

Dear Editor,

We thank you and the reviewers for the constructive comments on our manuscript. We are pleased to submit a revised version of this manuscript with modifications to the manuscript, as suggested by the reviewers.

Response to Reviewers' Comments

Reviewer #1:

1. **I would like the authors to simplify the results section and Discussion - making it clearer and more succinct. There are also quite a few grammatical errors, particularly in the Discussion section.**

Response: We have simplified the Results section and Discussion. We tried our best to correct the grammatical errors.

2. **I would also like the authors to express how they feel these data will be used in the clinical field and what they would plan to do next to advance this work.**

Response: We have revised the Discussion following the reviewer's comment.

Reviewer #2:

Major :

1. **Figure 5 does not support the authors' argument that VEGF shRNA and yCDglyTK exerts synergistic tumor cytotoxicity because black, blue, and pink lines are almost overlapped.**

Response: We admitted that the black and pink lines somewhat overlapped during the early stage of our *in vivo* study. However, on day 24, when compared with blank control group, yCDglyTK/5-FC group and shVEGF group showed about 46% and 48% tumor growth inhibition, while the combination showed 66% tumor growth inhibition. We do believe the combination had the strongest anti-tumor effect. We have removed the word "synergistic".

2. **Figures 5 and 6B6C provide discrepant results. CPNP/yCDglyTK+5Fc could inhibit tumor growth (Figure 5) while it could not reduce VEGF expression and MVD.**

Response: CPNP/yCDglyTK+5-FC exerts its anti-tumor effect through its ability to convert 5-FC to 5-FU.

3. **In figure 4A, the authors should present statistical comparison; otherwise, the degree of sensitivity to 5Fc treatment between each group can not be determined.**

Response: We have revised this part according to reviewer's suggestion.

Minor:

1. The authors should clarify what antigen the primary antibody recognizes.

Response: We have made revision following reviewer's comment.

2. In figure 6, the units of vertical lines should be described.

Response: We have added the units of vertical lines.

3. How did the authors determine that 36.8% of transcriptional activity is high.

Response: We have revised the description of this part.

4. The authors should present proof that nanoparticle exhibits low toxicity in this experimental setting. Especially, it is desirable to present that known toxicities by liposome are not observed by nanoparticle.

Response: We have added a supplementary figure S1 to show that nanoparticle exhibits low toxicity.

We thank you and the Reviewers again for your considerable efforts in reviewing our manuscript.

Sincerely,

Yongheng Chen, Ph.D.