**To the Editor,**

Many thanks for your time in reviewing our manuscript, entitled “A promising animal model recapitulating the features of human pancreatic cancer” We really appreciate the helpful comments and suggestions on our manuscript from yourself and three reviewers.

Following your suggestion and reviewers’ critical and insightful comments, we have revised our manuscript constructively. We have addressed the issues raised by each Reviewer in the revised manuscript, all changes have been marked in yellow color.

All co-authors have reviewed and approved of the revised manuscript. We have uploaded all files that you required. We hope that our manuscript can be accepted and published in your journal. Please let me know if you have any additional questions.

With kind regards,

Yaohe Wang

**Point to Point responses to the reviewers’ comments**

*Reviewer #1: The author states that there are currently no simple and reliable animal models that can mimic these features for accurate disease modelling. Is it really that no animal model could mimic the feature of the human pancreatic cancer? In addition, it is well known that the immune system is involved in the tumorigenesis and development. However, this model is dependent on immuno-deficient Syrian hamsters. This model cannot completely mimic human pancreatic cancer.*

**Response:** Many thanks for this reviewer’s comment. We completely agree with that the immune system is involved in the tumorigenesis and development. The ideal animal model should be immune-competent, which also can faithfully recapitulate all features of human pancreatic cancer. However, xenografting of human tumor cells into immuno-deficient mice has become the gold standard and been the most commonly used animal models for assessing tumor progression and preclinical efficacy of cancer drugs. Unfortunately this cannot be done using immune-competent models. Currently xenografting of human pancreatic cancer cells into immune-deficient mice are the most commonly used animal models, but rarely present multiple sites of metastasis. In this study we demonstrated that xenografting of human pancreatic cancer into immune-deficient Syrian hamster can present the distinguishing features of human pancreatic cancer, such as the multiple sites of metastasis, stromal reaction and the communication between stromal cells and pancreatic cancer cells. These suggest that immune-deficient Syrian hamster is a promising animal model recapitulating the features of human pancreatic cancer. In order to reduce the confusion to the readers, we have now specified this “xenograft animal models of human pancreatic cancer” in the title and the text in our revised manuscript.

*Reviewer #2: Thank you for the opportunity to review this interesting paper. In this paper, the authors wanted to exploit a new animal model that can faithfully recapitulate the features of human pancreatic cancer. The topic is relevant and the article is well written. However, I have several remarks and I think that some points need to be further analyzed. 1.Predictive variables for recapitulating the metastatic features of pancreatic cancer were insufficient. More predictive variables such as immunohistological and pathological features of hepatic, abdominal, or pulmonary metastasis should have been considered. 2. Morbidity and mortality in the IL2RG-/- Syrian hamster should have been considered. 3. It would be more persuasive if the abbreviation of PaCa is not used, and it is usually referred to PC or PDAC.*

**Response**: We really appreciate this Reviewer's helpful comments and suggestions for improving the quality of this manuscript. The major objective of this study is to confirm that the immune-deficient Syrian hamster is a promising xenograft model of human pancreatic cancer, recapitulating several key features of human pancreatic cancer, in particular multiple sites of metastasis, similar to human pancreatic cancer. For this reason we only presented the results of histopathological diagnosis to demonstrate whether xenografting human pancreatic cancer cells into immune-deficient Syrian hamster could have metastasis and which organs have got metastasis, but not primarily investigated the predictive variables in a great depth for recapitulating the metastatic features of pancreatic cancer as reviewer suggested. Following this reviewer's comment, we added more information about the histopathological features of metastatic tumors in hepatic, abdominal and pulmonary organs, kidney, diaphragm, stomach, adrenal gland, and peritoneum in the orthotopic model, shown in the new Figure 5. Obviously, it is important to comprehensively investigate the predictive variables further such as molecular genetics and biomarkers using a series of technologies as this reviewer suggested, for example immunohistochemistry staining and genetic analysis etc. These studies are ongoing and will publish separately.

Regarding the morbidity and mortality in the IL2RG$^{-/-}$ hamsters, in our revised manuscript, we have presented that IL2RG KO Syrian hamsters can survive over 72 weeks (1.5 years), and median survival time is about 89 weeks (shown in supplementary Figure S4).

Finally following this reviewer's suggestion, we have changed the abbreviation of PaCa into PC in our revised manuscript.

*Reviewer #3: No further comments.*

Response: We appreciate the Reviewer's time for reviewing our manuscript. Following the suggestion, we have polished the English further.