Editorial

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Regenerative Medicine

Making it personal: the prospects for autologous pluripotent stem cell-derived therapies

"...the autologous approach is not currently feasible for clinical therapy, given the costs of making individual cell lines..."

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The now familiar, yet extraordinary, discovery of the capacity for terminally committed adult cells to be reprogrammed to a pluripotent stem cell (PSC) state has raised the enticing possibility that any adult cell could be used to autologously replace diseased or damaged tissue. Furthermore, the recent development of direct transdifferentiation techniques have added to the interest in developing cellular replacement therapies derived from the patient's own cells. However, is this realistic from a practical, scientific and ultimately financial perspective?

The first human transplantation of an autologous pluripotent stem cell derived product took place in Japan in September 2014 [1]. The clinical trial, based at the RIKEN Institute (Japan), involved the transplantation of a sheet of retinal pigmentary epithelium cells generated from induced PSCs (iPSCs) for the treatment of age-related macular degeneration. This first treated patient has shown no adverse effects at 12 months and her visual acuity, which had been declining prior to the procedure, stabilized following the treatment [2]. However, during the safety testing of the second patient's iPSCs, genetic sequencing revealed several mutations that were not present in the patient's original fibroblasts. Three single nucleotide variations and three copy number variants were identified. These genetic changes are well recognized to occur in the iPSC reprogramming process [3,4], and in the case of this second patient one of the single nucleotide variations identified is listed in a curated database of somatic cancer-associated mutations, although only linked to a single cancer [5].

There are currently no clear guidelines on how to interpret such genetic data. The cell line with these mutations had been tested *in vivo* and reportedly shown no evidence of tumorgenicity [6], albeit within the lifespan of experimental animals. While the study investigators felt that these data indicated the cells were safe to transplant, a decision was made to suspend the trial while further evaluation was undertaken. A recent change in the regulatory environment in Japan, together with the uncertainty surrounding the oncogenic potential of the cells, were cited as the reasons for the decision [6]. The trial investigators have also now indicated that they feel that the autologous approach is not currently feasible for clinical therapy, given the costs of making individual cell lines, and have amended their protocol to use allogenic cells [5].

The present challenges for developing an autologous therapy are considerable. The quality and safety of each iPSC line is variable, and in the case of the first transplanted patient, 30 lines were generated in order to select a satisfactory cell line. Masayo Takahashi, the principal investigator of this study, estimates that the safety testing alone cost US$500,000 [2]. The total cost per patient treated is estimated to be US$1,000,000. Even if these costs could be met, it is difficult to envision the capacity, at least in the short

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term, to generate the number of cell lines needed to serve the populations affected by the target diseases.

Autologous iPSC-derived therapies face greater regulatory hurdles than allogeneic approaches [7] given the individual nature of the therapeutic so developed. The central issue is that each patient cell line developed for therapy will individually require comprehensive characterization and safety analysis. In the development of allogeneic therapies, the cell product can be extensively characterized and studied over long periods of preclinical assessment – and then can be used for many different patients. In the autologous setting, the time available for this assessment is much shorter and, in some circumstances, it may not be feasible to complete long-term animal safety studies in a clinically relevant time frame. For this reason, some proponents of the autologous approach argue for a more permissive regulatory approach for such treatments. However, the inherent variabilities in the starting material, the reprogramming process and the output from differentiation make it difficult to establish a manufacturing process that delivers a comparable cell product between patients. As a result, it is difficult to justify any change to the regulatory requirements that does not require strict characterization and safety analysis of each individual cell line.

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There are also other reasons why autologous transplantation may not be desirable. In patients with Mendelian disease, the transplantation of tissue that carries the mutation that lead to the disease in the first place is unlikely to be an optimal therapy – and even though this could be corrected, this brings with it another level of uncertainty and regulatory scrutiny. Indeed, the impact of genetic background upon long-term graft function may still be relevant in patients with diseases that have a complex genetic basis – such as Parkinson's disease.

An alternative to the autologous approach is the development of iPSC haplobanks. The idea of these banks is to provide an established source of clinical-grade pluripotent stem cells from selected homozygous HLA-typed donors to provide HLA-matched cells for as large a proportion of the population as possible. It has been demonstrated, for example, that a stem cell bank for 150 selected donors could match 93% of the UK population [8]. A similar figure has been calculated for Japan [9] where plans for such a bank are underway [5]. It is anticipated that a global network of mutually recognized iPSC banks could provide access to cellular therapeutics for the majority of people [10]. This approach offers the benefits of a cellular replacement material that is closely matched to the patient without the challenges associated with generating a new cell line for each individual patient. It is not clear whether this approach will eliminate or simply reduce the need for immunosuppression and this may vary depending on the site of transplantation and the nature of the graft [11].

Haplobanking is not without its disadvantages [12]. To achieve coverage of the population with a relatively small number of cell lines requires acceptance of a mismatch at up to two HLA loci. This imperfect match will contribute to the need for immunosuppression in these 'matched' transplants. In more ethnically diverse populations, the number of cell lines required will be much greater, and it is likely that there will always be some individuals who cannot be matched from a haplobank. There are also practical shortcomings to the haplobanking approach that arise from the limited number of cell lines generated from each donor. We cannot necessarily assume that any cell type can be generated from a single-banked cell line, despite its theoretical pluripotency. This will be particularly the case when a specific subtype of cell is required for therapy. In our experience, only a fraction of stem cell lines, all genuinely characterized as pluripotent, are capable of robustly being differentiated to the A9 dopaminergic subtype of neurons required for transplantation in Parkinson's disease [13]. There is no current method for determining this potential prospectively and it will not be possible to predict which cell lines in a haplobank will be called upon to produce a particular cell type for a patient.

The principal reason for interest in autologous, or HLA-matched therapies, is the elimination or reduction of the need for immunosuppression. There has been some uncertainty about the immunogencity of autologous pluripotent stem cells and their differentiated progeny. In 2011, a study demonstrated that iPSC-derived teratomas do elicit an immune response in syngeneic hosts [14]. However, subsequent studies have demonstrated that terminally differentiated cells derived from iPSCs can be transplanted into syngeneic hosts without eliciting any significant immune rejection response [15,16].

It is important to recognize that the requirements for immunotherapy are not necessarily absolute for allogeneic cell transplantation and will vary depending on the site and nature of the graft. In allogeneic solid organ transplantation, a population of patients exists whose grafts have survived despite the cessation of immunotherapy (usually for unavoidable medical reasons). These patients are being actively studied in an attempt to identify the factors that might contrib-

ute to the development of their immune tolerance to the allograft [17]. In the field of neural transplantation, where grafts are transplanted to a relatively immunologically privileged site, long-term immunosuppression appears not to be necessary [18,19]. This therefore undermines one of the major advantages in using iPS-derived cells, and raises questions as to whether it is more sensible, at least with neural grafting, to concentrate on the better characterized human embryonic stem cell lines.

The challenges of autologous transplantation faced by the RIKEN group have led to a shift away from this approach as a viable clinical therapy of a personalized nature, at least in the short to medium term. The immediate priority for the field is to establish whether PSC-based cellular therapies can provide effective treatment for human disease. If this is established, there will be a stronger impetus for further refinement including alternate cellular sources to minimize or eliminate the need for immunosuppression, as well as alleviate the ethical issues linked to some sources of stem cells. While it is always precarious to make predictions about the future of major new technologies, it seems that for now the focus will be on undertaking clinical trials utilizing allogeneic cellular material, either from well-established stem cell lines or HLA-matched to the patient using national iPSC haplobanks.

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References

1 Cyranoski D. Japanese woman is first recipient of next-generation stem cells. Nature News (2014). www.nature.com/news

2 Chakradhar S. An eye to the future: researchers debate best path for stem cell-derived therapies. *Nat. Med.* 22(2), 116–119 (2016).

3 Gore A, Li Z, Fung HL *et al.* Somatic coding mutations in human induced pluripotent stem cells. *Nature* 471(7336), 63–67 (2011).

4 Hussein SM, Batada NN, Vuoristo S *et al.* Copy number variation and selection during reprogramming to pluripotency. *Nature* 471(7336), 58–62 (2011).

5 Garber K. RIKEN suspends first clinical trial involving induced pluripotent stem cells. *Nat. Biotechnol.* 33(9), 890–891 (2015).

6 Kagimoto HTS. The path forward. *Cell Gene Therapy Insights* 1(1), 19–20 (2015).

7 Carpenter MK, Couture LA. Regulatory considerations for the development of autologous induced pluripotent stem cell therapies. *Regen. Med.* 5(4), 569–579 (2010).

8 Taylor CJ, Peacock S, Chaudhry AN, Bradley JA, Bolton EM. Generating an iPSC bank for HLA-matched tissue transplantation based on known donor and recipient HLA types. *Cell Stem Cell* 11(2), 147–152 (2012).

9 Nakajima F, Tokunaga K, Nakatsuji N. Human leukocyte antigen matching estimations in a hypothetical bank of human embryonic stem cell lines in the Japanese population for use in cell transplantation therapy. *Stem Cells* 25(4), 983–985 (2007).

10 Turner M, Leslie S, Martin NG *et al.* Toward the development of a global induced pluripotent stem cell library. *Cell Stem Cell* 13(4), 382–384 (2013).

11 Solomon S, Pitossi F, Rao MS. Banking on iPSC – is it doable and is it worthwhile. *Stem Cell Rev.* 11(1), 1–10 (2015).

12 De Rham C, Villard J. Potential and limitation of HLA-based banking of human pluripotent stem cells for cell therapy. *J. Immunol. Res.* 2014, 518135 (2014).

13 Grealish S, Diguet E, Kirkeby A *et al.* Human ESC-derived dopamine neurons show similar preclinical efficacy and potency to fetal neurons when grafted in a rat model of Parkinson's disease. *Cell Stem Cell* 15(5), 653–665 (2014).

14 Zhao T, Zhang ZN, Rong Z, Xu Y. Immunogenicity of induced pluripotent stem cells. *Nature* 474(7350), 212–215 (2011).

15 Araki R, Uda M, Hoki Y *et al.* Negligible immunogenicity of terminally differentiated cells derived from induced pluripotent or embryonic stem cells. *Nature* 494(7435), 100–104 (2013).

16 Guha P, Morgan JW, Mostoslavsky G, Rodrigues NP, Boyd AS. Lack of immune response to differentiated cells derived from syngeneic induced pluripotent stem cells. *Cell Stem Cell* 12(4), 407–412 (2013).

17 Newell KA, Asare A, Sanz I *et al.* Longitudinal studies of a B cell-derived signature of tolerance in renal transplant recipients. *Am. J. Transplant.* 15(11), 2908–2920 (2015).

18 Barker RA, Drouin-Ouellet J, Parmar M. Cell-based therapies for Parkinson disease-past insights and future potential. *Nat. Rev. Neurol.* 11(9), 492–503 (2015).

19 Kefalopoulou Z, Politis M, Piccini P *et al.* Long-term clinical outcome of fetal cell transplantation for Parkinson disease: two case reports. *JAMA Neurol.* 71(1), 83–87 (2014).