Biomaterials for Image-guided Drug Delivery

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Statement of purpose: Delivering drugs to a desired site, while minimizing systemic toxicity, has long been recognized as a challenging goal. Encapsulation within a nanoparticle facilitates a decrease in off-target effects, can increase circulation time and can enhance local delivery. Methods to activate nanoparticles with exogenous energy or using endogenous cellular properties have been studied to improve local efficacy. To develop such methods and agents, the pharmacokinetic profile must be optimized. Imaging-based quantitative pharmacokinetic assays and models can greatly simplify this process. Here, we review the methods for image-based assessment of particle stability, local targeting and local activation.

Methods, materials and analytical procedures used: We have developed multiple strategies to label particles for imaging with positron emission tomography (PET), ultrasound and optical imaging. We describe the approaches for labeling and demonstrate the utility of each approach.

Results: For PET imaging, we have developed a conjugation scheme for the attachment of a fluorine-18 label to a lipid molecule prior to incorporation in a nanoparticle (1). Alternatively, pre-formed and drug-loaded liposomes can be labeled with copper-64; we have attached 6-[p-(bromoacetamido)benzyl]-1,4,8,11-tetraazacyclotetradecane- N,N',N'',N'''-tetraacetic acid (BAT) to a lipid or polymer (2). Also, we have developed a maleimide-thiol approach to attach chelators to lipid or polymer constructs (3). Vehicles containing an optical label within the particle core, together with a PET label on the shell, have been evaluated in tumor models, resulting in the development of a pharmacokinetic model for uptake by the reticuloendothelial system and tumors and the stability of the particle (4). With a hydrophilic probe, we have demonstrated increases in 24 hours tumor accumulation of hydrophilic molecules by 10-200 fold (5). Alternatively, with an amphipathic probe (such as luciferin), ultrasound-mediated release has been demonstrated by increasing radiance in response to the sound energy (6). Our optimized methods for combining particle administration and ultrasound result in improved anti-tumor efficacy.

Conclusions: Multiple imaging modalities prove to be useful in the development of activatable strategies for the delivery of chemotherapeutics.

References

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