Nortriptyline-mediated attenuation of alpha-synuclein pathology in Parkinsons disease

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USA

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Nortriptyline-mediated attenuation of alpha-synuclein pathology in Parkinsons disease

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4

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Parkinson's disease & PD-related disorders

Keywords

Nortriptyline, alpha synuclein, Tricyclic Antidepressive Agents, attenuation, Parkinson Disease

Research Abstract

? DESCRIPTION (provided by applicant): Parkinson’s disease (PD) pathology is characterized by the formation of intraneuronal inclusions called Lewy bodies (LBs) and Lewy Neurites (LNs),

that are comprised primarily of misfolded, fibrillar ?-synuclein (?-syn). One therapeutic strateg to slow disease progression is to reduce these toxic aggregates by preventing the native/monomeric form of ?-syn from aggregating. There is substantial need for new, efficacious disease-modifying therapies in PD. Despite the fact that antidepressants have already been shown to be safe and efficacious for depression in PD, the effects of these drugs on disease progression remain unknown. However, previous work from our laboratory suggests tricyclic antidepressants (TCAs) slow disease progression in both preclinical toxin models (Paumier et al., 2014) and in a retrospective analysis of data from an early cohort of patients with PD (Paumier et al., 2012). Together these findings, and others (Jeannotte et al., 2009a, Jeannotte et al., 2009b, Trushina et al., 2009, Chung et al., 2010, Chadwick et al., 2011, Zschocke et al., 2011, Valera et al., 2014), support the notion that antidepressants have disease-modifying potential within an existing framework of established safety. The objective of the proposed studies is to determine whether NOR can be a disease- modifying treatment for PD. We will test our central hypothesis that NOR attenuates the accumulation/aggregation of ?-syn that occurs in PD, resulting in nigrostriatal preservation. Our hypothesis has been formulated on the basis of our own preliminary findings that NOR is a potent inhibitor of ?-syn aggregation in vitro and in vivo. Rationale for the proposed studies is related to the inability to assess engagement of the ?-syn target in the clinic and subsequently link neurobiological changes directly to improvement. Absent a clinical biomarker for target engagement desirable for a prospective clinical trial, we propose to further develop the case for clinical use of NOR by: 1.) testing in nonhuman primates, and 2.) mining data from subjects enrolled in the ongoing Parkinson’s Progressive Marker Initiative (PPMI) clinical trial. We predict that the capacity of NOR to reduce the rate of?-syn aggregation will prevent the spread and resulting dysfunction associated with LB-like pathology and this prevention of aggregation will be correlated with neurobiological benefit.

Lay Summary
PUBLIC HEALTH RELEVANCE To date, there are no pharmacologic approaches available to limit the misfolding and aggregation of alpha-synuclein (?-syn) implicated in parkinsonian pathology. The proposed research will validate an already approved, safe and efficacious pharmacological therapy that can reduce ?-syn pathology in the brain. Based on preliminary findings using our recently characterized rat synucleinopathy model, we hypothesize that the tricyclic antidepressant, nortriptyline attenuates the accumulation and aggregation of pathological ?-syn.

Further information available at:

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Investments > €500k

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Parkinson's disease & PD-related disorders

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