Live Real-Time MR Imaging of Drug-Delivery Systems

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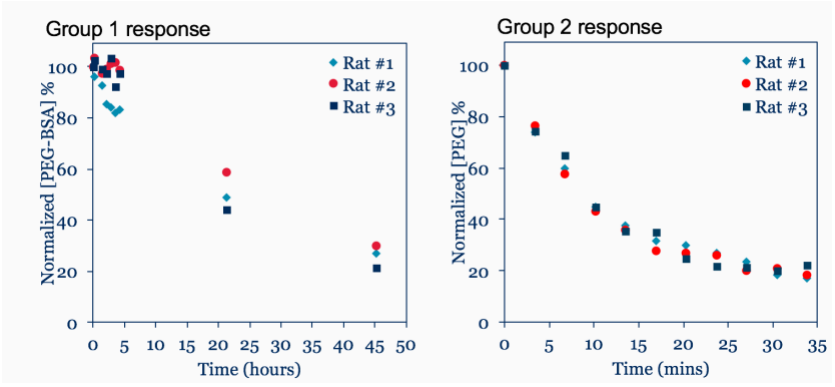
Introduction

Our collaborators have developed several new anti-cancer compounds which exhibit unprecedented action against brain tumor cells and orthotopic animal models. However, these compounds exhibit high toxicity and off-target effects. To remedy this, we utilize a class of FDA-approved drug delivery systems consisting of the copolymer polyethylene glycol polylactide (PEG-PLA). PEG-PLA encapsulates lipophilic drugs and is biotinylated for targeting to brain, prostate, or bone marrow tumour cells. Preliminary animal studies show improved targeting of the anticancer compounds to breast cancer tumor models, using intravenous bolus of either PEG-PLA or biotin-PEG-PLA. Our goal is to investigate the use of these drug delivery systems to: i) Enhance partitioning of cancer drugs to brain and breast tumors in mouse and rat models, ii) Demonstrate "real-time" ^{1}H Magnetic Resonance Imaging (MRI) and MRS to directly quantify drug delivery systems in animals, thereby measuring partitioning and clearance, iii) Optimize targeting and biodistribution of our lead cancer drugs. We will test PEG:PLA ratios, co-polymer size, drug loading protocols and adjuvants which regulate vasodilation to optimize tumor partitioning, and iv) Explore cancer drug cocktails that in drug delivery systems might work more efficaciously, and compare our results with biodistribution and clearance profiles of other nanomedicines (*e.g.* Doxil and Abraxane).

Quantitative MRI is generally pursued via (paramagnetic) contrast agents and is fraught with challenges. Here, we use the robust methylene signal from the PEG component of the delivery system, while employing diffusion-edited imaging and selective excitation pulses to filter out water signal in MRI. We can now profile biodistribution and clearance of drug delivery systems or (PEGylated) nanomedicines over minutes to days. By monitoring real-time profiles, we will be able to optimize the delivery system for the drugs of interest in animal models.

Results and Discussion



Six rats were injected with either ^{13}C-PEG-BSA (25 mg / mL PEG) (Group 1) or ^{13}C-PEG (50 mg / mL) (Group 2). Using a specially built ^{1}H / ^{13}C volume coil around the tail, the blood concentration of ^{13}C-PEG was directly measured on an 11.1 T MRI Imager (AMRIS Facility, MagLab, Gainesville, Florida), as shown.

More recently, we have conducted experiments on rats using direct 1H detection of the PEG component of PEG-PLA-Biotin drug delivery systems in animal models. PEG-PLA-biotin exhibited relatively rapid clearance to the bladder. We are therefore optimizing the concentration and size of the drug delivery system for subsequent MRI imaging experiments at the AMRIS facility in 2018.

Conclusions

PEGylated drug delivery systems can be directly imaged by ^{1}H MRI for purposes of better understanding partitioning and clearance. It is critical to first optimize the delivery system concentrations and size to avoid renal filtration and improve MRI sensitivity.

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