SUPPLEMENT ARTICLE

Dengue Human Infection Model: Introduction

M. Cristina Cassetti[1] and Stephen J. Thomas[2]

[1]Virology Branch, National Institute of Allergy and Infectious Diseases, Bethesda and [2]Viral Diseases Branch, Walter Reed Army Institute of Research, Silver Spring, Maryland

Dengue is an expanding public health problem in tropical and subtropical regions. An estimated 390 million infections occur annually, of which 96 million are clinically overt [1]. Transmission occurs between humans and *Aedes* vector species in endemic, hyperendemic, and/or epidemic patterns [2]. Multiple dengue virus (DENV) types cocirculate in most endemic regions with seasonal predominance of 1 or 2 DENV types in any given area [3]. The increasing dengue burden is driven by several factors including increased urbanization, world population growth, increased international trade and travel, and changes in human behavior that increase mosquito breeding sites (eg, discarded tires and plastic containers). Vector control has been largely unsuccessful at reducing transmission. There are no anti-DENV therapeutics to protect against or treat dengue infection and disease. Although there are numerous vaccine candidates in preclinical and clinical development, none have been licensed for use.

The world needs a dengue vaccine but several development challenges confront the field. First and foremost is the requirement to develop a multivalent vaccine to account for the multiple DENV types (DENV 1–4) capable of causing disease and death. Second are the complex immunologic processes that occur after wild-type infection. These processes are not well understood, making it difficult to predict what a protective immune response may be and to make vaccine development decisions [4, 5]. Third, no validated small animal or nonhuman primate model of dengue disease comprehensively approximates the human in vivo infection and disease experience [6, 7]. For these reasons and others, no immune correlate of protection has been defined. Because of this, vaccine developers are required to make inferences about a candidate's potential for clinical benefit based on its ability to protect a nonhuman primate from viremia after wild-type challenge and by measuring immunogenicity (ie, DENV type-specific neutralizing antibodies) in small to moderate-sized phase 1 and 2 studies. Dengue vaccinologists require development tools, which more accurately predict an immune profile's ability to prevent or significantly attenuate disease after natural infection [8–10]. The limited success of the world's first dengue vaccine efficacy trial underscores this need [11].

For this reason, vaccine and drug developers, immunologists, and entomologists are exploring the idea of a dengue human infection model (DHIM). The concept is to consistently produce, in healthy volunteers, an uncomplicated illness with clinical, biochemical, and immunologic findings consistent with dengue. The concept of a DHIM is not novel. The literature describes the development and use of DHIMs since the early 1900s [12–23]. Hundreds of volunteers have been experimentally infected with DENVs by means of various methods (ie, needle, mosquito) and administration strategies (ie, inoculation into subcutaneous space, mucous membrane exposure). Numerous seminal scientific discoveries and observations have been made using experimental human dengue infection including (but not limited to) the following: (1) identifying the viral etiology of dengue; (2) identifying transmission mechanisms; (3) defining viral incubation periods in mosquitoes and humans; (4) defining the period of infectivity in mosquito and humans; (5) describing the clinical and clinical laboratory features of uncomplicated dengue illness; (6) identifying the existence of multiple DENV types; (7) documenting the development of homotypic immunity after infection; (8) documenting the development of transient, heterotypic, cross-protective, and disease-attenuating immunity against other DENV types after infection with a single type; (9) demonstrating the development of anti-DENV

Correspondence: Director, Viral Diseases Branch, Walter Reed Army Institute of Research, 503 Robert Grant Ave, Silver Spring, MD (stephen.j.thomas3.mil@mail.mil).

The Journal of Infectious Diseases 2014;209(S2):S37–9

DOI: 10.1093/infdis/jiu061

neutralizing antibodies after exposure; and (10) supporting the development of early dengue vaccine candidates.

Recent dengue human infection studies have been used to explore serial ultrasonographic findings, characteristics of cellular immune responses, and the clinical and clinical laboratory findings after experimental infection of flavivirus-naive and previously vaccinated (experimental candidate) individuals [24–27].

In 2011, the Walter Reed Army Institute of Research (WRAIR) and the National Institutes of Health cosponsored a workshop designed to reintroduce the DHIM concept. The workshop was attended by dengue vaccine and drug developers, immunologists, entomologists, regulatory affairs personnel, and developers and users of the controlled malaria human infection model. This supplement reviews and documents the proceedings of that meeting, as follows.

Ken Eckels and Arthur Lyons of the WRAIR discuss aspects of the dengue human infection experiments executed by the US Army between 1999 and 2001. Eckels reviews the manufacturing and production process of DENV strains, DENV human infection strain candidate pedigree, and the attenuation process. Regulatory requirements and the process of creating and submitting investigational new drug applications to US Food and Drug Administration are also touched on. Lyons provides an overview of the clinical, biochemical, radiologic, virologic, and serologic findings and observations made by the WRAIR group during 2 human infection experiments (1999–2001). In experiment 1, investigators explored potential DENV human infection strains in flavivirus-naive individuals and selected DENV-1 and DENV-3 strains for continued testing based on safety and reactogenicity performance parameters. In experiment 2, investigators called back previous recipients of experimental tetravalent live virus dengue vaccines to receive challenge with either DENV-1 or DENV-3. Volunteers with postvaccination neutralizing antibodies against DENV-1 were assigned to be challenged with the DENV-1 human infection strain, and previous vaccine recipients who demonstrated a DENV-3 neutralizing antibody response were assigned to challenge with the DENV-3 strain. Two flavivirus naive controls were assigned to each group. Four articles describe the results of these experiments [24–27].

Timothy Endy from the State University of New York Upstate Medical University, Syracuse, discusses proposed DHIM performance parameters and reviews influenza human infection model performance and past dengue human infection experiments. He also proposes clinical and biochemical parameters that a DHIM should achieve to adequately support drug and vaccine development and basic science efforts.

Alan Rothman from the University of Rhode Island, Providence, reviews aspects of dengue immunology and its complexities. He also discusses potential uses of a DHIM to explore dengue immunology, with a focus on the exploration of immune correlates of protection, and reviews the limitations of a DHIM tool to explore basic immunology concepts.

James Whitehorn of the London School of Hygiene and Tropical Medicine, United Kingdom, describes the concepts presented at the meeting by Cameron Simmons, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam. Whitehorn also describes the use of a DHIM to support anti-dengue drug development; reviews the case for developing anti-dengue therapeutics, touching on current status; discusses the immunologic mechanism for how a prophylactic or therapeutic may work, and reviews DHIM limitations.

Christopher Mores, Louisiana State University, Baton Rouge, expands on the concept presented at the meeting by Jason Richardson, WRAIR that a mosquito-delivered dengue human infection strain could improve a DHIM. He discussed previous experience with mosquito-based human infection models and its immunologic implications and reviews the lessons learned and challenges of using mosquitoes in the context of human infection models and a DHIM specifically.

Michelle Spring, Armed Forces Research Institute of Medical Science, Bangkok, Thailand reviews the Controlled Human Malaria Infection Model (CHMI) as presented during the meeting by Mark Polhemus, Veterans Administration Medical Center, Syracuse, New York. The CHMI is now considered one of the most characterized and reproducible human challenge models, and it is commonly used to conduct an initial assessment of the efficacy of malaria vaccines before further evaluation in field studies and/or pediatric populations. Spring reviews how vaccine efficacy demonstrated using the CHMI model paralleled efficacy demonstrated in field studies, validating the utility of the human challenge model as an initial vaccine evaluation tool.

The growing global health burden of dengue disease and the ongoing challenges in developing vaccines and drugs against this infection have underscored the need for better models to elucidate the mechanism of dengue pathogenesis and evaluate interventions before large field efficacy trials. If successful, a DHIM could be used to study clinical and immunologic pathogenesis, explore virus-vector-host interactions, and inform vaccine and drug developers as they make development decisions. A DHIM could facilitate vaccine immunogenicity assay development and the optimization, qualification, and validation processes required for these assays to support regulatory strategies and product licensing applications. It could also help define a correlate and surrogate of protection, and once drug or vaccine safety and efficacy was proven in field testing in endemic settings, it could assist the process of bridging these data to nonendemic populations who may benefit from a therapeutic or vaccine (eg, travelers and military personnel).

Notes

Disclaimer. The opinions expressed herein are those of the authors and are not necessarily those of the US government, the National Institutes of Health (M. C. C.), or the Department of Defense (S. J. T.).

Potential conflicts of interest. Both authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature **2013**; 496:504–7.
2. World Health Organization. Dengue: Guidelines for diagnosis, treatment, prevention and control: new edition. Geneva, Switzerland: WHO, **2009**.
3. Gubler DJ. Dengue, urbanization and globalization: the unholy trinity of the 21st Century. Trop Med Health **2011**; 39:3–11.
4. Rothman AL. Dengue: defining protective versus pathologic immunity. J Clin Invest **2004**; 113:946–51.
5. Rothman AL. Immunity to dengue virus: a tale of original antigenic sin and tropical cytokine storms. Nat Rev Immunol **2011**; 11:532–43.
6. Zompi S, Harris E. Animal models of dengue virus infection. Viruses **2012**; 4:62–82.
7. Cassetti MC, Durbin A, Harris E, et al. Report of an NIAID workshop on dengue animal models. Vaccine **2010**; 28:4229–34.
8. Thomas SJ. The necessity and quandaries of dengue vaccine development. J Infect Dis **2011**; 203:299–303.
9. Thomas SJ, Endy TP. Critical issues in dengue vaccine development. Curr Opin Infect Dis **2011**; 24:442–50.
10. Thomas SJ, Endy TP. Vaccines for the prevention of dengue: development update. Hum Vaccin **2011**; 7:674–84.
11. Sabchareon A, Wallace D, Sirivichayakul C, et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. Lancet **2012**; 380:1559–67.
12. Graham H. Dengue: a study of its mode of propagation and pathology. Med Rec New York **1902**; 61:204–7.
13. Graham H. The dengue: a study of its pathology and mode of propagation. J Trop Med **1903**.
14. Ashburn P, Craig C. Experimental investigations regarding the etiology of dengue fever. J Infect Dis **1907**; 4:440–75.
15. Cleland JB, Bradley B, Macdonald W. Further experiments in the etiology of dengue fever. J Hyg (Lond) **1919**; 18:217–54.
16. Siler JF, Hall MW, Hitchens AP. Dengue: its history, epidemiology, mechanism of transmission, etiology, clinical manifestations, immunity, and prevention. Philippine Islands Bureau of Science monograph 20. Manila, Philippines: Bureau of Printing, **1926**.
17. Simmons JS, St. John JH, Reynolds FoHK. Experimental studies of dengue. Manilla: Bureau of printing, **1931** Philippine islands Bureau of science.
18. Sawada T, Sato H, Sai S. On the experimental dengue infection in man. Nippon Igaku **1943**; 3324:529–31.
19. Sabin AB, Schlesinger RW. Production of immunity to dengue with virus modified by propagation in mice. Science **1945**; 101:640–2.
20. McCoy O, Sabin AB. Dengue. Preventive medicine in World War II. Washington, DC: Office of the Surgeon General, **1946**:29–62.
21. Hotta S. Experimental studies on dengue. I. Isolation, identification and modification of the virus. J Infect Dis **1952**; 90:1–9.
22. Sabin A. Research on dengue during World War II. Am J Trop Med Hyg **1952**; 1:30–50.
23. Yaoi H. A summary of our studies on dengue. Yokohama Med Bull **1958**; 9:1–20.
24. Sun W, Eckels KH, Putnak JR, et al. Experimental dengue virus challenge of human subjects previously vaccinated with live attenuated tetravalent dengue vaccines. J Infect Dis **2013**; 207:700–8.
25. Gunther VJ, Putnak R, Eckels KH, et al. A human challenge model for dengue infection reveals a possible protective role for sustained interferon gamma levels during the acute phase of illness. Vaccine **2011**; 29:3895–904.
26. Statler J, Mammen M, Lyons A, Sun W. Sonographic findings of healthy volunteers infected with dengue virus. J Clin Ultrasound **2008**; 36:413–7.
27. Mammen M, Lyons A, Innis B, et al. Evaluation of dengue virus strains for human challenge studies. Vaccine. In press.