Immune evasion strategies of HSV and the potential value of developing mRNA candidate vaccines against HSV

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Female reproductive tract: portal of entry for sexually transmitted pathogens

- Women’s health is severely understudied
- Huge human costs in the developing world

Human immunodeficiency virus 1

Human Papillomaviruses

Herpes simplex virus 2

Antiviral immune responses in the genital tract: clues for vaccines
• ~half a billion people had genital infection with HSV type 2
• More women (313.5 million) than men (178.0 million) were infected.
• ~3.6 billion had oral HSV type 1 infection.
Stages of herpes simplex virus infection

Mucosal epithelia

Sensory neuron

Primary infection

Reactivation

Nature Reviews Microbiology volume 6, pages 211–221 (2008)
HSV-1 and HSV-2 use immunoevasins to escape antibody-dependent clearance

**a** Neutralizing antibodies

**b** Escape mutations

**c** Immunoevasins

**d** Vaccine strategies

G C binds the complement C3 and inhibits complement-mediated virus neutralization and the lysis of infected cells.

G E/G I complex acts as an FcR decoy on the viral envelope.

Major challenges

- Most vaccines rely on antibodies.
- HSVs evade antibody responses.
- Most infections start locally in a tissue.
- Current vaccines fail to establish mucosa immunity.
- Do circulating memory T cells protect the host?
Do circulating memory T cells confer protection?

Immune

Parabiosis

Attenuated HSV-2 (ivag)

5 weeks

Circulating memory T

Tissue resident memory T cells ($T_{RM}$)

Immune

Naive

Parabiosis

$T_{RM}$

No $T_{RM}$
Circulating memory T cells only partially protect the host against HSV-2 challenge

<table>
<thead>
<tr>
<th>Group #</th>
<th>Symbol</th>
<th>HSV-2 challenge</th>
<th>Number of mice</th>
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<tbody>
<tr>
<td>1</td>
<td>●</td>
<td>Naive WT</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>■</td>
<td>Immune WT</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>△</td>
<td>Immune WT</td>
<td>20</td>
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$T_{RM}$ secrete IFN$\gamma$ to block virus replication
Discovery of a new type of lymphoid structure; memory lymphocyte cluster

- Local viral infection establishes memory lymphocyte clusters.
- MLC is an organized outpost full of virus-specific T cells ready to defend against local viral challenge.

Prime and Pull Vaccine Strategy
Prime and Pull establishes tissue resident memory T cells

Prime

- Attenuated HSV-2 (s.c.)

Pull

- Chemokines CXCL9, CXCL10 (ivag)

5 days

5 weeks

Analyze tissues for CD8 T cells

HSV-specific CD8 T cells

Prime and Pull protects mice from lethal herpes infection

Prime and Pull therapeutic vaccine cures existing disease

Bernstein D et al. NPJ Vaccines (2019)
mRNA vaccines against HSV

BNT163 candidate vaccine encodes three HSV-2 glycoproteins, gC, gD and gE to help prevent HSV cellular entry and spread and counteract the immunosuppressive properties of HSV.

NCT05432583: Phase 1 Clinical Trial in Healthy Volunteers to Study the Safety, Tolerability, and Immune Responses After Vaccination With an Investigational Vaccine Designed to Prevent Genital Herpes Lesions

An HSV-2 nucleoside-modified mRNA genital herpes vaccine containing glycoproteins gC, gD, and gE protects mice against HSV-1 genital lesions and latent infection

Kevin P. Egan, Lauren M. Hook, Alexis Naughton, Norbert Pardi, Sila Awasthi, Gary H. Cohen, Drew Weissman, Harvey M. Friedman

Version 2 Published: July 27, 2020 • https://doi.org/10.1371/journal.ppat.1008795

Moderna’s herpes simplex virus (HSV) vaccine candidate (mRNA-1608)
Final thoughts

mRNA or any other vaccine approaches against genital herpes might benefit from incorporating the Prime and Pull approaches to inducing robust mucosal immunity.

Other strategies to recruit T and B cells to the genital mucosa can be combined with conventional mRNA vaccines to prevent and treat genital herpes.