Author's response to reviews

Title: A small molecular agent YL529 inhibits VEGF-D-induced lymphangiogenesis and metastasis in preclinical tumor models in addition to its known antitumor activities

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Author's response to reviews: see over
Dear editor,

We are submitting the manuscript entitled “A small molecular agent YL529 inhibits VEGF-D-induced lymphangiogenesis and metastasis in preclinical tumor models in addition to its known antitumor activities” for review and publication in the *BMC Cancer*. We believe that following aspects of this manuscript will make it interesting to general readers of *BMC Cancer*:

In present study, we described the pharmacological activity profiles of YL529, a novel small molecular compound as potential new anticancer agents discovered in our laboratory by computer-aided drug design, high-throughput screen and *de novo* synthesis. The chemical structure of YL529 is novel and its structure is different from other inhibitors used in clinical.

YL529 is an orally active inhibitor, exhibited antitumor activities with the following features: 1) YL529 inhibited the activities of a panel of protein kinases in enzyme level firstly reported by our group and inhibit tumor growth. Moreover, YL529 also inhibited the activities of other kinases like VEGFR3 in protein enzyme level *in vitro*. 2) The mechanisms investigation showed that YL529 inhibited the expression level of phosphorylation of VEGFR3, proliferation, migration, invasion and tube formation of human limbal epithelial cells (HLECs) at low concentration. Moreover, YL529 inhibited the proliferation of VEGF-D-LL/2 tumor both in vitro and in vivo via JNK/VEGFR3 signaling pathway. 3) *In vivo*, it induced regression of established VEGF-D-LL/2 tumor xenografts in C57/BAL/6 mice in a dose-dependent manner (37.5-150 mg/kg). The histologic analysis revealed tumors treated with YL529 show a reduction in microvessels density and increased apoptosis *in vivo*. 4) YL529 was well tolerated and no adverse effects on clinical condition during oral administration of murine tumor xenograft models in mice.

Collectively, the data shown that YL529 is a novel, orally active bioavailable inhibitor with potent anti-lymphangiogenesis and metastasis activity together with antitumor efficacy both *in vitro* and *in vivo*, might provide a relatively non-toxicity therapy for tumors and its well therapeutic will show its enormous potential for future investigation.
All authors have agreed to be so listed and have approved its content, and its submission to *BMC Cancer*.

We trust that the manuscript meets the high standard of *BMC Cancer* and we are very appreciated it if you would contact me by e-mail.

Sincerely Yours,
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