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Category: Predoc
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Title: Intranasal nanoparticle vaccination elicits a persistent, polyfunctional CD4 T cell responses in the murine lung specific for a highly conserved influenza antigen that are sufficient to mediate protection from influenza virus challenge

Abstract: Disease outbreaks caused by influenza A viruses result in considerable human morbidity, mortality, and economic burden each year. The best available tool to combat influenza virus infection is yearly administration of subunit vaccines enriched for the highly variable surface glycoprotein hemagglutinin. However, current vaccination regimens often fail to elicit sufficiently protective immune responses, especially in the case of antigenic mismatch between circulating and vaccine viruses, or the emergence of novel zoonotic influenza viruses. To overcome these limitations, there is an urgent need for novel vaccination regimens with improved protective efficacy. In this study, we evaluated the potential of a nanoparticle vaccine presenting the highly conserved influenza nucleoprotein (NP) to elicit lung localized CD4 T cell immunity. By poising a population of multifunctional CD4 T cells specific for a highly conserved viral antigen directly at the site of infection in the lung, we aimed to generate durable and broadly protective immunity against influenza virus infection. Using cytokine ELISpots, in vivo antibody labeling techniques, and multiparameter flow cytometry we find that nanoparticle immunization elicited lung-resident effector CD4 T cell populations localized to three distinct compartments within the lung: vasculature, tissue, and airway. Nanoparticle vaccination potentiated a population of airway-localized NP-specific CD4 T cells that responded robustly to restimulation with cognate antigen via production of multiple antiviral cytokines and cytotoxic degranulation, and did so at a frequency higher than lung tissue, lung vasculature, or peripheral CD4 T cells. Durable lung localized CD4 T cell responses were found to persist for at least nine months post-vaccination. We found that adoptive transfer of CD4 T cells elicited by nanoparticle vaccination protected naïve mice from lethal influenza virus challenge, and that nanoparticle vaccination had a protective advantage compared to existing intranasal influenza vaccines. Lung localization, polyfunctionality, and long-term persistence in vivo, coupled with the protective potential of vaccine-elicited CD4 T cells suggest the validity of pursuing intranasal vaccine approaches for induction of broadly protective immunity that can respond to influenza virus challenge.