



# NEWS RELEASE

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## Experimental Smallpox DNA Vaccine Protects Primates from Lethal Monkeypox

In the first successful study of its kind, scientists have shown that a DNA-based vaccine for smallpox can protect nonhuman primates from monkeypox, a disease that resembles smallpox in humans. The study, performed at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) and published in the May issue of the *Journal of Virology*, suggests a promising alternative approach to conventional smallpox vaccination.

Smallpox, a devastating disease caused by the variola virus, was eradicated in 1979 through the efforts of the World Health Organization (WHO). Currently, infectious variola (one of a class of viruses called orthopoxviruses) is known to exist only in two WHO-sanctioned repositories, one in Russia and the other in the United States. However, there is concern that undisclosed reference stocks of the virus may exist, and its potential as a biological weapon has led to the production and stockpiling of smallpox vaccine and the immunization of some healthcare workers.

The USAMRIID team, led by Jay W. Hooper, Ph.D., based its DNA vaccine on four genes from vaccinia virus—the same virus used in Dryvax, the licensed smallpox vaccine. Because Dryvax contains live virus, it carries a high risk of complications for people with suppressed immunity and other conditions. A DNA vaccine would not have the adverse side effects commonly associated with a live virus vaccine.

“This work represents important progress toward a smallpox vaccine that is as effective as the current product, but safer,” said Colonel Erik A. Henchal, commander of USAMRIID. “It is yet another example of how USAMRIID research to protect military service members can contribute to the overall public health.”

As smallpox no longer occurs naturally, experimental vaccines cannot be tested for their ability to prevent the disease in humans. Thus, licensing of future vaccine candidates will include studies of immune response and protection in nonhuman primates. Monkeypox currently provides the best nonhuman primate model of an orthopoxvirus infection.

According to Hooper, the four-gene combination DNA vaccine (known as 4pox) had already been tested extensively in mice, where it protected 100 percent of the animals from challenge. It had also been shown to elicit a robust immune response in nonhuman primates. The next step was to design a challenge experiment using rhesus macaques.

In the study, animals were divided into four groups. One contained two monkeys vaccinated with the human smallpox vaccine, Dryvax. Another consisted of two monkeys

vaccinated with a smallpox DNA vaccine containing just one gene, called L1R. A third contained three monkeys vaccinated with an unrelated DNA vaccine for Hantaan virus. The test group consisted of three monkeys vaccinated with the 4pox DNA vaccine.

The DNA vaccine technique involves immunizing with plasmid DNA that encodes one or more specific virus genes. When the plasmid DNA is introduced into the cells of a vaccine recipient, using a harmless device called a “gene gun,” the cloned gene is expressed and presented to the immune system, which begins to produce protective antibodies against the virus.

Following challenge with a lethal dose of monkeypox virus, the four groups of animals were closely monitored. Monkeys vaccinated with Dryvax showed no signs of clinical disease. Those receiving the L1R DNA vaccine developed severe monkeypox, but recovered, suggesting that this gene alone confers some protection. Monkeys vaccinated with the Hantaan virus vaccine developed monkeypox and died 7 to 14 days after challenge. Most importantly, monkeys immunized with the 4pox DNA vaccine were protected not only from lethal monkeypox, but also from severe disease.

“So far, other approaches have used live virus as the basis for a smallpox vaccine,” Hooper commented. “This is the first time that parts of the virus have been used and shown to work in primates as a protective vaccine for any of the orthopoxviruses.”

According to Hooper, epidemiological studies have shown that Dryvax protects humans against both smallpox and monkeypox. All the orthopoxviruses—vaccinia, monkeypox, and variola—are highly similar in the majority of their nearly 200 proteins, which partially accounts for the cross-protection among these viruses. However, the precise immune mechanisms by which the smallpox vaccine elicits immunity to both smallpox and monkeypox remains largely unknown. Thus, identifying protective immunogens—the proteins that trigger an immune response—is essential for developing and testing next-generation smallpox vaccines.

There are two major forms of infectious orthopoxvirus: the intracellular mature virion (IMV), and the extracellular enveloped virion (EEV). Both IMV and EEV are involved in poxvirus infection, and both must be targeted for a vaccine to work. The 4pox DNA vaccine contains two IMV-specific and two EEV-specific genes. Hooper and his team hypothesize that the high level of protection conferred when combinations of IMV and EEV immunogens are used is due to the targeting of different forms of the virus at different stages of infection and by different mechanisms.

Hooper’s colleagues on the study included Elizabeth G. Thompson, Catherine L. Wilhelmsen, Michael S. Zimmerman, Mohamed A. Ichou, Scott E. Steffen, Connie S. Schmaljohn, Alan L. Schmaljohn, and Peter B. Jahrling.

USAMRIID, located at Fort Detrick, Maryland, is the lead medical research laboratory for the U.S. Biological Defense Research Program, and plays a key role in national defense and in infectious disease research. The Institute’s mission is to conduct basic and applied research on biological threats resulting in medical solutions (such as vaccines, drugs and diagnostics) to protect the warfighter. USAMRIID is a subordinate laboratory of the U.S. Army Medical Research and Materiel Command.

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**Reference:** JW Hooper *et al.* Smallpox DNA Vaccine Protects Nonhuman Primates against Lethal Monkeypox. *Journal of Virology* 78. 9: 4433-4443 (2004).