Development of an Animal Model for Pharmacokinetics of Injectable Magnetic Micro/nanospheres

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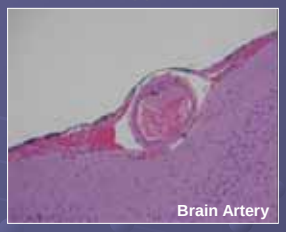
Introduction

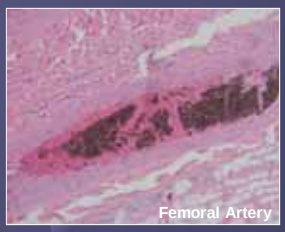
The scope of work was to gather proof-of-principle data using animal models to show that magnetic nanoparticles can be used to deliver drugs or to selectively and rapidly remove biological, chemical, and radioactive biohazards from humans. Conceptually, the magnetic nanoparticles are biostabilized with polyethylene glycol chains to avoid rapid bioclearance (immune system response) and are biodegradable to confer non-toxicity and biocompatibility. The nanoparticles can carry a variety of specific toxin-binding receptors (antibodies/chelators) bound to the surface or encapsulated drug. Once injected, the particles circulate freely through the bloodstream, offering selective capture and sequestration of blood-borne toxins to the surface receptors or magnetically concentrated in the diseased tissue.

In Vivo Experiment Setup

At left, general setup of circulating blood in animal model for injection and sample removal. At right, arterial catheterization into the abdominal aorta of the primate model. Continuous extracorporeal blood circulation in the rat was achieved via carotid-jugular cannulation and external pump support with filtration of magnetic nanoparticles using 1-mm-diameter closed-loop tubing and a single NdFeB magnet (0.4 T at surface, 18 mm diameter).

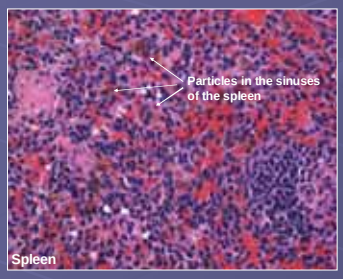
Magnetic Trapping

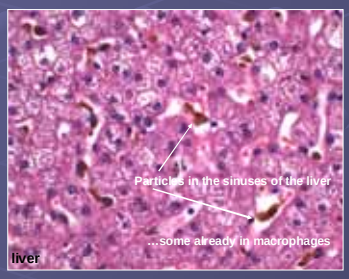


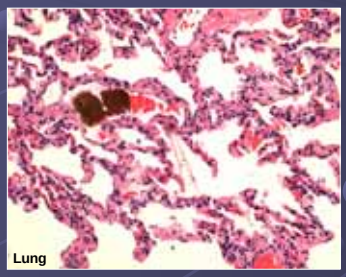


Experiments show modest trapping of magnetic microspheres in the superficial arteries of the brain after placement of a 0.4-T NdFeB magnet against a primate skull. Trapping in the femoral artery was very successful in the primate model using same magnet.

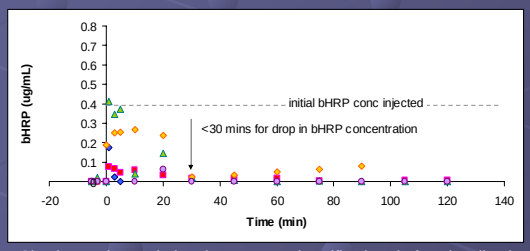
Histology





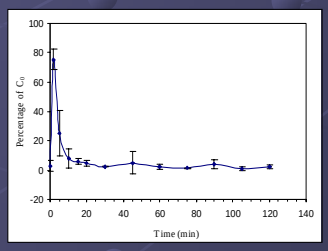


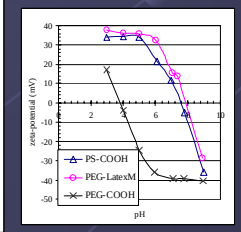
In Vivo Simulant Toxin Kinetics



- Simulant toxin needed to demonstrate detoxification via functionalized magnetic nanospheres
- Simulant biotoxin (bHRP) biocleared in rats in <30 min
- Stealth biotoxin needed to avoid rapid bioclearance for future *in vivo* microparticle experiments
- Need better biomarker as target antigen

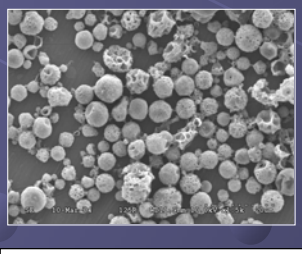
In Vivo Particle Kinetics

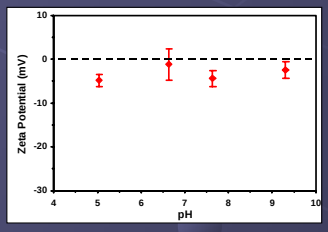


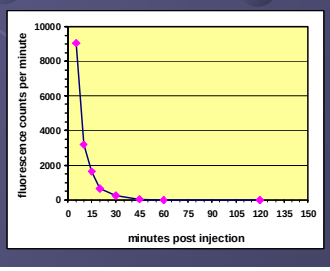


- 3-µm polystyrene magnetic spheres conjugated with PEG 6000 via carboxyl bridges
- Particle survived *in vivo* less than 10 min
- Insufficient PEG coverage noted by negative surface charge

Fluorescent-Labeled Microspheres







- PLA-PEG microspheres labeled with rhodamine for particle tracking in experiments
- Rhodamine encapsulation sufficient for flow cytometry detection; however, surface not sufficiently masked by PEG
- May need to synthesize branched PEGs

Future

- Rat and monkey models provide good working models for drug delivery studies and detoxification experiments
- We are evaluating several biomarkers to use as model toxin in place of horseradish peroxidase
- We need to reduce size of spheres and increase PEG conjugation
- Labeling spheres with ^{111}In via hydrophobic DTPA dissolved in PLA-PEG should reduce the uncertainties introduced by rhodamine encapsulation

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