AN INTERVIEW WITH...

Shinya Yamanaka

The 2010 March of Dimes Prize in Developmental Biology has been awarded to Shinya Yamanaka of the Center for iPS Cell Research and Application (CiRA), Kyoto University, Japan, and the Gladstone Institute of Cardiovascular Disease in San Francisco, USA, for his work on reprogramming adult cells to form induced pluripotent stem (iPS) cells. The prize recognizes researchers whose work has contributed to our understanding of the science that underlies birth defects. Mary Muers talked to Shinya Yamanaka about his research career, the path to achieving reprogramming and his personal perspective on being a stem cell scientist.

Why did you decide to make the transition from medicine into laboratory research?
I was an orthopaedic surgeon many years ago, but I found that I was not talented, so I thought that I could not help many patients by doing surgery. Also, even a very good surgeon cannot help large numbers of patients. For those two reasons I decided to move to basic medical research instead of medical practice.

How did you become interested in stem cells?
Well, it is a long story. I got my Ph.D. in pharmacology, and during my training as a Ph.D. student I became very interested in knockout (KO)-mouse technology. So, after graduating I decided to continue my research instead of going back to the clinic. In order to learn the KO-mouse technology I decided to come to the United States and I became a postdoctoral fellow at the Gladstone Institute in San Francisco. That was how I came across embryonic stem (ES) cells, because we needed mouse ES cells to make KO mice. It was about 15 years ago and at that time ES cells were just a tool for making KO mice, not a research target. But, during my postdoctoral training I identified a new gene that I thought was important in cancer. In order to study the function of that gene I made KO mice and it turned out that the gene I was studying was very important for pluripotency in ES cells — so that's how I got interested in ES cells themselves.

What made you believe that you would be able to turn a somatic cell into a stem cell?
In 1996 Dolly the sheep was born and also, many years previously in 1962, John Gurdon had shown that adult frog cells can be reprogrammed. From those experiments we knew that it was possible to reprogram adult cells. There were also other important studies, including beautiful work in flies that identified a gene called *Antennapedia* (*Antp*). It is a kind of master regulator gene: if you express it in antennae, legs develop instead of antennae. *MyoD* was found to be similarly important in muscle. From those experiments we knew that transcription factors can change the fate of cells. But we were not sure whether we could reprogram cells by using transcription factors — I just thought we should try.

How did you choose which factors to try?
ES cells have factors that maintain their pluripotency during long-term culture. Therefore, I hypothesized that if we overexpressed those pluripotency maintenance factors in somatic cells, we might be able to induce pluripotency. Instead of trying to identify pluripotency inducing factors, we decided to search for pluripotency maintenance factors in ES cells.

When did you realize that you had achieved reprogramming?
We had generated an assay system by which we could convert reprogramming into drug resistance. Using that assay system we tested many candidate factors to see whether they could generate induced pluripotency. We had 24 candidate factors and of course in the beginning we tested each individual candidate. None of them worked — we did not see any reprogramming. But when we simply combined all of the 24 factors we got drug-resistant colonies.

At that time did you expect that your work would launch a new field of research?
We thought it would be very important, but at that time my brain was full of regenerative medicine, so I was thinking that this technology would be very helpful in regenerative medicine. Soon afterwards, I realized through talking to many other scientists that iPS cells will also be useful in drug discovery and toxicology. When we published that first paper in *Cell*, we did not anticipate this kind of excitement — it is more than we expected!

What will have been achieved in iPS cell research a year from now and 10 years from now?
A year from now I really expect that some applications in toxicology and drug discovery will be realized — they are just around the corner. Ten years from now? It is difficult to make predictions. We hope that we will be able to use these cells in regenerative medicine, but it is too early to say. There are many, many hurdles before clinical application of these cells. These cells are like babies: they have great potential but we cannot predict what will happen — like Tiger Woods when he was a baby! At the moment iPS cells are less safe that human ES cells, but many of the difficulties are just technical. I am really hoping that we can overcome the technical issues regarding safety and regarding efficacy in differentiation within a few years. So, I hope that 10 years from now we will be able to use these cells in stem cell therapy, but it is difficult to make a prediction.

iPS cells have had a lot of media attention. Does that put researchers under pressure?
I do sometimes feel pressures, not only from the media but also from patients. But in a sense it is good — although the competition is very tough on scientists I think it is very good for patients because it speeds up everything.

What advice would you give a young person interested in following a career in research?
I think you should be open-minded. We make a hypothesis and we do experiments to test that hypothesis, so when the results are against that hypothesis we naturally are very disappointed. But those results could offer the chance of a new discovery — this happened to me a few times. That is why science is so interesting and so much fun — it is unpredictable.