

# CiRA Foundation Activity Report



## Message

### Cooperating with various organizations for the practical application of iPS cells

On April 1, 2020, we began the CiRA Foundation and are now into our third year. Over this time there has been a consistent increase in research institutions and companies using iPS cells manufactured by the CiRA Foundation. They also use our outsourced services for quality evaluation. And this year we made the first shipment of our iPS cell stock to an overseas university.

To realize the practical application of regenerative medicine using iPS cells, universities need to cooperate with industry. It is also vital for more companies to contribute to the research and development of regenerative medicine. To encourage more companies to join this effort, the CiRA Foundation has launched the “P.S. i LOVE YOU” PROJECT with 19 participating companies and is actively communicating about its work.

The research and development of regenerative medicine using new iPS cell-based medical technologies are very costly both in terms of money and time. For most companies, entering this field entails a significant risk. To lower the entry barriers for companies, the CiRA Foundation provides iPS cells and relevant technologies at affordable prices. On behalf of all of us at the CiRA Foundation, I want to thank our donors and the many people who support our activities.

In Japan, clinical research using iPS cells continues to progress. Notably, regarding clinical research results for transplantation medicine, the research group led by Professor Kohji Nishida at the Graduate School of Medicine, Osaka University has reported that the transplantation of iPS-cell derived corneal epithelium works well for visual recovery. However, the speed of iPS cell research differs for each disease and each disorder. The CiRA Foundation is devoted to supporting research and development as much as possible toward the practical application of iPS cell-based medicine.



Shinya YAMANAKA  
Representative Director  
CiRA Foundation

# Realizing the development of iPS cell-based therapies for cerebral infarction

The CiRA Foundation is participating in a joint research project that is developing therapies for cerebral infarction. This project is in partnership with the research group led by Professor Jun Takahashi. This April, Professor Takahashi became Director of the Center for iPS Cell Research and Application (CiRA), Kyoto University.

The Takahashi laboratory is researching intractable neurological diseases using iPS cells. In 2018, they began a physician-initiated trial for Parkinson's disease with physicians at Kyoto University Hospital. Seven patients have received the cell transplantation as scheduled, and their health conditions are under observation. We manufactured the dopaminergic progenitors used in this trial at our cell preparation facility (Facility for iPS Cell Therapy, or FiT). Following this work, Professor Takahashi and his team are using iPS cells to develop transplantation therapies for cerebral infarction. We are responsible for manufacturing the cells derived from the iPS cells for the transplantation, the quality evaluation of the cells, the offering and management of clean cell production facilities, and the consultation for the clinical application, among other aspects associated with the project.

To realize cell transplantation to patients, the manufacturing of cells is a critical first step. We manufacture cells at FiT, which offers a clean environment that fulfils conditions above those found in experimental laboratories. Materials and machines commonly used in experiment laboratories are rarely applicable for the manufacturing of cells to be used in transplantation therapies.

Compared with iPS cells for research use, the manufacturing of iPS cells for clinical use is challenging. We have accumulated expertise and equipment for this purpose. We are committed to working with the Takahashi laboratory and others like it to provide iPS cell technologies to patients in need as quickly as possible.



**Jun TAKAHASHI**

Director and Professor,  
Center for iPS Cell Research and  
Application (CiRA), Kyoto University  
(Director, CiRA Foundation)

We have manufactured cells for a clinical trial with the CiRA Foundation. We have great confidence in the CiRA Foundation and are happy to work with them again and again. Its contributions have been critical for us overcoming the many challenges of developing new therapies. The technology and expertise we obtained by working with the CiRA Foundation on the cell production for our Parkinson's disease clinical trial are a great asset to us. For cerebral infarction, the types of cells and clinical conditions differ. We will therefore face new challenges, but I am certain we can overcome them by working together.



**Daisuke DOI**

Junior Associate Professor,  
Center for iPS Cell Research and  
Application (CiRA), Kyoto University

We developed new cell-based preparations for cell transplantation therapies for Parkinson's disease and now for cerebrovascular disorders such as cerebral infarction (or stroke). Our experience with Parkinson's disease has been a great advantage for our work on cerebral infarction, but there are also many different challenges. Cooperating with the CiRA Foundation gives us confidence that we will develop new therapies for patients in need.

## Tomoko ICHISAKA

Manager,  
Manufacturing Control Unit, Manufacturing Section  
CiRA Foundation

In general, for any clinical trial, many people are involved in the project, including hospital staff and the patient. All these stakeholders must work together. The Manufacturing Section is crucial for devising the best strategy for the cell production. We are motivated by hearing of successful cell transplantations and improved patient health.

## Activities of the CiRA Foundation

### ■ Clinical Applications

September 2021

#### Transplantation of natural killer cells for ovarian cancer treatment

Natural killer cells produced from our iPS cell stock were administered to patients suffering from ovarian clear cell adenocarcinoma as part of the clinical trial conducted by the research group led by Professor Shin Kaneko at the Center for iPS Cell Research and Application (CiRA), Kyoto University, in collaboration with the National Cancer Center Hospital East.

December 2021

#### Transplantation of neural precursor cells for spinal cord injury

Neural precursor cells produced from our iPS cell stock have been administered to patients suffering from spinal cord injury as part of the clinical research conducted at Keio University Hospital. In March 2022, the safety of the cells was confirmed.

April 2022

#### Transplantation of corneal epithelial cell sheets for visual recovery

Corneal epithelial cell sheets produced from our iPS cell stock were transplanted to patients suffering from exhausted corneal epithelial stem cells, a condition that leads to poor vision. Osaka University reported that the visual acuity of three patients improved significantly in one year. (A fourth patient had developed cataracts, making evaluation difficult.) For one patient, visual acuity improved from 0.15 to 0.7.

April 2022

#### Transplantation of iPS cell-derived platelets for thrombocytopenia

The Megakaryon Corporation has manufactured platelets from our iPS cell stock. These platelets were transplanted into patients with thrombocytopenia. Evaluation of the efficacy and safety is ongoing. Megakaryon is now in discussion with the proper authorities to license the cells as a commercial product.

### ■ Activities

#### Introducing the CiRA Foundation online

The Center for iPS Cell Research and Application (CiRA), Kyoto University, from which the CiRA Foundation spawned, regularly holds tours of its facilities. A recent online tour included our Facility for iPS Cell Therapy (FiT).

※Please use the QR code to see the video.

※Language : Japanese only

July 2021



#### Basic agreement with VCCT, Inc.

We signed a basic agreement with VCCT, Inc., for the development of medical therapies for retinal diseases. The agreement includes research information sharing and the provision of material in order to advance the my iPS Project.

October 2021



#### Joint research agreement with CellFiber, Co., Ltd.

To accelerate our adoption of automated cell culture systems for cell banking, we are using the company's unique technology called CellFiber, which enables the mass cultivation of cells at less cost. As of June 2022, part of the verification process was completed.

November 2021



#### Regenerative Medicine Open Innovation Seminar

We held a seminar in association with the Kansai Bureau of Economy, Trade and Industry (METI), Kyoto City and the Advanced Science, Technology & Management Research Institute (ASTEM). The seminar targeted companies interested in joint research with us. More than 70 people attended.

December 2021



#### Joint research agreement with National Yang Ming Chiao Tung University (Taiwan)

We signed a joint research agreement with the university to develop new technology for iPS cell production using the expertise and technology of the two institutions. The agreement includes sending one of our staff to the university for a specified period.

January 2022



#### First shipment of our iPS cell stock for clinical use to an overseas partner

We provided our iPS cell stock for clinical use to iPS Bio, Inc., a start-up stem cell company in Korea. This was the first shipment of our iPS cell stock for clinical use to an overseas company. We aim to send our cells to more companies around the world.

March 2022



#### Yuko KITANO wins the Hanamizuki Prize for her work on the my iPS Project

This prize is awarded annually to recognize the exceptional work of one of our staff. This year, Yuko Kitano won the Hanamizuki Prize for her work to expand iPS cells and differentiate them to myocardial lineages in floating culture.

April 2022



A day in the life of members of the CiRA Foundation

## The Quality Test Team of the Quality Section

The Quality Section evaluates and assures the quality of iPS cells manufactured by the CiRA Foundation and the quality of cells for transplantation produced using iPS cells.

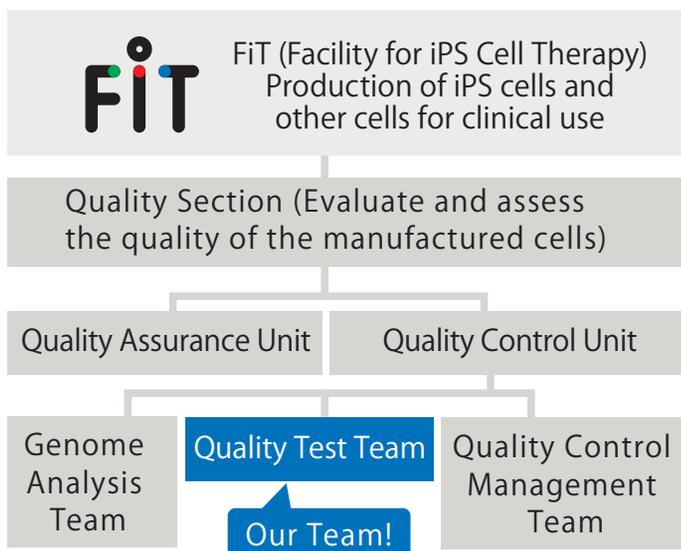
They evaluate various items regarding cells, including the genomics, characteristics, and contamination (sterility). We also confirm the condition of the reagents and the materials used for iPS cell production.

In this article, we describe the daily work of three members from the Quality Test Team. Their work is critical, as they check on bacterial infection in the cells or in the production area (the number of bacteria must be controlled within defined limits).

iPS cells and other cells produced by the CiRA Foundation are all living cells. Therefore, we cannot apply sterilization treatments or processes typically used for drugs and medicines, which makes bacteria a critical issue. It is very important to prevent bacteria contamination at all stages of the cell production and all the way to the shipment of the cell product. For every process, such as replacement of the iPS cell culture solution and transfer of iPS cells from one culture dish to another culture dish, we extract part of the culture solution and test it for bacteria contamination.

In the cell production area, a permissible number of bacteria per specified area is defined for each process. Appropriate control is necessary to prevent bacterial contamination. To confirm the number of bacteria, we collect bacteria floating in the air or adhering to surfaces, like desks and machines. We cultivate them for several days and then check their number and type. Based on criteria, we can then conclude if bacteria in the cell production area have been controlled appropriately. While many of our colleagues focus on iPS cells, our attention is on microorganisms.

Most types of cells for transplantation are unusable once they are frozen. Therefore, the cells must be delivered shortly after their production, which means we have to test them by using special method late into the night and finish our reports by the next morning. Although the work can feel tedious at times and is sometimes difficult, it is essential for us to assure the quality of the cells we deliver. The work also gives us great satisfaction, because these cells are being used in clinical testing and clinical trials. We are all committed to assuring the quality of the cells.



Saki TOMITA



Kyoka HIGUCHI

The appearance of bacteria!

Mie YAMAMOTO

