Plugging the Leak: Is DSS a case of "aseptic" shock?

Paul Young, Naphak Modhiran, Dan Watterson, David Muller and Kate Stacey

School of Chemistry & Molecular Biosciences, University of Queensland, Brisbane AUSTRALIA

In the absence of therapeutic treatment options for dengue virus infected individuals there is an ongoing and pressing need for antiviral drug development. We previously revealed that the highly conserved non-structural protein, NS1 activates cells via Toll-like receptor (TLR) 4, which *in vivo* may lead to an over-robust inflammatory response that contributes to vascular leak. We further showed that TLR4 antagonism inhibits NS1-mediated activation of peripheral blood mononuclear cells (PBMC) and NS1-induced vascular leak *in vitro,* and reduces dengue virus-induced vascular leakage in a mouse model. This discovery suggested that TLR4 antagonists could be effective in therapeutic intervention of dengue infection.

Given the considerable efforts made over the last 20 years to develop TLR4 antagonists as sepsis inhibitors, we explored the potential of re-purposing leading sepsis inhibitor candidates that have been through extensive clinical trials, as inhibitors of NS1-mediated TLR4 activation.

In addition, given the role that NS1 plays in mediating dengue induced pathology, we have also examined the therapeutic potential of antibodies specific for NS1 and the efficacy of prophylactic vaccine approaches employing NS1 as the immunogen.

Our group has been investigating the dengue virus NS1 protein for more than 30 years. We have progressed understanding of its role in virus replication, the value of its secreted form as a diagnostic biomarker, its role in the pathogenesis of severe disease and developed both therapeutic and vaccine approaches to infection control that target its function. This presentation will highlight some of our latest research on this rather enigmatic protein.