Novel compound blocks replication of Zika and other viruses

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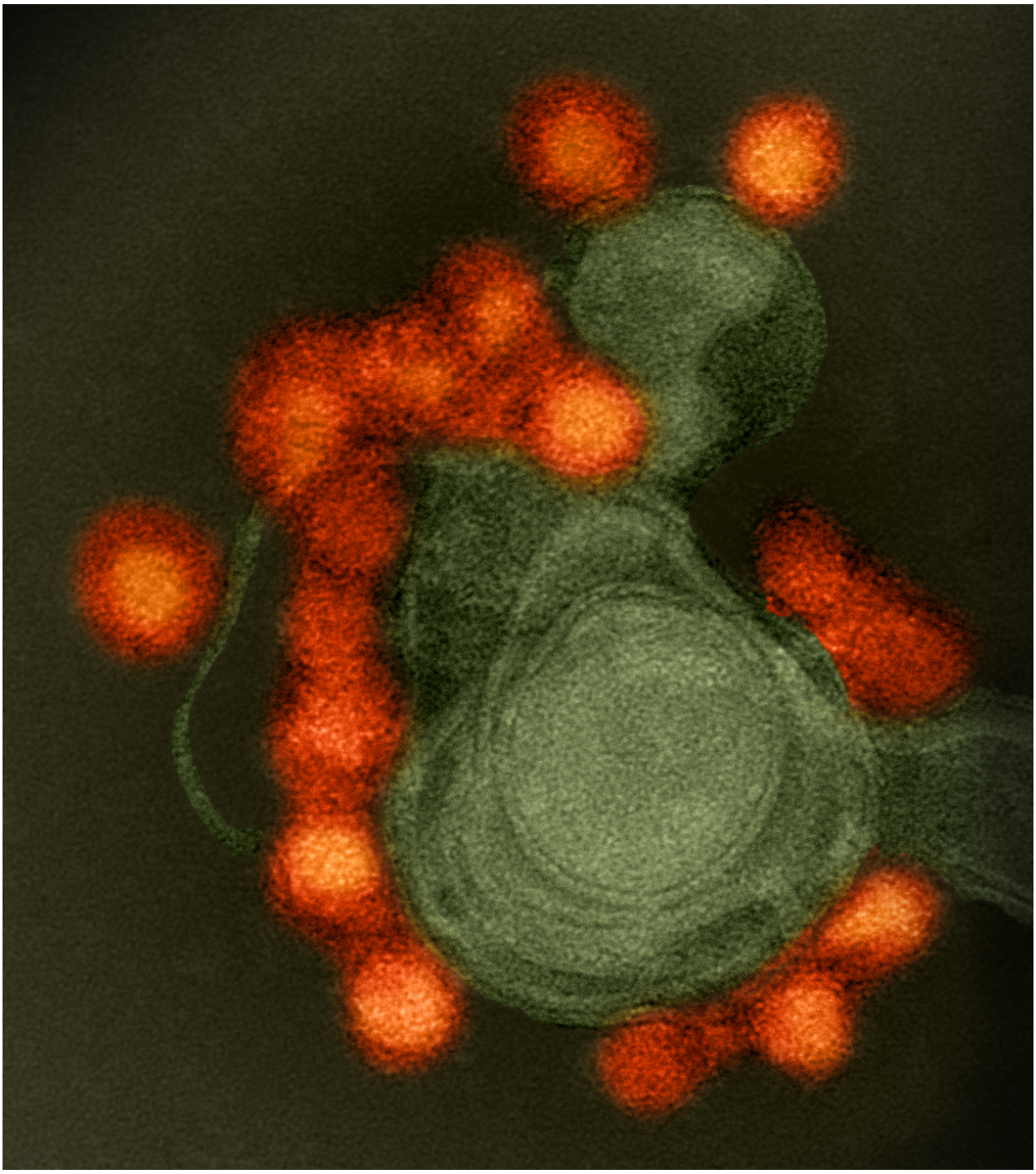

Transmission electron microscope image of negative-stained, Fortaleza-strain Zika virus (red), isolated from a microcephaly case in Brazil. The virus is associated with cellular membranes in the center. Credit: NIAID

The cells of vertebrates have evolved pathways that act like an internal defense, inhibiting viral infections by preventing replication of the pathogens. Drugs that activate those existing systems suggest a promising novel approach to treating dangerous infections by Zika and other viruses, say researchers from the Vaccine and Gene Therapy Institute at Oregon Health and Science University (OHSU), in Portland.

In a new study published this week in *mBio*, the scientists report on a novel compound that triggers a cell's innate antiviral system, inhibiting replication of Zika, Chikungunya, and Dengue viruses.

Recent outbreaks of Zika and Chikungunya infections that began in Latin and South America and spread to other continents—as well as the ongoing presence of Dengue—have spurred disease researchers to search for new antiviral medications. No treatments are available for the three infections, and only Dengue has a vaccine, which is licensed in some Asian and South American countries where the disease is endemic.

The three viruses spread by way of the same mosquito species and elicit similar symptoms. Chikungunya emerged in the Americas in Caribbean islands in 2013, and since then it has infected more than a million people on five continents. Zika was first identified 70 years ago, but a 2015 outbreak that began in Brazil has spread to 50 countries and, according to estimates from the World Health Organization, will infect three to four million people this year. Zika infection during pregnancy can cause severe birth defects, including microcephaly. More than 350 million people are infected with Dengue annually; the virus is a leading cause of illness and death among children in some countries.

Virologist Victor R. DeFilippis, at OHSU, led the work. He predicts that cellular innate immune responses may be pharmacologically harnessed to block infections as a kind of antiviral immunotherapy. "The tools that we need to fight off virus infection are programmed into our cells as a result

of evolution," he says. "I think that's a potentially lost opportunity for the identification of novel broad-spectrum antiviral strategies."

Interferons are proteins, secreted by cells, that are known to induce protection against a wide variety of infections, including viral. In the new paper, DeFilippis and his colleagues report on a novel small molecule, which they named AV-C, that triggers the built-in cellular defenses by activating the interferon system. In lab experiments, the researchers treated human fibroblasts with AV-C and, six hours later, infected the cells with one of the three viruses. The drug kept the viral presence low, leading them to conclude that AV-C establishes a cellular state antagonistic to replication. AV-C also triggered secretion of other proinflammatory cytokines, suggesting that it may have potential to enhance vaccine efficacy.

The researchers also investigated whether the molecule has potential therapeutic effects by administering it to cells after infection with Zika and Chikungunya. For Zika, the results were promising. AV-C did block Zika replication in the cells when administered as late as 16 hours post-infection. For Chikungunya, however, the molecule failed to block replication when given just two hours post-infection.

Next, says DeFilippis, the researchers need to evaluate the clinical utility of the drug in animal models. Early experiments in mice suggest AV-C does not inhibit virus replication in those animals, but DeFilippis hopes to test it in other species, such as nonhuman primates.

He sees AV-C as the first of a family of compounds worth exploring. He and his team found the drug by using high-throughput screening to examine 51,000 different compounds that might trigger the innate response. After they narrowed down their list to a few promising candidates, AV-C was one of the first they studied in earnest.

"There are potential drugs out there we haven't really taken a look at," says DeFilippis. "We're characterizing a number of other agents that are just as promising, and many are even more promising."

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