Cathepsin D Activation: A Target to Reduce Alpha-Synuclein Pathology in a Parkinson’s Model

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Cathepsin D Activation: A Target to Reduce Alpha-Synuclein Pathology in a Parkinson's Model

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The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract
Increased levels of a nerve cell protein named alpha-synuclein are linked to two common brain conditions: parkinsonism and dementia. To the detriment of >1.1 Mill Canadians and Americans, these alpha-synuclein-linked brain diseases remain incurable and progressive due to the lack of

cause-directed therapy. Such targeted therapy involves – for example – the use of statin drugs to lower cholesterol levels to minimize the risk of stroke and heart attacks. Few biological ‘scissors’ (enzymes) have been explored for their ability to remove excess alpha-synuclein, which acts like the ‘bad cholesterol of Parkinson disease’ in the statin analogy. Two teams (one led by the applicant) recently identified a first “target”, in the form of a protein-degrading enzyme called cathepsin D. Cathepsin D contributes to the elimination of alpha-synuclein in nerve cells grown in tissue culture dishes and seems to act similarly in brains of flies, mice, sheep, and humans. This proposal seeks to carry out the next step in translational research following the identification of the target; it is called ‘target validation’. We will test the hypothesis that enhanced cathepsin D activity in the adult nervous system is capable of lowering excess amounts of alpha-synuclein in the brain of mice. We will cross an existing, human alpha-synuclein-expressing Parkinson’s mouse model, which was recently published by a collaborator, with a second mouse strain which we have created; the latter carries extra copies of the human cathepsin D gene. In a related step of target validation, we seek to better define the conditions under which cathepsin D operates and by which we can pharmacologically manipulate the target. The successful demonstration that alpha-synuclein pathology in mice can be modified by cathepsin D activation would represent an essential step forward to ultimately treat alpha-synuclein-related diseases at their root cause.

Lay Summary
Further information available at:

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