In the lab: An mpox mRNA vaccine that's outperforming its old-school predecessor

November 17 2023, by Delthia Ricks

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The recent global mpox outbreak trained a bright spotlight on the need for safe and effective Orthopoxvirus vaccines, especially in light of

continuously looming zoonotic threats and the potential for these pathogens to spread rapidly worldwide.

Now, a collaborative group of U.S. scientists is testing a candidate mRNA mpox nanoparticle vaccine with the hope of developing an immunization that is superior to the current mpox shot.

The research team mostly hails from the private and federal institutions that produced one of the highly successful COVID mRNA vaccines: Moderna Inc., in Cambridge, Mass., and the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Md. The new study also included collaboration with the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick Md.

Writing in Science Translational Medicine, the researchers say the aim of the new mRNA vaccine for mpox is to have a shelf-ready inoculation in the event of a future outbreak. Having a vaccine in hand, they say, alleviates scrambling to figure out what might work most effectively as cases mount and doctors ask for the best immunization strategy to ward off additional infections.

In 2022, already battle fatigued amid a knock-down-drag-out fight against the ever-mutating SARS-CoV-2 menace, the global health community had to quickly pivot to take on an emerging mpox outbreak that had swiftly circled the globe. While the mpox outbreak didn't reach the scale of the coronavirus pandemic, it did reignite panic about the unexpected emergence of a zoonotic virus and how best to mount combat against it.

"Mpox virus caused a global outbreak in 2022," writes Dr. Alec Freyn, lead author of the new research involving the investigational mRNA nanoparticle vaccine.

"Although smallpox vaccines were rapidly deployed to curb spread and disease among those at highest risk, breakthrough disease was noted after complete immunization. Given the threat of additional zoonotic events and the virus's evolving ability to drive human-to-human transmission," Freyn continued, "there is an urgent need for an mpox-specific vaccine that confers protection against evolving mpox strains and related orthopoxviruses."

The vaccine administered in the mpox outbreak was a modified vaccinia Ankara shot, which was effective in reducing disease severity and transmission, despite its drawbacks. Modified vaccinia Ankara is an attenuated—weakened—strain of the vaccinia virus, a large and complex enveloped virus with a double-stranded DNA genome.

It's a member of the poxvirus family but is much less dangerous than the smallpox virus, which explains why it's used in vaccines against smallpox and mpox (smallpox was eradicated from the planet in 1977 after a centuries-long, disease-causing run that killed millions).

Freyn and colleagues say if a next-generation vaccine had been available, the global health community might have seen better immunization performance. With the investigational vaccine that is under development, the future of immunization technology against mpox looks promising, he and his team say.

Relying on animal model research, scientists tested the new mRNA shot by vaccinating mice that were later administered a lethal dose of vaccinia virus. In a stunning outcome, animals immunized with the candidate mRNA nanoparticle vaccine were able to thwart a lethal infection. Several different experiments were conducted to test the vaccine's efficacy as well as to compare it head-to-head with the old-school shot.

The mRNA vaccine performed as well—often better—than the modified vaccinia Ankara shot in its ability to elicit immune responses and protect against lethal infection. Overall, the mRNA nanoparticle vaccine proved to be the superior immunization.

"We demonstrate that an mRNA-lipid nanoparticle vaccine encoding a set of four highly conserved mpox surface proteins involved in virus attachment, entry, and transmission can induce mpox-specific immunity and heterologous protection against a lethal vaccinia virus challenge," Freyn added.

"Compared with modified vaccinia virus Ankara, which forms the basis for the current mpox vaccine, immunization with an mRNA-based mpox vaccine generated superior neutralizing activity against mpox and vaccinia virus and more efficiently inhibited spread between cells," Freyn noted.

The research team included virologists and vaccinologists from Moderna as well as from two key divisions of NIAID: the Vaccine Research Center as well the agency's Laboratory of Viral Diseases. The USAMRID contributor was from the Army lab's Virology Division.

The new data support further development of mRNA vaccines targeting orthopoxviruses to allow rapid response in the event of an outbreak, Freyn and his team say.

Indeed, the scientists concluded that the research reinforced their initial hypothesis that an mRNA-based mpox vaccine confers robust protection against orthopoxviruses.

More information: Alec W. Freyn et al, An mpox virus mRNA-lipid nanoparticle vaccine confers protection against lethal orthopoxviral challenge, *Science Translational Medicine* (2023). DOI:

10.1126/scitranslmed.adg3540