Reviewer's report

Title: Tracking the transcriptional host response from the acute to the regenerative phase of experimental pneumococcal meningitis

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Reviewer: Damiana DM Chiavolini

Reviewer's report:

"Tracking the transcriptional host response from the acute to the regenerative phase of experimental pneumococcal meningitis, by Wittwer, Grandgirard, Rohrbach and Leib reports the transcriptomic changes in the cortex and hippocampus during experimental pneumococcal meningitis in an infant rat model. This study will provide very good scientific basis for developing new drugs and treatments against this disease.

Though scientifically sound and compelling, the organization of this manuscript (particularly the results section) needs thorough improvement.

Major compulsory revisions.

1. Results section, page 5. The “Clinical parameters of meningitis” paragraph appears limited in its current state and results are not illustrated in any table or figure. It is obvious that the authors have extensively published on this subject before, but there are no references to past work to justify the paucity of detail included here. Please extend this section and cite any relevant past papers, if results are exactly the same as those observed in previous manuscripts. For instance, be more exhaustive with respect to “altered state” and “reduced weight gain”. What are the actual values and percentages? A table would probably be ideal to summarize the clinical parameters. This table could also contain the median scores of apoptotic cells reported in the next paragraph.

2. Results section, pages 5 and 6 “Inflammatory parameters”. Similarly to the previous comment, it would be extremely useful and important to see the cytokine data summarized in a figure or at least in a table. The cytokine profile was conducted by Luminex analysis, extensively described in the Materials and Methods section, but results are not reported with appropriate detail.

Overall, the infant rat meningitis model is the base of this entire study and an accurate description, or at least a fairly detailed summary is required.

3. Results section, page 6. Are results in the PCR paragraph reported or summarized anywhere? There is no reference to the primers in Table 1 here, and in fact Table 1 is never mentioned in the text of the manuscript. Please resolve.

4. Results section, pages 10 and 11. It is unclear why figures were made for gene expression in the hippocampus, but not for the cortex. Please resolve or
explain.

5. Results section, pages 11 and 12. In the first part of the “Time and tissue intersection” paragraph, I am assuming that the text is referring to Figures 6 and 7. Please cite appropriately or explain.

6. Results section, page 12. Please report the findings illustrated in Figure 9 in greater detail, indicating what factors are more important in each tissue at 24 and 72 hours post-infection.

Overall, please be careful when reporting data, and make sure that all text and figure legends match.

7. Discussion section, page 13. In the part regarding the use of 3 animals per time point, there is appropriate discussion of the control of sample variability. Would the use of more animals eliminate the need for this type of control? Please comment in the discussion.

Minor essential revisions

1. Abstract, Page 2. Please add the “Methods” subtitle to the abstract.

2. Abstract, Page 2. In the “Results” subsection please specify the tissue types (cortex and hippocampus) studied, instead of vaguely referring to “both tissue types…”

3. Results, page 7. Cite figures and panels correctly and consistently. For instance, in the “Spatial and temporal gene expression” section, add “Figure 2A” after 2974 transcripts. “Figure 1A” is the incorrect citation here, please change.

4. Results, pages 8 and 9. Remove “Figure 4” and “Figure 5” next to the paragraph titles.

5. Discussion, page 15, line 3. Please fix the incomplete sentence, “furthermore there is evidence…”

6. Discussion, pages 18-21. The “Regulation of the host defence: tissue and time intersection” paragraph is repeated twice. Please remove.


9. Figure legend 1, page 39. Please add more information to this legend. This should be a guide for a better understanding of a fairly complex experimental overview.

10. Figure legends 5 and 6, page 40. Please expand both legends.

11. Please check throughout the manuscript the use of italics for Streptococcus
pneumoniae.

12. Please check throughout the manuscript the use of commas and punctuation in general. This will greatly improve the text flow.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.