Transforming Medicine with the Unlimited Potential of iPS Cells

T-CiRA

Takeda-CiRA Joint Research Program
for iPS Cell Applications

Our Vision of New Therapies

The Concept behind the T-CiRA Logo

The four colors of the logo symbolize the four genes used to induce the first ever iPS cells. They also represent the interaction among patients, researchers, clinicians and iPS cells. The red of the "T" is one of CiRA's image colors as well as the symbol color of Takeda. The paper crane depicted in the center of the emblem represents our good wishes and hopes for patients. The tricolor circle embodies the importance of diversity as we work together to create innovative treatment options.

What is T-CiRA?

CiRA × Takeda = ∞

Combined strengths, high hopes

T-CiRA is a 10-year joint research program established by the Center for iPS Cell Research and Application (CiRA) , Kyoto University and Takeda Pharmaceutical Company Limited (Takeda) which began in fiscal 2016. Until now, in Japan, realizing agile commercialization of results from outstanding research conducted at universities has been somewhat of a challenge. However, a direct collaboration like T-CiRA, between academia and a pharmaceutical company is expected to enable a smoother transition of achievements in research to clinical applications.

During T-CiRA's 10-year program, approximately 100 researchers, chiefly from CiRA and Takeda, are working collectively on various projects to realize clinical application of iPS cell technologies. Their aim is to develop innovative treatment options through the use of disease modeling technology, next-generation drug discovery platform technology, cell therapy and genome editing therapy in areas such as cancer, intractable and rare diseases, gastrointestinal diseases and neuropsychiatric disorders.

The roles of CiRA and Takeda

〈CiRA〉

- To direct the research program
- To provide iPS cell technologies
- To provide drug development targets and assay systems
- To provide principal investigators, researchers and postdoctoral fellows

〈Takeda〉

- To provide collaborative funding of 20 billion yen over a 10-year period
- To provide more than 12 billion yen worth of research support
- To provide R&D know-how
- To provide research facilities at Shonan Health Innovation Park
- To provide platforms for drug discovery
- To provide access to compound libraries
- To provide researchers

*The T-CiRA program is managed and operated by the Global Advanced Platform at Takeda.

Ongoing Challenges to Benefit Patients

In 2006, our team reported the generation of iPS cells. This was a worldwide first. iPS cells can proliferate indefinitely and can be differentiated into various cell types that are present in the body. They even have the great and unprecedented advantage that they can be created from the cells of individuals.

Using the potential of iPS cell technologies, we hope to cure diseases and injuries for which there are currently no effective therapeutic options. In order to do that, we must bring basic research conducted in the academic world to the stage of clinical development. That is why we initiated T-CiRA, the 10-year joint research program between Takeda Pharmaceutical Company Limited (Takeda) and the Center for iPS Cell Research and Application (CiRA), Kyoto University.

Unlike standard collaborative research, T-CiRA uses a system in which academic researchers conduct research at Takeda's laboratory at Shonan Health Innovation Park together with Takeda's researchers. For a collaborative research program between a pharmaceutical company and academia, the reach of the T-CiRA program is extensive and has already brought forth revolutionary results.

Our further aim at T-CiRA is to nurture all of the research projects in progress at T-CiRA to the clinical development stage. It is the hope of all members participating in T-CiRA to deliver new treatment options through iPS cell technologies to patients as early as possible.

Shinya Yamanaka

Director of T-CiRA
Director Emeritus and Professor of
Center for iPS Cell Research
and Application, Kyoto University

Delivering Hope through Innovative Treatments

T-CiRA is an industry-academia joint research program aimed at creating innovative medicine through iPS cell technologies. The mission of T-CiRA is to germinate treatment options from academic ideas and nurture them to the clinical applicability stage, then entrust them to suitable partners for practical development.

T-CiRA is conducting research into cancer, intractable and rare diseases, gastrointestinal diseases and neuropsychiatric disorders which are difficult to cure with conventional therapies and which threaten quality of life for patients. To engage in these issues, we have taken advantage of the unique characteristics of iPS cells to develop innovative research such as cellular therapies and small-molecule medicines, and we have achieved steady results over the past seven years.

One of the results is the iCART program, an approach that supports the stable production of immune T cells from iPS cells for cancer immunotherapy. iCART was transferred to Takeda in 2019 and since that time we have undertaken the practical use of innovative immunotherapy. In 2021, T-CiRA also transferred the iCM program for severe heart failure and the iPIC program for type 1 diabetes using iPS cells to Orizuru Therapeutics, Inc., bringing both programs closer to clinical application.

To deliver new therapies based on other projects, we continue to foster cooperation with Takeda R&D and external partnerships to help pass our human resources and experience on to the next stage. Through the T-CiRA program, we will inspire drug discovery innovation from Shonan, where we are located, to contribute to the future of medicine.

Yasushi Kajii

Head, R&D Japan Region
R&D Regional and Business Operations
Takeda Pharmaceutical
Company Limited

T-CiRA's Values

Vision

A world with the prospect of better health
through the infinite power of science

Purpose

Transform medicine with the unlimited potential of
iPS cells

Mission

Discover the seeds of treatment options and
nurture them for clinical applications

Identity

INNOVATORS
Opening up new possibilities in healthcare without fear of failure

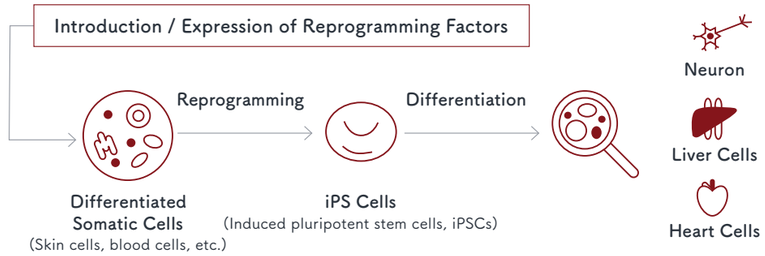
PIONEERS
Always keeping up with patients' needs using the wisdom of science

SCIENTISTS
Conducting next-generation research
for drug discovery within an industry-academia collaboration

What we do: Transform medicine with the unlimited potential of iPS cells

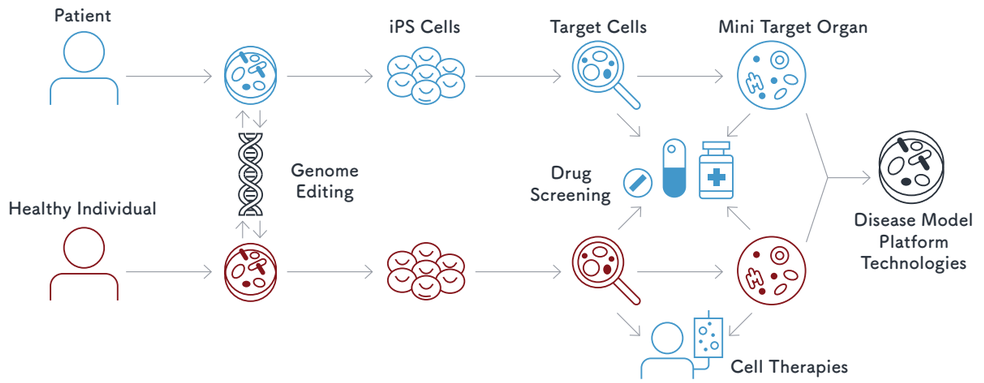
What are iPS cells?

iPS cells are established by introducing reprogramming factors into human somatic (differentiated) cells.
iPS cells can differentiate into any type of cell in the body and proliferate indefinitely in culture.



Innovative Research Conducted using iPS Cell Technologies

T-CiRA is conducting cutting-edge research into the clinical applications of iPS cells in drug discoveries, cell therapies and platform technologies. *In vitro* human disease models based on iPS cells and mini-organoid cells (known as "diseases in a dish") help scientists and physicians understand the pathophysiology or mechanism of various diseases. iPS cell-derived cells or mini organs are used to screen drugs in both efficacy and potential safety assessments. We also expect applications in regenerative medicine and transplanting iPS cell-derived cells, tissues or mini organs.



T-CiRA: Delivering Innovative Treatments

Main Areas of Research

At T-CiRA, projects involving cancer, intractable and rare diseases, gastrointestinal diseases and neuropsychiatric disorders are being developed through the use of iPS cell (iPSC) technologies.

Human iPS Cells

Cell Type	Research Target	Category
Immune cells T cells	•Cancer immunotherapy •Autoimmune disease •Rejection in allogenic transplantation	Cell Therapy
Enteric neuron iGUT	•Hirschsprung's disease	Cell Therapy Platform Technology
Renal stromal cells Kidney organoid	•Renal fibrosis •Nephrotoxicity	Drug Discovery Platform Technology
Liver organoid	•Coagulation / Complement related diseases •Drug induced liver injury (DILI)	Drug Discovery Platform Technology
Skeletal muscle cells	•Duchenne muscular dystrophy	Genome Editing Therapy
Cardiomyocyte	•Hypertrophic cardiomyopathy •Dilated cardiomyopathy	Drug Discovery
Motor neuron cells Cortical neuron cells Astrocytes Brain organoid	•Amyotrophic lateral sclerosis (ALS) •Autism spectrum disorder (ASD) •*NGLY1* deficiency	Drug Discovery

Immune Cell Therapy Project

Development of a novel immunotherapy using iPSC-derived immune cells

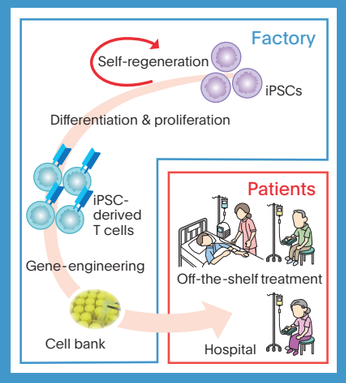
Shin Kaneko
CiRA

Gene-engineered iPSC-derived T cells for cancer immune cell therapy

In this project, we are developing a novel cancer immune cell therapy using iPSC-derived immune cells as therapeutic options. In chimeric antigen receptor (CAR) T-cell therapy, T cells are collected from a patient's blood and cancer-attacking genes are introduced into the T cells. These T cells are cultured and then transplanted back into the patient's body. Cell processing in this way requires significant time and cost. In order to solve these issues regarding CAR T-Cell Therapy, we have established a method to culture T cells using human iPS cells, safely and on a large scale. We are working toward realizing "off-the-shelf" cancer immune cell therapy by combining iPSC-derived immune cells developed at T-CiRA with Takeda's technology.

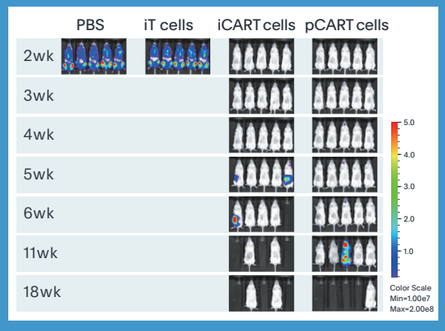
Research Overview

The objective is to create methods where T cells aimed at cancer immune cell therapy are differentiated from iPSCs and mass-cultured. The antitumor effects and safety of the obtained iPSC-derived T cells (iT) are assessed through various assay systems.



Research Progress

To examine the potential of iPSC-derived T cells (iT), we assessed their antitumor effects in models of CD19-positive B cell leukemia. When iPSC-derived T cells expressing anti-CD19 chimeric antigen receptor (iCART) were administered to mice bearing human CD19-positive B cell leukemia, the resulting tumor-suppressing effect was found to be equivalent to that of human peripheral blood T cells expressing the same anti-CD19 CAR (pCART). Graft-versus-host disease (GvHD)-like symptoms including weight loss and hair loss were observed in the group treated with pCART but not in the iCART treated group.



Perspective

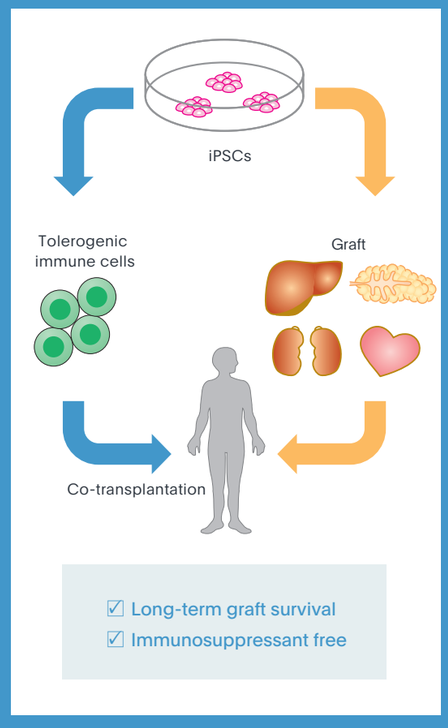
We are developing methods to manufacture iPSC-derived T cells as well as genetic modification technology optimization for iPSC-derived T cells aiming to develop new therapeutic options for cancer patients. We will advance development into clinical trials as swiftly as possible by demonstrating their medicinal efficacy and confirming their safety in preclinical studies.

iPSC-derived immune cells for immune tolerance development

In addition to cancer immune cell therapy, we are working on the development of clinical applications of novel immunological tolerance therapy utilizing our immune cell induction technology developed at T-CiRA. For example, transplantation requires immunosuppressive drugs to prevent rejection, but the drugs may in turn cause adverse reactions. We therefore aim to enable organ transplants that maintain full functionality over the long term without the administration of immunosuppressive drugs by differentiating human iPS cells into immune cells with immunosuppressive potential against a specific antigen and transplanting these immune cells into the patient simultaneously with tissue for transplant made from the same human iPS cells.

Research Overview

We develop methods where selected candidates for cell products that can induce immune tolerance from human iPSCs are differentiated and mass-cultured. Immune tolerogenic capacity and safety of the obtained cells are assessed through various assay systems.



Research Progress

New differentiated cell lines for multiple types of immune cells that are considered to have immune tolerogenic capacity have been established and analyzed for cell properties. Various preclinical studies are now being conducted to evaluate the immune tolerogenic capacity of the cells.

Perspective

We aim to deliver new therapeutic options to patients receiving immunosuppressants after organ transplantation and those suffering from intractable diseases caused by abnormalities in the immune system such as autoimmune diseases. By confirming the efficacy and safety of our therapeutic options in preclinical studies, we will continue to conduct research and development to move forward to early clinical studies and to reach our goal of practical use of our products.

Future of iPSC PART 1

An Accelerated Process

After joining Takeda, I was a pharmacological researcher in the field of drug discovery for cancer and autoimmune diseases. In 2015, when the T-CiRA program was established, I joined the team led by Professor Shin Kaneko since I thought I could make the most of my background in the fields of both cancer and immunology. Doing drug discovery research using iPSCs as a new material was an attractive challenge for me.

The Immune Cell Therapy Project is trying to develop cytotoxic T cells which fight against cancer cells, by creating T cells (cells for protecting the body from foreign intruders) from iPSCs and applying the gene manipulation technique to them. The team has completed the basic research stage and is now in the final process for delivering the new treatment to patients.

Fundamentally, I am a researcher in a basic research field, but now at T-CiRA, I am engaging in activities which are more closely related to the clinical field, such as working as a lead operator of cell production for non-clinical safety studies and for clinical use. I also work with cell therapy specialist teams at Takeda based here at Shonan Health Innovation Park and in Boston.

This is the first experience in my career, including the projects I was involved in before joining T-CiRA, to see a project having a prospect of clinical application in the five years since launch. It is truly amazing to achieve such progress particularly in a study combining iPSC-derived cell therapy and immunotherapy.

One of the appeals of T-CiRA is that researchers from Takeda can always communicate directly with academic researchers, which helps accelerate our studies. My main goal—as well as my dream—is to see our current studies bear early fruit and help as many patients as possible.

Suguru Arima

Principal Scientist,
Global Advanced Platform, Research
Takeda Pharmaceutical Co., Ltd.
<Immune Cell Therapy Project>

"Sync": Ties Promoting iPS Cell Technologies

In the T-CiRA Organoid Medicine Project, led by principal investigator Professor Takanori Takabe, we use miniature organs derived from iPS cells to reproduce what happens physiologically in the bodies of patients to study new approaches for drug discovery and disease research. I specialize in stem cell biology, hematological vascular biology and systems biology, and I use theoretical informatics and experimental techniques multilaterally to develop new miniature organ technology especially focused on blood vessels that connect organs in the human body. For me, T-CiRA is a place where I can take on big challenges. Being at the frontline of drug discovery, we can conduct effective research for developing new treatment methods. In addition, T-CiRA puts priority on research, which motivates me as a basic researcher. The ultimate goal of iPSC technologies is to contribute to society by providing each patient with appropriate treatment tailored to their individual needs.

Patients and families have high expectations for iPSC research. Through patient cell donation, a circle connecting patients and researchers has been created. At the same time, iPSCs are full of personal information, such as the donor's genetic information and medical history. To use them safely, it is necessary to cooperate not only with researchers and physicians who use them but also specialists with various skills, such as information science specialists handling the management, maintenance and mining of big data, and machine engineering specialists who develop devices for safe and stable handling of iPSCs.

The circle of people created by iPSC technologies and harmony among specialists necessary for the technology to make social contributions—these are important points of view in building my future career as a scientist. With these aspects in mind, I will continue to take on various challenges.

Norikazu Saiki

Project Assistant Professor,
Organ and Tissue Neogenesis Consortium, Division of Advanced Multidisciplinary Research, Tokyo Medical and Dental University <Organoid Medicine Project>

Organoid Medicine Project

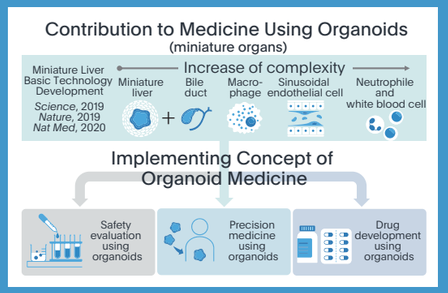
Miniature liver technology as a platform for research towards pharmaceutical applications

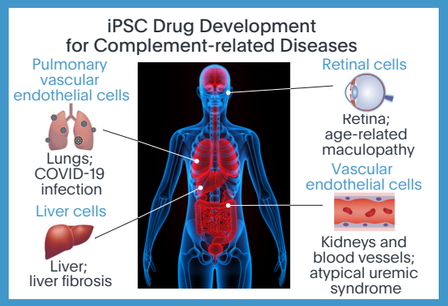
Takanori Takebe
Tokyo Medical and Dental University

A miniature liver (liver organoid) is a three-dimensional mini-sized human liver with vascular structures created using human iPS cells. The miniature liver mimics the early stages of organ development *in utero*. Using this innovative technology, we will reproduce the complex phenomena found in patients' bodies, explore new therapeutic drugs for intractable diseases and develop new drug discovery processes to help analyze rare adverse events, which could not be predicted with conventional drug discovery research.

Research Overview

• We will apply the genome-wide screening technology to iPSC-derived miniature organs (organoids) to help elucidate pathological mechanisms of rare diseases and search for therapeutic targets.
• We also will establish new methods for reproducing complex disease pathologies *in vitro* by further advancing the technology for creating liver organoids with the introduction of cells that were not previously included.
• Focusing on diseases related to complements and coagulation with high unmet medical needs, we aim to elucidate pathological mechanisms and develop therapeutic drugs for those diseases using miniature liver.





Research Progress

• We demonstrated that susceptibility of drug-induced liver injury (DILI) can be predicted from the polygenic risk score (PRS) calculated from individual genome-wide data by combining human iPSC-derived miniature liver, human liver cells and clinical data.
• We constructed high-throughput screening systems to detect vascular endothelial dysfunction *in vitro* caused by accumulation of compliments, using complement factors secreted from human iPSC-derived miniature liver and human iPSC-derived endothelial cells and found new drug candidate compounds.
• We showed that addition of fatty acids and other substances to human iPSC-derived miniature liver induces fatty liver and expression of inflammation and fibrosis markers. This resulted in our creation of the world's first *in vitro* model that mimics liver fibrogenesis with limited treatment options.

Perspective

The method for creation of human iPS cell-derived liver organoids is a revolutionary technology, and we aim to use it to recreate the complex phenomena occurring in the bodies of patients to develop novel therapeutic drugs for intractable diseases that have no established methods of treatment.

Neural Crest Cell Project

A new research platform with human iPSC-derived neural crest cells and its applications for drug discovery and regenerative medicine

Makoto Ikeya
CiRA

Neural crest cells (NCCs) play an important role in development and growth. These cells differentiate into diverse cell type lineages such as bones and peripheral neurons, suggesting their great potential for clinical applications. In this project, we aim to establish methods to maintain and culture human iPSC-derived NCCs and differentiate them into various types of cells such as enteric neurons and kidney organoids. Moreover, we hope to construct an *in vitro* disease model in combination with related technologies. We aim to apply this technology to cell therapy for congenital intestinal diseases and drug discovery for diseases related to the kidney and nervous system.

Research Overview

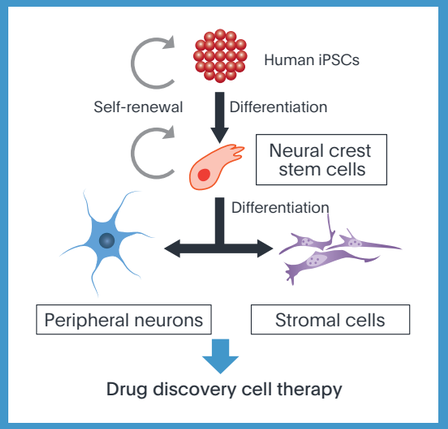
• Neural crest cells (NCCs) are a unique cell population that exists only in the early stages of development, and there are many areas in the research of human neural crest cells in particular that are yet to be clarified.
• It is extremely difficult to maintain the undifferentiated state of neural crest cells while culturing them *in vitro* (neural crest stem cell maintenance culture). However, if basic technologies using human iPS cells could be established, neural crest cells have the potential for a wide range of applications.

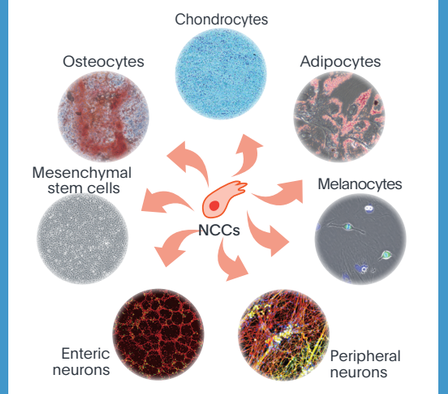
Research Progress

• We have established the technology for *in vitro* maintenance culture of neural crest stem cells created from human iPS cells while maintaining their pluripotency.
• We have established multiple protocols for differentiation of neural crest cells into enteric neuron progenitors and kidney stromal cells, and we have filed patent applications. These differentiated functional cells will be used for drug discovery research and for cell therapies.

Perspective

Taking advantage of the technologies using NCCs, we aim to contribute to developing cell therapies and drugs that have never existed before to deliver innovative therapeutic methods to patients suffering from diseases.





Neural crest cells (NCCs) differentiated into various cell types, e.g., mesenchymal stem cells, chondrocytes, melanocytes or peripheral neurons.

Genome Editing Therapy for Muscular Dystrophy Project

Development of novel gene therapy for Duchenne muscular dystrophy using genome editing and delivery technologies

Akitsu Hotta
CiRA

Duchenne muscular dystrophy (DMD) is caused by a mutation in the dystrophin gene, which causes gradual loss of skeletal muscles. It is known as an intractable disease and there is no effective treatment. However, genome editing technology holds great promise in developing a new treatment option. In this project, we aim to develop cutting-edge delivery technologies which will deliver the genome editing tool, a key for genetic repair, to the patient's skeletal muscle tissue and restore the dystrophin protein. While confirming its efficacy and safety in both patient derived iPS cells and animal disease models, we are working to establish a new gene therapy to benefit patients.

Research Overview

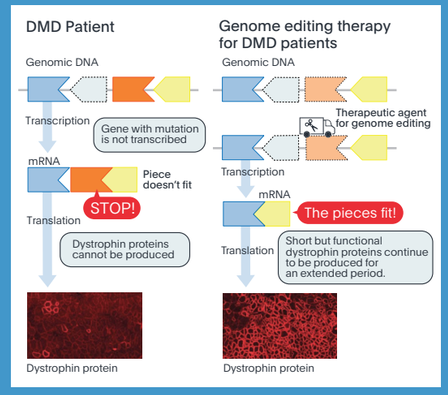
• We aim to sustain the restoration of dystrophin protein for an extended period by repairing exons in the dystrophin genes at the DNA level using genome editing technology.
• Taking advantage of a cutting-edge drug delivery technique, we will enable delivery of genome editing tools to a large area of skeletal muscles by repeated administration.
• We will develop clinically applicable genome editing drugs by evaluating the effects of genome editing in iPS cells derived from DMD patients and animal models of the disease.

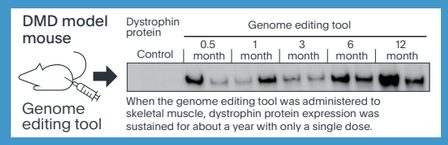
Research Progress

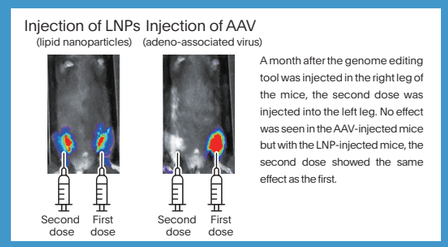
• We have created a nanoparticle technology (using lipid nanoparticles and virus-like particles) that delivers genome editing tools to muscles.
• We confirmed that delivery of one dose of the nanoparticles using the above technique to the skeletal muscles of DMD model animals induced sustained dystrophin protein expression for about one year.
• While repeated administration using conventional virus delivery techniques is challenging, the lipid nanoparticles we developed could be administered repeatedly.

Perspective

For over 30 years it has been known that muscular dystrophy is caused by genetic mutations, but it has not been possible to treat the mutations themselves. With genome editing technologies and cutting-edge delivery technologies, it is now becoming possible to repair genetic mutations simply with injections. We intend to continue working on research and development in collaboration with experts in various fields to achieve greater therapeutic efficacy and more robust safety, to make this new therapy widely available.







Future of iPSC PART 2

Understanding Patients' True Needs

I was originally engaged in drug discovery research targeting diabetes and obesity. Exercise is said to be effective in preventing these diseases, and my study focused on skeletal muscles in search of a drug which can produce the same preventive effect as exercise. T-CiRA was established in 2015 with a planned launch of a new project targeting serious muscular diseases, and I decided to join the muscular disease project led by Associate Professor Akitsu Hotta. We are focusing on Duchenne muscular dystrophy, among other muscular diseases. As an approach for treating this intractable disease, we are proceeding with drug discovery research based on genome editing technology to develop new treatment modalities. Drugs created by this technology are expected to realize long-lasting treatment effects with lower dosages.

Recently, our technology in developing drugs for Duchenne muscular dystrophy is attracting attention in its possible applications for Takeda's neuroscience drug discovery unit's neuromuscular disease research. We have started collaborative research with that unit, which is accelerating the speed of our research, giving us a great boost.

In drug discovery research, it is very important to understand patients, and I found reading articles and research papers is not enough to obtain deep understanding of patients' symptoms and needs, so I have been actively participating in public programs and events on muscular dystrophy. I believe such patient engagement activities are important because they allow me to know patients' inner thoughts and help eliminate self-righteousness from drug discovery research. Every time I see patients' and their families' high expectations for the development of therapeutic drugs, I reaffirm my strong resolve to deliver new treatment options that will bring smiles to their faces.

Hiroyuki Hozumi

Principal Scientist, Global Advanced Platform, Research
Takeda Pharmaceutical Co., Ltd.
<Genome Editing Therapy for Muscular Dystrophy Project>

Where the Spirit of Inquiry Blossoms

After finishing my master's program in biology, I joined Takeda and engaged in identification of new treatment target molecules and screening of small molecular compounds until I left to go abroad. After working as a technician at cancer-related research centers in the US and Japan, I went through a doctoral course. My laboratory was located in an environment where I could do research close to patients which gave me motivation. At the same time, however, I often encountered situations in which I would think that I could do my studies more efficiently if I were in a pharmaceutical company.

After a maternity and childcare hiatus, I sought to resume my research career, when I encountered a research paper on phenotype screening based on patient derived iPS cells published by a T-CiRA project team. I thought, at T-CiRA, I would be able to make the most of the skills I had acquired in drug discovery research at Takeda, and basic research skills developed in academia. I was also grateful that Shonan Health Innovation Park, where T-CiRA is located, has an onsite day-care center.

T-CiRA has the merits of both academia and a pharmaceutical company and offers an ideal research environment for me. With deep knowledge in iPSC-based regenerative medicine, CiRA leads the realization of clinical applications. On the other hand, Takeda has rich compound libraries, state-of-the-art analytical instruments and know-how in creating new therapeutic drugs. The system for cooperation among projects is working well, as we share information among projects, which helps to accelerate research.

As a researcher, I wish to contribute to realizing the future for patients with intractable diseases, a future where they can continue to hold jobs, enjoy hobbies and live happy lives.

Fumika Inazuka

Researcher
Center for iPS Cell Research and Application, Kyoto University
<Cardiomyopathy Project>

Cardiomyopathy Project

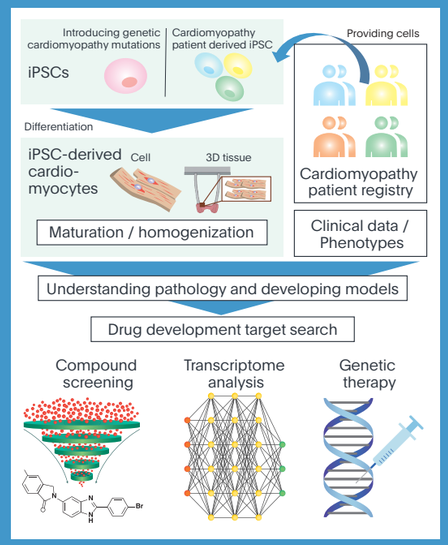
Drug discovery and treatment development for refractory cardiomyopathy

Yoshinori Yoshida
CiRA

Abnormalities in cardiac muscles can lead to disorders such as enlargement and hardening of the heart (hypertrophic cardiomyopathy) and reduced contractility (dilated cardiomyopathy), resulting in deterioration of the blood pumping function of the heart. Genetic mutations and viral infections have been known to cause cardiomyopathy, but quite a few cases have no known cause. Aiming to develop novel therapeutic drugs for cardiomyopathy, we are trying to reproduce its pathology with iPSC-derived cardiomyocytes and explore targets for drug development. In addition, we are working on studies to deliver cell therapy to a broad spectrum of patients.

Research Overview

• Our goal is to create iPSC-derived cardiomyocytes that replicate the pathology of cardiomyopathy, such as cell enlargement and malalignment of a sarcomere that plays a key role in myocardial contraction, by introducing genetic mutations that cause cardiomyopathy and identifying targets for the development of novel drugs to improve such abnormal phenotypes.
• To this end, we will develop and improve techniques to make iPSC-derived cardiomyocytes more homogeneous and mature into 3D tissues, in order to create more sophisticated models that reproduce the pathology of cardiomyopathy.
• We aim to create iPSC-derived cardiomyocytes with low immunogenicity for transplantation and develop a less-invasive approach for cardiac cell transplantation using such cells, which will allow for adequate cell engraftment even with low dosage immunosuppressants.



Research Progress

• We screened about 10,000 compounds using iPSC-derived cardiomyocytes which reproduced the pathology of hypertrophic cardiomyopathy and identified novel compounds that inhibit enlargement of cardiac muscle cells. Assessment of its efficacy, toxicity and mechanism of action is in progress in various studies using cells, tissues, and animal models.
• We identified a marker (CD151) that can be used to enrich iPSC-derived ventricular or atrial cardiomyocytes.
• We identified a compound (ERR agonist) that facilitates structural, metabolic and electrophysiological maturation of cardiomyocytes derived from iPS cells. The disease model of hypertrophic cardiomyopathy treated with the ERR agonist enables us to observe more prominent pathology.

Perspective

Using sophisticated reproduction of the pathology of cardiomyopathy through iPSC-derived cardiomyocytes, we aim to elucidate the underlying cause of worsening of disease conditions as well as find effective targets for drug development by taking advantage of various research and analysis techniques.

ALS/ASD Drug Discovery Project

ALS/ASD drug discovery and development using patient derived iPSCs

Haruhisa Inoue
CiRA

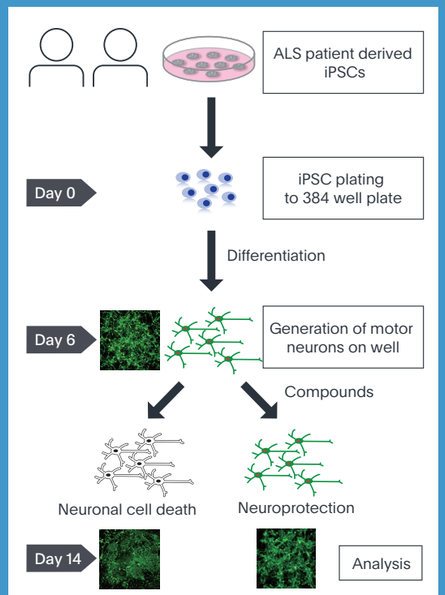
Amyotrophic lateral sclerosis (ALS), a progressive intractable disease in which motor neurons are damaged and the muscles atrophy, and autism spectrum disorder (ASD), a neurodevelopmental disorder, are neurodegenerative diseases for which there are still no effective treatments. We are using neurons differentiated from patient derived iPS cells to clarify the mechanisms underlying these diseases. We are working on discovering novel therapeutic drugs by using AI-based hit prediction models and uncovering drug seeds from Takeda Pharmaceutical's library of compounds.

Research Overview

We are working on studies to deliver innovative drugs to patients with amyotrophic lateral sclerosis (ALS) and autism spectrum disorder (ASD).

Research Progress

• We succeeded in identifying a "drug seed" that shows protective effects against the death of motor neurons derived from iPSCs of ALS patients using the high-content and high-throughput assay system that targets the death of motor neurons.
• We established a high-throughput assay system using neurons derived from iPSCs of ASD patients. We are planning to further search for compounds in Takeda's library that will lead to novel therapies.



The assay platform was established in CiRA, Kyoto University, and was introduced to T-CiRA joint research program.

Perspective

We are aiming to discover new "drug seeds" by utilizing patient derived iPS cells and screening them against Takeda's compound library.

NGLY1 Deficiency Project

Development of therapeutic agents for rare hereditary diseases using iPS cells

Tadashi Suzuki
RIKEN

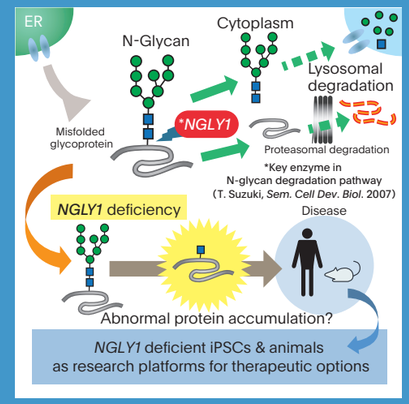
NGLY1 deficiency, which was discovered in 2012, is an extremely rare genetic disorder with symptoms that include developmental delay, motor disorder and epileptic symptoms. The cause is a mutation in the *NGLY1* gene that codes an enzyme called peptide: *N*-glycanase that removes sugar chains from glycoprotein. Through a combination of basic research findings, iPS cell technology and a drug discovery platform, we will develop innovative therapeutics targeting *NGLY1* deficiency which presently does not have any therapeutic options.

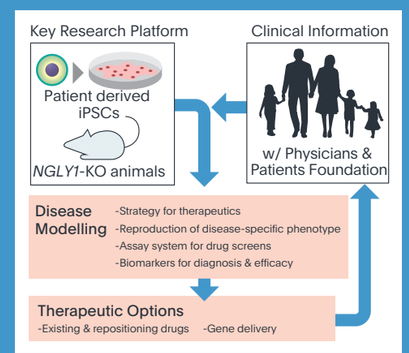
Research Overview

• We will advance the understanding of *NGLY1* deficiency pathology through the use of patient derived iPS cells.
• We are assessing the efficacy of *NGLY1* gene replacement therapy using adeno-associated virus (AAV) vectors.
• We are working on development of drugs to alleviate symptoms and improve QOL using patient derived iPSCs and disease model animals.
• We will develop diagnostic drugs that can be used for early diagnosis and assessment of treatment efficacy.

Research Progress

• We identified a number of drugs that improve abnormalities (hypofunction of mitochondria) observed in neurons developed from patient derived iPSCs in the library of approved drugs.
• We characterized *NGLY1* knockout animals as a disease model.
• We found that introduction of human *NGLY1* genes into the cerebral ventricle of the disease model rat via AAV vectors improved its motor function.
• With the aim of establishing a diagnostic method for *NGLY1* deficiency, we successfully developed a substrate to detect enzymatic activity of *NGLY1* present in cells and tissues.





Perspective

• We will provide therapeutic options to treat patients with *NGLY1* deficiency and to improve their quality of life through research using brain organoids induced from patient derived iPS cells and animal models of the disease.
• We will help promote clinical trials of the gene therapy developed by Grace Science Foundation, the organization for *NGLY1* deficiency patients in the US.
• We are working toward developing methods to diagnose *NGLY1* deficiency with high accuracy and bringing them into clinical application.

A Patient's Story

The Story of Grace: Living with *NGLY1* Deficiency

Matt Wilsey Chairman, President and Co-founder, Grace Science Foundation

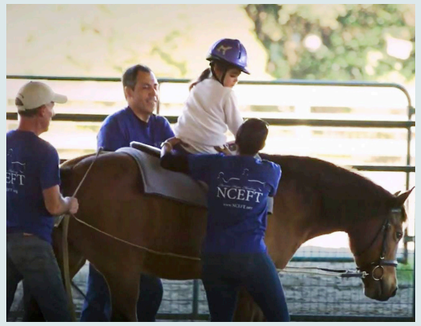
I would like to talk to you about my daughter Grace. She is a sweet, lovable little girl. She's eleven years old and fascinated by music and books. She loves to eat and is very social. In 2013 Grace was diagnosed with *NGLY1* deficiency. She was only three at the time.

NGLY1 deficiency is an extremely rare genetic disease which was first reported in 2012. There are less than 100 diagnosed patients worldwide. *N*-glycanase is an enzyme that removes glycans (sugar chains) from glycoproteins. When a mutation of the *NGLY1* gene which codes *N*-glycanase occurs, the enzyme cannot remove excess sugar. *NGLY1* deficiency is a global developmental disease so it basically affects every system in the body. It can lead to delays in growth, muscle loss and movement disorders. While Grace is 11 years old, she acts almost like a two-year-old. She can barely walk. I think communication is the hardest facet of the disease.

My background is tech entrepreneur. When Grace was diagnosed, I shifted gears fully to dedicate myself to understanding this disease, treating it and eventually curing it. I quickly learned that there was almost no research being done about *NGLY1* deficiency. My wife and I embarked on a challenge to help not only Grace but others with *NGLY1* deficiency by starting the Grace Science Foundation.

At Grace Science Foundation, scientists are building on the discovery made by Dr. Shinya Yamanaka, the world-renowned scientist and Nobel Laureate. Dr. Tadashi Suzuki of RIKEN, who first discovered the *NGLY1* gene and is working on the *NGLY1* Deficiency Project at T-CiRA, is also a member of the research team at the Foundation.

Grace is now working on a therapy involving riding horses, which helps to strengthen her core. When she first started, she could barely put her legs on either side of the horse, but now, she can even ride backwards and sideways with assistance.



At Grace Science Foundation, we help scientists around the world find treatments and cures. My hope is that finding a cure for *NGLY1* deficiency will lead to discoveries in cures for other diseases. It just takes one little spark to unlock a disease and you can do that. The more brilliant minds there are working on this, the faster we will get to a solution. In June 2021, Dr. Tadashi Suzuki and his team reported the possibility of a gene therapy targeting the central nervous system as a treatment for *NGLY1* deficiency. I hope that such breakthroughs accelerate and bring us closer to treatments for cures that will enable *NGLY1* deficiency patients to lead independent lives.

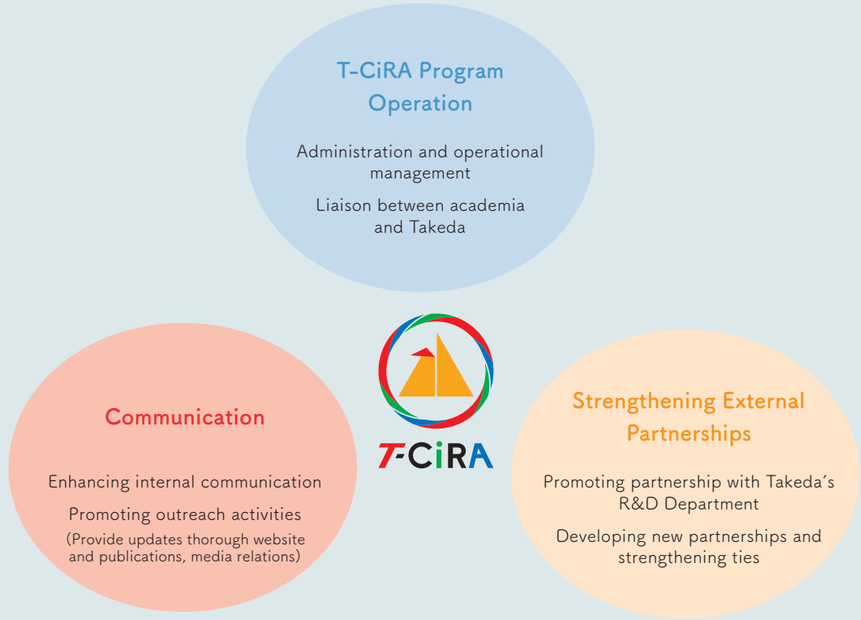
*This story is intended solely to promote awareness of *NGLY1* deficiency.

Supporting the Progress of Research

T-CiRA is a joint research program comprised of about 100 researchers primarily from CiRA and Takeda. Members representing both industry and academia work together to advance various projects, using iPS cell technology. The Global Advanced Platform at Takeda is responsible for overall management and administration of the program.

The Global Advanced Platform office provides the support that project members need to advance their research. We strive to create an environment that brings members together for seamless communication and sharing of information. We undertake outreach activities that provide timely updates about the research projects to the world. We also focus on developing partnerships that ensure and accelerate the practical application and commercialization of the research conducted at T-CiRA. In support of ongoing research projects conducted at T-CiRA, we make every effort to support the expansion and strengthening of existing and future partnerships to fulfill the goals of the program.

Operational Management Structure of T-CiRA



Please direct enquiries to Global Advanced Platform office, located inside Shonan Health Innovation Park.
E-mail: T_CiRA@takeda.co.jp

Publications List

2018

1 Enhancing T Cell Receptor Stability in Rejuvenated iPSC-Derived T Cells Improves Their Use in Cancer Immunotherapy
Atsutaka Minagawa et al.
Cell Stem Cell, 2018 Dec; 23: 850-858
<Immune Cell Therapy Project>

2019

2 iPS drug discovery strategy using liver organoid technology [in Japanese]
Eri Kawakami, Takanori Takebe
Saibo [*The Cell*], 2019 Apr
<Organoid Medicine Project>

3 Organoid Models of Development and Disease Towards Therapy
Yasunori Nio, Takanori Takebe
Medical Applications of iPS Cells,
Springer Nature eBOOK, 2019 Apr; 149-168
<Organoid Medicine Project>

4 Phenotypic Drug Screening for Dysferlinopathy Using Patient Derived Induced Pluripotent Stem Cells
Yuko Kokubu et al.
Stem Cells Transl Med, 2019 Jun; 8: 1017-1029
<Intractable Muscular Disease Project>

5 Identification of 2,6-Disubstituted 3*H*-Imidazo[4,5-*b*]pyridines as Therapeutic Agents for Dysferlinopathies through Phenotypic Screening on Patient Derived Induced Pluporient Stem Cells
Hiroyuki Takada et al.
Journal of Medicinal Chemistry,
2019 Oct; 62 (20): 9175-91877
<Intractable Muscular Disease Project>

2020

6 The possibility and challenges of organoid medicine [in Japanese]
Momoko Oohori et al.
Jikken Igaku [*Experimental Medicine*],
2020 Jan; 38 (1): 44-49
<Organoid Medicine Project>

7 Extracellular nanovesicles for packaging of CRISPR-Cas9 protein and sgRNA to induce therapeutic exon skipping
Peter Gee et al.
Nature Communications,
2020 Mar; 11: Article Number 1334
<Genome Editing Therapy for Muscular Dystrophy Project>

8 Insulin-Deficient Diabetic Condition Upregulates the Insulin-Secreting Capacity of Human Induced Pluripotent Stem Cell-Derived Pancreatic Endocrine Progenitor Cells After Implantation in Mice
Taisuke Mochida et al.
Diabetes, 2020 Apr; 69 (4): 634-646
<Beta Cell Therapy Project>

9 Ngly1−/− rats develop neurodegenerative phenotypes and pathological abnormalities in their peripheral and central nervous systems
Makoto Asahina et al.
Human Molecular Genetics,
2020 Apr; 29 (10): 1635-1647
<*NGLY1* Deficiency Project>

10 Polygenic architecture informs potential vulnerability to drug-induced liver injury
Masaru Koido et al.
Nature Medicine, 2020 Oct; 26 (10): 1541-1548
<Organoid Medicine Project>

11 Current status and future perspectives of HLA-edited induced pluripotent stem cells
Keiko Koga, Bo Wang, Shin Kaneko
Inflammation and Regeneration,
2020 Oct; 40: Article number 23
<Immune Cell Therapy Project>

12 Prediction of Compound Bioactivities Using Heat-Diffusion Equation
Tadashi Hidaka et al.
Patterns, 2020 Dec; 1 (9): 100140
<ALS/ASD Drug Discovery Project>

2021

13 The promise of human organoids in the digestive system
Masaaki Funata et al.
Cell Death & Differentiation, 2021 Jan; 28: (1) 84-94
<Organoid Medicine Project>

14 A clinically applicable and scalable method to regenerate T-cell from iPSCs for off-the-shelf T-cell immunotherapy
Shoichi Iriguchi et al.
Nature Communications,
2021 Jan; 12: Article number 430
<Immune Cell Therapy Project>

15 JF1/B6F1 Ngly1 -/- mouse as an isogenic animal model of *NGLY1* deficiency
Makoto Asahina et al.
Proceedings of the Japan Academy, Ser. B Vol. 97 No. 2, 2021 Feb; 89-102
<*NGLY1* Deficiency Project>

16 ERR γ enhances cardiac maturation with T-tubule formation in human iPSC-derived cardiomyocytes
Kenji Miki et al.
Nature Communications,
2021 Jun; 12: Article number 3596
<Cardiomyopathy Project>

17 Reversibility of motor dysfunction in the rat model of *NGLY1* deficiency
Makoto Asahina et al.
Molecular Brain, 2021 Jun; 14: Article number 91
<*NGLY1* Deficiency Project>

18 A muscle fatigue-like contractile decline was recapitulated using skeletal myotubes from Duchenne muscular dystrophy patient derived iPSCs
Tomoya Uchimura et al.
Cell Reports Medicine, 2021 Jun; 2 (6): 100298
<Intractable Muscular Disease Project>

19 Loss of peptide: N-glycanase causes proteasome dysfunction mediated by a sugar-recognizing ubiquitin ligase
Yukiko Yoshida et al.
PNAS, 2021 Jul; 118 (27) e2102902118
<*NGLY1* Deficiency Project>

20 Research on autism and dementia using iPS cells [in Japanese]
Keisuke Shibata et al.
Saibo [*The Cell*], 2021 Oct
<ALS/ASD Drug Discovery Project>

21 A method for assaying peptide: N-glycanase/N-glycanase 1 activities in crude extracts using an N-glycosylated cyclopeptide
Hiroto Hirayama et al.
Glycobiology, 2022 Feb; 32 (2): 110-122
(Originally published 2021, Nov)
<*NGLY1* Deficiency Project>

22 Orai1-STIM1 regulates increased Ca2+ mobilization, leading to contractile Duchenne muscular dystrophy phenotypes in patient derived induced pluripotent stem cells
Tomoya Uchimura, Hidetoshi Sakurai
Biomedicines, 2021 Nov; 9 (11): 1589
<Intractable Muscular Disease Project>

23 Emerging human liver organoid platform for basic and clinical research [in Japanese]
Masaaki Funata et al.
Jikken Igaku [*Experimental Medicine*],
2021 Nov; 39 (18): 2870-2876
<Organoid Medicine Project>

24 Low immunogenicity of LNP allows repeated administrations of CRISPR-Cas9 mRNA into skeletal muscle in mice
Eriya Kenjo et al.
Nature Communications,
2021 Dec; 12: Article number 7101
<Genome Editing Therapy for Muscular Dystrophy Project>

25 Ameliorative effect of anti-complement factor antibody on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected macaque
Yasunori Nio
Translational and Regulatory Sciences,
2021 Dec; 3 (3): 98-101
<Organoid Medicine Project>

2022

26 Assay for the peptide:N-glycanase/NGLY1 and disease-specific biomarkers for diagnosing *NGLY1* deficiency
Hiroto Hirayama, Tadashi Suzuki
J Biochem, 2022 Feb; 171 (2): 169-176
<*NGLY1* Deficiency Project>

27 Delivery of CRISPR-Cas tools for *in vivo* genome editing therapy: Trends and challenges
Eman A. Taha, Joseph Lee, Akitsu Hotta
Journal of Controlled Release,
2022 Feb; 342: 345-361
<Genome Editing Therapy for Muscular Dystrophy Project>

28 Generation of human GAPDH knock-in reporter iPSC lines for stable expression of tdTomato in pluripotent and differentiated culture conditions
Daisuke Kamiya et al.
Stem Cell Research, 2022 Apr; 60: 102704
<Neural Crest Cell Project>

29 Generation of a human SOX10 knock-in reporter iPSC line for visualization of neural crest cell differentiation
Teruyoshi Yamashita et al.
Stem Cell Research, 2022 Apr; 60: 102696
<Neural Crest Cell Project>

A Mission to Benefit the World

At T-CiRA, researchers from academia and Takeda are working together as one team to accelerate research on projects dealing with development of cell therapy and drug discovery platforms. T-CiRA began in fiscal 2016 as a 10-year program. Since then, it has proven itself as a source of innovation in iPS cell technologies by steadily making achievements and producing results.

Our mission is to discover the seeds of treatment options and nurture them for clinical application. In order to deliver on this mission, we are determined to overcome challenges and develop innovative ideas, bringing our medical discoveries and applications to the world.

Research Advancing to Clinical Applications

Three programs undertaken with T-CiRA were passed on to optimal business partners for further clinical development. One was the iCART Program for cancer treatment, which was transferred to Takeda in 2019 and is undergoing development; the iCM Program and iPIC Program were both transferred to Orizuru Therapeutics, Inc., a new company established in 2021 with the aim of developing regenerative medicine products using iPS cells. T-CiRA will continue to transfer research projects which are nearing clinical development to the best partners, in order to fulfill our mission to make timely delivery of innovative treatment options to patients.

iPS Cell-derived CAR T-Cell Therapy (iCART) Program

The program aims to stably provide CAR T-cell therapy for cancer treatment using T-cells derived from iPS cells.

CAR T*-cell therapy is a type of immunotherapy against cancer. In this treatment, a type of immune cells called T cells which detect and attack cancer cells are collected from the blood of a patient, genetically engineered and cultured outside of the patient's body, and then returned to the patient to treat cancer. This approach, however, uses the patients' own T cells, which takes time and cost; thus, in the T-CiRA program, we pursued research on how to produce T cells from iPS cells suitable for clinical application. We eventually discovered a more efficient method for culturing T cells and confirmed its statistically significant antitumor effect in experiments on mice.

We named the T cells derived from iPS cells, iCART cells. The iCART Program led by Professor Shin Kaneko of CiRA was transferred to Takeda in July 2019. This transfer will enable the provision of T cells to patients more quickly and at lower cost thus equalizing therapeutic opportunities.

* CAR T: CAR stands for chimeric antigen receptors, and T for T lymphocytes.

iCART Program
Date of transfer: July 2019
Company: Takeda Pharmaceutical Co., Ltd.

iPS Cell-derived Cardiomyocyte (iCM) Program
iPS Cell-derived Pancreatic Islet Cell (iPIC) Program

The two programs are aiming for clinical application of a new cell therapy method for patients with severe heart failure using human iPS cell-derived cardiomyocytes (iCMs), and a new treatment for patients with type 1 diabetes using transplanted human iPS cell-derived pancreatic islet cells (iPSCs).

In hand with the advancement of two T-CiRA programs, Orizuru Therapeutics, Inc. was newly established as a framework for accelerating realization of iPS cell therapy in a timely and effective manner. The company was launched using external funds and is located within the complete ecosystem of Shonan Health Innovation Park.

One of its two programs is the iCM Program led by CiRA's Associate Professor Yoshinori Yoshida. The team succeeded in the production of highly purified and safe cardiomyocytes through a simple differentiation process using a unique purification method that they developed. They named the cardiomyocytes differentiated from human iPS cells, iCM. Transplantation of iCMs with strong engraftment ability could facilitate cardiac myogenesis, which might enable recovery of heart functions in patients with severe heart failure who have had limited treatment options. Such treatment could reduce the mental and physical burden on the patients.

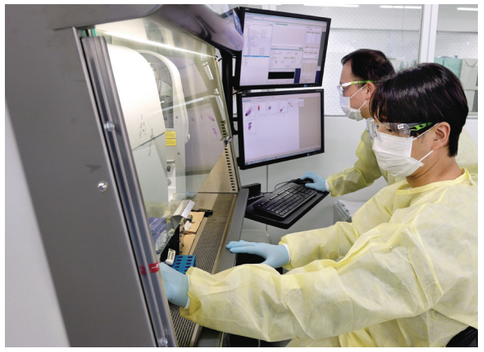
The other is the iPIC Program, led by CiRA's Junior Associate Professor Taro Toyoda. The team successfully cultured a large quantity of homogenous human iPS cell-derived pancreatic islet cells, iPICs, using a culturing system that they developed. The iPICs are mainly characterized by successful differentiation into and generation of insulin-secreting β cells and glucagon-secreting α cells both of which play key roles in diabetes, as well as less malignant transformation. The goal of this program is to cure brittle type-1 diabetes by transplanting iPICs to patients with the disease whose blood sugar level is difficult to control and thereby stimulating physiological insulin production.

iCM and iPIC Programs
Date of transfer: July 2021
Company: Orizuru Therapeutics, Inc.

Inside T-CiRA

T-CiRA's laboratories are located at Shonan Health Innovation Park (iPark) in Fujisawa City, Kanagawa Prefecture, along with CiRA's branch office. The laboratories cover a total area of 7,500m^2. Approximately 100 researchers from CiRA, Tokyo Medical and Dental University, RIKEN and Takeda are working side by side on iPS cell research every day.

The facility is equipped with all necessary resources, including the world's most advanced equipment and access to Takeda's vast and rich compound library. It provides a "one stop" environment where everything from basic research to clinical application research can be conducted. In addition, iPark is home to many companies and organizations in the area of next-generation medical care, AI and venture capital. It serves as a vital ecosystem of life sciences in Japan and fertile grounds for prompting technological innovation.



Making Discoveries Together

People from diverse backgrounds work together at T-CiRA. We hold monthly meetings for active discussions among researchers. Various events are held to support communication among all T-CiRA members, and we also create opportunities for researchers to interact with patients. These communication activities both within and outside T-CiRA broaden researchers' horizons and help lead to major innovations.

Monthly Meetings

All project members come together once a month for a debriefing session to report their project's progress, These discussions allow participants to speak freely and provide opportunities for everyone to see and understand research concepts and progress in projects other than their own, giving new perspectives and sometimes developing into collaboration among different projects. Members from Takeda's overseas R&D departments such as Boston and San Diego also participate online.

Interactions with Patients

In conducting drug discovery research, it is important to understand that patients having the same disease may have different symptoms and needs. At T-CiRA, we invite patients and patient groups to speak with project members. These occasions allow researchers to both discover their symptoms and needs and share the status and progress of their research.

Retreat

Before the COVID-19 pandemic, we held a 2-day overnight offsite meeting "Retreat" once a year. T-CiRA members would enjoy morning runs and have meetings to discuss the future of T-CiRA and what they wanted T-CiRA to be. Being together for two days away from their research environment, members were able to interact and build firm relationships. Due to the ongoing COVID situation, an online Retreat was held in February 2022. It proved to be a pleasant diversion for all participants.

Research Publications

Many research papers from T-CiRA's project teams have been published in prestigious scientific journals. In order to increase opportunities for such findings to be known to academia, industries and the general public, we initiate sessions where researchers present their papers to the media. This serves as a great opportunity for researchers to learn effective ways to explain their findings to the general public.

"One T-CiRA"

"One T-CiRA" is a communication tool that allows all members of T-CiRA to share information smoothly. This online system can be accessed freely by any member, regardless of their affiliation, position or project framework. It is useful for sharing a wide range of information, from discussions on science to reports on events conducted by each project.

Chronology and Achievements

December 2015
CiRA and Takeda establish "Takeda-CiRA Joint Research Program for iPS Cell Applications (T-CiRA)." T-CiRA is located at Takeda's Shonan Research Center (currently: Shonan Health Innovation Park). Research in clinical applications of induced pluripotent stem (iPS) cells in six core areas including cancer, heart failure, diabetes mellitus, neuro-degenerative disorders and intractable muscular diseases begins.

November 2016
Yokohama City University enters T-CiRA. A project to apply the method to produce miniature livers from human iPS cells (miniature liver technology) to drug discovery starts.

March 2017
RIKEN enters T-CiRA. Research to study treatments for *NGLY1* deficiency starts.

July 2019
First iPS cell-derived CAR T-Cell Therapy created by T-CiRA transferred to Takeda to begin process development toward clinical testing.

July 2021
iPS cell-derived cardiomyocytes (iCMs) and iPS cell-derived pancreatic islet cells (iPICs), which were developed as part of T-CiRA, transferred to Orizuru Therapeutics, Inc. (OZTx).

Research Achievements (as of March 2023)

182 Presentations at Scientific Conferences

54 New Patent Applications

8 Programs Supported by Public Funds

38 Publications in Scientific Journals

Major Media Coverage

T-CiRA and the CiRA / Takeda relationship

March 5, 2016	*The Yomiuri Shimbun*
August 25, 2016	*The Mainichi Shimbun*
October 27, 2016	*The Chemical Daily*
January 2, 2017	*Nikkei Biotechnology & Business*
February 14, 2017	*Nikkan Kogyo Shimbun*
March 15, 2017	*The Kyoto Shimbun*
April 13, 2017	*Ryu's Talking Live*, TV Tokyo
September 11, 2017	*The Professionals*, NHK (Japan Broadcasting Corporation)
November 20, 2017	*The Asahi Shimbun*
January 29, 2019	*The Chemical Daily*
August 11, 2021	*The Nikkei* and others
December 21, 2021	*Nikkei News Plus 9*, BS TV Tokyo

T-CiRA's research at Shonan iPark

January 1, 2020	*Yakuji Nippo*
August 23, 2021	*Nikkei Sangyo Shimbun*

T-CiRA's research projects

September 25, 2018	*Nikkan Kogyo Shimbun* and others [ALS/ASD Drug Discovery Project]
July 10, 2019	*Nikkei Sangyo Shimbun* and others [Intractable Muscular Disease Project]
July 17, 2019	*The Nikkei* and others [iCart Program]
February 19, 2020	*The Chemical Daily* and others [iPIC Program]
June 2, 2020	*Nikkan Kogyo Shimbun* and others [iCART Program]
September 8, 2020	*The Chemical Daily* and others [Organoid Medicine Project]
November 12, 2020	*Nikkei Biotechnology & Business* and others [ALS/ASD Drug Discovery Project]
June 16, 2021	*QLife Pro Medical News* and others [*NGLY1* Deficiency Project]
June 21, 2021	*The Kyoto Shimbun* and others [iCM Program]
December 8, 2021	*The Nikkei* and others [Genome Editing Therapy for Muscular Dystrophy Project]
September 15, 2022	*The Kyoto Shimbun* and others [Neural Crest Cell Project]

In the Beginning:
Our Philosophy and Ultimate Goal

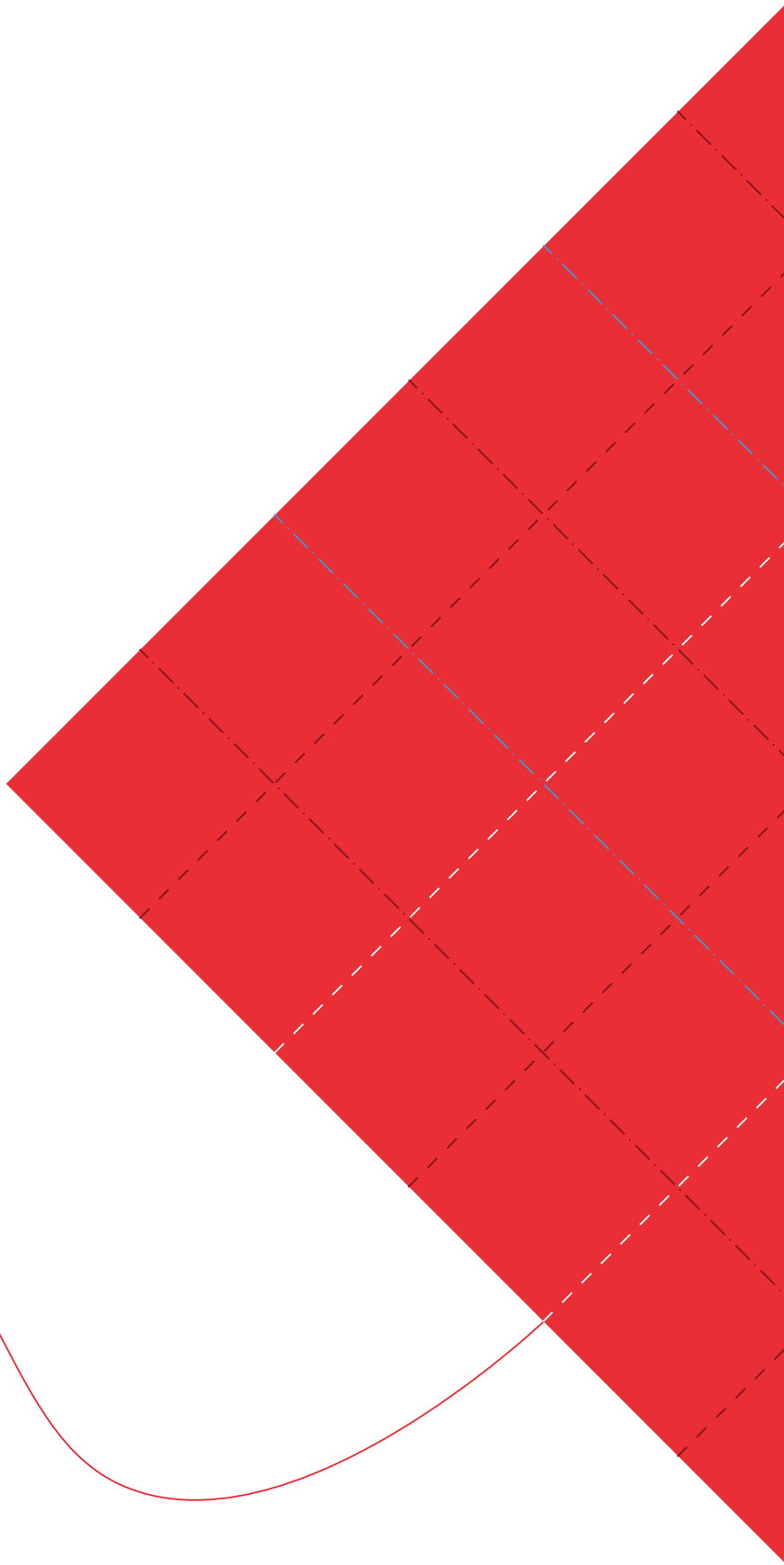
I am excited that we will be able to collaborate with CiRA, the world's leading institute dedicated to pioneering iPS cell research. Through this partnership, our company will provide significant assistance over a long period to CiRA's research into iPS cell technology applications, which is a vital part of the Japan Revitalization Strategy. It is our hope to deliver innovative drugs and cell therapies that meet patient needs as soon as possible through this collaboration between Takeda and CiRA.

Christophe Weber
President & CEO, Takeda

This 10-year joint research program with Takeda, Japan's largest pharmaceutical company, will become a powerful engine to realize medical applications using iPS cells. We sincerely appreciate Takeda's commitment to iPS cell research. This partnership will contribute to the development of new therapies to cure not only major diseases but also rare ones.

Shinya Yamanaka
Director and Professor of Center for
iPS Cell Research and Application (CiRA),
Kyoto University

*Both Mr. Weber and Dr. Yamanaka's messages were provided in December 2015, when T-CiRA was established. Titles appear as they were at the time.



For inquiries regarding T-CiRA

Global Advanced Platform, Research
Takeda Pharmaceutical Company Limited
(Located at Shonan Health Innovation Park)
Phone: +81 (0) 466-32-2111
Email: T_CiRA@takeda.co.jp

https://www.takeda.com/science/research-and-development/partnerships/t-cira/

Published May 2023