489d Real-Time Transport of Polymer Nanoparticles in Cervical Vaginal Mucus

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Topical delivery of drugs and genes to the cervical vaginal (CV) tract based on nanoparticle (NP) systems has potential clinical applications, such as treatment of cancer and prevention of sexually transmitted diseases (STDs). An often overlooked obstacle is the mucosal barrier lining the CV tract, which NPs must overcome in order to reach underlying cells and avoid clearance.

Previous methods provided only ensemble-averaged transport rates hence limiting the insight into complex transport phenomena that control NP transport in CV mucus. This problem is resolved here by the use of Multiple Particle Tracking, which allows for detailed quantitative analysis of individual NP movement in physiologically thick mucus. Furthermore, the measurements reported here were performed on cervicovaginal secretions present in the vagina, and therefore are more appropriate for vaginal delivery of NP than prior measurements that were performed on mucus obtained by vacuum extraction from the endocervical canal. In order to improve the transport of NP across the mucosal network, we investigated the effects of size, PEGylation, and presence of ligands on NP transport in undiluted human CV mucus.

The movement of hundreds of fluorescently labeled nanospheres of different sizes and surface modification was quantified using MPT within 4 hrs after sample collection. A high-speed axiovert camera (VE-1000, Dage-MTI) was used to capture movies at 15 frames/sec and 100x resolution. Mean-square displacement (MSD) and effective diffusivity (Deff) of nanospheres were obtained through analysis of the movies using MetaMorph software (Universal Imaging).

PEGylation drastically reduces the number of immobile particles in CV mucus across all NP sizes (100-500nm), and increases the number of diffusive particles. PEGylation also improves the overall transport rates of similar sized particles undergoing subdiffusive transport for all particle sizes. 200nm particles exhibited the fastest transport properties overall in CV mucus, both in the form of minimized percentage of immobile particles and maximized percentage of diffusive particles. 200nm particles also had a higher transport rate within the subdiffusive population. Accounting for both PEGylation and size, 200nm PS-PEG nanoparticles transport the fastest in CV mucus as demonstrated by the highest effective diffusivity over the entire population of NP. The presence of ligands such as transferrin on the end of poly(ethylene glycol) chains appear to substantially reduced the transport of nanoparticles, and the reduction in transport is dependent on the density of ligands on the surface on nanoparticles.

PEGylation may enhance particle transport rates by reducing interactions between nanoparticles and the mucosal fiber network. By preventing protein adsorption and minimizing interactions with the fiber network, PEGylation eliminates virtually all immobilization via electrostatic and chemical means, as evident with 200nm and 500nm particles. The reduced interaction upon PEGylation leads to a decreased number of subdiffusive particles and an increased number of diffusive particles. The unexpected slower transport properties of 100nm particles compared to 200nm particles might be explained using principles from gel permeation chromatography (GPC). For particles of various sizes traveling in a network with heterogeneous pore sizes, smaller particles have a greater tendency to diffuse into small pores/pockets, resulting in an overall reduced transport. When the size of particles are sufficiently large (i.e. 500nm), the tendency to encounter resistance from fibers of the mucosal network increases significantly and particles may ultimately be unable to diffuse deep within the network, hence slower transport.