WHAT'S HOT IN... BIOLOGY , July/August 2008

Three Teams Reprogram Adult Cells for Pluripotency

by Jeremy Cherfas

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Sometimes one just has to wait. A media outpouring greeted the publication in June 2007 of three papers that showed how adult skin cells can be turned into pluripotent stem cells, capable of becoming any sort of cell. Now, a year later, the judgement of the authors' peers agrees with that of the press, and the results appear in the Top Ten list. Or rather, some of them do.

The two papers published back to back in *Nature*, from Shinya Yamanaka's group at Kyoto University and from Rudolf Jaenisch's group at the Whitehead Institute, MIT, are there at #5 and #7. The third, published in the inaugural issue of a new journal, *Cell Stem Cell* (N. Maherali, *et al.*, 1(1): 55-70, July 2007), is not, as its 28 citations during January-February 2008 were good enough to achieve Hot Paper status but not quite sufficient for the current Top Ten. Kathrin Plath at UCLA School of Medicine, one of two lead authors on that paper, tells *Science Watch*® that "it's too bad for us," and speculates that one reason for the slight lag in citations might be that *Cell Stem Cell*, being so new, was not included in PubMed's database until February 2008, just after *Science Watch*'s analysis for this issue. That might have made it harder for some researchers to cite.

Whatever the reason, all three groups discovered essentially the same thing: that inserting a small group of four genes into an adult skin cell "reprograms" that cell into something very like an embryonic stem cell. Of course, none of the papers actually goes as far as to call the reprogrammed cells "stem cells"—the media, including *Science Watch*, did that. But that is essentially what they are.

Biology Top Ten Papers

Rank	Papers	Cites Jan-Feb 08	Rank Nov-Dec 08
1	E. Bettelli, *et al.*, **"Reciprocal developmental pathways for the generation of pathogenic effector T_H17 and regulatory T cells,"** *Nature*, 441(7090): 235-8, 11 May 2006. [Harvard Med. Sch., Boston, MA] *040YP	69	1
2	The ENCODE Project Consortium (E. Birney, *et al.*), **"Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project,"** *Nature*, 447(7146): 799-816, 14 June 2007. [80 institutions worldwide] *178FV	49	4
3	M. Veldhoen, *et al.*, **"TGFß in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells,"** *Immunity*, 24(2): 179-89, February 2006. [MRC Natl. Inst. Med. Res., London, U.K.; Howard Hughes Med. Inst., U. Calif., San Francisco] *014KN	48	3
4	P.R. Mangan, *et al.*, **"Transforming growth factor-ß induces development of the T_H17 lineage,"** *Nature*, 441 (7090): 231-4, 11 May 2006. [U. Alabama, Birmingham; NIDCD, NIH, Bethesda, MD] *040YP	47	5

5	K. Okita, T. Ichisaka, S. Yamanaka, **"Generation of germline-competent induced pluripotent stem cells,"** *Nature*, 448(7151): 313-7, 19 July 2007. [Kyoto U., Japan; Japan Sci. Tech. Agency, Kawaguchi] *191GC	46	†
6	G.A. Tuskan, *et al.*, **"The genome of black cottonwood *Populus trichocarpa* (Torr. & Gray),"** *Science*, 313(5793): 1596-1604, 15 September 2006. [39 institutions worldwide] *083YS	42	†
7	M. Wernig, *et al.*, **"*In vitro* reprogramming of fibroblasts into a pluripotent ES-cell-like state,"** *Nature*, 448(7151): 318-24, 19 July 2007. [5 U.S. institutions] *191GC	40	†
8	N.J. Krogan, *et al.*, **"Global landscape of protein complexes in the yeast *Saccharomyces cerevisiae*,"** *Nature*, 440(7084): 637-43, 30 March 2006. [10 institutions worldwide] *026OY	39	†
9	A.-C. Gavin, *et al.*, **"Proteome survey reveals modularity of the yeast cell machinery,"** *Nature*, 440(7084): 631-6, 30 March 2006. [Cellzome AG, Heidelberg, Germany; EMBL, Heidelberg; MPI-MG, Berlin, Germany; Austrian Acad. Sci., Vienna] *026OY	37	†
10	M. Komatsu, *et al.*, **"Loss of autophagy in the central nervous system causes neurodegeneration in mice,"** *Nature*, 441(7095): 880-4, 15 June 2006. [Tokyo Metro. Inst. Med. Sci., Japan; Juntendo U. Sch. Med., Tokyo; Osaka U. Grad. Sch. Med., Japan] *052SL	36	†

SOURCE: Thomson Scientific's Hot Papers Database. Read the Legend.

The stiffest test for pluripotency is that the cells should be capable of forming the germline cells that give rise to future generations. All three groups passed. By injecting the induced pluripotent stem (iPS) cells into early-stage blastocysts, the researchers generated adult mice that included cells derived from iPS cells in all their tissues, including germline cells. Mating these chimeric mice with normal mice produced embryos in which all cells were produced from iPS cells and, for Yamanaka's group, live offspring.

The reprogramming to produce iPS cells really does seem to be complete. For example, normal female cells inactivate one of the two X chromosomes. Pluripotent cells from Plath and Konrad Hochedlinger's team reactivate the silenced X chromosome and then randomly silence one of them when they differentiate.

The reason for the interest in iPS cells is not hard to fathom. Stem cells offer the potential for many different kinds of therapy, replacing damaged or defective tissues. With research on embryonic stem cells severely curtailed, especially in the United States, any improvement in the ability to generate pluripotent cells from non-embryonic tissue is bound to attract attention. Furthermore, the ability to make stem cells specific to an individual patient makes these cells even more useful as replacements. Until the publication of these three papers, the preferred approach was to insert an adult nucleus into a fertilized egg. Somatic cell nuclear transfer (SCNT) gave rise to Dolly the cloned sheep and brought down Woo Suk Hwang in South Korea, after he fraudulently claimed to have created human stem cells this way.

The SCNT approach is still being pursued, but induction of pluripotency now seems to be in greater favor. Of course, problems remain. One of the genes inserted into the skin cells to reprogram them was c-Myc, a known oncogene. Yamanaka reported that around 20% of the offspring derived from iPS cells developed tumors, which would not be acceptable in therapeutic use. Yamanaka then reported a modified protocol for inducing pluripotency that not only avoided the tumorigenicity associated with c-Myc but also resulted in the generation of a higher percentage of iPS cells (see M. Nakagawa, *et al.*, *Nature Biotech.*, 26(1): 101-6, January 2008; DOI: 10.1038/nbt 1374). At the same time Yamanaka and a group led by James Thomson at the University of Wisconsin passed another milestone by using the same sort of technique to induce human skin cells to become pluripotent. Other types of adult cell followed in turn.

A separate hurdle is that these early studies use a retrovirus to insert the reprogramming genes into the adult cells. This method inserts the genes more or less at random into the DNA, which could result in the disruption of essential functions. This, in addition to the use of c-Myc, could have been responsible for some of the tumors seen. Many groups are working on more benign viral vectors and some are even trying to avoid the need to insert the actual genes, preferring to concentrate on the signals those genes are producing.

The clinical importance of being able to create stem cells from a patient's own cells cannot be overstated,

one reason progress has been so rapid. The big breakthroughs will undoubtedly figure here in *Science Watch*, and eventually in practical medicine. One just has to wait.

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Keywords: stem cells, pluripotency, ES-like stem cells, Shinya Yamanaka, Rudolf Jaenisch, Kathrin Plath, reprogramming cells, induced pluripotent stem cells, iPS.

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