Reviewer's report

Title: Lubiprostone ameliorates the cystic fibrosis mouse intestinal phenotype

Version: 2 Date: 20 July 2010

Reviewer: Jonathan Kaunitz

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Comment:
The authors have revised the manuscript somewhat by adding some of the citations suggested by the reviewers. Nevertheless, many of the reviewers' comments have not yet been answered satisfactorily.

Major Compulsory Revisions

1. As Dr. De Jonge stated in his review, the main intestinal phenotype of CFTR -/- mice is intestinal obstruction and decreased survival. The phenotypic changes reported by the authors, such as bacterial overgrowth and delayed intestinal transit although present, are less well characterized.

2. Although the literature is divided about the mechanism of action of lubiprostone with regard to intestinal anion secretion, the preponderance of the data strongly favors lubiprostone acting as a local prostaglandin that activates CFTR in most cases. I am aware of few in situ data obtained from intact organisms that support the alternative explanation.

3. The authors make several statements stating that lubiprostone "may" increase bicarbonate secretion, even this was clearly shown in rats in ref. 20.

4. The authors use rhoadmine dextran to measure intestinal transit. Although the authors state that it is a "nondigestible, nonabsorbable tracer", dextran is fermented by colonic flora into butyrate (Olano-Martin E, Mountzouris KC, Gibson GR, Rastall RA. In vitro fermentability of dextran, oligodextran and maltodextrin by human gut bacteria. Br J Nutr. 2000 83:247-55). Given the marked differences of intestinal bacterial colonization between the groups, would the use of this marker add artifact to the measurements?

5. The authors speculate that some of their findings may be due to changes in the hydration status of mucus. Yet, mucus in biological systems in considered to be 99% hydrated. If the authors area aware of intestinal mucus in healthy living animals that is not fully hydrated, these data should be cited.

6. Since the authors did not measure immune cell function but rather reported expression changes of immune-function related genes, I reiterate my prior comment that the data should not be reported as the "innate immune response" or equivalent. Lacking direct measurements of mast cell migration or actual measures of immune function, it is exceedingly difficult to interpret expression
changes of this nature.

7. The Discussion is overly long and speculative and would thus benefit from deletion of many of its sections, despite the authors statements to the contrary.

Minor Essential Revisions

The authors should consider combining Figs. 2 and 3

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:

Yes, reserach support from Takeda NA.