**Nanoparticle vaccines and their interactions with immune cells - implication for new and improved vaccines for influenza**

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Current seasonal influenza vaccines provide protection that is highly strain-specific, resulting in costly global surveillance efforts and annual reformulation. Protein-based, self-assembling nanoparticles have tremendous potential as novel vaccine platforms – demonstrating superior immunity compared to soluble protein vaccines in a number of contexts including influenza. However, immune mechanisms that underpin this greater immunogenicity remain poorly defined.

We recently undertook an in-depth characterization of the immunogenicity of a prototypic protein-based nanoparticle vaccine, based on a spherical ferritin core with eight trimeric influenza haemagglutinin (HA) spikes on the surface. Vaccination of mice with HA-ferritin nanoparticles elicited 10-fold higher serum antibody titers and greater protection against experimental influenza challenge compared to vaccination with soluble HA protein. Confocal microscopy of draining lymph nodes following HA-ferritin vaccination revealed markedly augmented germinal center reactions compared to soluble HA. Quantification by flow cytometry confirmed large increases in both bulk and HA-specific germinal center B cells compared to soluble HA vaccination. Using an activation-induced marker assay to measure T follicular helper responses, we found no evidence that the ferritin carrier supported HA-specific B cells via linked recognition.

Our findings suggest the display of antigens in highly ordered and repetitive arrays by nanoparticles directly drives the the generation of improved immune responses, in a mechanism that is likely intrinsic to B cells without the requirement of T helper cells. Better understanding the basis of nanoparticle vaccine immunogenicity will facilitate the rational design of nanoparticle vaccines for broad and durable protection against diverse pathogens.