Author's response to reviews

Title: Elevated PDGF-BB Concentrations in Premature Neonates Who Develop Chronic Lung Disease

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PDF covering letter
Responses to reviewers

Reviewer 1
Most answers and revisions made by the authors are satisfactory. However, I still have methodological problems with the manuscript. In humans with pulmonary fibrosis increased expression of PDGF-A and PDGF-B mRNA and protein has been demonstrated in alveolar macrophages, and PDGF-B appeared the most abundantly expressed. This favours the formation of the PDGF-BB dimer and (finally) secretion of PDGF-BB by these cells. Since alveolar macrophages do comprise a considerable population in TA from these infants I still feel that the methodology of the authors (centrifugation of TA containing cells (alveolar macrophages) at high speed) may have artificially released this growth factor from the cells and thereby influenced the measurements. The authors should make a comment in their manuscript that they are aware of this and why they think their methodology does not significantly influence the PDGF results.

*We have added the following paragraph to the discussion. “In our study we employed a higher centrifugation speed than other studies. This may cause lysis of the cellular components (ie macrophages) of the TA. Thus TA PDGF-BB concentrations may reflect total PDGF-BB and not just free secreted growth factor.”*

On page 14 the authors mention a study by Currie et al, so they should also add this to their reference list.

*The reference has been added to the revised manuscript.*

Reviewer 2
1. Statistics. The authors’ comment that Bonferroni corrected repeated t tests yield the same conclusion as the repeated measures ANOVA. This strengthens their contention that the differences they observe truly reflect population differences. It would be worthwhile for the authors to mention this in their Results or Discussion.

*Since ANOVA for repeated measures is the most appropriate test we believe that mentioning other tests such as repeated t tests is unnecessary and might confuse the reader as to the validity of the results.*

2. Number of samples in Figures 4 and 5. I disagree that the numbers of samples examined are not germane. Presumably, the total number of samples for each comparison is 50. It would matter to the reader, however, if one of the bars in a graph that showed "no difference" represented only 5 subjects, as the reader might infer that the chance of Type II error was high. The reader could calculate the number of samples represented in each bar by gleaning the information from Tables 1 and 2, but it would be better for the authors to provide the numbers in the Figure legends or in the Figures themselves.

*I am not quite sure what I was thinking when I made the comment they were not germane. They have been added to the revised figures.*
3. Formatting/spelling errors.
   a. Page 9 1st para, line 15. Should be: "According to manufacturer's specifications,....."

   Corrected in revised text

   b. Page 12, last line. There is a hanging "(vs.)." The results are missing.

   Added to the revised text

   c. Figure 3. On my copy of this, the bar colors did not appear in the legend.

   This has been corrected.

Discretionary Revisions (which the author can choose to ignore)
1. Reviewer 1 comments: The authors may wish to include their response to comment #5 (Relationship to gestational age) in the text of the manuscript. It strengthens the manuscript.

   We added the following line to the revised manuscript: “We found no relationship between PDGF-BB concentrations and gestational age (data not shown).”

2. Reviewer 2 comments: The authors may wish to include their explanation regarding storage sites of PDGF-BB in the text of the manuscript. It strengthens the manuscript.

   This is mainly in the manuscript already. We have added the paragraph regarding centrifugation (see above).

3. Timing of peak PDGF-BB levels in infants not requiring O2 at 28 days. The authors state on pg. 12 that peak PDGF-BB levels in these infants were seen at 2.9 days. Figure 2 appears to show a peak at 4-5 days. The authors may wish to clarify this apparent discrepancy (which is, I think, the product of differing definitions).

   This is not an error or difference in definitions but related to the order in which division of numbers occur. Ie, if you have a few high values the average value on a specific day is high which then makes the peak appear later. If you average the day on which an individual’s peak concentration occurs you get a different result.