

The CiRA Foundation is now in its fourth year. Through our main project, the iPS Cell Stock Project, we have distributed iPS cells to more than 70 research institutes and companies, and more than 10 of these projects have used our iPS cells in clinical trials, with some having confirmed already the safety and efficacy of the treatment.

Since September 2023, the CiRA Foundation has been participating as a subcontractor for a new program related to regenerative medicine operated by the Center for iPS Cell Research and Application, Kyoto University. This program will receive government support for five years.

Also in 2023, in addition to our usual donations, the campaign, "Deliver iPS Cells to Everyone", received generous support for our work. I sincerely thank all of our donors.

In order to meet your expectations, the entire staff will continue our efforts toward the practical use of iPS cells.



Shinya Yamanaka
President

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

From September 6, 2023, to November 20, 2023, the CiRA Foundation held the "Deliver iPS Cells to Everyone" campaign to recruit 1,000 monthly donors in Japan. Ultimately, we received support from 2,748 donors, plus 115 donors who increased their monthly donations.

During this period, we also held online events to inform everyone about our activities: the three lectures in total provided basic knowledge on iPS cells, research ethics, and quality control methods for iPS cells.

In addition, we received many messages of hope for the clinical application of iPS cell technology, such as "I hope for the development of research" and "I want to support a future in which many incurable diseases will be cured".

We would like to express our sincere gratitude for your strong support. With our supporters' thoughts and expectations in mind, we will continue our efforts to "deliver iPS cells to everyone". (Philanthropy Office)



Thank you so much
for your support

What is the HLA genome-edited iPS cell stock?

The CiRA Foundation began providing clinical grade cells - "HLA genome-edited iPS cell stock" in June 2023. This stock has a lower risk of an immune reaction when used in a cell therapy. Below is some information about their special properties.



| Pre-manufactured and stockpiled iPS cell stock |

The "HLA-homozygous iPS cell stock" provided by the CiRA Foundation was created with the cooperation of the Japanese Red Cross Society, the Japan Marrow Donor Program, and the Cord Blood Bank, with the help of blood donors who are homozygous at three HLA loci (an immune type of combination that is less likely to cause immune reactions.)

When used in regenerative medicine, iPS cells are differentiated before transplanted into patients. However, it takes nearly a year and costs tens of millions of yen to produce one iPS cell stock. Shortening that time and cost is why multiple iPS cell stocks have been prepared by the CiRA Foundation.

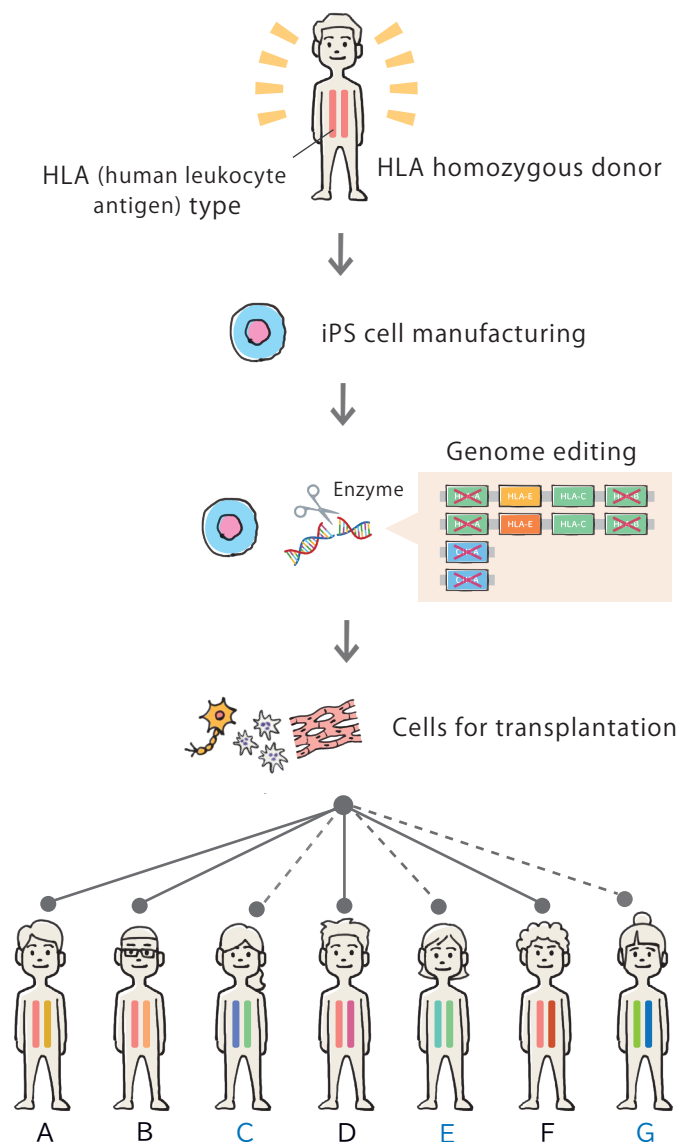
| More patients eligible for treatment |

At the CiRA Foundation, we envision a future in which iPS cell stocks are used as raw material for cell therapies, not only for patients in Japan but throughout the world. To match the immune types of more patients, we have turned our attention to genome editing technology, which was awarded the Nobel Prize in Chemistry in 2020. Genome editing technology uses an enzyme that acts as molecular scissors to cut DNA and rewrite genetic information. It is a popular technique in many laboratories around the world and is used not only in medical research but also in many other fields, including agriculture and fisheries.

Using this technology, we generated the "HLA genome-edited iPS cell stock" from HLA homozygous iPS cell stocks.

Although this HLA genome-edited iPS cell stock has great potential, it has not yet been used in any clinical trial. We are planning to conduct more research on the safety and efficacy of these cells through joint research with universities and companies to which we provide iPS cells.

We will continue our research and development to provide better iPS cells by integrating new technologies.



Even if the HLA type is not the same as that of the donor, as in the case of patients C, E, and G, the risk of an immune reaction will be smaller if using genome editing technology.

Working at the CiRA Foundation Secretariat of the iPS Cell Stock Review Committee



What exactly do you do before distributing iPS cells?

There are many things to do and many people involved in the iPS cell stock distribution process, such as checking details of the organization that wishes to obtain iPS cell stock and contracting with partnering institutions. We interviewed the staff in charge of the work.

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iPS cell stock is manufactured and stockpiled by the CiRA Foundation. Why does it take several months from request to distribution?

We are committed to expeditious procedures to promote research. On the other hand, the iPS cell stock is made from the blood of healthy donors and contains a lot of personal genetic information about the donors, so it must be handled with care.

We take the utmost measures to ensure that the privacy of donors is not compromised after the distributed iPS cell stock leaves the CiRA Foundation.

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2

How exactly do you protect privacy?

The first distribution of an iPS cell stock was made in the summer of 2015, before the CiRA Foundation was established. At that time, the basic policy and review criteria for the distribution were established, and an iPS Cell Stock Review Committee was set up.

The committee checks the following and other points of the institutions requesting the cells. 1) Are they likely to contribute to the development of regenerative medicine for the benefit of patients suffering from illness or injury? 2) Are they conducting research and development that has the potential to lead to new therapies? 3) Can the cells be used appropriately by them? Only if satisfying these and other questions do we provide the iPS cell stock.

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3

What is the role of the secretariat of the iPS Cell Stock Review Committee?

The secretariat confirms information on institutions that wish to obtain the iPS cell stock and coordinates between the iPS Cell Stock Review Committee, which decides whether or not to provide the cells, and the institutions that wish to obtain the iPS cell stock, including arrangements for the cell transportation.

In order to ensure that the process goes smoothly and trouble-free, a contract is concluded in advance with the organization to which the cells will be provided. This process involves building a relationship of trust between the organizations and involves thorough discussions and document exchange to reach a mutual agreement. It is not unusual for the process to take several months or more.

Teamwork across departments!



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4

Are there any precautions that should be taken when sending cells to research institutions or companies?

The provided iPS cell stock will be transplanted into patients after cell differentiation. The iPS cell stock must be stored with a certain level of quality in anticipation of the eventual administration of the cells to humans in clinical trials.

During the period between the production of the iPS cells and their distribution, the cells are stored in liquid nitrogen tanks at temperatures between -150 and -190 °C to preserve the quality. Otherwise, they cannot be used for the transplantation or research. This temperature must be maintained during the transport from departure to arrival, too.

For the shipment of cells, we coordinate the shipping schedule, arrange the containers, and make arrangements with the carrier.

In addition, when exporting cells or providing technology overseas, we carry out security trade control procedures within the CiRA Foundation in accordance with the relevant laws and regulations.

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5

Please tell us about the challenges and rewards of your daily work.

Even after working hard and meticulously preparing the cell shipments, unexpected events occur.

In the past, there was a case in which the iPS cells were not delivered properly due to a problem with the local customs. It was very frustrating that iPS cells produced from donor blood could not be delivered.

Based on this experience, even after the cells leave Japan and are entrusted to a carrier, we, the secretariat, check the status of the cells until they actually arrive at the recipient institution. We do not rest until we receive word from the recipient institution that the cells have arrived safely and are being cultured without problems.

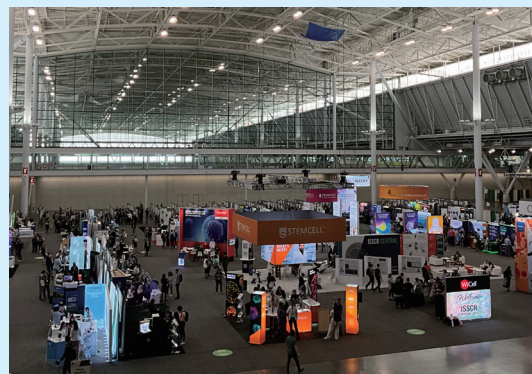
When we receive a report of the safe arrival and progressing research, we are happy to know that our activities made an impact.

June 2023

CiRA Foundation booth at ISSCR

The International Society for Stem Cell Research (ISSCR), the largest annual gathering of stem cell researchers in the world, was held June 14-17 in Boston, USA.

We exhibited a booth to inform about our activities, and our researchers presented their research results.



October 2023

Canon EXPO 2023

An exhibition introducing new products and future technologies of the Canon Group was held in Yokohama from October 18 to 20. A model of their automated autologous iPS cell production system, which is being developed in collaboration with the CiRA Foundation, was displayed.

Our staff members attended the exhibition and discussed future developments. It was a valuable opportunity for the CiRA Foundation, as many people deepened their understanding about us through the exhibition.



December 2023

Regenerative Medicine Open Innovation Seminar 2023

We held a seminar in association with the Kansai Bureau of Economy, City of Kyoto, Trade and Industry (Kansai Regenerative Medicine Industrial Consortium: KRIC), Advanced Science, Technology & Management Research Institute of Kyoto (ASTEM), and the Kyoto Municipal Institute of Industrial Technology and Culture.

The seminar targeted companies interested in joint research with us. Approximately 50 people attended.

