# A Triumph for Ethical Stem-Cell Research

## Nobel Prize Winner Finds Another Way

by E. Christian Brugger

The field of ethically legitimate stem-cell research got a boost on Oct. 8, when the Nobel Assembly in Sweden announced that its coveted prize in physiology or medicine would go to Japanese researcher Shinya Yamanaka. Yamanaka transformed the field of stem-cell research and regenerative medicine in 2006-2007, when he published a series of groundbreaking papers demonstrating that mature differentiated (mammalian) cells, such as skin cells, could be "reprogrammed" to become pluripotent stem cells. He first demonstrated the process using mouse cells and later using human cells. "Pluripotency" refers to the capacity of an immature cell to develop into specialized cell types. Before it develops into a mature cell, such as a blood cell, cardiac cell or neural cell, a cell exists in an undifferentiated state. This unspecialized cell is called a "stem cell." It's like a blank slate waiting to be drawn upon or a lump of clay awaiting a form.

If the stem cell is capable of taking the form of (or developing into) all cell types in the body, it is called pluripotent. If it is capable of becoming only the kind of cell in a single family of cells (e.g., those found in the heart), it is multipotent. If its capacity is limited to a single cell type, it is unipotent. A cell's type (also called its "fate") is determined by genes. A single gene is like a line out of an instruction manual. The sum total of one's genes ("genome") constitutes the whole manual. Genes provide instructions for making, operating and repairing all the parts of the human body, so genes direct the undifferentiated stem cell towards its particular cell fate. Genes are also responsible for preserving the state of pluripotency.

### Era of Stem-Cell Research

The era of stem-cell research was launched in 1981, when pluripotent stem cells were first isolated from mouse embryos and cultivated in the laboratory by British researcher Martin Evans. The scientific community recognized at once the enormous potential that this newfound ability to isolate, multiply and store pluripotent stem cells promised for medicine and research with humans. But an ethical hurdle stood in the way: To exploit the potential, human embryos — lots of them — would need to be created and lethally experimented upon. In 1998, the first successful isolation of human embryonic stem cells (hESCs) was reported by a lab at the University of Wisconsin-Madison. The Promethean allure of "miraculous cures" prompted many in the scientific community to become comfortable with the morally repugnant research.

### Yamanaka: Trailblazer

Shinya Yamanaka apparently was not one of them. I do not know if he himself ever performed embryo-destructive research. Nor do I know if he ever used tissue cultures derived from aborted babies when other non-tainted tissues were available. Both of these are morally unacceptable. But Yamanaka certainly made clear to the world that he was resolute on finding an alternative to embryo-destructive research. He famously told *The New York Times* in 2007: "When I saw the embryo, I suddenly realized there was such a small difference between it and my daughters. I thought, "*We can't keep destroying embryos for our research. There must be another way*."

Yamanaka asked what genes were responsible for preserving the state of pluripotency (i.e., by what genetic mechanism does a pluripotent stem cell remain pluripotent?). If he could identify the genes responsible, he thought, he might be able to introduce the same genes into the genome of a differentiated somatic cell, such as a skin cell, and thus prompt the cell — literally "reprogram" it — to a state of pluripotency. In 2007, Yamanaka's dream of producing pluripotent stem cells from mature body cells without the need for human embryos became a reality. The four genes he identified acted as "reprogramming factors" de-differentiating the mature cell back to a condition of developmental immaturity — to a state of pluripotency. These induced pluripotent stem cells (iPSCs) were proof of the principle that cells could be directly reprogrammed.

Yamanaka's pioneering discovery opened a new branch of stem-cell research almost overnight — just as the scientific community was waking up to the fact that hESCs may never produce the miracle cures that some had hoped for and the media so irresponsibly and uncritically hyped. Some of the most prominent cell biologists in the world, including Ian Wilmut (who cloned Dolly the sheep) and James Thomson (who first isolated hESCs in 1998 at the University of Wisconsin), have announced they are going over to iPSC research as a preferred method of

creating pluripotent stem cells. Even the California Institute for Regenerative Medicine (CIRM), created in 2004 to funnel $3 billion of taxpayer money into embryo-destructive stem-cell research, has begun awarding grants for iPSC research and the banking of iPS cells.

### Future of Stem-Cell Research

The choice for Yamanaka is not, to be sure, the Nobel Foundation's way of giving a thumbs-up to ethical stem-cell research, at least not intentionally. To ensure that nobody mistook its motivations, Nobel jointly awarded the 2012 prize to an elderly British cloning scientist named John Gurdon, who pioneered the cloning process known as somatic cell nuclear transfer. Gurdon is a resolute defender of embryo-destructive research (see J. B. Gurdon and J. A. Byrne, "*The First Half Century of Nuclear Transplantation*," Proceedings of the National Academy of Sciences, July 8, 2003, Vol. 100, No. 14, 8051). Nevertheless, Yamanaka's prestigious award is indeed a triumph for ethical research.

Since 2007, I have been asked many times whether the discovery of induced pluripotent stem cells has spelled the demise of embryonic stem-cell research. After all, if we no longer need to destroy human embryos to create pluripotent stem cells, why keep doing it? When the question is put to secular scientists, the official reply is: "We need both types of stem cells: induced pluripotent stem cells and embryonic stem cells (ESCs]; both promise benefits." And yet, because of the undeniable disappointment of ESC research, fewer scientists are taking it up, and fewer grant dollars are being spent on it. *Scientific American*, lamenting the "disappointment," opined in 2009: "Practicable ESC-based therapies are years away."

### Can They Be Misused?

Most any science can be used wrongly, especially if it's used in ways that harm or destroy human life. But since the production of pluripotent stem cells from somatic cells by reprogramming need not involve bringing into existence, experimenting upon or destroying human embryos, iPSC research in itself seems to me to be morally unproblematic. Having said this, iPSCs have not yet yielded any clinical benefits. Because of the concern with cancer causation and tumor formation, the cells are not ready to be used to treat human diseases. Using them prematurely, therefore, and subjecting patients to disproportionate risks of harm would be unethical. Moreover, if researchers tried to use direct cellular reprogramming (the process used to make iPSCs) to produce human embryos, that is, if, rather than create pluripotent cells, they tried to create "totipotent" cells (e.g., cells such as the human zygote with a complete capacity for organismic development), then it would be just another type of unethical embryo-exploitative research.

Reprogramming would also be unethical if it were used to create female or male gametes (eggs or sperm cells) with the intent of using them for assisted reproduction in humans. In fact, a milestone towards this dubious goal was announced on Oct. 4, when Japanese researchers published an article in the journal Science saying that they'd successfully transformed (mouse) iPSCs into viable mouse oocytes (eggs) and then used the eggs to produce healthy, fertile mouse pups.

### Adult Stem-Cell Research

Thus far in the field of stem-cell research, only adult stem cells (ASCs) have yielded clinical benefits. The headline of a *USA Today* article in 2010 read: "Adult stem-cell research far ahead of embryonic." This is no exaggeration. Tens of thousands of successful treatments with ASCs are performed each year. To date, none have been performed using ESCs. *The Journal of the American Medical Association* reported in 2010 that in one year (2006) more than 50,000 transplants were performed around the world using ASCs obtained from bone marrow, peripheral blood and umbilical cord blood. Catholic News Agency reported recently that since investors are increasingly demanding results and not just hype, they are shifting their money towards ASC research.



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