Manuscript NO: 54640
Title: Identification of an immune-related gene-based signature to predict prognosis of patients with gastric cancer

Dear Editor and the Referees,

Thank you very much for your time and effort in reviewing our manuscript entitled "*Identification of an immune-related gene-based signature to predict prognosis of patients with gastric cancer*". To aid in the re-review of this manuscript, we have included a point-by-point response to each comment. The reviewers' comments are *italicized* and placed in square brackets. In addition, within the revised manuscript, we have used "highlight" to denote major revisions in response to the reviewers' comments.

We appreciate the excellent suggestions and comments by the reviewers. As a consequence of the valuable suggestions, we believe that our manuscript has been improved.

Dear Reviewer 02537403 (SPECIFIC COMMENTS TO AUTHORS):

In this study, the authors analyzed the transcriptome RNA-seq data of gastric cancer identifying 4259 DEGs; among them, 181 up-regulated and 354 down-regulated DEGs were IRGs. These IRGs demonstrated to be enriched in immune-related processes such as humoral immune response, phagocytosis, B cell mediated immunity, and cytokine-cytokine receptor interaction. Also, it was explored the potential molecular mechanism of gastric cancer, showing the existence of 67 TFs differentially expressed in gastric cancer, whose implications in the pathogenesis of gastric cancer has to be elucidated. Moreover, 183 survival-related IRGs were identified for gastric cancer; 70 hub IRGs were associated with overall survival of gastric cancer. PPI network indicated that IL6, F2R and AGT were the top three hub genes, mainly involved in gastric cancer-related pathways such as Rap1, PI3K-Akt signaling pathways and cytokine-cytokine receptor interaction. Among 438 samples, in 323 occurred genetic alterations, the most frequent ones being represented by deletions and amplifications of the hub IRGs.

Most important, the authors designed an immune-related prognostic signature, consisting of 10 hub IRGs which can independently predict the overall survival of patients with gastric cancer (including S100A12, CGB5 and LGR6), with an excellent performance. Patients with high risk demonstrated a poorer overall survival time than those with low risk according to the median value of risk score. Finally, it is a very interesting research with important clinical relevance due to the identification of differentially expressed IRGs and subsequent design of a prognostic signature which may provide a promising perspective for

the treatment of gastric cancer. Moreover, this immune gene prognostic signature was positively correlated with immune cell infiltration, especially macrophages, and inflammatory responses. Therefore, it could effectively predict gastric cancer patients' survival and identify patients who will benefit from immunotherapy. I would suggest avoiding the expression "and so on" for too many times.

Reply: Thanks for the excellent comments. We have avoided the expression "and so on" for too many times in this manuscript. Furthermore, we have tried our best to polish our manuscript. As the consequence of the insight suggestions, we believe that our manuscript has been improved.

Dear Reviewer 03270518 (SPECIFIC COMMENTS TO AUTHORS):
Many compliments.

Reply: We appreciate your approval of our manuscript. We have tried our best to improve our English language of this manuscript. We believe that our manuscript has been improved. Thank you very much for your time and effort in reviewing our manuscript

Science Editor
Please provide the decomposable figure of Figures, whose parts are movable and editable. So you can put the original pictures in PPT and submit it in the system. Please provide the decomposable figure of all the figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. - image files.ppt" on the system. Make sure that the layers in the PPT file are fully editable. For figures, use distinct colors with comparable visibility and consider colorblind individuals by avoiding the use of red and green for contrast. Please read these four important guidelines carefully and modify your figure(s) accordingly: First, all submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes. Second, for line drawings that were automatically generated with software, please provide the labels/values of the ordinate and abscissa in text boxes. Third, please prepare and arrange the figures using PowerPoint to ensure that all graphs or text portions can be reprocessed by the editor. Fourth, in consideration of color-blind readers, please avoid using red and green for contrast in vector graphics or images.

Reply: Thank you very much for taking the time to review our manuscript. We have provided the decomposable figure of Figures, whose parts are movable and editable. We have put the original pictures in PPT and submitted it in the system. We have provided the decomposable figure of all the figures, whose

parts are all movable and editable, and we have organized them into a PowerPoint file, and submit as “Manuscript No. - image files.ppt” on the system. Furthermore, the layers in the PPT file are fully editable. For figures, we have used distinct colors with comparable visibility and have considered colorblind individuals by avoiding the use of red and green for contrast. However, in this manuscript, all drawings were automatically generated with software, therefore, it is difficult to provide all labels/values of the ordinate and abscissa in text boxes.