

# **Ebola virus crisis**

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***Molecular basis of viral pathogenicity***

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# Jean Mérieux INSERM BSL 4 Laboratory





- ❖ **The molecular basis of high pathogenicity**
- ❖ **Emergency of highly pathogenic viruses**
- ❖ **Lessons from current Ebola crisis**

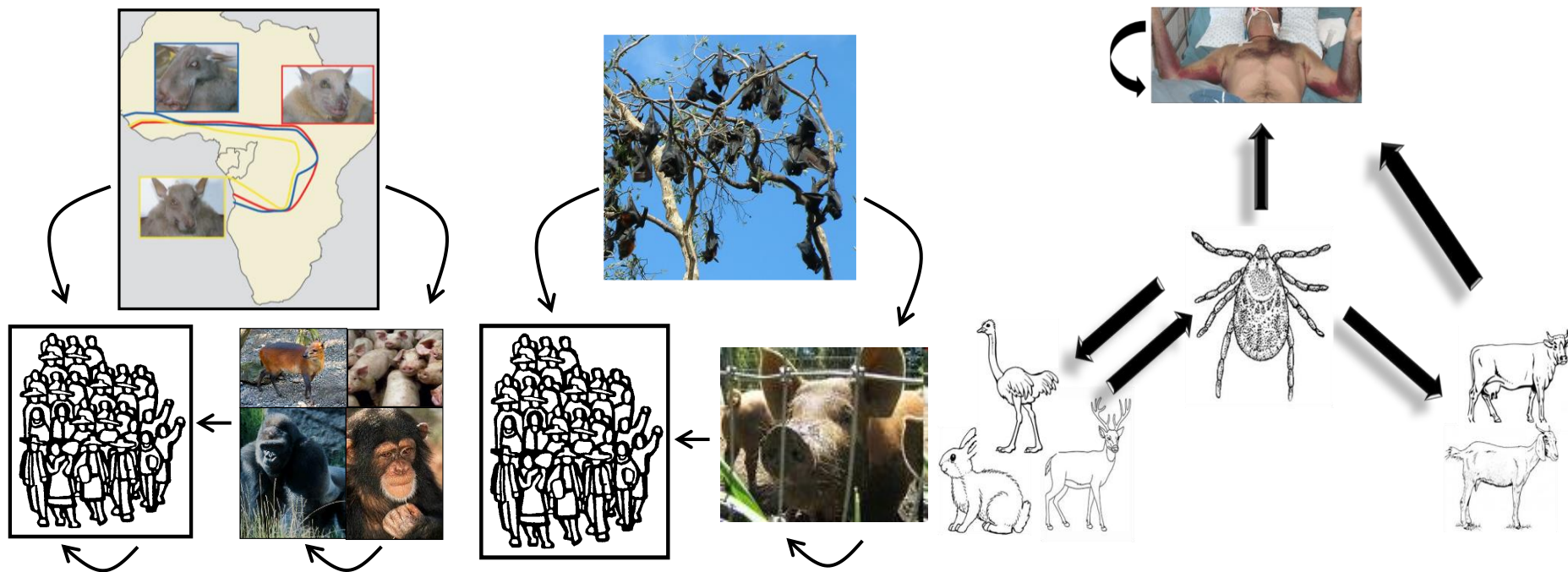


# *BSL P4 viral agents*

**Ebola and Marburg viruses / Filoviridae**

**Nipah virus / Henipaviridae**

**Crimean-Congo hemorrhagic fever virus / Bunyaviridae**



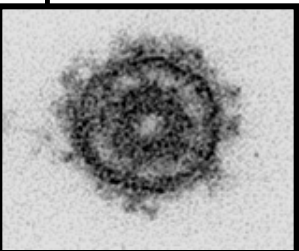
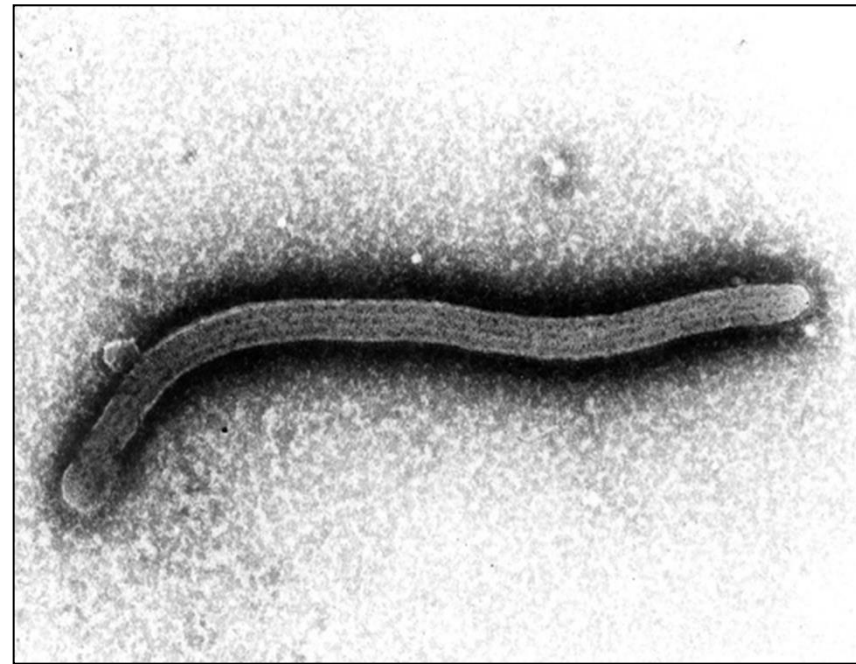
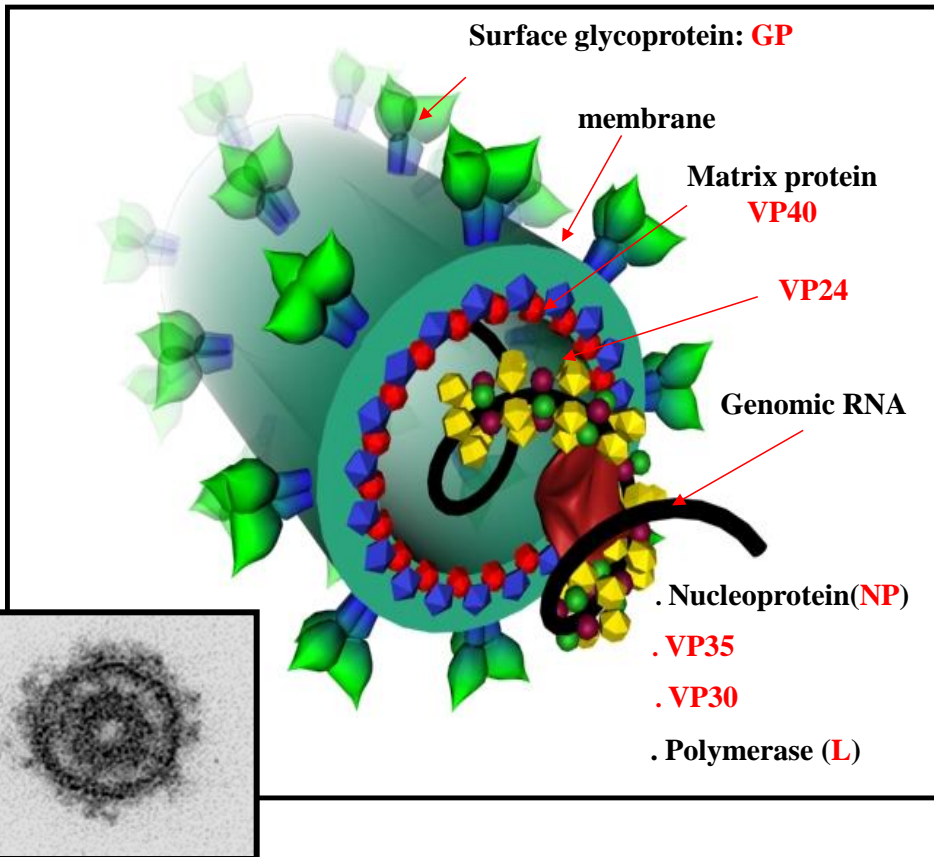
# *BSL P4 viral agents*

- ✦ Infections kill up to 60-90% of patients
- ✦ Spread through human-to-human or animal-to-human contacts
- ✦ Intercontinental virus transfer / Potential bio-terrorism agent
- ✦ Currently no vaccines or treatments are available for human use
- ✦ Molecular bases of high pathogenicity are not well understood

# Ebola virus

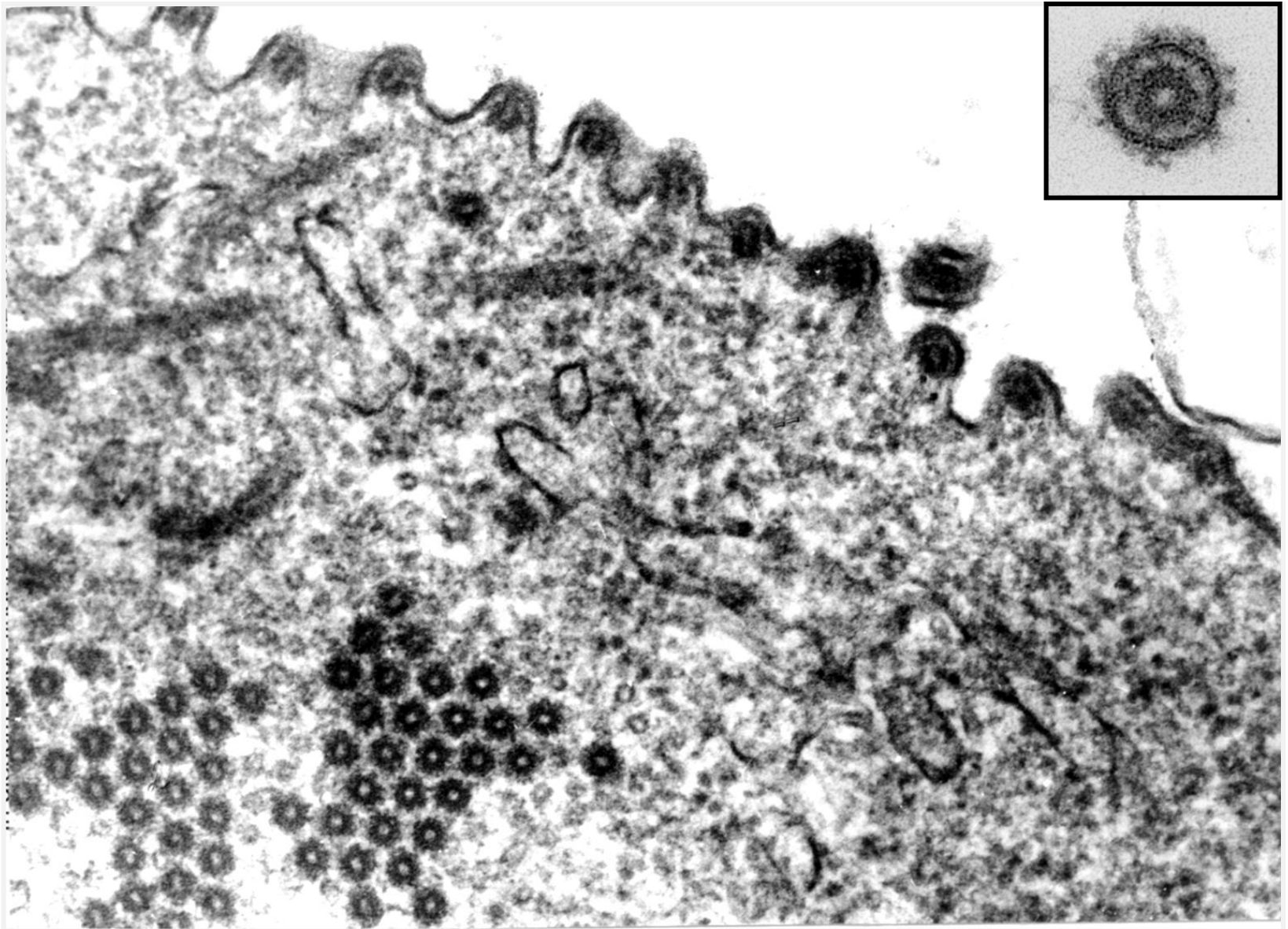


- Enveloped, non-segmented negative-stranded RNA containing virus
- 7 structural proteins and 3 non-structural soluble proteins

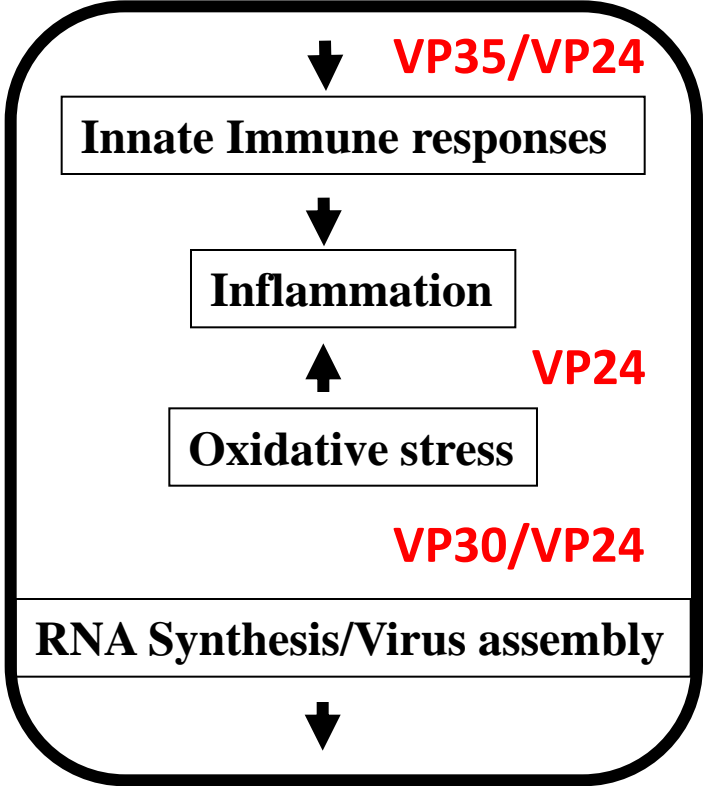




# Massive virus replication



**EBOV and MARV**



“Masking” phenomenon/ GP gene editing and virus adaptation

*Reynard et al., J Virol 2009; Volchkova et al., JID 2011*

Role of EBOV GP shedding

*Esquero-Perez et al., Plos Pathogenes 2014*

VP35 and VP24 are IFN antagonists

*Prins et al., J Virol 2010; Mateo et al., J Virol 2010.*

Molecular determinants of virulence

*Mateo et al., JID 2011*

Disregulation of host inflammatory responses

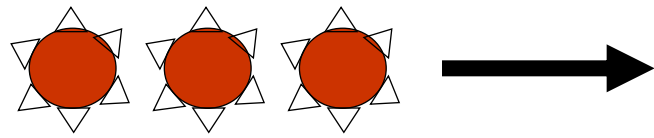
*Leung et al., JID 2011; Page et al., Cell Reports 2014*

Molecular switch: RNA replication versus transcription

*Martinez et al., J Virol 2010, JID 2011*

Role of VP24 in viral nucleocapsids assembly

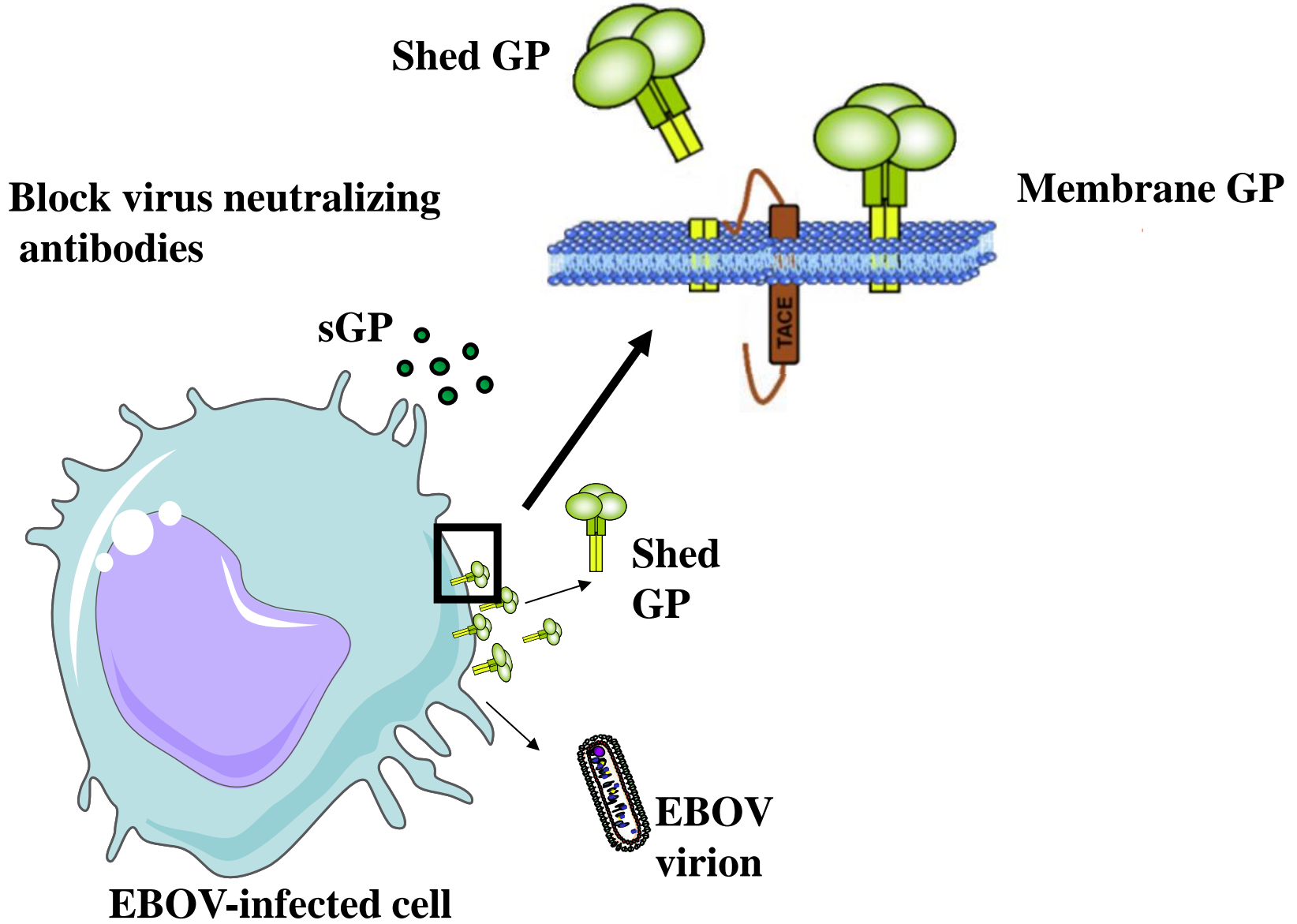
*Mateo et al., JID 2011*



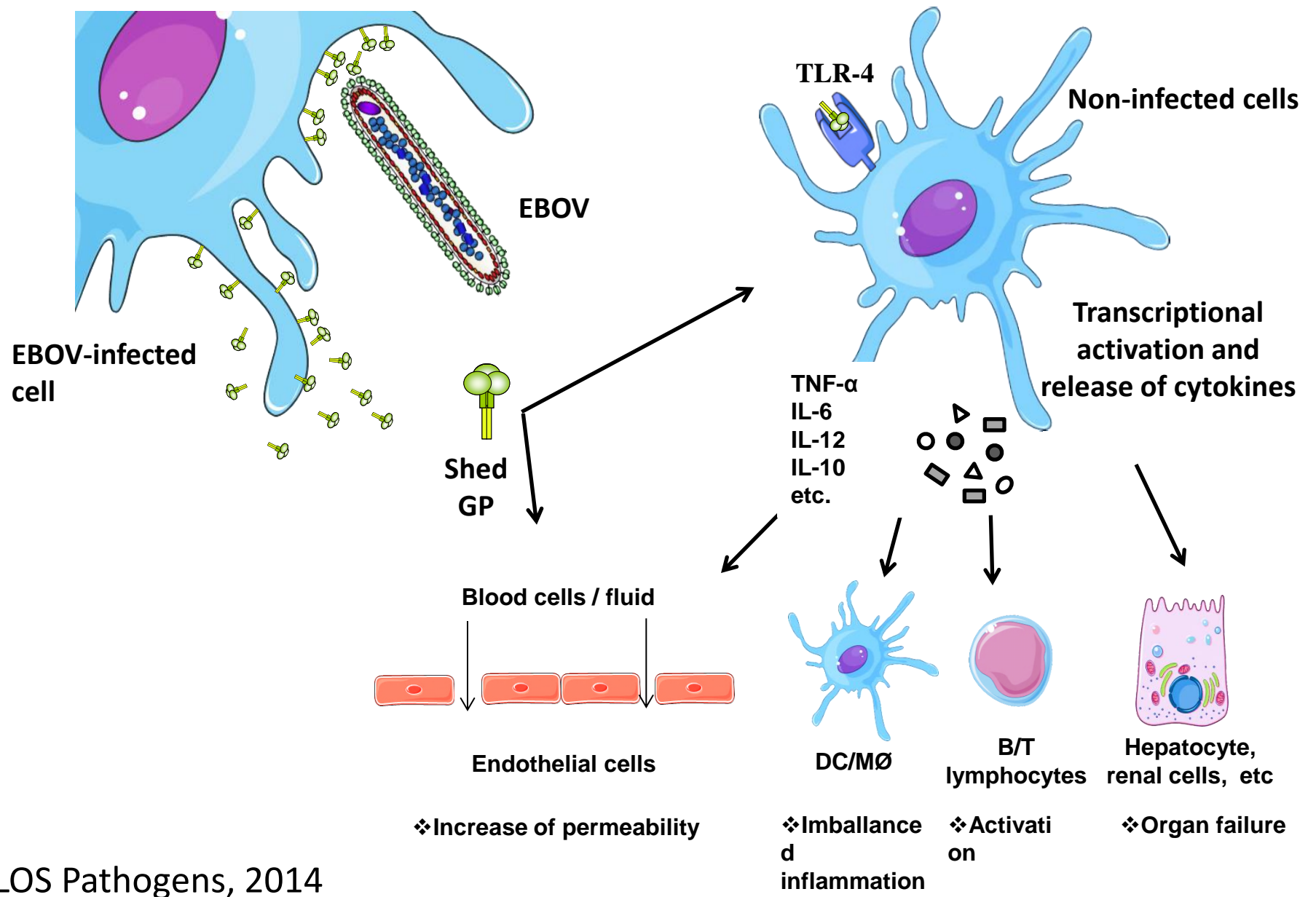
**High pathogenicity**



# Shedding of EBOV surface glycoprotein GP



# Shed GP of Ebola virus Triggers Systemic Immune Activation and Increased Vascular Permeability



# Factors that contribute to high pathogenicity

- ❖ **High efficiency of replication and viral pantropism**
- ❖ **Multiple antagonists of innate immunity**
- ❖ **Excessive and dysregulated host responses to viral replication**



« Loaded gun »





# Virus –host interaction (I)

## Natural reservoir



- ❖ Low virus replication
- ❖ Asymptomatic infection

High level of virus adaptation

# Virus –host interaction (II)



**Accidental  
hosts**

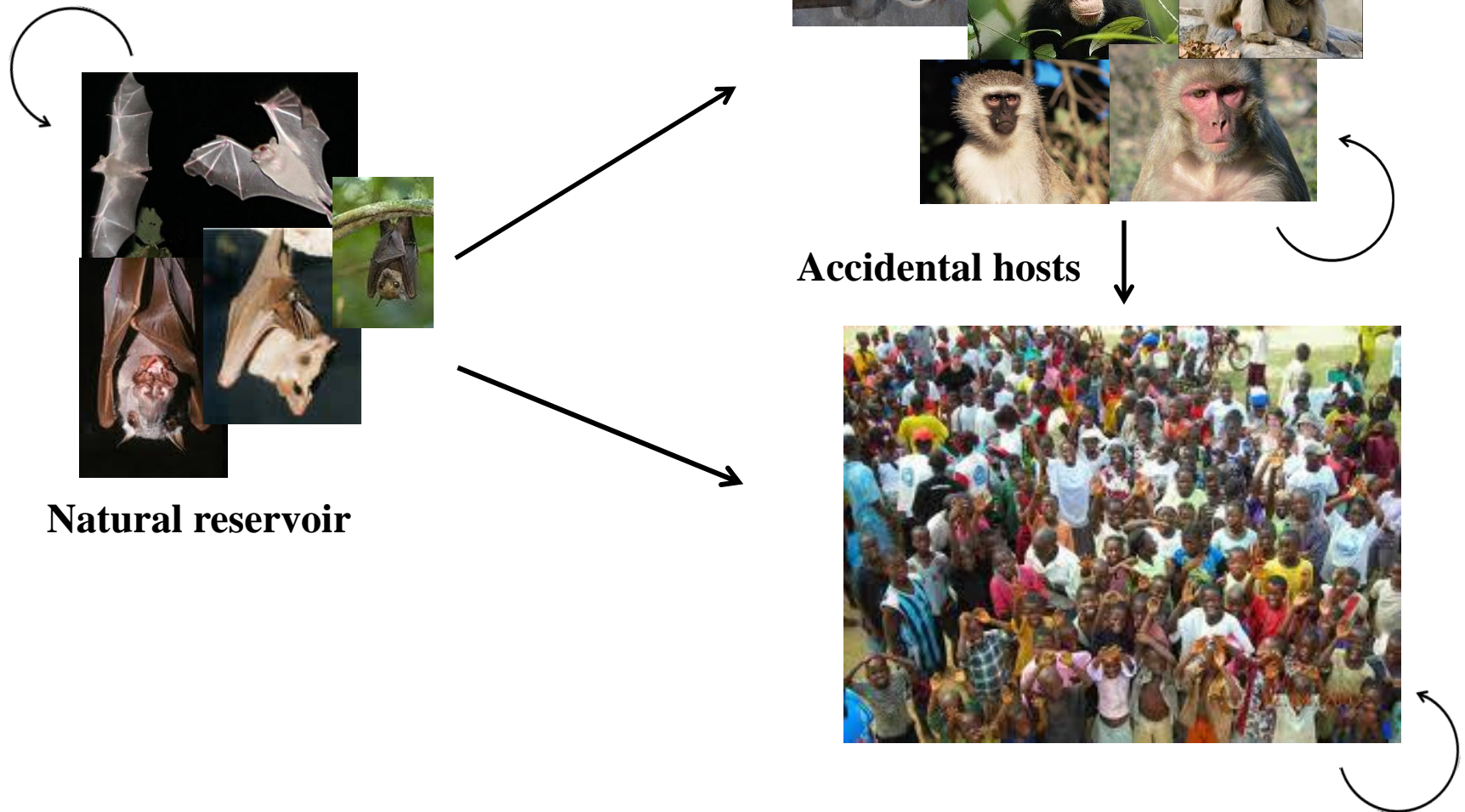


❖ **High level of virus replication**

❖ **High pathogenicity**

**Low level of virus adaptation**

# Virus emergence (I)





# Virus emergence (II)

## Local infections



Strict  
Quarantine



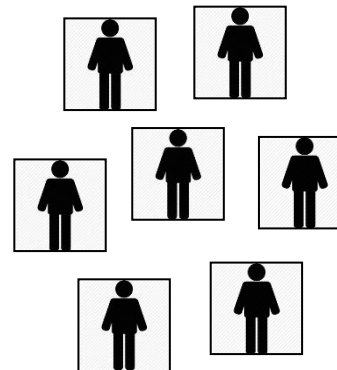
End of outbreak



Difficult to apply  
quarantine



Low Level  
Health Care



Virus spread

Nosocomial  
infection

# Lessons from current Ebola crisis:

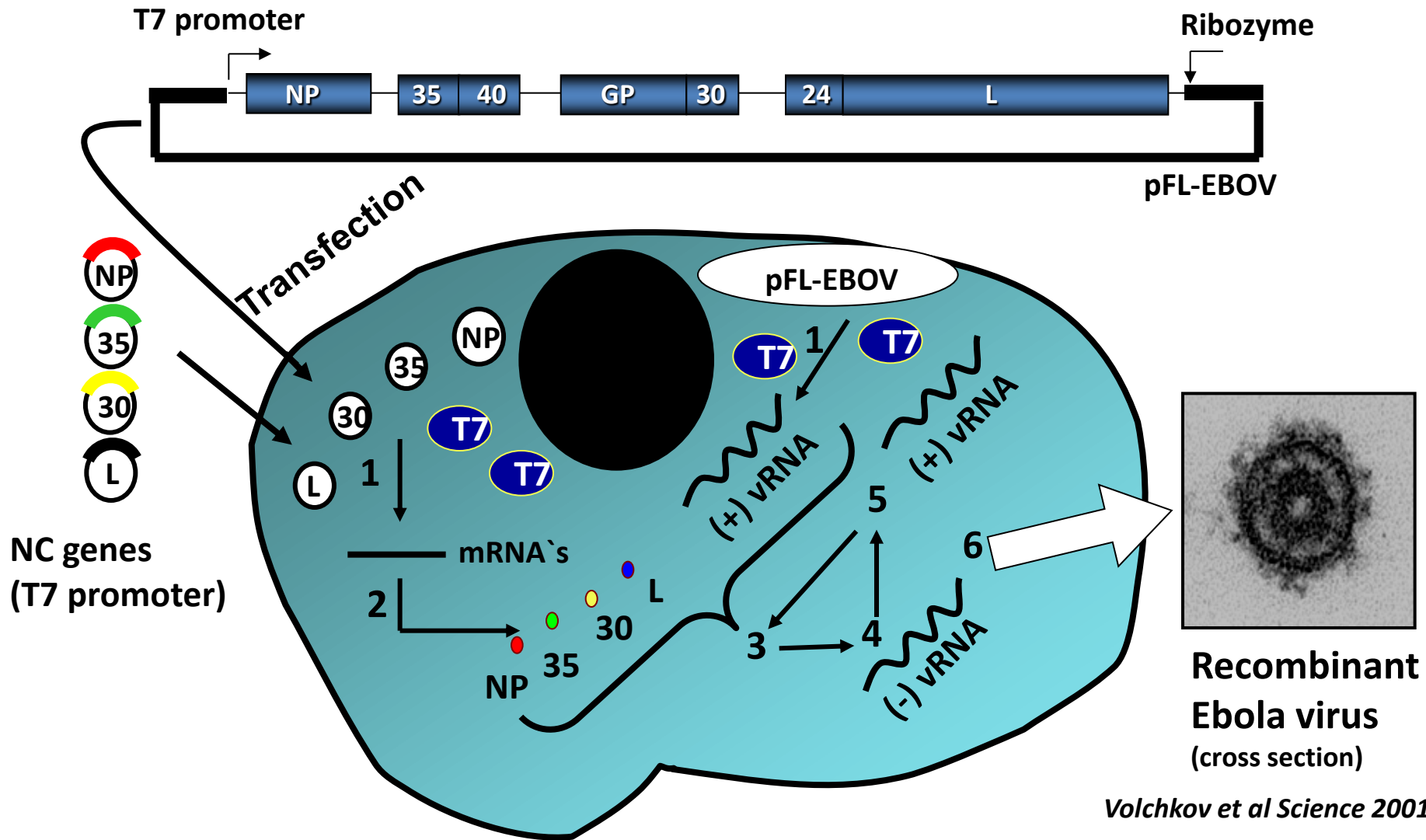
- **Always keep watching for known highly pathogenic viruses.**
  
- **Preparedness:**
  - ❖ **Diagnosis**
  - ❖ **Vaccine**
  - ❖ **Therapeutics**

} **For all known highly pathogenic viruses.**
  
- **Exploring the link between Academic Science and Industrials.**
  
- **Keep moving forward. Learn more on molecular basis of high pathogenicity.**
  
- **Search for new, related viruses (African henipa- and filoviruses)**

**BACK UP**



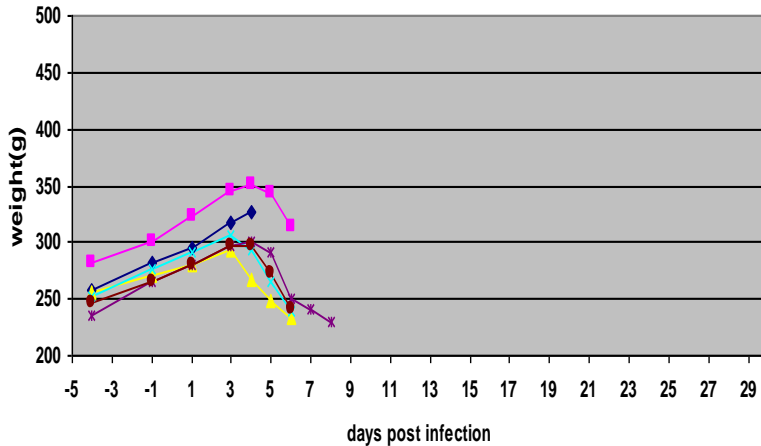
# Reverse genetics approach



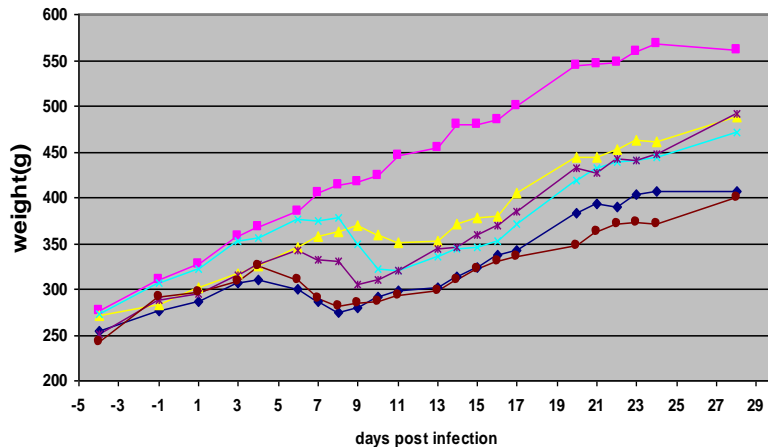
**Ebola and Marburg viruses, Nipah virus and CCHF virus**

# EBOV mutant is completely attenuated

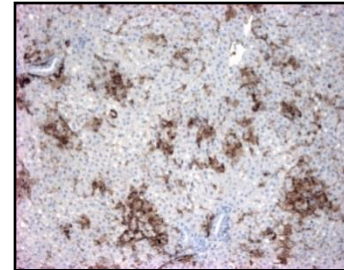
**WT**



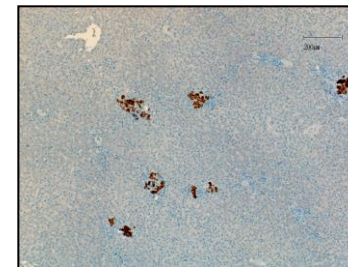
**NE**



**$\alpha$ VP40**



**D7**



**D16**



**D27**