

Development of a global network of induced pluripotent stem cell haplobanks

“An international network of mutually recognizable iPSC banks would enable the broadest access to this new generation of cellular therapeutics for people of different ancestral backgrounds.”

Keywords: allogeneic • global • haplobank • HLA-matching • iPSC • rejection • transplantation

When protocols were first described for the derivation of induced pluripotent stem cells (iPSC) from adult somatic cells by the introduction of a small number of selected transcription factors [1–3] it was suggested that such cells would be ideal for patient-specific cell therapy. While clinical-grade autologous cells could be produced, this seems unlikely to occur on a large scale because of the costs and time that are involved, at least with present protocols. Rather it has been suggested by several groups [4–6] that a useful partial match should be obtained by establishment of banks of cells from individuals homozygous at the major HLA antigens. Other approaches which may contribute to the protocols for cell therapy are reviewed elsewhere in this special issue and include induction of tolerance by a number of different routes.

If cells or tissues from one person are transferred into another, they will almost always be destroyed by immune rejection in the absence of immunosuppression. While there is a great deal of experience of preventing rejection of cells of the hematopoietic lineage, as well as tissues and solid organs, very little is known about the response to transfer of cells or tissues derived from pluripotent cells. In particular, there are very few studies in nonhuman primates or humans. In a comparison of immune response and survival of iPSC-derived neurons in a cynomolgus monkey model of Parkinson's disease, the immune response was less and cell survival greater when autologous cells were transferred than when there was an MHC mismatch between the cells and the recipient model animal [7].

In this study, no comparison was made with cells that provided a partial match by choosing donor animals homozygous at the major MHC antigens as such animals have not yet been identified.

As we have discussed elsewhere [6], it is necessary to consider several potential sources of rejection:

- Carbohydrate blood group antigens such as the ABO system. Donor cells will preferably be of group O because groups A, B or AB would be more likely to suffer rejection if transplanted into a patient with an incompatible ABO blood group, although the strength of the immune response to different transplanted tissues is variable [PECHANSKI M, PERS. COMM.];
- HLA incompatibility between donor cells and the recipient gives rise to rejection. When transplanting solid organs, the greatest benefit comes from matching HLA-A, HLA-B and HLA-DR [8] when matching reduces the incidence of rejection and the requirement for immunosuppression. However, as HLA-C and HLA-DQ are in close linkage to HLA-B and -DR, respectively, in most cases donor-recipient pairs matched for B and DR will also be matched for C and DQ. While one would ideally wish to match as many antigens as possible, in practice the most effective choice may be to identify as donors individuals homozygous at these three selected antigens and to transfer with no mismatch between donor and



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recipient;

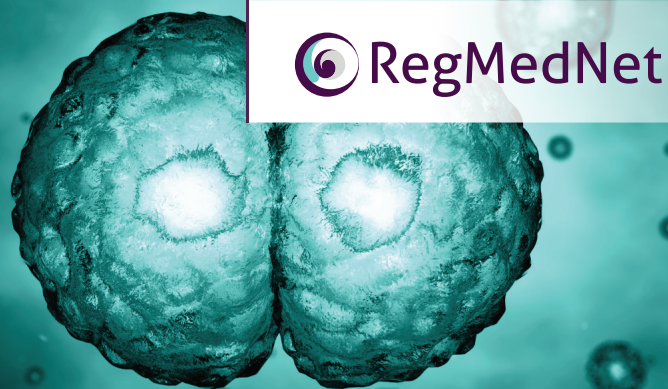
- However, it should be recognized that there are other HLA loci and minor histocompatibility antigens which are capable of causing rejection. In the case of those haplotypes which are relatively common, it will be possible to take the opportunity to match for additional loci (see below). As many of the latter reside on the Y chromosome, it would be preferable to build the HLA haplobank from female donors where possible;
- Providing HLA matching in the form of homozygote donors to minimize T-cell-mediated rejection may leave donor cells susceptible to natural killer (NK) cell mediated killing [9];
- Finally, there is evidence that pluripotent stem cells and their derivatives can be immunogenic, perhaps as a result of antigen rearrangements arising from the derivation and culture protocols, although this interpretation is controversial [9].

It is in this context that it has been proposed that iPSC should be derived from selected individuals who are homozygous at the HLA-A, HLA-B and HLA-DR loci (see below). A number of analyses have been

completed to estimate the practicality of this approach. How many individuals would have to be screened to identify the pool of donors that would be required? Given the most common homozygous genotypes, to what proportion of the population would they provide a beneficial match? How many lines would be required to provide a useful match to the population being considered? While broadly similar conclusions are drawn in the different analyses, there are differences in the heterogeneity of populations which are reflected in the need for more lines. The degree of sharing (and therefore redundancy) of conserved HLA haplotypes between ethnic groups has not been fully assessed, but may be expected to reduce the total number of lines required to populate a global iPSC haplobank. For example, the two most useful homozygous HLA haplotypes that match 20% the Japanese population would provide little utility for the UK population, but there is considerable haplotype sharing between the UK and American populations [5,10]. Moreover, the use of HLA homozygous lines would address the growing difficulty in providing suitable HLA matched tissue for transplantation in individuals of mixed race descent. In most cases, the analyses have been at the simplest level variously known as ‘first field’ or ‘2-digit typing.’

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In their extensive consideration of the UK population, Taylor and colleagues [5] first considered the full range of combinations of the known different HLA types that might be present in the population. There were found to be 13,860 possible combinations of the known HLA-A, -B and -DR specificities each representing a potential homozygous HLA-typed iPSC donor. By using the haplotypes of 10,000 organ donors as representative of the actual UK population they then estimated how many of these theoretical lines would be required to provide a zero mis-match to all of these 10,000 individuals. A zero HLA mismatch for at least 1 (between 1– and 1687) of the 10,000 potential UK recipients was provided by each of 4757 of the 13,860 (34.2%) theoretical homozygous HLA combinations, with the remainder of the potential combinations matching none of the potential recipients. A minimum of 405 of these theoretical homozygous HLA-A, -B and -DR combinations would be needed to provide such a match to all 10,000 theoretical recipients. Among these 405 haplotypes, the ten highest ranked homozygous combinations matched 53% of potential recipients. The first 150 theoretical homozygous HLA-A, -B and -DR combinations provided a match for 94% of potential recipients.



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Finally, they considered how many of these 405 theoretical homozygous HLA types were to be found among 17 million individuals who have volunteered to donate hematopoietic stem cells (Bone Marrow Donors Worldwide). They found 236 (58.3%) of the 405 theoretical HLA combinations required, and these would provide a zero mismatch for 95.5% of potential UK recipients. The highest ranked 150 of the 236 would provide a zero HLA-A, -B -DR mismatch for 93.2% of potential UK recipients, with a maximum of 19,398 and minimum of ten potential donors for the most, and least, frequent homozygous HLA donor types, respectively [5]. In the case of those haplotypes that are available in a large number of donors, it will be possible to match some of the minor antigens in addition to the three major haplotypes. When first using the haplobanks, extensive studies will be possible to identify the loci that provide the greatest benefit.

Equivalent calculations have been made for several different populations. Nakatsuji *et al.* [11] estimated that 30 homozygous cell lines selected from 15,000 individuals would match 82.2% of the Japanese population at the HLA antigen level for HLA-A, HLA-B and HLA-DR, while 50 homozygous lines selected from 24,000 individuals would match 90.7% of that population [11]. Similarly, when focusing on higher resolution HLA allele level matching, 140 homozygous lines selected from 160,000 individuals would provide a match for 90% of the Japanese population [12]. It seems that there is less genetic variation in the Japanese population so that fewer donors are required.

By contrast, in more diverse populations more donors are required. Gourraud and colleagues [13] used a probabilistic model to estimate the number of donors required to construct a haplobank in populations from four different ancestral backgrounds. A bank of 20 homozygous cell lines would require the screening of some 26,000 Northern Europeans and would match more than 50% of that population, but would require the screening of 110,000 African Americans to achieve a match to only 22% of the respective population. A bank of 100 homozygous cell lines from each population would match around 78% of Northern Europeans, 63% of Asians, 52% of Hispanics but only 45% of African Americans.

Given the large numbers of individuals who would need to be screened, particularly if gender and blood group are taken into account, we suggest that examination of established cohorts of HLA-typed individuals such as those on platelet apheresis panels, hematopoietic stem cell donor registries, donors to cord blood banks [5,10] and those whose HLA-types can be imputed from genome-wide association studies [14] would provide the most effective way to identify potentially suitable donors. Not only have all of

these groups been haplotyped, but they have all consented already to donate tissue or blood for other reasons and so may be particularly receptive to requests to contribute to a haplobank. Work to establish iPSC banks has been initiated in several countries including Japan, United Kingdom, France and the United States of America.

An international network of mutually recognized iPSC banks would enable the broadest access to this new generation of cellular therapeutics for people of different ancestral and ethnic backgrounds. However, a number of challenges will have to be addressed if this vision is to be realized [6]. It is critical that these cell lines are acceptable across the range of international regulatory bodies if the cells are to have global clinical applicability. It will be essential that agreement is reached over all of the procedures involved in the procurement, production, characterization and monitoring of the cell lines. This will include all steps from donor selection, screening and consent, as well as those related to clinical Good Manufacturing Practice (GMP), quality assurance and regulatory compliance. Thought needs to be given to the use of common nomenclature, identity and potency assays and reference standards to ensure comparability of assessment. There will also be a need to determine the effect of cell therapy upon the patients over a period of several years, monitoring for both adverse and beneficial effects.

The proposal to establish a global network of haplobanks offers great advantages in two ways. There is the prospect of cell lines being available for the entire human population at a fraction of the cost than would be involved in the provision of patient-specific autologous cells. In addition, there is considerable potential saving for companies and funding agencies if the members of the network collaborate to complete the preparatory work required to establish quality criteria for the cell lines and agreement on all of the regulatory procedures.

Working together to establish such a global network of haplobanks would offer enormous advantages to the biotechnology industry, clinical community, health-care providers and most particularly the patients who will benefit from the emerging methods of cell therapy.

Disclosure

The opinions reflect the opinions of the authors and do not represent the policies of the governments or institutions to which we are affiliated. None of the authors were paid to provide any opinion presented; and the effort was not funded by any commercial entity mentioned in this article. Several of the authors lead efforts to establish stem cell banks. I Wilmut, NG Martin, M Pechanski, D Turner and M Turner have no conflicts.

Financial & competing interests disclosure

S Leslie is a founding partner in Peptide Groove LLP. M Rao serves as a consultant for several companies in the stem cell space and was a founder of Q therapeutics. S Yamanaka is a scientific advisor of iPS Academia Japan without salary. CJ Taylor is supported by the NIHR Cambridge Biomedical Research Centre.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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