Medical countermeasures against Rift Valley fever

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RVF research in Umeå

- Kinetics of RVFV infection in mice

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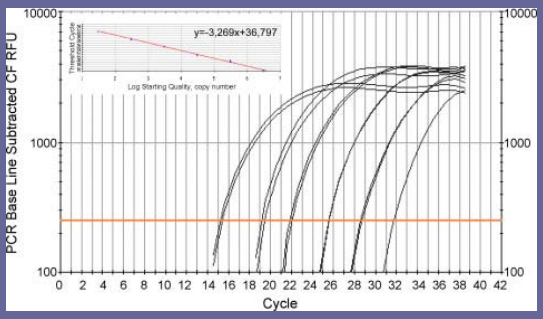
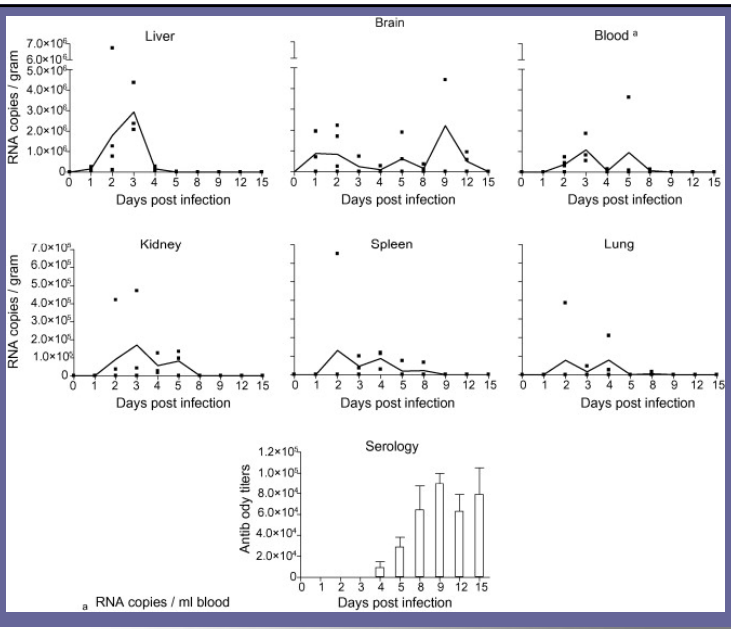
Quantitative real-time PCR

- Detect and quantify the RVFV (genomes)
- Primers that target the S-segment

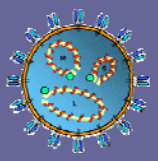




Kinetics of RVFV infection in mice

Näslund J et al. *Journal of Virological Methods. 151:277–82. 2008.*

RVF research in Umeå



- Kinetics of RVFV infection in mice
- RVFV vaccination in mice

Treatment and Vaccines

Anti viral

- No specific for RVFV exist

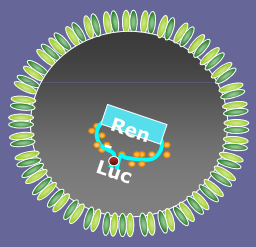
Vaccines

- Animals
  - Smithburn vaccine strain – attenuated through neuroadaption
  - Formalin inactivated RVFV
- Humans (only for high risk personnel)
  - TSI-GSD-200

Vaccine Candidates

- Clone 13 - natural isolate
- MP12 - chemically induced attenuation
- R556 - reassortant of Clone 13 and MP12
- Genetically engineered RVFV
- Viral vectors – Adenovirus, Alphavirus, newcastle disease virus
- DNA vaccine
- Virus-like particles

VLP vaccination against RVFV

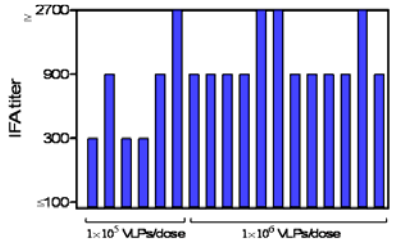


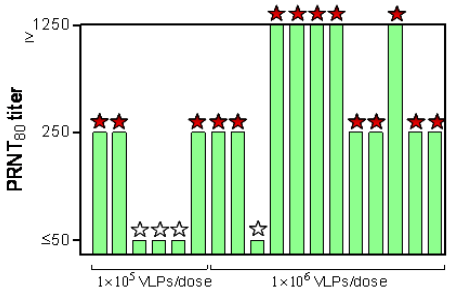
- Intra peritoneal immunised mice (C57Bl/6).
- 2 different doses.
- Challenged with wild type RVFV.

RVF VLPs are immunogenic in mice

Vaccination with RVF VLPs induce virus neutralizing antibodies

RVF VLPs are immunogenic in mice





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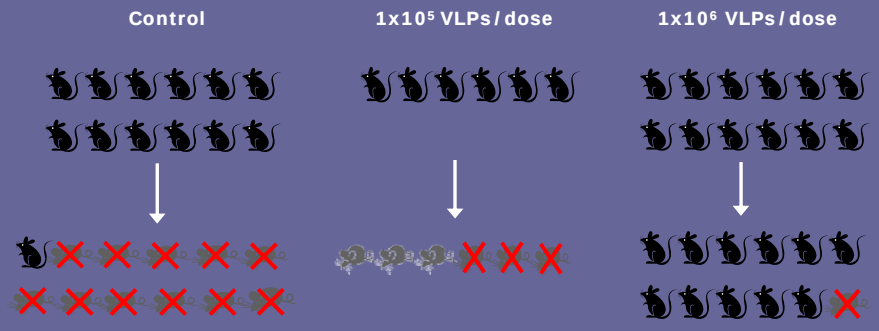
VLP vaccination against RVFV

Outcome



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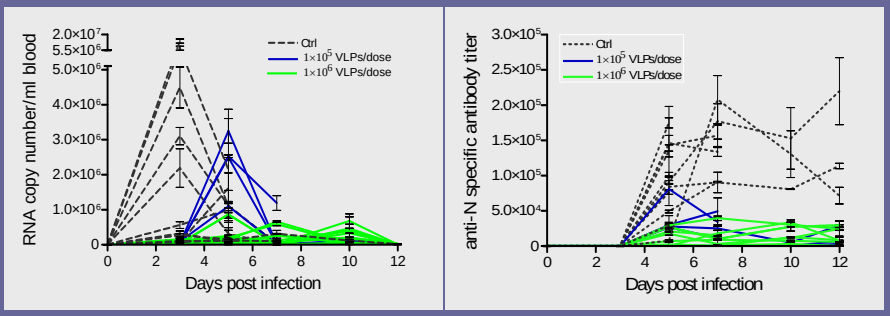
Vaccinations with RVF VLPs suppress viral replication after challenge



VLP vaccination against RVFV

Näslund et al., Virology, 2009

RVF research in Umeå

- Kinetics of RVFV infection in mice
- RVFV vaccination in mice
- Field sampling

Field sampling

- Nobuto filter strips
- Dried in blood samples with known amounts of virus
- Measure RNA load and infectivity

Field sampling

- RVFV RNA was not detected
- Blood stored on filter paper less than 48h may contain viable RVFV particles

RVF research platform in Umeå

- Animal model
- Mosquito transmission facilities
- BSL-3 lab
- RVFV with reporter genes (BSL 2)
- VLPs with marker dyes
- Small inhibitory compound screening platform
- Cell line library
- qRT-PCR, antibodies (serology)
- Collaboration with scientists in endemic countries

RVFV in Umeå

Magnus Evander, Umeå University
Clas Ahlm, Umeå University
Göran Bucht, FOI Umeå
Nina Lagerkvist, Umeå University and Karolinska Inst.
Maria Baudin, Umeå University

Thank you for your attention!!

Collaboration

Friedemann Weber, Marburg University, Germany
Rosemary Sang, Icipe, Kenya
Michéle Bouloy, Pasteur Institute, France
Åke Lundkvist, Karolinska Institute
Osama Ahmed Hassan, Sudan

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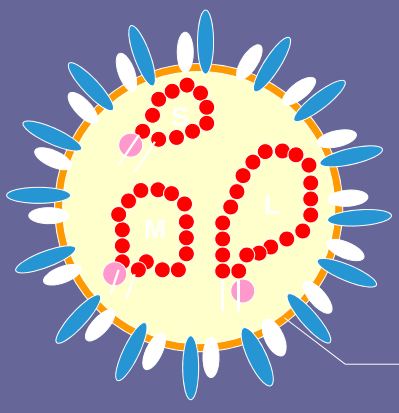
Rift Valley Fever Virus

Bunyaviridae, Phlebovirus

S segment
↓
N protein
NSs protein

M segment
↓
Gn, Gc proteins
NSm protein

L segment
↓
L protein



N Protein
L Protein
RNP
Gc Protein
Gn Protein
Lipid envelope

RNP = RiboNucleoProtein

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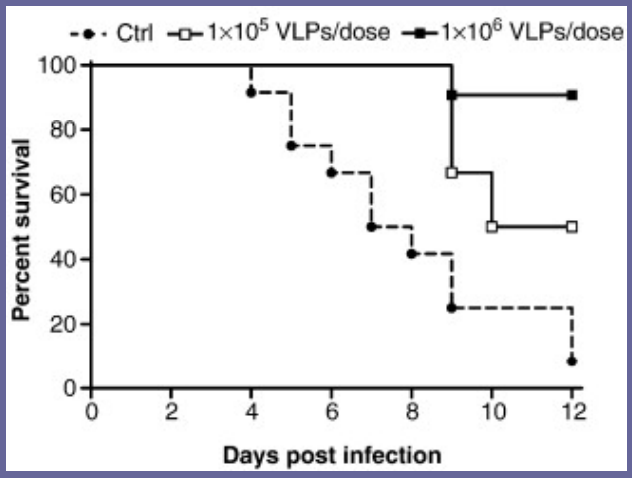
Vector competence for RVFV Viruses in Swedish mosquitoes

47 different blood-feeding mosquitoes in Sweden
Competent for RVFV transmission?
RVFV infection kinetics in mosquitoes

Virus surveillance in Swedish mosquitoes



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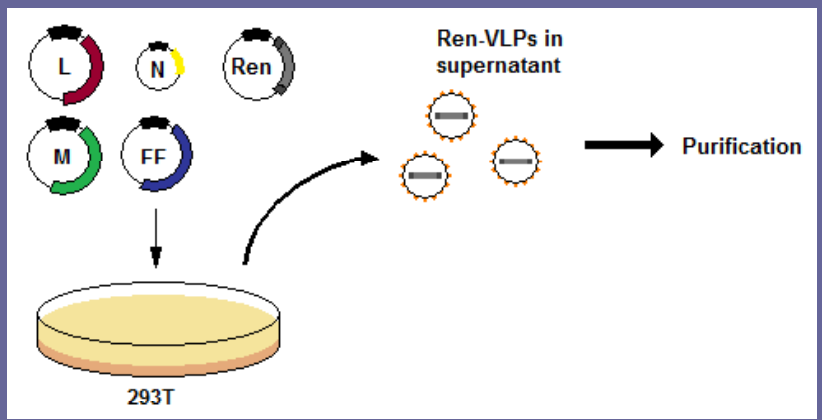
Advantages and disadvantages of animal models for Rift Valley fever.

Model	Advantages	Disadvantages
Mouse	• Highly susceptible to RVFV • Infected mice usually die in 2 weeks, and are suitable for RVFV challenge study • Acute hepatitis and lethal meningoencephalitis at late stage • Cost-effective	• No hemorrhagic fever • No ocular diseases
Rat	• Varied susceptibility among inbred strains • Suitable for studying host genes responsible for RVFV-resistant phenotype • Similar pathological changes to those in mice • A report suggests the presence of uveitis after aerosol challenge • Cost-effective	• The inbred strains of same name derived from different breeding colonies have different susceptibility to RVFV. • Age-dependent difference in susceptibility
Hamster	• Highly susceptible to RVFV • Similar pathological change to those seen in mice • Often used for experimental RVFV transmission by mosquitoes	• No hemorrhagic fever • No ocular diseases • Limited research resources
Gerbil	• Encephalitis with minimum liver diseases • Useful for studying neuroinvasiveness	• No significant diseases except for Encephalitis • Age-dependent difference in susceptibility • Limited research resources
Rhesus monkey	• Lethal hemorrhagic fever • Similar susceptibility to humans • Important for testing the safety of vaccines or antivirals before clinical trial	• No ocular diseases reported • Less than 20% develop hemorrhagic fever • Requirement of ABSL4 or BSL3+ space to keep monkeys • Expensive
Adult sheep, ewe	• A report suggests the occurrence of hemorrhagic fever and edema of corneal and choroidal edema with inflammation • High rate of abortion and fetal malformation • Suitable for veterinary vaccine study	• Susceptibility varies among different breeds • Requirement of ABSL4 or BSL3+ for large animals • Limited research resources • Expensive
Lamb	• Highly susceptible to RVFV • Lethal acute hepatitis • Important to evaluate the effect of collostrum from vaccinated ewes	• Neurovirulence is not prominent • No hemorrhagic fever • No ocular diseases • Requirement of ABSL4 or BSL3+ for large animals • Limited research resources

RVF Virus-Like-Particles (VLP)



L = viral polymerase
M = viral glycoproteins G_c and G_n
N = nucleocapsid protein
Ren = minireplicon construct
FF = firefly luciferase