

Format for ANSWERING REVIEWERS



April 25, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: WJG Editorial revised.doc).

Title: Therapeutic potential of siRNA/miRNA in hepatocellular carcinoma

Author: Farra Rossella, Grassi Mario, Grassi Gabriele, Dapas Barbara.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 17297

The manuscript has been improved according to the suggestions of reviewers; all text modifications have been reported in dark orange.

Reviewer #1

1) The authors reviewed the therapeutic potential of siRNA/miRNA in hepatocellular carcinoma and focused on siRNAs/miRNAs molecular targets and relevant delivery systems. Though the authors described in detail molecular targets for HCC from three approaches and liver directed delivery systems, there are other molecular targets that are not mentioned. The authors should add these in this article.

We agree with the referee that there are other possible markers as we mentioned in the paper on page 4 line 12 from top quoting ref 19. However, because we focussed on the most recent published works (we considered 2014-15 works only), not all possible targets have been discussed in our manuscript.

2) In addition, the number of references was insufficient that should be appropriately add. In conclusion, I think this article should be published on this journal, but need to minor revision.

We limited the number of references as our manuscript is not a full review but just an Editorial which, because of its nature, has to be necessarily shorter. Despite this, due to the point number 1 raised by reviewer 2, we have added 3 additional very recent publications (27, 28, 29) together with a comment in the text (page 11 lines 1-12 from bottom; page 12 lines 1-16 from top). Additionally, table 2 has been updated consequently.

Reviewer #2

1) Authors reviewed current concepts and delivery methods for si/miRNA treatment in hcc. Although there is not any new contribution from authors, manuscript is concisely summarized literature.

To fulfil the referee request, in the revised manuscript we have introduced and commented two recent works from our group (references 27 and 29) on page 11 lines 1-12 from bottom and on page 12 lines 1-16 from top. Additionally, table 2 has been updated consequently.

Reviewer #3

1) The authors reviewed the therapeutic potential of siRNA/miRNA in hepatocellular carcinoma and focused on gene targets and delivery system. Though experimental studies have shown promising results in cancer therapy by using animals, clinical efficacy still needs to be further studied. Of note, the liver blood supply system is different with dual blood supplies: Portal vein and hepatic artery. Normal liver is mostly supplied by portal vein;

however, the HCC is mostly supplied by hepatic artery. The regular IV route for siRNA/miRNA may not provide effective treatment to HCC. The authors should mention and discuss this in this paper.

According to the review comment, this important consideration has been introduced on page 16 lines 4-8 from bottom.

Reviewer #4

1) The authors focus their discussion on the most recent advances in the identification of siRNAs/miRNAs molecular targets and on the development of suitable siRNA/miRNAs delivery systems in HCC. Despite further improvements in the use of siRNA/miRNAs as potential novel anti HCC drugs are necessary, the progresses achieved in the last years fully justify further efforts in the field. On one hand, the use of siRNAs/miRNAs is considered to have a great therapeutic potential. This is substantially due to the fact that it is possible to generate siRNAs/miRNAs silencing the expression of any genes implicated in HCC. On the other hand, it is substantially due to the lack of appropriate delivery systems. Examples of liver directed delivery systems are described in the literature. Last but not least, improvements in the possibility to discriminate between HCC and normal liver cells is still necessary. The review is good at logic, I think it should be published on this journal.

We wish to thank the reviewer for the appreciation of our work.

Editor

1) First, could you give me the word version document about your article? So I can edit them easily?

Attached you can find the word version of our manuscript

2) In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:

Acceptable file formats: .mp3, .wav, or .aiff

Maximum file size: 10 MB

To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.

We have done our best to produce an audio file in .wav format.

3) Please provide the decomposable figure of Figures, whose parts are movable and can be edited. So please put the original picture as word or ppt or excel format so that I can edit them easily.

Attached you can find the ppt version of the figure.

4) Please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please revise throughout. The author should provide the first page of the paper without PMID and DOI. PMID (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) DOI (<http://www.crossref.org/SimpleTextQuery/>) (Please begin with DOI: 10.**). For those references that have not been indexed by PubMed, a printed copy of the first page of the full reference should be submitted.

In the revised manuscript PubMed citation numbers and DOI have been added to all references: additionally, all the authors have been added to each reference.

We trust that our revised manuscript will meet your and the reviewer's approval.

Looking forward to hearing from you soon, please receive my best regards.

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

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'G. Grassi'.

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