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Biodefense solutions to protect our nation

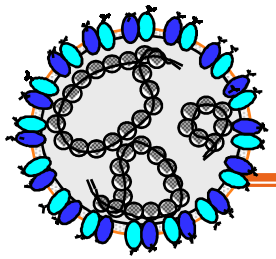
# Phase 1 Clinical Trial of DNA Vaccines for Hemorrhagic Fever With Renal Syndrome Delivered by Intramuscular Electroporation


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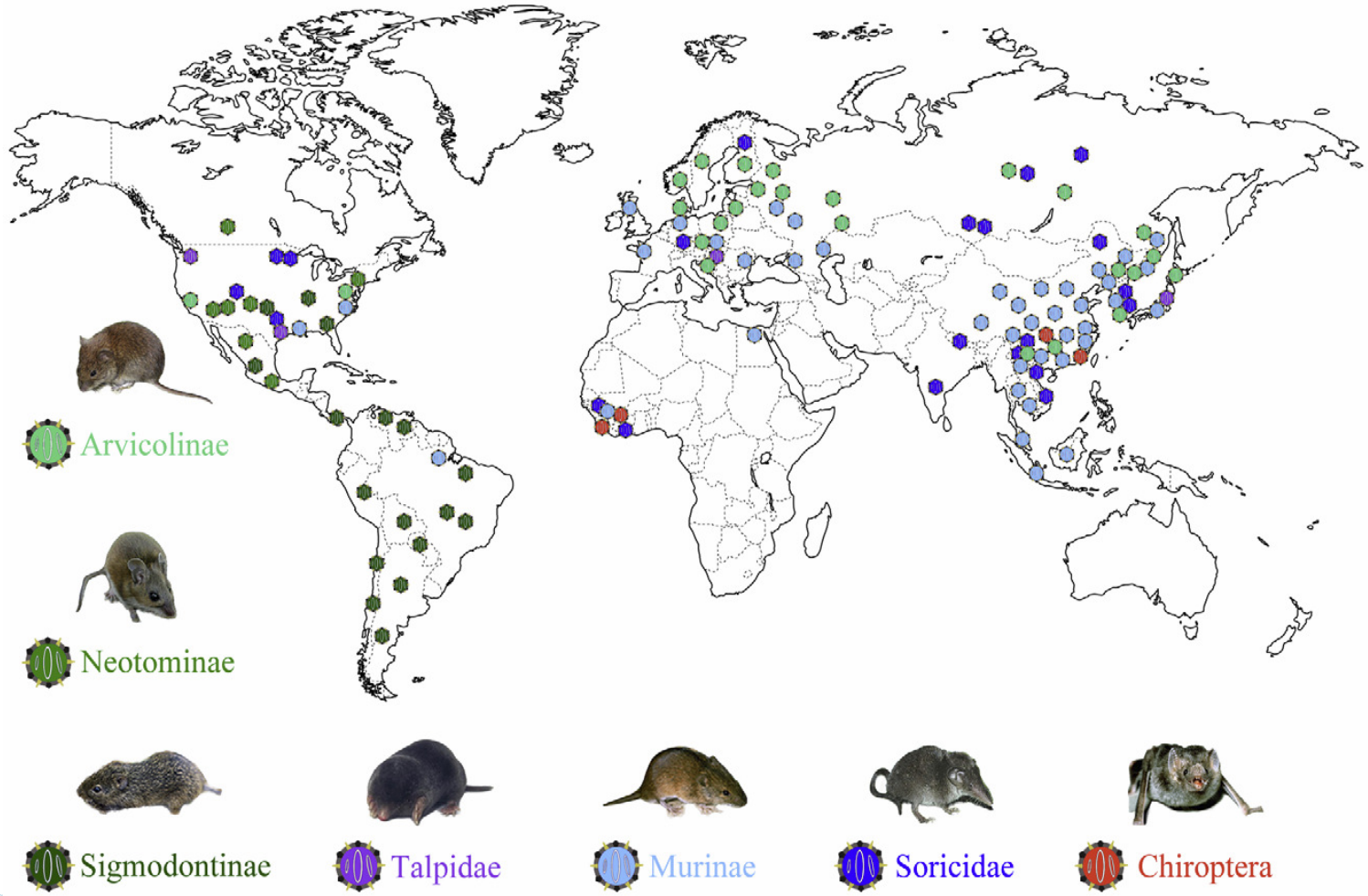
4th International Conference on Vaccines & Vaccination
Valencia, Spain
September, 2014



*Bunyaviridae*

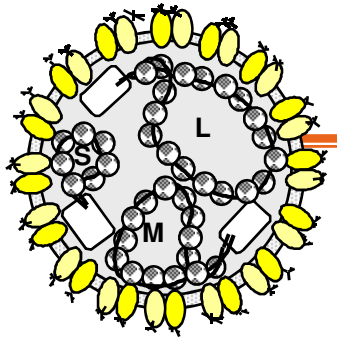
# Hantaviruses and Their Hosts

**Hantaviruses have been detected in >50 species of rodents, shrews, moles and bats**



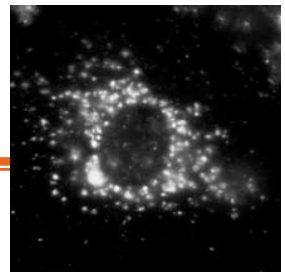

Guo WP, et al. (2013) PLoSPathog 9(2): e1003159.

# Hantaviruses




NIAID Category A
Priority Pathogens





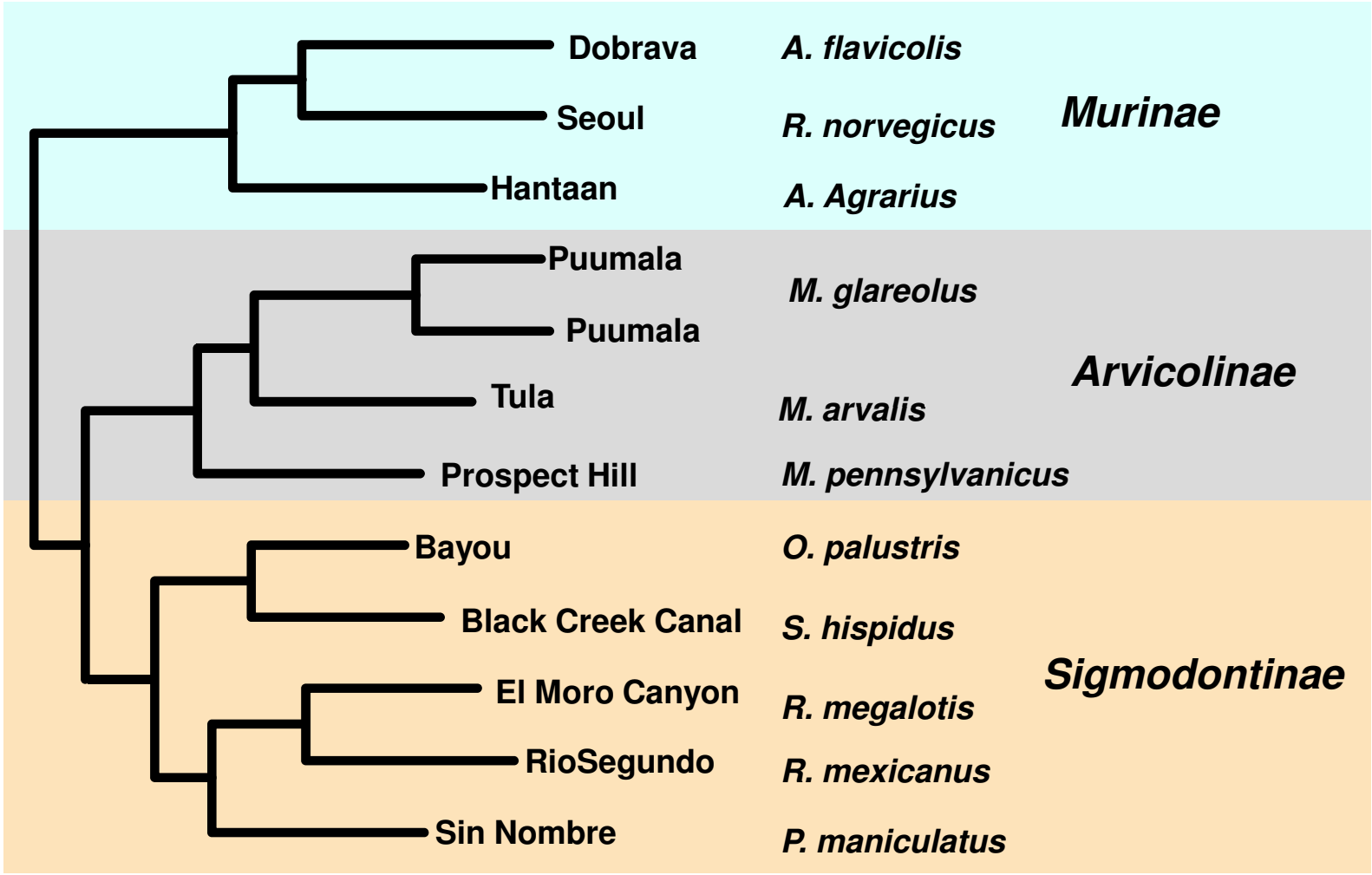
## Pathogenic Hantaviruses

- Persistently infected rodents
- Transmitted in aerosols of rodents' urine, feces, saliva

| | | | |
|---|---|---|---|
| Hantaan virus<br>Dobrava virus<br>Seoul virus<br>Puumala virus | Old World Rodents | HFRS | Mortality ~1%-15% |
| Sin Nombre virus<br>Andes virus<br>And more….. | New World Rodents | HPS | Mortality ~40% |

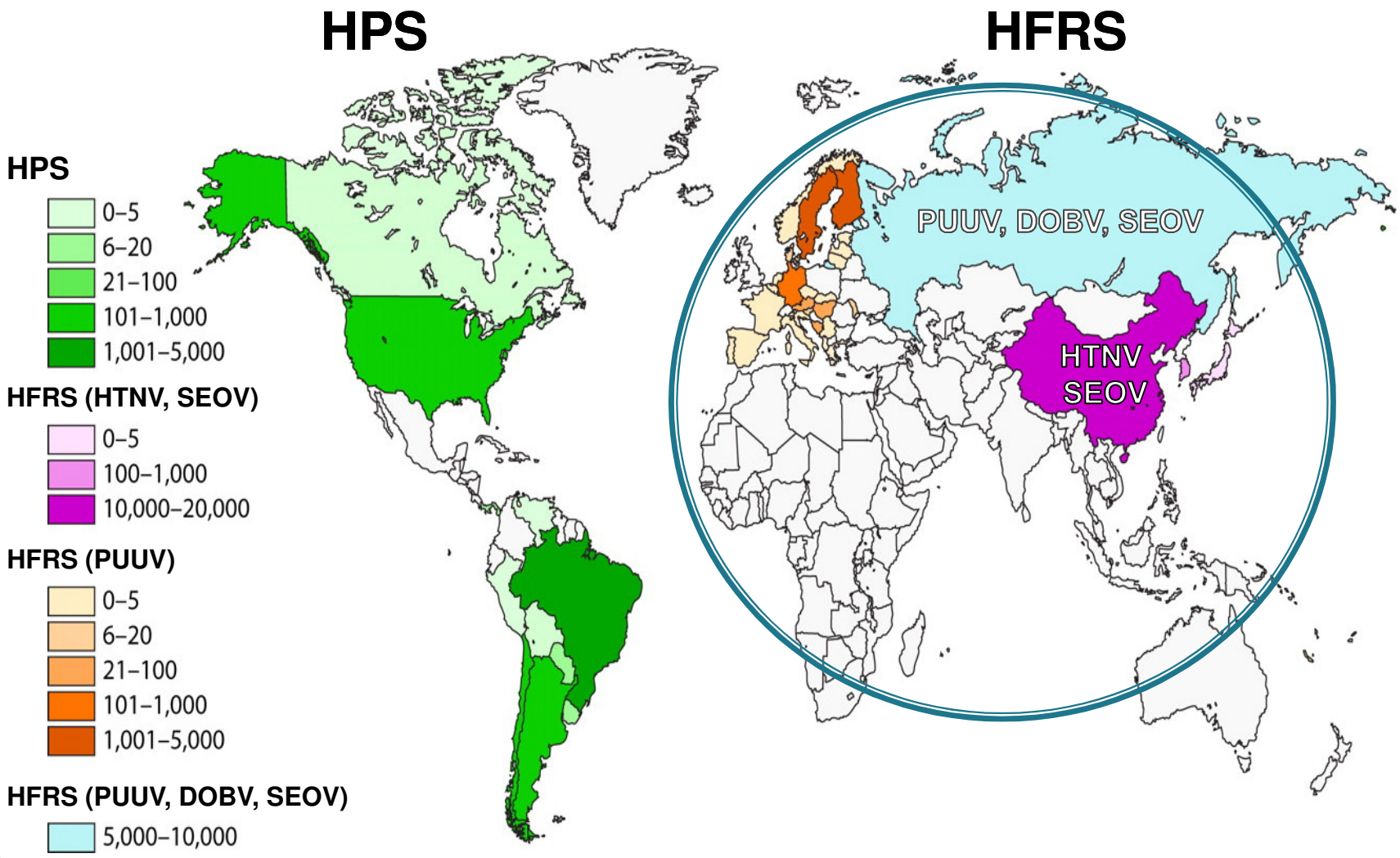
# Phylogeny and Rodent Hosts

## Coevolution Postulated for >100 MY*



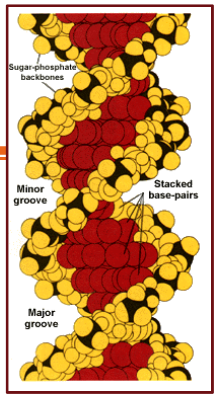

*Plyusnin, A., Sironen, T., 2014. Virus research 187, 22-26.

# Hantaviruses and Diseases



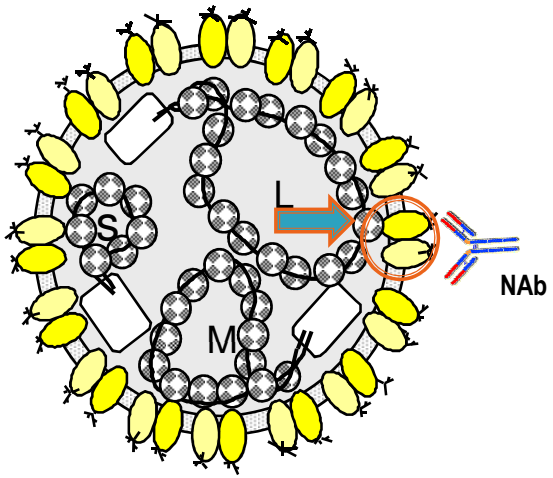

Map adapted from Jonsson CB, et al. Clinical Microbiology Reviews. 2010;23(2):412-41.

# DNA Vaccines
## Desirable Characteristics



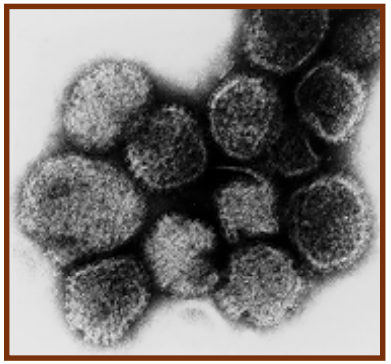

- **Easily Manufactured**
  - Can be quickly designed and produced in response to emerging or genetically engineered threats
  - DNA has established and approved manufacturing procedures
- **Safe**
  - Plasmids are replication defective
  - Not transmissible person to person or into the environment
- **No Pre-existing Vector Immunity**
- **Flexible Platform**
  - Easily combined to form multivalent vaccines
  - Can be delivered by a variety methods
    - **Gene gun**
    - **Electroporation**

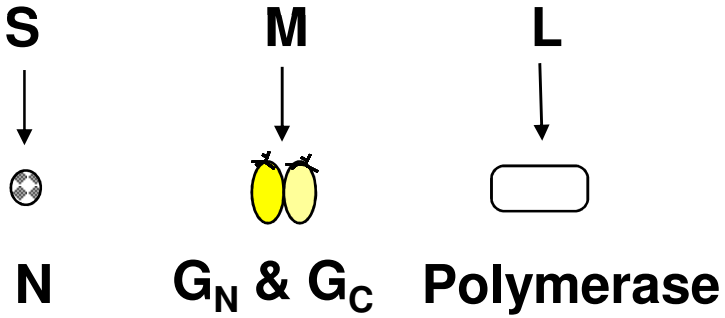
# Hantaviruses




*Bunyaviridae*

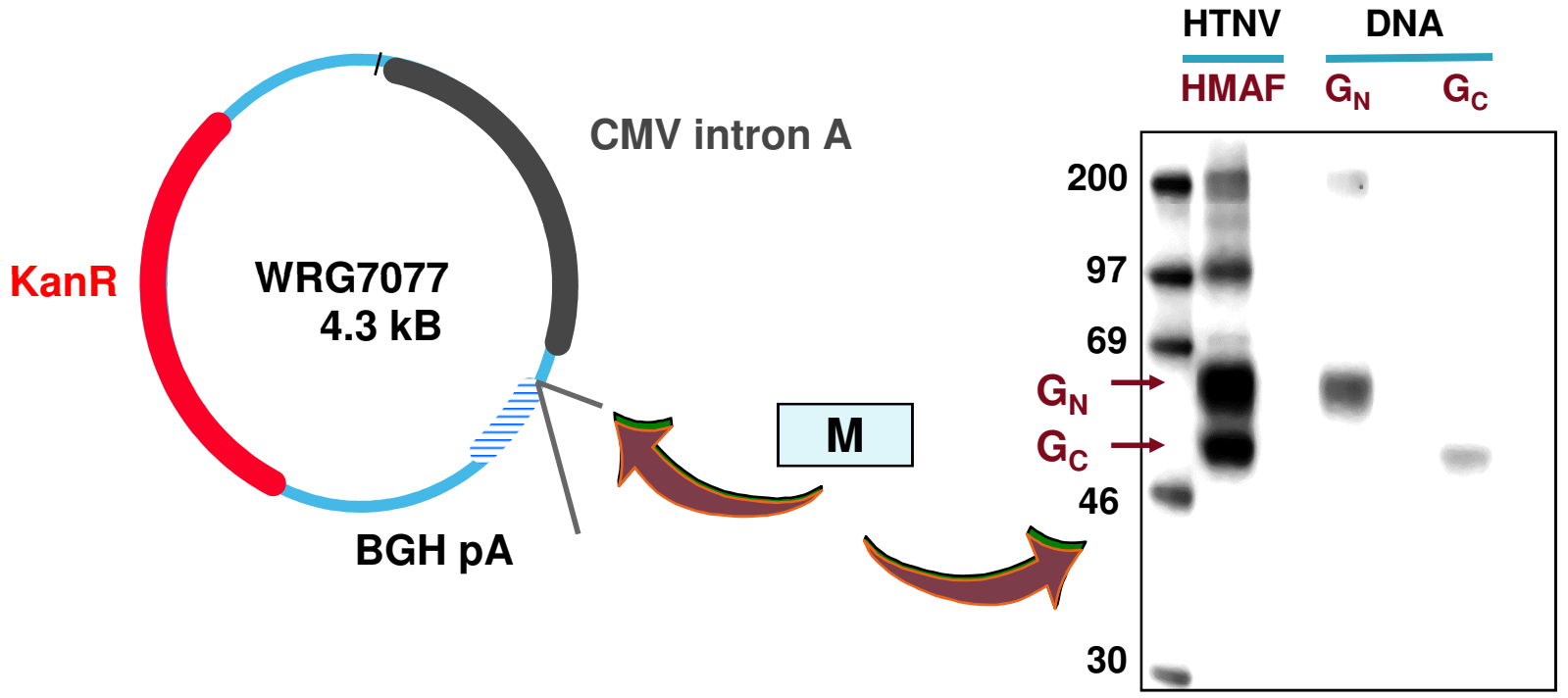
**enveloped, ~100 nm**
**ssRNA, (-),**
**3 segments**






**Immunity: Neutralizing antibodies**

# Hantaan Virus M Segment DNA Vaccine




**Immune precipitation of HTNV or DNA vaccine expression products with polyclonal mouse sera (HMAF) or monoclonal antibodies ($G_N$,$G_C$ )**

# Hamster Protection Studies

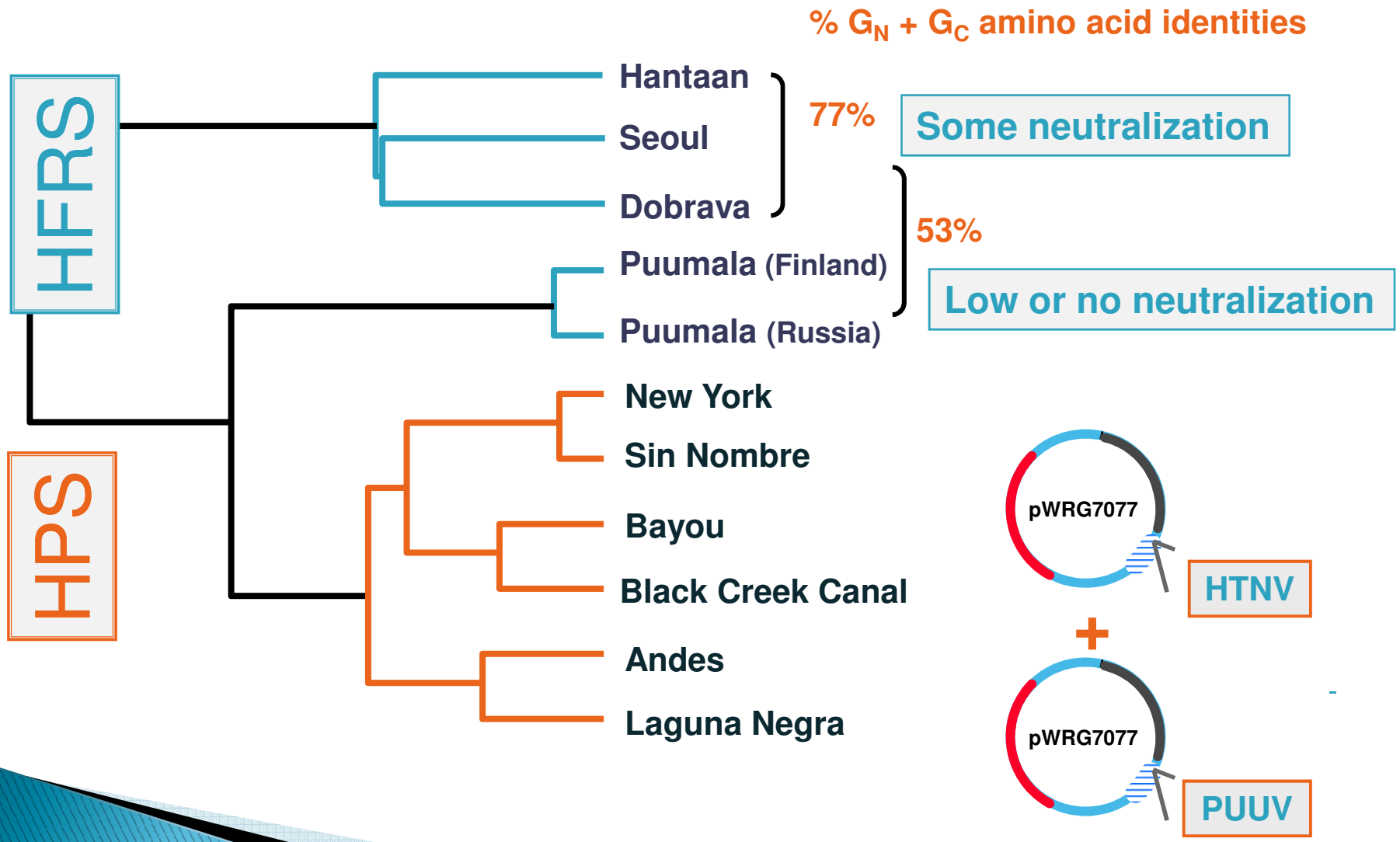
## HTNV DNA Vaccine



- Elicits neutralizing antibodies in hamsters
- Protects hamsters from infection with HTNV
- Protects most hamsters from SEOV or DOBV infection
- Does not protect hamsters from PUUV infection

Hooper, et al., 1999 Virology, 255:269; Hooper, et al., 2001 J Virol, 75:8469;
Brocato, et al., 2013 Clin Vaccine Immunol, 20: 218

# Hantaviruses



# Hamster Protection Studies

## Co-delivery of HTNV and PUUV DNA Vaccines

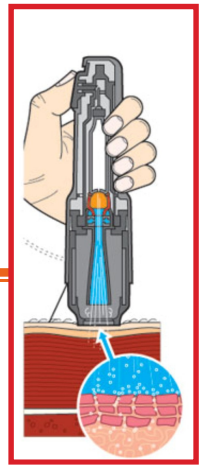


- Mixed HTNV and PUUV DNA vaccines elicit neutralizing antibodies in hamsters only to PUUV.
- Could not overcome this with higher ratio of HTNV:PUUV DNA
- For Phase 1 (Gene Gun) study the HTNV and PUUV DNAs were administered separately.

Spik KW, et al. *Vaccine* (2008)19;26(40):5177-81

# Phase 1 Study

## Gene Gun Delivery of HFRS DNA Vaccines



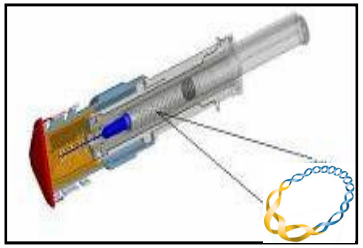
- Phase 1 Study: 3 vaccine groups of 9 subjects
  - HTNV DNA
  - PUUV DNA
  - Both DNAs delivered as separate administrations
- The vaccines were well tolerated and immunogenic
- Some volunteers produced high-titer neutralizing antibody responses ($PRNT_{50}$ >1000)
- Overall sero-conversion rate for study was <50%
- Improved delivery needed

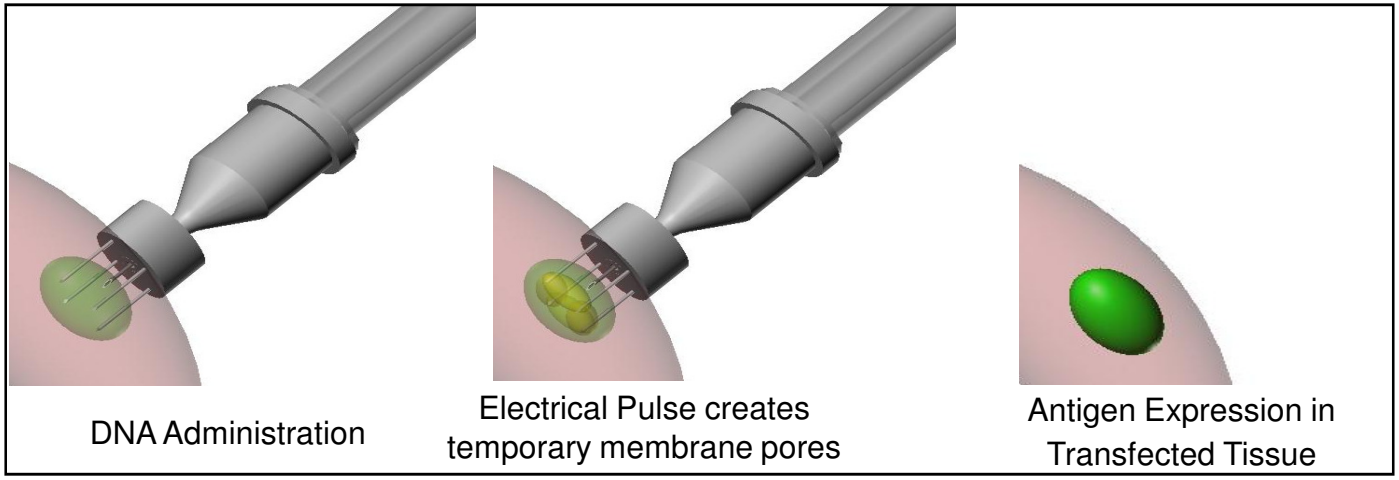
**Boudreau, et al. 2012, Vaccine 30, 1951-1958.**

# Electroporation-based DNA Vaccination



ichor
medical systems





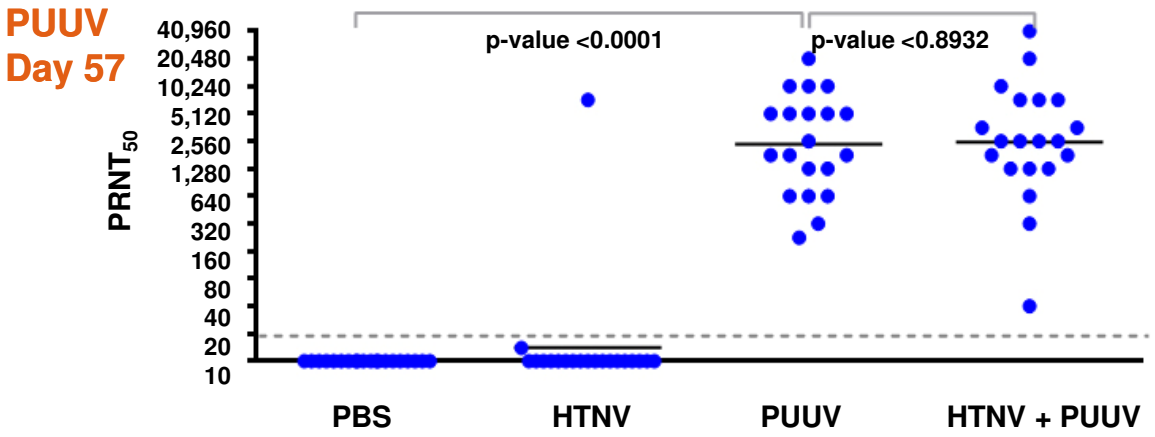
# GLP Preclinical Safety Studies

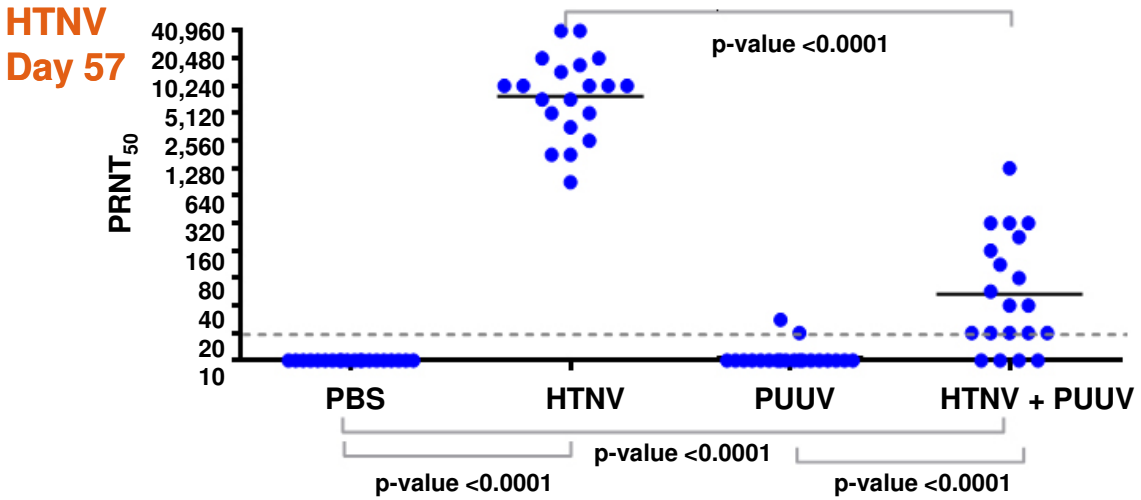
## Neutralizing Antibody Responses



N=20
2 mg DNA
IM-EP days 1, 15, 29, 57

- No vaccine-related mortalities or systemic clinical abnormalities
- No notable changes in mean body weights or food consumption
- No vaccine-related effects in mean body temperatures
- No observed changes during ophthalmic examinations




Hooper, J.W. et al., Clin Micro Inf : 2014 20 Suppl 5, 110-117.

# Phase 1 Clinical Study

## IM-EP Delivered HTNV + PUUV DNA Vaccines



- Three study groups: HTNV, PUUV, HTNV+PUUV DNA Vaccines
  - Determine if electroporation delivery improves seroconversion rate
  - Assess potential interference between hantavirus DNA vaccines in humans

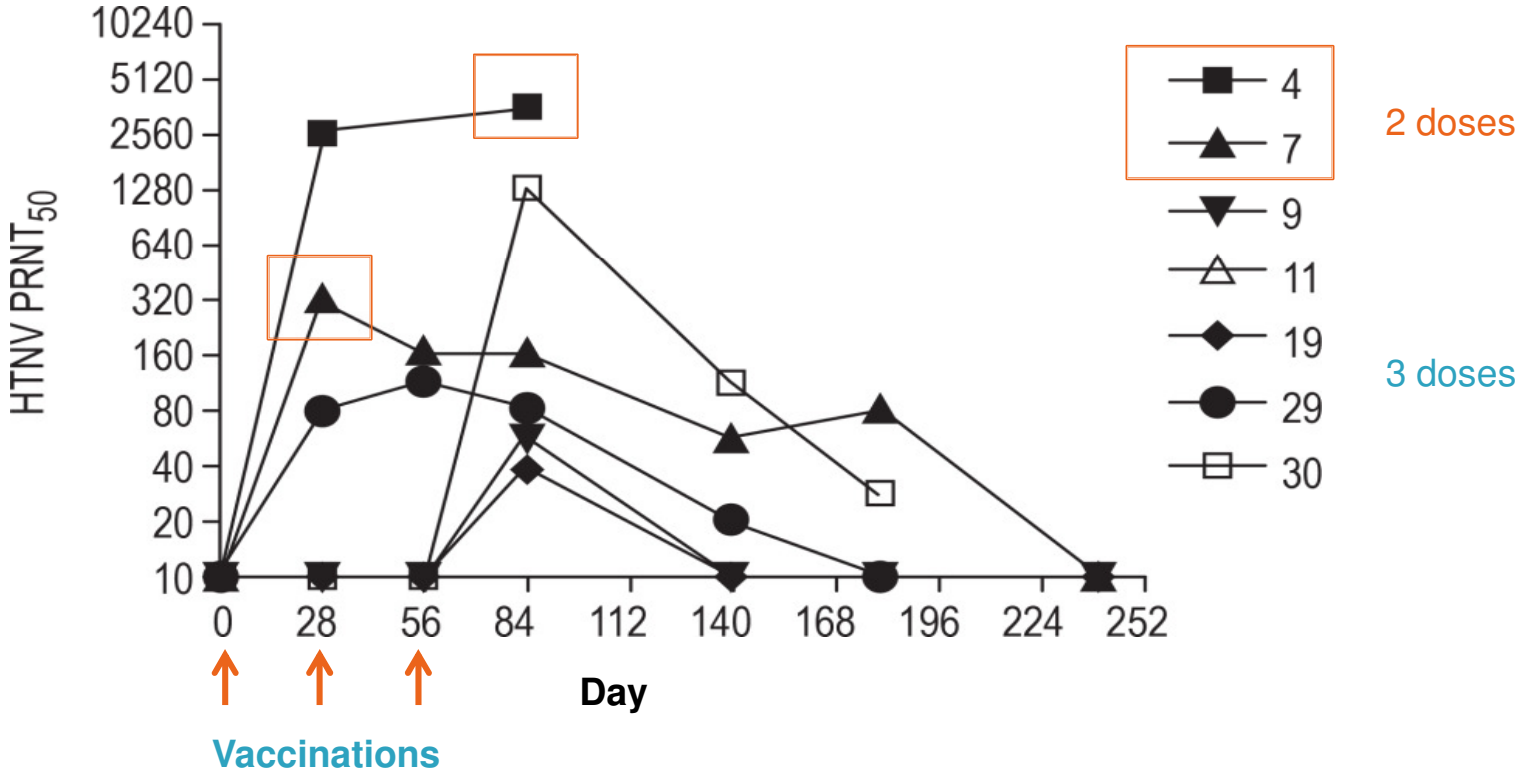
**Hooper, J. W., et al. 2014. Clin Microbiol Infect 20, Suppl 5:110-117.**

# Phase 1 Study IM-Electroporation

## Neutralizing Antibody Responses

**HTNV Vaccine: 2 mg DNA/1ml PBS, 3X at 4 wk intervals**

**Seroconversions: 7/11 = 64%**

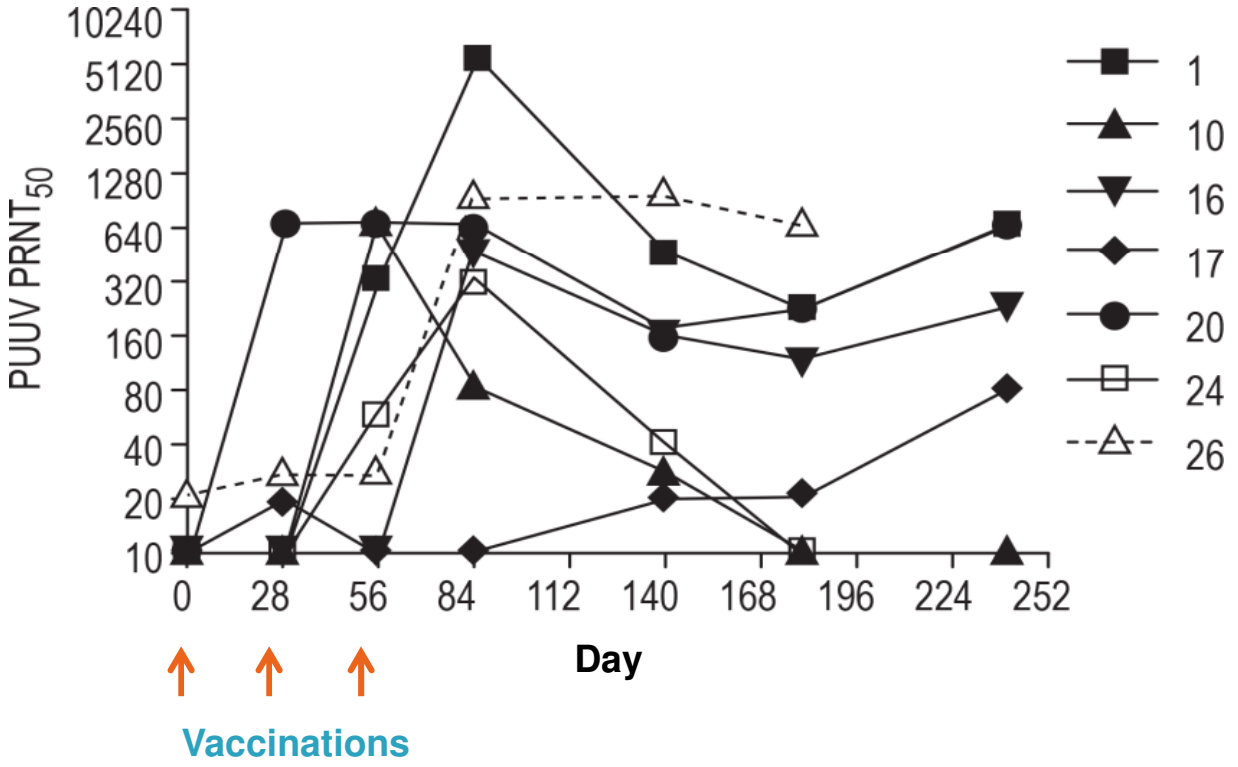


# Phase 1 Study IM-Electroporation

## Neutralizing Antibody Responses

**PUUV Vaccine: 2 mg DNA/1ml PBS, 3X at 4 wk intervals**

**Seroconversions: 6/8 = 75%**

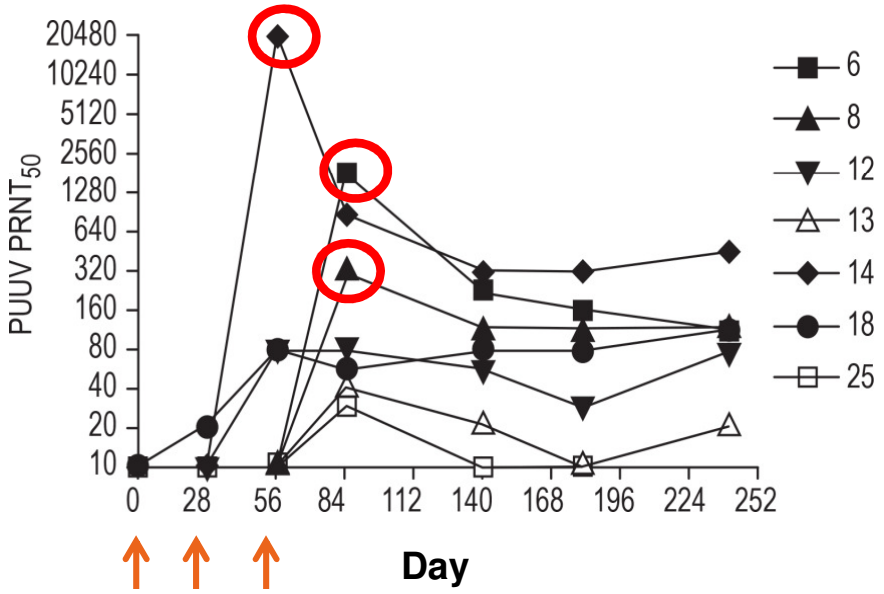


# Phase 1 Study IM-Electroporation

## Neutralizing Antibody Responses

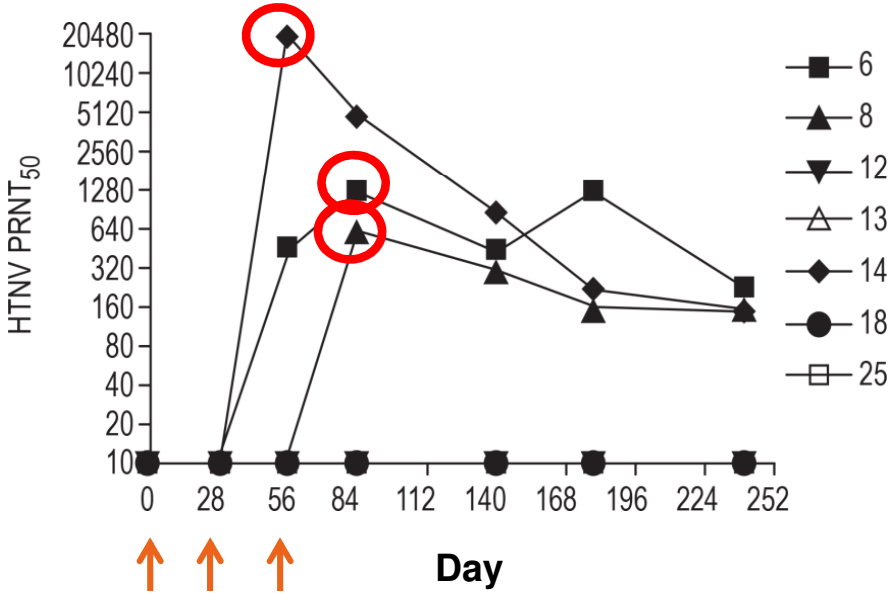
**HTNV+PUUV Vaccines: 1 mg each DNA/1ml PBS, 3X at 4 wk intervals**

**PUUV Seroconversions: 7/9= 78%**




Vaccinations

**HTNV Seroconversions: 3/9= 33%**

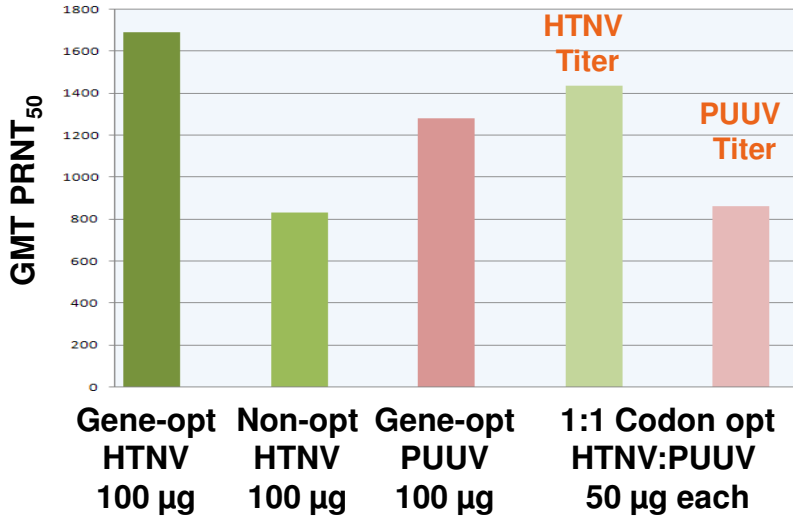



Vaccinations

# Summary:

## HFRS DNA Vaccines, IM-EP Delivery

- HTNV and PUUV DNA vaccines delivered by intramuscular electroporation were safe and immunogenic in a Phase 1 clinical study
- Interference of mixed vaccines continued to be problematic
- Mixed, gene-optimized HTNV and PUUV DNA vaccines developed and shown to be immunogenic in hamsters when given alone or as a mixture by IM-EP



# In progress: Phase 2a Dose ranging

## Hantavirus DNA Vaccines Delivered by IM-EP

- Using modified HTNV DNA-no interference in animal studies
- Two schedules and two doses assessed

| Group # | # of Subjects | Vaccine | Dose (mg) | Volume (ml) | Schedule |
|---|---|---|---|---|---|
| 1 | 30 | HTNV/PUUV | 2.0 | 1.0 | Days 0, 28, 56 (180) |
| 2 | 30 | HTNV/PUUV | 2.0 | 1.0 | Days 0, 56 (180) |
| 3 | 30 | HTNV/PUUV | 1.0 | 1.0 | Days 0, 28, 56 (180) |
| 4 | 30 | HTNV/PUUV | 1.0 | 1.0 | Days 0, 56 (180) |
| total | 120 | | | | |

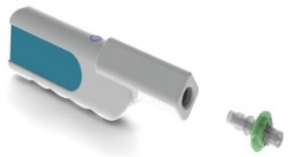
**Funded by the Military Infectious Diseases Research Program**

# Next: Phase 1 Clinical Study

## Comparison of IM and ID EP with Mixed Optimized DNA Vaccines for HTNV and PUUV



IM EP



ID EP

All Groups to be vaccinated on days 0, 28, 56

| Group #total | # of Subjects | Vaccine Candidate | Dose/route | Volume |
|---|---|---|---|---|
| 1 | 10 | HTNV | 0.6 mg / ID EP | 200 µl |
| 2 | 10 | HTNV | 2.0 mg / IM EP | 1000 µl |
| 3 | 10 | PUUV | 0.6 mg / ID EP | 200 µl |
| 4 | 10 | HTNV+PUUV | 4.0 mg / IM EP | 1000 µl |
| 5 | 10 | HTNV+PUUV | 1.2 mg / ID EP | 200 µl |
| 6a | 5 | none | - / IM EP | 1000 µl |
| 6b | 5 | none | - / ID EP | 200 µl |
| total | 60 | | | |

**NIAID Contract: HHSN272201200019C**

# Acknowledgements




Current USAMRIID



"New" USAMRIID

Opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the U.S. Army or the Department of Defense. The research described herein was sponsored by the Military Infectious Disease Research Program

Research was conducted in compliance with the Animal Welfare Act and other federal statutes and regulations relating to animals and experiments involving animals and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, National Research Council, 1996. The facility where this research was conducted is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

All clinical study procedures took place at the Walter Reed Clinical Trials Center. Recruitment was conducted according to current Good Clinical Practice (GCP) guidelines. The Clinical Protocol and Informed Consent forms were approved by the Walter Reed Army Institute of Research (WRAIR) Scientific Review Committee Sponsor's Representative Team (Division of Regulated Activities and Compliance, USAMMDA), the WRAIR Institutional Review Board (IRB), Department of the Army's Office of Research Protections, Human Research Protection Office (ORP, HRPO), Sponsor's Representative (acting for the OTSG of the Army), USAMRMC Commanding General, Commander, WRAIR. The study was sponsored by the Office of the Surgeon General, Department of the Army under IND 13688 using an open-label, single-center design.

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