AUTHOR COMMENTARIES - 2009

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Shinya Yamanaka

Featured Scientist from *Essential Science Indicators*SM

Due to the recent reversal of stem cell research restrictions in the United States, stem cells are back in the news. According to Essential Science Indicators *from Thomson Reuters, the most-cited Hot Paper when searching on "stem cell*" is "Induction of pluripotent stem cells from adult human fibroblasts by defined factors" (Takahashi K,* et al., Cell *131[5]: 861-72, 30 November 2007), which accumulated 442 citations from its publication up to February 28, 2009.*

The chief researcher behind this paper is Dr. Shinya Yamanaka, who is the Director of the Center for iPS Cell Research and Application (CiRA), at the Institute for Integrated Cell-Material Sciences (iCeMS) at Kyoto University in Japan. Dr. Yamanaka's citation record in the field of Molecular Biology & Genetics includes 24 papers cited 2,274 times, and he has several other Highly Cited Papers in other fields of the database as well.

In this interview, ScienceWatch.com *talks with Dr. Yamanaka about the 2007* Cell *paper as well as a 2008* Nature Biotechnology *paper and their impact on the stem cell research field.*

SW: Would you tell us a bit about your educational background and research experiences?

I received my M.D. at Kobe University in 1987. After working as a resident in orthopedic surgery at National Osaka Hospital for two years, I decided to enter the path to live as a scientist and got a Ph.D. in medicine at Osaka City University in 1993. Soon I moved to the United States with my family to work as a postdoctoral fellow at the Gladstone Institute of Cardiovascular Disease, in San Francisco, CA. After returning to Japan in 1996, I worked as an assistant professor at Osaka City University School of Medicine and got an associate professor position at the Nara Institute of Science and Technology in 1999. In 2004, I landed a professorship at Kyoto University.

SW: How did you get involved in stem cell research?

When I was working as a postdoc at the Gladstone Institute of Cardiovascular Disease, one of my purposes there was to master techniques to generate knockout and transgenic mice. Embryonic stem cells became a research material for me to make those mice. While making a transgenic mouse that showed high expression of APOBEC1 protein in its liver, I found that liver cancer occurred. Analysis of the cancer led me to the discovery of a new gene, NAT1, which I found is

essential to embyrogenesis and differentiation potential of mouse embryonic stem cells. I became fascinated by embryonic stem cell research thanks to this experience. When I had my lab at the Nara Institute of Science and Technology, I decided to make embryonic stem cells my lab's main research theme.

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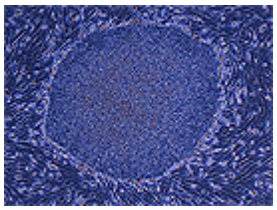

Human induced pluripotent stem cell.

Photo courtesy of Dr. Shinya Yamanaka, Kyoto University.

SW: Your team's November 2007 *Cell* paper, "Induction of pluripotent stem cells from adult human fibroblasts by defined factors," is the most-cited Hot Paper on the subject of stem cells. Would you talk a little about this paper—its goals and findings?

In August 2006, we reported in *Cell* that our lab generated ES-like cells by introducing four genes—Oct 3/4, Sox2, Klf4, and c-Myc—into mouse fibroblast cells (Takahashi K, Yamanaka S, "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors," *Cell* 126[4]: 663-76, 25 August 2006). We named the cells "induced pluripotent stem cells" (iPS cells). The next thing we were trying to achieve was, needless to say, the reprogramming of human differentiated cells.

The 2007 *Cell* paper describes how we generated human iPS cells. We added one procedure—lentiviral transduction of ecotropic receptor of retrovirus before transduction of the same set of the four genes into adult skin cells by retrovirus. The procedure improved the efficiency of retroviral transduction and secured the safety of researchers actually conducting the induction procedure. We successfully demonstrated that human iPS cells were similar to ES cells in terms of many aspects, including morphology, proliferation, gene expression, and teratoma formation. We also showed that the iPS cells differentiated into functional cells such as neurons and cardiac cells. Thus, the putative set of the four reprogramming factors was shown to be effective in human cells.

SW: Another of your papers, the 2008 *Nature Biotechnology* paper, "Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts," (Nakagawa M, *et al*, 26[1]: 101-6, January 2008) is the most-cited Hot Paper on stem cells in all of 2008. Why do you think this paper is being cited so much so quickly?

We showed the effectiveness of the putative set of the four reprogramming factors in mouse and human fibroblasts in our two papers—one published in *Cell* in 2006 and the other in 2007. Considering tumorigenicity attributed to the c-Myc insertion in the host genome, we clearly demonstrated in the *Nature Biotechnology* paper that Myc-devoid iPS cells can be generated by a modified protocol. Moreover, the paper includes extensive comparison of reprogramming effects of Sox, Oct, Klf, and Myc family genes. The data may be thought-provoking to many stem cell biologists who have just started iPS research.

SW: What are the hoped-for (or already realized) applications for these pluripotent stem cells?

"Direct reprogramming technology easily provides new pluripotent stem cells without any ethical controversy."

The applications for iPS cells that I believe will be realized in a few years are disease model development, drug discovery, and toxicology. I also expect to make the iPS cell technology available in regenerative medicine, such as cell transplantation, when its safety is secured. I believe that iPS cell technology should be applied to *in-vitro* use first. In contrast, it will still require years of basic research before we can overcome various obstacles, such as tumor formation, and realize regenerative medicine. My main focus is to make my best efforts in order to bring the iPS cell technology to patients at the earliest possible moment.

SW: How much does the political climate affect your research, if at all?

Since I announced in November 2007 that my lab generated human iPS cells, the Japanese government and lawmakers have provided strong financial support to advance iPS cell research, probably because the iPS cell technology originated in Japan. I do not see that the political climate affects iPS cell research in Japan, unlike in the US, where the change of the administration from the Republican to the Democratic resulted in reversing the nation's policy on embryonic stem cell research.

SW: Where do you hope to take this research in the future?

Direct reprogramming technology easily provides new pluripotent stem cells without any ethical controversy. There are still technical issues in iPS cells, which I hope will be resolved soon. Although

vigorous examinations to confirm the safety of iPS cells, prior to clinical applications, are absolutely necessary, I believe that iPS cells will provide great benefits to patients through drug discovery and toxicology studies in the near future, and then through cell transplantation therapy in the long-term future.

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Shinya Yamanaka's current most-cited paper in *Essential Science Indicators*, with 632 cites:

Mitsui K, *et al*., "The homeoprotein Nanog is required for maintenance of pluripotency in mouse epiblast and ES cells," *Cell* 113(5): 631-42, 30 May 2003. Source: *Essential Science Indicators* from Thomson Reuters.

Additional Information:

Special Topic of Stem Cells

KEYWORDS: INDUCED PLURIPOTENT STEM CELLS, IPS, ADULT HUMAN FIBROBLASTS, DEFINED FACTORS, KNOCKOUT MIC, TRANSGENIC MICE, HUMAN DIFFERENTIATED CELLS, LENTIVIRAL TRANSDUCTION, OCT 3/4, SOX2, KLF4, C-MYC, REPROGRAMMING FACTORS, DISEASE MODEL DEVELOPMENT, DRUG DISCOVERY, TOXICOLOGY, CELL TRANSPLANTATION THERAPY.

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