

## RESPONSES TO REVIEWERS

### Reviewer 1 (Code: 02916427)

*1. Tumor heterogeneity is a common phenomenon in several types of cancer. How about gastric cancer? In this innovative model, how to find the key cancer cells, which majorly impact the oncological outcomes?*

Tumor heterogeneity may exist for gastric cancer. However, in our prior paper (Gao M et al. 2018), we discovered identical genomic profiles from organoids created from multiple different sites on a single patient's tumor. We also performed immunostains of GC organoids for the stem cell markers LGR5 and TROY, which revealed positive immunostaining indicating the presence of cancer cells.

*2. The response of chemotherapy drug in this innovative model may not reflect the actual responses in human. It is because that the differences in pharmacokinetics and drug-dosing regimens between in a patient and in vitro.*

Thank you for your comments. We hope to test whether organoids can accurately predict clinical response in a future human clinical trial.

### Reviewer 2 (Code: 01560441)

*1. Organoid technology provides the ability to mimic gastric cancer more accurately than traditional in vitro models, and displays different morphologies based on the histology and molecular subtypes of the primary tumor from which they originate. It was insufficient description of histology and molecular subtypes in the review.*

Thank you for your comments. A more detailed description of the subtypes of gastric cancer was provided in the section, "Representation of histological and molecular subtypes." In previous publications (Yan HHN et al 2018, Nanki K et al 2018), GC

organoids were created from every tumor subtype as defined by the TCGA and Lauren classifications.

*2. Despite the broad prospects of organoids, there are still many difficulties to be solved, such as the difficulty of controlling maturity and the lack of blood vessels. The paper should also describe its shortcomings.*

We agree with the reviewer. We have added a paragraph on the limitations of GC organoid to the conclusion section of the manuscript.