Adam's fibroblast? The (pluri)potential of iPCs

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Two groups of scientists have just announced what is being described as a leap forward in human stem cell research.[1–3] Both have found ways of producing what are being called "induced pluripotent cells" (iPCs), stem cells that they hope will demonstrate the same key properties of regeneration and unrestricted differentiation that human embryonic stem cells (hESCs) possess, but which are derived from skin cells not from embryos. In simple terms, these scientists have succeeded in reprogramming skin cells to behave like hESCs.

Stem cell research has been hailed as one of the most important and exciting areas of science, because it is believed that these types of cells will not only play an important part in regenerative medicine, but also yield valuable scientific information. These latest developments in cell reprogramming represent a milestone for stem cell science. No longer does the paradigm of irreversible cell specialisation hold true; instead, almost any type of cell might have the potential to become any other.

The advent of techniques for producing these iPCs has also been hailed as an ethical breakthrough. Up until now, the production of hESCs has required a process (unacceptable to some) which involves the destruction of embryos. Many of these embryos are available as by-products of IVF; but in addition, the process of somatic cell nuclear transfer (therapeutic cloning) to produce cloned embryonic stem cells requires a supply of human oocytes, which must currently be harvested from female donors at no insignificant cost. In a nutshell, iPCs seem to enable us to produce "embryo-free" human pluripotent stem cells, and in a "gender-neutral" way—that is, without the need for human oocytes.

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The response from the scientific community, ethical commentators and the public has, however, reflected an inherent confusion over the ethical significance of this research. The anti-embryo research lobby have applauded iPCs as a source of "ethical stem cells", presumably as opposed to "unethical" human embryonic stem cells; and welcomed by some scientists as a more "socially acceptable" form of stem cell research, presumably in response to the qualms of the same lobbyists. More generally, it has been widely assumed that the derivation of stem cells without the use of eggs or the destruction of embryos solves all the major ethical issues pertaining to stem cell research. This, as we shall see, is not the case.

It has seldom been noticed that the reprogramming of cells which has made possible the production of embryo-free gender-neutral pluripotent stem cells also involves a radical destabilisation of our assumptions about the way cells and human bodies develop, and hence of the meaning of all the stages of the process of human development. An embryo is often considered to be important because it is the precursor to a fully-fledged human being, but its status as the entity from which a new human individual develops has been successively challenged by scientific advances. Embryo splitting (twins) and recombination, cloning and parthenogenetic development have all thrown into question our concept of the embryo as the single individual that has the capacity to develop into a unique human being. Now with the possibility that any cell can be reprogrammed to an embryonic state, the embryo's significance as the starting point for human life and hence its status as a morally important being seems further threatened. Moreover, while it is probable that iPCs are not totipotent in a way that would make them the moral equivalent of embryos it is not yet clear whether this is true.

It is ironic, therefore, that those who are most preoccupied with preserving the human embryo and asserting its moral value have so enthusiastically welcomed this scientific breakthrough that may diminish, in comparative terms, the embryo's status. It has sometimes been argued that an embryo has the right to life in virtue of its interest in experiencing what has sometimes been called a "future of value",[4] because of its potential to be a person. Yet if skin cells and possibly other cells can be reprogrammed to embryonic status, are all of these now embryos *in potentio* in the same way as in some sense, an embryo is a person *in potentio*? Those who value the embryo for its potentiality might well feel obliged to value all cells that might be reprogrammable for the same reason. It may be possible not only to reprogramme skin cells to become pluripotent stem cells but also to reprogramme them to become the sorts of additional cells needed to make an embryo, those that will form the extra-embryonic membrane and placenta. An alternative might be to insert iPCs into an embryo to realise their potential to form a new person or part of a new person.[5] The question then arises as to whether there is an obligation to release the potential contained in every cell by reprogramming them, so that every skin cell can experience its future of value!

Two further points remain to be considered.

The attitude taken by some scientists in response to iPC research seems to suggest that the wider social acceptability of a scientific process is an argument for preferring iPCs to alternatives. This is dangerous for two reasons. The first is that wide social acceptability is related necessarily neither to scientific merit, therapeutic promise, social utility nor to good moral reasoning. It would be a bad day for scientific progress and for human welfare if priority-setting in science were dictated by the degree of opposition to a particular practice.

This does not, of course, mean that scientists are not, nor should not, be publicly accountable. They are accountable and indeed are regulated by a number of proven mechanisms: by the necessity for ethics committee approval, by peer review, by the ability to justify their research in scientific terms and obtain funding and ultimately by law and by the courts. What should not determine the scientific agenda is a sort of popularity contest in which scientists themselves prioritise their research in terms of something akin to public approval ratings. The public interest is best served by allowing successful science to emerge by the usual experimental methods, not by trying to

anticipate the outcome of the ethical debate.

The success of iPC research, then, should not be seen as a call to abandon hESC research altogether. It is too early to know whether stem cells produced in this way will prove as effective, either therapeutically or scientifically, as "genuine" hESCs. Indeed, without continuing research on hESCs, we would have no benchmark by which to assess the usefulness of iPCs. The mere fact that some people find hESC research unpalatable or unacceptable is not a scientific reason that it should not be done—nor a reason to prefer iPC research.

This is not the place for a full account of the reasons why hESC research is ethical, but some basic points should be borne in mind. The first is that all current embryo research takes place on embryos less than 14 days old. At this stage, lacking any brain or central nervous system and before most of its cells have begun to specialise, an embryo can be neither the subject of rights or interests; at this stage embryos can neither be hurt nor harmed. They are not subjects in any sense. This is why embryo research is ethical and should also be legal. It also explains why the legal systems of most jurisdictions have consistently refused to protect the human embryo in any way comparable to human individuals that have been born and obtained an existence independent of their mother, and why the European Court of Human Rights has consistently refused to recognise a right to life in the embryo.[6]

There are many reasons which could and have been given in support of these contentions, but one thought experiment is, we believe, both convincing and conclusive. Imagine: the IVF lab is on fire. A fireman realises that the roof is about to collapse and that he has time to rescue one of the only two groups of occupants other than himself in the lab. He can rescue either a tray of 1000 frozen embryos, or the lab technician, who is already unconscious because of the smoke. We know of no-one who sincerely believes that there is even anything to consider in this choice. It would be both morally and legally inexcusable to carry anything from that lab but the threatened person. No court of conscience or law would exonerate the fireman who chose the tray of embryos; and the relative moral significance of the embryos is such that were there 10 000 on the tray rather than 1000, the answer would be the same.[7] This example shows, among other things, that the prospect of saving even one person is worth the sacrifice of any number of embryos. So long as embryonic stem cell research holds out such a prospect, even remotely, then the same must be true.

iPC research is attractive both for the elegance of the science and for two other reasons. The first is that it does not require the gathering and use of human eggs; the second and consequent reason, that it is genuinely gender-neutral because it does not impose a disproportionate burden on one gender over the other. Its ability to avoid the burdens and risks of egg collection is a distinct practical advantage, but does not necessarily represent an ethical advantage, providing that the use of human eggs can itself be demonstrated to be ethical. True, the process of harvesting oocytes involves some risks and costs; but if these are undertaken voluntarily by the donor as well as appropriately balanced against the potential benefits, it is not unethical.

If it were the case that iPCs provided an exact alternative to therapeutic cloning, then imposing the additional risks of egg harvesting would not be acceptable, but the fact is that we do not yet know whether the iPCs produced by reprogramming somatic cells are scientifically equivalent to hESCs produced by therapeutic cloning.

Research is scientific if it is well-calculated to answer a question that is worth answering and susceptible of answer. The importance of science research is related to the significance of the question and the impact that the answer has on our understanding of the world. Both iPC and hESC research are directed towards related questions of similar importance and utility. Until we have reason to believe that one approach rather than the other is better calculated to deliver the answers that we seek, we have no scientific reason for preference.

Further reading

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4. **Marquis D.** Why abortion is immoral. *J Philos* 1989;**86**:183–202.
5. The capacity of reprogrammed pluripotent cells to form viable embryos has already been demonstrated in mice**. Wernig M,** Meissner A, Foreman R, *et al*. In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state. *Nature* 2007;**448**:318–24; the same might in theory be possible with human iPCs.
6. In: **The European Court of Human Rights [CASE OF Vo vs France**. (*Application no. 53924/00*) Strasbourg 8th July 2004], and most recently in [EVANS vs The United Kingdom (*Application no. 6339/05*) Judgment. Strasbourg, 7 March 2006].
7. Variants of this thought experiment have been proposed in numerous instances: for example, **Sandel MJ.** The ethical implications of human cloning. *Perspect Biol Med* 2005;**48**:241–7.