Dengue fever (DF) is a re-emerging disease caused by four serotypes of dengue virus which are transmitted by Aedes mosquitoes. Because of increased urbanization and travel, climate changes and decreased vector-control efforts, the incidence of DF has dramatically increased during the last 50 years causing an estimated 50 to 100 million cases per year worldwide, primarily in tropical and sub-tropical areas. While infection with one serotype of the virus confers life-long protection against the same serotype, it may enhance the severity of infection with a different serotype (immune enhancement). The more severe forms of the disease, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) cause significant morbidity and mortality especially in young children and no vaccines or drugs are currently available to treat or prevent infection. One of the main obstacles to the development of dengue therapies and vaccines has been the lack of animal models that faithfully recapitulate human pathogenesis and predict which immune responses protect from disease and which might cause enhanced disease.

NIAID, with support from the Office of Rare Diseases at the NIH, held a workshop on September 18-19. 2008 to discuss the animal models currently available for dengue, identify the most appropriate models to address different scientific questions and highlight the most promising models that should be further defined or developed. The workshop involved investigators from academia, government and industry that utilize dengue animal models to study the basic mechanisms of pathogenesis and to evaluate vaccines and antiviral drugs.

The first session of the workshop focused on dengue animal models currently available to study the mechanisms of dengue pathogenesis, including the phenomenon of immune enhancement. Several models were reviewed: humanized mouse models, interferon (INF) receptor-deficient mouse models (AG129), non-human primates and the Yucatan miniature pig. Although each of these models illustrated some aspects of dengue disease and immune enhancement, further studies should address viral replication, cellular and tissue tropism, immune responses and mechanism of pathogenesis. There was general consensus that new models need to be developed to recapitulate the full spectrum of dengue disease in an immune-competent host. Until more clinically relevant models are developed, clinical studies remain essential to answer important questions about the immune responses and pathogenesis of dengue.

The second session of the workshop focused on the review of models that are currently used to evaluate vaccines and therapeutics for dengue. Different steps of vaccine and drug development, including the evaluation of vaccine attenuation, efficacy and toxicology, require animal models with different characteristics. None of the dengue animal models currently available are ideal...
individually for regulatory purposes, but in combination they should be able to support the clinical evaluation of vaccines and therapeutics.

In summary, significant progress was presented on the development of several animal models for dengue; however it is clear that additional research needs to be done. Current animal models need to be further characterized to elucidate the mechanisms of pathogenesis and improved so they are more suitable for the evaluation of drugs and vaccines. New animal models are needed to fully recapitulate dengue disease in an immune-competent host. As research on animal model development is expensive and difficult to fund under basic grant mechanisms, workshop participants suggested that some NIH resources be dedicated to this important task through special funding programs or contract mechanisms. It was also suggested that the NIH take a leadership role in developing standardized sets of reagents and protocols for the research community to expedite progress in this area.