

Health & Physiology

New treatment options for Zika virus infection

by **Rachel P. M. Abrams**¹ | Postdoctoral Research Fellow; **Avindra Nath**¹ | Senior Investigator

doi.org/10.25250/thescbr.brk544

¹: National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA

This Break was edited by Akira Ohkubo, Associate Editor - TheScienceBreaker

Despite the devastation caused by the 2015–2016 Zika virus outbreak, there are no approved treatments or vaccines. We screened over 100,000 compounds that were designed to treat other diseases, and identified three classes of compounds with anti-Zika activity. The identification of these promising drug candidates will help to prepare us for the next possible Zika virus outbreak.



Image credits: Pixabay

The recent outbreak of the Zika virus in South America in 2015–2016 had devastating consequences, involving at least 200,000 human infections. The Zika virus mostly spreads among people through bites from infected mosquitoes, but can also spread through sexual transmission. The number of infections are likely underestimated, as most infected adults show no or only mild symptoms and recover quickly. However, when a pregnant woman becomes infected, the Zika virus can infect the fetus and interfere with its brain development. As a result, the baby can be born with disabilities, such as an abnormally small head, called [congenital Zika syndrome](#). Thousands of babies were born during the 2015–2016 Zika virus epidemic with this severe syndrome. Moreover, in some cases, adult patients

developed life-threatening neurological disorders such as encephalitis, myelitis, and Guillain Barré syndrome.

While infection numbers have decreased in South America, the Zika virus has not disappeared, and spread to other continents could cause another outbreak. Despite the impending threat of another outbreak, the world is unprepared – there are no vaccines or drugs available for its prevention or treatment. Therefore, it is vital to have drug candidates that are already known to be safe in humans ready if another outbreak occurs.

We embarked on a study to identify inhibitors of Zika virus infection by screening over 100,000 candidate

compounds. These compounds were originally designed to treat other diseases, but we aimed to determine if any of them could be effective against the Zika virus infection as well. For the screening, we focused on a crucial part of the viral life-cycle, a process called protein processing. The Zika virus is a particle in which the viral genetic material is covered and protected by proteins and lipids. Like many other viruses, the Zika virus hijacks our cells for its reproduction. When the virus reproduces within human cells, the viral proteins are produced from the genetic material of the virus. These newly-produced proteins are inactive and need to be ‘processed’ to become functional.

To perturb the protein processing, we targeted its key actor, the [viral protease](#). A protease is a molecule that acts as a scissor to chop the large, inactive protein into small, functional pieces. By interrupting the viral protease, we should be able to block the protein processing and, in turn, the viral infection. To put this idea to test, we synthesized the Zika virus protease in the laboratory and tested around 10,000 drug candidate compounds for their ability to inhibit it. Using those results, we developed an artificial intelligence-based software program to accelerate the time-consuming laboratory testing procedure. By virtually screening around 100,000 compounds, we selected about 400 compounds that likely inhibit the Zika virus protease.

These molecular-level experiments were not sufficient to ensure these drug candidates indeed worked in physiological conditions against the living virus. Therefore, we carried out further screening to

assess the candidate drugs’ effectiveness at inhibiting infection in cells cultured in the laboratory. These experiments allowed us to select around 80 promising drug candidates. We further confirmed the efficacies of these 80 potential drugs in cultured human brain stem cells, which are the immature cells that the Zika virus infects in a fetal brain.

Collectively, our research enabled us to propose a new library of promising drugs against the Zika virus infection. This library includes three groups of compounds, which were originally developed for different purposes. The first group – namely the gamma-secretase modulators – was expected to treat Alzheimer’s disease but has remained unsuccessful. Further investigation is required to identify the least toxic compound with the best activity against the Zika virus. The second group – the FLAP inhibitors – were developed for treating inflammatory conditions and are known to be very safe. The third group – tetracyclines – are a class of widely-used, FDA-approved antibiotics that were first discovered in the 1940s. When tested in a mouse model, the most potent tetracycline, methacycline, reduced Zika virus infection and the associated neurological deficits.

In summary, we identified several promising therapeutic candidates for the treatment of Zika virus infection. Some of these compounds could be rapidly tested in preventative or treatment-based clinical trials in the near future. The identification of these drug candidates will help us to be more prepared for the next Zika virus outbreak.