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Synthetic DNA-delivered antibodies protect against Ebola in preclinical studies

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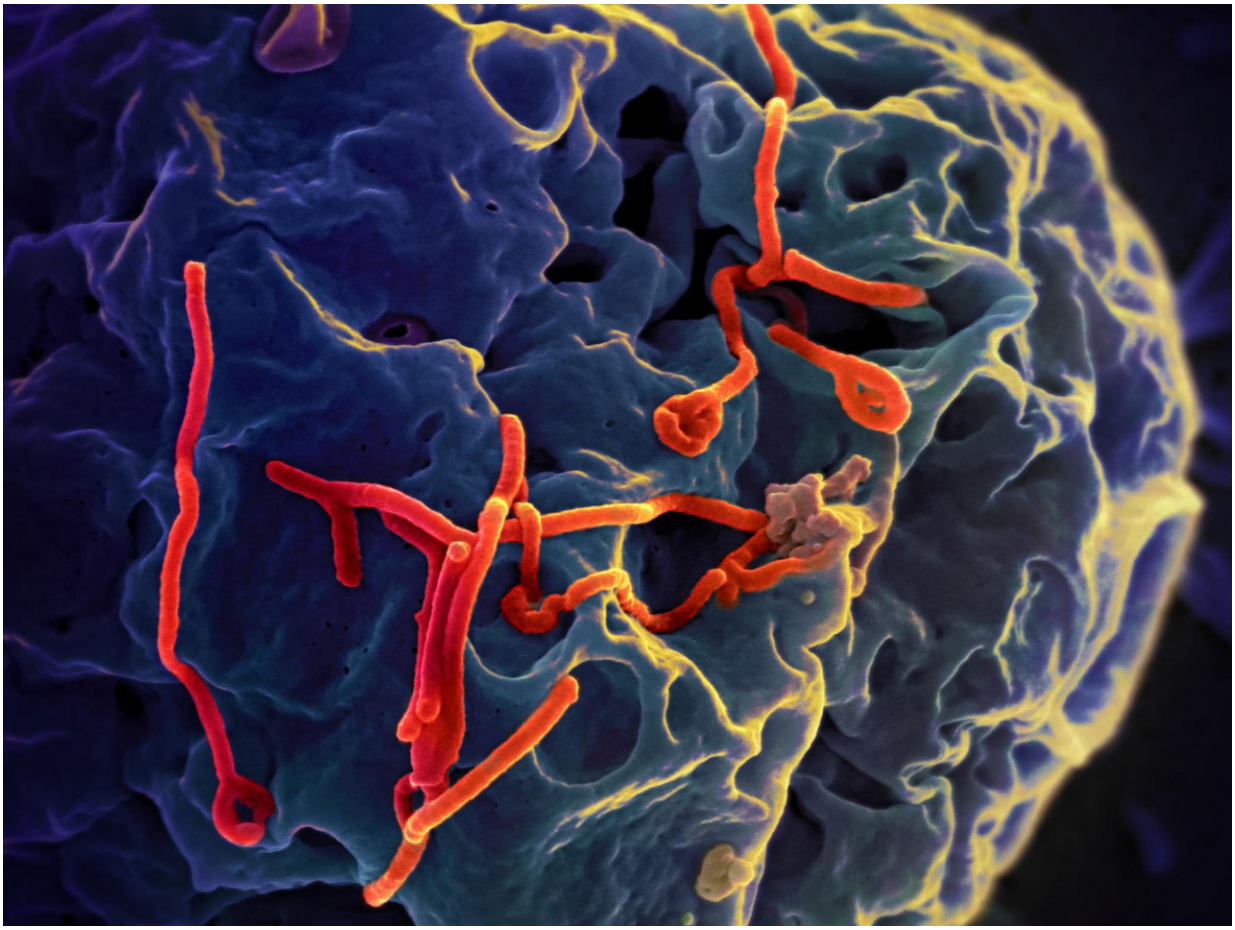

Ebola virus particles (red) on a larger cell. Credit: NIAID

Scientists at The Wistar Institute and collaborators have successfully

engineered novel DNA-encoded monoclonal antibodies (DMAbs) targeting Zaire Ebolavirus that were effective in preclinical models. Study results, published online in *Cell Reports*, showed that DMAbs were expressed over a wide window of time and offered complete and long-term protection against lethal virus challenges. DMAbs may also provide a novel powerful platform for rapid screening of monoclonal antibodies enhancing preclinical development.

Ebola virus infection causes a devastating disease, known as Ebola virus disease, for which no licensed vaccine or treatment are available. The 2014-2016 Zaire Ebola virus epidemic in West Africa was the most severe reported to date, with more than 28,600 cases and 11,325 deaths according to the Center for Disease Control. A new outbreak is ongoing in the Democratic Republic of Congo, with a death toll of more than 200 people since August. One of the experimental avenues scientists are pursuing is evaluating the safety and efficacy of monoclonal antibodies isolated from survivors as promising candidates for further development as therapeutics against Ebola virus infection. However, this approach requires high doses and repeated administration of recombinant monoclonal antibodies that are complex and expensive to manufacture, so meeting the global demand while keeping the cost affordable is challenging.

"Our studies show deployment of a novel platform that rapidly combines aspects of monoclonal antibody discovery and development technology with the revolutionary properties of synthetic DNA technology," said lead researcher David B. Weiner, Ph.D., executive vice president and director of Wistar's Vaccine & Immunotherapy Center, and W.W. Smith Charitable Trust Professor in Cancer Research.

The team designed and enhanced optimized DMAbs that, when injected locally, provide the genetic blueprint for the body to make functional and protective Ebola virus-specific antibodies, circumventing multiple

steps in the antibody development and manufacturing process. Dozens of DMAbs were tested in mice and the best-performing ones were selected for further studies. These proved to be highly effective for providing complete protection from disease in challenge studies.

"Due to intrinsic biochemical properties, some monoclonal antibodies might be difficult and slow to develop or even impossible to manufacture, falling out of the development process and causing loss of potentially effective molecules," added Weiner. "The DMAb platform allows us to collect protective antibodies from protected persons and engineer and compare them rapidly and then deliver them in vivo to protect against infectious challenge. Such an approach could be important during an outbreak, when we need to design, evaluate and deliver life-saving therapeutics in a time-sensitive manner."

"We started with antibodies isolated from survivors and compared the activity of anti-Ebola virus DMAbs and recombinant monoclonal antibodies over time," said Ami Patel, Ph.D., first author on the study and associate staff scientist in the Wistar Vaccine and Immunotherapy Center. "We showed that in vivo expression of DMAbs supports extended protection over traditional antibody approaches."

The researchers also looked at how DMAbs physically interact with their Ebola virus targets, called epitopes, and confirmed that DMAbs bind to identical epitopes as the corresponding recombinant monoclonal antibodies made in traditional bioprocess facilities.

The Weiner Laboratory is also developing an anti-Ebola virus DNA vaccine. Preclinical results from this efforts were published recently in the *Journal of Infectious Diseases*.

More information: Ami Patel et al, In Vivo Delivery of Synthetic Human DNA-Encoded Monoclonal Antibodies Protect against

Ebolavirus Infection in a Mouse Model, *Cell Reports* (2018). DOI: 10.1016/j.celrep.2018.10.062