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viewpoint

To be, or not to be?

Are induced pluripotent stem cells potential babies, and does it matter?

Katrien Devolder

In July 2009, two research groups independently reported the first successful generation of adult mice from induced pluripotent stem cells (iPSCs; Kang *et al*, 2009; Zhao *et al*, 2009). These experiments are part of ongoing research into the differences and similarities between iPSCs—which are derived from normal somatic cells by the activation of certain key genes—and embryonic stem cells (ESCs). If iPSCs are found to be similar to ESCs in terms of their ability to differentiate into any cell type, it might make the use of the latter in research redundant in the long term. This would be beneficial to biomedical research on stem cells and their medical use, as iPSCs are likely to be cheap and easy to produce and would circumvent many of the ethical issues posed by research using human ESCs (hESCs). However, the very same research results might raise ethical challenges for those who accept iPSC research but reject hESC research as ethically objectionable: similarities could cast doubt on one of the main arguments against hESC research, that of 'potentiality'.

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To create mice from iPSCs, the authors of both 2009 publications used a technique called tetraploid complementation. This method has been used successfully with mouse ESCs to produce viable mice and is the most stringent test of the pluripotency of stem cells. It involves creating tetraploid embryos by fusing the blastomeres of two-cell-stage embryos. As they have twice the normal number of chromosomes, tetraploid embryos cannot develop normally and do not result in an animal. The tetraploid embryos are grown to the blastocyst stage, injected with mouse ESCs and implanted in the uterus of a surrogate mouse. The resulting pups are derived solely from the ESCs, with the tetraploid embryos acting as a substitute trophectoderm: they form the placenta and the membranes that nourish and protect the developing organism but do not contribute to the 'embryo proper' (Nagy *et al*, 1990; Li *et al*, 2005). Tetraploid complementation experiments show that mouse ESCs and iPSCs have not permanently lost the capacity to grow into live offspring. Although moral issues prevent these experiments from being carried out in humans, hESCs and human iPSCs (hiPSCs) might have the same capacity, despite some differences in human and mouse stem cell populations (Li *et al*, 2009). On the basis of these results, some have concluded that we must regard hESCs and hiPSCs as potential human beings (Denker, 2009).

Some critics of the use of human embryos for research believe that a human embryo should not be harmed or destroyed because it has significant value from the moment of conception by virtue of its potential to develop into a human being (The President's Council on Bioethics, 2002; Condic *et al*, 2009). However, many bioethicists and others have pointed out weaknesses in the potentiality argument. An initial problem is one of logic: acorns are not oak trees, nor are eggs chickens or omelettes. Just because something has the potential to become something different, we should not regard it as if it has already realised that potential. Unless and until we achieve immortality, all of us share one important and inexorable potential: we are all potentially dead—but it does not follow that we must be treated as though we are already dead (Devolder & Harris, 2005). If we intend to treat something that has the potential to become something different in a special way, then additional arguments are needed.

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The second difficulty with the potentiality argument relates to its scope. If the human embryo has the potential to become a human being and is supposedly morally important by virtue of that potential, then every other cell or group of cells with a similar potential must be assigned equal moral status. This is sometimes called 'the extension argument' (Annis, 1984). In keeping with the extension argument, some have suggested that the development of somatic cell nuclear transfer means that we must now treat every cell in the body as having special moral significance, which has obviously absurd implications (Magill & Neaves, 2009). For reasons that I explain later, this version of the extension argument is somewhat problematic. However, the recent experiments showing that iPSCs can produce live offspring through tetraploid complementation now allow us to develop an extension argument that shows more convincingly the failure of the potentiality argument. Indeed, the

results raise an interesting dilemma for those who support the use of iPSCs but not hESCs in research. Faced with the finding that iPSCs could also be regarded as potential human beings, opponents to the use of hESCs must now either treat iPSCs as morally significant entities worthy of protection, or admit that early embryos do not derive their significance from the potential they possess. One way out of the dilemma would be to demonstrate that iPSCs lack some morally significant kind of potential that embryos possess, and several authors have adduced arguments in support of this position.

The most common argument to demonstrate the moral difference between iPSCs and/or hESCs and embryos is that iPSCs and/or hESCs alone cannot give rise to a full-grown organism (Condic *et al*, 2009). Whereas embryos have the capacity to produce their own trophoblast, which is necessary for embryonic development, hESCs and iPSCs require the provision of a surrogate trophoblast by tetraploid helper cells.

Although this observation is true, it is not clear why it is morally relevant. A blastocyst consists of two distinct cell types: the inner cell mass (ICM) cells, which becomes the embryo proper and, eventually, the adult human being; and trophoblast cells, which contribute to the placental support system. Although the trophoblast is essential for the further development of the embryo, it does not become part of the full-grown organism. Arguably, it is the ICM cells that are of moral significance, as the trophoblast merely provides the appropriate environment for these cells to develop into the embryo.

For the sake of argument, let us suppose that a couple undergoing *in vitro* fertilization can only produce embryos with a defective trophoblast. Suppose further that tetraploid complementation has become a routine technique with human cells and that the only way to fulfil the reproductive wishes of the parents is

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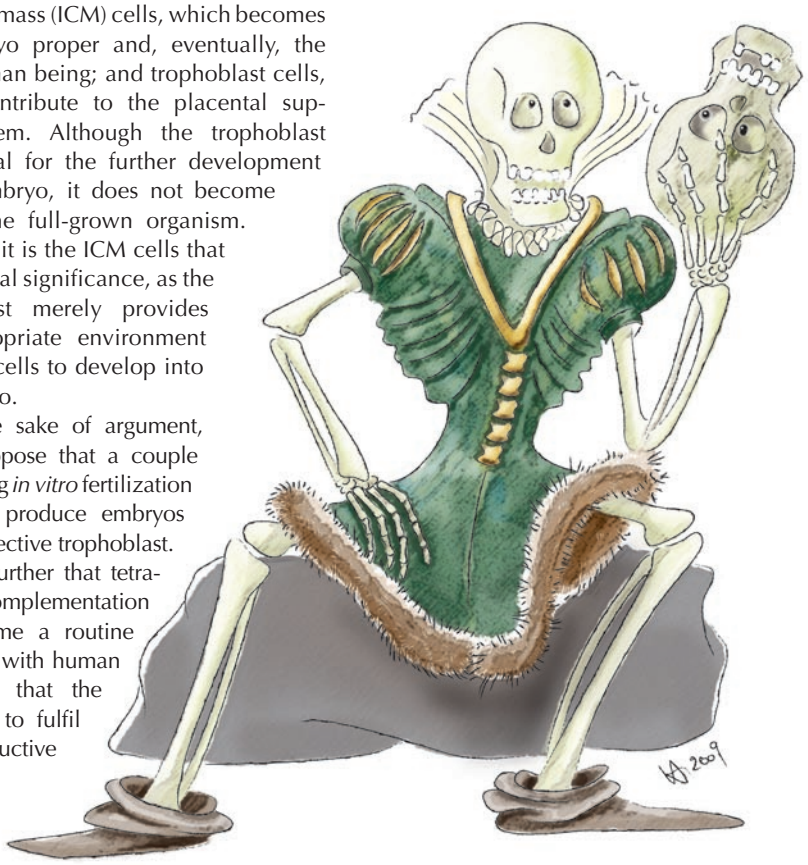
to replace the defective trophoblast with tetraploid helper cells. To circumvent the moral issue of using embryos to provide a surrogate trophectoderm, let us also suppose that it can be derived from iPSCs—there is now considerable experimental evidence demonstrating that hESCs can differentiate into trophoblast lineages (Gerami-Naini *et al*, 2004; Harun *et al*, 2006), so the same might be true for iPSCs. Would those who think that 'potential' is what defines moral value object to helping the parents to fulfil their reproductive wish? Probably not. Yet, the structure of the full embryo—ICM plus trophoblast—has been compromised. This would suggest that it is the potential of the ICM cells that is valued by people who believe moral status is to be derived from 'potential'. But, it would be difficult to differentiate the potential of these cells from that of iPSCs or ESCs: ICM cells, iPSCs and ESCs all require a trophoblast or another suitable substitute to develop.



The fact that the trophoblast and the embryo proper are in constant interaction, and that the latter needs nutrients and signals from the former to develop further, does not make this less plausible. After all, cell potency always depends on interaction with a context (Camporesi, 2007; Testa *et al*, 2007; Baertschi & Mauron, 2008). This is as true for ESCs and iPSCs as it is for zygotes. A cell can exist in many states in the body or in the lab, depending on what sort of information it receives. To develop into an embryo, a fetus and a full-grown human being, a zygote must implant in the uterus and communicate and interact with neighbouring cells, the extracellular matrix and the blood or lymph, and must not be exposed to dangerous substances. Likewise, the development of ESCs and iPSCs into a fetus and an adult organism depends on continuous interaction with a similarly supportive environment. The fact that this environment is provided by researchers is morally irrelevant, as this is also the case with *in vitro* embryos that are implanted in a woman's uterus.

One possible reply is that, unlike iPSCs and ESCs, the zygote has some sort of force inside it that determines what it will become. The context or environment merely allows the zygote's potential to be expressed. iPSCs and ESCs, by contrast, need external manipulations that determine to what the cells will give rise. The first type of potential is typically referred to as 'intrinsic' or 'active', the second type—possessed by ESCs or iPSCs—as 'extrinsic' or 'passive'. Stephen Holland, a bioethicist at the University of York, UK, uses the example of a conker and a horse chestnut tree to illustrate these potentials. To become a horse chestnut tree, a conker just needs 'appropriate circumstances', but for the tree to be turned into a table, an external agent—a carpenter—is needed (Holland, 2003). The potentiality argument is based on the view that entities with intrinsic potential to become full-grown human beings should not be used for research.

This argument might show that somatic cells, at least, lack intrinsic potential, as one could argue that only the cell resulting from nuclear transfer—that is, after the somatic cell has been fused with an enucleated egg—has intrinsic potential. Only after this event does a new cell exist that could give rise to live offspring. However, Holland's

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argument might be weaker against iPSCs, as an embryo can be created entirely from iPSCs by simply transferring them into an appropriate environment—no new cell needs to be created. It would be similar to placing a conker in fertile soil.

In any case, we have to ask ourselves whether the defenders of the potentiality principle really do think that intrinsic potential is of significant moral importance. Suppose that a fertility clinic creates an *in vitro* embryo in the context of a fertility treatment. The embryo is damaged, which makes it impossible for it to develop beyond the stage of an eight-week-old fetus. Fortunately, researchers know how to repair it by using some relatively simple genetic manipulations so that it will again be capable of developing into a baby. Most defenders of the potentiality argument would support the application of science to restore the embryo to its full potential. However, the damaged embryo does not have the intrinsic potential to develop into a human being; thus, according to the potentiality view, we do not have any reason to rescue it. If defenders of the potentiality argument think we should rescue it, then this is because external agents and their actions are part of what makes an embryo possess potential. But iPSCs and ESCs also have the potential to become a human being when certain actions are performed by external agents.

Recent advances in iPSC research are promising from both scientific and medical points of view, yet they also present a serious challenge to those who oppose the generation and use of hESCs for research. Although iPSCs, ESCs and embryos are not identical in their potential to develop into a human being, they do all have an inherent capacity to give rise to adult organisms when placed in an appropriate environment. This presents a dilemma for opponents of embryo research: if they continue to appeal to the potentiality argument, they also risk undermining the use of iPSCs for research. Alternatively, if they reject the potentiality argument, they must eschew restrictions on embryo research or seek some other basis for them.

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CONFLICT OF INTEREST

The author declares that she has no conflict of interest.

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