Disease Progression of Two Genetically Diverse Strains of Crimean-Congo Hemorrhagic Fever Virus in NHPs

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Crimean-Congo Hemorrhagic Fever Virus (CCHFV)

- Member of the newly created Nairoviridae (formerly bunyaviridae/nairovirus)
- Enveloped, segmented –ssRNA genome
- Spread to humans
  - Tick bites
  - Animals (butchers)
  - Nosocomial
- Causes VHF: liver damage, neurological, coagulation abnormalities. Lethal ~20%
- BSL-4 agent
- No licensed drugs or vaccines
Crimean-Congo Hemorrhagic Fever Virus Has a Wide Geographical Distribution
CCHF Clinical Disease

Exposure:
- Tick bite
- Crushing infected tick
- Nosocomial
- Blood or tissues of infected animals


CCHF NHP Modeling

- NHPs historically refractory to CCHFV challenge, canonical reference strain IbAr 10200 (Nigerian isolate) produces asymptomatic profile

- Recently, Heinz Feldmann’s group at Rocky Mountain Laboratory has developed a successful challenge model using Cynomolgus Macaques and a European isolate, Kosova Hoti

Cynomolgus Macaque
(Macaca fascicularis)

High Viral Dose ($10^6$ IU) by IV or combined SC/IV route
CCHF NHP Modeling

• CCHFV strains display considerable diversity at both the genetic and proteomic levels; does this contribute to differences in pathogenicity?

• We wanted to compare the established Hoti model against an Asiatic isolate of the virus, Afg09-2990

  GPC; Hoti vs. Afg09 = 85% protein cons.

  N; Hoti vs. Afg09 = 97% protein cons.
Extending the CCHF NHP Model-Overview

Kosova Hoti strain

- IV challenge (5 X 10^6 pfu)
- Temperature telemetry monitoring, daily serology, clinical observations
- Humane euthanasia as needed or end of study sacrifice

Afg09-2990 strain

- Clinical Score/ Fever Data
- Viremia
- Blood Chemistry/ Hematology
- Serum Chemokines
- IgM/IgG/neut abs
- Tissue Pathology; H&E/IHC/ISH
CCHF NHP Disease Course

Viremia, Clinical Score, and Fever

IgM, IgG, and Neutralization

Blood Chemistry, Hematology, and Serum Cytokines

- Sublethal disease state was established in all animals
- Rapid onset of symptoms, especially fever in both virus groups
CCHF NHP Disease Course

Fever Profile

Petechial Rash-day 3
Extending the CCHF NHP Model-Summary

USAMRIID
- Rapid fever response to both strains
- Prolonged fever and elevated clinical profile
- Depressed platelets and lymphocytes
- Elevated liver enzymes
- Elevated serum cytokines
- IgM and IgG response

RML
- Higher morbidity and mortality
- Longer incubation period

Future Directions
- Examine host factors that might determine disease severity
- Evaluate medical countermeasures (e.g. vaccines and therapeutics) in the Cynomolgus Macaque model
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Research was conducted under and IACUC-approved protocol in compliance with the Animal Welfare Act, PHS Policy, and other Federal statues and regulations relating to animals and experiments involving animals. The facility where this research was conducted is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, National Research Council, 2011.