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Re: Manuscript No: 88552; "Verteporfin fluorescence in antineoplastic-treated pancreatic cancer cells found concentrated in mitochondria"

Dear Dr. Ma,

Thank you very much for your decision letter and additional advice on our manuscript. We also thank the reviewers for their review of our revised manuscript and further comments. We are pleased to have the opportunity to address their additional concerns, and all amendments that are in direct response to the concerns of the reviewers are highlighted in the revised manuscript. In addition, our point-by-point responses to the latest comments are listed below this letter.

With best wishes,
Sincerely,

Zhi-Chang Ba, Ph.D.

Point-to-point responses to reviewer's comments

Reviewer #1

Summary of the manuscript. The experimental study reported by Zhang et al. showed that photodynamic therapy using verteporfin as a photosensitizer in addition to chemotherapeutic drugs, i.e., gemcitabine, significant decreased the survival of pancreatic cancer cell lines. The present study was well organized. The major point is only the future usefulness in the clinical setting.

Major comments. 1. Concerning resectable pancreatic cancer or border-line resectable disease, neoadjuvant chemotherapy, e.g., gemcitabine and S-1, has been reported as effective concerning down-staging or postoperative survival. Can the authors describe about future clinical treatment of photodynamic therapy using verteporfin in combination with neoadjuvant chemotherapeutic drugs for patients with resectable pancreatic cancer?

Response: Thanks for your positive comment and insightful suggestion on the present study. We have added discussion of the clinical promise of photodynamic therapy with verteporfin in combination with neoadjuvant chemotherapeutic drugs for patients with resectable pancreatic cancer:

> PDT is non-invasive and causes less damage than surgery, and is safer. If the effectiveness of PDT can be improved by more targeted photosensitizers, when combined with neoadjuvant therapy this technology has bright prospects for treating resectable PC.

Reviewer #2

This is a good, preliminary study which can suggest new lines of research and - potentially - treatment for PC.

The methods are well described. One general comment: why are many words colored in red? is this a revised manuscript? I was not informed of this. Another comment, can the Authors expand on the future lines of research that may stem from the present study?

Response: Thanks for your positive comment and thoughtful suggestion. We regret our carelessness. We have changed the red words to black. And we have added extended future research directions for the current study:

> PDT can also be used in the treatment of esophageal, bladder, and gastric cancers. It is possible to apply neoadjuvant therapy combined with photodynamic therapy and antitumor drugs and photosensitizers for different cancers.