PARKINSON'S DISEASE & STEM CELLS: FACT SHEET

INTRODUCTION

Parkinson's disease (PD) is a common, chronic and incurable neurodegenerative disorder of the brain. It typically presents with a resting tremor, slowness of movement, rigidity, and problems with walking. Additionally, there are numerous non-motor features associated with this condition. The pathology within the brain is widespread, but there is always a critical loss of dopaminergic neurons in an area of the brain called the substantia nigra. These cells project to another area of the brain called the striatum, where they release the neurotransmitter dopamine. This pathway is critical for the normal control of movement and certain aspects of cognition.

Since the 1960's, it has been possible to replace the lost dopamine in PD with drugs (such as L- dopa or dopamine agonists), producing significant clinical benefits, especially in the early stages of disease. However, over time, these drugs create side effects, prompting the need for a more effective way to replace the lost dopamine input. One approach to address this is by transplanting dopaminergic neurons into the striatum.

RATIONALE FOR USING CELL-BASED THERAPIES FOR PD

The most logical and obvious cellular replacement therapy approach for PD is the engraftment of dopaminergic cells of the type lost to the disease process - the A9 nigral midbrain dopamine cells. Implanting these cells in the brain of patients with PD needs to be done at the site where dopamine normally works. If successful, it should yield a clinical response equivalent to that seen with dopamine drugs. This cellular replacement therapy, while not curing patients of PD, has the theoretical advantage over drug therapies in that the grafted nerve cells will release dopamine in a physiological way at the site where it is needed. By doing so, it should avoid the side effects seen with dopamine drugs.

CLINICAL STATUS OF CELL-BASED THERAPIES AND CLINICAL TRIALS FOR PD

Beginning in the 1980s, attempts have been made to repair the PD brain using dopamine-producing cells, with the most successful to date using human fetal ventral mesencephalic tissue. When grafted into patients with PD, these cells can survive long-term in large numbers, release dopamine, make synapses with the host brain, and significantly improve PD for years. However, the use of fetal tissue faces major logistical and ethical challenges, as the cell implanted cannot be standardized, resulting in each patient receiving a slightly different cell transplant. This variability may explain some of the side effects observed in trials using this approach[1].

As a result, a more acceptable and reliable source of dopamine cells is needed. Over the last 15 years, technologies and protocols have evolved to the point that midbrain dopamine neurons can now be made from both embryonic stem (ES) and induced pluripotent stem (iPS) cell sources, which show good survival in animal models of PD and demonstrate functional benefits[2-5]. This work has progressed to the point where the first in-human clinical trials have started. The first one was initiated at Kyoto University in Japan 2018 (UMIN000033564). In this trial, all patients received dopamine neurons derived from the same donor iPSC line (allogeneic cells).

Similar clinical trials using ES cells have also been initiated in both the USA and Europe. The USA trial conducted by BlueRock Therapeutics (NCT04802733) has been completed and showed that the approach was well tolerated with no major safety issues and with some early signs of graft survival and effect. A phase 2 trial is planned. In Europe, the STEM-PD trial (NCT05635409), an academic trial involving Lund University/University Hospital in Sweden and Cambridge University/University Hospital in UK was initiated in 2023 and is still ongoing.

In addition, a single case report of a patient receiving autologous iPSC-derived dopamine cells has been published[6]. In this case, the iPSCs were made from the patient's own cells, turned into dopamine cells, and then implanted into their brain. There are other groups working on similar approaches, including targeting specific forms of PD.

ADDITIONAL RESOURCES

About Stem Cells
www.aboutstemcells.org

EuroStemCell
www.eurostemcell.org

GFORCE-PD
www.gforce-pd.com

World Parkinson Coalition
www.worldpdcoalition.org

CENTERS WORKING ON THE CLINICAL APPLICATION OF STEM CELLS FOR PD

The major groups leading this work have formed a global alliance called G-FORCE PD. Their latest joint publication was at the end of 2017[7]. However, many other groups and companies are now working in this field, including BlueRock Therapeutics (part of Bayer), Novo Nordisk, Sumitomo, and Aspen Neuroscience.

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