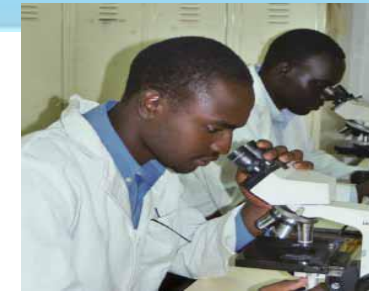
Institut Pasteur International Network : the 33rd Pasteur Institute in Conakry

Institut Pasteur de Guinée

One network, multiple international programs on ID



The IPGui on the UGANC campus

Institut Pasteur de Guinée

- Renovation and equipment of a « *Laboratoire Pasteur* »

  -> opened June 2018

- Building and equipment of the « *INSTITUT PASTEUR DE GUINÉE* »

  -> end 2019

Platforms

- Diagnosis : Molecular, serology
  - Large spectrum detection tools
- Biobank
- BSL3

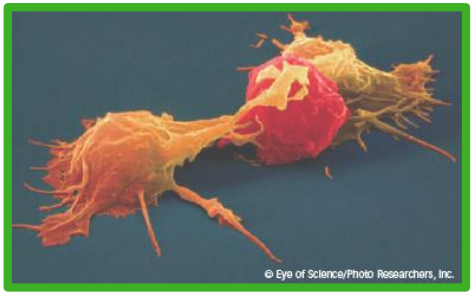
Two/three Research units

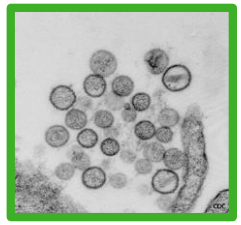
- Virology
  - Viral Haemorrhagic Fevers
  - Rabies
- Entomology
  - Arboviroses (RVFV, CCHFV, YFV, Zika…)
- Others

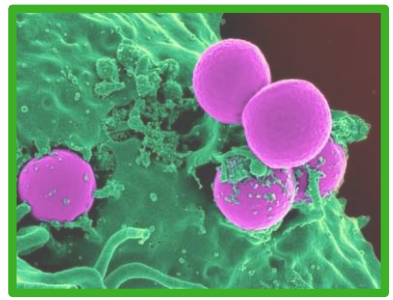
Reinforcing competences *teaching/training curriculum*

- **Molecular biology applied to pathogen detection (UGANC, Conakry)**
  - Theoretical ***(Nov 2016, Feb 2017)***
  - Practical ***(Oct 2018, Nov 2018)***
- **One Health (Vet School, Dalaba)** ***(March 2017)***
- **Lab managment (IPPS, Fondation Mérieux)** ***(Feb 2018, June 2018)***
- **Fellowships for Masters / Lab training**
  - 2 Dakar; 1 Yaounde; 1 Madagascar; 4 France
- **Collaboration with Guinean Universities/Institutions**
  - Master of Microbiology (viro, bacterio, parasito)
  - Veterinary program (Guinea – Sierra Leone)
- **Collaboration with International Institutions**
  - Institut Pasteur Network
  - Friedrich Loeffler Institute (Germany)…

Institut Pasteur de Guinée



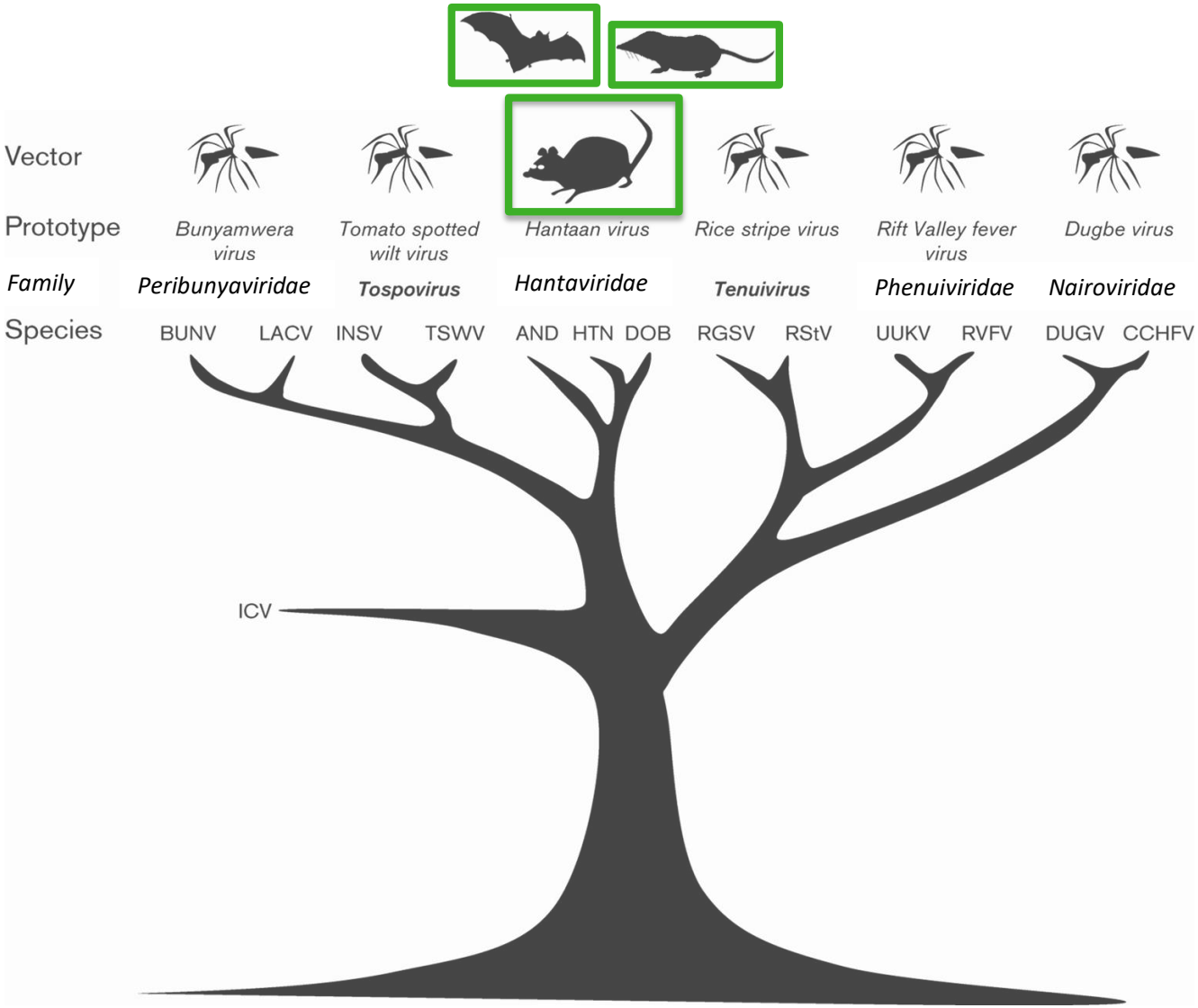




Molecular and functional diversity of Hantaviruses

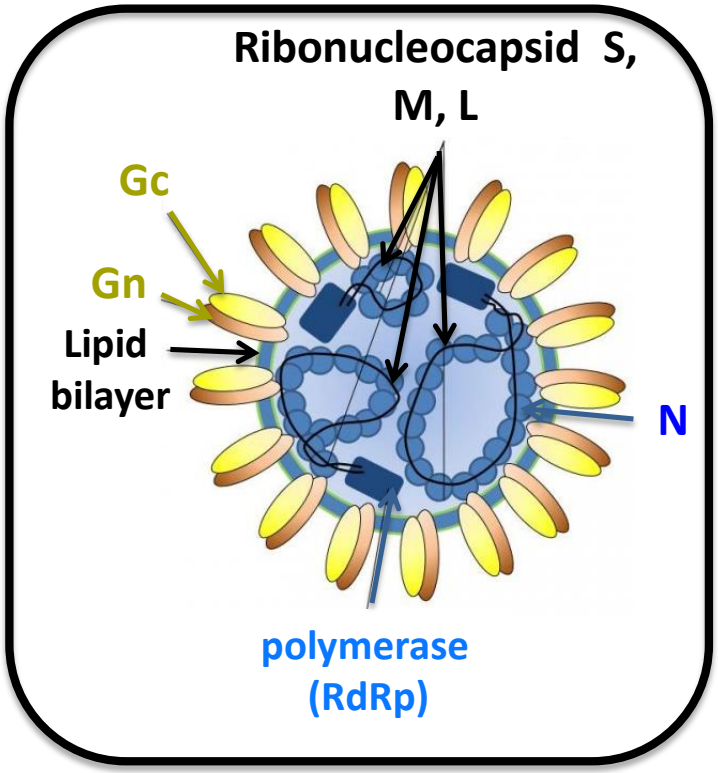
Hantaviruses: emerging pathogens

✓ Order *Bunyavirales*



✓ Genome

Tri-segmented negative strand RNA



Walter C T , and Barr J N J Gen Virol 2011;92:2467-2484

Hantavirus history

Hantaan river

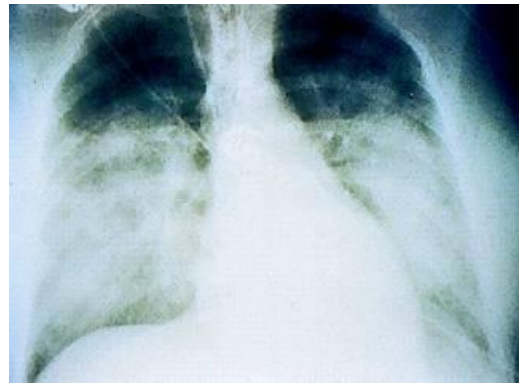
- **1951-1954** : Korean war
  - **Korean Hemorrhagic Fever** (associated with renal syndrom)
  - > 3000 US soldiers (10-15% mortality)
- **1976: Hantaan virus isolated** from ***Apodemus agrarius*** near Hantaan river (*Lee HW J Kor Soc Vir 1977; 7: 1-9)*
- **1979 : Seoul virus** among persons manipulating **rats** in **Korea** (*Lee J Infect Dis 1982;146:638-644*)
- **1980** : **Puumala virus** in **Europe** causing Nephropathia Epidemica (NE) and found in ***Myodes glareolus*** **(bank vole)** *(Brummer-Korvenkontion J Infect Dis 1980;141:131-4)*

Hantavirus discovery in the new world: 1993

Before 1993

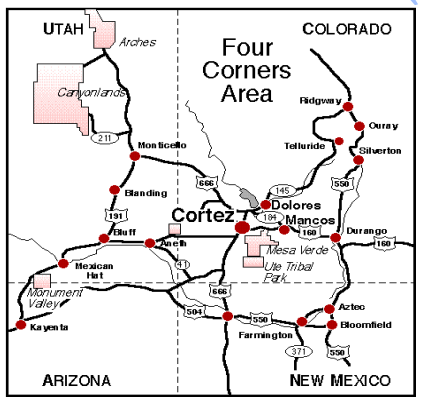
Sin Nombre Virus 1993 :

- unexplained human epidemics
- acute respiratory distress syndrom
- > 50% mortality



Prospect Hill Virus

Microtus pennsylvanicus



- serum cross reactivity with Hantaan, Seoul, Puumala
- identification of a new hantavirus: **Sin Nombre virus**

Peromyscus maniculatus

Nichol, Science 1993 ; 914-917

Kziazek, Am J Trop Med Hyg 1995

New hantaviruses discovered in the Americas

After 1993

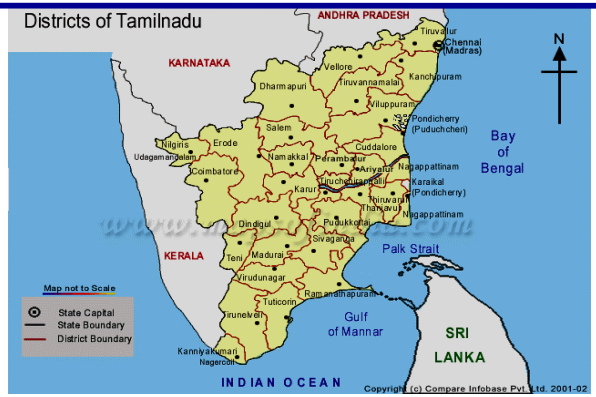
One virus species associate with one rodent species

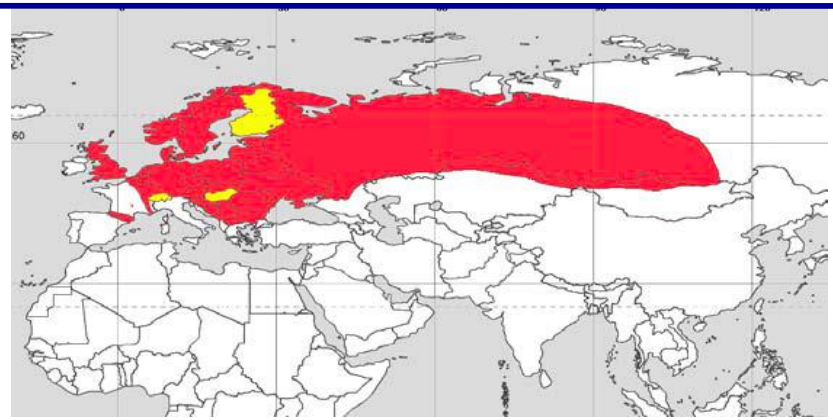
Hantavirus with CardioPulmonary Syndrom (HCPS)

Non pathogenic viruses

MacNeil et al, Virus Research, 2011

First hantaviruses isolated in shrews and bats





virus Thottapalayam

Carey et al. Ind. J. Med. Res. 1971

EUROPE :
- **Switzerland**
- **Finland**
- **Hungaria**
- **Russia…**

virus Seewis

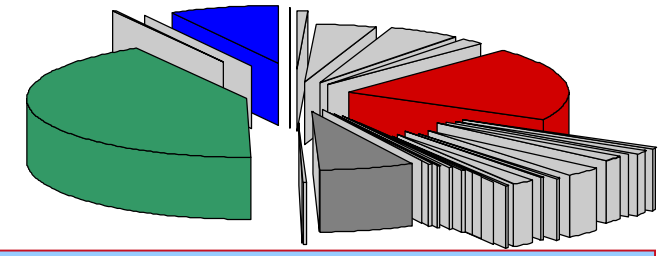
Song et al., Virology J. 2007
Kang et al., Virology J. 2009
Yashina et al., VB Zoon Dis. 2010

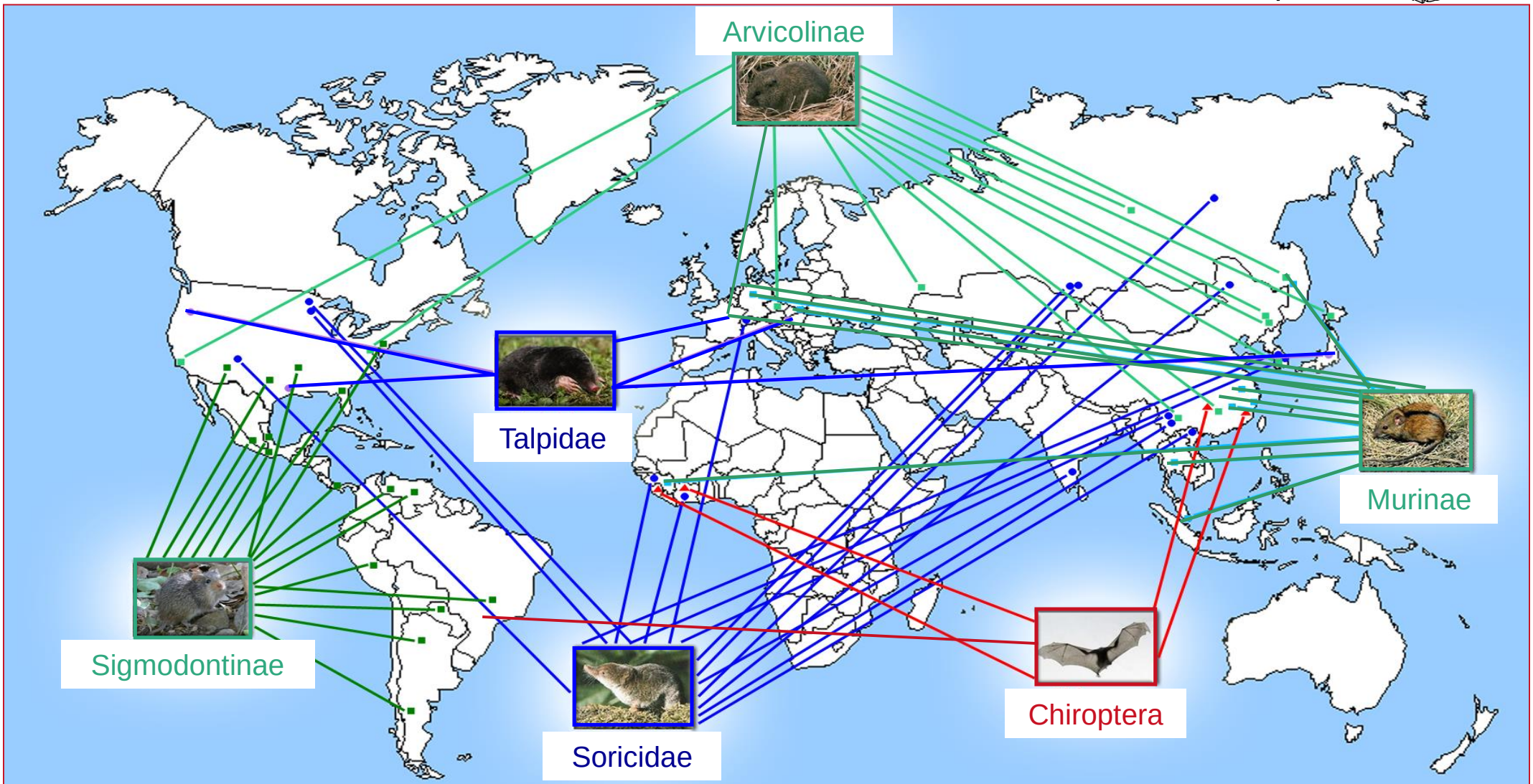
virus Mouyasué
- **Ivory Coast**

Sumibcay et al.2012
Virology journal

Hantaviruses : a story of rodents, insectivores and bats

- Rodentia: 42.02%
- Chiroptera: 20.5%
- Soricomorpha: 7.9%
- Primates: 6.94%

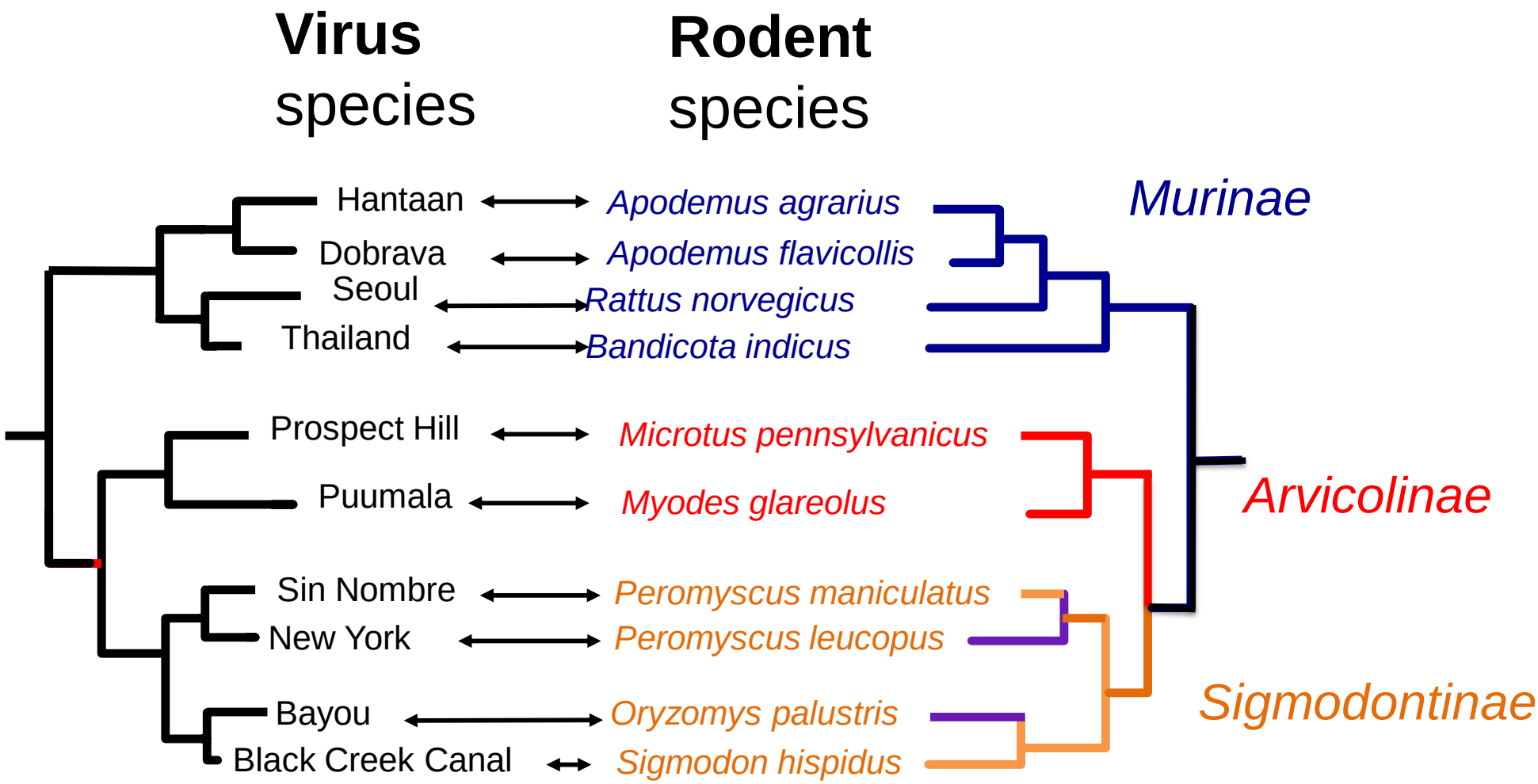




adapted from Guo W-P et al, Plos Path, 2013

Phylogeny of hantaviruses : co-speciation with reservoirs or cross-species transmission ?

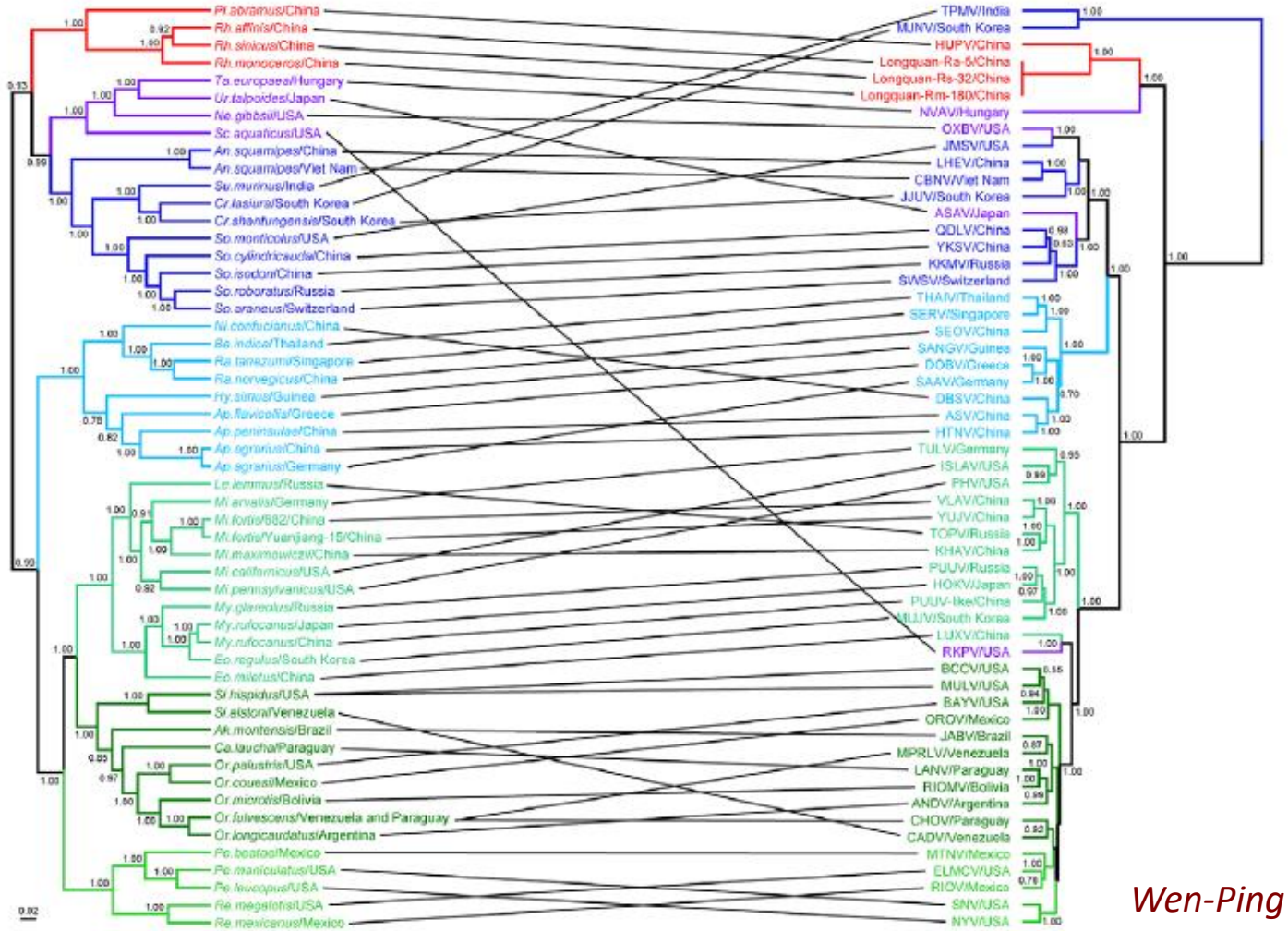
More simple with rodents only



Plyusnin and Sirone, Virus Res 2014

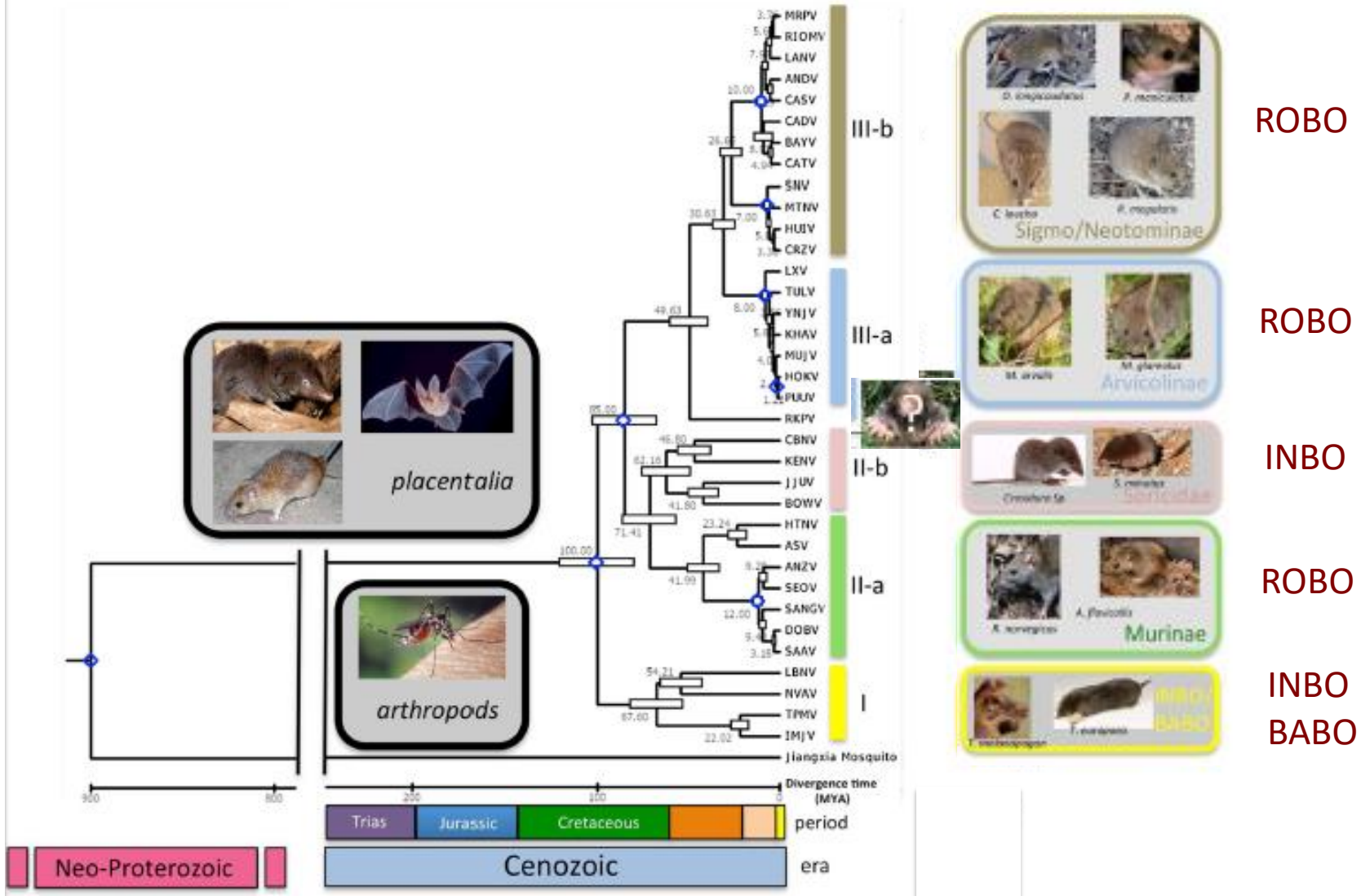
Phylogeny of hantaviruses : co-speciation with reservoirs or cross-species transmission ?

More complex adding insectivores and bats



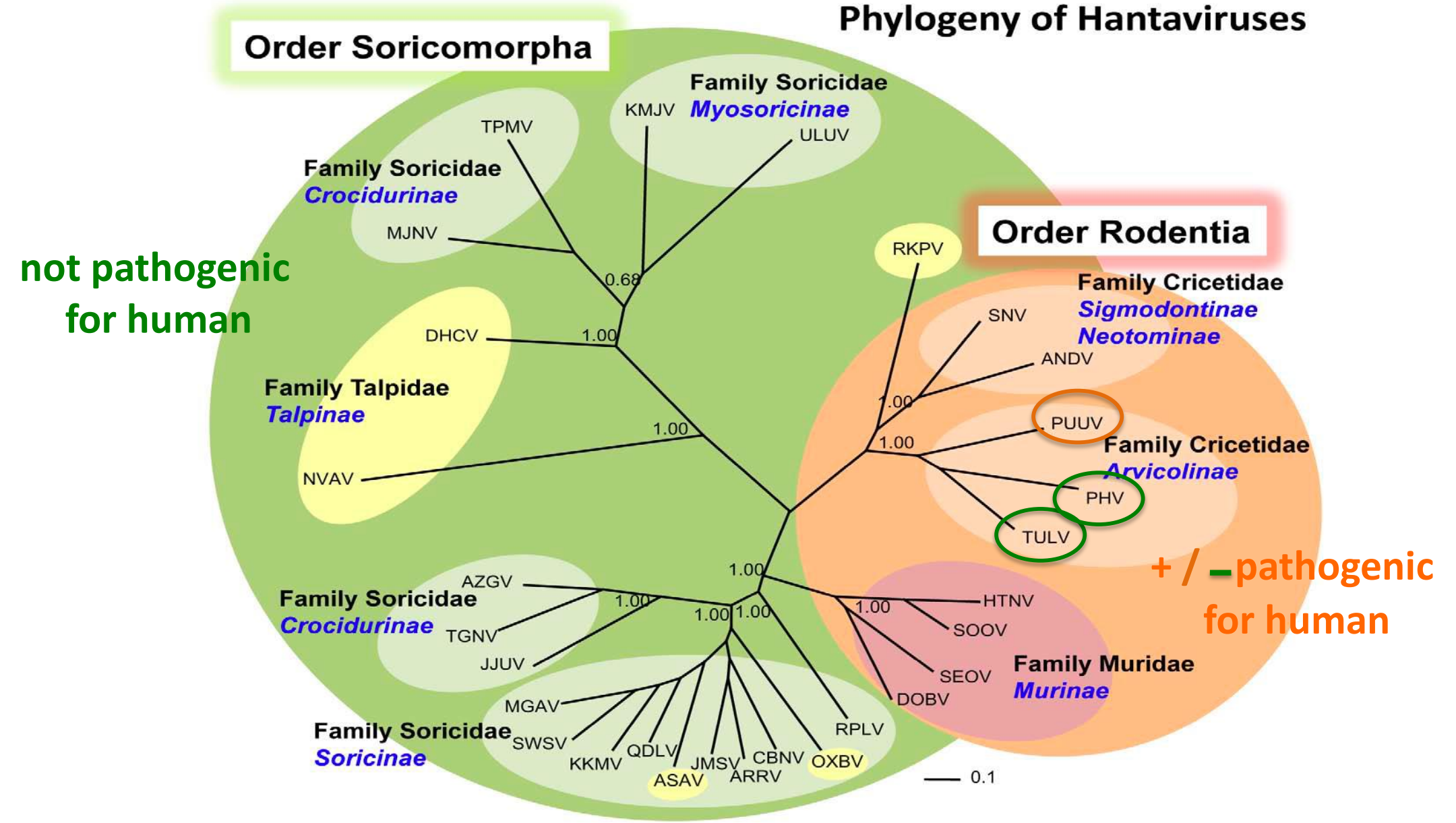
Wen-Ping Guo et al,
PLoS Pathog 2013 9(2): e1003159

Phylogeny of hantaviruses using fossils : insect origin ?



Castel, Tordo et Pyusnin, Virus Res 2017

Only rodent hantaviruses are pathogenic in human



Worldwide distribution of rodent-borne hantaviruses

Microtus arvalis

Tula

Puumala

Arvicolinae

Myodes glareolus

Prospect Hill

Arvicolinae

Sin Nombre

Sigmodontinae

Dobrava

Murinae

Hantaan

Apodemus flavicolis

Murinae

Seoul

Rattus rattus

Neotominae

Andes

Rodent reservoir: persistent and asymptomatic

Humans: - Hemorrhagic Fever with Renal Syndrome (**HFRS**) 150.000 cases/year 0-15% death

- Hantavirus Cardio-Pulmonary Syndrome (**HCPS**) 1000 cases/year 30-40% death

- **non pathogenic**

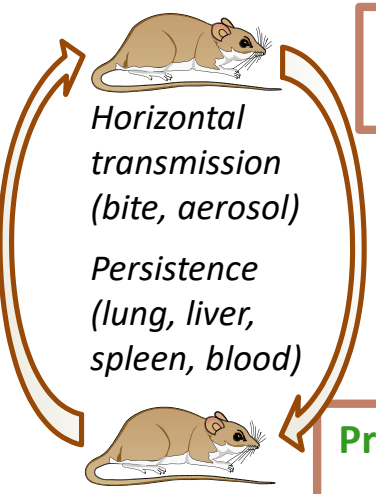
Hantavirus model and objectives

Comparative *in vitro* study of hantavirus interactions with their hosts

❑ in different situations

Reservoir *Arvicolinae*

Human



Horizontal transmission (bite, aerosol)

Persistence (lung, liver, spleen, blood)

Puumala PUUV → asymptomatic

Myodes glareolus

Tula TULV → asymptomatic

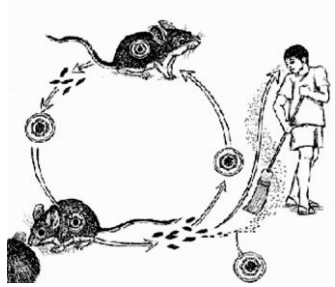
Microtus arvalis

Prospect Hill PHV → asymptomatic

Microtus pensylvaticus

Excreted in urine, feces

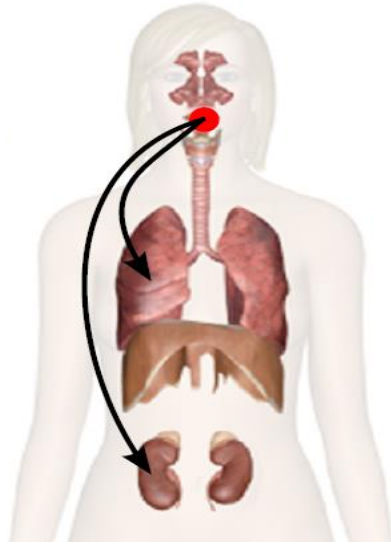
Transmission by aerosol



Mild HFRS Nephropathia epidemica

not pathogenic

not pathogenic



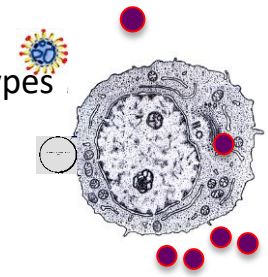
❑ at different levels

➢ Molecular

Search for host factors

- Yeast 2-hybrid
- Proteomics

Pseudotypes
Plasmid



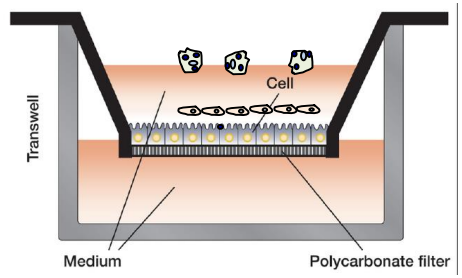
➢ Cellular

Virus cycle

- Entry / tropism
- Maturation / assembly
- Exit / cell to cell passage
- Host factor activation

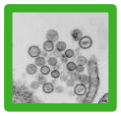
➢ Systemic

Propagation and barriers



❑ on different cells

- Tissues (epithelium, endothelium, immune system), Organs (lung, kidney)
- Species (human, rodent)

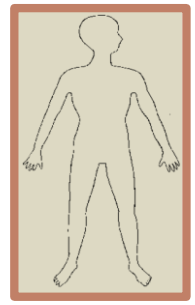


Hantavirus

Persistent infection
asymptomatic

Aerosol transmission
occasionnally

TULV
Non
pathogenic



PUUV
Nephropathia
epidemica

Activation of the host
immune response

Alteration of the
endothelial cell barrier
→ vascular leakage

Strong pro-
inflammatory
response

Tolerance ?

Tolerance

Different interactions with the immune system ?

Neutrophils (PMN) / NK
* Susceptibility to infection?
* Phenotypic and functional
modulation?

Persistence

Pathogenicity

Tissue damages

?

?

PUUV / TULV

Escape of the
immune system?

Conclusions

- Understand why Hantaviruses are persistent/asymptomatic in animal reservoirs but may be pathogenic in Human
  - ✓ Comparing human and rodent cells susceptibility
  - ✓ Comparing human and rodent partners of viral proteins (2-hybrid)

- Understand if the different outcomes in humans and rodents involve distinct interactions with the immune system which may provoke alteration of the endothelial barrier

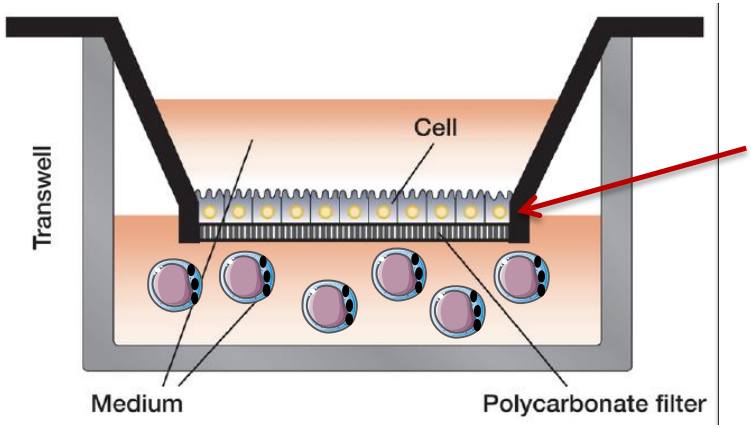
  - ✓ Neutrophils (PMN) from healthy human donors are very poorly sensitive to infection by PUUV (pathogenic) and TULV/PHV (non pathogenic)

  - ✓ No correlation with surface expression of “hantavirus” receptors

  - ✓ The pathogenic PUUV increases the survival of Neutrophils through delayed apoptosis, the non-pathogenic TULV/PHV do not.
    - ➢ Trojan horse for virus dissemination ?
    - ➢ Shaping the adaptive immune response ?

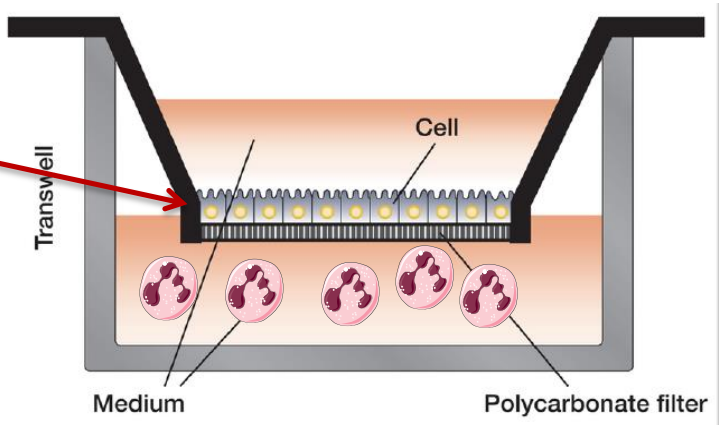
Perspectives: How immune cells interact with epithelial and endothelial barrier?

NK



Infected cells

Neutrophils



- Evaluation of neutrophils and NK cells activation
- Barrier alteration: trans-epithelial resistance
- Virus propagation across barriers (junctions alteration or via immune cells)

Acknowledgements

Stratégies Antivirales IP, Paris

N. Tordo

F. Baychelier-Tine

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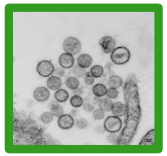
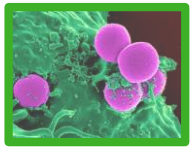




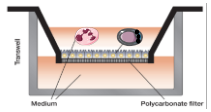
antigone anticipating the global onset of novel epidemics

Collaborators France

PE Ceccaldi

A. Vidy

IP, Paris



P. Marianneau

S. Murri

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Collaborators Europe

C. Drosten

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M. Muller

R. Ulrich

A. Rang

S. Essbauer

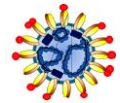
Germany

A. Plyusnin

O. Vapalahti

T. Sironen

Finland



A. Zvirbliene

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Sweden

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