Using reporter human iPS cells to study fate, function and Parkinsons disease

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USA

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Using reporter human iPS cells to study fate, function and Parkinsons disease

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1

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

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Midbrain structure, induced pluripotent stem cell, Parkinson Disease, Dopamine, Reporter

Research Abstract

DESCRIPTION (provided by applicant): Understanding the principles and processes governing the differentiation of a midbrain dopamine (mDA) phenotype in developing neurons is important

not only for brain ontogeny but also for the study and treatment of diseases such as Parkinson’s disease (PD). In the last decade, a great deal of insight has been gained into the transcriptional machinery regulating mDA differentiation in the embryonic mouse brain. Importantly, many of those same processes appear to be shared by human induced pluripotent stem (hiPS) cells as they differentiate into mDA neurons in the dish. Thus, when human neural progenitors (hNPs) derived either from human embryonic stem (hES) cells or adult induced pluripotent stem (hiPS) cells commit to the mDA differentiation pathway, they express many of the same mDA-specific genes/proteins (Lmx1a, Aldh1a1, Nurr1, Pitx3, TH, etc.). Importantly, regardless of the differentiation protocol used, the maximum yield of mDA neurons rarely exceeds 20% of total cells. This heterogeneity of cell types in mDA-differentiated stem cell cultures combined with the current lack of suitable cell surface markers for the selection of mDA cells, has significantly impacted the field, hampering our ability to study the mechanisms underlying mDA differentiation or to develop stem cells as a model for the study of PD in vitro or as a treatment modality in vivo. Thus, in this proposal, our goal is to create novel reporter hiPS stem cell lines using zinc finger nucleases to insert GFP-tagged mDA transgenes into the adeno-associated virus (AAVS1) safe harbor genomic integration site. These fluorescently labeled cell lines will allow us to purify cells to homogeneity at distinct stages during the mDA differentiation process and proceed with important proof-of-concept studies on the genetic and epigenetic factors governing mDA specification, midbrain regionalization and physiological function. In addition, we will use these reporter lines and DA-specific neurotoxins and PD-related genetic mutations to develop a stem cell model of PD for future studies in culture on PD pathogenesis and potential PD treatments.

Lay Summary

In this proposal, we will create reporter cells lines of human induced pluripotent stem cells isolated from normal subjects and Parkinson’s patients. These cells will be purified and used in studies to assess the effects of genetic, epigenetic and pathological factors on dopamine neuron development and function. The overall goal of this work is to establish a model cell system for future studies on midbrain dopamine differentiation, for pathogenetic and environmental mechanisms important in Parkinson’s disease (PD), for the production of a high throughput screen for PD drug discovery and ultimately for the development of cell-based therapies in PD.

Further information available at:

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