In 2006, a report from Shinya Yamanaka’s laboratory changed the landscape of stem cell research for good.1 Until that point, generating a source of patient-identical pluripotent stem cells, a major stepping stone in the quest for stem cell therapies, would only have been possible by cloning a human, generating an embryo, and deriving embryonic stem cells, all of which would involve challenging techniques and a burden of ethical issues.

The article by Yamanaka offered the potential of a new and easier method. By introducing 4 genes into terminally differentiated adult mouse fibroblasts, he could reverse the cells’ fates and render them embryo-like.1 And 1 year later, he did the same with human cells.2

Induced pluripotent stem cells, as the resulting cells were called, were shown to share the characteristics and features of embryonic stem cells, including the ability to give rise to every tissue type of the body.3,4 Thus, in principle, a patient might one day be able to donate some cells and in a matter of weeks have those cells converted into a source of stem cells ready to produce any required cell type—heart cells to fix an infarction injury, for example.

The technique is still a long way from being feasibly used in the clinic, but over the last 6 years, Yamanaka and other researchers have made several adjustments and improvements toward that goal.5–8 For example, it is now possible to make induced pluripotent stem cells without integrating viral vectors into the cells’ genomes, which was a major safety concern.5

In the shorter term, induced pluripotent stem cells will be useful for creating patient-identical disease model cells in which the pathological process can be studied and drugs can be tested. The production of induced pluripotent stem cells has also spurred the development of similar techniques, for example, researchers can now convert heart fibroblasts directly into myocytes by similar methods.

Considering his contributions to the stem cell field, it may be surprising to learn that Yamanaka, who is currently Director of Center for iPS Cell Research and Application at Kyoto University in Japan and also a senior investigator at the Gladstone Institute of Cardiovascular Disease in San Francisco, initially trained as an orthopedic surgeon. He told Circulation Research about his early days of fixing (and breaking) bones, what he thinks are the keys to success in science, and what have been the best and worst moments of his career. It is possible, of course, that his answer to the best-moment question would have been different, had this interview taken place after the 8th of October 2012, the day Yamanaka learned that he and John Gurdon of the University of Cambridge, UK, were to be awarded the Nobel Prize in Physiology or Medicine.

What Was Life Like Growing Up in Osaka?

My father was an engineer and ran a small factory. I used to watch him making small parts for sewing machines every day, and so I used to break down gadgets such as radios and clocks to see how they worked. But I often failed to put them back together. When I was a child, I wanted to become an engineer like my father.

When Did You First Become Interested in Science?

There was no specific event. I was good at mathematics and science classes at school. My favorite book was science-fiction series called “Perry Rhodan”. I also liked reading a certain monthly scientific magazine for elementary school children. This magazine came with various kits for doing your own experiments. I remember one time I was doing an experiment with an alcohol lump that came with the magazine. It dropped onto a table that was covered by a quilt and the table caught in fire. I was severely scolded by my mother.

You Chose to Study Medicine at College. Why Was That?

My father used to tell me that I should become a medical doctor, instead of taking over his business. I do not know why he said so, but he might have thought that I was not cut out for business.
But that was not the only reason. When I was a high school student, I was also inspired by Dr Torao Tokuda who, in the 1970s, founded a hospital group that revolutionized the Japanese medical system.

**You Then Trained as an Orthopedic Surgeon. Why?**
Throughout my junior high and high school years, I practiced judo, and as an undergraduate at Kobe University, I played rugby. While doing these sports, I managed to break various bone, >10 times, in fact. Going to orthopedic clinics frequently, I naturally wanted to become an orthopedic surgeon.

**Why Did You Decide to Drop Surgery and Do a PhD?**
After I started working as an orthopedic surgeon at a hospital, I found that my surgical skills were not as good as I expected. In addition, treating many patients with intractable diseases and injuries, such as rheumatism and spinal cord injury, I realized that there are many diseases that even talented surgeons and physicians cannot cure. I therefore became interested in basic medical science, with the hope that it might enable the development of new therapies.

**As a Young Scientist, Who Were You Inspired By, and Why?**
Many researchers inspired me. One of them is Dr Robert Mahley, who was then president of the Gladstone Institutes in San Francisco when I worked as a postdoctoral fellow there in early 1990s. He taught me that having a vision and working hard toward it is the key to success as a scientist. I always keep these words in mind.

**How Did Your Work on iPS Cells First Begin?**
Around 2000, I became an associate professor and principle investigator at the Nara Institute of Science and Technology. I had my own laboratory for the first time. One of the first things I had to do was to set a long-term research goal to attract talented graduate students to my laboratory. At the time, I was interested in embryonic stem (ES) cell research, and Dr James Thomson had recently reported the generation of the first human ES cells.

ES cells have associated ethical issues, however, because to generate the cells, embryos have to be destroyed. This had been an obstacle to the promotion of ES cell research in some countries, including the United States and Japan. So I decided to make my laboratory’s goal ambitious to generate ES-like stem cells from somatic cells, without using embryos. I knew that making such cells would be extremely difficult, and I thought that it might take decades to achieve the goal.

**It Did Not Take So Long, After All. How Did the Discovery Come About?**
My initial hypothesis was that the factors that maintain pluripotency of mouse ES cells may induce pluripotency in somatic cells. With tremendous efforts by students and technicians in my laboratory, especially Yoshimi Tokuzawa, Kazutoshi Takahashi, and Tomoko Ichisaka, we identified many factors that either are specifically expressed by or have important roles in mouse ES cells. By 2004, we had collected 24 initial candidates that might be able to induce pluripotency and established an assay system to evaluate these candidates.

**What Happened Next?**
When Kazutoshi Takahashi introduced the mixture of all 24 genes into mouse fibroblasts via retroviral vectors, we observed several colonies of cells that were similar to ES cells in terms of their morphology, proliferation, and gene expression. Bit-by-bit, we narrowed down the 24 factors to just 4 that are essential to induce pluripotency. When we succeeded in generating ES-like cells with those 4 factors, I was anxious that they were really the pluripotent cells that we were looking for and repeated the experiments over again to make sure of it.

**Would You Say This Was Your Favorite Moment of Your Career So Far?**
Actually, one of my favorite moments of my career is a very early one as a young scientist. When I was a PhD student at Osaka City University, I was assigned to perform an experiment to study the role of a blood lipid named platelet-activating factor in lowering blood pressure in dogs. The hypothesis my boss set up was that giving an inhibitor of another lipid, thromboxane A2, activated by platelet activating factor would prevent the blood pressure from going down. But my experiment showed a completely opposite result. I was so excited with the unexpected outcome that I became more intrigued by research. This study became my PhD dissertation, and I was delighted when it was published in *Circulation Research* in 1993.

**What Has Been the Lowest Point of Your Career?**
Two incidents rescued me from the post-America depression. One incident is that Dr Thomson generated human ES cells in 1998. This encouraged me in my own ES cell research endeavors, and the other incident is that I started my own laboratory at Nara Institute of Science and Technology, which offered an excellent research environment.

**How Did You Overcome This Low Point?**
I stay in the United States for a few days every several weeks to take care of my small laboratory at Gladstone. It is meaningful to visit the United States and meet scientists there to get latest information on stem cell research and related fields.

**You Now Have Laboratories in Both Japan and the United States. How Do You Split Your Time Between Them?**
Like many Japanese researchers, I worked hard from early in the morning till late at night as a young scientist.
How Important Is Hard Work Compared With Other Scientific Attributes?
Hard work is important to achieve a goal, but you need to have a clear vision too.

Do You Still Work Just as Hard or Even Harder?
I no longer perform experiments by myself. Now, as the director of the Center for iPS Cell Research and Application at Kyoto University, I have to bear additional responsibilities for running the center to achieve our goals, that is, bringing iPS cell technology to the clinic as soon as possible. In some ways, this means I am working harder.

What Advice Would You Give to Young Scientists?
The same advice that Dr Robert Mahley gave to me: have a vision and work hard. I also think that young scientists should not be disappointed with results that deny your hypothesis, but they should try to dig into the failures because you may encounter unexpected discoveries.

What Are Your Strengths and Weaknesses?
One of my strengths is that I am good at making a decision, and one of my weaknesses is my bones—as I said, I often broke them.

What Are the Best and Worst Things About Your Job?
Science is full of surprises. I am always thrilled with unexpected results of experiments by my laboratory members. The worst thing is that since I announced the discovery of iPS cells, I have been too busy and have not had sufficient time to carry out research activities and to spend with my family.

What Current Projects in Your Laboratory Are You Particularly Excited About?
My laboratory is working on generating clinical-grade iPS cells and establishing evaluation methods to decide the best origin and the best generation method to improve production of such iPS cells.

Disclosures
None.

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Shinya Yamanaka: Purveyor of Pluripotency
Ruth Williams

Circ Res. 2013;112:233-235; originally published online December 10, 2012;
doi: 10.1161/CIRCRESAHA.112.281105
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/112/2/233

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