Scientists try brincidofovir against Ebola

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Credit: Ryan Parks/UC San Diego Health Sciences Marketing and Communications

With the Ebola crisis ongoing, much attention is focused upon finding a drug capable of slowing – if not stopping – the infectious, deadly and terrifying virus.

There is Zmapp, of course, the experimental biopharmaceutical produced by a San Diego-based biotech firm that was used briefly before supplies ran out. There are other anti-Ebola drugs reportedly

under development in Oregon, Canada and China.

And there is brincidofovir, a compound with a decidedly unwieldy name that was discovered more than a decade ago by researchers at UC San Diego. Brincidofovir (pronounced brin-SIGH-doh-fo-veer) wasn't invented to fight Ebola – the scientists were actually looking for a new way to fend off the menace of bioterrorism – but it may represent one of the best chances yet to conquer a virus that has killed more than 4,500 people, almost all in stricken West Africa.

In 1999, Dr. Karl Hostetler, then a professor of medicine in UC San Diego School of Medicine, got a call from officials at the National Institute of Allergy and Infectious Diseases. They posed a question: Could he help create a new drug to protect Americans if bioterrorists unleashed smallpox – the one-time global scourge now restricted to a few high-security labs?

There was already a drug called cidofovir that might serve, but it required an injection. NIAID officials wanted a pill, something safe, stable and broadly effective against not just smallpox, but other highly infectious, deadly viruses that might be deployed as bioweapons.

"There was a lot of talk and fear about such attacks at the time," recalled Hostetler, now professor emeritus. "It's still a legitimate concern."

Hostetler, who studied the lipid molecules necessary to build cell membranes and was working on improved ways to deliver therapeutic drugs inside cells, agreed to help. Funding from NIAID arrived within days.

Over the next few years, he and colleagues created multiple analogs or variations of cidofovir. The first was brincidofovir. In cultured cell tests, the compound proved active against an array of viruses, blocking their

ability to replicate.

"With any disease that causes high mortality, the idea isn't so much to absolutely stop viral replication as to slow it down so that the patient's immune system can catch up and ultimately eradicate the infection," Hostetler said.

One of the viruses seemingly impacted by brincidofovir is Ebola, though Hostetler's focus at the time was elsewhere. Brincidofovir targets double-stranded DNA viruses like herpes, cytomegalovirus, Epstein-Barr, hepatitis and papillomavirus. Ebola is an RNA virus. It replicates differently.

"Brincidofovir is the first broad-spectrum antiviral for DNA viruses. It's not unprecedented that it might also work against RNA viruses like Ebola, but back then, the greatest interest was in DNA viruses," he said.

Unable to arouse outside interest and investment in brincidofovir, Hostetler founded Chimerix in Durham, N.C. to further develop the drug – both for smallpox and for other diseases. These efforts have progressed measurably. Phase 3 trials under the Food and Drug Administration's (FDA) animal rule are planned next year for a smallpox treatment. Phase 3 human trials are underway for brincidofovir as a therapy for cytomegalovirus and adenovirus – common viruses that can cause fever, diarrhea, conjunctivitis and bladder infections, but in persons with weakened or suppressed immune systems are life-threatening.

Hostetler left Chimerix in 2012, well before the company began to seriously investigate brincidofovir's activity against Ebola. But he has closely watched developments from the outside the company and has seen some of Chimerix' in vitro data describing brincidofovir's activity against Ebola.

(Full disclosure: Hostetler has no advisory or consulting role with Chimerix, but does retain founder's stock in the company. He would receive royalties, per university regulations, if brincidofovir reaches market.)

"The data are impressive.The drug appears to be effective against Ebola in vitro at concentrations similar to that reported for several DNA viruses that brincidofovir successfully treats in humans. In other words, the in vitro evidence so far suggests it might be an effective treatment, even though Ebola is an RNA virus."

Brincidofovir may have some advantages over other Ebola drugs under investigation.

First, it's a small molecule drug, which means that unlike Zmapp, whose antibodies must be grown in a plant model, a time-consuming process, the manufacture of brincidofovir is comparatively quick and easily scaled up.

Second, brincidofovir has been clinically tested on more than 1,000 human subjects, many of whom were desperately ill, and many of whom were children. Such cases suggest the drug isn't likely to make a sick patient worse. The other potential Ebola drugs have yet to be clinically tested in humans.

Finally, there is science explaining how brincidofovir may work against an RNA virus like Ebola. It's not a complete mystery. It's not magic. And Hostetler notes both the U.S. Centers for Disease Control and the FDA wouldn't be supportive of accelerating brincidofovir's development if they didn't think they had cause.

"The FDA wouldn't have given emergency investigational new drug status to brincidofovir if it hadn't already seen some encouraging data."

Hostetler said he's optimistic about brincidofovir, but added that everything depends upon the results of further rigorous, controlled, large-scale studies. Some of that can happen in the United States, but the real testing ground will be Africa, Ebola's home turf.

"You need to evaluate where there are enough patients," he said.

Meanwhile, he is busy doing battle against a different virus – human papillomavirus (HPV), a sexually transmitted infection that is linked to cervical cancer. In 2012, he founded Hera Therapeutics (his fourth biotech startup after Vical, Triangle Pharmaceuticals and Chimerix) to develop a topical agent to treat HPV. He hopes to launch its phase 1 clinical trial in about a year.

"I should have retired 10 years ago, but I still have ideas," he said.

Provided by University of California - San Diego