May 28, 2015

Dear Editor,

Please find enclosed the revised manuscript in Word format (file name: 18311-Review.doc).

Title: Nanomedicine and Drug Delivery Strategies for Treatment of Inflammatory Bowel Disease

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 18311

The manuscript has been improved according to the suggestions of the reviewers:
1 The format has been updated.

2 Revisions have been made according to the suggestions of the reviewers.
Reviewer 1
Minor comments
(1) Page 8 line 4 "addressing"
Answer: We have corrected the text accordingly.

(2) Page 9 line 22 "facilitate"
Answer: We have corrected the text accordingly.

(3) In the conclusion part please provide the reader with a message regarding the mechanism(s) facilitating the interaction of nanoparticles and the cell membrane as well as clear message concerning the intracellular uptake of the drug and the vehicle.
Answer: We have revised the conclusion accordingly. Specifically, we have added the following text: "ASO, siRNA and anti-inflammatory molecules with drug delivery vehicles generally undergo cellular internalization by paracellular transport or endocytosis into intestinal epithelial cells. Specialized differentiated epithelial cells called M cells are involved in the predominant uptake of nanoparticles in healthy intestinal mucosa. In intestinal inflammation, a loss of mucous-gel layers and the epithelial barrier through enterocyte damage and increased delivery of immune cells to the mucosal tissue have been shown to lead to the preferential accumulation and uptake of nanomedicines by both enterocytes and macrophages. Therefore, the topical therapy of nanomedicine by oral and rectal administration can be effective in treating the inflammation site. Important factors in targeting the intestine are not only the use of nano-size molecules but also the implementation of additional strategies to enhance drug delivery

to inflamed intestinal mucosa and achieve maximal retention time in tissues."

(4) Finally it might be interesting for the readers to give in the text some information concerning the oral nano-delivery systems for colon targeted drug delivery in IBD (Hua et al Nonomedicine 2015 Mar 14. Pii: S1549-9634(15)00068-4)

Answer: We agree with this comment and have added the reference (reference 78).

78 Hua S, Marks E, Schneider JJ, Keely S. Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: Selective targeting to diseased versus healthy tissue. Nanomedicine 2015 [PMID: 25784453 DOI: 10.1016/j.nano.2015.02.018]

Reviewer 2

Major:

1. I feel that the authors are very committed to nanoparticles. Their benefits are overestimated in my opinion. There should be more critical part in the discussion section (which is very short compared to length of the whole manuscript). E.g.: Rectally administered nanoparticles (and their delivery systems) won't raise the attention of a clinician, as locally administered 5-ASAs are effective, tolerable and cheap medications. More criticism should be used in the IL-10 section, also.

Answer: We have revised the conclusion accordingly. Specifically, we added the following text to the conclusion: 'ASO, siRNA and anti-inflammatory molecules with drug delivery vehicles generally undergo cellular internalization by paracellular transport or endocytosis into intestinal epithelial cells. Specialized differentiated epithelial cells called M cells are involved in the predominant uptake of nanoparticles in healthy intestinal mucosa. In intestinal inflammation, a loss of mucous-gel layers and the epithelial barrier through enterocyte damage and increased delivery of immune cells to the mucosal tissue have been shown to lead to the preferential accumulation and uptake of nanomedicines by both enterocytes and macrophages. Therefore, the topical therapy of nanomedicine by oral and rectal administration can be effective in treating the inflammation site. Important factors in targeting the intestine are not only the use of nano-size molecules but also the implementation of additional strategies to enhance drug delivery to inflamed intestinal mucosa and achieve maximal retention time in tissues." In addition, we added the following sentence to the IL-10 section: "Topical therapy using nanotechnology, such as oral and rectal administration, might improve efficacy and safety by localizing the effect of IL-10 to the inflammation site, thus preventing side effects."

2. In the same time, adverse events (infection, tumour-issue, antibodies, allergy, etc.) with the conventionally used biologics are emphasized. Indicating the exact odds ratios regarding these side effects would make the manuscript more balanced.

Answer: We have revised the introduction accordingly. Specifically, we added the following text: "Seventy cases of mycobacterial infections were reported in patients receiving anti–TNF-α Abs by 2001, and the incident rate was more than 10 times the expected background rate. Several studies have shown

an association between anti–TNF-α Abs and cancers such as non-Hodgkin's lymphoma (NHL) and cutaneous malignancies. A standardized incidence rate of NHL in over 16,000 IBD patients was reported to be 5.5 (95% CI: 4.4-6.6), and the odds ratio of developing cutaneous malignancies was reported to be 2.07 (95% CI: 1.28-3.33)".

3. A table reviewing the possible delivery systems and their mechanisms of action would enhance the value of the manuscript. It is not easy to understand the text fulfilled with lots of abbreviations.
Answer: We have added 3 tables to the revised manuscript summarizing the nanomedicines and their abbreviations.

Minor:
1. Significance of Smad7 ASO treatment is emphasized in the abstract. As the manuscript overviews lots of modalities, it is not favoured to stress one in the abstract section, in my opinion.
Answer: We agree with this comment and have deleted the corresponding sentence regarding Smad7 from the abstract.

2. Authors should check the formal requirements of WJG (reference numbering are correct?)
Answer: We have consulted the formal requirements of WJG.

3. Certolizumab and golimumab are also the members of anti-TNF families, these should be mentioned in the last paragraph of page 3.
Answer: We have added certolizumab and golimumab accordingly.

Sincerely yours,

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