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Trends and Challenges in iPS Cell Research

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1 Introduction

1-1 What are iPS Cells?

Our bodies are composed of cells differentiated into each organ within the limited period after fertilization, and the process of differentiation was long believed to be irreversible.

The advancement of research in cell differentiation, however, revealed the existence of stem cells possessing multi-potency after body development with the discoveries of embryonic stem cells (ES cells) by culturing early embryo and mesenchymal stem cells, multipotent cells in our bodies. Since then, there have been extensive efforts to find and obtain these multi-potent cells.

In August 2006, Professor Shinya Yamanaka of Kyoto University succeeded in generating cells with pluripotent differentiation potential in mice by inserting just four genes (Oct3/4, Klf4, Sox2, c-Myc) into their mature skin cells, and named them induced pluripotent stem cells (iPS cells).[1] This groundbreaking new fact, which differentiated mature cells possess pluripotency, overturned the traditional belief that differentiation after fertilization was a one-way process and proved that it was rather a plastic phenomenon. The four genes required to induce pluripotency are called Yamanaka factors. In addition, on July 20, 2007, one year after the discovery of iPS cells in mice, Prof. Yamanaka and his colleagues reported and proved that iPS cells could be generated with human cells.[2] This, in other words, means that "a large amount of differentiating cells with the identical genes of the patient" can be prepared whenever necessary.

Human iPS cells were produced by inserting the same four genes (Oct3/4, Klf4, Sox2, c-Myc) used for murine iPS cells. Their method was simple and required no special equipment or technique, and was thus highly versatile. In addition, Prof. Yamanaka reported that insertion of only three genes (Oct3/4. Klf4. Sox2) could achieve iPS cells[3] making the method safer without the use of carcinogenic c-Myc gene. Moreover, the initial method using retrovirus vectors[NOTE 1], a possible carcinogen, is now improved with the use of plasmid vectors[NOTE 2] with less carcinogenic risks.[4] Plasmid vectors, with their ability to insert genes without damaging the genes of the targeting cells, are believed to be safer than retrovirus. Recently, a group from Max Plank Institute for Molecular Biomedicine in Germany succeeded in producing murine iPS cells by inserting only one gene, Oct4, with some chemical agents[5].

1-2 Expectations for Science and Medicine

The importance of the discovery of iPS cells, as mentioned above, is the demonstration that the ability to differentiate into various organs was not exclusive to fertilized oocytes, but differentiated cells could achieve pluripotency as well with gene insertion. This proved the novel concept that pluripotency in differentiated cells could be re-set to a similar level as fertilized oocytes of early embryo. In other

[NOTE1]
Retrovirus vectors are used to carry the genes to be inserted into the target cells.
[NOTE2]
Plasmid vectors are non-viral cyclic DNA gene carriers for gene insertion.

words, it changed the entire strategy from "searching for" pluripotent cells to "generating" them with the establishment of an innovative technique that have the convenience of being able to "prepare whenever necessary," thus providing "pluripotent cells with individually conserved genetic character" at all times.

The expected benefits of iPS cells go beyond research to applications in medicine and drug development with their potential for generating appropriate cells whenever necessary. Expectations are high especially in (1) application in drug development where evaluation of the safety and efficacy of candidate compounds can be done with human cells and tissues differentiated from human iPS cells rather than traditionally used animal tissues or cells, (2) application in regenerative medicine for patients who need repair and regeneration of tissues or function disordered in a disease by regenerating and grafting tissues and organs generated from iPS cells derived from the patients' own cells, (3) in preparation of establishing an iPS cell bank with a collection of various types of human iPS cells, ready to provide a wide range of patients at any time, and (4) for treatments of congenital and intractable diseases[6, 7].

2 Scientific Innovation Triggered by iPS Cells

2-1 Application for Drug Development

The earliest practical application of iPS cells is expected to be in the field of pharmaceutical research for developing new drugs.

The best way to evaluate the safety and efficacy of most drug candidates is with humans, though this comes with many risks. In addition to the obvious risks, since access to human cells and human disease model cells has been widely limited, these evaluations have been conducted mostly with animal cells and animal disease models such as mice. There are many issues, however, with the evaluations using animal models, such as a long development period. In addition, there have been incidents of finding unforeseen side effects and altered efficacy after the drug had been on the market due to frequent interspecies differences between humans and the animal model, in toxicity and efficacy.

With the discovery of iPS cells, drug efficacy can be evaluated with human disease models differentiated from iPS cells derived from patients with the target disease right from the start. In addition, this technique allows access to certain cell types that are impossible to obtain from actual humans, such as cerebral neurons and cardiac muscle cells, and use them in evaluation. The use of iPS cells is expected to speed up the drug development process as well as obtain more information about side effects due to highly accurate evaluation with human cells.

Research and development of a toxicity-evaluation tool using human cardiac muscle cells generated from iPS cells started in October 2008 as a commissioned project of the New Energy and Industrial Technology Development Organization (NEDO). This project aims to establish a technique to evaluate early cardiac toxicity using iPS cells, with their technology to measure the pulsation of cardiac muscle cells developed in the existing NEDO project [8]. Since human myocardial cells were difficult to obtain, drug evaluation had to be conducted with animal model cells such as mice. With the available technology to generate human myocardial cells from iPS cells, efficacy and side effects of candidate drugs can be evaluated directly, enabling the development of drugs with better efficacy and fewer side effects in the future. In addition, omission of evaluation with animal cells is expected to contribute to a shortened development period and reduction of development cost.

The National Institute of Biomedical Innovation has produced iPS cells from patients with various diseases and is planning to differentiate them into cells such as hepatic cells, which are required for the evaluation of the toxicity, and metabolism of candidate drugs. This project is aiming to establish a technology for drug development by preparing iPS cells and differentiated cells derived from iPS cells of different sexes, ages, cell types and genetic backgrounds. Subsequent contribution to the improvement of drug safety (due to detailed toxicity evaluation in screening) is expected.[9]

In the future, the application of this technology will go beyond general drug development, and enable a pre-administration check of drug efficacy and toxicity with the cells differentiated from iPS cells derived from the patients' own cells, allowing optimization of the dosage and prevention of side effects by applying it for individual administration management and detailed individual treatment.

2-2 Application for Regenerative Medicine and Cellular Medicine (Treatment with Autologous Cells)

One of the biggest dreams with iPS cells is their application in regenerative medicine. This is due partly to their pluripotency. The difficulty of obtaining necessary cells for treatment has slowed down regenerative medicine as cell therapy. However, the discovery of iPS cells, cells possessing pluripotency made from skin cells, has shed hopes for abundant access to iPS cells for regenerative medicine and necessary cells and/or tissues differentiated from them for graft treatment (Figure 1).

The discovery of iPS cells has also shed special attention to autologous cell treatment, a type of treatment using patients' own cells. This means, skin cells taken from a patient will be turned into iPS cells to obtain necessary cells and tissues via differentiation and culturing in order to use them for the treatment of the patient him/herself, the provider of the cells. Since these cells come from the patient, they will not be labeled foreign when they are returned in the body, and thus pose no risk of immunological rejection.

iPS cells are not ideal for emergency use since it takes more than a few weeks to generate them. However, in cases where disease onset can be predicted, new medical divisions such as "emergency responsive medicine" and "preventative medicine" may now be operable. For example, for patients with high risks of cardiac infarct, preparation of myocardiac cells differentiated from iPS cells generated from their cells is now possible before the infarct attack.

A research team at the University of Tokyo, led by Professor Hiromitsu Nakauchi, has succeeded in differentiating iPS cells generated from human skin cells into thrombocytes via megakaryocytes by adding growth factors and co-culturing with bone marrow cells. This knowledge enables the generation of blood-related cells, such as white blood cells and red blood cells, and the concept of blood transfusion will be changed greatly in the future.

In January 2009, the Food and Drugs Administration (FDA) of the United States approved Geron Corporation, an American venture company, to conduct a clinical test to treat eight to 10 patients with paraplegia[NOTE 3] with human ES cells[10]. This is the world's first clinical test using human ES cells, and the United States is expected to take the lead in the field of iPS cell application as well.

iPS cells will be applied in regenerative medicine in the near future when the safety of iPS cells is verified and safe differentiated cells derived from iPS cells are established.

2-3 Use of Cell Bank (Homologous Cell Treatment)

Another approach for cell therapy using iPS cells is to make them more general by building cell banks. This is not only for autologous cell therapy where iPS cells are used only for the provider of the cells but also for cell therapy for all patients, which is termed homologous cell therapy (human to human, using another person's cells).

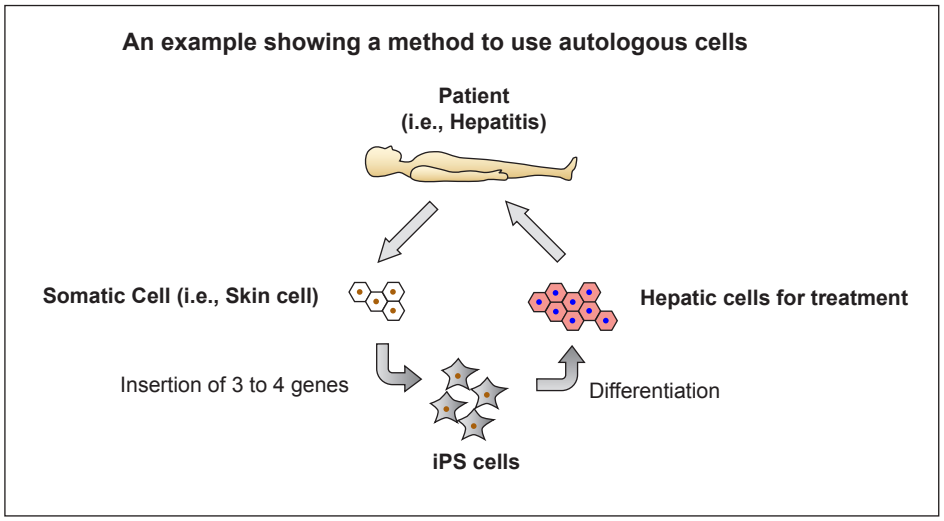

Figure 1 : Conceptual Diagram of Augologous Celll Therapy
(Conceptual diagram showing autologous cell therapy using iPS cells)

Prepared by the STFC

Human cells have different types of histocompatibility antigen (HLA) on the cell surface, and a mismatch in the antigen type is recognized as foreign and subsequently triggers immunological rejection and elimination. According to a calculation by Professor Norio Nakatuji and his colleagues of the Institute for Frontier Medical Sciences of Kyoto University, to eliminate a mismatch that causes the immunological rejection, preparation of 170 different types of iPS cells can be used for 80% of the Japanese population[11, 12]. This suggests a possible use of iPS cells produced by other people's cells in graft treatment in regenerative medicine by preparing many different HLA type cells to minimize the risks of rejection.

Treatment using this type of cell bank has been proposed by Professor Hideyuki Okano of Keio University. For cell therapy in a life-or-death emergency, such as treatment of spinal damage where grafting of nerve cells is ideally conducted on the 9th day post injury, iPS cells of the patients cannot be prepared in time. Therefore, for cases like this, it is ideal to build a bank within a cell bank for iPS cells without immunological rejection as well as a nerve cell bank using iPS cells for the treatment for spinal cord injury.[13]

One example of current progress was demonstrated by principal research associate Hajime Ogushi of the National Institute of Advanced Industrial Science and Technology, who has succeeded in producing iPS cells from mesenchymal stem cells contained in pulled wisdom teeth. Since wisdom teeth were traditionally discarded, they are regarded as a great candidate for the cellular source for building an iPS cell bank[14].

Resources at the iPS cell bank and cell bank derived from iPS cells for treatments are now expanding from homologous to heterologous cell therapy, and they are expected to be applied for emergency treatment of frequent injuries.

2-4 Treatment of Congenital and Intractable Diseases

iPS cells are expected to open up a new way for the treatment of congenital and intractable diseases presently with no radical cure. This involves generation of iPS cells from the cells of patients with congenital diseases or genetically intractable diseases, their differentiation following the repair of damaged genes at the DNA level, and grafting them back to the body to regenerate normally functioning tissues and/or organs. Alternatively, the treatment could be done by grafting normal healthy cells derived from iPS cells to the lesions of patients with intractable diseases. Hemophilia, congenital immunodeficiency and Parkinson's disease are among the target diseases.

Already, a research team at Harvard University in the United States has reported that they produced iPS cells using skin or bone marrow cells of patients with 10 different diseases, such as dystrophy, Down syndrome, diabetes and Parkinson's disease.[15, 16] Another research team at Harvard reported a successful generation of iPS cells from elderly patients with amyotrophic lateral sclerosis (ALS) for the same purpose[17]. The United States seems to be leading the application of iPS cells by far at the moment.

In our country, collaboration between Kyoto University and Keio University has lead to a report at a Keio University symposium on February 4, 2009, that the grafting of nerve cells differentiated from human iPS cells into mice with spinal injuries on the ninth day post injury has resulted in significant recovery of motor ability compared to mice receiving no treatment post injury. This, though a preliminary experiment using mice, is the first case to show the efficacy of iPS cells in an animal disease model.

At Osaka University, in collaboration with Kyoto University and Tokyo Women's Medical University, a myocardiac sheet was constructed with myocardiac cells differentiated from iPS cells derived from mouse fibroblast. When this myocardiac sheet was grafted in the infarct region of a cardiac infarct model created by ligation of the left anterior descending artery in mice, improvement in cardiac dysfunction and the suppression of a left ventricle enlargement was found.[18]

2-5 Repairing Organs

Yet another new challenge has started to re-construct normally functioning organs and tissues by producing iPS cells from patients with acquired dysfunction in some parts of the body and by re-differentiating them inside the patient's body.

Professor Nakauchi at the Institute of Medical Science of Tokyo University has cultured fertilized

[NOTE3]
Paralysis in both legs below the waist

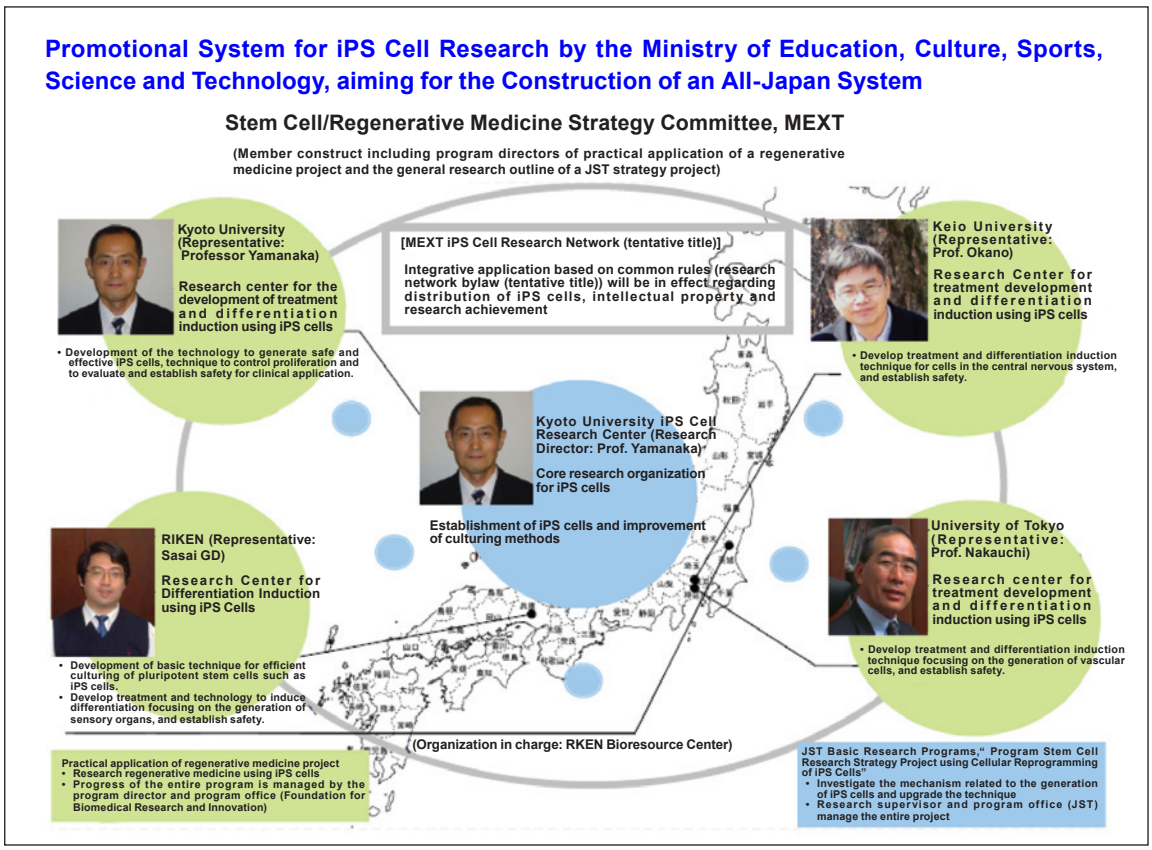

Figure 2 : Promotional System for iPS Cell Research by the Ministry of Education, Culture, Sports, Science and Technology, aiming for the Construction of an All-Japan System

Provided by reference[20]

oocytes, taken from mice with a deficit of genes to form a pancreas, to blastocyst and then injected iPS cells produced from normal mice. These blastocysts were subsequently implanted in a surrogate mother, and the resulting offspring formed pancreases with normal functions. Similarly, they have succeeded in forming kidneys, and the generation of these organs with bigger animals, such as pigs, is expected[19]. If this method proves to be successful in pigs, kidney transplants for patients with severe kidney dysfunctions are no longer just a pipedream since kidneys can be produced from differentiated iPS cells derived from the patient and by injecting them into pig blastocysts.

3 Research System

3-1 National Research Collaboration System

As mentioned above, iPS cells are expected to be a source for drug development research as well as tools for frontier treatment for diseases. In addition, since this was discovered first by Prof. Yamanaka of Kyoto University, an "All Japan System" for research is now being constructed in order to lead in basic research and their use in the industry (Figure 2).

For the "Project to Achieve Regenerative Medicine," four organizations, Kyoto University (Representative: Prof. Shinya Yamanaka), Keio University (Representative: Prof. Hideyuki Okano), University of Tokyo (Representative: Prof. Hiromitsu Nakauchi) and RIKEN (Representative: Dr. Yoshiki Sasai, Group Director), were chosen to strengthen the research using human iPS cells. With these four core institutions, they formed a network devoted for iPS cell research using human iPS cells, with each institution progressing in the research responsibly (Table 1).

As a core institution to progress iPS cell research in our country along with the four core organizations, the Center for iPS Cell Research and Application (CiRA: Research Supervisor: Prof. Shinya Yamanaka) was founded at Kyoto University in January 2008. CiRA is in charge of developing a safe and efficient technique to produce iPS cells, developing growth control technology, establishing safety for clinical application and developing necessary technology for the application. In details, it sets eight goals, shown

Table 1 : Four Research Centers Chosen as Human iPS Cells Research Centers and Abstracts of their Research

Title		
Title	Representative Researcher	Abstract
Integrative Research Center for iPS Cell Research at Kyoto University		
Kyoto University	Shinya Yamanaka	In order to advance human iPS cells research correctly and quickly from its initial stage for their use in regenerative medicine, we aim to contribute not only in Japan but around the world by collaborating with rich resources of researchers at the Institute for Frontier Medical Sciences, Kyoto University Hospital and the Institute for Integrated Cell-Material Sciences, as well as with organizations outside of Kyoto University, such as Osaka University, with CiRA as the core research center. Goal: 1) To reveal the basic essence of iPS cells, 2) to develop safe and effective methods to generate iPS cells, 3) to develop technology to control proliferation and differentiation induction of iPS cells, 4) to develop treatment technology using differentiated cells in disease-related projects, 5) to establish safety and evaluation techniques for clinical application, 6) to build a system to manage and operate intellectual property related to iPS cell research, 7) to found a basis of medical ethics specialized for iPS cells, 8) to standardize an iPS cell-generation technique, and to tirelessly progress iPS cell research in Japan with effective collaboration with related organizations outside of school, active utilization of resources of researchers and by sharing information.
Research Center for Practical Application of iPS cells, ES cells and Somatic Stem cells in Regenerative Medicine		
Keio University	Hideyuki Okano	We aim to deepen our basic knowledge of the mechanisms of autonomous replication, differentiation and epigenetic control and culturing techniques on human iPS cells, ES cells, and somatic stem cells. In order to achieve actual practice of regenerative medicine, we aim to progress internationally top-level clinical research with primate models, to verify safety and efficacy with the use of these iPS cells, with a special focus on diseases involving the central nervous system, hepatopoietic system, cardiovascular system and sensory system. In addition, build a firm basis of human iPS cell research by generating and self-processing many different HLA types of human iPS cells.
Development of Next Generation Gene and Cell Therapy Using iPS Cells		
University of Tokyo	Hiromitsu Nakauchi	With the Center for Stem Cell Therapy Research at the Institute of Medical Science Research, as the core research center, organize a collaborative research system with 4 departments—the Department of Medical Research, University of Tokyo Hospital, Institute of Molecular and Cellular Biosciences and the Graduate School of Arts and Sciences—we aim to advance research in preparation of preclinical tests. As well as establishing a system to generate high quality human iPS cells derived from patients with careful consideration of safety and ethics, we aim to develop a system to regenerate a variety of organs such as blood, blood vessels, bone. cartilage, skeletal system, cardiac muscles, liver, pancreas and nerves from iPS cells. In addition, we also aim to develop new methods of gene-repair treatments using the characteristics of iPS cells for diseases such as hemophilia and congenital immunological dysfunction as well as to educate resources of researchers in regenerative medicine.
Total Center for Technological Development of Differentiation Induction/Grafting as well as Technological Support for Human Pluripotent Stem Cells		
©RIKEN	Yoshiki Sasai	We conduct technological development for highly efficient differentiation induction of human ES cells and iPS cells into neuronal, sensory and blood cells. At the same time, we aim to develop a culturing technique to improve safety, and to establish the basic methods for purification of generated usable cells. In addition, through grafting research using animal models, analyze their function in vivo, and establish the basis for medical application such as in cell therapy. In particular, with the goal of a practical use of human iPS cells, conduct preclinical tests on medium-sized animals for grafting of retinal cells (pigment epithelial cells), and establish a technology that is clinically applicable for age-related muscular degeneration and pigmentary retinal degeneration Through the collaboration between the main research center (Center for Developmental Biology) and the secondary research center (Bioresource Center) as a support center, contribute to the development of technology, resources and infrastructure by providing lecturing and transferring techniques, building, banking and providing useful cell strain, and by adjusting protocol in order to apply human stem cells such as iPS cells in regenerative medicine research in Japan.

Prepared by the STFC based on Reference[21]

in Table 1, and takes charge of basic research to reveal the essence of iPS cells and to develop a safe differentiation induction technique.

Keio University is the research center for practical application of iPS cells in regenerative medicine. They are in charge of applying their knowledge and expertise from their prior research of practical use of stem cells with ES cells and somatic stem cells before the discovery of iPS cells. In addition, in order to use iPS cells for the diseases shown in Table 1, they are aiming to achieve regenerative medicine by driving forward pre-clinical research, including tests with a primate model and confirmation of its safety. They focus on the development of a differentiation technique (especially in the central nervous system), confirmation of safety and research for treatment development. In addition, they have their eye on constructing iPS cell bank with many HLA type human iPS cells (goal: 200 strains) to target diseases in the central nervous system, hematopoietic system, cardiovascular system, and sensory system.

At the University of Tokyo, lead by the Stem Cell Treatment Research Center at the Institute of Medical Science Research, development of differentiation induction, safety confirmation and treatment development technology research will be undertaken. In addition, they will investigate specific diseases shown in Table 1.

At RIKEN, the development of basic technology for efficient culturing of iPS cells, the development

Table 2 : Major iPS Cell Research Organizations Other than the Four Selected Organizations and the Focus of Their Research

Research Organization	Research Focus
Tohoku University	Development of regenerative treatment using autologous cornea cells generated from iPS cells
Nagoya University	Development of novel vascular regenerative treatment using vascular precursor cells derived from iPS cells
Nagoya City University	Actualization of stem cell treatment for periventricular leukomalacia
Osaka University	Treatment of cardiac disease such as myocardiac hypertrophy using myocardial cells generated from iPS cells
Kyushu University	Development of a safe and highly efficient method to differentiate hematopoietic stem cells using human iPS and ES cells
Kumamoto University	Development of the basis for differentiation control from iPS cells to pancreatic βcells and for regenerative medicine for diabetes
National Center of Neurology and Psychiatry	Development of stem cell graft treatment for dystrophy
National Institute of Biomedical Innovation	Build evaluation database on pharmaceutical efficacy and side effects using iPS cells
National Institute of Advanced Industrial Science and Technology	Development of grafting treatment using genetically modified mesenchymal stem cell for severe congenital metabolic bone disease

Produced at Science & Technology Trends Research Center based on references[22-24]

of differentiation induction especially in sensory system as well as safety confirmation and treatment development will be undertaken.

Some universities and research organizations other than the four aforementioned organizations indicated in Table 1 have started research using iPS cells (Table 2). Most are researching with aims to develop treatment for congenital diseases and genetically intractable diseases.

3-2 International Research Collaboration

International research collaboration is still in the initial stage of relationship-building. As I will address later, there seem to be many difficulties to overcome to build a friendly international collaborative relationship with the current vigorous international competition for the rights to the intellectual property.

Under this condition, CiRA has agreed to form a partnership with an American corporation, Novocell, Inc. in September 2008, to research the differentiation of iPS cells to pancreatic cells. Novocell, Inc. has had previous success in creating pancreatic cells using ES cells, and now they will take the challenge of making pancreatic cells from iPS cells. This is aiming at the development of a radical cure for diabetes, and will be a big step in this area, anticipating high demand.[25]

In addition, CiRa has signed an agreement on research collaboration with the University of Toronto in Canada in October 2008. This was for exchanging information about the induction, maintenance and differentiation technique of iPS cells for studying pathological conditions and developing treatments for intractable diseases using disease-specific iPS cells created from the cells of the patients.[26]

The Japan Science and Technology Agency (JST) has concluded a collaborative agreement for stem cell research with the California Institute for Regenerative Medicine (CIRM) of the United States in November 2008. Based on the agreement, they will support various international collaborative research activities by hosting seminars and interaction among researchers and international symposiums. In addition, they are planning to improve the environment for research interactions through sharing and transmission of information about iPS cell research and by hosting a research retreat for young researchers in iPS cell research[27].

3-3 Importance of Strategy for Intellectual Property

As I have mentioned, iPS cells are expected to be used in the development of drugs and novel medical treatments. However, due to this industrialization, iPS cells will be an intellectual property and whenever they are used directly or indirectly, there will be a charge to be paid to the holder of the patent. Since iPS cells and the associated technology were first discovered by Kyoto University, they are believed to have an advantage in many technological contents which are to be patented. However, with the rapid

cycle of research reports from many countries, such as the United States, a significant number of patents will likely be applied by these research organizations and corporations.

Publicized patent information to date indicates the first patent application on murine iPS cell generation by Kyoto University was on December 13, 2005 (Japanese Patent). Similarly, the international application date including human iPS cell generation methods (aforementioned Japanese application date is the priority date) was December 6. On the other hand, application dates from others include Wisconsin University in the United States on March 23, 2007, Massachusetts Institute of Technology's Whitehead Institute for Biomedical Research on April 7, 2007, Harvard University on May 30, 2007, and Bayer AG of Germany on June 15, 2007. Thus based on the application date, Kyoto University holds an advantageous position over the other patent applicants. In fact, on September 12, 2008, the first patent on the iPS cell generation methods by Kyoto University was accepted in Japan.[28] What is approved as rights, whether this patent is approved in other countries, and the approval of patents applied afterwards all depend on the content of the right requisition of patent application as well as the way that patents are regarded in each country. Therefore, it is necessary to pay attention to the transition in order to confirm whether the rights on truly necessary contents are protected.

Kyoto University has started their effort to control their intellectual property by first setting a specialized division, iPS cell research intellectual property support, in the Office of Society-Academia Collaboration for Innovation in April 2008, and subsequently in August 2008, Intellectual Property Office in the Research Strategy Division at CiRA.[29]

On the other hand, the Japan Pharmaceutical Manufacturers Association (JPMA) has proposed that it is necessary for there to be an all-Japan support system that includes the industrial arena's knowledge about strategy in intellectual property for iPS cell-related research accomplishment, at public and private dialogue with the ministers from Ministry of Economy, Trade and Industry, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labor and Welfare in April 2008.[30, 31] However, at this time, consortium is yet to be achieved. JPMA has started their own action and founded an intellectual property support project in November 2008 with contributions from 13 companies on the executive board as one-year support, by analyzing and advising on the strategy for intellectual property of iPS cell-related research results, with a special focus on rights acquisitions in the United States.[32~34]

In June 2008, iPS Academia Japan was founded to manage patented intellectual property on an iPS cell-generation method by Kyoto University, and to approve the rights to conduct patent discovery for companies aiming to develop medical treatment and drugs using the method.[35] Their principle is to provide nonexclusive license for free to non-profit organizations, such as universities, and provide a nonexclusive license onerously to profit-making organizations. To date (February 2009), they have started negotiations with more than 10 companies.

4 Challenges in the Future

4-1 Standardization of iPS Cells

As we are still at the stage of gaining basic knowledge regarding the iPS cell generation, the definition of iPS cells -what exactly are iPS cells- is still vague. Standardization of iPS cells, criteria to define iPS cells, and technological development for standardization are urgently needed for practical application of iPS cells. In particular, clones with different differentiation abilities obtained in the process of generating iPS cells require basic verification, such as the difference between the clones (inter-clone variance) and the way to controlling the changes within one clone over culturing and successive subculture (intra-clone variance).

In the future, iPS cells are expected to be used all over the world, and Japanese research teams are desired to take a lead role in their universal standardization.

4-2 Treatment of Human Diseases

Development for treatment of diseases in humans is one of the major possibilities with the use of iPS cells. Therefore, we should focus on whether it is actually possible and if so how this can be achieved. Especially, efforts should be made to develop treatments for genetic diseases and intractable diseases without any existing treatment. In addition, their adaptation for regenerative medicine with high demands should be made immediately. As I stated in 2-5, the United

States seems to take the lead in this area using their resourceful achievement with stem cell research.

One of the greatest contributions of the iPS cell discovery to human kind is that it gives hope and expectations for treatment to intractable and congenital disease patients. Therefore, we need to select candidate diseases on which to focus, as well as organize teams of clinical doctors and develop researchers for each disease to tackle the target intractable and congenital diseases.

4-3 Guideline for Clinical Application

In order to achieve a successful application of iPS cells in regenerative medicine and disease treatment, we need to build a seamless flow from basic research to applied research. Currently, the guideline for clinical tests using human iPS cells[36] seems to be applicable for tests using iPS cells. However, it is important to construct a guideline specifically for iPS cells that actively guides a user through basic research to their application, following the evaluation of 1) efficacy (benefit) and 2) safety (risks) of iPS cells, to achieve appropriate and speedy application using the results obtained. Therefore, research institutions, directing ministries and the industry should interact with each other to hold detailed yet active discussions in order for each opinion to be reflected directly on the guideline.

The FDA in the United States has already permitted Geron Inc. to conduct a clinical test using ES cells. In addition, in March 2009, President Obama signed an Exclusive Order to lift restrictions on federally funded embryonic stem cell research. Since the knowledge obtained from ES cell research is applicable to iPS cells, clinical application of iPS cells in the United States is expected to accelerate in the future.

In Japan, the application of regenerative therapy to patients has lagged behind the Western countries in the past due to overly strict policy for regenerative medicine as well as delayed revision of science and technology policies as they advanced. We can only hope for a quick setting of the policy for the clinical application of iPS cells. If, however, the policy is too conservative, the development of Japanese iPS cell therapy will be limited. This may result in the American medical industry and their supporters, with liberal approval to polish their pioneering medical technology, to reap all of the reward alone.

4-4 Strategy for Intellectual Property

As I mentioned, practical application of iPS cells is expected to start with the application for drug development followed by use in cell therapy. In particular, their clinical application for the treatment of intractable diseases is expected to be initiated by the United States following their first clinical application of ES cells to be conducted only about 10 years after their initial basic research. Considering the size of the market and the speed of practical application, it is important to get the patent in the United States as well as in Japan.

The method of generating iPS cells has been patented in Japan now. However, patenting of iPS cells themselves independent of their generation methods and of iPS cells and their differentiated cells derived from patients with intractable diseases is still the very basic aspect of the patents. In addition, although medical procedures could not be patented here, since they can be patented in the United States, a strategy to aim for an American patent is very important. For example, though both Europe and Japan have a “first come first served” policy on patenting, meaning the first submitted application is accepted even when the difference is only by a day or the content be identical, since the United States has “first to invent first served” policy, the date of the invention/discovery is critical and experiment notes act as important evidence. Therefore, the management of experiment notes of all researchers researching iPS cells is the basis for getting an American patent. At the “Life Science Intellectual Property Forum” on January 28, 2009, co-hosted by JPMA and the Japan Bioindustry Association, revision of the application method was discussed to include the American caveat policy to act on the ever so rigorous iPS cell-related research field with a shortening interval between new patent applications and presentations at academic conferences.

As shown here, considering the importance of the American patent of Intellectual Property, it is necessary to cooperate with those in the private sector who have extensive experience in obtaining American and international patents. In addition, patent application should be submitted as soon as a discovery is made in research, and in that sense, research and action for intellectual property rights need to be done simultaneously. Therefore, I emphasize the importance of the aforementioned system by JPMA,

"iPS cell intellectual property consortium."

Presently, building a systemic strategy for obtaining intellectual property rights is the most urgent issue to overcome, with new research results coming everyday.

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Doctor of Medical Science
Dr. Sumi is currently working on research development and operation using biotechnology after doing research on the biochemistry of blood, regeneration of nerve cells and drug development. He strongly believes that Japan can lead the world with iPS cells research and that these cells can potentially overthrow the economic recession!

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