Elucidating early pathogenic mechanisms of neurodegeneration in Parkinson’s disease through a humanized dynamic in vitro model

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Principal Investigators
Institution
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Country

European Commission

Title of project or programme

Elucidating early pathogenic mechanisms of neurodegeneration in Parkinson's disease through a humanized dynamic in vitro model

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5.0

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Research Abstract

Our understanding of Parkinson’s disease (PD) pathogenesis is currently limited by difficulties in obtaining live neurons from patients and the inability to model the sporadic, most frequent, form of PD. It may be possible to overcome these challenges by reprogramming somatic cells from patients into induced pluripotent stem cells (iPSC). In preliminary studies, we have generated a collection of 50 iPSC lines representing both sporadic PD and familial PD patients, and identified distinct PD-related neurodegeneration phenotypes arising, upon long-term culture, in DAn differentiated from these PD-iPSC. Here, I propose to take advantage of this genuinely

human PD model to investigate: i) mechanistic insights responsible for the PD phenotype identified in our model (by combining molecular and biochemical analyses to study mitochondrial function and redox profile, as well as genome-wide transcriptional profile of control versus PD-patient specific iPSC-derived DAn); ii) early functional alterations in patient-specific iPSC-derived DAn, which would predate neurodegeneration signs and provide valuable information as to ways to prevent, rather than rescue, neurodegeneration in PD patients (by electrophysiological recordings in in vitro reconstructed neuronal/glial networks to assess synaptic dynamics together with neuronal excitability); iii) further refinements in our iPSC-based PD model, including the generation of iPSC lines representing asymptomatic patients carrying pathogenic mutations, and the correction of known mutations by gene edition, all of which will allow exploring the relationship between pathogenic mutations and the genetic makeup of patients; and iv) whether DAn degeneration in PD is solely a cell-autonomous phenomenon, or whether it is influenced by an altered cross-talk between DAn and glial cells. These studies may impact significantly on our understanding of PD pathogenesis and on the development of new therapy strategy.

Lay Summary
Further information available at:

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Investments > €500k

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European Commission

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Parkinson's disease & PD-related disorders

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