Author's response to reviews

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

Authors:

Iakov N Rudenko (rudenkoi@mail.nih.gov)
Ruth Chia (chiarp@ninds.nih.gov)
Mark R Cookson (cookson@mail.nih.gov)

Version: 2 Date: 12 December 2011

Author's response to reviews: see over
Response to reviews

We thank the reviewers for their thoughtful and helpful comments that have allowed us to improve our manuscript. We have made a series of changes to the manuscript, which we outline here in response to each reviewer’s comments in italics. We have not repeated positive comments, although they were appreciated by the authors, for reasons of space.

Reviewer 1

Comment: 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.

Response: We agree of course that this is important and now include a section “From bench to bedside: clinical trials and future prospects” (pps 7-9 of the revised version) that expands previous parts of the review to provide more emphasis on translational aspects.

Comment: 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?

Response: We have included several examples of these in vivo models, emphasizing that most of the transgenic animals don’t have dopaminergic cell loss but that some of the viral models do (eg the bottom of p7)

Comment: Will the agents that are discussed in this review as potential candidates cross the blood-brain barrier?

Response: The best available kinase inhibitor, LRRK2-IN1, does not and we highlight what an important issue this in the revised review (p5 and top p8)

Comment: What are the risks of side effects and the expected safety/tolerability issues?

Response: We include two short paragraphs discussing on target and off-target toxicity issues (2nd and 3rd paragraphs, p8)

Comment: 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…).

Response: We have briefly included some of these issues, including discussion of biomarkers (p9)

Comment: Finally, the authors should better explain the chances that targeting at LRRK2 mechanisms will have an impact on sporadic PD as opposed to the genetic mutation cases.

Response: We have included a paragraph on sporadic PD (pp8-9).
Reviewer 2
Comment: The manuscript does not seem to be updated when it comes to LRRK2 and other mutations. They don’t discuss the EIF4G1 mutations in familial PD, recently published, which is involved in the regulation of factor eIF4E.
Response: We included mention of the eIF4E mutation (p6, reference 64)
Comment: They should also include the LRRK2 N1437H mutation, reported by Scandinavian and German groups.
Response: This is now added (p4 and in the figure)
Comment: They don’t mention LRRK2 and the risk for cancer. How would the use of kinase inhibitors change that risk?
Response: We mention the cancer risk, although we are not quite sure if kinase inhibitors would be helpful here and state this (p9).

Reviewer 3
Comment: Overall, this is an excellent short review, which covers its topic extremely well. It is concise and up-to-date as well as well-written.
Response: Thanks for the positive comments, we don’t see any specific changes requested that are not covered by other reviews.