DEVELOPMENT OF A RODENT MODEL OF PARKINSON'S DISEASE USING RECOMBINANT ADENO-ASSOCIATED VIRAL MEDIATED OVEREXPRESSION OF HUMAN ALPHA SYNUCLEIN


Elan Pharmaceuticals, South San Francisco, CA, USA

Introduction: Parkinson's disease (PD) is the second most common neurodegenerative disease. It is characterized by substantial loss of dopaminergic neurons in the substantia nigra pars compacta and severe decrease in the levels of dopamine in the striatum. The mechanisms contributing to the pathological events that underlie neuronal degeneration in PD are not well understood, but strong genetic and biochemical evidence exists suggesting that alpha-synuclein plays an essential role. Animal models of PD have been developed using recombinant viral vectors to overexpress human alpha-synuclein protein in the substantia nigra pars compacta.

Aim: Our goal is to develop an animal model that recapitulates alpha-synuclein associated neuropathology and neuronal dysfunction in the nigral-striatal pathway similar to that seen in PD.

Methods: We have developed an animal model of PD using recombinant adeno-associated viral (AAV) vectors to mediate the expression of either wildtype or mutant (E46K) human alpha-synuclein in the adult rat substantia nigra.

Results: Robust human alpha-synuclein expression is achieved by four weeks after transduction. Human alpha-synuclein expression in the substantia nigra resulted in loss of tyrosine hydroxylase immunoreactivity and large decreases in striatal dopamine levels by 8 weeks post-transduction. Furthermore, we have established correlations between the levels of alpha-synuclein protein expression and the severity and timecourse of neurodegeneration and correlations between striatal dopamine deficits and impaired performance in motoric behavioral assays.

Conclusion: This model recapitulates critical aspects of nigral/striatal degeneration observed in PD and should prove to be useful for understanding mechanisms of alpha-synuclein toxicity and PD drug target validation.