

**iPSCs Brief: Good Science, Good Morals. Spread the Word!**

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Culture of Life Fellow in Ethics, Dr. Christian Brugger, explains the development, process, ethics and scientific contributions of Induced Pluripotent State Stem Cells.

When news broke last November that adult skin cells had been reprogrammed into pluripotent stem cells a doubt was born. Embryonic-like stem cells (iPSCs) without killing embryos? Does this portend the end of embryo-destructive experimentation? Op eds flirted favorably with the idea. Scientists even came clean about long-standing doubts with killing embryos. As Chinese medicine says, ‘good wind’ was blowing. On day three the push-back came. An explosion of editorials insisting that embryo-destructive experimentation was necessary. It must continue! It WILL continue! Both methods would progress side by side. And so on. But the doubt was born.

The news of iPSCs is to the defense of the embryo what an opening on the Supreme Court would be to the defense of the fetus: a tremendous opportunity. Whether the scientific community will capitalize on the opportunity and avert the cultural catastrophe of federal funded human embryo cultivation and destruction is yet to be seen.

It is instructive to review the extraordinary events of the last few months. Two teams of scientists, one led by James Thomson<sup>[i]</sup> at the University of Wisconsin, Madison, and one by Shinya Yamanaka<sup>[ii]</sup> at the University of Kyoto in Tokyo, simultaneously published papers showing that human fibroblasts (skin cells) could be coaxed back to a state of pluripotency if injected with a complex of four genes. What does “coaxed back to a state of pluripotency” mean?

There are over 200 types of cells in the human body (e.g., liver, skin, cardiac, neural, etc.). Contrary to what one might think cell types are not distinguished by their genomes (i.e., differences in their DNA sequences). With little exception, all the cell types in the human body possess an identical DNA sequence. This sequence is divided into approximately 35,000 genes each of which potentially codes for a biological characteristic of the organism. But not all the genes in a cell are turned on. In any given cell, only 1/3 of the genes are active, the rest are silenced. This is what accounts for differences in cell types. Cell identity is determined by which genes are active and which are silenced. This pattern of gene expression (the on-off sequence) is called the cell’s epigenetic state. So the biological identity of a cell is determined by its epigenetic state.

Epigenetics is also associated with cell potency. Potency refers to the cell’s capacity for differentiation and development. Skin cells are highly specialized cells capable of differentiating into a single cell type—their own. But a pluripotent stem-cell is



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able to differentiate and develop into most all the cell types of the human body. The undifferentiated epigenetic state of pluripotency then is developmentally prior to the highly specialized state of a skin cell. The extraordinary breakthrough of the Wisconsin and Tokyo teams was to show that a cell, whose epigenetic state had been fixed for a single type of cell proliferation, could be reprogrammed back to the undifferentiated state of pluripotency. One commentator likened it to “hitting rewind”.<sup>[iii]</sup>

The teams harvested adult skin cells, called fibroblasts, and cultured them in vitro. Four genes were then introduced into the cultured skin cells using a retrovirus delivery system. After several weeks in culture, colonies of embryonic-like stem cells formed. When tested they behaved almost identically to embryonic stem cells in culture. The four genes had apparently worked together to re-program the epigenetic state of the cell from the highly specialized state of a fibroblast back to the undifferentiated state of a pluripotent stem cell. The clinical promise was immediately evident. Patients donating their own fibroblasts, and having them reprogrammed back to a state of pluripotency, would have a ready supply of genetically matching stem cells—“patient specific”—avoiding all problems with tissue rejection. Most extraordinary of all, it was accomplished without the need for a single embryo.

Some problems existed with the early procedures. One of the four genes used to carry out the reprogramming, c-MYC, together with the retroviral delivery system both were known potentially to cause cancer in patients after transplantation. Experts said the problems would rapidly be overcome. And within weeks of the November publications, Yamanaka published a second paper illustrating that the problematic c-MYC gene could be eliminated and reprogramming successfully carried out using only three genes, although with reduced efficiency.<sup>[iv]</sup> But even the efficiency problems are being overcome. The Yamanaka and Thomson procedures are being picked up by other labs and efficient iPS cell production is beginning without c-MYC. Testing also suggests that the use of retroviral gene delivery systems may not be a problem. Labs are finding that the virus can be removed after iPS cells are made and that normal cells are retained with no mutations. Most recently, a study was published (again by the Yamanaka lab) suggesting that iPS cells could be generated without using retroviral integration at all.<sup>[v]</sup>

The science is rapidly advancing on this ethically acceptable solution to the problem of embryo destructive experimentation. For those who have ears to hear, let them hear: an opportunity has presented itself which could pass by if we don't take advantage of it. *Spread the word.*

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<sup>[i]</sup> Yu, J. et al. “Induced pluripotent stem cell lines derived from human somatic cells,” *Science* advance online publication 20 November 2007. doi: 10.1126/science.1151526 | [Article](#)

<sup>[ii]</sup> Takahashi K. et al. “Induction of pluripotent stem cells from adult human



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[\[iv\]](#)Nakagawa, M. et al. “Generation of induced pluripotent stem cells without Myc from mouse and human fibroblasts,” *Nat. Biotechnol.* Advance online publication 30 November 2007. doi: 10.1038/nbt1374 | [Article](#)

[\[v\]](#)Aoi, Takashi et al. “Generation of Pluripotent Stem Cells from Adult Mouse Liver and Stomach Cells,”

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