Reviewer’s report

Title: Lubiprostone ameliorates the cystic fibrosis mouse intestinal phenotype

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Reviewer: Jonathan Kaunitz

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General: The authors submit a paper describing the effect of lubiprostone on the intestinal phenotype of the CF mouse. They tested the hypothesis that mucus turnover is slowed in CF due to diminished fluid secretion, leading to bacterial overgrowth.

Comment:

1. Although bacterial overgrowth has been reported in CF (e.g. Fridge J Ped. Gastroenterol Nutr 2007 44:212, 2007), the most commonly reported GI problem is recurrent obstruction and constipation, which has been treated successfully with lubiprostone (O’Brien Ann Pharmacotherapy 2010 44:577). The manuscript should include a bit more background information.

2. Although there is controversy surrounding the mechanism of lubiprostone, the authors have omitted perhaps the most compelling publication, Bijvelds (Gastroenterol 2009 137:976). In the paper, the authors showed that the effects of lubiprostone were entirely inhibited by prostaglandin EP4 antagonists whereas a CLC-2 channel inhibitor was without effect in three model systems. Furthermore, almost all in situ data supports a basolateral localization of the CLC-2 channel in the enterocyte. In light of these data, the predominance of the data favors lubiprostone acting as a prostaglandin.

3. The authors use an indirect means to assess mucus secretion, measurement of intervillous (crypt) width. Since they hypothesize that lubiprostone increases the rate of mucus turnover, they should measure it directly, perhaps by the methods described in ref. 21.

4. Lubiprostone substantially increased bacterial overgrowth in normal mice. Is this effect clinically important? Given that lubiprostone is approved to treat IBS, and bacterial overgrowth may worsen IBS, it would seem that this effect of lubiprostone would impair its therapeutic effects in the IBS population.

5. The authors stated on p. 15 that lubiprostone “…decreased the innate immune response…”. This seems like too strong a statement given the data presented, since it is difficult to extrapolate changes in RNA expression with an immune response. In general, the gene chip analysis does not seem to add much to the authors’ main argument and should be deleted.

6. If lubiprostone is a CLC-2 channel activator, why does it affect motility? Would it not be more likely that it acts as a PG, which has well known effects on
motility? Although the author has previously measured altered motility in CF mice, is this also true in humans? In one article (Tonelli, J Cyst Fibros. 2009 May;8(3):193-7), gastroparesis was unusual and is thought the be due to lung disease or diabetes in most cases. In general, the motility data adds little to testing the stated hypothesis and could be deleted.

7. The Discussion could be reduced by 30% by deleting much of the speculation and focusing on the core findings.

8. Fig. 4. It seems that that n is much lower for controls than for the lubi groups. Is this the case? Could this bias the interpretation?

9. How valid is the method described for the quantitation of intestinal flora in the absence of standard culturing techniques?

Minor:
1. Please use the term “anion channel” rather than the confusing “Cl- HCO3-channel”, especially since the nature of the ionic species transported by CFTR remains controversial.

2. Also, please use the term “anion exchangers” rather than “anion transporters that exchange…”

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

Quality of written English: Acceptable

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

Declaration of competing interests:

I have received research funding and meeting support from Takeda Pharmaceuticals in the past 5 years.