297d Long-Circulating Nanoparticles through Red Blood Cell Attachment

Elizabeth L. Chambers and Samir Mitragotri

Polymeric nanoparticles have been extensively studied for use as intravascular drug delivery vehicles. Unfortunately polymeric particles are rapidly cleared from circulation by the reticuloendothelial system (RES) preventing their effective use as sustained drug delivery vehicles. When polymeric particles are introduced into vascular circulation they are opsononized and subsequently removed from vascular circulation by macrophages primarily located in the liver, spleen and lungs. Previous attempts to improve vascular circulation have focused on coating the particles with polymer brushes, such as polyoxamines, polyoxamers, and polyethylene glycol, to prevent opsononization. However, circulation lifetimes of surface-modified particles are still limited.

We report on a novel method of increasing intravascular particle circulation by anchoring the nanoparticles to the surface of red blood cells (RBCs). We hypothesize that particles adhered to RBCs can escape phagocytosis due to the ability of RBCs to evade macrophages. RBC-anchored particles may therefore remain in circulation for long periods of time. This method is motivated by the strategy adopted by certain bacteria, for example hemobartonella, that adhere to RBCs and remain in circulation for several weeks.

RBC bound polystyrene particles of various surface chemistries (hydrophobic, electrostatic, and biotin-avidin binding forces) and sizes (100nm – 1.1μm) were tested in an *in vivo* rat model. RBC bound particles exhibited dramatically improved intravascular circulation lifetimes compared to unbound particles. The circulation lifetime was dependant on the surface chemistry and size of the particle. Furthermore, the RBC was not removed from circulation due to particle attachment.

RBC bound particles were eventually removed from circulation. We hypothesized that particle clearance is due to physical detachment of the particle from the RBC surface followed by phagocytosis in the liver and spleen. To test our hypothesis we studied the biodistribution of particles, the effect of liver and spleen blockage and the effect of shear stress on particle-RBC attachment. Our results show that particle clearance is due to the separation of the particle from the RBC and that the length of circulation is dependant on the nature (hydrophobic, electrostatic and biotin-avidin) and strength of binding. These results indicate that increasing the strength of binding may increase the circulation lifetime of RBC bound particles making them a good potential candidate for drug delivery purposes.