Preclinical targeting of the tumor microenvironment

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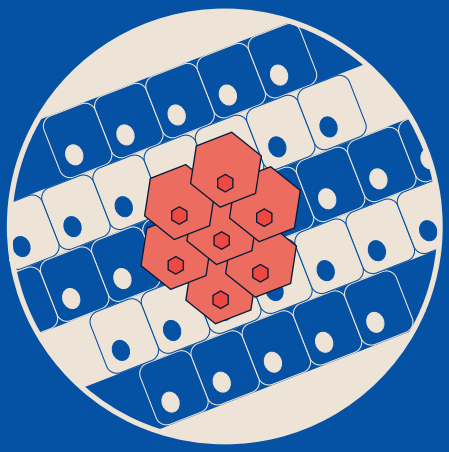

Chapter 5B

Bevacizumab-induced vessel normalization hampers tumor uptake of antibodies – response

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We would like to reply to the letter by Huang *et al.* on the impact of vascular changes induced by antiangiogenic therapy on tumor uptake of other drugs in relation to our findings of reduced antibody uptake after bevacizumab treatment (1). Their comments focus on the bevacizumab dose used and whether vessel normalization was demonstrated.

They consider the bevacizumab dose we used high and suggest that this resulted in "inadequate" rather than "normalized" tumor vessels. The concept of too high bevacizumab dosing is interesting and might have a major impact if translated to the clinic. Jain's group reported on findings in a preclinical study with 10, 20 and 40 mg/kg of the mouse anti-VEGFR2-antibody DC101 where the highest dose resulted neither in vessel normalization nor improved efficacy of immunotherapy (2). It is unclear whether these findings with anti-VEGFR2-antibody can be translated directly to our results with bevacizumab, which binds VEGF-A, affecting both VEGR1 and VEGFR2 signaling.

In our mouse model, one modest dose of 5 mg/kg bevacizumab reduced the tumor uptake of radiolabeled trastuzumab and aspecific control IgG by 38% and 27% respectively after only 2 days. On day 6, after three 5 mg/kg bevacizumab doses, this decrease was even more pronounced for radiolabeled trastuzumab, -bevacizumab and -IgG (1). Moreover, these decreases are all within the described vascular normalization time window (3). We found increased pericyte coverage after bevacizumab treatment, indicating structural vessel normalization. This may not prove functional vessel normalization. However, tumor histology showed no difference in already low percentages of necrosis, tumor viability or proliferation index between animals receiving bevacizumab or placebo. This is not in line with inadequate vasculature caused by high-dose antiangiogenic therapy (3).

Our findings of reduced uptake of antibodies after antiangiogenic therapy are supported by two preclinical studies. One 10 mg/kg dose of the cross-reactive anti-VEGF-antibody B20-4.1 decreased tumor trastuzumab uptake by 50% after 2 days (4) and 10 mg/kg bevacizumab decreased tumor cetuximab uptake by 40% after 4 days (5). Importantly, our findings are also supported in the clinical setting as a study in renal cell carcinoma patients showed 47% decrease of ^{89}Zr-bevacizumab tumor uptake after 10 mg/kg bevacizumab (6). Furthermore, large phase 3 trials showed only modest effects of bevacizumab combined with trastuzumab in HER2 positive breast cancer, and negative effects when combined with cetuximab or panitumumab in colorectal cancer.

Combining bevacizumab with chemotherapy, in a dosage that is high according to Huang *et al*, showed also disappointing results as it did not improve overall survival in breast and ovarian cancer. Nonetheless, chemotherapy with a relatively low-dose of 5 mg/kg bevacizumab in metastatic colorectal and a high-dose of 15 mg/kg in non-small cell

lung cancer (NSCLC) every 2 weeks improved overall survival (7, 8). Jain (3) suggested that the reduced tumor uptake of radiolabeled docetaxel in NSCLC patients may be the consequence of a too high bevacizumab dose of 15 mg/kg (9). However, also 24 hours after 7.5 mg/kg bevacizumab, radiolabeled 5-fluorouracil uptake decreased 20% in liver metastases of colorectal cancer patients (10).

This illustrates that many aspects of the interplay between vessel normalization, anti-angiogenic therapy dosing and combination with other anticancer drugs still need to be clarified. Like Huang *et al.*, we are interested in using imaging for this purpose. Small exploratory studies could visualize effects of antiangiogenic drugs on distribution of other labeled drugs, provide serial information on whole body drug distribution and guide rational trial design for large combinatorial studies. The ultimate goal is optimal drug delivery to individual tumors.

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