On the hunt for a dengue antiviral: Scientists comb through scores of compounds to find a drug for 'breakbone fever'

March 19 2021, by Delthia Ricks

Credit: CC0 Public Domain

The 'dengue belt' stretches around much of the planet crossing continents, cultures and time zones, a vast region linked by a common

fate: a mosquito-borne disease that can be prevented for a select number of people with a somewhat quirky vaccine. Dengue, however, remains a source of misery for many, a viral infection without an antiviral to treat it.

The need for an antiviral is enormous. Forty percent of the world's population—about 3 billion people—resides in regions at risk of dengue infection, according to the U.S. Centers for Disease Control and Prevention. Each year up to 400 million people are infected, 100 million get seriously sick and 22,000 die of severe dengue.

Scientists are increasingly conducting what once was an arduous task of finding "a needle in a haystack," pinpointing a compound from an existing archive of thousands of compounds. The reason for such hunts is to find a compound capable of treating any given disease. In general, so-called 'big data' scans are allowing hunts through massive libraries of chemical data. This type of search has been mounted to uncover a compound to treat dengue, and a discovery by one research group has already begun to produce positive results.

"Dengue virus is a mosquito-borne flavivirus that lacks any effective antiviral treatments," wrote Dr. Stephanie A. Moquin, first author on a research paper about a big data hunt for a dengue antiviral. The research, conducted by a team from the Novartis pharmaceutical company, was published in *Science Translational Medicine*.

"There are four serotypes of dengue virus, all of which can cause disease, including dengue fever, dengue shock syndrome [and] dengue hemorrhagic fever. Thus, an antiviral drug needs to be effective against all four serotypes," according to Moquin and her colleagues.

Although a vaccine was approved in 2019 to prevent infection, it remains of limited use. The inoculation is prescribed only for people

between the ages of nine and 45 and it can be administered only to those who previously were infected. Worse, the vaccine has the dubious reputation of causing severe disease in some people. That's one reason that scientists have been on the hunt for an antiviral capable of effectively treating the infection.

An efficacious antiviral would be immediately welcomed into the pharmaceutical armamentarium. The mosquito-transmitted virus can cause an excruciatingly painful constellation of symptoms—a disease marked by soaring fever, headache, swollen glands and an indescribable amount of pain in the joints. It's no accident that ages ago the viral disease was widely known as breakbone fever.

Moquin and her team hail mostly from the global laboratories and research centers of the pharmaceutical giant, which is headquartered in Basel, Switzerland. Although Novartis experts dominated the hunt for a dengue antiviral, they were aided by the Institute of Antiviral Research at the University of Utah. Novartis team members were scattered all over the United States—California, New Jersey and Massachusetts, and they collaborated with colleagues at the Novartis Institute for Tropical Medicine Research in Singapore.

The team had at their disposal—and used as their primary source—the vast Novartis compound library, which afforded a staggering number of details about potential candidates. Similar searches in recent months have involved the compound libraries of other pharmaceutical companies as scientists have searched for potential medications that can be re-purposed to treat COVID-19. Such searches are not new to pharmaceutical drug development, and increasingly have been used in the hunt for medications to address a wide range of conditions: antibiotic resistance, cancer and heart disease, for example. The hunts also can include searches of shelved and forgotten compounds from other eras.

Scientists search the libraries of chemical compounds for potential drugs that can keenly attack specific disease-causing targets.

"We performed a high-throughput phenotypic screen using the Novartis compound library and identified candidate chemical inhibitors of dengue virus," Moquin reported. "This chemical series was optimized to improve properties such as anti-dengue virus potency and solubility. "The lead compound, NITD-688, showed strong potency against all four serotypes of dengue virus and demonstrated excellent oral efficacy in infected AG129 mice."

AG129 mice are deficient in alpha, beta and gamma interferon receptor-signaling. Interferons are a group of signaling proteins made and released by host cells in response to the presence of viruses. Generally, a virus-infected cell releases interferons—chemical messengers—that cause neighboring cells to bolster their defenses. AG129 mice are commonly used in dengue research.

What scientists found in the small animal tests was surprising—a substantial reduction in viremia when mice were treated orally at 30 milligrams per kilogram twice daily for 3 days starting at the time of infection. Viremia is the amount of virus in the bloodstream. Treatment with the compound, NITD-688, also resulted in further viremia reduction when mice were treated again 48 hours after infection.

To test their hypothesis that NITD-688 may indeed be a potent antiviral with a high level of specificity for all four serotypes of the dengue virus, the team additionally tested the compound in laboratory rats and dogs, and additionally found the compound to be well-tolerated and produced a sharp decline in viremia.

The compound works against the virus because it inhibits the activity of a key dengue virus protein: NS4B. That molecule is vital to the dengue

virus's replication complex, and therefore essential to the viral life cycle. NS4B works in tandem with another viral protein, NS4A. But with NS4B disabled by the newly identified compound, the pair can no longer perform their jobs maintaining vital functions of the virus.

Dengue viruses are spread by two mosquito species that are common throughout many parts of the world, and especially in the dengue belt. Aedes aegypti, for example, originated in Africa, but is found around the globe, including throughout much of the United States, according to the CDC. Aedes albopictus is the other mosquito carrier of dengue viruses. It too, is found globally. In addition to dengue, the same two mosquito species transmit Zika and chikungunya viruses.

The ongoing concern about these mosquitoes—flying hypodermic needles—is that their range throughout the dengue belt is where they do considerable harm. Dengue is often a leading cause of illness in areas that are at risk. The belt covers Central America and the Caribbean, most of South America, sub-Saharan Africa, India, and South East Asia, according to the World Health Organization.

So far, the future looks bright for the drug candidate, NITD-688. "Pharmacokinetic studies in rats and dogs showed a long elimination half-life and good oral bioavailability," Moquin wrote. "Extensive in vitro safety profiling along with exploratory rat and dog toxicology studies showed that NITD-688 was well tolerated after 7-day repeat dosing, demonstrating that NITD-688 may be a promising preclinical candidate for the treatment of dengue."

More information: Stephanie A. Moquin et al. NITD-688, a pan-serotype inhibitor of the dengue virus NS4B protein, shows favorable pharmacokinetics and efficacy in preclinical animal models, *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.abb2181