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

One network, multiple international programs on ID

Regions

- Americas
- Medit.
- Europe
- Asia Pacific
- Sub-Saharan Africa
- Conakry

BSL3
The IPGui on the UGANC campus

- 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 management (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)…
Molecular and functional diversity of Hantaviruses
Hantaviruses: emerging pathogens

✓ Order Bunyavirales

Vector

Prototype

Family

Species

Bunyamwera virus
Tomato spotted wilt virus
Hantaan virus
Rice stripe virus
Rift Valley fever virus
Dugbe virus

Peribunyaviridae
Tospovirus
Hantavirus
Tenuivirus
Phenuiviridae
Nairovirus

BUNV LACV INSV TSWV AND HTN DOB RGSV RSV UUKV RVFV DUGV CCHFV ICV

✓ Genome

Tri-segmented negative strand RNA

Ribonucleocapsid S, M, L

Gc
Gn
Lipid bilayer
N
polymerase (RdRp)

Hantavirus history

- **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 syndrome
- > 50% mortality
- serum cross reactivity with Hantaan, Seoul, Puumala
- identification of a new hantavirus: Sin Nombre virus

Prospect Hill Virus
Microtus pennsylvanicus

Nichol, Science 1993; 914-917

Peromyscus maniculatus
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

EUROPE:
- Switzerland
- Finland
- Hungary
- 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

Suncus murinus

Sorex araneus

Neoromicia nanus
Hantaviruses: a story of rodents, insectivores and bats

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

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

About 5500 mammal species
Phylogeny of hantaviruses: co-speciation with reservoirs or cross-species transmission?

More simple with rodents only

Virus species

Hantaan
Dobrava
Seoul
Thailand

Prospect Hill
Puumala

Sin Nombre
New York
Bayou
Black Creek Canal

Rodent species

Apodemus agrarius
Apodemus flavicollis
Rattus norvegicus
Bandicota indicus

Microtus pennsylvanicus
Myodes glareolus

Peromyscus maniculatus
Peromyscus leucopus

Oryzomys palustris
Sigmodon hispidus

Murinae
Arvicolinae
Sigmodontinae

Plyusnin and Sirone, Virus Res 2014
Phylogeny of hantaviruses: co-speciation with reservoirs or cross-species transmission?

More complex adding insectivores and bats

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

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
  - Puumala (PUUV) - asymptomatic
    - Horizontal transmission (bite, aerosol)
    - Persistence (lung, liver, spleen, blood)
  - Tula (TULV) - asymptomatic
  - Prospect Hill (PHV) - asymptomatic

Reservoir Arvicolinae
- Excreted in urine, feces
- Transmission by aerosol
- Mild HFRS
- Nephropathia epidemica
- 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

Aerosol transmission occasionally

Persistent infection asymptomatic

Tolerance

Different interactions with the immune system?

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

Pathogenicity

Escape of the immune system?

Tolerance?

Alteration of the endothelial cell barrier → vascular leakage

Strong pro-inflammatory response

Tissue damages

PUUV / TULV

Activation of the host immune response

Non pathogenic

Nephropathia epidemica

Aerosol transmission occasionnally

Hantavirus

Persistence

Tolerance
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?

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