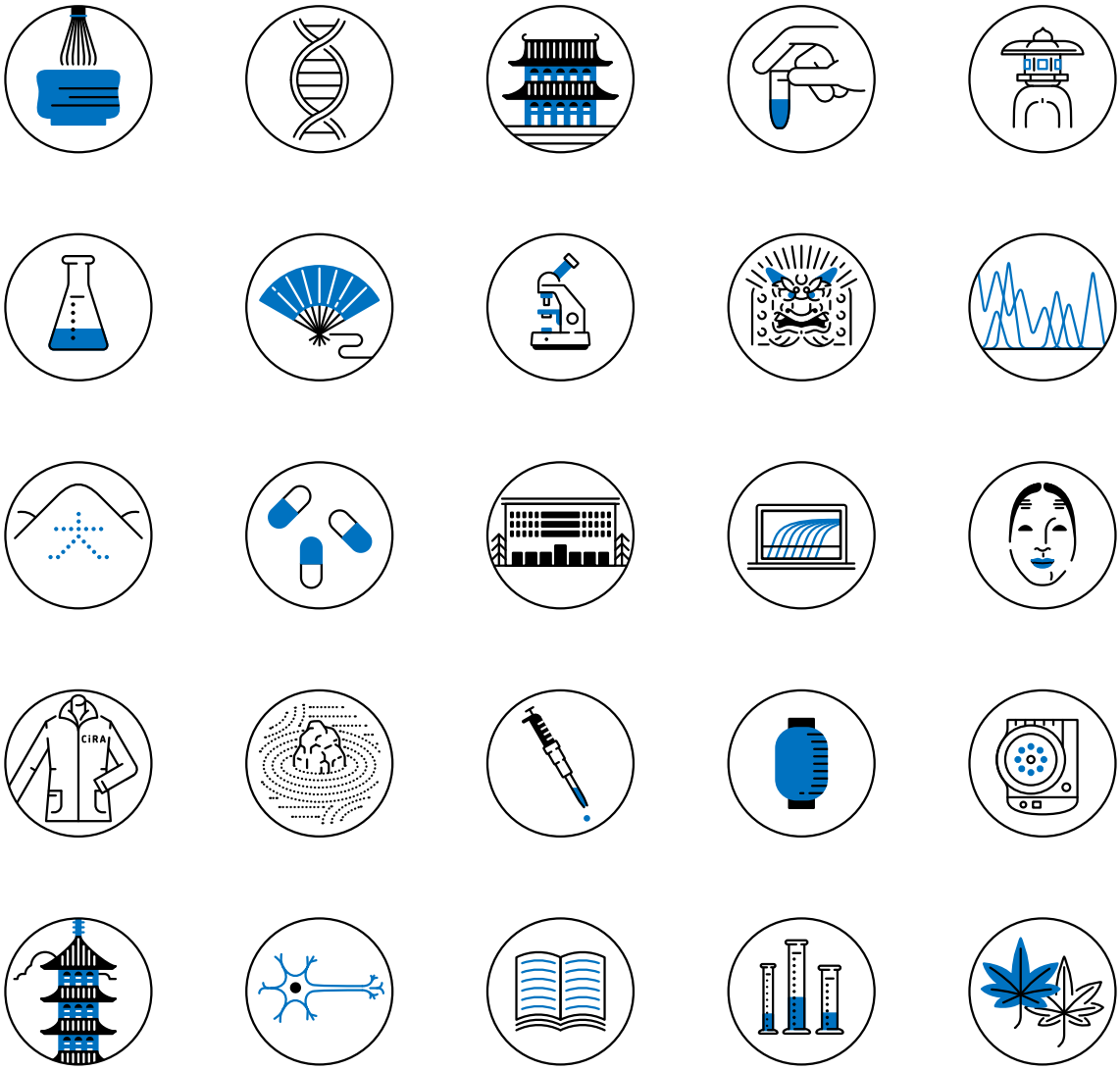
Center for
iPS Cell
Research and
Application,
Kyoto University

Annual Report 2018

CiRA



Contents

*The data in this report reflects activities from April 1, 2018, through March 31, 2019.

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, engages in research activity towards its mission of achieving the clinical application of iPS cells. It has set itself four related goals to achieve by the year 2030:

CiRA Vision 2030

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

2_ Produce new drugs for intractable diseases and personalized medicine 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

Fiscal year 2018 saw the start of a clinical trial and a clinical research based on work carried out at CiRA. In August 2018, in collaboration with Kyoto University Hospital, we launched a physician-initiated clinical trial that aims to realize an iPS cell-based therapy for Parkinson's disease. In October, cell transplants were carried out in the first enrolled patient. This clinical trial draws on an iPS Cell Stock for Regenerative Medicine. In September, the Japanese government gave approval for autologous iPS cell-derived platelets to be used in a clinical research in a patient with aplastic anemia accompanied by platelet transfusion refractoriness.

There was also significant progress in the iPS Cell Stock for Regenerative Medicine. In partnership with industry, we launched one project to build a master cell bank from our iPS cell stock and another to develop technology for the generation of high-quality clinical-grade iPS cells. As a strategy to ensure the long-term continuation of our iPS cell stock project, we also submitted to the Japanese government a proposal to establish a public interest incorporated foundation that will operate the project.

CiRA is also progressing with research to open new frontiers in medical science using iPS cells. In fiscal year 2018, we clarified the properties of T cells generated from cancer patient-derived iPS cells by analyzing their gene expressions. We also succeeded in strengthening the antigen specificity of T cells through genome editing and optimization of culture conditions. Further, to regulate the behavior of specific cell types, we developed artificial RNA-based logic circuits that make it possible to control cell fate precisely.

In fiscal year 2018, we again received many generous donations to our iPS Cell Research Fund. To use this fund effectively for the rapid development of iPS cell-based therapies, we at CiRA are united to advancing our research activities.

March 2019

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


Yoshiya Kawaguchi
Professor


Wataru Fujibuchi
Professor


Yoko Hamazaki
Professor


Hirohide Saito
Professor


Knut Woltjen
Associate Professor


Takuya Yamamoto
Associate Professor


Yasuhiro Takashima
Junior Associate Professor


Masato Nakagawa
Junior Associate Professor


Keisuke Okita
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


Jun K. Yamashita
Professor


Haruhisa Inoue
Professor


Kenji Osafune
Professor


Shin Kaneko
Associate Professor


Yoshinori Yoshida
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


Noriyuki Tsumaki
Professor


Megumu Saito
Associate Professor


Makoto Ikeya
Associate Professor


Hidetoshi Sakurai
Associate Professor


Akitsu Hotta
Junior 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

Uehiro Research Division for iPS Cell Ethics

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

Department Head


Misao Fujita
Professor


Jusaku Minari
Associate Professor

Research Highlight

2018 – 2019

1 Basic Research

Regulating cell fate with artificial RNA logic gates

Synthetic RNA-based logic computation in mammalian cells
Nature Communications

Department of Life Science Frontiers
Hirohide Saito
(Professor)

As a technology to manipulate cell fate, some groups are developing artificial logic gates that regulate intracellular gene expressions. Specifically, Professor Hirohide Saito and his research team have been working on RNA-based artificial logic gates that do not modify the genome. In previous years, they reported logic gates, ON/OFF switches that exploit differences in the activity of selective micro-RNAs (miRNA) to regulate protein expressions (output).

This year, they reported an advancement in their technology to regulate the output with higher precision. They refined their artificial RNA logic gates to successfully construct the full range of basic logic gates (AND, OR, NAND, NOR, XOR). When these logic gates are introduced into cells, the activity of multiple endogenous miRNAs acts as the input signal. The logic gates were used to elicit fluorescence or cell death in the target cell only.

This technology makes it possible to regulate cell function accurately using RNA expression and is expected to contribute to research areas such as cell purification for therapeutic applications.

Genome editing technology to create iPS cells with reduced risk of immune rejection

Targeted disruption of HLA genes via CRISPR-Cas9 generates iPSCs with enhanced immune compatibility
Cell Stem Cell

Department of Clinical Application
Akitsu Hotta
(Junior Associate Professor)

Department of Cell Growth and Differentiation
Shin Kaneko
(Associate Professor)

In transplantation therapies, the HLA types of the cell donor and the transplant recipient must be compatible. Otherwise, the transplant may be attacked by the recipient's immune cells, such as killer T and NK cells and fail to engraft. However, patient-donor matching is not trivial. By manipulating the genes responsible for HLA expression, it is possible to mute the killer T and NK cell response.

The research teams of Junior Associate Professor Akitsu Hotta and Associate Professor Shin Kaneko have developed a genome editing method for this purpose. By knocking out both HLA-A and HLA-B alleles and one HLA-C allele, they were able to prevent killer T and NK cell reactions to the transplant. In addition, they estimated that seven different iPS cell lines made using this method would provide compatibility with more than 95% of the Japanese population and 12 cell lines would cover most of the world's population.

Research Highlight

2018 – 2019

2 Regenerative Medicine

Successful generation of rejuvenated killer T cells from human iPS cells for cancer immunotherapy

——Success with both genome edited patient-derived iPS cells and human iPS cell stock

Enhancing T cell receptor stability in rejuvenated iPSC derived T cells improves their use in cancer immunotherapy
Cell Stem Cell

Gene insertion into human iPS cell-derived T cells produces helper T cell-like functions

Generation of TCR-expressing innate lymphoid-like helper cells that induce cytotoxic T cell mediated anti-leukemic cell response
Stem Cell Reports

Department of Cell Growth and Differentiation

Shin Kaneko
(Associate Professor)

Cancer could be called a national disease in Japan, as almost half of the population will experience a positive diagnosis. Several therapies exist, with ranging successes, but in recent years immunotherapy has dominated.

In the immune system, the body's dendritic cells, helper T cells, killer T cells and other cell types work in coordination to eliminate cancerous cells. For instance, when dendritic cells recognize cancer cells, helper T cells are activated. The activated helper T cells in turn activate dendritic cells, which then present an antigen on the cancer cell surface to killer T cells, causing the killer T cells to proliferate and attack the cancer. However, due to continual and chronically activation, the immune cells take a phenotype known as "exhaustion", in which they experience reduced function and numbers, allowing the cancer cells to proliferate.

Associate Professor Shin Kaneko and his research team have succeeded in creating iPS cells from exhausted killer T cells from cancer patients and differentiated them back into fully functional or "rejuvenated" killer T cells. Although the rejuvenated cells have properties similar to those of the normal killer T cells, T cell receptor (TCR) rearrangement during the differentiation process reduces their ability to recognize the targeted antigen, thus risking their ability to target cancer cells. By performing genome editing so that undesirable rearrangement does not occur, the team showed that it was possible to induce rejuvenated killer T cells capable of mounting effective attacks on cancer cells *in vivo* and *in vitro.* Furthermore, they could stably generate killer T cells with desired antigen-specificity by using iPS cells from the iPS cell stock .

Finally, they succeeded in endowing T cells generated from iPS cells with the function of helper T cells. One type of killer T cell can only recognize one cancer cell antigen, but helper T cells can activate a wide range of killer T cell types, allowing a response to a number of antigens.

These research findings raise hopes of a new cancer immunotherapy based on the transplant of iPS cell-derived rejuvenated immune cells.

Research Highlight

2018 – 2019

Turbulence makes possible the large-scale platelet production required for clinical use

Turbulence activates platelet biogenesis to enable clinical
Cell

Department of Clinical Application
Koji Eto
(Professor)

Human iPS cell-derived platelets are expected to be one of alternative systems of platelet transfusions. Current methods using iPS cells, however, fall far short of producing the more than 100 billion platelets required for one transfusion.

In their newest report, Professor Koji Eto and his research team discovered that turbulence is key to platelet production. By incorporating this turbulence into bioreactors, they succeeded in creating more than 100 billion platelets in one session.

Molecularly, the turbulence stimulated megakaryocytes to release the soluble factors IGFBP 2, MIF, and NRDC to promote the production of platelets with normal function. The researchers showed made platelets that functioned normally when transfused into two animal models.

Based on these findings, the group has received approval to transfuse autologous iPS cell-derived platelets into a paitent with aplastic anemia and platelet transfusion refractoriness.

Oxidative stress causes proliferation of DUX4, the causative gene of facioscapulohumeral muscular dystrophy

A patient-derived iPSC model revealed oxidative stress increases facioscapulohumeral muscular dystrophy-causative DUX4
Human Molecular Genetics

Department of Clinical Application
Hidetoshi Sakurai
(Associate Professor)

Facioscapulohumeral muscular dystrophy (FSHD) is a genetic disease in which progressive muscular degeneration causes muscular weakness. The cause is thought to be abnormal expression of the DUX4 gene, which is toxic to skeletal muscle. Because the progression of symptoms varies widely among patients, unknown external factors are also thought to be involved.

To elucidate these external factors, Associate Professor Hidetoshi Sakurai and his research team have been investigating the mechanism of FSHD by FSHD patient-derived iPS cells to generate skeletal muscle cells. They found that DUX4 was expressed at high levels in iPS cell-derived myocytes and that this expression was increased by oxidative stress. When one mutation of SMCHD1, one of the causative genes of FSHD, was repaired with CRISPR/Cas 9 in the patient iPS cells, the level of DUX4 expression was reduced even when the cells were exposed to oxidative stress.

This research suggests that the oxidative stress brought on by excessive exercise, muscular damage, inflammation, and other triggers may be an external factor stimulating the progression of FSHD.

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 Director, CiRA, Kyoto Univ.

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 about how somatic cells are reprogrammed into iPS cells. Our laboratory's research aims to elucidate biological phenomena.

Research Progress

Establishing a global-standard iPS cell culture method

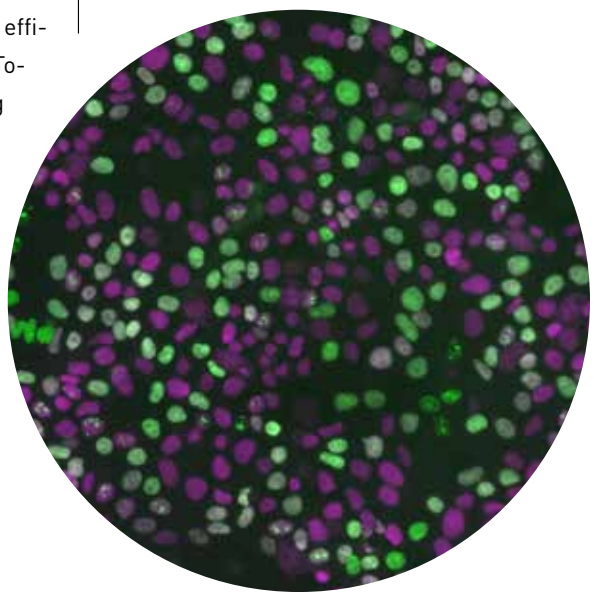
iPS cell generation has been progressing not only here at CiRA, but in countries around the world, leading to a diverse range of iPS cell technologies. For instance, there are differences in source tissues, reprogramming factors and reprogramming induction methods. These differences result in variations in cell properties, cell safety, and the efficiency of the generation process. Toward practical application in drug discovery and regenerative medicine, we have been working to develop safe and effective technology for iPS cell generation and evaluation that can serve as a global standard. So far, we have succeeded in establishing iPS cell culture methods that has low risk of carcinogenesis and is free of animal-derived substances.

Toward a new life science and new medical treatments

To promote the clinical application of iPS cells, further research is needed on the maintenance of pluripotency and chromosome stability. We have established the role played in pluripotency by the Nat1 gene, which we identified in 1997 as a gene essential to the differentiation potential of embryonic stem cells.

Going forward, in addition to clinical applications, we envisage that iPS cells will also contribute to basic research aimed at better understanding of cell differentiation and reprogramming.

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



Members

・Mio Iwasaki (Assistant Professor)
・Tsuyoshi Tabata

Using iPS cells as a tool for research in developmental biology

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

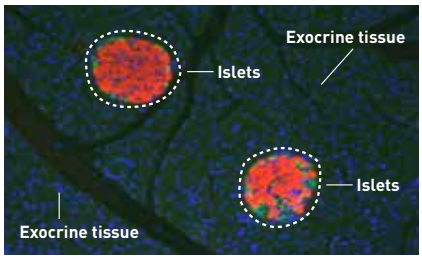
Summary

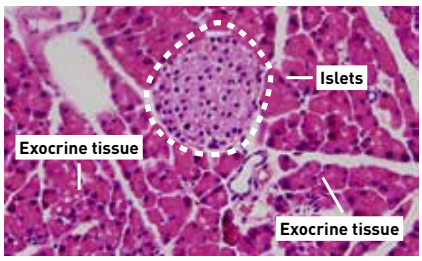
The pancreas contains both exocrine tissue, which secretes digestive enzymes, and endocrine tissue, which secretes hormones. Aiming to generate three-dimensional pancreatic tissue from human iPS cells, we are investigating pancreas development and maturation. We are also studying development of the digestive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

Research Progress

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

The pancreas acts both as a digestive and an endocrine organ. Its two corresponding tissue types, exocrine tissue and pancreatic islets, are formed almost simultaneously and coexist throughout its lifetime. In fiscal year 2018, we discovered that exocrine tissue-derived TFF 2 inhibits cell death in fetal-stage endocrine cells. We will keep identifying other exocrine tissue-derived factors that suppress the activity of endocrine cells.





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.

Elucidating the mechanism of "epithelial barriers" formation

There are a number of locations in the human body where junctions form between different types of epithelial cells.

In fiscal year 2018, we achieved fundamental insights into the mechanism of one of these sites, the junction of the esophagus and the stomach.

Not only during development, but also during tissue regeneration or when cancer develops, cells communicate with each other to regulate tissue morphology. We are conducting basic research to deepen our understanding of cell behavior in the regulation of three-dimensional structures.

Members

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

Profile

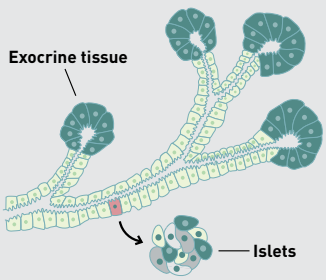
1988 M.D., Faculty of Medicine, Kyoto Univ.
1997 Ph.D., Graduate School of Medicine, Kyoto Univ.
1999 Postdoctoral Fellow, Dept. of Cell Biology, Vanderbilt Univ.
2002 Assistant / Assistant Professor, Graduate School of Medicine, Kyoto Univ.
2009 Lecturer, Graduate School of Medicine, Kyoto Univ.
2011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

Publication Highlights

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

(2) Sox9 and reprogramming of liver and pancreatic progenitors
Kawaguchi Y
J Clin Invest (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.*
Nat Genet (2011) 43 (1) : 34-41



Factors from exocrine tissue are needed to differentiate islets.

Department of Life Science Frontiers

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 Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) Stem cell based methods to predict developmental chemical toxicity
Takahashi H *et al.*
Methods Mol Biol (2018)
1800: 475-483

(2) Japanese patent application
No.5931

(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

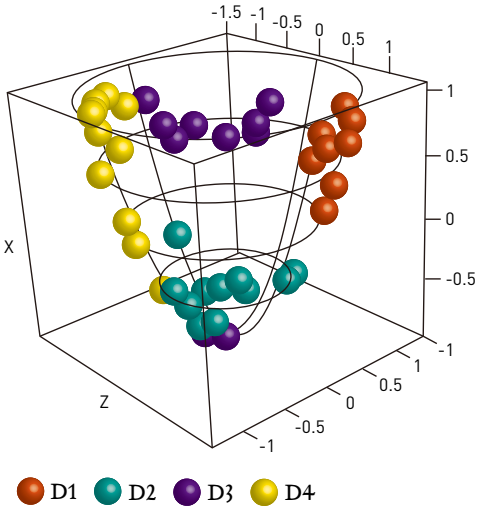
As an informatics laboratory, we are engaged in theoretical cell analysis. To date, with the aim of constructing an artificial intelligence-based system to predict the toxicity of a substance by the reaction in ES cells, we have set up a consortium consisting of companies and researchers in related fields.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

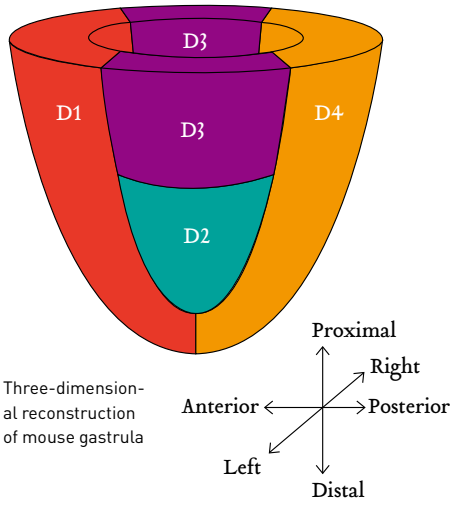
Research Progress

Developing a stem cell toxicity testing system and a stem cell information database

Utilizing artificial intelligence technology, we constructed a highly accurate compound toxicity prediction system using human ES cells and gene network data.

Our laboratory also conducts wet experiments that provide a wide range of omics data, such as gene expression data and epigenetic data including methylome information, which we integrate to calculate intercellular distances with the aim of reconstructing computer-based three-dimensional tissues. As an achievement of 2018, we submitted a related international patent application. Also, Japan's largest stem cell database –SKIP– was transferred to our laboratory from Keio University, which promoted further integration of international stem cell databases.





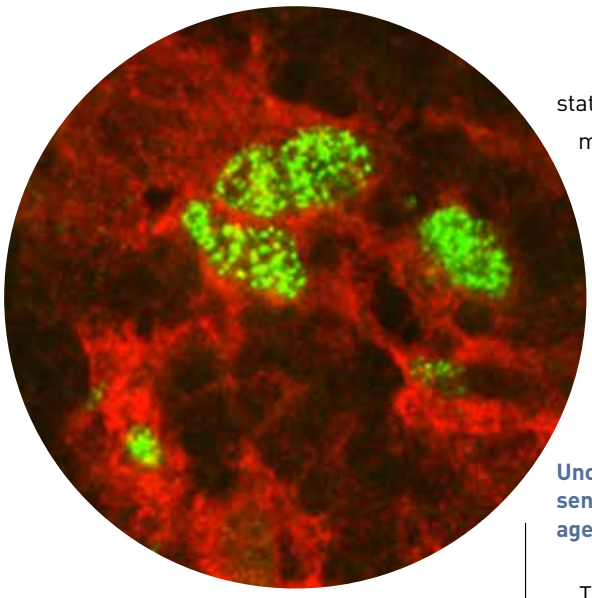
Three-dimensional reconstruction of mouse gastrula

Members

- Ying Chen
- Emma Hasna Maud Goune
- Kazunori Jikihara
- Teruhiro Kamoto
- Tsuneo Kido
- Kenta Kobayashi
- Yuji Kozakura
- Takayuki Nakayama
- Kayo Obata
- Ayano Osakada
- Hironori Otsuki
- Susumu Sawada
- Naila Shinwari
- Hiroki Takahashi
- Haruka Takaoka
- Wan Yun Tian
- Masami Ueno
- Junko Yamane

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

We have identified the stem cells of thymic teacher cells that educate developing T cells and found that their activity begins to decline in advance of age-related thymic atrophy. Based on these findings, we are studying the mechanisms of thymic involution and T-cell aging and investigating novel strategies to reconstitute thymic function using iPS cell technologies.

Research Progress

Understanding and reproducing the thymus, the organ producing T cells

We have recently revealed that some particular thymic epithelial cells in a state of senescence release a range of molecules which regulate the thymic microenvironment and thereby contribute to the production of T cells [Wang et al. Int. Immunol (2018)]. Building on the findings of this basic research, we are working to reconstitute thymic function using iPS cells.

Uncovering the mechanism of T-cell senescence and its involvement in age-related diseases

The thymus shrinks rapidly after adolescence. We have discovered that, prior to this so-called thymus involution, the activity of thymic epithelial stem cells undergoes a marked decline. More recently we have additionally found that thymic involution and subsequent reduced production of new T cells induce a compensatory proliferation in the body's T cells even in the absence of infection, and that this process results in an increase in CD8 T cells, which are strong producers of inflammatory cytokines(1). This suggests the possibility that this unique group of T cells, which increases with aging, contributes to the onset and pathology of metabolic diseases involving chronic inflammation.

Members

- Kouhei Kometani (Assistant Professor)
- Tomoko Ikari
- Chiyomi Inoue
- Takeshi Ito
- Norihide Jo
- Mika Sawada
- 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 Professor, CiRA / Graduate School of Medicine, Kyoto Univ.

Publication Highlights

(1) CXCR3high CD8+ T cells with naïve phenotype and high capacity for IFN-γ production are generated during homeostatic T-cell proliferation
Kato A *et al.*
Eur J Immunol (2018)
48(10) : 1663-1678

(2) Medullary thymic epithelial stem cells: role in thymic epithelial cell maintenance and thymic involution
Hamazaki Y *et al.*
Immunol Rev (2016)
271(1) : 38-55

(3) 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

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 Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) Synthetic mRNA devices that detect endogenous proteins and distinguish mammalian cells
Kawasaki S *et al.*
Nucleic Acids Res (2017)
7: 45(12): e117

(2) Mammalian synthetic circuits with RNA binding proteins for RNA-only delivery
Wroblewska L *et al.*
Nat Biotechnol (2015)
33(8): 839-841

(3) Synthetic RNA-based logic computation in mammalian cells
Matsuura S *et al.*
Nat Commun (2018)
9: 4847

Summary

MicroRNA and protein activity varies with cell type. This insight enabled us to construct systems for regulating the expression of genes introduced into cells.

Research Progress

Regulating cell fate with synthetic RNA-based logic circuits

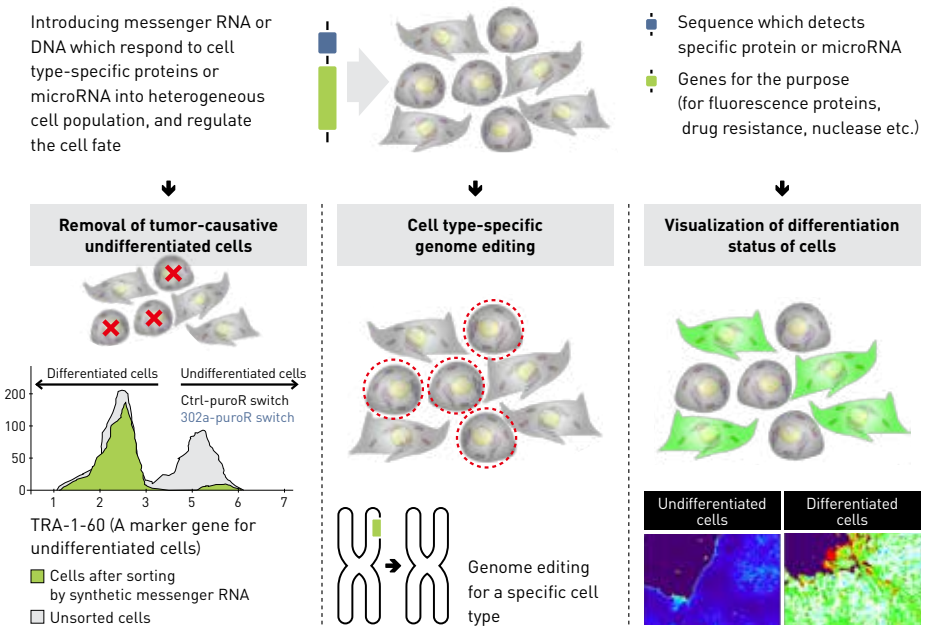
With iPS and iPS-derived cells, we need to regulate cell fate by cell type, for instance by distinguishing target cells and other cell populations or by selectively removing unwanted cells(1). To do this, we have developed systems to detect differences in the intracellular environment(2).

In fiscal year 2018, we developed this system further to construct logic circuits capable of detecting a number of different microRNA types simultaneously(3). By successfully creating within the cell the system analogous to a computer's logical operator, we have made it possible to achieve more precise regulation of cell fate in response to the cell type.

Members

- Yoshihiko Fujita (Assistant Professor)
- Sae Akamine
- Kazuma Fukuya
- Karin Hayashi
- Moe Hirosawa
- Shunsuke Kawasaki
- Shin-Il Kim
- Kaoru Richard Komatsu
- Kenjiro Kotake
- Sora Matsumoto
- Satoshi Matsuura
- Emi Miyashita
- Tomohiro Miyazato
- Megumi Mochizuki
- Hideyuki Nakanishi
- Miho Nishimura
- Hirohisa Ohno
- Hiroki Ono
- Malvin Leonardo Pardi
- Shunsuke Sumi
- Teruo Susumu
- Nobuhiro Tsushi
- Shunsuke Wada
- Mari Yamagata
- Ryo Yamamoto

Using biomolecules to regulate cell fate



Engineering genomes and cell functions

Knut Woltjen Ph.D., Associate Professor

Summary

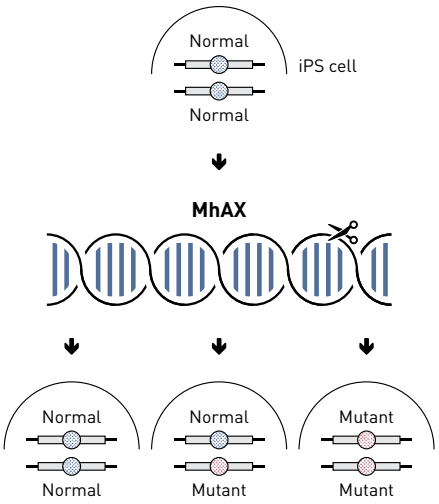
Pioneering genome engineering technologies in human iPS cells for nearly a decade, the Woltjen Laboratory develops cell engineering strategies for disease modelling and improved stem cell therapies. Employing molecular biology tools such as DNA transposons, programmable nucleases, and site-specific recombinases, 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 micro-homology-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.

Simultaneously derive an isogenic iPS cell panel



Our research into somatic cell reprogramming mechanisms uses *piggyBac* transposon technology, and our studies revealed a fundamental difference in cloned Klf4 that affects protein stoichiometry, influencing both the initiation and stabilization of true iPS cells(1). Using this system, we have recently identified transcriptional regulators which suppress the growth of partially reprogrammed cells and streamline the establishment of induced pluripotency.

Members

- Janin Grajcarek
- Mayumi Ikeda
- Harunobu Kagawa
- Shin-Il Kim
- Suji Lee
- Tomoko Matsumoto
- Thomas Luc Maurissen
- Michiko Nakamura
- Anika Reinhardt
- Jose Fabian Oceguera Yanez

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.
2018 Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) OVOL1 influences the determination and expansion of iPSC reprogramming intermediates
Kagawa H *et al.*
Stem Cell Reports (2019) 12(2): 319-332

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

(3) 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

Department of Life Science Frontiers

Comprehensive analysis of changes accompanying the somatic cell reprogramming process

Takuya Yamamoto Ph.D., Associate Professor

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 Assistant Professor, CiRA, Kyoto Univ.
2016 Junior Associate Professor, CiRA, Kyoto Univ.
2018 Associate Professor, CiRA, Kyoto Univ.

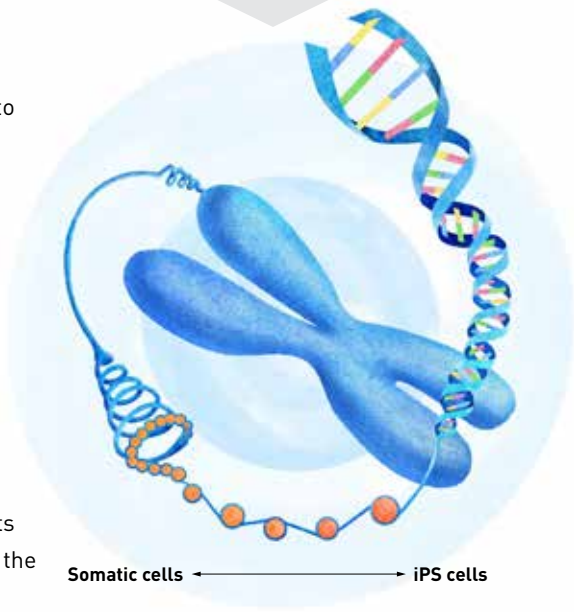
Publication Highlights

(1) Hybrid cellular metabolism coordinated by Zic3 and Esrrb synergistically enhances induction of naive 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.*
Nat Commun (2017)

(3) Generation of human oogonia from induced pluripotent stem cells in vitro
Yamashiro C *et al.*
Science (2018) 362: 356-360

Genome-wide analysis(NGS)
Molecular biology
Bioinformatics



Summary

The aim of our research group is to uncover the fundamental principles underlying biological phenomena. To do this, we use cell fate-altering processes including somatic cell reprogramming as the target experimental system to clarify how information is extracted from the genomic DNA and how the extracted information is fed into cell function and cell properties. Our laboratory conducts comprehensive analysis to achieve the above mentioned goal.

Research Progress

Understanding the regulatory mechanism of the somatic cell reprogramming process

We have established that two transcription factors, Zic3 and Esrrb, acting together with Oct4, Sox2, and Klf4, can dramatically increase the effectiveness of mouse somatic cell reprogramming. We additionally demonstrated that transcription networks including Zic3 and Esrrb act in concert with the metabolic network to regulate the somatic cell reprogramming process(1). In fiscal year 2018, we performed metabolome analysis of the transition from primed pluripotent stem cells to naïve pluripotent stem cells, thus shedding light on metabolic regulatory mechanisms in naïve pluripotent stem cells.

Elucidating the regulatory mechanism of pluripotent stem cells

Our analysis of the chromosome higher-order structure has revealed that differentiation-related gene loci separate from the nuclear membrane in somatic cells during reprogramming to colocalize in pluripotent stem cells(2). In fiscal year 2018, we focused on genome domains of unknown function, or gene deserts, and identified an iPS cell-specific chromosome structure, thereby discovering a new connection between higher-order structures and the maintenance of pluripotency.

Members

- Junya Asahira
- Hiroki Ikeda
- Mayumi Ikeda
- Mio Kabata
- Eri Kawaguchi
- Joonseong Lee
- Ryoji Mabuchi
- Satoko Sakurai
- Yuko Sogabe

Early development and regenerative medicine using naïve human iPS cells

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

Summary

iPS cells and ES cells can be subdivided into two types according to which developmental stage they are closest: a naïve type found in mice that is closer to the fertilized egg; and a primed type found in humans and a more advanced developmental stage. It is thought that the naïve type can differentiate with higher efficiency into a wider range of cells.

We have been progressing with research to reset human iPS cells into the naïve state and have achieved a world-first success in this area. We are also engaged in research to visualize the initial stages of development in vitro.

Research Progress

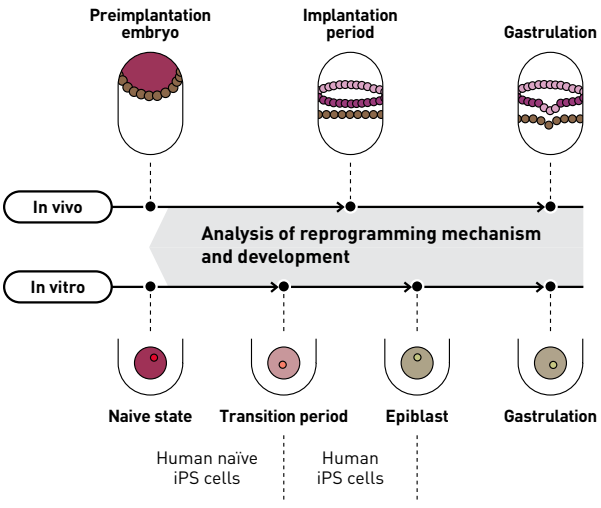
Human naïve iPS cells and regenerative medicine

Because human naïve iPS cells have low methylation levels resembling fertilized eggs, it is expected that they may have wider differentiation potential and offer higher differentiation efficiency. Our aim is to realize regenerative medicine based on human naïve iPS cells, and we are accordingly engaged in detailed analysis of the process of reprogramming into the naïve state.

Human naïve iPS cells and early development

In fiscal year 2018, we concentrated especially on inducing differentiation into extra-embryonic cells. At the same time, taking as our model the common marmoset, whose developmental pattern is similar to that of humans, we are progressing with the analysis of early development and research into naïve iPS cells.

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.

Members

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

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 Junior Associate Professor, CiRA, Kyoto Univ.

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) Reduced MEK inhibition confers a growth advantage and improves genomic stability in naïve human ES cells
Stefano BD *et al.*
Nature Methods (2018)
15 (9) : 732-740

(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

Unlocking the somatic cell reprogramming mechanism by uncovering protein functions

Masato Nakagawa Ph.D., Junior Associate Professor

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 Junior Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

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

(2) A novel efficient feeder-free culture system for the derivation of human induced pluripotent stem cells
Nakagawa M *et al.*
Sci Rep (2014) 4: 3594

(3) Promotion of direct reprogramming by transformation-deficient Myc
Nakagawa M *et al.*
PNAS U S A (2010) 107 (32) : 14152-14157

Summary

To clarify the somatic cell reprogramming mechanism, we are investigating the action of the Yamanaka factors. We are also researching iPS cell maintenance culture methods that are feeder-free (i.e., without using animal cells) and the associated mechanisms.

Research Progress

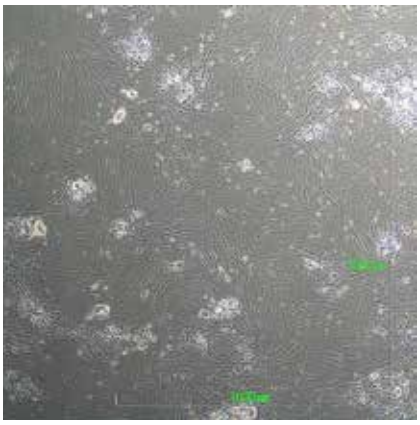
Understanding the somatic cell reprogramming mechanism

We are elucidating the molecular functions of Sox2, Oct3/4, Klf4, and c-Myc, the first identified reprogramming factors. Of the four, we have taken special interest in the function of c-Myc, a member of the Myc family. The Myc gene has several isoforms (c-Myc, N-Myc, L-Myc <My cl>). In human cells, L-Myc is more efficient than c-Myc at generating iPS cells, but the reason for this is unclear.

To investigate this puzzle, we are reprogramming using the Sendai virus and RNA induction systems. Within one week after introduction of the reprogramming factors, a difference was apparent between the functions of c-Myc and L-Myc. Going forward, we intend to clarify L-Myc function during this period.

Members

・Chiaki Akifuji
・Takahiko Imai
・Yoko Uematsu
・Yuka Kawahara
・Chiho Sakurai
・Akihide Shimizu
・Yukie Seto
・Jun Mukougawa



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

Klf4 is also an important reprogramming factor, but its function has not been analyzed in detail. We used proteomics analysis to investigate the expression level and modification status. We are investigating this hypothesis.

Developing efficient culture methods for human iPS cells

We have developed an efficient method for the generation and maintenance of human iPS/ES cells that does not use feeder cells (feeder-free culture). To maintain these cells in the undifferentiated state, the growth factor bFGF must be added to the culture medium, but the mechanism involved is unclear. It is thought that as bFGF binds to the receptor, a signal gets transmitted into a cell and that maintains the cell undifferentiated. However, our recent research findings suggest that there may actually be a different mechanism at work, which we are now seeking to clarify.

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

Keisuke Okita Ph.D., Junior Associate Professor

Summary

Understanding the reprogramming mechanism is crucial for the medical application of iPS cells. We have identified genes that affect the reprogramming efficiency. We are researching to elucidate the reprogramming mechanism and ways that destabilize cell identity.

Research Progress

Clarifying the somatic cell reprogramming mechanism

A full understanding of the reprogramming mechanism is essential for generating high quality iPS cells and achieving clinical application. We are tackling this challenge through a gene-based approach and have investigated over 2,000 genes, of which HLX, HHEX, and Srf were found to improve reprogramming efficiency.

In further analysis, we established that Srf is involved in maintaining the stability of differentiated cells. Failure of this mechanism leads to disease, and when Srf is forcibly expressed in mice, abnormalities arise in the pancreas, stomach, and colon. We have also identified a number of genes that block reprogramming and are researching ways to improve iPS cell quality by controlling these genes.

Application to endangered species

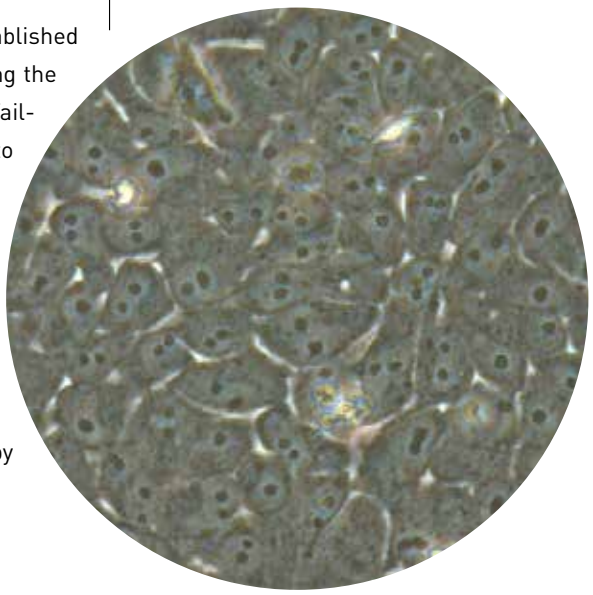
In Japan, there are more than 30 mammal species such as the Iriomote cat that are listed as endangered.

Using iPS cell technology, it may be possible to save species for which conservation measures are now too late. Zoos and other facilities worldwide have frozen stocks of somatic cells of endangered and extinct animal species. It is thought that individual reproduction could be achieved by generating iPS cells from these somatic cells and applying assisted reproduction technology. We are currently engaged in related technology development.

Members

- Tomomi Eto
- Mari Hamao
- Takashi Ikeda
- Yasuko Matsumura
- Mizuki Minata
- Yukie Seto
- Masafumi Shibata
- Yoko Uematsu

iPS cells derived from cynomolgus monkey



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 Junior Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

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

Department of Life Science Frontiers

Capturing biological phenomena with ultra-high resolution

Akira Watanabe Ph.D., Assistant Professor

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 Junior Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) Autologous induced stem-cell-derived retinal cells for macular degeneration (in Japanese)
Mandai M, Watanabe A *et al.* *New Engl J Med.* (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 (in Japanese)
Watanabe A
Experimental Medicine (2015) 33 (1): 2-6

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, which is why we have developed single cell analysis tools. Using these tools, we could detect the beginnings of cancer-like properties in cells.

Research Progress

Understanding the mechanism of cell fate

In fiscal year 2018, our research focused mainly on establishing a methodology for single-cell multi-omics to clarify the mechanism of cell fate determination. Genomics practice hitherto has observed average conditions in multi-cell populations, but reports indicate that the behavior of individual cells differs widely.

By operating a number of single-cell analysis platforms and using them to analyze transcription conditions at the single-cell level in several thousand different cells, we were able to identify cell groups which were undetectable under previous classification systems. This has made it possible for instance to elucidate the transcription characteristics of a cell group representing less than 10% of the total. We have also developed a new technique for characterizing the time-series change in transcription networks.

Based on these results, we identified factors involved in the regeneration of the kidney and pancreas. Additionally, by integrating DNA methylation analysis with epigenetic analysis, including chromatin status analysis with ATAC-seq, we realized multi-omics analysis. We discovered that these epigenetic conditions reflect the cell history and succeeded in visualizing the process of cell carcinogenesis. In this way, through basic research concentrating on single-cell analysis and through the building of platforms for drug discovery, we are progressing to observe all biological phenomena at the single-cell level.

Members

- Akiko Hasegawa
- Ryotaro Kabai
- Unyanee Kato
- Noda Katsura
- Tomoko Kita
- Ryo Kitano
- Saki Matsushima
- Chihiro Okada
- Satoko Sakamoto
- Midori Sakiyama

Understanding cell fate by multi-omics analysis including genomics

Unravelling the mechanism of germ cell genesis

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

Research Progress

Recapitulating the germ cell formation process in vitro

From mouse ES/iPS cells, we succeeded in the in vitro induction of primordial germ cell-like cells that contribute to creating sperm and egg cells and healthy offspring. Further, we have clarified the transcription and signaling mechanisms that induce primordial germ cells, elucidated the epigenetic reprogramming mechanism, developed a method to proliferate primordial germ cells, induced sperm stem cells from primordial germ cells *in vitro*, identified the mechanism of oocyte differentiation and meiosis, and generated offspring in mice that were infertile due to sex chromosome abnormalities. We also succeeded in inducing human primordial germ cell-like cells from human iPS cells. Moreover, we progressed with research using cynomolgus monkeys to identify the development coordinates of the pluripotency spectrum in mice, monkeys, and humans, and pinpointed the early-stage amnion as the origin of primate germ cells.

In fiscal year 2018, we succeeded in maturing primordial germ cell-like cells induced from human iPS cells into oogonia. We are now engaged in further research to recapitulate the process of human germ cell formation.

Members

・Yoji Kojima (Assistant Professor)
・Shihori Yokobayashi (Assistant Professor)
・Sayaka Takeshima

Profile

1995 M.D., Faculty of Medicine, Kyoto Univ.
1999 Ph.D., Graduate School of Medicine, Kyoto Univ.
2009 Professor, Graduate School of Medicine, Kyoto Univ.
2018 Adjunct Principal Inventigator, CiRA / Professor, Kyoto University Institute for Advanced Study / Director, Institute for the Advanced Study of Human Biology

Publication Highlights

(1) Generation of human oogonia from induced pluripotent stem cells in vitro
Yamashiro C *et al.*
Science (2018) 362: 356-360

(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

Elucidating the mechanism that determines protein quantity

Mio Iwasaki Ph.D., Assistant Professor

Research Progress

Development of protein quantification methods

Proteins are essential macromolecules that regulate cell function. Observing differences in protein expression levels and modification status between cell types may therefore lead to more efficient control of cell reprogramming and differentiation.

In fiscal year 2018, we developed a method for protein quantification known as RiMS (removal of interference mixture MS/MS spectra) that allows highly accurate protein quantification without repeated measurement of samples or use of high-sensitivity mass spectrometry. Additionally, by comparing human ES/iPS cells and fibroblasts, we succeeded in isolating several hundred gene groups that display marked differences between mRNA volume and protein volume. Next, we intend to explore the factors controlling these volumes to identify critical genes in cell fate.

Members

・Yuka Kawahara
・Sayaka Takeshima
・Tsuyoshi Tabata

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 Assistant Professor, CiRA, Kyoto Univ.

Publication Highlight

(1) The jPOST environment: an integrated proteomics data repository and database
Ishihama Y *et al.*
Nucleic Acids Res (2019)
47 (D1) : D1218-D1224

Department of Cell Growth and Differentiation

Understanding skeletal system diseases to develop innovative therapies

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

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 Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) In vitro bone-like nodules generated from patient-derived iPS cells recapitulate pathological phenotypes of bone disease
Kawai S *et al.*
Nat Biomed Eng (2019)
doi: 10.1038/ s41551-019-0410-7

(2) Enhanced mTOR signaling triggered by Activin-A in chondrogenesis of fibrodysplasia ossificans progressiva (FOP)
Hino K *et al.*
J Clin Invest (2017)
127(9) : 3339-3352

(3) Neofunction of ACVR1 in fibrodysplasia ossificance progressiva
Hino K *et al.*
PNAS U.S.A (2015)
112(50) : 15438-15443

Summary

The skeletal system is made up of bone, cartilage, ligament, tendons, and other cell types. Diseases of the skeletal system can be caused by genetics, trauma, and other acquired conditions, 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

Physician-initiated clinical trial for intractable disease

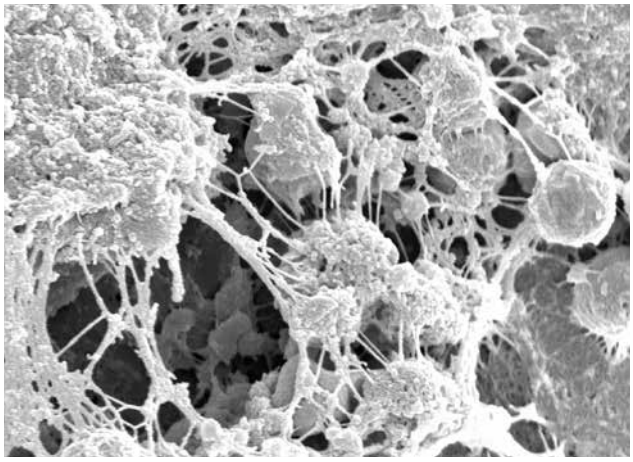
Our research using patient-derived iPS cells identified a therapeutic drug candidate for fibrodysplasia ossificans progressiva (FOP). A joint multicenter physician-led clinical trial began in September 2017 at 4 centers in Japan, with the enrollment of the planned number of subjects completed in fiscal year 2018.

Successful development of high-efficiency bone differentiation method

By adapting retinoic acid signaling, we succeeded in establishing a method to induce bone cells in a period of just 10 days. Using this method, we reproduced *in vitro* the pathological conditions of the intractable disease osteogenesis imperfecta and established a therapeutic drug screening system. We also achieved the first successful visualization of the differentiation process using time lapse images taken with confocal microscopy. This system is expected to become a useful tool for understanding the bone differentiation process, with applications ranging from the analysis of genetic diseases to drug discovery for more general diseases such as osteoporosis.

Members

- Hiroyuki Yoshitomi (Associate Professor)
- Cantas Alev (Assistant Professor)
- Yonghui Jin (Assistant Professor)
- Yoshiko Uesughi
- Takeshi Kamakura
- Rena Kashimono
- Shunsuke Kawai
- Yuko Koyama
- Sun Liping
- Sanae Nagata
- Megumi Nishio
- Mizuki Ohtsuka
- Yann Pretemer
- Mitsuru Soen
- Tomoyuki Takeya
- Sakura Tamaki
- Makoto Watanabe
- Rie Yamamoto
- Yoshihiro Yamanaka
- Hisayo Yashida
- Marie Yoshino



Bone cells differentiated from iPS cells

Opening new horizons in cardiac regenerative therapy with iPS cells

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

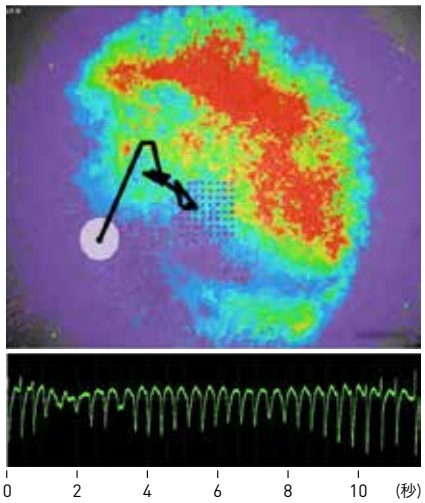
Summary

We are conducting research to ultimately generate heart cells and tissues from iPS cells. Based on 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 heart and blood vessel tissues

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 of differentiating human iPS cells into vascular endothelial cells(3) and commercialized this technology in an iPS cell-derived endothelial cell product and a cardiomyocyte product. Additionally, we aim to use human iPS cells to create cardiac tissue-like structures (HiCT) including heart muscle, blood vessels, and interstitial tissues for cardiac regenerative therapy within the next few years (joint research with Kyoto University School of Medicine, Dept. of Cardiovascular Surgery/Institute for Frontier Life and Medical Sciences).



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.

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.

Members

- Yuji Agawa
- Daisuke Heima
- Takuhiro Hoshino
- Yurie Kaji
- Tsugumitsu Kandou
- Masahide Kawatou
- Yu Kinoshita
- Yajing Liu
- Víctor López-Dávila
- Hidetoshi Masumoto
- Tomohiro Minakawa
- Chisato Murayama
- Kae Nakamura
- Toshikazu Nishie
- Yuki Oichi
- Hiroaki Osada
- Mizuho Shino
- Chinatsu Suzuki
- Ayano Tabata
- Masafumi Takeda
- Yasuhiro Tosaka
- 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 Professor, CiRA, Kyoto Univ.

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.*
Nat Commun (2017) 8: 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

Drug discovery using iPSC models of intractable neurological diseases and dementia

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

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 Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) 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

(2) 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

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

Summary

Amyotrophic lateral sclerosis (ALS) and Alzheimer's disease are intractable diseases caused by the degeneration of neurons in the central nervous system. We use patient-derived iPS cells to establish disease models, which will contribute to reveal disease mechanism and to discover therapeutic drugs. Accordingly, we have investigated drug efficacy and explored compounds or cocktails to treat these diseases.

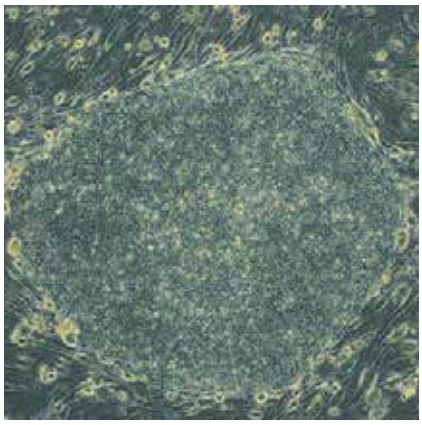
Research Progress

Elucidating the pathology of intractable neurological diseases and feedback to clinical practice

Using iPS cells from patients with intractable neurological diseases, such as ALS and Alzheimer's disease, we have been progressing with research aimed at developing drug discovery platforms, transplant therapies, and precision medicine. Our research can thus be described as going "from bedside to dish" and "from dish to bedside."

In cooperation with research groups in Japan and overseas, we have used motor neuron cells generated from ALS patient-derived iPS cells to carry out compound screening for therapeutic drugs. This resulted in the identification of a molecular pathway as a target for ALS treatment and the discovery of an existing drug that suppresses degeneration in motor neurons. In March 2019, clinical trials on ALS patients were begun.

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(2).



ALS patient-derived iPS cells

Members

- Keiko Imamura (Assistant Professor)
- Takayuki Kondo (Assistant Professor)
- Haruhiko Banno
- Takako Enami
- Mikie Iijima
- Risa Inoue
- Naoko Kasai
- Nozomi Kawabata
- Michiyo Miyake
- Ayako Nagahashi
- Takeshi Niki
- Sayaka Omori
- Shinichi Sueta
- Mika Suga
- Dang Ngoc Anh Suong
- Ayumi Suzuki
- Ruri Taniguchi
- Kayoko Tsukita
- Tan Ghee Wan
- Toshifumi Watanabe
- Yuichiro Yada

Novel regenerative medicine for the kidney, pancreas, and liver

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

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 highly efficient method of differentiating iPS cells into nephron progenitor cells.

Toward the development of cell-based therapies for kidney disease, we have also identified a combination of cell surface antigens, which can sort kidney progenitor cells from iPS cells.

Pancreas regeneration

We identified the low-molecular compound AT7867, which promotes the proliferation of human iPS cell-derived pancreatic progenitors, and the compound sodium cromoglicate, which stimulates the differentiation of pancreatic progenitors into pancreatic endocrine cells, and used them to develop a method to induce pancreatic islet cells (see Figure).

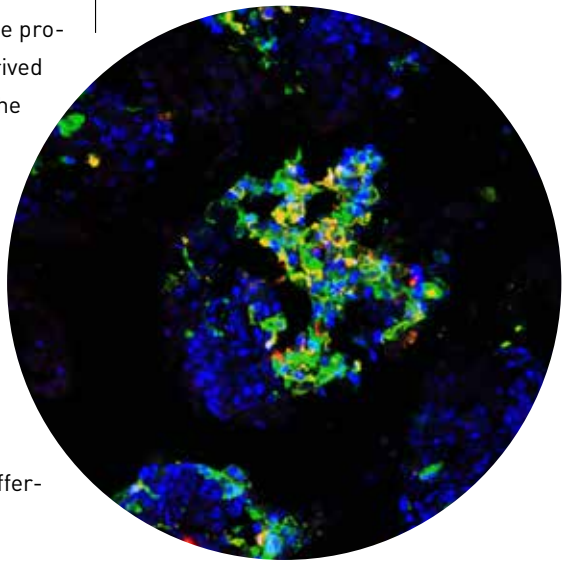
Liver regeneration

We established a method to differentiate iPS cells into bile duct epithelial cells, one of the constituent cell types of the liver. Going forward, we aim to create models of diseases that cause lesions in the bile duct, such as autosomal dominant polycystic kidney disease (ADPKD).

Members

- Taro Toyoda (Junior Associate Professor)
- Shin-Ichi Mae (Assistant Professor)
- Toshikazu Araoka
- Ayako Date
- Hirofumi Hitomi
- Azusa Hoshina
- Maiko Igami
- Chihiro Inui
- Ryo Ito
- Yoshikazu Kameda
- Tomoko Kasahara
- Naoko Katagiri
- Azuma Kimura
- Yasuyo Kitai
- Shuhei Konagaya
- Maki Kotaka
- Yang Liu
- Kyoko Matsuse
- Atsushi Mima
- Takahito Minami
- Erika Moriguchi
- Shiho Morimoto
- Makoto Nasu
- Miyuki Ochiai
- Ryu Okada
- Shiori Okumura
- Makoto Ryosaka
- Ramin Banan Sadeghian
- Aya Shibasaki
- Tatsuya Shimizu
- Katsutaro Yasuda
- Fumihiko Shiota
- Tomomi Sudo
- Hiromi Tanaka
- Erika Tsuji
- Hiraku Tsujimoto
- Katsutaro Yasuda
- Ryuji Yokokawa

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



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 Professor, CiRA, Kyoto Univ.

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) Monitoring and robust induction of nephrogenic intermediate mesoderm from human pluripotent stem cells
Mae SI *et al.*
Nat Commun (2013) 4:1367
(2018) 495 (1) : 954-961

Department of Cell Growth and Differentiation

Clinical application of rejuvenated T cells

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

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 Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) Enhancing T cell receptor stability in rejuvenated iPSC-derived T cells improves their use in cancer immunotherapy
Minagawa A *et al.*
Cell Stem Cell (2018)
23 (6) : 850-858

(2) Generation of TCR-expressing innate lymphoid-like helper cells that induce cytotoxic T cell-mediated anti-leukemic cell response
Ueda N *et al.*
Stem Cell Reports (2018)
10 (6) : 1935-1946

(3) Generation of HIV-resistant macrophages from iPSCs by using transcriptional gene silencing and promoter-targeted RNA
Higaki K *et al.*
Mol Ther Nucleic Acids (2018)
12: 793-804

Summary

Cytotoxic T lymphocytes (CTL) recognize and destroy viruses, cancer cells, and other foreign bodies. By applying iPS cell technology, we are establishing a high volume of high-quality CTLs. Our research is using this strategy to establish new therapies for cancer and viral infections.

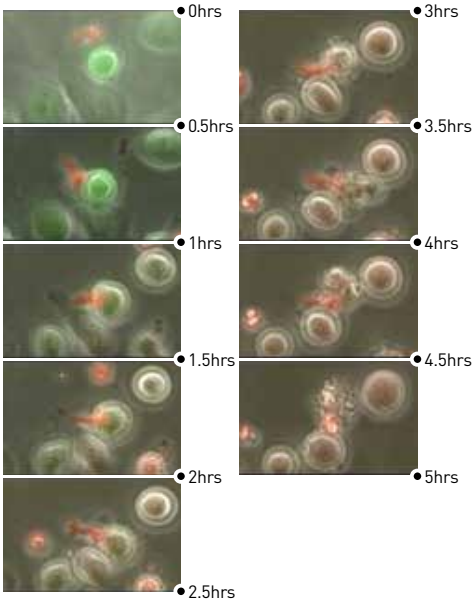
Research Progress

Toward the realization of iPS cell-based immune regenerative therapy

In fiscal year 2018, we reported technology to stabilize the cancer antigen specificity of killer T cells differentiated from cancer patient-derived iPS cells and from CiRA's iPS Cell Stock; the regeneration of immune cells with leukemia antigen-specific helper function; and the regeneration of HIV infection-resistant macrophages.

Using public funds, we investigated the anticancer immune function of reprogrammed tumor-infiltrating lymphocytes, the immunological regulation of HIV infection, and non-clinical safety research based on iPS cell-derived killer cells expressing chimeric receptor genes. Through joint research with a number of private-sector enterprises on projects including the T-CiRA program, we are moving forward with applied research to find a wide range of practical uses for our laboratory results.

Rejuvenated T lymphocytes attack and destroy cancer cells



Red cells: rejuvenated T lymphocytes
Green cells: cancer cells

Members

- Maika Akizuki
- Sayaka Chuganji
- Anri Fujishiro
- Ken Fukumoto
- Yoichi Higuchi
- Eri Iami
- Yoshitaka Ishiguro
- Shoichi Iriguchi
- Akihiro Ishikawa
- Takeshi Ito
- Yoshihiro Iwamoto
- Sanae Kamibayashi
- Yohei Kawai
- Ryota Kobayashi
- Hirokazu Koizumi
- Jung Young Kul
- Ayako Kumagai
- Kaede Makino
- Hiroki Maruyama
- Atsutaka Minagawa
- Yuta Mishima
- Yasuyuki Miyake
- Tadayo Miyasaka
- Kengo Nakagoshi
- Kazuki Nakane
- Munekimi Nanao
- Katsura Noda
- Yusuke Nozaki
- Kohei Ohara
- Nozomi Okamoto
- Junichi Ookawara
- Reiko Saikawa
- Yoshie Sakamoto
- Keisuke Saso
- Eri Sato
- Sara Shiina
- Hiroaki Suzuki
- Hitomi Takakubo
- Shinichiro Takayanagi
- Tomoaki Tanaka
- Masahiro Tanaka
- Tatsuki Ueda
- Bo Wang
- Masazumi Waseda
- Nariaki Yanagawa
- Hisashi Yano
- Yutaka Yasui

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

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

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 heart and blood.

Research Progress

Myocardial regenerative medicine

We reported that optimizing the maturation stage of cardiomyocytes improves the engraftment efficiency in a mouse model of myocardial infarction. We also established new observation techniques using electron microscopes and other tools to confirm that formation of T tubules and other maturation processes *in vivo*. We are now engaged in research to increase the therapeutic efficacy of cell transplants.

Members

- Kenji Miki (Assistant Professor)
- Kazuhisa Chonabayashi
- Takeshi Ego
- Kohei Fujiwara
- Yuya Fujiwara
- Yuhei Fukushima
- Takeshi Hatani
- Azusa Inagaki
- Julia Junghof
- Manabu Kasamoto
- Deboda Kehl
- Misato Koakutsu
- Yuta Kogure
- Antonio Lucena-Cacace
- Ai Mieda
- Yuki Morimoto
- Rena Nakayama
- Megumi Narita
- Misato Nishikawa
- Aya Ogura
- Chikako Okubo
- Daniel Otero-Albiol
- Masako Sasaki
- Yukie Seto
- Kazuma Suda
- Tadashi Takaki
- Ming-Heng Tsai
- Yoko Uematsu
- Masayuki Umeda
- Hidaka Yokota

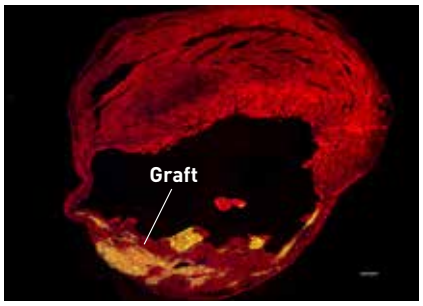
Disease models based on disease-specific iPS cells

We are using gene editing technology to construct models of hypertrophic cardiomyopathy from iPS cells. For arrhythmias, we constructed an analysis system adaptable to high-throughput screening by using a membrane potential-sensitive dye to measure the action potential of cardiomyocytes.

In addition, cardiomyocytes differentiated from iPS cells are immature, which compromises their use in research.

We are developing methods to control the cell maturation. Other diseases modelled include myelodysplastic syndrome and heritable sideroblastic anemia.

At 3 months



At 6 months

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

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 Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) Induced pluripotent stem cells ten years later：for cardiac applications
Yoshida Y, Yamanaka S
Circ Res (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

Department of Clinical Application

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

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

Profile

1986 M.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 Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) Three-dimensional induction of dorsal, intermediate and ventral spinal cord tissues from human pluripotent stem cells
Ogura T *et al.*
Development (2018) 145: dev162214

(2) MHC matching improves engraftment of iPSC-derived neurons in non-human primates
Morizane A *et al.*
Nat Commun (2017) 8: 385

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

Summary

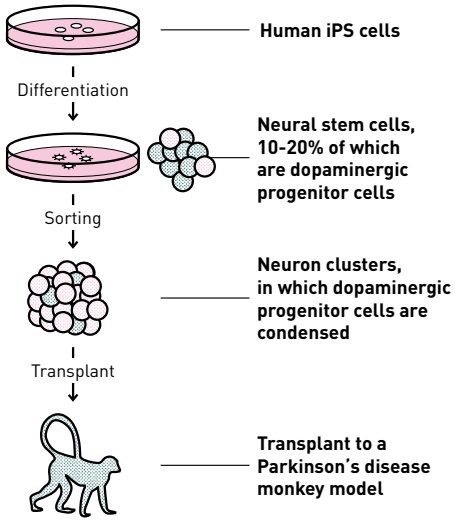
Parkinson's disease is an intractable neurological disease characterized by gradual loss of dopaminergic neurons and the impairment of motor functions. We have carried out experimental transplantations with iPS cell-derived cells in animal models as a radical therapy.

Research Progress

Start of physician-initiated clinical trials

The fiscal year 2018 saw the launch of a physician-initiated clinical trial of iPS cell-based transplantation therapy for Parkinson's disease (see figure right). Using the iPS Cell Stock at CiRA, we induced iPS cells into dopaminergic progenitor cells and purified the cells. After confirming safety and efficacy in animal models and getting approval, we began enrolling patients on August 1, 2018, and operated on the first subject in October.

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

Generating spinal cord organoids

As our next target after Parkinson's disease, we are considering paralysis caused by stroke or brain injury. In the fiscal year 2018 reported on the induction of cerebellar and spinal cord organoids(1). We have established that, when inducing spinal tissue from ES/iPS cells, adjusting the concentration of ventralizing and dorsalizing factors makes it possible to construct three-dimensional structures in a way that mimics individual development.

Members

- Daisuke Doi (Assistant Professor)
- Asuka Morizane (Assistant Professor)
- Hiromasa Adachi
- Tomoka Ashida
- Seiya Baba
- Yudai Fujita
- Kaori Fukushima
- Brice Luc Grinand
- Yulius Hermanto
- Satoe Hiramatsu
- Yuko Ishii
- Markus Karlsson
- Yuki Katano
- Tomohisa Kato
- Tetsuhiro Kikuchi
- Takahiro Kitahara
- Kei Kubota
- Hiroaki Magotani
- Aya Mihara
- Hitomi Nakamura
- Yuki Ozaki
- Hideya Sakaguchi
- Bumpei Samata
- Rena Shiga
- Takafumi Shimogawa
- Mika Soen
- Yusuke Sugao
- Hideaki Takahashi
- Rika Takaichi
- Yoshie Tanikawa
- Ryohei Tomita
- Sadaharu Torikoshi
- Ryosuke Tsuchimochi
- 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 products. However, platelets in particular can only be stored for 4 days after collection, making reliable supplies difficult. We developed an efficient and safe method to create platelet products from iPS cells. We are clarifying the platelet production mechanism, exploring new compounds involved in platelet production, and investigating the role of fluid dynamics in platelet generation as we progress toward commercialization.

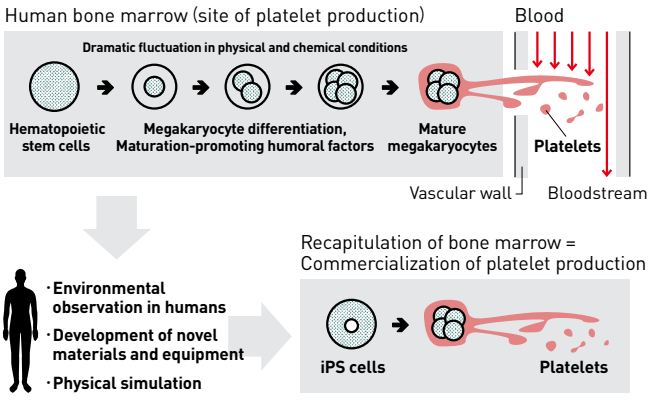
Research Progress

Development of a production system capable of meeting clinical demand

It has become possible to produce platelets from iPS cells, but the efficiency rate of this production is still far behind that of the production that occurs in our bodies. In joint research, we studied the fluid dynamics of platelet release into the blood and discovered that the turbulence of the bloodflow is an important factor. Based on this finding, we developed a new culture apparatus with which we succeeded in producing high-quality platelets on the scale of the 100 billion required for a single transfusion.

We also discovered the possibility of a new pathway involved in platelet biogenesis. This system will contribute not only to the development of a platelet transfusion system independent of donors, but also clarification of the platelet biogenesis mechanism.

Research for commercialization of iPS cell-derived platelet production



Members

- Naoshi Sugimoto (Assistant Professor)
- Marina Akasaka
- Rei Ashine
- Valerie Bolitis Barber
- Si Jing Chen
- Shima Date
- Hiroshi Endo
- Charlotte Flahou
- Kosuke Fujio
- Yasuo Harada
- Kanae Hashimoto
- Kazuya Hashimoto
- Natsumi Higashi
- Akira Ishii
- Yukitaka Ito
- Maki Kawato
- Takaaki Kayama
- Maya Kimura
- Yuki Kurahashi
- Toshie Kusunoki
- Takuya Matsumoto
- Sachiyo Misumi
- Miyuki Morizumi
- Itsuro Motegi
- Jun Mukai
- Sou Nakamura (Specially-Appointed Assistant Professor)
- Machi Nishikoji
- Kimiko Nonomura
- Hiroyuki Okunaga
- Akiko Shigemasa
- Asahi Shimada
- Shin Shimizu
- Ieva Stirblyte
- Katsumi Suezawa
- Mizue Suzuki
- Do Thi Thanh Tam
- Yasuhiko Tosa
- Michiko Ueda
- Rajneesh Varma
- Sanae Yoshikawa
- Akinori Yuzuriha

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 Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) Turbulence activates platelet biogenesis to enable clinical scale ex vivo production
Ito Y *et al.*
Cell (2018) 174 (3) : 636-648

(2) A β1-tubulin-based megakaryocyte maturation reporter system identifies novel drugs that promote platelet production
Seo H *et al.*
Blood Adv (2018) 2 (17) : 2262-2272

(3) Platelet production from induced pluripotent stem cells
Sugimoto N, Eto K
J Thromb Haemost (2017) (9) : 1717-1727

Department of Clinical Application

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 Professor, CiRA, Kyoto Univ.

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.*
Nat Commun (2016) 7: 10959

(3) Proposal of patient-specific growth plate cartilage xenograft model for FGFR3 chondrodysplasia
Kimura T *et al.*
Osteoarthritis Cartilage (2018)
26: 1551-1561

Human iPS cell-derived cartilage tissue

Summary

Cartilage disease impairs bone growth and joint movement. We aim to develop relevant therapies by using iPS cell technology. Our research includes investigating the efficacy of candidate drugs in disease-bearing chondrocytes generated from patient-derived iPS cells and exploring regenerative medicine by replacing damaged articular cartilage with transplants created from iPS cells.

Research Progress

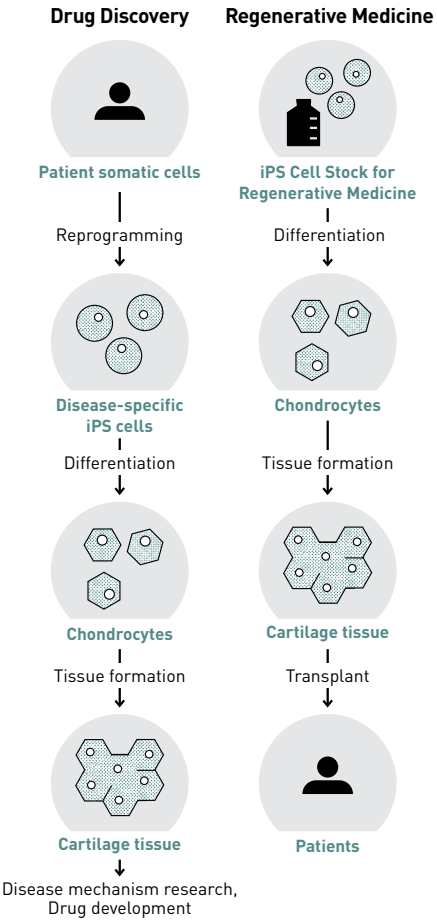
Exploring drug therapies for skeletal dysplasia

In the fiscal year 2018, we carried out subcutaneous transplants of cartilage created from human iPS cells, demonstrating that the complex structure of human epiphyseal plate can be recreated in mice. We also succeeded in recreating diseased epiphyseal plate in an animal model and established that the model can be used to analyze pathological conditions and test drug efficacy.

Development of regenerative therapy for articular cartilage

We aim to realize regenerative therapies by replacing damaged cartilage with transplants made from iPS cells. In the fiscal year 2018, we studied in detail the phenomenon of integration in iPS cell-derived cartilage and analyzed the associated molecular mechanism.

Cartilage disease research with iPS cells



Members

- Akihiro Yamashita (Assistant Professor)
- Xike Chen
- Kaori Fujita
- Fumiko Hamada
- Asami Harumatsu
- Nanao Horike
- Yuki Iimori
- Tomoko Ikari
- Yuui Ishida
- Takashi Kamatani
- Tomoko Kato
- Tsubasa Kita
- Tomohito Kobayashi
- Azuma Kosai
- Maasa Koshimoto
- Saeko Koyamatsu
- Yuki Makita
- Makiko Matsuoka
- Miho Morioka
- Yuri Murata
- Hiromi Nishino
- Aoi Okamoto
- Yuuki Okutani
- Tomonori Ozaki
- Masumi Sanada
- Toshika Senba
- Nobuyuki Shima
- Yoshiaki Takei
- Hiromi Takemoto
- kie Watanabe

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 disease phenotype, we aim to elucidate disease mechanisms and establish therapies for intractable pediatric diseases. Focusing on diseases which appear during the neonate or infancy stage, we are investigating causes at the molecular and genetic level.

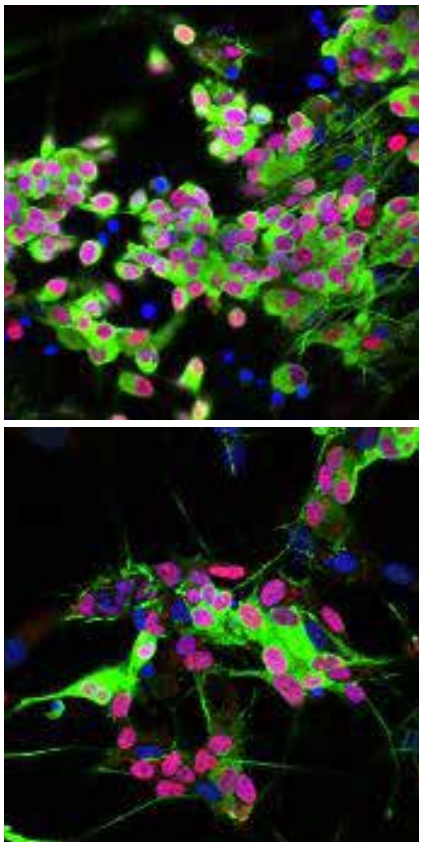
Research Progress

Elucidating the pathology of inflammatory diseases

We generated iPS cells from Nakajo-Nishimura syndrome patients, induced them to differentiate into monocytes and macrophage lineages, and investigated their function. We found that reactive oxygen is elevated in patient-derived cells, but that when this trend is inhibited, the inflammatory reaction is also suppressed.

Developing a highly efficient differentiation method for sympathetic nerve cells

We developed a system for differentiating sympathetic nerve cells from iPS cells that has higher efficiency (80%) compared to standard methods. Further, our system does not use serum, cells or other animal-derived constituents and has no need for cell isolation.



Sympathetic neurons derived from pluripotent stem cells (upper, derived from ES cells; lower, derived from iPS cells). Red, PHOX2B (a specific transcription factor for sympathetic neurons). Green, dopamine beta hydroxylase. Blue, nucleus. Scale bar, 50 μm.

Members

- Akira Niwa (Assistant Professor)
- Mitsujiro Osawa (Assistant Professor)
- Yoko Arai (Nishinaka)
- Tatsuhiko Arakawa
- Seiko Benno
- Hsi Chang
- Nishida Chizu
- Lin Chuang-Yu
- Toshikawa Hiromitsu
- Jose Ichishima
- Ryunosuke Ikeda
- Akihiro Ikenaka
- Naoya Kase
- Yuri Kawasaki
- Yoko Kitagawa
- Chiaki Kubota
- Takafumi Mano
- Hiroyuki Matsubara
- Shiori Matsuo
- Shoko Matsuo
- Asuka Morii
- Emiri Nakamura
- Sayaka Nishimura
- Monika Ohno
- Ryo Ota
- Norikazu Saiki
- Ryosuke Sugimoto
- Li Siqiaozhi
- Ryoichi Sugimura
- Jingxin Wang
- Harumi Watanabe
- Masami Yamashita
- Takahito Yasuda

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 Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) Efficient derivation of sympathetic neurons from human pluripotent stem cells with a defined condition
Kirino K *et al.*
Sci Rep (2018) 8 (1) : 12865

(2) Lysosomal membrane permeabilization causes secretion of IL-1β in human vascular smooth muscle cells
Ono H *et al.*
Inflamm Res (2018) 67 (10) : 879-889

(3) Pluripotent stem cell model of Nakajo-Nishimura syndrome untangles proinflammatory pathways mediated by oxidative stress
Honda-Ozaki F *et al.*
Stem Cell Reports (2018) 10 (6) : 1835-1850

Department of Clinical Application

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

Makoto Ikeya Ph.D., Associate Professor

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 Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) An mTOR signaling modulator suppressed heterotopic ossification of fibrodysplasia ossificans progressiva
Hino K *et al.*
Stem Cell Reports (2018)
S2213-6711(18): 30430-2

(2) Modeling human somite development and fibrodysplasia ossificans progressiva with induced pluripotent stem cells
Nakajima T *et al.*
Development (2018)
145: dev165431

(3) Activin-A enhances mTOR signaling to promote aberrant chondrogenesis in fibrodysplasia ossificans progressiva
Hino K *et al.*
J Clin Invest (2017)
127(9): 3339-3352

Summary

We are researching new therapies for diseases related to bone and cartilage using patient-derived iPS cells. For instance, we recapitulated the pathological conditions of fibrodysplasia ossificans progressiva (FOP) from patient-derived iPS cells and reported a new drug screening system that revealed one drug candidate that could prevent the ossification seen in FOP.

Research Progress

Identifying drugs that inhibit disease progression

Working with the Toguchida lab, we identified rapamycin (sirolimus) as a candidate drug to inhibit disease progression of FOP, and in the fiscal year 2018 we identified two further candidate compounds.

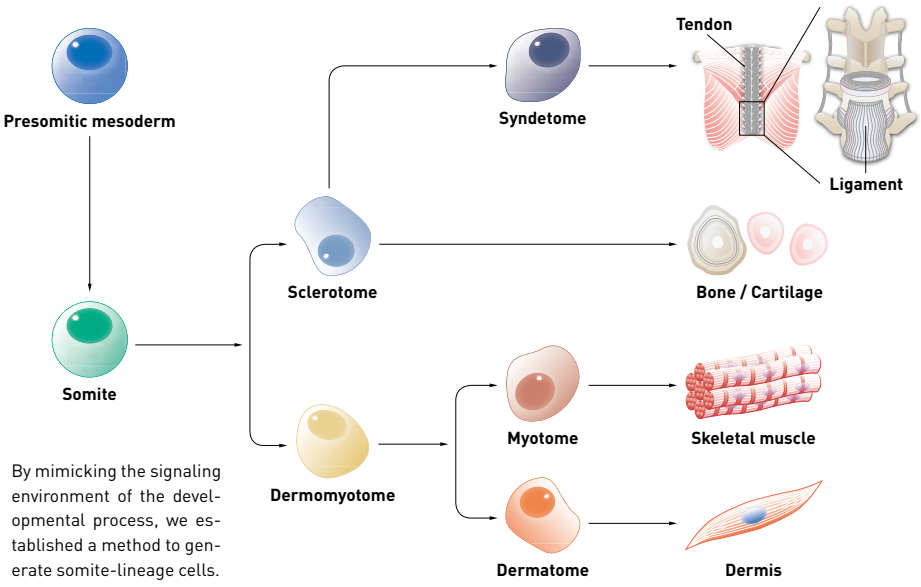
From basic research to practical application

Elsewhere, our research involves modeling the pathology of diseases caused by neural crest cell abnormalities, developing induction methods for cells difficult to induce and applying these techniques for regenerative medicine and drug discovery.

Members

- Yayoi Toyooka (Assistant Professor)
- Nicholas James Boyd-Gibbins
- Mamoru Ishii
- Daisuke Kamiya (Specially-Appointed Assistant Professor)
- Wako Matsuura
- Chiaki Mihara
- Yukiko Nakagawa
- Taiki Nakajima
- Mai Tanaka
- Mei Terashima
- Naoki Yamada
- Chengzhu Zhao

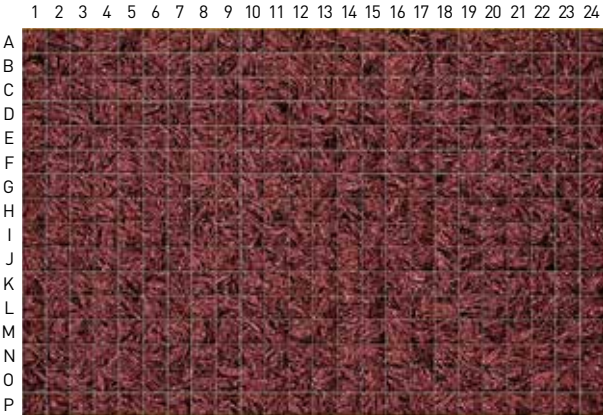
Stepwise induction of somite-lineage cells



By mimicking the signaling environment of the developmental process, we established a method to generate somite-lineage cells.

Novel therapies for intractable muscular diseases

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



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

IF: MHC+DAPI

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 cells, and the other strategy is regenerative medicine by transplanting skeletal muscle stem cells differentiated from clinical-grade iPS cells.

Research Progress

Progress with iPS cell-based disease modeling and drug discovery research

In the fiscal year 2018, we published a disease model of facioscapulohumeral muscular dystrophy (FSHD) (1).

We induced iPS cells from FSHD patients and differentiated them into myocytes. We found that oxidative stress is involved in the regulation of causative gene, the DUX4 expression in these myocytes. We also found that the DNA damage response was downstream of the oxidative stress. We are now constructing a screening system aimed at discovering a drug to target these new disease-modifying factors.

Toward therapeutic application of skeletal muscle stem cells for regenerative medicine

In the fiscal year 2018, we took forward research to validate the efficacy and safety of transplant therapy using skeletal muscle stem cells derived from the CiRA iPS Cell Stock. We have obtained data indicating efficacy of the transplant in animal models and will now investigate long-term safety in order to establish a clinical therapy.

Members

- Meni Arai
- Kana Ishii
- Rukia Ikeda
- Sayaka Ido
- Tomoya Uchimura
- Airi Ota
- Jun Otomo
- Atsuya Kato
- Hiroki Kato
- Machiko Kaneshiro
- Yuko Kokubu
- Megumi Gotou
- Chinami Saka
- Masae Sato
- Yusaku Sato
- Tatsuya Jonouchi
- Nana Takenaka
- Midori Tanaka
- Mingming Zhao
- Aya Harada
- Mikiko Fukuda
- Kei Fujiwara
- Mitsuru Honda
- Yasutomo Miura
- Mayuho Miki
- Minas Nalbandian

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 Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) A patient-derived iPSC model revealed oxidative stress increases facioscapulohumeral muscular dystrophy-causative DUX4
Sasaki-Honda M *et al.*
Hum Mol Genet (2018) 27 (23) : 4024-4035

(2) A human iPS cell myogenic differentiation system permitting high-throughput drug screening
Uchimura T *et al.*
Stem Cell Res (2017) 98-106

(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

Department of Clinical Application

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 Junior Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

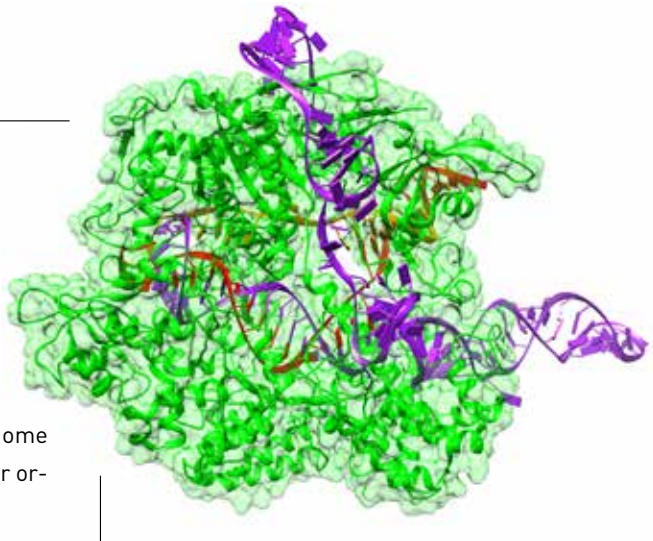
(1) Site-specific randomization of the endogenous genome by a regulatable CRISPR-Cas9 piggyBac system in human cells
Ishida K *et al.*
Scientific Reports (2018) 8(1): 310

(2) Srf destabilizes cellular identity by suppressing cell-type-specific gene expression programs
Ikeda T *et al.*
Nat Commun (2018) 11: 9(1): 1387

(3) Efficient mRNA delivery system utilizing chimeric VSVG-L7Ae virus-like particles
Zhitnyuk Y *et al.*
Biochem Biophys Res Commun (2018) 505(4): 1097-1102

Summary

Orphan diseases are rare conditions with no effective treatment available. More than half of these diseases are said to involve genetic 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 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].

Currently, we are developing a technique for the delivery of CRISPR-Cas 9 without using the *piggyBac* vector. We are also developing a method to prevent immune rejection by modifying the HLA gene of iPS cells, which should accelerate iPS cell-based analysis of gene functions and research into disease therapies.

Members

- Peter Gee
- Naoko Ishihara (Fujimoto)
- Kumiko Iwabuchi
- Akihiro Kagita
- Yuto Kita
- Mandy Lung
- Yukiko Nakagawa
- Yuya Okuzaki
- Miyuki Ono
- Noriko Sasakawa
- Kei Watanabe
- Huaigeng Xu

Contributing to transplantation medicine through development of an iPS cell stock

Naoko Takasu M.S., Professor

Summary

With a view to the practical application of regenerative medicine, in which iPS cells differentiated into the target cell type are used for transplantation, CiRA has set up the Facility for iPS Cell Therapy (FiT), which is building a stock of healthy donor-derived iPS cells resistant to immune rejection. To create a high-quality supply of clinical-grade iPS cells with a consistently high level of pluripotency, we are developing next-generation technologies using novel genes to realize highly efficient generation methods.

Research Progress

Toward a higher-quality iPS cell stock

Among the iPS cells produced using current methods, cell properties differ not only between different cell lines but also within the same cell line, resulting in wide variability in cell characteristics such as the pluripotent ability to differentiate into the target cell type. This issue is one of the main obstacles to the practical realization of iPS cell-based regenerative medicine and needs to be resolved as soon as possible. We are responding by developing next-generation technologies that use novel genes for a stable supply of iPS cells of higher and more consistent quality.

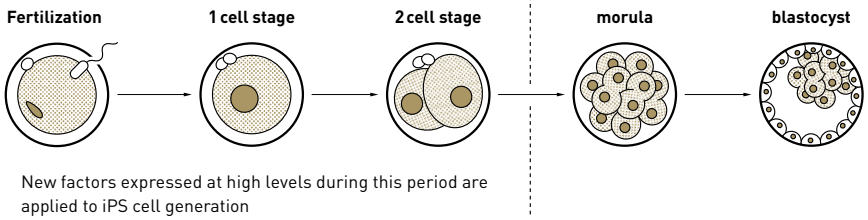
Applying egg cell-specific proteins to iPS cell generation

Immediately after fertilization, the human egg acquires totipotency to differentiate into all tissue types, with an important part in this process played by proteins present in large numbers in the egg cell. It is reported that the genes of these proteins can also be useful in generating iPS cells more efficiently. Focusing on this insight, we isolated the genes of proteins specific to egg cells and applied them in the generation of iPS cells. Currently, to establish whether the iPS cells created with these novel genes are suitable as iPS cells for the next generation of regenerative medicine, we are using a range of investigative techniques including comprehensive gene analysis and differentiation to the three germ layers.

Members

・Ryoko Hirohata ・Akira Kunitomi

Fertilized egg acquire totipotency in the early development stage



New factors expressed at high levels during this period are applied to iPS cell generation

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 Professor, CiRA, Kyoto Univ.

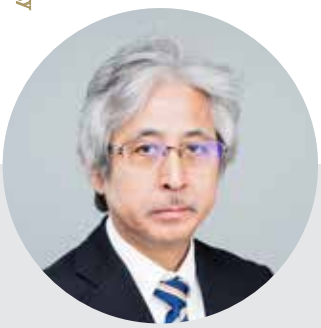
Publication Highlight

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

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 Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) In vitro disease modeling of Hermansky-Pudlak syndrome type 2 using human induced pluripotent stem cell-derived alveolar organoids
Korogi Y *et al.*
Stem Cell Reports (2019)
12 (3): 431-440

(2) Proposal for "Fundamental principles for microscopic observation of cultured cells"
Nakamura K *et al.*
Tiss Cult Res Commun (2018)
37 (2): 123-131

(3) Reduction of lipid accumulation rescues Bietti's crystalline dystrophy phenotypes
Hata M *et al.*
PNAS U.S.A (2018)
115 (15): 3936-3941

Summary

To promote the medical application of human iPS cells, we had ever carried out training programs to research institutions and researchers in areas such as the establishment of iPS cell lines, cell maintenance and culture, and quality evaluation methods. Furthermore, we develop teaching materials and work for the formulation and widespread adoption of technology guidelines based on Good Cell Culture Practice (GCCP), which is a set of basic principles designed to maintain the quality level of cell culture technology.

We also support other research laboratories through activities including the ethical review of research plans.

Research Progress

Activities to promote the wider adoption of iPS cell technology

In the fiscal year 2018, we produced a video for iPS cell beginners summarizing the experimental techniques for feeder-free passage culture and frozen storage of iPS cells. It was posted on the CiRA website together with the materials produced in the fiscal year 2017 on feeder-free iPS cell line establishment. We also published a scientific paper, *Fundamental principles of cultured cell observation*, which proposes minimum standards for assessing cell growth, etc., detecting problematic abnormalities, and judging cell suitability during the cultured cell observation period (2).

Finally, as Chair of CiRA's Ethical Review Board, we reviewed more than 20 CiRA research plans.

Basic Principles for Culture Cell Observation

Principle 1
Check that the microscope settings are correct

Principle 2
Observe cells with the naked eye before microscopic observation

Principle 3
Observe the whole area of culture vessel

Principle 4
Observe the condition of each individual cell

Principle 5
Pay attention to the timing of the observation

Principle 6
Record and retain the results of the observation

Principle 7
Share the observation results

Video teaching material on the frozen storage method for human iPS cells

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 common equipment. Among the cardinal items of common equipment are fluorescence-activated cell sorters (FACS), microscopes and other cell imaging instruments, 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 through these 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 Associate Professor, CiRA, Kyoto Univ.
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.*
Am J Med Genet A (2014) 164A (1): 213-219

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

Data-based discussion of ethical issues of iPS cell technology

Misao Fujita Ph.D., Professor

Profile

1992 Graduated from Faculty of Human Sciences, Univ. of Tsukuba
2006 Ph.D., Graduate School of Medicine, Kyoto Univ.
2008 Project Assistant Professor, Graduate School of Medicine, The Univ. of Tokyo
2009 Assistant Professor, Graduate School of Medicine, The Univ. of Tokyo
2013 Associate Professor, CiRA, Kyoto Univ.
2018 Professor, CiRA, Kyoto Univ.

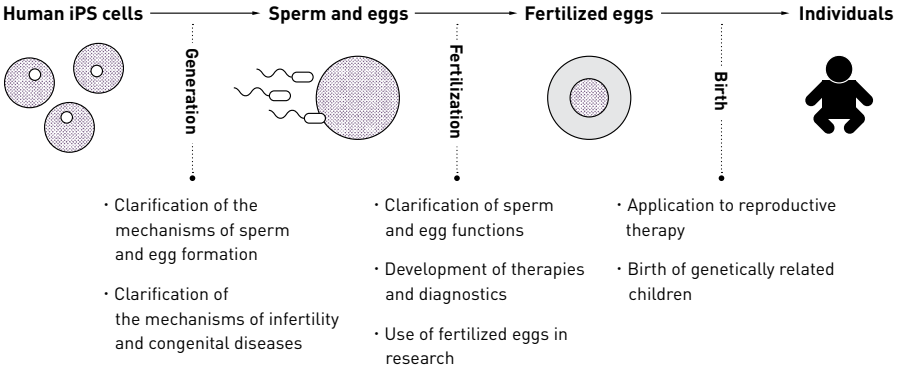
Publication Highlights

(1) A rebuttal of Akabayashi and colleagues' criticisms of the iPSC stock project
Fujita M *et al.*
JME (2019) doi: 10.1136

(2) 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 Transl Med (2017) 6 (8): 1749-50

(3) Recent court ruling in Japan exemplifies another layer of regulation for regenerative therapy
Ikka T *et al.*
Cell Stem Cell (2015) 17 (5): 507-508

Research on the creation of germ cells



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 on genome-editing technology and research using human iPS cells to create germ cells.

Research Progress

Ethical issues in genome-editing technology

New genome-editing technology can modify genomic DNA with good accuracy and have expectations for new therapies and other benefits for human health and society. On the other hand, the birth of twins using this technology in the fall of 2018 sparked worldwide debate. We have analyzed the ethical issues on the birth of humans born from genome-edited fertilized eggs and have adopted the stance that should be prohibited.

Research into the creation of germ cells

iPS cells have been used to successfully create the cells from which human eggs and sperm originate. In a questionnaire covering 3,096 members of the public, we found that the highest levels of expectation from this technology were directed toward the development of therapies and clarification of pathologies rather than application to reproductive therapy, and that there were strong concerns regarding the risk to unborn children and the phenomenon of designer babies.

Members

・Jusaku Minari (Associate Professor)
・Taichi Hatta (Assistant Professor)
・Tsutomu Sawai (Assistant Professor)
・Kyoko Akatsuka
・Kinuko Kasama
・Yuko Kuyama
・Keiko Mizuno
・Mika Suzuki
・Miki Tanigawa

Increasing the public credit in cutting-edge life science research

Jusaku Minari Ph.D., Associate Professor

Summary

Research into iPS cells and other cutting-edge life sciences relies not only on public support, but also the public's willingness to donate blood samples and other biological materials. Working with specialists from various fields in Japan and overseas, we explore a range of issues such as how to promote communication between researchers and the public, how to establish rules and guidelines to govern research, and how to respond to the social impact of research findings.

Research Progress

Society and life science research

To promote consideration towards the pubic and public confidence, we are currently addressing two exploratory items within the ISLE (Innovation for Science, Life and Ethics) project adopted by the Japan Science and Technology Agency.

Initiatives under the ISLE project

The two exploratory items are as follows. First, we are studying the optimal regulatory framework for life science research. Here, focusing on government guidelines, we have been looking into the background to their formulation and associated issues. Specifically, I have used our findings among other things in the revision of the guidelines as a member of the revision committee from the fiscal year 2018.

The other line of research concerns how to create dialogue with the public. Here, we are engaged in discussion with specialists from a wide range of fields in the world on the optimal design of questionnaires and workshops to identify public perceptions and attitudes. We are also designing formats that integrate elements of art and design to include people with no great interest in life science research, allowing them to encounter the progress of the research and the associated ethical and social issues, express their own ideas and impressions, and experience new perspectives and value concepts. In the fiscal year 2018, in the framework of the Sado Island Galaxy Art Festival 2018, we organized a workshop on the subject of Connections between Humans and Nature.

Members

・Kinuko Kasama ・Miki Tanigawa

Workshop in the framework of the Sado Island Galaxy Art Festival 2018 (Aug 19 2018 at the Sado Island, Niigata Prefecture)

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 Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) Tensions in ethics and policy created by National Precision Medicine Programs
Minari J, Brothers KB, and Morrison M
Human Genomics (2018) 12: 22

(2) Ethical, social and policy considerations for realizing genomic medicine (in Japanese)
Minari J
BIO Clinica (2018) Vol.33, 63-66

(3) The novel approach of AMED in realizing genomic medicine. (in Japanese)
Minari J, Kato O, Sakurai M and Saito A
Idenshi Igaku MOOK (2018) Vol.33, 168-172

Group photograph taken in front of the CiRA main building (Apr.2,2019)

Honors and Awards (2018.4-2019.3)

Research Promotion Awards, Honorary Doctorates, etc.

Month	Name of the Award	Awardee	Lab
2018.5	The 1st Kazuhiko Yamada Award (Japan IDDM Network)	Shinya Yamanaka	Yamanaka Lab.
2018.6	German Innovation Award Gottfried Wagener Prize	Makoto Ikeya	Ikeya Lab.
2018.8	JST/NEDO Award for Academic Startups 2018 JASVE President's Award	Jun K. Yamashita	Yamashita Lab.

Young Investigator Awards, Poster Awards, etc.

Month	Name of the Award	Awardee	Lab
2018.5	Japan Human Proteome Organisation MSP2018 Excellent Presentation Award	Mio Iwasaki	Yamanaka Lab.
2018.5	The 52nd Congress of Japanese Physical Therapy Association Excellent Award	Nana Takenaka	Sakurai Lab.
2018.6	Travel Grant Winner of the 23rd Congress of the European Hematology Association	Si Jing Chen	Eto Lab.
2018.6	ISSCR Travel Award for the 2018 ISSCR Annual Meeting in Melbourne	Nana Takenaka Yuko Kokubu	Sakurai Lab.
2018.7	FASEB Science Research Conference: Poster prize	Kana Ishii	Sakurai Lab.
2018.8	The 4th Annual Meeting of Japan Muscle Society Student's Award Best Excellent Award	Mitsuru Honda	Sakurai Lab.
2018.9	FY2018 Faculty of Medicine Kyoto University Young Investigator Award (KMYIA)	Masahide Kawatou	Yamashita Lab.
2018.9	The 2nd JCS Council Forum on Basic CardioVascular Research Poster Award	Daisuke Heima	Yamashita Lab.
2018.10	The 80th Annual Meeting of the Japanese Society of Hematology Best Poster Awards	Naoshi Sugimoto	Eto Lab.
2018.10	The 23rd International Annual Congress of the World Muscle Society: The President's Prize for Best First-time Presenter	Mitsuru Honda	Sakurai Lab.
2018.10	Best Poster Presentation in ESID 2019	Megumu Saito	Saito M Lab.
2018.11	47th Annual Meeting of the Japanese Environmental Mutagen Society (JEMS) Best Presentation Award (Oxford Journals Collection Award)	Ryota Kobayashi	Kaneko Lab.
2018.12	Abstract achievement award of the 60th American Society of Hematology (ASH) Annual Meeting	Akinori Yuzuriha	Eto Lab.
2019.2	The 20th Takeda Science Foundation Symposium on Bioscience: Excellent Poster Award	Kaoru Richard Komatsu	Saito H Lab.

Internal Award

Month	Name of the Award	Awardee	Lab
2019.1	The 6th CiRA Prize	Jun Takahashi	Takahashi Lab.
2019.3	The 1st CiRA Encouragement Award	Atsutaka Minagawa Sou Nakamura Bo Wang Huaigeng Xu	Kaneko Lab. Eto Lab. Kaneko Lab. Hotta Lab.

Publications (2018.4-2019.3)

2018

April

01 – Takahashi J
Stem cells and regenerative medicine for neural repair
Current Opinion in Biotechnology
52: 102-108

02 – Mitsuda Y, Morita K, Kashiwazaki G, Taniguchi J, Bando T, Obara M, Hirata M, Kataoka TR, Muto M, Kaneda Y, Nakahata T, Liu PP, Adachi S, Sugiyama H, Kamikubo Y
RUNX1 positively regulates the ErbB2/HER2 signaling pathway through modulating SOS1 expression in gastric cancer cells
Scientific Reports
8(1): 6423

03 – Rand TA, Sutou K, Tanabe K, Jeong D, Nomura, M, Kitaoka F, Tomoda E, Narita M, Nakamura M, Nakamura M, Watanabe A, Rulifson E, Yamanaka S, and Takahashi K
MYC releases early reprogrammed human cells from proliferation pause via retinoblastoma protein inhibition
Cell Reports
23(2): 361-375

04 – Hata M, Ikeda HO, Iwai S, Iida Y, Gotoh N, Asaka I, Ikeda K, Isobe Y, Hori A, Nakagawa S, Yamato S, Arita M, Yoshimura N, Tsujikawa A
Reduction of lipid accumulation rescues Bietti's crystalline dystrophy phenotypes
Proceedings of the National Academy of Sciences of the United States of America
115(15): 3936-3941

05 – Ikeda T, Hikichi T, Miura H, Shibata H, Mitsunaga K, Yamada Y, Woltjen K, Miyamoto K, Hiratani I, Yamada Y, Hotta A, Yamamoto T, Okita K, Masui S
Srf destabilizes cellular identity by suppressing cell-type-specific gene expression programs
Nature Communications
9: 1387

06 – Endo K and Saito H
mRNA engineering for the control of mammalian cells in medical applications
Applied RNA Bioscience
95-114

07 – Minari J, Brothers KB and Morrison M
Tensions in ethics and policy created by National Precision Medicine Programs
Human Genomics
12: 22

08 – Kanda K, Sakamoto J, Matsumoto Y, Ikuta K, Goto N, Morita Y, Ohno M, Nishi K, Eto K, Mikura Y, Nakanishi Y, Ikegami K, Yoshikawa T, Fukuda A, Kawada A, Sakai Y, Ito A, Yoshida M, Kimura T, Chiba T, Nishi E, Seno H
Nardilysin controls intestinal tumorigenesis through HDAC1/p53-dependent transcriptional regulation
JCI insight
3(8): e91316

09 – Hoshina A, Kawamoto T, Sueta SI, Mae SI, Araoka T,Tanaka H, Sato Y, Yamagishi Y, Osafune K
Development of new method to enrich human iPSC-derived renal progenitors using cell surface markers
Scientific Reports
8: 6375

10 – Sugie T, Suzuki E, Yamauchi A, Yamagami K, Masuda N, Gondo N, Sumi E, Ikeda T, Tada H, Uozumi R, Kanao S, Tanaka Y, Hamazaki Y, Minato N, Toi M
Combined effects of neoadjuvant letrozole and zoledronic acid on $\gamma\delta$T cells in postmenopausal women with early-stage breast cancer
The Breast
38: 114-119

May

11 – Tadokoro Y, Hoshii T, Yamazaki S, Eto K, Ema H, Kobayashi M, Ueno M, Ohta K, Arai Y, Harada K, Oshima M, Oshima H, Arai F, Yoshimura A, Nakauchi H, Hirao A
Spred1 safeguards hematopoietic homeostasis against diet-induced systemic stress
Cell Stem Cell
22(5): 713-725

12 – Takei T, Edahiro Y, Mano S, Masubuchi N, Mizukami Y, Imai M, Morishita S, Misawa K, Ochiai T, Tsuneda S, Endo H, Nakamura S, Eto K, Ohsaka A, Araki M, Komatsu N
Skewed megakaryopoiesis in human induced pluripotent stem cell-derived haematopoietic progenitor cells harbouring calreticulin mutation
British Journal of Haematology
181(6): 791-802

13 – Yokobayashi S and Saitou M
Reconstitution of germ cell development in vitro
Cell Biology of the Ovary
1-19

14 – Kashida S and Saito H
Design of ligand-controlled genetic switches based on RNA interference
Synthetic Biology: Parts, Devices and Applications
Chapter 8

15 – 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

2018

16 – Allison TF, Andrews PW, Avior Y, Barbaric I, Benvenisty N, Bock C, Brehm J, Brüstle O, Damjanov I, Elefanty A, Felkner D, Gokhale PJ, Halbritter F, Healy LE,Hu TX, Knowles BB, Loring JF, Ludwig TE, Mayberry R, Micallef S, Mohamed JS, Müller FJ, Mummery CL, Nakatsuji N, Ng ES, Oh SKW, O'Shea O, Pera MF, Reubinoff B, Robson P, Rossant J, Schuldt BM, Solter D, Sourris K, Stacey G, Stanley EG, Suemori H, Takahashi K, Yamanaka S
Assessment of established techniques to determine developmental and malignant potential of human pluripotent stem cells
Nature Communications
9(1): 1925

17 – Kawai A, Goto T, Shibata T, Tani K, Mizutani S, Nishikawa A, Shibata T, Matsumoto S, Nagata K, Narukawa M, Matsui S, Ando M, Toguchida J, Monden M, Heike T, Kimura S, Ueda R
Current state of therapeutic development for rare cancers in Japan, and proposals for improvement
Cancer Science
109(5): 1731-1737

18 – Ueda N, Uemura Y, Zhang R, Kitayama S, Iriguchi S, Kawai Y, Yasui Y, Tatsumi M, Ueda T, Liu TY, Mizoro Y, Okada C, Watanabe A, Nakanishi M, Senju S, Nishimura Y, Kuzushima K, Kiyoi H, Naoe T, Kaneko S
Generation of TCR-expressing innate lymphoid-like helper cells that induce cytotoxic T cell-mediated anti-leukemic cell response
Stem Cell Reports
10(6): 1935-1946

19 – Shibata H, Komura S, Yamada Y, Sankoda N, Tanaka A, Ukai T, Kabata M, Sakurai S, Kuze B, Woltjen K, Haga H, Ito Y, Kawaguchi Y, Yamamoto T, Yamada Y
In vivo reprogramming drives Kras-induced cancer development
Nature Communications
9: 2081

June

20 – Wuriyanghai Y, Makiyama T, Sasaki K, Kamakura T, Yamamoto Y, Hayano M, Harita T, Nishiuchi S, Chen J, Kohjitani H, Hirose S, Yokoi F, Gao J, Chonabayashi K, Watanabe K, Ohno S, Yoshida Y, Kimura T, Horie M
Complex aberrant splicing in the induced pluripotent stem cell-derived cardiomyocytes from a patient with long-QT syndrome carrying KCNQ1-A344Aspl mutation
Heart Rhythm
15(10): 1566-1574

21 – Hiratsuka S, Tomita T, Mishima T, Matsunaga Y, Omori T, Ishibashi S, Yamaguchi S, Hosogane T, Watarai H, Omori-Miyake M, Yamamoto T, Shibata N, Watanabe A, Aburatani H, Tomura M, High KA, Maru Y
Hepato-entrained B220+CD11c+NK1.1+ cells regulate pre-metastatic niche formation in the lung
EMBO Molecular Medicine
10(7): e8643

22 – Aiba T, Saito T, Hayashi A, Sato S, Yunokawa H, Maruyama T, Fujibuchi W, Ohsako S
Does the prenatal bisphenol A exposure alter DNA methylation levels in the mouse hippocampus?: An analysis using a high-sensitivity methylome technique
Genes and Environment
40: 12

23 – Ueda N, Uemura Y, Zhang R, Kitayama S, Iriguchi1 S, Kawai1 Y, Yasui Y, Tatsumi M, Liu TY, Mizoro Y, Okada C, Watanabe A, Nakanishi M, Senju S, Nishimura Y, Kuzushima K, Kiyoi H, Naoe T, Kaneko S
Regeneration of TCR expressing Innate Lymphoid helper cells that induces cytotoxic T cell-mediated anti-leukemic immunity in HLA Class II and bcr-abl peptide restriction
Stem Cell Reports
10(6): 1935-1946

24 – Honda-Ozaki F, Terashima M, Niwa A, Saiki N, Kawasaki Y, Ito H, Hotta A, Nagahashi A, Igura K, Asaka I, Li HL, Yanagimachi M, Furukawa F, Kanazawa N, Nakahata T, Saito MK
Pluripotent stem cell model of Nakajo-Nishimura syndrome untangles proinflammatory pathways mediated by oxidative stress
Stem Cell Reports
10(6): 1835-1850

25 – Nishimura K, Takeda M, Yamashita JK, Shiojima I, Toyoda N
Type 3 iodothyronine deiodinase is expressed in human induced pluripotent stem cell derived cardiomyocytes
Life Sciences
203: 276-281

26 – Takahashi H, Qin XY, Sone H, Fujibuchi W
Stem cell-based methods to predict developmental chemical toxicity
Computational Toxicology
1800: 475-483

July

27 – Tsuburaya N, Homma K, Higuchi T, Balia A, Yamakoshi H, Shibata N, Nakamura S, Nakagawa H, Ikeda SI,

2018

Umezawa N, Kato N, Yokoshima S, Shibuya M, Shimonishi M, Kojima H, Okabe T, Nagano T, Naguro I, Imamura K, Inoue H, Fujisawa T, Ichijo H
A small-molecule inhibitor of SOD1-Derlin-1 interaction ameliorates pathology in an ALS mouse model
Nature Communications
9(1): 2668

28 – Yu L, Li J, Hong J, Takashima Y, Fujimoto N, Nakajima M, Yamamoto A, Dong X, Dang Y, Hou Y, Yang W, Minami I, Okita K, Tanaka M, Luo C, Tang F, Chen Y, Tang C, Kotera H, Liu L
Low cell-matrix adhesion reveals two subtypes of human pluripotent stem cells
Stem Cell Reports
11(1): 142-156

29 – Hatani T, Miki K and Yoshida Y
Induction of human induced pluripotent stem cells to cardiomyocytes using embryoid bodies
Methods in Molecular Biology
1816: 79-92

30 – Lee S, Huh JY, Turner D, Lee S, Robinson J, Stein J, Shim SH, Hong CP, Kang MS, Nakagawa M, Kaneko S, Rao M, Kurtz A, Stacey G, Marsh S, Turner M, Song J
Repurposing the cord blood bank for haplobanking of HLA-homozygous iPSCs and their usefulness to multiple populations
Stem Cells
36(10): 1552-1566

31 – Ito Y, Nakamura S, Sugimoto N, Shigemori T, Kato Y, Ohno M, Sakuma S, Ito K, Kumon H, Hirose H, Okamoto H, Nogawa M, Iwasaki M, Kihara S, Fujio K, Matsumoto T, Higashi N, Hashimoto K, Sawaguchi A, Harimoto KI, Nakagawa M, Yamamoto T, Handa M, Watanabe N, Nishi E, Arai F, Nishimura S, Eto K
Turbulence activates platelet biogenesis to enable clinical scale ex vivo production
Cell
174(3): 636-648

32 – Ogura T, Sakaguchi H, Miyamoto S, Takahashi J
Three-dimensional induction of dorsal, intermediate and ventral spinal cord tissues from human pluripotent stem cells
Development
145: dev162214

33 – Machida K, Arai D, Katsumata R, Otsuka S, Yamashita JK, Ye T, Tang S, Fusetani N, Nakao Y
Sameuramide A, a new cyclic depsipeptide isolated from an ascidian of the family Didemnidae
Bioorganic & Medical Chemistry
26(13): 3852-3857

34 – Kato A, Takaori-Kondo A, Minato N, Hamazaki Y
CXCR3high CD8+ T cells with naïve phenotype and high capacity for IFN-γ production are generated during homeostatic T-cell proliferation
European Journal of Immunology 48(10): 1663-1678

35 – Zhao C and Ikeya M
Generation and applications of induced pluripotent stem cell-derived mesenchymal stem cells
Stem Cells Internationa
doi: 10.1155/dev9601623

36 – Hashii Y, Yoshida M, Hara J, Nishimura S, Yumura-Yagi K, Horibe K, Nakahata T
Acid-suppressing drugs and a Low 1 level of antithrombin as risk factors for l-asparaginase-associated pancreatitis: A case-control study in the Japan Association of Childhood Leukemia Study (JACLS)
Journal of Pediatric Hematology/Oncology
40(5): 374-378

August

37 – Ishigami M, Masumoto H, Ikuno T, Aoki T, Kawatou M, Minakata K, Ikeda T, Sakata R, Yamashita JK, Minatoya K
Human iPS cell-derived cardiac tissue sheets for functional restoration of infarcted porcine hearts
PLoS One
13(8): e0201650

38 – Kimura T, Ozaki T, Fujita K, Yamashita A, Morioka M, Ozono K, Tsumaki N
Proposal of patient-specific growth plate cartilage xenograft model for FGFR3 chondrodysplasia
Osteoarthritis and Cartilage
26(11): 1551-1561

39 – Sasaki-Honda M, Jonouchi T, Arai M, Hotta A, Mitsuhashi S, Nishino I, Matsuda R, Sakurai H
A Patient-derived iPSC Model revealed oxidative stress increases facioscapulohumeral muscular dystrophy-causative DUX4
Human Molecular Genetics
27(23): 4024-4035

40 – Tanaka K, Ogawa G, Mizusawa J, Naka N, Kawai A, Takahashi M, Hiruma T, Matsumoto Y, Tsuchiya H, Nakayama R, Hatano H, Emori M, Hosaka M, Yoshida Y, Toguchida J, Abe S, Asanuma K, Yokoyama R, Hiraga H, Yonemoto T, Morii T, Matsumoto S, Nagano A, Yoshikawa H, Fukuda H, Ozaki T, Iwamoto Y
Prospective comparison of various radiological response criteria and pathological response to preoperative chemotherapy and survival in operable high-grade soft tissue sarcomas in the Japan Clinical Oncology Group study JCOG0304
World Journal of Surgical Oncology
16(1): 162

41 – Kanaji T, Vo MN, Kanaji S, Zarpellon A, Shapiro R, Morodomi Y, Yuzuriha A, Eto K, Belani R, Do MH, Yang XL, Ruggeri ZM, Schimmel P
Tyrosyl-tRNA synthetase stimulates thrombopoietin-independent hematopoiesis accelerating recovery from thrombocytopenia
Proceedings of the National

2018

Academy of Sciences of the United States of America
115(35) : 8228-8235

42 – Nakai R, Ohnuki M, Kuroki K, Ito H, Hirai H, Kitajima R, Fujimoto T, Nakagawa M, Enard W, Imamura M
Derivation of induced pluripotent stem cells in Japanese macaque (Macaca fuscata)
Scientific Reports
8(1) : 12187

43 – Taichi Hatta, Keiichi Narita, Kazuhiro Yanagihara, Hiroshi Ishiguro, Toshinori Murayama, Masayuki Yokode
Crossover mixed analysis in a convergent mixed methods design used to investigate clinical dialogues about cancer treatment in the Japanese Context
Journal of Mixed Methods Research
doi: 10.1177/dev1558689818792793

44 – Di Stefano B, Ueda M, Sabri S, Brumbaugh J, Huebner AJ, Sahakyan A, Clement K, Clowers KJ, Erickson AR, Shioda K, Gygi SP, Gu H, Shioda T, Meissner A, Takashima Y, Plath K, Hochedlinger K
Reduced MEK inhibition preserves genomic stability in naive human embryonic stem cells
Nature Methods
15(9) : 732-740

45 – Nakajima T, Shibata M, Nishio M, Nagata S, Alev C, Sakurai H, Toguchida J, Ikeya M
Modeling human somite development and fibrodysplasia ossificans progressiva with induced pluripotent stem cells
Development
145(16) dev: 165431

46 – Kirino K, Nakahata T, Taguchi T, Saito MK
Efficient derivation of sympathetic neurons from human pluripotent stem cells with a defined condition
Scientific Reports
8(1) : 12865

September

47 – Ifuku M, Iwabuchi KA, Tanaka M, Lung MSY, Hotta A
Restoration of dystrophin protein expression by exon skipping utilizing CRISPR-Cas9 in myoblasts derived from DMD patient iPS cells
Methods in Molecular Biology
1828: 191-217 9/1 2018

48 – Sogabe Y, Seno H, Yamamoto T, Yamada Y
Unveiling epigenetic regulation in cancer, aging, and rejuvenation with in vivo reprogramming technology
Cancer Science
109(9) : 2641-2650

49 – Toki T, Yoshida K, Wang RN, Nakamura S, Maekawa T, Goi K, Katoh MC, Mizuno S, Sugiyama F, Kanezaki R, Uechi T, Nakajima Y, Sato Y, Okuno Y, Sato-Otsubo A, Shiozawa Y, Kataoka K, Shiraishi Y, Sanada M, Chiba K, Tanaka H, Terui K, Sato T, Kamio T, Sakaguchi H, Ohga S, Kuramitsu M, Hamaguchi I, Ohara A, Kanno H, Miyano S, Kojima S, Ishiguro A, Sugita K, Kenmochi N, Takahashi S, Eto K, Ogawa S, Ito E
De novo mutations activating germline TP53 in an inherited bone marrow failure syndrome
The American Journal of Human Genetics
103(3) : 440-447

50 – Takasaki A, Hirono K, Hata Y, Wang C, Takeda M, Yamashita JK, Chang B, Nakaoka H, Okabe M, Miyao N, Saito K, Ibuki K, Ozawa S, Sekine M, Yoshimura N, Nishida N, Bowles NE, Ichida F
Sarcomere gene variants act as a genetic trigger underlying the development of left ventricular noncompaction
Pediatric Research
84(5) : 733-742

51 – Higaki K, Hirao M, Kawana-Tachikawa A, Iriguchi S, Kumagai A, Ueda N, Bo W, Kamibayashi S, Watanabe A, Nakauchi H, Suzuki K, Kaneko S
Generation of HIV-resistant macrophages from iPSCs by using transcriptional gene silencing and promoter-targeted RNA
Molecular Therapy Nucleic Acids
10(6) : 793-804

52 – Seo H, Chen SJ, Hashimoto K, Endo H, Nishi Y, Ohta A, Yamamoto T, Hotta A, Akira Sawaguchi A, Hayashi H, Koseki N, Murphy GJ, Fukuda K, Sugimoto N, Eto K
A β1-tubulin-based megakaryocyte maturation reporter system identifies novel drugs that promote platelet production
Blood Advances
2(17) : 2262-2272

53 – Karagiannis P, Nakauchi A and Yamanaka S
Bringing induced pluripotent stem cell technology to the bedside
JMA Journal
1(1) : 6-14

October

54 – Chen X, Yamashita A, Morioka M, Senba T, Kamatani T, Watanabe A, Kosai A, Tsumaki N
Integration capacity of human induced pluripotent stem cell-derived cartilage
Tissue Engineering Part A
25(5-6) : 437-445

55 – Yamashita A, Tamamura Y, Morioka M, Karagiannis P, Shima N, Tsumaki N
Considerations in hiPSC-derived cartilage for articular cartilage repair
Inflammation and Regeneration
38: 17

56 – Moriya Y, Kawano S, Okuda S, Watanabe Y, Matsumoto M, Takami T, Kobayashi D, Yamanouchi Y, Araki N, Yoshizawa AC, Tabata T, Iwasaki M, Sugiyama N, Tanaka S, Goto S, Ishihama Y
The jPOST environment: an

2018

integrated proteomics data repository and database
Nucleic Acids Research
47(D1): 1218-1224

57 – Masumoto H and Yamashita JK
Human iPS cell-engineered three-dimensional cardiac tissues perfused by capillary networks between host and graft
Inflammation and Regeneration
38: 26

58 – Ono H, Ohta R, Kawasaki Y, Niwa A, Takada H, Nakahata T, Ohga S, Saito MK
Lysosomal membrane permeabilization causes secretion of IL-1β in human vascular smooth muscle cells
Inflammation and Regeneration
67(10): 879-889

59 – Yamashiro C, Sasaki K, Yabuta Y, Kojima Y, Nakamura T, Okamoto I, Yokobayashi S, Murase Y, Ishikura Y, Shirane K, Sasaki H, Yamamoto T, Saitou M
Generation of human oogonia from induced pluripotent stem cells in vitro
Science
362(6412): 356-360

60 – Sakikubo M, Furuyama K, Horiguchi M, Hosokawa S, Aoyama Y, Tsuboi K, Goto T, Hirata K, Masui T, Dor Y, Fujiyama T, Hoshino M, Uemoto S, Kawaguchi Y
Ptf1a inactivation in adult pancreatic acinar cells causes apoptosis through activation of the endoplasmic reticulum stress pathway
Scientific Reports
8: 15812

61 – Taoka K, Arai S, Kataoka K, Hosoi M, Miyauchi M, Yamazaki S, Honda A, Aixinjueluo W, Kobayashi T, Kumano K, Yoshimi A, Otsu M, Niwa A, Nakahata T, Nakauchi H, Kurokawa M
Using patient-derived iPSCs to develop humanized mouse models for chronic myelomonocytic leukemia and therapeutic drug identification, including liposomal clodronate.
Scientific Reports
8: 15855

62 – Tsuji O, Sugai K, Yamaguchi R, Tashiro S, Nagoshi N, Kohyama J, Iida T, Ohkubo T, Itakura G, Isoda M, Shinozaki M, Fujiyoshi K, Kanemura Y, Yamanaka S, Nakamura M, Okano H
Laying the groundwork for a first-in-human study of an induced pluripotent stem cell-based intervention for spinal cord injury
Stem Cells
37(1): 6-13

November

63 – Hatani T, Funakoshi S, Deerinck TJ, Bushong EA, Kimura T, Takeshima H, Ellisman MH, Hoshijima M, Yoshida Y
Nano-structural analysis of engrafted human induced pluripotent stem cell-derived cardiomyocytes in mouse hearts using a genetic-probe APEX2
Biochemical and Biophysical Research Communications
505(4): 1251-1256

64 – Zhitnyuk Y, Gee P, Lung MSY, Sasakawa N, Xu H, Saito H, Hotta A
Efficient mRNA delivery system utilizing chimeric VSVG-L7Ae virus-like particles
Biochemical and Biophysical Research Communications
505(4): 1097-1102

65 – Hino K, Zhao C, Horigome K, Nishio M, Okanishi Y, Nagata S, Komura S, Yamada Y, Toguchida J, Ohta A, Ikeya M
An mTOR signaling modulator suppressed heterotopic ossification of fibrodysplasia ossificans progressiva
Stem Cell Reports
211(5): 1106-1119

66 – Sumitomo A, Siriwach R, Thumkeo D, Ito K, Nakagawa R, Tanaka N, Tanabe K, Watanabe A, Kishibe M, Ishida-Yamamoto A, Honda T, Kabashima K, Aoki J, Narumiya S
LPA induces keratinocyte differentiation and promotes skin barrier function through the LPAR1/LPAR5-RHO-ROCK-SRF axis
Journal of Investigative Dermatology
139(5): 1010-1022

67 – Matsuura S, Ono H, Kawasaki S, Kuang Y, Fujita Y, Saito H
Synthetic RNA-based logic computation in mammalian cells
Nature Communications
9(1): 4847

68 – Woltjen K and Bortvin A
Editorial overview: Embroidering the canvas of life
Current Opinion in Genetics & Development
52: ii-iv

69 – Konishi Y, Terai K, Furuta Y, Kiyonari H, Abe T, Ueda Y, Kinashi T, Hamazaki Y, Takaori-Kondo A, Matsuda M
Live-cell FRET imaging reveals a role of extracellular signal-regulated kinase activity dynamics in thymocyte motility
iScience
10: 98-113

70 – Ohno H, Akamine S and Saito H
RNA nanostructures and scaffolds for biotechnology applications
Current Opinion Biotechnology
58: 53-61

December

71 – Minagawa A, Yoshikawa T, Yasukawa M, Hotta A, Kunitomo M, Iriguchi S, Takiguchi M, Kassai Y, Imai E, Yasui Y, Kawai Y, Zhang R, Uemura Y, Miyoshi H, Nakanishi M, Watanabe A, Hayashi A, Kawana K, Fujii T, Nakatsura T, Kaneko S
Enhancing T cell Receptor Stability in Rejuvenated iPSC-derived T cells improves their use in cancer immunotherapy.
Cell Stem Cell
23(6): 850-858

2018 - 2019

72 – Wang J, Sekai M, Matsui T, Fujii Y, Matsumoto M, Takeuchi O, Minato N, and Hamazaki Y
Hassall's corpuscles with cellular-senescence features maintain interferon alpha production through neutrophils and pDC activation in the thymus
International Immunology
31(3) : 127-139

73 – Niki T, Imamura K, Enami T, Kinoshita M, Inoue H
Establishment of human induced pluripotent stem cell line from a patient with Angelman syndrome carrying the deletion of maternal chromosome 15q11.2-q13
Stem Cell Research
34: 101363

74 – Wang J, Sekai M, Matsui T, Fujii Y, Matsumoto M, Takeuchi O, Minato N, Hamazaki Y
Hassall's corpuscles with cellular-senescence features maintain IFNα production through neutrophils and pDC activation in the thymus
International Immunology
31(3) : 127-139

75 – Sakaue S, Hirata J, Maeda Y, Kawakami E, Nii T, Kishikawa T, Ishigaki K, Terao C, Suzuki K, Akiyama M, Suita N, Masuda T, Ogawa K, Yamamoto K, Saeki Y, Matsushita M, Yoshimura M, Matsuoka H, Ikari K, Taniguchi A, Yamanaka H, Kawaji H, Lassmann T, Itoh M, Yoshitomi H, Ito H, Ohmura K, R Forrest AR, Hayashizaki Y, Carninci P, Kumanogoh A, Kamatani Y, de Hoon M, Yamamoto K, Okada Y
Integration of genetics and miRNA-target gene network identified disease biology implicated in tissue specificity
Nucleic Acids Research
46(22) : 11898-11909

January

76 – Iriguchi S and Kaneko S
Toward the development of true "off-the-shelf" synthetic T-cell immunotherapy
Cancer Science
110(1) : 16-22

77 – Karagiannis P, Takahashi K, Saito M, Yoshida Y, Okita K, Watanabe A, Inoue H, Yamashita JK, Todani M, Nakagawa M, Osawa M, Yashiro Y, Yamanaka S, Osafune K
Induced pluripotent stem cells and their use in human models of disease and development
Physiological Reviews
99(1) : 79-114

78 – Fujita M and Tabuchi K
A rebuttal to Akabayashi and colleagues' criticisms of the iPSC stock project
Journal of Medical Ethics
doi: 10.1136/dev105248

79 – Jo N, Sogabe Y, Yamada Y, Ukai T, Kagawa H, Mitsunaga K, Woltjen K, Yamada Y
Platforms of in vivo genome editing with inducible Cas9 for advanced cancer modeling
Cancer Science
110(3) : 926-938

80 – Karagiannis P, Yamanaka S and Saito MK
Application of induced pluripotent stem cells to primary immunodeficiency diseases
Experimental Hematology
71: 43-50

81 – Liu Y and Yamashita JK
AMPK activators contribute to maintain naïve pluripotency in mouse embryonic stem cells
Biochemical and Biophysical Research Communications
509(1) : 24-31

82 – Matsui S, Ochiai M, Yasuda K, Mae SI, Kotaka M, Toyoda T, Yamamoto T, Osafune K
Differentiation and isolation of iPSC-derived remodeling ductal plate-like cells by use of an AQP1-GFP reporter human iPSC line
Stem Cell Research
35: 101400

February

83 – Boisson B, Honda Y, Ajiro M, Bustamante J, Bendavid M, Gennery AR, Kawasaki Y, Ichishima J, Osawa M, Nihira H, Shiba T, Tanaka T, Chrabieh M, Bigio B, Hur H, Itan Y, Liang Y, Okada S, Izawa K, Nishikomori R, Ohara O, Heike T, Abel L, Puel A, Saito MK, Casanova JL, Hagiwara M, Yasumi T
Rescue of recurrent deep intronic mutation underlying cell type-dependent quantitative NEMO deficiency
The Journal of Clinical Investigation
129(2) : 583-597

84 – Sekai M, Wang J, Minato N, Hamazaki Y
An improved clonogenic culture method for thymic epithelial cells
Journal of Immunological Methods
467: 29-36

85 – Kasirer-Friede A, Tjahjono W., Eto K, Shattil SJ
SHARPIN at the nexus of platelet integrin, immune and inflammatory signaling
Proceedings of the National Academy of Sciences of the United States of America
116(11) : 4983-4988

86 – Hirata K, Kodama S, Nakano Y, Minaki-Nakagawa Y, Aoyama Y, Sakikubo M, Goto T, Yoshida M, Masui T, Yamamoto T, Uemoto S, Kawaguchi Y
Exocrine tissue-driven TFF2 prevents apoptotic cell death of endocrine lineage during pancreas organogenesis
Scientific Reports
9: 1636

87 – Mae SI, Ryosaka M and Osafune K
Protocol to generate ureteric bud structures from human iPS cells
Methods in Molecular Biology
1926: 117-123

88 – Kagawa H, Shimamoto R, Kim SI, Oceguera-Yanez F, Yamamoto T, Schroeder T, Woltjen K
OVOL1 influences the determination and expansion of iPSC reprogramming intermediates
Stem Cell Reports
12(2) : 319-332

2019

89 – Suga M, Kondo T, Imamura K, Shibukawa R, Okanishia Y, Sagara Y, Tsukita K, Enami T, Furujo M, Saijo K, Nakamura Y, Osawa M, Saito MK, Yamanaka S, Inoue H
Generation of a human induced pluripotent stem cell line, BRCi001-A, derived from a patient with mucopolysaccharidosis type I
Stem Cell Research
36: 101406

90 – Nakazeki F, Tsuge I, Horie T, Imamura K, Tsukita K, Hotta A, Baba O, Kuwabara Y, Nishino T, Nakao T, Nishiga M, Nishi H, Nakashima Y, Ide Y, Koyama S, Kimura M, Tsuji S, Naitoh M, Suzuki S, Izumi Y, Kawarai T, Kaji R, Kimura T, Inoue H, Ono K
MiR-33a is a therapeutic target in SPG4-related hereditary spastic paraplegia human neurons
Clinical Science
133(4): 583-595

March

91 – Torisawa Y, Mishima Y and Kaneko S
Developing thymus-on-a-chip and cancer-on-a-chip for cancer immunotherapy
Impact
29(2): 33-35(3)

92 – Terada Y, Jo N, Arakawa Y, Sakakura M, Yamada Y, Ukai T, Kabata M, Mitsunaga K, Mineharu Y, Ohta S, Nakagawa M, Miyamoto S, Yamamoto T, Yamada Y
Human pluripotent stem cell-derived tumor model uncovers the embryonic stem cell signature as a key driver in atypical teratoid/rhabdoid tumor
Cell Reports
26(10): 2608-2621

93 – Korogi Y, Gotoh S, Ikeo S, Yamamoto Y, Sone N, Tamai K, Konishi S, Nagasaki T, Matsumoto H, Ito I, Chen-Yoshikawa TF, Date H, Hagiwara M, Asaka I, Hotta A, Mishima M, Hirai T
In Vitro Disease Modeling of Hermansky-Pudlak Syndrome Type 2 Using Human Induced Pluripotent Stem Cell-Derived Alveolar Organoids
Stem Cell Reports
12(3): 431-440

94 – Takaki T, Inagaki A, Chonabayashi K, Inoue K, Miki K, Ohno S, Makiyama T, Horie M, Yoshida Y
Optical recording of action potentials in human induced pluripotent stem cell-derived cardiac single cells and monolayers generated from long QT syndrome type 1 patient
Stem Cells International
doi: 10.1155/ dev7532657

95 – Xu H, Wang B, Ono M, Kagita A, Fujii K, Sasakawa N, Ueda T, Gee P, Nishikawa M, Nomura M, Kitaoka F, Takahashi T, Okita K, Yoshida Y, Kaneko S, Hotta A
Targeted disruption of HLA genes via CRISPR-Cas9 generates iPSCs with enhanced immune compatibility
Cell Stem Cell
24(4)566-578

96 – Ichishima J, Suzuki NM, Samata B, Awaya T, Takahashi J, Hagiwara M, Nakahata T, Saito MK
Verification and rectification of cell type-specific splicing of a Seckel syndrome-associated ATR mutation using iPS cell model
Journal of Human Genetics
64: 445-458

97 – Goto H, Nishio M, To Y, Oishi T, Miyachi Y, Maehama T, Nishina H, Akiyama H, Mak TW, Makii Y, Saito T, Yasoda A, Tsumaki N, Suzuki A
Loss of Mob1a/b in mice results in chondrodysplasia due to YAP1/TAZ-TEAD-dependent repression of SOX9
Development
145(6): 1-11

98 – Imai T, Tanaka H, Hamazaki Y, Minato N
Rap1 signal modulators control the maintenance of hematopoietic progenitors in bone marrow and adult long-term hematopoiesis
Cancer Science
110(4): 1317-1330

Kyoto University announced in January 2018 that a specially-appointed assistant professor at CiRA had conducted research fraud. In response, past articles the researcher first authored were voluntary reevaluated by CiRA faculty members. As a result, the following research paper published in Cell Stem Cell in 2012 was retracted. The researcher was punitively dismissed in March 2018.

Publication

Protein Kinase A Determines Timing of Early Differentiation through Epigenetic Regulation with G9a
Cell Stem Cell
10(6): 759-770 (2012)

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

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)
- Yoriko Indo
- Akito Tanaka
- Daisuke Seki

Facility for iPS Cell Therapy (FiT)

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

- **Head:** Shinya Yamanaka (Professor)
- **Deputy Head:** Naoko Takasu (Professor)

Manufacturing Department

- **Supervisor:** Masayoshi Tsukahara (Specially Appointed Professor)
- Kanehiro Eguchi
- Hinako Gotoda
- Soichiro Kagei
- Ayumi Matsunaga
- Yuko Obara
- Akiko Okada
- Youhei Osako
- Yoshichika Yagyu
- Kyoko Tanimura

Manufacture and management unit

Manufactures clinical-grade iPS cells and differentiated cells from clinical-grade iPS cells.

- Naoko Hayakawa
- Norihito Hirai
- Tomoko Ichisaka
- Akiko Kadotani
- Kumiko Kan
- Mitsuyo Kawada
- Yukiko Kobayashi
- Sayaka Maezori
- Yuki Matsubayashi
- Noriko Matsunaga
- Shun Minobe
- Eri Nishikawa
- Takuo Nishimura
- Atsushi Nishizawa
- Yoko Ohtagaki
- Momoko Okabe
- Aki Sasaki
- Yukiko Sasaki
- Wataru Shimamoto
- Maho Yokoi

Research and Development Department

- **Supervisor:** Masayoshi Tsukahara (Specially Appointed Professor)

CMC research and development unit

- Hiromi Dohi
- Yuko Kitano
- Sonoka Matsuda
- Miyuki Mouri
- Krol Rafal Przybyslaw
- Yoshiko Sato
- Anna Ueda
- Masafumi Umekage

Quality Department

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

Quality management unit

Evaluates iPS cells by genome analysis, karyotype analysis and microbial infection. Conducts collaborative research and analysis with external partners.

- Ichiro Fukuoka
- Sho Hasegawa
- Takaaki Hikichi
- Satoko Hinatsu
- Koichi Kaneko
- Tomoaki Kato
- Ayane Kawakami
- Fumiyo Kitaoka
- Kazuhiko Kitajima
- Masako Kudo
- Junko Kuwabara
- Akiko Matsumoto
- Noriko Mori
- Kasumi Nakao
- Chika Nakashima
- Mika Nishimura
- Masaki Nomura
- Yuki Nouguchi
- Haruna Ogawa
- Tokiko Ohkame
- Yusuke Ohkame
- Kazuhide Ohnishi
- Keiko Oono
- Mayumi Sakagami
- Tomoko Takahashi
- Ito Teramoto
- Saki Tomita
- Mie Yamamoto
- Atsuyo Yoshioka

Quality certification unit

Conducts quality assurance and inspection of cell production.

- Naoki Amano
- Yoshie Umeda
- Ryosaku Tomioka
- Yasuko Nakai
- Shuichi Yano
- 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 equipment at CiRA.

- **Head:** Naoki Harada (Associate Professor)
- Tomoko Furubayashi

FACS Group

Supports the analysis of cell properties by flow cytometers.

- Kanae Mitsunaga (Assistant Professor)
- Yuki Goshima

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:** Koji Eto (Professor)
- Michihiro Tanaka (Assistant Professor)
- Shinsuke Dokan
- Toyokazu Fujita
- Aoi Kuginuki
- Jun Nishikawa
- Shinya Nishikawa
- Hikari Nishina
- Hiromi Nose
- Kenichi Otsuka
- Noriko Saiwaki
- Kotaro Shiraishi
- Shinichi Yamashita
- Katsuya Yanagi

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)

Academic Research Support Group

- Toru Kawamura (GL・Specially-Appointed Associate Professor)
- Miho Saito
- Sayaka Takeshima

Human Resource Group

- Toru Kawamura (GL・Specially-Appointed Associate Professor) (～2018.8.31)
- Kumi Higashi(GL) (2018.9.1～12.31)
- Rie Kato (GL) (2019.1.1～)
- Hitomi Imagawa
- Aya Iwayama
- Masayuki Kan
- Shinsuke Morisawa
- Shinya Tomita
- Masakazu Watanabe

Secretary Group

- Fumitaka Watanabe (Deputy GL) (～H30.8.31)
- Rie Kato (GL) (～H30.12.31)
- Kumi Higashi (GL) (H31.1.1～)
- Keiko Kamegawa
- Takako Nakata
- Mitsuki Otsuki

Fundraising Group

- Fumitaka Watanabe (GL)
- Junya Hirasada
- Hiromi Imanishi
- Chikako Kanda
- Yuriko Kawakatsu
- Fusao Koyama
- Yoko Matsumoto
- Tomoyo Ogawa
- Kaori Ono
- Aiko Tokunaga
- Mika Yamagishi

Common Secretary Group

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

2018–2019

Research Institute Support

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)
- **Deputy Head:** Atsushi Onodera

Regenerative Medicine Support Group

- Hiromi Dohi (GL)
- Ayumi Matsunaga (SGL)
- Hiroko Endo
- Tadaaki Hanatani
- Shoko Matsui
- Yumie Matsumura
- Hisae Takenakajima
- Keiko Ukita

Ethics and Inspection Group

- Keiichi Tabuchi (GL, Associate Professor)
- Ayumi Matsunaga (SGL)
- Shoko Matsui
- Yumie Matsumura

Contract and Drug Discovery Group

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

Intellectual Property Group

- Nobuko Tachikawa (GL)
- Hiroko Endo
- Miwa Nakagawa
- Chie Saneyoshi
- Ayumi Suzuki
- Mika Uchiyama

Planning and Coordination Office

Manages research funds and coordinates laboratory and office space.

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

International Public Communications Office

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

- **Head:** Akemi Nakamura
- Peter Karagiannis (Specially-Appointed Junior Associate Professor)
- Hidenari Kato
- 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:** Masakazu Watanabe
- **Deputy Head:** Satoshi Okuyama

General Affairs

- Hina Furuya (Manager)
- Yuko Kitano (Assistant Manager)
- Kana Ikeshita
- Kohta Katsukawa
- Aya Kita
- Sumie Minakuchi
- Mayu Mochi
- Megumi Murase
- Akiko Nakagawa
- Rie Oyagi
- Sakiko Tsubota

Personnel Affairs

- Shinya Tomita (Manager)
- Aya Iwayama (Assistant Manager)

Financial Affairs

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

CiRA Advisors

Scientific Advisers

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

Management Adviser

- Hiromichi Mizuno

Communication Adviser

- Hidenari Kato
- Motoaki Nishiwaki

GL=Group Leader SGL=Sub Group Leader

2018-2019

Research Activities

1 CiRA Seminars

Date	Lecture Title	Speaker	Affiliation
2018.4.20	Regenerative medicine through the allogeneic transplantation of chondrocyte sheets for the treatment of osteoarthritis of the knee	Takumi Takahashi Masato Sato	Tokai University
2018.5.22	CRISPR/Cas-assisted genetics in intestinal organoids	Bon-Kyoung Koo	Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA)
2018.5.23	Microarray dataset from Open TG-GATEs	Yoshinobu Igarashi	National Institute of Biomedical Innovation, Health and Nutrition
2018.5.25	High-throughput screening using imaging ~Basics and application of High-content screening (HCS)	Noriko Oshima Takenobu Kuji Mitsuo Yamaguchi Ryo Shioda Takanobu Matsubara	GE Healthcare Japan Thermo Fisher Scientific Molecular Devices PerkinElmer Yokogawa Electric Corporation
2018.5.25	Ethics of organ transplantation ── from the perspective of medical anthropology ──	Yousuke Shimazono	Center for Global Initiatives
2018.6.1	Clinical trials act and regenerative medicine	Shimon Tashiro	National Cancer Center Center for Public Health Sciences
2018.7.4	Ethical guidline of human biomedical science research ── Roots and international development of bioethics ──	Rihito Kimura	Waseda University
2018.7.20	Improving the performance, efficiency, and flexibility of targeted sequencing	Bryan N. Höglund	Technical Director of Twist Biosciences
2018.7.24	Clinical features of frontotemporal dementia	Manabu Ikeda	Osaka University
2018.7.24	Unconventional aggregate pathologies and their modifier in C9orf72-FTLD/ALS	Koji Mori	Osaka University
2018.8.7	Prothymosin α plays multifunctional robustness roles against fatal stresses in neurons	Hiroshi Ueda	Nagasaki University
2018.8.27	Dual process models, behaviour change, and the ethics of health promotion	Rebecca Brown	University of Oxford
2018.8.27	How to take responsibility for your health in an epistemically polluted environment	Neil Levy	Macquarie University/ University of Oxford
2018.8.27	Epistemology and ethics of promissory health claims in the adveillance economy	Douglas Sipp	RIKEN
2018.9.6	Reprogramming stem cell-based strategies for skeletal muscle repair and (re)generation	Francesco Saverio Tedesco	University College London (UCL)
2018.9.6	Klf5 regulates skeletal muscle differentiation, regeneration and development	Shinichiro Hayashi	National Center of Neurology and Psychiatry
2018.9.7	Blastoids: Blastocyst-like structures generated solely from stem cells	Nicolas Rivron	Hubrecht Institute for Developmental Biology and Stem Cell Research/ MERLN Institute for Technology-Inspired Regenerative Medicine
2018.9.26	Genetic and pharmacologic intervention of heterotopic ossification caused by aberrant BMP signaling in mice	Yuji Mishina	University of Michigan

2018-2019

Research Activities

Date	Lecture Title	Speaker	Affiliation
2018.9.27	Nanoparticle-based local translation system revealed novel mRNA function as translation-coupled nascent protein scaffold ~insight from in vitro studies~.	Shunichi Kashida	Ecole Normale Supérieure
2018.10.16	Current progress in early diagnosis and drug discovery for human prion diseases	Noriyuki Nishida	Nagasaki University
2018.10.23	Human immunology	Hideki Ueno	Icahn School of Medicine at Mount Sinai
2018.10.31	The current status and issues of General Data Protection Regulation ~A survey report of GDPR~	Mayumi Kusunose	RIKEN
2018.11.12	Visualizing ATP dynamics in live mice	Masamichi Yamamoto	Kyoto University
2018.11.16	Scaffold-free Bio-3D printing for solid organ fabrication	Koichi Nakayama	Saga University
2018.11.16	The evolution of thymopoietic microenvironments	Ryo Morimoto	Max Planck Institute for Immunobiology and Epigenetics
2018.12.11	Unlocking silenced enhancers for reprogramming to naïve pluripotency	Kenjiro Adachi	Max Planck Institute for Molecular Biomedicine
2018.12.14	Compassionate use and the “right” to try unapproved drugs	Arthur L. Caplan	NYU School of Medicine
2019.1.8	Deconstruction of pluripotency	Masaki Kinoshita	University of Cambridge
2019.1.30	Publishing in Nature Communications	Fiona Carr	Nature Communications
2019.2.6	Life and dignity of human	Toshihiko Dohzono	Shizuoka University
2019.3.28	Synthetic cell biology: Total synthesis of cell function and its biomedical applications	Takanari Inoue	Johns Hopkins University

2018-2019

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 (U.S., Indonesia, Spain, China, Canada and Japan) joined in 2018. 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 CiRA researchers present their latest research. 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, October 29-30, was held near Lake Biwa. CiRA participants presented posters or gave an oral presentation about their research. The retreat also invited 3 external speakers to attend.

Guest Speakers

Shuji Nakamura
(University of California, Santa Barbara)
Yoichi Ochiai
(Pixie Dust Technologies, Inc. / Tsukuba University)
Tadahisa Kagimoto (Healios K.K.)

Best Oral Presentation Award

1st : Takeshi Ito (Hamazaki Lab.)
2nd: Huaigeng Xu (Hotta Lab.)
3rd: Mitsuru Honda (Sakurai Lab.)

Outstanding Poster Award

Jose Ichishima (Saito M Lab.)
Taiki Nakajima (Ikeya Lab.)
Kazuya Hashimoto (Eto Lab.)
Chiaki Mihara (Ikeya Lab.)
Sadaharu Torikoshi (Takahashi Lab.)
Yuta Mishima (Kaneko Lab.)
Naoko Katagiri (Osafune Lab.)
Ieva Stirblyte (Eto Lab.)
Julia Junghof (Yoshida Lab.)
Tomoko Kita (Watanabe Lab.)

(1)

(2)

(1)
Commemorative photo at CiRA Retreat

(2)
A discussion at CiRA Retreat

2018–2019

Research Activities

5 CiRA Internal Communication

The CiRA internal events were held from 2018 to promote communication among CiRA members.

Every month "Tell us, Researcher! CiRA's Research" was held as an interaction between support staffs and researchers. Also, CiRA Networking Events were held to promote more communications. An internal magazine, "Wiki CiRA" was installed to notify the event news to CiRA members.

"Tell us, Researcher! CiRA's Research" Speakers

1st:	2018.5.8	Junya Toguchida
2nd:	2018.6.5	Shinya Yamanaka
3rd:	2018.7.3	Naoko Takasu
4th:	2018.9.11	Jun Takahashi
5th:	2018.10.2	Misao Fujita
6th:	2018.11.14	Haruhisa Inoue
7th:	2018.12.4	Yoshiya Kawaguchi
8th:	2019.1.29	Hirohide Saito
9th:	2019.2.20	Koji Eto
10th:	2019.3.26	Yoko Hamazaki

total 650 people joined

Club Activities at CiRA

CiRUN (Marathon),ChoiRA (Chorus), Shogi club, Ping-pong club

CiRA Networking Events

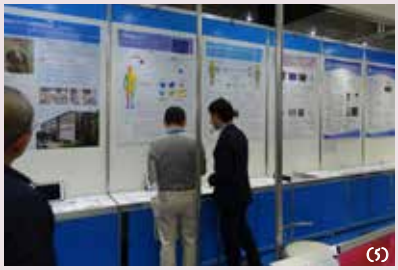
1st:	2018.4.20	Takoyaki Welcome Party. 126 people joined.
2nd:	2018.5.25	Hot dog Party. 96 people joined.
3rd:	2018.7.19	International Party. 36 people joined.
4th:	2018.11.22	Quiz Party. 44 people joined. Guest: Masakazu Higuchi, iCeMS, Kyoto University
5th:	2019.2.16	CiRA Alumni Party. 75 people joined.

(3)

(4)

6 Booth Exhibit

CiRA exhibited a booth at BioJapan 2018 which was held from October 10 to 12, 2018 in Yokohama. Top business development, licensing, alliance management professionals, R&D personnel, and biotech company executives participated this event and came by CiRA booth and CiRA's presentation.



(5)

(3)
CiRA Exchange Meeting

(4)
"Tell us, Researcher! CiRA's Research"

(5)
CiRA booth at BioJapan 2018

※People joined at Club Activities or CiRA Exchange Meetings pay their own expense.

2018–2019

General Public Outreach

1 CiRA Symposium

CiRA holds symposia for the general public each year.

September 25, 2018

Present and Future of iPS Cells
This event was a joint symposium with Kobe Shimbun. The event was held in Kobe city.
521 people joined.
[Speakers]
Michiko Mandai (RIKEN)
Shinya Yamanaka, Makoto Ikeya (CiRA)

February 2, 2019

Research and Regulation of Human Cells
This event was held as an annual meeting of the Uehiro Foundation on Ethics and Education.
This event was held at the Kyoto University Museum. Approx. 20 people joined.
[Speakers]
Taichi Hatta, Tsutomu Sawai, Mika Suzuki, Kyoko Akatsuka (CiRA)

March 24, 2019

iPS Cells and Future Health
This event was held in Naha city, Okinawa.
Approx. 650 people joined.
[Speakers]
Shinya Yamanaka, Yoshinori Yoshida, Taro Toyoda (CiRA)

2 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 Kyoto, Sendai, Kumamoto and Okinawa.

June 26, 2018

Regenerative medicine using iPS cells ~a challenge to Parkinson's disease~
This 24th CiRA Café was held at CiRA. Approx. 30 people joined.
[Speaker]
Jun Takahashi (CiRA)

August 26, 2018

Listen to and discuss iPS cells
This event discussed the use of iPS cells to treat muscular dystrophy.
This event was held at Sendai city, Miyagi.
18 people joined.
[Speakers]
Toshiaki Takahashi (Sendai Nishitaga Hospital)
Hidetoshi Sakurai (CiRA)

March 17, 2019

Listen to and discuss iPS cells
This event was held in Kumamoto city. 11 people joined.
[Speakers]
Satoshi Yamashita (Kumamoto University)
Akitsu Hotta, Hiroyuki Wadahama (CiRA)

March 23, 2019

Opening Lecture for iPS cells
This event was held in Naha city, Okinawa.
Approx. 30 people joined.
[Speaker]
Ayaka Nakauchi (CiRA)

(1)
Professor Yamanaka at the symposium "Present and Future of iPS Cells" (credit: Kobe Shimbun)

(2)
Panel discussion at the symposium "Present and Future of iPS Cells" (credit: Kobe Shimbun)

(3)
A talk at "Research and Regulation of Human Cells"

(4)
Panel discussion at "Research and Regulation of Human Cells"

(5)
Professor Takahashi at "Regenerative Medicine Using iPS cells ~A Challenge to Parkinson's Disease~"

(6)
Junior Associate Professor Hotta at "Listen to and discuss iPS cells"

2018–2019

General Public Outreach

3 Seminar and Workshop

The following events were held to share our activities and research results with the public.

August 2, 2018

Science Writing Workshop
This event was held to share the experience of Santa Fe Science Writing Workshop held in May 2018. This was held at CiRA. 13 people joined.
[Speaker]
Peter Karagiannis (CiRA)


(7)


(8)

September 10, 2018

Regenerative Medicine from Bench to Bedside
This event was a joint seminar with Snowbank held in Shibuya, Tokyo. 23 people joined.
[Speakers]
Yoshimasa DAZE Arai (Snowbank)
Naoko Takasu (CiRA)
[Panel Discussion]
Yoshimasa DAZE Arai (Snowbank)
Tomoyuki Suzuki (Mitsubishi Research Institute)
Naoko Takasu, Hiroyuki Wadahama (CiRA)

March 12, 2019

Science Event Seminar
This event was held to share the experience of New Scientist Live held in London, in September 2018. Approx. 20 people joined.
[Speaker]
Hiroyuki Wadahama (CiRA)

4 Programs for children

The following events were held to get children interested in iPS cells and science in general.

July 24, 2018

Let's study iPS cells
As a part of the summer schools run by the Kyoto City Board of Education and by the Otsu City Science Museum, CiRA held a science seminar for 40 junior high school students.
[Lecturer]
Noriyuki Tsumaki (CiRA)

August 4 and 5, 2018

iPS Cells: Play and Learn!
CiRA exhibited a workshop in the event "Science Square" at National Museum of Nature and Science, Tokyo. 60 elementary school students attended the workshop.

August 6, 2018

Create and Learn! The secrets of iPS cells.
This event was a joint workshop with Morioka Science Group held at Children's Science Center in Morioka city, Iwate. 40 elementary school students attended the workshop.

August 20 and 21, 2018

iPS Cells: Play and Learn!
This workshop was held as a part of "Mirai Summer Camp", organized by Mori Building, Roppongi, Tokyo. Approx.90 elementary school students attended the workshop. A lecture was held together with the workshop.
[Lecturer]
Shoichi Iriguchi (CiRA)

November 4, 2018

Become an iPS cell expert!
This event was a joint program with Kansai TV held at Osaka city. Approx.600 people visited the event mostly with their children. CiRA exhibited a booth and an interactive game, as well as a movie which shows CiRA interior and an interview of a researcher.


(9)


(10)

(7)
Peter Karagiannis at the science writing workshop

(8)
Speakers at "Regenerative Medicine from Bench to Bedside" Tomoyuki Suzuki, Yoshimasa DAZE Arai, Naoko Takasu, and Hiroyuki Wadahama from the left.

(9)
A science seminar on July 24

(10)
An interactive game at Kansai TV

General Public Outreach

5 Booth Exhibit

CiRA exhibited booths at pubic events to show iPS cells and stem cell card games.

April 18 and 19, 2018

Knowledge Capital School
This event was held in Knowledge Capital in Osaka city as an event for a general public communication.

November 10 and 11, 2018

Snow Bank Pay it Forward 2018 "Tokyo Snow Festival" (Tokyo)
This event was to promote blood donation and registration for marrow donor program. Approx. 159 people visited.


(1)


(2)


(3)

6 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, eight tours on four were held on June 2, Sep 1, Dec 1 in 2018 and Feb 2 in 2019 (one was scheduled on July 7 but cancelled due to typhoon). More than 280 people participated in those tours.

7 International Session

CiRA opened a session with a collaboration with RIKEN at the AAAS 2018 Annual Meeting on February 15 in Washington D.C., titled "The role of stem cells for the future medicine." We shared our latest research outcome and talked some issues associated with medical application.

Speakers

Paul Knoepfler (University of California, Davis)
Akishi Onishi (RIKEN)
Knut Woltjen (CiRA)

Organizers

Jens Wilkinson (RIKEN)
Ayaka Nakauchi (CiRA)

(4)

(1)
CiRA booth at Knowledge Capital School

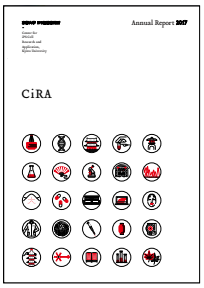
(2)
People playing stem cell card games at CiRA booth

(3)
CiRA booth at Snow Bank Pay it Forward 2018

(4)
Session at AAAS 2018 Annual Meeting
Knut Woltjen, Akishi Onishi, Paul Knoepfler, and Ayaka Nakauchi
From the left

2018–2019

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_CiRA Annual Report (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.

iPS Cell Research Fund

In the FY 2018 the iPS Cell Research Fund collected nearly 4.8 billion yen from approximately 25,000 donations. In addition, the fund received many recurring gifts and bequests. This surpasses the Fund's performance from the year before, making it again the best annual performance of the Fund.

As of March 31, 2019, the iPS Cell Research Fund had a balance of over 14 billion yen. This money is being used to convert iPS cell research novel into innovative treatments. Expenditure from the fund was used to purchase state-of-the-art equipment for iPS cell research and totaled up to 700 million yen, which is 200 million yen more than last year.

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 2018 Financial Report (April 1, 2018-March 31, 2019)

Revenue	Number of Donations	Amount (yen)
Individual	23,551	3,199,834,072
Corporation / Organization	1,161	1,605,599,613
Total	24,712	4,805,433,685

Expenditures	Amount (yen)
Personnel	361,113,711
Research projects	213,680,807
Intellectual property	37,600,129
Other operating expenses (*portion to Kyoto University)	147,089,921 (111,601,227)
Total	759,484,568

	Amount (yen)
FY 2018 Balance	14,341,438,119

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

2018–2019

Intellectual Property

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

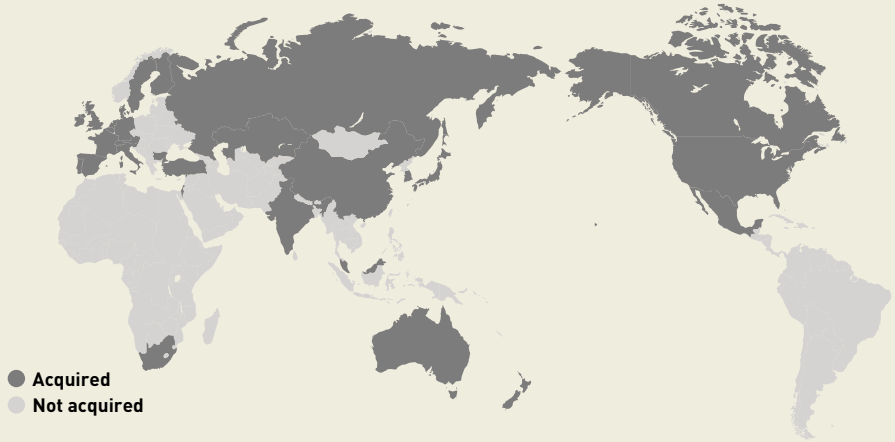
In FY 2018, patents related to basic technology for iPS cells were granted in Europe and India. Including these countries, patents owned by CiRA have been granted in 32 countries and 1 region (see figure below) by the end of March 2019. Other patents include IP for the production of iPS cells and for 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, 2019)**

Nations and Regions	Number of Patents
Japan	38
U.S.A.	29
China	14
European Union *1	19
Singapore	7
Australia	6
Canada	10
Hong Kong *2	4
Eurasia *3	2
U.K. *4	2
Korea	10
Mexico	3
New Zealand	2
South Africa	2
Israel	4
Malaysia	1
India	3
Total	156

*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, 2019)**



2018–2019

Major Research Projects

1 Research Center Network for Realization of Regenerative Medicine

Sponsored by the Japan Agency for Medical Research and Development (AMED), this program promotes the practical application of iPS cells by establishing a research system that facilitates research on safety and standards, the construction of iPS cell stock for regenerative medicine, and aims for realization of regenerative medicine by disease and tissue. 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 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 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 Asso-ciate 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.

T-CiRA
(1)

(1)
T-CiRA logo

2018–2019

Major Research Projects

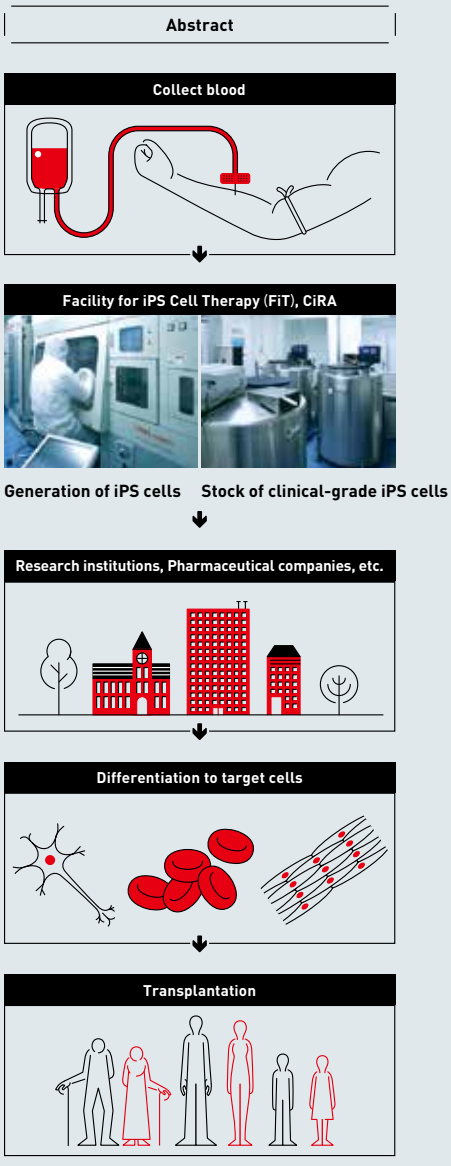
3 iPS Cell Stock for Regenerative Medicine

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 (p.49) in collaboration with the Facility for iPS Cell Therapy (FiT(p.47)). Full-scale operation began in FY 2013 with the aim of establishing an iPS cell stock that covers 30-50% of the Japanese population.

The recruitment of donors is being done in partnership with the Japanese Red Cross Society (JRCS). To hasten blood collection for more iPS cell lines, CiRA began teaming with Kaijo Bldg. Clinic in Tokyo and with the Japanese Red Cross Nagoya Daiichi Hospital. Already working with Kyoto University Hospital, CiRA can now collect blood from Kyoto, Nagoya, and Tokyo.

In 2015, CiRA began distribut iPS cells from its iPS cell stock. These cells were made from donors that have the most frequent homozygous HLA in Ja-pan and should serve approximately 17% of the Japanese population. After completing its second HLA-homozygous iPS cell line in 2017, the iPS cell stock completed its third and fourth HLA-homozygous iPS cell line in 2018. Those lines are estimated to match 40% of the Japanese population.

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 Card Blood Bank.



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, 2019)

Professors	15 (4)
Associate Professors	11 (1)
Junior Associate Professors	6 (0)
Assistant Professors	23 (0)
Researchers	114 (73)
Research Assistants	68 (80)
Research Support Staff	43 (10)
Administrative Staff	12 (6)
Total	292(174)

Number of Students :

Dept. of Life Science Frontiers	28
Dept. of Cell Growth and Differentiation	21
Dept. of Clinical Application	24
Total	73

People from outside, such as, concurrent members, collaborators, contractors are shown in parentheses.

Organization Chart (as of March 1, 2019)

Director
Shinya Yamanaka

Deputy Directors
Junya Toguchida
Jun Takahashi
Naoko Takasu
Hirohide Saito

Assistant Directors
Shinsuke Morisawa
Fusao Koyama
Masayuki Kan
Hidenari Kato

Advisor
Tatsutoshi Nakahata

Faculty Council

Faculty Forum

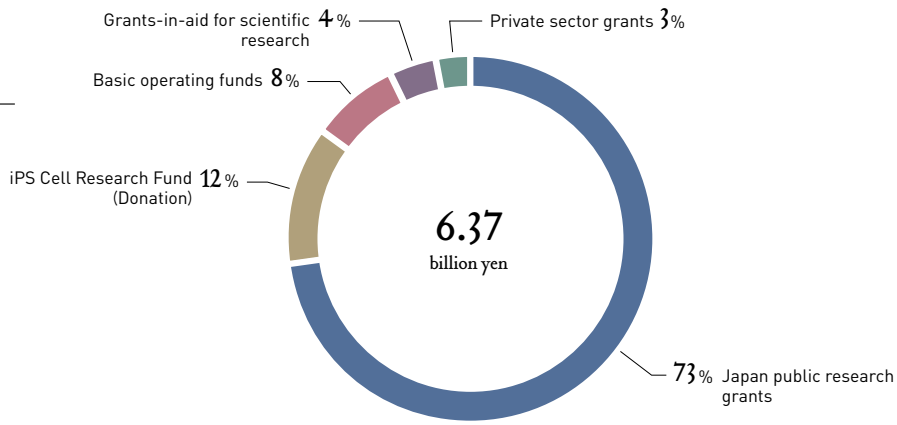
Research Departments
- Life Science Frontiers
- Cell Growth and Differentiation
- Clinical Application
- Fundamental Cell Technology
  - Drug Discovery Technology Development Office
  - Common Equipment Management Office
  - Information Security Office
- Uehiro Reserch Division for iPS Cell Ethics

Animal Research Facility
Facility for iPS Cell Therapy (FiT)

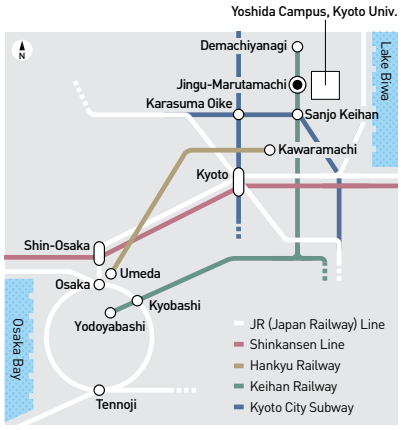
Research Support Division
Director's Office
Planning and Coordination Office
Medical Applications Promoting Office
International Public Communications Office

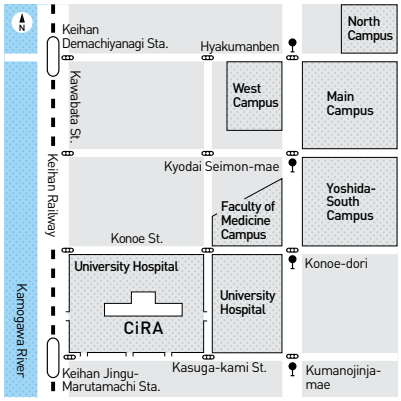
Administration Division
CiRA Administrative Office

Fiscal Budget Implementation (as of March 31, 2019)



Access





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

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Credit

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