

ANSWERING REVIEWERS

Dear Editor,

We have the pleasure to contact you for submitting the revised version of Manuscript No. 28727, entitled “Immunomodulatory Oligonucleotide IMT504: Effects on Mesenchymal Stem Cells as a First-in-Class Immunoprotective/Immunoregenerative Therapy” by Zorzopulos et al. We are very grateful to the Reviewers, whose suggestions, queries and corrections have been carefully analyzed and considered. All suggestions were found to be pertinent and the manuscript has been accordingly modified.

Please, find below the reviewers’ comments and corresponding answers.

Reviewer 02446027:

The authors review the use of IMT504 for resolution of inflammation and regeneration in several of human diseases. The topic is of considerable interest since IMT504, the prototype of a major class of immunomodulatory oligonucleotides, induces expansion of MSCs and may useful for clinical trial in patients with osteoporosis, diabetes or sepsis. Since osteoporosis, diabetes mellitus are chronic diseases affecting millions of people worldwide and the prevalence of these diseases is increasing and it is a serious health problem. Therefore, review on the treatment options for these diseases, and focuses on IMT504 for resolution of inflammation and regeneration in several of human diseases is a beneficial. Overall the review is complete, and contains the most important information about the IMT504 in treatment of many diseases. However, there are several concerns about the manuscript which need to be improved. Therefore, I cannot recommend acceptance of the manuscript in its present form. The manuscript needs minor revision.

1. The manuscript is long, and there are some spelling, grammar and syntax errors that require attention. For example, on page 9: dierentiation should correct to, differentiation, on page 19: abbreviation for interferon is IFN not INF. Some more of these examples can be found throughout the manuscript. The authors should go over the entire manuscript for the correction.

Spelling, grammar and syntax errors found throughout the manuscript were corrected. Proofreading test was done by an English language editor and by two of the authors from the US (David Horn and Steven Opal).

2. Some of the references were old. For example, reference number 2, 3, 4, 11 ext. The authors need to add new, up-to-date references to the reference section.

References 2, 3, 4 and 11 are historical. Therefore, cannot be up dated.

3. The year that some of the references were published are wrong and needs to be corrected. For example, reference number 49: The correct year of published this paper is: 2014 Not 201, or reference number 70: The correct year of published this paper is: 2013 Not 201. The authors should go over the entire reference section for the correction.

The entire Reference Section was revised and corrected.

Reviewer 02446101:

In this manuscript, you introduced IMT504. The research is very helpful to the following researchers. Generally speaking, this manuscript was well written. However, there are some language mistakes. For example, ‘intricate’ was spelt as ‘intrincate’. In all, my opinion is to accept after minor revision.

Spelling, grammar and syntax errors found throughout the manuscript were corrected. Proofreading test was done by an English language editor and by two of the authors from the US (David Horn and Steven Opal).

Reviewer 02446243:

In the present manuscript the authors reported that IMT504, the prototype of a major class of immunomodulatory ODNs, induces in vivo expansion and likely activation of MSCs. They used the IMT504 in preclinical models of neuropathic pain, osteoporosis, diabetes and sepsis demonstrating interesting functions and future perspectives for clinical applications. The aim of these experimental trials was to solve most, if not all, of the problems related to the therapeutic applications of MSC external delivery that can be already used. The use and the application of the IMT504, could be an alternative or synergic candidate for the treatment of several of the inflammatory disorders likely responsive to MSC transplant. I found this paper really rich in details, correctly written in scientific English and really interesting in all of its parts. However in the description of the activation of MSC, I think the authors could add more details, in order to strengthen the manuscript. Moreover the authors should also specify if, during their studies, have found some interesting changing in the modulation of pluripotency, in the differentiation of MSCs and eventually in the maintenance of their status. I believe that the present manuscript could be published in WJSC after the minor review requested

According to the suggestion of the reviewer, we have added more information about MSC activation including citation of a recent review on the subject:

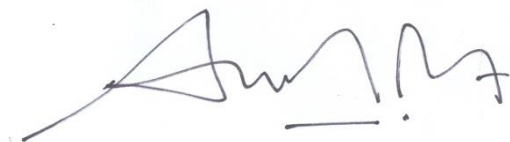
“Among them, the pro-inflammatory cytokines interferon-gamma (IFN- γ), tumor necrosis-alpha (TNF- α), interleukin-6 (IL-6) and IL17A and stimulation of the receptors TLR3 and TLR4 have been proposed as main signals for switching MSC differentiation to its anti-inflammatory and pro-resolving differentiation stage (de Witte SF, Franquesa M, Baan CC1, Hoogduijn MJ. Toward Development of iMesenchymal Stem Cells for Immunomodulatory Therapy. Front Immunol. 2016; 6:648. [PMID: 26779185 DOI:10.3389/fimmu.2015.00648])”.

Information on the modulation of pluripotency, in the differentiation and maintenance of the status of the MSCs during treatment are very important issues that would be answered in future contributions.

A file with highlighted changes made to the manuscript according to the peer-reviewers' comments is attached together with the language certificated file locked for submission by FP Servicing BPG. Also, a file containing figures as ppts is included, as requested.

Regarding to plagiarism, the manuscript was uploaded for iThenticate.com analysis. It is worth to note that every sentence stated before by us or other authors was always followed by its corresponding reference.

Yours very truly,

A handwritten signature in blue ink, appearing to read 'Alejandro Montaner', with a horizontal line underneath.

Dr. Alejandro Montaner

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