

## Musings

# Musings on genome medicine: is there hope for ethical and safe stem cell therapeutics?

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### Abstract

Although most stem cell therapy has been non-controversial, therapy based on pluripotent stem cells has raised both ethical and safety concerns. Despite these concerns, the use of cells derived from pluripotent stem cells has recently been approved for clinical trials. We suggest that recent advances in the field have provided avenues to develop pluripotent cells that raise far fewer ethical concerns. Moreover, advances in cell sorting, gene modification and screening have allowed the development of safer therapeutic approaches. Continued advances in this rapidly evolving field are likely to allow therapy to be delivered in a safe and effective manner without socially divisive ethical controversy in the not-so-distant future.

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### The current state of stem cell therapies

Cell therapy of some sort has been available for many years, most notably hematopoietic cell therapies, which use adult bone marrow stem cells to treat the donor themselves or a related person. Commercial products, such as Carticell, Epicell and limbal stem cells, are used worldwide for tendon repair and esthetic surgery. More recently, allogenic transplants and xenotransplants of skin, pancreatic islets, cord blood or mesenchymal stem cells have been used, and trials involving embryonic stem cell (ESC)-derived [1] and fetal-derived neural stem cells [2] have been approved.

Three different modalities of cell therapy have emerged that take into account the differing regulations governing processed and unprocessed cells [3]. First is a personalized medicine point-of-contact model, in which cells are harvested from the same (or a related) individual, undergo minimal processing and are delivered immediately to the recipient. Second is a model akin to what is used for cord blood, which involves an indeterminate period of storage with minimal processing. And third is a drug-delivery model, in which the manufactured product (cells in this case) is approved under a Biologic License Application (BLA). Under any model, the ethical and safety issues

raised by potential pluripotent stem cell therapies are significant hurdles that must be overcome if the medical promise of this field of research is to be realized.

### Ethical concerns

Most cell therapy has not provoked much controversy, but an exception is ESC therapy, about which important moral and ethical issues have been raised (reviewed in [4]). These concerns include donor and consent issues associated with obtaining eggs and the issue of destruction of embryonic human life [5]. Countries around the world have enacted guidelines defining what is permissible for pluripotent stem cell research. These regulations range from an outright ban on such work to narrowly defined permissions [6]. All these guidelines reflect decisions about when during embryonic development human life begins as well as measures to protect egg donors and to reduce the likelihood of embryo destruction.

Scientists working within these guidelines, in concert with ethicists, have proposed several alternative sources of stem cells that would be morally acceptable [4]. These include single cells from a blastocyst, dead embryos, non-embryo sources of stem cells created using altered nuclear transfer [7], parthenogenetic stem cells and germ-cell-derived stem cells. Initially, many of these alternatives were greeted with skepticism, but research has proven each of these approaches to be possible. Thus, such alternative sources of stem cells offer a path to ethically acceptable therapeutic interventions using pluripotent cells. The recent change in US Federal policy regarding funding of stem cell research [8] has reduced, but not eliminated, funding restrictions (for example, the Dickey-Wicker amendment prohibiting the use of Federal funds for embryo-destructive research remains in place). However, the recently released National Institutes of Health guidelines for stem cell research [9] have raised concerns about the eligibility of existing stem cell lines for Federal funding [10]. Nonetheless, the change in US

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ESC, embryonic stem cell; iPSC, induced pluripotent stem cell.

policy will undoubtedly increase funding for stem cell research and thereby benefit stem cell researchers.

Yamanaka and colleagues took a different approach, by trying to reprogram adult cells to a pluripotent state [11]. They reasoned that pluripotency was maintained by ESC-specific factors and that a combination of such factors might be sufficient to reprogram adult cells. In a careful series of experiments they showed that, when co-expressed, as few as three factors could successfully reprogram an adult cell to become pluripotent. This work was first done in mice [12] and was rapidly replicated in human cells by a large number of laboratories [13-15]. Such induced pluripotent stem cells (iPSCs) have properties very similar to blastocyst-derived stem cells, including similar developmental capabilities, patterns of gene expression and epigenetic states [16]. Induced pluripotency offers a relatively efficient and reproducible way of generating pluripotent cells that does not raise any of the moral and ethical concerns associated with obtaining human eggs or with destruction of human embryos.

### Is pluripotent stem cell therapy safe and can it be made safer?

Experiments have shown that undifferentiated pluripotent cells, irrespective of their origin, cannot be safely transplanted into patients; for example, as few as two undifferentiated embryonic stem cells transplanted to a mouse produce tumors [17]. In mature tissue, pluripotent cells do not receive appropriate differentiation signals, and they continue to proliferate, forming benign tumors (teratomas) that can transform into malignant teratocarcinomas. Thus, a critical component of ensuring the safety of pluripotent stem cell therapy is developing effective methods for differentiating cells and for depleting any undifferentiated cells from the transplant pool.

Three different approaches that require minimal manipulation have been proposed. The simplest has been to use a depletion strategy based on the identification of ESC-specific markers [18,19]. A parallel approach that has been developed by several commercial providers focuses on positive rather than negative selection, using cell-type-specific markers [20,21]. An alternative strategy has been to develop a toxin specific to pluripotent stem cells. Yap and colleagues [22] identified an antibody to podocalyxin that seems to induce rapid death of pluripotent but not differentiated cells. Zeng and colleagues have shown that several small molecule drugs exist that have a similar effect (X Zeng, personal communication).

A second safety concern with pluripotent cell therapy is that transplanted cells will induce an immune response, leading to failure of the therapy. Although long-term immune suppression is available, it produces significant medical complications. Initial optimism that ES-like cells

would be immune privileged has not been borne out, and these cells are in fact rejected by the immune system like other transplants. Therefore, with the exception of patient-specific iPSCs, the risk of an immune response remains a concern. Several strategies to address immune rejection have been proposed [23]. Perhaps the simplest is to maintain a bank of cells, akin to a blood bank. It should be possible to develop lines from individuals that are homozygous for key alleles in the HLA domains so that fewer cell lines would be required. Others have put forward the possibility of engineering cells to develop immunologically null lines. A third proposed solution has been to use nuclear transfer to create patient-specific lines, but this approach has proven technically difficult and it raises several significant practical and ethical issues, including the difficulty of obtaining human eggs in sufficiently large numbers and the concerns over producing cloned human embryos for use in research and therapy [24].

Finally, in the case of iPSC lines, there were initial concerns about the use of retroviral- or lentiviral-based random integration of multiple copies of several genes into the cells' genome. Minimizing this risk has been the subject of intense effort in the past year or so, and recently some novel solutions have been demonstrated [25]. Several groups have shown that small molecules, episomal vectors or proteins and zero footprint technology can be used to induce pluripotency without the possible risks associated with viral-based integration [16].

### Conclusions

Personalized medicine using stem cells is now a practical possibility because of the convergence of two distinct fields: genomic research, which has developed techniques to analyze cells on a genome-wide scale using a very small sample size (even single cells), and direct reprogramming, which has allowed researchers to obtain cells of virtually any phenotype from any human genotype. The unprecedented ability to rapidly compare, screen and analyze single cells (or pure populations of cells) at any stage of development will radically change our research methodologies and lead to novel discoveries and therapies.

Therapies based on tissue-specific stem cells are currently benefiting patients with a wide range of medical conditions, and there is considerable hope that the future holds even greater promise. The use of pluripotent stem cells for medical therapies is still in its infancy, and developing such therapies has been hampered by the practical and ethical issues associated with egg donation and embryo-destructive research. However, recent research has validated multiple alternative sources of pluripotent stem cells that are ethically uncompromised. Rapid development of adult cell reprogramming has made this approach much safer for patients and brought the hope of pluripotent stem cell therapeutics much closer to a practical reality.

## Competing interests

MR is an employee of Life Technologies, which funds a stem cell research group and manufactures stem-cell related products.

## Authors' contributions

MR and MLC conceived and designed the article, provided financial support, wrote the manuscript and approved the final version. MLC also provided administrative support.

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