Format for ANSWERING REVIEWERS

December 10th 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (New strategies of gene therapy for hepatic fibrosis: 14607-review.doc).

Title: NEW STRATEGIES OF GENE THERAPY FOR HEPATIC FIBROSIS

Author: Salazar-Montes A, Hernández-Ortega LD, Lucano-Landeros S and Armendáriz-Borunda J.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 14607

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

3 References and typesetting were corrected

One point by point response letter is included at the end of this document.

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

Sincerely yours,

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POINT BY POINT RESPONSE

Reviewer 1

1.- The authors provide an overview of the main strategies used in gene therapy for liver fibrosis. Although this manuscript is rich in content and generally updated as far as literature is concerned, there are some concerns mainly regarding its structure. For example, it is not clear to the reader that the text is divided in three main parts: 1.NON-VIRAL VECTORS divided into DNA PLASMIDS and LIPOSOMES, 2. VIRAL VECTORS divided into ADENOVIRUSES-BASED SHUTTLE VECTORS, AAV VECTORS and NOVEL VIRAL VECTORS FOR GENE THERAPY and finally 3. BLOCKING MOLECULES FOR INHIBITION OF DELETERIOUS GENES.

Response

This review presents in a global manner the published information about different strategies in gene therapy for experimental liver fibrosis. Due to the fact that there are several vectors for gene delivery, we considered convenient to present the available information by blocks in the two generic groups used in gene therapy. Those two main blocks of information regards viral and non-viral vectors. An additional third part of this review concerns a novel strategy using blocking molecules. Thus, inside each group, it is shown the most relevant information obtained from the different authors dealing with liver fibrosis treatment.

2.- I would appreciate the authors' response to the following comments: Please check and correct references 5-14 according to their order in the text. Reference 52 is missing & Eun-Joong et, al. and Jinxia L, et.al are not mentioned in the references. Please, correct.

Response

All references have been checked and corrected according to the observations of the referee.

3.- In the section "non viral vectors", I would suggest quoting references for the methods which are not analyzed thoroughly, i.e. polymers.

Response

This reference has been included.

4.- In the section "DNA plasmids", there appears to be a need for a small introduction about DNA plasmids similar to the introductions used for the rest strategies you deal with.

Response

A paragraph with this information has been included.

5.- The title "(AUGMENTATION OF LIVER REGENERATION ALR)" is redundant.

Response

This title has been removed and the information included as part of the paragraph.

6.- MMP13 is mentioned amongst the therapy targets in the design of anti-fibrotic strategies for chronic liver diseases but is not analyzed as MMP1, MMP8, MMP9.

Response:

Information of gene therapy protocols using MMP13 has been included.

7.- The section "DECOY MOLECULES" should be incorporated in "BLOCKING MOLECULES FOR INHIBITION OF DELETERIOUS GENES", amongst ANTISENSE OLIGONUCLEOTIDES, siRNA, and miRNAs with a general introduction about new gene therapy approaches based on short DNA or RNA technology.

Response:

These indications have been properly done.

8.- The advantages and disadvantages of gene therapies mentioned here, as well as the potential effectiveness of gene therapy for liver fibrosis in humans should be addressed in the discussion section of the manuscript.

Response:

This information was already incorporated in discussion.

9.- Furthermore, the authors could explore whether there is progress in research overcoming the side effects of application of gene therapy in the clinical practice.

Response:

At this moment, no gene therapy protocol against human liver fibrosis has been reported in the clinical trial web sites and it is already included in discussion.

10.- Conclusively, the manuscript could be organized better and more attention should be given in syntax, spelling and grammar, for successful publication.

The entire manuscript has been revised and corrected. PLEASE NOTE ALL THE CORRECTIONS ARE UNDERLINED.