POINTWISE REPLY TO THE REVIEWERS' COMMENTS

At the outset we are very grateful to all the reviewers and the editor for provisionally accepting our manuscript subject to the approval of the revisions which we have incorporated in this version.

We have made substantial revision by going through the manuscript and removing sections and paragraphs which were adding to the word count and leading to redundancy.After reading our edited manuscript we agree that by condensing the information we have increased the readability of our article.

Reviewer 1

The topic has been well compiled by the authors.

Reply: We are very grateful for appreciating and approving our manuscript.

Reviewer 2

Overall, the authors have done a commendable work in their manuscript, reviewing literature and pathogenesis/ tumorigenesis of breast cancer and various genetic pathways. They have also highlighted the role of stem cells in breast cancer and potential target for precision medicines. However, the manuscript is extremely lengthy (>9000 words) and has significant redundancy. It appears to be in a thesis format but needs to be converted into a review article, which appears to be the intention of the submission. Ideally, the goal should be 3500-4500 words for a review article as it highlights major points, does justice to the title of the manuscript and is a succinct review of current literature on the topic. It is also important to maintain interest for the readership. My recommendation is to significantly cut down on word count and sections that are not related to stem cells and only briefly touch upon other pathways. For example, micro RNA section can be significantly cut down to highlight major studies and their connection to stem cells rather than complete tumorigenesis. Similarly, CDKs, NF-kB in tumorigenesis, HER2 pathway, PI3K/Akt pathway and BRCA pathway need to be summarized only in a small paragraph and their role stem cell activation or regulation in breast cancer can be highlighted in a table format. Pathways regulating cancer stem cells is beautifully highlighted in the manuscript and need to be the focus of the review hence the need to cut down the abovementioned sections.

Reply:We are very grateful for the indepth critique and erudite comments of the reviewer and are also very happy to note that apart from the length of our review you have found our article interesting and appreciated the figures which are all original and prepared by us using the Biorender application tool.

We have thoroughly gone over the review and have substantially cut down on the word count from >9000 by more than 5000 words,without compromising on the scientific value and the current knowledge in this very exciting field.We hope you will allow us to retain the edited version .As suggested we have removed information not directly related to stem cells and tried to bring out only the salient features of the other pathways which contribute to tumorigenesis.

As suggested, we have drastically cut down on the section of miRNA, CDKs, NF-kB in tumorigenesis, HER2 pathway, PI3K/Akt pathway and BRCA. We have added a new table **(Table 1)** in which we have summed up the contribution of the pathways in CSCs in a easier to read manner .We hope you will now find our review much improved and suitable for publication.

Reviewer 3

The following needs to be addressed: (1) As a review article for stem cell therapy, it is necessary to focus on this background and concepts, as well as some specific contents and latest progress on this field. (2) This manuscript detailly lists some cellular pathways and findings, but you do not point out the relationship between future direction and clinical practice. (3) The readability of this paper is not strong enough. This article is too long, including lots of figures, and it is not easy to catch your highlights and main opinions.

Reply: We are grateful for the comments and have reduced our article by over 5000 words and removed the redundancy. By keeping our focus on breast cancer stem cells and their pathway aberrations, the data for the drugs targeting these aberrant cells has now come into focus.

The concept of BCSCs is still in its infancy with respect to its targeting in the clinical setting. We have gone through the various clinical trials and listed them in **Table 2 and Figure 5**.As most of the trials are still ongoing most of the data is still not available in the public domain. However after reducing the length of the review, the highlights and main opinions would now come to the forefront. However the data regarding promising drugs which will lead to their incorporation in

the clinical setting in the near future as well as the challenges that need to be overcome have been mentioned in the section on Drugs targeting the pathways.

Observations made by Editor

4. **LANGUAGE QUALITY**

Reply: We have resolved all issues regarding the grammar ,punctuation etc, so as to increase the readability of the manuscript .

Science Editor

5 Issues raised: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s)

Reply : This is a review article and hence no direct funding was involved as no experiments were conducted.The first author Ms Sabiha Khan received fellowship from CCRH .We have added the grant number F.No. 17-03/2019-20/CCRH/Tech/ Coll/ Amity/7284 .

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Reply:All the figures are original. We have used the Biorender software to prepare the figures. The figures are embedded in the review article and we have also uploaded all the figures in jpeg format in the PPT 64843-Figures

(3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and

Reply: As suggested we have extensively added the PMID and DOI for all the references.

(4) If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease.

World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Reply: All the figures are original and hence no copyright violation is there.

We have carefully gone over the guidelines as per the document on Guidelines and requirements for revised submission for Review articles

We have also done the following

1.Added a running title -Targeting breast cancer stem cells

2.Corrected the format for names of authors and co-authors

3.We have added the PMID and DOI for references cited in the article

4.We have added the figures which were prepared using the Biorender package in the file labelled as 64843-Figures.ppt

5. We have made a word document for Table 1 and Table 2 in editable form with file name as 64843-Tables.doc.