Author's response to reviews

Title: Clinical significance of L-type Amino Acid Transporter 1 Expression as a Prognostic marker and Potential of New Targeting Therapy in Biliary Tract Cancer

Authors:

Kyoichi Kaira (kkaira1970@yahoo.co.jp)
Yutaka Sunose (ysunose@showa.gunma-u.ac.jp)
Yasuhiro Ohshima (ohshima.yasuhiro@jaea.go.jp)
Noriko S Ishioka (ishioka.noriko@jaea.go.jp)
Kazuhisa Arakawa (k-arakawa@maebashi.jrc.or.jp)
Tetsushi Ogawa (t-o-gawa@takasaki-hosp.jp)
Noriaki Sunaga (nsunaga@gunma-u.ac.jp)
Kimihiro Shimizu (kmshimizu@gmail.com)
Hideyuki Tominaga (htomi@med.gunma-u.ac.jp)
Noboru Oriuchi (oriuchi1@gmail.com)
Hideaki Itoh (h-ito@maebashi.jrc.or.jp)
Shushi Nagamori (nagamori@pharma1.med.osaka-u.ac.jp)
Yoshikatsu Kanai (ykanai@pharma1.med.osaka-u.ac.jp)
Aiko Yamaguchi (ayamaguchi@gunma-u.ac.jp)
Atsuki Segawa (asegawa@med.gunma-u.ac.jp)
Munenori Ide (idem@gunma-u.ac.jp)
Masatomo Mori (mmori@med.gunma-u.ac.jp)
Tetsunari Oyama (oyama@med.gunma-u.ac.jp)
Izumi Takeyoshi (takeyoshi@gunma-u.ac.jp)

Version: 3 Date: 26 August 2013

Author's response to reviews: see over
To Referee

Thank you for your generous comments for our paper.

1) Discretionary Revisions:
The following points should be addressed in the discussion:

• Is LAT1 a tumor-specific drug target?
• Is LAT1 expressed in normal tissues? Discuss your findings about benign lesions.
• At which point in the carcinogenesis/adenoma-carcinoma sequence is LAT1 overexpressed? E.g., any data from colon cancer available?

Re) We have no available data from colon cancer. However, we had previously evaluated the protein expression of LAT1 by immunohistochemistry in patients with from low-grade to high-grade pulmonary neuroendocrine tumor. Our report indicated that the expression of LAT1 tended to increase from low-grade to high-grade malignancy. Recently, we described the different expression of LAT1 between pancreatic cancer and pancreatic benign lesion. In this report, LAT1 expression was not observed in pancreatic adenoma, whereas, LAT1 was highly expressed in pancreatic cancer. Previous experimental data also demonstrated that LAT1 is overexpressed in tumor tissue, and LAT2 is dominantly expressed in normal tissue. In the protein expression level of human tissue specimens, there was no evidence of LAT1 expression in normal tissues. We believe that LAT1 is tumor-specific amino acid transporter and has a potential target of tumor-specific therapeutics. We added above sentences in the Discussion section.

• Does animal models based on LAT1 overexpression exist?
Re) Kobayashi K. et al. has established LAT1-overexpressed glioma and reported that overexpression of LAT1 enhanced the rates of tumor growth in vivo (Ref. Neurosurgery 2008, 62(2), 493-504). However, there is no animal model based on LAT1 overexpression in other cancers.

2) Minor Essential Revisions:
• Page 7: the authors state that the TNM stages were adopted from staging for
pancreatic cancer. Not those for bile duct cancer?

Re) I am sorry that pancreatic cancer is mistaken. This sentence was corrected as bile duct cancer.

• Figure 1: show picture of benign lesion or normal tissue

Re) The representative figure of benign lesion was also added as Figure 1B. Therefore, Figure 1 was changed to Figure 1A.

• Table 1: UICC stage 1-4 → please precise: pathological (pT) or clinical tumor extent (cT)

Re) UICC stage on Table 1 shows pathological disease staging. In Table 1, some corrections were made.

3) Major Compulsory Revisions:

• none

Re) Thank you for your generous comment.