Author’s response to reviews

Title: S100A4-neutralizing antibody suppresses spontaneous tumor progression, pre-metastatic niche formation and alters the T-cell polarization balance

Authors:

Birgitte Grum-Schwensen (bigru@regionsjaelland.dk)
Jörg Klingelhofer (klingelhofer@sund.ku.dk)
Mette Beck (mkbeck@cbs.dtu.dk)
Charlotte Menné Bonefeld (cmenne@sund.ku.dk)
Petra Hamerlik (pkn@cancer.dk)
Per Guldberg (perg@cancer.dk)
Mariam Grigorian (grigorian@sund.ku.dk)
Eugene Lukanidin (el@cancer.dk)
Noona Ambartsumian (ambartsumian@sund.ku.dk)

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Dear Editor

We would like to transfer the manuscript, entitled “S100A4-neutralizing antibody suppresses spontaneous tumor progression, pre-metastatic niche formation and alters the T-cell polarization balance.” by Birgitte Grum-Schwensen, Jörg Klingelhöfer, Mette Beck, Charlotte Menné Bonefeld, Petra Hamerlik, Per Guldberg, Mariam Grigorian, Eugene Lukanidin and Noona Ambartsumian, from Molecular Cancer to BMC Cancer, and to be considered for publication.

In recent years, it has become evident that tumor progression is a result of a cross-talk between cancer cells and surrounding stroma. Immune cells exhibit remarkable plasticity in their ability to shift from anti-tumor to pro-tumor phenotype depending on the context of the tumor microenvironment. Recently it was shown that therapeutic re-education of immune cells in order to exhibit tumor suppressing function could be an efficient way to combat cancer.

In previous work, others and we established that S100A4, a member of the S100 family, promote metastasis formation. Accordingly, S100A4 upregulation in a variety of cancer types correlates with poor outcome in patients. The pro-metastatic S100A4 is known as an inducer of inflammatory processes and has been shown to attract T-cells to the tumor. Targeting S100A4 by a neutralizing antibody blocked metastasis formation. However, the mechanism of antibody action and the effect of S100A4 on T-cells is not clear.

Here we tested the hypothesis whether S100A4 can regulate T-cell lineage differentiation towards a pro-tumorigenic (Th2) phenotype and provide evidence of the efficacy of the antibody in blocking tumor progression in a spontaneous breast cancer model.

The following major novel findings are presented in the manuscript:

(i) S100A4 regulates T-cell pattern differentiation. In particular it induces changes in the T-cells’ Th1/Th2 polarization balance and subsequently in the cytokine expression
The S100A4 neutralizing antibody, 6B12, can reverse the Th1/Th2 balance of T-cells.

(ii) The 6B12 antibody executes its activity at the pre-malignant stage of tumor and pre-metastatic stage of metastasis by blocking the attraction of T-cells to the site of growing tumor.

We believe that *BMC Cancer* would be an excellent journal in which to publish this paper as it describes molecular mechanisms and conceptual advances about the role of S100A4 in cancer progression and metastasis and also potential therapeutic implications. The topic of the paper should therefore be of general interest to a wide audience, including molecular biologists and cancer researchers working in both basic and clinical fields, and to investigators working in the area of cancer immunology.

The content of the manuscript is original and it has not been published or accepted for publication, either in whole or in part, in any form. No part of the manuscript is currently under consideration for publication elsewhere.

The authors have no conflict of interest to declare. All animal studies were approved by the relevant institutional review boards.

Sincerely,

**Jörg Klingelhöfer and Noona Ambartsumian, PhD**

Associate Professors, PhDs

**University of Copenhagen - Neuro-Oncology Group**

Symbion Science Park

Fruebjergvej 3, Box 39

2100 Copenhagen Ø