November 1, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (13891-review.doc).

Title: Role of E3 ubiquitin ligases in Gastric Cancer

Author: Yachao Hou Jingyu Deng

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13891

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
(1) Reviewed by 00537853
This review summarizes the role of E3 ubiquitin ligases in gastric cancer development, progression and prognosis. Furthermore, Authors aimed to discuss the preclinical and clinical studies of novel treatment strategies targeting aberrant E3 ubiquitin ligases in cancer patients. I believe that, to completely fit Authors'aim, the paragraph: "TARGETING E3 UBIQUITIN LIGASES FOR GASTRIC CANCER THERAPY" should be expanded. Several phrases should be also corrected: - Page 5: "MDM2 as a potential predictor for for benefit from adjuvant chemotherapy with fluorouracil-leucovorin–oxaliplatin (FLO) in resectable GC patients". - Page 10: "Some studies found that CHFR promoter methylation status may provide useful as a value predicting the malignant behaviors and molecular diagnostic marke for GC". - Page 12: "Despite further study is must which needs a better understanding of biological functions of many E3 ubiquitin ligases..".

Responses to reviewer:

Answers to reviewer: Thanks for the suggestion of reviewer. The paragraph: "TARGETING E3 UBIQUITIN LIGASES FOR GASTRIC CANCER THERAPY"has been expanded,as follows: The SCF, also known as CRL(Cullin-RING ubiquitin Ligase) ,was the largest family of ubiquitin ligases that promoted the degradation of about 20% of UPS-regulated proteins [88, 89], including cell cycle regulatory proteins, transcription factors, oncoproteins and tumor suppressors among others [90, 91]. Post-translational neddylation of CUL, a process triggered by the NEDD8-activating enzyme E1 subunit 1 (NAE1), was required for CRL/SCF activation. Recently, MLN4924 was discovered via a high-throughput screen as a specific NAE1 inhibitor and first-in-class anticancer drug [92, 93]. The efficacy and mechanism of action of MLN4924 has been tested in vitro and in mouse models and has revealed promising anticancer activity of a wide-ranging of malignancies [94-99], but not including GC. MLN4924 was currently in multiple phase I clinical trials in both solid tumor and hematological malignancies [88]. We believed that MLN4924 may be used for patients with GC in the near future.

Several phrases should be also corrected: - Page 5: "MDM2 as a potential predictor for for benefit from adjuvant chemotherapy with fluorouracil-leucovorin–oxaliplatin (FLO) in resectable GC patients". - Page 10: "Some studies found that CHFR promoter

methylation status may provide useful as a value predicting the malignant behaviors and molecular diagnostic marke for GC". - Page 12: "Despite further study is must which needs a better understanding of biological functions of many E3 ubiquitin ligases.." have been corrected in the article.

(2) Reviewed by 02438007

This manuscript makes an extensive review on E3 ubiquitin ligases function and its contribution to gastric cancer development. The role of E3 ubiquitin ligase inhibitors in the treatment of GC is also discussed. This review is useful and clearly.

Responses to reviewer:

Answers to reviewer: Thanks for the suggestion of reviewer. According to the suggestion that the article not revise.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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