Study paves way for new vaccines to protect infants against infections

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A new Penn Medicine study puts researchers within closer reach of vaccines that can protect infants against infections by overcoming a mother's antibodies, which are known to shut down immune defenses initiated by conventional vaccines. That hurdle largely explains why vaccinations for infectious diseases like influenza and measles not given until six to 12 months of age. Findings from the preclinical study were published online today in *Science Translational Medicine*.

The research team, led by Scott E. Hensley, Ph.D., an associate professor of Microbiology, and Drew Weissman, MD, Ph.D., a professor of Infectious Diseases in the Perelman School of Medicine at the University of Pennsylvania, found that a specialized modified-RNA (mRNA) influenza vaccine developed at Penn successfully protected young mice against the infection in the presence of maternal antibodies. The study suggests this protection occurred because the vaccine programs cells to constantly churn out new antigens for a prolonged period of time, rather than delivering a one-time shot of a viral protein.

"Around the world, every year, many young infants become infected and often die from infections because of a lack of effective vaccines to protect them earlier in life," Weissman said. "mRNA-based vaccines could potentially help prevent that. What's more, it would not only be effective against influenza but also other pathogens, as the vaccine's platform is easily adaptable to different antigens."

Elinor Willis, a doctoral student in the department of Microbiology and Penn Vet, served as first author on the paper.

Developing effective vaccines that protect infants in the presence of maternal antibodies has proven difficult because the antibodies can bind to vaccines and prevent them from eliciting good immune responses.

"Maternal antibodies are kind of a double-edged sword: they are great to have around when you are young because they can protect you from infection, but it's tough to vaccinate when there are high levels of them," Hensley said. "Today's strategy is to wait awhile for these antibodies to decline. This isn't ideal because the timing can be imprecise, so there is almost always a period where the young infant is susceptible to disease."

mRNA vaccines have emerged as leading candidates for protection against pathogens in adult clinical studies. Instead of delivering lab-grown viral proteins like a traditional vaccine, mRNA vaccines introduce an mRNA sequence that programs cells to produce antigens to mimic the disease. The result is a more powerful immune response and broader protection.

For this study, the Penn lab turned to the what is known as a nucleoside-modified mRNA encapsulated in lipid nanoparticles (mRNA-LNP) vaccine. In the past, Hensley and Weissman showed that this vaccine, which expresses hemagglutinin (HA) proteins, elicited robust

antibody responses and protected adult animals from influenza.

To determine its ability to overcome maternal antibodies, the researchers first established a mouse model to show how the antibodies protect young mice against influenza and how they inhibit immune responses elicited by conventional vaccinations. Next, the researchers tested the mRNA vaccine platform in the mouse model and found that it elicited very strong antibody responses, both in the presence and absence of maternal antibodies, and protected the mice from the virus.

The vaccine essentially "slips under the radar," Hensley said, gets into cells, and then starts continuously producing the antigen for the immune system to respond to in what's called "prolonged germinal center reactions." The finding suggest that maternal antibodies eventually drop below a certain level and the antigen is still there to generate an immune response from the child.

The researchers continue to investigate the vaccine in mouse models to better understand mechanistically why this vaccine works so well in the presence of a mother's antibodies and hope to translate the promising results into human studies in the future.

"It could be a real game changer," Hensley said. "Imagine a world where an infant is born or comes into the clinic very early in life and can receive vaccines that have antigens not just for the flu but a multitude of different pathogens. Wouldn't that be something?"

More information: "Nucleoside-modified mRNA vaccination partially overcomes maternal antibody inhibition of de novo immune responses in mouse pups," *Science Translational Medicine* (2020). stke.sciencemag.org/lookup/doi … 26/scisignal.aav5701

Provided by Perelman School of Medicine at the University of Pennsylvania

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