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 principle 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 Research Center
- To provide platform 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.
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 iPSC, led by nine principal investigators.

**ALS drug discovery and development using patient-derived iPSCs**

Dr. Inoue’s team conducts research into amyotrophic lateral sclerosis (ALS), a neurodegenerative disease for which there is no effective cure. They aim to develop new therapeutic drugs using patient-derived iPSCs and Takeda’s compound libraries.

**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.
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.

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 human iPSC cell stock for regenerative medicine with Takeda’s experience in drug production.

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

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.

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

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 proprietary 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.

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

- Even 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.
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 within 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.

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

Neural crest cells 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 cultures of human iPSC-derived neural crest stem cells 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.

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.

Neural crest cells are a unique cell population that exists only in the early stages of development. Much about them remains unknown, especially human neural crest cells.

It is very difficult to cultivate neural crest cells in vitro while maintaining their undifferentiated state. But if basic technologies to maintain neural crest cells can be established using human iPSCs, the application possibilities are extensive.
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.
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 Research Center as a branch of CiRA. Here, over 100 researchers from CiRA, Yokohama City 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 trial applications.
In order to foster a sense of unity among those engaged in our T-CiRA research activities, a total of 122 T-CiRA researchers and T-CiRA support members came together at the T-CiRA Retreat.

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

A morning run with Prof. Yamanaka was also planned. We shared our desire with him to complete the long road to applying iPSC research to drug discovery.

Every month, Prof. Yamanaka visits the Shonan Research Center 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 that treatment methods derived from iPSC research can be realized as soon as possible.

Mr. Matt Wilsey (representative of the Grace Science Foundation, an AGLY1 deficiency patient group) visited T-CiRA. He expressed his hope that T-CiRA can provide innovative new drugs to patients suffering from intractable diseases without established effective treatments.

Together with our partners, towards the future of drug discovery
A Nobel Prize was only the beginning

A History of iPS Cell Research at CiRA

2006  Prof. Shinya Yamanaka published establishment of a mouse iPS cell line
2007  Prof. Shinya Yamanaka published establishment of a human iPS cell line
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 Clinical 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 and Medicine
2014  RIKEN’s Masayo Takahashi led clinical research using human iPS cells, during which a transplant surgery was conducted
2015  Shipment of iPS cell stock for regenerative medicine use began
       T-CiRA Joint Program for iPS Cell Applications began

A History of Stem Cell Research at Takeda

2006  Stem cell research began on somatic stem cells and mouse ES cells
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 (pancreatic β cells, nerve cells) began
       Takeda conducted joint research with Prof. Haruha Inoue of CiRA on iPS cells derived from patients with Alzheimer’s and ALS
2012  Takeda conducted joint research with Prof. Kenji Osafune of CiRA on insulin-producing cells using 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

A brighter future for patients through innovative new treatment options
2025 – The year new therapies will become reality

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

T-CiRA takes a novel approach toward treatments of patients who were previously without effective therapeutic options. Our projects are progressing rapidly, using the power of IPS cells to formulate new therapeutic options. Working closely together, university and pharmaceutical industry researchers are mapping uncharted territory to discover innovative solutions. Take the case of Amyotrophic Lateral Sclerosis (ALS) a fatal neurodegenerative disease.

If our drug screening for this disease succeeds, the nerve degeneration that causes the disease could be halted entirely. Similarly, if a project to create insulin-secreting pancreatic β cells succeeds, patients suffering from diabetes mellitus may no longer need insulin injections. Our dream is that patients will receive therapeutic options discovered directly through our 10-year collaborative research effort.

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

https://www.takeda.com/T-CiRA/