Editorial

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Regenerative Medicine

Stem cell therapies for Parkinson's disease: are trials just around the corner?

"The candidate to date that is the closest to being trialed are dopaminergic neurons derived from embryonic stem cells."

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Parkinson's Disease (PD) is the second most common neurodegenerative disorder of the CNS and typically presents around the age of 70 years [1]. It is currently incurable and leads to progressive disability, despite responding well to dopaminergic drug therapies early on in its clinical course. While the condition is defined by the loss of the dopaminergic nigrostriatal neurons and the formation of α-synuclein Lewy bodies, it is now recognized that the pathology and clinical features extend well beyond this pathway. This, coupled with the problems of long-term levodopa therapy has led to the search for better, more biologically relevant therapies and one such approach involves transplants of dopaminergic cells grafted into the brain to replace those lost to the disease process [2]. This approach is not designed to cure patients of PD but will help treat more effectively the dopaminergic responsive elements of the disease for which there are already many effective competing therapies, including deep brain stimulation, apomorphine infusions and DuoDopa® (Abbott Laboratories, North Chicago, IL, USA) delivery (for review see [3]). Thus, as it currently stands, any stem cell-derived dopaminergic cell-based therapy will only give a therapeutic response that is as good as that already seen with the pre-existing dopaminergic therapies. Therefore, any such therapy will not only have to produce this clinically significant benefit, but also have advantages over these pre-existing agents – either practically, therapeutically in the long-term, economically or a combination thereof.

What types of stem cells are being considered for use in PD?

Stem cells, by definition, have the inherent ability to differentiate into any cell type of the human body. They can either be sourced from embryos (embryonic stem cells; ESCs), a variety of differentiated tissues (adult stem cells) or generated from a source of adult somatic cells (induced pluripotent stem cells; iPSCs). All of these sources are being considered for cell-based therapies for PD, but the most advanced work is currently being undertaken with ESCs [4,5], stem cell-derived long-term self-renewing neuroepithelial-like stem cells [6] and iPSCs [7]. Using different protocols, dopaminergic neurons from all these sources have been generated and some have even shown promising results when transplanted into rodent and non-human primate models of PD in terms of survival, integration and behavioral recovery.

What have we already learned from dopamine cell therapy trials in patients with PD?

Dopaminergic cell-based therapies for PD have been trialed for over 30 years using a variety of cell sources, but the most effective to date have involved allografts of human fetal ventral mesencephalon (hfVM) tissue. Transplants of hfVM contain the developing midbrain dopaminergic neurons and have been shown to provide clinical benefits lasting well over a decade in some patients [8] with normalization of dopaminergic innervation of the transplanted striatum [9]. However other studies have not shown such

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clear benefits and even reported significant side effects, such as graft-induced dyskinesias [10,11]. The reasons for these disparate results have been debated and may relate to issues around patient selection, tissue preparation and implantation, immunosuppression, primary end points, as well as trial design more generally [2]. Whatever the reasons, there is no doubt that as a proof of principle, dopamine cell therapies can survive in the human PD brain, reinnervate the striatum and produce long-lasting clinical benefits – whether it is possible to do this reliably and consistently is still not clear and is the subject of a new trial, TRANSEURO [13]. In the context of stem cells though, it means that if we can produce an authentic nigral dopaminergic cell from a stem cell source, then in principle it should be able to produce significant long-lasting benefits to the patient. Indeed, it may even be able to do this while minimizing the risk of some of the side effects seen with hfVM grafts, such as graft-induced dyskinesias, which have been attributed to contaminating non-dopaminergic cells within the grafted tissue, especially the serotoninergic neurons that develop adjacent to the dopaminergic cells of the midbrain.

What will the dopamine neuron differentiated from a stem cell have to do?

At the very least, grafted dopaminergic neurons differentiated from stem cells will have to be equivalent to hfVM tissue in terms of being able to innervate and restore dopamine levels in the striatum to a degree that alleviates the motor features of the disease. To do so, the cells will need to survive long-term, innervate the striatum and functionally connect with the host striatal cells. In order for such cells to be able to do this, they should be phenotypically identical to A9 dopaminergic neurons in terms of their morphology, fiber outgrowth and innervation pattern, transcriptional profile, synapse formation, electrophysiological activity and neurotransmitter release. If these characteristics can be realized, then the cells should be able to behave like the normal nigral dopaminergic cell and thus on grafting should normalize behavior, or at least the dopamine responsive elements of the condition. In addition to displaying these functional characteristics, the cells also need to be safe which means they should not: present any risk of forming masses/tumors; migrate away from the site of grafting and integrate into unaffected neural circuits; be able to de-differentiate back to the cell of origin.

Where are we with stem cell-derived dopamine cells?

The candidate to date that is the closest to being trialed are dopaminergic neurons derived from ESCs. The generation of human ESCs was initially done in 1998 with the first reports that they could be differentiated into dopaminergic neurons coming a few years later [12]. Many human ESC lines have now been generated that are well characterized and quality controlled and this includes two human ESC-based sources that have already been approved by the US FDA for early stage clinical trials in humans. While immunogenicity leading to graft rejection can occur with human ESCs, this problem could be avoided by banking stocks of immunologically diverse donor cells to cover the wide diversity of *HLA* types. In recent years, authentic midbrain dopaminergic neurons have been generated using protocols developed by the groups of Lorenz Studer and Malin Parmar. The first is a floor plate-based protocol that generates midbrain dopaminergic neurons that survive and integrate with functional benefits in the long-term [5], whereas the second protocol is based on embryoid body formation and dual SMAD inhibition with similar long-term survival and benefit [4]. One of these protocols has also demonstrated the scalability of this approach by transplanting ESC-derived dopaminergic neuron precursors in non-human primates [5].

> "...the point at which we can undertake trials with [embryonic stem] cells is fast approaching and brings with it many challenges..."

Other sources of stem cells are also being considered for clinical trials, especially iPSCs, with trials planned in Japan next year. The advantage of these cells over ESCs is that they could be generated from the host somatic cells and thus should be more immunocompatible. However, the use of iPSCs for stem cell-based therapy will require their derivation, expansion and differentiation under transgene-free, xeno-free and feeder-free conditions, which is not currently possible, although much progress has been made towards that end recently.

When should we go to trials & what should they look like?

While we have come a long way in making authentic nigral dopamine cells from stem cells sources, it is clear that we have still not produced such a cell. Although the dopamine cells derived from ESCs have many of the necessary characteristics, there are still issues of fiber growth and innervation potential. Nevertheless the point at which we can undertake trials with these cells is fast approaching and brings with it many challenges in terms of which patients to graft, with how many cells, with what sort of primary end point. These discussions are now being taken on by an international

consortium from Europe, North America and Japan working around this common issue (G-FORCE) and which had its first meeting in London in May 2014. As such, we are now not just discussing whether we can take stem cell-derived dopamine cells to trial, but when.

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