Takeda-CiRA Joint Program
for iPS Cell Applications

T-CiRA
Reprogramming the Future

For inquiries regarding T-CiRA

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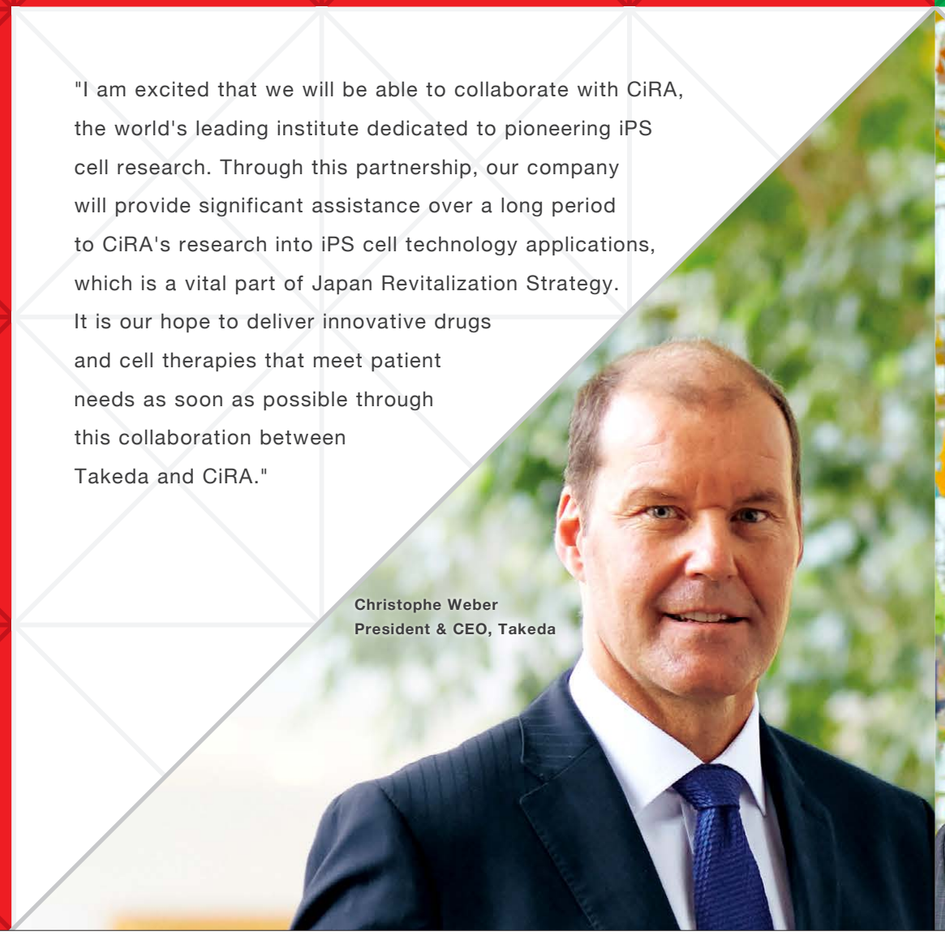
https://www.takeda.com/what-we-do/t-cira/

2019.10

ENGLISH

Changing the future of healthcare through regenerative medicine and drug discovery

"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 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 program with Takeda, Japan's largest pharmaceutical company, will become a powerful engine to realize medical applications using iPS cells. We sincerely thank 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."

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

CiRA × Takeda = ∞

Combined strengths, high expectations

T-CiRA is a joint research program conducted by Takeda Pharmaceutical Company and Kyoto University's Center for iPS Cell Research and Application (CiRA). Until now, the lack of bridges linking universities and pharmaceutical companies in Japan has deterred agile commercialization of the results from outstanding research conducted at universities. T-CiRA acts as a bridge across this so-called "Death Valley" of lost opportunity. In Europe and the US, venture companies commercialize university research and pass it on to pharmaceutical companies. T-CiRA promises a smoother research-development-commercialization process through direct links between Takeda and the university. CiRA and Takeda are collaborating for 10 years on research into clinical applications for iPS cell technologies, aiming to develop innovative therapies through regenerative medicine and drug discovery for use in areas such as heart failure, diabetes mellitus, neuro-psychiatric disorders, cancer and intractable muscle diseases.

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

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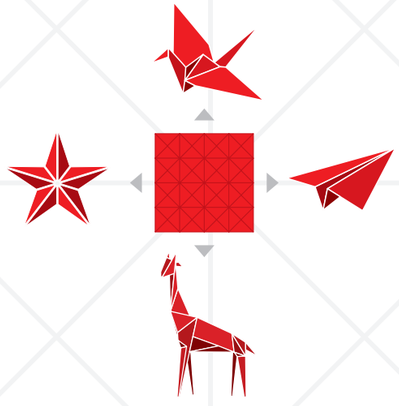
〈Takeda〉

- 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

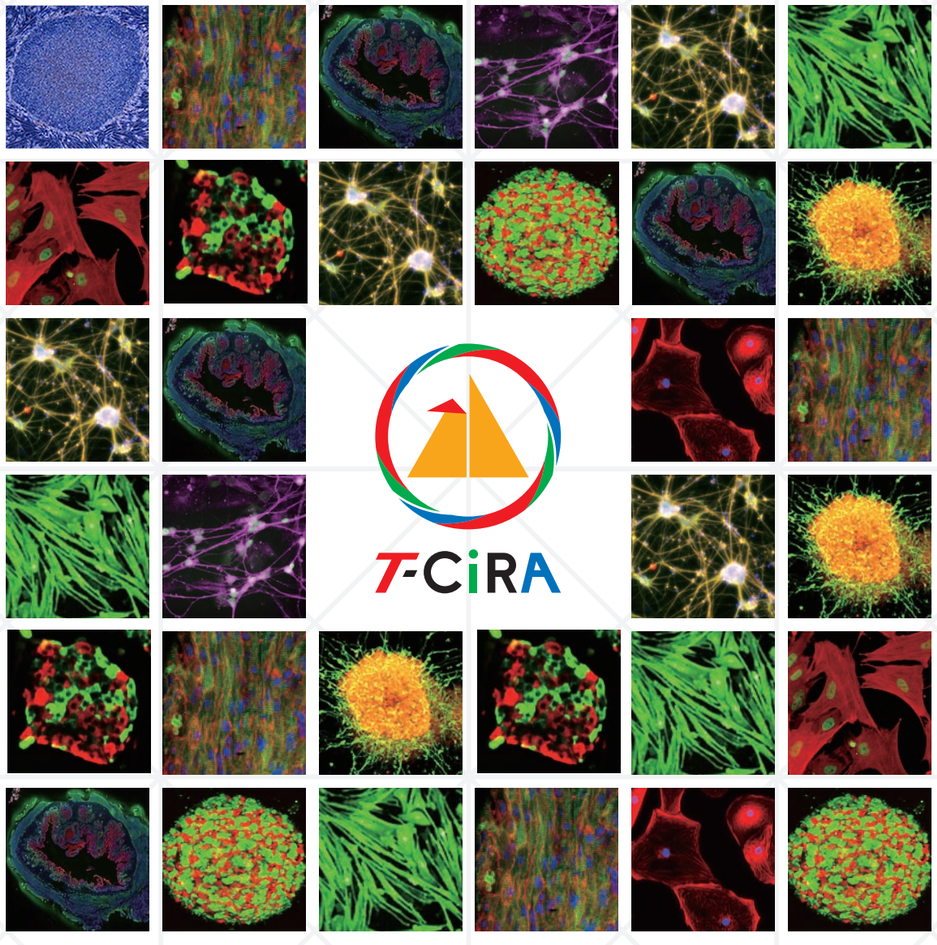
Concept behind the T-CiRA logo

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 both CiRA's image color and the symbol color of Takeda. The paper crane in the center of the emblem represents our hopes and prayers for patients. The tricolor circle embodies the importance of diversity as we work together to create innovative treatment options.



Booklet Concept

Just as iPS cells have the potential to become a variety of cell types and T-CiRA can shape our future of medication, a sheet of paper can take on many forms through *origami*, the art of paper folding.



T-CiRA

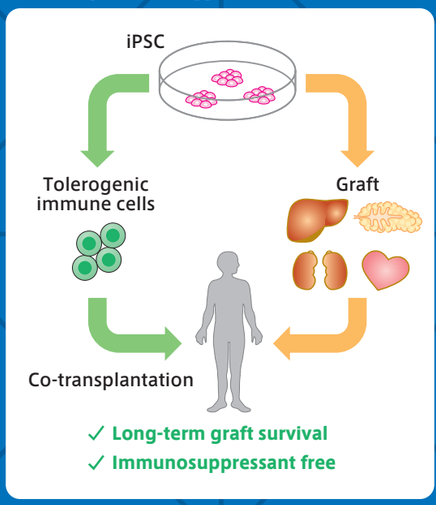
Game-Changing Therapeutics to be Delivered from the T-CiRA Joint Program

We are committed to providing innovative treatments to patients through iPS cell technology. At T-CiRA, several novel research projects are underway for creating medical applications of iPS cells, led by nine principal investigators.

〈Immune Tolerance Project : Development of a novel immunological tolerance therapy in transplantation〉

Dr. Kaneko's team is trying to develop a novel clinical approach using iPSC-derived tolerogenic immune cells. We aspire to realize a transplantation tolerance which leads to well-functioning graft without immunosuppressive drugs in an immunocompetent host.

<Concept/Strategy>

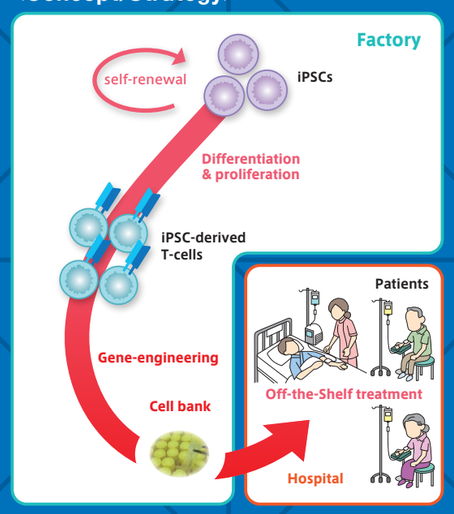


〈T-Cell Cancer Therapy Project : Development of a novel immunotherapy using iPSC-derived cancer antigen-specific T-cells〉

Dr. Kaneko's team is trying to develop a novel cancer immunotherapy using iPSC-derived immune cells. We aspire to realize "off-the-shelf" allogeneic products for cancer patients by combining CiRA's iPS Cell Stock for Regenerative Medicine with Takeda's experience in drug production.

Shin Kaneko

<Concept/Strategy>



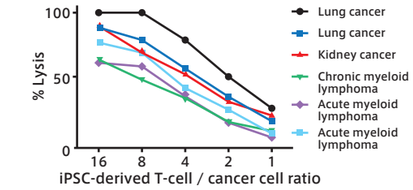
<Concept>

- T-cell receptor (TCR) gene that targets cancer cells is introduced into iPSCs derived from super donors, which can provide a match for a large population of patients.
- T-cells are differentiated from iPSCs, mass-cultured and stocked using manufacturing methods industrialized and standardized.
- The stockpiled T-cells can be administered to HLA-matched cancer patients and a marked therapeutic effect can be expected on cancers expressing the relevant antigen.

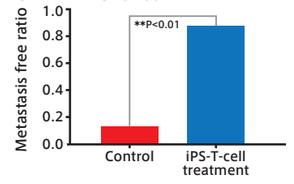
<Progress>

- iPSC-derived T-cells demonstrated *in vitro* tumor antigen-specific cytotoxicity against various types of cancer cell lines (A), the suppression of tumor metastasis (B) and tumor growth in mice.

A: In vitro anti-tumor effect



B: In vivo anti-tumor effect



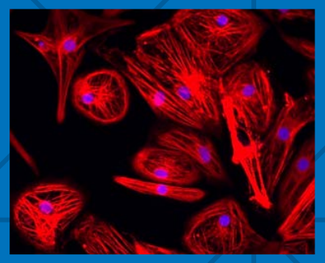
Treatment with iPSC-derived T-cell suppressed the tumor metastasis in mouse xenograft model, whereas metastasis was observed in 90% of control mice.

Yoshinori Yoshida

〈Cardiac Cell Therapy Project : Development of an iPSC-based cell therapy platform and application to novel therapy for heart failure〉

Dr. Yoshida's team aims to create iPSC-derived cardiomyocytes suitable for regenerative therapy and drug discovery research using new technologies such as microRNA-switch technology developed at CiRA. With these cardiomyocytes, they aim to develop cell therapies against heart failure alongside next-generation drug discovery platform and new therapeutic drugs.

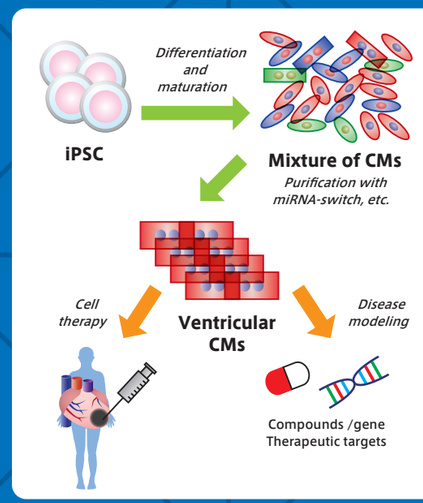
- Human iPSCs are differentiated into cardiomyocytes (CMs), which are then matured.



Red : cardiac troponin T

- Subpopulations of cardiomyocytes, such as ventricular cardiomyocytes, are selectively acquired from iPSC-derived cells with varied characteristics using miRNA-switch and other techniques. These cells are used for cell therapy and compound screening.

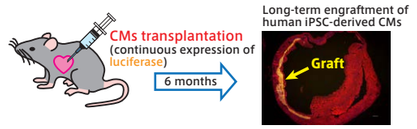
<Concept/Strategy>



<Progress>

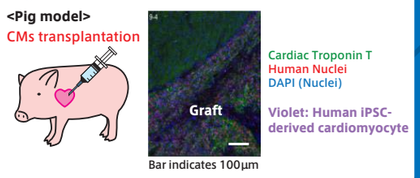
Engraftment of human iPS cell-derived cardiomyocytes (CMs) in mouse and pig model

<Myocardial infarction mouse model>
(Reported from CiRA, Kyoto Univ.: Sci Rep 2016 Jan 8;6:19111)



Technology transfer to T-CiRA

<Pig model>
CMs transplantation

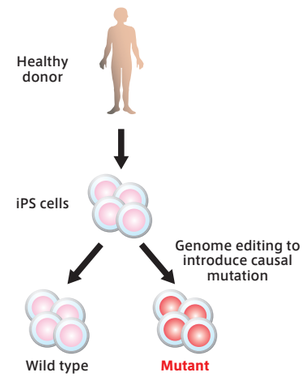


Engraftment of human iPSC-derived cardiomyocytes is confirmed in a large animal model

〈Cardiac Disease Drug Discovery Project : Drug discovery for genetic cardiac disease using a novel iPSC-based platform〉

Dr. Yoshida's team is also trying to create iPSC-derived cardiomyocytes which are harboring the causal mutation for cardiomyopathy by genome editing. With these cardiomyocytes, they aim to develop new therapeutic drugs for genetic heart failure such as hypertrophic or dilated cardiomyopathy and catecholaminergic polymorphic ventricular tachycardia.

<Concept/Strategy>



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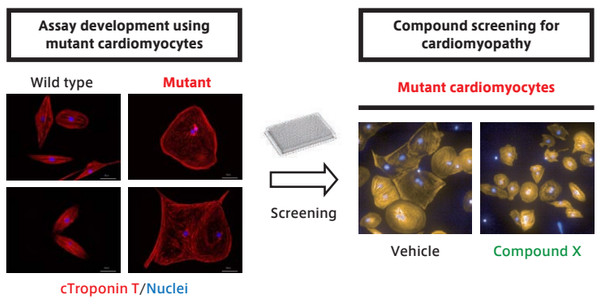


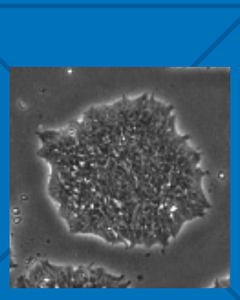
➢ **Confirmation of hypertrophy and sarcomere disarray in mutant cardiomyocytes**

➢ **Identification of "seed compounds" which ameliorated abnormal phenotypes of mutated cardiomyocytes from Takeda's compound library**

Taro Toyoda

〈Beta Cell Project: Research on Cell Therapy against Type 1 Diabetes〉

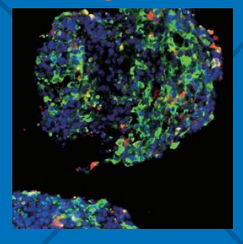
Dr. Toyoda's team is conducting research into cell therapy against type 1 diabetes mellitus involving transplants of iPSC-derived pancreatic cells. Their current research aim is to develop new treatments based on islet transplantation, but without the current limitations of such transplantation.



iPS cells

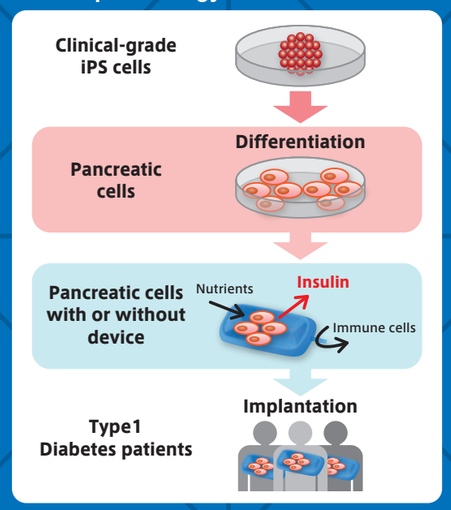
Differentiation

Insulin
Glucagon Nuclei



Endocrine cell clusters

<Concept/Strategy>



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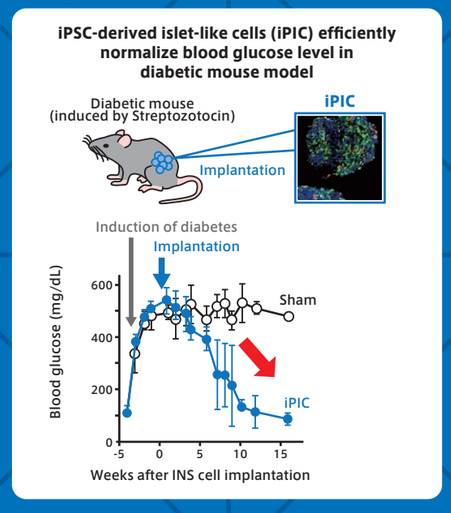
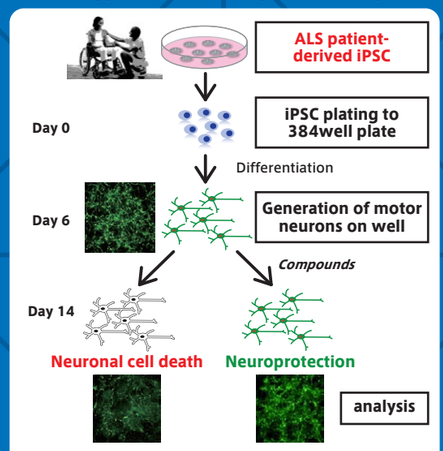


Dr. Inoue's team is conducting researches to deliver new therapeutic options to patients suffering from amyotrophic lateral sclerosis (ALS) and autism spectrum disorder (ASD) for which there is no effective cure. They aim to identify and develop new therapeutic drugs using patient-derived iPS cells and Takeda compound libraries.

Haruhisa Inoue

〈ALS/ASD Drug Discovery Project : ALS/ASD drug discovery and development using patient-derived iPSCs〉

<Strategy for ALS Drug Discovery>



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

<Progress>

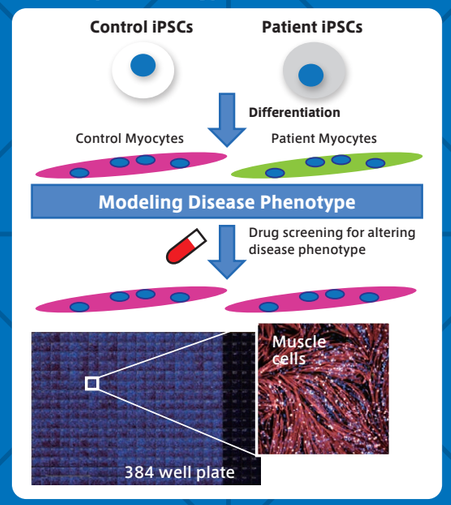
- We identified "new seed compounds" which are effective against motor neuron loss using the high-content and high-throughput screening systems with motor neurons differentiated from iPS cells from patients with ALS.
- We also established high-throughput screening systems with neurons differentiated from iPS cells from patients with ASD. We have plans to screen seed compounds which can lead to new therapies for ASD.

Hidetoshi Sakurai

〈Muscular Dystrophy Project : Drug discovery for intractable muscular disease using patient-derived iPSCs〉

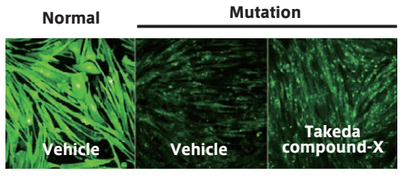
Dr. Sakurai's team will create novel therapeutic drugs for intractable muscular diseases such as Miyoshi myopathy and Duchenne muscular dystrophy and investigate muscular disease models. To achieve this goal, they utilize patient-derived iPSCs as a tool for disease modeling and drug screening.

<Concept/Strategy>



<Progress>

Miyoshi Myopathy : Identified "drug seeds" elevating dysferlin protein levels by high-content and high-throughput drug screening using patient iPSC-derived myotubes.
Optimization of seed compound is underway to deliver a novel therapeutic drug.



Recovery of dysferlin protein level (detected by immunocytochemistry)

Y. Kokubu *et al* (2019) STEM CELLS Translational Medicine

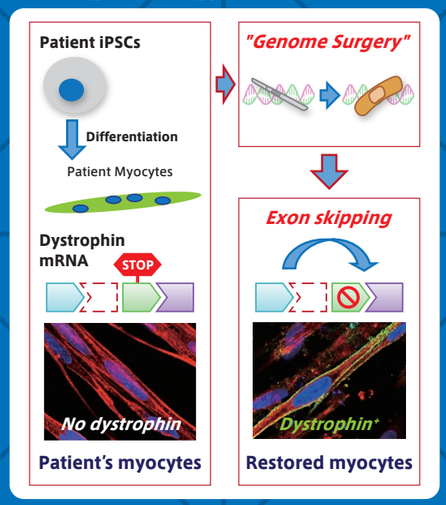
<Concept>

- Both iPSCs derived from healthy subjects and patients are differentiated into skeletal muscle cells (myotubes) on 384-well plates.
- A high-throughput drug screening and evaluation system are developed by visualizing pathological changes observed only in patient iPSC-derived myotubes.
- Compounds that improve pathological changes are selected and optimized.

<Progress>

- Miyoshi myopathy : Identification of "seed compounds" from Takeda compound library (left panel)
- Duchenne muscular dystrophy : Identification of a therapeutic target for abnormal Ca2+ metabolism in patient iPSC-derived myotubes.

<Concept/Strategy>



Akitsu Hotta

〈In Vivo Genome Editing project : Therapeutic genome editing for congenital muscular dystrophy〉

Dr. Hotta's team aims to correct the causal genetic mutations involved in severe muscular dystrophy using state-of-the-art genome editing and delivery technologies. The team aims to develop technology that will enable them to create new gene therapies while, at the same time, confirming repair efficiency and safety using patient-derived iPS cells.

<Concept>

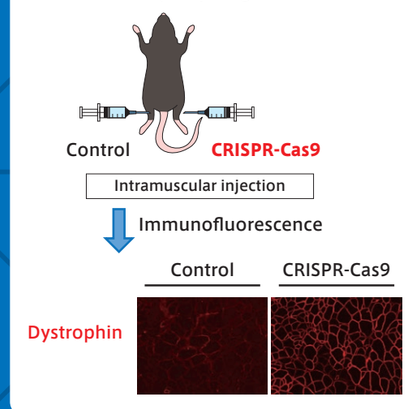
- When patient-derived iPS cells, which harbor a genetic mutation in the dystrophin gene, are differentiated into skeletal muscle cells, dystrophin protein expression is absent.
- By using genome editing technology to skip exons that carry a genetic mutation, it is possible to rescue the expression of dystrophin protein that retains some degree of functionality.

<Progress>

- Restoration of dystrophin protein expression by genome editing system in muscular dystrophy mice harboring "humanized dystrophin gene".

<Progress>

Muscular dystrophy mice harboring *"humanized dystrophin gene"*

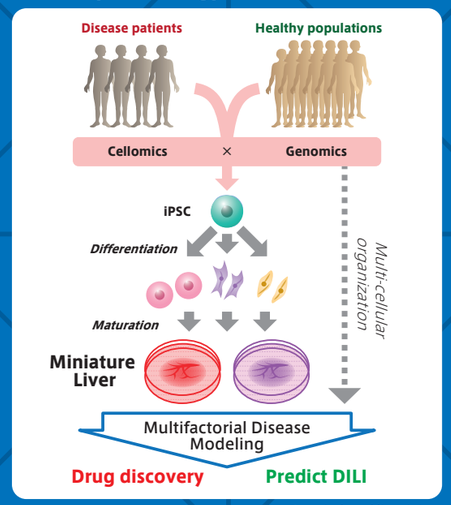


Takanori Takebe

〈Organoid Medicine Project : Miniature liver technology as a platform for research towards pharmaceutical applications〉

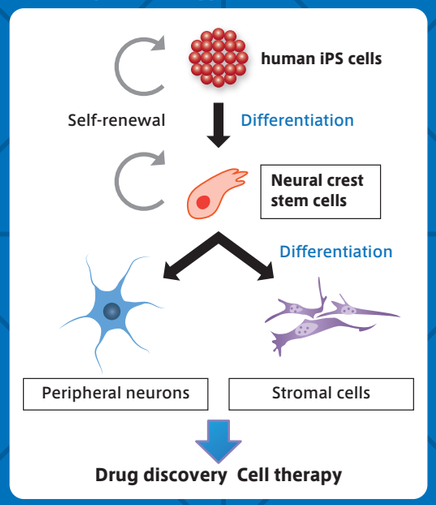
Based on human iPSC-derived miniature liver technology developed at Yokohama City University, Dr. Takebe's team is developing an innovative system that can reproduce the complex phenomena found in patients' bodies. This research will create a novel drug discovery system for intractable diseases and a novel predictive platform for expression analysis of rare adverse events unforeseen in traditional drug discovery research.

<Concept/Strategy>



DILI: Drug-induced liver injury

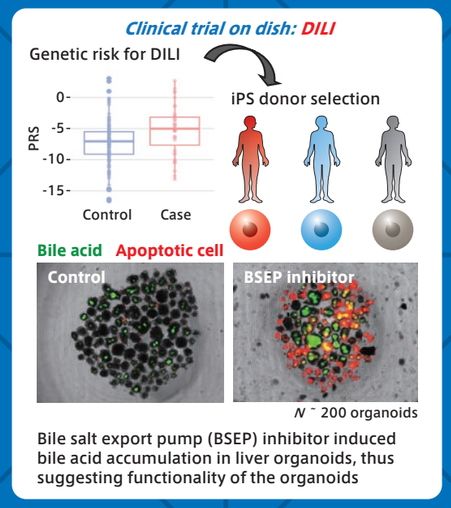
<Concept/Strategy>



Makoto Ikeya

〈Neural Crest Cell Project : A new research platform with human iPSC-derived neural crest cells and its applications for drug discovery and regenerative medicine〉

Neural crest cells (NCCs) differentiate into diverse cell type lineages such as bones and peripheral neurons, suggesting their great potential for clinical applications. Dr. Ikeya's team aims to create methods to maintain and culture human iPSC-derived NCCs and to induce them to differentiate into various types of cells. Moreover, they hope to construct an *in vitro* disease model in combination with related technologies and apply it to drug development and regenerative medicine.

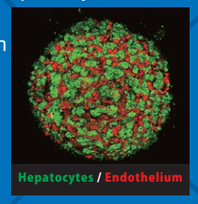


N ~ 200 organoids

Bile salt export pump (BSEP) inhibitor induced bile acid accumulation in liver organoids, thus suggesting functionality of the organoids

<Concept>

- Genomic information is used for the strategy to create iPSCs that allows the team to establish a method of screening donors that could be useful for predicting the phenotype of rare diseases.
- Furthermore, by creating a mini-liver consisting of multiple types of cells, the team will construct a method to reproduce complex patient pathology in vitro.
- By integrating these two proprietary methods of genome research and cellome research, the team will contribute to the creation of an innovative drug discovery system.



<Concept>

- Neural crest cells are a unique cell population that exists only in the early stages of development. However, much about them remains unknown.
- It is very difficult to culture neural crest cells *in vitro* while maintaining their undifferentiated state. But if basic technologies to maintain neural crest cells are established using human iPSCs, the application possibilities are extensive.

<Progress>

- The team identified multiple differentiation protocols to induce various cell types from NCCs. The differentiated functional cells will be used for development of drug discovery and cell therapy platform.

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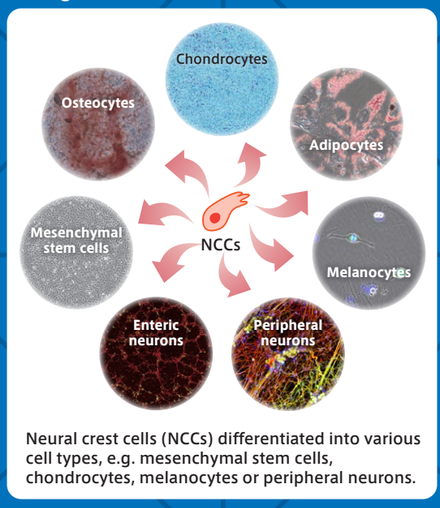
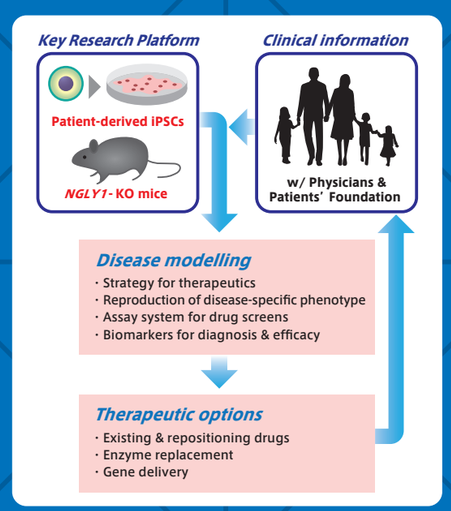


Neural crest cells (NCCs) differentiated into various cell types, e.g. mesenchymal stem cells, chondrocytes, melanocytes or peripheral neurons.

Tadashi Suzuki

〈NGLY1 Deficiency Project : Development of therapeutic agents for rare hereditary diseases using iPS cells〉

Dr. Suzuki's team is focusing on a deficiency in the *NGLY1* gene that encodes for the de-*N*-glycosylating enzyme *N*-glycanase. They will develop innovative therapeutics for *NGLY1* deficiency, a rare inherited disease that presently does not have any therapeutic options, through a combination of basic research findings, iPSC technology and a drug discovery platform.



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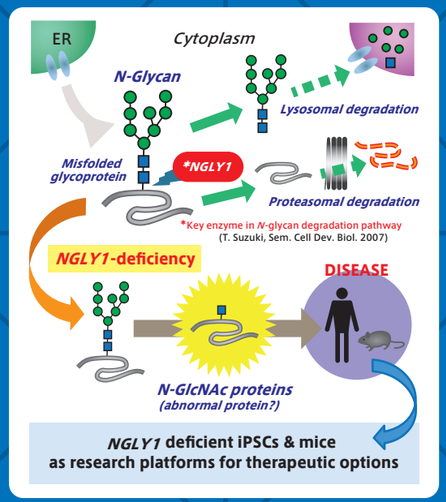

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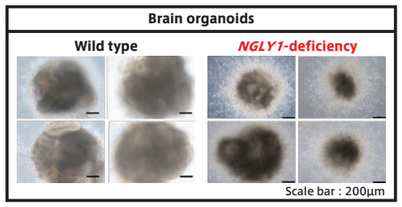


▸Recent data suggested abnormalities in brain organoid developed from patient-derived iPSCs

- Many large neural tissues that have greatly expanded in wild type brain organoids but not in *NGLY1*-deficiency organoids (day 20).
- *NGLY1*-deficiency organoid which has failed to produce neuroepithelial buds, instead displaying extended cell processes consistent with direct neural differentiation.

Giving shape to hopes – with agility

Cutting-edge technology leads our center for drug creation

The T-CiRA research laboratory has been established at the Shonan Health Innovation Park as a branch of CiRA. Here, over 100 researchers from CiRA, Tokyo Medical and Dental University, RIKEN and Takeda work together using iPS cell technologies.
The lab features the latest equipment and resources, creating a one-stop research environment that begins with fundamental research and culminates in research for clinical trials.

① Shonan Health Innovation Park (iPark), Kanagawa, Japan
② The latest in state-of-the-art high-content screening devices, allowing for simultaneous high-resolution photography across four wavelengths
③ High-throughput screening devices to unearth seeds for drug discovery from compound libraries
④ A laboratory where researchers from academia and Takeda work together

Together with our partners, towards the future of drug discovery

〈T-CiRA Retreat〉 In order to foster a sense of unity among those engaged in our T-CiRA research activities, a total of 160 T-CiRA researchers and T-CiRA support members came together at the T-CiRA Retreat.

A morning run with Prof. Yamanaka took place. We shared our desire with him to complete the long road to applying iPS cell research to drug discovery.

The participating researchers gave oral and poster presentations and deepened their understanding of mutual projects through spirited discussions.

〈T-CiRA Monthly Meeting〉

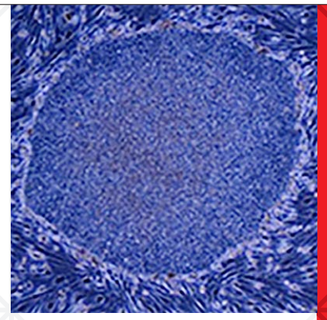
Every month, Prof. Yamanaka visits the Shonan Health Innovation Park and participates in the T-CiRA monthly meeting. At the meeting, a serious discussion takes place on individual project plans and their progress, in order to accelerate research towards realization of therapies using iPS cells.

〈Articles and programs on T-CiRA〉

Printing / Broadcast Date	Printing / Broadcasting Program
January 25, 2016	Yomiuri Shimbun
March 5, 2016	Yomiuri Shimbun
June 11, 2016	Diamond Weekly
August 25, 2016	Mainichi Shimbun
October 24, 2016	Kansai Joho Netto ten. (Yomiuri Television)
October 27, 2016	The Chemical Daily
January 2, 2017	Nikkei Biotech ONLINE
February 14, 2017	Nikkan Kogyo Shimbun
February 21, 2017	Nikkan Kogyo Shimbun
February 21, 2017	The Chemical Daily
March 15, 2017	Kyoto Shimbun
April 13, 2017	The Cambrian Palace (TV Tokyo series)
Sep 11, 2017	The Professional (NHK series)
Nov 20, 2017	Asahi Shimbun
Jan 2, 2018	Nikkei Biotech ONLINE
September 25, 2018	Nikkan Kogyo Shinbun
January 29, 2019	The Chemical Daily
July 10, 2019	The Nikkei Business Daily
July 17, 2019	The Nikkei
July 18, 2019	Nikkei Biotech ONLINE

(As of August, 2019)

A Nobel Prize was only the beginning



A History of iPS Cell Research at CiRA

2006 Prof. Shinya Yamanaka published establishment of mouse iPS cells.
2007 Prof. Shinya Yamanaka published establishment of human iPS cells.
2008 Creation of disease-specific iPS cells began.
Initial patent granted in Japan for creation of iPS cells.
2010 The Center for iPS Cell Research and Application, Kyoto University, was established.
2011 Division for iPS Cell Application Development established at Kyoto University Hospital.
Patents obtained in the US and Europe for creation of iPS cells.
2012 Prof. Shinya Yamanaka was awarded the Nobel Prize in Physiology or Medicine.
2015 Shipment of iPS Cell Stock for regenerative medicine began.
T-CiRA Joint Program for iPS Cell Applications began.
2017 The first transplant to an AMD patient using CiRA's iPS Cell Stock was conducted in a clinical research led by RIKEN's Dr. Masayo Takahashi.
A clinical trial for a FOP drug candidate, which is based on the findings of Drs. Junya Toguchida and Makoto Ikeya, started.
2018 A clinical research to transplant iPS cell-derived platelets to a patient with refractoriness to platelet transfusion, which is based on Dr. Koji Eto's findings, was approved by the Ministry of Health, Labour and Welfare.
The first transplant to a Parkinson's Disease patient using CiRA's iPS Cell Stock was conducted. The clinical trial is based on Dr. Jun Takahashi's findings.
2019 A clinical trial for an ALS drug candidate, which is based on the findings of Dr. Haruhisa Inoue, started.

A brighter future for patients through innovative new treatment options

A History of iPS Cell Research at Takeda

2008 iPS cell research began with a focus on neuronal differentiation, pancreatic β cell differentiation and cardiomyocyte differentiation.
Prof. Shinya Yamanaka provided two kinds of human iPS cell clones to Takeda.
2010 Takeda participated in the Advanced Medical Development Project (a Japan's National project) led by Prof. Shinya Yamanaka: "Project to Accelerate Medical Applications of iPS Cells".
2011 Disease-specific iPS cells were introduced and fundamental research on regenerative medicine began.
Takeda conducted joint research with Prof. Haruhisa Inoue of CiRA on iPS cells derived from patients with Alzheimer's disease and ALS.
2012 Takeda conducted joint research with Prof. Kenji Osafune of CiRA on insulin-producing cells derived from iPS cells.
2013 Various differentiated cells and human disease models created.
2014 Takeda participated in the National project "Application of disease-specific iPS cells for intractable diseases".
2015 T-CiRA Joint Program for iPS Cell Applications began.
2019 First iPSC-derived CAR T-cell therapy created by T-CiRA Joint Program entered process development toward clinical testing

Research Achievements

56

Presentations at Scientific Conferences

28

New Patent Applications

T-CiRA

4

Publications in Scientific Journals

5

Programs Supported by Public Fund

As of September, 2019

Publications from T-CiRA Joint Program

◆Enhancing T Cell Receptor Stability in Rejuvenated iPSC-Derived T Cells Improves Their Use in Cancer Immunotherapy

Atsutaka Minagawa, Toshiaki Yoshikawa, Masaki Yasukawa, Akitsu Hotta, Mihoko Kunitomo, Shoichi Iriguchi, Maiko Takiguchi, Yoshiaki Kassai, Eri Imai, Yutaka Yasui, Yohei Kawai, Rong Zhang, Yasushi Uemura, Hiroyuki Miyoshi, Mahito Nakanishi, Akira Watanabe, Akira Hayashi, Kei Kawana, Shin Kaneko

Cell Stem Cell, 2018, vol.23, 850-858

◆Phenotypic Drug Screening for Dysferlinopathy Using Patient-Derived Induced Pluripotent Stem Cells

Yuko Kokubu, Tomoko Nagino, Katsunori Sasa, Tatsuo Oikawa, Katsuya Miyake, Akiko Kume, Mikiko Fukuda, Hiromitsu Fuse, Ryuichi Tozawa, Hidetoshi Sakurai

Stem Cells Translational Medicine, 2019, vol.8, 1017-1029

◆Organoid Models of Development and Disease Towards Therapy

Yasunori Nio, Takanori Takebe

Medical Applications of iPS Cells, Springer Nature eBOOK, 2019, 149-168

◆Identification of 2,6-Disubstituted-3*H*-imidazo[4,5-*b*]pyridines as Therapeutic Agents for Dysferlinopathies through Phenotypic Screening on Patient-Derived iPSCs

Hiroyuki Takada, Akira Kaieda, Michiko Tawada, Tomoko Nagino, Katsunori Sasa, Tatsuo Oikawa, Akiko Oki, Tomoya Sameshima, Kazumasa Miyamoto, Makoto Miyamoto, Yuko Kokubu, Ryuichi Tozawa, Hidetoshi Sakurai, Bunnai Saito

Journal of Medicinal Chemistry, in Press

2025 – The year new therapies will become reality

University and Pharmaceutical working hand in hand –to solve unprecedented challenges.

T-CiRA Joint Program takes innovative approaches toward clinical solutions for rare and intractable disease patients who were previously without effective therapeutic options. Our projects are progressing rapidly, using the power of iPS cells, to formulate novel therapeutic options. Working closely together, academic and pharma researchers are mapping uncharted territory to discover breakthrough solutions. Our approaches with iPS cells could provide transformative progress in Neuroscience, Gastroenterology, Oncology and Rare Diseases, as well as type I diabetes and heart failure, accompanied by outcomes as small molecule drugs, cell therapy and gene therapy. Our dream is that patients will receive such life-changing therapeutic options discovered through our 10-year collaborative research effort.

Yasushi Kajii
Head of T-CiRA Discovery

Delivering innovative therapeutic options to our patients, as soon as possible. That's our mission, every day.

T-CiRA is constantly evolving. Please visit our website to track our exciting journey.

T-CiRA

Reprogramming the Future

Please visit our website

T-CiRA Search

https://www.takeda.com/what-we-do/t-cira/