

Gene Carriers Modified with PEG Demonstrate Increased Transport and Stability in Mucus as Explored with High-Resolution Nanoparticle Tracking

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Introduction. The successful delivery of DNA to the epithelia of the lungs, gastrointestinal (GI) tract, vagina, and nose is limited by inefficient particle transport through mucus, which forms a continuous barrier over the epithelial cell surface. High molecular weight glycoproteins and macromolecules, the primary constituents of mucus, form a fine network with interfiber spacings approximately 100 - 500 nm in diameter. Particles small enough to diffuse through the microscopic pores may still be unable to overcome this barrier due to adhesive interactions.

Experimental. To reduce interactions of particles with mucus, we used poly(ethylene glycol) (PEG), a non-mucoadhesive polymer, to surface-modify non-viral gene carriers formulated from polyethylenimine (PEI). Standard polystyrene (PS) particles were also modified with PEG as controls.

Using real-time multiple particle tracking (MPT), we measured the mean squared displacements (MSD) of individual particles in mucus from patients with cystic fibrosis or synthetic mucus that accurately mimics lung or GI mucus and quantified the effects of surface modification with PEG on the rate of gene carrier transport. MPT allowed us to quantify the transport rates of individual particles with ~10 nm and 33 ms spatiotemporal resolution. Statistical analysis of the individual particle transport rates was used to quantify the heterogeneities in transport rates.

Results and Discussion. The average rate of transport of PEI or standard-sized polystyrene (PS) particles surface-modified with PEG increased by approximately 10-fold. Furthermore, the percentage of particles undergoing diffusive transport in mucus, as determined by measuring the linearity in the slope of the MSD, was increased for PEI particles modified with PEG by approximately 10%. Particle formulations were optimized for rapid transport, stability in mucus, cell uptake, and transfection efficiency in mucus-covered lung or GI cells.