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Getting Stem Cells Right

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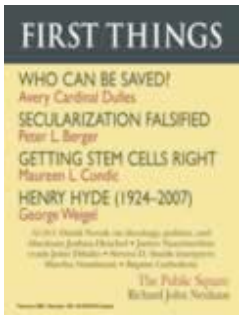

A true, no-cost resolution of a conflict, where the interests of all parties are served without compromise, is an exceedingly rare thing. Yet just such an unlikely resolution may be in hand for one of the most acrimonious conflicts of recent times: the debate over human embryonic stem cells.

Research groups in Japan and the United States have shown that ordinary human skin cells can be converted to stem cells with all the important properties of human embryonic stem cells by a process termed direct reprogramming. Like embryonic stem cells, reprogrammed cells are pluripotent, able to generate all the cells of the body, and so they have been named induced pluripotent stem cells (IPSCs). Unlike human embryonic stem cells, however, IPSCs are genetically identical to patients and are generated without destroying human embryos or using either human or animal eggs.

Producing IPSCs is remarkably simple. First, adult skin cells are removed by a biopsy procedure similar to a blood draw. The skin cells are treated in the laboratory with gene-therapy viruses that contain four reprogramming factors. Over approximately two weeks, the reprogramming factors convert some of the adult skin cells into IPSCs. No embryos are produced and no embryos are destroyed; the skin cells simply transform into cells that are the functional equivalents of human embryonic stem cells.

Direct reprogramming is one of the most exciting scientific discoveries of modern times, and it significantly alters both the political and the scientific landscape of stem cell research. The availability of an ethically and scientifically uncompromised source of pluripotent stem cells should be warmly embraced by all parties as a truly win-win resolution to the long-standing controversy over embryo-destructive research.

Or so one would think. Despite the initial euphoria with which both scientists and ethicists greeted these remarkable findings, the stalwarts of unrestricted stem cell research almost immediately began the solemn chant of “research must go forward on all fronts.” The International Society for Stem Cell Research, one of the largest

professional associations of stem cell biologists, issued a press release the day the studies appeared cautioning that "these findings do not obviate the need for research using human embryonic stem cells; rather the different avenues of human stem cell research should be pursued side by side." This sentiment was echoed even more strongly a week later by the editors of *Nature* magazine, who stated "this is exactly the wrong time to constrain research on human embryonic stem cells."

It is important to ask whether the interests of science and of society are indeed served by allowing research to move forward using all sources of pluripotent stem cells: from human embryos, from direct reprogramming, and from (as yet theoretical) human cloning. Studies of pluripotent human stem cells will undoubtedly advance our understanding of human biology. Patients may someday benefit from new therapies based on stem cell research. These are noble purposes. Yet do we really need to continue research on pluripotent stem cells derived from human embryos when we can obtain cells with the same properties in an ethically uncompromised way? Do we need to pursue human cloning as a means of generating patient-specific stem cells when we can produce them so readily from adult skin?

Regardless of how one views the ethical status of human embryos, the existence of an alternative source of pluripotent stem cells radically undermines the justification for human embryonic stem cell research. Even President Clinton's bioethics commission concluded that embryo destruction posed a moral problem and was justifiable only if there were no alternatives, stating in the 1999 report entitled "Ethical Issues in Human Stem Cell Research ": "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. . . . 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."

Clearly, the advent of direct reprogramming warrants a serious revisiting of the contention that "no less morally problematic alternatives are available." In all relevant practical terms, IPSCs are functionally equivalent to stem cells from embryos. James Thomson, the first person to isolate human embryonic stem cells and the author of one of the two studies on direct reprogramming, notes in his paper that IPSCs "meet the defining criteria" for embryonic stem cells "with the significant exception" that the cells "are not derived from embryos."

Although direct reprogramming is still in its scientific infancy, there are *already* a number of important reasons why IPSCs are superior for scientific research—reasons that

have nothing to do with ethical concerns over destroying human embryos. First, the ability to generate patient-specific stem cell lines for research on human genetic diseases is a tremendous scientific advantage. IPSCs are available now, compared to the merely theoretical prospects of obtaining patient-matched stem cells from human embryo cloning. Moreover, direct reprogramming can generate multiple stem cell lines from an individual patient without any additional cost or effort—an enormous scientific advantage. Thus, scientists can begin studying human diseases immediately using these cells, and this is likely to be the most significant early application of this technology.

In addition to these important scientific advantages, direct reprogramming offers a number of practical advantages. IPSCs are simpler to produce than stem cells from human embryos, and they are ethically uncompromised and therefore fully eligible for federal funding. These features make the cells attractive to scientists who have avoided embryo-destructive research from technical, ethical, or financial concerns. Direct reprogramming also does not involve human embryos or human eggs and is therefore subject to simpler regulatory requirements, another practical advantage that will attract more scientists to this area and speed the pace of discovery.

These practical advantages do not merely reflect current federal policies that might be altered by the next presidential administration. They reflect the intrinsic superiority of IPSCs on a practical front.

IPSCs also offer a significant ethical advantage, even for those who do not consider destruction of human embryos to be an ethical problem. Because direct reprogramming does not use human eggs, research can be conducted without subjecting women to the medical risks associated with egg donation. The difficulty of obtaining human eggs has been a serious problem for research on both human embryonic stem cells and human cloning. A recent *New York Times* editorial noted that, despite a $100,000 advertising campaign mounted by "respected stem cell researchers at Harvard," not a single woman has stepped forward, a situation the editorial refers to as "the vexing egg donor problem." The dearth of egg donors is not terribly surprising in light of the medical risks associated with this procedure. A significant percentage of women who donate eggs experience serious complications that include both sterility and death.

In a seemingly last-ditch effort to justify a line of research that is clearly compromised on scientific, practical, and ethical fronts, advocates of human embryonic stem cells are quick to assert that the direct-reprogramming breakthrough was based on information obtained from the study of human embryonic stem cells—therefore proving that human embryo research is critical to scientific advancement.

What this argument fails to point out is that IPSCs were first produced from cells of an adult mouse, using information from studies of mouse embryonic stem cells. The factors identified in these animal studies proved sufficient to reprogram adult *human* cells as well. Research on human embryos may have contributed to the

development of IPSCs, but it can hardly be seen as critical.

The destruction of human embryos is no more critical for advancing research on direct reprogramming. While it will be interesting to compare pluripotent stem cells derived from direct reprogramming to those derived from human embryos, scientists have twenty-one lines of human embryonic stem cells available for federal funding to make these comparisons, and there is no scientific justification to clone and destroy human embryos to obtain new human stem cell lines.

Despite the astonishing scientific advance of direct reprogramming, it is important to remain realistic about the possibility of developing pluripotent stem cell therapies. Direct reprogramming will not be a panacea for treatment of all human medical conditions. Because of problems with immune rejection, safety (cancer risk), and efficacy (ability to produce clinically useful cells), there are currently no medical treatments using pluripotent stem cells. Direct reprogramming resolves the significant problem of immune rejection by producing patient-matched cell lines. The serious issues of safety and efficacy, however, remain for IPSCs, just as they do for embryonic stem cells.

Indeed, the risks associated with IPSCs may be greater at this time because of the use of gene-therapy viruses for reprogramming, though the need for such viruses is likely to be eliminated as the technique is further refined. The risk of tumor formation, common to all pluripotent stem cells, can theoretically be addressed by converting stem cells into mature cells. Yet despite considerable effort, efficient conversion of pluripotent stem cells into clinically useful cells has not been accomplished. Because of these remaining hurdles, no immediate therapies should be expected from human pluripotent stem cells, whether they are derived from embryos or from direct reprogramming.

The final argument of those still supporting research on human embryos is that freedom of scientific inquiry demands that research be unrestricted—that science and society will be harmed by placing limits on what scientists can investigate.

Yet science, like all human endeavors, must operate within the constraints of ethical values. No one seriously believes that freedom of scientific inquiry should trump all other considerations. Good science does not demand that all avenues of inquiry be pursued. The Tuskegee experiments on African American men with syphilis and the Nazi experiments on Jews and disabled persons were not legitimate avenues of scientific investigation and were not justified by the useful information they yielded.

Many Americans consider research on human embryos to be fundamentally wrong. Even some who do not share this conviction are nonetheless uneasy with using human embryos as research material. James Thomson recently remarked in an interview with the *New York Times*, “If human embryonic stem cell research does not make you at least a little bit uncomfortable, you have not thought about it enough.” *Good* research, research that truly advances our knowledge, enhances our lives, and ennobles our culture, must respect both scientific and ethical standards. IPSC research meets the highest standards of science, and it respects the ethical standards of many Americans who object to human embryonic stem cell research as deeply immoral.

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