"As to diseases ,make a habit of two things —
to help, or at least *do no harm*."
— Hippocrates, *The Epidemics* —

DO NO HARM
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Q & A
INDUCED PLURIPOTENT STEM CELLS:
MAKING EMBRYONIC STEM CELLS OBSOLETE

Q: What are induced pluripotent stem cells?

A: Induced pluripotent stem cells (iPSCs) are cells that possess the same pluripotent characteristics of embryonic stem cells; however, they are not obtained from embryos, nor using eggs or cloning.

Q: If they are not obtained from embryos, where do they come from?

A: Induced pluripotent stem cells are obtained by taking an ordinary somatic (body) cell, such as a skin cell, and reprogramming it to an embryonic-like pluripotent state; the somatic cell is *induced* to become a pluripotent cell, much like a computer is reprogrammed to run a different program.

Q: Must embryos be destroyed in order to obtain iPS cells?

A: Embryos DO NOT need to be destroyed in order to obtain iPS cells.

Q: Why is this development so important to the stem cell debate?

A: From the outset, the ability to reprogram ordinary body cells back to an embryonic-like undifferentiated, pluripotent state had been considered the "holy grail" of stem cell research. That is because the ability to reprogram ordinary body cells provides researchers an almost limitless supply of readily obtainable pluripotent stem cells in an ethically acceptable and non-contentious way.

Q: How do scientists view the iPS cell breakthrough in terms of the current debate over human embryonic stem cell research and human cloning?

A: The ability to reprogram ordinary body cells to a pluripotent state is considered one of the major scientific advances of recent times. Many scientists all over the world have strongly suggested that this advance should end the current debate over the use of stem cells derived from the destruction of human embryos, and that iPS cells represent the future of regenerative medicine, with human embryonic stem cells now becoming obsolete:

James Thomson, author of one of the 2 papers describing the human iPS cell technique:

- "The human iPS cells described here meet the defining criteria that we originally proposed for human ES cells, with the notable exception that the iPS cells are not derived from embryos. Similar to human ES cells, human iPS cells should prove useful for studying the development and function of human tissues, for discovering and testing new drugs, and for transplantation medicine. For transplantation therapies based on these cells, with the exception of autoimmune diseases, patient-specific iPS cell lines should largely eliminate the concern of immune rejection." (*Science*, 21 December 2007).

- "The world has changed…It is the beginning of the end of the controversy that has surrounded this field…Over time, these [induced pluripotent stem] cells will be used in more and more labs. And human embryo stem cell research will be abandoned by more and more labs." (*Boston Globe* 11/21/07)

- "The induced cells do all the things embryonic stem cells do. It's going to completely change the field. ….They are probably more clinically relevant than embryonic stem cells." (Medical News Today, 11/26/07).

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Ian Wilmut, cloning pioneer and creator of Dolly the sheep:

- "The fact that introduction of a small number of proteins into adult human cells could produce cells that are equivalent to embryo stem cells takes us into an entirely new era of stem cell biology." (*The Scotsman*,1/21/07).
- "[Reprogramming is] 100 times more interesting [than cloning]…I have no doubt that in the long term, direct reprogramming will be more productive" *The [London] Telegraph* 11/10/08).

Sir Martin Evans, British stem cell researcher and 2007 Nobel Laureate for Medicine:

- "This is going to be the way forward. …We've all been waiting for this" (*Wall Street Journal* 11/21/07).

Monash University Professor Richard Boyd, one of Australia's leading stem cell experts:

- "There is a definite move now towards this new [iPS] area which is potentially so much easier and free of the ethical stresses that surround classical embryonic stem cell research… By comparison with the classical embryonic stem cell process, which requires us to use thousands of eggs, this is much more efficient, technically much easier and it solves some of those more emotional dilemmas" (*The Sydney Morning Herald*, 11/21/07)

Q: In what ways are iPS cells preferable to human embryonic stem cells?

A:

- Embryos DO NOT need to be destroyed to obtain iPS cells, thus overcoming the ethical problems associated with embryonic stem cells.
- The process of obtaining iPS cells is relatively easy; the process of deriving stem cells from the destruction of embryos is far more difficult.
- The process of obtaining iPS cells is quite efficient, giving researchers a ready supply of pluripotent stem cells; the process of obtaining human embryonic stem cells is highly inefficient, requiring the destruction of numerous embryos just to obtain one stem cell line.
- Because the iPS cells originate from a patient's own body cell, the induced stem cells are specific to and genetically identical to that patient.

Q: What about human cloning? Are iPS cells preferable to obtaining stem cells from human cloning?

A: They are preferable in one very real way: iPS cells exist now*, while human cloning has not yet been successful, so obtaining stem cells from human cloning remains only a theoretical possibility.*

Beyond this fact iPS cells are preferable to cloning, on both ethical and practical grounds, to obtain patient specific stem cells because:

- iPS cells are patient specific, but they avoid the ethical problems associated with cloning human embryos and destroying them for their stem cells.

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- No eggs are needed to obtain iPS cells; to be practical, human cloning would require eggs on an enormous scale, leading to the exploitation of women and presenting them with very real medical risks associated with hyperovulation.

- Realizing the superiority of iPS cells, Ian Wilmut, the first scientist to clone a mammal, Dolly the sheep, has abandoned cloning to pursue iPS cell research. According to Prof. Wilmut, "changing cells from a patient directly into stem cells has got so much more potential," and "in the long term, direct reprogramming will be more productive."

Q: But wasn't human embryonic stem cell research instrumental in achieving the iPS cell breakthrough? If we stop hESC and human cloning, wouldn't we be putting the possibility of future breakthroughs at risk?

A: No. Human embryonic stem cell research had nothing to do with the iPS cell breakthrough.

Japan's Shinya Yamanaka is the scientist credited with the original iPSC breakthrough and one of two scientists to develop human iPSC (the other being James Thomson of the University of Wisconsin, who was also the first to isolate human embryonic stem cells). Both scientists worked independently and published their results in November, 2007

- According to Yamanaka, human embryonic stem cells (hESCs) were ***not*** crucial to his work. Yamanaka's initial work in reprogramming utilized mice, not human, embryonic stem cells and he used the same method for human iPSC production. According to him, "Neither eggs nor embryos are necessary. ***I've never worked with either***" (*Nature*, June 7 2007, p 618, emphasis added).

- In fact, it was precisely Yamanaka's ethical concerns to *avoid* lethal experiments with human embryos that led to his breakthrough. Recalling looking at a human embryo through a microscope several years earlier, Yamanaka said: "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''*** ("Risk Taking in His Genes;" *The New York Times*, 12/11/07).

Q: Aren't certain viruses, and genes associated with cancer in humans, used in creating iPS cells, thus making them unsuitable for use in patients?

A: The original reports of reprogramming did use certain viral vectors, as well as a gene associated with cancer in humans. However, rapid advances in reprogramming have shown that iPS cells can be created without the use of dangerous viruses, even without the use of any viruses, and also without the use of any cancer-causing genes.

Q: Do we know that iPS cells are really the equal to human embryonic stem cells?

A: James Thomson, author of one of the 2 papers first describing the iPS cell procedure, and the first to isolate human embryonic stem cells, has said that iPS cells "meet the defining criteria" of embryonic stem cells, but "with the significant exception that the iPS cells are not derived from embryos."

Q: But shouldn't researchers continue to pursue all types of stem cell research, including human embryonic stem cell research and cloning?

A: In September, 1999, then-President Clinton's bioethics commission was the first to call for federal funding of human embryonic stem cell research. However, realizing the moral problems associated with such research, it laid down the following condition:

- ***"In our judgment, the derivation of stem cells from embryos remaining following infertility treatments is justifiable only if no less morally problematic alternatives are available for advancing the research***…

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> The claim that there are alternatives to using stem cells derived from embryos is not, at the present time, supported scientifically***. We recognize, however, that this is a matter that must be revisited continually as science advances.***" (National Bioethics Advisory Commission, *Ethical Issues in Human Stem Cell Research* (Sept. 1999), Volume I, p. 53 (emphasis added).

That was 10 years ago. The iPS cell breakthrough (along with the many advances using adult stem cells to treat patients) clearly provides the less morally problematic alternative for advancing the research."

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