Author's response to reviews

Title: CNS Activity Of Pokeweed Anti-Viral Protein (PAP) In Mice Infected With Lymphocytic Choriomeningitis Virus (LCMV)

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Author's response to reviews: see over
Dear BioMed Central Editorial Team,

On behalf of the authors of this manuscript, I would like to thank the editorial staff and Drs. Herrath and Bausch for the most helpful and constructive comments that were received in such a timely fashion. We sincerely hope that we have addressed all the reviewers’ concerns sufficiently. Please see below our point-by-point responses to the reviewers’ required/suggested revisions.

Response to Reviewer #1: Matthias von Herrath

A. Major Compulsory Revisions

None were listed

B. Minor Essential Revisions

1) There are numerous spelling mistakes and grammatical errors throughout the paper that need to be addressed. Paragraph 2 of the Background section needs particular attention.

We thank the reviewer for his note. We have made every effort to correct all grammatical and spelling errors.

2) Also, in the Results section the authors state twice that the mice that died immediately after intracerebral injection, due to accidental brain injury are “invaluable”. This is the wrong use of the word invaluable. Presumably the authors mean that these mice were excluded from the data analysis and if so this should be stated.

We have replaced the word “invaluable” with “excluded from data analysis”.

C. Discretionary Revisions

The authors use cumulative proportion surviving as the y-axis for the graph of Figure 1, with a scale of 0 – 1, but proportion surviving in percent (0 - 100) for the table below. They should change one of these to make it consistent and easier to understand. In my view proportion surviving (in percent), is easier to follow.

We have taken the reviewer’s suggestion and made the adjustment to the figure.

Response to Reviewer #1: Daniel Bausch

A. Major Compulsory Revisions

The results of the study are fairly clear, but the “Discussion” section fails to address various pertinent issues. The following should be addressed:

The included responses were incorporated into the Discussion section.

1) A very vigorous dosing regimen was employed in the study, including two pre- and four post-challenge doses. Do the authors think that they would get the same favorable results if the PAP was given only post-challenge?

Future studies will examine the therapeutic activity of PAP against LCMV in post-challenge settings.

2) The authors are encouraged by the possibility that PAP appears to have activity in the CNS. However, the blood-brain barrier was breached by the intracerebral administration of the challenge dose, potentially artificially facilitating PAP’s penetration into the CNS. Is there data on PAP’s normal penetration into the CNS?

It is possible that PAP penetrate the blood brain barrier only when the latter is impaired by a viral infection. Therefore, PAP may not be useful in pre-challenge prophylaxis against LCMV-mediated CNS infection.

3) The authors are encouraged by the results of their study and the possibility that PAP may be useful for HIV infections involving the CNS. However, LCMV infections primarily infect the leptomeninges and ependyma, whereas HIV may entail true neuronal involvement.

While these results suggest that PAP crosses the blood brain barrier and may therefore be beneficial in other
viral infections affecting CNS, they need to be interpreted with due caution for HIV infections involving the CNS since LCMV affects leptomeninges while HIV affects neurons.

4) The study does not demonstrate definitive anti-LCMV activity of PAP. The pathogenesis of LCMV infections in some mouse models is immune mediated. Is it possible that PAP is acting via immunomodulatory effects rather than direct anti-viral activity? 

While these results support the notion that the antiviral activity spectrum of PAP covers LCMV as well, an immunomodulatory effect of PAP may also contribute to the observed prophylactic efficacy of PAP against LCMV.

B. Minor Essential Revisions
The manuscript should be revised for various errors in format and grammar, including:

1) The “Results” section of the abstract contains no data, only stated conclusions. Please correct. 

The following sentence was added to the abstract: 
The median survival time of PAP-treated mice was >21 days as opposed to 7 days median survival for the control (p = 0.0069).

2) The “Methods” section does not mention how many animals were used. In addition, as the effects of LCMV on mice can be age-dependent, the age of the animals should be included.

The n-values and age of the animals are thus included.

3) There is significant repetition throughout the body of the manuscript. For example, there is no need to again state the dosing schedule, in the first paragraph of the “Results” section when it appears, appropriately, just above in the “Methods” section. Various other similar repetitions can be found.

We have removed the repetitive statements.

4) Once the abbreviation “LCMV” for “lymphocytic choriomeningitis virus” is defined, the authors should simply use “LCMV,” without writing out the long version of the virus name each use.

This correction has been made.

5) Please correct the typo on the bottom of page 2 which I presume should be “anti-HIV” rather than “anti-HVI”.

This correction has been made.

6) On pages 5 and 6 the word “invaluable” is incorrectly used to mean “not able to be evaluated.” Please correct.

This correction has been made. Please note response to reviewer #1.

7) On the top of page 3 it is stated that pokeweed has had “clinical use.” This is usually taken to imply use in humans, but the cited reference pertains to mice. I recommend that the authors amend the sentence to read “…clinical use of PAP in mice [2]”.

This correction has been made.

Discretionary Revisions
None were suggested.

Please do not hesitate to contact me if you require further information or corrections.

Best Regards,

Heather Tibbles