March 10, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8763-reviewR1.doc).

Title: MicroRNA in cancer therapeutic response: friend and foe

Author: Jingyan Xue, Jixiao Niu, Jiong Wu, Zhao-Hui Wu

Name of Journal: *World Journal of Clinical Oncology*
ESPS Manuscript NO: 8763

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated as suggested.

2 Revision has been made according to the suggestions of the reviewer
(1) *The title of this manuscript suggests that the article is focused on breast cancer; however, the presentation on pages 3, 4, 5 and part of p. 6 and 7 barely mention breast cancer which finally appears in the bottom half of pages 6 and 7. There is no obvious heading that the introduction to miRs has transitioned into breast cancer. The authors need provide in Introduction and then transition into and focus primarily on miRs in breast cancer. After discussing the role or function of a miR in breast cancer one could then refer to its role in other cancers for comparative purposes.*

We appreciate the suggestion from the reviewer and have modified our manuscript accordingly. The overriding goal of this review is to discuss some recent progress in understanding versatile pathophysiological roles of miRNAs in various cancer stages, particularly in cancer treatment, along with brief background. We aimed to cover different types of cancer in general while using breast cancer as a focal point. We realized the original title was not broad enough to describe all the content this review tried to cover. Therefore, the title has been modified which is now more balanced and informative.

(2) *The title "miRNAs in cancer initiation" should focus on breast cancer and indicate in the Introduction that miRNAs are important for cancer initiation. The section on cancer initiating is very confusing since the authors point out that many of the miRs included in this section have other functions; e,g, "miR-21 has been demonstrated to mediate cell survival and proliferation". It is confusing to discuss this under the heading "cancer initiation".*

We have changed the section title to “miRNAs in cancer development”.

(3) *The idea of a single miR targeting multiple proteins and a single protein targeted by multiple miRs (with examples) should be emphasized in the Introduction since this is an important source of cell context-dependent differences among different cell lines.*

We thank the reviewer for raising an important point and have added related content in both abstract and introduction section.

(4) *The idea of miRNA therapeutics can involve more than antagimirs, siRNAs and sponges because*

miRNA expression can possibly be regulated by anticancer agents or other drugs (e.g. PNAS 108, 4394, 1011; Cancer Res. 72, 335, 2011; JBC 286, 4027, 2011; 285, 24707, 2010).

We agree that miRNA alteration by anti-cancer agent is also an important aspect when considering application of miRNAs as therapeutic agents in cancer treatment. We have included the suggested literatures and discussion in “miRNA as cancer therapeutics” section.

(5) *Previous studies have demonstrated that miR-335 is pro-metastatic in ER-negative breast cancer (Nature 451, 147, 2008; Genes Dev. 25, 226, 2011) and a recent report showed drug-induced induction of miR-335 could inhibit breast cancer metastasis (Mol. Cancer Therap. 11, 108, 2012) and these papers were not discussed under the "cancer metastasis" heading.*

We have included discussion related to miR-355 as suggested.

(6) *The authors also mentioned miR-17-92 under the "miRNAs in cancer initiation" heading but only referred to the results in "B cell lymphoma in mice". There is an extensive and somewhat contradictory literature on miR-17-92 and paralogs in breast cancer which have not been referenced or discussed in the review (PNAS 107, 8231, 2010; 106, 15732, 2009; Breast Cancer Res. Treat. 126, 565, 2011; Cancer Res. 69, 8742, 2009; Mol. Cell Biol. 26, 8191, 2006; J. Cell. Biol. 182, 509, 2008; Oncogene 31, 1034, 2012). MiR-27a also plays a role in breast cancer (Mol. Cancer Therap. 11, 1421, 2012; Breast Cancer Res. Treat. 136, 21, 2012; Mol. Carcin. 52, 591, 2013; Cancer Res. 67, 11001, 2007). These omissions and other possible omissions need to be addressed since there is some concern that this article does not adequately cover this field.possible omissions need to be addressed since there is some concern that this article does not adequately cover this field.*

We have added suggested content in revised manuscript. As limitation of the space, this review did not intend to discuss exhaustively the literatures related to miRNA functions in cancer. Alternatively, we cited several comprehensive reviews published recently for readers to acquire extended information.

3 References and typesetting were corrected

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

Sincerely yours,

Jingyan Xue, M.D.

Department of Breast Surgery, Fudan University Shanghai Cancer Center,
Department of Oncology, Shanghai Medical College,
Fudan University, Shanghai,200032, China;
Center for Cancer Research,
University of Tennessee Health Science Center, Memphis, TN 38163, USA ;
Jxue7@uthsc.edu

Telephone: +1-901-448-2155

Fax: +1-901-448-3910