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Axel T. Lehrer
University of Hawaii, USA

Teri-Ann S. Wong
University of Hawaii, USA

Michael M. Lieberman
University of Hawaii, USA

Chih-Yun Lai
University of Hawaii, USA

Eleanore Chuang
University of Hawaii, USA

See next page for additional authors

Authors

Axel T. Lehrer, Teri-Ann S. Wong, Michael M. Lieberman, Chih-Yun Lai, Eleanore Chuang, David Clements, Jaime Horton, Oreola Donini, Theodore W. Randolph, Kendall B. Preston, Liana O. Medina, and Thomas W. Geisbert

DEVELOPMENT OF A THERMOSTABLE, MULTIVALENT FILOVIRUS VACCINE BASED ON RECOMBINANT SUBUNIT PROTEINS

Axel T. Lehrer, University of Hawaii
lehrer@hawaii.edu
Teri-Ann S. Wong, University of Hawaii
Michael M. Lieberman, University of Hawaii
Chih-Yun Lai, University of Hawaii
Eleanore Chuang, University of Hawaii
David Clements, Hawaii Biotech, Inc.
Jaime Horton, Hawaii Biotech, Inc.
Oreola Donini, Soligenix, Inc.
Theodore W. Randolph, University of Colorado, Boulder
Kendall B. Preston, University of Colorado, Boulder
Liana O. Medina, University of Texas Medical Branch
Thomas W. Geisbert, University of Texas Medical Branch

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Ebola Virus Disease (EVD) is the most prominent example of filovirus disease but despite being characterized as a Category A Priority Pathogen by NIH/NIAID over a decade ago, it lacked public and private research resources due to the absence of a commercial market. Transmission from wild animals into the human population typically causes outbreaks of limited scale in endemic areas located in the forested regions of Central Africa and the Philippines (for *Reston ebolavirus*). In the past decade, a *Zaire Ebolavirus* (EBOV) outbreak causing more than 11,000 deaths in several West African countries started to reveal the true epidemic potential that filovirus infections can have when entering an urban setting in a highly mobile society. In addition a persistent outbreak in the Democratic Republic of the Congo has continued since August 2018 despite significant progress with the clinical development of several EBOV vaccine candidates (one of which recently gained regulatory approvals in Europe, the U.S. and several African countries) and the advanced testing of promising EBOV specific therapeutics. Despite this significant progress, additional research is needed in particular on understanding the mechanism of protection and defining immune correlates of protection for Ebola and other filoviruses do develop fast and efficacious strategies for outbreak control as the incidence of outbreaks and total case numbers has significantly increased over the last decades.

For our multivalent filovirus vaccine candidate, we have developed scaleable production methods using antigen-specific immunoaffinity chromatography methods to produce well-characterized lots of soluble recombinant filovirus glycoproteins (GP) from EBOV, *Marburg marburgvirus* (MARV) and *Sudan ebolavirus* (SUDV) using stably transformed *Drosophila* (S2) cells. Yields and stability of purified antigens are promising and the immunogenicity of highly purified recombinant subunits and admixtures formulated with or without clinically relevant adjuvants was demonstrated in mice, guinea pigs and macaques. Strong antigen-specific IgG titers as well as virus neutralizing titers are observed after administering two or three doses of adjuvanted formulations. Since being able to demonstrate that both humoral and cell-mediated immunity are elicited by recombinant GP and protection has been demonstrated in rodents, our formulation development is mainly driven by immunogenicity and efficacy testing in non-human primates.

Recent challenge studies using the “gold-standard” cynomolgus macaque models demonstrate that vaccination with formulations of recombinant EBOV, MARV or SUDV subunits and an emulsion-based adjuvant consistently produce high anti-EBOV IgG and virus neutralizing titers. Such vaccination prevents viremia subsequent to live virus challenge with the homologous live virus and protects animals from terminal filoviral disease. Most importantly, we also demonstrated promising durability of protection of our monovalent EBOV vaccine candidate. Currently ongoing work being discussed focuses on the development of bi- and trivalent vaccine formulations and the testing of thermostable formulations containing recombinant subunits as well as the adjuvant in a single vial.

Our results demonstrate that formulations based on insect cell expressed subunit can be used to produce thermostable, multivalent and durable vaccines for protection against high-consequence pathogens which are highly immunogenic in multiple animal species and are capable of providing effective vaccine protection against live virus challenge.