Singaporean Society for Immunology

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SgSI Seminar Series: Infectious Diseases

Date & Time: 20 November 2014 (Thursday), 4.30 - 5.45pm

*Venue: Aspiration, Matrix Level 2M, Biopolis

Host: Dr. Katja Fink, SIgN

Registration is based on first-come first-served.
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Dr. Sylvie Alonso

Associate Professor
NUS

Experimental In Vivo Model of Enhanced Dengue Disease Severity through Maternally Acquired Heterotypic Dengue Antibodies

Dengue (DEN) represents the most serious arthropod-borne viral disease. DEN clinical manifestations range from mild febrile illness to life-threatening hemorrhage and vascular leakage. Early epidemiological observations reported that infants born to DEN-immune mothers were at greater risk to develop the severe forms of the disease upon infection with any serotype of dengue virus (DENV). From these observations emerged the hypothesis of antibody-dependent enhancement (ADE) of disease severity, whereby maternally acquired anti-DENV antibodies cross-react but fail to neutralize DENV particles, resulting in higher viremia that correlates with increased disease severity. Although *in vitro* and *in vivo* experimental set ups have indirectly supported the ADE hypothesis, direct experimental evidence has been missing. Furthermore, a recent epidemiological study has challenged the influence of maternal antibodies in disease outcome.

Here, using the immuno-compromised AG129 mice that are Type I&II interferon (IFN)-receptors deficient mice, we have developed a mouse model of ADE where DENV2 infection of young mice born to DENV1-immune mothers led to earlier death which correlated with higher viremia, elevated pro-inflammatory cytokines and increased vascular leakage compared to DENV2-infected mice born to dengue naïve mothers. In this ADE model we demonstrated the role of TNF-α in DEN-induced vascular leakage. *In vitro* ELISA and ADE assays confirmed the cross-reactive and enhancing properties towards DENV2 of the serum from mice born to DENV1-immune mothers. Lastly, age-dependent susceptibility to disease enhancement was observed in mice born to DENV1-immune mothers, thus reproducing epidemiological observations.

More recently, we have established this ADE model in the Type I IFN receptor deficient A129 mice. Interestingly, while mice display early death, increased virus titers and elevated pro-inflammatory cytokines, no vascular leakage could be observed.

Overall, this work provides direct *in vivo* demonstration of the role of maternally acquired heterotypic dengue antibodies in the enhancement of dengue disease severity and offers a unique opportunity to further decipher the mechanisms involved.

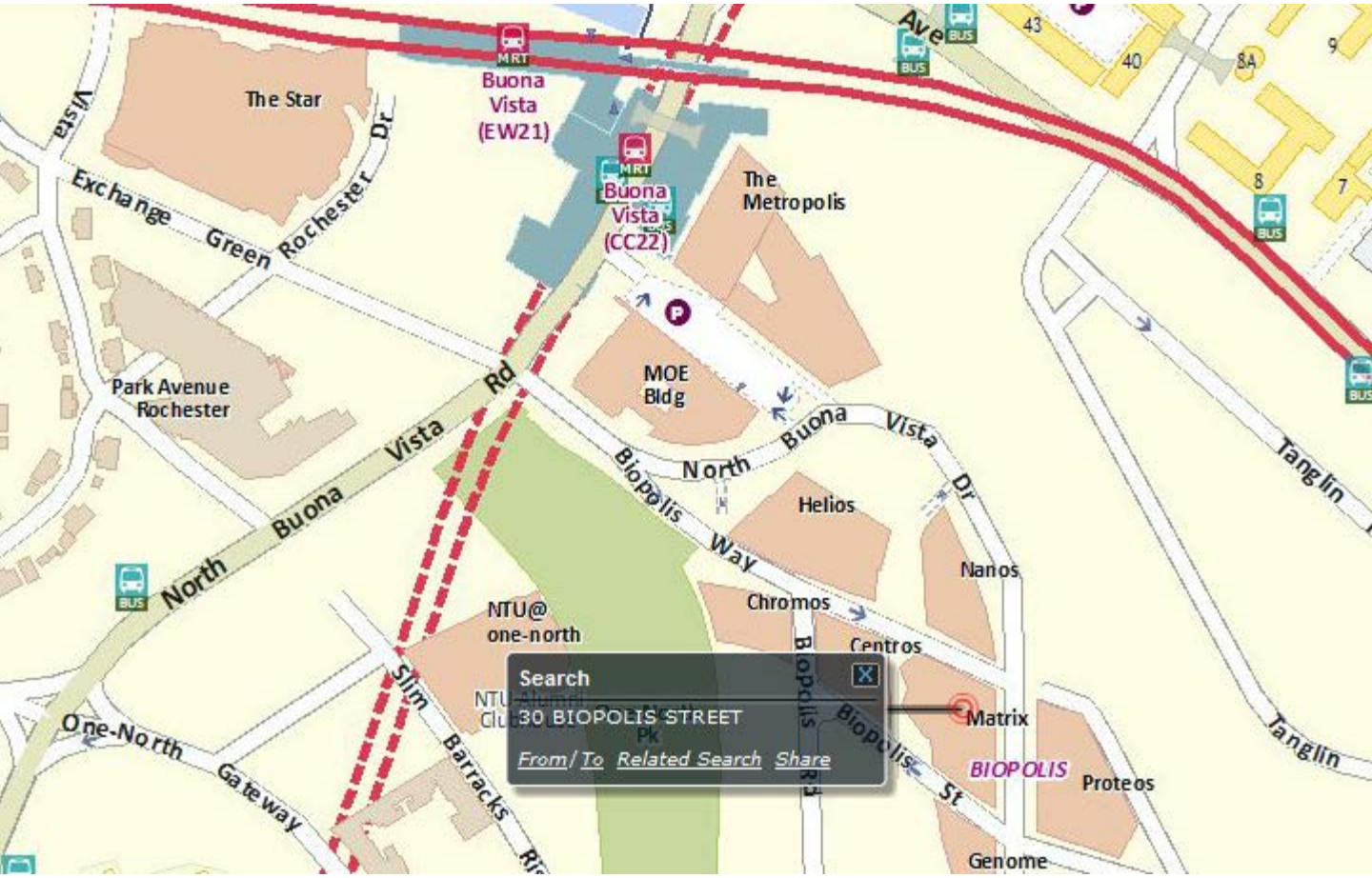
Dr. Eng Eong Ooi

Associate Professor
Duke-NUS

Dengue virus trims the interferon response for epidemic transmission

Dengue virus (DENV) is a positive-stranded RNA virus that causes frequent and recurrent epidemics throughout the tropical world. Multiple factors contribute to dengue epidemics. Epidemiological observations have identified the association between the emergence of novel DENV genotypes with epidemic dengue transmission. However, the mechanism by which differences in viral genome sequence result in competitive exclusion or virus survival for epidemic transmission, is unknown. We have been examining one such outbreak in Puerto Rico where the emergence of a new DENV-2 strain co-incided with the epidemic of 1994. Our findings suggest a role for subgenomic DENV RNA strands in modulating the interferon response during acute infection and provide new insights into the molecular epidemiology of dengue.

*Address: 30 Biopolis Street, Singapore 138671
Nearest Bus Stop: Buses 91, 92, 95, 74, 191, 196, 198, 200 (walk 5 min)
Nearest MRT Station: Buona Vista CC22/EW21 (walk 5 min)



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