Pathogen-Mimetic Nanovaccine Protects Against Lethal Influenza Virus Infection

Frances C. Knight[1], Pavlo Gilchuk[2,3], Amrendra Kumar[2,3], Kyle W. Becker[1], Sema Sevimli[1], Max E. Jacobson[1], Naveenchandra Suryadevara[2,3], Lihong Wang-Bishop[1], Kelli L. Boyd[2], James E Crowe, Jr.[2], Sebastian Joyce[2,3], and John T. Wilson[1]

[1]Vanderbilt University, Nashville, TN
[2]Vanderbilt University Medical Center, Nashville, TN
[3]Department of Veterans Affairs Tennessee Valley Healthcare System, Nashville, TN

Background: Administration of vaccines at mucosal surfaces (e.g., the lungs) with pathogen-like nanoparticles mimics the route of natural infection and can generate tissue-resident memory T cells (T_{RM}), which are ideally positioned to trigger a protective immune response against subsequent pathogen encounter. Pulmonary immunization with subunit vaccines is an attractive approach because these are safer than vaccines based on live or attenuated microbes; they are less likely to create inflammation and damage in the lung tissue and cannot revert to a virulent form. They also have several advantages for use in global health, including the possibility of needle-free intranasal delivery. However, subunit vaccines are also less immunogenic than live or attenuated vaccines, and are inefficient at generating $CD8^+$ T cells, which are necessary for defense against many intracellular pathogens, including viruses like influenza.

Methods: To address this, we have developed a pH-responsive nanoparticle (NP) delivery platform that can be loaded with protein antigen and nucleic acid adjuvant.[1] The small size of the particle (~20-40 nm) and its dual-loading capacity allows it to mimic viruses in the way it delivers cargo intracellularly and stimulates the immune system. The particle leverages endosomal acidification after cellular uptake to release antigen into the cytosol, where it can be processed by the MHC-I presentation pathway, resulting in a $CD8^+$ T cell response and lung-resident memory T cells. Here, we loaded the NP platform with influenza nucleoprotein antigen and CpG DNA adjuvant to create an NP vaccine (Flu-NP/CpG) targeted toward generating nucleoprotein-specific $CD8^+$ T cells. We used a combination of flow cytometry techniques and a lethal influenza challenge model in mice to characterize the immune response to the NP vaccine and show that it can protect against virus-induced morbidity.

Results: Tissue-resident memory T cells in the lungs are commonly identified by their expression of the surface markers CD69 and CD103. Using a combination of MHC-I tetramer and surface marker staining via flow cytometry, we showed that the NP vaccine induced significantly more antigen-specific $CD8^+$ T_{RM} cells in the lungs than control groups. We also showed that the route of administration was important—intranasal immunization was more effective than systemic administration—and that the pH-sensitive nature of the nanoparticle enhanced the tissue-resident response. Finally, in a lethal murine challenge model, the NP vaccine significantly increased survival of mice infected with H1N1 influenza virus (PR8) and allowed for recovery from weight loss after infection.

Conclusion: This work represents a novel use of materials engineering principles to design a vaccine that can generate lung-resident memory T cells and protect against a respiratory pathogen that poses a significant threat to public health. Further work is being done to determine the innate immunological mechanisms by which this vaccine generates a T_{RM} response and protects against infection.

[1]Wilson JT, Keller S, Manganiello MJ, et al. (2013). pH-Responsive Nanoparticle Vaccines for Dual-Delivery of Antigens and Immunostimulatory Oligonucleotides. ACS Nano, 7(5):3912-3925.

[2]Knight FC, Gilchuk P, Kumar A, et al. (2019). Mucosal Immunization with a pH-Responsive Nanoparticle Vaccine Induces Protective CD8+ Lung-Resident Memory T Cells. ACS Nano, 13(10):10939-10960.