Herpes simplex virus vaccines

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Herpes simplex virus (HSV) types 1 and 2 cause herpes labialis and genital herpes respectively, although genital herpes caused by HSV-1 is increasing in adolescence. Adult HSV-1 seroprevalence in western countries is 55% to 80% (80% in Australia) and acquired in two peaks, in infancy and adolescence. HSV-2 seroprevalence is highly variable geographically, reaching 12% in Australian adults but up to 90% in African countries[1,2]. After initial HSV-1 or 2 infection, asymptomatic shedding occurs in the mouth and genital tract respectively in nearly all infected subjects. Complications of HSV-1 include keratitis and blindness and life-threatening encephalitis. Severe complications of HSV-2 include acute urinary retention, meningitis and neonatal herpes (25% fatality). In addition, prior infection with HSV-2 consistently enhances HIV acquisition three- to fourfold. In immunosuppressed persons, HSV-1 and 2 may cause indolent ulcers, oesophagitis and pneumonia. Ultimately, a childhood vaccine effective against both HSV-1 and 2 disease is needed.

An effective HSV vaccine has been sought for more than 50 years. Inactivated, subunit or attenuated HSV vaccines were ineffective. Theoretically, a vaccine which prevents all aspects of the HSV-1/2 infectious cycle is required, that is, to prevent initial mucosal infection, colonisation of the dorsal root ganglion and subsequent reactivation resulting either in asymptomatic genital tract shedding (and therefore spread) or clinical disease. However, prevention of initial infection requires induction of sterilising immunity, which is difficult to achieve, focusing attention on preventing or reducing shedding and disease. Choosing the appropriate immune mechanisms to stimulate has been difficult. Induction of both neutralising antibody and T cell immunity (both CD4 and CD8 lymphocytes) will be necessary, as both have been shown to be important in immune control of initial HSV infection. Innate immune mechanisms such as interferon-secreting plasmacytoid and myeloid dendritic cells, NK cells, macrophages and gamma-delta T cells may also be important as these cells are present in human lesions[3-5]. Which of the over 80 HSV proteins expressed during cellular infection are potential inducers or targets for these immune cells? Neutralising antibody is directed against HSV surface glycoproteins B (gB) and D (gD) whereas the CD8 lymphocyte response appears to be much broader. The CD4 lymphocyte response is intermediate, mainly directed at structural proteins, especially gD.

Recently vaccine companies have attempted more targeted approaches to vaccine development, using the above principles. As viral peptides or proteins are not immunogenic enough to induce the correct type or magnitude of immune response, they must be combined with an adjuvant that induces the correct form of immune response and replaces the TLR legends in the original virus. Chiron used a candidate vaccine containing HSV-2 gD and gB with an adjuvant, MF59, biased to Th2 responses which induced higher neutralising antibody levels than in infected subjects but it failed to be protective[6]. GSK used another gD2 candidate vaccine, containing the AS04 adjuvant (or dMPL), which stimulates DCs via TLR4 to produce Th1 response. In 2002 the two large trials conducted in consort design were reported to show 73% efficacy against genital herpes disease in women seronegative for both HSV-1 and HSV-2 but no efficacy against men or HSV-1 seropositive women[7]. However a third recent (HERPEVAC) trial in randomly selected HSV-1 and HSV-2 negative women is reputed to show the vaccine was safe but without significant overall efficacy, leading to cessation of its development. Comparison of the effects in the different recipient populations may help guide further vaccine development[8]. The design of future vaccine candidates should be aimed at also inducing innate, immune and CD8 T cell responses[9]. Many other candidates, including DNA vaccines, different peptide-adjuvant combinations, HSV-viral vector recombinants and replication-defective mutants are under development or in early trials[8].

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Biographies

Tony Cunningham, AO, MBBS, MD, is Executive Director of the Westmead Millennium Institute and Research Centres at the Westmead Hospital and of the Centre for Virus Research. He is Professor of Research Medicine and Sub-Dean (Research) at the Western Clinical School at the University of Sydney. He is also Director of the Australian Centre for HIV and Hepatitis Virology Research. He trained in infectious diseases, clinical virology and virology research at the University of Melbourne and as a postdoctoral fellow at Stanford University. His major research interests are in HIV and Herpes simplex virus biology and immunology, especially in relation to the development of vaccines and microbicides. In 2010, Tony was awarded an Officer in the Order of Australia for "service to medicine, particularly in the field of viral research and through the development and leadership of medical and biomedical research."

Dr. Min Kim is working on Herpes Simplex Virus (HSV) Immunology as NHMRC senior research officer at the Centre for Virus Research, Westmead Millennium Institute and Sydney Medical School, University of Sydney with Professor Anthony L. Cunningham's lab since 2004. She received her PhD in Virology in 1993. Her research as postdoctoral fellow at Seoul National University was on antiviral mechanism of 28-deacetylsendanin on HSV-1. After migration to Australia in 1999, she worked on dendritic cell research in Non Hodgkin's Lymphoma patients in Dr. Derek Hart's lab and on Kunjin Virus in Professor Edwin Westaway's lab. Her major research interest is the development of a vaccine for genital herpes.