



Discussion

Summary and recommendations from a National Institute of Allergy and Infectious Diseases (NIAID) workshop on “Next Generation Herpes Simplex Virus Vaccines”



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At an NIAID workshop entitled “Next Generation Herpes Simplex Virus Vaccines: The Challenges and Opportunities” on October 22–23, 2012, researchers agreed that there was a great medical need for a herpes simplex virus (HSV) vaccine and recommended increased focus on all stages of herpes vaccine research, development, and testing, including basic vaccine discovery research, development and manufacturing of vaccines, human immunology, and clinical trials. While the need for an HSV vaccine has been recognized for decades, in the last 17 years only recombinant HSV glycoprotein D (gD) alone or with gB has been tested in randomized, double-blind, placebo controlled human trials to prevent genital herpes. In 2012, the results of the Herpevac Trial for Women, the largest HSV vaccine trial to date, involving over 8000 women who were seronegative for HSV-1 and HSV-2 were reported. The vaccine failed to reach its primary endpoint, reduction in occurrence of genital herpes disease due to either HSV-1 or HSV-2. While there was modest reduction in HSV-1 genital disease, there was no reduction in HSV-2 genital disease. The goal of the meeting was to reassess the status of the field, identify gaps in knowledge, and propose new approaches and solutions to fill the gaps.

The medical need for a herpes vaccine was summarized as:

1. *Morbidity caused by herpes infections.* There are 500,000 cases of oral herpes and 300,000 cases of genital herpes each year in the US. These include 20,000 cases of ocular herpes and 1500 cases of central nervous system disease. Acute herpetic disease causes discomfort and psychological burden in immunocompetent individuals, but serious disseminated disease can occur in immunodeficient or immunosuppressed individuals. The burden of HSV-2 infection is greatest among African-Americans with 59% infected by the ages of 40–49, indicating an important health disparity.

2. *Risk of vertical transmission to neonates.* There are 1500 cases of neonatal herpes each year in the US. Neonates infected during delivery continue to have life-threatening disease, and this increases the need for Cesarean sections in mothers with new genital herpes infection.
3. *Increased risk of HIV infection.* The risk of transmission of HIV-1 is increased by 4-fold if the HIV-infected individual is HSV-2 seropositive and the risk of acquisition of HIV-1 is increased by 2–3-fold if the HIV-uninfected individual is HSV-2 seropositive. Thus, an effective HSV vaccine should help to reduce the spread of HIV. Another indirect approach to reduce HIV infection, male circumcision, has previously shown to be effective.

The challenges facing development of next-generation herpes vaccines that were identified and the recommendations proposed to address these were as follows:

1. The participants identified difficulties in comparison of the results of vaccine studies and immunologic assays between different investigators due to a lack of standardized reagents and assays, including an HSV antibody neutralization assay. Efforts should be made to develop standardized reagents for preclinical vaccine development including challenge virus stocks, immunogens, adjuvants, and sera with known HSV neutralizing activity. These reagents should be made broadly available to the research community. NIAID’s Resources for Researchers program offers a variety of resources that can be explored for this purpose (<http://www.niaid.nih.gov/labsandresources/resources/Pages/default.aspx>).
2. The participants noted that different experimental endpoints are often used to study vaccine candidates in animal models compared with the endpoints used in clinical trials in humans. They recommended that animal studies utilize endpoints that more closely match those used in clinical trials. In addition, it is known that the immune system of humans has many differences from that of small animals, and this can result in different virus–host cell interactions. The participants recommended that additional animal models be developed. These models should more closely mimic human infection and the human immune response to

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¹ On behalf of the workshop participants listed in [Appendix A](#).

the virus and help to identify correlates of protection both for infection and for disease. Different vaccine candidates should be compared in animal models. In particular, comparisons should be made with vaccines that have already been tested in human clinical trials, rather than simply with placebos.

3. Efforts should be made to help facilitate the development and manufacturing of select vaccines. NIAID's Vaccine Development Services (<http://www.niaid.nih.gov/LabsandResources/resources/dmid/vaccine/Pages/default.aspx>) may help to further these efforts. NIAID's Vaccine Development Services include safety and toxicity testing, non-clinical immunogenicity and efficacy studies, process development, pilot and cGMP manufacture, and several other services. This NIAID program is designed to fill critical gaps in a product development plan. The goal is to assist the process of vaccine development by providing support which will de-risk the process at key points in order to advance products that address public health needs.
4. The participants recognized the need for clinical testing of additional vaccine candidates, in part through the use of smaller iterative clinical trials to hone vaccine design. This would be greatly aided by developing a better understanding of the natural history of herpes infection. Several recommendations were made to assist in this effort:
 - (a) Adaptive clinical trial design to accelerate the testing of more vaccine candidates.
 - (b) Clinical trials in populations at high-risk for infection with HSV to obtain preliminary data on efficacy.
 - (c) A laboratory infrastructure to identify immune parameters that correlate with protection from HSV disease, shedding or infection.
 - (d) Design of HSV vaccine trials to capture data both on genital infection or disease and on rates of HIV acquisition or transmission.

These studies could be considered for incorporation into existing clinical trial networks or sites.

5. More detailed immunologic analyses of samples from previous trials should be performed (e.g., might include the Herpevac Trial for Women).
6. The participants felt that an HSV Vaccine Working Group should be established. This Group would be made up of researchers from academia, government, and industry to promote public-private partnerships, to decide on needed common preclinical and clinical reagents and prototype animal models, to help design clinical trials, and to promote a forum for continuing discussion of HSV vaccine development.

Finally, the meeting chairs, Lawrence Corey and David Knipe, summarized that the workshop highlighted both the need and the potential for developing a safe and effective HSV vaccine. HSV offers a unique opportunity to study the host–viral interactions of a persistent viral infection in humans. Novel interactions of HSV-2 with the host have been demonstrated in both human and animal models and offer windows into new insights into the pathogenesis of this virus and host immune responses. Translating these observations into effective HSV vaccines is the challenge. The most rapid path to the optimal prophylactic and therapeutic herpes vaccines will require intensified efforts in both animal models and human studies to understand the mechanisms of immunization and identify the optimal immunogen(s), the types of immune responses induced, and the correlates of protective immunity. Increased academic, industrial, and government collaboration and partnerships

are needed. Industry has highlighted the importance of “de-risking” their investment, as correlates of protection for either a prophylactic or therapeutic vaccine are as yet undefined. Evaluation of novel prophylactic vaccines has potential to help stem the high acquisition rate of HSV-2 in adolescent populations in sub-Saharan Africa that poses a growing health concern. Existing clinical trials networks may offer the infrastructure to facilitate evaluation of novel vaccines. The academic community can provide the scientific leadership for such efforts. Conversely, the academic sector needs the expertise of industry to develop and manufacture novel immunogens for clinical trials. This “Global Alliance” is needed to accelerate the development of herpes vaccines. The establishment of a Herpes Vaccine Working Group and the implementation of the recommendations from the workshop will enhance the pace of research toward an efficacious herpes simplex virus vaccine.

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Conflict of interest statement

DMK is a consultant to Sanofi Pasteur and coinventor of a patent covering the use of replication-defective mutants as herpes simplex vaccines, which has been licensed by Harvard University to Sanofi Pasteur.

LC reports holding stock in Immune Design, and is a co-inventor on several patents associated with identifying T-cell antigens to HSV-2 that are directed at an HSV-2 vaccine. J.I.C. has a Cooperative Research and Development Agreement (CRADA) with Sanofi Pasteur that provides funding to evaluate an HSV-2 vaccine in a clinical trial, and a CRADA with Immune Design Corporation that provided funding to test a therapeutic HSV-2 vaccine in an animal model. CDD reports no conflicts of interest.

Appendix A. List of workshop participants

Elizabeth Adams, Jeff Alexander, Kenneth Bagley, Lynn B. Barclay, Christopher Beisel, Abbie Bellamy, Robert Belshe, Lbachir BenMohamed, David Bernstein, Nigel Bourne, Heather Bradley, Nathalie Broutet, Jill Brown, David Burns, Cathy Cai, Danilo Casimiro, Mark Challberg, Cara J. Chrisman, Jeffrey I. Cohen, Lawrence Corey, Hagit David, Carolyn Deal, Simon Delagrave, Walla Dempsey, Betty Dodet, Lesia Dropulic, Emily Erbelding, Marian Ewell, Ali Fattom, Anthony Fauci, Neil Finlayson, Doran Fink, Jessica Flechtner, Timothy Fouts, Harvey Friedman, Ulrich Fruth, Gary Fujii, Anne Gershon, Jonathan Glock, Jennifer L. Gordon, Heather Greenstone, Dennis L. Guberski, Susan Guerry, Marc Gurwith, Barbara Hahn, William Halford, Thomas C. Heineman, Seth Hetherington, Thomas Hiltke, David M. Knipe, David Koelle, Philip R. Krause, Philip LaRussa, Catherine Laughlin, Peter Leone, Daniel Li, Douglas Lowy, Lauri Markowitz, Gregg N. Milligan, Tulin Morcol, Luwy Musey, Anthony Nesburn, Deborah Palliser, Dorothy L. Patton, Carlos V. Paya, Christine Posavad, Elizabeth Rogers, Kenneth L. Rosenthal, Susan L. Rosenthal, Robert P. Ryall, George R. Siber, Jonathan Smith, Deborah Spector, Sean M. Sullivan, Shuang Tang, Anna Wald, Ken-ying Wang, D. Heather Watts, Lisa L. Wei, Richard Whitley, Peter Wolff, Kejian Yang.