Reviewer's report

Title: TIP peptide inhalation in experimental acute lung injury: effect of repetitive dosage and different synthetic variants

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Reviewer: Maurizio Cereda

Reviewer's report:

The study by Dr. Hartmann et al. describes the use of TIP peptides (analogues of the lectin-like domain of TNF-# with an effect on alveolar fluid re-absorption) to attenuate pulmonary edema in a double-hit model of lung injury. This study builds on the authors' previously published work, where a single-dose TIP peptide decreased lung edema. In the current work, the authors show that: a second dose of TIP peptide a further decreases edema (but does not improve lung function); two variants of the molecule have similar effects.

Major compulsory revisions:

Methods
Lung injury model: the authors imply that the model adopted is a surfactant depletion (Hit#1) followed by VILI (Hit #2, presumably atelectrauma). However, the use of the term “second hit” is a little misleading, as it builds the expectation that an inflammatory injury is present. The tidal volume used (10 ml/kg) is relatively mild compared with previous work by other authors. Furthermore, ventilation at zero PEEP was started only after 45 minutes following the end of the SL procedure, and injury may not have had time to be established.

Results
Second paragraph: were the differences in AFC between groups significant?

Discussion
Page 11, Paragraph 1. This is supposed to be a paragraph on the comparison between peptides A and B, but only the effects of A are discussed (not tested in the current work). Again, there is no rationale provided for the A vs. B comparison. Also, how do they differ and why was a difference expected? Why do the authors think there was no effect of the peptide type?

Page 11, Paragraph 2, last line: how can the authors state with confidence that there was VILI? Based on the results of their previous work (Figure 1 in ref 14), there was limited additional accumulation of edema during five hours ventilation after lavage, in animals not receiving TIP peptide.

Page 12, lines 3-7. It is not clear what the authors are saying. Despite improved edema, the additional TIP-A dose did not improve lung function. This can have several explanations but the one chosen by the authors in not convincing. Again, it is not clear whether or not VILI was being produced and, even if that were the
case, it does not explain why oxygenation should not get better while edema does.

Page 12, lines 10-12: Are the authors trying to say that the tested agents may affect blood flow distribution independently of their effects of edema? The point they are trying to make here is unclear.

Limitations paragraph: again, the limitations of this model should be stated more clearly.

Minor Essential Revisions
Introduction
The introduction is short and nicely written.
While the need for a study on repeat dosing is self-explanatory, it is not clear why it is important to study different TIP peptide variants. Please briefly explain.
Page 4 line 5: please remove “in different severity stages”: this part of the sentence is confusing and does not add any contribution to the statement being made.
Page 4, line 18: “In succession to a study that approved… “please rephrase to improve language.
Protocol and drug: the authors should specify what category of nebulizer they used.
Discussion
Page 10, paragraph 2, line 6. References 18 and 19 do not address the presence of additional injury after prolonged ventilation of surfactant depleted lungs at this tidal volume.
Page 11, Paragraph 2: the effects of the second treatment dose on AFC should be addressed.
Page 11, Paragraph 2, last sentence: it is not clear to me what a statement on the inflammatory properties of TIP peptides add to this part of the discussion.
Page 12, paragraph 2, lines 6-9: please remove the term “clinical”. It is not clear what the authors mean by “clear cut differentiation”.

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

Quality of written English: Needs some language corrections before being published

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

Declaration of competing interests:
I declare that I have no competing interests