

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

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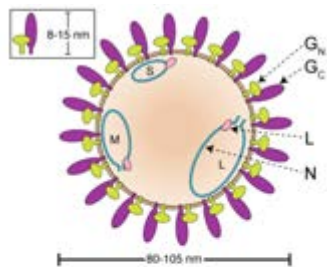
United States Army Medical Research Institute of Infectious Disease  
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# Crimean-Congo Hemorrhagic Fever Virus (CCHFV)



Hyalomma (hard-bodied) tick

- 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**

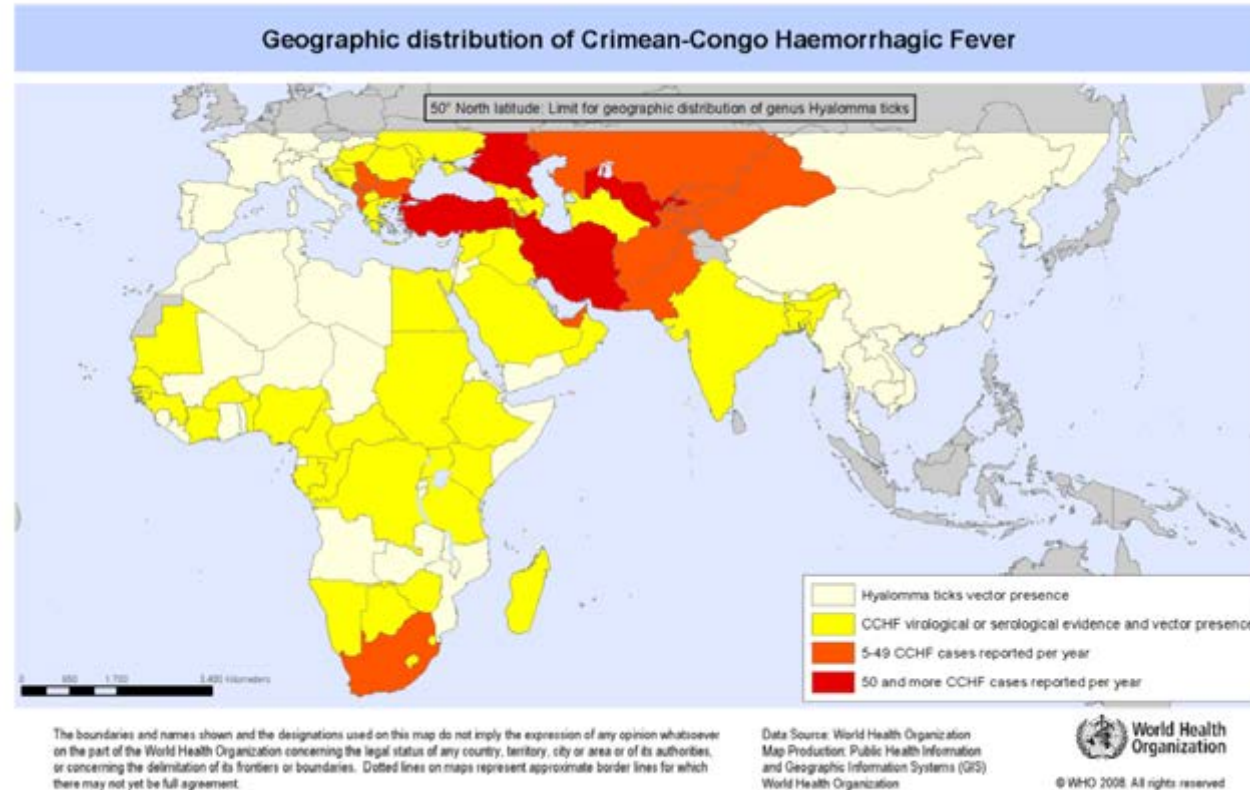


Virus Image from Taylor S. Virology ELS. March 2009



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# Crimean-Congo Hemorrhagic Fever Virus Has a Wide Geographical Distribution



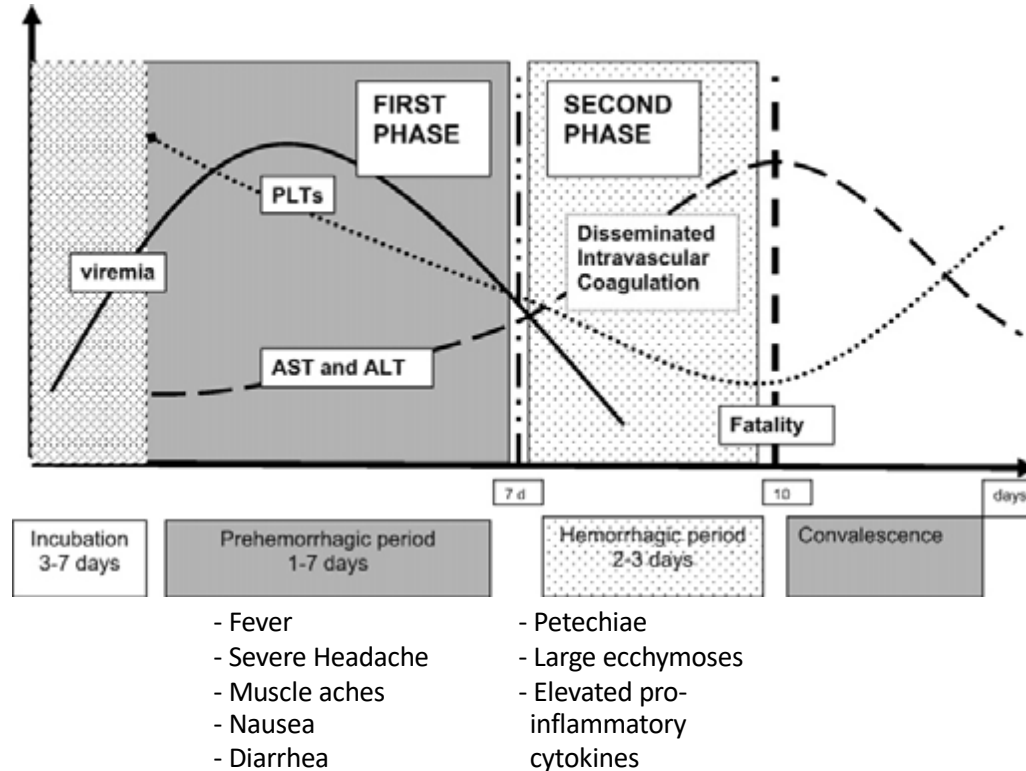
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# CCHF Clinical Disease



Exposure:

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



Whitehouse C., Antiviral Res (2004)

Ergonul. 2008. Antiviral Res . 78(1):125-31(2007)



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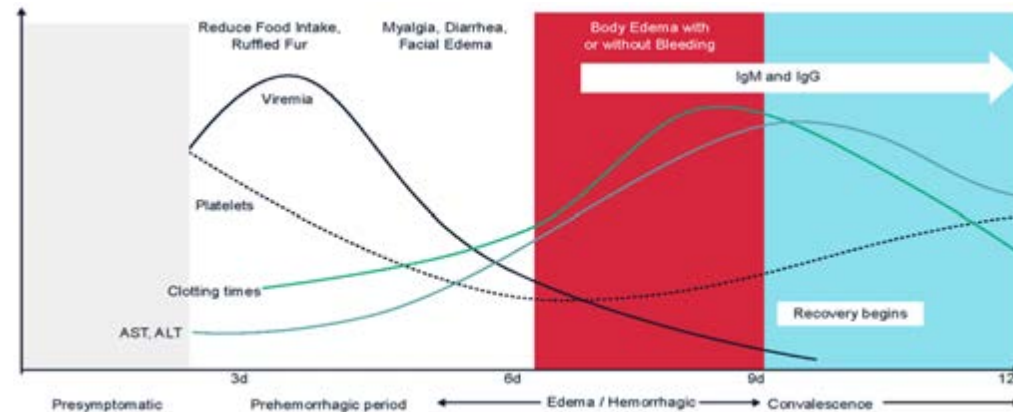
# CCHF NHP Modeling

- 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*)

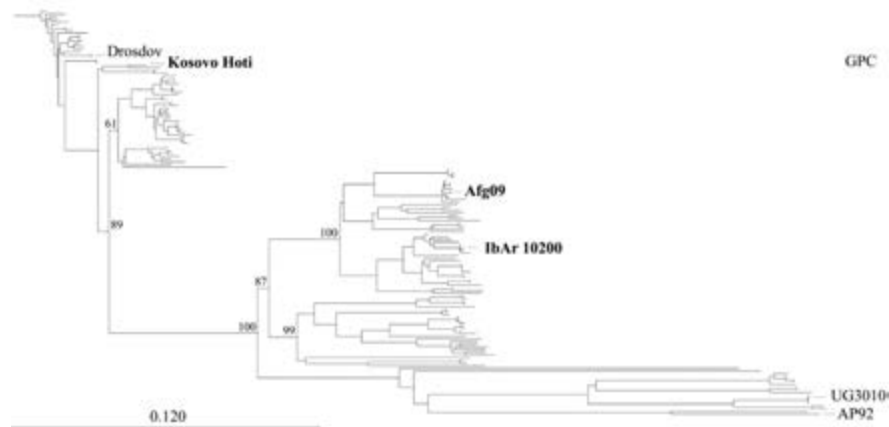
High Viral Dose ( $10^6$  IU) by IV or combined SC/IV route



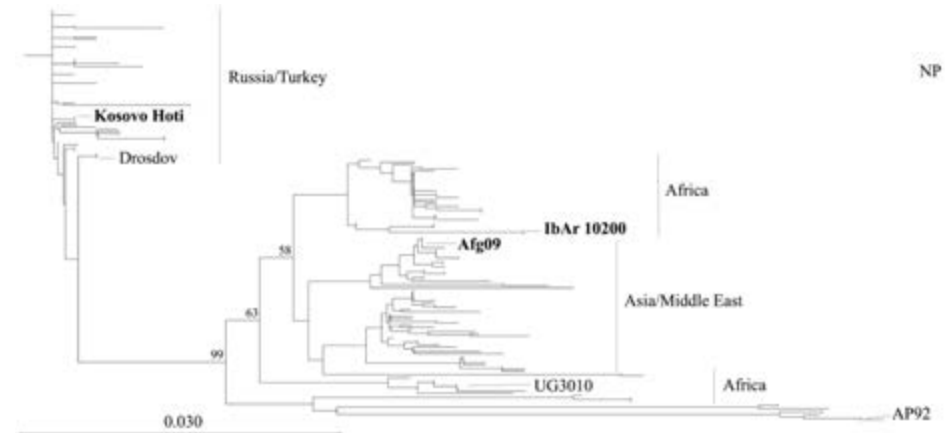
# CCHF NHP Modeling

- CCHFV strains displays 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 a Asiatic isolate of the virus, Afg09-2990

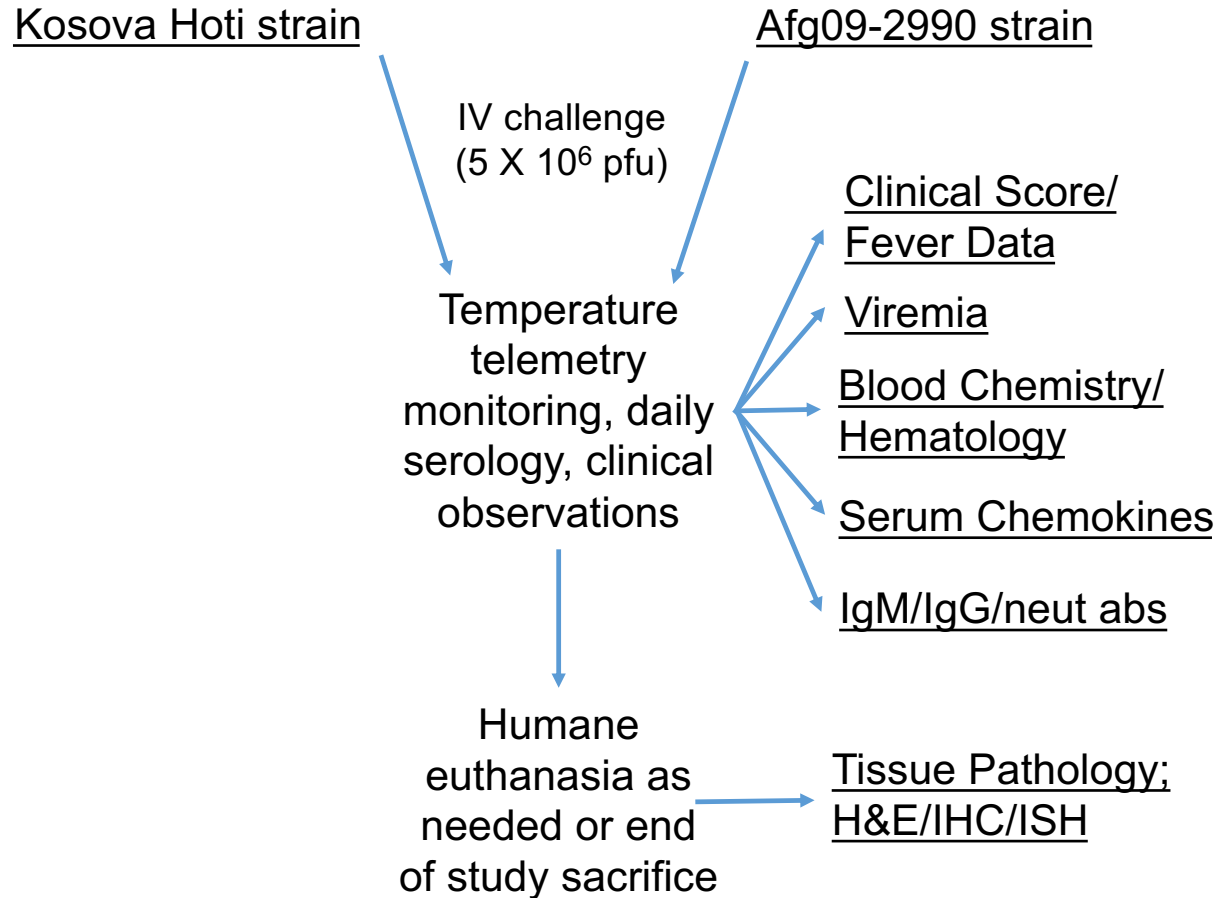
GPC; Hoti vs. Afg09= 85% protein cons.



N; Hoti vs. Afg09= 97% protein cons.



# Extending the CCHF NHP Model-Overview

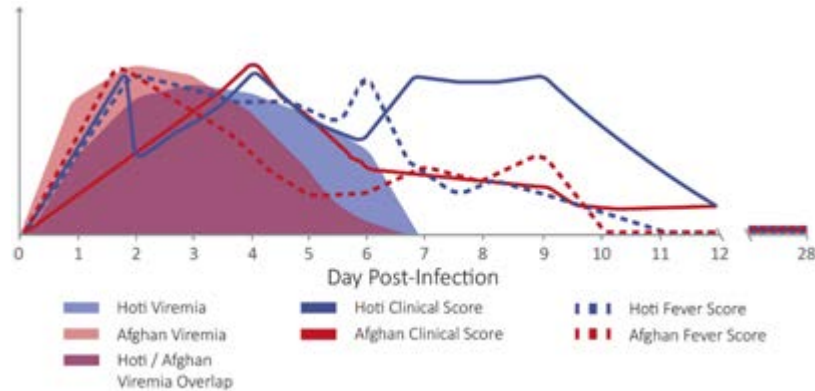


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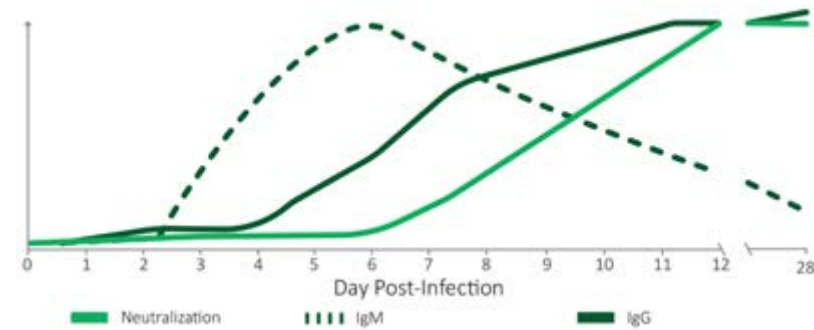
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# CCHF NHP Disease Course

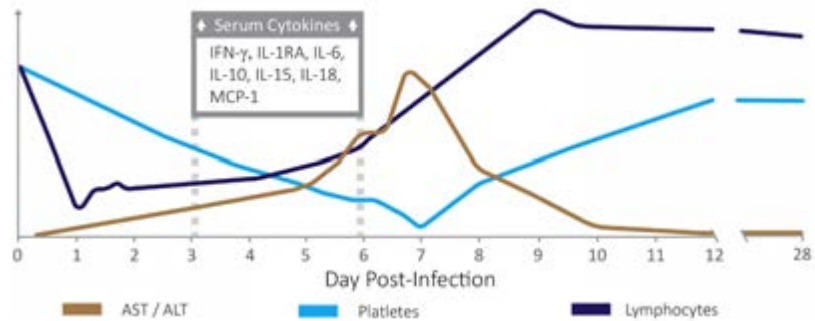
Viremia, Clinical Score, and Fever



IgM, IgG, and Neutralization



Blood Chemistry, Hematology, and Serum Cytokines

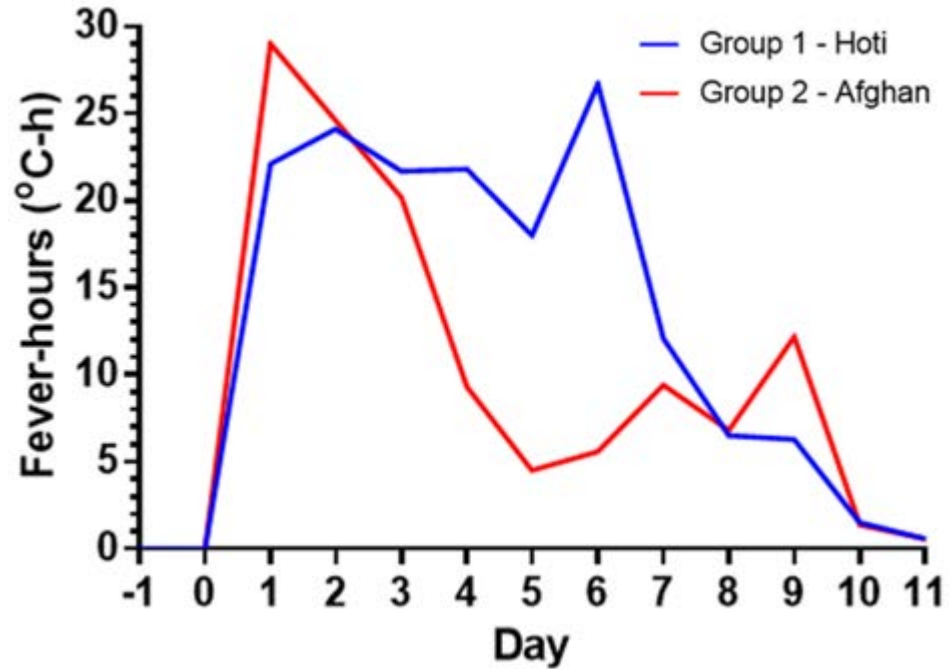


- Sublethal disease state was established in all animals
- Rapid onset of symptoms, especially fever in both virus groups





# CCHF NHP Disease Course



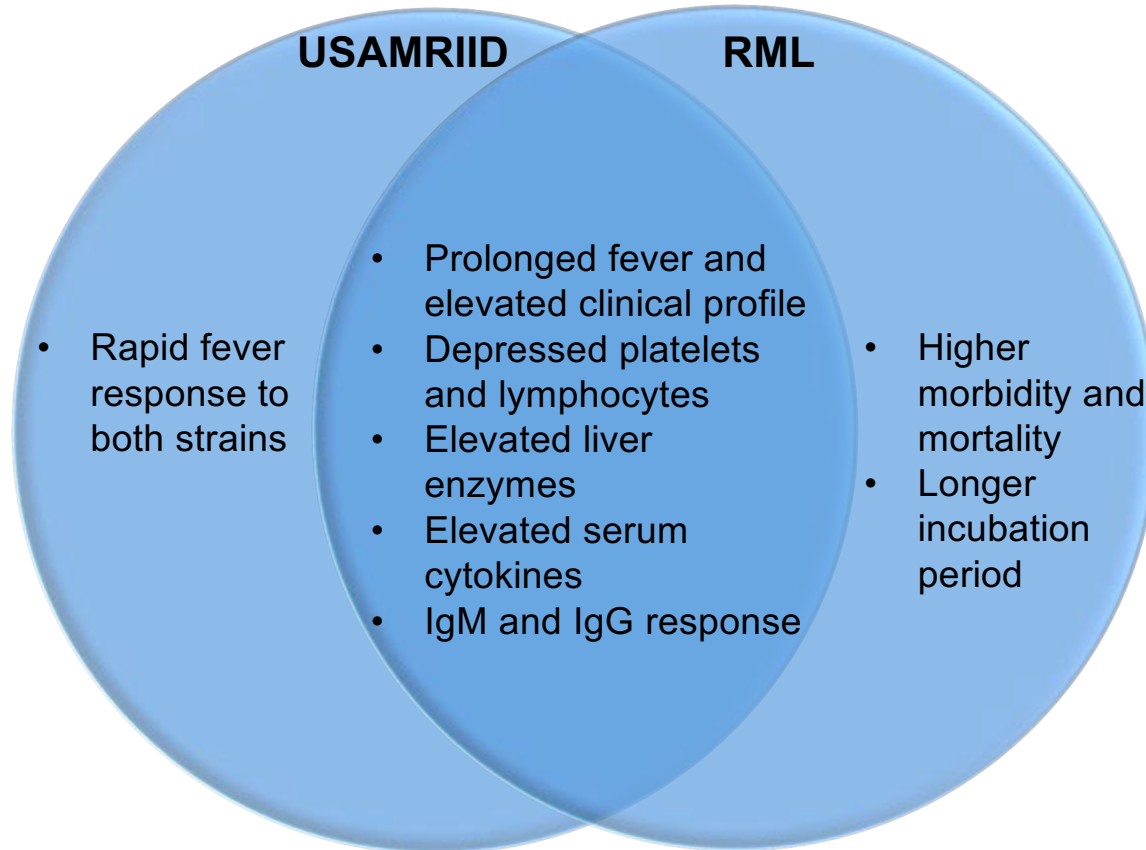
Fever Profile



Petechial Rash-day 3



# Extending the CCHF NHP Model-Summary



## 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 statutes 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.



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