Reviewer's report

Title: Is Inhibition of Kinase Activity the Only Therapeutic Strategy for LRRK2-associated Parkinson's Disease?

Version: 1 Date: 10 November 2011

Reviewer: Olivier Rascol

Reviewer's report:

Major Compulsory Revisions

The discovery of the role of LRRK2 in the pathophysiology of Parkinson’s disease (PD) has been a major breakthrough in our understanding of the disease. Translating this discovery into therapeutics is now a major challenge. The authors are carefully reviewing in this manuscript a number of molecular mechanisms that can represent potential targets for this purpose. Such strategies are well explained. The major limits of this review, as it stands, is that it restricts its topic to such molecular aspects, while it would be useful for the reader to understand what are the next steps in the development of these concepts for translation into therapeutics in PD patients. Nothing is said about the problem of the “in vivo” animal models, beyong such mechanistic “in vitro” cell cultures experiments. What are the phenotypes of LRRK2 in “ in vivo” models ? How predictive are these models expected to be for potential effects in humans ? Will the agents that are discussed in this review as potential candidates cross the blood-brain barrier ? What are the risks of side effects and the expected safety/tolerability issues ? Moreover, the authors should briefly add at the end of this review some general comments on the current limitations of the next steps of development, that is the clinical ones, with the failure of most previous attempts, and the main reasons for that (lack of reliable biomarkers- and how the LRRK-2 hypothesis could change this problem, difficulties in finding the right dose, assessment of PD progression on long term follow-up while most patients will receive efficacious symptomatic medications concomittantly…).

Finally, the authors should better explain the chances that targeting at LRKK2 mechanisms will have an impact on sporadic PD as opposed to the genetic mutation cases.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.