Filovirus Pathogenesis: Considerations for Vaccination Strategies

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Filovirus Infections Cause Systemic Disease in Most All Tissues

**Ideal Filovirus Vaccine:**
Maintain Robust, Circulating, and Durable Humoral Protection

Have Potent and Durable Cellular Component to Bolster Humoral Protection

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Lymph node: infection of macrophages and dendritic cells leading to depletion of lymphocytes and impairment of the host immune response

Liver: infection or necrosis of hepatocytes leading to dysfunction and decreased production of clotting factors

Adrenal gland: infection or necrosis of adrenal cortical cells leading to an impaired synthesis of steroids

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The Lancet 2011 377:849-862 DOI: (10.1016/S0140-6736(10)60667-8)
Can Route of Infection Impact Vaccine Efficacy?

- Decades of filovirus vaccination development focused on **IM challenge** as a stringent bar, modeling “worst case” needle stick scenario.
- Most infections in nature likely are due to **mucosal exposures**
  - Conjunctival, Nasal, Oral, and Aerosol Challenge can result in delayed lethal disease in Nonhuman Primates in a dose dependent manner
    - Prasad et. al. 2023 Natural history of nonhuman primates after oral exposure to Ebola virus variant Makona JID, Nov 13:228
    - Cross et. al. 2023 Natural history of nonhuman primates after conjunctival exposure to Ebola Virus, Scientific Reports 13 (1) 4175
    - Alfson et. al. 2017 Development of a Lethal Intranasal Exposure Model of Ebola Virus in the Cynomolgus Macaque
    - Prasad et.al. 2023 Pathogenesis of Aerosolized Ebola Virus Variant Makona in Nonhuman Primates, JID, Nov 13:228
- NHP models suggest prolonged disease course after mucosal challenge can allow for wider and more systemic spread into immune privileged sites
- **Limited published data on vaccine protection against mucosal challenge routes**
- **Is IM vaccination really the best route? What about Mucosal, Dermal, Combos?**
Antigen Selection: *One glycoprotein to rule them all?*

- Primary Antigen for Vaccine Design has been **Glycoprotein** to drive Humoral Protection in most vaccines where some Evidence of Cellular Protection has been shown to also be present for some vaccines.

- Live attenuated vaccines expressing the EBOV glycoprotein have clearly shown that **only limited cross reactivity** to other filoviruses supporting the notion that *blended, chimeric, or sequential vaccination strategies may be the path forward as a “PAN-Filovirus vaccine”*

- Limited focus on **NP** despite potential to direct towards **Cellular Immunity**.
  - **Recent:** saRNA vaccines suggest a benefit from addition of NP to vaccination
What can we learn from Natural Survivors?

Ebola Virus Disease Survivors Show More Efficient Antibody Immunity than Vaccinees Despite Similar Levels of Circulating Immunoglobulins

Till Koch 1,2,3, Monika Rottstegge 2,3, Paula Ruibal 2,3, Sergio Gomez-Medina 2,3, Emily V. Nelson 2,3, Beatriz Escudero-Pérez 2,3, Matthias Pillny 4, My Linh Ly 1,2,3, Fara Raymond Koundouno 5, Joseph Akoibore 5, N’Faly Magassouba 6, Christine Dahlke 1,2,3, Stephan Günther 2,3, Miles W. Carroll 7, Marylyn M. Addo 1,2,3 and César Muñoz-Fontela 2,3,4.
Filoviruses can Persist in Survivors

Importance of Clearance of Systemic Infections

Ebola-Specific CD8$^+$ and CD4$^+$ T-Cell Responses in Sierra Leonean Ebola Virus Survivors With or Without Post-Ebola Sequelae

A

CD8$^+$ T-cell response to any EBOV-specific antigen

*P = .02

Survivors with positive response, %

84%

16/19

Survivors Without positive response

47%

7/15

B

CD4$^+$ T-cell response to any EBOV-specific antigen

*P = .03

Survivors with positive response, %

63%

12/19

Survivors Without positive response

27%

4/15
Is there Benefit to Vaccination of Survivors?

Can boosting humoral response serve as a barrier to shedding from sanctuary sites?

Can potent cellular responses serve to clear out sanctuary sites from stubborn infections?
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