Dengue viruses (DENV) include four serotypes (DENV-1 - DENV-4) that belong to the Flaviviridae family and cause one of the most significant arthropod-borne viral infections of humans with about 100 million infections and 25,000 deaths annually. DENV causes classic dengue (“break-bone”) fever (DF) and more severe and sometimes fatal dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS). In tropical and subtropical regions of Asia and the Americas, DF and DHF are among the most serious public health problems. The incidence and geographical distribution of these diseases has dramatically changed in the last few decades and dengue has started to affect several areas with temperate climates like the southern regions of the US and Europe. The World Health Organization (WHO) has estimated that the numbers of reported dengue cases worldwide has increased 30 fold in the last 50 years. No vaccines or drugs are currently available to control this disease and their development has been hampered by the lack of predictive animal models and the need for vaccines/therapies that are effective against all four viral strains. Vaccines against related flaviviruses (yellow fever and Japanese encephalitis) are available and this suggests that a vaccine against dengue should be feasible. Several experimental dengue vaccines are currently being evaluated in the clinic (mostly live-attenuated viruses) and have generated robust immunological responses, including neutralizing antibodies. Thus, they appeared promising as it was widely believed that the presence of neutralizing antibodies would be a correlate of protection. However the recent results of a Phase IIb trial of the most advanced vaccine under development (Sabchareon A., at al. Lancet 2012) indicated that that the overall vaccine efficacy was only 30.2 percent and the DEN 2 component of the vaccine was not effective at preventing disease. These findings revealed that significant knowledge gaps remain in understanding the immunological basis of protection against dengue.

The primary goal of this consultation was to review the progress, unexpected results, and known mechanism of protection of dengue vaccines. This two and a half day meeting featured presentations by subject matter experts from government agencies, academia, and industry who reviewed lead candidate dengue vaccines under development, mechanisms of acquired immune protection against dengue infection/disease, and pathogenic mechanisms of dengue infections that may impact protection. The meeting agenda can be found at this link: https://respond.niaid.nih.gov/conferences/denguevaccine2013/Pages/Agenda.aspx. A total of 168 scientists from 13 countries participated in this meeting.
Progress in several areas important to dengue vaccine development was reported during this meeting. Advances have been made in understanding the quality of immune responses that are required for dengue neutralization, factors that affect variability in dengue neutralization tests, and differences between type-specific and heterotypic immune responses. Researchers have identified new epitopes that are targeted by dengue neutralizing antibodies following vaccination or natural infection including some that target quaternary/structural epitopes that are only present on intact viral particles. Several presentations reviewed factors that affect dengue neutralization tests, including the structural heterogeneity of viral particles during propagation in cell culture, temperature in which particles are prepared, and the specific viral genotypes that are used. The role of T cells in vaccine-induced protection was discussed and data suggest that T-cell responses against non-structural dengue proteins can contribute to vaccine-induced protection and prevention of antibody-dependent enhancement of disease (ADE) in a mouse model. Progress was reported in the development of animal models for dengue including the development of improved mouse models and the use of salivary gland extracts in intradermal infection of mice to model mosquito bites. The latter part of the meeting focused on the role, risks, and benefits of dengue human challenge models to address questions that are important to the development of vaccines, including correlates of protection, dosing schedule, and durability of immune responses.

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