

Dear editor,

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript, we appreciate editor and reviewers very much for their positive and constructive comments and suggestions on our manuscript entitled “Emerging potential of ubiquitin-specific proteases and ubiquitin-specific proteases inhibitors in breast cancer treatment, Manuscript NO.: 78504”.

We have studied reviewer’s comments carefully and have made revision which marked in red in the paper. Point-by-point responses to the reviewers are listed below this letter.

Reviewer #1:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Major points

1. You should clarify what the reader should understand about ubiquitin-specific proteases and ubiquitin-specific protease inhibitors.

Response: Thanks for your kind suggestion. According to your suggestion, we enriched the manuscript. Ubiquitin-specific proteases (USPs) are emerging as potential therapeutic targets in breast cancer and several USP inhibitors have been developed. The manuscript helps readers to know the research status of USPs and their inhibitors in breast cancer, providing more reference to explore the mechanism and discover new potential drugs for breast cancer treatment. Based on the suggestions given by the reviewer, we modified our manuscript. In addition to these revisions, I have checked the whole manuscript and correct the English language errors under the guidance of English professor. I hope the revision could meet the standard for publication. But if you have any other comments, please do not hesitate to let us know. We will modify the manuscript as soon as possible. Thanks again for your kindness !

2. Abstract should state the main points of the paper.

Response: Thanks for your valuable suggestions to improve the quality of our manuscript. Here we make further enrichment of the abstract.

“Breast cancer is the most frequently diagnosed cancer in women, accounting for 30% of new diagnosing female cancers. Emerging evidence suggests that ubiquitin and ubiquitination played a role in a number of breast cancer etiology and progression processes. As the primary deubiquitinases in the family, ubiquitin-specific peptidases (USPs) are thought to represent potential therapeutic targets. The role of ubiquitin and ubiquitination in breast cancer, as well as the classification and involvement of USPs are discussed in this review, such as USP1, USP4, USP7, USP9X, USP14, USP18, USP20, USP22, USP25, USP37, and USP39. The reported USPs inhibitors investigated in breast cancer were also summarized, along with the signaling pathways involved in the investigation and its study phase. Despite no USP inhibitor has yet been approved for clinical use, the biological efficacy indicated their potential in breast cancer treatment. With the improvements in phenotypic discovery, we will know more about USPs and USPs inhibitors, developing more potent and selective clinical candidates for breast cancer.”

Minor points

1. You should correctly number the subheadings.

Response: Thank you for your comments and we correct the numbers of subheadings.

2. You should not full spell the word once expressed as an abbreviation such as ubiquitin specific peptidase (USP).

Response: Thanks for your kind suggestion. We have revised the manuscript based on your suggestion.

3. You made many careless and mistakes such as "could n promote" and " inhibit".

Response: We are very sorry for our incorrect writing in the current version of the manuscript. According to your suggestion, I have checked the whole manuscript and correct the English language errors under the guidance of English professor.

4. You made many strange expressions such as " leading to a variety of diseases,

such as tumorigenesis" and ideal candidates as cancer targets for drug development".

Response: Thanks for your kind suggestion. According to your suggestion, I have checked the whole manuscript and correct the English language errors under the guidance of English professor Guangtai Shen. Based on the contribution of Guangtai Shen to the previous guide and current revision of the manuscript, we added him as corresponding author. The revised content was marked in red in manuscript. I hope the revised manuscript could meet the standard of the magazine.

5. Table 1 should contain reference numbers.

Response: Thanks for your comments. We have added the reference numbers in Table 1.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Nice article.this will definitely act as a game changer in breast cancer patients treatment.

Response: We thank you very much for your positive comments on our manuscript.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors:

The abstract is too short and non informative, kindly elaborate and shift the image provided in the abstract to the introduction segment of the main manuscript.

Response: Thanks for your valuable suggestions to improve the quality of our manuscript. Here we make further enrichment of the abstract and shift the image from abstract to the introduction segment.

“Breast cancer is the most frequently diagnosed cancer in women, accounting for 30% of new diagnosing female cancers. Emerging evidence suggests that ubiquitin and ubiquitination played a role in a number of breast cancer etiology and progression processes. As the primary deubiquitinases in the family, ubiquitin-specific peptidases (USPs) are thought to represent potential therapeutic targets. The role of ubiquitin and ubiquitination in breast cancer, as well as the classification and involvement of USPs are discussed in this review, such as USP1, USP4, USP7, USP9X, USP14, USP18, USP20, USP22, USP25, USP37, and USP39. The reported USPs inhibitors investigated in breast cancer were also summarized, along with the signaling pathways involved in the investigation and its study phase. Despite no USP inhibitor has yet been approved for clinical use, the biological efficacy indicated their potential in breast cancer treatment. With the improvements in phenotypic discovery, we will know more about USPs and USPs inhibitors, developing more potent and selective clinical candidates for breast cancer.”

The tables are good and well structured, however they must be referenced adequately, the results which are depicted in them must have been picked up from published literature and kindly add the reference number in tables too.

Response: Thanks for your kind suggestion. We have added the reference numbers in Tables.

Few references are incomplete for example number 7, 8, 14 page number is missing, kindly check all

Response: Thank you again for your comments and we were really sorry for the mistakes made in paper. We checked all references and add the missing page numbers.

We have tried our best to revise our manuscript according to the comments. Attached please find the revised version, which we would like to submit for your kind consideration. If there are any other modifications we could make, we would like very much to modify them and we really appreciate your help. Thank you very much for

your help, looking forward to hearing from you.

Thank you and best regards

Yours sincerely