The Development of Human ES-Derived Dopamine Neurons for Clinical use in Parkinson's Disease

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting a million people in the US alone. The advent of deep brain stimulation (DBS) has made a significant impact on the quality of life of a subset of patients. However, reconstruction of basal ganglia circuitry remains an ultimate goal that stands a better chance of addressing various aspects of the disease in a permanent and sustained manner.

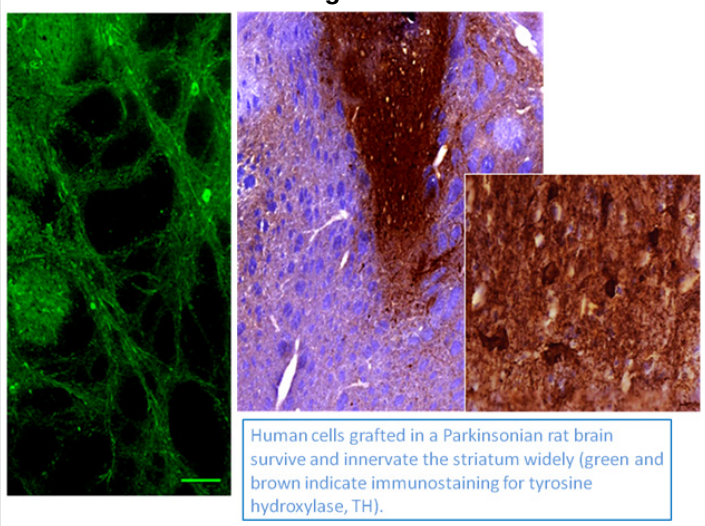
Methods

Our team has developed robust protocols for the derivation of dopamine neurons (DA)from human embryonic stem cells (ES) (Kriks et al. Nature 20011). We subsequently formed a consortium, supported by a 15 million dollar grant from New York State, that aims at translating these findings into a clinical trial of cell therapy for PD.

Results

Key milestones will be described including the development of a large cell bank, validation assays , safety testing, and finally validation and efficacy in vivo in an animal model of Parkinson's disease. Our data show that human ES-derived DA neurons survive grafting both in rodents and in primates; they extend complex neurites that innervate the striatum and result in the reversal of behavioral deficits in parkinsonian rats. There were no teratomas or overgrowth of neural progenitors. Key challenges in translating the work included the translation of our cell differentiation protocol to large scale production, using only GMP-compliant sources, the identification and validation of a cryopreservation medium that maintained high viability, and the

Figure 1



Human cells grafted in a Parkinsonian rat brain survive and innervate the striatum widely (green and brown indicate immunostaining for tyrosine hydroxylase, TH).

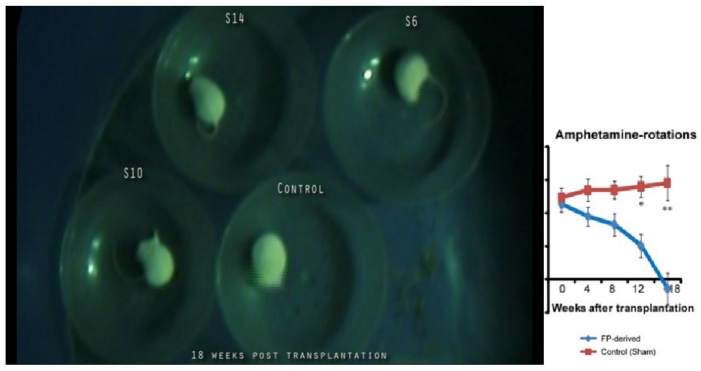
Conclusions

Ongoing work is focused on achieving FDA approval, anticipated in late 2017 and implementing a first in human clinical trial of embryonic stem cell-derived dopamine neurons for PD.

Learning Objectives

Novel potential therapy for Parkinson's disease
Cell-based therapies

Figure 2



Amphetamine-induced rotations as a measure of clinical parkinsonism in a rat model. Grafted animals cease rotations or even exhibit contralateral rotations, while sham controls maintain high rotation scores

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