Characterization of dengue-specific T cell responses in Hawaii and French Polynesia

Allison Imrie1, Munkhzul Sukhbaatar1, Janet Meeks1, Claudine Roche2, Van-Mai Cao-Lormeau2.
1Department of Tropical Medicine, Medical Microbiology, and Pharmacology, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, Hawaii; 2Institut Louis Malardé, Papeete, French Polynesia.

Corresponding author: Allison Imrie        imrie@cyllene.uwa.edu.au

Dengue is a mosquito-borne illness which is present in endemo-epidemic form throughout the year in much of the Pacific. The disease is caused by any one of four dengue viruses (dengue virus (DV) serotypes 1-4), RNA viruses of the family Flaviviridae. Most patients experience dengue fever and typically recover after about 5-6 days, but about 5-30% of cases develop the more severe dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). DHF/DSS frequently occurs during secondary infection with any of the 4 dengue viruses. Onset of the most severe symptoms occurs when viral load drops and fever remits, suggesting that the vascular leakage leading to shock is the result of immunopathology. We are studying the role of cross-reactive dengue-specific memory T cells and their capacity to produce excessively high or low levels of cytokines and other immunomodulatory molecules, when they are activated by heterologous dengue serotypes in a secondary infection. To do this we first need to characterize the nature of dengue-specific cell mediated immune responses in Pacific Islanders, whose HLA frequencies may be distinct from Asian and Caucasian populations, the most studied groups to date.

Between 2005-2007 we recruited individuals infected with dengue in Hawaii and French Polynesia between 1975 and 2001, with well described single or multiple DV1, DV2, and DV3 infections. Using a peptide library we synthesized based on the epidemic DV1 strain Hawaii2001, we mapped T cell epitopes in the dengue NS3 and NS5 genes, the highly conserved viral protease and RNR-dependent RNA polymerase, respectively. Responses were detected in 15/32 subjects up to 14 years after infection, measurable directly ex-vivo. We identified a highly immunodominant epitope at NS5_329-337, in 8 subjects, restricted by HLA B*5502, a molecule frequently expressed in Polynesian populations. Our current studies of dengue-specific T cell cross-reactivity focus on this response, and will be discussed. This is the first study of dengue-specific cellular immunity in Pacific Islanders.