CiRA Foundation Activity Report

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CiRA Foundation

Message

For the 10th anniversary of the iPS Cell Stock Project for Regenerative Medicine, the CiRA Foundation published a peer-review paper summarizing the results of the project in the journal Med on November 16, 2022 (U.S. Eastern Standard Time). We expect that this paper will be of great help to companies using iPS cells in the field of regenerative medicine. We are grateful to the blood donors whose generous cooperation has helped us build the iPS cell stock. In addition, the Japanese Red Cross Society, the Public Cord Blood Bank, and the Japan Marrow Donor Program have assisted with the recruitment of HLA-homozygous donors. In addition, this project would not have been possible without the cooperation of many other people, including financial donors, research institutions and companies to whom we provided the iPS cell stock, and government officials. We would like to express our sincere gratitude to all of you who have cooperated with us and to the many people who send us encouragement daily.

Shinya YAMANAKA, Representative Director, CiRA Foundation

News

May 2022 C4U, CiRA, and the CiRA Foundation sign a joint research agreement

The C4U Corporation has developed CRISPR-Cas3 technology that is expected to improve the safety and ease of genome editing. A joint research agreement on genome editing using this technology has been concluded among the three organizations.

June 2022 The CiRA Foundation published a peer-review article on the production of HLA genome-edited iPS cells for medical use.

The CiRA Foundation's Research and Development Center published a peer-review on their work regarding the production of genome-edited iPS cells for medical use as well as for assessing their quality.

September 2022 Toshiba and the CiRA Foundation sign a joint research agreement

A joint research agreement was signed with the aim of using liposomes provided by Toshiba for gene delivery in the generation of iPS cells for medical use.

November 2022 A peer-review article by the CiRA Foundation and summarizing research findings on the iPS cell stock was published.

A peer-review article summarizing the methods for producing and evaluating the quality of iPS cells in the iPS cell stock, as well as data analysis methods and information on sources for the stock was published.

Symposium co-hosted with CiRA

We hosted a symposium with the Center for iPS Cell Research and Application (CiRA), Kyoto University, in November 2020, at which we introduced differences between CiRA and CiRA Foundation and the roles of each organization. Lectures and panel discussions were also given. A video of the event will be posted on YouTube soon.

Crowdfunding report on the "Deliver iPS Cells to Everyone" campaign.

From September 6, 2022, to November 20, 2022, the CiRA Foundation held the "Deliver iPS Cells to Everyone" campaign to recruit 1,000 monthly donors in Japan. During this period, we aimed to recruit 1,000 new donors. Ultimately, we received support from 1,048 donors, plus 93 donors who increased their monthly donations. These donations will be used by the CiRA Foundation for public interest purposes. During the period, we also held online events, such as interviews with donors, basic seminars on iPS cells, and a seminar on the "production of iPS cells for clinical use". Many of you helped us spread the information on social media and distributed posters and flyers. We would like to express our sincere gratitude for your strong support. We will continue our efforts to "deliver iPS cells to everyone".

Interview

Dr. Kohji NISHIDA, M.D, Ph.D., on his work to cure corneal epithelial stem cell exhaustion

Dr. Nishida has been conducting clinical research since 2019 to restore vision by transplanting corneal sheets made from iPS cells. In April 2022, it was announced that three of the four patients had regained their vision using his experimental therapy. The other patient developed cataracts, making the measurement of vision inconclusive. In some cases, corrected visual acuity recovered from 0.15 to 0.7.

We visited Dr. Nishida, who also serves on the CiRA Foundation's board of directors, and asked him about overcoming past challenges and his vision for the future.

Kohji NISHIDA, M.D, Ph.D.

Professor & Chairman, Department of Ophthalmology
Associate Dean, Graduate School of Medicine, Osaka University
Director, CiRA Foundation

What is the cornea?

It is the most forward part of the eye and serves as its lens. In healthy eyes, it is normally transparent but needs replacement if it grows cloudy.

What is corneal epithelial stem cell exhaustion?

This is a condition in which the cornea becomes cloudy due to the loss of corneal epithelial stem cells, which are mainly located at the border between the iris and sclera and is usually caused by damage to the cornea due to disease or injury.

What is the current status of corneal transplantation?

It is one of the oldest and most widely used treatment methods. However, there is a worldwide shortage of donors, and there are many postoperative issues such as rejection and infection. The success rate is 20~30%.

Q1 What challenges have you overcome in treating keratoconus?

NISHIDA: To overcome the lack of donors and the low success rate of corneal transplants, we had been developing treatments using the (epithelial) cells of the patient's own oral mucosa before we came across iPS cells.
In some cases, the patient's vision was restored, while in others, the patient's vision deteriorated again after surgery. I believe this is because cells of the oral mucosa could have served as a substitute for the cornea but were not completely transformed into corneal cells.

Q2 Then you moved on to research using iPS cells?

NISHIDA: Yes. First, it was a long road to get to this stage. I met Dr. Yamanaka for the first time in 2007.
I then used iPS cells to study the mechanism of how the cornea develops, and it took me about l0 years to write the paper. At the time, research on embryonic stem (ES) cells was ongoing, but there was no research on the use of ES cells to create corneal epithelium, so I had to start from scratch.

Q3 Why did you use our iPS cell stock for your clinical research?

NISHIDA: I think the main reason was that we had built a lot of trust for information sharing.

Q4 In April 2020, you reported that 3 out of 4 patients had their vision restored. What was your reaction?

NISHIDA: I think this is a very good result.
Of course, we had conducted many experiments and tests in the past, so we were confident that we would succeed, but I was very nervous as we watched the progress.

Q5 What do you think are the future prospects based on your work?

NISHIDA: Research on the corneal epithelium at the university has been completed. We will hand the baton to Raymei Inc. and hope to conduct clinical trials within a year or two. Our goal is to see standard clinical use by 2026 or so.
At the university, we will continue our research on corneal endothelial cells, which are located in the innermost part of the cornea.

Working at the CiRA Foundation

Unit 3, Manufacturing Control, Manufacturing Section

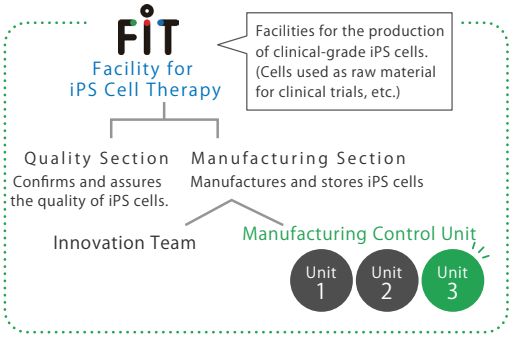
The Manufacturing Control Unit performs various tasks such as facility management and contract manufacturing for companies and research institutes. Within the unit is Unit 3, which manufactures the iPS cell stock, the raw material used to create transplantable cells for clinical trials, and its manager, Ms. Tomoko ICHISAKA.

Members of the Manufacturing Control Unit, Manufacturing Section (ICHISAKA is in the back row, far left).

Q1 The Manufacturing Section of the CiRA Foundation has 3 units. What are your main duties in Unit 3?

ICHISAKA：The CiRA Foundation has a clean facility called "FiT", which manufactures iPS cells and other cells for transplantation. Our main role is to produce and store cells in FiT. The iPS cell stock is designed to be immune compatible with more people in Japan. We have provided it to many research institutes and companies.

Members of the unit checking that the cell production happens in a germ-free environment.



Q2 What other tasks are performed within Unit 3?

ICHISAKA：We also make written records of the manufacturing process, purchase reagents and materials, inspect products, install and maintain the equipment used.

Unit 3 members conducting cell culture training

Q3 You worked at the Center for iPS Cell Research and Application (CiRA), Kyoto University, before joining the CiRA Foundation and have more than 10 years of experience in this work. Since when did you want to pursue this career?

ICHISAKA：When I was in junior high and high school, iPS cells did not exist, so I did not anticipate my current career path. However, when I was in high school, I became interested in biotechnology when I learned of plants grown by fusing two types of vegetable cells. I also have always loved living things, so that was another motivation for me to pursue a career in science.
During my university days, I was culturing passion fruit cells. After that, I worked at an animal experiment facility, where I became involved with iPS cells by a stroke of good luck.

Q4 When have you best used your past experience?

ICHISAKA：Many laboratory instruments are similar, and if you have worked with animal cells, there are many similarities in working with human cells.
I have had the pleasure of working with Dr. Yamanaka, the President of the CiRA Foundation, since my days as a technical officer at the Nara Institute of Science and Technology (NAIST), and I am happy to have been involved in the application of iPS cell technology, including the creation of mouse iPS cells, the creation of iPS cells from human skin and blood cells, and the creation of differentiated cells using these cells as raw materials.

Q5 Unit 3 has 18 members. What kind of person do you think is best suited for its work?

ICHISAKA：Currently, we have a variety of members, including those who originally had cell culture experience, those who had laboratory experiment experience, and those who had no experience and are learning from scratch. I believe that those who can notice the smallest details and reproduce results following procedures are best suited for this position.

Q6 It sounds like cooking, making the same tasty dish from the same recipe.

ICHISAKA：Indeed, there are quite a few people who like to cook and are certified dietitians, so it may have something in common. Also, teamwork is important, so being able to communicate well with everyone is a must.

Q7 I always see how busy your team is. What do you do on your days off to refresh yourself?

ICHISAKA：I am not sure if I can call it a hobby, but I like to drink. It is quite fun to go to a convenience store and find different kinds of beer.

Q8 Please tell us about what is rewarding and motivating for you and your team at work.

ICHISAKA：What is most rewarding and motivating for all of us is the fact that the iPS cells we produce are used to create the differentiated cells needed for clinical research and trials, and that these cells are successfully transplanted, ultimately benefiting patients.
I sincerely hope that iPS cell technology will be put to practical use in the future and that as many patients as possible will receive the treatment they need.

Mr. Shinsuke YOSHIDA,
Senior Manager, Research and Development Center (center)

Shinsuke Yoshida begins life in Taiwan

In 2021, the CiRA Foundation signed a joint research agreement with National Yang Ming Chiao Tung University in Taiwan, and Shinsuke Yoshida, a researcher at the CiRA Foundation Research and Development Center, has been conducting research there since the summer of 2022. We asked him about the experience.

Q1 Please tell us what kind of research you are conducting in Taiwan.

YOSHIDA: The research is using technology cultivated in the semiconductor industry at National Yang Ming Chiao Tung University and the CiRA Foundation's experience in the establishment of clinical-grade iPS cells that can be used as raw materials for regenerative medicine. Specifically, we are developing an automated cell culture system that can easily produce iPS and other cells and a method to confirm cell quality only by high-resolution observation that does not destroy the cells.

Q2 What is the campus environment like?

YOSHIDA: The campus is located in Hsinchu City (also known as Taiwan's Silicon Valley) in the northwestern part of Taiwan, where TSMC, the world's largest semiconductor contract manufacturer, has its headquarters.
I am currently conducting research at the Guangfu and Boai campuses. The members of the research team include students from Malaysia, making it a very international environment.

Q3 What do you enjoy there?

YOSHIDA: I like to stroll around the lush green campus. Between the two campuses I mentioned, there is also National Tsing Hua University. A student-friendly environment, including a library, student cafeteria, and athletic facilities, is available. Also, encouraging messages are posted in various places on campus, and it is fun to suddenly find these. Reading those messages reminds me of the importance of remembering our original intentions.

The historical phrase 飲水思源 is carved on a stone statue on campus. The message is that when drinking water, we should not forget the source of the water or the hard work of the person who dug the well. In other words, the basis of the things and favors we have are from others.

Q4 What are your current challenges and future plans?

YOSHIDA: I am gradually getting used to discussions and talks in English, but my current problem is that I am not yet proficient in the local language (Taiwanese).
We still have a long way to go to achieve our goals, but we are working on them every day with the mindset of “three steps forward, two steps back / the journey of a thousand miles begins with a single step”.
In the future, I hope to contribute to the establishment of manufacturing facilities for iPS cell-related products for medical use and to help provide treatment to patients around the world through the practical application and industrialization of regenerative medicine in Taiwan.

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