A novel nanoscale probe facilitates non-invasive quantification of tumor EPR status and helps predict chemotherapy outcomes in a rodent breast cancer model

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Introduction: Nanoscale therapeutic interventions are increasingly important elements of cancer therapy [1]. Nanoparticle-based chemotherapeutics have been approved for clinical use, such as Doxil® [2] and Abraxane® [3], or undergo clinical evaluation . However, the success of nanoparticle-based cancer chemotherapy is primarily dependent on the access these agents have to tumors via the leaky vasculature, the so called Enhanced Permeation and Retention (EPR) effect [4]. Yet, the extent of vascular permeability to nanoparticles in individual tumors varies widely [5, 6], resulting in a correspondingly wide range of responses to the therapy. However, there exist no tools currently to rationally determine whether tumor blood vessels are amenable to nanocarrier mediated therapy in a patient-specific manner today. An a priori determination of the extent of vascular permeability would therefore facilitate personalized therapy, and spare potential non-responders from the rigors of a chemotherapy regimen.

Methods: To address this need, we developed a long-circulating liposomal contrast *nanoprobe*, for X-ray imaging. Using a clinical mammography unit, we probed the tumor vascular permeability to the nanoprobe in a rat breast tumor (MAT BIII mammary adenocarcinoma), and subsequently treated the animals with liposomal doxorubicin of similar composition and particle size as the probe (and as the clinically used liposomal chemotherapy), to evaluate the probe's predictive efficacy.

Results: The high iodine content (155 mg of iodine per mL) and the method of use allowed detection and quantification of the intratumoral, extravascular accumulation of the nanoprobe showing a widely variable vascular permeability. It would be expected that a long-circulating agent would produce undistinguishable extravascular and intravascular signal making determination of the degree of EPR unfeasible. Here, we identified a dose that produces undetectable signal from the blood while the accumulation of the agent produces adequate signal for detection. We were able to identify two subgroups prior to treatment: a 'good prognosis' and a 'bad prognosis' subgroup and indeed these demonstrated differential tumor growth rates.

Conclusions: In this work, we demonstrate what is to our knowledge, the first contrast agent capable of predicting the therapeutic outcome of a clinically used chemotherapy using a simple, fast and commonly used imaging modality (such as mammography).

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