THE discovery of induced pluripotent stem cells (iPSCs) is anticipated to change medical research and treatment. Japan has invested heavily in this technology, beginning with the creation of CiRA, an institute devoted to the research and application of iPSCs at Kyoto University. Sharing investment has been industry. The most recent example is the comprehensive partnership between CiRA and Takeda Pharmaceutical Co. Ltd. announced last April.

Over the past decade, stem cells have captured the imagination of the public as a potential miracle cure. Stories abound about stem cell discoveries that hinted at the possibility of new treatments for patients suffering from debilitating diseases and injuries. Yet, stem cells have been used as treatments for decades. What distinguishes the recent stem cell excitement from the past?

Stem cells come in many types, but the latest attention is specifically about pluripotent stem cells (PSCs). PSCs emerge at the very early moments of development and have the ability to self renew and differentiate into various cell types of the adult body, which means they have the potential to replace any cell that is diseased or destroyed. Unfortunately, unlike other stem cells, PSCs do not exist in the adult body.

PSCs can be created in the laboratory, however. The first of these were embryonic stem cells (ESCs). More than any stem cell discovered before them, ESCs have shown remarkable curative potential for various diseases and injuries. However, their use has been subject to stringent laws, as their acquisition requires the destruction of fertilized embryos, which has created controversy among the public and led to relatively severe limitations in their use for research. More recently, another PSC type, induced pluripotent stem cells (iPSCs), was reported. Unlike ESCs, iPSCs can be generated from adult cells and avoid the aforementioned ethical concerns. Equally important, they share the same fundamental properties as ESCs and are therefore expected to have the same curative potential.

Somewhat paradoxically, while they can be acquired from the body, iPSCs do not actually exist in the body. They are created by Professor Shinya Yamanaka and other researchers at Kyoto University. Prior to iPSCs, it was believed that a cell develops unidirectionally, from a primitive to mature state, with no possibility of reversal. Thus, once a fertile egg differentiates into a somatic cell – for example, a skin cell – it will forever be a skin cell until it dies. Yamanaka and his team, however, showed that a cell’s fate need not be final. They demonstrated that by inducing specific genes, they could reprogram a differentiated cell to the pluripotent state, i.e. an iPSC. Because iPSCs are pluripotent, they can be differentiated into different cell types of the body. In other words, one can reprogram skin cells into iPSCs, which can then be differentiated into any cell type of choice – neural cells, pancreatic cells, muscle cells, etc. Theoretically just about any cell type in the human body can be reprogrammed into any other cell type using Yamanaka’s discovery.

The impact of this realization cannot be exaggerated. Since the first reports by Yamanaka on iPSCs from mouse fibroblasts in 2006 and human fibroblasts in 2007, there has been an explosion in cell
reprogramming science. The potential of iPSCs as medical treatments has already been demonstrated in a long list of cells and tissues. Even though it has still not been 10 years since their birth, international conferences on iPSCs are abound, with the next one happening in Kyoto in March 2016.

In recognition of his discovery, Yamanaka was awarded the Nobel Prize in Physiology or Medicine in 2012, only six years after the first iPSC report. Moreover, the first clinical research involving iPSC-based cell therapy is already ongoing in Japan, as a patient suffering from age-related macular degeneration received a transplant of retinal cells derived from iPSCs generated from her own somatic cells. The advancement of cell reprogramming science has startled almost everyone in the field, including Yamanaka. “I am impressed with the rapid progress of iPSC research.”

CiRA
In response, Kyoto University founded the Center for iPS Cell Research and Application (CiRA) in 2010 and appointed Yamanaka its director. Now in its sixth year, the institute has already seen its staff more than double. The core of CiRA research is to develop iPSC technologies for medical therapies, especially for intractable diseases. Over this time, CiRA researchers have established methods to generate and evaluate clinical-grade iPSCs for quality and safety so that they can be used in humans. In the next few years, CiRA is anticipating clinical research using iPSC-based therapies to treat Parkinson’s disease and blood diseases, with treatments for other diseases expected thereafter. In addition, CiRA is building an iPSC stock for regenerative medicine, from which clinical-grade iPSCs will be made available to research institutes and companies around the world that are investigating new cell therapies.

Along with cell therapies, iPSCs have shown great value for drug discovery. Work by CiRA researchers has suggested that iPSCs can be used to separate subpopulations of diseased patients that respond positively to a drug from those that do not. More recently, a CiRA research team has shown the benefits of iPSCs for drug repositioning. The possibility of finding new drugs and reducing R&D costs has encouraged a number of pharmaceutical companies to explore iPSCs as a tool for drug discovery.

The Japanese government has responded unequivocally to the discovery of iPSCs, as it recognizes them a foundational technology on which to promote not only the nation’s science and technology, but also economic growth. Appropriately, it has supported CiRA with abundant research funding. CiRA also distinguishes itself from other research institutes in Japan by the generous number of private donors that contribute money to its research.

However, even these funds are not enough for CiRA’s ultimate goal of iPSC-based cell therapies when considering the cost of translating an academic discovery into a widely used treatment, a translation commonly known as the “Valley of Death” in commercialization. Consequently, CiRA has partnered with industry for the study of diseases and development of new therapies. Current examples include work with Sumitomo Dainippoin Pharma Co. Ltd. on treatments for fibrodysplasia ossificans progressiva, a rare but horrifying disease where tissue ossifies, and with Fujifilm Corp. for Alzheimer’s disease, a form of the most common dementia. The latest, T-CiRA, was announced in April and is the largest yet.

CiRA features a gallery in its main building where visitors can access information about CiRA and iPS cell research. The gallery is open to the public 8:30-17:15 on weekdays and 9:00-17:00 on Saturdays. CiRA also offers tours of its facilities to the general public. For details, please visit the CiRA website.

WEB www.cira.kyoto-u.ac.jp/e/about/contact/ (The tour schedule and availability are limited)
T-CiRA
Takeda, Japan’s biggest pharmaceutical company, teamed with CiRA to create T-CiRA, or Takeda-CiRA Joint Program for iPS Cell Applications. The program aims to combine the respective expertise in iPS cells of CiRA and drug development of Takeda for the innovation of iPS cell-based medicines. T-CiRA is extraordinary in its size and length, as Takeda has pledged 20 billion yen (app. US$ 160 million) for 10 years plus another 12 billion yen for infrastructure.

Also making it extraordinary is the speed at which T-CiRA came to fruition. One of the first destinations Takeda President and Chief Executive Officer Christophe Weber visited after taking over his post in 2014 was CiRA. At the time, Yamanaka planned little more than a handshake and a smile. “I was just going to say, ‘Hi. Welcome to Japan.’” Instead, the introduction quickly escalated into a partnership that Yamanaka hopes will redefine drug discovery research. Formal discussions about T-CiRA began the beginning of 2015 and were finalized in April. “T-CiRA is extraordinary in view of scale, time and budget,” says Atsushi Onodera, one of the officials at CiRA responsible for the agreement.

T-CiRA aims to employ up to 100 researchers, with the two institutes directly hiring half each. The initial plan is to develop drugs in areas such as heart failure, diabetes, mellitus neuro-psychiatric disorders and cancer, which are all strengths of CiRA. However, as new scientists are hired, there is an expectation that the number of diseases for study will increase. T-CiRA projects will be located at the Takeda Shonan Research Center, which is much closer to Tokyo than it is to Kyoto, the home of CiRA. The reason, explained Yamanaka, is that he wanted a wall between the science done at T-CiRA and that done at CiRA alone. “I wanted a clear separation between T-CiRA and any other efforts.” The purpose, he added, was to assure other potential industrial partners that collaborative projects with CiRA will in no way be encroached by this one.

Yamanaka expects T-CiRA will become the paradigm for successful translation of academic inventions to the clinic, not just iPS cell-based ones. He also expects that the large investment will attract leading scientists from around the world to CiRA and the field of iPSCs. “This 10-year joint program with Takeda will become a powerful engine to realizing medical applications using iPS cells.” Weber shares his enthusiasm. “I am excited that we will be able to collaborate with CiRA, the world’s leading institute dedicated to pioneering iPS cell research.”

In part because the speed in which T-CiRA was formed, many of the details about the project, including how current CiRA staff will be involved, need to be clarified. Wherever T-CiRA leads, Yamanaka looks forward to hiring bright minds committed to iPS cell research. “Any talented scientist will be welcome as long as he or she wants to find new cures to intractable diseases by using iPSCs.”

The CK Project: For the Unprecedented Aging Society to Come
The hope of all members participating in the CK project is to create a truly healthy society.

Innovative Techno-Hub for Integrated Medical Bio-Imaging Project for Developing Innovation Systems Creation of innovation centers for advanced interdisciplinary research area program, known as the CK Project is a ten-year national project supported by the Ministry of Education, Culture, Sports, Science, and Technology (MEXT). The project aims to create a healthy society through promoting cutting-edge research and development, improving quality of life (QOL), and reducing medical expenses for the future aging society. As of April 2015, one hundred
A novel technology integrating ultrasound and optical imaging, Photoacoustic mammography (PAM) enables the visualization of neo-vascular cancer networks. Other related researches which are underway include development of the technique for the medical image fusion of ultrasound and MRI, and development of the disease-specific diagnostic agent for photoacoustic imaging.

Clinical Laboratory for PAM
Kyoto Univ. Hospital

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Program Co-Director, Professor, Advanced Biomedical Engineering Research Unit, Center for the Promotion of Interdisciplinary Education and Research

The Center for Innovation in Immunoregulative Technology and Therapeutics (The AK Project), an open innovation laboratory for drug discovery and development, was established in 2007 by Kyoto University and Astellas Pharma. The AK Project works in the field of immunology area to develop innovative therapeutics to overcome intractable diseases, e.g. allergies, autoimmune diseases, and chronic inflammation. The project seeks to invent a drug discovery model for the post genome era that is capable of producing game-changing drugs in Japan.

At the Fusion Laboratory on the Medical School Campus of Kyoto University, fifteen groups led by young principal investigators (PIs) and two groups from Astellas work closely with each other under the guidance of three key researchers from the Medical School: Prof. Shuh Narumiya, Prof. Nagahiro Minato, and Prof. Shimon Sakaguchi. Each group carries out independent research to identify unique targets. A prominent feature of the AK Project is collaboration with clinical departments, which search for biomarkers and verify the clinical significance of drug targets found in the Fusion Lab. A satellite laboratory located in the Astellas Research Institute in Tsukuba conducts high-throughput screening and compound optimization. The members share clinical information and samples, knowledge on molecular mechanisms, and drug discovery skills. The AK Project has an intellectual property (IP) office in the Fusion Lab, where two IP managers handle all IP matters, such as patent applications, publications, and contracts, on-site.
Finding functional or healthy components in food materials through metabolomics approaches is an emerging research area in food science. The findings will be key to developing new processing methods for functional foods. Tomatoes are known to have at least 5,000 metabolites (ingredients) in which functional or palatable chemicals are likely to be included.
Food-Sci

Fuji Oil Soybean Renaissance Laboratory
Joint research to develop innovative soy foods.

Soybeans contain many nutrients. The fat and protein content is very high (20% and 35%, respectively) and the nutritional values of both are excellent. Soybeans are, therefore, a beneficial food for humans. Although globally 200 million tons of soybeans are produced per year, only 10% of that is utilized for human food, with most being used for animal feed. The quantity of soybeans used as a protein source for humans is very relevant in light of the food shortage problem caused by global population growth. As described above, however, the amount used for human food is small, and the major reason for this is that there are few soy food products which have an appealing taste and high applicability as food material.

In order to increase the usage of soybean for food, our joint research has begin to develop basic technologies for new soy food products which have an appealing taste and high applicability to various foods.

Fig. 1 shows a microscope photograph of the cut surface of soybean cotyledon. The photograph shows that the structure of cotyledon is not homogeneous. Many particles can be seen in soybean cotyledon, and each particle is covered by a membrane and contains various kinds of materials. These components are considered as effective factors in designing the taste and texture of soy food products.

Our research is investigating in detail the properties of soybean components, and the mutual interaction between them under different conditions using latest methods (for example, the field-flow fractionation system in Fig. 2). Soybeans contain many functional components beneficial to human health, especially for the prevention of metabolic syndrome. Therefore, the physiological effects on humans also require further study.

Eventually, we aim use our study results to propose innovative soy foods with excellent flavor and functionality. We have named our collaborative project the “Soybean Renaissance.”

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WEB www.fujiol.co.jp/fujiol_e/news/150316.html