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Challenges in the clinical development of stem cell therapy

Nataša Levičar[1] & Nagy A Habib[†1]

"Despite advances made in the past few years and the accumulating body of evidence supporting the contribution of stem cells in tissue regeneration, many questions regarding their clinical application need to be addressed..."

[1]Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, Du Cane Road, London, W12 0NN, UK
[†]Author for correspondence:
Tel.: +44 208 383 8973
Fax: +44 208 383 3212
E-mail: nagy.habib@imperial.ac.uk

The idea behind cell therapy is not new; it was proposed many years ago. However, the significant research activities in the regenerative medicine field started in the 1970s. Over the last decade the advances in the understanding of stem cell biology have made the prospect of tissue regeneration a potential clinical reality. A potential strategy to replace, repair and restore the function of damaged tissues or organs is stem cell transplantation. Cell therapeutics may perform better than current treatments such as medical devices, recombinant proteins and chemical compounds. Despite advances made in the past few years and the accumulating body of evidence supporting the contribution of stem cells in tissue regeneration, many questions regarding their clinical application need to be addressed [1]. Processes to produce cell-based therapeutics are not standardized yet and are highly variable. The critical challenge for translating stem cell therapy into the clinic is to deliver safe, effective and affordable therapies to patients.

Types of cells and routes of administration for specific clinical scenarios would need to be determined in order to maximize potential therapeutic benefit. Furthermore, it is necessary to determine the quantity of cells needed for transplantation to achieve best possible therapeutic effect. The type of patients that would benefit from this treatment must be determined. The desirable features of stem cells for therapy include rapid expansion *in vitro* and minimal immunogenicity and regenerative properties when transplanted into injured organs.

Possible candidate cells to be used include various stem cells such as adult stem cells, embryonic stem (ES) cells and recently generated pluripotent stem cells (iPS) [2] that closely resemble ES cells. ES cells have an unlimited self-renewal ability and the capacity to differentiate into any specialized cell type, therefore, could represent an unlimited cell source for tissue regeneration. However, research on these cells has been hampered or banned in some countries because of the ethical concerns about destroying human embryos to obtain them. Another major limiting factor for their usefulness in clinical therapy lies in their risk of uncontrolled growth and potential danger of teratoma formation and immunological intolerance [3,4]. In spite of this, the US biotechnology company Geron have performed the first US FDA-approved clinical trial using ES-derived glial oligodendrocytes in patients with acute spinal cord injury. The results have not been published yet, but the trial is aiming to elucidate whether ES cells are safe to use in patients and also if they improve patients' sensation in the trunk or legs. Using iPS cells can bypass ethical and immunological issues and may offer the possibility of developing patient-specific cell therapeutics. However, the use of oncogenic viruses to make the iPS is considered unsafe for clinical applications and there is a possibility of tumour genesis. Improved induction methods more suitable for clinical use are under development [5]. Moreover, patient-specific therapy is associated with high cost and regulatory issues. Currently,

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the majority of ongoing clinical studies [101] use adult stem cells derived from bone marrow, which are the best characterized and most widely understood adult stem cells. Although their differentiation potential is limited in comparison to the ES cells, they can still differentiate into a variety of cell lineages. Their growth potential is limited and they are found in low frequency, but using autologous cell therapy removes the need for immunosupression. Several recently published articles have discussed the regeneration potential of adult stem cells [6]. Studies have suggested that patients with diseases as diverse as heart disease, stroke and spinal cord injury may benefit from adult stem cell therapy.

However, the processes by which stem cells contribute to tissue regeneration *in vivo* are unclear. It is debatable whether any improvement is due to direct participation of stem cells in the regeneration of damaged tissue or via bystander mechanisms on the host microenvironment. Hence, stem cell therapy remains primarily a research challenge rather than a readily usable clinical therapy for widespread use. In addition, the fate of stem cells given for therapeutic purposes is also unknown, as not many of the studies have attempted to track the cells or demonstrated their presence in the tissue following transplantation. To determine cell fate after transplantation, it is necessary to control their behavior in pathological conditions. Understanding these mechanisms will become of the utmost importance before clinical cell transplantation can be performed safely and with high efficacy.

Other clinical considerations that are needed to be determined include cell-therapy safety, cell expansion, cell delivery to the targeted tissue and long-term survival and functioning of transplanted cells. A viable and cost-effective cell therapy requires easily isolated cells with a stable cell growth profile and scalable cell expansion process. Characterization and standardization of stem cell populations is crucial for the success of stem cell-based therapy and will most likely be dependent on the choice of cells for transplantation. Therefore, the developmental stage (i.e., progenitors or fully differentiated cells) in which stem cells should be transplanted is very imporant to determine.

Usually, there are a large numbers of cells needed for transplantation. Cells are amplified *in vitro* for a long period of time, which could lead to genetic and epigenetic changes. Genetic and phenotypic stability along with biological activity should be performed to ensure a stable product. Moreover, expansion protocols to produce sufficient amount of cells to treat patients need to be significantly scaled up. Currently, most of the expansion protocols developed have been used for research purpose only or to produce sufficient amount of cells for animal studies, which is significantly less than for clinical requirements.

Although some stem cell therapy is already being used clinically, it is critical to optimize further and determine how the cells are best deployed. Delivery of the intact product to the intended site is very important in developing successful cell therapy and researchers must consider how they will deliver the cells, either via injection, surgical procedure or another process. Some stem cell products even require scaffolds for the reconstruction of damaged organs, which should be taken into consideration when delivering the product to the patient.

Turning cells into effective, safe and affordable therapies is a challenging and complex process even after determining all of the basic parameters. Cell therapies require aseptic processing of living cells and delivery of a living-cell product often with a limited shelf-live. Dependent on the cell type, therapy and delivery route, the manufacturing process may involve some or all of the following steps: cell isolation and enrichment, expansion, encapsulation or seeding on support, freezing, packaging or shipping and delivery to patient [7]. To fulfill manufacturing requirements, researchers must comply with a vast range of regulations, which can vary greatly between international regulatory agencies such as the FDA and EMA [8]. The regulations for regenerative medicine products are largely undefined and standards and guidelines are evolving because the standards for safety, efficacy and consistency have not been fully established. Furthermore, to fully accept regenerative medicine therapeutics as novel therapeutic tools, they must outperform current existing treatment(s) and be cost effective.

Most of the current cell-therapeutic products involved in clinical trials use patient' own autologous cells. Autologous therapies pose greater challenges as they are potentially much more expensive to manufacture. Furthermore, patient-specific cell therapies have greater inherited variability since the quantity and quality of starting stem cell material varies as does cell growth and behavior. Autologous therapy is further associated with logistical issues related to the practicalities of delivering cells to the patients. Ideally, more practical off-the-shelf products should be developed. Some allogeneic regenerative products are already being evaluated in clinical trials. Demonstrating that allogenic cell therapy has clinical benefit, means there is a potential to treat thousands of patients with expanded adult stem cells from a single donor, although the potential immunorejection is of concern. Allogeneic cell therapeutics are more aligned with the pharmaceutical business practice of centralized product production and distribution to healthcare providers [9], possibly entering the clinical practice easier.

However, it seems that the 'one cell fits all' approach will not lead to successful cell therapeutics as it is more and more clear that different pathologies require different

cell types or delivery systems for therapy. According to Ährlund-Richter *et al.*, it is anticipated that over time three main models of cell therapy will develop [10]. The first model is a personalized medicine model, where the cells will be isolated from the same patient or closely related relative. Following the isolation, the cells will be manipulated in the laboratory and then transplanted back into the patient. In the second, termed the banking model, the isolated cells will be stored and exposed to minimal processing. In the third manufacturing model, the cells would be manipulated and manufactured centrally. A single batch of cells will be then used for a large number of patients.

There have been enormous advances made in the regenerative medicine field in the recent years and an understanding of the therapeutic areas in which stem cells have clinical efficacy is likely to emerge over the next few years. However, there are several obstacles and challenges beyond those posed by the research to overcome [11]. First, to determine the safety and efficacy of stem cell therapy in controlled multicenter clinical trials is of paramount importance. Second, regulatory agencies will have to define new criteria to evaluate the risks associated with specific stem cell products. Finally, in order to bring stem cell therapeutics into the clinic on a routine basis, they will need to be manufactured at a cost-effective scale, to make them financially competitive and viable. Hopefully, some cell products developed in the near future will fulfill these criteria and make a successful transition from bench to bedside.

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