

New Advances in iPS Cell Research Do Not Obviate the Need for Human Embryonic Stem Cells

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Recently three different studies were published demonstrating that mouse fibroblast (skin) cells can be directly reprogrammed to behave like embryonic stem cells (Okita et al., 2007; Wernig et al., 2007; Maherali et al., 2007). These studies advanced a breakthrough announced last year in which a quartet of genes (Oct-3/4, Sox2, c-Myc, and Klf4) were discovered to induce pluripotency in mouse cells, albeit incompletely (Takahashi and Yamanaka, 2006). Now a second generation of these induced pluripotent stem cells (called iPS cells) has been made to do almost everything mouse embryonic stem cells can do. When mouse iPS cells were injected into mouse blastocysts, they contributed to all tissue types in the resulting adult mice, including sperm and oocytes (Okita et al., 2007; Wernig et al., 2007; Maherali et al., 2007). And one research team produced fetal mice derived entirely from iPS cells—a key criterion for embryonic stem cells (Wernig et al., 2007).

Media reports of these stem cell advances have enlivened the public's hopes of one day producing human iPS cells from collected skin biopsies to generate patient-specific stem cells for disease research, drug development, and new cell-based therapies. Consequently, some policymakers and citizens might be tempted to jump to the conclusion that research on human embryonic stem cells (hES cells) is unnecessary in light of the emerging possibility of human iPS cell research. Indeed, this misguided

impression could be further fueled by President Bush's latest stem cell bill veto, at which time he referred to these new stem cell studies as a galvanizing reason for his opposition to hES cell research and part of his motive for issuing an executive order to provide public funds for "alternative" forms of human stem cell research (Associated Press, 2007; Department of Health and Human Services, NIH, 2007).

However, it would be a serious mistake to conclude that recent developments in iPS cell research (or, for that matter, any other so-called "alternative" source of pluripotent stem cells) avert the need for ongoing research on hES cells. There are many important reasons why iPS cell research must be conducted hand in hand with hES cell research. In advancing these reasons we do not mean to imply that hES cell research is not of paramount importance in its own right. There are overwhelming scientific justifications for proceeding with hES cell research, which is precisely why it is important for the public to maintain a realistic perspective on iPS cell research vis-à-vis hES cell research.

First, progress toward socially beneficial applications of stem cell science would be indefensibly delayed if iPS cell research is pursued at the expense of further hES cell research. Research on iPS cells has barely begun, and there is much to learn. For example, tumorigenicity and safety are major concerns for iPS cells, as one of the pluripotency-inducing transcription factors, c-Myc, seemed to contribute

to cancer in 20% of chimeric mice (Okita et al., 2007). Even if c-Myc could be substituted, the retroviruses used to insert the pluripotency-inducing factors might themselves lead to cancer and deleterious mutations. Although the current research suggests that retroviruses are needed only to activate skin cells' change to iPS cells, and that endogenous genes seem to maintain pluripotency thereafter, it is unclear at this point whether other modifications will be necessary and what limitations these modifications may pose for possible therapeutic applications. The fact that all mouse iPS cell clones contain numerous integrations of retroviruses suggests that activation or inactivation of additional genes may be required for their induction. Thus it could take many years to understand fully what iPS cells are capable of doing. All the while, hES cells are currently available and should be used for research that may produce important translational scientific work from the bench to the bedside. Therefore, hES cell research should not be fettered or slowed down, especially during this time at which the unique challenges facing iPS cell research remain unresolved.

Second, there is the related point that, despite tremendous efforts, iPS cell research might not translate to human cells. To date, iPS cells have only been generated in experimental mice. There may be significant and unforeseen differences between mice and humans that may prevent human body cells from being similarly

reprogrammed. In the case of cellular transformation, mouse fibroblasts can be transformed with two active oncogenes, but human fibroblasts require four or more oncogenes. Recall that it took 15 years of research to identify the genetic differences between human and mouse cancer cells and even longer between the isolation of mouse and human ES cells. It is therefore unpredictable when, if at all, human iPS cells will be generated. From a public policy standpoint aimed at advancing responsible science, prudence calls for ongoing hES cell research, as human iPS cell research may not succeed.

Third, in the felicitous event that human iPS cells are generated in due course, hES cells will have to be used as important controls to examine the safety and abilities of human iPS cells. In the case of mouse iPS cells, we (K.H., R.J., and S.Y., unpublished data) were able to improve the selection method by using ES cells as a control. It must be emphasized that at present ES cells derived from embryos represent the only pluripotent cells that are genetically unmodified. In the course of early human iPS cell research, up-to-date knowledge of hES cells will be essential for informing sci-

entists' understanding and analyses of human iPS cells.

Fourth, even if human iPS cells are derived, there are invaluable avenues of research that may not be easily pursued with reprogrammed skin cells. For example, early postimplantation development of the human embryo is experimentally difficult to access. In vitro differentiation of hES cells represents a unique experimental system to study early stages of human development.

Thus, we hold that research into all avenues of human stem cell research must proceed together. Society deserves to have the full commitment of scientific inquiry at its service. And science is a practice that works best when it is approached with an open and creative mind. Research into one approach can inspire new ideas in unpredictable and exciting ways. As a case in point, the inspiration for iPS cell research came from an earlier stem cell study in which human body cells were reprogrammed by fusion with hES cells (Cowan et al., 2005). From this earlier study it was hypothesized that hES cells have defined factors that induce pluripotency, thus leading to the first iPS cell breakthrough in 2006 (Takahashi and Yama-

naka, 2006). In short, the recent advancements in iPS cell research would not be possible if it were not for the many years of dedicated hES cell research that preceded them. We cannot support the notion that iPS cell research can advance without hES cell research.

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