CELLULAR THERAPIES

Cellular Therapies comprises a spectrum of approaches to transplanting human cells into patients. Its usually though of as a sub-set of Regenerative Medicine, though it overlaps on the one hand with established clinical practice in blood transfusion, tissue and organ transplantation, and on the other with experimental approaches in gene therapy and tissue engineering. Recent advances in our understanding of stem cell and developmental biology, coupled with significant Government investment both in the UK and internationally along with rising public expectation, have led to a significant increase in the number of novel cellular therapies entering clinical trial. The regulatory environment has evolved rapidly, but there remain a number of open issues, some of which overlap with SaBTO's remit.

Broadly speaking Cellular Therapies can be categorised according to the extent of cell manipulation involved during manufacture:

- Category 1: minimally manipulated cell therapies: either of autologous or allogeneic origin. The paradigm here is Haematopoietic Stem Cells derived from bone marrow, mobilised peripheral blood or umbilical cord blood which are usually cryopreserved as a mononuclear cell preparation and thawed just prior to transplantation. However preparation of enriched cell populations on the basis of immunophenotypic markers such as CD34 or CD133 either for haematopoietic transplantation or under clinical trial for other indications (for example to improve post-myocardial infarction perfusion) would also fall into this category. Separation of islet cells from pancreata through digestion, centrifugation and washing also falls into this category. SaBTO provides safety advice on these products where required, whilst the products themselves are regulated under the EU Tissues and Cells Directive[1] and Human Tissues (Quality and Safety) Act[2] by the Human Tissue Authority.

- Category 2: somatic cell therapies in which autologous or allogeneic cells, donated by living or deceased donors, are isolated or cultured for a limited period of time *in vitro* (usually a matter of days or weeks) prior to transplantation into one, or potentially a handful of, recipients. Examples include corneal epithelial stem cell transplantation for the treatment of ocular surface disorders; mesenchymal stem cells for the treatment of autoimmune diseases or to ameliorate graft versus host disease; CMV- or EBV-specific cytotoxic T lymphocytes to treat disseminated infection or lymphoma respectively in immunosuppressed patients. These cellular therapies are regulated as Advanced Therapy Medicinal Products (ATMPs). Whilst there is considerable overlap with category 1 cellular therapies in terms of donor selection and microbiological screening (for example: corneal epithelial stem cell and corneal transplantation; mesenchymal and haematopoietic stem cell transplantation and CTL with DLI respectively), the extended cell culture process clearly introduces further complexity in terms of (*inter alia*) the risk of in-process contamination and the character and function of the final product.

- Category 3: pluripotent stem cell lines are derived either from *in vitro* blastocysts (human embryonic stem [hES] cells) or genetic reprogramming of adult cells (induced pluripotent stem [iPS] cells). Such cell lines will proliferate indefinitely in culture and can also differentiate into most if not all of the cell types present in an adult. They therefore open the possibility of scalability and of a single (allogeneic) donor contributing multiple cell or tissue products to multiple recipients over an extended period of time. Examples include hESC-derived retinal pigment epithelium cells for Stargardt's Macular Dystrophy, neural stem cells for patients disabled by ischaemic stroke, or iPS-derived red cells or platelets. Both the donor selection and microbiological screening risks are amplified in this context by the potentially high number of recipients of each donation, as are the risks during manufacture (for example a pluripotent stem cell line may go through several passages followed by a complex multi-step differentiation protocol, amounting to several months in culture). These kinds of cellular therapy products are also ATMPs.

  ATMPs are subject to the ATMP Regulations[3]. The Competent Body in the United Kingdom is the Medicines and Healthcare products Regulatory Agency.

In this author's opinion the complexity of cellular therapy products is likely to increase in the longer term since tissues (as we all know) do not comprise single cell suspensions but complex three dimensional structures comprising multiple cell types and extra-cellular components.

The most significant open issues relate to category 3 cellular therapeutics, the first of which have now started to reach clinical trial. These include (*inter alia*):

- In the majority of instances hES cell lines are derived from supernumerary morula / blastocysts generated during routine clinical *in vitro* fertilisation (ivf), often some months or years after the original procurement of the gametes. The donor selection and screening procedures are self-evidently quite different from those involved in a routine blood or tissue donation. In addition only a minority of ivf generated embryos will be used to generate clinical grade hES cell lines. Open issues include the extent to which it is necessary and appropriate to re-approach the donors to ascertain further medical history or perform further microbiological screening and the extent to which testing of the hES cell line itself can be considered a suitable alternative strategy.

- For iPS cell lines, the donor of the skin or blood sample can be more easily subject to a donor selection / screening process – but there are open issues around whether current donor selection criteria are sufficient: is a family propensity to disease of importance (for example of early onset cardiovascular disease if endothelial cells are to be derived); is the post-donation medical history of the donor of relevance (for example if the donor were to develop Parkinson's Disease would one continue to use neurons derived from his/her cell line); is genetic screening of the donor justifiable / required and if so under what circumstances?

- Microbiological screening – whilst donors can be screened for known pathogens there are many potential pathogens in the human population which we don't currently screen for – some undetectable (such as prion diseases), some pathogenic in some recipients but not others (such as Hepatitis E or HHV8), some of uncertain pathogenicity (such as TTV), some probably as yet unknown.

- Traceability – what are the implications for the donor and his/her family if genetic or other abnormalities are discovered during the life history of the cell line – perhaps years or decades after the original donation?

- Persistence of or reversion to pluripotency, leading to a risk of teratoma or differentiation into alternative lineages *in vivo* leading to inappropriate tissue formation.

- Neoplasia induced by genetic or epigenetic manipulation or potentially by the culture process itself. Such neoplasia could express itself generically or potentially in the context of a specific lineage, immediately or after long duration.

- Dissemination of the cellular therapy leading to ectopic tissue formation.

- Immunological rejection of the transplanted cell or tissue.

Finally, it's important to recall that cellular therapies are complex living systems which will be subject to dynamic change in response to the *in vivo* environment once transplanted, raising the possibility if not likelihood that the therapeutic will evolve in its structure, function and/or dispersion during the life-time of the recipient.

Recommendation:

Since SaBTO's remit includes advising on the safety of blood, cells, tissues and organs for transfusion / transplantation including the microbiological safety of gametes and stem cells in liaison with the relevant regulatory authorities, it would be prudent for the Committee to undertake to keep itself informed on the rapid developments in this field and be prepared to offer advice / recommendations as or when appropriate.

References

1. EU Tissues and Cells Directives 2004/23/EC, 2006/17/EC and 2006/86/EC
2. Human Tissues (Quality and Safety for Human Application) Regulations 2007
3. Regulation (EC) No: 1393/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amended Directive 2001/83/EC and Regulation (EC) No 726/2004.

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