December 11, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6174-review.doc).

Title: The Hedgehog signaling pathway as a new therapeutic target in pancreatic cancer
A review paper

Author: Hideya Onishi, Mitsuo Katano

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6174

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) *It would be helpful to present some target genes of this signaling, which are affected by activation of the Hedgehog pathway and play a crucial role in carcinogenesis. The authors are encouraged to present target genes of this pathway which are typically dysregulated in cancer cells.*

According to your suggestion, we added the sentences as below, "One of the target genes of Hh signaling; Ptch and Gli1 regulate the transcription of the Hh responsive genes by themselves [16]. Other target genes of Hh signaling are the cell cycle regulator Cyclin D1, p21 and N-Myc which plays imporatnat role for carcinogenesis and is also typically dysregulated in the cancer cells [7, 17, 18]." (Page 5, Line 17-21)

(2) *The authors are encouraged to provide more information concerning the influence of the Hedgehog pathway on the cellular/molecular level and its effect on proliferation and invasion.*

According to your suggestion, we discussed about the influence of the Hedgehog pathway on the cellular/molecular level and its effect on proliferation and invasion as below, "Some other molecules affected by the activation of Hh signaling may also contribute to the induction of malignant potential in pancreatic cancer. Decrease in Cyclin D1by the inhibition of Hh signaling induces the G0/G1 arrest and inhibits cell proliferation [37]. Matrix metalloproteinase (MMP)-9 and MMP-2 locate the downstream of Gli1 and are involved with the invasiveness in pancreatic cancer [38, 39]." (Page 7, Line 6-10)

(3) *Are there any data indicating that the activity of Hedgehog signaling correlates with patients' outcome?*

We discussed about your suggestion as below, "Although exact patients' outcome has not been reported yet, Sekulic *et al* has shown that the independently assessed response rate was 30% and 43%, and the median duration of response was 7.6 months using two-cohort study with GDC-0449 (Visnodegib) in metastatic and locally advanced basal-cell carcinoma [68]. " (Page 10, Line 20-23)

(4) *How feasible will be the incorporation of the Hh signaling in every day clinical routine? A more detailed prospective how and when Hh signaling can be used in future clinical life should be discussed more in detail.*

We discussed about your suggestion as below, "Hh inhibitor can successfully inhibit tumor growth and invasiveness *in vitro* and can be a promising drug, however, in clinical trial, it is not easy to verify the

effectiveness of Hh signaling inhibitor. This reason may be that the actual function of Hh signaling molecules are not fully understood [79, 80]. Hh signaling inhibitors should be effective in cancers in which Hh components are mutated such as basal cell carcinoma, basal cell nevus syndrome and medulloblastoma because Hh signaling is constitutively activated [81]. And in these cancers, Hh signaling inhibitors may become the first use drug in future clinical life. However, for other tumors, appropriate combination therapy may be required for the effective therapy." (Page 12, Line 3-11)

(5) *Are there studies with animal models consistent with the role of Hh signaling in pancreatic CSCs or Hh up-regulation under hypoxia conditions?*

We have not detected the animal models concerning Hh up-regulation under hypoxia in pancreatic cancer. Then we introduced animal models consistent with the role of Hh signaling in pancreatic CSCs as below, "Han *et al* has revealed that suppression of Hh signaling by arsenic trioxide leads to the inhibition of the viability of pancreatic CSCs using animal models [51]. " (Page 8, Line 2-4)

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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