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SUPPLEMENT ARTICLE

Whole-Inactivated and Virus-Like Particle Vaccine Strategies for Chikungunya Virus

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Chikungunya virus (CHIKV) is a global public health threat, having been identified in >60 countries in Asia, Africa, Europe, and the Americas. There is no cure for or licensed vaccine against CHIKV infection. Initial attempts at CHIKV vaccine development began in the early 1960s. Whole-inactivated and virus-like particle (VLP) vaccines are 2 of the current approaches being evaluated. Success of these approaches is dependent on a safe, well-tolerated vaccine that is immunogenic and deployable in regard to manufacturing, stability, and delivery characteristics.

Keywords. chikungunya virus; vaccine; whole-inactivated vaccine; virus-like particle vaccine; alphavirus.

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus in the family *Togaviridae* that causes a febrile, systemic illness associated with disabling polyarthralgias [1]. CHIKV is a global public health threat for which a preventive vaccine is needed. Initial attempts at vaccine development for CHIKV began in the early 1960s, after the virus was isolated from a member of the Makonde tribe in Tanzania in 1952 [2–5] and identified by the East African Virology Research Institute (now the Ugandan Virology Research Institute). CHIKV has reemerged sporadically roughly every 2 to 50 years [6, 7]. Notably, a 2005 outbreak that started in Kenya and spread across the Indian Ocean mainly by viremic travelers was found to have been propelled by a specific mutation in the E1 protein that increased the viral infectivity of the *Aedes albopictus* vector, enabling broader dissemination of CHIKV [8]. Vaccine development efforts in turn were reignited; CHIKV vaccine candidates using diverse platforms emerged, including live-attenuated vaccines, which were immunogenic but accompanied by arthralgia in clinical trials [9, 10]; recombinant modified vaccinia Ankara, measles, and adenovirus-vectored vaccines [11–14]; a chimeric alphavirus vaccine [15, 16]; and DNA vaccine candidates [11, 17–19]. Herein, we focus discussion on 2 additional platforms for CHIKV vaccine development: whole-inactivated and virus-like particle (VLP) approaches.

WHOLE-INACTIVATED VACCINES

Whole-inactivated vaccines may provide an enhanced safety profile over traditional live vaccines as the inactivated viral pathogen is inactivated and thus nonreplicating and cannot revert to its virulent form [20, 21]. Whole-inactivated antiviral vaccines are currently licensed for polio, hepatitis A, Japanese encephalitis, influenza, and rabies, and a Vero cell culture–derived whole-virus inactivated Ross river virus vaccine has successfully advanced to phase 3 clinical trial evaluation [22]. Virus inactivation is achieved through chemical or physical methods; however, the inactivation process has the potential to alter viral epitopes and adversely affect immunogenicity because the native structure of the viral antigen is not always maintained. In turn, administration of multiple doses, booster injections, or the addition of adjuvant is often required to achieve protective humoral immune responses [20].

Beginning in the early 1960s, inactivation of CHIKV has been achieved through formalin, β-propiolactone, 1,5 iodonapthyl azide, binary ethyleneimine, or UV irradiation, enabling evaluation of whole-inactivated CHIKV vaccine candidates in preclinical trials [4, 23–26]. A formalin-inactivated CHIKV vaccine prepared in African green monkey tissue culture was previously evaluated in 16 healthy adults and shown to be well tolerated and immunogenic [4]. More recently, a Vero cell–cultured, formalin-inactivated Alhydrogel-adjuvanted CHIKV candidate vaccine based on the East-Central-South African CHIKV strain isolated during the 2006 epidemic in India was shown to elicit high-titer enzyme-linked immunosorbent assay (ELISA) and neutralizing antibodies in mice [27].

VLP VACCINES

VLP vaccines consist of self-assembled viral structural proteins that mimic the conformation of wild-type virus [28]. By displaying antigenic epitopes that resemble wild-type virus in

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a high-density display, VLP vaccines are immunogenic and induce highly neutralizing antibody titers [29]. VLPs provide an enhanced safety profile as they are nonreplicating, noninfectious constructs. Because live virus is not used in manufacturing, neither viral attenuation nor viral inactivation is needed during vaccine production, and this also enables low-containment manufacturing. VLP vaccines have been used against hepatitis B virus and human papillomavirus, and at least 2 VLP candidate vaccines are being evaluated for CHIKV [30–32].

One mammalian cell–produced CHIKV VLP candidate vaccine is in advanced clinical development following encouraging preclinical and early phase clinical evaluation. Expression vectors encoding the CHIKV structural proteins (C-E3-E2-6K-E1) from the West African CHIKV strain 37 997 transfected into 293 T HEK cells result in the production of VLPs that resemble wild-type virus with E1 and E2 glycoproteins organized into heterodimers [31]. In preclinical testing in nonhuman primates, this VLP vaccine generated neutralizing antibody to both homologous and heterologous CHIKV strains and provided protection from viremia in a live CHIKV challenge model; the mechanistic correlate of protection was demonstrated to be CHIKV-specific neutralizing antibody [31].

In 2011, this CHIKV VLP nonadjuvanted vaccine candidate was evaluated in phase 1 testing in 25 healthy adults ages 18–50 years. The vaccine was well tolerated and without dose-limiting toxicity. Subjects received a 3-dose regimen of either 10, 20 or 40 mcg at weeks 0, 4 and 20 by intramuscular injection. All subjects developed robust neutralizing antibody titers following the first or second vaccination (geometric mean titers of the half maximum inhibitory concentration, 2688 in the 10-μg group, 1775 in the 20-μg group, and 7246 in the 40-μg group), as well as durable humoral responses that persisted at least 6 months following completion of the regimen [33]. Neutralizing antibody titers, assessed by a previously described reproducible, quantitative assay [34], reached levels inferred to be protective following natural infection [35, 36], by comparison to human convalescent neutralizing antibody responses in the same assay. Based on this phase 1 safety and immunogenicity data, the 20-μg dose on a 0- and 1-month schedule was advanced into phase 2 evaluation in a randomized, placebo-controlled trial in CHIKV-endemic regions of the Caribbean (Clinicaltrials.gov NCT02562482).

EFFICACY EVALUATIONS

A promising vaccine could be used in outbreak settings where attack rates are high in relatively naive populations. Approaches to evaluate efficacy of a vaccine against an emerging viral disease that may be sporadic in nature may include a traditional randomized controlled trial or the "ring" vaccination approach, which was recently successfully used in the West African Ebola epidemic [37]. Complications related to efficacy evaluation in the context of sporadic outbreak include issues related to subclinical infections masking cases of disease [38] and difficulties in defining the primary source of exposure in the case of mosquito and human vector.

Efficacy data will contribute to the demonstration and validation of a correlate of immunity. The CHIKV envelope antigens are highly immunogenic in several platforms; there is good evidence that neutralizing antibody activity is a correlate of immunity. Therefore, it appears that vaccine development is biologically feasible. If this can be proven in human field trials, it may be feasible to license vaccines on the basis of their safety and immunogenicity.

SUMMARY

CHIKV represents a rapidly emerging global infection in which the debilitating arthritis and high attack rates create a public health imperative to develop a safe and effective vaccine. In addition to people living in CHIKV-endemic regions, target populations include travelers and guest workers, such as military personnel, in such regions. Just as the epidemic has spread in Asia because of the extended range of the *A. albopictus* mosquito, it is likely that similar adaptations will eventually occur in the Americas to extend the scope of that epidemic, so the relevant populations for vaccination may also expand.

Ultimately, a successful vaccine will need to be well tolerated, safe, devoid of significant vaccine-associated adverse events such as arthralgia or arthritis, and induce high levels of durable efficacy in the general population. In addition, it will need to have manufacturing, stability, and delivery characteristics that make it cost-effective. Whole-inactivated vaccine approaches may have relatively low manufacturing costs, but the virus would have to be grown under high-level containment, and steps would need to be taken to ensure that antigenicity is not altered by the inactivation process. VLP vaccines have the advantage of maintaining authentic structures and antigenicity and are very safe. If they can be produced efficiently and achieve sufficient stability, they would serve as ideal immunogens. Both the whole-inactivated and VLP-based approaches can induce high levels of antibody, but they may require more than a single dose for optimal immunogenicity. Conversely, replication-competent chimeric or vectored approaches may induce a lower level of antibody but may achieve maximal immunogenicity after a single dose, and therefore, if effective, could also be suited for outbreak intervention, using a ring vaccination approach. Accordingly, it will be important to advance >1 vaccine technology platform into field testing to provide the data needed to determine approaches that best fit the public health needs of a particular region or population.

Notes

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