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Glucocerebrosidase Gene Therapy for Parkinson's disease

Mutations in the GBA1 gene coding for the lysosomal enzyme glucocerebrosidase (GCase) are related to increased incidence of synucleinopathies such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Although the mechanisms through which GCase regulates the homeostasis of alpha-synuclein still are not fully understood, the identification of reduced GCase lysosomal activity as a common feature sustaining the neuropathological findings underlying PD and DLB -even when considering sporadic forms of these synucleinopathies- has recently attracted strong interest in the field. Accordingly, a number of novel strategies focused on increasing GCase activity to reduce alpha-synuclein burden and preventing dopaminergic neuronal death have been designed. Here we have performed bilateral injections of a recombinant adeno-associated viral vector serotype 9 coding for the mutated form of human alphasynuclein (rAAV9-SynA53T) for disease modelling purposes, both in mice as well as in nonhuman primates (NHPs), further inducing a progressive neuronal death in the substantia nigra pars compacta (SNc). Next, another rAAV9 coding for the GBA1 gene (rAAV9-GBA1) was unilaterally delivered in the SNc of mice and NHPs one month after initial insult with rAAV9-SynA53T, together with the contralateral delivery of an empty rAAV9 (rAAV9-null) for control purposes. Obtained results showed that rAAV-mediated enhancement of GCase activity reduced alpha-synuclein burden, leading to improved survival of dopaminergic neurons together with a reduction in microglial-driven pro-inflammatory phenomena. Furthermore, the trans-synaptic "prionlike" spread of mutated alpha-synuclein was impeded upon treatment with rAAV9-GBA1. Data reported here support the use of glucocerebrosidase gene therapy as a disease-modifying treatment for PD and related synucleinopathies, also including sporadic forms of these disorders.

Biography

José Luis Lanciego Pérez is currently ahead of the Functional Neuroanatomy of Basal Ganglia Lab at the Center for Applied Medical Research, University of Navarra. He has been working in the field of basal ganglia-related neurodegenerative disorders for more than 20 years. He has published more than 100 papers in indexed journals, with an H index of 35 (May, 2019). In December 2006, his group received the credentials of "group of excellence" in the field of neurodegenerative disorders, issued by the Spanish Ministry of Health. At present, his research group has a narrow focus on the implementation of a number of different gene therapy strategies targeting neurodegenerative disorders caused by the pathological aggregation of misfolded proteins.

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