

Dear Ya-Juan Ma,

The manuscript entitled “Anticancer effect of adenosine on gastric cancer through diverse signaling pathways” (MS# 18469) has been revised following referee’s comments. Revised corrections are indicated in the highlighted text.

I hope that all concerns raised by the referee have been addressed to his/her entire satisfaction.

I look forward to hearing from you about the acceptability of this paper for publication in *World Journal of Gastroenterology*.

Thank you for your re-consideration.

Sincerely yours,

Prof. Tomoyuki Nishizaki, MD & PhD  
Division of Bioinformation, Department of Physiology  
Hyogo College of Medicine  
Anticancer effect of adenosine on gastric cancer through diverse signaling pathways

### **Answer to Referee's comments**

The authors have compared their new drug HUHS1015 in vitro and in subcutaneous tumor nude mouse models of human stomach cancer, with favorable results versus cisplatin, paclitaxel, and irinotecan. The use of an orthotopic model of stomach cancer, available since 1993 (Cancer Res. 53, 1204-1208, 1993; Investigational New Drugs 17, 343-359, 1999), would have made the study of HUHS1015 much stronger, especially to determine antimetastatic efficacy. The authors need to discuss this point and cite the references indicated above.

**Answer:** We greatly appreciate the referee's important advice. According to his/her advice, we have cited references and discussed usefulness for the orthotopic model of stomach cancer as follows: In the present study, the anticancer effect of drugs was assessed using a subcutaneous implantation model of stomach cancer. Tumors subcutaneously implanted are grown in a very different micro-environment from the tissue of origin of the tumors, which may result in the lack of metastases and the altered drug responses. To address these problems, a surgical orthotopic implantation (SOI) model has been developed [13,14]. We are currently attempting to obtain the more physiological effect of HUHS1015 on gastric cancer using the SOI model.

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From: \$B@>:j(B \$BCNG7(B <tomoyuki@hyo-med.ac.jp>  
To: y.j.ma <y.j.ma@wjgnet.com>  
Subject: Re: 18469  
Date: 2015/8/10 10:42:13  
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Dear Prof. Ma,

The manuscript (#18469) has been revised following editor's comments.  
We are submitting a revised version of the manuscript entitled  
"Anticancer effect of adenosine on gastric cancer through diverse  
signaling pathways" to World Journal of Gastroenterology.  
According to the editor's comment, we have added the following  
paragraph "Especially, specific potential inhibitors and targets of A3  
adenosine receptor and AMP, respectively, could be used  
therapeutically" to the discussion.

I hope that all concerns raised by the editor have been addressed to  
his entire satisfaction.

I look forward to hearing from you about the acceptability of this  
paper for publication in World Journal of Gastroenterology.

Thank you for your consideration.

Sincerely yours,

Prof. Tomoyuki Nishizaki, MD & PhD  
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Hyogo College of Medicine