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Developing an asymptomatic mucosal herpes vaccine: the present and the future

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“...this recent discovery could lead to a viable strategy for developing an asymptomatic T-cell-based vaccine against herpes infection and other diseases.”

The development of prophylactic and therapeutic vaccines against infectious diseases has been a great success in medical science. During the last two decades, several mucosal vaccine strategies have been identified, providing renewed optimism that effective control of mucosal infectious agents through vaccination is feasible [1]. However, mucosal vaccines developed for many mucosal pathogens, including HIV-1 and herpes simplex virus (HSV), are either ineffective or unavailable.

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Herpes simplex virus-1 and -2 infect mucosal surfaces and then establish lifelong latency in neurons of sensory ganglia. During latency, viral DNA replication and gene expression are limited, and no new viral progeny are made [2]. Reactivation occurs sporadically, and the virus returns to the mucosal surfaces, replicates and is shed in mucosal fluids (e.g., tears and vaginal fluids). HSV-1 and -2 replication can cause serious diseases at every stage of life, including fatal disseminated disease in newborns and cold sores, genital ulcerations, eye disease and fatal encephalitis in adults [3–14]. Together, ocular and genital herpes represent an enormous reservoir for horizontal and vertical transmission [3–8]. The rapid spread of herpes infection, which occurs mostly during unrecognized asymptomatic shedding, is reflected in more than 1 million new cases per year in the USA alone [3–7,15].

Despite the availability of many interventional strategies, such as sexual behavior education, barrier methods and costly guanine nucleoside antiviral drug therapies (e.g., acyclovir and derivatives), controlling the spread of ocular and genital herpesvirus still remains a challenge, as clinical manifestation rates have continued to rise over the last decade [16–22]. An effective immunoprophylactic and/or immunotherapeutic mucosal vaccine would be the most cost-effective approach that would be helpful, not only in developed nations, but also in developing regions, such as sub-Saharan Africa, where 70% of high-risk HIV-negative individuals and 85% of HIV-infected individuals are seropositive for HSV-1 and/or -2. To date, however, no clinical herpes vaccine is available. Several challenges face herpes vaccine development, including the lack of knowledge regarding the protective antigens and derived epitopes, and the uncertainty about effector mechanisms involved in protective immunity.

“Despite the availability of many interventional strategies ... controlling the spread of ocular and genital herpesvirus still remains a challenge...”

A mucosal herpes vaccine that could reduce symptomatic disease or, at least, decrease the threshold of infection is thought to be a reasonable approach, even if full protection cannot be achieved. However, a vaccine that reduces symptomatic disease without reducing asymptomatic shedding could inadvertently increase transmission from asymptomatic individuals who think they are not infectious. Therefore, a therapeutic vaccine should aim to reduce both recurrent shedding and recurrent disease.

The existence of HSV-seropositive asymptomatic HSV individuals who shed the virus suggests that their immune system may somehow control the disease while failing to prevent reactivations and/or shedding. This raises two vital questions:

- Why, under the same circumstances of reactivation and shedding, do asymptomatic individuals control recurrent disease while symptomatic individuals do not?
- What are the differences between asymptomatic and symptomatic individuals in terms of herpes infection, disease and immunity?

The recent discovery of two different non-overlapping sets of T-cell epitopes on HSV target antigen glycoproteins, gD and gB, might provide an answer to the previous questions [23–25]. It is also possible that this recent discovery could lead to a viable strategy for

developing an asymptomatic T-cell-based vaccine against herpes infection and other diseases.

Until now, many advanced techniques in molecular medicine have been applied to develop a vaccine against HSV; nevertheless, a vaccine has remained elusive because of the subtle and successful adaptation of HSV to its human hosts by developing many immunoevasion strategies. The vaccine trials that have undergone clinical evaluation include subunit vaccines, attenuated live-virus vaccines, replication-defective virus vaccines, naked DNA vaccines and viral-vector vaccines. Most of these strategies elicited protective immunity in animal models, but none has yet been effective in humans. While acyclovir and related nucleoside analogs provide successful modalities for treatment and suppression, HSV remains highly prevalent worldwide and is a major cofactor fueling the HIV epidemic [26]. Antiviral drugs (e.g., acyclovir) can reduce recurrent herpetic disease by approximately 45%, but do not completely prevent virus replication and/or reactivation. The cost, the incomplete protection and the emergence of drug-resistant HSV strains, combined with compliance problems of taking multiple doses of the drug daily, suggest that an effective therapeutic vaccine would be a better approach to decrease HSV-1 reactivations and recurrent ocular herpes disease [27–30].

“We hope the newly introduced HLA-transgenic rabbit model ... solves many hurdles associated with the preclinical phase of herpes vaccine development.”

An effective therapeutic mucosal vaccine must increase key immune effectors, even in the presence of stress factors, to control reactivations in sensory ganglia and/or virus replication in mucosal tissues, such as the cornea and genital tract [1]. CD8⁺ T cells are believed to be one such key immune factor. However, a major complication of therapeutic vaccine using whole virus or whole proteins is, while they could induce protective asymptomatic CD8⁺ T-cell responses, they might also simultaneously trigger harmful symptomatic T-cell-mediated incidental damage in the cornea. Thus, a herpes vaccine (either genital or ocular) when given to latently infected individuals could exacerbate herpes disease by increasing nonprotective, pathogenic immune responses. An example of this is vaccination of mice with HSV-1 glycoprotein gK, which significantly exacerbated herpetic eye disease following ocular HSV-1 challenge [31,32]. Thus, an effective therapeutic vaccine against herpes must induce strong protective asymptomatic CD8⁺ T-cell responses, without inducing damaging symptomatic CD8⁺ T-cell responses. One way to achieve this goal is to identify and remove symptomatic epitopes on HSV target antigens during the process of vaccine construction. The next generation vaccine should be composed of asymptomatic epitopes only.

In preclinical studies, an appropriate animal model is required to demonstrate safety, immunogenicity and protective efficacy of a candidate vaccine. In this note, newly developed HLA-transgenic rabbits are an excellent model for recurrent ocular shedding and eye disease, while an as yet to be developed HLA-transgenic guinea pig model would be excellent for studying recurrent genital shedding and disease. In addition, the newly introduced needle-free mucosal (i.e., topical ocular and intravaginal) lipopeptide vaccines provide an unprecedented strategy that might target ocular and genital herpes and would probably help provide heterologous protection from HIV-1 [33]. In fact, mucosal self-

adjuvanting lipopeptide vaccines are easy to manufacture, simple to characterize, extremely pure, cost effective, highly immunogenic and safe. We hope the newly introduced HLA-transgenic rabbit model (and, perhaps in the future, the HLA-transgenic guinea pigs) with spontaneous reactivation and recurrent herpes disease that can mount a T-cell response to HLA-restricted human CD8⁺ T-cell epitopes, solves many hurdles associated with the preclinical phase of herpes vaccine development.

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