New Zika clone could be new model for developing vaccine

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Stopping the explosive spread of Zika virus - which can lead to birth defects in babies born to infected mothers - depends on genetic insights gleaned through new tools and models. Researchers at the National Institutes of Health recently cloned an epidemic strain of the virus, creating a model that can help biologists develop and test strategies for stopping the pandemic.

In the latest issue of *mBio*, the researchers reported that the cloned virus replicated successfully in multiple cell lines, including placental and brain cells - tissue particularly vulnerable to damage from Zika. The clone will be used for the development of a live but attenuated vaccine.

"Our goal is to create long-term immunity after one short immunization," says study leader and molecular biologist Alexander Pletnev, at the National Institute of Health's National Institute of Allergy and Infectious Diseases in Bethesda, Maryland.

The goal of Pletnev's group is to create a live, attenuated vaccine similar to the ones used in humans against other harmful viruses like polio, yellow fever, and Japanese encephalitis. Following up on their lab studies, Pletnev and his collaborators recently began mouse studies of the cloned virus. Pletnev says he invites other researchers to use his lab's ZIKV clone to investigate and ultimately stop the harm caused by Zika.

The virus was first identified nearly 70 years ago in Uganda, but for decades it circulated only in a small geographic area in equatorial Africa

and Asia, and mostly among primates. The current epidemic began in early 2015 in Brazil, and since then has spread throughout South and Central America. In February 2016, the World Health Organization declared the pandemic a public health emergency. Five months later, the US Centers for Disease Control and Prevention reported the first case of mosquito-borne infection in the US in residents of Florida, in a neighborhood near Miami. (The virus can also be transmitted through sex.)

The biological behavior of viruses is often unpredictable, which makes it difficult for scientists to figure out how to stop them, says Pletnev. Zika belongs to the Flavivirus group of viruses, which also includes West Nile, dengue, and yellow fever. Viruses in this family each have a single strand of RNA, but they're notoriously difficult to manipulate and clone. With the tools of reverse genetics, biologists can study single-stranded RNA by using viral complementary DNA, or cDNA. Flaviviruses, however, are often toxic to their bacterial hosts, and biologists have pursued a variety of ways around the problem.

Pletnev and his group, including researchers from the University of Texas and the US Food and Drug Administration, began with a viral strain collected from an infected, febrile patient in Brazil in 2015. To reduce toxicity and increase the stability of the ZIKV cDNA clone during growth in Escherichia coli bacteria, they added introns - or specific nucleotide sequences - to the full viral cDNA genome. High-throughput sequencing revealed that the virus derived from the cDNA clone had less genetic diversity than its wild-type parent strain, and subsequent experiments showed that the clone was attenuated, compared to its parent.

The researchers made a few more genetic tweaks to customize their clone to grow in Vero cells - a line derived the kidneys of African green monkeys, commonly used in human vaccine manufacture.

In addition to their work on Zika, which began in early 2016, Pletnev's group has worked extensively on other Flaviviruses. They produced a vaccine for West Nile virus, currently in clinical trials, and have worked on developing vaccines against St. Louis and Japanese encephalitis.

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