NEW HOT PAPERS - 2009

November 2009

PDF

Hans R. Schöler talks with *ScienceWatch.com* and answers a few questions about this month's New Hot Paper in the field of Clinical Medicine. The author has also sent along an image of his work.

Photo: MPI Muenster/Sarah Eick

Article Title: Pluripotent stem cells induced from adult neural stem cells by reprogramming with two factors

Authors: Kim, JB;Zaehres, H;Wu, GM;Gentile, L;Ko, K;Sebastiano, V;Arauzo-Bravo, MJ;Ruau, D;Han, DW;Zenke, M;Scholer, HR

Journal: NATURE, Volume: 454, Issue: 7204, Page: 646-U54, Year: JUL 31 2008

* Max Planck Inst Mol Biomed, Dept Cell & Dev Biol, Rontgenstr 20, D-48149 Munster, Germany.
* Max Planck Inst Mol Biomed, Dept Cell & Dev Biol, D-48149 Munster, Germany.
* Univ Aachen, Sch Med, Rhein Westfal TH Aachen, Inst Biomed Engn, Dept Cell Biol, D-52074 Aachen, Germany.

SW: Why do you think your paper is highly cited?

Tremendous debate has arisen in both the scientific community and the general public over the past decade regarding the derivation and use of human embryonic stem cells. Though the derivation of human embryonic stem cells is fraught with ethical considerations, the potential application of these cells in areas such as regenerative medicine, for example, may lead to curative therapies and thus holds immense clinical utility.

The discovery of induced pluripotent stem ("iPS") cells, first in mice and then in humans, has opened up new avenues for generating pluripotent cells from the somatic cells of individual patients, thereby obviating ethical concerns.

Originally, iPS cells were generated via the retroviral gene transfer of the four transcription factors: Oct4, Sox2, Klf4, and c-Myc. However, as Klf4 and c-Myc are well-known oncogenes, the iPS cells generated by and expressing these factors were not of clinical use.

Our paper was the first demonstration of reducing this cocktail to the two factors Oct4 and Klf4, making iPS generation not only easier in the lab, but also potentially safer in the clinic.

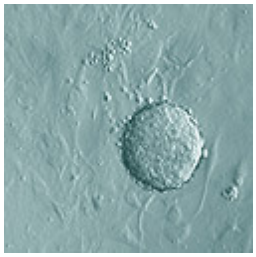
The iPS cells generated were similar to embryonic stem cells, as judged by molecular and developmental properties, including their ability to contribute to development of the germline and to form chimeras. The success of this work lies in the ability to complement already existing factors. The somatic cells used in our study express higher endogenous levels of two of the above transcription factors—Sox2 and c-Myc—and thus the addition of Oct4 and Klf4 completed the necessary quartet.

With this paper, we are the first lab to prove the hypothesis that the

number of exogenously added reprogramming factors can be reduced when using somatic cells that express appropriate endogenous levels of the complementing, or remaining, reprogramming factors. Further work may see the use of small-molecule compounds in lieu of gene transfer to induce the endogenous expression of these factors.

Finally, since we used adult neural stem cells as the starting somatic cell population, we are also the first lab to generate iPS cells from adult stem cells, thereby combining adult, embryonic, and iPS cell research in one report.

[+] enlarge



Colony of iPS cells that originate from reprogramming of neural stem cells with two factors.

Photo: "MPI Muenster/ Jeong Beom Kim"

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

The genetic complementation of endogenous factors with exogenous factors to generate iPS cells can be considered a new discovery in the field of cellular reprogramming. By reducing the number of exogenous factors needed to successfully generate iPS cells, we have simplified the gene transfer methodology, while, at the same time, rendering the generated iPS cells potentially safer.

SW: Would you summarize the significance of your paper in layman's terms?

The generation of pluripotent stem cells ("allrounder") from somatic cells from each individual patient is feasible with the addition of just two factors. Subsequent work, which we have published in *Cell* and *Nature* this year, narrows down the factors even further.

In the latter we show direct reprogramming of human neural stem cells by Oct4. Thus we know now that the transcription factor Oct4 alone can do the job in both mice and humans. Just think about it for a moment: just one factor can turn a somatic stem cell into cell that can give rise to every cell within our body. Oct4 is the earliest expressed gene known to encode a transcription factor which is developmentally regulated during mammalian embryogenesis.

SW: How did you become involved in this research, and were there any problems along the way?

Our lab has had a long-standing interest in reprogramming research. We have looked at methods to induce pluripotency in the mouse system using somatic cell nuclear transfer and cell fusion. A key ingredient in this work has been the development of a reliable reprogramming marker system consisting of an Oct4 promoter–GFP transgene.

But it all started 20 years ago, when I described and cloned the transcription factor Oct-4, which we associated with cellular pluripotency. The scientific community at that time speculated that a cocktail of "reprogramming" factors might be applied to somatic cells in an effort to induce pluripotency. Shinya Yamanaka was the first scientist to conclusively bring this idea to fruition in the mouse system (Takahashi K, Yamanaka S, "Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors," *Cell* 126[4]: 663-76, Aug 25, 2006).

Since that discovery, we have accomplished three major feats that have allowed us to undertake our study. We have developed the technologies to cultivate neural stem cells and to transfer the transcription factors into somatic cells as well as the methodology to compare the generated iPS cells at the molecular and developmental levels to embryonic stem cells.

SW: Where do you see your research leading in the future?

The direct reprogramming of almost any type of somatic cell using gene transfer is now readily feasible in the lab. The replacement of gene transfer technology with recombinant proteins and/or small molecules is now possible, but with very low efficiency. The routine use of these new technologies to develop iPS cells would be a huge step forward.

For example, patient-specific iPS cells and cells derived from them would be of great value in drug discovery and toxicology studies. The ultimate goal is to enable the safe and effective use of iPS-derived cells in cell transplantation therapy. However, many hurdles must be overcome before the clinical utility of iPS cells comes to pass.

SW: Do you foresee any social or political implications for your research?

Intense debate on human embryonic stem cell research continues in my home country of Germany and in the USA, where I had my lab for five years. Personally, I feel a sense of relief since these alternate

cells—induced pluripotent stem cells—have been developed and are now on the market.

Although human embryonic stem cells are still the gold standard of pluripotent cells, clinical applications with pluripotent stem cells may be more easily achieved with iPS cells. Well, we will see.

Professor Dr. Hans Schöler
Department Cell and Developmental Biology Director
Max Planck Institute for Molecular Biomedicine
Münster, Germany
Web

KEYWORDS: HUMAN SOMATIC-CELLS; HUMAN FIBROBLASTS; DEFINED FACTORS; EXPRESSION; MOUSE; GENERATION; ONCOGENE; GENES; SOX2; P53.

PDF

back to top

2009 : November 2009 - New Hot Papers : Hans R. Schöler on Pluripotent Stem Cells

Science Home | About Thomson Reuters | Site Search