Messages from Modern Inventors to the Next Generation

12. *iPS cells* - Dr. Shinya Yamanaka, Center for iPS Cell Research and Application, Kyoto University

The physical body of a human being is composed of countless cells. Certain types of illnesses are caused when cells are lost or lose their function. Therefore, it is thought that such illnesses can be cured with new cells that replace the lost cells.

Dr. Yamanaka succeeded in making iPS (induced pluripotent stem) cells. iPS cells are similar to ES (embryonic stem) cells which can be changed into all types of cells including nerve, muscle, bone and all other types of cells. iPS cells are generated by introducing four genes into skin cells of a human.

What inspired you to become an inventor/researcher?

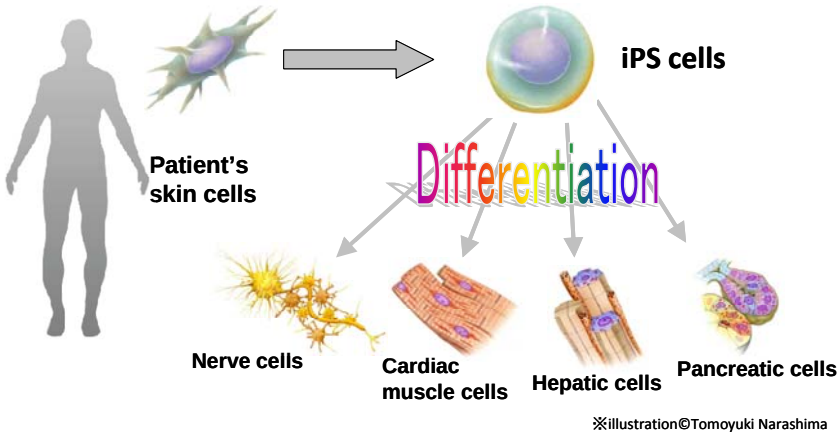
With my father's advice and encouragement, I had been thinking about becoming a medical doctor since my childhood. I was passionate about judo during my junior and senior high school days and about rugby as a university student. As a result, my bones were broken more than ten times. So I was therefore very much indebted to my orthopedists. Accordingly, I entered the School of Medicine at Kobe University with plans to become an orthopedist. During my residency, however, I realized that I was not talented in surgery and quite incapable of being an orthopedist. Also, during those days as a physician, I encountered patients who were suffering from rheumatism (a disease causing joint and other rheumatic pains with no cure), spinal cord damage, and other

types of intractable diseases/irreparable injuries. I started thinking that I would like to be of some help to those patients, so I decided to become a researcher considering the significance of basic research to unravel the causes of human disease.

What kinds of challenges have you faced as an inventor/researcher, and how have you overcome those challenges?

When I had my first laboratory as an associate professor at the Nara Institute of Science and Technology in 1999, I decided that the purpose of my laboratory would be "to generate undifferentiated cells like ES cells from somatic cells." At that time, many researchers were already involved in the study of 'cell differentiation' (the process by which cells become structurally and functionally different from one another and develop a mature phenotype), which is the royal road to research, by using ES cells. With little chance to win due to my late entry into the competition, I decided to choose a new approach.

By that time, it was already known that somatic cells could be turned into the pluripotent state by using cloning technology (e.g., using a lamb's somatic cells and an oocyte, a completely identical lamb was born.). However, no one had ever succeeded in changing somatic cells into undifferentiated cells directly (i.e., cells before they are differentiated) without using an oocyte. Although I first thought that it would take many decades for us to achieve success, we were able to do so earlier than expected thanks to the great help of the brilliant lab members. Utilizing published databases, we were also able to narrow down, in an unexpectedly short period of time, the number of genes that are idiosyncratically expressed in ES cells. This led us to the discovery of four genes which initialize somatic cells followed by the successful establishment of iPS cells.



Differentiation of iPS cells:
The iPS cells generated from human skin cells are transformed into various types of cells in a human body.

What gives you joy as an inventor/researcher?

There is much pleasure that I gain from my work as a scientist. The first one is to experience a surprise. We researchers first form a hypothesis and then conduct an experiment to prove the hypothesis. I sometimes happen to face unexpected experimental results which do not necessarily disappoint me. The unknown reasons for the result thrillingly cause me to ask myself why the result occurred. This question makes me form another hypothesis and probe the reasons for the result while leading me to a new discovery.

Another pleasure is the opportunity to interact with many people who are involved in all kinds of research activities. Nothing can be achieved alone. The activities of a researcher include reading predecessors' papers, discussing and refining ideas with colleagues, and receiving other researchers' offers of samples which are required for experiments. An experiment cannot be successfully performed without the support of technician, researchers and students. It is also essentially important to discuss the results of an experiment with many other researchers including rivals at domestic and international academic conferences. In addition, I have recently had quite a few opportunities to give lectures and thus have had more chances to meet a variety of people including patients. It is indeed a joy for me to be engaged in research work while collaborating with many people. My objective is for "iPS cells to be used in clinical

applications that significantly benefit patients". It will take time to achieve this goal, and when I do so, I will be able to realize true joy as a researcher and a doctor.

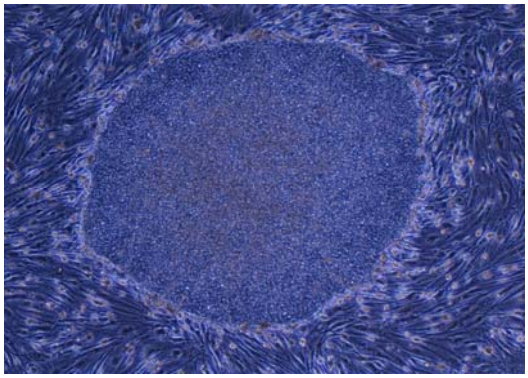
Open laboratory in the Center for iPS Cell Research and Application, where researchers, technicians and students conduct experiments

What message would you like to convey to the next generation?

"Vision and Hard Work" is the phrase that I learned from a professor at the Gladstone Institute of Cardiovascular Diseases in San Francisco, California, in the United States where I studied as a postdoctoral fellow. The phrase implies that it is important for one to first have a long-term vision and then to make every effort to realize that vision. Both "vision" and "hard work" are necessary.

I believed that it would take me many decades to successfully complete my research when I started to study iPS cells. At the same time, however, I decided to form a hypothesis suggesting that "the genes involved in maintaining the pluripotency of ES cells (i.e., maintaining the undifferentiated state of ES cells) should be a factor which makes it possible to transform somatic cells into undifferentiated cells." In order to prove that this hypothesis was correct, I decided to study the system for maintaining the pluripotency of ES cells, which was still unknown at that time. This study, as a result, made a significant contribution to the establishment of iPS cells. The first hypothesis here was the "vision" and the effort patiently and earnestly made in performing daily experiments was the "hard work." These two factors were successfully combined to achieve an outstanding result.

Looking back, I collaborated with many students, researchers and technicians, who all contributed steady and strenuous efforts to make the research project a success. I was able to consistently pursue my research goals thanks to their continuous support and advice. In closing, let me add that I just cannot sufficiently express my gratitude to all of the people, including my family members, who supported me.



Human iPS cells: In view of future research on iPS cells, which can be differentiated into various cell types, it is highly expected that a variety of illnesses may be cured with iPS cells in the future.