May 8, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: refractory UC treatment revised manuscript final 2015.5.8.doc).

Title: **Advances in refractory ulcerative colitis treatment: a new therapeutic target, Annexin A2**

Author: Satoshi Tanida MD, PhD, Tsutomu Mizoshita MD, PhD, Keiji Ozeki MD, PhD, Takahito Katano MD, PhD, Hiromi Kataoka MD, PhD, Takeshi Kamiya MD, PhD, and Takashi Joh MD, PhD

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 18017

The authors thank you for your letter on 30-April-2015. Likewise, we greatly acknowledge your kind suggestions on our manuscript. We have precisely revised our manuscript in line with comments from reviewers.

We are looking forward to hearing from you.

Sincerely,

Satoshi Tanida, M.D. PhD
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1. My comment to the suggestions of the reviewer (#68485).

(1) This is an interesting manuscript especially the section on Annexin A2. It is well written, however, the review section on UC therapy is rather cursory and could do with grading of evidence. However, the section on ANX A2 and especially the in vitro data showing inhibition with siRNA is novel. I would suggest a re-submission as an original article removing the initial review aspect and rather concentrate, explore the in vitro data and subsequent discussion on potential therapeutics.

Thank you for your comments. I received an invited letter to recommend to submit a review article on a new strategy for patients with IBD refractory to conventional medications and potential of Annenxin A2 as a new molecular target for the IBD treatment. Currently, calcineurin inhibitors, TNF-α blockade and vedolizumab, which block or neutralize the production and functions of inflammatory cytokines and adhesive molecules, are currently effective for the treatment of patients with refractory UC due to their high rate of remission induction and maintenance. It is very important to know the efficacy and limitation of currently available conventional and new agents. So, I would like to state the efficacy and limitation of ever-changing therapeutic agents for the UC treatment and emphasize the potential of Annenxin A2 as a new molecular target.

Now, I am making progress the experiments investigating the involvement of Annexin A2 in IBD development in IBD model mouse. I will submit an original article on the involvement of Annexin A2 in IBD development in IBD model mouse.

2. My comment to the suggestions of the reviewer (#227388)

(2) The author give a bird's overview of existing treatment of Inflammatory Bowel Disease with super-selected references in most instances. I am delighted to see that authors introduced a new chapter (Annexin A2) opening in the ever-changing ever-evolving field of management of Inflammatory Bowel Disease. The manuscript is backed by adequate cross-referencing.

Thank you for your comments. I would like to state the efficacy and limitation of ever-changing therapeutic agents for the UC treatment and emphasize the potential of Annenxin A2 as a new molecular target.

3. The manuscript has been revised according to the suggestions of the reviewer (#36951). (#36951).

(3) It is need the modification of the introduction too long and conclusion are less clear.

Thank you for your comment. I have shortened the introduction and have clarified the conclusion.

4. My comment to the suggestions of the reviewer (#71779).

(4) Exhaustive review.

Thank you for your comment.