



<Photo Left to Right> Masayoshi TSUKAHARA (Executive Director), Shinya YAMANAKA (President), Naoko TAKASU (Senior Executive Director), Tadaaki HANATANI (Executive Director)

On June 14, we began providing the HLA genome-edited iPS cell stock for clinical use. This stock was developed after more than two years of research together with collaborating institutions. We have provided many cell lines from the iPS cell stock to institutions and companies for research purposes and plan to continue doing so. This year, Naoko Takasu was appointed as Senior Executive Director, and Masayoshi Tsukahara and Tadaaki Hanatani were appointed as Executive Directors of the CiRA Foundation. (See photo)

## February 2023 The distribution of iPS cells for research using cells from healthy donors

We have started to provide iPS cells for research using blood cells from healthy donors. The provision system has been improved by simplifying the contracting procedure, such that iPS cells can be provided in as little as one week after the application for the provision is accepted.

## March 2023 Charity marathon with Foundation donors

A charity marathon for donors to the CiRA Foundation was held along the Yodogawa River (Osaka City). A total of 362 participants joined the five runs: half marathon, 10 km, 5 km, 2 km, and half relay marathon. The event garnered 144,800 yen in donations to the organizer of the event, excluding operating and other expenses.



## Collaborative Research Contract with Knowledge Palette, Inc

Using the technology of Knowledge Palette, a biotechnology company in Japan, we clarify the characteristics of iPS cells and iPS cell-derived cells. We aim to promote the further industrialization of iPS cells by realizing simpler and more stable production as well as quality control.



## April 2023 Provision of a new clinical grade iPS cell line made using Sendai virus

Sendai virus (SeV)-iPS cells are conformable to the donor eligibility regulations of Japan, the U.S., and Europe. Adding these cells to the iPS cell stock expands the number of iPS cell lines for clinical use.

## Signed Letter of Intent with Transformative Cell Processing Company (TCPC)

Leveraging the strength of both Taiwan's semiconductor technology and the CiRA Foundation's medical research, a new partnership seeks to present solutions that bring iPS cell therapy from basic research to industrial applications.



## The first Hanamizuki Award Ceremony held

The CiRA Foundation holds an annual fiscal year meeting in April. The last three meetings have been held online, but this year the meeting was held in person. At the Hanamizuki Award Ceremony, which recognizes employees for their work on management and operations at the Foundation, the following two individuals and teams were awarded prizes for their outstanding work.



<Left>Masaki NOMURA  
(Team Leader, Genome Analysis Team)  
Contributing to the improvement of the number of genome analysis contracts.

<Right>Megumi YAMAUCHI  
(Group Leader, Financial Affairs Group)  
Contributed to the establishment of a financial infrastructure system.

<Left>Tomoko ICHISAKA  
<Center right>Shun MINOBE  
<Right> Yasuka OGURA  
(Members of HLA genome-editing and manufacturing)  
They were the core of the CiRA Foundation's manufacturing efforts and were instrumental in obtaining the first HLA genome-edited iPS cell lines for clinical use.

## June 2023 Provision of HLA genome-edited iPS cell stock for clinical use

To minimize the risk of immune reactions, we have started providing iPS cells modified with genome editing technology for clinical use. We expect that these cells will be used as raw materials for therapeutic cells globally.

## Dr. Shin KANEKO, M.D, Ph.D., on his work to cure cancer patients.



Shin KANEKO, M.D, Ph.D.

Deputy Director / Professor / Principal Investigator, Dept. of Cell Growth and Differentiation Center for iPS Cell Research and Application (CiRA), Kyoto University

Dr. Kaneko is developing clinical immune cells made from iPS cells for use in cancer treatments. Since September 2021, a clinical trial using immune cells made from the iPS cell stock for ovarian cancer have started. The patients were ineligible for surgery and did not respond well to anti-cancer drugs and other treatments. We asked Dr. Kaneko about his impression of working with the CiRA Foundation and his vision for the future.

### What is cancer?

Cancer is a disease in which cells in body begin to grow and spread uncontrollably due to genetic damage. In Japan, one out of every two people will develop cancer in their lifetime. Medical science is increasing the survival rate every year. In addition to anticancer drugs, surgery, and radiation therapy, immunotherapy is now regarded as one of the main treatment methods.

### What are immune cells?

Also known as white blood cells, these cells protect the body from viruses and cancer cells. Dr. Kaneko is researching and developing a therapy in which two types of immune cells, T cells and NK cells, are produced from iPS cells and used in cancer therapies.

#### Q1 Please describe your work.

Originally, as a hematologist, I was involved in research on gene therapies. Even if a bone marrow transplant is performed on a leukemia patient, the leukemia may recur. In response to this, I was researching a method to treat patients by administering immune cells from a healthy donor. However, there were many challenges, such as the need to collect immune cells from the donor each time. In 2007, I was shocked and stimulated by the news that iPS cells could be established from human cells, and I decided to devote myself to research on the integration of iPS cell technology and immunotherapy.

#### Q2 Will the treatment methods you are developing solve the problem of side effects on healthy cells seen with current anti-cancer drugs and radiation therapy?

I believe that anticancer drugs and radiation therapy will continue to be used, and we are not developing anything to replace them. We are working to increase the number of treatment options as much as possible. Normally, cancer cells divide faster than normal cells. Controlling cancer in accordance with the timing of cell division is an excellent treatment method using anticancer drugs and radiation therapy. If immunotherapy, which we are developing, can be added to these therapies to further target and attack cancer cells, it may be possible to proceed with treatment without causing too much damage to normal cells. However, unlike drugs or radiation, it is difficult to control how the cells in immunotherapy work because the cells to be administered are living organisms. It depends on the patient's physical condition and disease state, and also on the administered cells themselves. I think the key point is how to reduce such variations and control the effects so that they can be predicted in advance.

#### Q3 In the clinical trials for ovarian cancer, you have worked closely with the CiRA Foundation to prepare iPS cell lines in the CiRA Foundation's iPS cell stock that were genome-edited and then differentiated into immune cells. Can you comment on the progress of this work?

The CiRA Foundation has both a manufacturing system and a quality control system in place that, I believe, enabled us to proceed quickly. In addition, the CiRA Foundation is neither a university nor a corporation, but a public interest incorporated foundation, so from the standpoint of someone like me who belongs to both a university and a corporation, I felt the Foundation was neutral and reliable. The clinical trial is still in the process of confirming safety and efficacy, but I am happy that we have been able to advance this far. I will do my utmost to bring this treatment method to patients as soon as possible.

#### Q4 In the above clinical trial, why were patients with ovarian cancer that had metastasized to the abdomen given NK cells?

NK cells induced from iPS cells attack cancer cells more potently. On the other hand, their ability to reach cancer cells by vascular administration is not high. Therefore, we thought it would be more effective to administer directly to the area where the cancer cells are gathered. Since the abdomen is covered by a membrane, we thought that the administered NK cells could stay and function near cancer cells.

#### Q5 What do you hope to focus on in the future?

I would like to further enhance NK cells generated from iPS cells, confirm their safety and efficacy, and promote research and development so that T cells generated from iPS cells can also be used as a treatment option as soon as possible. Currently, we are focusing on the application of cancer therapy, but we would like to produce more immune cells and expand the range of therapeutic targets, such as autoimmune diseases.



I have been in charge of the manufacturing management for this project since its inception (before the establishment of the CiRA Foundation). In order to manufacture a product used for treatment, it is essential to ensure not only its performance but safety. To achieve this, it is necessary to comply with a vast number of management standards that were not necessary during the university research phase. Over the years since its launch, we have supported the project through hardships and difficulties to meet these requirements. Manufacturing cannot be done by one person. It is my job to coordinate the various people involved and to manage the manufacturing objectively, including troubleshooting, in order to create an environment where workers can manufacture with peace of mind. I would like to continue to work together and contribute to the project.

Aki SASAKI, Unit 2 Manager, Manufacturing Control Unit, Manufacturing Section

## Working at the CiRA Foundation Tsuguharu OHMURA, Attorney at Law, Contract Management Office

Taking challenges  
from Japan to the world!

The CiRA Foundation is engaged in the manufacturing, quality evaluation, and storage of iPS cells, as well as joint research with research institutions and companies. In relation to this, the Contract Management Office performs many tasks, such as concluding contracts, complying with the laws and regulations of the relevant countries, and considering regulatory compliance in various situations, including when providing and receiving cell data and when shipping cells overseas. In this interview, we spoke with Mr. Ohmura of the Contract Management Office, the department in charge of legal affairs.



Q What inspired you to become a lawyer?

1 It was the influence of a senior member of my high school kendo club. He was four years older than me and a freshman at one of the esteemed schools of law in Japan. He was serious and full of enthusiasm, a live-action version of the "good and cool senior" in manga. He enthusiastically told me about his university life, taking lectures, and how interesting legal theory was, and since I was (probably still am) a simple person, I was strongly inspired by his enthusiasm.

Q What was your career path?

2 After graduating from high school, I went on to a school of law as an undergrad, enrolled in law school, and obtained my Juris Doctor degree in Japan. I was fortunate enough to pass the bar exam the year I graduated. After becoming a lawyer and practicing, I have a total of more than 10 years of experience in law firms and as a senior counsel in corporations.

Q You have experience studying abroad, right?

3 I studied at Columbia Law School in New York, USA, from 2017 to 2018. I was a Fulbright scholar, a program operated jointly by the U.S. government and the governments of other countries. Many Nobel Prize laureate professors in Japan were recipients of this program. I still remember April 16, 2017, when I was informed that I had been moved up from the alternate list. I was listening to my father's old radio in the living room of my parents' house, and I remember being so honored that I flipped the radio over with a flourish as I stood up to receive the incoming call. The scholarship not only covered my tuition and living expenses, but also provided frequent opportunities for networking with researchers, engineers, politicians, dancers, and practitioners from around the world. The establishment of these connections and networks will last a lifetime.

In law school, I researched and studied the U.S. legal system known as Class Action. Since I had never studied in foreign countries, I had to devote all my energy. I was stuck in the law school library all year round, but that time became the foundation of what I am doing now.



Mr. Joseph M. Young, the US Chargé d'Affaires ad interim in Japan with Mr. Ohmura at the U.S. Embassy in Tokyo. (Photo courtesy of the U.S. Embassy to Japan)

Q What kind of work does the Contract Management Office of the CiRA Foundation do?

4 We are handling a wide range of contracts and various laws and regulations. For example, our work includes collaborative research agreements to provide the iPS cell stock to companies and research institutions and negotiating and coordinating the terms of agreements to have the cells used overseas, not only in Japan. Since the rules and regulations differ from country to country, we need to confirm and adjust them.

Q Even if we say we are "providing iPS cells to foreign countries," we still have to consider various measures and adjustments to follow laws and regulations, no?

5 Each team member has different tasks, but we all have an important role. First, iPS cells are manufactured from the blood of donors, so it is very important to consider how to protect the personal information of the donors. Second, because iPS cells are cultured and differentiated into a target cell, it is important to negotiate the terms of the contracts and property rights such as ownership of the iPS cells. In addition to that, the establishment and differentiation of the iPS cells use advanced scientific technology that might be covered by intellectual property rights. The laws and regulations regarding the handling of somatic cells differ between Japan and other countries. To fill this gap in terms of law, it is necessary to adjust agreements to follow the jurisdiction of our collaborators as well.

Q Isn't it hard to deal with such a wide range of content?

6 The encounter with difficult legal issues is a challenge, but it is also the beginning of something truly fun and interesting. Law itself has existed since pre-Roman times, so there is a vast body of academic papers written by brilliant professors of law and lawyers from all over the world at various times. However, what about iPS cells, which are self-renewing, can change their properties, and are subject to property rights, but also contain personal information of the donor and are established with advanced technology protected by intellectual property rights? Reprogramming a cell and then differentiating it into another cell, such as a nerve cell or a cardiac muscle cell or altering its genes... such things would never have occurred to Roman-era lawmakers. There are of course many papers written from the viewpoint of medicine and physiology. However, there are few articles written by professors of law and lawyers on stem cell-related research, including iPS cells, that encompass private law such as ownership and credit relations, data privacy law, ethics, intellectual property, regulatory compliance such as cell production, quality assurance, and storage, and taxation.

Q There are no precedent cases and no sufficient documentation to address the complexed legal issues, are there?

7 Because of the current situation, instead of asking "How can we bring foreign rules to Japan?", we can think of rules for technologies born in Japan and disseminate them out to the world. I am even more enthusiastic when I think that this will ultimately benefit patients.

Q How are the team members and the environment?

8 I think it is an open and challenging environment. I also think that this is largely reflected in the personality of the office manager, Ms. Hisae Takenakajima, who is always willing to incorporate new things. Recently, we started to distribute internal-only videos to help CiRA Foundation staff understand the details of contracts. Personally, I would be really happy if I could also provide consultation to anyone who is considering a career path as a lawyer like me in the future, tell them how interesting and rewarding this job is, and engage in other such activities.



\*The Contract Management Office was selected as a finalist for the ALB Law Award Japan 2023 in two categories: Healthcare and Pharmaceutical and In-House Team of the Year.

Mr. Tsuguharu Ohmura and Ms. Yoko Taniguchi at the ALB Law Award Japan 2023, Award Ceremony.

Thank you very much for supporting the CiRA Foundation. We are financially supported by public funds, business profits, and donations. In fiscal year 2022, donations and supporting membership fees from individuals and corporations totaled approximately 1.9 billion yen.

We would like to take this opportunity to thank you for your warm support.

	Number of donations	Amount of donations
Membership	69	¥ 28,140,000
Donations	248,271	¥ 1,874,940,911
Total	248,340	¥ 1,903,080,911

We use the following and other costly equipment for the quality evaluation and testing of manufactured iPS cells. Since regular maintenance is necessary for long-term use of these equipment, donations have been used for equipment upgrades.

### 1. Single cell library preparation system

This system enables the comprehensive analysis of gene expressions in individual cells. We use it to evaluate the quality of iPS cells and their differentiated cells.



### 2. Sonicator

We analyze the entire human genome, which consists of approximately 6 billion base pairs, to confirm that there are no abnormalities in the genome of clinical iPS cells.

This equipment enables an accurate and stable analysis.



### 3. DNA amplification system

This system efficiently amplifies minute amounts of DNA in a short time. It is widely used in cell quality testing and molecular biological research using next-generation sequencers, such as gene mutation analysis and gene expression analysis. We use it to analyze DNA and RNA contained in iPS cells and their differentiated cells.



Your donations are also used for our implementation of business for public interest purposes. All of us at the CiRA Foundation would like to express our sincere gratitude to you.

