Author’s response to reviews

Title: Pathway activity profiling of growth factor receptor network and stemness pathways differentiates metaplastic breast cancer histological subtypes

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Author’s response to reviews:

Dr. Andrea H. Bild
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August 15, 2019

Dr. Catherine Rice
Senior Assistant Editor
BMC Cancer
Dear Dr. Rice,

We would like to again thank the editorial staff and the reviewers for contributing helpful feedback to our manuscript, “Pathway activity profiling of growth factor receptor network and stemness pathways differentiates metaplastic breast cancer histological subtypes”/BCAN-D-19-00164. We have revised the manuscript as described in response to each point below. Thank you again for the opportunity to revise this manuscript and for your consideration of its publication in BMC Cancer.

Sincerely,

Jasmine A. McQuerry

&

Dr. Andrea H. Bild

Professor, Department of Medical Oncology and Therapeutics Research

City of Hope
Editor’s Comments

Editor Comments:

1 - Please ensure the corresponding and other author details in the submission system and on the manuscript are in agreement.

The author details have been verified.

2 - If you wish to acknowledge someone by their full name in the Acknowledgements, please ensure you have obtained permission from them to so do.

We have obtained permission to use the full name of the individual acknowledged in the manuscript.

3 - At this stage, please upload your manuscript as a single, final, clean version that does not contain any tracked changes, comments, highlights, strikethrough or text in different colours. All relevant tables and figures should also be clean versions. Figures (and additional files) should remain uploaded as separate files. Should you wish to respond to these revision requests, please include the information in the designated input box only.

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Reviewer 2 Comments

I strongly disagree with author's reasoning for dismissing what I still see as a valid concern. Publication in Nature, high number of citations and curation by Broad Institute cannot absolve of caveats associated with having to make imperfect assumptions. This is not a critical issue that should hinder paper publication, but this attitude hurts the advance of scientific knowledge.

We sincerely thank the reviewer for their commitment to advancing scientific knowledge and wish to provide more rationale regarding the method chosen. The reviewer’s original suggestion to ensure overexpression of growth factor receptor network and stemness genes achieves levels comparable to those seen in tumors is well taken. While different tumors often show a broad range of expression of these genes, expression by the adenovirus system is tested to fall within the range of expression in tumor cells if feasible. Additionally, the pathway activation system used herein, based on the Bild et al. Nature (2006) system, is focused on isolating the transcriptional effects from a pathway’s activation. This system is designed to minimize background signal and noise to best isolate the effects specific to a pathway. Thus, normal mammary epithelial cells are used with low serum and conditioned media to decrease background signals not relevant to the pathway studied. Importantly, activation of upstream pathway components, such as growth factor receptors and genes such as RAS, et cetera, activate downstream transcription factors with unique genomic “signatures”. Alternatively, if a pathway was activated in a cancer cell, in which there are extensive levels of oncogenic signaling, it would be challenging to isolate the transcriptional effects specific to a single pathway’s activation.