Author’s response to reviews

Title: Molecular Targeted Photoimmunotherapy for HER2-positive Human Gastric Cancer in Combination with Chemotherapy Results in Improved Treatment Outcomes Through Different Cytotoxic Mechanisms

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Response to first reviewer’s report:

I would suggest alternate language be used on line 369, as more in-vivo data is needed to determine if this method is "practical". I may say "promising" or "a potential therapy" as I do not feel that the data presented support or address the practicality of the therapy (PIT).

We agree with your suggestion. We have replaced a word on line 369.

Response to third reviewer’s report

Though 5-FU is a suitable combination partner with PIT for preclinical studies, future efforts would be of interest to observe if synergy is also obtained when PIT is combined with cisplatin chemotherapy. Currently in the clinic patients are treated with the triplet of a fluoropyrimidine, cisplatin, and trastuzumab if they have HER2-overexpressing disease. If the authors I have any results with cisplatin therapy it would be of interest

At this time, we have not tested cisplatin treatment in combination with PIT, however, we would like to do this as one of our important tasks to build preclinical data for future clinical translation in patients with HER2-expressing gastric cancer.
NCI-N87 is well-known to be a HER2-overexpressing cell line. Have the authors pursued the same experiments with other HER2-overexpressing gastric cancer cell lines to see if similar results are obtained to help ensure this is not a phenomenon restricted to a single cell line. Further along those lines is have any experiments been pursued testing their therapy in HER2-overexpressing patient-derived xenografts mouse models which may be an even better representation of intratumoral heterogeneity.

We have not tested other HER2-expressing human gastric cancer cells, however, recent unpublished data suggest that the phototoxic effects of trastuzumab-IR700 with NIR light depended on HER2-specific IR700 signal intensities, or HER2 expression levels (this was confirmed using human breast cancer cells). Intratumoral heterogeneity may be one of the major limitations of PIT treatment because our colleague’s paper suggest that PIT treatment is not effective for the cells which mAb-IR700 cannot bound specifically to the cells (RSC Adv. 2015 Mar 3;5(32):25105-25114). In terms of clinical translation for epithelial cancers, which frequently show intratumoral heterogeneity, combination treatment of PIT with chemotherapy would be preferable to treat effectively.

For the X- and Y-axes of Figures 1A and 1B, I would recommend including units/numbers to enable the reader to have a better interpretation of scale for these 2 figures.

We have modified Figures 1A and 1B.