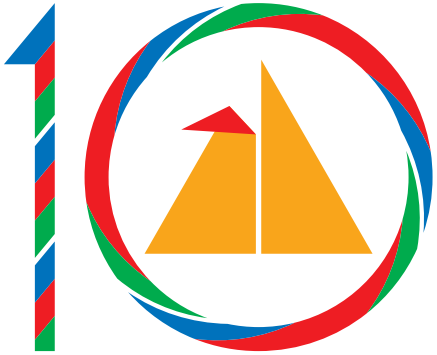


The Journey of 10 Years

T-CiRA

Takeda-CiRA Joint Research Program for iPS Cell Applications

Transform medicine with the unlimited potential of iPS cells

INDEX

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.

Research Achievements of T-CiRA
(as of March 2025)

Presentation at Scientific Conferences

246

New Patent Applications

58

Establishment of new company

1

Programs Supported By Public Funds

8

Publications in Scientific Journals

66

Clinical Trial

1

(As of October 2025)


T-CiRA
2019


T-CiRA
Reprogramming the Future

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
October 7, 2021	The Humanience, NHK (Japan Broadcasting Corporation)
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 project

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]
August 4, 2024	The Nikkei and others [Organoid Medicine Project]
June 8, 2025	NHK "The Human Body III, Episode 4" [Organoid Medicine Project]

Immune Cell Therapy Project

Research and development of human iPS cell-derived immune cell therapy

PI

Shin Kaneko

A decade is a long time—not only for industry–academia collaboration but also in a person's life. Inspired by Director Shinya Yamanaka's exhortation at T-CiRA—"Recognize this as the greatest opportunity of your research career, and pursue it with the conviction that if you miss this chance, practical application will never happen"—we adopted as our project motto: **"Bring to the world a product worthy of Professor Yamanaka's biography."**
For ten years we faced every step head-on—from basic research on T-cell regeneration therapy, through translational work, to practical application. That journey became an irreplaceable experience for every member of our team. I express my heartfelt gratitude to all T-CiRA colleagues. I believe that those who shared a decade of challenges and achievements will continue to lead the world in regenerative medicine and contribute to patients' well-being, and I look forward to the day when we can work together again.

Results

Our work centered on two thrusts: (1) developing therapies for solid tumors using iPSC-derived cytotoxic (killer) T cells, and (2) establishing methods to temper excessive immune responses using iPSC-derived regulatory T cells. The former began as a CiRA technology-introduction project within T-CiRA. We established a manufacturing process for killer T cells that demonstrated promising efficacy and transferred the technology to Takeda. In subsequent collaboration with Takeda, we advanced CMC and regulatory readiness, culminating in a spin-out to a startup company. This pathway—from basic discovery, to translation, to practical application—exemplifies how the team operated seamlessly across the entire value chain. Domestic clinical trials are expected to begin soon, and we eagerly anticipate the culmination of this decade of development.
The latter program yielded numerous valuable advances, including novel protocols for inducing regulatory T-cell differentiation, which will be instrumental for future development. As a therapeutic modality, this approach is highly promising, and CiRA will continue to drive its rigorous advancement.

Membership List:

Shin Kaneko (PI), Akira Hayashi (Co-PI), Shoichi Iriguchi (Sub-PI), Keiko Koga (Sub-PI), Atsushi Matsuda (Sub-PI), Wang Bo, Tomoko Ishii, Chihiro Kaneko, Keitaro Kanie, Kei Higaki, Ryohei Takada, Eri Imai, Momoka Yamada, Qingyi Guo, Takayuki Sato, Haruka Ban, Maki Shioiri, Kazuki Nakazono, Tamaki Kono (30 alumni).

Looking back on T-CiRA

- **Akira Hayashi** (Co-PI, Takeda)

Over the past decade, we have dedicated ourselves to advancing iPSC-derived immune cell technology, and made significant progress in establishing robust differentiation and proliferation processes and demonstrating preclinical efficacy. I am confident that iCART will advance to clinical application through the dedicated efforts of our colleagues at Alloy. I am deeply grateful to everyone who shared this journey with us and to all who supported us with unwavering commitment.

- **Shoichi Iriguchi**
  (Sub-PI, CiRA)

In T-CiRA, I have had a rare opportunity to a part of a novel attempt where university researchers conduct joint research at the laboratory of a pharmaceutical company for 10 years. I would like to express my gratitude to all the members of Takeda who believed in and refined the seed technology of Kaneko Laboratory in CiRA, as well as to everyone I met in Shonan, and ask for your continued association with us.

- **Yoshiaki Kassai** (Co-PI, Takeda, currently Alloy Therapeutics)

Through T-CiRA, we navigated numerous challenges together, experiencing the excitement of sparking innovation while growing profoundly as individuals. Those days serve as my bedrock. Even now, as I pursue my lifework, I am deeply grateful to be surrounded by such exceptional peers (who have surprisingly stuck by me). I am confident that our paths will remain connected and that, together, we will continue to drive global change as true innovators.

Organoid Medicine Project

Organoid-guided drug safety and discovery program

PI

Takanori Takebe

T-CiRA made me keenly aware that drug discovery research is truly a collective effort. We were fortunate to work with extraordinally colleagues across domains, whose contributions made these achivements possible. We would like to express our sincere gratitude to all of the participants throughout the time. Innovation often emerges at the boundaries between different disciplines, and the strength of people and organizations becomes most evident when we face difficulties. A representative example is that, despite the adversity of the pandemic, we were united to publish a high-impact paper to elucidate key COVID-19 related disease mechanism in Cell Stem Cell in such a short period of time. I hope to continue embracing challenges without fearing difficult paths, and to keep working with you to deliver meaningful results to patients.

Results

Our study uncovered the common genetic basis of drug-induced liver injury using iPS cell–derived liver organoids and patients' sample contributing to drug discovery and personalized medicine. Secondly, we devised next-generation vascularized organoid platform that can dictate the sinusoidal structure of the liver, demonstrating potential applications for a Hemophilia A in regenerative medicine. *Finally, this new vascularized organoid platform aid identify a therapeutic candidate for currently intractable endothelial dysfunction syndrome thought in-depth molecular pathobiological mechanisms*
Overall, this work has led to 10 patent filings, 14 publications, 26 presentations at academic conferences, and 3 media features.

Membership List:

Norikazu Saiki, Shutaro Kawamura, Rio Omura, Hirokazu Matsumoto, Masaaki Funada, Kohei Deguchi, Taeko Yoshida, Eri Kawakami, Tamaki Kono, Tadahiro Shinozawa (23 alumni).

Looking back on T-CiRA

- **Tadahiro Shinozawa** (2016 – 2018, Co-PI, Takeda)

Through my experience with T-CiRA, I have witnessed the fusion of different idea creation and thinking processes between academia and corporate researchers. In addition to this achievement, we expect that this new research culture will lead to the acceleration of drug discovery research and the early delivery of innovative drugs to patients.

- **Yasunori Nio** (2016 – 2022, Sub-PI → Co-PI, Takeda)

It was a team formation where researchers with different skill sets got together. Academia-industry researchers may have been unsure of themselves due to the difference in mindsets between industry researchers and researchers with different skills. However, we overcame such confusion and realized that we could sublimate research papers and patents by leveraging each other's strengths. I look forward to seeing how they will be implemented in society and be useful.

- **Hirokazu Matsumoto** (2022 – 2025, Co-PI, Takeda)

By being closely exposed to highly specialized, cutting-edge research, I was able to spend truly stimulating days. I learned not only about the research content itself but also about presentation techniques and slide creation from diverse perspectives based on innovative ideas. I am deeply grateful for this invaluable experience..

- **Masaru Koido** (2016 – 2018, Sub-PI, Yokohama City University)

Driven by the mission to challenge conventional paradigms in predicting drug-induced liver injury, the team engaged in close collaboration, integrating diverse expertise and perspectives.
I look forward to the day when T-CiRA's many achievements lead society toward transformation.

- **Norikazu Saiki** (2018 – 2025, Sub-PI, Institute of Science Tokyo)

I am truly grateful that we were able to produce results while experiencing the process of basic research shifting to and synchronizing with the industry. At the same time, with new issues and missions for achieving true social implementation, we believe that the 10-year anniversary is the new beginning of T-CiRA initiated research and a ray of light for the future.

- **Eri Kawakami** (2016 – 2025, Takeda)

In challenging complex diseases such as DILI, aHUS, COVID-19, and SOS, and facing data sincerely,I gained many new insights and serendipity. In collaboration beyond organizational boundaries, our discovery through repeated hard work will become the foundation for the future. We will take steps to take on the next challenge, bearing in mind the preciousness of our years together and the appreciation.

- **Masaaki Funada** (2019 – 2025, Takeda)

I found that people with different specialties and positions engaged in honest discussions from diverse perspectives gave me new realizations through the friction of opinions that led to results. It is our hope that the research findings from this project will lead to the realization of medical treatment in the future.

Neural Crest cell Project

Studies using human iPS cell-derived neural crest cells

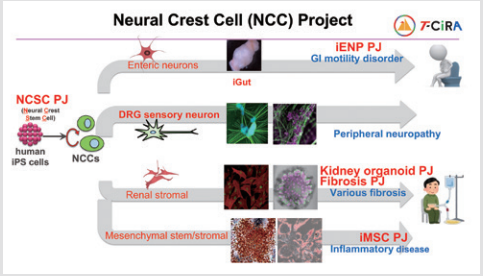
PI

Makoto Ikeya

My ten years at T-CiRA have been an incredibly valuable experience, where I was able to promote neural crest cell research through the collaboration between academia and industry. I am deeply grateful for the tremendous support from Takeda and for the colleagues who have challenged this journey together. The path is still ongoing, but based on the achievements obtained so far, I will continue to expand and develop my research towards social implementation.

Research theme

In this project, the research was conducted based on the method for inducing differentiation from iPS cells to neural crest cells developed by Associate Professor Ikeya. As a result, we established a technology to stably culture neural crest cells prepared from iPS cells while maintaining the multipotency. We also developed a method to expand enteric neural progenitor cells and demonstrated that the cells restore intestinal motility in a Hirschsprung's disease model mice. This achievement demonstrates the applicability of this technology to cell therapy. Furthermore, we differentiated neural crest cells into renal stromal cells, identified multiple molecules involved in renal fibrosis, and presented the possibility of new drug discovery targets. In addition, we established a method for differentiation into mesenchymal stem cells (MSC) using no animal-derived raw materials and demonstrated that the prepared MSCs exhibit immunosuppressive effects. As described above, iPS cell-derived neural crest cells were used to construct a platform that can be applied to future drug discovery research and cell therapy.



Membership List:

Yayoi Toyooka, Daisuke Kamiya, Teppei Akahoshi, Hirokazu Matsumoto, Teruyoshi Yamashita, Yusaku Komoike, Taiki Nakajima, Hideyuki Hiyoshi (20 alumni).

Looking back on T-CiRA

- **Hirokazu Matsumoto** (Co-PI, Takeda)

Ikeya PJ was familiar with the environment where we could discuss at any time, beyond the framework of themes and affiliations, about differentiation methods related to sensory neurons, renal interstitial cells, enteric neurons, etc. induced by NCC and various disease research. I am sure that these experiences have allowed us to spend such an exciting and meaningful time and will be a great asset for our members going forward.

- **Daisuke Kamiya** (Sub-PI, CiRA)

For eight years after the launch of T-CiRA, I was in charge of the work of kidney and MSC at Ikeya PJ. Now that I am working in a venture company, I realized once again that, in T-CiRA, various people supported me and created an environment where I could concentrate on my research. I have had many learning opportunities, and I myself have achieved great growth. Thank You!

- **Yayoi Toyooka** (Sub-PI, CiRA)

I deeply appreciate Dr. Ikeya and Dr. Yamanaka for hiring me when I was in a difficult situation to continue my research career due to my family circumstances. I also appreciate Dr. Matsumoto's efforts to exploring ways to utilize the NCSC in drug discovery. I was so grateful to Funada-san, Shinohara-san, and Inukai-san, who talked to me occasionally while I didn't have acquaintances. I wish Takeda continued success in the future.

- **Teruyoshi Yamashita** (Sub-PI, Takeda)

In 2017, I was drawn to the Ikeya Project by my long-standing interest in neural crest cell research. Together with wonderful colleagues, we pursued our work under the slogan "Make the World go round by Neural Crest cells" and achieved results that could lead to regenerative medicine for enteric nervous system. Although T-CiRA is coming to an end, I will continue to explore ways to contribute to the social implementation of these technologies in some form.

Genome Editing Therapy for Muscular Dystrophy Project

Development of novel gene therapies for Duchenne muscular dystrophy using genome editing and in vivo delivery technologies

PI

Akitsu Hotta

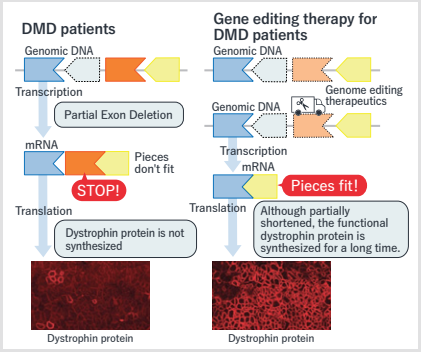
When we started this project 10 years ago, there was no method to safely deliver genome-editing enzymes to skeletal muscle. Thanks to the efforts of the project members and the support of many people, we were able to develop a number of groundbreaking delivery methods. I believe that it is my mission to bring these results to patients. I am truly grateful to everyone who have supported the project, and I am also proud to have been able to conduct this pioneering research together

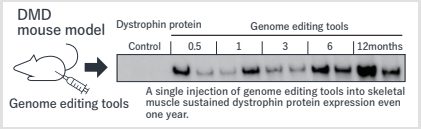
Research theme

Duchenne muscular dystrophy (DMD) is an intractable disease in which the skeletal muscles are gradually damaged. It is caused by abnormalities in the *dystrophin* gene. In this project, we developed a drug-delivery technology to deliver genome editing tools that are key for gene repair as a new treatment method.

Results

We developed nanoparticle technologies (lipid nanoparticles and virus-like particles) and protein-based delivery technology that can deliver genome-editing tools to skeletal muscles. Among them, lipid nanoparticles were able to be administered multiple times, showing the potential for a radical treatment of genetic mutation.





Membership List:

Naoto Inukai, Makoto Asahina, Takanori Tabata, Youichi Naoe, Naoko Fujimoto, Hiroyuki Hozumi, Taisuke Mochida, Dongyang Li, Megumi Ozawa, Kaori Konno, Aya Takino, Masataka Ifuku, Tomomi Iwasaki, Kumiko Iwabuchi, Kentaro Otake, Rumiko Ochiai, Eriya Kenjo, Tsukasa Sugo, Masami Tanaka, Ryuichi Tozawa, Ryuichi Nishigaki, Yukimasa Makita, Satoru Matsumoto, Peter Gee

Looking back on T-CiRA

- **Naoto Inukai** (Co-PI, Takeda)

Over ten years with T-CiRA, I gained invaluable experiences beyond everyday work. Meeting and working with all T-CiRA members is something I truly treasure.

- **Makoto Asahina** (Takeda)

I was responsible for in vivo efficacy studies, through which I gained deep insights into LNP-based delivery.

- **Youichi Naoe** (CiRA)

Thank you for giving me the opportunity to be involved in drug discovery research.

- **Hiroyuki Hozumi** (Takeda)

I had the privilege of gaining various valuable experiences beyond my research activities.

- **Dongyang Li** (CiRA)

I am honored to have taken part in the T-CiRA project and gained lots of knowledge and experience.

- **Kaori Konno** (Orizuru)

Thank you for being involved in this project.

- **Takanori Tabata** (Takeda)

These past four years, I have been supported by many people, and I am filled with gratitude. Thank you.

- **Naoko Fujimoto** (CiRA)

I appreciate the opportunity to participate in the T-CiRA project.

- **Taisuke Mochida** (Takeda)

We successfully demonstrated in vivo muscle stem cell editing in a pioneering study, delivering new value to society.

- **Megumi Ozawa** (Orizuru)

It was a very valuable experience to be involved in the project. Thank you.

- **Aya Takino** (Orizuru)

Thank you very much for giving me the opportunity to gain such a valuable experience.

Cardiomyopathy Project

Human iPS cell-based drug discovery for intractable cardiomyopathy

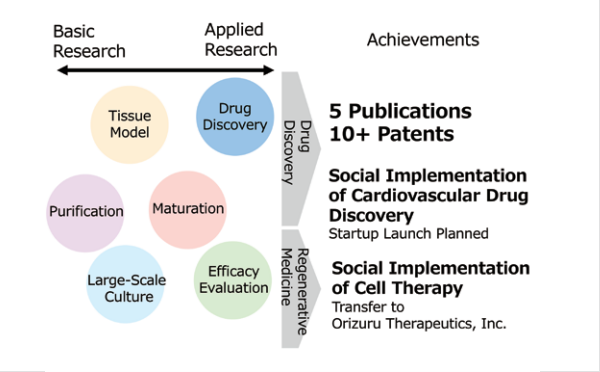
PI

Yoshinori Yoshida

It has been ten years since the launch of T-CiRA. During this period, together with many colleagues, collaborators, and members of Takeda and CiRA, we have advanced our projects in drug discovery and regenerative medicine using human iPS cell-derived cardiomyocytes. We sincerely appreciate your continued support. Although T-CiRA project has concluded, we remain committed to accelerating our research and development to address unmet medical needs in the cardiovascular field, building on the technologies and scientific advances developed through T-CiRA.

Results

Human iPS cell–derived cardiomyocytes are often immature, heterogeneous, and available only in limited quantities, limiting their use in drug development and cell therapy. Our team has established methods to generate cardiomyocytes that more faithfully recapitulate the human heart and can be produced at scale with high reproducibility, enabling applications in drug discovery and regenerative medicine. Building on these technologies, we have further advanced this platform, and parts of it have been transferred to Orizuru Therapeutics, Inc., as a cell therapy platform for clinical implementation. We are also planning to launch a new startup to translate our 3D cardiac tissue technology into innovative cardiovascular drug discovery.



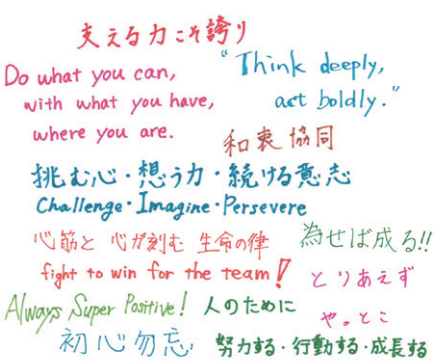
Membership List:

Kohei Deguchi, Yuya Fujiwara, Shunsuke Funakoshi, Kenichi Imahashi, Fumika Inazuka, Naoto Inukai, Shigeru Kondo, Hirokazu Matsumoto, Yuki Naka, Misato Nishikawa, Tomoyuki Nishimoto, Masako Sasaki, Ayaka Sakoda (30 alumni).

Looking back on T-CiRA

Throughout this period, more than thirty members have joined this project and we have steadily accumulated robust data using a wide range of methods and perspectives. Each experiment was performed with precision to ensure consistent generation of high-quality cardiomyocytes, and compound treatment conditions were carefully optimized. We also paid close attention to every step of animal experiments, including the insertion and removal of needles. These reliable data were made possible by technical skills that take years to develop. The obtained data were carefully analyzed, discussed, and integrated with previous studies to interpret the findings and uncover their significance. We have persistently overcome unexpected challenges and continued to advance toward achieving our research goals. During periods when progress was difficult, including the COVID-19 pandemic, we repeatedly reflected on our mission and carefully considered the value of our research within society beyond academia. We take great pride not only in contributing to basic science through publishing our findings but also in advancing them toward social implementation.

Members who have moved on from the project continue to pursue new challenges in their respective fields—conducting research at overseas institutes, joining new organizations, and founding startups—to create the next wave of social value. The driving force behind these achievements lies in the steady, day-to-day research efforts accumulated throughout this project. Each member has contributed a message under the theme “MOTTO,” expressing their individual approach to advancing our mission. We hope that everyone will share these thoughts together with the trajectory of our progress.



“MOTTO”

ALS/ASD Project

Drug discovery research for amyotrophic lateral sclerosis (ALS) and autism spectrum disorder (ASD) using patient-derived iPS cells

PI

Haruhisa Inoue

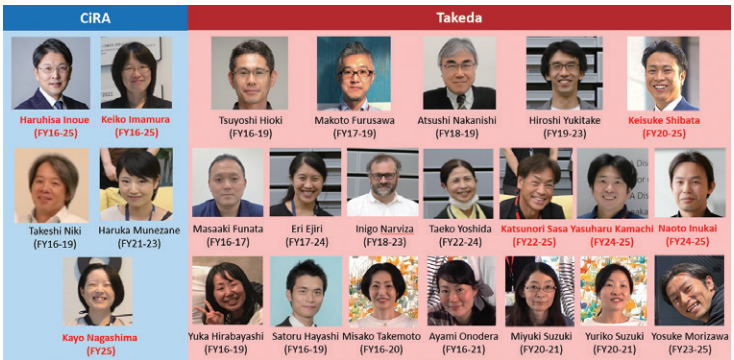
This joint project, conducted over a period of 10 years with the generous support of Takeda, has successfully achieved its intended goals. We would like to express our deepest gratitude. This initiative has produced multifaceted outcomes, including a deeper understanding of intractable neurological diseases, the establishment of a new drug discovery platform, the development of human resources, and the formation of an industry–academia collaboration network. These accomplishments represent a new starting point for future drug discovery research and medical applications, and will continue to support research activities that contribute to society.

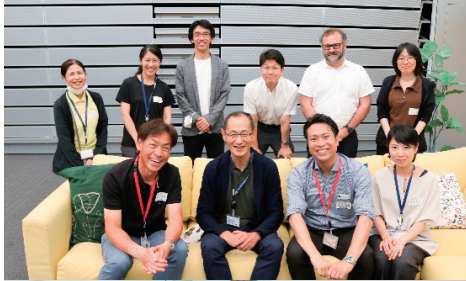
Research theme

Amyotrophic lateral sclerosis (ALS), a progressive and intractable disease in which motor neurons are damaged and muscles atrophy, and autism spectrum disorder (ASD), a neurodevelopmental disorder, both have a profound impact on patients' lives, and no effective treatments are currently available. To address this, we conducted research to identify potential *drug seeds* using neurons derived from patient-specific iPS cells. By employing a high-content, high-throughput evaluation system—targeting motor neuron degeneration in ALS and deficits in neurite outgrowth and neuronal activity in ASD—we successfully identified *drug seeds* that can protect or ameliorate abnormalities observed in patient-derived iPSC neurons. Furthermore, we accelerated our research by integrating AI-based hit prediction models and automated cell-culture platforms, with the goal of delivering meaningful results to patients as quickly as possible.

Membership List:

Total members: 24 * Closing members





Looking back on T-CiRA

- **Keisuke Shibata** (Co-PI, Takeda)

This project has taken on many challenges over the past 10 years, guided by Prof. Inoue's strong belief in "delivering results to patients." Within this groundbreaking industry–academia collaboration, the insight and passion of academic researchers made each day deeply valuable and provided tremendous learning opportunities for the Takeda members as well. I sincerely hope that the achievements and knowledge accumulated over the past decade will lead to further research and innovation in the years to come.

- **Keiko Imamura** (CiRA)

Through our 10 years of joint research, we have learned a great deal from the collaboration between industry and academia. In particular, the insights gained from the differences in our perspectives and ways of thinking have greatly contributed to the advancement of our work. Moving forward, we will continue to promote research that bridges the results of iPS cell studies to real-world implementation. I would like to express my heartfelt appreciation to all those who have supported us along the way.

- **Misako Takemoto** (Takeda)

I would like to express my sincere gratitude for this important milestone of T-CiRA. The years I spent conducting research on treatments for neurological disorders using iPS cells were not without challenges, but they were invaluable experiences that contributed greatly to my personal and professional growth. I look forward to the day when the seeds planted here will begin to flourish.

NGLY1 deficiency Project

Elucidation of the pathogenic mechanisms of NGLY1 deficiency and development of therapeutic strategies

PI

Tadashi Suzuki

T-CiRA was truly a major turning point in my research career. With the team's support, we achieved results that contributed to GS-100, the clinical trial for gene therapy for NGLY1 deficiency. I had never worked with iPS cells before this project—embarrassingly—but through this experience I realized their tremendous value. Thank you very much!

Results

①Contribution to early patient diagnosis through the development of NGLY1 activity assays and diagnostic methods

②Development of specific biomarkers for NGLY1 deficiency

③Successful generation of a highly specific and sensitive NGLY1 antibody

④Transient suppression of convulsion-like behaviors in Ngly1-deficient mice by intranasal oxytocin administration

⑤Elucidation of the involvement of FBS2 in the pathogenic mechanisms of NGLY1 deficiency

⑥Generation of systemic Ngly1-deficient rat and mouse models with rescued embryonic lethality

⑦Functional recovery of Ngly1-deficient rats through AAV administration and its translation toward gene therapy in human

⑧Phenotypic analysis of patient-derived iPSC–derived motor neurons and brain organoids, and screening of candidate therapeutics among approved drugs

⑨AI-based identification of approved drugs as candidate therapeutics for NGLY1 deficiency

Looking back on T-CiRA

- **Hiroto Hirayama** (RIKEN)

I succeeded in (1) developing a method to detect NGLY1 activity and a diagnostic method, and (2) developing a biomarker specific to NGLY1 deficiency during my research on NGLY1 deficiency PJ. These findings are important findings that contribute to the development of early diagnosis of the disease.

- **Yuriko Tatsuta** (RIKEN)

Mainly responsible for the development of a detection method for NGLY1, which had no good detection method, and the search for a biomarker for NGLY1 deficiency. To develop a method to detect NGLY1, a simple activity assay was established, a specific antibody was generated, and biochemical analysis of NGLY1 was performed using the established activity assay.

- **Reiko Fujinawa** (RIKEN)

Because an animal step length measuring device was not available, paints were smeared on the soles of animals, and the footprints of animals were measured with a ruler. It was very difficult to make the animals walk “straight,” but by improving the environment, we were able to collect and measure the footprints with good reproducibility.

- **Mr. Yukimasa Maita** (Takeda)

We submitted a paper and presented at a scientific meeting on the inhibitory effect of oxytocin on convulsion-like behavior in Ngly1-deficient mice, followed by a joint press release with RIKEN.

- **Makoto Asahina** (Takeda)

We are proud to have contributed to the development of AAV gene therapy in humans by establishing a systemic Ngly1-deficient rodent model that avoided embryonic death and verifying the efficacy of intracerebroventricular injection of AAV.

- **Ryuichi Tozawa** (Takeda)

I was involved in the operation and promotion of the project as Co-PI from the launch of the project to May 2021. As a project that contributes to the development of treatments for the ultra-rare disease NGLY1 deficiency, we obtained significant results in pathophysiology analysis using disease iPS cells and disease model animals, examination of treatment candidates, and development of biomarker analysis methods with close cooperation of patient groups.

- **Mr. Yukitake** (Takeda)

Although it was a short time, working with members of Suzuki PJ who were enthusiastic about contributing to the treatment of NGLY-1 deficiency was a precious opportunity for me. Thank you.

Intractable Muscular Disease Project

Drug Discovery Research for Intractable Muscular Diseases

PI

Hidetoshi Sakurai

The research to reproduce the pathology using iPS cells derived from patients with muscular dystrophy, which had started at my university, was actually used as a drug discovery tool through participation in a major project called T-CiRA. This was a very valuable experience for me as well. The university's ability to create new things, the outstanding drug discovery technologies and uncompromising professional approach to research, which Takeda has cultivated over many years, combined well to produce these results.

Research theme

We constructed a stable skeletal muscle differentiation induction system that can withstand drug screening from patient-derived iPS cells, and replicated pathological conditions and proceeded drug screening. For Miyoshi myopathy, we established a high-throughput screening system using a high-content image analyzer to identify drugs that increase dysferlin expression from the existing drug library. In addition, we conducted large-scale phenotypic screening using the Takeda compound library to identify candidate compounds as potential drug discovery targets and developed the results for pharmacological evaluation. In Duchenne muscular dystrophy, we have identified a molecular mechanism that causes calcium overload and its inhibitors. In addition, we established a method for mature skeletal muscle differentiation, created a model of electrically stimulated muscle fatigue-like contractility reduction, and identified therapeutic drug candidates from existing drugs. In addition, to increase throughput, we developed a system for evaluating contraction by light stimulation without electrodes.

Membership List:

Ryuichi Tozawa, Naoto Inukai, Tomoya Uchimura, Yuko Kokubu, Tomoko Nagino, Masahiro Oka, Tatsuo Oikawa, Toshiki Tanaka, Ayuka Inatsuka, Motoko Fukuda, Katsunori Sassa, Taeko Yoshida, Minako Ogawa, Akiko Kume, Kyoyo Mikami, Yosuke Iseki, Michiko Isobe

Looking back on T-CiRA

- **Ryuichi Tozawa** (Co-PI, Takeda)

From the start of the project in 2015 to May 2021, I supported the operation and promotion of the project as Co-PI. I consider the fact that we have been able to effectively advance drug discovery research for rare intractable diseases, for which Takeda could not engage in full-scale, through the approach of iPS cell drug discovery, which combines the disease iPS cell utilization technology from CiRA and the drug discovery know-how from Takeda to be a major accomplishment.

- **Tatsuo Oikawa** (Sub-PI, Takeda)

Members with different specialties came together, and under the strong leadership of Dr. Sakurai, we were able to identify candidate drug discovery targets by setting a drug screening system using iPS cells and establishing a preclinical evaluation system in a short period of time. It is a significant result that we were able to communicate the potential of iPS cell drug discovery from Sakurai PJ.

- **Yuko Kokubu** (Sub-PI, CiRA)

As I failed drug discovery research once as a pharmaceutical company researcher and relearned iPS cell technology in academia, HTS and drug discovery research using disease-specific iPS cells derived from patients with muscular dystrophy at T-CiRA was one of my life goals. The experience of publishing a paper together with the members of Takeda and progressing a hit compound to the next stage, although the development was discontinued, is a great asset. I would like to contribute to society through new drug development in the future.

- **Katsunori Sassa** (Takeda)

I am very proud to participate in the industry-academia joint T-CiRA. While I were able to appreciate the difficulty of using iPS cells in drug discovery research, I were surprised at how wide the range of indications was. I would like to thank all involved.

Beta cell Project

Research on cell therapy for type 1 diabetes mellitus

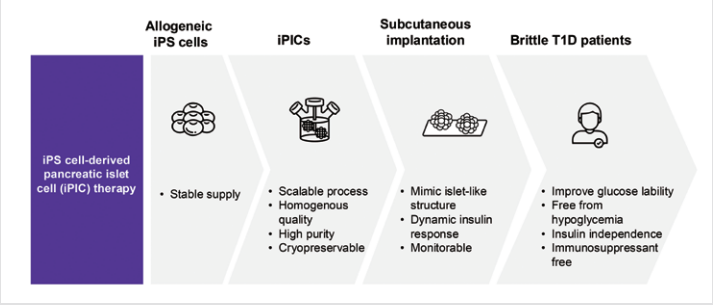
PI

Taro Toyoda

It is thanks to the exceptional environment of T-CiRA, where diverse experts gather for high-level discussions, that our basic academic research has reached the major milestone of starting a clinical trial. The valuable experiences gained through this industry-academia collaboration and the opportunity to meet colleagues who share the same vision, are treasures of my life. We will continue to strive to build upon these achievements for the future and further advance regenerative medicine using iPS cells.

Research theme

Building upon the differentiation method toward pancreatic cells discovered by Dr. Toyoda, we established allogeneic iPS cell-derived pancreatic islet cells (iPICs), suitable for cell therapy, which secrete insulin in response to blood glucose levels in vivo. We also independently developed a diabetic immunodeficient porcine model to demonstrate the efficacy of iPICs in large animals. Furthermore, using gene expression analysis, we established a purification method to selectively remove off-target cells occasionally arising during iPIC production. Additionally, in collaboration with a manufacturer, we developed culture bags for the mass production of homogeneously sized iPICs. These steps laid a crucial foundation for the transition to clinical trials. These achievements were transferred to Orizuru Therapeutics, Inc. in 2021 and led to the initiation of an investigator-initiated clinical trial of the iPIC sheet product OZTx-410 for people with type 1 diabetes mellitus.



Membership List:

Ryo Ito, Hikaru Ueno, Hiroaki Sugiyama, Shuhei Konagaya, Akifumi Yoshihara, Noriko Yamazoe, Kensuke Sakuma, Taisuke Mochida, Hideyuki Hiyoshi, Yutaka Tanoue, Midori Yamasaki, Hirokazu Matsumoto, Kenji Osafune (46 alumni).

Looking back on T-CiRA

• Hirokazu Matsumoto (Co-PI, Takeda)

It is deeply moving that iPICs have entered a clinical trial 10 years after we started setting up the lab with Dr. Toyoda to launch T-CiRA in the fall of 2015. During this time, under the leadership of Dr. Osafune and Dr. Toyoda, we were able to tackle and solve various issues as a team, and I think that it was the best shared experience for the members who were involved. I sincerely hope it will reach patients as a product!

• Ryo Ito (Sub-PI → Co-PI, Takeda)

Four years have passed since Orizuru Therapeutics, Inc. inherited the results of the Beta Cell Project in 2021. We started the first clinical trial of allogeneic iPS cell-derived pancreatic islet therapy, taking a major first step toward practical application. I believe this was achieved thanks to the high-level discussions at T-CiRA, where leading experts in iPS cell research gather, and Takeda's extensive support from the early stages of research, including CMC. We will continue to energize the field of cell therapy!

• Shuhei Konagaya (Sub-PI, CiRA)

We successfully started the clinical trial of iPICs. Many people reached out to me at the time, and I was humbled once again by the number of people involved. We received cooperation from many parties, including Takeda Pharmaceutical and the device and material manufacturers we conducted joint research with. It was a valuable experience for me to collaborate with experts in fields rarely encountered in academia, such as CMC and safety assessment. I will continue to work hard to deliver the products to patients!

Message

Principal, Izumo Associates, LLC

Seigo Izumo

Reflections on T-CiRA

T-CiRA represents an unparalleled large-scale industry-academia collaboration based on human iPS cells—one of the most revolutionary discoveries in the history of medicine. It is one of the greatest honors of my life to have had the opportunity to establish T-CiRA program under the leadership of Professor Shinya Yamanaka, the father of iPS cells, and to work closely with many esteemed scholars from academia together with dedicated staff from Takeda.

Over the past decade, T-CiRA has yielded numerous scientific insights, original publications and intellectual properties. Several projects have now been out-licensed to biotechnology ventures with the aim of advancing toward clinical trials. I have unwavering faith that the innovative treatments originating from T-CiRA will, in time, reach patients around the world. Moreover, the invaluable experience of researchers from both academia and the pharmaceutical industry collaborating side by side at T-CiRA will surely serve as a critical foundation of their future careers.

I wish to express my deepest gratitude to all those who have contributed to the establishment of T-CiRA. In particular, I would like to thank Takeda CEO Christophe Weber, the late Dr. Tachi Yamada (then Chief Medical Scientific Officer), and Dr. Nagahiro Minato, President of Kyoto University. Their wholehearted support and endorsement of our bold vision to revolutionize regenerative medicine—and of T-CiRA's unprecedented collaborative framework bridging academia and industry—were instrumental in bringing this initiative to life.

President, Representative Director and CEO Orizuru Therapeutics, Inc.

Kenji Nonaka

For better Society through iPS Cell Technology

On the occasion of the conclusion of the T-CiRA Program, I would like to extend my deepest gratitude to all those who have contributed to its success. Orizuru Therapeutics, Inc. (hereinafter referred to as "OZTx") has inherited both the intellectual property and the human expertise associated with the cardiomyocyte and islet cell programs from that program, and commenced its business operations in 2021. Both pipeline projects have progressed steadily; in particular OZTx-410, the lead candidate of the islet cell program, has successfully advanced to the clinical development phase. Our platform business, primarily composed of technical staff formerly engaged in T-CiRA, has been able to provide continuous support for that program as well as other related initiatives. With profound respect and appreciation for the aspirations embodied by T-CiRA and the forefront of iPS cell technology, OZTx remains steadfast in its commitment to carrying forward this mission, striving to serve as a bridge to a better society through the continued advancement of research and development.

Chief Executive Officer
iPark Institute Co., Ltd.

Toshio Fujimoto

The Future of Medicine Pioneered by Industry-Academia Collaboration

T-CiRA represented a new model of industry-academia collaboration, accelerating practical applications by combining Japan's cutting-edge technology with the nation's leading pharmaceutical company. For all of you, this decade must have been one where the exhilaration of leading the era and the pressure of carrying immense expectations were in constant tension. You have proven the effectiveness of this collaboration model by spawning several clinical programs, and on top, T-CiRA's presence itself enriched the ecosystem community. While it is generally said that it takes 30 years to move from technological discovery to practical application, that timeframe for iPSC technology is set to be significantly shortened. Your decade of effort is now being passed on to patients. I sincerely hope you will continue to pioneer new possibilities in medicine.

President & CEO
Axcelead Drug Discovery Partners, Inc.

Yoshinori Ikeura

The foundation of knowledge built by T-CiRA and the baton to the next generation

When Christophe was appointed president of Takeda Pharmaceutical Company Limited, he was asked what science Japan was proud of and mentioned iPS research without hesitation. This is a scene that I still vividly recall. After that, thanks to the efforts of many people, T-CiRA was born. With patient-derived iPS as the core, we have promoted disease models, drug discovery platforms, and cell/gene therapies as the Trinity, and built an unwavering foundation of knowledge: 246 presentations at academic conferences, 58 patents, and 66 papers by the end of October 2025. At Shonan iPark, researchers from CiRA and Takeda have lined up with each other to create a new drug discovery ecosystem under the direction of Professor Shinya Yamanaka. As Axcelead, we are very proud that we were able to contribute through the establishment of various evaluation systems. The two programs of iPS-derived cardiomyocytes and pancreatic islet cells, which are the emblastic achievements, were transferred to Orizuru Therapeutics in 2021, making solid progress toward clinical application. T-CiRA is not an end. It is an entity that the results, people, and "ways of working together " will be passed down to the next generation. The journey we have taken together from launch to support has been invaluable to me.

Future Prospects

T-CiRA Director
Director Emeritus and Professor, Center for iPS Cell Research and Application (CiRA), Kyoto University
President, CiRA Foundation
Senior Investigator, Gladstone Institute of Cardiovascular Disease

Shinya Yamanaka

Transformative Outcomes from an "Unprecedented Industry-Academia Collaboration" towards the Next Stage of Practical Application

T-CiRA can be described simply as an "unconventional industry-academia collaboration."
One of the most important features of our system is that academic researchers visit Takeda's laboratories to advance research and development side-by-side with Takeda's researchers, leveraging our compound library and world-class facilities.
I have witnessed firsthand how researchers from industry and academia, exchanging ideas daily in the same space and pooling their respective strengths, have produced results beyond imagination. Furthermore, for us in academia, conducting research while experiencing the cutting edge of pharmaceutical development up close was an invaluable experience beyond compare.
This revolutionary framework proved its true worth as multiple projects over the decade paved a solid path toward practical application. As research and development progressed, I observed the discussions advance from the perspective of a basic scientist while witnessing firsthand how the projects steadily moved closer to tangible results. Each time, my heart raced at the sheer power of industry and academia uniting to tackle challenges together.
I am confident that the wisdom and collaborative spirit cultivated through T-CiRA will become the driving force to transform healthcare in the future. Indeed, our vision of "Transforming Medicine with the Unlimited Potential of iPS Cells" began taking shape here.
Finally, at the conclusion of the T-CiRA program, I would like to express my heartfelt gratitude to all of those who have supported this challenge. I would like to extend my wishes to Takeda and all the researchers involved in the research for the future.

R&D Japan Region Head, Global Regions, Takeda R&D

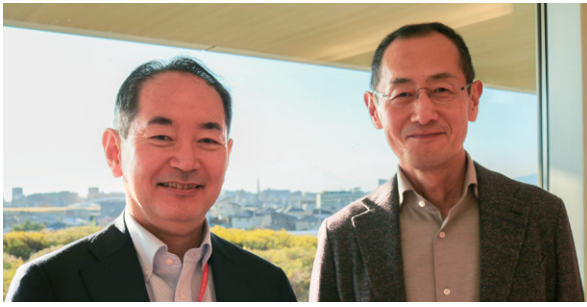
Yasushi Kajii

Medical revolution that unlocks the future: Challenges and achievements of T-CiRA

T-CiRA accomplished great achievements with challenges as a unique industry-academia collaboration program. Although 10 years of the program duration may seem long, it was a very short time to link iPS cell technology discovered only 10 years before, of which there were many unknowns at the starting point of the program, to a new business. Nevertheless, as a result of the enthusiasm and dedication of the researchers who participated in this program from both academia and Takeda, we were able to make certain steps toward social implementation of new medical innovations.

For example, clinical studies aimed at gene therapy for ultra-rare diseases for which there is no treatment method, and iPS cell therapy for diseases for which there is no treatment method other than organ transplantation, are being conducted as the results of T-CiRA. These clearly demonstrate the social significance of T-CiRA.

In addition, as one of the persons involved in the management of this program, I am very proud that the researchers who participated in T-CiRA at various positions are playing important roles in new environments. Thus, this unique program also played a significant role in the development of human resources to promote innovation. I sincerely hope that the impact of T-CiRA will show up even more clearly in various academic, clinical and business settings in the future.



Publications List

1. Ifuku, M. & Hotta, A. iPS細胞とゲノム編集の融合による新展開. 日本臨牀 75, 788-794 (2017).
2. Makita, Y. et al. 筋ジストロフィー治療応用を目指したゲノム編集技術の開発動向. Clinical Calcium 27, 67-75 (2017).
3. Ifuku, M. et al. Restoration of Dystrophin Protein Expression by Exon Skipping Utilizing CRISPR-Cas9 in Myoblasts Derived from DMD Patient iPS Cells. Methods Mol Biol. 1828, 191-217 (2018). https://doi.org/10.1007/978-1-4939-8651-4_12.
4. Iwabuchi, K. & Hotta, A. ゲノム編集によるデュシェンヌ型筋ジストロフィーの治療戦略. 医療応用をめざすゲノム編集 12,122-136 (2018).
5. Iwabuchi, K. & Hotta, A. ゲノム編集技術とその応用の現状. 血液フロンティア 28, 343-352 (2018).
6. Minagawa, A. et al. Enhancing T Cell Receptor Stability in Rejuvenated iPSC-Derived T Cells Improves Their Use in Cancer Immunotherapy. Cell Stem Cell 23, 850-858 e854 (2018). https://doi.org/10.1016/j.stem.2018.10.005
7. Kawakami, E. & Takebe, T. 肝オルガノイド技術を用いたiPS創薬戦略. 細胞 51, 173-177 (2019).
8. Kokubu, Y. et al. Phenotypic Drug Screening for Dysferlinopathy Using Patient-Derived Induced Pluripotent Stem Cells. Stem Cells Transl Med 8, 1017-1029 (2019). https://doi.org/10.1002/sctm.18-0280
9. Nio, Y. & Takebe, T. Organoid Models of Development and Disease Towards Therapy. (Springer Nature eBOOK, 2019).
10. Saiki, N. & Takebe, T. 肝臓オルガノイドのシングルセル解析. 実験医学 37, 61-67 (2019).
11. Takada, H. et al. Identification of 2,6-Disubstituted 3H-Imidazo[4,5-b]pyridines as Therapeutic Agents for Dysferlinopathies through Phenotypic Screening on Patient-Derived Induced Pluripotent Stem Cells. J Med Chem 62, 9175-9187 (2019). https://doi.org/10.1021/acs.jmedchem.9b01100
12. Asahina, M. et al. Ngly1 -/- rats develop neurodegenerative phenotypes and pathological abnormalities in their peripheral and central nervous systems. Hum Mol Genet 29, 1635-1647 (2020). https://doi.org/10.1093/hmg/ddaa059
13. Gee, P. et al. Extracellular nanovesicles for packaging of CRISPR-Cas9 protein and sgRNA to induce therapeutic exon skipping. Nat Commun 11, 1334 (2020). https://doi.org/10.1038/s41467-020-14957-y
14. Hidaka, T. et al. Prediction of Compound Bioactivities Using Heat-Diffusion Equation. Patterns (N Y) 1, 100140 (2020). https://doi.org/10.1016/j.patter.2020.100140
15. Koga, K., Wang, B. & Kaneko, S. Current status and future perspectives of HLA-edited induced pluripotent stem cells. Inflamm Regen 40, 23 (2020). https://doi.org/10.1186/s41232-020-00132-9
16. Koido, M. et al. Polygenic architecture informs potential vulnerability to drug-induced liver injury. Nat Med 26, 1541-1548 (2020). https://doi.org/10.1038/s41591-020-1023-0
17. Mochida, T. et al. Insulin-Deficient Diabetic Condition Upregulates the Insulin-Secreting Capacity of Human Induced Pluripotent Stem Cell-Derived Pancreatic Endocrine Progenitor Cells After Implantation in Mice. Diabetes 69, 634-646 (2020). https://doi.org/10.2337/db19-0728
18. Oohori, M., Nio, Y., Kawakami, E. & Takebe, T. オルガノイド医療の可能性と課題. 実験医学 38, 44-49 (2020).
19. Asahina, M. et al. JF1/B6F1 Ngly1(-/-) mouse as

an isogenic animal model of NGLY1 deficiency. Proc Jpn Acad Ser B Phys Biol Sci 97, 89-102 (2021). https://doi.org/10.2183/pjab.97.005

20. Asahina, M. et al. Reversibility of motor dysfunction in the rat model of NGLY1 deficiency. Mol Brain 14, 91 (2021). https://doi.org/10.1186/s13041-021-00806-6

21. Funata, M., Nio, Y. & Takebe, T. 肝臓におけるヒューマン・オルガノイド研究の最前線. 実験医学 39, 2870-2876 (2021).

22. Funata, M., Nio, Y., Erion, D. M., Thompson, W. L. & Takebe, T. The promise of human organoids in the digestive system. Cell Death Differ 28, 84-94 (2021). https://doi.org/10.1038/s41418-020-00661-3

23. Iriguchi, S. et al. A clinically applicable and scalable method to regenerate T-cells from iPSCs for off-the-shelf T-cell immunotherapy. Nat Commun 12, 430 (2021). https://doi.org/10.1038/s41467-020-20658-3

24. Kawakami, E. & Takebe, T. 肝臓オルガノイドによるマイメディシン. 医学のあゆみ 276, 86-92 (2021).

25. Kenjo, E. et al. Low immunogenicity of LNP allows repeated administrations of CRISPR-Cas9 mRNA into skeletal muscle in mice. Nat Commun 12, 7101 (2021). https://doi.org/10.1038/s41467-021-26714-w

26. Miki, K. et al. ERRgamma enhances cardiac maturation with T-tubule formation in human iPSC-derived cardiomyocytes. Nat Commun 12, 3596 (2021). https://doi.org/10.1038/s41467-021-23816-3

27. Nio, Y. Ameliorative effect of anti-complement factor antibody on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected macaque. Translational and Regulatory Sciences 3, 98-101 (2021).

28. Nio, Y., Oohori, M. & Takebe, T. 幹細胞・オルガノイドを用いた肝線維化研究の最前線. 医学のあゆみ 279, 777-781 (2021).

29. Shibata, K., Imamura, K., Yukitake, H. & Inoue, H. iPS 細胞を用いた自閉症と認知症の研究 細胞 53, 671-675 (2021).

30. Uchimura, T. & Sakurai, H. Orai1-STIM1 Regulates Increased Ca(2+) Mobilization, Leading to Contractile Duchenne Muscular Dystrophy Phenotypes in Patient-Derived Induced Pluripotent Stem Cells. Biomedicines 9 (2021). https://doi.org/10.3390/biomedicines9111589

31. Uchimura, T., Asano, T., Nakata, T., Hotta, A. & Sakurai, H. A muscle fatigue-like contractile decline was recapitulated using skeletal myotubes from Duchenne muscular dystrophy patient-derived iPSCs. Cell Rep Med 2, 100298 (2021). https://doi.org/10.1016/j.xcrm.2021.100298

32. Yoshida, Y. et al. Loss of peptide:N-glycanase causes proteasome dysfunction mediated by a sugar-recognizing ubiquitin ligase. Proc Natl Acad Sci U S A 118 (2021). https://doi.org/10.1073/pnas.2102902118

33. Fujihira, H., Asahina, M. & Suzuki, T. Physiological importance of NGLY1, as revealed by rodent model analyses. J Biochem 171, 161-167 (2022). https://doi.org/10.1093/jb/mvab101

34. Hirayama, H. & Suzuki, T. Assay for the peptide:N-glycanase/NGLY1 and disease-specific biomarkers for diagnosing NGLY1 deficiency. J Biochem 171, 169-176 (2022). https://doi.org/10.1093/jb/mvab127

35. Hirayama, H., Tachida, Y., Seino, J. & Suzuki, T. A method for assaying peptide: N-glycanase/

N-glycanase 1 activities in crude extracts using an N-glycosylated cyclopeptide. Glycobiology 32, 110-122 (2022). https://doi.org/10.1093/glycob/cwab115

36. Hiyoshi, H. et al. Characterization and reduction of non-endocrine cells accompanying islet-like endocrine cells differentiated from human iPSC. Sci Rep 12, 4740 (2022). https://doi.org/10.1038/s41598-022-08753-5

37. Kamiya, D. et al. Generation of human GAPDH knock-in reporter iPSC lines for stable expression of tdTomato in pluripotent and differentiated culture conditions. Stem Cell Res 60, 102704 (2022). https://doi.org/10.1016/j.scr.2022.102704

38. Kamiya, D. et al. Induction of functional xeno-free MSCs from human iPSCs via a neural crest cell lineage. NPJ Regen Med 7, 47 (2022). https://doi.org/10.1038/s41536-022-00241-8

39. Saiki, N. & Takebe, T. 胆道疾患研究最前線 肝臓オルガノイド研究の最前線. 消化器・肝臓内科 11, 1-9 (2022).

40. Taha, E. A., Lee, J. & Hotta, A. Delivery of CRISPR-Cas tools for in vivo genome editing therapy: Trends and challenges. J Control Release 342, 345-361 (2022). https://doi.org/10.1016/j.jconrel.2022.01.013

41. Yamashita, T. et al. Generation of a human SOX10 knock-in reporter iPSC line for visualization of neural crest cell differentiation. Stem Cell Res 60, 102696 (2022). https://doi.org/10.1016/j.scr.2022.102696

42. Fujiwara, Y. et al. ERRgamma agonist under mechanical stretching manifests hypertrophic cardiomyopathy phenotypes of engineered cardiac tissue through maturation. Stem Cell Reports 18, 2108-2122 (2023). https://doi.org/10.1016/j.stemcr.2023.09.003

43. Ishiguro, Y. et al. Lineage tracing of T cell differentiation from T-iPSC by 2D feeder-free culture and 3D organoid culture. Front Immunol 14, 1303713 (2023). https://doi.org/10.3389/fimmu.2023.1303713

44. Kawakami, E. et al. Complement factor D targeting protects endotheliopathy in organoid and monkey models of COVID-19. Cell Stem Cell 30, 1315-1330 e1310 (2023). https://doi.org/10.1016/j.stem.2023.09.001

45. Sakuma, K. et al. CDK8/19 inhibition plays an important role in pancreatic beta-cell induction from human iPSCs. Stem Cell Res Ther 14, 1 (2023). https://doi.org/10.1186/s13287-022-03220-4

46. Tachida, Y., Hirayama, H. & Suzuki, T. Amino acid editing of NFE2L1 by PNGase causes abnormal mobility on SDS-PAGE. Biochim Biophys Acta Gen Subj 1867, 130494 (2023). https://doi.org/10.1016/j.bbagen.2023.130494

47. Yoneyama, Y. & Saiki, N. オルガノイドの移植とライブイメージング. 実験医学 42, 802-809 (2023).

48. 宗實悠佳, Yukitake, H., Imamura, K. & Inoue, H. iPS細胞データと人工知能を用いた神経変性疾患研究. 実験医学 41, 2531-2536 (2023).

49. Fujihira, H. et al. ELISA-based highly sensitive assay system for the detection of endogenous NGLY1 activity. Biochem Biophys Res Commun 710, 149826 (2024). https://doi.org/10.1016/j.bbrc.2024.149826

50. Hirayama, H. et al. Development of a fluorescence and quencher-based FRET assay for detection of endogenous peptide:N-glycanase/NGLY1 activity. J Biol Chem 300, 107121 (2024). https://doi.org/10.1016/j.jbc.2024.107121

51. Hiyoshi, H. et al. Identification and removal of unexpected proliferative off-target cells emerging after iPSC-derived pancreatic islet cell implantation. Proc Natl Acad Sci U S A 121, e2320883121 (2024). https://doi.org/10.1073/pnas.2320883121

52. Kassai, Y. 免疫系オルガノイドの現状と展望：免疫細胞療法や疾患モデルへの応用. 実験医学 42, 744-749 (2024).

53. Kitabatake, Y. & Inukai, N. 動き始めたゲノム編集の医療応用. 実験医学 42, 6 (2024).

54. Makita, Y., Asahina, M., Fujinawa, R., Yukitake, H. & Suzuki, T. Intranasal oxytocin suppresses seizure-like behaviors in a mouse model of NGLY1 deficiency. Commun Biol 7, 460 (2024). https://doi.org/10.1038/s42003-024-06131-7

55. Munezane, H. et al. Elimination of the extra chromosome of Dup15q syndrome iPSCs for cellular and molecular investigation. Eur J Cell Biol 103, 151446 (2024). https://doi.org/10.1016/j.ejcb.2024.151446

56. Nakanishi-Koakutsu, M. et al. CD151 expression marks atrial- and ventricular- differentiation from human induced pluripotent stem cells. Commun Biol 7, 231 (2024). https://doi.org/10.1038/s42003-024-05809-2

57. Yamasaki, M. et al. Xenogenic Engraftment of Human-Induced Pluripotent Stem Cell-Derived Pancreatic Islet Cells in an Immunosuppressive Diabetic Gottingen Mini-Pig Model. Cell Transplant 33, 9636897241288932 (2024). https://doi.org/10.1177/09636897241288932

58. Yano, H. et al. Human iPSC-derived CD4(+) Treg-like cells engineered with chimeric antigen receptors control GvHD in a xenograft model. Cell Stem Cell 31, 795-802 e796 (2024). https://doi.org/10.1016/j.stem.2024.05.004

59. Yukitake, H. 非臨床創薬研究におけるヒト由来サンプルの利活用. 日本薬理学雑誌 159, 290-294 (2024).

60. Asahina et al. AAV9-mediated NGLY1 gene replacement suppresses non-epileptic convulsions in Ngly1-/- rats. Biochem Biophys Res Commun. 790:152823. (2025). doi: 10.1016/j.bbrc.2025.152823. Online ahead of print.

61. Fujiwara, Y. et al. A polystyrene-film-based device for engineered cardiac tissues enables accurate analysis of drug responses on contractile properties. Lab Chip (2025). https://doi.org/10.1039/d4lc00691g

62. Hirayama H. et al. Structural characterization and insights into the formation of N-acetylglucosaminylasparagine and its derivatives in NGLY1-deficient models and patients. Glycobiology. (2025). doi: 10.1093/glycob/cwaf065. Online ahead of print.

63. Kawamura, S. et al. Modeling antithymocyte globulin-induced microvasculopathy using human iPSC-derived vascularized liver organoids. Cell Rep. Med. 102433 (2025). https://doi.org/10.1016/j.xcrm.2025.102433

64. Saiki, N. et al. Self-organization of sinusoidal vessels in pluripotent stem cell-derived human liver bud organoids. Nat. Biomed. Eng. (2025). https://doi.org/10.1038/s41551-025-01416-6.

65. Takaki, T. et al. Simultaneous optical recording of action potentials and calcium transients in cardiac single cells differentiated from type 1 CPVT-iPS cells. Front Physiol 16, 1579815 (2025). https://doi.org/10.3389/fphys.2025.1579815

66. Yang K. et al. The STING pathway drives noninflammatory neurodegeneration in NGLY1 deficiency. J Exp Med. 222(10), e20242296. (2025). doi: 10.1084/jem.20242296.

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