

## Peer Review File

Article Information: <https://dx.doi.org/10.21037/tcr-23-345>

### Reviewer A

The manuscript entitled “Progress in Transition Metal-mediated Bioorthogonal Catalysis for the Treatment of Solid Tumors” by Wan and co-workers overviews the most recent advances on the field of bioorthogonal catalysis devoted to cancer therapy. The review is timely and it can be accepted after the following questions are addressed:

1) References related to Vincent Rotello’s group are important and should be included in the revised version of the manuscript.

**Reply 1:** Vincent Rotello’s group has extensively and deeply studied the construction of transition metal nanoenzymes, and we have added some new literature, specifically referred to references 41 to 43.

**Changes in the text:** We have modified our text as advised (see Page 12, line 223-238).

2) A general Figure including the main types of nanoparticles, complexes, hybrids should be included for the general reader. In general, the authors should clearly state when the articles refer to complexes or nanoparticles. Sometimes, it remains ambiguous.

**Reply 1:** We have added a general Figure (Figure 2).

**Changes in the text:** We have modified our figures (see Page 31, line 607).

3) A general Figure summarizing the key reaction covered by bioorthogonal catalysis should be included.

**Reply 1:** We have added a general Figure (Figure 1)

**Changes in the text:** We have modified our figures (see Page 31, line 607).

4) Line 21, check spelling for “transition”.

**Reply 4:** We have made changes.

**Changes in the text:** We have modified our text as advised (see Page 2, line 21).

5) Line 55, change “reaction” by “type of catalysis”

**Reply 5:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 4, line 55).

6) Line 63, check the spelling for nanozyme

**Reply 6:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 4, line 63).

7) Lines 65-66: please re-write the sentence

Reply7: We have made changes.

**Changes in the text:** We have modified our figures (see Page 4, line 65-66).

8) Line 107: specify the type of Pd catalyst (complex, nanosheet, nanoparticle...)

**Reply 8:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 6, line 107).

9) Line 116: check O<sub>2</sub> superindex

**Reply 9:** After we checked with the references, it was not mislabeled

**Changes in the text:** We have modified our figures (see Page 7, line 116).

10) Line 141: change induce by induced (in general, check verbal tenses to place them in past tense)

**Reply 10:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 8, line 141-142).

11) Line 178: replace by “showed” (check all the verbs)

**Reply 11:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 10, line 178).

12) Line 215: Unciti-Bruceta and Santamaria’s groups...

**Reply 12:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 11, line 215).

13) Line 216: substitute by “in situ reduced in CO ambient to form...”

**Reply 13:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 11, line 216).

14) Line 226: define NZ

**Reply 14:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 12, line 226).

15) Line 228: revise nanomases

**Reply 15:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 12, line 228).

16) Line 232: demonstrated rather than demonstrate

**Reply 16:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 12, line 235).

17) Line 238: catalyzed instead of catalyze

**Reply 17:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 12, line 241).

18) Lines 240-243: re-write these sentences for the sake of clarity

**Reply 18:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 13, line 244-247).

19) Lines 255-256: The Unciti Broceta and the Santamaria teams further tested multiple noble-metal based nanoalloys.

**Reply 19:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 13, line 259-260).

20) Line 276: Include references.

**Reply 20:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 14, line 280).

21) Lines 285-286: ...”group was seriously damaged in the in vivo experiments”

**Reply 21:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 15, line 289-290).

22) Line 287: increased

**Reply 22:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 15, line 290-291).

23) Line 294: used

**Reply 23:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 15, line 298).

24) Lines 353-354: rewrite this lines for better understanding

**Reply 24:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 18, line 364-365).

## **Reviewer B**

The review article entitled "Progress in Transition metal-mediated bioorthogonal catalysis for the treatment of solid tumore" " by Xiaotian Wan and co-workers is a collection of information on the contemporary popular topic of treatment od tumors based on transition metal compounds. The article was written based on 65 references which are quite „fresh". References have been selected correctly. The drawings and tables were made aesthetically and clearly. The work is written in rather general terms. However, I have a few comments on the article, which will improve the article as a whole and make it even more interesting for readers of "TCR" journal.

1. In the title of point 3.1. it is necessary to write which specific metal ions were taken into account.

**Reply 1:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 5, line 84).

2. The manuscript must be polished for editorial errors, e.g. Latin phrases must be written using italic e.g. „in vitro"

**Reply 2:** We have made changes.

**Changes in the text:** We have checked the full text for Latin phrases and written it in italics.

3. Line 88 – „transition metals" authors need to add which exact metal ions Chen et al. studied (24)

**Reply 3:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 5, line 88).

4. Point 3.3.1 - Is too concise - contains only 5 sentences. It is necessary to expand the consideration of this topic:

- Reduction and Oxidation Reactions
- Ligand Substitution Reactions
- Coordination Chemistry Reactions

**Reply 4:** Since there are fewer bioorthogonal reactions related to gold, we add a discussion of the literature.

**Changes in the text:** We have modified our figures (see Page 17, line 342-348).

5. Line 99 – „good anti-proliferative activity” is too general a term, you need to expand the discussion on this topic, give what digital values, incubation time, etc.

**Reply 5:** We have made changes.

**Changes in the text:** We have modified our figures (see Page 6, line 98-100).

6. Throughout the manuscript, the discussion of the mechanisms of interaction of specific metal ions, e.g. Au(I), with other compounds present in cells needs to be expanded.

**Reply 6:** Since this review focuses on the application of transition metal-mediated bioorthogonal catalytic reactions in cancer therapy, only a superficial discussion of the relationship between gold and thiols has been made. It is also because of the complexity of the biological environment that it is difficult to apply various materials in vivo. We believe that this mechanism needs a lot of literature support and is not very relevant to our subject, so we do not discuss it.

**Changes in the text:** No changes at present

7. In the Conclusion part Authors need to add, for example, some kind of summary table of the literature analysis presented in this paper, e.g., a summary of metal ions and their participation in specific reactions in the treatment of tumors.

**Reply 7:** We have added a general Figure (Figure 2).

**Changes in the text:** We have modified our figures (see Page 31, line 607).

8. I propose to add a Future and Perspectives section to the manuscript as well.

**Reply 8:** In accordance with the format requirements of your journal, it has been written into the "Conclusion" section.

**Changes in the text:** We have modified our figures (see Page 19-20, line 388-410).