A New Era of Medicine with iPS Cells

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Thank you very much, Chairman, for your introduction. My name is Shinya Yamanaka, from Japan, and it is a great honor to have become a new member of this Academy. I will do my best to contribute to this Academy.

I started my career as a physician, not as a scientist. Actually I was an orthopedic surgeon twenty-five years ago, but after seeing many patients suffering from intractable diseases and injuries such as spinal cord injury and cancers, I decided to change my career. I decided to become a scientist, because it is science which can generate and develop new therapies for patients suffering from intractable diseases.

However, making new therapies through basic science is easy to say, but it's very difficult to actually achieve. However, very luckily, we were able to develop this new method to generate stem cells, Pluripotent Stem Cells, directly from our somatic cells, such skin cells. In 2006 by introducing these four factors, four genes, in the mouse skin cells we were able to reset the fate of skin cells back into a pluripotent state. So we designated these new stem cell lines iPS cells – induced Pluripotent Stem Cells. In the following year, 2007, we and others were able to recapture the same reprogramming in human skin cells.

iPS cells have two important properties: the first one is the immortality. We can expand iPS cells as much as we want. The second important property is pluripotency. From iPS cells, after expansion, we can generate virtually all types of somatic cells that exist in our body such as brain cells, muscle cells, heart cells, blood cells and so on. So now, in addiction to skin cells, we can make iPS cells from many types of somatic cells, such as peripheral blood cells; all we need is a very small amount, like 5 ml of blood cells. By introducing that small number of factors we can convert blood cells into stem cells – iPS cells. Once they become iPS cells, we can expand these cells as much as we want to a large quantity. And after expansion, by applying certain kinds of growth factors, we can convert iPS cells into many types of different cells, such as beating heart cells, and blood cells, skin cells, many types of cells.

In 2010, four years ago, our university, Kyoto University, decided to open a new research institute to facilitate medical applications of iPS cells technology. The name of our research institute is Center for iPS Cell Research and Application (CiRA). For us, this one word, "application", is very important, because this is our goal. Our goal is not just writing papers, our goal is to realize applications of these new stem cells technologies.

This is what we want to achieve within next five or ten years. There are two major applications of this technology. The first one is a kind of *in vivo* application, also known as Cell Therapy. The other one is *in vitro* application, so we use iPS cells and iPS cell-derived somatic cells in laboratories, in toxicology testing, in disease modeling and in drug screening. So *in vivo* application and *in vitro* application: those are two major applications.

Let me give you a few examples of *in vivo* application cell therapy. The first application is Age-related Macular Degeneration. This is a major cause of blindness in many countries, including our own country. Dr. Masayo Takahashi in Riken Institute, in Kobe has just started the very first clinical trial using iPS cells in human patients. She generated a functional sheet of retinal pigmental epithelial cells from a patient's own iPS cells, then she transplanted this sheet back into the patient's eye just last month, September 12th. So we are now checking the safeness and efficacy of this new treatment using iPS cell-derived retinal cells.

Another application is Parkinson Disease. Dr. Jun Takahashi in our Institute, who is also a brain surgeon, has developed a robust and very efficient way to generate dopaminergic neurons from human iPS cells, which he is now testing. He is planning to help to treat patients suffering from Parkinson Disease by transplanting these dopaminergic neurons into the brain of patients. He is now testing this strategy in a monkey model of Parkinson Disease. He is hoping to initiate human clinical trials as early as next year.

Another application – this is not a neurological application, but also this is a very important application: Dr. Koji Eto of our Research Institute has developed ways to generate blood cells, platelets and erythrocytes from human iPS cells. He is hoping to bring this strategy to patients as blood transfusion.

Many countries, including Japan, within the next ten or fifteen years, will be short on blood donors, because Japan is an aging society so after ten years we won't have enough numbers of blood donors, so we need to develop some other alternatives. This is one of our hopes.

We have been collaborating with Dr. Yoshiki Sawa, of Osaka University, who is a heart surgeon. He can now make this beating sheet of cardiac myocytes from human iPS cells. He has transplanted this kind of cardiac sheet into a pig model of cardiac ischemia and he observed functional recovery. So, again, he is hoping to translate this strategy into human patients within next three to four years.

Japan is different from other countries such as the US. We only have a very small number of cases of cardiac transplant each year to help these patients. Many patients are dying while they are waiting for a cardiac transplant, so we hope that this strategy can help those patients in the new future.

As for spinal cord injuries, we have been collaborating with Keio University, Dr. Hideyuki Okano. This is our strategy: we can make neural stem cells from iPS cells, and by transplanting these neural stem cells into the site of injury we hope to obtain functional recovery in patients suffering from spinal cord injuries.

Also, we are now trying to apply this technology into cancer treatments, Cancer Immunotherapy. In patients suffering from cancer, their immune system tries to kill cancer cells, especially T-lymphocytes of patients try to kill cancer cells. However, in most cases, cancer cells are stronger so T-lymphocytes of patients are defeated by cancer cells. However, by applying iPS cell technology, we can rejuvenate cancer-attacking T-lymphocytes. We can rejuvenate and we can expand T-lymphocytes. Dr. Shin Kaneko of our Institute is now developing this new cancer treatment. This can be applied to many types of human cancers, including pancreatic cancer.

Let me give you another example of iPS cell technology, which is disease modeling and drug screening. Let me use ALS – Amyotrophic Lateral Sclerosis – as an example. ALS is also known as Lou Gehrig Disease in the US. Lou Gehrig was a wonderful, brilliant, baseball player back in the 1930s, more than seventy or eighty years ago. However, at his peak he suddenly became ill, became sick. He suffered from ALS, Amyotrophic Lateral Sclerosis, which forced him to retire when he was only 35 or 36 years old, and only few years later he passed away. ALS is a motor neuron disease. In these patients the motor neurons degenerate and eventually die. Because of this, these patients progressively lose their ability to move their muscles, so in the end they cannot move at all, and of course they cannot breathe without the help of a respirator. However, they can still think, they can still sense, they can still hear because only motor neurons are specifically affected. Other types of neurons are intact. So, again, patients can think, can sense, can feel, but in the end they cannot communicate at all, so it is a very, very difficult, tough condition for patients and also for their family members. We still don't have any good cures for this ALS.

You know, we have mouse and rat models of ALS, and many drugs have been developed on rodent mouse and rat models. They are very effective on mice, but unfortunately none of them are effective on human patients. So we need to use human cells, instead of mouse or rat models, to understand and to develop a new effective cure for these patients. However, as you can imagine, it is impossible to obtain motor neurons from patients, because if you remove motor neurons a patient or a donor will completely lose the ability to move that particular muscle, so we cannot ask patients or any individuals for a motor neuron biopsy. That's one of the causes of why we don't have good cures for these patients.

However, now that we can use iPS cell technology, all we need is a small amount of blood cells, or skin samples from patients. They don't mind providing us their blood cells or skin cells. Then we can convert patients' blood cells or skin cells into iPS cells, we can expand iPS cells to a large quantity and then we can generate motor neurons from iPS cells.

Dr. Haruhisa Inoue, in our Institute, has been conducting this kind of strategy, so he generated iPS from control individuals, as well as from ALS patients.

When iPS cells are undifferentiated we did not see any differences between control and patients. However when Dr. Inoue differentiated iPS cells into motor neurons, he observed marked differences, many differences. One obvious difference is a morphological difference. As you know, brain cells – neurons – have a long projection known as a neurite. So, as you can see here, motor neurons derived from iPS cells also have long neurites. However, in motor neurons from ALS-patient iPS cells, he noticed that projection neurites are significantly shorter. This is the average of multiple patients and control individuals. ALS motor neurons have only 50% length in neurite ranks.

Using this as a model system, Dr. Inoue is now screening thousands of chemicals to find good drug candidates for ALS patients. He did find some good candidates, such as anacardic acid. So, as you can see here, anacardic acid can divert the abnormal morphology of ALS motor neurons back into the normal morphology. We are hoping that one of these candidates will help ALS patients in the near future. So, again, this is what we want to achieve.

We really want to bring iPS cell technologies into patients, into clinics, in cell therapy and in drug discovery. So again, we, the Center for iPS Cell Research and Application, has been working very hard to realise those

medical applications of iPS cells. We have more than 300 scientists and admin people in this building, so we really hope that in the new future we can contribute to new therapies for patients suffering from intractable diseases and injuries. Thank you very much.