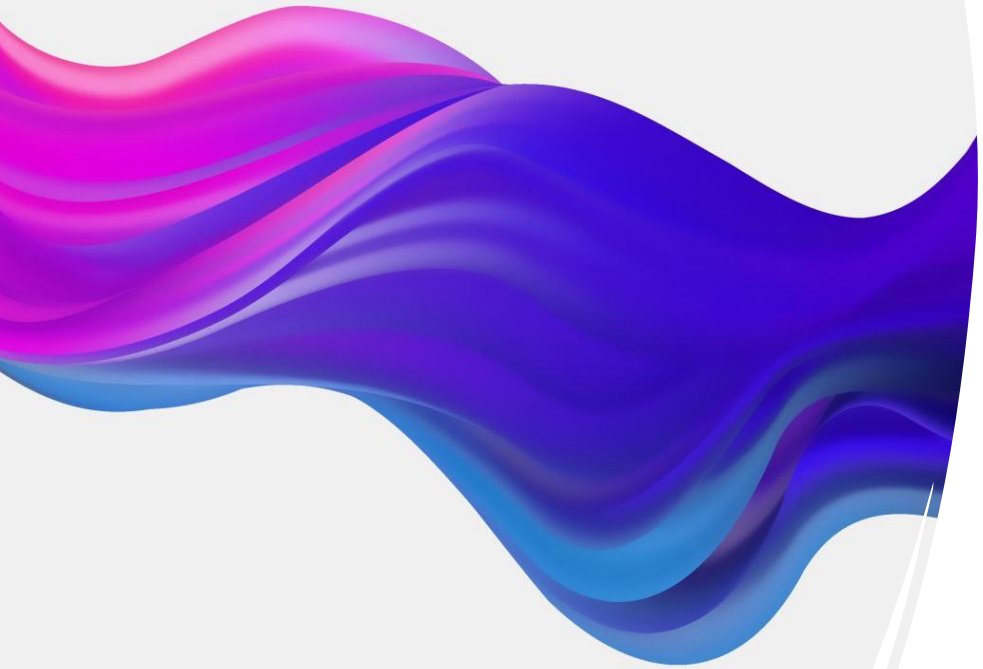


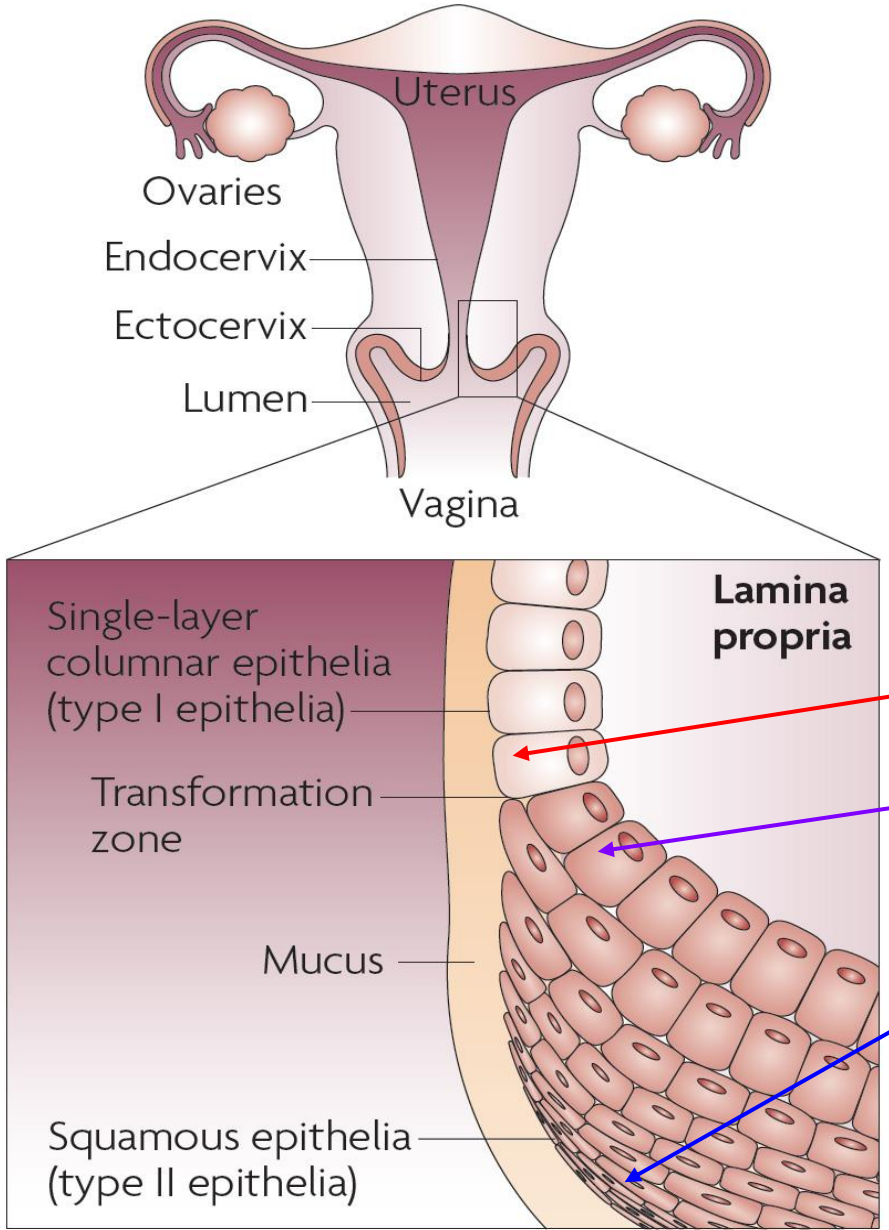
Immune evasion strategies of HSV and the potential value of developing mRNA candidate vaccines against HSV

Akiko Iwasaki, Ph.D.

Immunobiology, Yale University

Howard Hughes Medical Institute

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

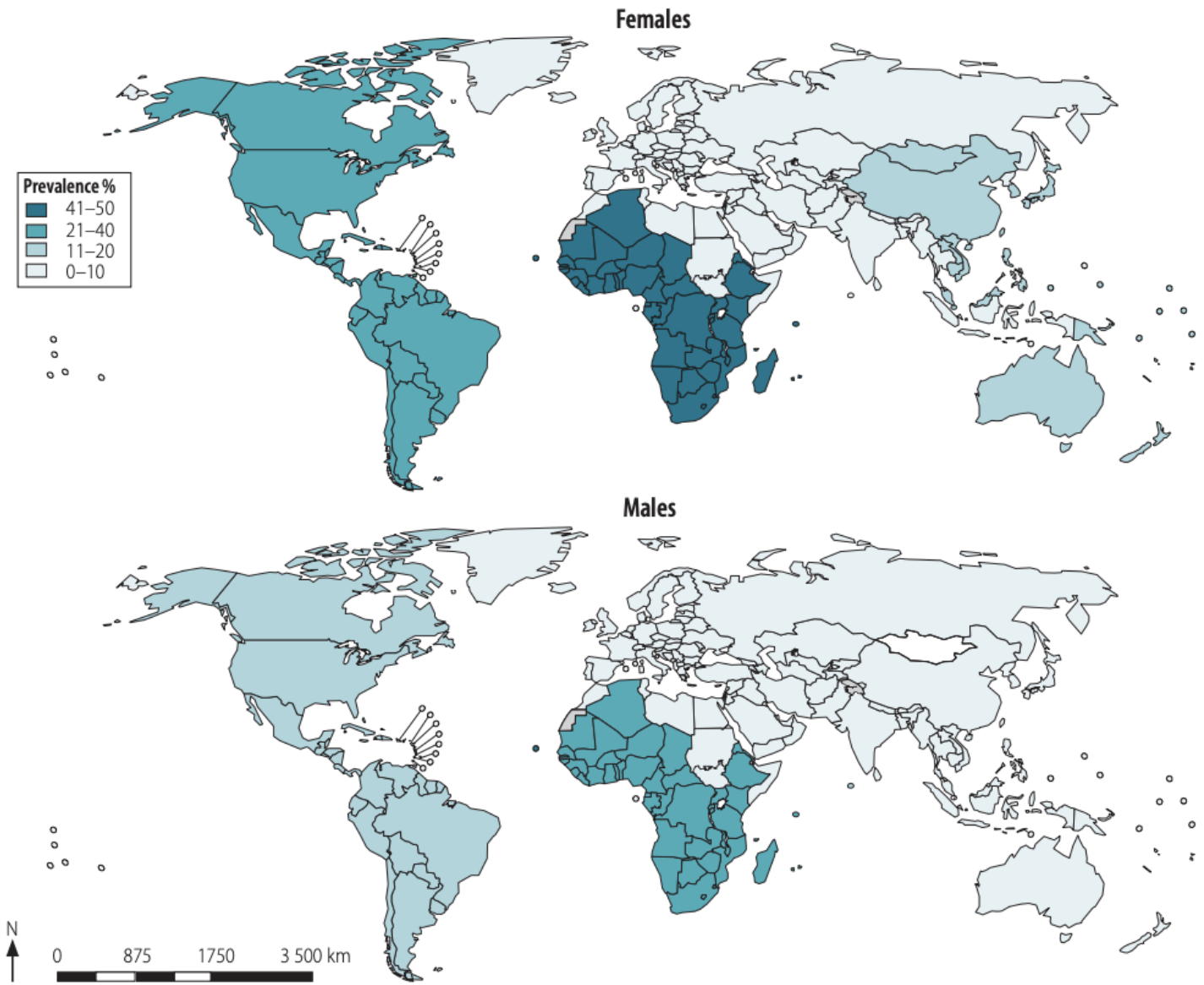
Herpes simplex virus 2

Antiviral immune responses in the genital tract: clues for vaccines

Akiko Iwasaki

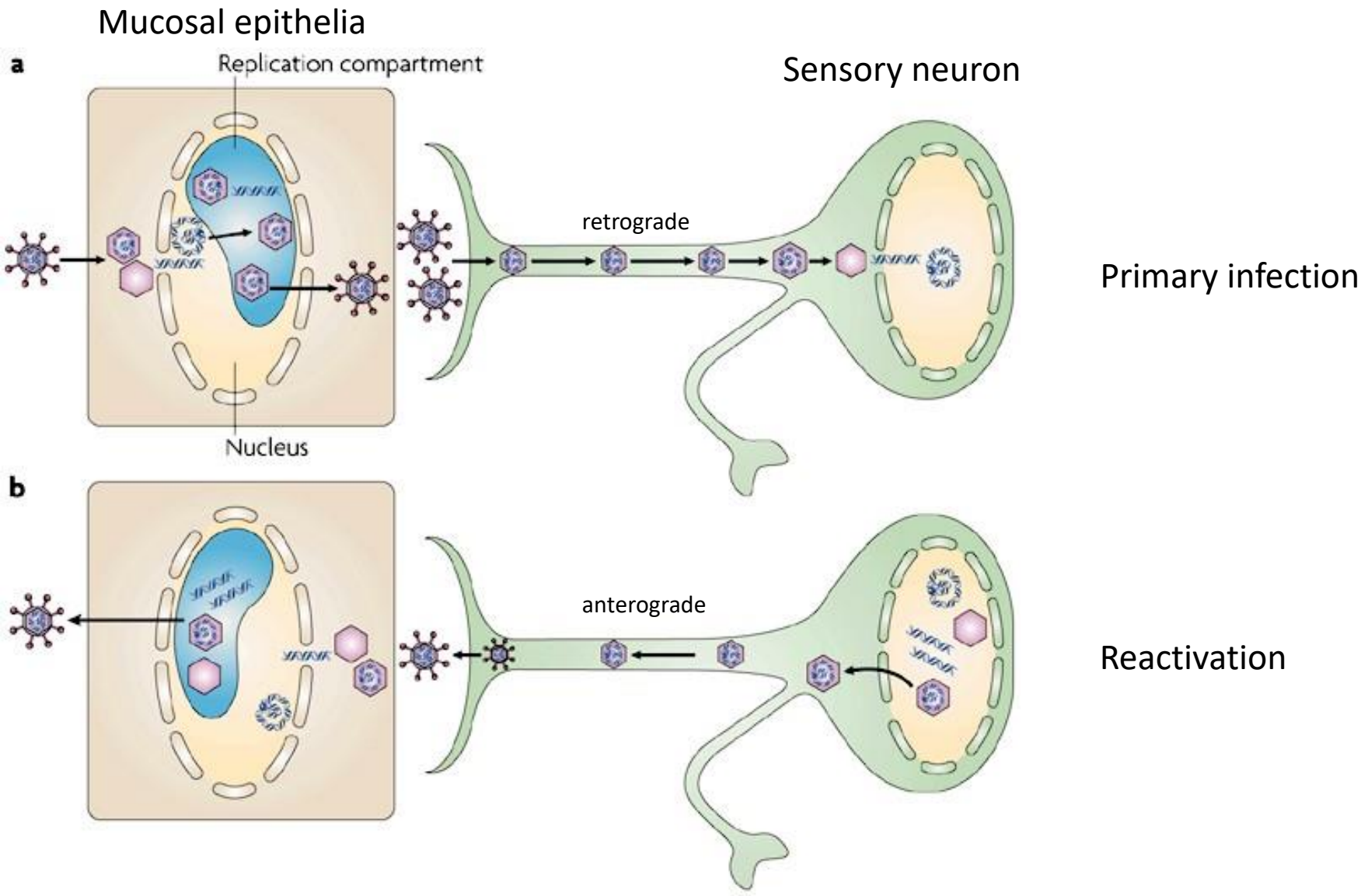
- ~half a billion people had genital infection with HSV type 2
- More women (313.5 million) than men (178.0 million) were infected.
- ~3.6 billion had oral HSV type 1 infection.

Fig. 2. **Map of regional estimates of the number and prevalence of herpes simplex virus type 2 infections in females and males, 2016**



Bulletin of the World Health Organization, 98 (5): 315 - 329

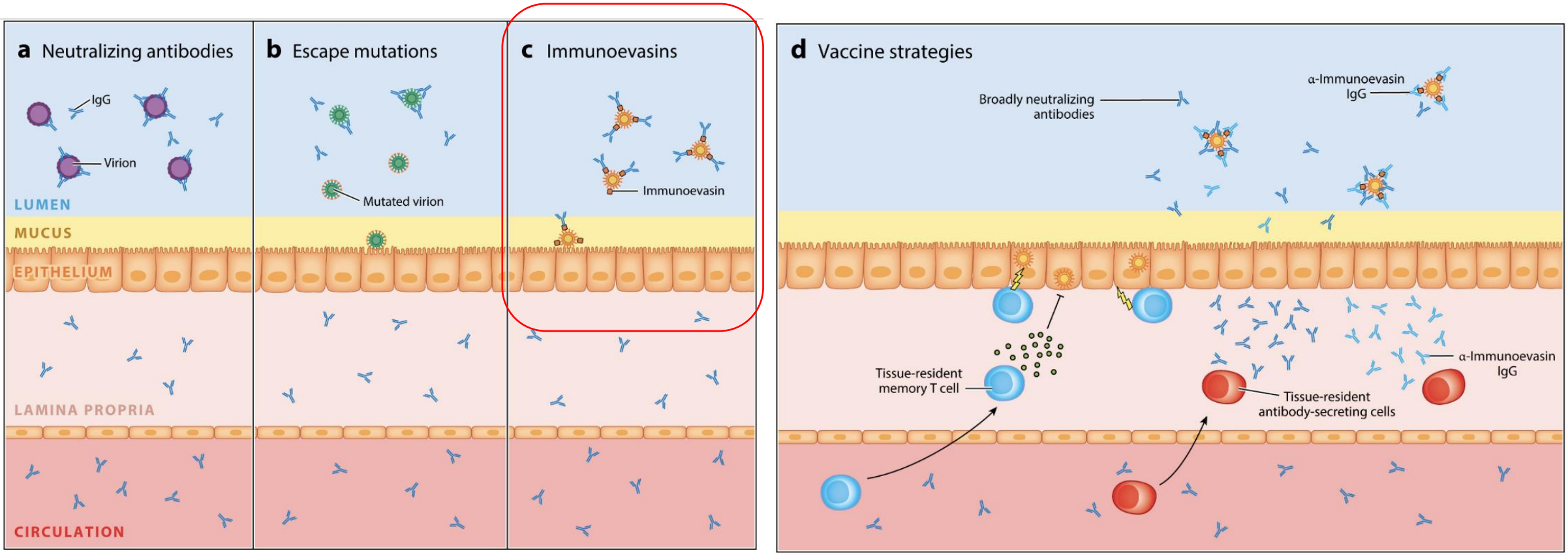
Stages of herpes simplex virus infection



Nature Reviews Microbiology volume 6, pages211–221 (2008)

Nature Reviews | Microbiology

HSV-1 and HSV-2 use immunoevasins to escape antibody-dependent clearance



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

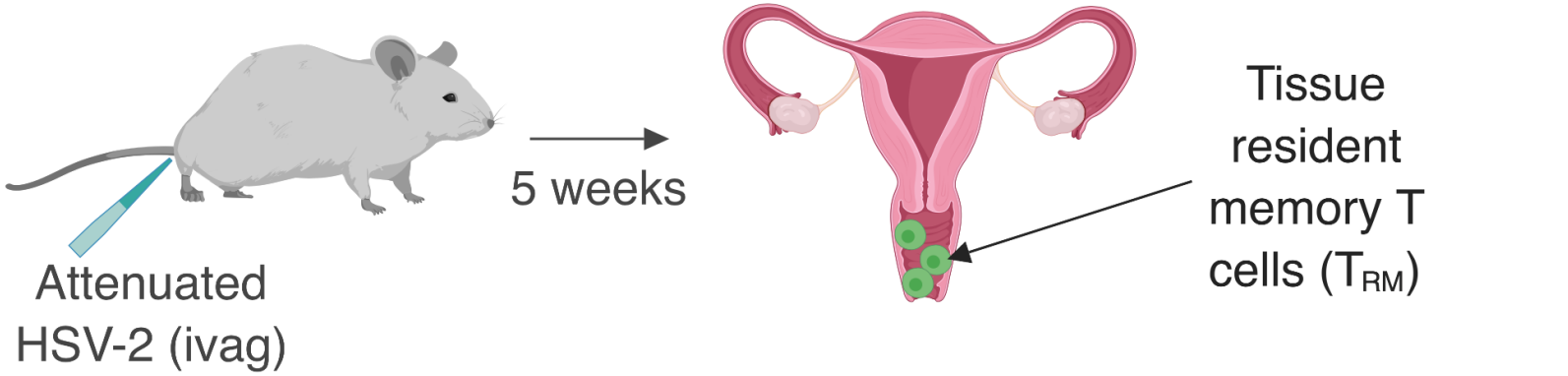
gE/gI complex acts as an FcR decoy on the viral envelope

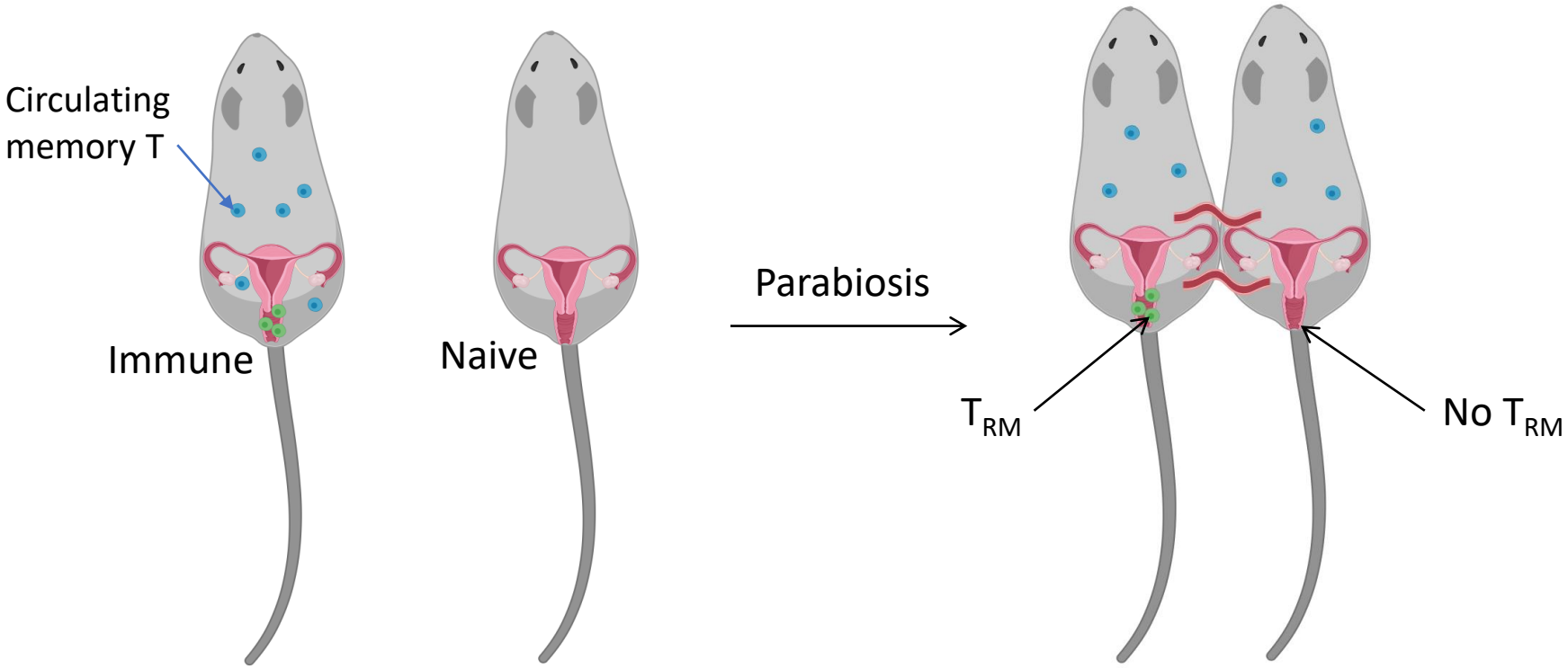
Iwasaki A. 2016.
Annu. Rev. Immunol. 34:575–608

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?

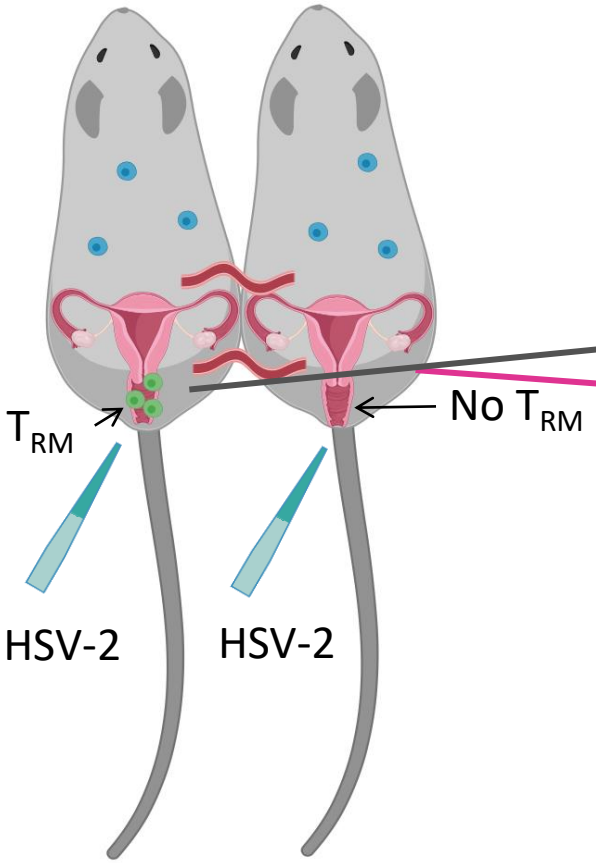
Do circulating memory T cells confer protection?

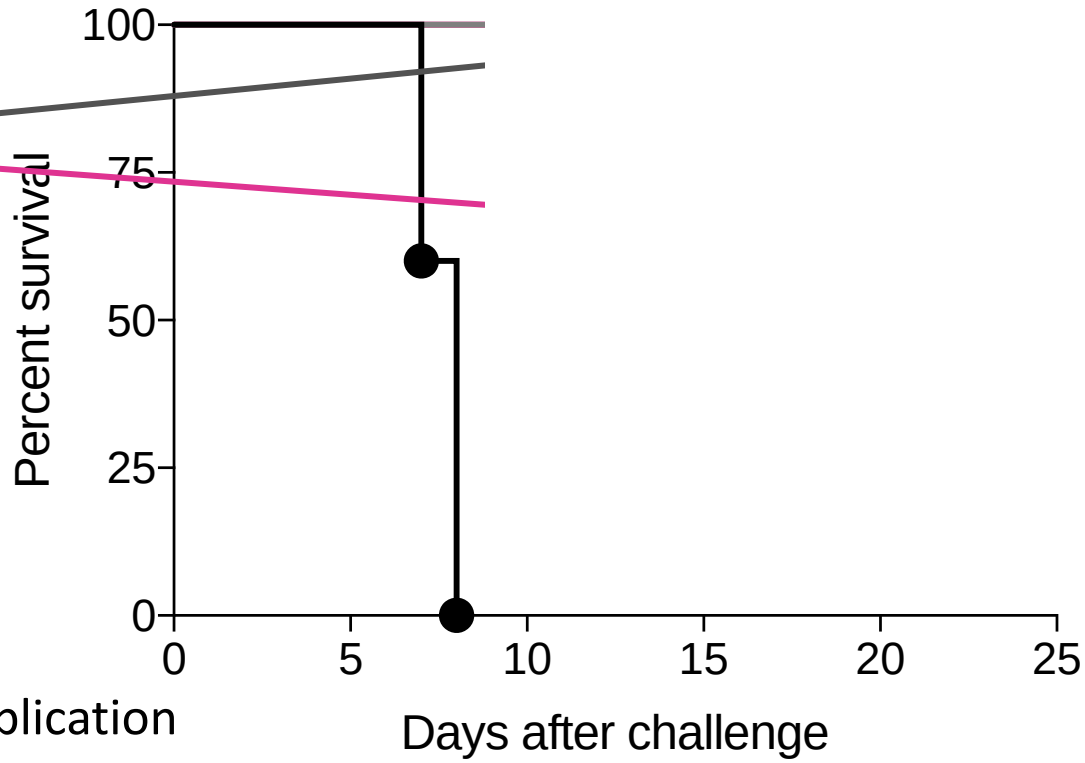




Circulating memory T cells only partially protect the host against HSV-2 challenge

Group #	Symbol		HSV-2 challenge	Number of mice
1	●	Naive WT	Naive WT	9
2	■	Immune WT	Immune WT	12
3	▲	Immune WT	Naive WT	20

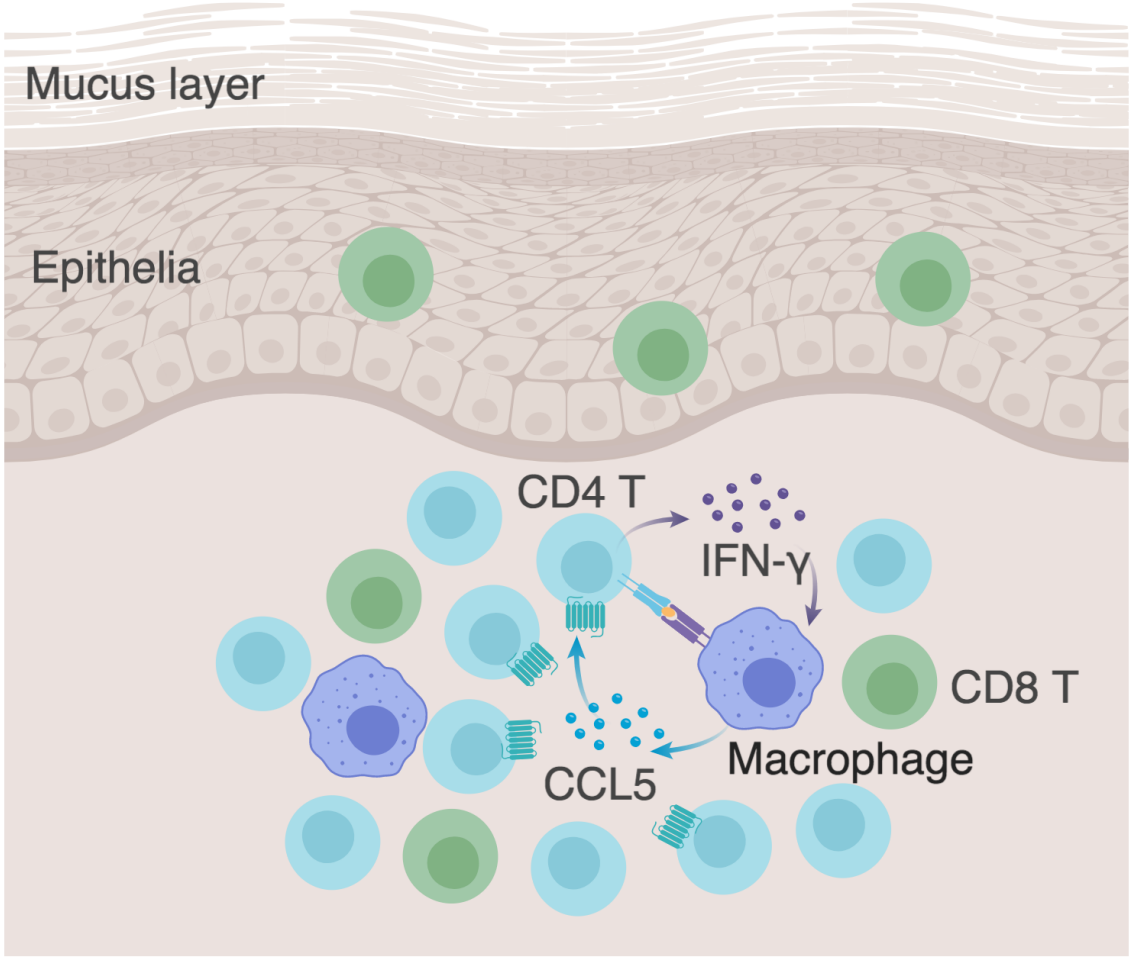




T_{RM} secrete IFNγ to block virus replication

Discovery of a new type of lymphoid structure; memory lymphocyte cluster

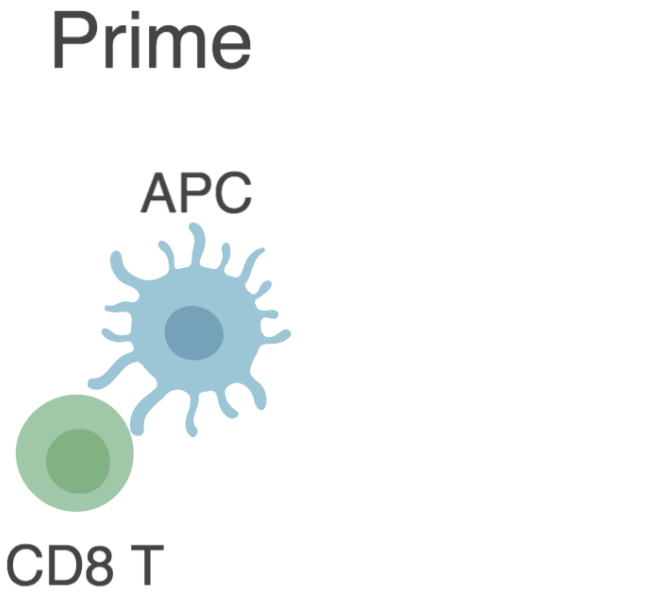
- Local viral infection establishes memory lymphocyte clusters.
- MLC is an organized outpost full of virus-specific T cells ready to defend against local viral challenge.



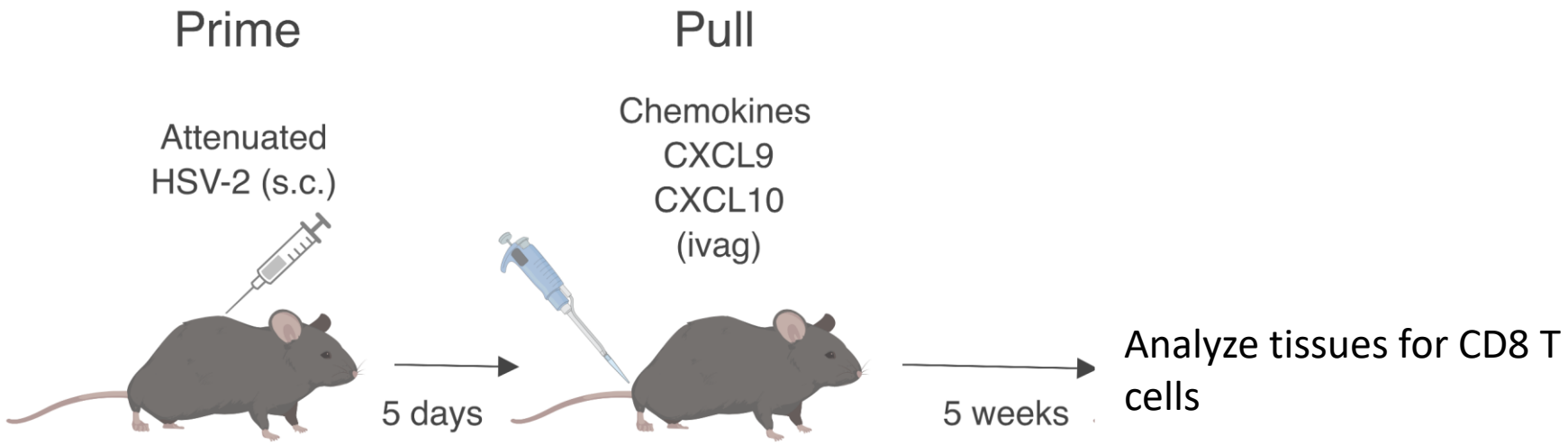
Memory lymphocyte cluster (MLC)

Iijima and Iwasaki *Nature* (2014)

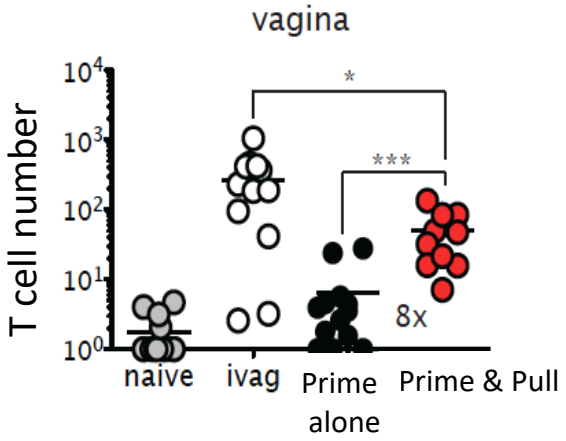
Prime and Pull Vaccine Strategy



Prime and Pull establishes tissue resident memory T cells

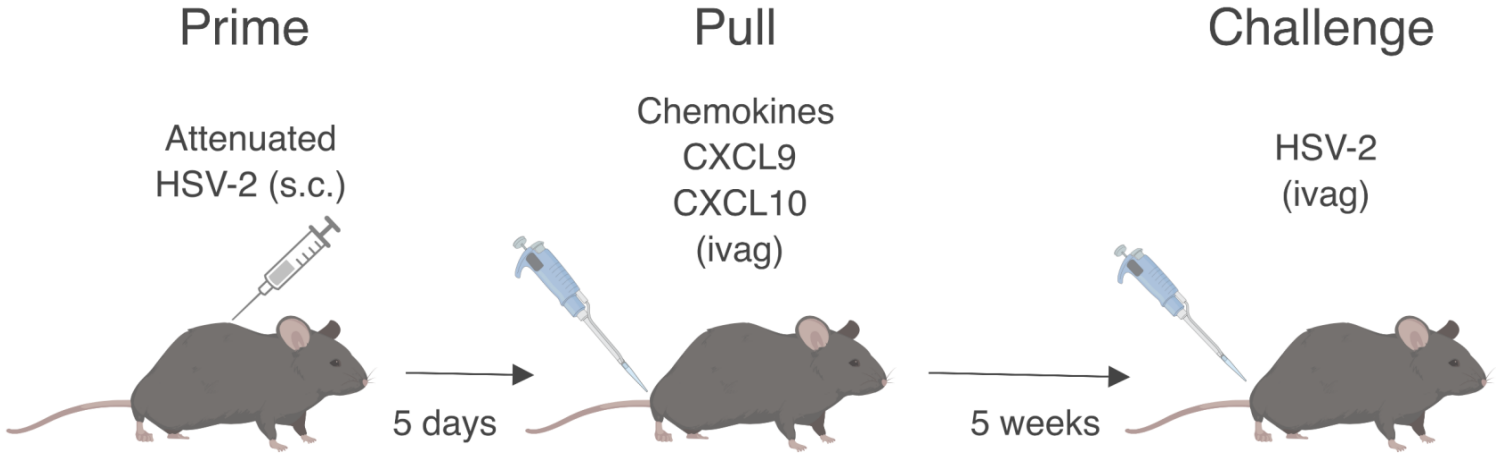


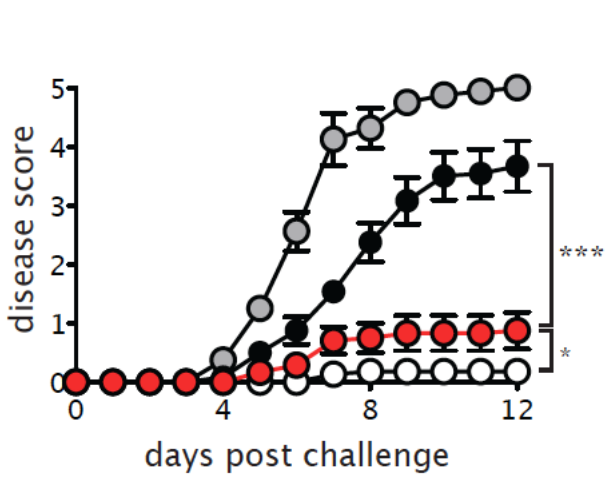
HSV-specific CD8 T cells

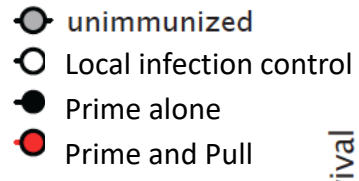


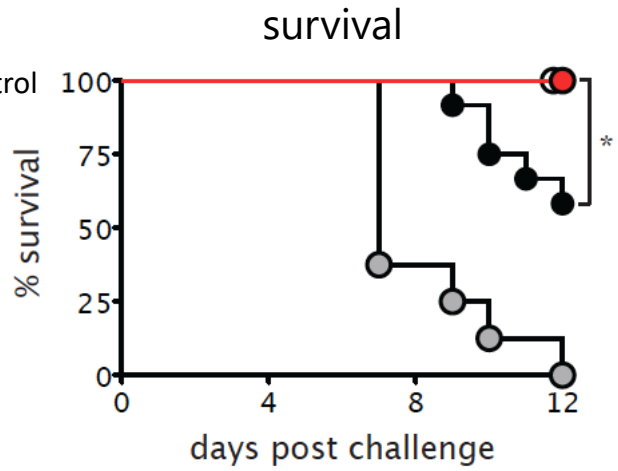
Shin & Iwasaki *Nature* (2012)

Prime and Pull protects mice from lethal herpes infection



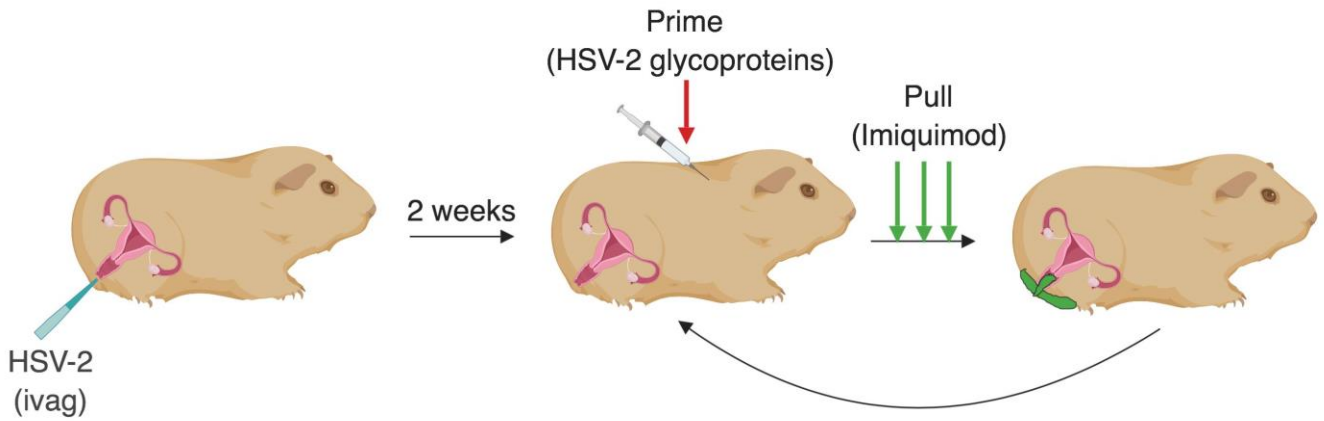


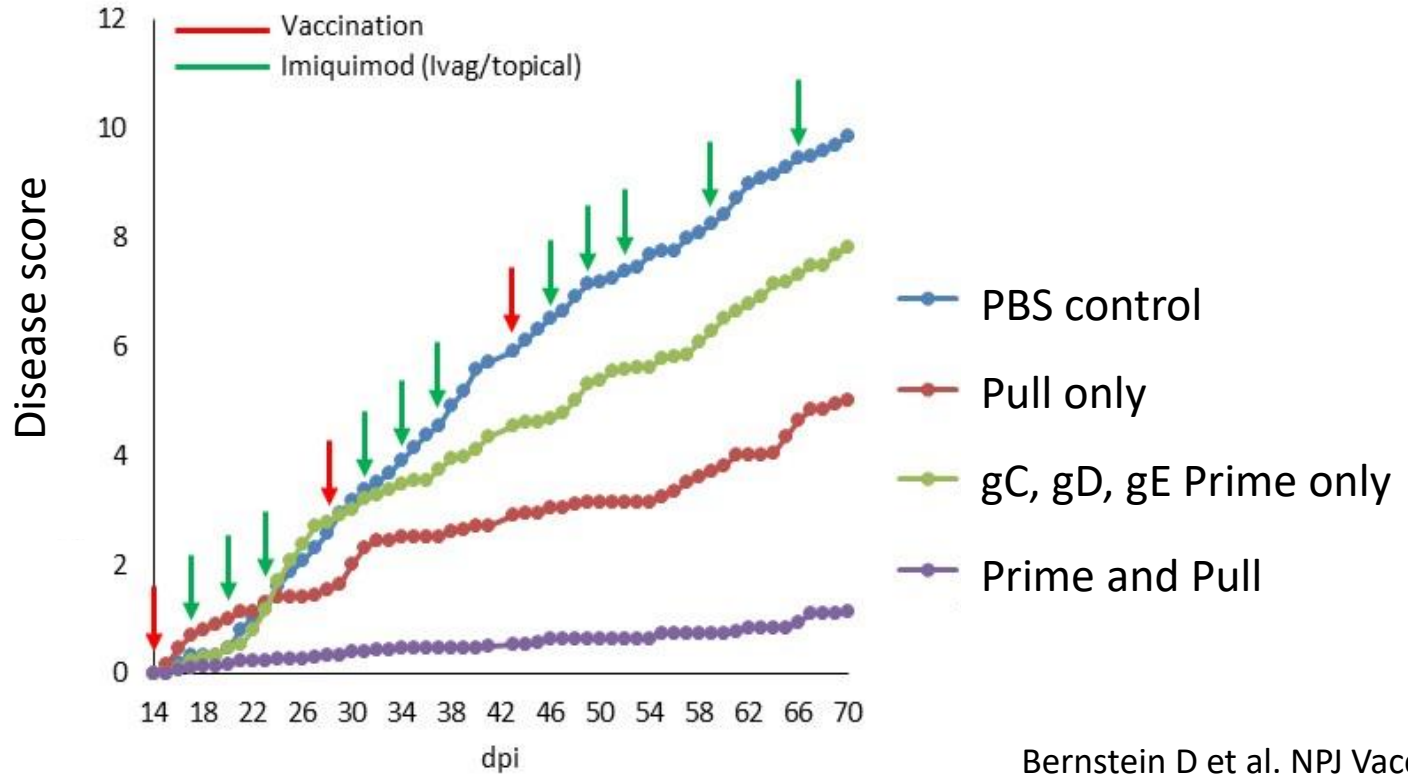




Shin & Iwasaki *Nature* (2012)

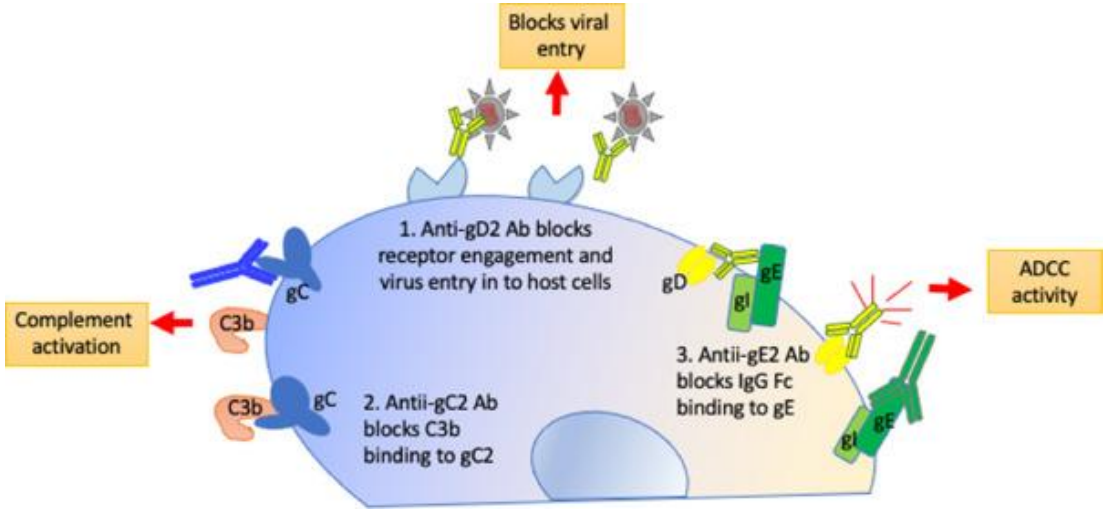
Prime and Pull therapeutic vaccine cures existing disease





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

PLOS PATHOGENS

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RESEARCH ARTICLE

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, Sita 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.