Takeda-CIRA Joint Program
for IPS Cell Applications

For inquiries regarding T-CIRA
Takeda Pharmaceutical Company Limited
Shoren Health Innovation Park

Phone: +81-3-6811-5756
Fax: +81-3-6811-5757
Email: T-CIRA@takeda.com


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 x 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.

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.

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

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.
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.

**T-Cell Cancer Therapy Project:**

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

**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 IPS-derived tolerogenic immune cells. We aspire to realize a transplantation tolerance which leads to well-functioning grafts without immunosuppressive drugs in an immunocompetent host.

**Concept/Strategy:**

- 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-cultivated 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:**
IPS-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.

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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.

(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.
Dr. Inoue's team is conducting research 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.

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.
**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.

**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.

**Progress**

- Miokshi myopathy: Identification of “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.

**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/Strategy**

- 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).

**Consortium**

- CERF: Collaborative effort of researchers and clinicians.
- CEM: Clinical evaluation and management.
- CTR: Corporate support and collaboration.

**Muscular dystrophy mice harboring “humanized dystrophin gene”**

Muscular dystrophy mice harboring humanized dystrophin gene show restored dystrophin expression and improved muscle function.

**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.
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**

- Disease patients
- Healthy populations
- Multifactorial Disease Modeling
- Miniature Liver
- Drug discovery
- Predict DILI (Drug-induced liver injury)

**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 types, such as the notochord, midline mesoderm, peripheral neural crest, and mesenchymal stem cells, suggesting their great potential for clinical applications. Dr. Ikeda'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 plan to construct an in vitro disease model in combination with related technologies and apply it to drug development and regenerative medicine.

**Concept**

- Genomic information is used for the strategy to create iPSCs that allow 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 cell line research, the team will contribute to the creation of an innovative drug discovery system.

**Progress**

- Neuronal 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 status. But if basic technologies to maintain neural crest cells are established using human iPSCs, the application possibilities are extensive.
- 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 platforms.
Tadashi Suzuki

(Glycogen Storage Disease Project: Development of therapeutic agents for rare hereditary diseases using iPSC cells)

Dr. Suzuki's team is focusing on a deficiency in the 'Glycogen Storage Disease' gene that encodes for the de-N-glycosylating enzyme 'Glycogen Phosphorylase'. They will develop innovative therapies for NCBI/GT 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.

<Concept/Strategy>

<Progress>

Recent data suggested abnormalities in brain organoids developed from patient-derived iPSCs.
- Many large neural tissues that have greatly expanded in wild type brain organoids but not in NCBI/GT-deficiency organoids (day 20).
- NCBI/GT deficiency organoids which has failed to produce neuropeptide 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 iPSC 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

In order to foster a sense of unity among those engaged in our T-CIRA research activities, a total of 180 T-CIRA researchers and T-CIRA support members came together at the T-CIRA Retreat.

A morning run with Prof. Yamaneaka 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 Retreat)

(T-CIRA Monthly Meeting)

Every month, Prof. Yamaneaka 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)

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(As of August, 2018)
ノーベル賞は、夢の通路点。

CIRAのiPS細胞研究の歩み

2006 山中伸弥教授がマウスiPS細胞創りを報告
2007 山中伸弥教授がヒトiPS細胞樹立を報告
2008 基本特異のiPS細胞の作製開始
2010 京都大学iPS細胞研究所（CIRA）設立
2011 京都大学医学部附属病院にiPS細胞治療開発部門を創設
アメリカ：ヨーロッパでiPS細胞作製に関わる特許取得
2012 山中伸弥教授がノーベル生理学・医学賞受賞
2015 再生医療用iPS細胞ストック初提供
T-CIRA Joint Program for iPS Cell Applications開設
2017 CIRAの再生医療用iPS細胞ストック供与の作業の開始
2018 井上治彦教授らの研究成果に基づき、ALS病変個体の治療開始

新たなプログラムを開始

タケダのiPS細胞研究の歩み

2008 神経分化、神経細胞分化および神経神経分化にフォーカスしたiPS細胞研究を開始
山中伸弥教授より2種のヒトiPS細胞クローンをタケダに導入
2010 山中伸弥教授がノーベル生理学・医学賞を受賞
「iPS細胞医療応用加速推進プロジェクト」の受注
2011 基本特異のiPS細胞の導入、再生医療分野研究（神経細胞、神経腫瘍）を開始
アルパハイマー病、ALS患者由来iPS細胞研究に関してCIRAの井上治彦教授と共同研究
2012 iPS細胞を用いたインスリン治療研究に関してCIRAの長崎順二教授と共同研究
2013 各種腫瘍分化、ヒト癌発生モデルの作製
2014 AMED事業「基本特異のiPS細胞を活用した再生医療」に参画
2015 T-CIRA Joint Program for iPS Cell Applications開始
2019 T-CIRA Joint Programが創製した初のiPS細胞由来CAR-T細胞療法臨床試験に向けた

新たなプログラムを開始

患者さんに明るい未来をもたらす、
革新的な治療法の提供のために。
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 Iriyuchi, Maiko Takiguchi, Yoshiaki Kassai, Eri Imai, Yutaka Yasui, Yohei Kawai, Rong Zhang, Yasushi Uemura, Hiroyuki Miyoshi, Mahito Nakanishi, Akira Watanabe, Akira Hayashi, Kei Kawano, Shin Kaneko
Cell Stem Cell, 2018, vol23, 860-868

Phenotypic Drug Screening for Dystrophinopathy Using Patient-Derived Induced Pluripotent Stem Cells
Yuko Kokubu, Tomoko Nagino, Katsunori Sasa, Tatsuo Okawa, Katsuya Miyake, Akiko Kume, Miikiko Fukuda, Hiromitsu Fuse, Ryuichit Tozawa, Hidetoshi Sakurai
Stem Cells Translational Medicine, 2019, vol8, 1017-1029

Organoid Models of Development and Disease Towards Therapy
Yasunori Nio, Takanori Takebe
Medical Applications of iPSCs, Springer Nature eBOOK, 2019, 149-168

Identification of 2,8-Disubstituted-3H-imidazo[4,5-2]pyridines as Therapeutic Agents for Dystrophinopathies through Phenotypic Screening on Patient-Derived iPSCs
Hiroyuki Takada, Akira Kaieda, Michiko Tawada, Tomoko Nagino, Katsunori Sasa, Tatsuo Okawa, Akiko Oki, Tomoyo Sameshima, Kazumasa Miyamoto, Makoto Miyamoto, Yuko Kokubu, Ryuichit Tozawa, Hidetoshi Sakurai, Bunmi Salto
Journal of Medicinal Chemistry, in press
2025年。新しい医療のカタチを実現したい。

大学と企業が手を携え、前例のない挑戦へ。

T-CiRAプログラムは、いまだに有効な治療法がない希少疾患や難病の解決に向けた革新的なアプローチを拡大しています。iPS細胞の利用を通じて新たな治療法に結びつけるプロジェクトが、着実に進行しています。大学および企業の研究者、直面手を携え、道なり道を頑なに歩み前進を元気にていく気持ちはあります。これまでは、面倒な解決策があるはずではありません。iPS細胞を用いた私たちの取り組みは、脳機能病や心原性疾患、糖尿病、がん、希少疾患といった領域に医学をもたらす進歩を提供しようとしており、手合医薬品、薬剤治療、遺伝子治療といった成果をもって現れるでしょう。私たち、生活を変えるこのような治療オプシヨンとして研究成果を患者さんの側まで届けることを実現するために、10年間の共同プログラムに取り組んでまいります。

患者さんに一日も早く革新的な治療オプションを届けたいという思いから、私たちは日々、挑戦しつづけます。

これから様々な新たなプロジェクトが開始し、T-CiRAは大きく成長しています。
今後の展開につきましては、T-CiRAのウェブサイトをご覧ください。

Reprogramming the Future

ウェブサイトをご案内
T-CiRA

https://www.b蒟蒻.com/jp/what-we-do/t-cira/