**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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**Version:** 9  
**Date:** 10 April 2015

**Author's response to reviews:**

Dear editor and reviewers,

We are grateful for your letter dated on 8 March, 2015, with regard to the comments for our 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 (MS: 9316125914519646)”. Many thanks for you and the reviewers for the valuable comments.

We have thoroughly revised the manuscript and addressed all the issues. The detailed explanations are included in the manuscript marked in blue or in the following up section of this letter point by point. We are looking forward to hearing from you at your earliest convenience time. Thanks again for your reconsideration.

Best regards

Sincerely Yours,

Yinglan Zhao, Ph.D

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Editor: (Comments to the Author)

Reviewer #1:

(Minor essential revision)

Q1: The lack of balance on VEGF-C (Q2) in the introduction and the lack of an experiment addressing its activity does leave a gap in this study.

A1: Thanks for this comment. We agree with the reviewer’s comment. According to the reviewer’s comment, we have revised the “Introduction” section, added some context, recently some other researchers like Hanahan D et al. and Stacker SA, et al have proved that VEGF-C plays a key role in lung cancer metastasis (Hanahan D and Weinberg RA, Cell 2011; Stacker SA, et al., Nat Rev Cancer 2014.). Up-regulating the expression of VEGF-C could increase the lymphangiogenesis, exacerbate tumor metastasis to local lymph nodes and distant organs. It may be best to do an experiment to addressing VEGF-C activity in present study. However, in our previous preliminary experiments, our result about the effect of VEGF-C for YL529 treatment is not obvious, and combined with the limitations of our experimental conditions#we chose to detection the expression of VEGF-D after YL529 treatment. Based on this, we revised the manuscript and added some comments in Background section to address that VEGF-C is very important in lung cancer metastasis. (Page 3, paragraph 2nd)

Q2: The “few reports” of VEGF-D in tumor metastasis should include the original reference Stacker et al., Nature Medicine 2001.

A2: Thanks for the comment. We agree with the reviewer’s comment. According to the reviewer’s comments, we updated and added the reference “Stacker SA, Caesar C, Baldwin ME, Thornton GE, Williams RA, Prevo R, Jackson DG, Nishikawa S, Kubo H, Achen MG. VEGF-D promotes the metastatic spread of tumor cells via the lymphatics. Nat Med 2001, 7:186-191” in the revised manuscript.


A3: Thanks for the comment. We agree with the reviewer’s comment that the reference #38 is not the original reference for this fact. And according to the reviewer’s suggestion, we revised and change the reference #38 “Kesari S, Bota DA:Fos-related antigen-1 (Fra-1) is a regulator of glioma cell malignant phenotype. Cancer biol Ther 2011, 11:307-310.” to “Debinski W, Slagle-Webb B, Achen MG, Stacker SA, Tulchinsky E, Gillespie GY, Gibo DM: VEGF-D is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. Mol Med 2001, 7:598-608.”in the “Reference” section of the manuscript. (Page 20, last three lines)

Q4:Page 11, the new sentence appears incomplete.
A4: Thanks for the comment. We are sorry to make a mistake in the new sentence. In the revised manuscript, we correct the mistake and make the sentence “Similar to the previous data from our group, this study uses a VEGF-D antibody that detects the mature form of VEGF-D, because the fully mature cleaved form of 21 kD has the greatest affinity for the receptors, and can bind and activate not only VEGFR-2 but also VEGFR-3” completed. (Page 11, paragraph 3rd, line 2nd to 5th)

Q5: Rounding of the numbers from two-decimal places is suggested.
A5: Thanks for the comment. According to the reviewer’s suggestion, we revised the rounding the numbers with two-decimal marked in blue in the revised manuscript.

Q6: Figure 7 is still quite confusing and does not adequately explain the different contributions of R2 and R3 on LEC and blood vessels. The diagram should as a minimum show the different contributions of R2 and R3 on LEC, and preferably compared to BEC on blood vessels.
A6: Thanks for this comment. According to the reviewer’s suggestion, we have revised the figure 7 and have described show the different contributions of VEGFR2 and VEGFR3 on LEC, and preferably compared to BEC on blood vessels.

Q7: Expressions like "the specific lymphangiogenic factor" will confuse readers about the specificity of VEGF-D and do not integrate the activity of VEGF-D seen on blood vessels by these workers and others. It will create an incorrect bias in the minds of the readers about the total activity of the factor.
A7: Thanks for the comment. According to the reviewer’s suggestion, we revised the manuscript and revised the expressions like "the specific lymphangiogenic factor" to avoid misleading readers.

Q8: Figure 7 is quite poor, and could provide so much more information and guidance to the readers.
A1: Thanks the reviewer for the comment. According to the reviewers’ recommend, we have revised the Figure 7 and added the related information and guidance to the readers.