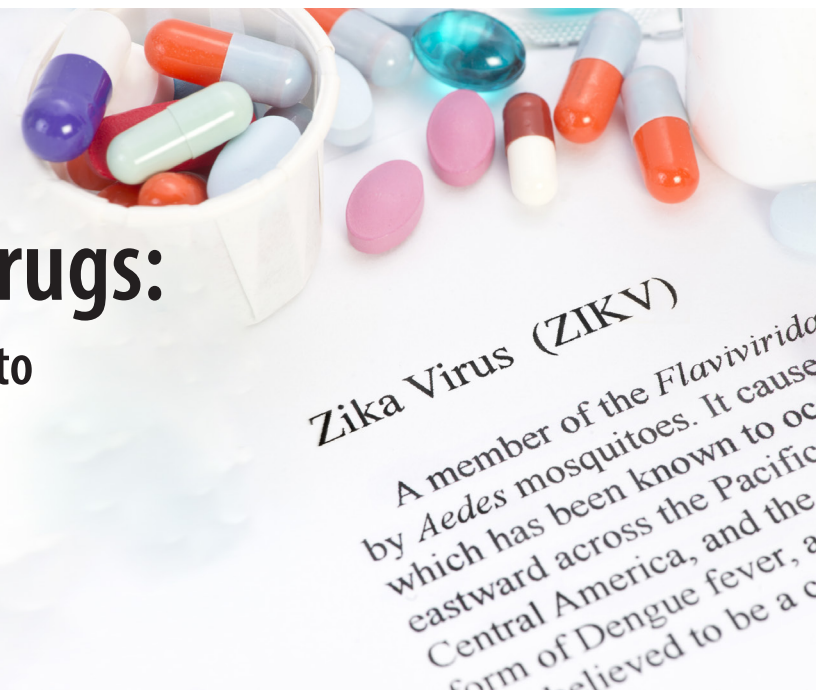


# New Tricks for Old Drugs:

## Using High-Throughput Screening to Repurpose Medications

by

Carlos C. Goller, Stefanie H. Chen, and Melissa C. Srougi  
North Carolina State University, Raleigh, NC



Zika Virus (ZIKV)  
A member of the *Flaviviridae*  
by *Aedes* mosquitoes. It causes  
which has been known to occur  
eastward across the Pacific  
Central America, and the  
form of Dengue fever, a  
believed to be a

### Introduction

As a first-year graduate student, you are excited to begin your research journey. You have acquired a coveted spot in a new lab on campus that studies the Zika virus. To get up to speed, you dive into the literature to learn more. From your background reading, you learn that the Zika virus was first isolated in 1947 from a rhesus monkey in the Zika Forest of Uganda (Dick *et al.*, 1952). It is a flavivirus that spreads to people mainly through mosquito (*Aedes aegypti* and *Ae. albopictus*) bites. It can also be spread through sexual transmission and from a pregnant woman to her fetus. Most people infected with the Zika virus experience mild symptoms such as fever, rash, joint pain, or red eyes (CDC, 2019; Ojha *et al.*, 2018). Symptoms can last for several days to a week, but infected individuals usually do not require hospitalization. Once infected with Zika, a person is likely to be protected from future infections due to a robust immune response that includes the development of IgM antibodies and memory cells.

Watch the following video for an overview of the impact of Zika virus infection in the United States and its territories:

- *Zika in Babies in US Territories, August*. Running time: 0:56 min. Produced by CDC, 2018.  
<<https://youtu.be/j5zJ3Lm3frk>>

From reading the literature, it is clear that there is a dire need for effective therapeutics to combat Zika virus infection. Excitingly, as a way to accelerate drug development, your new research lab has taken a novel approach to fighting Zika virus by performing drug repurposing screens. This strategy identifies new uses for FDA-approved and investigational drugs that are outside the scope of the original medical indication. For example, drugs that have been approved for use to treat cancer, HIV, hepatitis C, etc., are tested for their effectiveness against other diseases, such as Zika. Since these drugs have already been demonstrated to be safe for use (via human clinical trials), they are less likely to fail safety standards, and the time frame of drug development is reduced. Thus, drug repurposing fast-tracks a drug's bench-to-bedside usage and saves substantial costs. Scientists from your lab recently published a paper where they performed a drug repurposing screen of ~6,000 approved drugs to identify compounds that either inhibit Zika virus infection or suppress infection-induced caspase-3 activity in different neural cells (Xu *et al.*, 2016). This high-throughput screen uncovered numerous active compounds against the Zika virus. For your first research project, you are tasked to look into these compounds and report back to the lab during your next meeting.



## Part II – PubChem

Now that you have a better understanding of the purpose and methodologies of the study, you can take a deep dive into the data. The researchers have deposited their screen results and assays in PubChem: <<https://pubchem.ncbi.nlm.nih.gov/>>. To access the data, use the PubChem search engine to search for BioAssay 1224859. Scroll down to the Protocol section.

### *Questions*

- Using the PubChem search results, describe how the researchers determined if a compound was active based on their screen.
- View the Data Table to explore the findings. How many active compounds were found in this assay?
- What is the potency range of the active compounds?



## Part IV – Future and Current Studies

8. Returning to PubChem BioAssay 1224859, select another active compound and list it below.
  - a. Why did you choose this compound? Has this compound been active in other screens?
  - b. What would you do next to test for the efficacy and selectivity of this compound particularly against Zika infection? (Propose an experiment that you could perform in your new lab and include your rationale behind the experiment. *Hint*: Look into what tests were done with the compound against its original target.)
  
9. Repurposing screens can be powerful tools for the “quick” identification of novel therapeutics, especially in fighting recently emerging viruses. One such novel virus, SARS-CoV-2, is the cause of the COVID-19 worldwide pandemic. Can you find information on PubChem for potential drugs that could be repurposed to combat COVID-19? Describe your workflow: how did you use PubChem to find these compounds/screens?
  
10. What was new to you in this activity? What is the significance of high-throughput screens such as these in the development of novel therapeutics?

## References

- Centers for Disease Control and Prevention (CDC). 2019. Zika virus [webpage]. <<https://www.cdc.gov/zika/index.html>>
- Centers for Disease Control and Prevention (CDC). 2021. Zika travel information [webpage]. <<https://wwwnc.cdc.gov/travel/page/zika-information>>
- Dick, G.W.A., S.F. Kitchen, and A.J. Haddow. 1952. Zika virus (I): isolations and serological specificity. *Transactions of The Royal Society of Tropical Medicine and Hygiene* 46(5): 509–20. <[https://doi.org/10.1016/0035-9203\(52\)90042-4](https://doi.org/10.1016/0035-9203(52)90042-4)>
- Ojha, C.R., M. Rodriguez, J. Lapierre, M.K. Muthu Karuppan, H. Branscome, F. Kashanchi, and N. El-Hage. 2018. Complementary mechanisms potentially involved in the pathology of Zika virus. *Frontiers in Immunology* 9: 2340. <<https://doi.org/10.3389/fimmu.2018.02340>>
- Xu, M., E. Lee, Z. Wen, *et al.*, 2016. Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen. *Nature Medicine* 22: 1101–7. <<https://doi.org/10.1038/nm.4184>>

*Internet references accessible as of September 27, 2021.*

