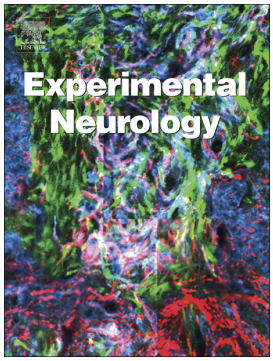

Achieving neuroprotection with LRRK2 kinase inhibitors in Parkinson disease

Andrew B. West

PII: S0014-4886(17)30203-0
DOI: doi: 10.1016/j.expneurol.2017.07.019
Reference: YEXNR 12584

To appear in: *Experimental Neurology*

Received date: 19 May 2017
Revised date: 11 July 2017
Accepted date: 28 July 2017

Please cite this article as: Andrew B. West , Achieving neuroprotection with LRRK2 kinase inhibitors in Parkinson disease, *Experimental Neurology* (2017), doi: 10.1016/j.expneurol.2017.07.019

Achieving Neuroprotection with LRRK2 kinase inhibitors in Parkinson Disease

Andrew B. West

Center for Neurodegeneration and Experimental Therapeutics, 1719 6th Ave. South, University of Alabama at Birmingham, Birmingham, AL 35294 abwest@uab.edu

Abstract

In the translation of discoveries from the laboratory to the clinic, the track record in developing disease-modifying therapies in neurodegenerative disease is poor. A carefully designed development pipeline built from discoveries in both pre-clinical models and patient populations is necessary to optimize the chances for success. Genetic variation in the *leucine-rich repeat kinase two* gene (*LRRK2*) is linked to Parkinson disease (PD) susceptibility. Pathogenic mutations, particularly those in the LRRK2 GTPase (Roc) and COR domains, increase LRRK2 kinase activities in cells and tissues. In some PD models, small molecule LRRK2 kinase inhibitors that block these activities also provide neuroprotection. Herein, the genetic and biochemical evidence that supports the involvement of LRRK2 kinase activity in PD susceptibility is reviewed. Issues related to the definition of a therapeutic window for LRRK2 inhibition and the safety of chronic dosing are discussed. Finally, recommendations are given for a biomarker-guided initial entry of LRRK2 kinase inhibitors in PD patients. Four key areas must be considered for achieving neuroprotection with LRRK2 kinase inhibitors in PD: 1) identification of patient populations most likely to benefit from LRRK2 kinase inhibitors , 2) prioritization of superior LRRK2 small molecule inhibitors based on open disclosures of drug performance, 3) incorporation of biomarkers and empirical measures of LRRK2 kinase inhibition in clinical trials, and 4) utilization of appropriate efficacy measures guided in part by rigorous pre-clinical modeling. Meticulous and rational development decisions can potentially prevent