PARTICLE SURFACE PROPERTIES DIRECT CELLULAR IMMUNE RESPONSES IN THE LUNG

Catherine A. Fromen, University of Michigan, Chemical Engineering
cfromen@umich.edu
Jeffery Noble, University of Michigan, Chemical Engineering
Anthony Zimmerman, University of Michigan, Chemical Engineering

Key Words: surface charge, vaccine, adjuvant
Nano- and micro-particulate carriers enable the site-specific delivery for controlled biological responses and can harness the intrinsic pathways by which the body responds to natural invaders. These particles are in the size range which naturally associates with many innate immune cells, including antigen presenting cells (APCs). Through controlled design properties, engineered nano- and microparticle drug delivery vehicles have the potential to expand the breadth of many therapeutic approaches, impacting immunological outcomes through cell-specific targeted delivery. However, in many applications, such as mucosal vaccines or controlled-release lung depot, optimal particle properties have not yet been identified. Physical properties such as size, shape, and surface chemistry are known to impact cellular interactions, particle margination, and biodistribution; as such, many particle design considerations have been established for systemic intravenous (IV) administration to create long-circulating drug delivery vehicles [3]. However, much less is known about particle design parameters which are critical to interfacing with and directing the immune system, especially through non-IV administration.

To this end, recent work has investigated the role of surface charge and functionality on pulmonary drug delivery carriers, as potential vaccine formulations or immune modulators. These results find that positively charged nanoparticle vaccine formulations induce robust antigen-specific mucosal and systemic antibody responses following pulmonary administration, whereas negatively charged nanoparticles fail to do so. Cationic nanoparticles were shown to produce superior antigen-specific IgG and IgA responses, as well as the upregulation of various co-stimulatory molecules, enhanced germinal center B cell formation, and CD4+ T cell activation, when compared to otherwise equivalent anionic particles [4]. In combination, these indicate that cationic particles by themselves provide an adjuvant-like effect when delivered to the airways. Adjuvants are molecules which enhance immune responses by stimulating various cellular pathways and are critical components of vaccine formulations [6]. These cationic particles showed increased association with pulmonary APCs following lung administration, including preferential association with lung dendritic cell populations, producing increased cytokine and chemokines in the lung [5]. Thus, cationic.

While cationic nanoparticles themselves can act as adjuvants, these responses can be enhanced by incorporating toll-like-receptor (TLR) ligands to the particle surface [7]. In this work, we have engineered a series of particles to investigate the role of adjuvant density on the particle. We incorporate two TLR adjuvant molecules, CpG and LPS, on the surface of both cationic and anionic particle carriers and quantify the immune response in various biological environments as a function of particle characteristics. As with unmodified particles, cationic formulations produce more robust responses than anionic formulations. Furthermore, our results indicate that when dosed at equivalent particle concentrations with varied adjuvant surface densities, particles with the highest adjuvant density per particle produce the largest in vitro stimulation; however, when dosed at equivalent adjuvant mass per sample, particles of the lowest adjuvant density, corresponding to the highest number of particles dosed, resulted in superior stimulation. These results indicate a trade-off between adjuvant density and particle number. Overall, we believe this work provides a set of design rules which inform particulate vaccine formulations, to ensure both potency and safety, with potential future applications for novel treatments for cancer, inflammation, and allergy.