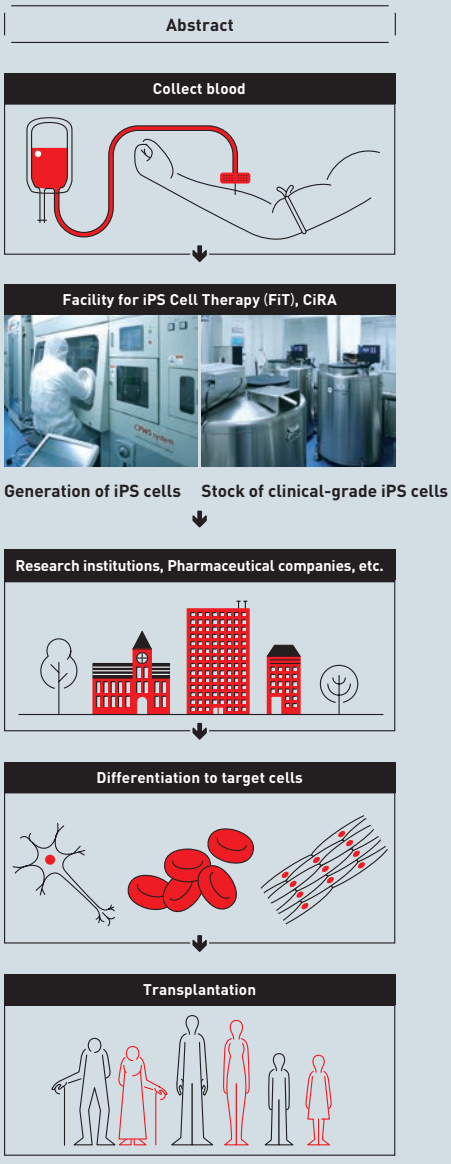
The iPS Cell Stock for Regenerative Medicine involves the collection of cells from health donors with homozygous HLA (human leukocyte antigen). The aim of the stock is to hold iPS cells of guaranteed quality and to supply these cells quickly to medical care institutions and research institutions when required. The project is being led by Professor Naoko Takasu and the Medical Applications Promoting Office in collaboration with the Facility for iPS Cell Therapy (FiT). Full-scale operation began in FY 2013 with the aim of establishing an iPS cell stock that covers 30-50% of the Japanese population.

In 2015, CiRA began distributing iPS cells from its iPS cell stock. These cells were made from donors that have the most frequent homozygous HLA in Japan and should serve approximately 17% of the Japanese population. In 2017, the iPS cell stock completed its second HLA-homozygous iPS cell line. The two lines are estimated to match 24% of the Japanese population.

To hasten blood collection for more iPS cell lines, in 2016 CiRA began teaming with Kaijo Bldg. Clinic in Tokyo and in 2017 with the Japanese Red Cross Nagoya Daiichi Hospital. Already working with Kyoto University Hospital, CiRA is now collecting blood from Kyoto, Nagoya, and Tokyo.

One of the lines distributed since August 2016 was halted in January 2017 because of errors in management. As a result, CiRA has revised its management system and used the same blood donation to make a new iPS cell-line. This line has been distributed since October 2017.

The efforts to make an iPS cell stock has depended on the continued cooperation of organizations like the aforementioned hospitals and the Japanese Red Cross Society, the Japan Marrow Donor Program, and umbilical cord banks.



CiRA Facts

History

Jan. 2008 ....The Center for iPS Cell Research and Application (CiRA) is founded as part of the Institute for Integrated Cell-Material Sciences (iCeMS), Kyoto University.
Apr. 2009 ....The iPS Cell Research Fund is set up.
Feb. 2010 ....The CiRA building is completed.
Apr. 2010 ....CiRA is recognized as an institute independent of iCeMS.
Apr. 2013 ....Uehiro Research Division for iPS Cell of Ethics is established.
Mar. 2015....The second CiRA building is completed.
Feb. 2017 ....The third CiRA building is completed.

Personnel (as of March 1, 2018)

Professors	14 (2)
Associate Professors	13 (1)
Junior Associate Professors	7 (0)
Assistant Professors	20 (0)
Researchers	125 (69)
Research Assistants	68 (86)
Research Support Staff	40 (9)
Administrative Staff	12 (5)
Total	299(172)

Number of Students :

Dept. of Life Science Frontiers	28
Dept. of Cell Growth and Differentiation	22
Dept. of Clinical Application	14
Total	64

Organization Chart (as of March 1, 2018)

Director
Shinya Yamanaka

Deputy Directors
Junya Toguchida
Koji Eto
Naoko Takasu
Hirohide Saito

Assistant Directors
Shinsuke Morisawa
Fusao Koyama

Advisor
Tatsutoshi Nakahata

Faculty Council

Faculty Forum

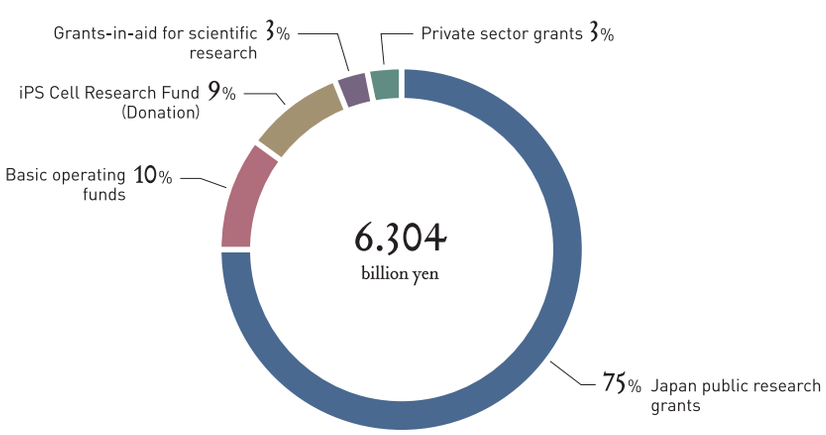
Research Departments
- Life Science Frontiers
- Cell Growth and Differentiation
- Clinical Application
- Fundamental Cell Technology
  - Drug Discovery Technology Development Office
  - Common Equipment Management Office
  - Information Security Office
- Uehiro Reserch Division for iPS Cell Ethics

Animal Research Facility
Facility for iPS Cell Therapy (FiT)

Research Support Division
Director's Office
Planning and Coordination Office
Medical Applications Promoting Office
International Public Communications Office

Administration Division
CiRA Administrative Office

Fiscal Budget Implementation (as of March 31, 2018)



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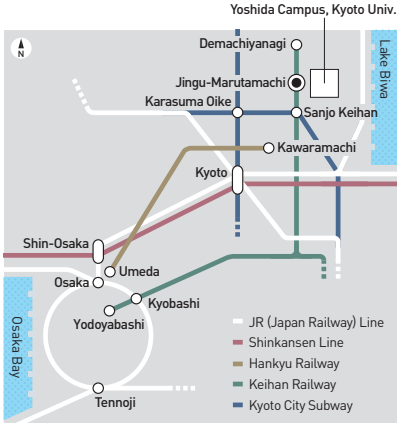

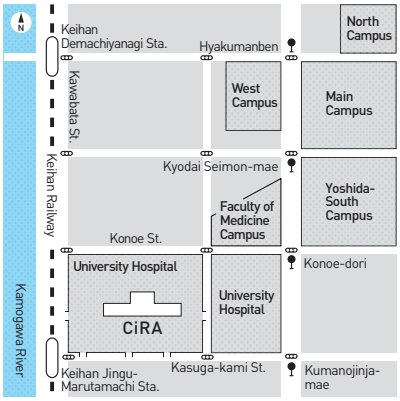

From Kansai International Airport to Kyoto
Take JR "Haruka" Kansai Airport Limited Express from Kansai airport and alight at Kyoto station

From Tokyo to Kyoto
Take JR Shinkansen bullet train at Tokyo station, and get down at Kyoto station

From Kyoto Station to CiRA
Take bus No. 206 bound for Gion via Kiyomizu-dera Temple, and get off at Kumano Jinja-mae

Contact

CiRA International Public Communications Office
53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto
606-8507, Japan
TEL: +81 75 366 7005
FAX: +81 75 366 7185
URL: www.cira.kyoto-u.ac.jp/e/

Credit

Publisher	Center for iPS Cell Research and Application (CiRA), Kyoto University
Producers	Ayaka Sasaki, Akemi Nakamura (CiRA)
Editors / Writers	Peter Karagiannis, Yoko Miyake, Ayaka Nakauchi, Misaki Ouchida, Hiroko Sata, Masaya Todani, Hiroyuki Wadahama, Director's Office, Medical Applications Promoting Office, Planning and Coordination Office, Administrative Office (CiRA), Sci-Tech Communications Inc.
Photography	Jussi Panula, KO SASAKI, International Public Communications Office (CiRA)
Art Direction	Mitsunobu Hosoyamada
Design	Hikaru Yokoyama (Hosoyamada Design Office)
Illustration	Shinji Hamana (Beach)
Print	HOKUTO PRINT Co., Ltd.
Publication Date	July 2018

Center for
iPS Cell
Research and
Application,
Kyoto University