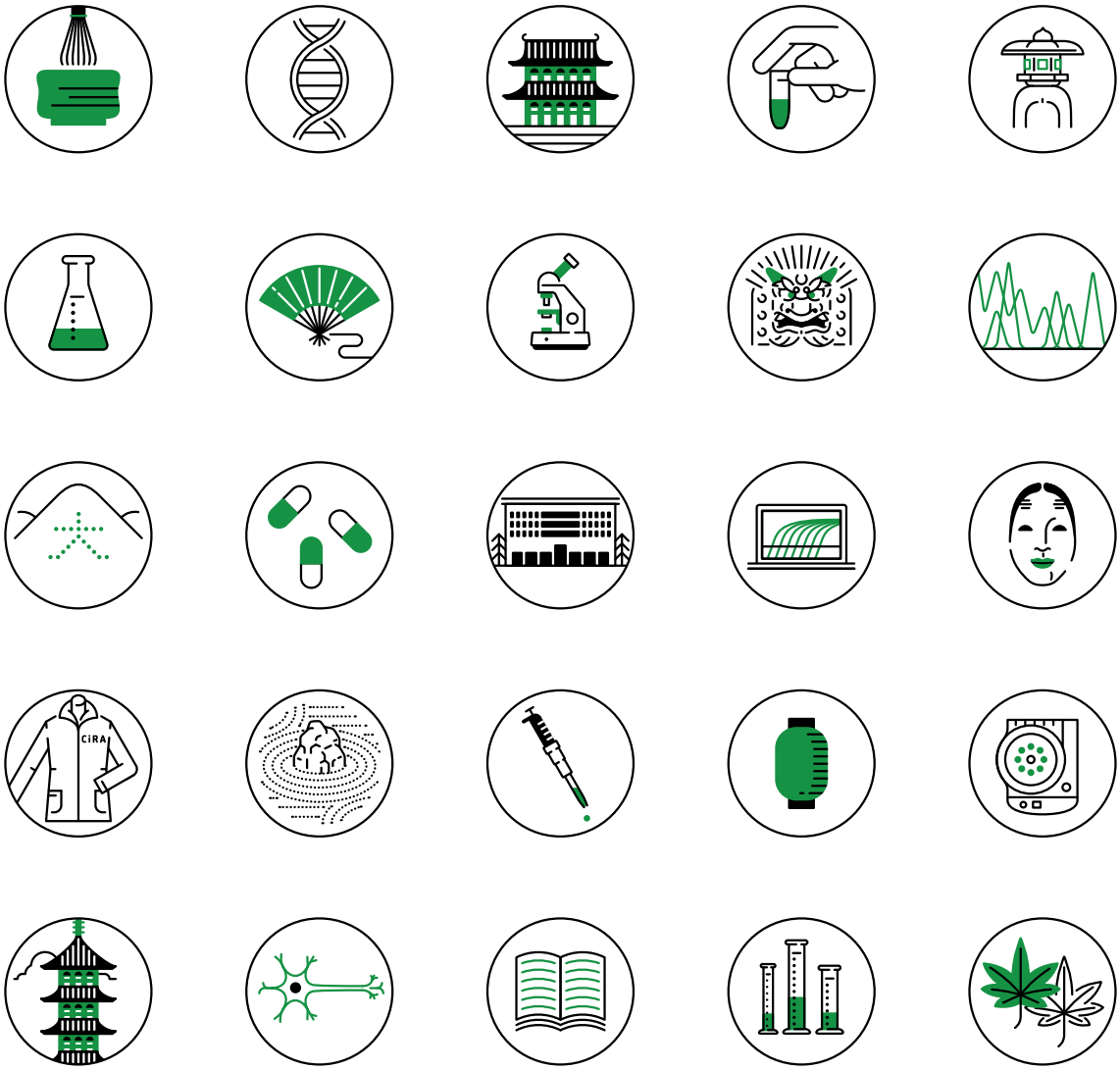
Center for
iPS Cell
Research and
Application,
Kyoto University

Annual Report 2019

CiRA



Content

*The data in this report reflects activities from April 1, 2019, through March 31, 2020.

Message from the Director

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

Shinya Yamanaka

Since its establishment in 2010, the Center for iPS Cell Research and Application (CiRA) has dedicated itself to the medical application of iPS cells. With this mission in mind, we have laid out our vision as below.

CiRA Vision 2030

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

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

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

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

Fiscal year 2019 has shown promising results for CiRA in terms of clinical studies. First, in January 2020, a collaboration with Kyoto University Hospital received approval for using iPS cells to treat articular cartilage damage. In this trial, cartilage prepared from the iPS Cell Stock will be transplanted. Second, in collaboration with Kyoto University Hospital and three other hospitals, a new drug trial for amyotrophic lateral sclerosis (ALS) started based on our iPS cell research.

We have also had noteworthy research accomplishments for regenerative medicine. The genome editing of iPS cells allowed our researchers to prepare platelets that have less risk of immune rejection in platelet transfusions. We also reported a new genome editing tool based on CRISPR-Cas3 and demonstrated its effects on repairing the gene mutations seen in iPS cells made from Duchenne muscular dystrophy patients.

T-CiRA, our collaborative project with Takeda Pharmaceutical Co.Ltd, also warrants mention. T-CiRA has prepared CAR-T iPS cells (iCART) and plans to start the first-in-human iCART trial in 2021 for cancer.

Finally, in September 2019, Kyoto University created the CiRA Foundation to promote the iPS Cell Stock Project. The reason was to sustain the project for the long term. The foundation officially takes over the stock project in April 2020.

As always, all these efforts are to benefit patients from iPS cell research as quickly as possible.

March 2020

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)


Kazutoshi Takahashi
Associate Professor (Junior 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


Kazuo Takayama
Junior 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 the 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 Highlights

2019 – 2020

1 Research Progress

Identification of abnormalities potentially arising during the generation of iPS cells and development of preventive techniques

—— toward the development of safe cell fate control technology

De novo DNA methylation at imprinted loci during reprogramming into naïve and primed pluripotency
Stem Cell Reports

Department of Life Science Frontiers
Takuya Yamamoto
(Associate Professor)

In somatic cells, a stable DNA methylation status is known to be maintained in CpG islands and imprint control regions. In the reprogramming process, major changes occur in the DNA methylation status, but what change takes place in CpG islands and imprint control regions are unclear.

In this study, we established that specific imprint control regions may acquire a high methylation status during reprogramming. Having demonstrated that this change occurs in the latter stage of the reprogramming process and involves Dnmt3a, we succeeded in generating iPS cells with normal imprinting by inhibiting the function of Dnmt3a. The fact that the DNA methylation abnormalities related to somatic cell reprogramming have been observed in pediatric cancers suggests that the same abnormalities may be implicated in the onset of these cancers. Because genome imprinting abnormalities are known to impair the function of stem cells, our findings may contribute to improving iPS cell quality. These findings should also contribute to methods for regulating cell senescence, which can cause functional impairments in individual cells.

Successful development of a new CRISPR-Cas3 genome editing tool

——successful repair of the DMD gene in human iPS cells

CRISPR-Cas3 induces broad and unidirectional genome editing in human cells
Nature Communications

Department of Clinical Application
Akitsu Hotta
(Junior Associate Professor)

Genome editing tools using CRISPR-Cas9 have been applied to a wide range of life science fields. However, there are safety concerns due to 'off-target' mutations occurring outside the intended region. There are also issues with intellectual property rights, In response, our research group focused on enzymes that, unlike Cas9, cleave DNA with a multi-protein complex. We found that Escherichia coli-derived Type I-E CRISPR-Cas3 can also be used in human cells. We established a CRISPR-Cas3 tool that triggers major deletions upstream of the targeted genome sequence with very little off-target effects and used it to successfully gene repair human iPS cells with mutations in the Duchenne muscular dystrophy (DMD) gene. It is expected that this new genome editing tool using the CRISPR-Cas3 system will find have applications drug discovery and gene therapy.

Research Highlights

2019 - 2020

Successful generation of 'universal' platelets from iPS cells using genome editing technology

iPSC-derived platelets depleted of HLA class-I are inert to anti-HLA class-I and NK cell immunity
Stem Cell Reports

Department of Clinical Application
Koji Eto
(Professor)

Platelet transfusion refractoriness (PLT) is a condition in which the transfusion is rejected if the platelets do not match the patient's HLA type. Gene manipulation to create a 'universal' platelet product with HLA class 1 deleted could be an effective solution.

Professor Koji Eto and his team used genome editing and iPS cells to produce platelets that do not express HLA class 1 (HLA-deleted iPS platelets).

They tested whether natural killer cells, which are known to attack cells that do not express HLA class 1, attack HLA-deleted iPS platelets. Culture experiments found that natural killer cells were no more likely to attack HLA-deleted iPS platelets than regular platelets.

Next, in a mouse model, they demonstrated that the HLA-deleted iPS platelets were able to circulate without being attacked by natural killer cells. These research results should help reduce the risk of PLT.

Ethical issues in research using cerebral tissue (cerebral organoid) grown in a culture dish from human pluripotent stem cells

The ethics of cerebral organoid research: Being conscious of consciousness
Stem Cell Reports

Uehiro Research Division for iPS Cell Ethics
Tsutomu Sawai
(Assistant Professor)

A three-dimensional tissue structure generated from pluripotent stem cells is known as an organoid. In 2019, CiRA researchers successfully induced cerebral organoids. Cerebral organoids to date have only reproduced localized structures that do not show consciousness. However, future cerebral organoids with more complex structures will require carefully testing for consciousness.

Assistant Professor Tsutomu Sawai and his team considered the question of how consciousness in organoids should be studied. Isolated, a cerebral organoid is unlikely to have consciousness, but, as the author point out, if a cerebral organoid were transplanted into an animal and acquired neural connections to perceive the outside world, it could possibly influence the consciousness of the animal.

The researchers do not believe that cerebral organoid research should be prohibited. However, they recommend that scientists should join philosophers and bioethicists to discuss the ethical issues associated with this research.

Research Highlights

2019 - 2020

2 Clinical research and clinical trials

Clinical trial for amyotrophic laterals sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a progressive disease in which the degeneration of motor neurons causes muscular atrophy and weakness.

Professor Haruhisa Inoue and his team differentiated ALS patient-derived iPS cells into motor neurons and used these cells to screen a range of different compounds for the ability to suppress death of motor neurons. As a result, they identified and reported bosutinib. Bosutinib was also found to suppress the death of motor neurons in ALS mouse model.

On the basis of these research findings, March 2019 saw the start of a clinical trial to evaluate the safety and tolerability of bosutinib in ALS patients.

Clinical research aimed at the regeneration of damaged knee joint cartilage

Body joints are points where two bones come into contact. Articular cartilage covers the bones at these contact points, allowing the joints to move smoothly and painlessly without causing damage to the bone.

At CiRA, the laboratory of Professor Noriyuki Tsumaki has been using iPS cell technology to prepare high quality articular cartilage at sufficient quantities to repair damaged cartilage in knee joints. In animal studies, the articular cartilage was confirmed to be safe (non-cancerous) and effective at regenerating cartilage at the transplanted site.

Based on these findings, the Ministry of Health, Labor and Welfare in January 2020 gave permission for Kyoto University Hospital to use the iPS cell-derived cartilage in humans as part of a clinical trial. The iPS cell-derived cartilage will be transplanted into damaged cartilage in the knee and tested for safety.

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.
2020 Representative Director, CiRA Foundation

Publication Highlights

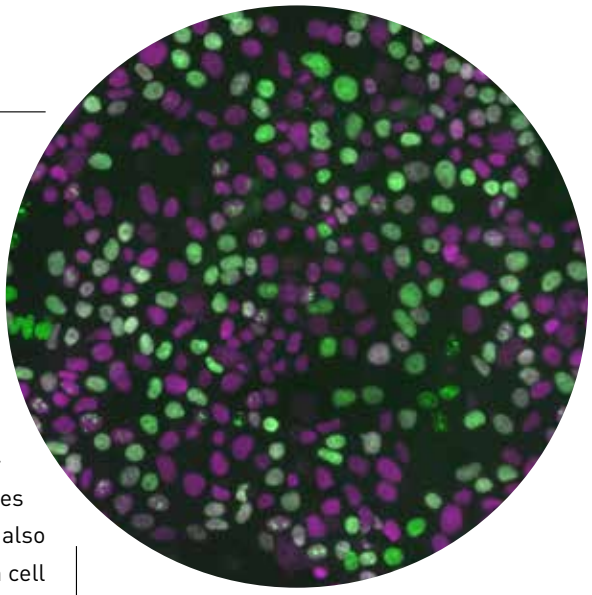
(1) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors
Takahashi K *et al.*
Cell (2006) 126 (4) : 663-676

(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 are reprogrammed somatic cells that have the ability to differentiate into almost any cell type of the body and to proliferate indefinitely. However, there are still many unknowns about the reprogramming mechanism. We are therfore analyzing genes involved in pluripotency. We are also working on the mechanism of germ cell genesis with iPS cells.



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

Research Progress

Establishing a global-standard iPS cell culture method

Technology for iPS cell generation has been progressing not only at CiRA, but in countries around the world. The result is different source tissues, reprogramming factors and reprogramming induction methods, leading to variations in iPS cell properties, safety, and generation efficiency. For drug discovery and regenerative medicine, we are developing safe and effective technology for iPS cell generation and evaluation that can serve as a global standard. We have also established iPS cell culture methods that have a low risk of carcinogenesis and are free of animal-derived substances.

New life sciences and new medical treatments

To promote the clinical application of iPS cells, we will continue to research the mechanism that maintains pluripotency and chromosome stability. Additionally, since 2018, we have hosted Professor Mitinori Saitou (Kyoto University) as an adjunct professor to drive forward research into the mechanism of germ cell development.

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

Members

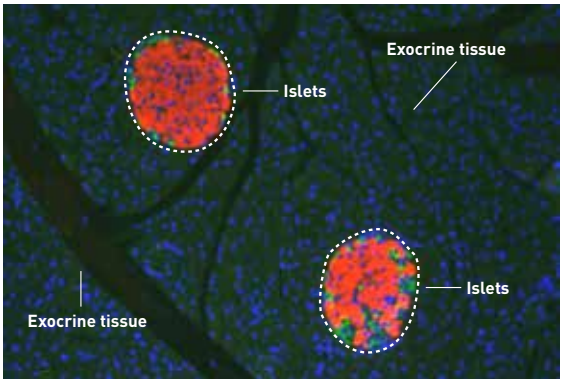
- Kazutoshi Takahashi (Associate Professor)
- Kiichiro Tomoda (Associate Professor)
- Mio Iwasaki (Assistant Professor)
- Yuka Kawahara
- Michiko Nakamura
- Tsuyoshi Tabata
- Sayaka Takeshima

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.



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

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

Research Progress

Understanding mechanisms regulating cell behavior in 3D tissue formation

During organ formation, regeneration after injury, and cancer, cells communicate with each other as the three-dimensional tissue structure is realigned, with individual cell behavior regulated by 'rules' within the cell community. We are using human iPS cells to study these rules in the digestive tract, pancreas and other human endodermal organs.

Exocrine-endocrine interaction during embryonic stage

Exocrine and endocrine cells are formed in the distinct portions in the branched ductal structure. In FY 2019, we identified exocrine-driven factor TFF2 prevents apoptotic death of endocrine cells during organogenesis. Similar exocrine-endocrine interaction is observed in adult pancreas, mediated by other factors.

Generating pancreatic endocrine progenitor cells from human iPS cells

Pancreatic islets develop from Nkx6.1-positive progenitor cells. In FY 2019, we discovered that FoxO1 inhibitors and Wnt stimulants activate the proliferation of human iPS cell-derived Nkx6.1-positive cells, making possible the production of pancreatic islet cells in large numbers.

Members

- Kenichiro Furuyama (Junior Assistant Professor)
- Yoshiki Aoyama
- Kaho Fujii
- Masanobu Habu
- Koji Hirata
- Masashi Horiguchi
- Ahmed Ibrahim Mohamed Ibrahim Aboahmed
- Toshihiko Masui
- Sakiko Minemura
- Ahmed Mohamed el Sayed Rashwan
- Chihiro Mori
- Kenzo Nakano
- Akiko Sankoda
- Nao Sankoda
- Ben Sasaki
- Asahi Sato
- Rina Tanaka
- Kunihiko Tsuboi
- Masahiro Yoshida

Profile

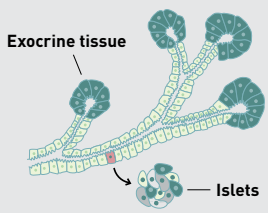
1988 M.D., Faculty of Medicine, Kyoto Univ.
1997 Ph.D., Graduate School of Medicine, Kyoto Univ.
1999 Postdoctoral Fellow, Dept. of Cell Biology, Vanderbilt Univ.
2002 Assistant / Assistant Professor, Graduate School of Medicine, Kyoto Univ.
2009 Lecturer, Graduate School of Medicine, Kyoto Univ.
2011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

Publication Highlights

(1) Senescence caused by inactivation of the homeodomain transcription factor Pdx1 in adult pancreatic acinar cells in mice
Horiguchi M *et al.*
FEBS Letters (2019)
593 (16): 2226-2234

(2) Exocrine tissue-driven TFF2 prevents apoptotic cell death of endocrine lineage during pancreas organogenesis
Hirata K *et al.*
Scientific Reports (2019) 9: 1636

(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 Chemical Risk Information Sharing Consortium
https://scchemrisc.stemcellinformatics.org/

(2) Novel computational model of gastrula morphogenesis to identify spatial discriminator genes by self-organizing map (SOM) clustering
Mori T *et al.*
Scientific Reports (2019) 9: 12597

(3) Integrated Collection of Stem Cell Bank data by MIACARM
https://icscb.stemcellinformatics.org/

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

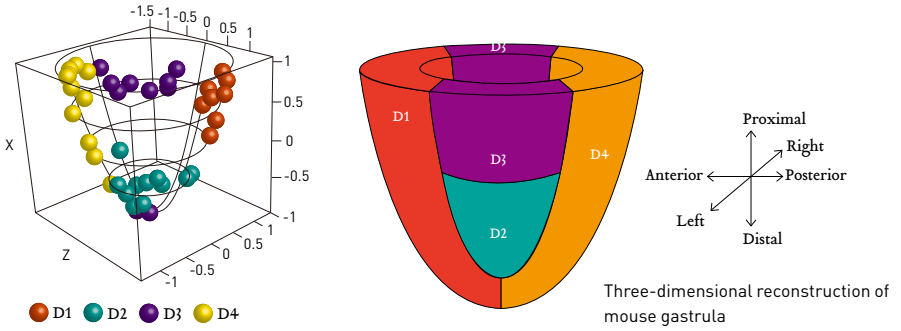
Stem cell toxicity testing system and a stem cell information database

Using artificial intelligence technology, we constructed a highly accurate compound toxicity prediction system based on human ES cell and gene network data. We have set up a consortium with more than 80 participants including corporations and researchers in the fields of pharmaceuticals, foods, and chemicals, and have begun work on creating a database of compound reactivities measured in undifferentiated cells (1). Our research laboratory also has an experimental group that provides epigenetic data on gene expressions and methylations, and a wide range of other omics data. We integrate these data to calculate information on intercellular distances so as to create 3D computer-based tissue models. In FY 2019, we published a related scientific paper on early mouse embryos (2).

We also proposed the MIACARM stem cell data standard, intended as a basic platform for data sharing with the world's 20 or more stem cell banks and published a relevant report. In FY 2017, we presented a scientific paper on the standardization of stem cell nomenclature and developed the Integrated Collection of Stem Cell Bank Data (3), which brings together 10,000 items of stem cell data from around the world.

Members

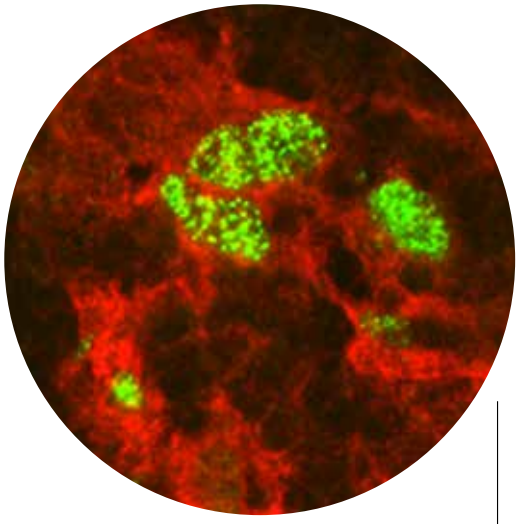
- Ying Chen
- Tomoka Hisaki
- Tsuneo Kido
- Kenta Kobayashi
- Kayo Obata
- Toshiaki Ogino
- Ayano Osakada
- Hironori Otsuki
- Yulia Panina
- Shuichi Sekine
- Naila Shinwari
- Hiroki Takahashi
- Masami Ueno
- Junko Yamane



Three-dimensional reconstruction of mouse gastrula

Controlling and rebuilding the immune system

Yoko Hamazaki Ph.D., Professor



Teacher cells in the thymic medulla educate T cells against autoimmune responses
Red: Claudin (expressed by teacher cells)
Green: Aire gene (identify the body's own tissue)

Summary

We identified the stem cells of thymic teacher cells, which 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 developing novel strategies to reconstitute thymic function using iPS cell technologies.

Research Progress

Understanding and reproducing the developmental process of the thymus

Abnormalities in the immune system can leave the body unable to combat infectious microorganisms and cancers and may lead to autoimmune disease. We identified the stem cells of "teacher cells" (thymus epithelial cells) in the thymus that have the task of educating T cells to not attack the body's own tissue.

Having succeeded in establishing an assay system for evaluating stem cell activity, we are now working to identify the factors that can activate declining thymic functions and using iPS cells to reproduce the structure and functions of the thymus.

Exploring the immune cell senescence mechanism and age-related diseases

Despite its crucial importance for T cell generation, the thymus shrinks rapidly from adolescence onward and reduces the production of new T cells. We found that T cells proliferate in response to the reduced T cell number in the body. This process results in an increase in the CD8 T cell population, which shows a high potential for producing inflammatory cytokines [1]. An animal model revealed that this fraction of CD8 T cells causes an aggravated inflammatory response. These findings suggest that the unique T cells generated during thymic involution may contribute to excess and/or chronic inflammation observed in metabolic diseases and other aging-related diseases.

Members

- Takeshi Ito (Assistant Professor)
- Kouhei Kometani (Assistant Professor)
- Tomoko Ikari
- Chiyomi Inoue
- Norihide Jo
- Aya Yonemura
- Rui Zhang

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

(2) Synthetic RNA-based logic computation in mammalian cells
Matsuura S *et al;*
Nature Communications, (2018)
9 (1) : 4847

(3) Numerical operations in living cells by programmable RNA devices
Endo *K et al;*
Science Advances (2019)
5 (8): eaax0835

Summary

MicroRNA and protein activity vary with cell type. This insight has enabled us to construct synthetic molecules that regulate exogenous genes in cells.

Research Progress

Development of RNA switch technology

Purity is crucial for translating iPS cell technology to medical treatment. We developed synthetic mRNA technology that detects differences in the intracellular environment and control cell fate accordingly. This technolgy switches the expression of exogenous genes on and off in response to specific microRNA or protein activity.

In FY 2019, we degined our switches to detect the activity of multiple microRNAs simultaneously to identify cell types by multivariate analysis in live cells to conduct genome editing only in cells with specific microRNA activity and to respond with high protein sensitivity.

These technologies will enable the accurate identification of and genome editing in target cell types and also the construction of complex synthetic gene circuits.

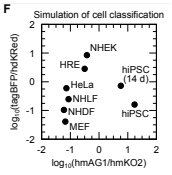
Members

- Yoshihiko Fujita (Assistant Professor)
- Hirohisa Ohno (Assistant Professor)
- Evgeniia Edeleva
- Yuki Hada
- Karin Hayashi
- Moe Hirosawa
- Shigetoshi Kameda
- Shunichi Kashida
- Shunsuke Kawasaki
- Kaoru Richard Komatsu
- Shodai Komatsu
- Kenjiro Kotake
- Takeru Kuwabara
- Sora Matsumoto
- Emi Miyashita
- Tomohiro Miyazato
- Megumi Mochizuki
- Hideyuki Nakanishi
- Miho Nishimura
- Hiroki Ono
- Malvin Leonardo Pardi
- Clarissien Ramongolalaina
- Yusuke Shiba
- Shunsuke Sumi
- Urtel Georg Christian
- Mari Yamagata
- Norika Yamaji

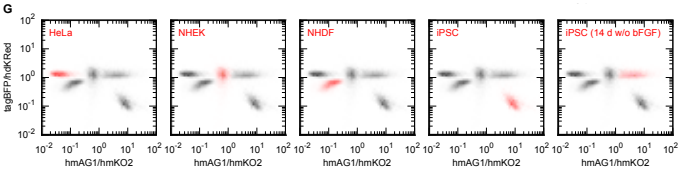
New functions of RNA switches responsive to proteins or microRNAs

1. Identification of cell types through simultaneous detection of multiple microRNAs

Simulation



Introduction of RNA switch into actual cell



Isolation of cells as per simulation using RNA switches to detect multiple microRNAs

2. Genome editing of target cells only using microRNA as a marker

Genome editing exclusively of target cells by detecting marker microRNA

Engineering genomes and cell functions

Knut Woltjen Ph.D., Associate Professor

Summary

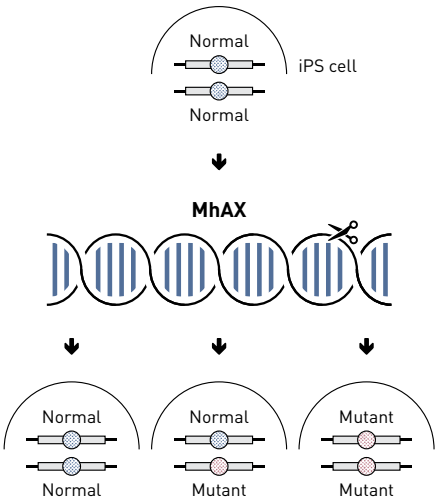
Pioneering genome engineering technologies in human iPS cells for over a decade, the Woltjen Laboratory develops cell engineering strategies for disease modelling and improved stem cell therapies. Employing molecular biology tools such as DNA transposons, programmable nucleases, and site-specific recombinases, we purposefully edit the human genome. Our methods have been applied to enhance reprogramming, and 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" gene editing in iPS cells (1). 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 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. We discovered that most deletion variants in the human genome are flanked by microhomology. We are exploiting this phenomenon to efficiently create pathogenic deletion mutations for disease models with both gain- and loss-of-function phenotypes (2).

Simultaneously derive an isogenic iPS cell panel



Our research into cell reprogramming mechanisms revealed a fundamental difference in cloned Klf4 that affects protein stoichiometry, influencing both the initiation and stabilization of true iPS cells (3). Using this system, we have identified transcriptional regulators that suppress the growth of partially reprogrammed cells and streamline the establishment of induced pluripotency.

Members

- Glicia Maria De Almeida
- Janin Grajcarek
- Mayumi Ikeda
- Harunobu Kagawa
- Suji Lee
- Mandy Siu Yu Lung
- Tomoko Matsumoto
- Thomas Luc Maurissen
- Michiko Nakamura
- Kazumi Nishikawa
- Jose Fabian Oceguera Yanez
- Anika Reinhardt
- Yusuke Ryu

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

(2) Genome-Wide Microhomologies Enable Precise Template-Free Editing of Biologically Relevant Deletion Mutations
Grajcarek *et al.*
Nature Commun (2019) 1-13

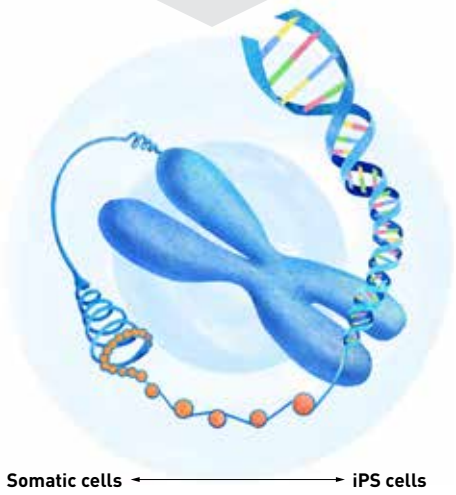
(3) OVOL1 influences the determination and expansion of iPSC reprogramming intermediates
Kagawa H *et al.*
Stem Cell Reports (2019) 12(2) : 319-332

Department of Life Science Frontiers

Comprehensive analysis of changes accompanying the somatic cell reprogramming process

Takuya Yamamoto Ph.D., Associate Professor

Genome-wide analysis(NGS)
Molecular biology
Bioinformatics



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, 1103-1117

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

(3) De novo DNA methylation at imprinted loci during reprogramming into naïve and primed pluripotency
Yagi M *et al.*
Stem Cell Reports (2019) 12, 1113-1128

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 to clarify how information is extracted from genomic DNA and used for cell function and cell properties. Our laboratory conducts comprehensive analysis to achieve this goal.

Research Progress

Genome imprinting abnormalities arising in somatic cell reprogramming

We have been researching the epigenetic regulation mechanism at work in somatic cell reprogramming. In FY 2019, we conducted a detailed analysis of DNA methylation and found that associated abnormalities were frequently observed in specific imprinting control regions in mouse and human somatic cell reprogramming [3]. We also developed a reprogramming technique to avoid these methylation abnormalities. Additionally, we demonstrated that the abnormalities are present at high frequency in pediatric cancers, suggesting that these abnormalities are involved in the cancer genesis. These research findings promise to contribute to the development of more stable iPS cell generation techniques.

Elucidating the mechanism specific to maintaining stem cell pluripotency

Following a comprehensive range of analyses, we identified a chromosome higher-order structure specific to pluripotent stem cells in FY 2019 [2].

When genome editing technology was used to remove a specific region from domains of unknown function, known as "gene deserts", there was a reduced expression of pluripotency-related genes that were distantly situated in terms of one-dimensional sequencing but nearby in three-dimensional terms. This finding suggests that the chromosome higher-order structure plays an important part in the pluripotent gene network.

Members

- Junya Asahira
- Joonseong Lee
- Mayumi Ikeda
- Mio Kabata
- Eri Kawaguchi
- May Koyama
- Ryoji Mabuchi
- Ryusaku Matsumoto
- Kazumi Nishikawa
- Satoko Sakurai
- Yuko Sogabe
- Kazunori Sunadome
- Akiko Yamakawa

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 that is 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 researching ways to reset human iPS cells into the naïve state. We are also engaged in research to visualize the initial stages of development in vitro.

Research Progress

Reprogramming naïve human iPS cells

We are the world's first research team to successfully reset existing human iPS / ES cells to the naive-type state. Naive-type human iPS cells are close to the fertilized egg stage and have wider differentiation potential and higher differentiation efficiency. We are further investigating the process of reprogramming to the naïve state.

Modeling early development

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

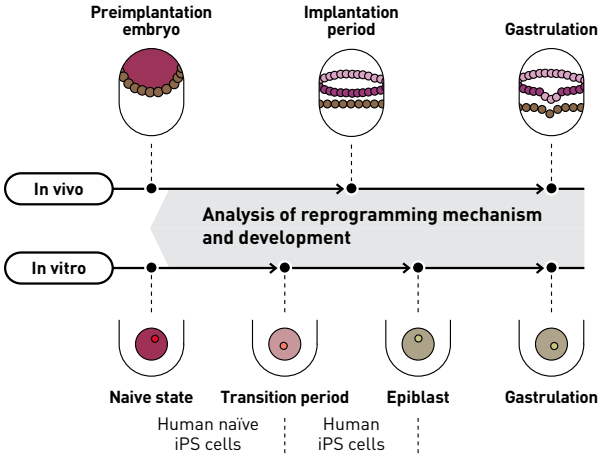
We are using naïve iPS cells to visualize early development in vitro.

In FY 2019, we induced differentiation to extra-embryonic cells, including the placenta and yolk sac, which is difficult with conventional iPS cells.

Members

- Hanaka Arai
- Yoshiki Iemura
- Mayumi Ikeda
- Shingo Io
- Belinda Yunita Kaswandy
- Haruko Kunitomi
- Minatsu Matsufuji
- Shungo Mochizuki
- Kazumi Nishikawa
- Takumi Okubo
- Katsunori Semi
- Akiko Shimada
- Masahito Takakura
- Mai Ueda

Research scheme using next-generation human iPS cells



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

Profile

1998 M.D., School of Medicine, Kobe Univ. / Dept. of Internal Medicine, Kobe University Hospital
1999 Dept. of Internal Medicine, Nishiwaki City General Hospital
2007 Ph.D., Graduate School of Medicine, Kobe Univ. / Research Associate, Center for Developmental Biology, RIKEN / Researcher, Wellcome Trust-MRC Stem Cell Institute, Univ. of Cambridge
2015 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) Removal of interference MS/MS spectra for accurate quantification in isobaric tag-based proteomics
Iwasaki M *et al.*
J Proteome Res (2019)
18 (6): 2535-2544

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

(3) Promotion of direct reprogramming by transformation-deficient Myc
Nakagawa M *et al.*
PNAS (2010)
107 (32): 14152-7

Summary

Many aspects of somatic cell reprogramming remain poorly understood. We are studying the molecular functions of the Yamanaka factors. The Yamanaka factors function as proteins. In general, many interact cluster together to form higher-order functional complexes that regulate various cellular functions by acting on intracellular sites. We are investigating whether the Yamanaka factors function in the same way. We are also updating methods for establishing and maintaining cell cultures to produce human iPS cells suitable for clinical application.

Research Progress

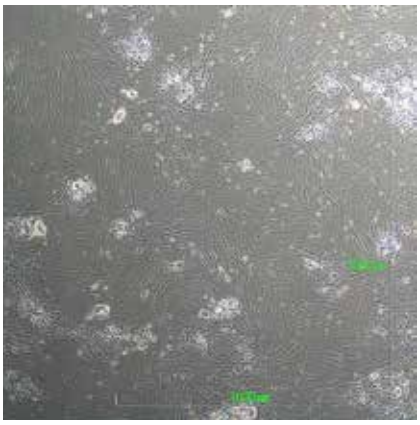
Elucidating the somatic cell reprogramming mechanism

The first four reprogramming factors to be discovered were Sox2, Oct3 / 4, Klf4, and c-Myc. We are elucidating the somatic cell reprogramming mechanism by studying their molecular functions, with current focus on Myc and Klf4. Myc is known as an oncogene but in recent years attention has come to focus on its multiple functions. Klf4 is also known to play a role in cancer.

In FY 2019, using methods including immunoprecipitation and affinity chromatography, we identified a number of proteins that bind to L-Myc and Klf4 (unpublished data), which we expect will give new insights on somatic cell reprogramming.

Developing efficient culture methods for human iPS cells

For the clinical application of human iPS cells, we have developed an efficient cell culture without using feeder cells. To maintain iPS cells in an undifferentiated state requires the addition to the culture medium bFGF, but the detailed mechanism of its action is unclear. Normally, the undifferentiated state is maintained through signaling receptors. but our research findings suggest that a separate mechanism may be at work.



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

Members

- Chiaki Akifuji
- Yu Shen Cheng
- Takahiko Imai
- Yuki Matsubayashi
- Jun Mukougawa
- Chiho Sakurai
- Akihide Shimizu
- Nao Tashiro
- Yoko Uematsu

The reprogramming mechanism and 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 and are researching the reprogramming mechanism and other ways that destabilize cell identity.

Research Progress

Analysis of the reprogramming mechanism

A full understanding of iPS cell induction is essential for generating high-quality iPS cells for clinical application. We tackled this still incomplete task through a gene-based approach and investigated over 2,000 genes, of which HLX, HHEX, and Srf were found to improve the reprogramming efficiency. Having further established that Srf is involved in maintaining the stability of differentiated cells, we are continuing with research into its biological function. We have also undertaken joint research into methods that suppress DNA methylation abnormalities during the reprogramming process as part of efforts to improve iPS cell quality.

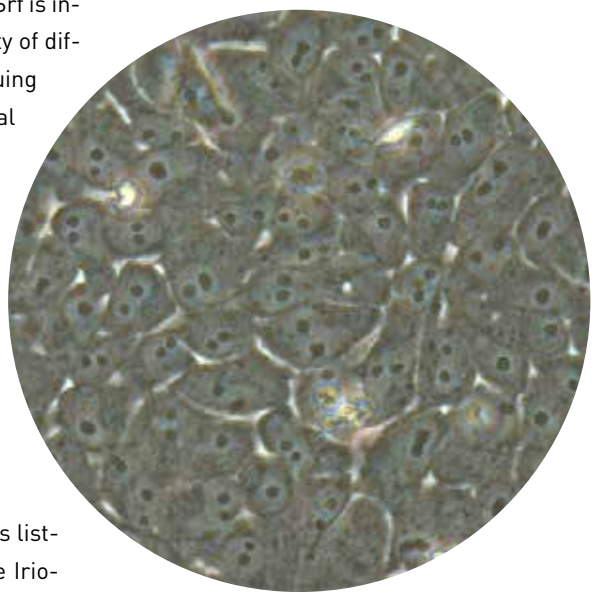
Application to endangered species

Japan has 30 mammal species listed as endangered, including the Iriomote cat. One example from the wider world is the northern white rhinoceros, with only two surviving individuals due to uncontrolled hunting. iPS cell technology may make it possible to save species where conservation measures are too late. Zoos and other facilities hold frozen stocks of somatic cells of endangered and extinct species. We believe that individual reproduction could be achieved by generating iPS cells from these stocks and applying assisted reproduction technology. We are engaged in related technology development.

Members

- Tomomi Eto
- Mari Hamao
- Kamonlak Leecharoenkiat
- Yasuko Matsumura
- Mizuki Minata
- Masafumi Shibata
- Malinee Tongbaen
- 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.
2020 Program-Specific Associate Professor, Kyoto University Graduate School of Medicine,

Publication Highlights

(1) Autologous induced stem-cell-derived retinal cells for macular degeneration
Mandai M, Watanabe A *et al.*
New Engl J Med (2017)
376(11) : 1038–1046

(2) Experimental Medicine Special Edition: Single Cell Genomics
Watanabe A, Suzuki Y *eds*.
Experimental Medicine Vol.37 No.20
Yodosha (2019)

(3) A modular differentiation system maps multiple human kidney lineages from pluripotent stem cells
Tsujimoto *et al.*
Cell Rep (2020), in press

Summary

Our research is 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 a multi-cell population, but reports indicate that the behavior of individual cells differs widely.

By operating a number of single-cell analysis platforms to analyze transcription conditions at the single-cell level in several thousand cells, we could identify cell groups which had been undetectable under previous classification systems, allowing us among other things to elucidate the transcription characteristics of minor cell populations. For example, we used single-cell analysis of kidney-lineage cells to recapitulate cell differentiation dynamics in early human development, for which no existing research material is available (2). Our research laboratory ceased activity as part of CiRA at the end of September 2019, but is continuing to deploy multi-omics technology for iPS cell-based regenerative medicine and drug discovery.

Understanding cell fate by multi-omics analysis including genomics

Members

- Kanae Echizen
- Akiko Hasegawa
- Azusa Hayano
- Ryotaro Kabai
- Unyanee Kato
- Yuki Kobayashi
- Saki Matsushima
- Katura Noda
- Chihiro Okada
- Kazuki Okuda
- Tatsuya Okumura
- Satoko Sakamoto
- Midori Sakiyama
- Yoshiaki Sato
- Masaki Yoshida

Research Progress

Understanding the mechanism of cell fate

By integrating DNA methylation analysis with epigenetic analysis, including chromatin status analysis with AT-AC-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 by building platforms for drug discovery, we are progressing to observe all biological phenomena at the single-cell level.

Mechanism and in vitro reconstitution of human germ cell development

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

Research Progress

What is a germ cell?

Germ cells differentiate into sperm and egg cells, the fusion of which creates a new individual and ensures the transmission of genetic and epigenetic information to the next generation. Clarifying the mechanism of germ cell formation will help us understand the mechanisms of genetic information transmission, epigenetic regulation, and infertility as well as the onset mechanism of genetic disorders.

Recapitulating germ cell development in vitro

By elucidating the mechanism of germ cell specification, we succeeded in the in vitro induction of primordial germ cell-like cells that contribute to sperm and egg cells. Using this system, we clarified the molecular mechanisms of germ cell development, including the epigenetic reprogramming mechanism and the mechanisms of oocyte differentiation and meiosis.

In FY 2019, we succeeded in developing a system for inducing primordial germ cell-like cells from cynomolgus monkey ES cells.

Members

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

Profile

1995 M.D., Faculty of Medicine, Kyoto Univ.
1999 Ph.D., Graduate School of Medicine, Kyoto Univ.
1999 Travelling Research Fellow/ Senior Research Associate, Gurdon Institute
2009 Professor, Graduate School of Medicine, Kyoto Univ.
2018 Professor, Kyoto University Institute of Advanced Study/ Director, Kyoto University Institute for the Advanced Study of Human Biology

Publication Highlights

(1) Induction of the germ-cell fate from pluripotent stem cells in cynomolgus monkeys
Sakai Y *et al.*
Biol Reprod (2020) 102 (3) : 620-638

(2) ZGLP1 is a determinant for the oogenic fate in mice
Nagaoka S I. *et al.*
Science (2020) 367, eaaw4115

Determining the mechanism of human somatic cell reprogramming

Kazutoshi Takahashi Ph.D., Associate Professor

Research Progress

Research on the molecular mechanism of somatic cell reprogramming has centered on transcription factors(1). Having discovered that post-transcription regulation plays an important role, we took interest in protein translation. We found that translation includes various mechanisms. We are clarifying new mechanisms and their significance.

In the early-stage of somatic cell reprogramming, we discovered that MYC stimulates translation of the RNA binding protein LIN41 through the microRNA Let-7. We also found that LIN41 inhibits the translation of CDKN1A gene, resulting in the proliferation of cells that have undergone reprogramming.

NAT1 has high homology with the translation initiation factor eIF4G. Noting NAT1 plays an important role in pluripotency, we successfully identified NAT1 protein complexes and their target RNA. Going forward, we hope to gain insights into the translation regulation of pluripotency by studying NAT1.

Members

・Michiko Nakamura ・Sayaka Takeshima

Profile

2005 Ph.D., Graduate School of Biological Sciences, Nara Institute of Science and Technology
2006 Assistant Professor, Institute for Frontier Medical Science, Kyoto Univ.
2015 Researcher. Gladstone Institutes, USA
2019 Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) MYC releases early reprogrammed human cells from proliferation pause via retinoblastoma protein inhibition
Rand TA *et al.*
Cell Reports (2018) 23, 361-375

Department of Life Science Frontiers

Elucidating the mechanism that determines protein quantity

Mio Iwasaki Ph.D., Assistant Professor

Profile

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

Publication Highlight

(1) Removal of interference MS / MS spectra for accurate quantification in isobaric tag-based proteomics
Iwasaki M *et al.*
Journal of proteome research (2019) 18(6):2535-2544

(2) The jPOST environment: an integrated proteomics data repository and database
Moriya Y. *et al.*
Nucleic acids research (2019) 47:D1218-D1224

Research Progress

Development of protein quantification methods

Proteins, which are the final product of gene expressions, are essential macromolecules that regulate cell function. Observing differences in protein expression levels and modification status among stem and differentiated cell types may lead to more efficient control of cell reprogramming and differentiation. However, compared to mRNA, proteins are difficult to quantify comprehensively and accurately.

We are developing technology for highly accurate quantitative analysis of proteins, creating a database of protein expression levels in various cell types, and investigating the effect on iPS cells of the mRNA to protein expression ratio on iPS cells. Based on highly accurate protein quantification using the method known as RiMS (removal of interference mixture MS / MS spectra), which we reported in FY 2019 (1), we successfully isolated several hundred gene groups with marked differences between mRNA and protein levels in a way specific to iPS cells. Because some of these genes are involved in the survival of iPS cells and are essential for the early stage of development, we are investigating why they undergo this kind of regulation.

Members

・Yuka Kawahara ・Sayaka Takeshima
・Tsuyoshi Tabata

Understanding skeletal system diseases to develop innovative therapies

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

Summary

The skeletal system is made up of bone, cartilage, ligament, tendons, and other 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.

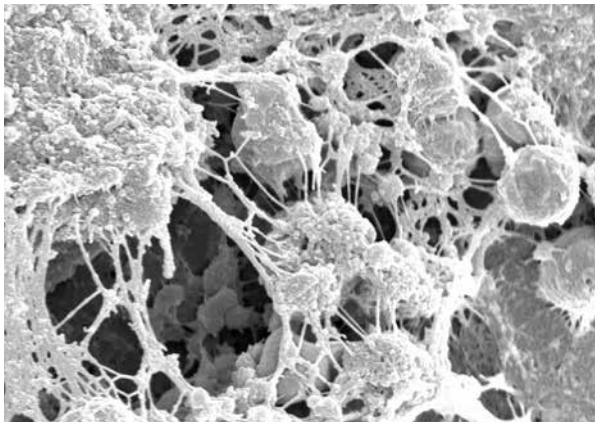
Research Progress

Physician-initiated clinical trial for an intractable disease

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disease in which heterotopic bone forms in the soft tissues of the body. Using patient-derived iPS cells, we identified activin A as the factor causing the ossification and that mTOR inhibitors suppress the ossification. Based on these findings, we started a clinical trial using the mTOR inhibitor sirolimus, already approved for pharmaceutical use, in 2017.

Successful development of high-efficiency bone differentiation

Most existing methods for the induction of bone differentiation are multi-staged and mimic the development process. By adapting retinoic acid signaling, we succeeded in inducing differentiated bone cells from iPS cells in just 10 days. Using this method, we reproduced in vitro the pathological conditions of osteogenesis imperfecta and established a drug screening system. Using confocal microscopy, we additionally achieved successful visualization of the bone cell differentiation from osteoblasts and migration into bone matrix and are now looking for factors that regulate the stages of differentiation.



Bone cells differentiated from iPS cells

Members

- Cantas Alev (Assistant Professor)
- Shunsuke Kawai (Assistant Professor)
- Mai Gozu
- Yonghui Jin
- Takeshi Kamakura
- Rena Kashimoto
- Jingchun Ma
- Sanae Nagata
- Hitomi Nakao
- Takaki Nakashima
- Megumi Nishio
- Mizuki Ohtsuka
- Yann Pretemer
- Mitsuru Soen
- Mai Sugimoto
- Liping Sun
- Sakura Tamaki
- Yoshiko Uesughi
- Makoto Watanabe
- Yoshihiro Yamanaka
- Hisayo Yasuda
- Marie Yoshino
- Hiroyuki Yoshitomi

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 patientderived iPS cells recapitulate pathological phenotypes of bone disease
Kawai S *et al.*
Nat Biomed Eng (2019)
3(7): 558-570

(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

Department of Cell Growth and Differentiation

New horizons in cardiac regenerative therapy with iPS cells

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

Profile

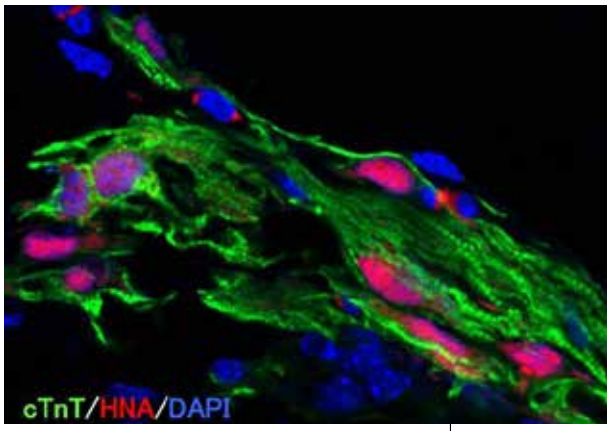
1990 M.D., Faculty of Medicine, Kyoto Univ.
1998 Ph.D., Graduate School of Medicine, Kyoto Univ.
2002 Assistant Professor, Graduate School of Medicine, Kyoto Univ.
2003 Associare Professor, Institute for Frontier Medical Sciences, Kyoto Univ.
2008 Associate Professor, iCeMS, Kyoto Univ.
2010 Associate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



CD82-positive cells at one month after transplantation to immunodeficient NOG mouse heart. Almost all the transplanted cells differentiated into cardiomyocytes.

Summary

We are conducting research to generate heart cells and tissues from iPS cells. Based on technology for generating cardiomyocytes and vascular cells, we are developing new cardiac regenerative therapies and disease models.

Research Progress

Regeneration of heart and blood vessel tissues

We use iPS cells to research the cardiovascular cell differentiation mechanism and develop regenerative therapy strategies. For example, we demonstrated that human iPS cells expressing CD82 are fated to become cardiomyocytes and show a high rate of autonomous cardiomyocyte differentiation following transplantation to animals (1).

We also developed an efficient method of differentiating human iPS cells into vascular endothelial cells (3), which we commercialized.

Additionally, we are using human iPS cells to create cardiac tissue-like structures (HiCT) including heart, blood vessel, and interstitial tissues for use in cardiac regenerative therapy.

New model of fatal arrhythmias

We created a three-dimensional structure consisting of 5-6 cell layers combining two different cell types, cardiomyocytes and interstitial cells. This successfully replicated the pathology, an achievement which promises to contribute to pharmaceutical safety evaluation, analysis of arrhythmia pathology, and development of therapies.

Elucidating new mechanisms that regulate stem cell differentiation

We identified a new role for exosomes in stem cell differentiation.

Members

- Yuji Agawa
- Takuhiro Hoshino
- Yurie Kaji
- Masahide Kawatou
- Ya Jing Liu
- Victor Lopez Davila
- Tomohiro Minakawa
- Chisato Murayama
- Akira Nakamura
- Kae Nakamura
- Yuki Oichi
- Hiroaki Osada
- Mizuho Shino
- Chinatsu Suzuki
- Ayano Tabata
- Masafumi Takeda
- Eriko Tominari
- Zhennan Yang
- Miki Yoshioka

Drug discovery using iPSC models of intractable neurological diseases and dementia

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

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. We have also investigated drug efficacy and explored compounds or cocktails to treat these diseases.

Research Progress

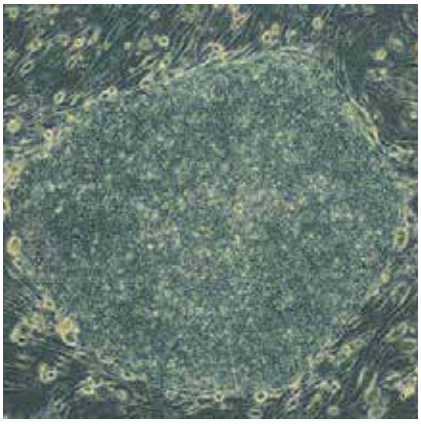
Elucidating the pathology of intractable neurological diseases

Using iPS cells from patients with ALS and Alzheimer's disease, we have been developing drug discovery platforms, transplant therapies, and high-precision medical treatments.

Going forward, we will continue using iPS cells and other stem cell technologies to understand the human central nervous system, elucidate associated pathologies, and ultimately feed this knowledge into clinical practice. Our research can thus be described as going "from bedside to dish" and "from dish to bedside."

The detailed mechanism of ALS, a disease in which the degeneration of motor neuron cells causes muscular atrophy and weakness, is not clear and there is no effective treatment available. In collaboration with research groups in Japan and overseas, we used motor neurons generated from ALS patient iPS cells to screen for therapeutic drug candidates and identified a molecular pathway as a target and an existing drug (1). In March 2019, iDReAM study for ALS patients begun.

One of the causes of Alzheimer's disease is thought to be the accumulation of amyloid β in the cerebral cortex. We conducted drug screening using Alzheimer's disease patient iPS cells and discovered a cocktail of three existing drugs which act synergistically to reduce amyloid β production (2).



ALS patient-derived iPS cells

Members

- Keiko Imamura (Junior Assistant Professor)
- Takayuki Kondo (Junior Assistant Professor)
- Dang Ngoc Anh Suong
- Haruhiko Banno
- Takako Enami
- Miwa Fujita
- Kiyomi Hatae
- Mikie Iijima
- Ikuyo Inoue
- Masataka Ishizuka
- Noriko Ito
- Nozomi Kawabata
- Yuya Kawasumi
- Eri Makino
- Michiyo Miyake
- Ayako Nagahashi
- Takeshi Niki
- Naoki Nishishita
- Mayu Okuda
- Taro Okunomiya
- Tomoko Saigo
- Ran Shibukawa
- Shinichi Sueta
- Mika Suga
- Ayumi Suzuki
- Kayoko Tsukita
- Yuichiro Yada

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

Department of Cell Growth and Differentiation

Novel regenerative medicine for the kidney, pancreas, and liver

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

Profile

1996 M.D., Faculty of Medicine, Kyoto Univ.
2003 Ph.D., Graduate School of Science, The Univ. of Tokyo
2005 Postdoctoral Fellow, Harvard Stem Cell Institute, Harvard Univ.
2008 Lecturer, iCeMS, Kyoto Univ.
2009 Associate Professor, iCeMS, Kyoto Univ.
2010 Associate Professor, CiRA, Kyoto Univ.
2014 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) pii : eaaj2300

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

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

Summary

A number of chronic diseases afflict the kidney, pancreas, and liver. By developing an efficient differentiation method of iPS cells, 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 to differentiate iPS cells into both nephron progenitor cells and ureteric bud cells. By combining these two cell types, we succeeded in reconstructing a kidney tissue uniting glomeruli, tubules, and collecting duct. We also identified a low-molecular compound that promotes the proliferation of nephron progenitor cells and used it to develop a method for in vitro expansion culture.

Pancreas regeneration

We identified a low-molecular compound for the proliferation of human iPS cell-derived pancreatic progenitor cells in vitro, which we differentiated into pancreatic islet-like tissue (see Figure). We also identified the downstream pathway.

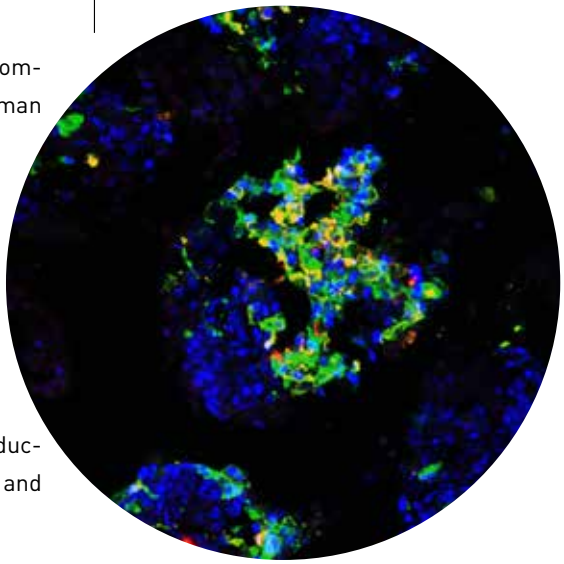
Liver regeneration

We induced erythropoietin-producing cells from human iPS cells and used these cells to identify a factor that promotes the production and secretion of erythropoietin.

Members

- Taro Toyoda (Junior Associate Professor)
- Shin-Ichi Mae (Assistant Professor)
- Toshikazu Araoka (Specially-Appointed Assistant Professor)
- Ayako Date
- Azusa Hayano
- Ryuichiro Hirayama
- Maiko Igami
- Chihiro Inui
- Ryo Ito
- Ryotaro Kabai
- Yoshikazu Kameda
- Naoko Katagiri
- Unyanee Kato
- Azuma Kimura
- Yasuyo Kitai
- Shuhei Konagaya
- Maki Kotaka
- Yang Liu
- Kyoko Matsuse
- Atsushi Mima
- Takahito Minami
- Hiroshi Mizuguchi
- Erika Moriguchi
- Aya Nozaki
- Miyuki Ochiai
- Ryu Okada
- Kazuki Okuda
- Tatsuya Okumura
- Takeya Otsuki
- Makoto Ryosaka
- Ramin Banan Sadeghian
- Satoko Sakamoto
- Midori Sakiyama
- Yoshiaki Sato
- Tatsuya Shimizu
- Fumihiko Shiota
- Tomomi Sudo
- Ryotaro Tabata
- Kosuke Toyohara
- Hiraku Tsujimoto
- Yoshiko Uesugi
- Akira Watanabe
- Tomohisa Yamamoto
- Katsutaro Yasuda
- Ryuji Yokokawa
- Masaki Yoshida
- Akifumi Yoshihara

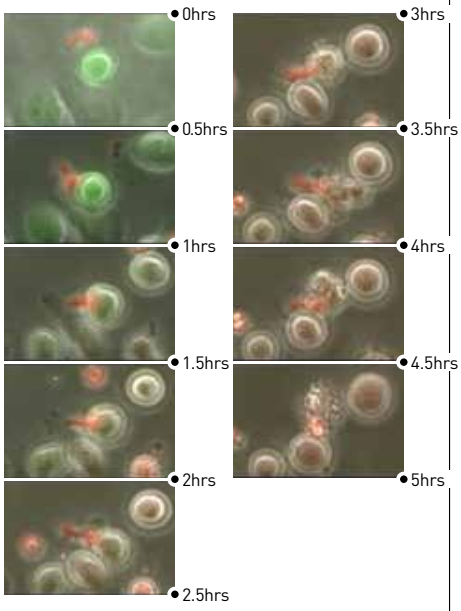
Immunostaining of islet cells differentiated from human iPS cells. Green: C-peptide, Red: Glucagon



Clinical application of rejuvenated T cells

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

Rejuvenated T lymphocytes attack and destroy cancer cells



Red cells: rejuvenated T lymphocytes
Green cells: cancer cells

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

We are using immune cells differentiated from iPS cells to regenerate the patient's immune system to combat cancer, infections, and other diseases. In FY 2019, we worked on regenerative research to create cytotoxic T lymphocytes expressing chimeric antigen receptors (CAR) from HLA-homozygous iPS cells. Meanwhile, we are preparing a physician-led clinical trial using CAR-expressing natural killer cells derived from HLA-homozygous iPS cells to treat ovarian tumors.

Elsewhere, we are reducing the antigenicity of cells differentiated from iPS cells through genome editing (joint research with the Hotta laboratory) and on induction methods for helper T cells and other new technologies.

Members

- Maika Akizuki
- Sayaka Chuganji
- Jerome Detuncq
- Anri Fujishiro
- Ken Fukumoto
- Saki Hasegawa
- Yoichi Higuchi
- Izumi Ihara
- Shoichi Iriguchi
- Yoshitaka Ishiguro
- Tomoko Ishii
- Akihiro Ishikawa
- Takeshi Ito
- Yoshihiro Iwamoto
- Young Kul Jung
- Sanae Kamibayashi
- Yohei Kawai
- Hirokazu Koizumi
- Ayako Kumagai
- Yuhi Kumakiri
- Kaede Makino
- Hiroki Maruyama
- Atsutaka Minagawa
- Yuta Mishima
- Yasuyuki Miyake
- Tadayo Miyasaka
- Kengo Nakagoshi
- Kazuki Nakane
- Satomi Nakata
- Munekimi Nanao
- Katsura Noda
- Yusuke Nozaki
- Nakaba Ochiai
- Kohei Ohara
- Sayaka Okamoto
- Junichi Okawara
- Reiko Saikawa
- Keisuke Saso
- Eri Sato
- Sara Shiina
- Hiroaki Suzuki
- Shinichiro Takayanagi
- Masahiro Tanaka
- Yoshie Tanikawa
- Tatsuki Ueda
- Bo Wang
- Masazumi Waseda
- Ryo Yakabe
- Nariaki Yanagawa
- Hisashi Yano
- Yutaka Yasui
- Munehiro Yoshida
- Chaoqi Zhang

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

Department of Cell Growth and Differentiation

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

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

Profile

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

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 maturity of cardiomyocytes improves the rate of engraftment in an animal model of myocardial infarction. We also established new observation techniques to observe T tubule formation and other maturation markers of cardiomyocytes transplanted into mouse heart tissue.

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)]

Disease models

We are using gene editing technology to construct a model of hypertrophic cardiomyopathy for drug screening. Meanwhile, for arrhythmic conditions such as long QT syndrome, we have established an analysis system using membrane potential-sensitive dye to measure optical action potentials.

Controlling the maturation

The immaturity of cells derived from iPS cells compromises their application. For example, cardiomyocytes derived from iPS cells are at the same immature stage as those of the fetal myocardium. By analyzing intracellular changes during cardiomyocyte differentiation, we are seeking to clarify the maturation mechanism.

Members

- Kazuhisa Chonabayashi
- Takeshi Ego
- Yuya Fujiwara
- Yuhei Fukushima
- Takeshi Hatani
- Azusa Inagaki
- Julia Junghof
- Manabu Kasamoto
- Yuki Kawamura
- Debora Kehl
- Misato Koakutsu
- Yuta Kogure
- Antonio Lucena-Cacace
- Kenji Miki
- Yuki Morimoto
- Yuki Naka
- Momoko Nakamura
- Rena Nakayama
- Megumi Narita
- Misato Nishikawa
- Chikako Okubo
- Rurika Okuda
- Hiroyuki Okunaga
- Shinichiro Oshima
- Masako Sasaki
- Shuji Shibutani
- Kaoru Shimizu
- Kazuma Suda
- Naoyuki Tahara
- Tadashi Takaki
- Kanae Tani
- Yu Tian
- Koki Tomita
- Yoko Uematsu
- Masayuki Umeda

Gene regulation technology with high spatiotemporal resolution and its application to iPS cell research

Kazuo Takayama Ph.D., Junior Associate Professor

Research Progress

Generation and clinical application of human iPS cell-derived liver and intestinal epithelial cells

There are strong expectations for iPS cell application to drug discovery. Because many drugs are administered in oral or injection form and are absorbed and metabolized in the intestine and liver, part of the drug discovery process evaluates drug pharmacokinetics and toxicity in these organs. In my research at Osaka University, I developed a technology for generating intestinal epithelial cells and liver cells from human iPS cells and utilized it for pharmacokinetics and drug toxicity experiments. High-functioning intestinal epithelial cells(1) and liver cells(2) from human iPS cells were generated from gene induction technology, gene modification technology, and extracellular matrices.

Because the generated cells provide a faithful model of the human intestine and liver in vivo, they promise to be useful in not only drug discovery, but also research to elucidate the mechanisms of human development and disease onset. I will be working, mainly with these cells to clarify the onset mechanism of inflammation and cancer. By faithfully reproducting spatiotemporally genetic abnormalities, I aim to investigate the impact on homeostatic maintenance in the intestine and liver. I am new to CiRA, having joined March 1, 2020, but am working hard every day to set my research on track as quickly as possible.

Profile

2015 Ph.D., Graduate School of Pharmaceutical Sciences, Osaka Univ. / Specially Appointed Assistant Professor, Graduate School of Pharmaceutical Sciences, Osaka Univ.
2018 Assistant Professor, Graduate School of Pharmaceutical Sciences, Osaka Univ.
2020 Junior Associate Professor, CiRA, Kyoto Univ.

Publication Highlights

(1) Generation of human iPSC-derived intestinal epithelial cell monolayers by CDX2 transduction
Takayama K *et al.*
Cell Mol Gastroenterol Hepatol (2019) 8 (3): 513-526

(2) Prediction of interindividual differences in hepatic functions and drug sensitivity by using human iPS-derived hepatocytes
Takayama K. *et al.*
Proc Natl Acad Sci U S A (2014) 111 (47): 16772-16777

Department of Clinical Application

"Building a Brain" 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) MicroRNA-based separation of cortico-fugal projection neuron-like cells derived from embryonic stem cells
Sunohara T *et al.*
Front Neurosci (2019)
doi: 10.3389 / fnins. 2019. 01141

(2) Self-organized synchronous calcium transients in a cultured human neural network derived from cerebral organoids
Sakaguchi H *et al.*
Stem Cell Rep (2019)
13 (3): 458-473

(3) Therapeutic effects of combined cell transplantation and locomotor training in rats with brain injury
Shimogawa T *et al.*
NPJ Regen Med (2019) 4: 13

Summary

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

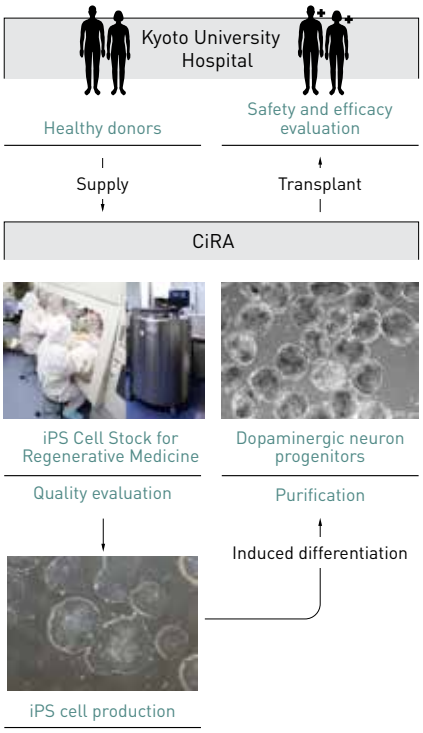
Research Progress

Physician-initiated clinical trials

FY 2018 saw the launch of a physician-initiated clinical trial of a cell transplant therapy for Parkinson's disease (see Figure). The primary evaluation items are safety-related, and the secondary evaluation items are efficacy-related.

In FY 2019, transplantations were conducted in three additional patients. The treatment is progressing well, and none of the patients are experiencing problematic adverse events.

Physician-initiated clinical trials



Generating cerebral organoids

As our next disease target, we are considering motor paralysis caused by cerebrovascular damage. In FY 2019, we reported the induction of human cerebral organoids [2]. We observed an early-stage cerebral cortex that mimics development, and the formation of neural networks and synchronous neuronal activity. It is expected that these findings will be applicable not only to regenerative medicine but also to developmental research and drug discovery.

Members

- Asuka Morizane (Junior Assistant Professor)
- Daisuke Doi (Assistant Professor)
- Tetsuhiro Kikuchi (Assistant Professor)
- Hiromasa Adachi
- Tomoka Ashida
- Seiya Baba
- Tone Enshu
- Yudai Fujita
- Kaori Fukushima
- Luc Brice Grinand
- Natsuko Hada
- Satoe Hiramatsu
- Megumi Ikeda
- Yuko Ishii
- Yuki Katano
- Takahiro Kitahara
- Tetsuya Kiyosumi
- Kei Kubota
- Hiroaki Magotani
- Aya Mihara
- Yuki Ozaki
- Fabian Raudzus
- Hideya Sakaguchi
- Bumpei Samata
- Rena Shiga
- Yusuke Sugao
- Hideaki Takahashi
- Rika Takaichi
- Ryosuke Tsuchimochi
- Emi Yamasaki
- Hokuto Yamashita
- Kenji Yoshida

Cherish the delusion and realize clinical innovation

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

Summary

Platelets 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.

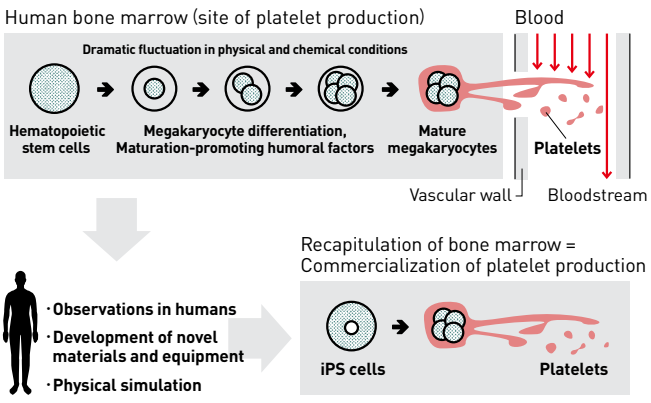
Research Progress

HLA-deleted universal iPS platelets

To ease the supply of donated blood, we are progressing with the clinical application of platelets generated from human iPS cells. One issue is the matching of human leukocyte antigen (HLA) class I. We tackled this issue by applying genome editing technology to iPS cells to engineer megakaryocytes with HLA class I deleted, thus creating "universal" HLA-deleted iPS platelets that can be used in transfusion irrespective of HLA class I type. However, NK cells attack cells with reduced HLA class I expression. Thus, we established a mouse model and confirmed that HLA class I-deleted platelets can circulate in the body without being rejected by the immune system.

This finding establishes platelets' unique immunogenic property of invisibility to NK cells and that HLA-deleted iPS platelets are a universal product useful against platelet transfusion refractoriness, laying the foundation for the commercial production of iPS platelets.

Research for commercialization of iPS cell-derived platelet production



Members

・Naoshi Sugimoto (Junior Associate Professor)
・Sou Nakamura (Assistant Professor)
・Qihao Chen
・Si Jing Chen
・Shima Date
・Masaki Endo
・Charlotte Flahou
・Kousuke Fujio
・Yasuo Harada
・Yamato Haraguchi
・Kanae Hashimoto
・Kazuya Hashimoto
・Natsumi Higashi
・Setsuko Inoue
・Yukitaka Ito
・Maki Kawato
・Takaaki Kayama
・Maya Kimura
・Yuki Kurahashi
・Toshie Kusunoki
・Takuya Matsumoto
・Miyuki Morizumi
・Itsuro Motegi
・Jyun Mukai
・Machi Nishikoji
・Kimiko Nonomura
・Akiko Shigemasa
・Asahi Shimada
・Shin Shimizu
・Ieva Stirblyte
・Hidehiko Sugino
・Ryohei Takada
・Do Thi Than Tam
・Yasuhiko Tosa
・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) iPSC-derived platelets depleted of HLA class-I are inert to anti-HLA class-I and NK cell immunity
Suzuki D *et al.*
Stem Cell Reports (2020)
14(1): 49-59

(2) Turbulence Activates Platelet Biogenesis to Enable Clinical Scale Ex Vivo Production
Ito Y *et al.*
Cell (2018)
174 (3): 636-648

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

Department of Clinical Application

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 consists of growth cartilage and articular cartilage, which are responsible for bone growth and joint movement, respectively. Damage to growth cartilage leads to skeletal dysplasia characterized by skeletal deformities and short stature, while defects in articular cartilage cause mobility impairment and pain associated with movement. To find a radical cure for these conditions, we are researching the molecular mechanism that regulates chondrocyte differentiation.

Research Progress

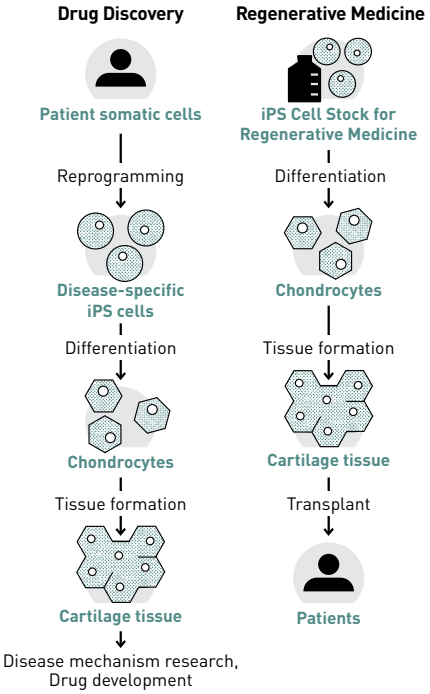
Chondrocyte differentiation

We established that chondrocyte differentiation is regulated by the enzyme SIK3. SIK3 is also involved in chondrocyte maturation and in the progression of osteoarthritis. Therefore, we believe that understanding this mechanism will be useful in achieving cartilage regeneration and analysing cartilage disease pathologies.

Regenerative therapies

Articular cartilage covers the surface of the bone to ensure smooth joint movement. Having poor self-repair ability, it fails to recover when damaged, leading to osteoarthritis or related conditions. Our aim is to realize regenerative medicine by transplanting iPS cell-derived cartilage to replace damaged articular cartilage. In FY2019, we continued with non-clinical studies to verify the safety and efficacy of our iPS cell-derived cartilage and received approval to begin transplantations in patients.

Cartilage disease research with iPS cells



Members

- Akihiro Yamashita (Assistant Professor)
- Kengo Abe
- Kaori Fujita
- Hiroki Hagizawa
- Fumiko Hamada
- Nanao Horike
- Yuki Iimori
- Takashi Kamatani
- Tomoko Kato
- Natsumi Kawasaki
- Kanako Konishi
- Azuma Kosai
- Maasa Koshimoto
- Saeko Koyamatsu
- Yuki Makita
- Makiko Matsuoka
- Miho Morioka
- Yuri Murata
- Hiroko Nakagawa
- Yuya Nishijima
- Hiromi Nishino
- Aoi Okamoto
- Yuuki Okutani
- Chie Ota
- Tomonori Ozaki
- Miyuki Sakamoto
- Masumi Sanada
- Nobuyuki Shima
- Yoshiaki Takei
- Hiromi Takemoto
- Kie Watanabe
- Yunpeng Zhang

Studying intractable pediatric diseases with disease-specific iPS cells

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

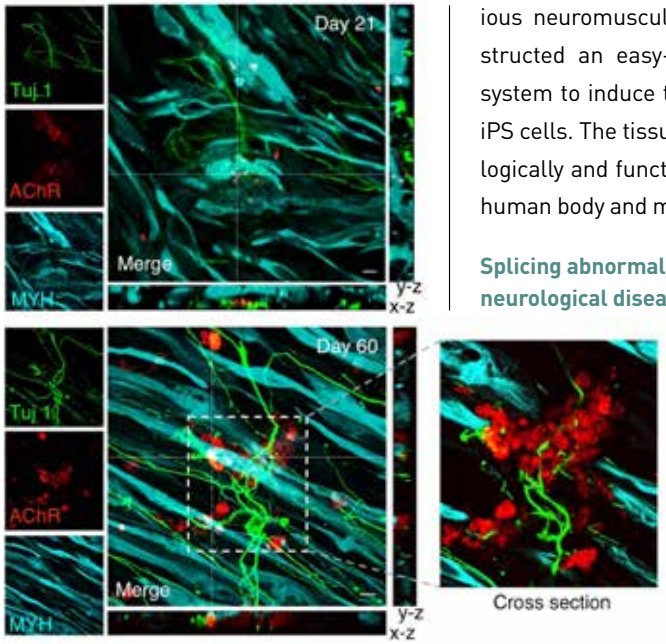


Figure: Neuromuscular junction generated from human pluripotent stem cells.

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

Modeling the neuromuscular junction

The neuromuscular junction (NMJ) provides an electrical connection between motor nerve endings and muscles. Abnormalities in its cells cause various neuromuscular diseases. We constructed an easy-to-use differentiation system to induce the NMJ from human iPS cells. The tissue resembled morphologically and functionally the NMJ in the human body and matured in culture.

Splicing abnormalities in immune and neurological diseases

We used iPS cells to model how ATR gene mutations cause nerve-specific splicing abnormalities in Seckel syndrome, a form of hereditary microcephaly. We also recapitulated primary immunodeficiency syndrome, confirming splicing abnormalities in the NEMO gene.

Differentiating blood cells from human iPS cells

We enhanced our blood cell differentiation system to induce the differentiation of functional natural killer cells and vascular endothelial cells.

Members

- Akira Niwa (Assistant Professor)
- Yoko Arai (Nishinaka)
- Ryoma Edo
- Akihiro Ikenaka
- Naoya Kase
- Yuri Kawasaki
- Yoko Kitagawa
- Chiaki Kubota
- Siqiaozhi Li
- Chuang-Yu Lin
- Takafumi Mano
- Shiori Matsuo
- Shoko Matsuo
- Asuka Morii
- Saori Nakano
- Chizu Nishida
- Sayaka Nishimura
- Monika Ohno
- Mitsujiro Osawa (Specially-Appointed Assistant Professor)
- Ryo Ota
- Yuta Otani
- Ryosuke Sugimoto
- 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) iPSC-derived functional human neuromuscular junctions model the pathophysiology of neuromuscular diseases
Lin CY *et al.*
JCI Insight (2019) 4 (18)

(2) Verification and rectification of cell type-specific splicing of a Seckel syndrome-associated ATR mutation using iPS cell model
Ichisima J *et al.*
J Hum Genet (2019)
64 (5): 445-458

(3) Rescue of recurrent deep intronic mutation underlying cell type-dependent quantitative NEMO deficiency
Boisson B *et al.*
J Clin Invest (2018)
129 (2): 583-597

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 iPS cells. For instance, we recapitulated the pathological conditions of fibrodysplasia ossificans progressiva (FOP) from patient-derived iPS cells and reported a drug screening system that revealed one drug candidate.

Research Progress

Ligament tissue regeneration using ligament cells

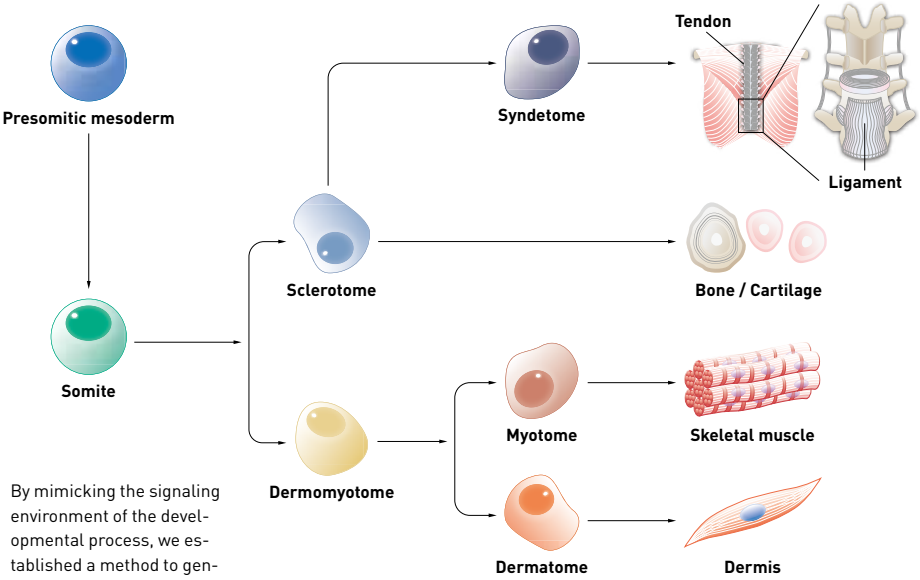
We established a method to induce dermal cells and ligament cells, previously considered difficult, via somites. Since ligament tissue cannot heal naturally in vivo once damaged, we are now investigating whether these induced ligament cells are applicable for regenerative medicine purposes.

Elsewhere, we are modeling the pathology of diseases caused by neural crest cell abnormalities and developing methods to induce mesenchymal cells via lateral plate mesoderm, applying our findings to regenerative medicine and drug discovery.

Members

- Yayoi Toyooka (Assistant Professor)
- Teppei Akaboshi
- Ziadoon Hameed Abed Al Akashi
- Nicholas James Boyd-Gibbins
- Yoshiko Inada
- Daisuke Kamiya (Specially-Appointed Assistant Professor)
- Wako Matsuura
- Chiaki Mihara
- Sadaki Mitsuzawa
- Yukiko Nakagawa
- Taiki Nakajima
- Nakako Shimazu
- Mai Tanaka
- Mei Terashima
- Keiko Yoshizawa
- Chengzhu Zhao

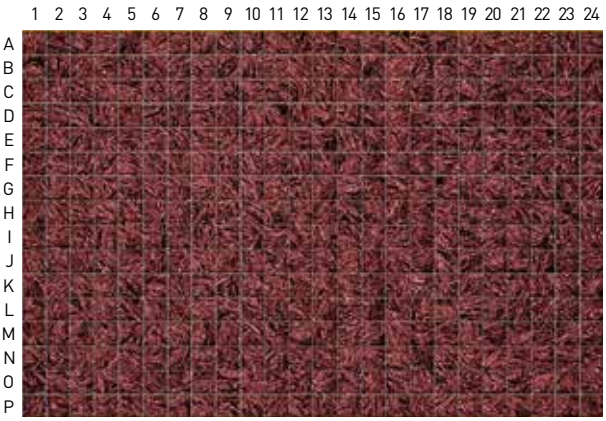
Stepwise induction of somite-lineage cells



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

Summary

We are studying the pathogenesis of and new therapies for intractable muscular diseases. The research involves two strategies: producing disease models and drug screenings using patient iPS cells, and regenerative medicine by transplanting iPS cell-derived skeletal muscle stem cells.

Research Progress

iPS cell-based drug screening research

In FY2019, through drug screening for dysferlinopathy patient iPS cell products, we identified a compound with therapeutic effects (1). iPS cell-derived muscle cells treated with nocodazole were found to recover the depleted membrane repair function.

Mesenchymal stromal cell transplantation for muscular dystrophy

In connection with Ullrich congenital muscular dystrophy, which occurs due to defective type VI collagen, we used human iPS cell-derived mesenchymal stromal cells developed by the Ikeya laboratory to pursue cell transplant research. When the mesenchymal stromal cells were directly injected into the muscles of a mouse model, we found that the expression of type VI collagen recovered, and the regeneration and maturation of muscle fibers were activated. Going forward, we intend to test the efficacy of systemic administration with a view to establishing a therapy.

Members

- Meni Arai
- Eri Arimoto
- Kei Fujiwara
- Mikiko Fukuda
- Megumi Goto
- Aya Harada
- Junjie He
- Yuma Hirano
- Mitsuru Honda
- Sayaka Ido
- Rukia Ikeda
- Fumika Inazuka
- Kana Ishii
- Tatsuya Jonouchi
- Machiko Kaneshiro
- Atsuya Kato
- Hiroki Kato
- Ryu Kawada
- Tomoki Kinoshita
- Yuko Kokubu
- Mayuho Miki
- Yasutomo Miura
- Yukiko Nakagawa
- Minas Nalbandian
- Airi Ota
- Jun Otomo
- Tomoka Sabuta
- Chinami Saka
- Masae Sato
- Yusaku Sato
- Toru Takaori
- Nana Takenaka
- Midori Tanaka
- Tomoya Uchimura
- Rika Yamanaka
- Akihiro Yasuhara
- Clémence Kiho Yoshioka
- Mingming Zhao

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) Phenotypic drug screening for dysferlinopathy using patient-derived induced pluripotent stem cells
Kokubu Y *et al.*
Stem Cells Transl Med (2019) (10): 1017-1029

(2) 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

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

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.
2019 Joint Academic Investigator, Bioethics and Safety Response Officr, Life Sciences Division, Ministry of Education, Culture, Sports, Science and Technology, Japan

Publication Highlights

(1) Targeted disruption of HLA genes via CRISPR-Cas9 generates iPSCs with enhanced immune compatibility
Xu H, Wang B *et al.*
Cell Stem Cell (2019)
24 (4): 566-578

(2) CRISPR-Cas3 induces broad and unidirectional genome editing in human cells
Morisaka H *et al.*
Nature Communications (2019)
10, 5302

(3) 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: 310

Summary

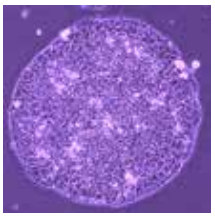
Orphan diseases are rare conditions with no effective treatment available. More than half of these diseases are said to involve genetic abnormalities. Our goal is to develop genome editing technology as a therapy for orphan diseases.

Research Progress

Preventing immune rejection by deleting HLA expression in iPS cells

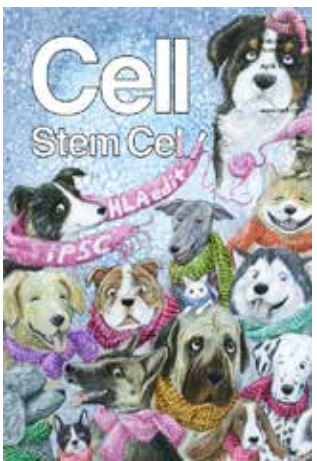
Cell transplant therapy using iPS cells has already reached the clinical trial stage in a number of diseases, but a mismatch of human leukocyte antigens (HLAs) between the transplanted cells and the patient is known to cause immune rejection. CiRA is establishing a HLA-homozygous cell stock by generating iPS cells from HLA-homozygous donors. A stock with 10 different cell lines will be able to cover almost half of the Japanese population, but to reach 90% or higher coverage will require 140 different cell lines. Meanwhile, there have been reports of disrupting genes required for cell surface presentation of HLAs. This would make it possible to avoid rejection by T cells, but would also disable the HLA-based suppression of natural killer cells, in addition to a loss of antigen presentation ability with HLAs.

In response, we developed genome editing technology using CRISPR-Cas9 to specifically disrupt HLA-A and HLA-B, but retaining HLA-C. Using this method, it was possible to prevent activation of CD8-positive T cells, CD4-positive T cells, and natural killer cells. If a stock of 12 different lines of such iPS cells can be established, it could possibly cover not only more than 95% of the Japanese population, but all main ethnic types, boosting rates of coverage worldwide. We believe that our research findings can benefit not only regenerative medicine using iPS cells, but also many other cell- and gene-based treatments.



An iPS cell in which CRISPR-Cas 9 genome editing technology has been used to delete HLA to reduce the risk of immune rejection

Our HLA study made the cover of Cell Stem Cell (Illustration: Misaki Ouchida)



Members

- Naoko Ishihara (Fujimoto)
- Kumiko Iwabuchi
- Akihiro Kagita
- Yuto Kita
- Mandy Lung
- Yukiko Nakagawa
- Youichi Naoe
- Natsumi Okawa
- Yuya Okuzaki
- Miyuki Ono
- Noriko Sasakawa
- Nakako Shimazu
- Kei Watanabe
- Huaigeng Xu

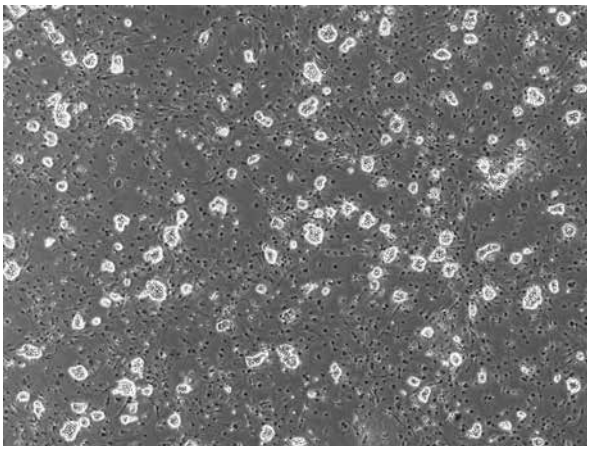
Contributing to transplantation medicine through development of an iPS cell stock

Naoko Takasu M.S., Professor

Summary

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 a wide variability in cell characteristics such as pluripotency. This issue is one of the main obstacles to the practical realization of iPS cell-based regenerative medicine. We are responding by preparing a stable supply of iPS cells of high and consistent quality.



Naïve-type human iPS cells generated from human dermal fibroblasts form small dome-shaped colonies

Research Progress

An iPS cell stock of high uniform quality

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 a wide variability in cell characteristics.

In human development, the egg, once fertilized, acquires totipotency, with an important part of this process played by proteins present in large numbers in the egg. The genes encoding these proteins are useful for more efficient iPS cell reprogramming. Thus, we are using linker histone H1F00 to generate iPS cells. Currently, we are testing whether these iPS cells are suitable for next-generation regenerative medicine.

Generating naive-type human iPS cells from somatic cells

In recent years, it has been proposed that pluripotent stem cells can be subdivided into naive and primed. The human iPS cells currently used widely for research and clinical applications are primed. However, naïve iPS cells are thought to have the ability to differentiate into a wider range of cells. Numerous methods can generate naive iPS cells by resetting primed iPS cells, but to obtain a stable supply for clinical purposes, direct generation from human dermal fibroblasts or peripheral blood mononuclear cells appears necessary. We are investigating such methods.

Members

- Ryoko Hirohata
- Akira Kunitomi (Specially-Appointed Assistant Professor)

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.

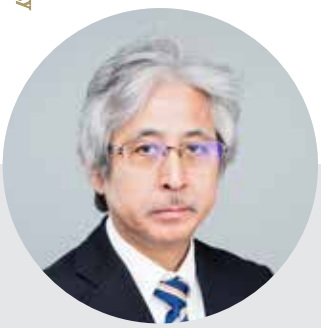
Publication Highlight

(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) Points of consideration for pluripotent stem cell culture
Working Group for Consideration of Good Cell Culture Practice
Tiss Cult Res Commun (2019) 38 (3): 135-143

(2) 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

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

Summary

To promote the medical application of human iPS cells, we develop teaching materials for the establishment and maintenance of iPS cell lines and for Good Cell Culture Practice (GCCP), which is a set of basic principles for quality of cell culture technology.

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

Research Progress

Promoting iPS cell technology

In FY 2019, we restructured video materials of experimental techniques for the establishment of iPS cell lines from blood cells, passage and frozen storage under feeder-free conditions as English version which were previously uploaded on CiRA website as Japanese version. The videos were supplied to our International Public Communications Office to promote the technologies for the researchers out of Japan. As last year, we published a review article, entitled Important Points for Pluripotent Stem Cell Culture. The article presents important 7 points which should be shared on the associated knowledge, principles and procedures for pluripotent stem cell culture[1]. We had coordinated the important points as a member of the Working Group for GCCP, which organized on the Research Project for Practical Applications of Regenerative Medicine operated by the Japan Agency for Medical Research and Development (AMED) from fiscal years 2017 to 2018.

To keep the technical level of CiRA staff for cell culture, we also twice held lecture courses on fundamental cell culture technology for the approximately 70 new staff. The courses were lectured on GCCP guidelines including the other practices published in fiscal years 2017 and 2018.

Lastly, we undertook ethical review of more than 35 research plans as the chair of the CiRA Ethical Review Board.

Item headings of the Important Points for Pluripotent Stem Cell Culture[1]

1. **Laws and ordinances, guidelines, consent statements and material transfer agreements to be checked before use of materials**
2. **Diversity of pluripotent stem cells**
3. **Culture equipment and materials**
4. **Thawing procedures**
5. **Medium replacement and passaging procedures**
6. **Freezing procedures**
7. **Culture monitoring**

English-language video teaching materials on human iPS cell technology

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.

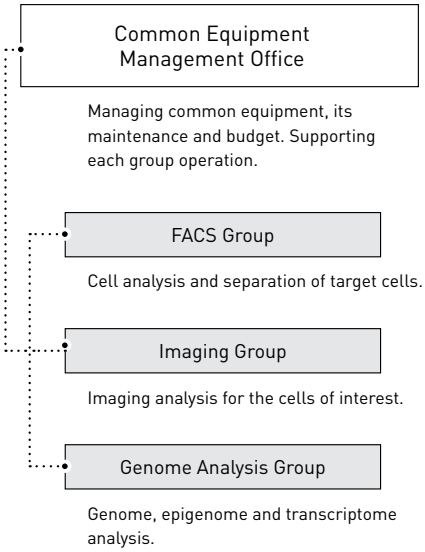
Research Progress

Operation of the Common Equipment Management Office

Common Equipment Management Office was reorganized in April 2017 and now supports CiRA researchers through three-groups (see Figure). The FACS Group possesses a number of flow cytometers adapted for multi-colored analysis of cell properties. The Imaging Group is equipped with confocal microscopes and the latest multiphoton microscopes for the live imaging of cells and tissues. The Genome Analysis Group possesses high-throughput sequencers for the full range of genome, epigenome and transcriptome analysis. We additionally possess a large number of real-time PCR machines, capillary sequencers and other devices, which require systematically planned management and maintenance. With the collaboration of the Information Security Office, in fiscal year 2019, we completed networking and data storage systems for all common equipment. We now are completing the digitization of equipment utilization records.

As office director, I support the progress of CiRA's research by setting appropriate annual budgets for the maintenance and updating of all common equipment, presenting an equitable charging system for researchers, and ensuring appropriate and effective operations.

Organization of CiRA Common Equipment Management Office



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.
2017 Part-time Lecturer, School of Medcine, Saga 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.

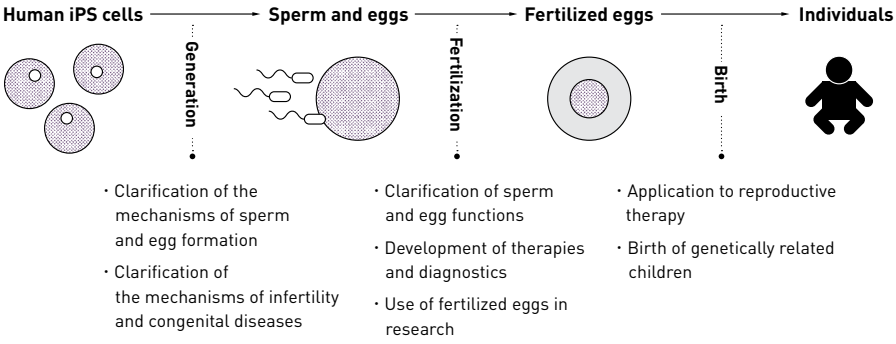
Publication Highlights

(1) The ethics of cerebral organoid research: being conscious of consciousness
Sawai T *et al.*
Stem Cell Reports (2019) 13 (3): 440-447

(2) A rebuttal of Akabayashi and colleagues' criticisms of the iPSC stock project
Fujita M *et al.*
JME (2019) 45 (7): 476-477

(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 in advance. To respond to this need, we carry out fact-finding surveys and opinion surveys. Findings from these surveys are useful when discussing the formulation of regulations.

Research Progress

Regenerative medicine

Despite the enactment of legislation on regenerative medicine, there is concern over the promotion of cell-based therapies whose safety and efficacy have not been established. We analyzed Japanese government to grasp the current situation of regenerative medicine in private clinics.

Artificial germ cells/ genome editing

It is theoretically possible to create germ cells from human iPS cells. Our survey found that the proportion of Japanese who accept the use of these cells in infertility treatment is lower than overseas. Legislation to regulate genome editing of the human embryo is currently under discussion by the Japanese government. We conducted a related survey on the associated degrees of acceptance, expectation, and concern for this research.

Policy proposals: human-animal embryos/ cerebral organoids

We published a paper that emphasized the importance of public discussions around chimeric animal-human brains. Additionally, we outlined ethical issues arising from cerebral organoids and argued that prohibition of this research would be premature at present.

Members

・Taichi Hatta (Assistant Professor)
・Tsutomu Sawai (Assistant Professor)
・Kyoko Akatsuka
・Kinuko Kasama
・Mika Suzuki
・Miki Tanigawa

Enhancing public trust in cutting-edge life science research

Jusaku Minari Ph.D., Associate Professor

Summary

Research into iPS cells relies on public trust. Working with specialists 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

Investigating the connections between life science research and society

Research into iPS cells raises the issues of how to ensure public trust. We are currently promoting research regarding public enagagement as part of the ISLE (Innovation for Science, Life and Ethics) project supported by the Japan Science and Technology Agency.

Two initiatives under the ISLE project

Under ISLE, we are following two lines of research. First, the optimal regulatory framework for life science research. I have delivered our research findings to the process revising governmental ethical guideline since FY2018. The other line of research concerns how to communicate with the public. Specifically, we are designing questionnaires and workshops to identify public perceptions and attitudes.

Initiatives on the regulation of iPS cell research

From FY2019, we have been exploring approaches to regulating the clinical application of iPS cell research. In concrete terms, we are seeking academic insights to contribute to the future amendment and implementation of regulations and frameworks for advanced medical treatment and patient-requested treatment. Specifically, by focusing attention on the boundaries between research and medical treatment and by questioning conceptions on each side, we hope to suggest better approaches to regulation regarding clinical application.

Members

・Kinuko Kasama
・Miki Tanigawa
・Kayo Takashima

A workshop organized as part of an art festival
(May 5, 2019, Karato Hall, Teshima, Kagawa 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) Dynamic consent: an evaluation and reporting framework
Prictor M *et al.*
J. Emp. Res. Hum. Res. Ethics (2020)15:175-186

(2) Meaning of ambiguity: a japanese survey on synthetic biology and genome editing
Hibino A *et al.*
Front. Sociol. (2019) 4: 81

(3) Letter in reply to: 'therapeutic misconception and the role of the Research Ethics Committee'
Takashima K *et al.*
Future Medicine (2019) 14: 719-720

Honors and Awards (2019.4-2020.3)

Research Promotion Awards, Honorary Doctorates, etc.

Month	Name of the Award	Awardee	Lab
2019.4	Commendation for Science and Technology by the Minister of Education, Culture, Sports, Science and Technology 	Junya Toguchida, Makoto Ikeya	Toguchida Lab. Ikeya Lab.
2019.5	The Japanese Orthopaedic Association Academic Achievement Award	Junya Toguchida	Toguchida Lab.
2020.2	The 3rd Future Foundation Award	Kazutoshi Takahashi	Yamanaka Lab.
2020.2	Shimazu Encouragement Award 	Hirohide Saito	Saito H Lab.
2020.3	The Japanese Society for Regenerative Medicine Johnson & Johnson Innovation Award	Koji Eto	Eto Lab.

Young Investigator Awards, Poster Awards, etc.

Month	Name of the Award	Awardee	Lab
2019.6	ISSCR Travel Award for 2019 ISSCR Annual Meeting in Los Angeles	Janin Grajcarek, Azuma Kimura, Taro Toyoda, Akira Ota, Kenji Osafune	Woltjen Lab. , Osafune Lab.
2019.6	ISSCR Abstract Merit Award for 2019 ISSCR Annual Meeting in Los Angeles	Taiki Nakajima, Azuma Kimura, Taro Toyoda, Akira Ota, Kenji Osafune	Ikeya Lab. , Osafune Lab.
2019.6	Japan Society of Hematology Travel Award	Kazuya Hashimoto	Eto Lab.
2019.6	The 92nd Annual Meeting of Japanese Tissue Culture Association Encouragement Award	Kyosuke Hino	Ikeya Lab.
2019.6	The 62nd Annual Meeting of the Japanese Society of Nephrology Best English Presentation Award	Hiraku Tsujimoto, Tomoko Kasahara, Shinichi Sueta, Makoto Ryosaka, Shinichi Mae, Toshikazu Araoka, Kenji Osafune	Osafune Lab.
2019.7	Bayer Yakuhin, Ltd x Sysmex -Pitch Your Dreams in KOBE2019 Highest Award	Kaoru Richard Komatsu	Saito H Lab.
2019.7	The 21st Annual Meeting of the RNA Society of Japan Best Presentation Highest Award	Kaoru Richard Komatsu	Saito H Lab.
2019.8	Japan Muscle Society Young Investigator Award	Kei Fujiwara	Sakurai Lab.

Month	Name of the Award	Awardee	Lab
2019.9	"Ishigane Ebihara Foundation Neuroscience Awards" for Parkinson's Disease Academic Research Award	Daisuke Doi	Takahashi Lab.
2019.9	RNA Frontier Meeting 2019 Best Presentation Award	Shunsuke Sumi	Saito H Lab.
2019.9	ISSCR/ KSSCR Poster Award	Suji Lee	Woltjen Lab.
2019.10	The 7th Skeletal Muscle Cells Study Gourp by Young Researchers Best Poster Award	Minas Nalbandian	Sakurai Lab.
2019.10	The Japanese Society of Hematology Encouragement Award	Sou Nakamura	Eto Lab.
2019.11	2019 ASN Kidney STARS Award	Hiraku Tsujimoto, Toshikazu Araoka, Makoto Ryosaka, Shinichi Mae, Kenji Osafune	Osafune Lab.
2019.12	The 36th Inoue Research Award for Young Scientists	Xu Huaigeng, Atsutaka Minagawa	Hotta Lab., Kaneko Lab.
2020.2	Japan Research Association for Immunotherapeutics (Egawa Prize) Young Scientist Award	Shoichi Iriguchi	Kaneko Lab.
2020.3	The 19th The Japanese Society for Regenerative Medicine (Basic research area)Encouragement Award	Wang Bo	Kaneko Lab.

Internal Award

Month	Name of the Award	Awardee	Lab
2019.9	Kyoto University Academic Day Prize	Hirohide Saito, Hirohisa Ohno, Shunsuke Kawasaki, Hiroki Ono, Shigetoshi Kameda	Saito H Lab.
2019.11	CiRA 2019 International Symposium Best Poster Presentation Award	Janin Grajcarek, Xu Huaigeng, Yuta Mishima	Woltjen Lab., Hotta Lab., Kaneko Lab.
2020.1	7th CiRA Prize 	Takuya Yamamoto, Knut Woltjen	Yamamoto Lab., Woltjen Lab.
2020.1	2nd CiRA Encouragement Award 	Tsutomu Sawai, Shunsuke Kawai	Uehiro Research Division for iPS Cell Ethics., Toguchida Lab.

Publications (2019.4-2020.3)

2019

April

01 – Inoue H, Nakamura Y
Medical Applications of iPS Cells -Innovation in Medical Sciences
Innovation in Medical Sciences
X, 190

02 – Morimoto H, Kanatsu-Shinohara M, Ogonuki N, Kamimura S, Ogura A, Yabe-Nishimura C, Mori Y, Morimoto T, Watanabe S, Otsu K, Yamamoto T and Shinohara T
ROS amplification drives mouse spermatogonial stem cell self-renewal
Life Science Alliance
2: e201900374

03 – Matsubara H, Niwa A, Nakahata T, Saito MK
Induction of human pluripotent stem cell-derived natural killer cells for immunotherapy under chemically defined conditions
Biochemical and Biophysical *Research Communications*
515 (1): 1-8

04 – 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

05 – Sawai T, Hatta T, Fujita M
Japan significantly relaxes its human-animal chimeric embryo research regulations
Cell Stem Cell
24 (4): 513-514

06 – Kou YT, Liu HT, Hou CY, Lin CY, Tsai CM, Chang H
A transient protective effect of low-level laser irradiation against disuse-induced atrophy of rats
Lasers in Medical Science
34 (9): 1829-1839

07 – Sekine S, Kaneko M, Tanaka M, Ninomiya Y, Kurita H, Inden M, Yamada M, Hayashi Y, Inuzuka T, Mitsui J, Ishiura H, Iwata A, Fujigasaki H, Tamaki H, Tamaki R, Kito S, Taguchi Y, Tanaka K, Atsuta N, Sobue G, Kondo T, Inoue H, Tsuji S, Hozumi I
Functional evaluation of PDGFB-variants in idiopathic basal ganglia calcification, using patient-derived iPS cells
Scientific Reports
9: 5698

08 – Sugimoto N, Eto K
αIIbβ3 changes gears in MKs and platelets
Blood
33 (16): 1700-1701

09 – Otomo N, Takeda K, Kawai S, Kou I, Guo L, Osawa M, Alev C, Kawakami N, Miyake N, Matsumoto N, Yasuhiko Y, Kotani T, Suzuki T, Uno K, Sudo H, Inami S, Taneichi H, Shigematsu H, Watanabe K, Yonezawa I, Sugawara R, Taniguchi Y, Minami S, Kaneko K, Nakamura M, Matsumoto M, Toguchida J, Watanabe K, Ikegawa S
Bi-allelic loss of function variants of TBX6 causes a spectrum of malformation of spine and rib including congenital scoliosis and spondylocostal dysostosis
Journal of Medical Genetics
56 (9): 622-628

10 – Nakajima T, Sakurai H, Ikeya M
In vitro generation of somite derivatives from human induced pluripotent stem cells
Journal of Visualized Experiments
146: e59359

11 – Iwasaki M, Tabata T, Kawahara Y, Ishihama Y, Nakagawa M
Removal of interference MS/MS spectra for accurate quantification in isobaric tag-based proteomics
Journal of proteome research
18 (6): 2535-2544

May

12 – Hishiyama Y, Minari J, Suganuma N
The survey of public perception and general knowledge of genomic research and medicine in Japan conducted by the Japan Agency for Medical Research and Development
Journal of Human Genetics
64 (5): 397-407

13 – Nakanishi H, Saito H
Endogenous signal-responsive transgene switch systems for visualization and purification of specific cells
Medical Applications of iPS Cells
doi: 10.1007/ 978-981-13-3672-0_6: 99-112

14 – Kunimoto K, Honda-Ozaki F, Saito MK, Furukawa F, Kanazawa N
Beneficial effect of methotrexate on a child case of Nakajo-Nishimura syndrome
The Journal of Dermatology
46 (10): e365-e367

15 – Yasumoto T, Takamura Y, Tsuji M, Watanabe-Nakayama T, Imamura K, Inoue H, Nakamura S, Inoue T, Kimura A, Yano S, Nishijo H, Kiuchi Y, David B. Teplow, and Ono K
High molecular weight amyloid b1-42 oligomers induce neurotoxicity via plasma membrane damage
FASEB Journal
doi: 10.1096/ fj.201900604 R

16 – Yagi M, Kabata M, Ukai T, Tanaka A, Shimada Y, Sugimoto M, Araki K, Okita K, Woltjen K,

2019

Hochedlinger K, Yamamoto T and Yamada Y
De novo DNA methylation at imprinted loci during reprogramming into naïve and primed pluripotency
Stem Cell Reports
12 (5): 1113-1128

17 Kanazawa N, Honda-Ozaki F, Saito MK
Induced pluripotent stem cells representing Nakajo-Nishimura syndrome
Inflammation and Regeneration
39 (11)

18 Yamamoto K, Kitawaki T, Sugimoto N, Fujita H, Kawase Y, Takaori-Kondo A, Kadowaki N
Anti-inflammatory modulation of human myeloid-derived dendritic cell subsets by lenalidomide
Immunology Letters
211: 41-48

June

19 Shimogawa T, Sakaguchi H, Kikuchi T, Tsuchimochi R, Sano N, Torikoshi S, Ito A, Aoyama T, Iihara K, Takahashi J
Therapeutic effects of combined cell transplantation and locomotor training in rats with brain injury
npj Regenerative Medicine
4 (13)

20 Sugimura R
Derivation of hematopoietic stem and progenitor cells from human pluripotent stem cells
Methods in Molecular Biology
2005: 37-41

21 Zhou Y, Zhang Y, Chen B, Dong Y, Zhang Y, Mao B, Pan X, Lai M, Chen Y, Bian G, Zhou Q, Nakahata T, Zhou J, Wu M, Ma F
Overexpression of GATA2 enhances development and maintenance of human embryonic stem cell-derived hematopoietic stem cell-like progenitors
Stem Cell Reports
13 (1): 31-47

22 Kawai S, Yoshitomi H, Sunaga J, Alev C, Nagata S, Nishio M, Hada M, Koyama Y, Uemura M, Sekiguchi K, Maekawa H, Ikeya M, Tamaki S, Jin Y, Harada Y, Fukiage K, Adachi T, Matsuda S, Toguchida J
In vitro bone-like nodules generated from patient-derived iPSCs recapitulate pathological bone phenotypes
Nature Biomedical Engineering
3 (7): 558-570

23 Kimura T, Nishiyama N, Negishi M, Nishiyama A, Takazawa T, Fujisawa T, Nakajima K, Kashimura S, Kunitomi A, Katsumata Y, Nishiyama T, Aizawa Y, Fukuda K, Takatsuki S
The durability of atrial fibrillation ablation using an oesophageal temperature cut-off of 38 degrees C
Heart, Lung and Circulation
28 (7): 1050-1058

24 Ohta R, Sugimura R, Niwa A, Saito MK
Hemogenic endothelium differentiation from human pluripotent stem cells in A feeder- and xeno-free defined condition
Journal of Visualized Experiments
(148)

25 Kashida S, Wang DO, Saito H, Gueroui Z
Nanoparticle-based local translation reveals mRNA as a translation-coupled scaffold with anchoring function
Proceedings of the National Academy of Sciences of the United States of America
116 (27): 13346-13351

26 Katsuno T, Belyantseva IA, Cartagena-Rivera AX, Ohta K, Crump SM, Petralia RS, Ono K, Tona R, Imtiaz A, Rehman A, Kiyonari H, Kaneko M, Wang YX, Abe T, Ikeya M, Fenollar-Ferrer C, Riordan GP, Wilson EA, Fitzgerald TS, Segawa K, Omori K, Ito J, Frolenkov GI, Friedman TB, Kitajiri SI
TRIOBP-5 sculpts stereocilia rootlets and stiffens supporting cells enabling hearing
JCI Insight
4 (12)

27 Shigemura T, Matsuda K, Kurata T, Sakashita K, Okuno Y, Muramatsu H, Yue F, Ebihara Y, Tsuji K, Sasaki K, Nakahata T, Nakazawa Y, Koike K
Essential role of PTPN11 mutation in enhanced haematopoietic differentiation potential of induced pluripotent stem cells of juvenile myelomonocytic leukaemia
British Journal of Haematology
187 (2): 163-173

28 Kokubu Y, Nagino T, Sasa K, Oikawa T, Miyake K, Kume A, Fukuda M, Fuse H, Tozawa R, Sakurai H
Phenotypic drug screening for dysferlinopathy using patient derived-induced pluripotent stem cells
STEM CELLS Translational Medicine
8 (10): 1017-1029

July

29 Masui T, Sato A, Nakano K, Uchida Y, Yogo A, Anazawa T, Nagai K, Kawaguchi Y, Takaori K, Uemoto S
Predictive value of the Ki67 index for lymph node metastasis of small non-functioning pancreatic neuroendocrine neoplasms
Surgery Today
49 (7): 593-600

2019

30 – Radulovic V, van der Garde M, Koide S, Sigurdsson V, Lang S, Kaneko S, Miharada K
Junctional adhesion molecule 2 represents a subset of hematopoietic stem cells with enhanced potential for T lymphopoiesis
Cell Reports
27 (10): 2826-2836.e5

31 – Kosai A, Horike N, Takei Y, Yamashita A, Fujita K, Kamatani T, Tsumaki N
Changes in acetyl-CoA mediate Sik3-induced maturation of chondrocytes in endochondral bone formation
Biochemical and Biophysical Research Communications
516 (4): 1097-1102

32 – Hirosawa M, Fujita Y, Saito H
Cell-type-specific CRISPR activation with microRNA-responsive acrllA4 Switch
ACS Synthetic Biology
8 (7): 1575-1582

33 – Ozeki-Hayashi R, Fujita M, Tsuchiya A, Hatta T, Nakazawa E, Takimoto Y, Akabayashi A
Beliefs held by breast surgeons that impact the treatment decision process for advanced breast cancer patients: a qualitative study
Breast Cancer
11: 221-229

34 – Nishida Y, Kawai A, Toguchida J, Ogose A, Ae K, Kunisada T, Matsumoto Y, Matsunobu T, Takahashi K, Nishida K, Ozaki T
Clinical features and treatment outcome of desmoid-type fibromatosis: based on a bone and soft tissue tumor registry in Japan
International Journal of Clinical Oncology
24 (11): 1498-1505

August

35 – Horiguchi M, Yoshida M, Hirata K, Furuyama K, Masui T, Uemoto S, Kawaguchi Y
Senescence caused by inactivation of the homeodomain transcription factor Pdx1 in adult pancreatic acinar cells in mice
FEBS Letters
593 (16): 2226-2234

36 – Suga M, Kondo T, Inoue H
Modeling neurological disorders with human pluripotent stem cell-dervied astrocytes
International Journal of Molecular Sciences
20 (16): 3862

37 – Kime C, Kiyonari H, Ohtsuka S, Kohbayashi E, Asahi M, Yamanaka S, Takahashi M and Tomoda K
Induced 2C expression and implantation-competent blastocyst-like cysts from primed pluripotent stem cells
Stem Cell Reports
13 (3): 485-498

38 – Zhang R, Kitayama S, Liu T, Ueda N, Tokumitsu Y, Mashima H, Ohdan H, Kaneko S, Uemura Y
In vitro detection of cellular adjuvant properties of human invariant natural killer T cells
Methods in Molecular Biology
2048: 121-130

39 – Iriguchi S, Kaneko S
In vitro differentiation of T cells: From nonhuman primate-induced pluripotent stem cells
Methods in Molecular Biology
2048: 93-106

40 – Ueda T, Kaneko S
In vitro differentiation of T cell: From CAR-modified T-iPSC
Methods in Molecular Biology
2048: 85-91

41 – Minagawa A, Kaneko S
Differentiating CD8$\alpha\beta$ T cells from TCR-transduced iPSCs for cancer immunotherapy
Methods in Molecular Biology
2048: 81-84

42 – Yasui Y, Hitoshi Y, Kaneko S
In vitro differentiation of T Cell: From human iPS Cells in feeder-free condition
Methods in Molecular Biology
2048: 77-80

43 – Kawai Y, Kaneko S
Redifferentiation of adaptive naïve-like CTL from T-cell-derived iPSC
Methods in Molecular Biology
2048: 71-75

44 – Iriguchi S, Kaneko S
In vitro differentiation of T cells: From human embryonic stem cells and induced pluripotent stem cells
Methods in Molecular Biology
2048: 59-70

45 – Sekai M, Wang J, Hamazaki Y
Clonogenic culture of mouse thymic epithelial cells
Methods in Molecular Biology
2019 (2048): 143-153

46 – Egawa N, Chung KK, Takahashi R, Lo EH, Inoue H, Arai K
Brief review: Can modulating DNA methylation state help the clinical application of oligodendrocyte precursor cells as a source of stem cell therapy?
Brain Research
doi: 10.1016/ j. brainres.2019.146386

47 – Sato T, Higashioka K, Sakurai H, Yamamoto T, Goshima N, Ueno M and Sotozono C
Core transcription factors promote induction of PAX3-positive skeletal muscle stem cells
Stem Cell Reports
13: 352-365

48 – Kanatsu-Shinohara M, Yamamoto T, Toh H, Kazuki Y, Kazuki K, Imoto J, Ikeo K, Oshima M, Shirahige K, Iwama A, Nabeshima Y, Sasaki H and Shinohara T
Aging of spermatogonial stem cells by Jnk-mediated glycolysis activation
Proceedings of the National Academy of Sciences of the United States of America
116: 16404-15409

49 – Motoike S, Kajiya M, Komatsu N, Horikoshi S, Ogawa T, Sone H, Matsuda S, Ouhara K, Iwata T, Mizuno N, Fujita T, Ikeya M,

2019

Kurihara H
Clumps of mesenchymal stem cell/extracellular matrix complexes generated with xeno-free conditions facilitate bone regeneration via direct and indirect osteogenesis
International Journal of Molecular Sciences
20 (16): 3970

50 Endo K, Hayashi K, Saito H
Numerical operations in living cells by programmable RNA devices
Science Advances
5 (8)

51 Takashima K, Inoue Y, Tashiro S, Muto K
Letter in reply to: 'Therapeutic misconception and the role of the Research Ethics Committee'
Regenerative Medicine
14 (8)

52 Wu JC, Garg P, Yoshida Y, Yamanaka S, Gepstein L, Hulot JS, Knollmann BC, Schwartz PJ
Towards precision medicine with human iPSCs for cardiac channelopathies
Circulation Research
125 (6): 653-658

53 Mori T, Takaoka H, Yamane J, Alev C, Fujibuchi W
Novel computational model of gastrula morphogenesis to identify spatial discriminator genes by self-organizing map (SOM) clustering
Scientific Reports
9: 12597 (2019)

54 Mitsuzawa S, Ikeguchi R, Aoyama T, Ando M, Takeuchi H, Yurie H, Oda H, Noguchi T, Ohta S, Zhao C, Ikeya M, Matsuda S
Induced pluripotent stem cell-derived mesenchymal stem cells prolong hind limb survival in a rat vascularized composite allotransplantation model
Microsurgery
39 (8): 737-747

September

55 Kikuchi S, Noguchi K, Wakai K, Hamazaki Y, Tozawa K, Jomori T, Sasako M, Miwa H
Propagermanium induces NK cell maturation and tends to prolong overall survival of patients with refractory cancer
Anticancer Research
39 (9): 4687-4698

56 Umekage M, Sato Y, Takasu N
Overview: an iPS cell stock at CiRA
Inflammation and Regeneration
39 (17)

57 Panina Y, Germond A, Watanabe TM
Rejuvenating cells to iPS: just how profound are the changes?
Atlas of Science

58 Komura S, Ito K, Ohta S, Ukai T, Kabata M, Itakura F, Semi K, Matsuda Y, Hashimoto K, Shibata H, Sone M, Jo N, Sekiguchi K, Ohno T, Akiyama H, Shimizu K, Woltjen K, Ozawa M, Toguchida J, Yamamoto T, Yamada Y
Cell-type dependent enhancer binding of the EWS/ ATF1 fusion gene in clear cell sarcomas
Nature Communications
10 (1): 3999

59 Takaishi K, Takeuchi M, Tsukamoto S, Takayama N, Oshima M, Kimura K, Isshiki Y, Kayamori K, Hino Y, Oshima-Hasegawa N, Mitsukawa S, Takeda Y, Mimura N, Ohwada C, Iseki T, Nakamura S, Eto K, Iwama A, Yokote K, Nakaseko C, Sakaida E
Suppressive effects of anagrelide on cell cycle progression and the maturation of megakaryocyte progenitor cell lines in human induced pluripotent stem cells
Haematologica
pii: haematol.2018.214841

60 Sakaguchi H, Ozaki Y, Ashida T, Matsubara T, Oishi N, Kihara S, Takahashi J
Self-organized synchronous calcium transients in a cultured human neural network derived from cerebral organoids
Stem Cell Reports
13 (3): 458-473

61 Sawai T, Sakaguchi H, Thomas E, Takahashi J, Fujita M
The ethics of cerebral organoid research: Being conscious of consciousness
Stem Cell Reports
13 (3): 440-447

62 Shiba T, Tanaka T, Ida H, Watanabe M, Nakaseko H, Osawa M, Shibata H, Izawa K, Yasumi T, Kawasaki Y, Saito MK, Takita J, Heike T, Nishikomori R
Functional evaluation of the pathological significance of MEFV variants using induced pluripotent stem cell-derived macrophages
Journal of Allergy and Clinical Immunology
144 (5): 1438-1441

63 Lin CY, Yoshida M, Li LT, Ikenaka A, Oshima S, Nakagawa K, Sakurai H, Matsui E, Nakahata T, Saito MK
iPSC-derived functional human neuromuscular junctions model the pathophysiology of neuromuscular diseases
JCI Insight
4 (18)

64 Araki H, Miura F, Watanabe A, Morinaga C, Kitaoka, F, Kitano Y, Sakai N, Shibata Y, Terada M, Goto S, Yamanaka S, Takahashi M, and Ito T
Base-resolution methylome of retinal pigment epithelial cells used in the first trial of human induced pluripotent stem cell-based autologous transplantation
Stem Cell Reports
13 (4): 761-774

65 Sugimoto N, Eto K
Reconstitution of the hematopoietic system and clinical applications of iPS cells
Rinsho Ketsueki
60 (9) : 1046-1055

66 Tachibana K, Yamane J, Haghparast SMA, Miyake J
Sialomucin and phosphorylated-ERM are inhibitors for cadherin-mediated aggregate formation
Biochemical and Biophysical Research Communications

2019

520 (1): 159-165

October

67 – Elbadry MI, Mizumaki H, Hosokawa K, Espinoza JL, Nakagawa N, Chonabayashi K, Yoshida Y, Katagiri T, Hosomichi K, Zaimoku Y, Imi T, Nguyen MAT, Fujii Y, Tajima A, Ogawa S, Takenaka K, Akashi K, Nakao S
Escape hematopoiesis by HLA-B5401-lacking hematopoietic stem progenitor cells in men with acquired aplastic anemia
Haematologica
104 (10): e447-e450

68 – Saito H, Yokobayashi Y
Editorial overview: Mammalian synthetic biology: from devices to multicellular systems
Current Opinion in Chemical Biology
52: A1-A2

69 – Nakanishi H, Saito H
Mammalian gene circuits with biomolecule-responsive RNA devices
Current Opinion in Chemical Biology
52: 16-22

70 – Takada H, Kaieda A, Tawada M, Nagino T, Sasa K, Oikawa T, Oki A, Sameshima T, Miyamoto K, Miyamoto M, Kokubu Y, Tozawa R, Sakurai H, Saito B
Identification of 2,6-disubstituted 3H-imidazo[4,5-b]pyridines as therapeutic agents for dysferlinopathies through Phenotypic Screening on patient-derived induced pluripotent stem cells
Journal of Medicinal Chemistry
62 (20): 9175-9187

71 – Arai HN, Sato F, Yamamoto T, Woltjen K, Kiyonari H, Yoshimoto Y, Shukunami C, Akiyama H, Kist R, Sehara-Fujisawa A
Metalloprotease-dependent attenuation of BMP signaling restricts cardiac neural crest cell fate
Cell Reports
29 (3): 603-616

72 – Sunohara T, Morizane A, Matsuura S, Miyamoto S, Saito H, Takahashi J
MicroRNA-based separation of cortico-fugal projection neuron-like cells derived from embryonic stem cells
Frontiers in Neuroscience
13: 1141

73 – Grajcarek J, Monlong J, Nishinaka-Arai Y, Nakamura M, Nagai M, Matsuo S, Lougheed D, Sakurai H, Saito MK, Bourque G, Woltjen K
Genome-wide microhomologies enable precise template-free editing of biologically relevant deletion mutations
Nature Communications
10: 4856

November

74 – Chonabayashi K, Yoshida Y, Kitawaki T, Nannya Y, Nakamura M, Oshima S, Hishizawa M, Yamashita K, Ogawa S, Takaori-Kondo A
Acute myeloid leukemia with a cryptic NUP98/ PRRX2 rearrangement developing after low-dose methotrexate therapy for rheumatoid arthritis
Annals of Hematology
98 (12): 2841-2843

75 – Prictor M, Lewis MA, Newson AJ, Haas M, Baba S, Kim H, Kokado M, Minari J, Molnár-Gábor F, Yamamoto B, Kaye J, Teare HJA
Dynamic consent: an evaluation and reporting framework
Journal of Empirical Research on Human Research Ethics
doi: 10.1177/ 1556264619887073

76 – Sakakura M, Ohta S, Yagi M, Tanaka A, Norihide J, Woltjen K, Yamamoto T, Yamada Y
Smarcb1 maintains the cellular identity and the chromatin landscapes of mouse embryonic stem cells
Biochemical and Biophysical Research Communications
519 (4): 705-713

77 – Yoshida T, Jonouchi T, Osafune K, Takita J, Sakurai H
A liver model of infantile-onset pompe disease using patient-specific induced pluripotent stem cells
Frontiers in Cell and Developmental Biology
7: 316

December

78 – Imamura K, Izumi Y, Banno H, Uozumi R, Morita S, Egawa N, Ayaki T, Nagai M, Nishiyama K, Watanabe Y, Hanajima R, Oki R, Fujita K, Takahashi N, Ikeda T, Shimizu A, Morinaga A, Hirohashi T, Fujii Y, Takahashi R, Inoue H
Induced pluripotent stem cell-based drug repurposing for amyotrophic lateral sclerosis Medicine (iDReAM) study: Protocol for a phase 1 dose escalation study of bosutinib for amyotrophic lateral sclerosis patients
BMJ Open
9 (12): e033131

79 – Morisaka H, Yoshimi K, Okuzaki Y, Gee P, Kunihiro Y, Sonpho E, Xu H, Sasakawa N, Naito Y, Nakada S, Yamamoto T, Sano S, Hotta A, Takeda J and Mashimo T
CRISPR-Cas3 induces broad and unidirectional genome editing in human cells
Nature Communications
10 (1): 5302

80 – Hibino A, Yoshizawa G, Minari J
Meaning of ambiguity: a Japanese survey on synthetic biology and genome editing
Frontiers in Sociology
4 (81)

81 – Suzuki D, Flahou C, Yoshikawa N, Stirblyte I, Hayashi Y, Sawaguchi A, Akasaka M, Nakamura S, Higashi N, Xu H, Matsumoto T, Fujio K, Manz MG, Hotta A, Takizawa H, Eto K, Sugimoto N
iPSC-derived platelets depleted of HLA class I are inert to anti-HLA class I and natural killer cell immunity
Stem Cell Reports
14 (1): 49-59

2019

82 Yamazaki D, Konishi Y, Morikawa T, Kobara H, Masaki T, Hitomi H, Osafune K, Nakano D, Kittikulsuth W, Nishiyama A
Failure to confirm an SGLT2 inhibitor-induced hematopoietic effect in non-diabetic rats with renal anemia
Journal of Diabetes Investigation
doi: 10.1111/ jdi. 13205

January

83 Li H, Neelankal John A, Nagatake T, Hamazaki Y, Jiang FX
Claudin 4 in pancreatic β cells is involved in regulating the functional state of adult islets
FEBS Open Bio
10 (1): 28-40

84 Torikoshi S, Morizane A, Shimogawa T, Samata B, Miyamoto S, Takahashi J
Exercise promotes neurite extensions from grafted dopaminergic neurons in the direction of the dorsolateral striatum in Parkinson's disease model rats
Journal of Parkinson's Disease
10 (2): 511-521

85 Takenaka-Ninagawa N, Goto M, Ikeda R, Sakurai H
Muscular dystrophy and rehabilitation interventions with regenerative treatment
Current Physical Medicine and Rehabilitation Reports
8: 17-29

86 Kawasaki S, Ono H, Hirosawa M, Saito H
RNA and protein-based nanodevices for mammalian post-transcriptional circuits
Current Opinion in Biotechnology
63: 99-110

87 Takahashi J
Preclinical evaluation of patient-derived cells shows promise for Parkinson's disease
The Journal of Clinical Investigation
130 (2): 601-603

88 Luo J, Qin L, Zhao L, Gui L, Ellis MW, Huang Y, Kural MH, Clark JA, Ono S, Wang J, Yuan Y, Zhang SM, Cong X, Li G, Riaz M, Lopez C, Hotta A, Campbell S, Tellides G, Dardik A, Niklason LE, Qyang Y
Tissue-engineered vascular grafts with advanced mechanical strength from human iPSCs
Cell Stem Cell
26 (2): 251-261

89 Ono H, Kawasaki S, Saito H
Orthogonal protein-responsive mRNA switches for mammalian synthetic biology
ACS Synthetic Biology
9 (1): 169-174

90 Minakawa T, Kanki Y, Nakamura K, Yamashita JK
Protein kinase A accelerates the rate of early stage differentiation of pluripotent stem cells
Biochemical and Biophysical Research Communications
524 (1): 57-63

91 Minato N, Hattori M, Hamazaki Y
Physiology and pathology of T-cell aging
International Immunology
pii: dxaa006

92 Nishimoto S, Mizuno T, Takahashi K, Nagano F, Yuzawa Y, Nishiyama A, Osafune K, Hitomi H, Nagamatsu T
CD140b and CD73 are markers for human induced pluripotent stem cell-derived erythropoietin-producing cells
FEBS Open Bio
10 (3): 427-433

February

93 Egawa N, Suzuki H, Takahashi R, Hayakawa K, Li W, Lo E, Arai K, Inoue H
From in vitro to in vivo reprogramming for neural transdifferentiation, an approach for CNS issue remodeling using stem cell technology
Journal of Cerebral Blood Flow and Metabolism
19; 271678 × 20910324

94 Murakami K, Yoshimura M, Nakagawa S, Kume T, Kondo T, Inoue H, Irie K
Evaluation of toxic amyloid 42 oligomers in rat primary cerebral cortex cells and human iPS-derived neurons treated with 10-Me-Aplog-1, a new PKC activator
International Journal of Molecular Sciences
21 (4): ijms-708437

95 Samata B, Takaichi R, Ishii Y, Fukushima K, Nakagawa H, Ono Y, Takahashi J
L1CAM Is a marker for enriching corticospinal motor neurons in the developing brain
Frontiers in Neuroscience
doi: 10.3389/ fncel.2020.00031

96 Parr CJC, Wada S, Kotake K, Kameda S, Matsuura S, Sakashita S, Park S, Sugiyama H, Kuang Y, Saito H
N1-Methylpseudouridine substitution enhances the performance of synthetic mRNA switches in cells
Nucleic Acids Research
gkaa070

97 Tsujimoto H, Araoka T, Nishi Y, Ohta A, Nakahata T, Osafune K
Small molecule TCS21311 can replace BMP7 and facilitate cell proliferation in in vitro expansion culture of nephron progenitor cells
Biochemical and Biophysical Research Communications
doi.10.1016/ j.bbrc.2020.02.130

98 Reinhardt A, Kagawa H, Woltjen K
N-terminal amino acids determine KLF4 protein stability in 2A peptide-linked polycistronic reprogramming Constructs
Stem Cell Reports
14 (3): 520-527

99 Hasegawa D, Imamura T, Yumura-Yagi K, Takahashi Y, Usami I, Suenobu SI, Nishimura S, Suzuki N, Hashii Y, Deguchi T, Moriya-Saito A, Kato K, Kosaka Y, Hirayama M, Iguchi A, Kawasaki H, Hori H, Sato A, Kudoh T, Nakahata T, Oda M, Hara J, Horibe K; Japan Association of Childhood Leukemia Study

2019

Group (JACLS)
Risk-adjusted therapy for pediatric non-T cell ALL improves outcomes for standard risk patients: results of JACLS ALL-02
Blood Cancer Journal
10: 23

March

100 Ohno H, Akamine S, Saito H
Synthetic mRNA-based systems in mammalian cells
Advanced Biosystems
doi.10.1002/ adbi.201900247

101 Ueda T, Kumagai A, Iriguchi S, Yasui Y, Miyasaka T, Nakagoshi K, Nakane K, Saito K, Takahashi M, Sasaki A, Yoshida S, Takasu N, Seno H, Uemura Y, Tamada K, Nakatsura T, Kaneko S
Non-clinical efficacy, safety, and stable clinical cell processing of iPSC-derived anti-GPC3 CAR-expressing NK/ ILC cells
Cancer Science
doi: 10.1111/ cas.14374

102 Nagaoka SI, Nakaki F, Miyauchi F, Nosaka Y, Ohta H, Yabuta Y, Kurimoto K, Hayashi K, Nakamura T, Yamamoto T and Saitou M
ZGLP1 is a determinant for the oogenic fate in mice
Science
367 (6482): eaaw4115

103 Sasaki B, Uemoto S, Kawaguchi Y
Transient FOXO1 inhibition in pancreatic endoderm promotes the generation of NGN3+ endocrine precursors from human iPSCs
Stem Cell Research
44: 101754

104 Nakanishi H, Saito H
Caliciviral protein-based artificial translational activator for mammalian gene circuits with RNA-only delivery
Nature Communications
11 (1): 1297

105 Sakai Y, Nakamura T, Okamoto I, Gyobu-Motani S, Ohta H, Yabuta Y, Tsukiyama T, Iwatani C, Tsuchiya H, Ema M, Morizane A, Takahashi J, Yamamoto T and Saitou M
Induction of the germ-cell fate from pluripotent stem cells in cynomolgus monkeys
Biology of Reproduction
102 (3): 620-638

106 Seki T, Kanagawa M, Kobayashi K, Kowa H, Yahata N, Maruyama K, Iwata N, Inoue H, Toda T
Galectin 3-binding protein suppresses amyloid-β production by modulating β-cleavage of amyloid precursor protein
Journal of Biological Chemistry
295 (11): 3678-3691

107 Gee P, Lung MSY, Okuzaki Y, Sasakawa N, Iguchi T, Makita Y, Hozumi H, Miura Y, Yang LF, Iwasaki M, Wang XH, Waller MA, Shirai N, Abe YO, Fujita Y, Watanabe K, Kagita A, Iwabuchi KA, Yasuda M, Xu H, Noda T, Komano J, Sakurai H, Inukai N, and Hotta A
Extracellular nanovesicles for packaging of CRISPR-Cas9 protein and sgRNA to induce therapeutic exon skipping
Nature Communications
11 (1): 1334

108 Yamamoto Y, Kojima K, Taura D, Sone M, Washida K, Egawa N, Kondo T, Minakawa E, Tsukita K, Enami T, Tomimoto H, Mizuno T, Kalaria N R, Inagaki N, Takahashi R, Shiba Harada M, Ihara M, Inoue H
Human iPS cell-derived mural cells as an in vitro model of hereditary cerebral small vessel disease
Molecular Brain
13 (38)

109 Takeuchi H, Imamura K, Ji B, Tsukita K, Enami T, Takao K, Miyakawa T, Hasegawa M, Sahara N, Iwata N, Inoue M, Tabira T, Hara H, Ono M, Trojanowski J, Lee V, Takahashi R, Suhara T, Higuchi M, Inoue H
Nasal vaccine delivery attenuates brain pathology and cognitive impairment in tauopathy model mice
npj Vaccines
5 (28)

CiRA Buildings

Main Building

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

The Second Building

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

The Third Building

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

Ancillary Facilities

Animal Research Facility

Small-sized animal room

X-ray room

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

- **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
- Ayumi Matsunaga
- Yoshiko Ohara
- Yohei Osako,
- Yoshie Tange
- Kyoko Tanimura
- Nanako Yamanishi

Manufacture and management unit

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

- Naoko Hayakawa
- Shusuke Hira
- Norihito Hirai
- Tomoko Ichisaka
- Akiko Kadotani,
- Kumiko Kan
- Hitomi Kanai
- Yukiko Kobayashi
- Sonoka Matsuda
- Noriko Matsunaga
- Shun Minobe
- Akiyoshi Miyasyo
- Miyuki Mori
- Kyoko Morino
- Yoshiki Nakashima
- Eri Nishikawa
- Yoko Otagaki
- Aki Sasaki
- Yukiko Sasaki
- Takeshi Shiranita
- Maho Yokoi

Research and Development Department

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

CMC research and development unit

- Tomoaki Kato
- Yuko Kitano
- Rafal Przybyslaw Krol
- 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.

- Tomohiro Akahoshi
- Hiromi Dohi
- Sho Hasegawa
- Takafusa Hikichi
- Maki Hira
- Koichi Kaneko
- Mitsuyo Kawada
- Ayane Kawakami
- Kazuhiko Kitajima
- Fumiyo Kitaoka
- Masako Kudo
- Junko Kuwahara
- Akiko Matsumoto
- Noriko Mori
- Yuki Noguchi
- Masaki Nomura
- Haruna Ogawa
- Yoshiko Ogawa
- Tokiko Okame
- Yusuke Okame
- Kazuhide Onishi
- Keiko Ono
- 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
- Yuji Arakawa
- Yasuko Nakai
- Kasumi Nakao
- Ryosaku Tomioka
- Yoshie Umeda
- Shinsuke Yoshida

Experiment Support

Drug Discovery Technology Development Office

Automated differentiation culture system

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

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

Common Equipment Management Office

Flow cytometer

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

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

FACS Group

Supports flow cytometric analysis.

- Kanae Mitsunaga (Assistant Professor)
- Kohei Furukawa

Imaging Group

Supports live imaging of cells and tissues (confocal microscopes and multiphoton microscope).

- Keiko Imamura (Junior Associate Professor)
- Shunsuke Kihara

Genome Analysis Group

Analyzes genomes and epigenomes with next generation sequencers.

- Takuya Yamamoto (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)
- Chisa Matsuda
- Hikari Nishina
- Noriko Saiwaki
- Shigeki Uchida
- Jun Nishikawa
- Hiromi Nose
- Kotaro Shiraishi
- Shinichi Yamashita

Research Support Division

Director's Office

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

- **Head:** Toru Kawamura (Specially-Appointed Professor)

Academic Research Support Group

- Toru Kawamura (GL・Specially-Appointed Professor) (~R1.8.31)
- Miho Saito (GL) (R1.9.1~)
- Ayaka Nakauchi
- Sayaka Takeshima

Secretary Group

- Kumi Higashi (GL)
- Keiko Kamegawa
- Mitsuki Otsuki

Common Secretary Group

- Fusao Koyama (GL)
- Mayumi Ikeda
- Yukiko Nakagawa
- Kazumi Nishikawa
- Katsura Noda
- Masumi Oishi
- Nakako Shimazu
- Yoko Uematsu
- Harumi Watanabe

2019–2020

Research Institute Support

Administration Division

Medical Applications Promoting Office

Supports the promotion of 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)
- Yuji Arakawa (Specially-Appointed Junior Associate Professor)
- Hiroko Endo
- Tadaaki Hanatani
- Yumie Matsumura
- Hisae Takenakajima

Ethics and Inspection Group

- Keiichi Tabuchi (GL, Associate Professor)
- Ayumi Matsunaga (SGL)
- Yuji Arakawa (Specially-Appointed Junior Associate Professor)
- Yumie Matsumura

Contract and Drug Discovery Group

- Atsushi Onodera (GL)
- Hisae Takenakajima (SGL)
- Suga Hasegawa
- Tomoko Miyata
- Satoshi Nishihama
- Kayoko Nishizawa
- Yoko Taniguchi
- Chiharu Yabuta

Intellectual Property Group

- Miwa Nakagawa (GL)
- Hiroko Endo
- Saiko Moriyama
- Chie Saneyoshi
- Nobuko Tachikawa
- Minako Tateno

Planning and Coordination Office

Manages research funds and coordinates laboratory and office space.

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

Human Resourses Development Office

Manages employment, personnel evaluation systems and interpersonal skill training

- **Head:** Masayuki Kan
- Rie Kato (GL)
- Hitomi Imagawa
- Aya Iwayama
- Shinsuke Morisawa
- Chie Nakamura
- Masakazu Watanabe
- Tomoaki Yamazaki

iPSC Research Fund Office

Conducts fund-raising activities and communicates with donors.

- **Head:** Fumitaka Watanabe
- Hiroe Kawabata
- Fusao Koyama
- Kaori Ono
- Aiko Tokunaga
- Kana Umegaki

International Public Communications Office

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

- **Head:** Akemi Nakamura
- Peter Karagiannis (Specially-Appointed Junior Associate Professor)
- Mito Kiyoi
- Yoko Miyake
- Ayaka Nakauchi
- Misaki Ouchida
- Ayaka Shida
- 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:** Tsutomu Baba
- **Assistant Head:** Yuriko Nakaue

General Affairs

- Hina Furuya (Manager)
- Masumi Ban (Assistant Manager)
- Chiaki Arase
- Kota Katsukawa
- Aya Kita
- Mitsunaga Koide
- Megumi Murase
- Akiko Nakagawa
- Rie Oyagi
- Hajime Seki
- Takuya Tanaka

Personnel Affairs

- Tomoaki Yamazaki (Manager)
- Aya Iwayama (Assistant Manager)

Financial Affairs

- Megumi Ikeda (Manager)
- Yuhi Tada
- Gakushi Yamamoto

iPSC Research Fund Affairs

- Yuriko Nakaue
- Sakiko Sunadome

CiRA Advisors

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

Management Adviser
- Hiromichi Mizuno

Communication Adviser
- Motoaki Nishiwaki

GL=Group Leader SGL=Sub Group Leader

2019-2020

Research Activities

1 CiRA Seminars

Date	Lecture Title	Speaker	Affiliation
2019.4.18	Challenges in ensuring hPSC quality —— The importance of maintaining and assessing high-quality human ES/ iPSC cultures for drug development and cell therapy ——	Andrew Gaffney	STEMCELL Technologies Inc.
2019.4.19	If it looks like a sheep, then it's a sheep: Sources of confusion in bioethical arguments	Greg Bognar	Practical Philosophy Department of Philosophy, Stockholm University
2019.4.26	Novel tools to examine intracellular phase transition and RNP granules	Zoher Gueroui	Department of Chemistry, Ecole Normale Supérieure
2019.5.7	Development of cancer-specific antibodies	Yukinari Kato	Department of Antibody Drug Development, Tohoku University Graduate School of Medicine
2019.5.10	Control of T cell differentiation and function through metabolism and epigenome crosstalk	Masakatsu Yamashita	Department of Immunology and Host Defenses, Ehime University Graduate School of Medicine
2019.5.15	Regulation of osteogenic and chondrogenic growth programs by FGF signaling pathways	David Ornitz	Department of Developmental Biology, Washington University School of Medicine
2019.5.21	Programming self-assembly of soft materials using DNA nanotechnology	William Benjamin Rogers	Department of Physics, Brandeis University
2019.5.27	Impact and outlook on the Act on the Safety of Regenerative Medicine	Kaoru Inoue	Kyoto Prefectural University of Medicine
2019.5.27	Status and issues regarding current cell therapies	Masao Sasai	Department of Medical Innovation, Osaka University
2019.6.3	Skin stem cells: coping with stress, inflammation and Cancer	Elaine Fuchs	Laboratory of Mammalian Cell Biology and Development. The Rockefeller University
2019.6.10	Risk, benefit, and ethics in early phase trials of novel therapies	Jonathan Kimmelman	Biomedical Ethics Unit, Mcgill University
2019.6.26	Development of effective small molecules that bind to DNA and RNA molecules associated with neurodegeneration	Kazuhiko Nakatani	The Institute of Scientific and Industrial Research (ISIR), Osaka University
2019.7.4	Harnessing experimental animals	Hiroshi Kiyonari	RIKEN Center for Biosystems Dynamics Research (BDR)
2019.7.5	Control of non-AUG codon translation by eIF5-mimic protein	Katsura Asano	Division of Biology, Kansas State University
2019.7.24	Multiple origins and distinct roles of osteoclasts derived from HSC independent embryonic precursors: Implications in bone homeostasis and repair	Yasuhito Yahara	Department of Orthopaedic Surgery, Faculty of Medicine, University of Toyama
2019.7.30	Research using fetal tissue: ethical issues and legal regulation	Yoshichika Mori	Faculty of Management Information, Hannan University
2019.8.21	My recent progress in mRNA-based biotechnologies	Kei Endo	Graduate School of Frontier Sciences, The University of Tokyo
2019.9.5	How to think about medicalization	Hazem Zohny	University of Oxford

2019-2020

Research Activities

Date	Lecture Title	Speaker	Affiliation
2019.9.5	How should we constrain physicians' discretionary space to ensure good medicine?	Doug Mcconnell	University of Oxford
2019.9.5	Benefit sharing in biomedical research using samples and data	Mayumi Kusunose	RIKEN Center for Integrative Medical Sciences
2019.9.27	Using SABER to amplify multiplexed FISH and IF signals in situ	Jocelyn Kishi	Wyss Institute for Biologically Inspired Engineering, Harvard University
2019.11.13	tRNA methylation: A global determinant of bacterial multi-drug resistance	Ya-Ming Hou	Department of Biochemistry and Molecular Biology, Thomas Jefferson University
2019.11.25	Defining the developmental trajectory of human pluripotent stem cell derived skeletal muscle	April Pyle	Department of Microbiology, Immunology and Molecular Genetics, UCLA
2019.12.20	Phasing biology	Kentaro Shiraki	Faculty of Pure and Applied Sciences, University of Tsukuba
2020.1.17	Nishida philosophy's theory of life	Tetsuro Nagaoka	Graduate School of Letters, Kyoto University
2020.1.21	Cellino tissue foundry: single-cell control, at scale	Marinna Madrid	Harvard University
2020.1.23	Waivers of informed consent for research: A legal and historical review and consideration of emerging practice	Jon F. Merz	Department of Medical Ethics & Health Policy, University of Pennsylvania
2020.1.27	Generating 3D organs of the urinary tract using human iPS cells	Minoru Takasato	RIKEN Center for Biosystems Dynamics Research(BDR)
2020.1.29	GC content shapes mRNA storage in human P-bodies	Dominique Weil	Laboratory of Developmental Biology, Institute of Biology Paris-Seine
2020.1.30	Boolean signaling inputs control predictable cell fate transitions in mouse pluripotency	Ayako Yachie	The Systems Biology Institute

2 CiRA Research Internship Program

CiRA set up a research internship program, which welcomes undergraduate and graduate students to conduct research in CiRA labs. 21 students from 8 countries (U.K., Germany, Hungary, Indonesia, Taiwan, U.S., Canada and Japan) joined in 2019. 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.

Research Activities

4 CiRA Retreat

The CiRA Retreat, 13-14 February, 2020, 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

Satoshi Omura (Kitasato University)
Elizabeth A. Blaber (NASA)
Azusa Inoue (RIKEN)

Best Oral Presentation Award

1st : Azuma Kimura (Osafune Lab.)
2nd: Mingming Zhao (Sakurai Lab.)
3rd: Yann Pretemer (Toguchida Lab.)

Outstanding Poster Award

May Koyama (Yamamoto Lab.)
Yoshiaki Takei (Tsumaki Lab.)
Yuki Iimori (Tsumaki Lab.)
Hirotsugu Maekawa (Toguchida Lab.)
Thomas Maurissen (Woltjen Lab.)
Akira Kunitomi (Takasu Lab.)
Eri Makino (Inoue Lab.)
Chiaki Akifuji (Nakagawa Lab.)

5 CiRA International Symposium

CiRA held its 7th international symposium, "iPSCs Changing the Future of Science and Medicine", in Kyoto from 27 -29 November 2019. 580 people attended, including 120 from overseas. The symposium invited 21 global leaders in stem cell research to speak about their work. There was also a Meet the Experts Lunch, which allowed students to talk directly to the speakers about their research projects.

Speakers

Sheila Chari (Cell Stem Cell) /
Kathy Niakan (Francis Crick Institute) /
Donald Ingber (Harvard Univ.) /
Hideyuki Okano (Keio Univ.) /
Tasuku Honjo, Mitinori Saitou (Kyoto Univ.) /
Jin-Soo Kim (Institute for Basic Science) /
Joao Monteiro (Nature Medicine) /
Hiromitsu Nakauchi, Stanley Qi,
Marius Wernig (Stanford Univ.) /
Yasushi Kajii (T-CiRA Discovery,
Takeda Pharmaceutical Company Limited) /
April Pyle (UCLA) /
Gordon Keller (Univ. Health Network) /
Timothy Kieffer, Peter Zandstra (Univ. of British Columbia) /
Takanori Takebe (Cincinnati Children's Hosp.) /
Magdalena Zernicka-Goetz (Univ. of Cambridge) /
Shinya Yamanaka, Hidetoshi Sakurai,
Shin Kaneko (CiRA)

(1)
Group photo at CiRA Retreat

(2)
Poster session at CiRA Retreat

(3)
A lecture at CiRA International Symposium

(4)
Professor Yamanaka at CiRA International Symposium

2019-2020

Research Activities

6 Booth Exhibit

CiRA exhibited a booth at BioJapan 2019, which was held on 9-10 October in Yokoyama. Top business development, licensing, and alliance management professionals, R&D personnel, and biotech company executives participated in the event.

(5)
CiRA booth at BioJapan 2019

(6)
CiRA Exchange Meeting

7 CiRA Internal Events

The CiRA internal events were held to promote communication among CiRA members and lab members.

Every month "Tell us, Researcher! CiRA's Research" was held as an interaction between support staff and researchers. Also, CiRA exchange meetings were held to promote more communications and lunch exchange meetings were held every month. An internal online magazine, WikiCiRA, was installed to notify event news to CiRA members.

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

[11th] 2019.4.9	Noriyuki Tsumaki	total 352 people joined
[12th] 2019.5.15	Kenji Osafune	
[13th] 2019.6.4	Wataru Fujibuchi	
[14th] 2019.7.9	Mitinori Saitou	
[15th] 2019.9.10	Isao Asaka	
[16th] 2019.10.29	Jun K. Yamashita	
[17th] 2019.11.26	Makoto Ikeya	
[18th] 2019.12.10	Hidetoshi Sakurai	
[19th] 2020.1.7	Shin Kaneko	

CiRA Exchange Meetings

[6th] 2019.5.24 Welcome Party. 93 people joined.
[7th] 2019.10.25 Halloween Party. 110 people joined.
[8th] 2019.12.24 CiRA Bar. 18 people joined

Lunch Exchange Meetings

Lunch exchange meetings were held 13 times
("Cherry Blossom Viewing Lunch",
"Networking Lunch for Moms and Dads",
"Networking Lunch for CiRA members wanting to study abroad" etc.).
Total 182 people joined.

Club Activities at CiRA

CiRUN (Marathon), ChoiRA (Chorus),
Ping-Pong club

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

2019–2020

General Public Outreach

1 CiRA Symposium

CiRA holds symposia for the general public each year.

August 20, 2019

Possibility of science to create the future
This event was a joint symposium with the Fukushima Future Center for Regional Revitalization, Fukushima University. The event was held at Koriyama City. About 700 people joined.
[Speakers]
Shinya Yamanaka, Mio Iwasaki (CiRA)

February 1, 2020

Our future with genome editing: ethical perspectives on editing the human genome
This event was held as an annual meeting of the Uehiro Foundation on Ethics and Education. This event was held at Kyoto University Museum, Approx. 20 people joined.
[Speakers]
Tsutomu Sawai, Taichi Hatta, Kyoto Akatsuka, Kayo Takashima, Mika Suzuki (CiRA)

(1) Prof. Yamanaka is speaking at Symposium "Possibility of science to create the future"

(2) Assistant Prof. Iwasaki is speaking at Symposium "Possibility of science to create the future"

(3) Group Photo of "Our future with genome editing: ethical perspectives on editing the human genome"

(4) Panel discussion of "Our future with genome editing: ethical perspectives on editing the human genome"

2 CiRA Café

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

August 19, 2019

CiRA Café × Grassroots science café in Fukushima
"Thinking about the future of iPS cell × Genome Editing"
It held at Koriyama city, Fukushima prefecture. 12 people joined.
[Speaker]
Hiroyuki Wadahama (CiRA)
[Graphic recording]
Misaki Ouchida (CiRA)

December 22, 2019

Listen to and discuss iPS cells
This event discussed the use of iPS cells to treat muscular dystrophy.
This event was held in Osaka. 24 people joined.
[Speaker]
Akitsu Hotta (CiRA)
Hiroyuki Wadahama (CiRA)

(5) Attendees of CiRA Café × Grassroots science café in Fukushima "Thinking about the future about iPS cell × Genome Editing"

(6) Graphic recording of CiRA Café × Grassroots science café in Fukushima "Thinking about the future about iPS cell × Genome Editing"

(7) Dr. Hotta is speaking at "Listen to and discuss iPS cells"

(8) Interaction with attendees at "Listen to and discuss iPS cells"

2019-2020

General Public Outreach

3 Programs for children

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

July 26, 2019

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]
Isao Asaka (CiRA)
[Support]
Ikeya Lab. (CiRA)


(9)


(10)

4 CiRA Tour

CiRA offers tours of its 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 fiscal year, six tours were held on May 11 and Sept. 14, 2019 and Feb. 1, 2020. More than 180 people participated in tours.

(7)
Prof. Asaka is speaking at "Let's study iPS cells"

(8)
Junior high school students at "Let's study iPS cells"

2019-2020

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.

2019-2020

iPS Cell Research Fund

Last fiscal year, the iPS Cell Research Fund collected nearly 5.2 billion yen from approximately 30,000 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, 2020, the iPS Cell Research Fund had a balance of over 18 billion yen. This money is being used to convert iPS cell research into innovative treatments. The total expenditure from the fund is 700 million yen, which is 50 million yen less 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
E-mail: ips-kikin@cira.kyoto-u.ac.jp

iPS Cell Research Fund FY 2019 Financial Report (April 1, 2019-March 31, 2020)

Income	Number of Donations	Amount (yen)
Individual	28,810	4,602,802,261
Organization / Corporation	1,277	622,701,734
Total	30,087	5,225,503,995

Expenditures	Amount (yen)
Personnel	384,902,137
Research projects	76,658,257
Intellectual property	47,608,973
Other operating expenses*	195,846,753 (134,974,366)
Total	705,016,120

	Amount (yen)
FY 2019 Balance	18,861,925,994

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

2019-2020

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.

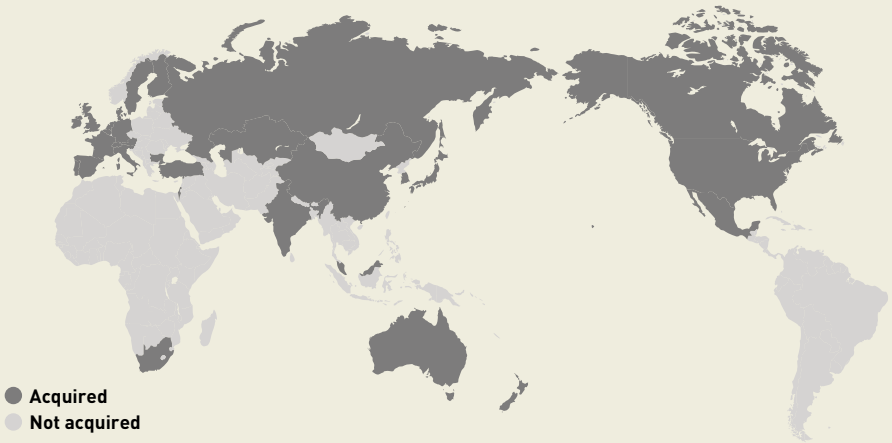
Patents based on discoveries by CiRA researchers have been granted in 32 countries and 1 region (see figure below) by the end of March 2020. Other patents include IP for the production of iPS cells and for the differentiation of iPS cells to various cells. iPS Academia Japan Inc. is mainly responsible for licensing iPS cell-related patents owned by Kyoto University.

1 **Acquired basic and related patents on iPS cell technology (as of March 31, 2020)**

Nations and Regions	Number of Patents
Japan	38
U.S.A.	32
European Union *1	24
China	14
Korea	13
Canada	12
Singapore	10
Australia	6
Hong Kong *2	5
India	5
Israel	4
Mexico	3
Eurasia *3	2
U.K. *4	2
New Zealand	2
South Africa	2
Malaysia	1
Total	**175**

*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, 2020)**



2019–2020

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 an iPS cell stock for regenerative medicine, and realizes regenerative medicine for diseased and damaged tissues. 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 the Realization of Regenerative Medicine, and the Program for Intractable Disease Research.

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 the Shonan Health Innovation Park in Fujisawa, Kanagawa Prefecture. T-CiRA is at minimum a 10-year project under the direction of CiRA. It aims to innovate medical applications of iPS cells. In this fiscal year, the project saw research progress in areas such as neurological disorders, intractable muscle diseases, cancer, heart failure and diabetes. These projects were led by CiRA Prof. Haruhisa Inoue, Assoc. Profs. Hidetoshi Sakurai, Shin Kaneko, Yoshinori Yoshida, and Makoto Ikeya, and Junior Assoc. Profs. Akitsu Hotta and Taro Toyoda. Prof. Takanori Takebe of Tokyo Medical and Dental 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.

In FY 2019, T-CiRA began using research from the Kaneko laboratory that combined iPS cell and chimera antigen receptor (CAR) T cell technologies to produce a new type of cell, iCART. Based on the terms of the agreement, Takeda will own the global commercial rights for iCART, while CiRA will receive income based on agreed upon milestones. The partnership aims to use iCART in clinical research by 2021.

T-CiRA (1)

(1)
T-CiRA logo

2019-2020

Major Research Projects

3 iPS Cell Stock for Regenerative Medicine

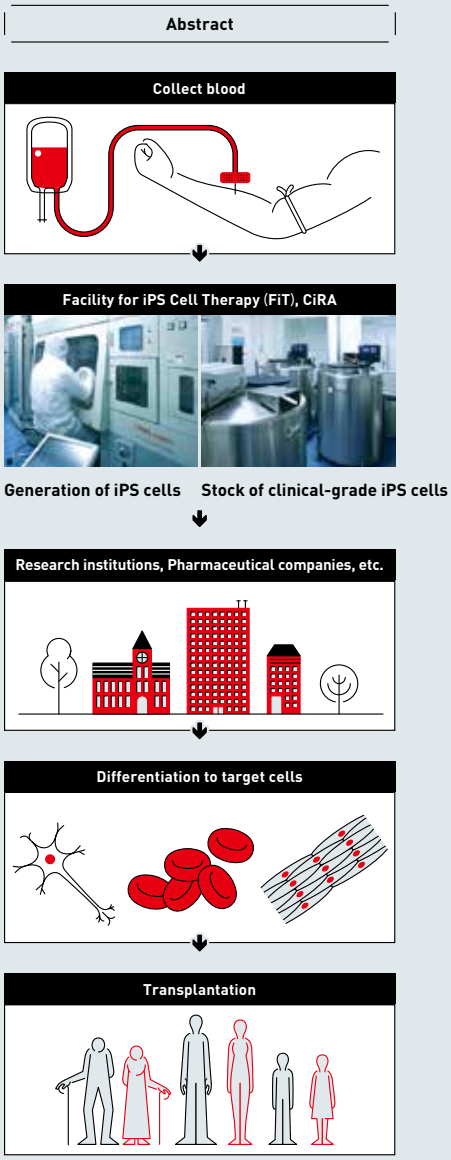
This stock project reprograms the blood of HLA homozygous donors into iPS cells at the Facility for iPS Cell Therapy (FiT: Facility for iPS Cell Therapy-(P.49). HLA homozygosity maximizes patient-donor matching. The stocked iPS cells are confirmed to be of high quality and made available to medical and research institutions around the world. The project is being led by Professor Naoko Takasu and the Medical Applications Promoting Office (p.51) in collaboration with FiT.

The recruitment of the donors is being done in partnership with the Japanese Red Cross Society (JRCS), Kaijo Building Clinic in Tokyo, the Japanese Red Cross Nagoya Daiichi Hospital, and Kyoto University Hospital, such that CiRA can now collect blood from Kyoto, Nagoya, and Tokyo.

At the moment, the stock makes available 4 iPS cell lines that were made by reprogramming peripheral blood and cord blood and match approximately 40% of the Japanese population.

For patients with rare HLA types, instead of seeking donors, the project is investigating the prospect of gene editing the HLA genes. This strategy could potentially reduce the number of iPS cell lines needed to serve a wide population. Further research is reducing the cost of autologous iPS cells so that patients can use their own reprogrammed cells for treatment.

In September 2019, Kyoto University created the CiRA Foundation to promote the iPS Cell Stock Project. In April 2020, CiRA transfered responsibility of the stock project to the CiRA Foundation.



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 Ethics is established.
Mar. 2015....The second CiRA building is completed.
Feb. 2017....The third CiRA building is completed.

Personnel (as of March 1, 2020)

Professors	15 (2)
Associate Professors	12 (0)
Junior Associate Professors	11 (0)
Assistant Professors	18 (0)
Researchers	125 (61)
Research Assistants	72 (89)
Research Support Staff	53 (11)
Administrative Staff	15 (5)
Total	321(168)

Number of Students :

Dept. of Life Science Frontiers	26
Dept. of Cell Growth and Differentiation	15
Dept. of Clinical Application	23
Total	64

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

Organization Chart (as of March 1, 2020)

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

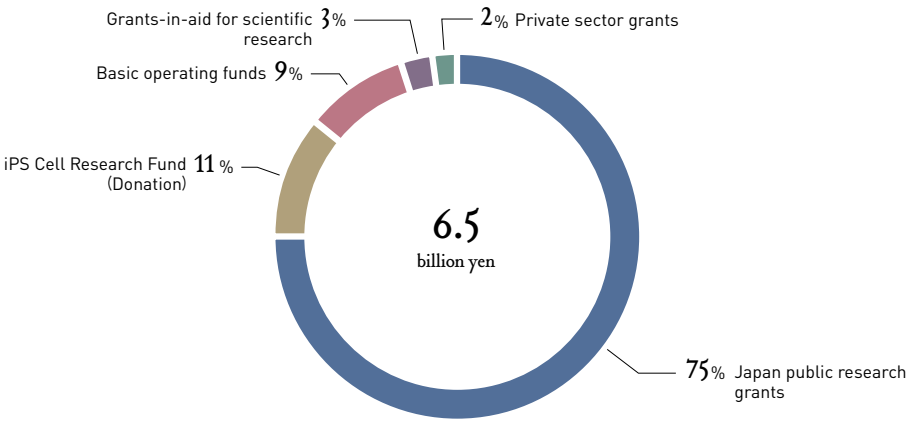
Research Departments
- Life Science Frontiers
- Cell Growth and Differentiation
- Clinical Application
- Fundamental Cell Technology
  - Drug Discovery Technology Development Office
  - Common Equipment Management Office
  - Information Security Office
- Uehiro Reserch Division for iPS Cell Ethics

Animal Research Facility
Facility for iPS Cell Therapy (FiT)

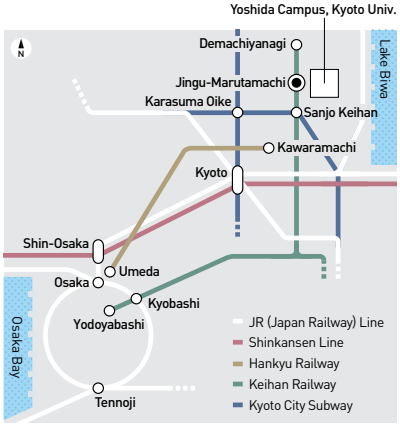
Research Support Division
Director's Office
Planning and Coordination Office
Medical Applications Promoting Office
Human Resourses Development Office
iPSC Research Fund Office
International Public Communications Office

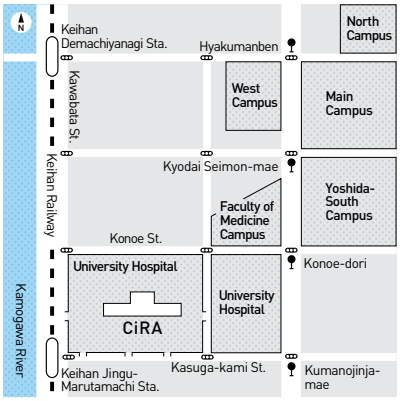
Administration Division
CiRA Administrative Office

Fiscal Budget Implementation (as of March 31, 2020)



Access





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

From Tokyo to Kyoto
Take JR Shinkansen bullet train from Tokyo station Kyoto station

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

Contact

CiRA International Public Communications Office
53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto
606-8507, Japan
TEL: +81 75 366 7005
FAX: +81 75 366 7034
URL: www.cira.kyoto-u.ac.jp/e/

Credit

Publisher	Center for iPS Cell Research and Application (CiRA), Kyoto University
Producers	Yoko Miyake, Akemi Nakamura (CiRA)
Editors / Writers	Peter Karagiannis, Mito Kiyoi, Misaki Ouchida, Ayaka Shida, Hiroko Sata, Masaya Todani, Hiroyuki Wadahama, Director's Office, Medical Applications Promoting Office, Planning and Coordination Office, Human Resourses Development Office, iPSC Research Fund Office, Administrative Office (CiRA), Sci-Tech Communications Inc.
Photography	Jussi Panula, KO SASAKI International Public Communications Office (CiRA)
Art Direction	Mitsunobu Hosoyamada
Design	Hikaru Yokoyama (Hosoyamada Design Office)
Illustration	Shinji Hamana (Beach)
Publication Date	October 2020

Center for
iPS Cell
Research and
Application,
Kyoto University