Disarming HIV with a 'pop': Researchers create molecule that can trick HIV into destroying itself

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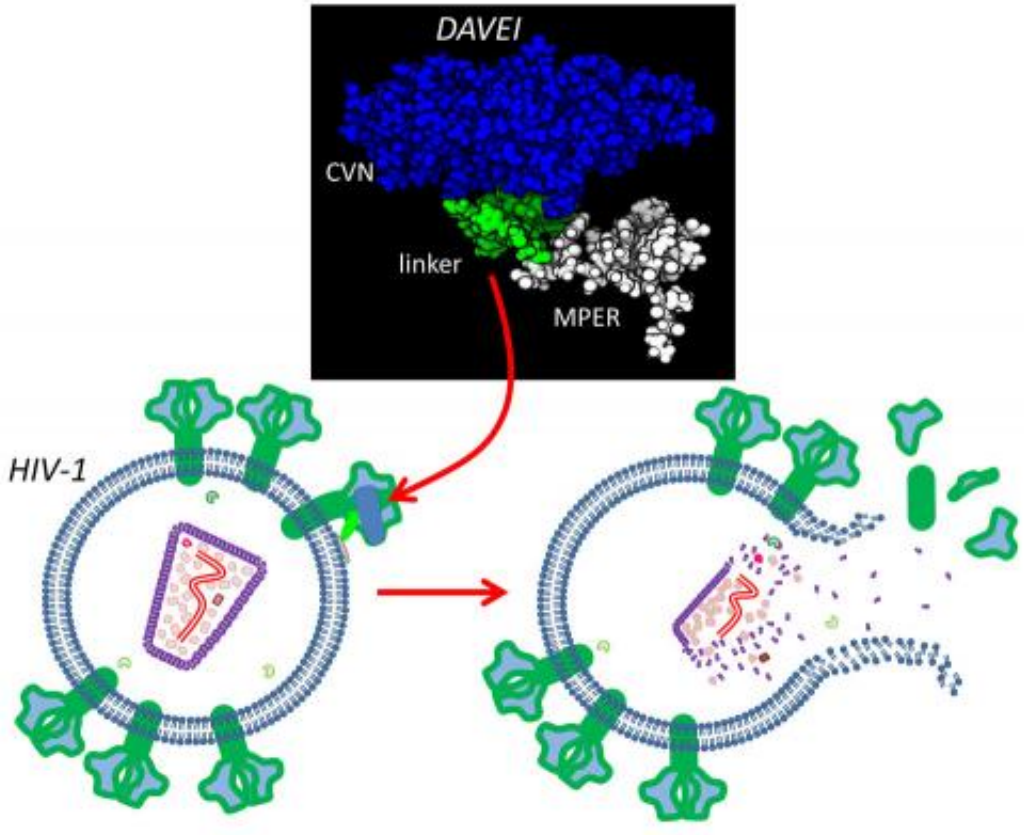

The Dual Action Virolytic Entry Inihibitor (DAVEI) molecule is comprised of two pieces: one called Membrane Proximal External Region (MPER) attaches to the viral membrane; the other, called cyanovarin (CVN) bonds with the virus's protein spike. The molecule is able to make the virus react as if it is attached to a healthy cell -- firing its protein spike and injecting its RNA into oblivion, thereby rendering it inert. Credit: Drexel University

Pinning down an effective way to combat the spread of the human immunodeficiency virus, the viral precursor to AIDS, has long been challenge task for scientists and physicians, because the virus is an elusive one that mutates frequently and, as a result, quickly becomes immune to medication. A team of Drexel University researchers is trying to get one step ahead of the virus with a microbicide they've created that can trick HIV into "popping" itself into oblivion.

Its name is DAVEI - which stands for "Dual Action Virolytic Entry Inhibitor"- and it can pull a fast one on HIV. DAVEI was invented and tested by scientists from Drexel's College of Engineering; School of Biomedical Engineering, Science and Health Systems; and College of Medicine, and is the latest in a new generation of HIV treatments that function by specifically destroying the virus without harming healthy cells.

"While several molecules that destroy HIV have recently been announced, DAVEI is unique among them by virtue of its design, specificity and high potency," said Dr. Cameron Abrams, a professor in Drexel's College of Engineering and a primary investigator of the project.

A team co-led by Abrams and Dr. Irwin Chaiken in the Department of Biochemistry and Molecular Biology in Drexel's College of Medicine, and including Dr. Mark Contarino and doctoral students Arangassery Rosemary Bastian and R. V. Kalyana Sundaram, developed the chimeric recombinantly engineered protein – that is, a molecule assembled from pieces of other molecules and engineered for a specific purpose, in this case to fight HIV. Their research will be published in the October edition of the American Society for Microbiology's *Antimicrobial Agents and Chemotherapy*.

The idea behind DAVEI was to design a molecule that hijacks the virus's fusion machinery, the tools it uses to attach to and attack a healthy cell, and trick the virus into destroying itself. HIV invades a healthy cell by first attaching via protein "spikes" that then collapse to pull viral and cell membranes together, fusing them and allowing the genetic contents of the virus to enter the healthy cell. The cell is rewired by the viral genetic material into producing more viruses instead of performing its normal function, which, in the case of cells infected by HIV, involves normal immunity. AIDS is the result.

"We hypothesized that an important role of the fusion machinery is to open the viral membrane when triggered, and it follows that a trigger didn't necessarily have to be a doomed cell," Abrams said. "So we envisioned particular ways the components of the viral fusion machinery work and designed a molecule that would trigger it prematurely," Abrams said.

They designed DAVEI from two main ingredients. One piece, called the Membrane Proximal External Region (MPER), is itself a small piece of the fusion machinery and interacts strongly with viral membranes. The other piece, called cyanovirin, binds to the sugar coating of the protein spike. Working together, the MPER and cyanovirin in DAVEI "tweak" the fusion machinery in a way that mimics the forces it feels when attached to a cell.

"For lack of a better term, DAVEI 'tricks' the virus into 'thinking' it is about to infect a healthy cell, when, in fact, there is nothing there for it to infect," Abrams said. "Instead, it releases its genetic payload harmlessly and dies."

Chaiken's lab has extensively investigated the molecular mechanisms of HIV-1 envelope protein interactions and structure-based design of agents that fight HIV. The researchers produced DAVEI by recombinant

protein engineering and used HIV-1 pseudoviruses to demonstrate that it can physically rupture and irreversibly inactivate the virus particles.

"DAVEI and other new-generation virolytic inactivators open up an important opportunity to develop a topical microbicide to block the transmission of HIV, and at the same time provide lead ideas to discover treatment strategies for people who are already infected," Chaiken said. "Our hope is that determining the structural driving forces of both inhibitors and viral entry machinery that enable spike inactivation will help to advance molecular designs with increased power, specificity and clinical potential for both prevention and treatment."

Provided by Drexel University