Science

The Scientific Context for the President's Stem Cell Order: iPS Cells

On Monday, March 9, 2009, President Barack Obama signed an executive order that not only overturned his predecessor's funding restrictions for embryonic stem cell research but also rescinded the Bush initiative that explicitly mandated federal funding for alternative methods of stem cell research that would avoid the destruction of human embryos (Executive Order 13435 of June 20, 2007). Ironically, the Jaenisch Laboratory at the Massachusetts Institute of Technology reported—*just one week before President Obama signed his executive order!*—that they had invented a safe way to create patient-specific iPS cells that brings this technology one step closer to human clinical trials (Frank Soldner et al., "Parkinson's Disease Patient-Derived Induced Pluripotent Stem Cells Free of Viral Reprogramming Factors," *Cell*, March 6, 2009). The researchers used viruses to introduce the four Yamanaka reprogramming factors (Oct4, Sox2, Klf4, and c-Myc) into skin cells taken from patients with Parkinson's disease. After the cells were reprogrammed to iPS cells, they introduced an enzyme called Cre, which was able to delete the reprogramming genes in the cells. As a result, they were able to efficiently create virus-free iPS cells that are virtually identical to the cells of the patients with Parkinson's disease who had donated the original skin cells. Significantly, the iPS cells without the reprogramming genes had a pattern of gene expression that resembled the pattern of human embryonic stem cells. Finally, the reprogrammed iPS cells from patients with Parkinson's disease were differentiated into the dopamine-producing nerve cells that are lost in the disease. These cells could be used to study the biology of Parkinson's as well as to develop drugs to treat symptoms. Eventually, of course, they could be used to replace the nerve cells whose demise caused the disease.

The invention of virus-free iPS cells in the Jaenisch laboratory is only one—but probably the most important—of the handful papers published this past quarter that highlight the rapid advances in the field of nuclear reprogramming. Using other innovative techniques, Keisuke Kaji and his colleagues at the University of

Edinburgh show that it is possible to use a single DNA fragment called a vector to introduce the four Yamanaka reprogramming factors into mouse cells ("Virus-Free Induction of Pluripotency and Subsequent Excision of Reprogramming Factors," *Nature*, March 1, 2009). They demonstrate that the four genes can then be removed using a cut-and-paste molecular machinery. Finally, the team combined this technique with the use of a "jumping gene" called piggyBac to generate virus-free iPS cells. Andras Nagy and his colleagues at the Mount Sinai Hospital in Toronto took this technology one step further to create iPS cells from both human and mouse skins cell ("piggyBac Transposition Reprograms Fibroblasts to Induced Pluripotent Stem Cells, *Nature*, March 1, 2009). They also showed that the piggyBac method could be used to generate iPS cell lines in which different combinations of the reprogramming factors are removed individually, making lines that are potentially useful for drug discovery and research.

Jeong Beom Kim and his colleagues, working at the Max Planck Institute for Molecular Biomedicine in Germany, were able to generate iPS cells using a single reprogramming factor ("Oct4-Induced Pluripotency in Adult Neural Stem Cells," *Cell*, February 6, 2009). The research team selected a particular kind of cell—a neural stem cell—that already expressed three of the four Yamanaka genes, and introduced Oct4 into these cells. This one factor was able to generate pluripotent stem cells (one-factor, or 1F, iPS cells) that are similar to embryonic stem cells in vitro *and* in vivo. Though their experiments were done with mouse cells, it should be relatively easy to translate this discovery into the human system.

Next, in a paper published in *Stem Cells*, Cesar Sommer and his associates used a single DNA fragment, called a lentiviral vector, to introduce the four Yamanaka genes into skin cells to reprogram them ("Induced Pluripotent Stem Cell Generation Using a Single Lentiviral Stem Cell Cassette," March 2009). Though this advance would have been a significant discovery six months ago, it has been superseded by the papers described above. Nonetheless, Sommer's paper illustrates well the rapid rate of scientific discoveries that are being made in the iPS field.

In the end, President Obama claimed that his directive would promote embryonic stem cell research and retire words like "terminal" and "incurable" from our vocabulary by providing cures for life-threatening diseases. However, as these recent discoveries demonstrate, induced pluripotent stem (iPS) cell research has the same therapeutic potential without the moral controversy. Scientifically, therefore, the Obama executive order was unnecessary.

Finally, research on human–animal hybrid embryos created by inserting human cell nuclei into hollowed-out egg cells from animals has revealed that these chimeric embryos do not develop normally (Young Chung, "Reprogramming of Human Somatic Cells Using Human and Animal Oocytes," *Cloning and Stem Cells*, February 2009). These findings are not unexpected given what we know about the biology of these "cybrid" embryos: scientifically, it is difficult imagining how a human genome could regulate either a cow or a rabbit cell. Research with these hybrid embryos was approved last year in the United Kingdom despite bitter opposition, and it is surprising that the scientists who were pushing for the approval of this research protocol did not anticipate these scientific problems.

The Scientific Context for the President's Stem Cell Order: Adult Stem Cells

Several days after President Obama's inauguration, the Food and Drug Administration announced that they would allow the world's first clinical trial of a therapy derived from human embryonic stem cells by Geron, a biotechnology corporation in Menlo Park, California. Geron's trial will involve injecting neural support cells derived from embryonic stem cells into the injury sites of eight to ten patients with severe spinal cord injuries. The hope is that the injected cells will help repair the damaged spinal cord, restoring the ability of some nerve cells to transmit neuronal signals. Not surprisingly, the Food and Drug Administration's approval of the clinical trial generated worldwide attention in the mainstream media.

Characteristically, however, the media failed to mention several recent reports describing the use of adult stem cells to treat spinal cord injury. For example, a team from the Akay Hospital in Ankara, Turkey, report that they have used bone-marrow derived-blood stem cells to improve the movement and sensation of nine patients with spinal cord injury (Seung Hwan Yoon, "Treatment of Chronic Spinal Cord Injured Patients with Autologous Bone Marrow-Derived Hematopoietic Stem Cell Transplantation: One-Year Follow-Up," *Cytotherapy*, June 2008). Another research group from Australia used stem cells taken from the nose to treat patients suffering from paraplegia (A. Mackay-Sim et al., "Autologous Olfactory Ensheathing Cell Transplantation in Human Paraplegia: A Three-Year Clinical Trial," *Brain*, September 2008). Three years after the procedure, the small group of patients showed only minimal improvement, though it was significant that none of them had developed tumors from the implanted cells. Finally, Geffner and associates were able to use bone marrow stem cells to improve the quality of life of eight patients with spinal cord injuries ("Administration of Autologous Bone Marrow Stem Cells into Spinal Cord Injury Patients via Multiple Routes Is Safe and Improves Their Quality of Life: Comprehensive Case Studies," *Cell Transplantation*, December 2008). Significantly, the recipients of the adult stem cells reported improved bladder function. Though certainly not cures, these studies are evidence of the clinical use of adult stem cells to treat spinal cord injury and to improve the quality of life of patients with spinal cord injury.

Finally, a paper by N. Amariglio and colleagues reported that transplanted fetal stem cells had caused a tumor in a teenage boy ("Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telanglectasia Patient," *PLoS Medicine,* February 17, 2009). The publication of this paper made headlines around the world. A nine-year old boy with a crippling disease that had left him in a wheelchair received stem cells from at least two aborted fetuses directly into various regions of his brain. (It is unclear exactly what the doctors were trying to accomplish, especially since the authors of the case report were themselves not involved in the experimental trial.) Four years later, however, the then-teenager was diagnosed with a benign brain tumor, which clearly had developed from the fetal cells that had been injected into his skull. It is the first known case of a tumor caused by a brain stem cell therapy. The researchers conclude that their case study should serve as a warning for others who wish to use fetal stem cells without further studies to determine the safety of this novel therapy.

Assisted Reproductive Technology, In Vitro Fertilization, and the California Octuplets

On January 26, 2009, Nadya Suleman, a single mom living with her parents in Whittier, California, gave birth to eight babies—six boys and two girls—nine weeks prematurely at the Kaiser Permanente Bellflower Medical Center. It appears that the octuplets were conceived in the laboratory using in vitro fertilization (IVF) to fertilize their mother's eggs with a donor's sperm in a test tube. This extraordinary birth has sparked a moral controversy and has increased calls to regulate the assisted reproductive technology (ART) industry.

This past quarter, several papers were published that highlight ongoing research in ART. First, a research team at the University of Oulu in Finland has shown that implanting single embryos into a woman is more effective and less costly than implanting two embryos at a time (Zdravka Veleva, "Elective Single Embryo Transfer with Cryopreservation Improves the Outcome and Diminishes the Costs of IVF/ICSI," *Human Reproduction*, March 24, 2009). The study compared the outcomes of more than thirty-six hundred assisted reproduction cycles at a major Finnish clinic from 1995 to 1999 and from 2000 to 2004, and revealed that the live birth rate was 5 percent higher for women who had only one embryo implanted at a time than for those who had received a double embryo transfer. A second paper published in the same journal, *Human Reproduction*, used a mathematical model to compare the cost effectiveness of seven in vitro ferilization strategies (Audrey A. A. Fidelers, "Cost-Effectiveness of Seven IVF Strategies: Results of a Markov Decision-Analytic Model," March 24, 2009). The researchers at the Academic Hospital Maastricht in the Netherlands concluded that implanting two embryos every time would result in more live births, but many of the pregnancies would involve multiple fetuses and the average cost per child would be more than twice that of a single-embryo approach. In sum, both of these studies—and there are others—suggest that single-embryo transfer should become the norm for IVF practices worldwide. Had this limit been in place, the mother of the California octuplets would not have been able to do what she did.

Next, it is estimated that more than 1 percent of babies born in the United States are conceived using ART. The argument is often made that IVF and the other assisted reproductive technologies are good because they help infertile couples bring "wanted" children into the world. Little is said, however, about the effects of these practices on the children themselves. A new study from the National Center on Birth Defects and Developmental Disabilities, part of the Centers for Disease Control and Prevention, has found that children who were conceived using ART, including *in vitro* fertilization and the use of donor eggs, are two to four times more likely to be born with certain types of birth defects, although the overall risk is still relatively low ("Assisted Reproductive Technology and Major Structural Birth Defects in the United States," *Human Reproduction*, February 2009). These risks include the risk for septal heart defects (twice more than normal), for cleft lip or cleft palate (more than twice the risk), and for gastrointestinal defects (four times more than normal). This study adds to the growing body of evidence that ART is associated with birth defects. The heightened risk is real.

Finally, a study published in the *American Journal of Epidemiology* has revealed that ovulation-inducing drugs—drugs often used in assisted reproductive technologies—appear to increase the overall risk of cancer (R. Calderon-Margalit et al., "Cancer Risk after Exposure to Treatments for Ovulation Induction," February 1, 2009). The research team at Haddassah–Hebrew University in Jerusalem examined data from 15,030 women enrolled in the Jerusalem Perinatal Study who gave birth between 1974 and 1976. The 567 women who received drug treatment to induce ovulation had a 36 percent increased risk of developing cancer at any site. The authors call for further studies to confirm their findings.

Can the Distribution of Condoms Stop the Spread of HIV/AIDS in Africa?

During his apostolic journey to Cameroon and Angola in March 2009, Pope Benedict XVI was widely criticized for his comments suggesting that the distribution of condoms would not necessarily halt the spread of HIV/AIDS in Africa. Within days, the *New York Times* published an editorial that denounced the Holy Father's statement: "Pope Benedict XVI has every right to express his opposition to the use of condoms on moral grounds, in accordance with the official stance of the Roman Catholic Church. But he deserves no credence when he distorts scientific findings about the value of condoms in slowing the spread of the AIDS virus." ("The Pope on Condoms and AIDS," March 17, 2009).

What is the scientific evidence for the link between condom distribution and the spread of the AIDS epidemic? Breaking from precedent, I would like to end this quarter's narrative by highlighting the scientific literature, not from the past quarter but from the past decade, that supports the Holy Father's comments.

First, it is clear that condom promotion is effective in reducing HIV/AIDS that is spread mainly through prostitution, as in Thailand, and also, to some extent, among other high-risk groups including men who have sex with men.[1] This is true despite the fact that condom use is not 100 percent effective at halting the transmission of HIV. One systematic review concludes that consistent use of a condom only results in an 80 percent reduction in HIV incidence.[2] However, there is also no evidence that condom use has had a primary role in contributing to the decline of HIV in more generalized, primarily heterosexual populations like those in Africa, probably because it is difficult to maintain consistent condom use within more regular and, typically, concurrent partnerships.[3] In fact, data point to a link between a greater availability and use of condoms and higher—and not lower—HIV infection rates.[4] This

[1] Norman Hearst and Sanny Chen, "Condom Promotion for AIDS Prevention in the Developing World: Is It Working?" *Studies in Family Planning* 35.1 (March 2004): 39–47.

[2] See S. C. Weller and K. Davis-Beaty, "Condom Effectiveness in Reducing Heterosexual HIV Transmission," *Cochrane Database of Systematic Reviews* 1 (2002): CD003255.

[3] James D. Shelton, "Ten Myths and One Truth about Generalized HIV Epidemics," *Lancet* 370.9602 (December 2007): 1809–1811.

[4] P. Kajubi et al., "Increasing Condom Use without Reducing HIV Risk: Results of a Controlled Community Trial in Uganda," *Journal of Acquired Immune Deficiency Syndromes* 40.1 (September 1, 2005): 77–82.

may be due in part to a phenomenon known as risk compensation, meaning that when one uses a risk-reduction "technology" such as condoms, one often loses the benefit (reduction in risk) by "compensating," or taking greater chances than one would take without the risk-reduction technology. In contrast, data suggest that one of the most successful strategies for reducing the spread of HIV/AIDS in this context involves programs that encourage monogamy and fidelity.[5] Thus, in the long run it appears that the most effective answer to the HIV/AIDS epidemic involves not promoting condom use, but encouraging male circumcision and challenging individuals to live virtuous and chaste lives that reduce multiple sexual partnerships.[6]

In sum, the empirical evidence supports the Pope. The *New York Times* is wrong. The distribution of condoms would not necessarily halt the spread of HIV/AIDS in Africa. In fact, it could make the AIDS epidemic worse.

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[5] James D. Shelton et al., "Partner Reduction Is Crucial for Balanced 'ABC' Approach to HIV Prevention," *British Medical Journal* 328 (April 10, 2004): 891–893.

[6] M. Potts et al., "Reassessing HIV Prevention," *Science* 320.5877 (May 9, 2008): 749–750.