New approach to stopping Dengue fever

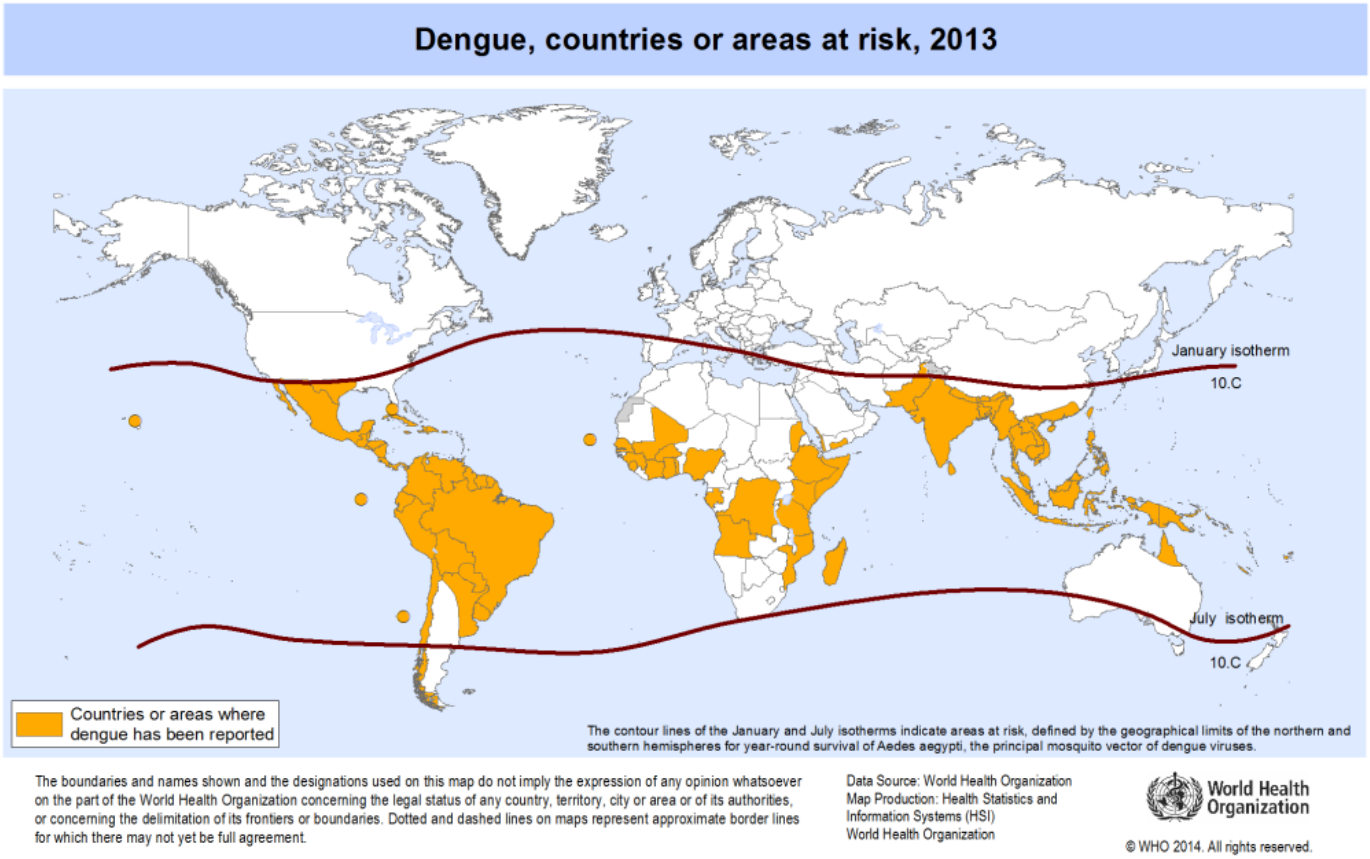
The virus that causes Dengue Fever, DENV, infects an estimated 390 million people per year, often leading to severe disease (used to be called Breakbone Fever for the pain it caused), hemorrhagic fever and often death. It's the fastest growing and most prevalent mosquito-borne virus in the world. Although a third of the world's population is at risk of infection, there currently aren't any effective antiviral treatments or vaccines.

A new study of the virus, led by Judith Frydman, a professor of biology and of genetics at Stanford, shows how disrupting a critical cellular pathway in the host can block the virus' life cycle at multiple steps. This strategy could offer novel therapies against Dengue virus, as well as other related human pathogens, such as West Nile Virus, Yellow Fever and Tick Borne Encephalitis.

DENV, like all RNA viruses, travels light, carrying only its genome coding for 10 proteins, and relies heavily on the host machineries to replicate. In particular, the infected host's cellular machinery that folds proteins, the so called “protein homeostasis “ or “proteostasis” machinery, is essential to produce and manage the viral proteome – the proteins that the virus expresses in order to survive and thrive in an infected host. This machinery consists of “molecular chaperones”, which, much like human chaperones, prevent inappropriate interactions and make proteins reach their mature and functional state. By studying how the cells proteostasis machinery is used by the virus, the Frydman lab obtained insights into a new and powerful strategy to fight viral infection.

Frydman’s group focused on Hsp70, a type of chaperone that is central to protein homeostasis. Hsp70’s main job is to help other proteins fold into their functional shape, and to then protect them from damage by environmental stresses. Hsp70 type proteins are present in almost all organisms. DENV, like many other viruses, also relies on Hsp70, in this case to help replicate the viral genome, and ultimately produce the viral proteins it needs to take control of the host cells and spread infection. By defining how Hsp70 components helps the virus replicate, the Frydman lab identified a strategy to block viral replication with very little toxicity to the host cell. In collaboration with the labs of Jason Gestiwicki and Raul Andino in UCSF and the lab of Ana Fernandez-Sesma in Mount Sinai, they tested a series of drugs that target the host activities required by the virus, and showed that the virus is much more dependent on this chaperone than the host. This produces a very good therapeutic window against the virus with little toxicity.

Most excitingly, inhibiting Hsp70 in human blood cells could block several strains of Dengue, without harming the host cells. This result provides a promising roadmap for addressing a virus for which there is currently no preventative treatment.



World Distribution of Dengue Fever in 2013 (from WHO)

A constant challenge with developing preventive therapies for DENV and other viruses, however, is that they can rapidly produce a mutant strain that becomes resistant to the drug. This also presents an opportunity for attacking the virus: Instead of hunting the virus itself, Frydman's team instead targeted one of the host's molecular networks upon which DENV relies. Restricting Hsp70 proves to be an attractive antiviral approach for a number of reasons.

First, because Hsp70 is involved in so many steps of the viral cycle, the virus could not produce mutant strains resistant to the drug, even after multiple attempts. This unusual lack of DENV drug-resistance to Hsp70-targetting compounds opens the way to both therapeutic and prophylactic use for short courses of treatment without losing effectiveness due to resistance, the major concern of most existing antivirals.

Secondly, because these compounds modulate Hsp70 rather than fully block its activity, they exhibit negligible toxicity to the relevant human target cells at concentrations that completely block

virus production.

Third, in the case of DENV, the antiviral dampened the release of virally-induced cytokines, which can contribute to severe forms of disease and create the “cytokine-storm” associated with haemorragic fever forms of Dengue.

Perhaps most promising, the compounds are effective against different serotypes of DENV and even different insect-borne flaviviruses, including West Nile virus, Yellow Fever and Tick Borne encephalitis. The broad spectrum action of these class of inhibitors suggest an antiviral strategy for pan-flavivirus antivirals with low potential for resistance.

These findings have major implications for our understanding of the interface between viral and chaperone biology, and provide a new way of thinking about strategies to develop a novel class of antivirals that will not be rendered ineffective by the emergence of drug-resistance. This unique property of targeting viral proteostasis therapeutically may close a fundamental gap in antiviral drug development.

Dr. Judith Frydman
Professor, Department of Biology
Stanford University, Stanford, CA
http://www.stanford.edu/group/frydman

Publication

Defining Hsp70 Subnetworks in Dengue Virus Replication Reveals Key Vulnerability in Flavivirus Infection.
Taguwa S, Maringer K, Li X, Bernal-Rubio D, Rauch JN, Gestwicki JE, Andino R, Fernandez-Sesma A, Frydman J
Cell. 2015 Nov 19