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: Wataru Araki

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The authors have shown that an oncology drug carmustine (BCNU) has an Abeta-reducing effect in CHO cells expressing APP. They present data on the effects of carmustine on APP processing, secretase activities, cytotoxicity, and TGFbeta levels. They have also demonstrated that chronic administration of carmustine could reduce amyloid plaques in APdE9 mice.

The paper describes original findings on a novel candidate drug for Alzheimer's disease. However, several points need to be clarified.

Major compulsory revisions

1) Only Thioflavin S staining was used to evaluate the inhibitory effect of BCNU on Abeta accumulation. Since this is a key finding in this paper, it is important to provide more definitive evidence by including more confirmatory data (Quantification of Ab with ELISA and/or immunohistochemical analysis with anti-Abeta).

2) The authors report that BCNU increases sAPPalpha levels, but not those of sAPPbeta or sAPPtotal. Considering that sAPPalpha is a major species of sAPP, it is unusual that only sAPPalpha is increased without any change in sAPPtotal. A graph of sAPPtotal should be included.

3) The authors suggest that decreased Abeta production by BCNU results from reduced endocytosis of APP from the cell surface and increased alpha-secretase processing of APP. How does the observed reduction of CTF levels fit in this hypothesis?

4) BCNU was shown to increase the level of TGFbeta in the conditioned media. Does BCNU affect the cellular level of TGFbeta as well?

Minor essential revisions

1) What assay condition (concentration of each compound) was used for Fig. 1A?

2) What culture condition was used for measurement of Abeta from 7WD10 cells.

3) In Fig. 6 BCNU levels are higher at 15 min than at 0 min. Why?

4) In Fig. 4B, LDH release is higher at 10-20 uM BCNU. Doesn't this reflect any cytotoxicity?
Quality of written English: Acceptable

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