Reviewer's report

Title: Striking reduction of amyloid plaque burden in an Alzheimer's mouse model after chronic administration of carmustine

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Reviewer: Mary Jo LaDu

Reviewer's report:

The authors have attempted to address some of the previous issues in the manuscript, however there are a number of major revisions in this manuscript that prevent publication. These issues include;

1) Although this reviewer recognizes that ‘drugs generally have a multi-target mechanism for biological effects’ TGFβ is proposed as a major mechanism in this study and yet there are no data on in vivo TGFβ levels after drug treatment. Attempts should be made to at least partially validate this mechanism if it considered important for drug efficacy.

2) Co-staining of microglia with an anti-Aβ antibody; The reduction in microglia may be related to the decrease amyloid load as described for other drugs that remove amyloid via microglia mediated clearance. Indeed after short-term treatment microglia levels may be increased in number and for both long- and short- term treatment they may be closer associated with plaques for clearance.

3) Short-term drug treatment would address many important questions including the immediate effects on APP processing, inflammation and microglia-dependent plaque clearance.

4) At least a basic identification of the proposed active metabolites in the brain would strengthen the manuscript, or even if possible addition of the active metabolites in vitro to determine if they also cause the observed effects.

5) The rationale for introducing and discussing the cell cycle reentry is still unclear. In the introduction the authors purport that cell cycle re-entry effects APP processing and in the discussion that BCNU may act to block cell cycle re-entry. However in the response to reviewers it is acknowledged that BCNU at low concentrations BCNU will not affect the cell cycle. Although the authors meant to highlight that anticancer drugs will affect the cell cycle, there are no data presented that BCNU acts via this mechanism for AD. This reviewer agrees it is an interesting potential for this class of drug, however the introduction and discussion of the idea is not validated in this manuscript with any data and is therefore speculation.

Quality of written English: Acceptable

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

I declare I have no competing interests