Rift Valley Fever: key immunological considerations for vaccine development

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Rift Valley fever virus

First Identified in the 1930’s
- Rift Valley of Kenya

Livestock pathogen
- Cattle, goats, sheep

Transmission to humans
- Mosquito: arbovirus
- Contact with blood/bodily fluids of affected livestock

Blue= endemic
Green= seropositive reports

https://www.cdc.gov/vhf/rvf/index.html
Human disease manifestations

3-6 days post infection

7

Self-limiting febrile illness >80%

14

Retinitis

Encephalitis

Days post-initial symptom onset

21

28

Overall mortality: 1-3%
Up to 60% of adults seropositive in endemic areas

Heptatitis
What are the key viral antigenic targets for a RVFV mRNA vaccine?

- **Surface glycoproteins Gn/Gc**
  - Target of neutralizing antibodies

- Nucleocapsid protein and the polymerase protein
  - Inside the virion
  - Intracellularly expressed

- Non-structural proteins NSm and NSs
  - Virulence factors
RVFV potential immune correlates

• Neutralization- functional ability of antibodies to block virus entry
  • Antibodies are directed against the viral surface glycoprotein (mostly Gn)
  • Plaque reduction neutralization titer: PRNT
  • Focus reduction neutralization titer: FRNT
  • Expressed as 50% or 80% reduction

• ELISA- quantitation of antibodies that bind to viral proteins

• Cellular immune assays- measure the ability of T cells to recognize viral proteins
  • Measured by the release of cytokines from the T cells, e.g. IFN-γ
Natural infection induces sustained RVFV humoral response

- Two villages in Kenya
- Sampled 3 years apart
- 13 individuals who were positive in 2006 also sampled in 2009
- All with PRNT80 over 100
- One with increased titer between sampling suggesting re-exposure
Natural infection induces long-lived robust immune responses

- Two cohorts in Kenya
- Longitudinal data in 5 individuals
- High titer virus neutralizing antibodies
- IgG1 predominant
- Gn/Gc specific T cell function also noted
Immune correlates of protection

- Not clearly defined for humans
- Often associated with neutralizing antibodies
- Very little data on human cellular immunity and no established correlates for cellular immunity
- Pre-clinical data in mice, hamsters, rhesus macaques
  - Passive transfer experiments
  - PRNT or FRNT levels correlates with protection from challenge
Immune correlates of protection-mice

- Naïve mice administered different amounts of immune serum from mice vaccinated with live attenuated DelNSs RVFV
- FRNT80 measure in mice 24 hours after transfer then mice challenged with WT RVFV
- Note differences in protection based upon challenge dose
- GMT FRNT$_{80}$ $\geq$ 74 was 100% protective at both challenge doses
Immune correlates of protection - NHPs

Table 2. Protection against RVFV infection by passive antiserum

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Antibody dosea</th>
<th>Pre-infection PRNTb</th>
<th>Viremia&lt;sup&gt;c&lt;/sup&gt;</th>
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<tr>
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<td></td>
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<td>Day</td>
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a ml/kg given i.m. on day −2; serum PRNT<sub>80</sub> 1:2,560
b GMT ± SEM of log<sub>10</sub> PFU/ml serum; number viremic in parenthesis
c Geometric mean titer or GMT (range)
d s.c. inoculation with 6.0 log<sub>10</sub> PFU of ZH501 FRhL<sub>1</sub> spleen, serum, spleen<sub>1</sub> on day 0
e i.v. inoculation with 4.1–4.7 log<sub>10</sub> PFU of ZH501 FRhL<sub>2</sub> on day 0

Experimental Rift Valley fever in rhesus macaques


Disease Assessment and Pathology Divisions. U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland, U.S.A.

Accepted December 12, 1987

- Rhesus macaques given 0.5 ml/kg down to 0.025 ml/kg of immune serum with a starting PRNT80 of 1:2560
- Challenged with WT ZH501
- Animals were protected from disease and had undetectable viremia following any dose of antibody
Does vaccination induce sufficient immunity? How long will vaccine mediated immunity last? Will boosters be necessary?

• Likely depends upon the platform and immunogen
• Lessons learned from prior vaccines
  • Formalin inactivated vaccine
  • MP-12- live attenuated
  • ChAdOx
  • DDVax (University of California Davis and Colorado State)-NHP data
  • RVFV-4S (Wageningen Bioveterinary Research)- NHP data
Formalin inactivated vaccine

- First vaccine tested in humans
- 1860 subjects
- 3 dose primary series (0,14,28d)
- Estimated that $\geq 1:40$ was protective
- Required boosting to maintain titers over time
MP-12- mutagenized live attenuated

- Single dose $1 \times 10^5$ PFU
- 62 subjects in Phase I and Phase II
- Estimated that $\geq 1:20$ was protective

18/19 seroconverted
8/9 maintained $\geq 1:20$ out to 5 years
ChAdOx1 RVFV vaccine

- Chimpanzee adenovirus vectors RVFV Gn/Gc
- Single dose $5 \times 10^9 - 5 \times 10^{10}$
- 15 subjects
- 12/15 seroconverted
- FRNT stable out to 3 months
- Phase I in Uganda recently completed
Summary- a RVFV mRNA vaccine?

• Gn/Gc most likely antigen
• Neutralizing antibodies are easy to measure and correlate well with protection in pre-clinical models
• Defining the true protective neutralization titer in human efficacy studies still needs to be done- tough given the sporadic nature of RVFV emergence in resource limited locations
  • WHO/CEPI sponsored international standards will help to coordinate this amongst groups
• Unknowns:
  • Will mRNA vaccination induce sufficient magnitude of neutralizing antibodies?
  • Will an mRNA vaccination induce durable immunity?
  • Will route or dose of exposure affect vaccine efficacy in humans?