Dear Editor Jia-Ping Yan:

Thank you for your letter dated on July-24-2019. We appreciate greatly for the reviewer's comments on the manuscript entitled "Up-regulated WISP1 correlates with poor prognosis and drug-resistance by reducing DNA repair in gastric cancer" (ID: 49533). Those comments are very constructive and help to improve the manuscript significantly. Attached is our point-by-point responses addressing the reviewer's concern and questions. The manuscript has been corrected accordingly, and all the changes have been highlighted in red. It is our hope that the manuscript is now qualify for publication in this journal.

Thanks again for your kind considerations.

Sincerely yours,

Lihua Zhang

Responses to the reviewer's concern

Review ID: 02544757

In the current study, Zhang et al assessed the association between expression of Wnt1-inducible signaling pathway protein-1 (WISP1) and clinical outcome of 150 patients. The author showed that overexpression of WISP1 correlated with poor overall survival in univariate and multivariate analyses. The authors also confirm the biologic function of WISP1 in gastric cancer cell lines via siRNA of WISP1. Overall, the manuscript is well presented. However, there are some comments may improve this manuscript. Major comments

1. In the abstract section, if the authors could provide the more information of 150 patients with gastric cancer (GC).

Response:

Thanks for the constructive comment. Accordingly, we add these lines to the patients' information **in lines 82-84.** They read: 150 patients who underwent surgery for GC between February 2010 and October 2012 at the Affiliated Hospital of Jiangnan University were selected for validation study.

2. Along this line, if patients received adjuvant chemotherapy, or received chemotherapy if disease recurred or develop metastases? What this the chemotherapy regimen in these patients? The response to chemotherapy is based on the RECIST or other guidelines?

Response:

Thanks for the comment. Accordingly, we add these lines to MATERIALS AND METHODS section **in lines 168-172.** They read: "Those patients who postoperatively received oxaliplatin-based or cisplatin-based first-line systematic chemotherapy were enrolled in the present study. Tumor assessment was performed after every 2 cycles of chemotherapy according to the Response Evaluation Criteria in Solid Tumors 1.1(RECIST 1.1) criteria, and the assessment was classified as a complete response (CR), a partial response (PR), stable disease (SD) and progressive disease (PD)".

3. Considering that 5-FU and cispaltin remain the standard regimen for GC, whether siRNA of WISP1 can enhance the sensitivity of 5-FU and cisplatin?

Response:

This is very good and interesting point. We are sorry that we did not performe such assay for the present study due to limited fund. We will address this issue in our further study. Accordingly, the sentence was added in the section of this study limitation **in lines 458-460.** It reads: "The effect of WISP1 siRNA on the sensitivity of the standard regimen i.e. 5-FU and cisplatin warrant further investigation.

4. As mentioned by authors that WISP1 can promote the proliferation, migration, and invasion of GC, whether siRNA of WISP1 can inhibit the proliferation, migration, and invasion in gastric cancer cell lines.

Response:

This is again a very good and interesting point. We are sorry we did not perform such assay for the present study due to limited fund. We will address this issue in our further study.

5. In the methods or results section, the targeted RNA sequences and protein sites of siRNA of WISP1 should be provided in details. The western blotting and the qRT-PCR to illustrate the expression level of proteins and mRNA of scramble WISP1 and siRNA of WISPI in two GC cell lines are strongly recommended.

Response:

This is a constructive comment. We update the section of method about RNA interference according to reviewer's suggestion **in lines 244-252.**

It reads: Chemically synthesized WISP1 siRNAs (siRNA-1, siRNA-2) and the matching scramble control siRNAs were purchased from Ribo Company (RiboBio, Guangzhou, China). Their corresponding sequences: NM_080838.3(628-646): GGACATCCATACACTCATT; NM_080838.3(885-903): GGAATCCCAATGACATCTT. The siRNAs were transiently transfected into MKN45 and AGS cells by using Lipofectamine 3000 reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. The western blotting and the qRT-PCR to illustrate the expression level of proteins and mRNA of scramble WISP1 and siRNA of WISPI in MKN45 and AGS cell lines.

Review ID: 03769068

The manuscript entitled "Up-regulated WISP1 correlates with poor prognosis and drug-resistance by reducing DNA repair in gastric cancer" submitted by Li-Hua Zhang et al. is a nice original article that shows that WISP1 expression might be useful as a prognosis marker for patients with Gastric Cancer. It is an well-written article with good tables and graphs. Two mistakes should be corrected: 1) the writing of the word "Introduction", at the first subtitle, is missing the first "i"2) The word "in" at the phrase "in GC cells, WISP1 has acted as an oncogene by promoting proliferation, migration, and invasion", in the introduction, must have its first letter being uppercase.

Response:

We thank the reviewer for the supportive comments. Accordingly, we have corrected the mistakes. 1) "INTRODUCTION" was added **in line 124.** 2)**The sentence was also revised in lines 148-149 reads: "**In GC cells, WISP1 has acted as an oncogene by promoting proliferation, migration, and invasion"

Review ID: 03478635

WISP1 expression is correlated with cancer proliferation. Core tip may be revised to describe how up-regulated expression of WISP1 is associated with cancer progression and drug resistance. The description about Cox multivariate survival analysis in TNM stage in Table 2 may be revised to include the more detailed explanation.

Response:

Thanks for the constructive comments. Accordingly, we revised the core tip **in lines 115-120**. It reads: "The present study for the first time revealed that Significantly upregulated WISP1 expression was associated with advanced cancer, drug resistance and poor prognosis in GC. WISP1 enhanced oxaliplatin resistance by reducing cell cytotoxicity through enhancing DNA repair. Overall, the findings of the present study suggest that WISP1 is a novel prognostic biomarker for GC and highlight the significance of WISP1 as promising therapeutic targets for GC.".

In the Cox multivariate analysis, the more detailed descriptions and explanation were included in result section and Table 2, e.g. "TNM stage (III vs I-II), T stage (T3-T4 vs T2-T1), chemotherapy outcome (SD/PD vs CR/PR) ".