February 8, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Chinnadurai et al_review.doc).

Title: Challenges in modelling mesenchymal stromal cell based clinical trials for inflammatory bowel disease in animal models

Authors: Raghavan Chinnadurai, Spencer Ng, Vijayakumar Velu, Jacques Galipeau

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 15765

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
Reviewer #00189171: Chinnadurai et al. reviewed the pitfalls of translating the results of mesenchymal stromal cell trials in inflammatory bowel disease. As a clinician, I could understand the most important viewpoints which should be take into considerations regarding this topic. A minor concern: Authors offer to perform the particular MSC procedure on at least two different models. Which pairs would be ideal to eliminate the methodologic inappropriateness, in their opinion? I have some formal advice: 1. Some of the information (page 3 - criterias define multiple MSCs;) are more detailed as it needed for a clinician. Summarizing these data in tables would make the paper more readable. 2. Authors refer the only one figure many times in the text. This figure could be divided into several parts. It would make it more simple and understandable.

Response: Thank you for your clinically insightful comments. We have made change as “Investigators may require the use of at least two of the models, for example an acute and a chronic colitis model, described above to validate their findings relevant to the clinical trials”. 1. Comprehensive analysis of defining MSCs were well reviewed by Dominici M et. al.(PMID 16923606) and Krampera M et al (PMID: 23602578). These references were cited for the readers to get further detailed insights on the defining characteristics of MSCs. 2. We divided the figure citation in to Figure 1 left and Figure 1 Right to make it more understandable for differences between murine and human respectively.

Reviewer # 00503539 The authors reviewed the available data, which utilize mesenchymal stem cells (MSCs) for mitigating colitis in animal models, and highlighted the challenges in translating studies into effective clinical therapies. As they mentioned, understanding of MSC mechanisms to reduce gut injury and inflammation is essential to inform the improvement of current ongoing and future clinical trials. This excellent, updated review article will provide much recent knowledge concerning MSC utilization for IBD patients to the readers of this journal.

Response: We appreciate your comments.

Reviewer # 00037018 This is an interesting and well-structured review on experimental approaches to test molecular mechanisms of mesenchymal stromal cells as immunomodulatory agents. This reviewer has no major concern on this review. Minor points are: Page 4, last

paragraph of section "Clinical trials...": the authors mention two major factors for variations in clinical outcome, but the subsequent list is not clear, please revise. Page 7, first paragraph: the authors state that reduced CD34 is a differential property to primary MSCs, but previously in the paper they wrote that lack of CD34 is a criteria to define multipotent MSC, please make this consistent Page 7, last sentence of second paragraph: please revise "mouse model of colitis mouse model". There are minor typos that this reviewer could spot: page 8 "Sjorgen Syndrome, and myelodisplastic" please remove ","; page 8 "xeogenic" maybe "xenogenic" Figure 1 may not be completely clear, in particular the fact that converstion of tryptophan to kyneurine or l-arginine to nitric oxide determine immunomodulatory activity, this could be written explicitly in the figure

Response: We appreciate your comments. Suggested changes have been addressed in the revised manuscript and editorial corrections were made.

Reviewer # 00038879

This is a nice, comprehensive review on a very interesting subject. My comments: 1. what the authors describe as an issue in testing MSC therapy for IBD (namely the lack of reliable animal models)is also an issue for any other type of medications, especially biologics. Hence I believe the authors should also briefly mention in their discussions the many trials failed with biologics for IBD (despite great promises of preclionical studies) and cite relevant reviews (i.e. Gut. 2012 Jun;61(6):918-32 and Expert Rev Clin Immunol. 2014 Feb;10(2):219-29) 2. The English can be improved - there are several typos of wrong sentences. Examples: - Abstract "inform the imrpovement of current ongoing..." - page 4 top: ""have been tested clinical trials..." and "..clinical trials aimed the safety...' - page 4 middle: "...which is contrast to the data..." - page 5 middle "...and is currently unknown of such effect..." - page 9 middle: "...suggested the defective of distribution..." - Figure legend, last sentence does not read well

Response: We appreciate your comments. Suggested editorial changes are reflected in the revised manuscript. We also discussed the overall challenge of translating biological therapy from mouse model of colitis into human inflammatory bowel diseases.

Reviewer # 00035901

In this review, the authors discuss the challenges and approaches of using appropriate animal models of colitis, not only to study putative MSC therapeutic efficacy and their mechanisms of action, but also the suitability of translating findings derived from such studies to the clinic. The present paper was well organized and well investigated. It will give us a new information in this field. I have no claim.

Response: We appreciate your comments

3. References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology.*

Sincerely yours,

Prof. Jacques Galipeau.
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