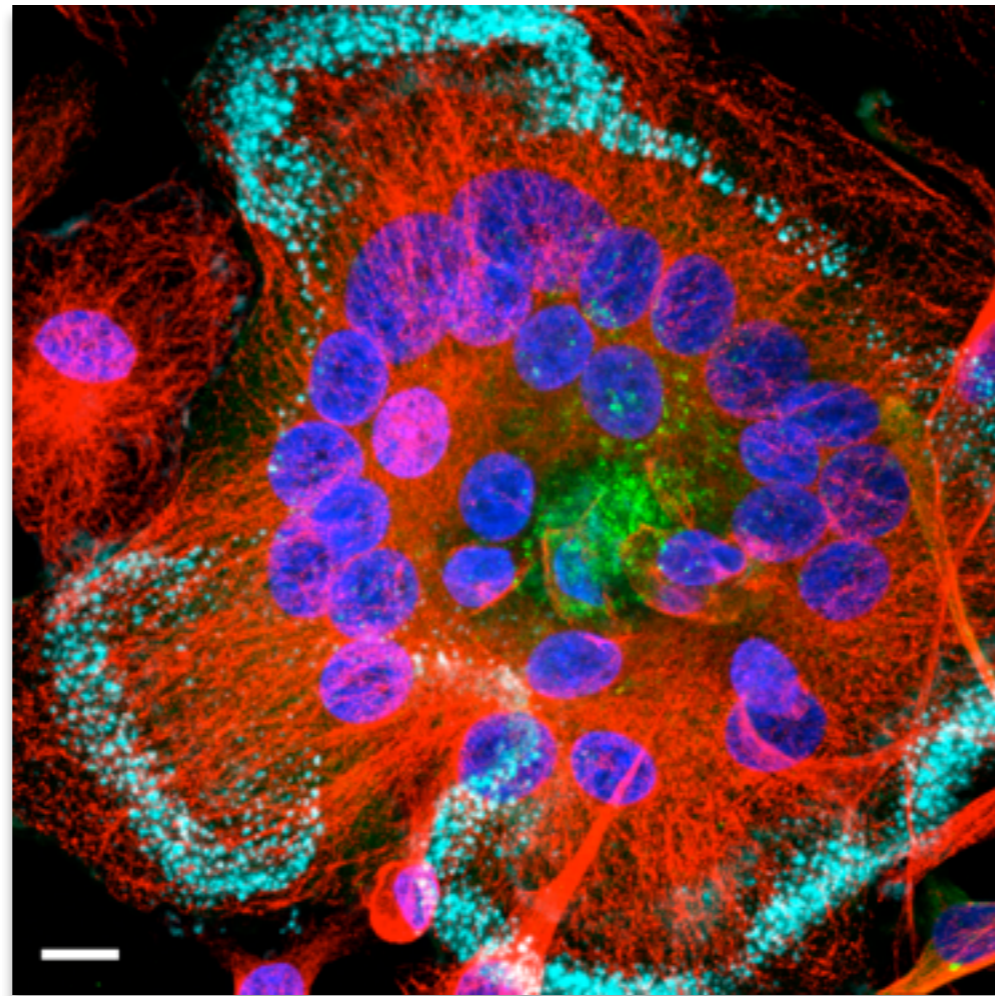
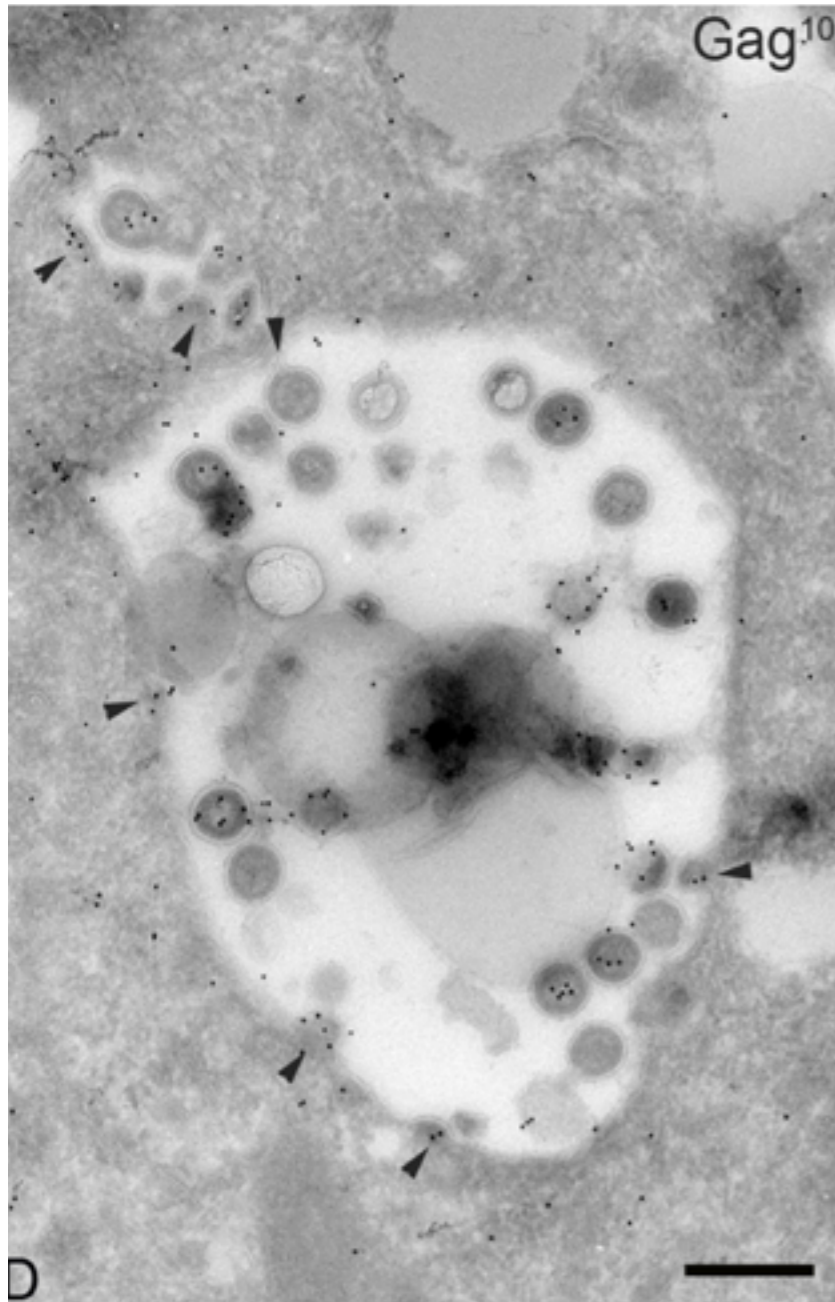


# Macrophage sensing of HIV-1 entry elicits a type I interferon response



# The HIV-1 life cycle in macrophages



*Macrophages are versatile cells* present in most tissues endowed with a variety of functions, including innate and adaptive immunity

*Macrophage paradox* : first line of defense against pathogens ...but many pathogens have selected MØ as their niche to replicate

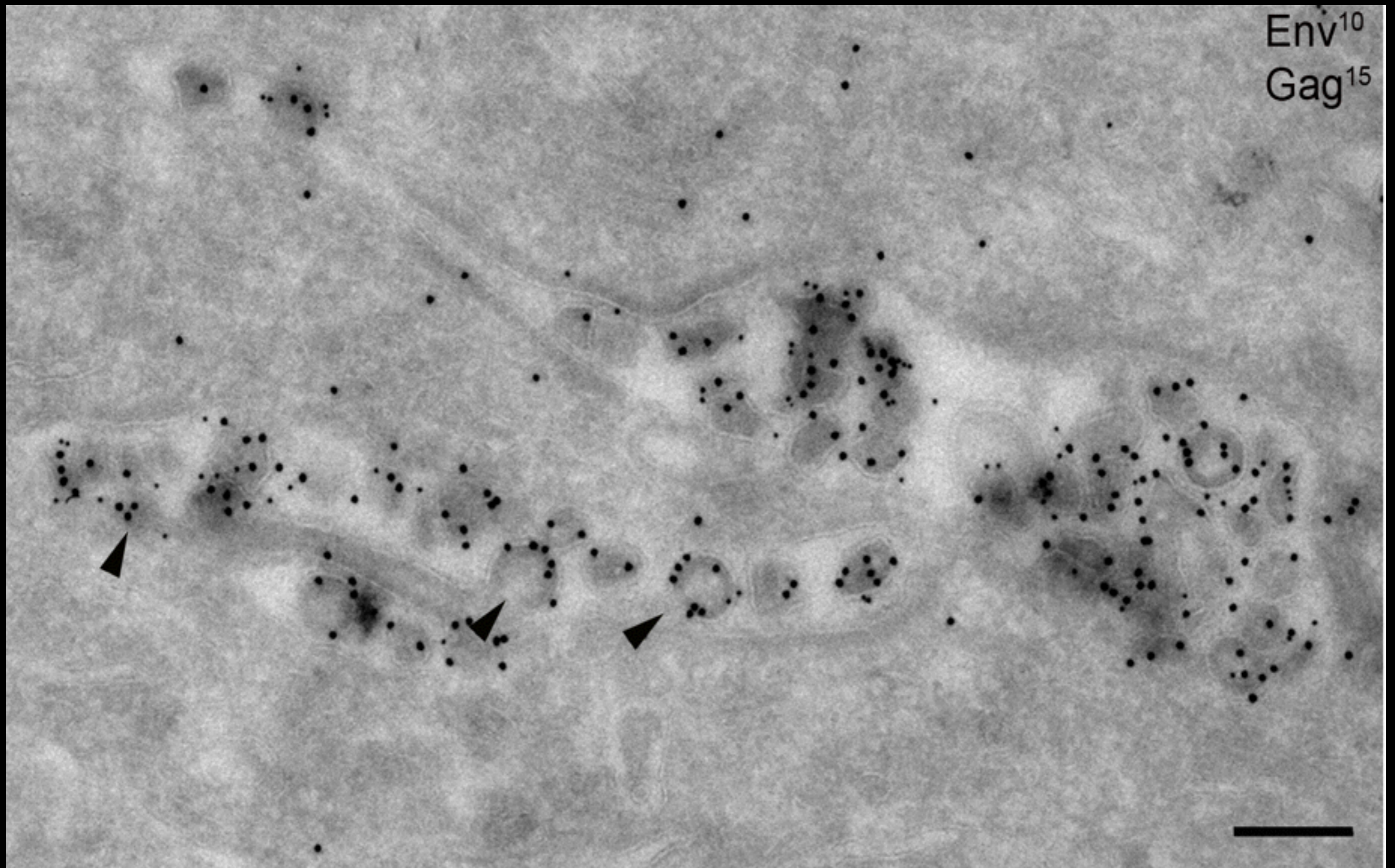
*HIV-1-infected macrophages:*

- have been found in many tissues & are involved from the onset of the infection to the pathogenesis
- retain infectious particles for extended periods of time (non cytopathic viral cycle)
- a crucial viral reservoir upon arrest of HAART

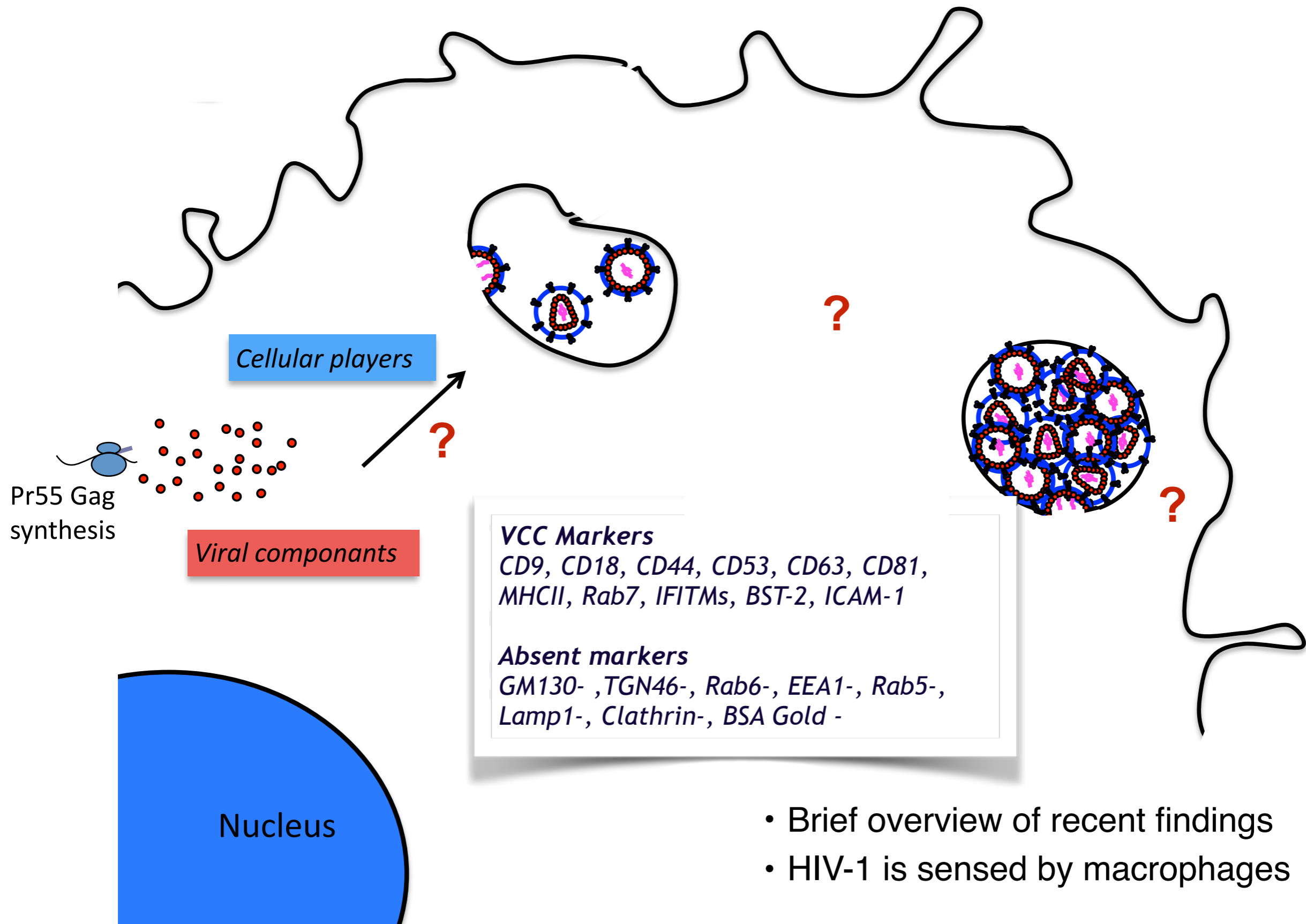
-> *HIV-infected macrophages represent a viral reservoir*



*The enigmatic Virus-Containing Compartment*

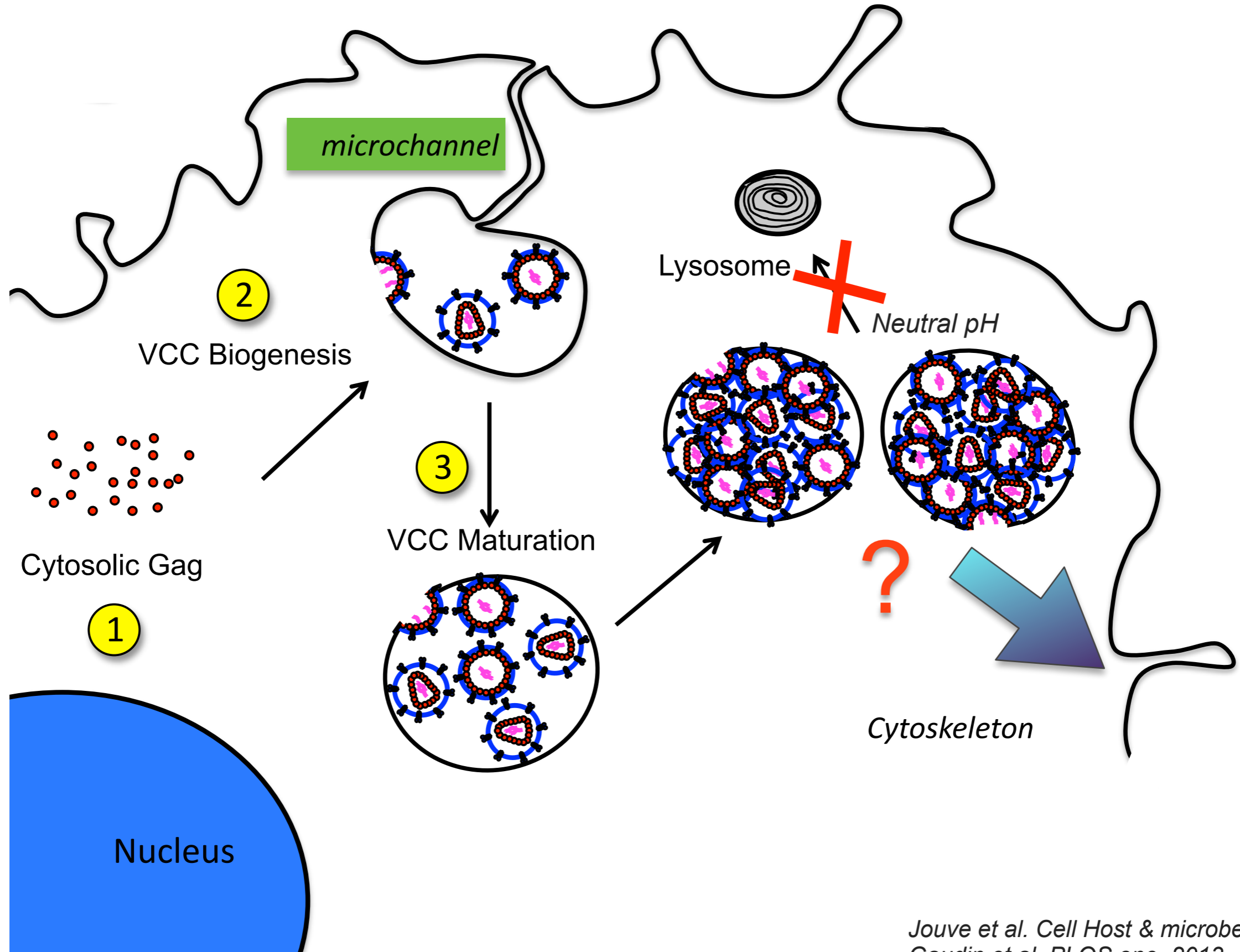


# The Virus-Containing Compartment is unique

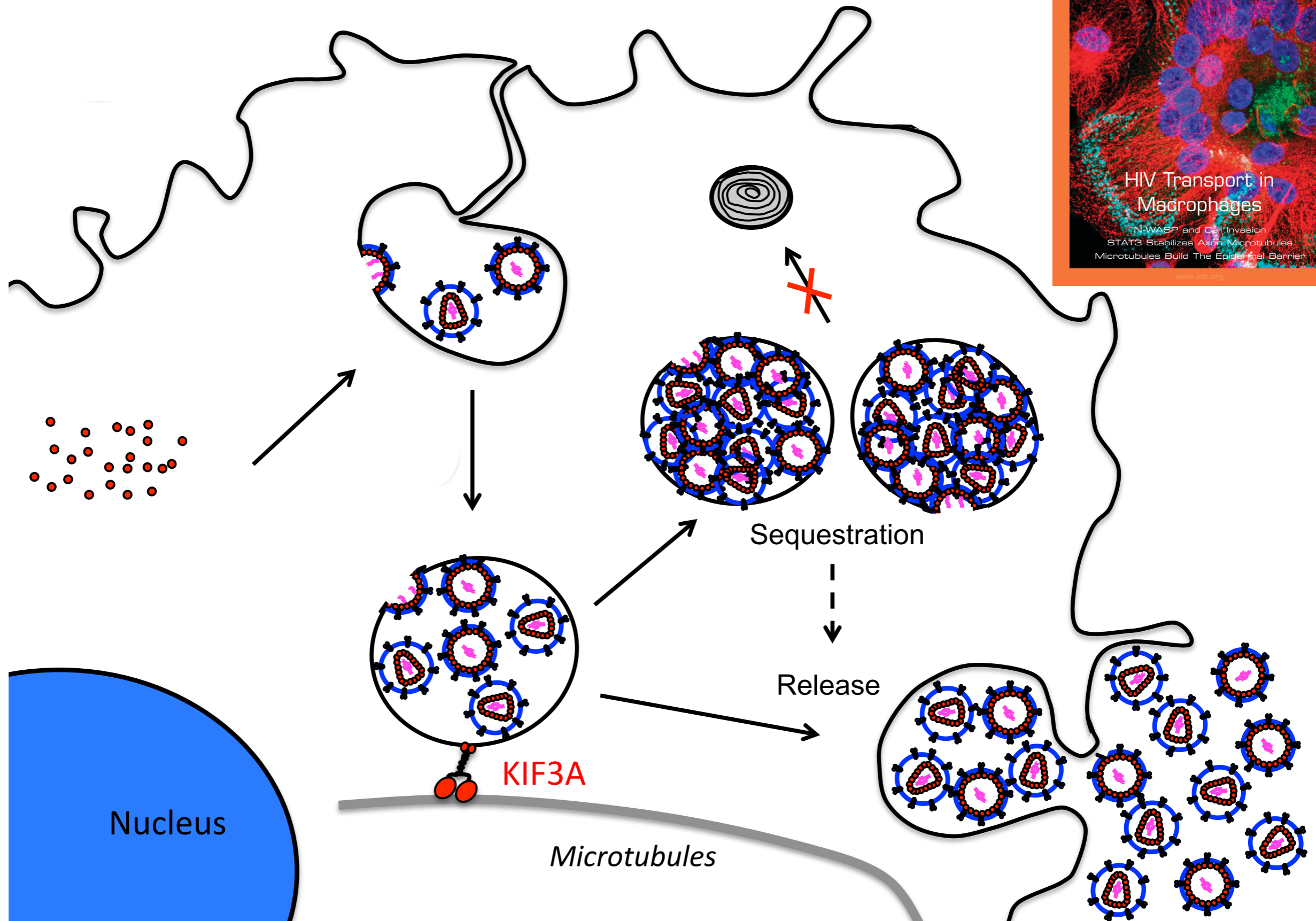




# Dynamics of the Virus-Containing Compartment



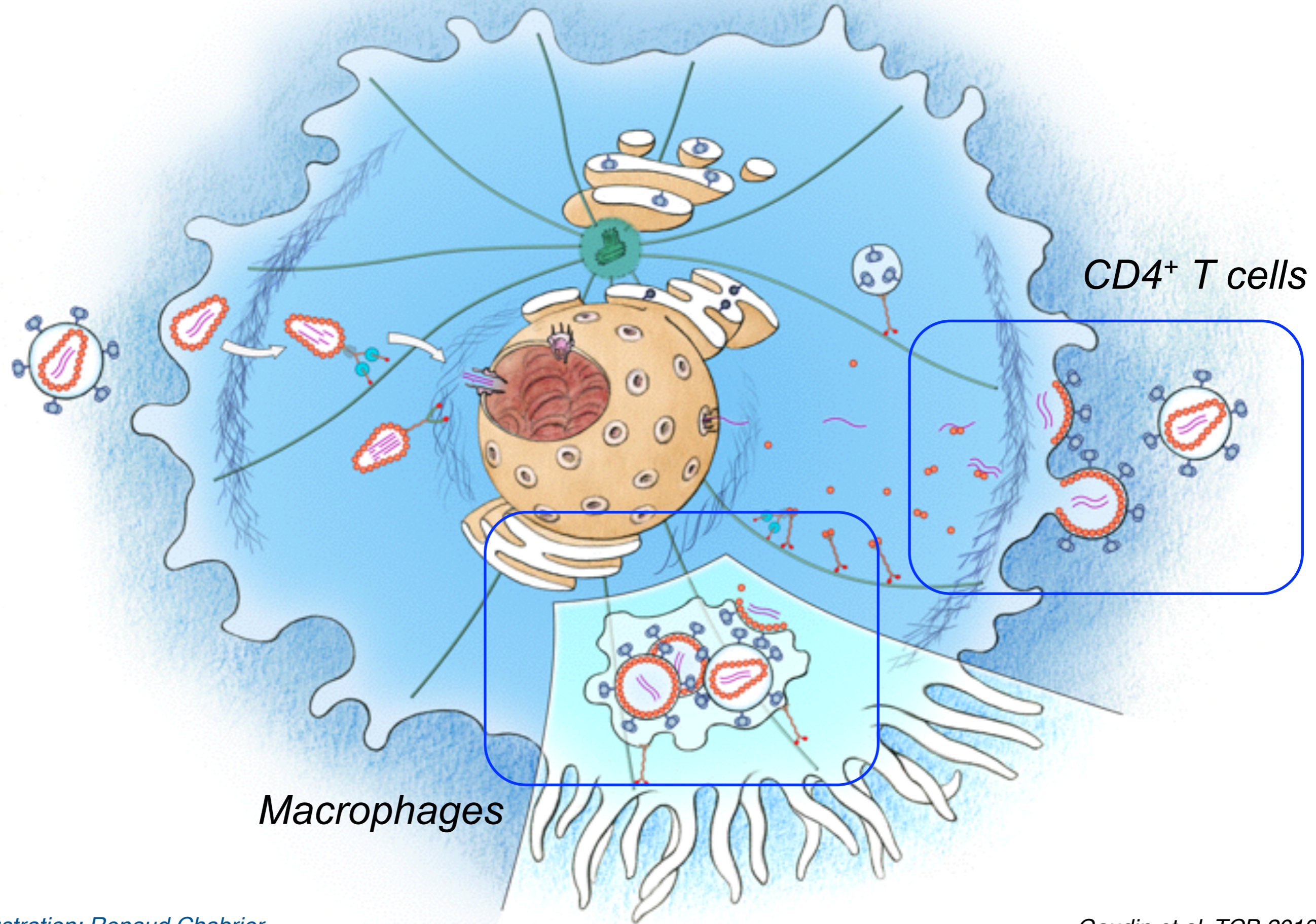
# KIF3A plays a critical role in the HIV cycle in macrophages



*Not in T lymphocytes -> first host protein macrophage-specific*



*Molecular basis of the macrophage specificity of the localization of HIV assembly?*

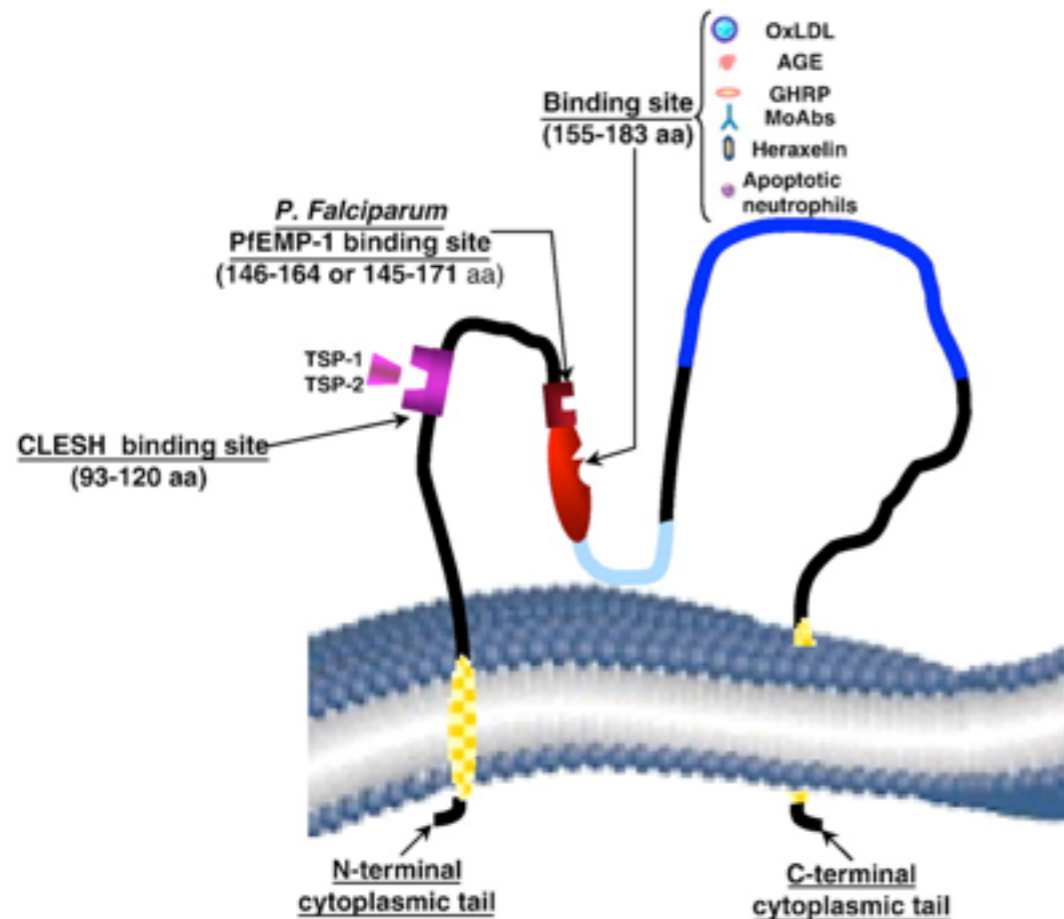


*CD4<sup>+</sup> T cells*

*Macrophages*



# The clustering-responsive Class B scavenger receptor III CD36 binds many ligands



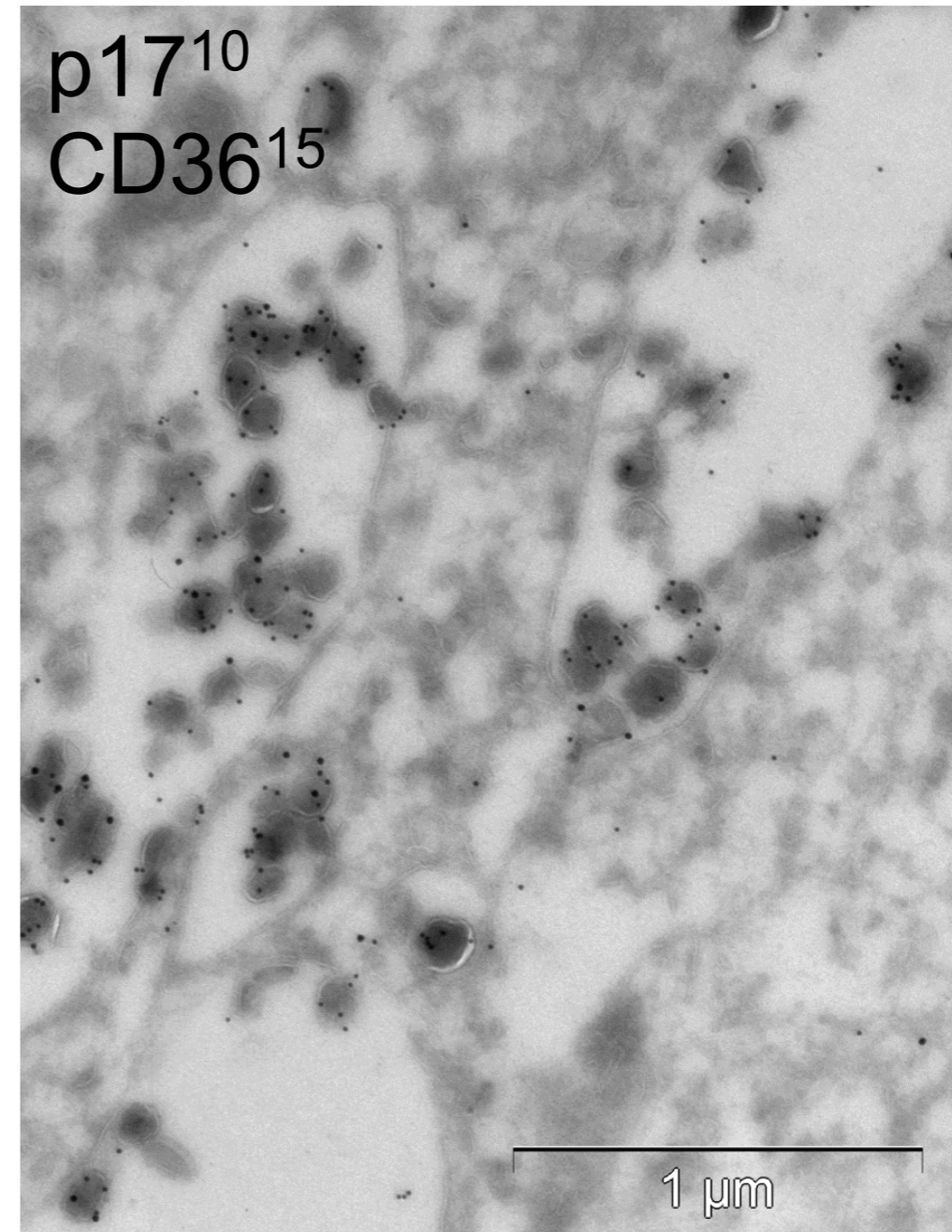
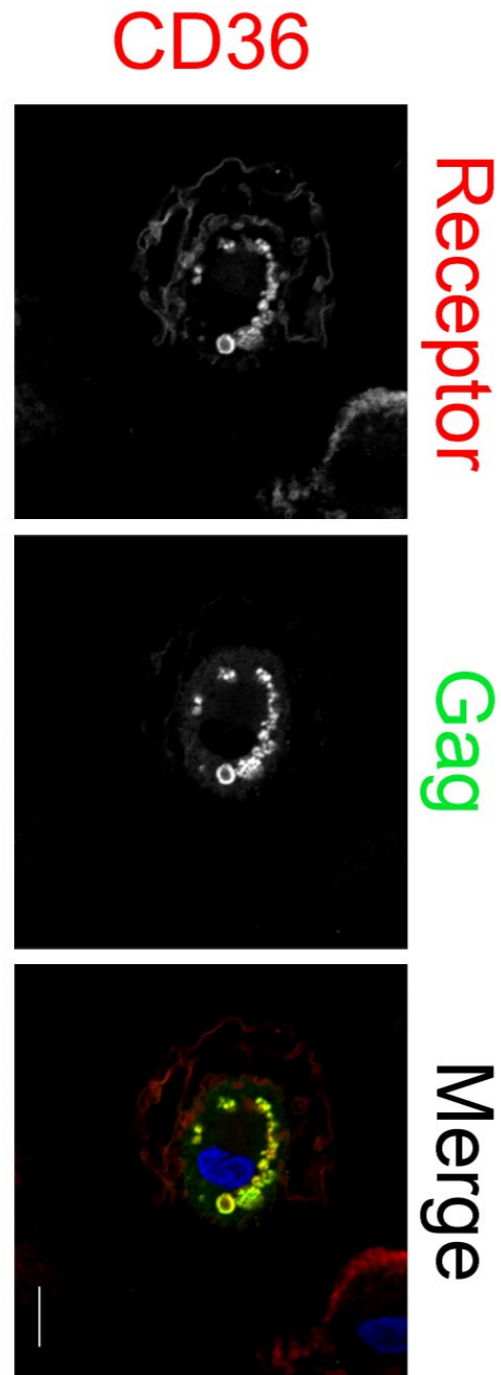
- Collagen
- Thrombospondin
- erythrocytes parasitised with *Plasmodium falciparum*
- **oxidised low density lipoprotein**
- native lipoproteins
- oxidised phospholipids
- long-chain fatty acids
- dead cells

CD36 is mainly expressed on the surface of platelets, endothelial cells, and macrophages.  
**Not in T lymphocytes**

CD36 is implicated in a wide range of processes, from lipid metabolism to innate immunity and tissue remodelling



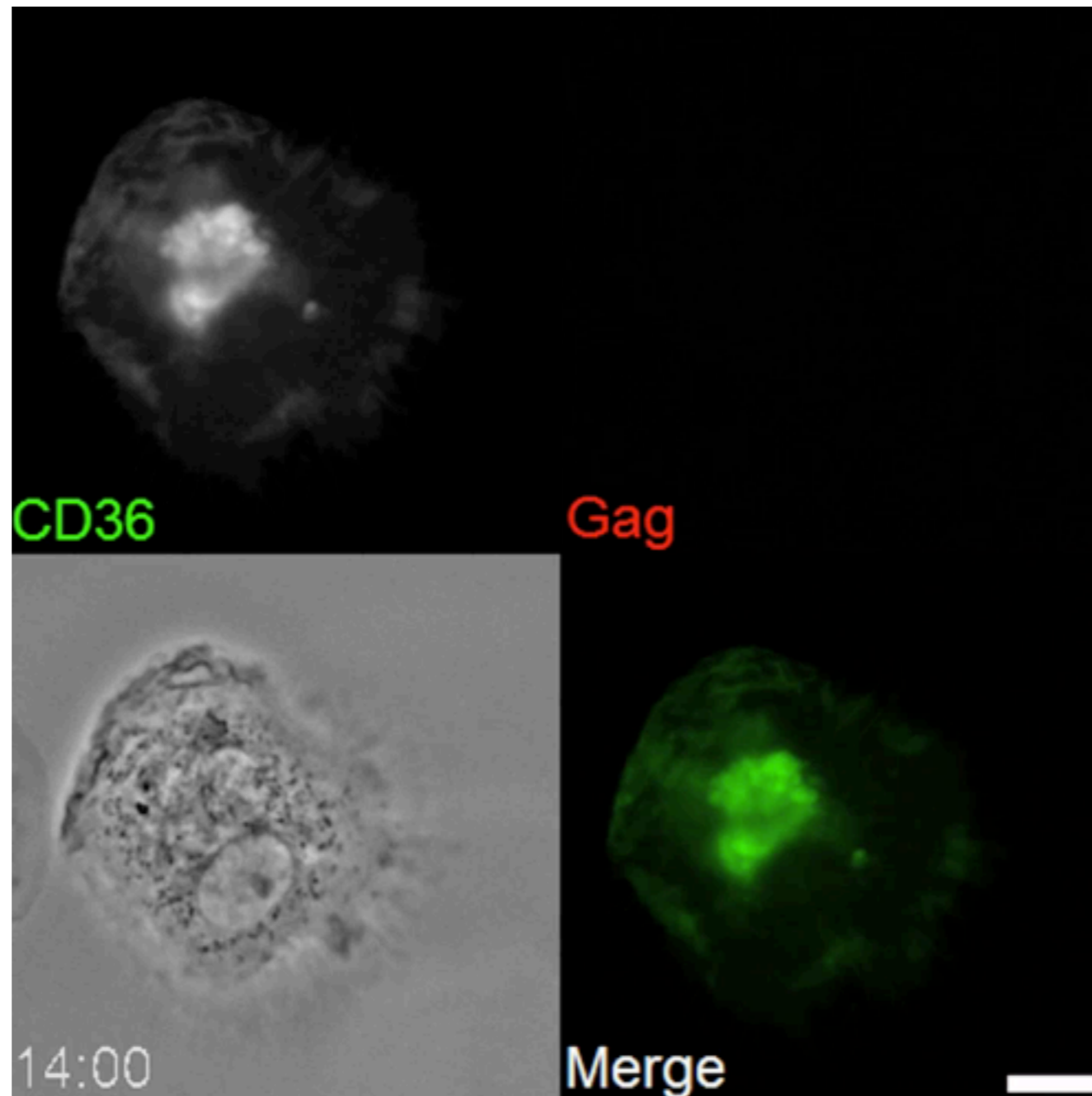
## The Virus-Containing Compartment contains CD36



*In uninfected macrophages: CD36<sup>+</sup> compartments are CD9<sup>+</sup>CD81<sup>+</sup>Lamp1<sup>-</sup> & can be connected to the PM*

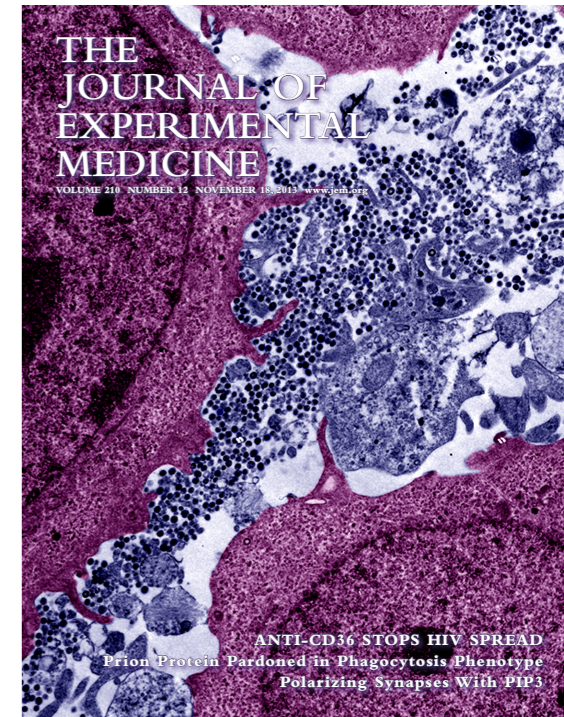
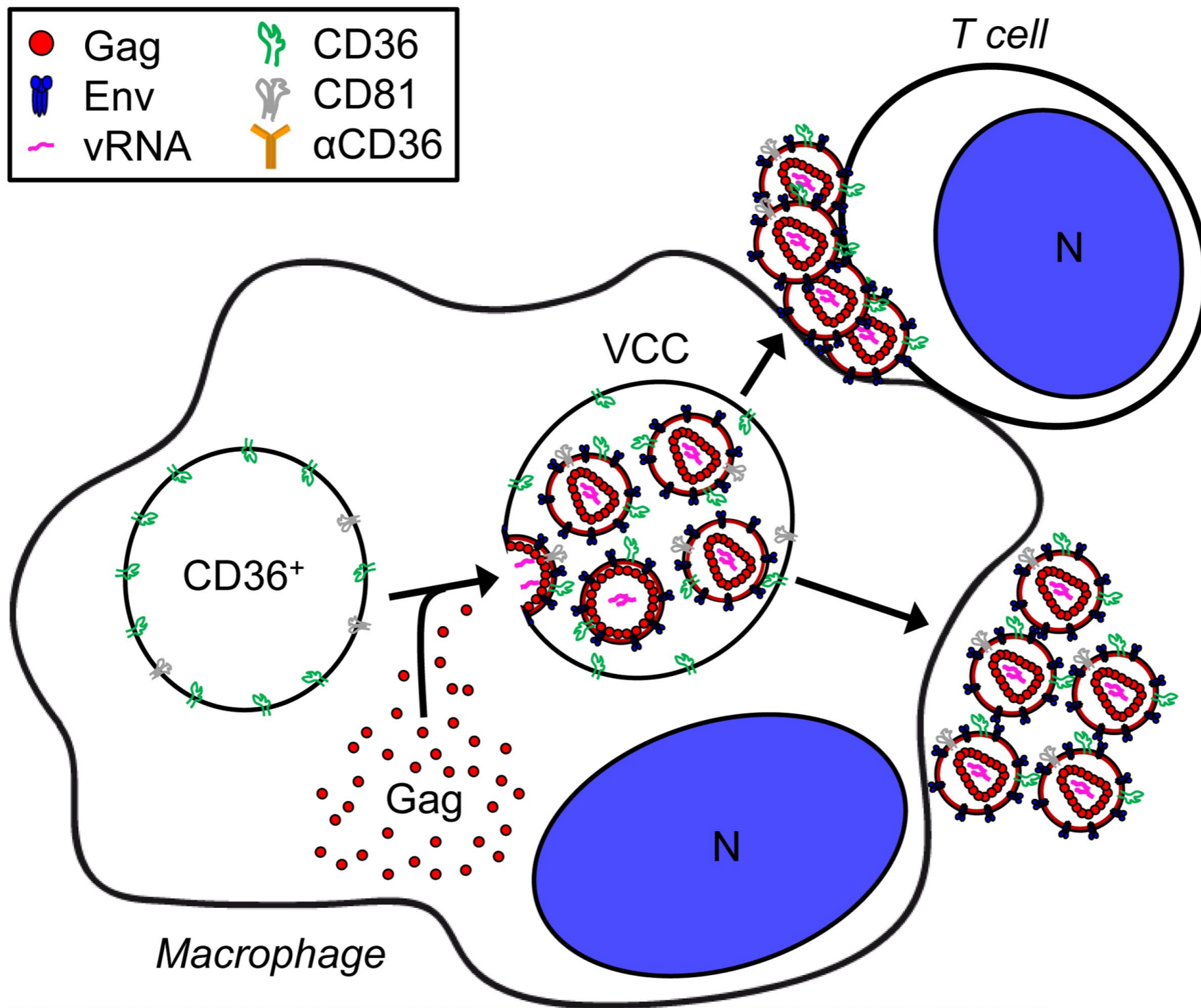
*Are CD36<sup>+</sup> compartments hijacked by HIV-1?*

# Upon HIV-1 infection, Gag is recruited to preexisting CD36+ compartments in macrophages





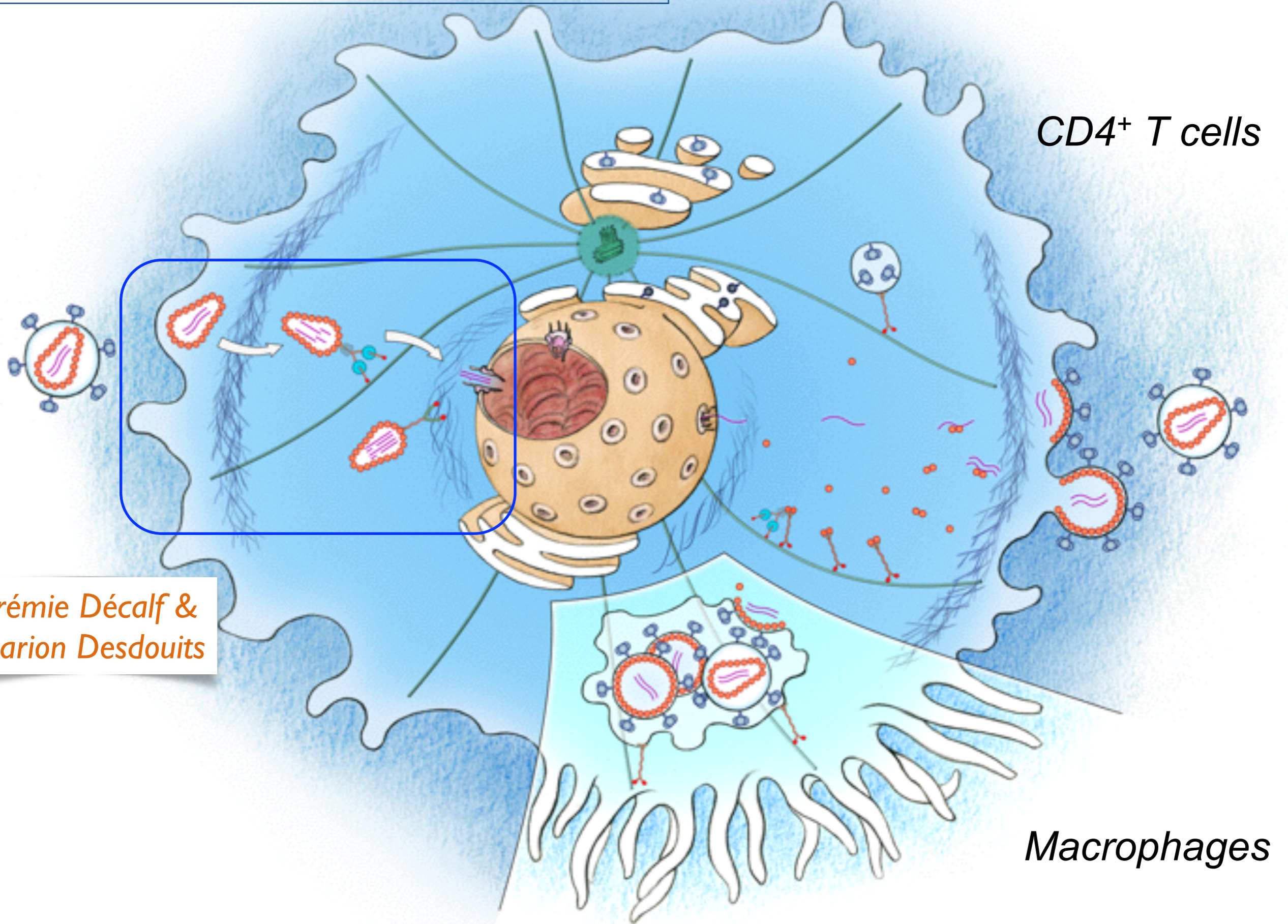
# HIV-1 cycle in macrophages & transmission to T cells



*p55 Gag promotes the coalescence of TEM and raft domains*



# Macrophages early sensing of HIV-1?



*CD4<sup>+</sup> T cells*

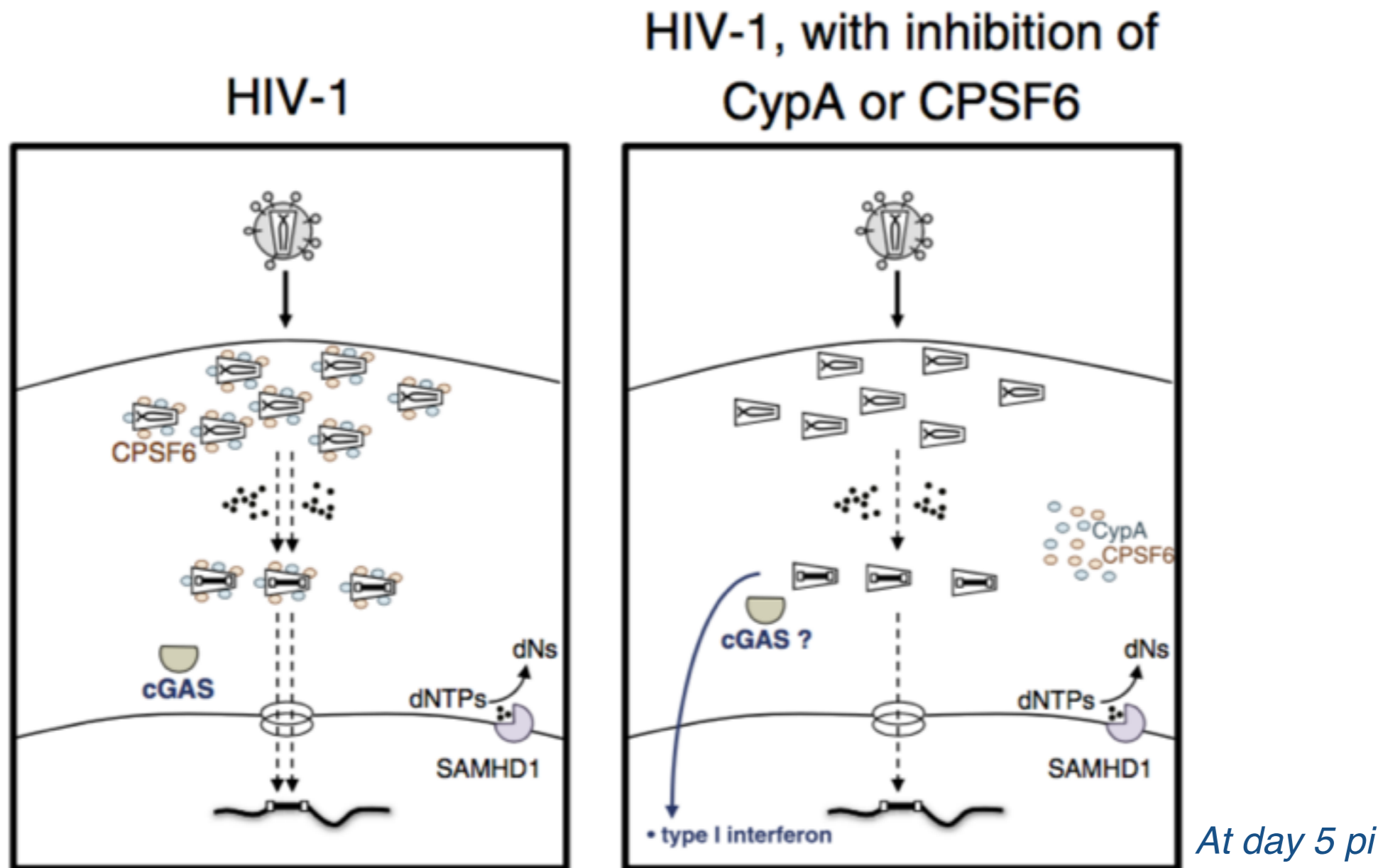
*Macrophages*

*Jérémie Décalf & Marion Desdouits*



# HIV infection in primary **human monocyte-derived macrophages**: sensing or no sensing ?

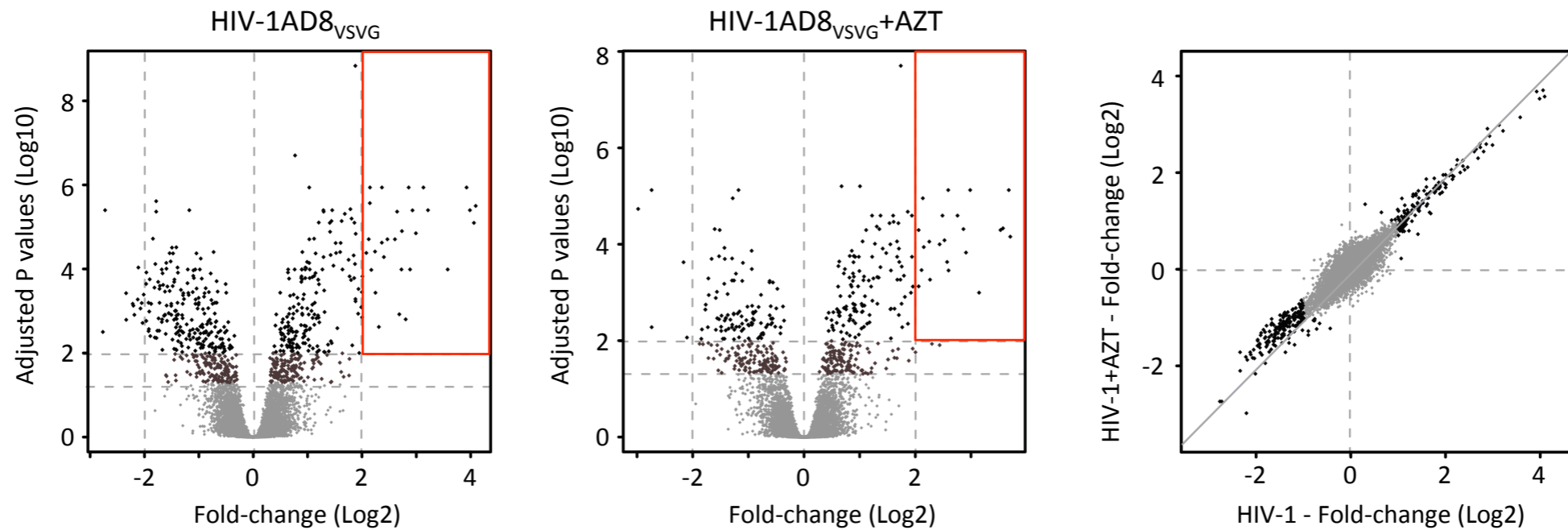
PAMPs



*Adapted from Lahaye and Manel 2015*

*At early steps absence of detectable type I IFN but clear ISG response  
-> ISG directly induced in an IFN-independent manner?*

# Macrophages response to HIV-1 infection is independent of the retrotranscriptase (RT) activity



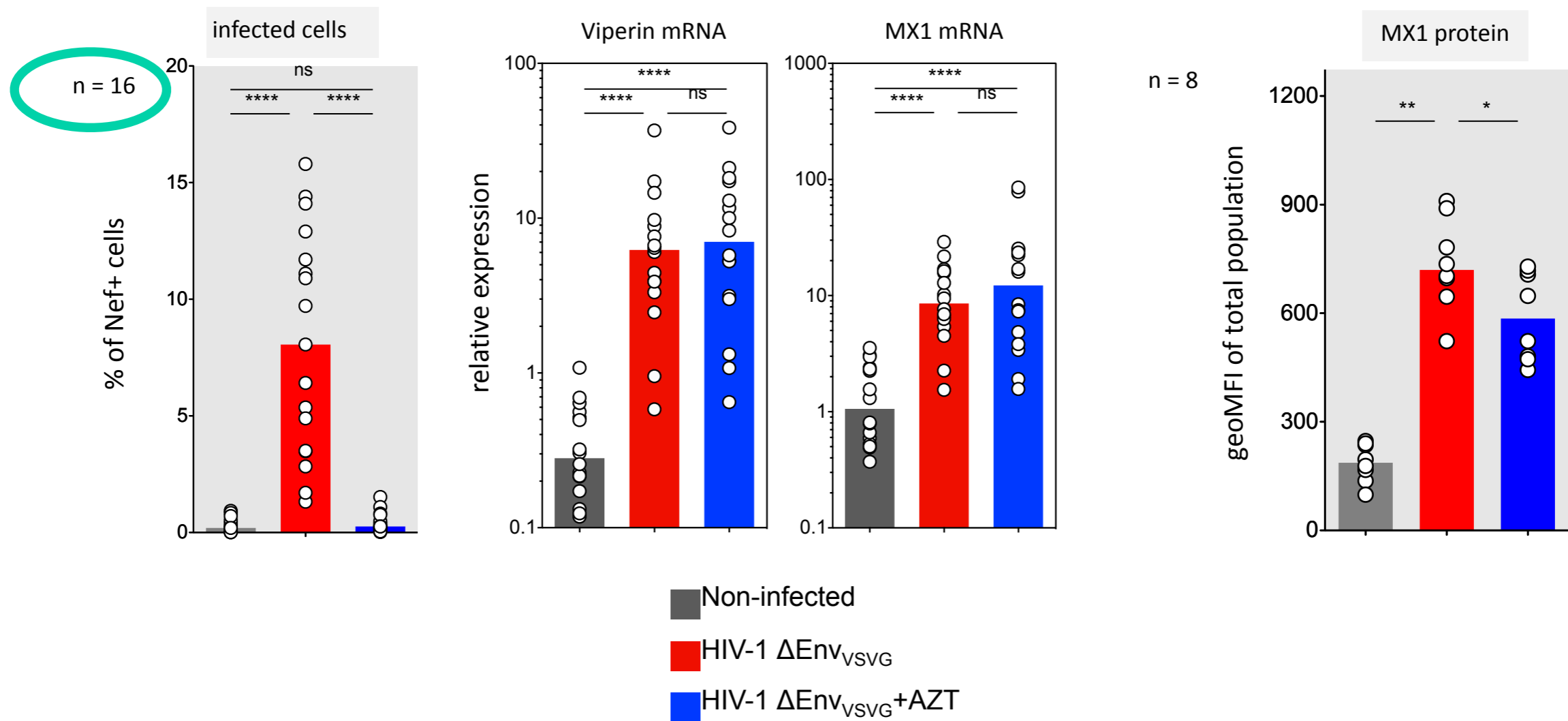
24 hours  
post infection

GSEA

*HIV-1 sensing by macrophages induces an ISG response observable from 8h post infection*

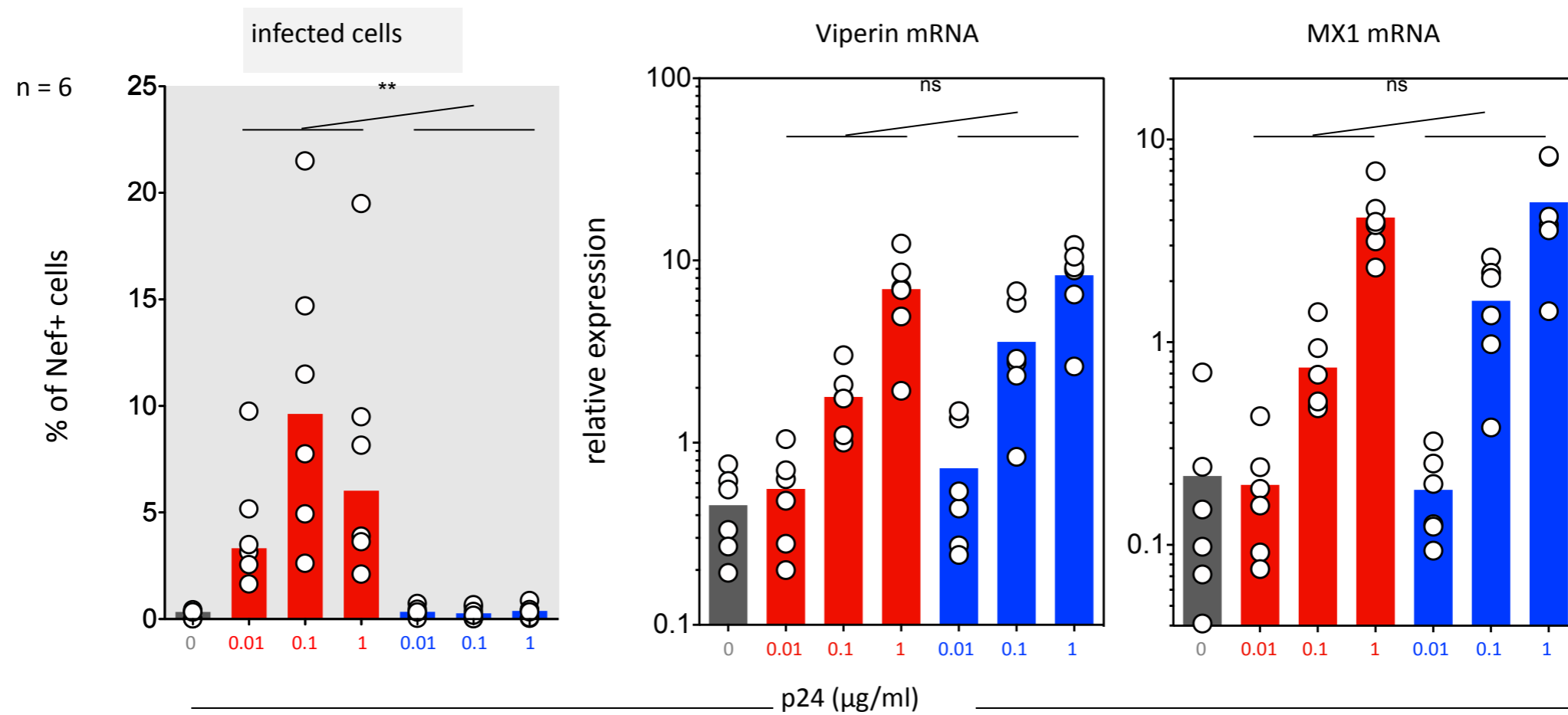


# HIV-1 induction of ISGs is reverse-transcription independent



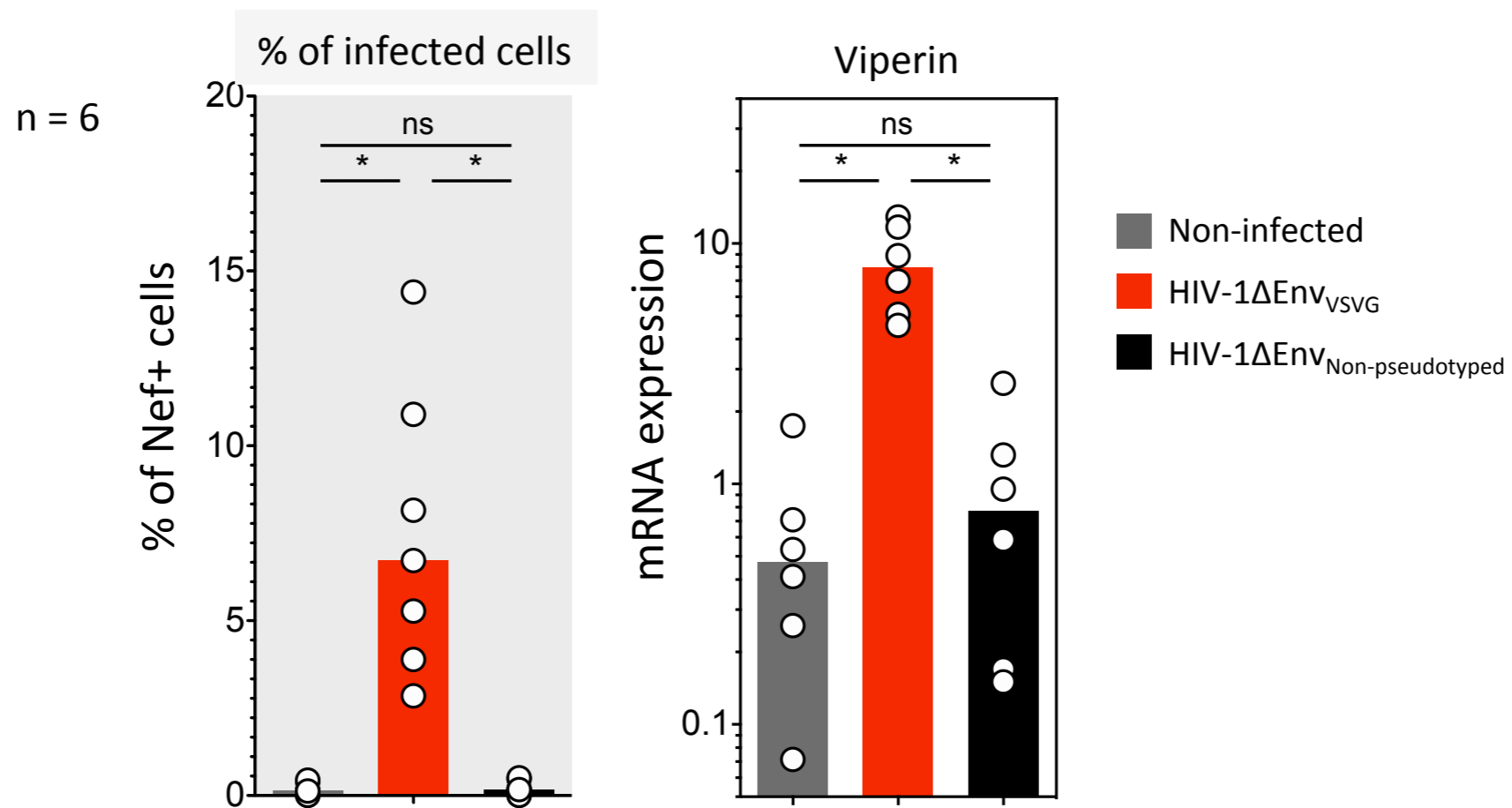
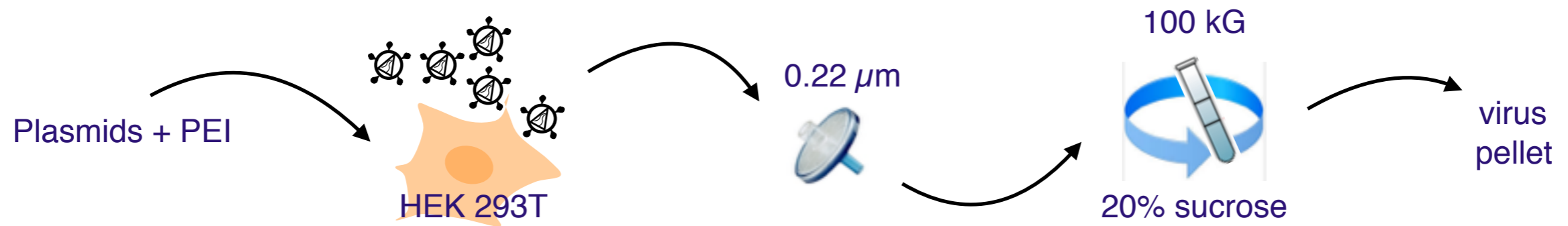
*Same results with Nevirapin instead of AZT*

# Virus titration suggests that sensing and replication are dissociated



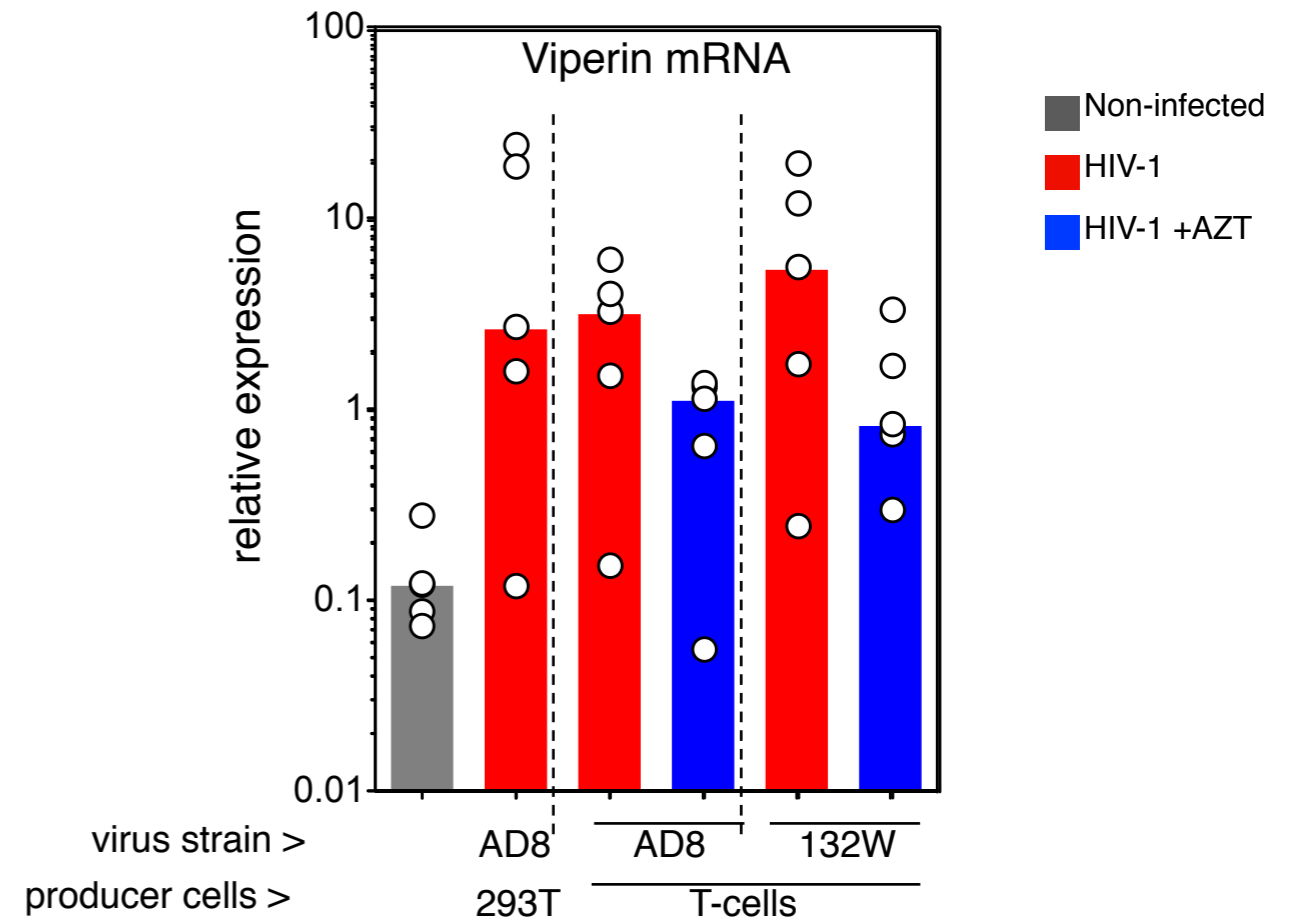
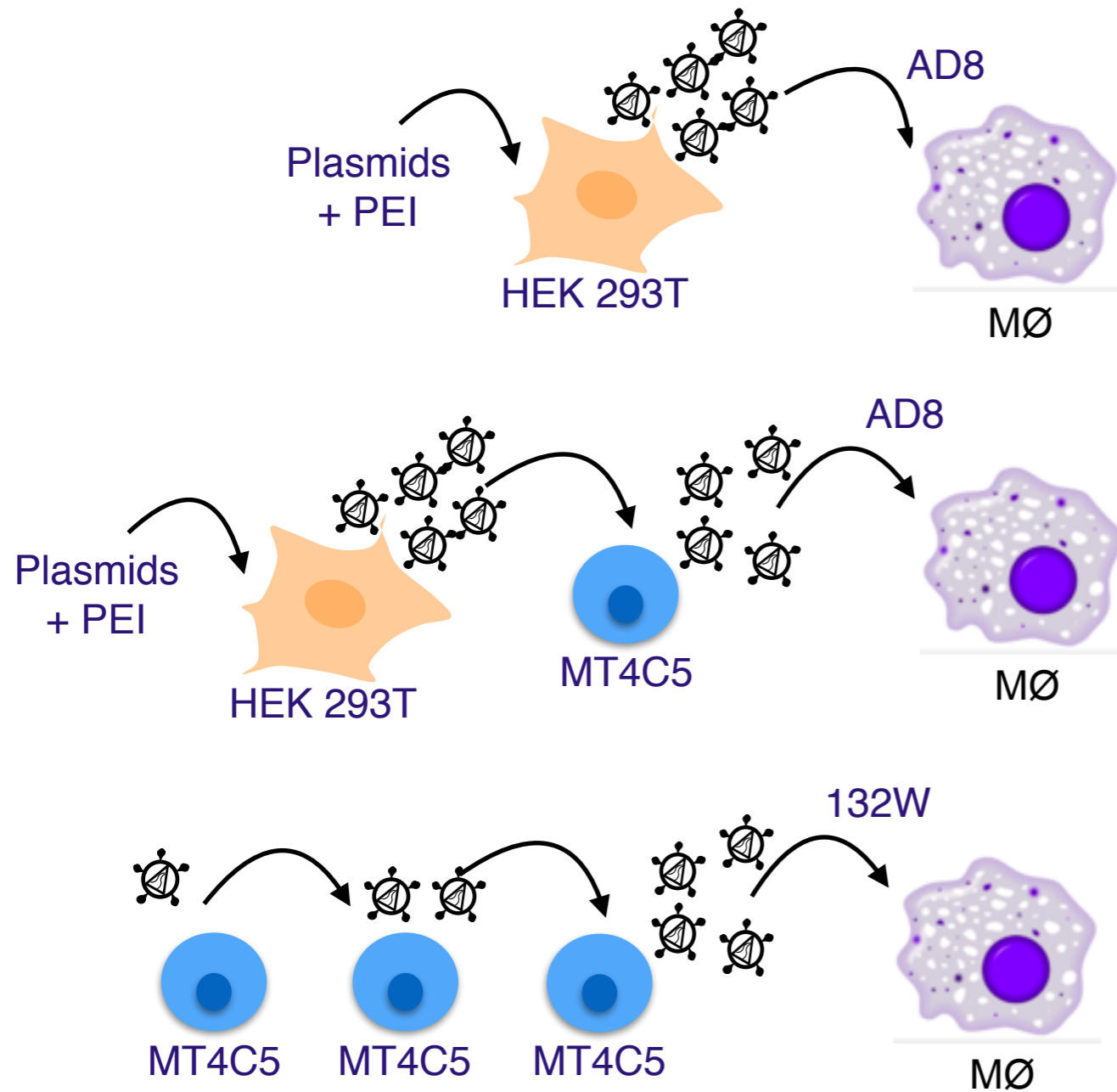


# Genuine sensing of viral infection or contamination? (1/2)



*Sensing is not due to contaminations present in the viral preparations, nor to cGAMP or plasmid DNA present in the viruses*

## Genuine sensing of viral infection or contamination? (2/2)

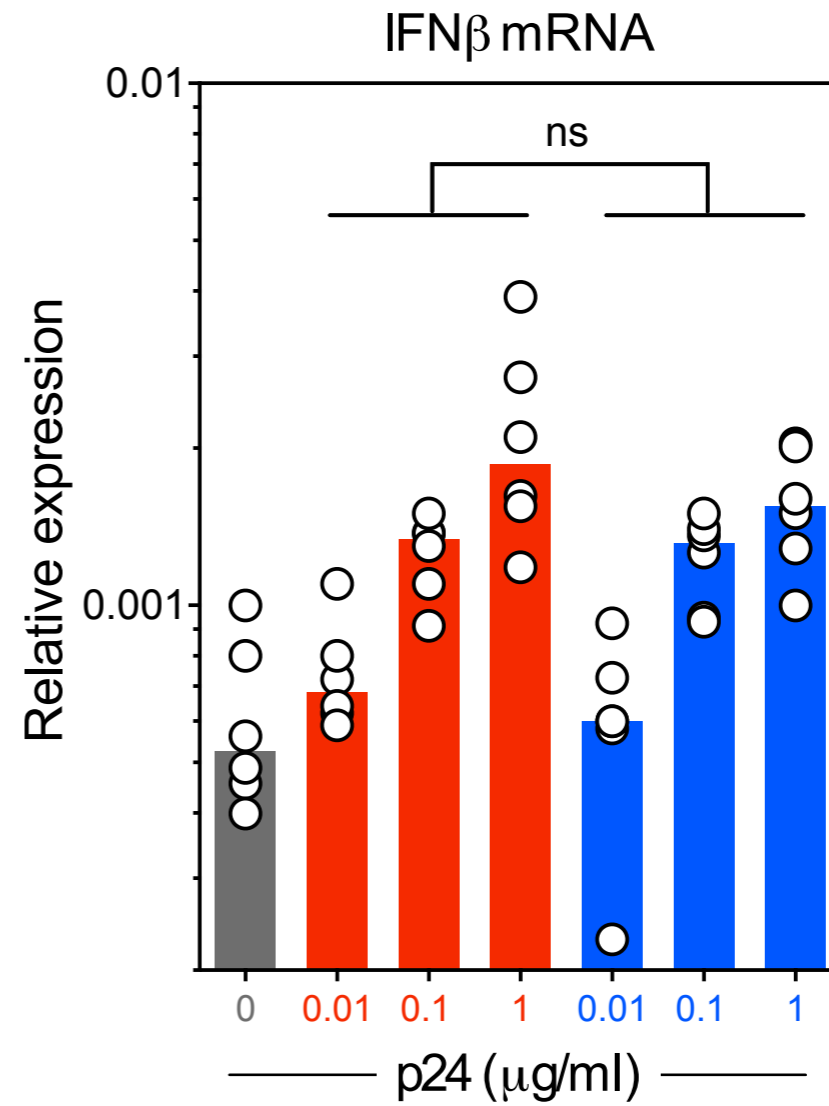
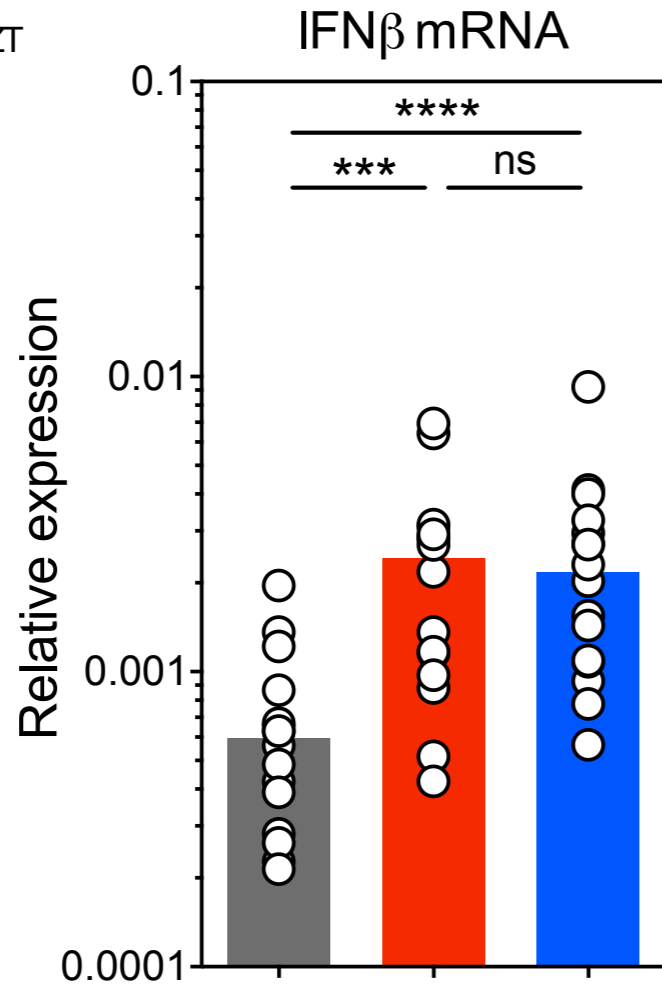


*Sensing requires an envelope, can occur with different viruses produced by different cells and leads to ISG expression*

# Is type I IFN responsible for the ISG signature?

- Non-infected
- HIV-1 $\Delta$ Env<sub>VSVG</sub>
- HIV-1 $\Delta$ Env<sub>VSVG</sub>+AZT

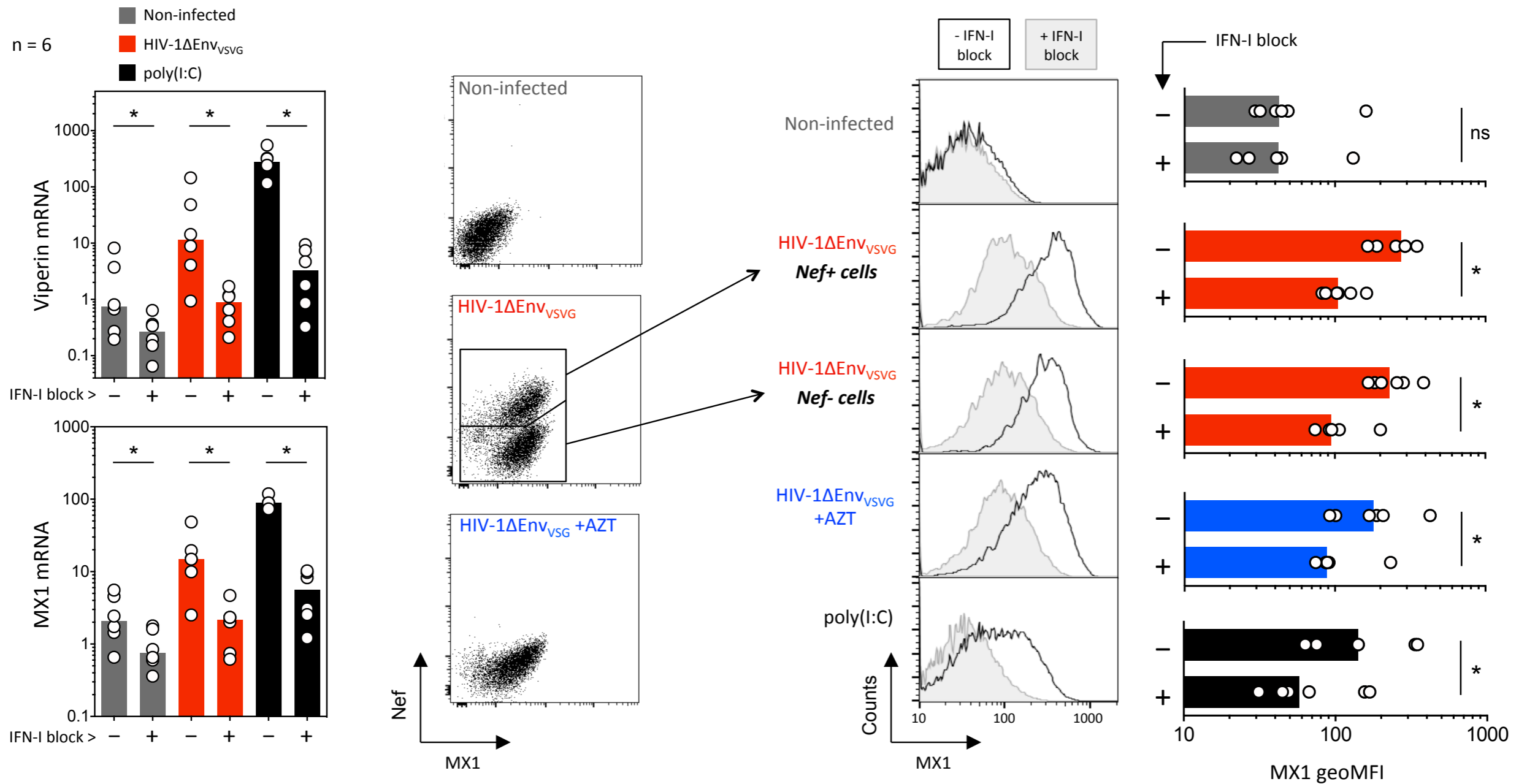
n = 16



*Macrophages produce type I IFN at low levels in response to HIV-1*

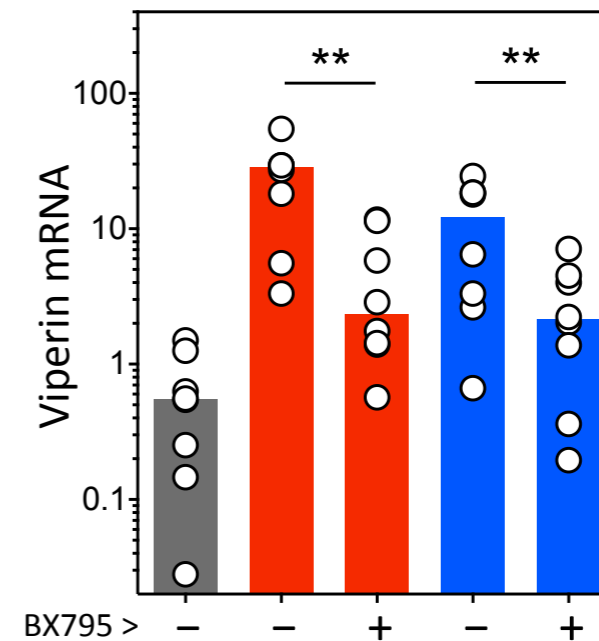
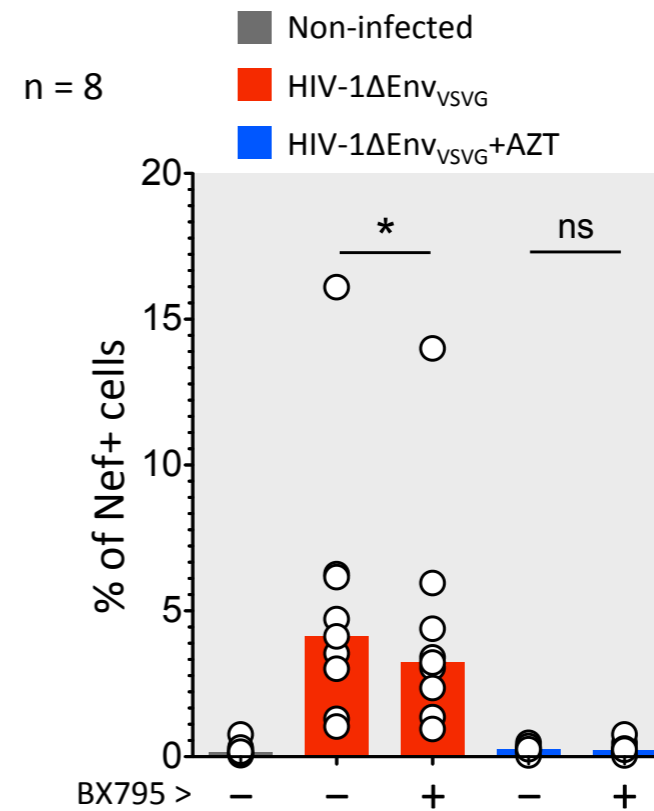
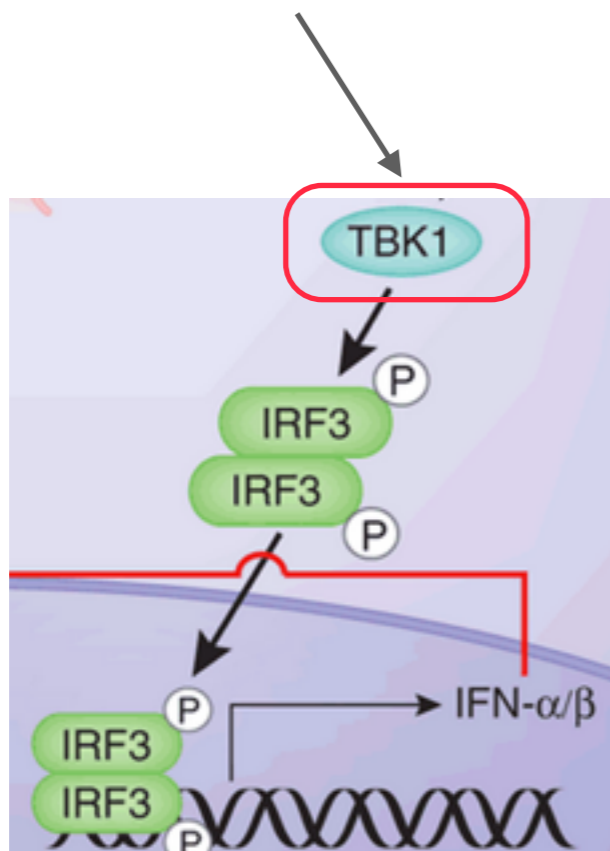
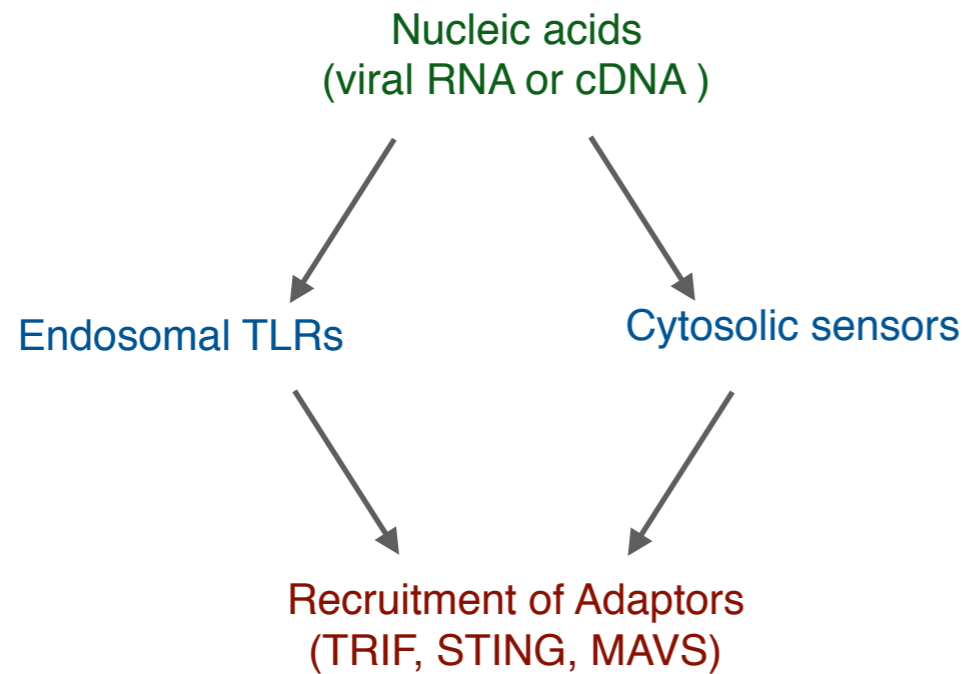


# The ISG induction is abolished by type I IFN neutralizing antibodies



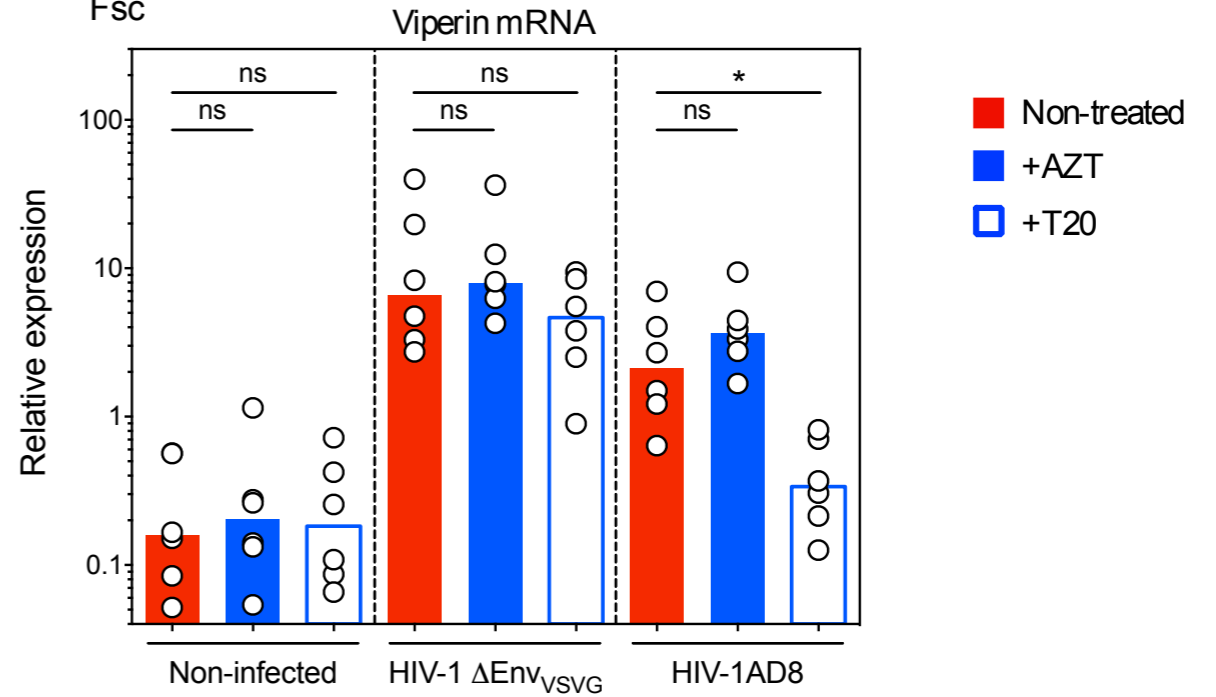
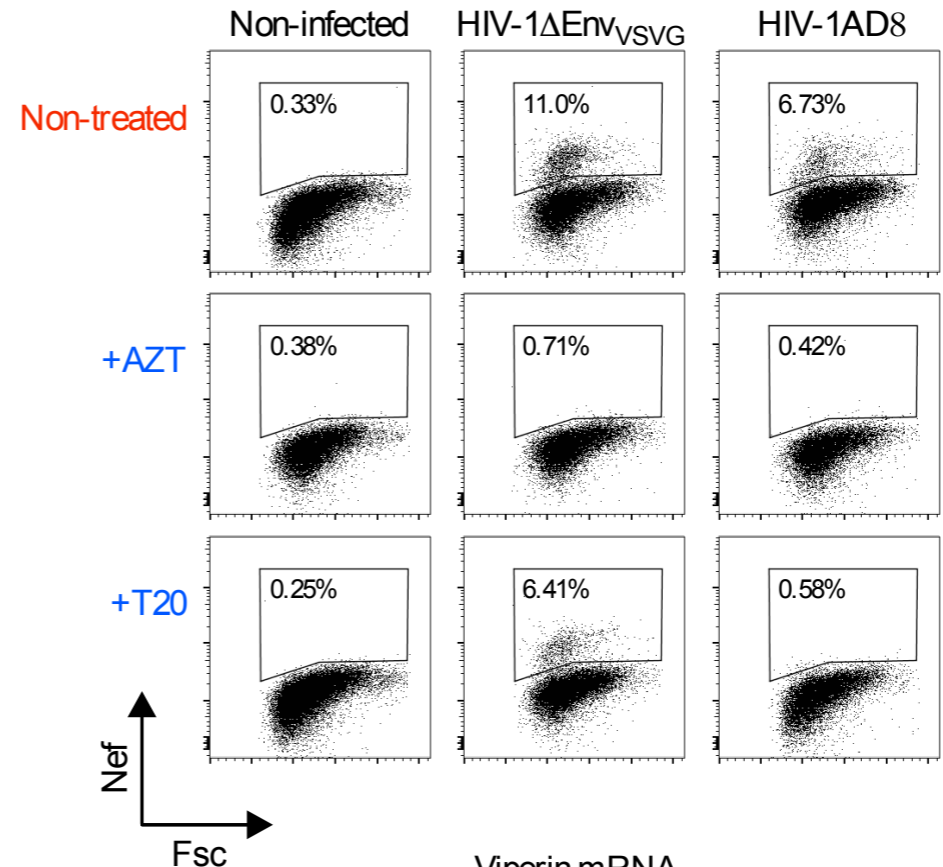
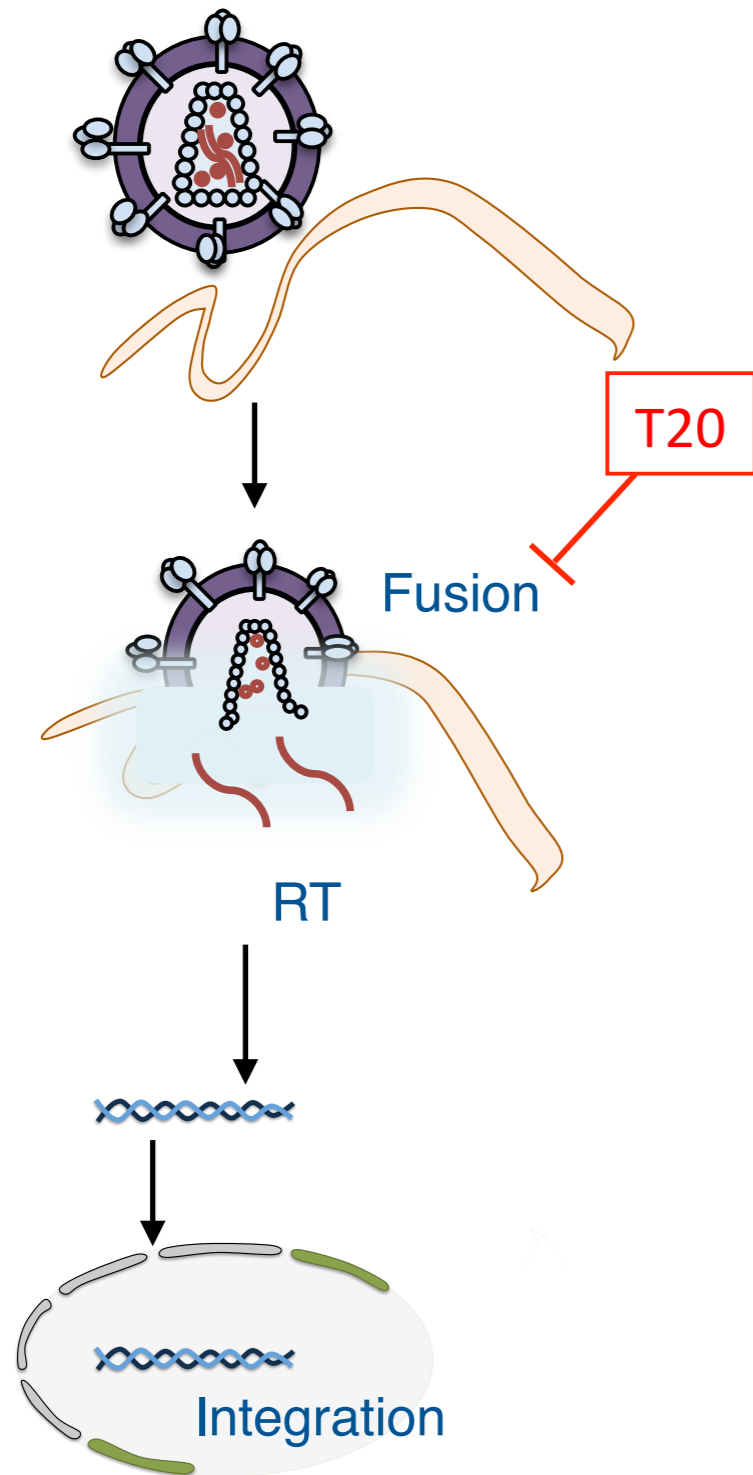
*Induction of MX1 protein expression is inhibited by type I IFN neutralizing antibodies in both uninfected and infected macrophages*

# TBK I: a key kinase for sensing



*M* $\emptyset$  response to HIV-1 is induced by a TBK I-dependent sensing

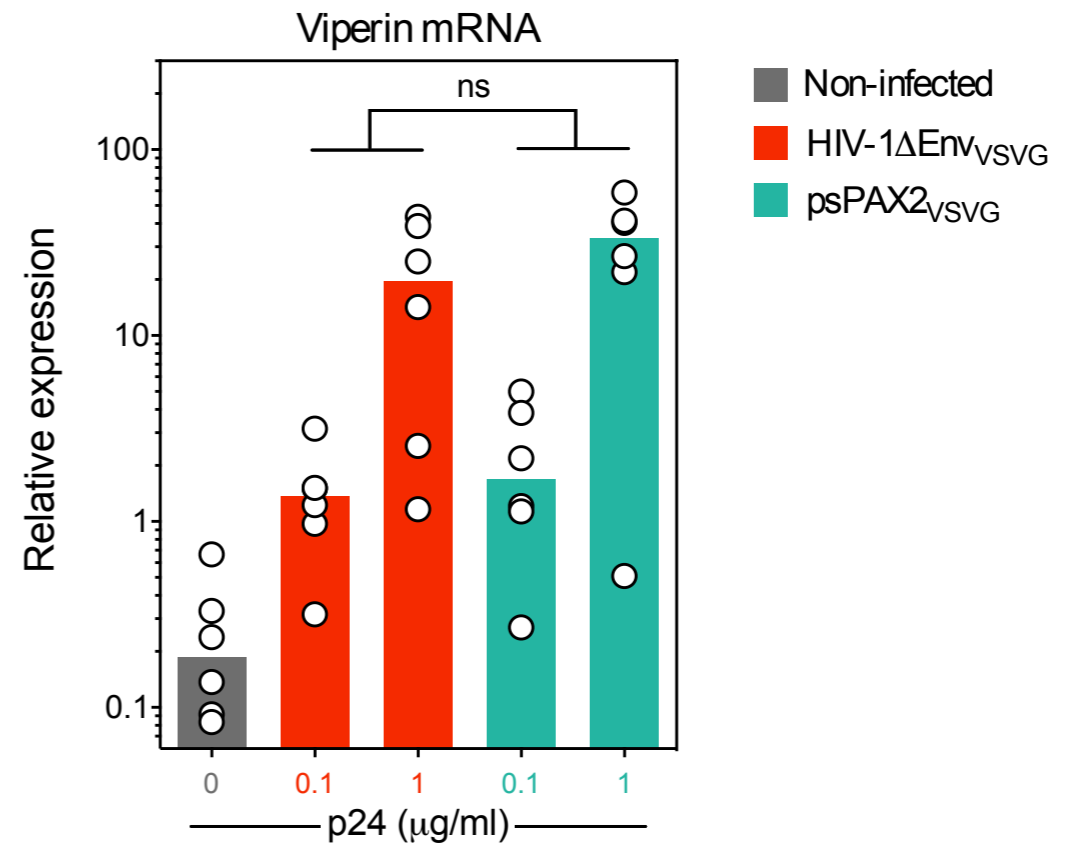
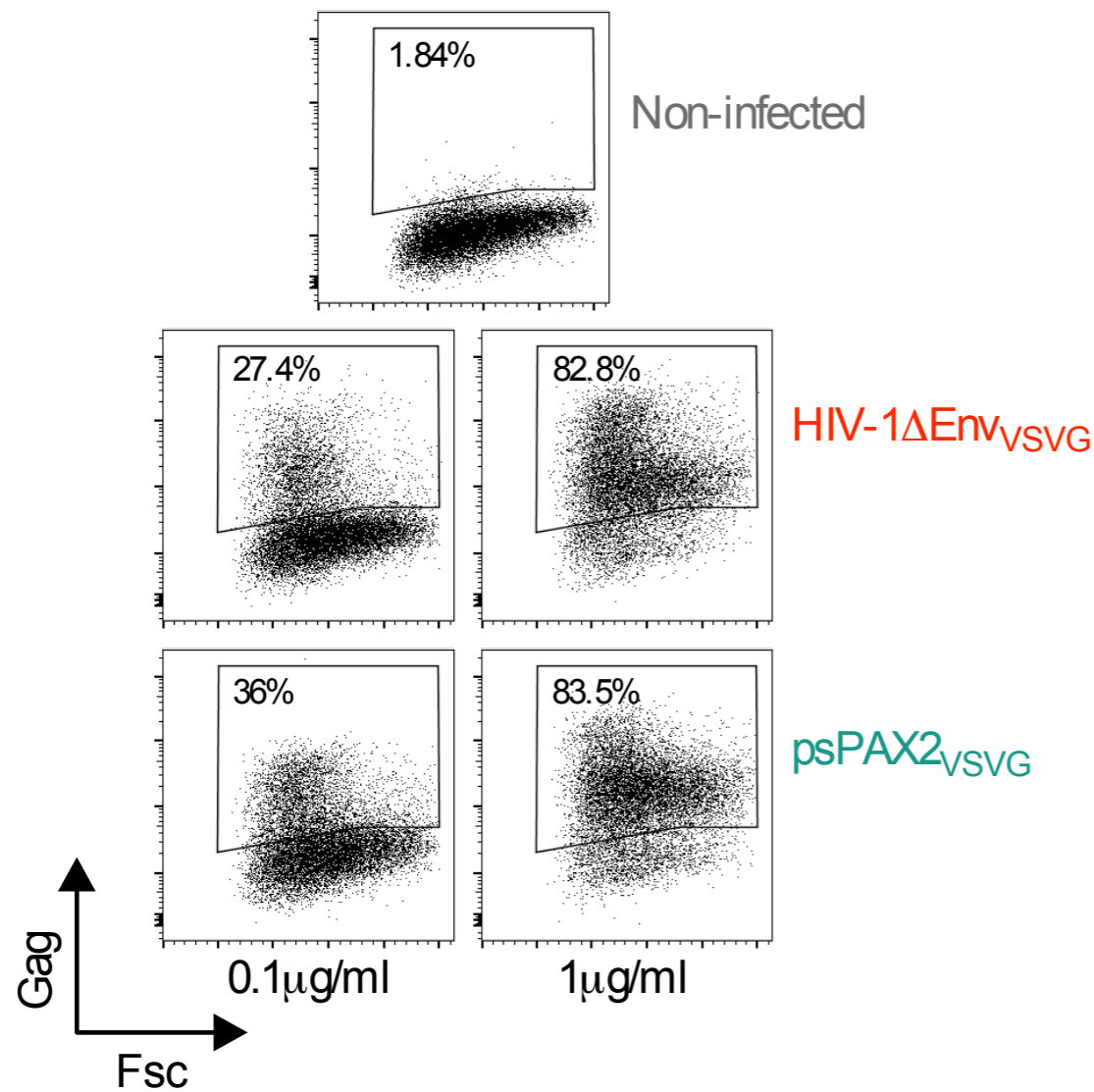
# HIV-1 fusion is required to trigger macrophage response to HIV-1



same results with the primary strain I32W produced by T cells



# Fusion of Virus-Like Particles can trigger sensing in macrophages



-> Nucleic acids are not required for sensing of incoming particles

VLPs pseudotyped with HIV Env (ADA) are sensed -> sensing does not depend on VSVg

# CONCLUSIONS

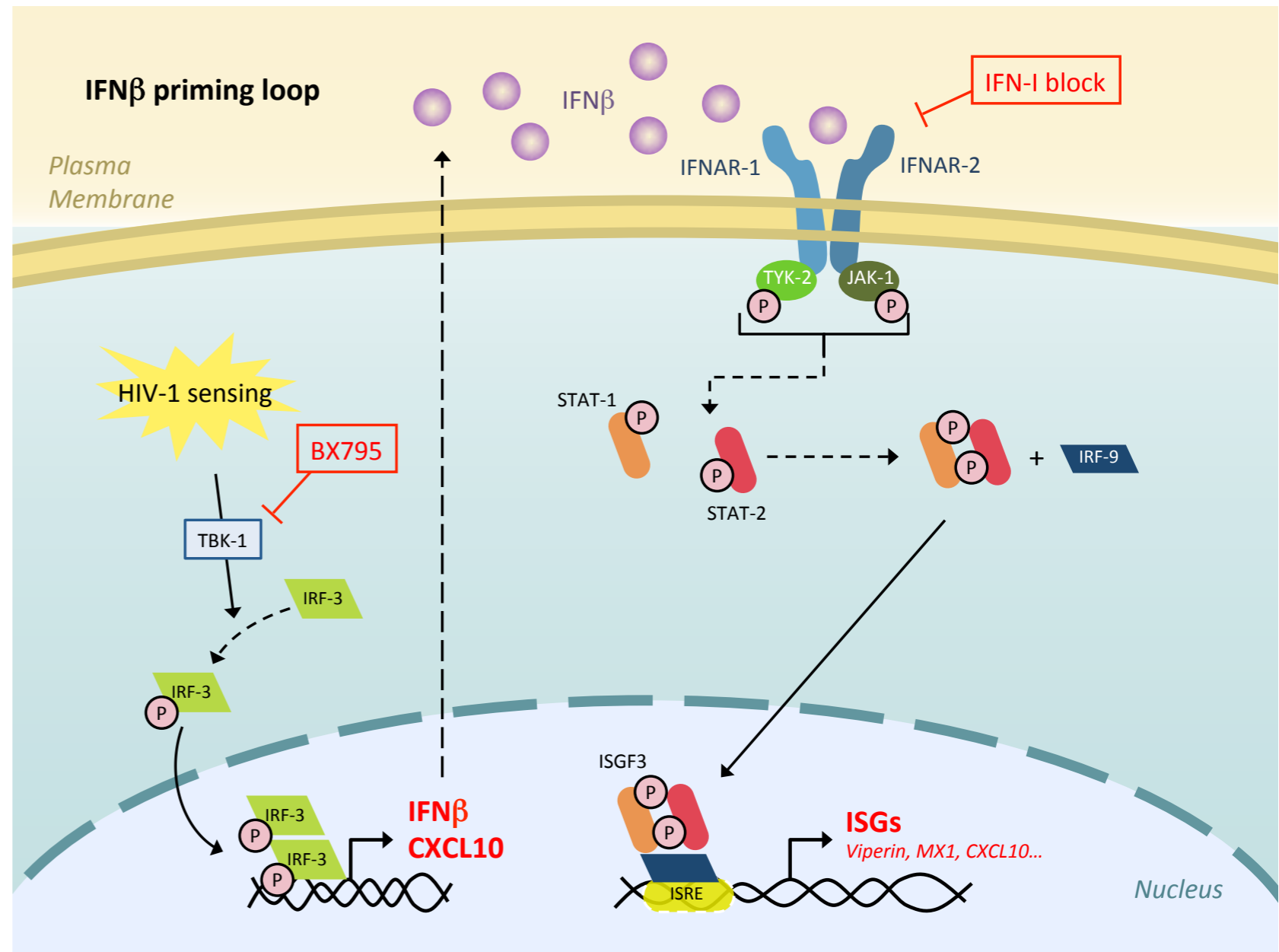
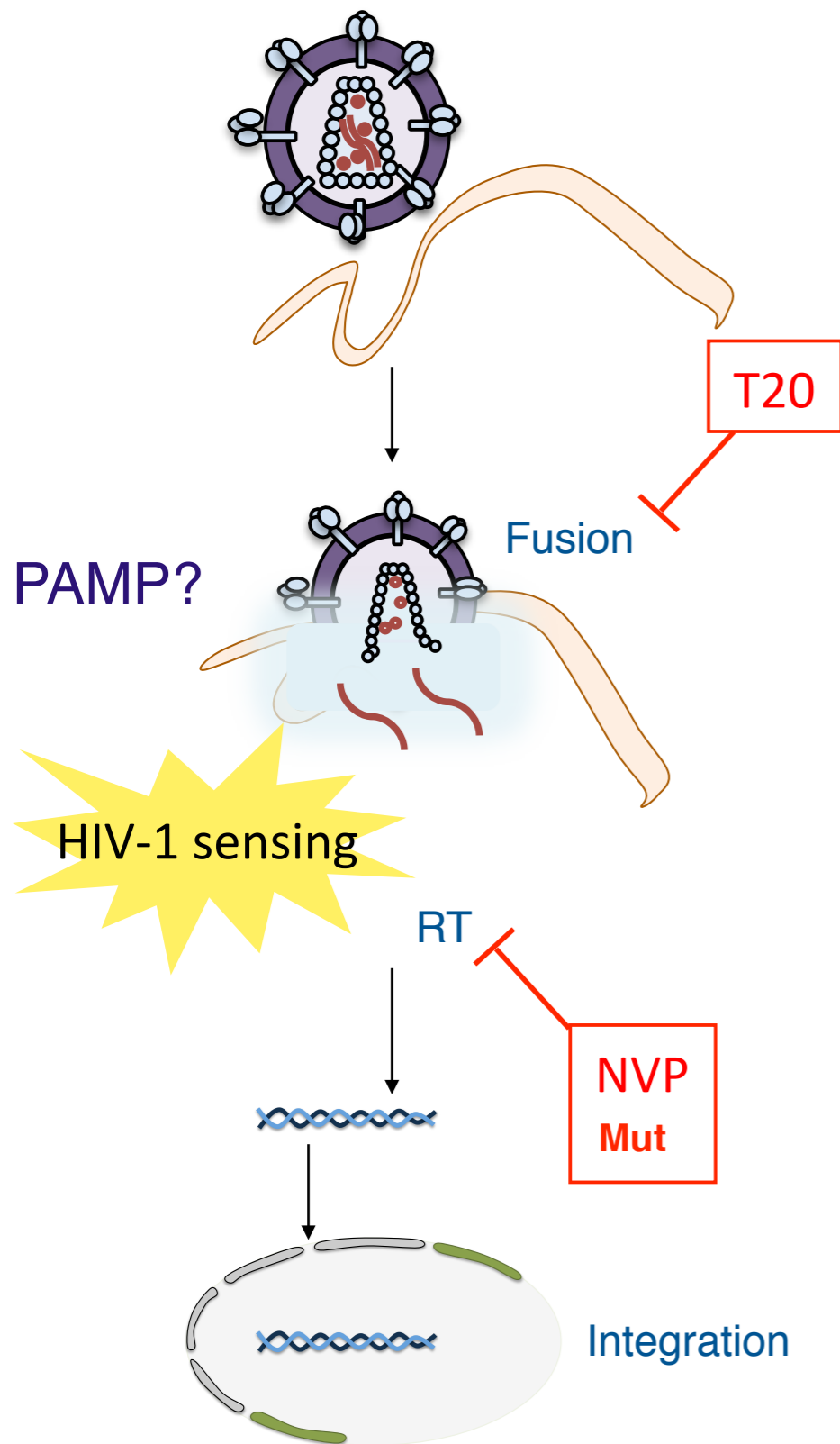
*Sensing requires an envelope, can occur with different viruses produced by different cells -> different receptors*

*Sensing occurs in 2 steps: 1) is RT-independent  
2) is RT-dependent but independent of the 1st one*

*ISG induction is TBK1- and type I IFN-dependent*

*Early sensing is protective -> weak type I IFN induction but efficient ISG upregulation*

# Early sensing of HIV-1 entry by macrophages



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Nicolas Ruffin

**Marion Desdouits**

Ester Gea Mallorquí

Laurent Zablocki

Francesca Graziano

Vasco Rodriguez

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*Aditi Varthaman*

*Andres Titarelli*

**Jérémie Décalf**

*Bruna de Alencar*

*Raphaël Gaudin*

*Stefano Berre*

*Alejandra Garcia-Cattaneo*

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*Franck Perez, Nelly Gareil,*

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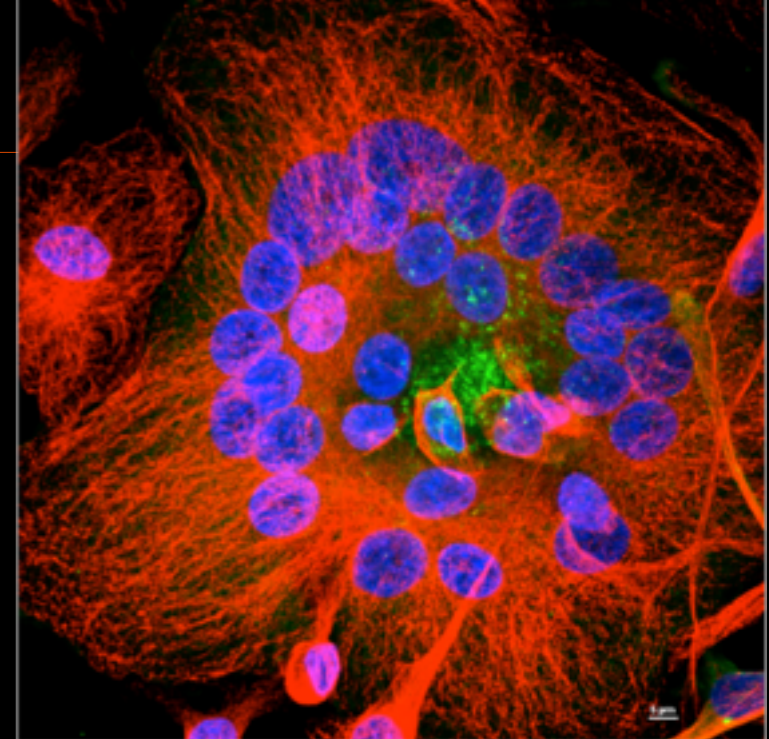
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