Somatic inactivation of the SNCA locus: a new approach to the understanding and treatment of Parkinsons Disease

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Country

USA

Title of project or programme

Somatic inactivation of the SNCA locus: a new approach to the understanding and treatment of Parkinsons Disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

378440.367

Start date of award

01/08/2015

Total duration of award in years

1

Keywords

alpha synuclein, Dependovirus, Parkinson Disease, synucleinopathy, SNCA gene

Research Abstract
? DESCRIPTION (provided by applicant): Parkinson’s disease is the second most prevalent neurodegenerative disorder in the United States. A continued lack of curative treatments poses a burden not only to PD patients but also to our society as a whole. Thus, the development of

disease modifying therapies is imperative. This will require paradigm-shifting strategies designed to modulate, not the cause of symptoms, but the molecular underpinnings driving neuronal dysfunction in the PD brain. Numerous genetic and biochemical studies firmly place the SNCA gene, which encodes for a-synuclein, at the center of the patho-molecular events driving onset and progression of genetic and sporadic forms of PD. Aberrantly polymerized forms of a-synuclein are the major component of Lewy bodies and Lewy neurites that are classically observed in PD. Also, a-synuclein inclusion pathology tracts with the neuronal degeneration that is observed in PD. Moreover, recent studies have suggested that a-synuclein fibrils could act in a “”prion-like”” mechanism to seed and spread a-synucleinopathy throughout, perhaps underlying the toxicity observed in PD and other forms of dementia. Because a-synuclein-induced pathology requires sustained a-synuclein expression, it is hypothesized that curtailing SNCA expression could impede the onset or progression of disease. Here, we propose to investigate the feasibility of a novel, paradigm- shifting gene targeting approach to inactivate the SNCA gene in somatic brain tissue. Experiments in aim-1 of this proposal will develop, test and determine whether adeno-associated virus (AAV)-delivery of a new CRISPR/Cas9 system into adult mammalian brain results in safe and effective inactivation of the SNCA locus. Results from this first set of experiments are expected to validate AAV-CRISPR/Cas9 as a novel, powerful tool that can be used by the entire neurodegenerative disease research community to query gene function in the brain. Proof-of-principle studies in aim-2 of this proposal will determine if AAV-CRISPR/Cas9-mediated inactivation of SNCA in a novel mouse model of a-synucleinopathy is efficient enough to modify the onset or progression of a-synuclein pathology in disease relevant areas of the brain. Results from these experiments are anticipated to provide the basis for further development of this novel molecular therapy for PD and other incurable neurodegenerative diseases.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A