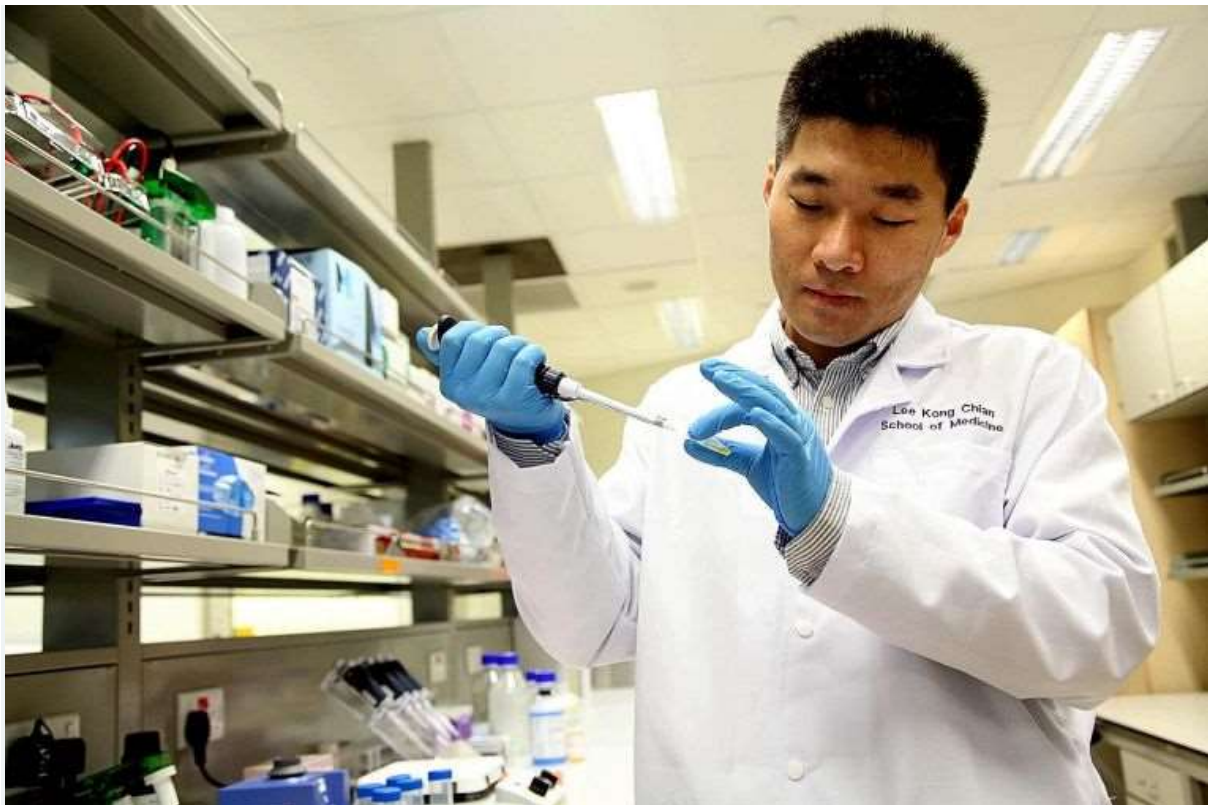


Small tweak leads to big dengue breakthrough for NTU team



Assistant Professor Luo Dahai's discovery is a significant step forward in the search for a potential drug to treat dengue and Zika. The scientist from NTU's Lee Kong Chian School of Medicine had put the quest on the backburner after repeated failures several years ago, but renewed interest when Zika broke out in 2016. PHOTO: NTU

NTU team finds that simple lab process used to engineer enzyme was negatively affecting results

[Samantha Boh](#)

A few years ago, scientists hit a wall in their quest to find a drug to treat dengue.

Despite trawling through millions of compounds, nothing seemed to have a hope of working against it and other related flaviviruses, like Zika. It took a break, and fresh eyes, for scientist Luo Dahai to expose a ray of hope.

He found that it was not the potential medicines which were at fault. Instead, a simple lab procedure used to engineer an enzyme in the test tube had gone awry.

It took Dr Luo and his team some time to tweak this process, and now his group at Nanyang Technological University (NTU) is developing new compounds which they hope can be developed into drugs to treat dengue and Zika.

"It's a fresh start," said Assistant Professor Luo, who is from NTU's Lee Kong Chian School of Medicine.

He is working with researchers from the Experimental Therapeutics Centre at the Agency for Science, Technology and Research (A*Star), the NTU School of Biological Sciences and Duke-NUS Medical School.

Flaviviruses cause a number of serious human diseases, including yellow fever, dengue, various types of encephalitis and hepatitis C. For years, Dr Luo had studied these viruses and how to inhibit them.

In particular, his team had focused their efforts on the NS2B-NS3 protease - an enzyme that digests viral proteins. Viral proteins are produced in a big chunk, he explained so, to work, they need to be cut into individual components.

Since flaviviruses need certain proteins to reproduce, the way to combat them is to somehow disrupt this process so that they will not be able to spread through their human host, or infect their next victim.

"If you find a way to kill the function of this enzyme, you stop the virus from replicating," he explained.

This had, until now, been a fruitless journey.

While potential compounds that could inhibit the function of the enzyme were identified, further tests on infected human cells and animal models were disappointing.

In 2013, Dr Luo put the effort on the backburner to focus on other projects. But when Zika broke out in 2016, he was motivated to give the research another go.

He and his team pored through literature on the subject to figure out what had been done and why there was no success. It struck him that for the last 15 years or so, an artificial linker - basically a string of amino acids - was used to create the NS2B-NS3 enzyme for laboratory experiments.

He did away with the artificial linker. Instead, he allowed the proteins to be produced as separate fragments, and then allowed them to combine naturally in cells.

"The idea is not special... We were just removing nine amino acids which were not supposed to be there," Prof Luo said.

This time, the process worked.

Papers on the findings were published in several scientific journals, including Science, over the past year.

For now, the team is revisiting compounds that were found to display some level of inhibition against the NS2B-NS3 enzyme in earlier dengue studies.

They have found some possible candidates and will be doing further experiments on the best five.

"We hope this will result in potent inhibitors and eventually antiviral drugs not just for dengue but for Zika and yellow fever as well," Prof Luo said.

Professor Ooi Eng Eong, deputy director of Duke-NUS Medical School's Emerging Infectious Diseases Programme, said the NTU finding is an important step forward in improving the understanding of how a key viral protein complex from the Zika virus works.

"Their findings provide new insights on how drugs can be designed to target this protein complex and disable its function," he added.

However, he noted that it will take some time for a drug to be developed.

"Although the findings are exciting and promising, successful development of a drug that targets this protein safely to inhibit Zika virus infection effectively, especially in expectant women, remains a very challenging task," Prof Ooi said.