Reviewer's report

Title: Blood vessel hyperpermeability and pathophysiology in human tumour xenograft models of breast cancer: a comparison of ectopic and orthotopic tumours

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Reviewer: Sven A Lang

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The manuscript by Ho and coworkers compares the effects of orthotopic vs. ectopic injection of tumour cells on permeability and pathophysiology in a breast cancer model. SC tumour cell implantation and injection into the mammary fat pad (MFP) were used. Subsequently, tumours were size matched and dextran accumulation (after i.v. tail vein injection) was assessed. Furthermore, immunohistochemical stainings for CD31, collagen IV, CD31/#SMA and LYVE-1 were performed. From their results the authors conclude that orthotopic (MFP) tumors are superior to ectopically implanted tumours to observe enhanced permeability and retention (EPR) effects.

In general, this is a very interesting study that adds novel arguments to the ongoing discussion for the use of orthotopic mouse models in preclinical cancer research. The study is well written and performed with appropriate methods. However, some points should be addressed and are listed below:

1. The study is based on results from 1 breast cancer cell line. Taking into account that unexpectedly several tumours in the SC group were smaller after 6 weeks post-injection than after 5 weeks, I would really recommend to validate at least the key results in 1 more cell line. This would significantly strengthen the study.

2. In my opinion the double staining for CD31/#SMA is weak. It is difficult to detect the violet cells although they are indicated this arrows. I would rather recommend performing immunofluorecent stainings.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: 'I declare that I have no competing interests'