Synthetic antibody rapidly protects mice and monkeys from Zika

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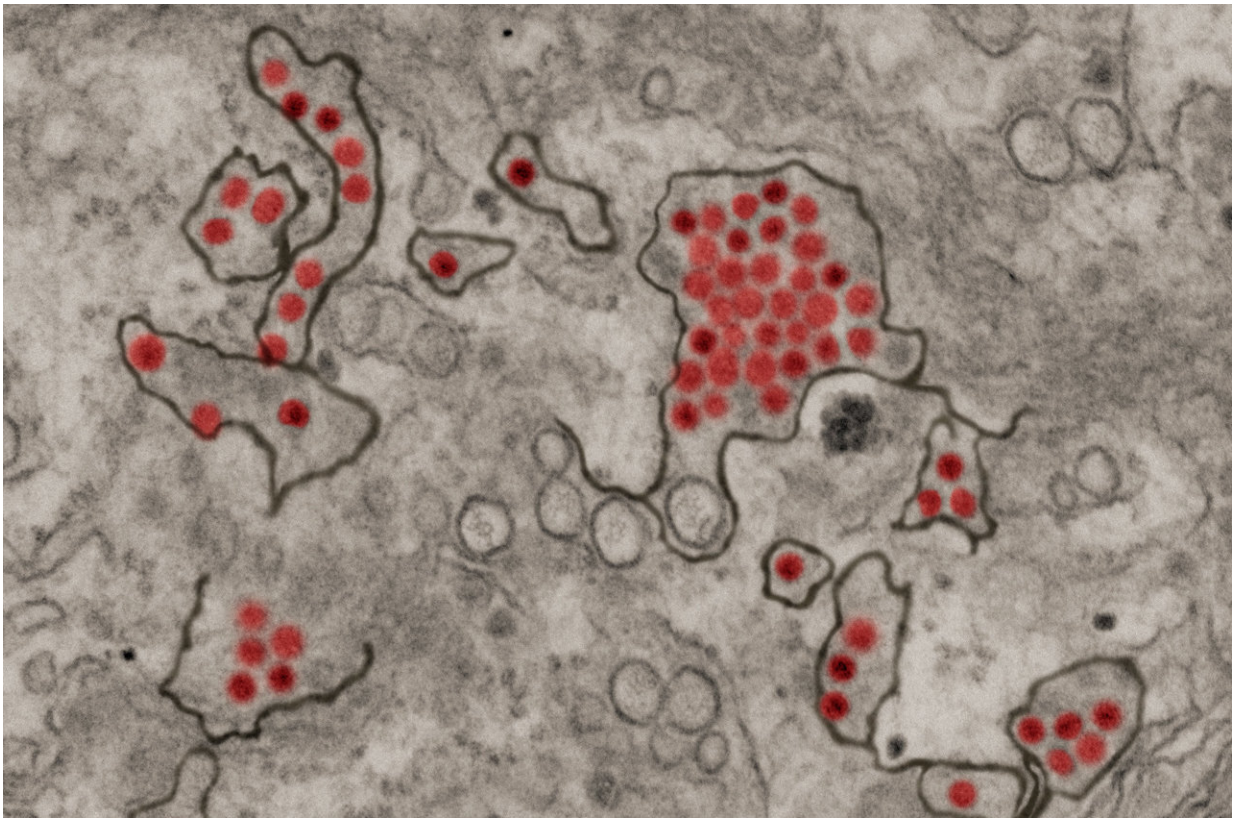

Zika virus particles (red) shown in African green monkey kidney cells. Credit: NIAID

A DNA-encoded monoclonal antibody prevents Zika infection in mice and non-human primates, researchers report April 5th in the journal

Molecular Therapy. Injections of synthetic DNA encoding the potent anti-Zika monoclonal antibody ZK190 resulted in high production of ZK190 for weeks to months, effectively controlling infection in all animals. The new platform for monoclonal-antibody gene delivery and expression, called DMAb-ZK190, may be valuable for conferring rapid, transient preventative protection against Zika infection in high-risk populations.

"The DMAb-ZK190 studies are the first demonstration of Zika virus infection control using a synthetic nucleic acid approach for antibody gene delivery," says senior study author David Weiner, executive vice president, director of the Vaccine & Immunotherapy Center and the W.W. Smith Charitable Trust Professor in Cancer Research at The Wistar Institute. "Additionally, this is the first evidence that such an approach can be efficacious in a non-human primate. Our study represents an important step forward for synthetic DMAb delivery, with the goal of human translation."

Zika is a mosquito-borne virus that has become an important global public health concern, with more than two billion people at risk. Zika virus infection carries significant risks during pregnancy, resulting in severe developmental defects in newborns. Neurological symptoms have also been observed in a subset of infected adults. Currently, there is no vaccine or specific medicine for Zika. Rapid preventative interventions for the Zika virus are a pressing global need for people living in endemic countries, travelers, and other high-risk populations.

Individuals who recover from infection develop antibodies that specifically protect against the Zika virus. However, the use of monoclonal antibodies for preventing infection is costly and challenging due to delivery and manufacturing limitations. This approach requires high doses and long infusion times as well as cold-chain storage and long-term antibody stability. In vivo delivery of synthetic nucleic acid that

encodes engineered monoclonal-antibody genes represents a possible alternative approach with great potential to alleviate these critical challenges.

"The large protein-coding capacity of synthetic DNA can be combined with the latest advances in in vivo cell transfection to deliver, in this case, fully encoded antibody cDNA sequences that will guide antibody production by the body's own cells," Weiner says. "Our platform has advantages in manufacturing, cost, temperature stability, and storage for such an encoded biologic molecule. These represent critical features to potentially improve accessibility of antibody-based biologics globally."

To test this approach, the researchers injected DMAb-ZK190 into the leg muscles of eight mice and then exposed the animals to a lethal dose of the Zika virus. Remarkably, the monoclonal antibody provided 100% protection against mortality and signs of illness. DMAb-ZK190 also completely protected against testicular damage and atrophy after exposure to either a low or high dose of the Zika virus.

While Zika virus infection is not lethal in non-human primates, three sequential injections of DMAb-ZK190 in rhesus macaques had a positive effect on controlling infection in all five animals and significantly lowered viral loads in four animals. DMAb-ZK190 achieved high expression levels persisting for more than 10 weeks in mice and more than 3 weeks in non-human primates.

"These data support further evaluation of DMAbs in general and moving this strategy forward for translation into humans," Weiner says. "While we are excited that we achieved in vivo expression of DNA-encoded antibody, as well as protection from viral challenge, additional work will be important for expression and longevity of this approach in non-human primates. We are focusing heavily on improving parameters of DMAb expression through additional genetic engineering and on improvements

in the platform in additional animal models."

More information: *Molecular Therapy*, Esquivel and Patel, et al.: "In vivo delivery of a DNA-encoded monoclonal antibody (DMAb) protects non-human primates against Zika virus." www.cell.com/molecular-therapy … 1525-0016(18)X0006-9 , DOI: 10.1016/j.ymthe.2019.03.005

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