M & I
Microbiology
and Immunology
University of North Carolina at Chapel Hill

DISSERTATION SEMINAR

Emily Gallichotte

"The Human Antibody Response to Denv2 Infection and Vaccination."

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2:00 p.m.
1131 Bioinformatics

Dissertation Advisors: Drs. Aravinda de Silva and Ralph Baric

Presented in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

ABSTRACT

Emily Gallichotte: "The Human Antibody Response to Denv2 Infection and Vaccination
(Mentors: Aravinda de Silva and Ralph Baric)

Dengue viruses (DENVs) are mosquito-borne flaviviruses that are estimated to infect 390 million people each year. Dengue is a major global public health concern because people infected with the virus can develop dengue fever or severe dengue hemorrhagic fever and shock syndrome. Vaccines offer the best hope for controlling the current global DENV pandemic. The major goal of my thesis project was to define the properties of neutralizing and protective human antibodies stimulated by natural DENV infections and the leading live attenuated DENV vaccines.

There are four antigenically distinct DENV serotypes, named DENV1 through DENV4. For my studies, I focused on DENV2 as a model to understand human protective immunity following infection or vaccination. Following natural DENV2 infections, individuals generate strongly neutralizing DENV2 serotype-specific antibodies, which provide protection against subsequent DENV2 infections. I characterized the properties and specific epitopes of multiple human DENV2 serotype-specific strongly neutralizing monoclonal antibodies, and discovered two major antigenic sites on domain III and domain I of the DENV2 envelope protein. Additionally, I found that the majority of DENV2 serotype-specific polyclonal antibodies present in immune sera also target quaternary epitopes as defined by these DENV2 monoclonal antibodies.

I sought to determine if DENV vaccination is able to elicit the same types of DENV2 antibodies implicated in protective immunity following natural infections. I observed that two different live DENV vaccines were able to elicit antibodies targeting epitopes similar to those targeted by antibodies following natural DENV2 infections, suggesting that these vaccines might be protective against DENV2 challenge.

Investigators studying DENV pathogenesis and vaccines had previously focused on the functional properties (neutralization) of human antibodies, with little consideration of the actual epitopes and mechanisms of protective immunity. Recent results from vaccine trials indicate that the mere presence of antibodies capable of neutralizing DENV in cell culture assays was not sufficient for protection from WT DENVs. My studies provide an in-depth view of the molecular specificity of serotype-specific human antibodies that neutralize DENVs. As a result of my thesis work, it is now possible to go beyond neutralizing antibodies and define the fine specificity and other properties of serotype-specific antibodies induced by infection or vaccination. My studies shed light on the protective immune response to DENV infections, which can ultimately be harnessed to evaluate current DENV vaccines, and improve the design of the next-generation of DENV vaccines.