

Small molecule hobbles dengue in vitro and in vivo

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A novel compound inhibits dengue virus, as well as other closely related important human pathogens. The research is published in the September 2011 issue of the journal *Antimicrobial Agents and Chemotherapy*.

Dengue virus causes an estimated about 50 million infections annually, resulting in half a million hospitalizations, and a 2.5 percent mortality rate, according to the <u>World Health Organization</u>. Neither antivirus therapy nor vaccines exist against dengue. The newly discovered inhibitor is also active against fellow flavivirus family members including <u>West Nile virus</u>, yellow fever virus, Japanese encephalitis virus, and tick-borne encephalitis virus. The compound works by preventing translation of RNA to protein, according to the report.

In the study, the researchers identified the small molecule inhibitor via high throughput screening of Novartis compound libraries, says corresponding author, Pei-Yong Shi of Novartis Institute for Tropical Diseases, Singapore. They then refined the original molecule to give it greater metabolic stability. Tests in a dengue mouse viremia model showed that "this compound significantly reduced peak viremia, demonstrating the in vivo efficacy of the inhibitor," according to the report.

However, despite the fact that the compound selectively inhibits protein translation in flaviviruses, in in vitro tests, it nonselectively inhibited viral and host translation. That raised the specter of side effects, and indeed, tripling the experimental dose in the mouse model caused



significant side effects, according to the report. Thus, the therapeutic window needs to be widened before the compound will be ready for clinical testing, the researchers report.

The compound is being developed under the auspices of the Novartis Institute for Tropical Diseases, which aims to develop novel therapeutics for neglected diseases, and to provide these new medicines to poor patients at cost prices," says Shi. "Dengue poses a public health threat to 2.5 billion people worldwide," most of them living in poverty or near poverty.

More information: Q.-Y. Wang, et al. 2011. A translation inhibitor that suppresses dengue virus in vitro and in vivo. <u>Antim. Agents</u> <u>Chemother</u>. 55:4072-4080

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