

# The Flavivirus NS1 protein: Unraveling Mechanisms of Pathogenesis of Dengue, Zika, and Beyond

The flavivirus nonstructural protein 1 (NS1) plays critical roles in immune evasion, virus replication, and pathogenesis. Here we show that NS1 proteins from multiple flaviviruses (dengue, Zika, yellow fever, West Nile, and Japanese encephalitis) trigger permeability in human endothelial cell lines from different tissues and induce vascular leak in mice in a tissue-specific manner that reflects disease tropism. This process is mediated by disruption of the endothelial glycocalyx-like layer and by remodeling of the intercellular junction complex. The specificity of NS1 interaction with endothelial cells is determined both by NS1 binding to glycans on the cell surface and by NS1 internalization via clathrin-mediated endocytosis. We also show how NS1 can facilitate virus dissemination by enabling viral passage across endothelial barriers. Finally, we identify cell binding determinants on NS1 as well as a conserved glycosylation site that is essential for internalization and therefore endothelial permeability. Together, this work describes the contribution of NS1 to disease pathogenesis due to vascular leak as well as virus dissemination and identifies and characterizes a new target for flavivirus therapeutics and vaccine strategies.

**Speaker:** **Prof Eva Harris**

**Division of Infectious Diseases and Vaccinology  
 Director, Center for Global Public Health  
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**Host:** **Prof Lok Shee Mei**

**Emerging Infectious Diseases Programme  
 Duke-NUS Medical School**

**Date:** **Wednesday, 29 May 2019**

**Time:** **12.00 PM - 1.00 PM**  
**(Light refreshments will be served at 11.30 AM)**

**Venue:** **Duke-NUS Medical School  
 Meeting Room 7C, Level 7**

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Dr. Eva Harris is a Professor in the Division of Infectious Diseases and Vaccinology in the School of Public Health and Director of the Center for Global Public Health at the University of California, Berkeley. She has developed multidisciplinary approaches to study the virology, pathogenesis, immunology, epidemiology, clinical aspects, and control of dengue, Zika, and chikungunya. Her work addresses viral and host factors that modulate disease severity and investigates immune correlates of protection and pathogenesis using *in vitro* approaches, animal models, and research involving human populations, the latter through long-term collaborations in Nicaragua. She has published over 265 peer-reviewed articles, as well as a book on her international scientific work. She was selected as a Pew Scholar and received a MacArthur Award, the Beijerinck Virology Prize, and a national recognition award from the Minister of Health of Nicaragua.



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