An interview with Masayo Takahashi, Project Leader at the Laboratory for Retinal Regeneration, RIKEN Center for Developmental Biology

iPS Cells — Breakthrough Technology That Could Herald Average Life Span of 100 Years

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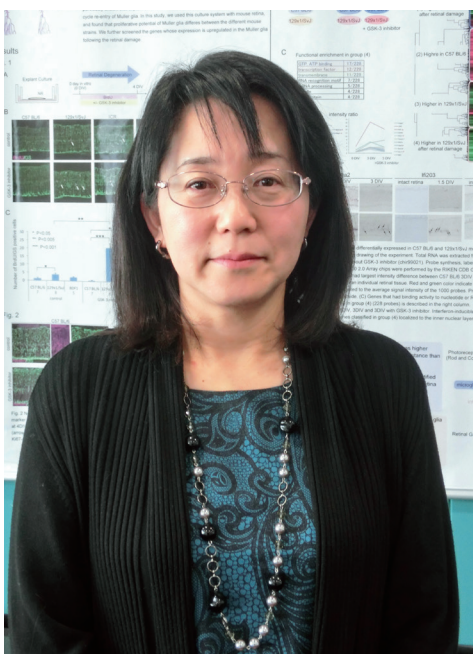
Introduction

At the end of last year, the British science journal *Nature* named 10 scientists around the world who had made "an invaluable contribution to the evolution of global science in 2014". Among them was Dr. Masayo Takahashi, a project leader at the Laboratory for Retinal Regeneration at the RIKEN Center for Developmental Biology in Kobe. Last September, she and her team were successful — for the first time in the world — in an operation to transplant retina cells generated from iPS (induced pluripotent stem) cells into a patient suffering from age-related macular degeneration.

This could be a stepping-stone to achieving a society where elderly people can enjoy good health for a long time. *Japan SPOTLIGHT* interviewed Dr. Takahashi to introduce her work to our readers and to discover what she thinks about the potential of medical science in the future.



Masayo Takahashi, Project Leader at the Laboratory for Retinal Regeneration, RIKEN Center for Developmental Biology

From Ophthalmologist to iPS Cell Researcher

JS: Could you tell us how you became involved in an operation using iPS cells, having started your career as an ophthalmologist?

Takahashi: I had been working for a clinic for more than 20 years and had engaged in a number of eye surgeries. During my working years as a clinician, I had a chance to study at the Salk Institute for Biological Studies in the United States in 1995. The laboratory is specializing in brain neuroscience, which discovered a new concept of neural stem cells. It had been said that once the central nervous system such as the brain or spinal cord is damaged, it cannot be restored. However, Dr. Fred Gage at the Salk Institute discovered that there was a neural stem cell in the adult brain that produces a new brain cell.

So we thought that there would be a potential for a new neural retinal cell being produced and incorporated as in the brain and a possibility of practicing regenerative medicine with the transplanted neural cell. At that time, I was the only ophthalmologist working in the institute on neural stem cells. I decided to move into research to discover a new remedy for eye disease, and to do this I thought that I should continue to work in clinics as well as conduct research.

JS: What is the most difficult part of this operation, the first in the world to use iPS cells?

Takahashi: A team of three doctors headed by Dr. Yasuo Kurimoto, head of the Department of Ophthalmology at the Institute of Biomedical Research and Innovation Hospital, was in charge of this operation. By itself, it was not necessarily a new operation but the use of iPS cells was original. The retinal cells that we made from iPS were very pure and there was very little risk of side effects. Even though many people think iPS cells could have a negative impact, operations using them would be much less risky than ordinary eye surgery. It was certainly a tense moment, but having assessed its safety a number of times by data we were convinced. This operation demonstrated the safety of iPS cells based on clinical research.

JS: Is clinical research difficult because it is not only research but is also expected to produce cures for patients?

Takahashi: Yes, it is difficult. What seems to make it more difficult for

people in other countries to understand about clinical research in Japan is that we have our own indigenous system with two tracks — clinical research and clinical trials. In the rest of the world, there are only clinical trials. In Japan, we have to do a clinical trial to get authorization for production and sale of a new medicine or new medical equipment from the Ministry of Health, Labour and Welfare, the regulatory authority for the medical industry, and also clinical research in accordance with a medical practitioners' law to explore new remedies and examine their physical effects.

In usual clinical trials for drugs, we have three phases for developing a new remedy or medicine and the first phase is the stage where we should confirm its safety before examining its effects. This operation which we started last September corresponded to the first phase for confirming safety.

iPS Cells & Public Policy

JS: Cabinet ministers adopted a strategy for promoting health and medical science in July 2014. One of the targets toward 2030 is to extend the nation's average life span in good health. Do you think iPS cells can provide promising medical remedies in this regard?

Takahashi: Yes. At some point in the future I think it is extremely likely that we will be able to treat currently intractable conditions using iPS cell-based approaches. Of course, we are not sure when we will reach this point — it may be in five years' time, or it may not come for another 20 years. But I think it should be possible to achieve by 2030.

JS: Eye therapies have often been cited as one promising area for application of iPS cells. How about other areas?

Takahashi: Eyes have long been a part of the body on which new treatments are used for the first time. For example, lenses for surgical implantation in intraocular prosthesis are one of the first and most successful artificial internal organs. New medicines, such as antibody drugs, have also succeeded well in eye treatment, and similarly this new remedy using iPS cells has now also begun with the eye.

In a country like Japan with a long average life span, maintaining quality of life in advanced age is an important societal problem, just the same as preventing premature death. These are measured by what we call Disability-Adjusted Life-Years (DALY). We can accept that a life lived with handicaps or unemployment due to the need to care for parents with disabilities is also a social loss, and it is said that in Japan eye diseases would cost society more than $80 billion a year. This means that eyes are a very important part of this pursuit of a society with good health and long life spans and could provide a major market for iPS cells. This technology could probably be introduced for other diseases, such as Parkinson's disease.

JS: How many patients with age-related macular degeneration, a disease your research can help cure, are there in Japan now?

Takahashi: It is said in Japan there are around 700,000 patients, more than 1% of the elderly population. In 2014, for example, there were 880,000 patients newly judged to be suffering from cancer by a medical doctor in Japan. We have many kinds of medicines to treat different types of cancer, but there are only a few medicines for this specific eye disease. This is one such disease where we can see unmet medical needs.

Encouraging iPS Cell Research by Deregulation

JS: Do you think a new law for regenerative medicine that came into effect in November 2014 would encourage your clinical research?

Takahashi: I think the Revised Japanese Pharmaceutical Affairs Law, which came into effect in November 2014, may have a more significant impact on our research than the new law for regenerative medicine. With this revision, Japan's Pharmaceutical Affairs Law has become the most encouraging one to promote regenerative medicine. The core part of the revision is a significant deregulation for the administrative approval process for regenerative medicine. According to this revised law, the administration authorizes a medicine quickly and industry with the help of academia has to confirm its validity in post-market research. Thus we will need to ensure promotion of regenerative medicine and its safety simultaneously through cooperation between the administration and academia. This is a big challenge for us.

This deregulation will be successful in attracting a variety of biotech companies from all over the world, not only the good ones but also the bad ones, due to the simplicity of the administration's approval process. Some venture firms aiming only to earn money could sell low-quality medicines on the Japanese market, so to avoid this we academics must take firm control of post-market research on medicines and authorize only those medical facilities with a confirmed commitment to conduct research.

The government has now given us the chance to promote regenerative medicine, so we want to promote and strictly control regenerative medicine simultaneously. This deregulation is possible only in Japan, where it has not been business but academia that thus been the main driver of regenerative medicine.

JS: This revision has made the approval process very rapid. Is that the essence of the reform?

Takahashi: Yes. The Pharmaceuticals and Medical Devices Agency (PMDA) recently announced that the medical drug lag has become zero. Japan used to be very far behind other countries in terms of the speed of the administrative approval process for new medicines, but now, thanks to this revised law, it has outstripped some other countries. This is amazing progress for us.

JS: Do you have any other expectations of the administration following such decisive deregulation?

Takahashi: We would like the administration to maintain this rule as much as possible, even if there are calls to strengthen regulations again in the future. In order to achieve this, we would need to make this revised law as successful as possible, and we in academia must feel a great responsibility for its success.

JS: Would it be possible for us to realize an average life span of 100 if such deregulation facilitates speedy innovation in medical science?

Takahashi: Whether we should have a 100-year average life span is another question altogether. But as far as eye treatment is concerned, we are optimistic that we can decrease blindness steadily.

International Cooperation in iPS Cell Research

JS: It is often said we can achieve breakthrough innovations in science and technology by open collaboration with other nations. Is this true of iPS cells as well?

Takahashi: Before this dramatic deregulation was applied to regenerative medicine, we were thinking that our startup company would take our developed medicines to the US Food and Drug Administration first for approval. But now that we have had such deregulation in Japan, we do not have to go to other countries first. Companies from other nations are now trying to come to Japan, attracted by the advantages created by this deregulation. So that now we can use Japanese technologies in our work and the industries affiliated to regenerative medicine can be raised inside Japan.

JS: So will foreign direct investment (FDI) to Japan increase in the area of iPS cells and regenerative medicine?

Takahashi: The city of Kobe is expecting exactly that. Many business firms including from overseas are now coming to Kobe following the public announcement of the news of our clinical research on iPS cells as the first such attempt in the world.

JS: FDI in Japan does not seem to be increasing significantly in spite of the government policy promoting it. But if regenerative medicine could bring an increase in FDI, that would be fabulous.

Takahashi: Yes. We could create a company like Toyota, which attracts attention all over the world, in the area of regenerative medicine. At the same time, we should promote our new regulation standards as shown in our revised Pharmaceutical Affairs Law to the rest of Asia, where no such rules have been adopted yet in medical services. We could set an example in this area for the rest of the region.

JS: This means that Japan could export its new rules to Asia?

Takahashi: I think we can certainly export the system defined in our Pharmaceutical Affairs Law to other nations. We have both clinical research and clinical trials in developing new medicines for practical use. This is very important. We are trying to develop new therapeutics as quickly as possible by using both. I believe we have now a big opportunity to export our standards. My concern is that there are some people, such as researchers engaged in basic research, who are excessively concerned about its risks and stress the importance of risk assessment. They are preventing us from promoting our trials, neglecting a big opportunity to attract FDI through Japan's iPS research or export our standards overseas.

Future Plans

JS: What treatments are you planning to conduct hereafter?

Takahashi: Fortunately, our patient whom we operated on last year is currently in the best condition that we could assume in advance. However, as I said, some experts consider our clinical research on autotransplantation to be excessively risky, so it will be increasingly difficult to achieve autotransplantation. I am therefore thinking about changing our clinical research from autotransplantation to allotransplantation for as many patients as possible.

JS: There seem to be many patients with eye disease or Parkinson's disease waiting for your new remedy to be developed and implemented.

Takahashi: Yes. In hospitals our patients always ask us for new treatments as soon as possible. On the other hand, there are some who tell us to be prudent, since they may involve risks.

It does not matter whether our procedure was the first such attempt in the world or not. It is more important that we discover how quickly we can create a new remedy for our patients. We have never created a new type of medicine yet in Japan, so we have not needed to prove a new remedy's effectiveness or safety until now. Overseas researchers are now admiring the supportive regulatory environment resulting from the recent revision of the Pharmaceutical Affairs Law, and we should take advantage of this situation.

However, the lack of experience I mentioned seems to create unnecessary concerns about risk and that prevents us from making further progress.

JS: In thinking about medical risks, public opinion is likely to be influenced by the ability of scientific experts to explain about advanced medical developments in understandable language. As science has a close impact on our daily lives today, this ability is very important, isn't it?

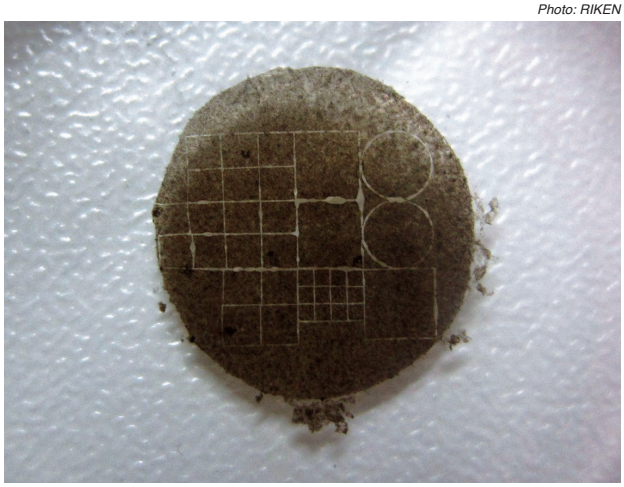
Takahashi: That is a difficult question. What is most important is that both experts and the public understand that it will take much effort and time to achieve a good public understanding of medical issues. I think we should have a consensus that it will be difficult to explain such issues to the public in easy language. The public should know there will be limits to their understanding of these issues.

JS: In the case of operations in a hospital, a doctor explains things so that even a non-expert can understand the medical science.

Takahashi: Yes, a medical doctor's ability to explain about a disease is clearly important. But I believe the human relationship between a doctor and a patient must be more important, since a medical doctor occasionally will not tell everything, even on the assumption of informed consent.

When an unfortunate accident happens, whether or not a doctor gives the full details of a patient's condition is not necessarily a crucial issue that would cause a conflict or eventual lawsuit. More important is whether a doctor and patient have achieved a relationship of trust or not through treatment, as this would be key to causing or preventing a

Photo: RIKEN



A sheet of retinal pigment epithelial (RPE) cells derived from iPS cells

conflict. No matter how detailed an explanation a doctor gives to a patient, a lack of trust between the two could result in a lawsuit. On the other hand, even though the doctor did not explain everything to the patient, a good relationship between the two might prevent litigation.

Potential of Japanese Science

JS: What do you think about the potential of Japanese science?

Takahashi: Dr. Masatoshi Koshiba, winner of the 2002 Nobel Prize for Physics, once told me, "We lived in the age of physics and engineering in the 20th century, but in the 21st century we are living in the age of life sciences. You can be a star of science. Please do your best to achieve great progress in life sciences."

Airplanes and automobiles used to be the engine of the world. In the future, medical and life sciences will be at the core of global innovation and development, according to him.

Japan's basic research in life sciences has reached the highest levels, but the capacity for innovation to put this high-level research into practical use is rather weak. The Japanese government is now aware of this and trying to evoke innovation by drastic deregulation for regenerative medicine. I think this is the right approach.

We medical scientists should take advantage of this good opportunity and refrain from being comfortable with less challenging research that involves taking no risks.

JS: Japanese tend to think they should not do anything if any risk has been observed. Of course, having no risk is impossible. It is more important to find out how to reduce risks.

Takahashi: Japanese mass media are also responsible for this risk-avoiding attitude. They always severely criticize medical services for any risks caused by medicine. We medical science experts would like to discover how effective a medicine may be, as well as its risks. There is no media that discusses its benefits. The media should consider its merits and demerits equally.

We need to maintain our efforts to achieve better communication with the media. In our case, we should tell the media about the merits and risks of iPS cells comprehensively. This is a good opportunity for us to improve the Japanese media's understanding of iPS cells, since the media's attention today is attracted to our research.

JS: Lastly, in the light of raising promising scientists in Japan, how do you think we should reform our education?

Takahashi: Even now, our education system is changing little by little. So far we have tended to have only teachers with little experience of risk-taking in their social life, but it will be a different story if we can have more ambitious and risk-taking teachers in academia. There are not so many, but even now there are people in their thirties thinking and acting on a larger scale, which was not the case in previous generations.

We should keep an eye on these young people emerging onto the main stage and if necessary help them to utilize their full capacities. They could change our education system. JS

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