Author's response to reviews

Title: State of Progress in Treating Cystic Fibrosis Respiratory Disease

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Author's response to reviews: see over
Dear BMC editor,
Please accept this revised version of our manuscript entitled “State of Progress in Treating Cystic Fibrosis Respiratory Disease”. We appreciate the contributions of the two reviewers and we have addressed their comments in the revised text and have given a point-by-point response to their comments below. In addition, we have made the editorial changes that you requested. We hope that this version will meet the approval of the reviewers and the editorial staff. Please let us know if there are any additional questions.

Sincerely,

Patrick A. Flume, MD

Reviewer 1:
1. The most important correction to be made is that when discussing the underlying pathophysiology of cystic fibrosis (CF) airway disease it is incorrect to state that the airway surface liquid (ASL) is dehydrated.

   We appreciate the reviewer’s more accurate description and we have incorporated this into the text. We have removed all use of the word dehydration in favor of volume depletion.

2. Associated with this misconception, is the statement that dehydration “creates ciliary dysfunction effectively halting the mucociliary escalator” as a cause of airway disease.

   As above, we have removed this description.

3. Phlegm in the CF airway is neither dehydrated nor viscous when compared with sputum from persons with asthma or chronic bronchitis. CF secretions are tenacious (adhesivity and cohesivity)

   As above, we have used this language to describe the events resulting in obstruction of the airways. Forgive us if we have actually stolen some of your text.

4. In the section on CFTR modulation, the authors accurately state that more than 1,800 CF gene mutations have been described in the SickKids database, however they also suggest that these can all be categorized as disease causing abnormalities of synthesis, processing, regulation, or channel conductance. Many, if not most of these, abnormalities have not been shown to be disease causing which has led to the unfortunate circumstance of patients with minimal or no symptoms being classified as having CF on the basis of having a non disease causing mutation identified through screening.
We accept that some of the identified mutations are associated with minimal features of disease and have tried to make this clear in the text.

5. In the discussion on the macrolide antibiotics, please note that macrolide antibiotics have been developed that have no antimicrobial properties but that have strong immunomodulatory properties (eg EM703 and Z18010) and that the 16-member macrolides have antimicrobial properties but are not effective immunomodulators. It is now believed that the mechanism of action for the macrolides is modulation of the extracellular regulated kinase (ERK1/2) and not antimicrobial effects.

We appreciate the comment and have edited the text accordingly.

Reviewer 2:

1. When discussing the early onset of lung disease (p. 4), would include the reference by Linane, et al (AJRCCM 2008) that PFTs in CF infants are abnormal by 6 m/o.

   We have included the Linnane reference as recommended.

2. Is “death” of the exocrine pancreas (p. 6) really the best term? How about fibrosis, which is the reason the disease was originally named CF in the first place?

   We have edited this text as suggested.

3. The other issue with gene therapy (p. 7) besides clinical benefit is whether gene transfer/expression can be stably maintained.

   We appreciated this comment and have amended the text accordinglyl.

4. When discussing CFTR modulation, may want to also discuss phenylbutyrate and ubiquinone inhibition.

   We appreciate the reviewer’s interest in completeness. However, neither of these approaches are viable and in clinical trials at this time. We are well over the requested word limit, so we would prefer to omit discussion of these approaches.

5. The results of TIGER-2 were recently published in JCF, so could add this citation. The authors also discuss potential reasons why TIGER-2 failed to show an effect, which might be useful to cite.
We have added the citation in JCF as well as conjecture as to reasons for TIGER-2 failure (which to our knowledge, have not been unambiguously determined)

6. In the discussion of Hydrators, may want to include the results of the recent ISIS trial.

   We have added the results of the ISIS trial as suggested.

7. In the discussion of ICS, should make it clear that there has never been an RCT that has studied ICS, but that 2 registry studies have shown ICS therapy is associated with better outcomes. On the other hand, should cite the WISE study, which showed that withdrawal of ICS was not associated with worse outcomes. Finally, should mention that the latest version of the CF treatment guidelines continue to recommend against their use, except if the patient has asthma.

   Thank you for the suggestions. We have included these points in the text and noted that efficacy endpoints employed in the withdrawal study were different from those of the retrospective registry studies

**Editorial requests:**

*Email addresses- We have included the email addresses of both authors on the title page.

*Copyright for use of figures – We have not requested permission to use the figures from the copyright holders; we believed this was typically done by the editorial office. Please let me know if I need to make the request. We have tried to upload only one copy of each figure.

*Competing interests – We have added a statement with our disclosures after the Conclusions.

*Authors’ contributions – Both authors contributed equally and this is noted in this section.

*Authors’ information – We do not believe this adds to the manuscript and have not added any information.