

## RESPONSE TO THE REVIEWS

### Reviewer #1

The authors review the current development strategies of nanomedicine-based therapies against cancer stem cells (CSCs) of the digestive system. The authors also review the several potential approaches to target CSCs of the digestive system, including targeting CSCs surface markers and signaling pathways. The topic is of considerable interest since cancer in the digestive system is fatal disease affecting millions of people worldwide and the prevalence of these diseases is increasing and it is a serious health problem. Therefore, review on the treatment options for this disease, and focuses on nanomedicine-based therapies in clinic is a beneficial. Consequently, development of effective therapeutic strategies against CSCs plays a key role to increase the efficacy of cancer therapy. Overall the review is complete, and contains up-to-date with the latest and most important information about nanomedicine in the treatment of CSCs. I believe that the manuscript is suitable for publication in the Journal. Although I recommend acceptance of the manuscript in its present form, but the manuscript has some typo error. The authors should go over the entire manuscript for the correction.

**Answer:** Thank you for your comment. We have went over carefully the entire manuscript and corrected all the errors.

### Reviewer #2

**Question 1:** The review is poorly written and very difficult to follow. There are no graphs, charts or tables to aid the reader.

**Answer 1:** Thank you for your comment. Accordingly, we have edited the whole manuscript carefully, and added one graph and one table to make the paper more clear and more persuasive.

**Question 2:** My main complaint is the use of the word stem cell. By definition stems cells must be capable of self-renewal and multilineage differentiation. By my reading, Weissman et al only suggest a stem cell may exist. The paper by Dick et al did not show multilineage differentiation. Thus by my reading the term stem cell being used in conjunction with cancer is actually a lineage committed progenitor (albeit expressing CD133), that is usually quiescent and therefore difficult to treat.

**Answer 2:** This is a great comment. However, a lot of research used the definition "cancer stem cells" widely [*Nat Rev Drug Discov* 2009;8,806-823; *Adv Exp Med Biol* 2013;734:145-79; *Acta Pharmacol Sin* 2013;34:732-40]. Also the review of the application of nanomedicine in cancer stem cells very hot [*Int J Nanomedicine*. 2015 Sep 10;10(Spec Iss):251-60. *Nanomedicine (Lond)*. 2015 Jan;10(1):143-60.].