Small molecules activating RET for the treatment of Parkinson’s disease

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Name of Fellow
Institution
Funder

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Contact information of fellow
Country

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Small molecules activating RET for the treatment of Parkinson's disease

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The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

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GDNF mimetics | Parkinson’s disease | RET receptor thyrosine kinase | glial cell line-derived neurotrophic factor | dopamine | dopaminergic neurons | drug development | drug design

Research Abstract

Parkinson’s disease (PD) is caused by degeneration and progressive loss of dopaminergic (DA) neurons of the substantia nigra. In Western countries more than 6 million people live with PD. Currently no cure for this disease is available, existing therapeutic strategies alleviate PD

symptoms but do not influence its cause or in other words do not prevent or slow down degeneration of DA neurons. Glial cell line-derived neurotrophic factor (GDNF) is one of the few molecules able to protect and repair DA neurons in animal models of PD. GDNF protein and the related factor neurturin were tested in five clinical trials, but the results have been inconclusive. The pharmacokinetic properties of these proteins complicate their therapeutic development. They do not pass blood-brain-barrier (BBB). Moreover, these factors diffuse poorly from the site of injection.
The purpose of current proposal is to combine expertises of the academic and industrial partner in the fields of computational/medicinal chemistry (industrial participant), molecular/behavioural neuroscience and neuropharmacology (academic participant) to develop small molecules passing BBB and efficiently protecting and repairing dopaminergic neurons in vivo. We have developed an initial set of hits that activate GDNF receptors that at 1-10 uM concentration protect and repair DA neurons in vitro. We plan to optimize existing molecules and develop new ones to achieve an active concentration in the range 1-10nM using rational drug design approaches and cell-based screening methods developed by us.
Successful compounds will be tested and optimized for ADMET and pharmacokinetic properties and studied in rat models of Parkinson’s disease to determine their safety, efficacy and other pharmacological characteristics. The expected outcome of this project is generation of safe drug-candidates efficient against Parkinson’s disease manifestations in laboratory animals.

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