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Towards an effective genital herpes vaccine: past lessons and future prospects

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Introduction

In 2007, the most effective means to acquire life-long immunity to genital herpes is to engage in romantic activity with a partner who is infected with herpes simplex virus 2 (HSV-2). Three out of four people who acquire HSV-2 in this manner are blissfully unaware of the molecular hitchhikers that they will carry for life, hidden away in neurons of their peripheral nervous system. Such persons derive a huge benefit from these molecular hitchhikers: life-long immunity from the disease of genital herpes.

The natural approach to acquiring HSV-2 has a serious downside: 2 to 5% of HSV-2 infected people endure considerable pain and distress, as they may experience recurrent outbreaks of genital herpes every three to twelve months for the rest of their lives. About 1.5 billion people worldwide are infected with HSV-2, and ~50 million suffer from recurrent outbreaks of genital herpes.

It is absurd to suggest that unprotected sex is the best means to vaccinate against HSV-2 and genital herpes. Yet, the sad reality in 2007 is that the medical community has about as much power to prevent genital herpes as doctors did who practiced in ancient Rome. The development of acyclovir in the late 1970s was a major breakthrough. It has provided a tool by which doctors and patients can restrict the severity and frequency of genital herpes outbreaks. However, a preventative vaccine that confers life-long protection against genital herpes continues to elude us.

Tens of thousands of studies have been published on herpes simplex virus 1 (HSV-1) and HSV-2 in the past fifty years. These studies provide a wealth of information about the epidemiology, clinical presentation, immunology, molecular biology, and animal biology of HSV-1. Given that HSV-1 and HSV-2 share a nearly identical set of 75 genes, we possess an amazingly detailed knowledge about the biology of the infectious agents that cause recurrent herpes.

So, how is it possible that progress in treating genital herpes has remained at a standstill for 30 years? I have grappled with this question for the past decade, and summarize my conclusions herein. My personal view is that a dichotomy in logic exists between **1.** the approaches being most seriously considered to prevent genital herpes, and **2.** the biology of herpes simplex virus infections. As the most thoroughly studied herpes vaccine candidate,

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the glycoprotein D subunit vaccine merits specific attention. However, I believe that the larger questions are:

- Why has an effective herpes vaccine eluded us for so long?
- What approaches are most likely to lead to an effective herpes vaccine?

HSV-2 subunit vaccines: what have we learned?

If one thinks of vaccine development in purely molecular terms, then an ideal HSV-2 vaccine would be a protein subunit of the virus that “jump starts” the adaptive immune response to HSV-2. Thus, HSV-2 vaccine development has focused on how to deliver immunodominant epitopes of HSV-2 to the immune system (1, 6, 25, 32, 38).

Glycoprotein D is an immunodominant protein of HSV-1 and HSV-2. Clinical trials have been performed to determine if HSV-2 glycoprotein D can be used to protect people from HSV-2 infection and genital herpes. On both counts, the glycoprotein D subunit vaccine is marginally effective (29–31). Likewise, glycoprotein 120 subunit vaccines fail to protect people against human immunodeficiency virus infection and AIDS (5, 33, 39). Other attempts to produce HSV-2 vaccines have included killed, inactivated HSV-2 vaccines (27, 28), and replication-defective viral vectors (3, 7, 9, 20). In each case, I have reservations about the likelihood of success of the approach.

Before proceeding, I wish to make clear my respect for the scientists who performed the studies on the HSV-2 glycoprotein D subunit vaccine. These individuals blazed a trail that simply did not exist ten years earlier. The glycoprotein D subunit may not be critical to the final formulation of a genital herpes vaccine, but what we have learned is invaluable. These studies have lifted a veil from the eyes of the scientific community, and have served as a catalyst that has scientists today asking the question, “What is necessary to attain an effective genital herpes vaccine?” There is no bigger success in science than to change (for the better) how your peers look at the natural world.

How are new cures devised?

In the past fifteen years, I have witnessed many ideas that were touted as a means to improve the prevention or management of genital herpes. Like subunit vaccines, these proposals generally share three traits that explain **1.** their scientific appeal and **2.** why the idea is unlikely to improve the clinical management of genital herpes.

- 1. *Each approach is simple in principle, and is thus accessible to a broad audience.*** Any student of virology and/or immunology should quickly be able to grasp why a protease inhibitor or subunit vaccine may block herpes simplex virus replication, hence yielding an antiviral effect. The scientific review process selects for ideas that instantly make sense to a diverse group of scientists.
- 2. *Each approach resembles two 20th century medical success stories.*** Penicillin and antibiotics made complicated surgeries possible, and eventually routine. Between 1950 and 1970, simple and effective vaccines were developed against the acute and potentially devastating infectious diseases of poliomyelitis, mumps, measles, rubella, whooping cough, diphtheria, and tetanus. Scientists have very strong positive associations with proposed treatments that resemble these successes.
- 3. *Each approach ignores the biology of persistent herpesviral infections.*** The diseases that antibiotics and most vaccines prevent are caused by *acute* infectious agents, where the drug or vaccine need only be effective for a period of days to weeks to achieve the desired clinical outcome. AIDS and genital herpes are caused

by viruses that colonize their human hosts for life. This *persistent* lifestyle confounds the feasibility of most “tried-and-true” approaches. It is highly unlikely that a sustainable victory over AIDS or genital herpes will be achieved through antiviral drugs or subunit vaccines.

In the case of genital herpes, I would suggest that the first critical step towards devising an effective vaccine lies in understanding the natural process by which protective immunity is maintained for a human lifetime in asymptomatic carriers of HSV-2.

Biology of HSV-1 and HSV-2 infections

Following a first exposure, HSV-1 or HSV-2 produces a robust infection in experimental animals such as mice, rabbits, or guinea pigs that leads to the establishment of 1,000 to 10,000 latently infected neurons throughout the peripheral nerves of the animal. It appears that viral reactivation occurs in one of these latently infected neurons about once per week. Most such “single-cell reactivation events” produce a handful of infectious virions. The capacity of this low-grade infection to emanate from the peripheral nerves is dependent on HSV’s capacity to thwart the host immune defenses.

Wald, Corey, and colleagues have spent a decade comparing the frequency of genital herpes disease versus HSV-2 replication in humans. Most reactivation events prove to be so brief (< 3 days) that HSV-2 spread is limited, and lesions do not form. Rather, clinical disease only occurs when HSV-2 reactivation events persist in the epithelium for 3 days or longer (34, 35). Such detailed studies have brought us full circle to nearly the same conclusion reached by Buddingh in 1953: asymptomatic carriers of HSV shed low levels of infectious virus at a surprisingly high frequency (4).

Therefore, the immunological memory that protects people from genital herpes does not appear to be conferred by a one-time encounter between viral antigens and lymphocytes. Rather, protective immunity against genital herpes is *actively maintained* by the frequent oscillation of HSV-2 between true “molecular latency” and “single-cell reactivation” events. This frequent source of endogenous HSV antigen appears to explain how billions of people worldwide remain strongly seropositive against HSV-1 or HSV-2 in the absence of herpetic disease (4, 14, 26).

Failed vaccines or flawed logic?

Past attempts to generate an effective genital herpes vaccine have ignored at least one of the four following points that should be considered in developing an HSV-2 vaccine.

1. Subunit vaccines lack antigenic complexity

The proteome of HSV-2 is sufficient to give rise to >1000 B cell and T cell epitopes. The permutations are staggering regarding how B cells, CD4⁺ T cells, and CD8⁺ T cells may collectively respond to a natural HSV-2 infection. It is unlikely that the host response to a single viral subunit faithfully mimics the natural protective immune response mounted against HSV-2.

2. Killed, inactivated vaccines lack immunological context

Within the cytoplasm of cells, intracellular proteins are constantly degraded into ~10 amino acid peptides that are exported to the cell surface in the context of MHC class I molecules. CD8⁺ T cells, a key component of antiviral defense, limit viral spread when they “see” *intracellular* viral peptides presented on the surface of virus-infected cells. Subunit and inactivated HSV-2 vaccines are *extracellular* antigens, and thus have only limited access to

the MHC class I antigen presentation pathway that primes the CD8⁺ T cell response against HSV-2.

3. Live, replication-defective HSV-2 vaccines are short-lived

Replication-defective HSV-2 mutants have been proposed as a means to vaccinate against genital herpes (3, 7, 9, 20). Because a single round of viral infection is initiated, *intracellular* viral antigens are generated and presented to CD8⁺ T cells. However, HSV-2 antigen expression is so short-lived that the net immunogenicity is likely 1/1000th of a natural infection. Replication-defective vectors are cleared from the body within weeks, whereas natural HSV-2 infections persist for life.

4. HSV-2 is not poliovirus

Clonal expansion of poliovirus-specific B cells and T cells explains how the Salk vaccine (inactivated poliovirus) confers protection against the crippling disease of poliomyelitis. However, our success in controlling acute viral pathogens does not provide a compelling basis for the assumption that “Salk-like” vaccines can be used to prevent the recurrent diseases caused by herpes simplex viruses.

Herpes simplex viruses are immune-escape artists

Just as sharks are highly evolved predators, herpesviruses are a remarkable product of co-evolution between virus and host. Herpesvirus genomes are ~10 times the size of the viruses that cause poliomyelitis, mumps, measles, and rubella. Within that extra order of magnitude of complexity, herpesviruses encode factors that counteract every level of host defense including innate, humoral, and cell-mediated immunity.

Specifically, HSV-1 and HSV-2 encode two viral proteins, ICP0 and ICP34.5, which counteract the innate interferon system (10, 11, 16, 17, 21, 22). Viral glycoproteins C, E, and I bind and neutralize key initiators of the humoral immune response, C3b and IgG (18, 23). Finally, ICP47 binds the TAP antigen transporter and delays viral peptide association with MHC class I molecules (12, 37). Thus, CD8⁺ T cells have difficulty recognizing HSV-infected cells before these virus factories can produce more progeny.

Given HSV's capacity to thwart the normal function of the host immune system, clonal expansion of HSV-specific lymphocytes alone is unlikely to confer life-long protection against genital herpes. Many of the past difficulties in vaccinating against genital herpes stem from the frequent assumption by immunologists that HSV is just another three-letter antigen, such as BSA[†] or KLH[‡]. The immune evasion potential of herpesviruses explains much about their ability to cause recurrent disease in healthy adults. Any genital herpes vaccine strategy should account for HSV-2's “Houdini-like” ability to escape detection and clearance by the human immune system.

A live vaccine to prevent genital herpes?

An important principle emerges from the epidemiology and natural history of HSV-1 and HSV-2 infections: *viral replication is necessary, but not sufficient, for HSV-1 and HSV-2 to produce human disease* (reviewed in Ref. 13, 15). Thus, I would suggest that a simple, but relatively unexplored approach to vaccinate against genital herpes would be to construct live, attenuated vaccine strains of HSV-1 and HSV-2 that:

[†]bovine serum albumin

[‡]keyhole limpet hemocyanin

1. establish latent infections in their human hosts,
2. reactivate subclinically to stimulate life-long protective immunity, and
3. are unable to produce clinical disease.

One would be correct to ask, “Are the risks of a live HSV-2 vaccine worth the benefits?” The answer to this question lies in the natural history of HSV-2. One-and-a-half billion people worldwide currently harbor *virulent, wild-type* strains of HSV-2. Three out of four of these infections produce no disease, but do confer life-long protection against exogenous HSV-2 infection. Therefore, latent infection is not, in and of itself, a problem. The problem is that when left to chance, 2 to 5% of HSV-2 infected people will experience recurrent outbreaks of genital herpes.

The immune evasion armor of herpesviruses has long been viewed as a barrier to vaccination (19, 36). Perhaps we have been looking at the problem backwards. Rather than lament the failure of subunit vaccines to penetrate HSV-2’s armor, we could focus on stripping this armor away and rendering HSV-2 vulnerable to host immune control. Deletion of key immune evasion genes represents a potential means to create live vaccine strains that are safe, but retain the immunogenicity of wild-type virus. Specifically, viral functions that could be disrupted to achieve this end are listed, as follows:

Genotype	Predicted Phenotype <i>in vivo</i>
1. ICP0 ⁻ virus	easily repressed by interferons (10),
2. ICP34.5 ⁻ virus	easily repressed by interferons (17),
3. ICP47 ⁻ virus	easily repressed by CD8 ⁺ T cells (24),
4. gE ⁻ virus	easily repressed by IgG antibodies (23), and
5. gC ⁻ virus	easily repressed by complement-driven inflammation (18).

Studies from my own laboratory indicate that ICP0⁻ viruses achieve an attractive balance between safety and efficacy in HSV-1. ICP0⁻ viruses are unable to produce disease in mice with severe-combined immunodeficiency (10). Yet, these same ICP0⁻ viruses induce a protective immune response in normal mice that is almost sterilizing: little to no replication of a lethal HSV-1 strain is detected in vaccinated mice just 24 hours after challenge (10). This is similar to the level of protection conferred upon mice by prior infection with wild-type HSV-1.

Conclusion

For thirty years, scientists have been trying to devise an effective herpes vaccine based on the constraint that a latent infection must not be established in the recipient. Despite the prevalence of this belief, human epidemiology tells us that latent HSV-2 infections are not a problem, and may actually be required to sustain protective immunity against genital herpes. Specifically, the available evidence indicates that:

1. Clinically latent HSV-2 infections exist in a dynamic equilibrium, and thus the human host is frequently re-exposed to endogenous HSV-2 antigens.
2. Asymptomatic HSV-2 carriers are the only persons who enjoy *bona fide* protective immunity against genital herpes, and their unique status may depend on frequent re-exposure to endogenous HSV-2 antigens.

Future Perspective

In my studies of the interface between herpes virology and immunology, I have found no compelling evidence to support the belief that a transient HSV-2 vaccine should mimic the process by which immunity to genital herpes is naturally maintained.

I would suggest that a safe and effective genital herpes vaccine lies within our grasp, and will come in the form of an attenuated vaccine strain of HSV-2. An effective genital herpes vaccine should mimic the natural behavior of HSV-2 infection, and ICP0⁻ or ICP34.5⁻ null viruses (2) represent two very safe alternatives to achieve this end.

Herpesviruses are as old as life itself (8), and have been beating the vertebrate immune system at its own game for tens of millions of years. So, who is the real master here? I suspect that when scientists are ready to bow to the teacher, and listen to the lessons that herpes simplex virus has to offer, then and only then will an effective genital herpes vaccine be forthcoming.

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Executive Summary

Primary message

- The proposal that subunit vaccines or replication-defective viruses can be used to vaccinate against genital herpes is inconsistent with the biology of HSV-2.

Major Points

- 75% of natural HSV-2 infections produce no disease in the infected person.
- Asymptomatic carriers of HSV-2 enjoy *bona fide* protective immunity against herpes.
- Frequent subclinical reactivation of endogenous HSV-2 infection may be necessary to sustain protective immunity against genital herpes.
- HSV-2 encodes a small arsenal of immune evasion proteins.

Conclusions

- Safety concerns have quashed consideration of live HSV-2 vaccines for three decades. In erring on the side of caution, perhaps we have overlooked the most feasible approach to vaccinate against genital herpes.
- Live, immune evasion-deficient mutants of HSV-2 represent a new and promising approach to develop an effective genital herpes vaccine.