Author's response to reviews

Title: STAT6 expression in glioblastoma promotes invasive growth

Authors:

   Barbara C Merk (bcm4u@virginia.edu)
   Jennifer L Owens (jlkalb@gmail.com)
   Maria-Beatriz S Lopes (msl2e@hscmail.mcc.virginia.edu)
   Corinne M Silva (silvacm@niddk.nih.gov)
   Isa M Hussaini (imh5c@cms.mail.virginia.edu)

Version: 3 Date: 5 April 2011

Author's response to reviews: see over
April 5, 2011

Melissa Norton, MD
Editor in Chief, BMC Cancer

SUBMISSION OF REVISED MANUSCRIPT

Dear Dr. Norton,

Enclosed please find the latest version of our manuscript, “STAT6 expression in glioblastoma promotes invasive growth.” We again wish to thank the reviewers for their thoughtful, constructive feedback; we have revised the manuscript to incorporate their suggestions. As requested, we have included a point-by-point response to each reviewer’s comments below, and have highlighted the newly revised sections of the manuscript.

We appreciate your help throughout the submission process, and hope that this revised manuscript will meet your expectations for acceptance.

Sincerely yours,

Barbara Merk
Referee #1: Janusz Rak

1. We thank the reviewer for this suggestion. We have re-phrased the discussion to clarify which mechanisms of STAT6 contribution to GBM pathophysiology we are proposing based on our own studies, and which additional potential effects have been described by others.

2. We agree completely. It is our belief- and the suggestion of the aforementioned studies’ authors- that the STAT6 -/- mice resist xenograft tumors due to enhanced anti-tumor immunity, and that this immunity is influenced primarily by the lack of STAT6 expression in the tumor microenvironment/ stromal cells (as opposed to the tumor cells themselves). We therefore propose that, based on the aforementioned studies and our own work, the potential benefits of STAT6 inhibition could be two-fold: enhanced anti-tumor immunity combined with growth inhibition/ decreased invasive potential of the tumor cells. We have clarified this point in our discussion.

We also wish to apologize for the lack of clarity in our previous response to this reviewer: it was precisely this point we were trying to make when explaining why the use of currently available animal models would not yield optimal in vivo data. While we agree that we could potentially confirm the slower growth/reduced invasion of STAT6-/- cells in these animals, a xenograft model would fail to take into account the effects of STAT6 inhibition in the stromal cells. Even if crossed with STAT6-/- animals (and thus achieving global STAT6 silencing), SCID mice would be unable to demonstrate the potential immunological advantage conveyed by inhibition of STAT6.

3. We have clarified our description of the Rembrandt analysis. STAT6 up- or down-regulation refers to a 2-fold (or greater) difference from the mean expression within the data set. For example, up-regulation among GBM patients refers to a 2-fold increase in STAT6 expression, compared to the average STAT6 expression levels in all patients in the GBM sub-population. Therefore, each patient sub-population (i.e. GBM, astrocytoma, all gliomas) has a distinct baseline, and expression levels are only compared to other patients in the same sub-population.

Referee #2: Ian Lorimer

1. We agree, and have revised our statement on the potential reasons why statistical significance is not reached in Figures 7B and 7C.

2. We thank the reviewer for pointing this out, and have revised these statements accordingly.

Referee #3: Julie Carrier
1. We agree that presenting the microarray data following our *in vitro* studies results in a more logical order of results, and have implemented this change.

2. We have changed the description of Tables 2 and 3. We thank the reviewer for pointing out this discrepancy.