

We thank the reviewers for their thoughtful review of our manuscript, and our manuscript has been improved according to the suggestions of reviewers.

### **1. Reviewer 503516:**

Yu-Cheng Zhang et described the possible use of circulating miRNAs as novel biomarkers useful for HCC diagnosis and prognosis. The manuscript is clear and well written; additionally it can be of great interest for the readers of the journal. Minor comments -Pag 4 line 22 from top after reference 9: I suggest introducing the reference: “Novel hepatocellular carcinoma molecules with prognostic and therapeutic potentials. Scaggiante et al., World J Gastroenterol 2014 February 7; 20(5): 1268 - 1288; doi:10.3748/wjg.v20.i5.0000” to give the readers the possibility to have a reference for other HCC diagnostic/prognostic markers. -Pag 4 line 23 from top: the word “are” is missing after “technologies”. -Pag 6 line 14 from bottom after reference 39: I suggest introducing the reference: “Scaggiante et al., Improving siRNA bio-distribution and minimizing side effects. Current Drug Metabolism 2011, 12, 11-23” to remind the readers that for any miRNA/miRNA considered as therapeutic molecule, the off targeting issue should be always considered. - Pag 8 line 9 from bottom: the words “abundant live-specific miRNAs” should be corrected with “abundant liver-specific miRNAs” - Pag 8 line 4 from bottom: an “a” should be added after the word “was”. - Pag 9 line 9 from top: an “of” should be added after the word “detection”. - Pag 9 line 14 from top: the sentence “Qi et al and Xu et al, their results suggest that serum” should be correct with “Qi et al and Xu et al, suggest that serum “ - Pag 10 line 4 from top: the name “tan” should be correct with “Tan”. -Pag 14 lines 1-2 from bottom and page 15 lines 1-4 from top: the final sentence of the manuscript is too long and difficult to understand. It should be rephrased and split in at least two sentences

### **Reviewer suggestions and authors Response:**

We thank the reviewer for extensive and helpful comments:

- 1) **Suggestion 1:** Pag 4 line 22 from top after reference 9: I suggest introducing the reference: “Novel hepatocellular carcinoma molecules with prognostic and therapeutic potentials. Scaggiante et al., World J Gastroenterol 2014 February 7; 20(5): 1268 - 1288; doi:10.3748/wjg. v20.i 5.0000 ” to give the readers the possibility to have a reference for other HCC diagnostic/prognostic markers.

**Authors Response 1:** The reference ( Novel hepatocellular carcinoma molecules with prognostic and therapeutic potentials) has been added.

- 2) **Suggestion 2:** Pag 4 line 23 from top: the word “are” is missing after “technologies”.

**Authors Response 2:** The word “are” has been added.

- 3) **Suggestion 3:** Pag 6 line 14 from bottom after reference 39: I suggest introducing the reference: “Scaggiante et al., Improving siRNA bio-distribution and minimizing side effects. Current Drug Metabolism 2011, 12, 11-23” to remind the readers that for any miRNA/miRNA considered as therapeutic molecule, the off targeting issue should be always considered.

**Authors Response 3:** The reference (Improving siRNA bio-distribution and minimizing side effects) has been added.

- 4) **Suggestion 4:** Pag 8 line 9 from bottom: the words “abundant live-specific miRNAs” should be corrected with “abundant liver-specific miRNAs”

**Authors Response 4:** The words “abundant live-specific miRNAs” have been corrected with “abundant liver-specific miRNAs”.

- 5) **Suggestion 5:** Pag 8 line 4 from bottom: an “a” should be added after the word “was”.

**Authors Response 5:** The word “a” has been added.

- 6) **Suggestion 6:** Pag 9 line 9 from top: an “of” should be added after the word “detection”.

**Authors Response 6:** The word “of ” has been added.

- 7) **Suggestion 7:** Pag 9 line 14 from top: the sentence “Qi et al and Xu et al, their results suggest that serum” should be correct with “Qi et al and Xu et al, suggest that serum.

**Authors Response 7:** This sentence has been corrected.

- 8) **Suggestion 8:** “ - Pag 10 line 4 from top: the name “tan” should be correct with “Tan”.

**Authors Response 8:** This word has been corrected.

- 9) **Suggestion 9:** -Pag 14 lines 1-2 from bottom and page 15 lines 1-4 from top: the final sentence of the manuscript is too long and difficult to understand. It should be rephrased and split in at least two sentences

**Authors Response 9:** All sentences have been corrected.

## **2. Reviewer 68723:**

This manuscript well reports background of micro RNA. The manuscript described current knowledge on micro RNA in HCC. Differentiating HBV related HCC from HCV related HCC was interesting. The authors focused on biomarkers as current diagnostic procedure of HCC. But practically, imaging plays a central role in diagnosis of HCC. Unfortunately, the review did not deal with imaging. This was understandable because the authors focused on biomarkers. To make this review more attractive, the following points should be addressed. Diagnostic procedure of HCC has been established with diagnostic imaging and tumor marker. Current problems are detection of small HCC (for example, <1cm), differential diagnosis of small HCC and regenerative nodule of liver cirrhosis. Another problem is detection of recurrence after treatment. How do the authors fit micro RNA into the current diagnostic system?

### **Authors Response:**

We thank the reviewer for helpful comments. Peer reviewer No 68723 wish the authors to fit microRNA into the current diagnostic system. In fact, criteria for the diagnosis of HCC have evolved over the past decade. Current methods for HCC diagnosis are classified in the following main categories: imaging (MRI, CT and ultrasound) and laboratory biomarker analysis (AFP). AFP is the most common used tumor marker for HCC diagnosis and prediction of prognosis, but current AASLD guidelines do not recommend AFP for screening or diagnostic purposes because of its low sensitivity and specificity. Researches into novel biomarkers for early HCC

detection continue. The authors think that circulating miRNAs as potential novel and ideal biomarkers for HCC surveillance should be firstly compared with AFP or be combined with ALP, which may improve the sensitivity and specificity of diagnosis of HCC. Therefore, the review highlights the recent progresses made regarding circulating miRNAs as diagnostic and prognostic biomarkers for HCC. Of course, more researches are required to verify the sensitivity and specificity of miRNAs for HCC.