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TITLE: Multimodal imaging of breast cancer metastasis targeting and antimetastatic nanotherapy

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ABSTRACT BODY:

Abstract Body: INTRODUCTION: As opposed to the routine use of nanomedicines for drug targeting to solid tumors, the highest medical need refers to targeting and treating metastasis. Little is known regarding the accumulation of polymers, liposomes and micelles in metastases, and no systematic analyses have been performed comparing drug targeting to different types (and sizes) of metastases. We here employ three different nanocarriers, an optically imageable metastatic mouse model and several different imaging techniques, to assess drug targeting and drug treatment of metastasis. With fluorophore-labeled nanomedicines, we show that metastases can be more efficiently targeted than primary tumors. In addition, we provide convincing proof-of-principle that docetaxel-loaded micelles are able to inhibit metastasis, also providing initial insights into the vascularity of different types of metastases within different organs.

METHODS: Female Nu/Nu mice were orthotopically implanted with $2x10^5$ 4T1-iRFP cells (exc 680 nm). Mice were non-invasively monitored for local tumor growth and metastatic colonization using hybrid 3D computed tomography - fluorescence molecular tomography (CT-FMT). Upon metastastic detection, fluorophore-labeled (488/750) polymers, liposomes and micelles were i.v. injected. At 72h, primary tumors and metastases were harvested for ex vivo fluorescence reflectance imaging (2D FRI), assessing the colocalization between metastases (680nm) and nanocarriers (750nm). In an initial therapy study, 4T1-iRFP bearing mice were i.v. treated with vehicle, free docetaxel (Taxotere 30 mg/kg), and core-crosslinked polymeric micelles containing docetaxel (CriPec 30 mg/kg). In addition, a single CriPec 90 mg/kg was administered. Animals were CT-FMT scanned for metastasis colonization, organs were harvested for histology and 1 mouse/group was perfused with the vascular casting agent Microfil (for high-resolution ex vivo CT imaging of blood vessels in tumors and metastases).

RESULTS AND DISCUSSION: Metastatic colonization was sensitively detected using CT-FMT (Fig.1A-C). Fluorophore-labeled polymers and liposomes efficiently colocalized with metastases (overlap between 680 and 750 signals, Fig.1B-C), with no accumulation in healthy areas in lungs, lymph nodes and ovary (Fig.1C). The therapeutic efficacy of docetaxel-loaded core-crosslinked polymeric micelles was found to be higher than that of the free drug, with smaller primary tumors and less lung metastases, as visualized and quantified using optical imaging, CT imaging and histology (Fig.1D-E). A single 90 mg/kg micelle dose was found to be more efficient than three 30 mg/kg doses of free drug. High-resolution ex vivo μCT provided initial insights on the microvascular network in different types of metastases, showing that those are more extensively and more homogenously vascularized than primary tumors (Fig.1F).

CONCLUSION: In summary, we here systematically show that different types of metastases - in particular lung, lymph node, bone and ovary - can be efficiently targeted and treated using nanomedicines. Initial evidence correlating vascular characteristics with metastatic drug targeting is also provided.

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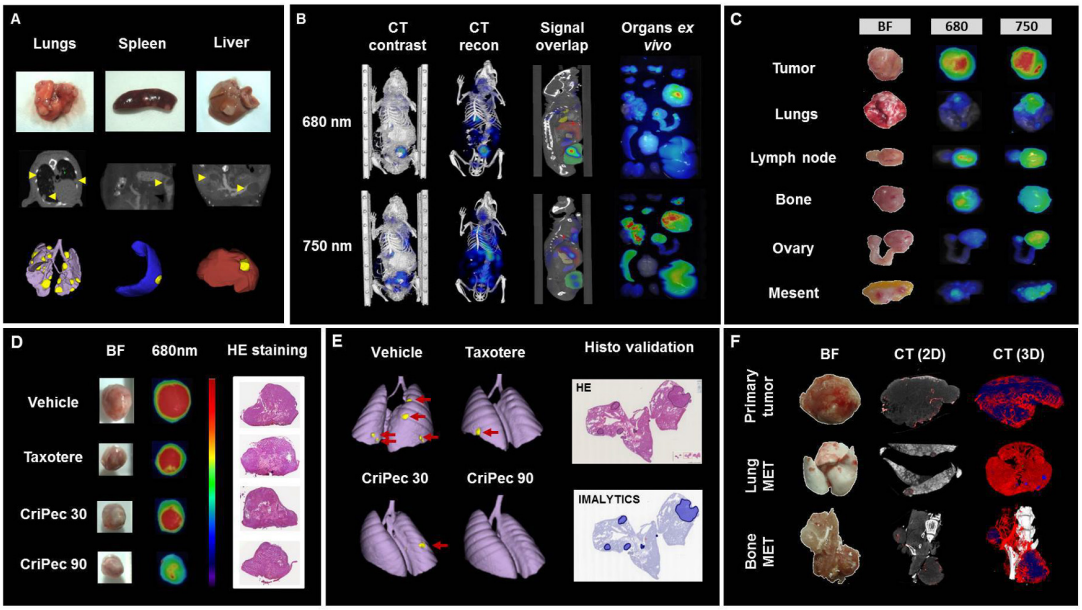

Figure 1: Imaging, targeting and treating breast cancer metastases using nanomedicine formulations. A: In vivo CT imaging of 4T1-iRFP breast cancer metastases in lung (top panels), spleen (middle panels) and liver (bottom panels). Metastases are segmented in yellow in the in vivo CT images, the respective organs (excised post-mortem) are shown on the left. B-C: Efficient and specific targeting of fluorophore-labeled polymers and liposomes to metastatic lesions in several different tissues, non-invasively in vivo in (B) and ex vivo 2D FRI (C). iRFP-expressing cancer cells are shown at 680 nm, fluorophore-labeled nanocarriers at 750 nm. Note the overlap between the 680 and 750 signals. BF: Bright-field images. D-E: Efficient anti-metastatic therapy using docetaxel-loaded core-crosslinked polymeric micelles (CriPec), exemplifying smaller primary tumors upon drug targeting (D) and less metastatic lung lesions (E), as also validated through histology by less necrotic areas upon treatment and also less lung metastases (lower number of lung metastases nodules, as well as lower relative area covered by the nodules (%)). F: High-resolution ex vivo CT imaging of blood vessels (red) in orthotopic breast cancer tumors and in lung and bone metastases upon Microfil perfusion. Analyses to correlate the efficiency of tumor and metastasis targeting with anatomical and functional blood vessel characteristics are currently ongoing. All images are based on own unpublished findings.