Format for ANSWERING REVIEWERS

March 17, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6556-2nd revised.doc).

Title: Gene therapy for preventing liver cirrhosis, where we are?
Revised title: Small RNA-and DNA-based gene therapy for the treatment of liver cirrhosis, where we are?

Author: Kyung-Hyun Kim and Kwan-Kyu Park

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6556

Thank you for your kind comments and useful suggestions that have helped us to improve our paper considerably.

As you suggested, now I re-submit my manuscript with almost complete revision addressing all the points raised by the reviewers.

I am including a letter of response to the reviewer's comments and highlighted the changes in the revised manuscript.

Again, I appreciate your kind suggestion.
Thank you for your consideration.

Best regards,

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Reviewer 1

The author searches many documents and gathers it up carefully. I have a question to ask you. How about the start time of the treatment to hold liver fiberization in check by a gene therapy? If the sustained infection of the hepatitis virus is established, will you perform it? Or is it after a diagnosis of the chronic hepatitis? May the fiber ingredient be eliminated? Is the gene therapy that I limited to liver cancer considered?

Answer to Reviewer 1

We are grateful to reviewer 1 for the critical comments and useful suggestions that have helped us to improve our paper considerably. As indicated in the following responses, we have incorporated all of these comments.

How about the start time of the treatment to hold liver fiberization in check by a gene therapy?

Answer 1.

Thank you for kind suggestion of our manuscript.

The start time of the liver fibrosis will be the initial point of inflammation. Sustained inflammation undergoes to the liver fiberization. Prevention of the accumulation of extracellular matrix during the liver fibrogenesis is the major point for the treatment in liver fibrosis. Based on our previous studies, the start time of gene therapy will be 2 or 3 weeks after CCl_4 administration in mouse.

If the sustained infection of the hepatitis virus is established, will you perform it?

Answer 2.

As your suggestion, sustained infection of the hepatitis is crucial factor for liver cirrhosis. If the causative agent for hepatitis is available, we are expecting to contribute our following research in near future.

Or is it after a diagnosis of the chronic hepatitis?

Answer 3.

The main purpose of gene therapy for liver cirrhosis in clinic is to apply these therapeutic approaches after a diagnosis of the chronic hepatitis.

May the fiber ingredient be eliminated?

Answer 4.

Patients, who have chronic hepatitis, go through sustained inflammation which leads to fibrosis in liver. During the fibrotic changes, there has already been the fiber ingredient (ECM) around liver tissue. Complete elimination of these fiber ingredients might be impossible. The point of therapeutic approaches is the prevention of the progression of liver fibrogenesis.

Is the gene therapy that I limited to liver cancer considered?

Answer 5.

As your query, gene therapy for liver cancer will be available to study. However, the different approach is required to gene therapy for liver cancer. Inflammation and fibrogenesis-related genes are key factors in liver fibrosis, whereas liver cancer will be focus on the prevention of proliferation in liver tissue.

Reviewer 2

During the review process the paper by Kim and Park has been improved impressively. Including of the two tables - Summary of studies using small RNA and DNA based therapies in liver cirrhosis - Advantages and disadvantages of small RNA- and DNA-based gene therapy Improved the review article considerably. Changing of title and eliminating lots of grammatical errors improved the revised version in addition. From my point of view the mansucript could be published now.

Answer to Reviewer 2

Thank you for your kind comments of our manuscript.

Reviewer 3

A good review on future perspective in patients with liver cirrhosis. English language needs improvement.

Answer to Reviewer 3

We are grateful to reviewer 3 for the critical comments and useful suggestions that have helped us to improve our paper considerably. We have edited this manuscript. Thank you for your kind comments of our manuscript.

Reviewer 4

To the authors,
Congratulations for this review. The manuscript is well written and has no major flaws.
I have some (relatively minor) concerns, as listed below:

1. Abstract:
    a. no need to abbreviate oligodeoxynucleotides.
    b. Last phrase , (for the treatment of liver fibrosis) should be liver cirrhosis (see the title of the review).
2. Introduction:
    a. Page 4, second and third phrases : please, make them more clear
    b. Page 4 first paragraph, last word: fibrogenesis or fibrosis?
3. Gene therapy and all over the text:
    a. There are too many abbreviations which make difficult to keep readers attention (e.g. in one single page there are nearly 50 abbreviations!)

b. Page 5, second paragraph, last phrase: "recently……@ the article was published more than a decade ago!!!

c. Tables 1 and 2 are not included in text!??

4. Conclusion section:
    a. Is too long, please rewrite it.
    b. Please delete "table 2…", " for example" (twice on page 13)
    c. You repeat three times "small RNA - and DNA-based therapeutics" in two consecutive paragraphs (page 13 and 14)
5. References: please, refer to the authors' instructions (e.g. first author underlined)
6. Figure 1: is it original? If not, please cite the reference including permission for reproduction .

Answer to Reviewer 4

We are grateful to reviewer 4 for the critical comments and useful suggestions that have helped us to improve our paper considerably. As indicated in the following responses, we have incorporated all of these comments into the revised version of our paper.

1. Abstract:
    a. no need to abbreviate oligodeoxynucleotides.
    b. Last phrase , (for the treatment of liver fibrosis) should be liver cirrhosis (see the title of the review).

Answer 1.

Thank you for kind suggestion of our manuscript.

As your suggestion, we revised abstract. (Revised and blue highlighted in abstract)

2. Introduction:
    a. Page 4, second and third phrases : please, make them more clear
    b. Page 4 first paragraph, last word: fibrogenesis or fibrosis?

Answer 2.

As your suggestion, we revised second and third phrases. We also revised the

last word of page 4 first paragraph from fibrogenesis to fibrosis. (Revised and blue highlighted in introduction)

3. Gene therapy and all over the text:
    a. There are too many abbreviations which make difficult to keep readers attention (e.g. in one single page there are nearly 50 abbreviations!)
    b. Page 5, second paragraph, last phrase: "recently……@ the article was published more than a decade ago!!!
    c. Tables 1 and 2 are not included in text!??

Answer 3.

As your suggestion, we revised all over text. Unnecessary abbreviations are deleted. Additionally, "recently" is deleted. Table 1 and 2 are included in conclusion section. For the smooth progression in text, table 1 and 2 change the order (Revised and blue highlighted in main text and conclusion)

4. Conclusion section:
    a. Is too long, please rewrite it.
    b. Please delete "table 2…", " for example" (twice on page 13)
    c. You repeat three times "small RNA - and DNA-based therapeutics" in two consecutive paragraphs (page 13 and 14)

Answer 4.

As your suggestion, we revised conclusion part. Additionally, "for example" (second paragraph) is deleted. (Revised and blue highlighted in conclusion)

5. References: please, refer to the authors' instructions (e.g. first author underlined)

Answer 5.

As your suggestion, we revised reference. (Revised and blue highlighted in reference)

6. Figure 1: is it original? If not, please cite the reference including permission for reproduction .

Answer 6.

Figure 1 is original. It does not need to permission for reproduction.