New mRNA and gene editing tools offer hope for dengue virus treatment

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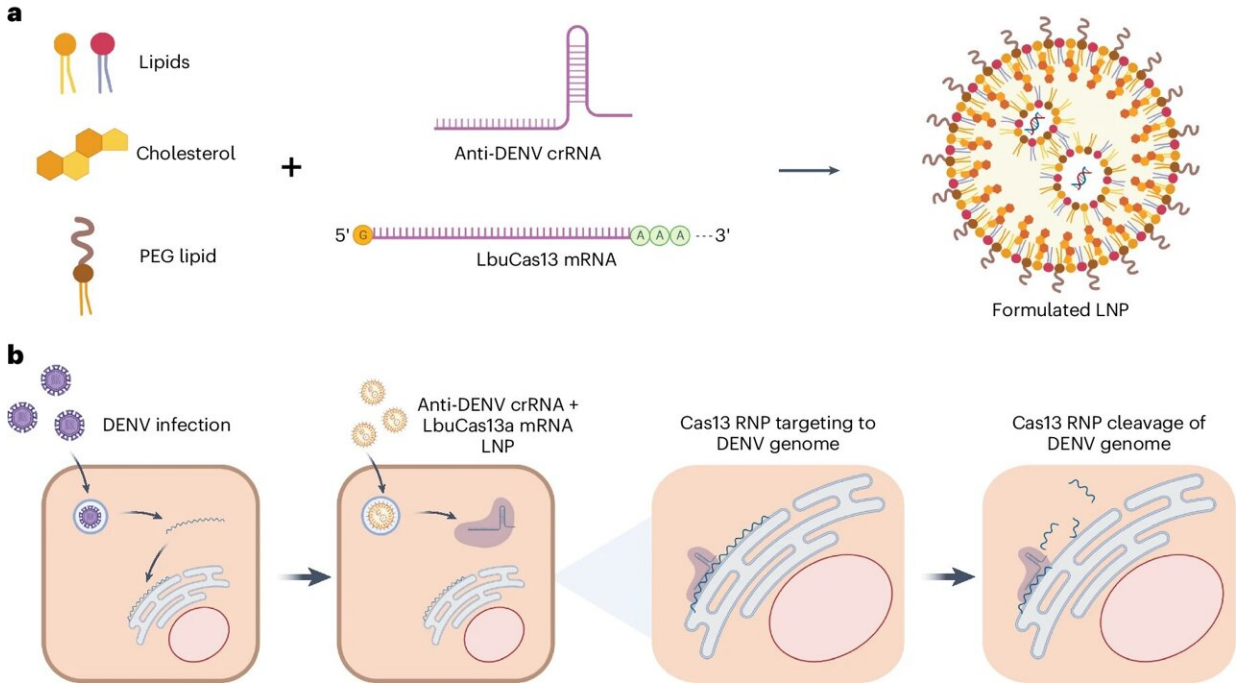

Schematic of the composition and mechanism of action of a mRNA-expressed anti-DENV LbuCas13a drug. Credit: *Nature Microbiology* (2024). DOI: 10.1038/s41564-024-01726-6

Dengue virus, a painful and sometimes fatal mosquito-borne infection well known in tropical countries, is surging rapidly across the planet. Now, 4 billion people live in places at risk for the disease, like the southeastern United States, which doesn't have an effective antiviral

treatment yet.

A team of researchers led by biomedical engineer Phil Santangelo has developed a breakthrough therapy to target and kill the virus using the gene editing tool CRISPR-Cas13. The team's systemic delivery of the treatment was successful in treating dengue virus in mice, as the researchers explain in a study appearing in *Nature Microbiology*.

Dengue is difficult to treat, in part because there are four different serotypes of the virus, which means four different targets for a vaccine. People infected with one serotype who then contract a second version of the virus can end up with a serious disease. That second attack can end up amplifying the first. Symptoms include fever, nausea, rash, aches and pains (including behind the eyes), and in some cases, internal bleeding, shock, and death.

"There are several challenges with trying to treat dengue, so we wondered, is it possible for us to produce an mRNA-based, CRISPR-based antiviral where one shot can clear the virus," said Santangelo, professor in the Wallace H. Coulter Department of Biomedical Engineering at Georgia Tech and Emory University. "And that's basically what we've shown."

New use for tech

With the global proliferation of the Aedes mosquito that spreads dengue and other viruses, the timing of such a treatment would be fortuitous.

"Unfortunately, climate change is enabling an increase of these virus-causing mosquitoes," Santangelo said. "So, it's a good idea to be prepared."

This is the first time an mRNA-based CRISPR treatment has worked

against systemic viral infections in animal models. But Santangelo demonstrated its efficacy in earlier studies focused on lung diseases, including a treatment for coronavirus. That was an inhalable treatment using polymeric nanoparticles—large, biodegradable molecules ideal for delivering medicine directly to the lungs.

For the dengue virus study, the team used lipid nanoparticles (LNPs), which are like tiny fat bubbles that transport drugs through the bloodstream and into cells. The nanoparticles carried a custom-coded messenger RNA (mRNA) molecule.

The mRNA was encoded with Cas13a (a CRISPR protein that can cut viral RNA) and guide RNAs (to direct the Cas13a to the viral RNA to be cut). The process basically created a set of instructions. When the encoded mRNA was delivered to infected cells via the LNPs, the cell used those instructions to build Cas13a and guide RNAs, which degraded the viral RNA within those targeted cells.

Military precision

A single dose of the treatment was given to mice infected with lethal doses of two serotypes of dengue virus, DENV-2 and DENV-3. All the treated mice survived with no unintended damage to their RNA. Following treatment, the researchers also looked for evidence of the virus in the mice's brains but couldn't find any.

"It looks like our treatment precludes the virus from getting into the brain," Santangelo said. "This may not be super critical for dengue, which doesn't end up in the human brain. But this discovery could be really important for Zika virus, Japanese encephalitis, West Nile, and other viruses that do affect the human brain."

Santangelo's team is now testing their approach on dengue's other

serotypes and will study the treatment in other viruses.

"We're very interested in trying these kinds of approaches to go after as many viruses as we can with one, potent treatment," said Santangelo, whose team included researchers from Georgia State University as well as Emory's Computational Core. "We're trying to find the most efficient way to kill these viruses. We're not quite there yet, but we're going to get there eventually."

More information: Mausumi Basu et al, mRNA-encoded Cas13 can be used to treat dengue infections in mice, *Nature Microbiology* (2024). DOI: 10.1038/s41564-024-01726-6

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