A novel drug re-positioning strategy for Parkinson’s: Simultaneous, high content screening for translatable small molecules which are beneficial for mitochondrial and lysosomal dysfunction in primary fibroblasts from Parkinson’s patients

https://neurodegenerationresearch.eu/survey/a-novel-drug-re-positioning-strategy-for-parkinsons-simultaneous-high-content-screening-for-translatable-small-molecules-which-are-beneficial-for-mitochondrial-and-lysosomal-dysfunction-in-primary/

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Funder

Parkinson's UK

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Country

United Kingdom

Title of project/programme

A novel drug re-positioning strategy for Parkinson's: Simultaneous, high content screening for translatable small molecules which are beneficial for mitochondrial and lysosomal dysfunction in primary fibroblasts from Parkinson's patients

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Parkinson's UK

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4.0

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Neuroprotection | Animal models | Cell biology

Research Abstract
Background: There is still no disease-modifying therapy for Parkinson’s. A drug re-positioning strategy has proved successful for other diseases. Pathogenesis of Parkinson’s is complex and novel approaches targeting multiple pathways are needed. Mitochondrial and lysosomal dysfunctions are important pathogenic mechanisms in Parkinson’s.

Hypothesis: I hypothesise that a drug screen (i) in patient tissue encompassing different causes of Parkinson’s, (ii) using a compound library designed to only include licensed drugs which have good brain penetrance and (iii) a screen which assesses the effect of the compounds on multiple pathways dysregulated in Parkinson’s; will provide lead compounds amenable to rapid translation to the clinic.

Objectives:
1. Compile a library of licensed drugs with good brain penetrability.
2. Screen this compound library in fibroblasts from patients with either familial or sporadic Parkinson’s to determine the effect on mitochondrial and lysosomal function.
3. Establish optimal concentration exposure time.
4. Determine mechanism of action by analysis of each pathway.
5. Validate compounds’ effectiveness in neuronal models.

Methods:
Objective 1: Chemoinformatic data-mining.
Objectives 2 and 3: High throughput screening of mitochondrial function (mitochondrial membrane potential (MMP)) and lysosome number.
Objective 4: In depth measurement of mitochondrial function using spectrophotometric and oxygen consumption methods. Measurement of lysosomal function using Western blotting and activity assays of cathepsin D processing through the lysosomal pathway.
Objective 5: Measurement of MMP and lysosome number in neurons.

Expected Outcome: Lead drugs identified using this strategy which are beneficial in patient cells could potentially be progressed rapidly to the clinic.

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Fellowships

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Parkinson's disease & PD-related disorders

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