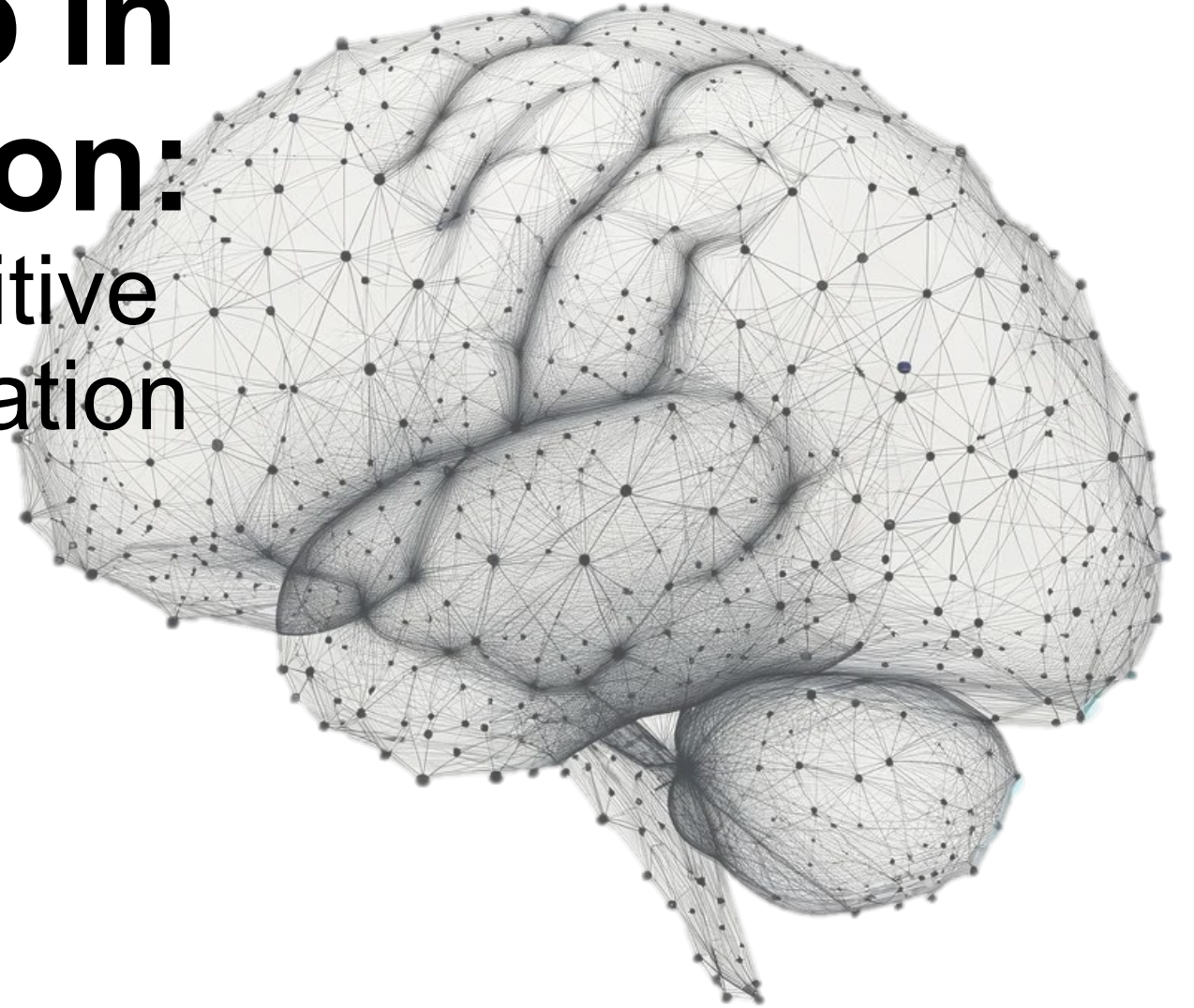


# Bridging the gap in neuroinflammation: RTP801 mediates cognitive impairment and inflammation

Pol Garcia-Segura and Cristina Malagelada, PhD

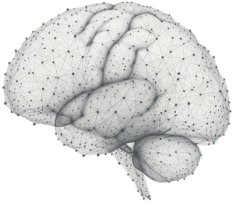
Dpt. of Biomedicine, Fac. of Medicine and Health Sciences  
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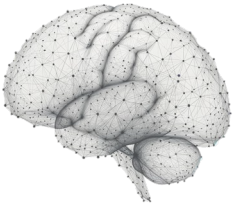
**HIV**  
**neuro**  
**psychiatry**

17th Edition  
Barcelona,  
May 31 and June 1, 2024



The authors declare no conflict of interest.

# HIV-associated neurocognitive impairment (NCI)



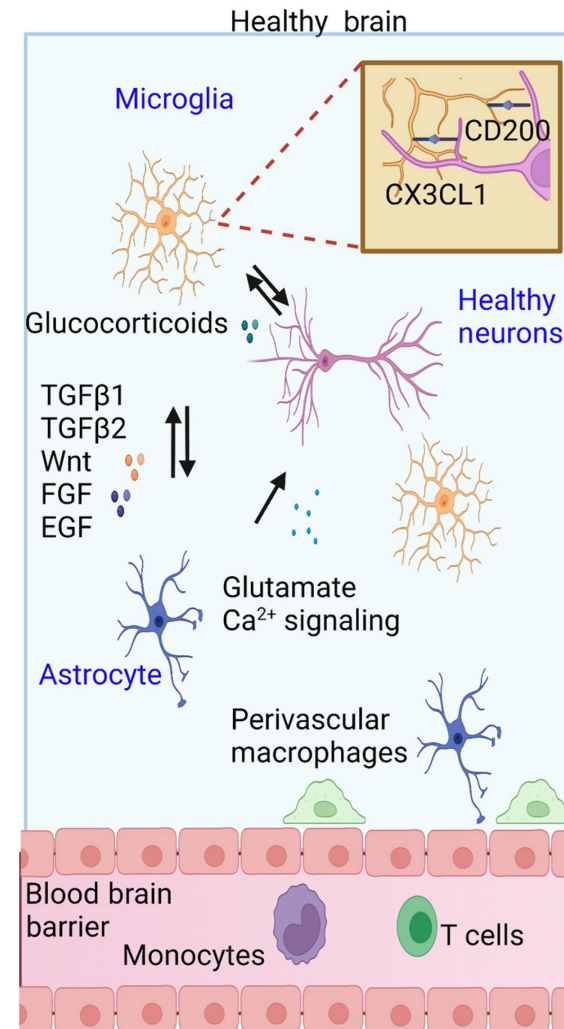
**15-60% HIV-1+** individuals present **neurocognitive impairment (NCI)**.

In the brain: HIV-1 infects and replicates in microglia (and astrocytes)

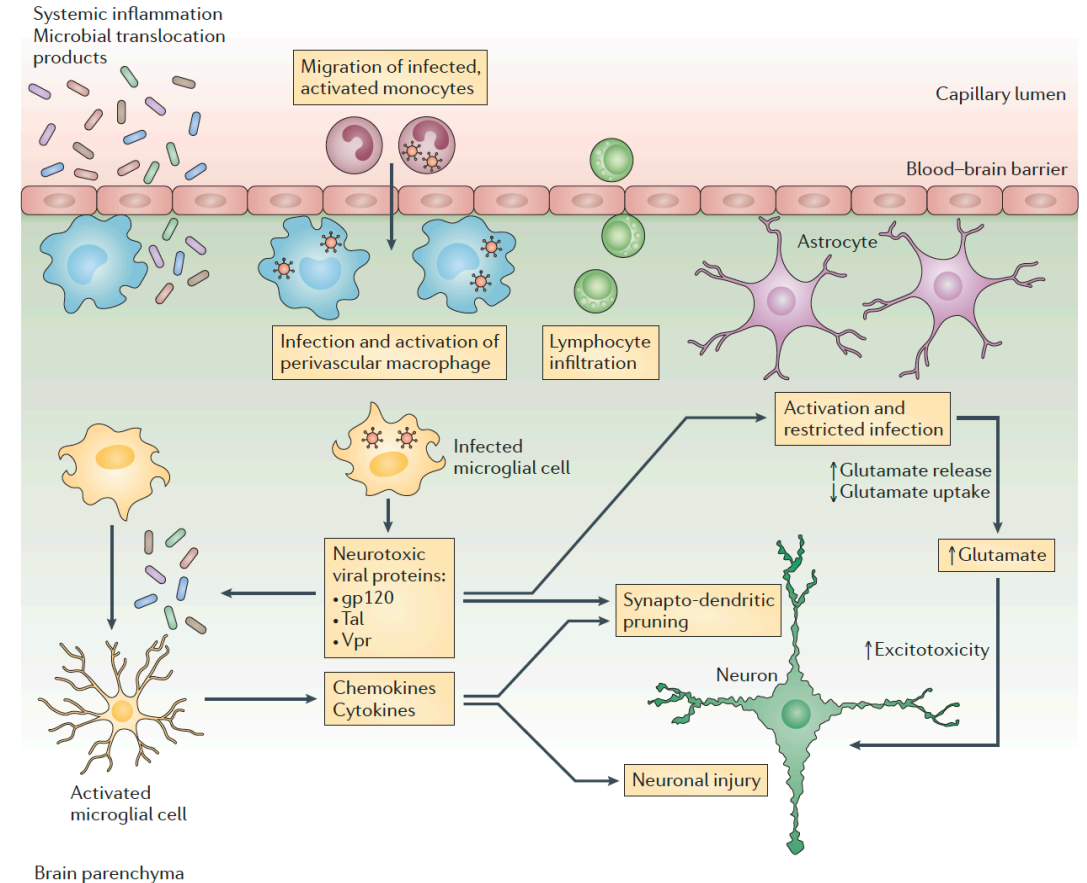
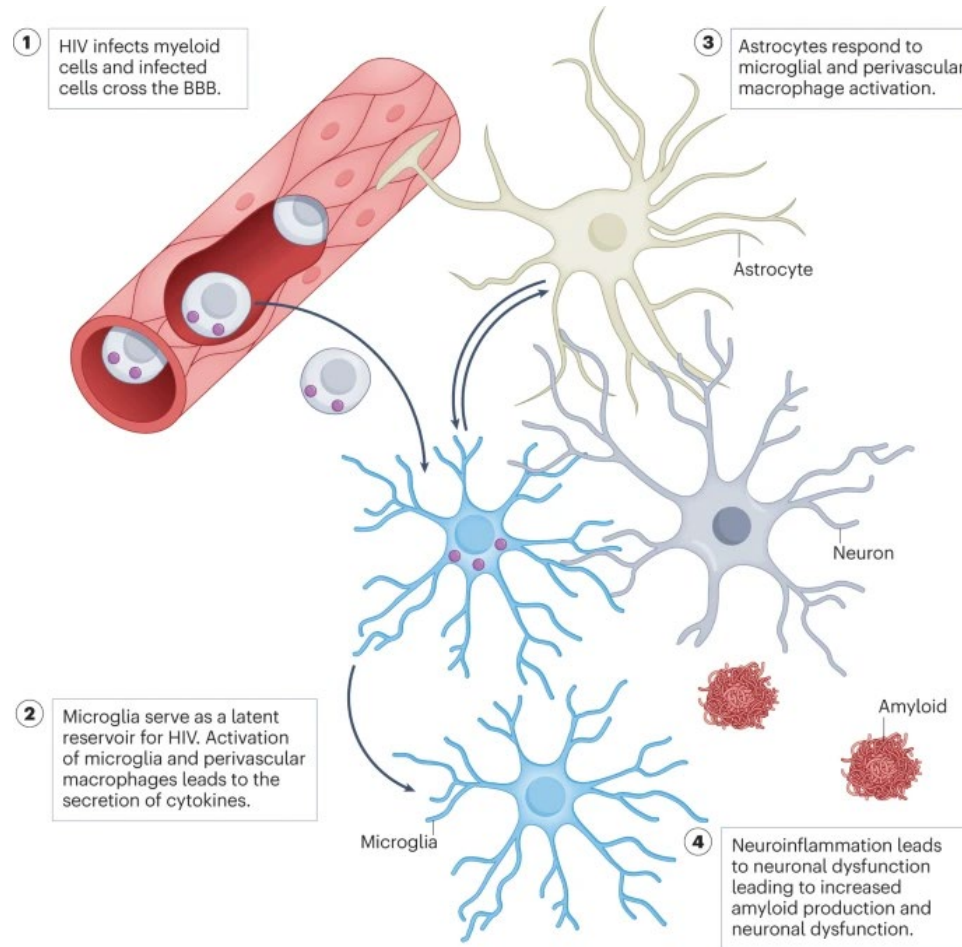
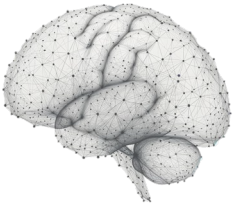
Mechanisms underlying HIV-associated NCI **still not clear**:

- systemic inflammation
- neuroinflammation
- a combination of the two

**Antiretroviral therapies (ART)**: extend lifespan and positively impact on cognitive performance but **do not abolish systemic or CNS inflammation**

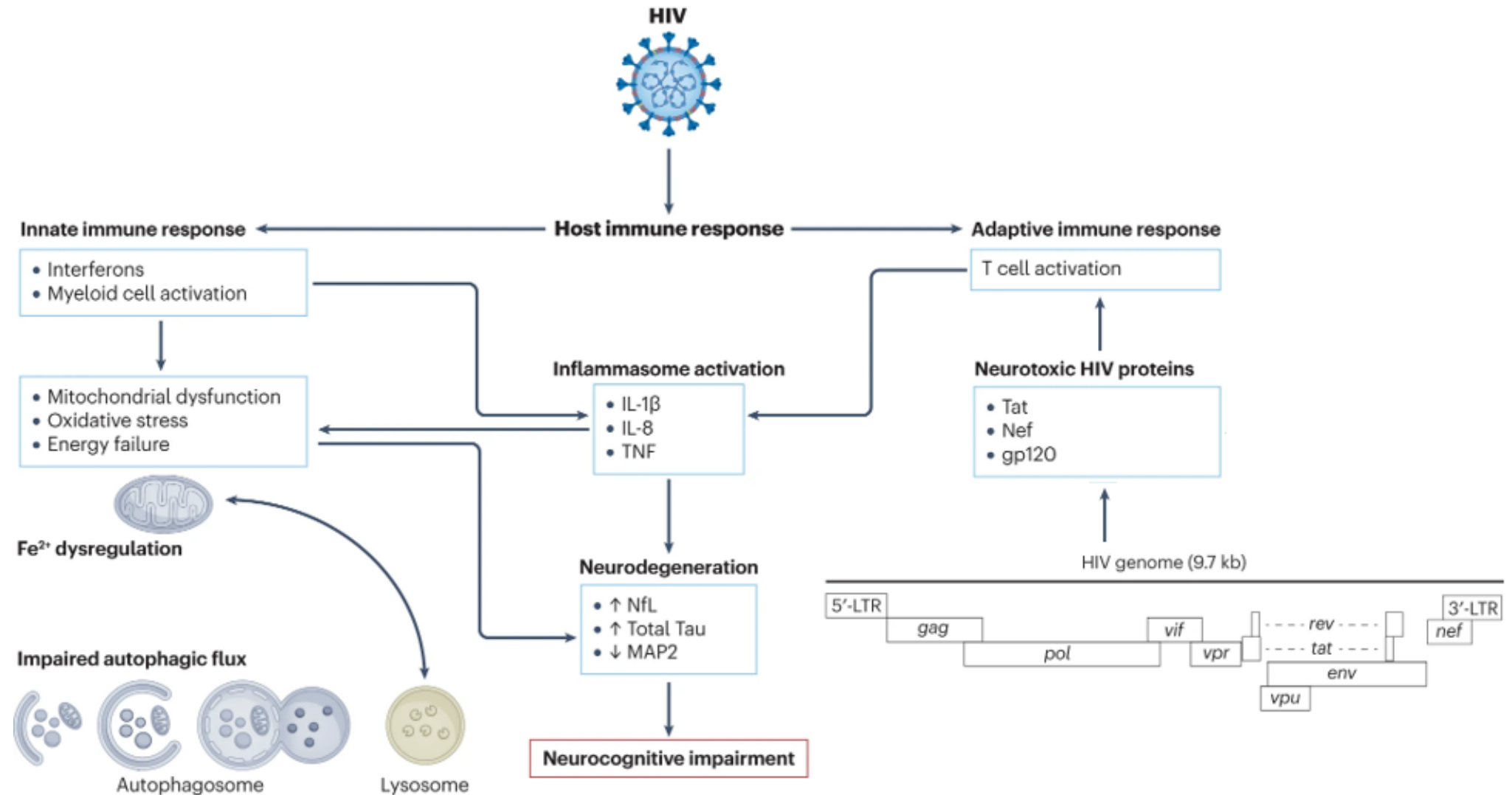
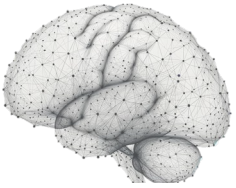


# Neuropathogenesis of HIV-associated NCI

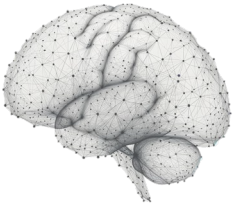


**HIV-associated NCI is caused by cellular crosstalk between glial cells and neurons**

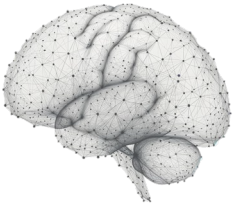
# Neuropathogenesis of HIV-associated NCI



Adapted from Ellis R.J *et al.*, Nature Reviews Neurology (2023)

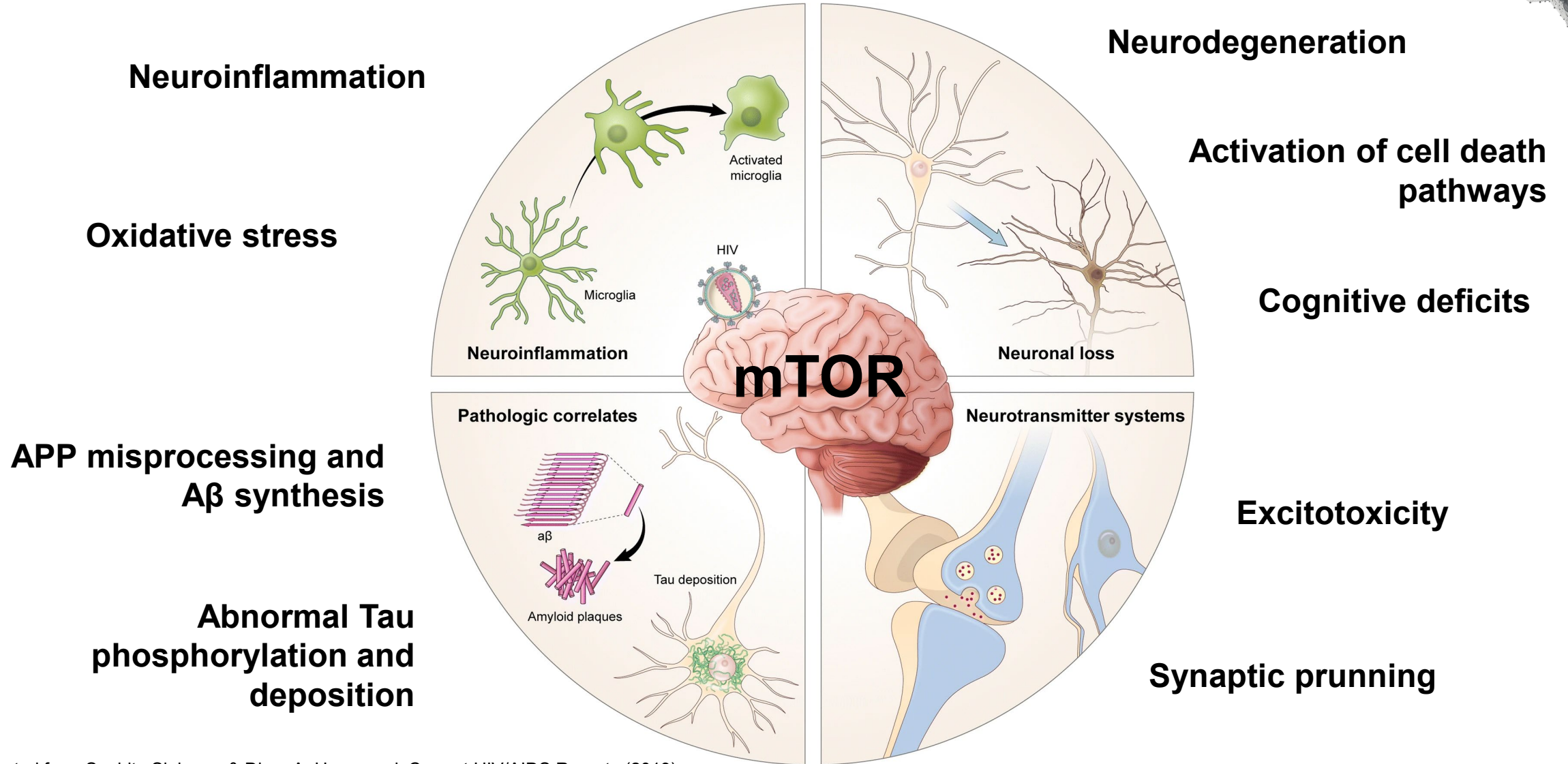
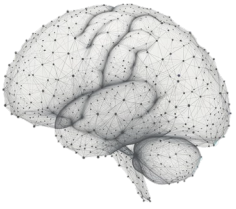


So then, why are we interested in  
**HIV-associated NCI?**



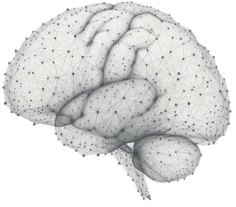
**Because HIV-associated NCI and AD share common pathogenic pathways**

# AD-like pathogenic mechanisms in HIV





# mTOR pathway in HIV-associated NCI

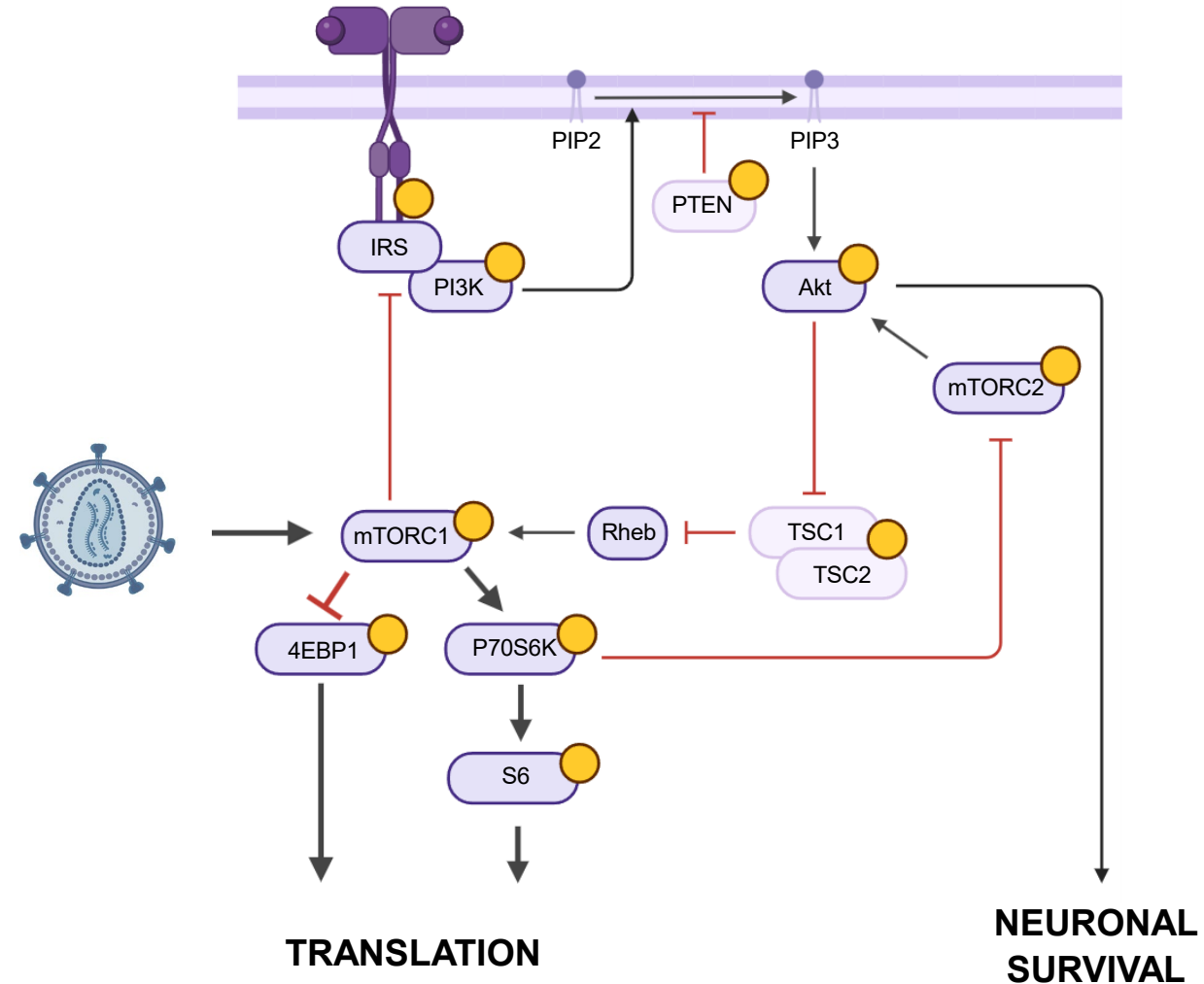


**HIV enhances mTORC1 activity to favor its replication**

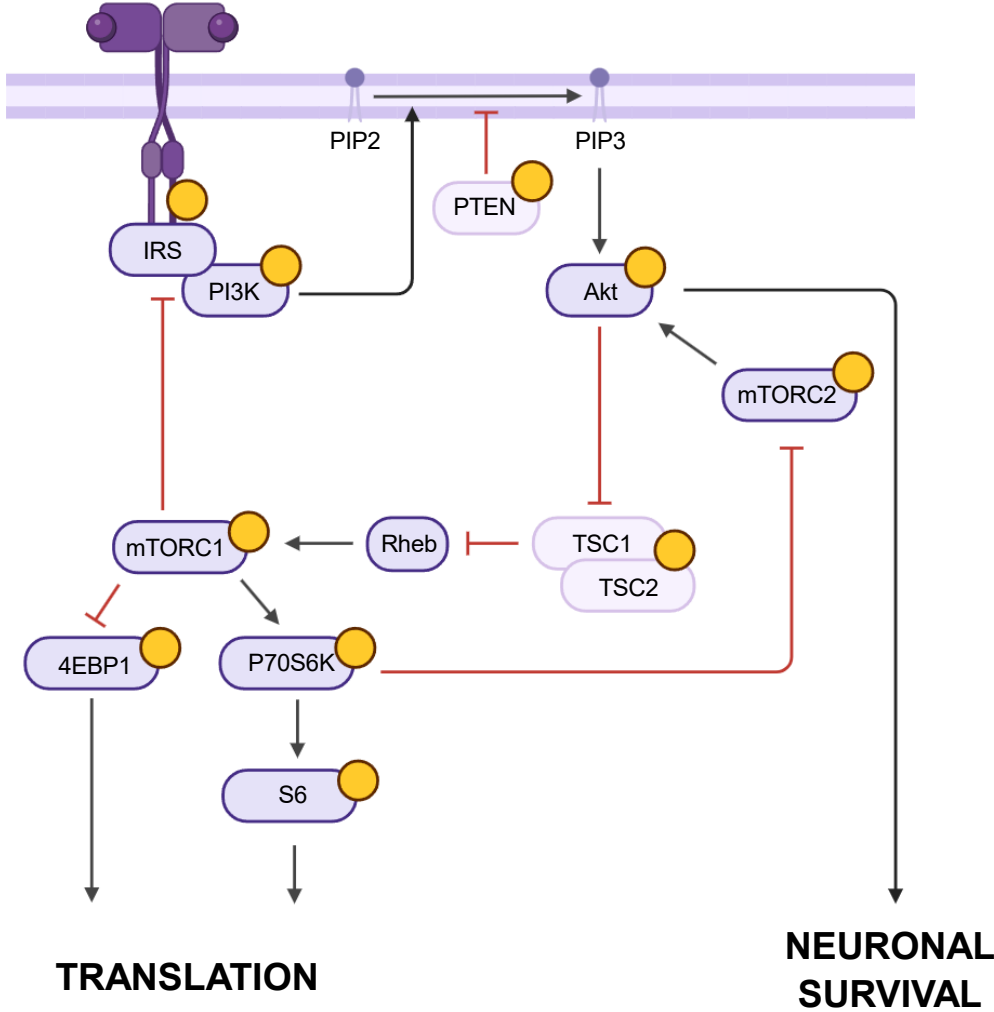
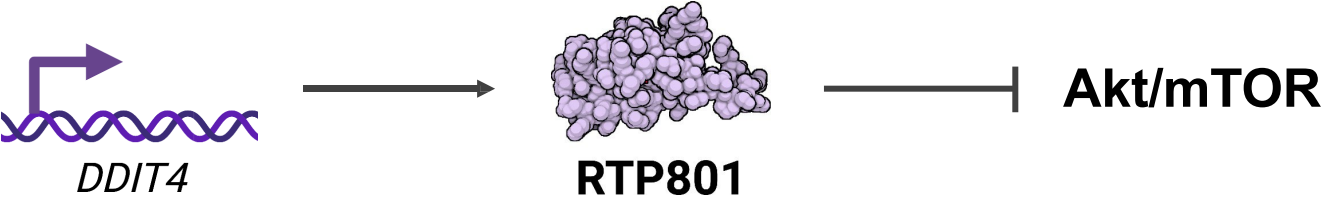
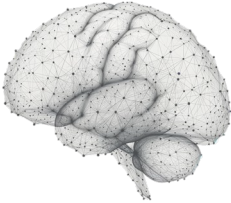
mTORC1 signaling disruption:

- **Apoptosis**
- **Autophagy**
- **Inflammation**

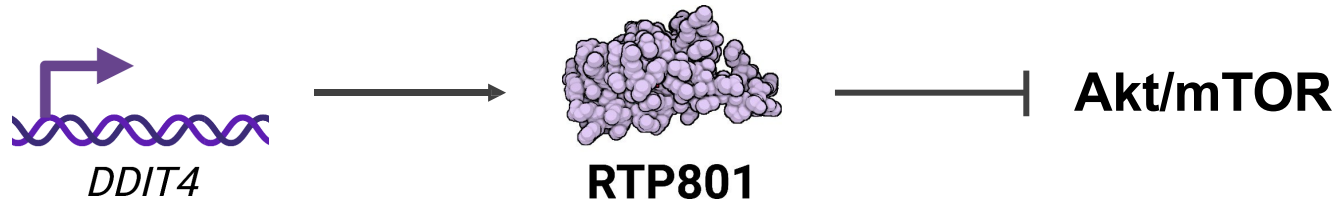
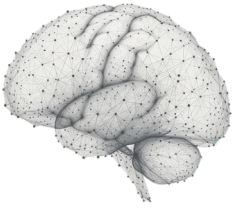
**mTOR inactivation is neuroprotective** and improves immune function and metabolism (~ early AD)



# RTP801/mTOR signaling pathway



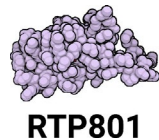
# RTP801/mTOR signaling pathway



RTP801/REDD1 has a **dual role:**

Shoshani T. et al., *Mol. Cell. Biol.*, 2002

- Pro-apoptotic (differentiated cells)
- Anti-apoptotic (proliferating cells)



**PD**

Malagelada, C. et al. *J. Neurosci.*, 2006

**HD**

Martín-Flores, N. et al. *Mol. Neurobiol.*, 2016

**AD**

Pérez-Sisqués, L. et al. *Cell Death Dis.*, 2021

In murine models:

**PD: MPTP**

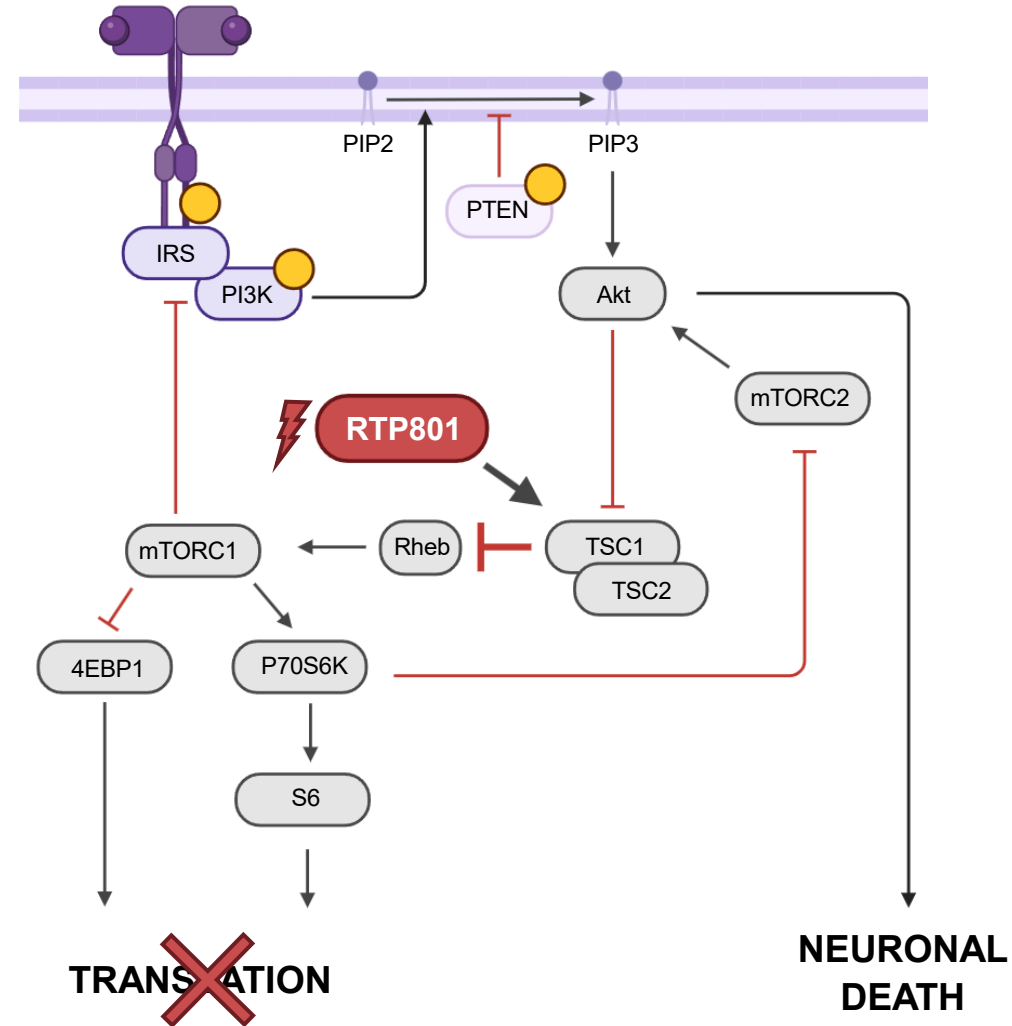
Malagelada, C. et al. *J. Neurosci.*, 2010

**HD: R6/1**

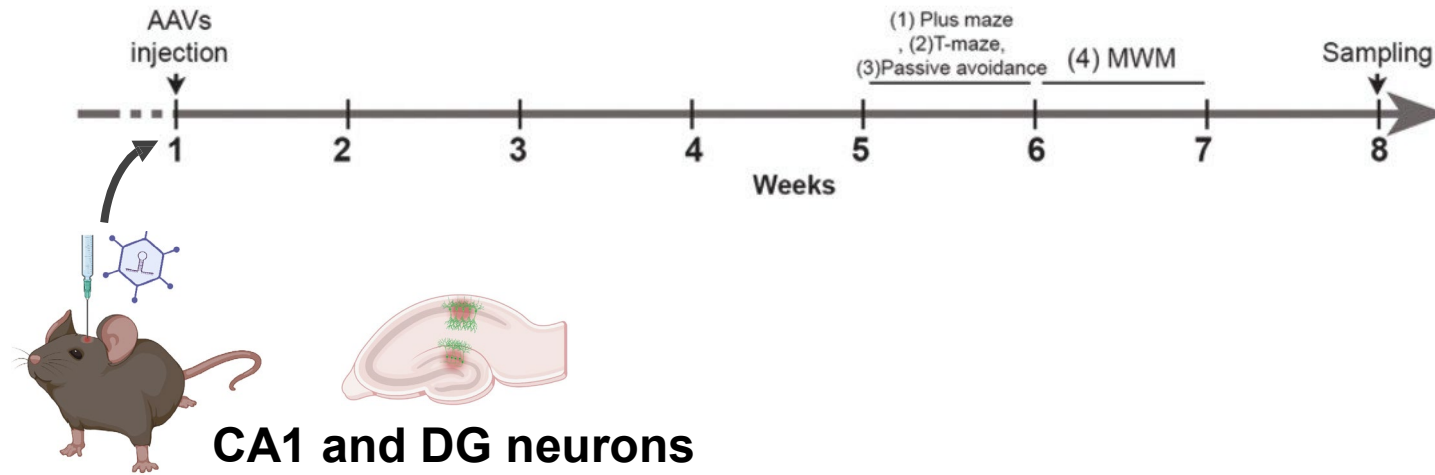
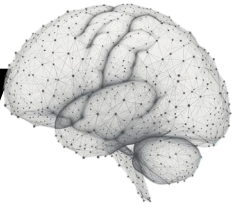
Martín-Flores, N. et al. *Cell Death Dis.*, 2016

**AD: 5xFAD, rTg4510**

Pérez-Sisqués, L. et al. *Cell Death Dis.*, 2021



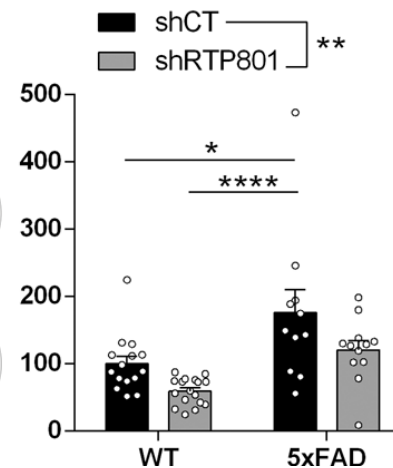
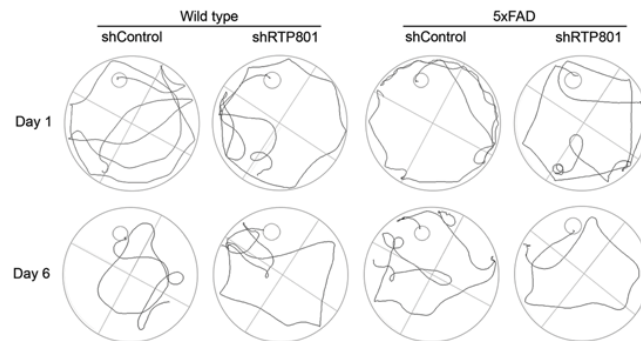
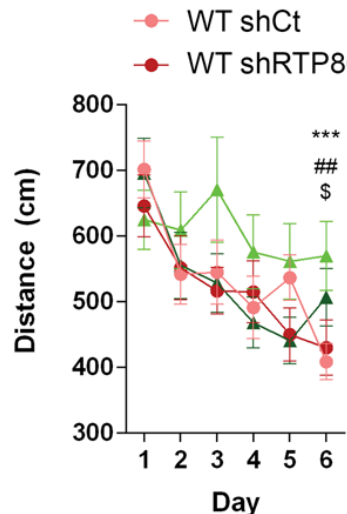
# RTP801 contributes to neuroinflammation and memory impairments in AD



Neuronal RTP801 silencing:  
**↓ Neuroinflammation**

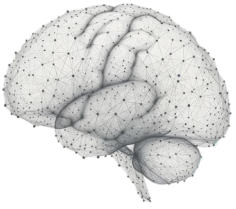
1. Decrease in GFAP & Iba1+ cells
2. Prevent inflammasome activation

**↑ Memory**



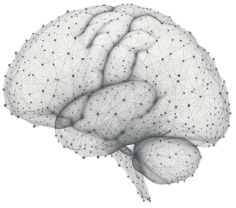
**Astrocytic RTP801 silencing in vivo in the same 5xFAD model shows similar results**

Chicote-González. *et al.* Unpublished, 2024

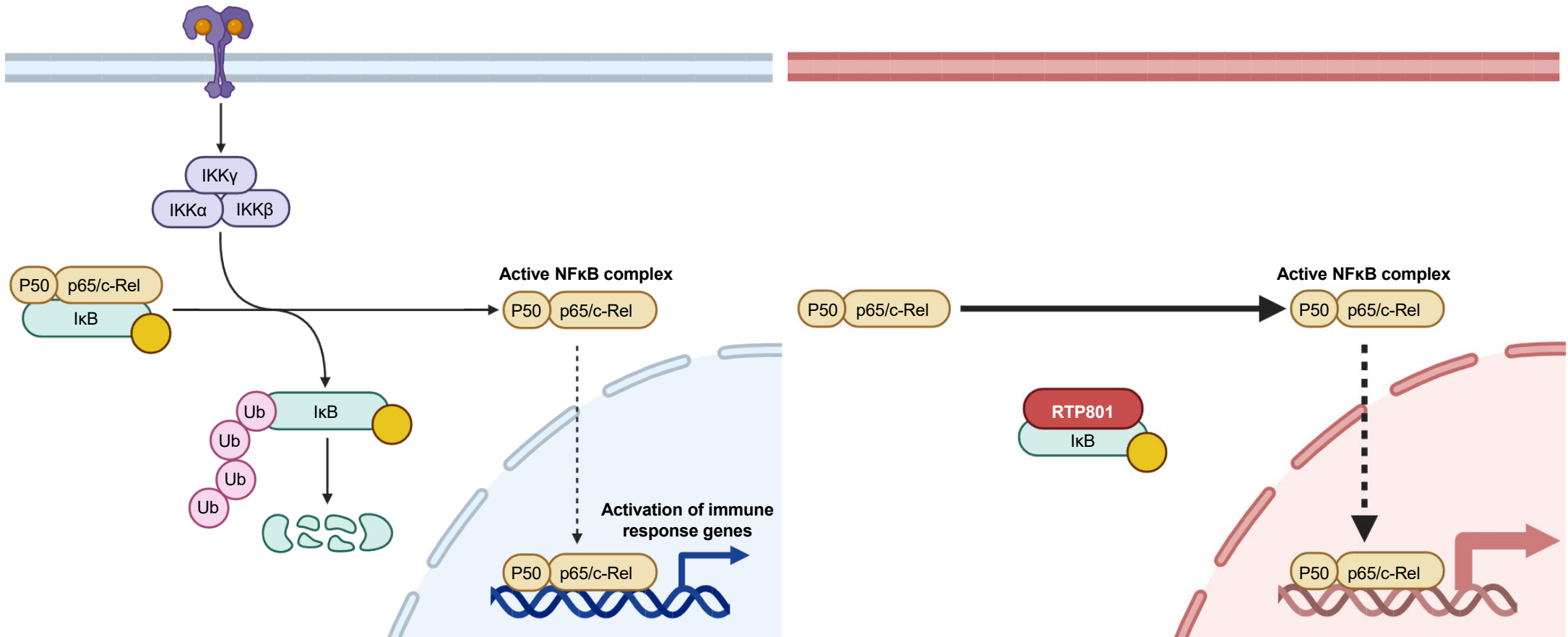


**RTP801 mediates cognitive  
impairment and inflammation,  
but... How?**

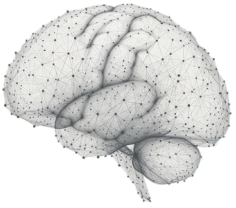
# RTP801 induces atypical NF- $\kappa$ B activation



RTP801 promotes atypical NF- $\kappa$ B activation by preventing the formation of the inactive NF- $\kappa$ B/I $\kappa$ B $\alpha$  complex through direct interaction with I $\kappa$ B $\alpha$

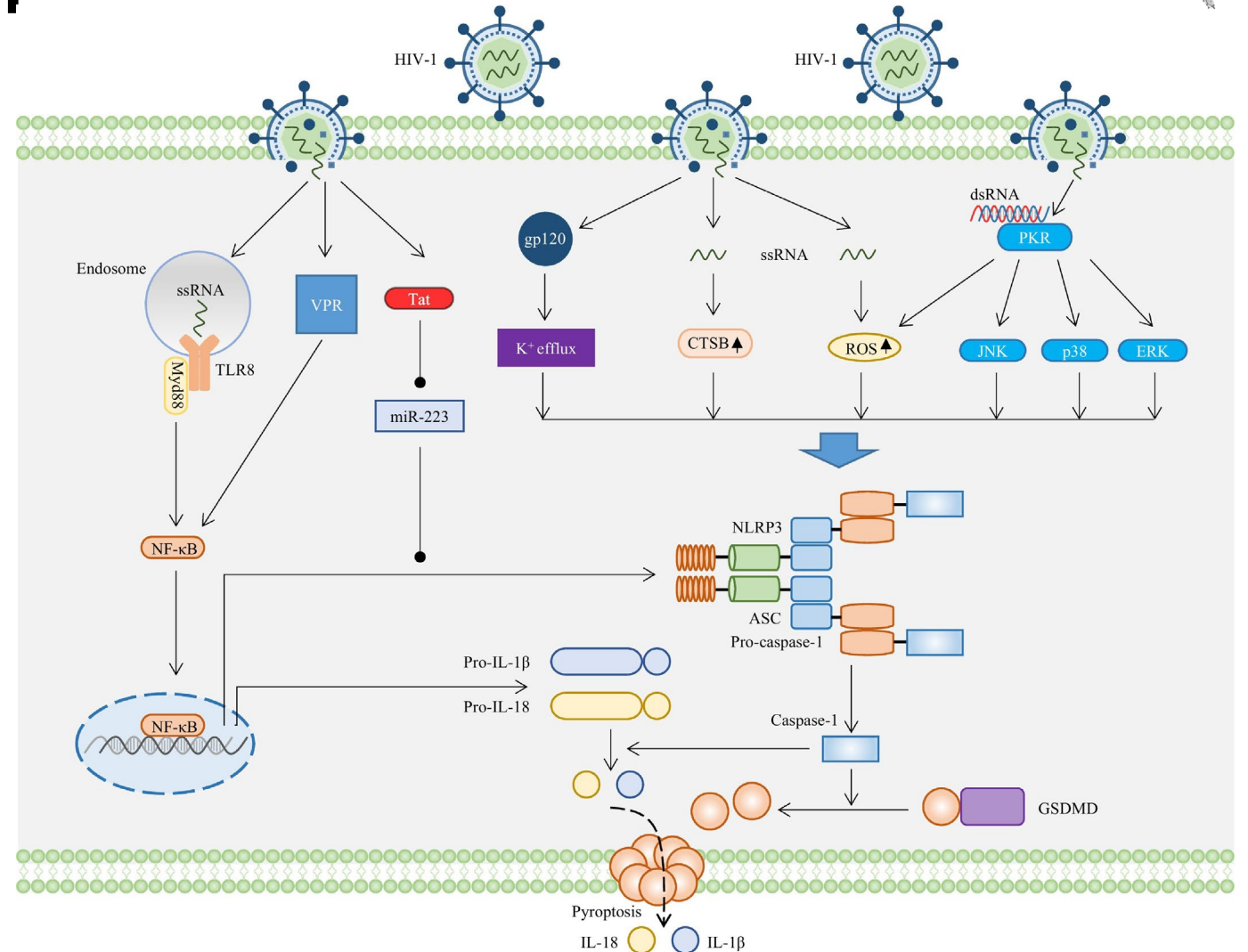


# RTP801 might promote HIV-induced NLRP3 inflammasome activation

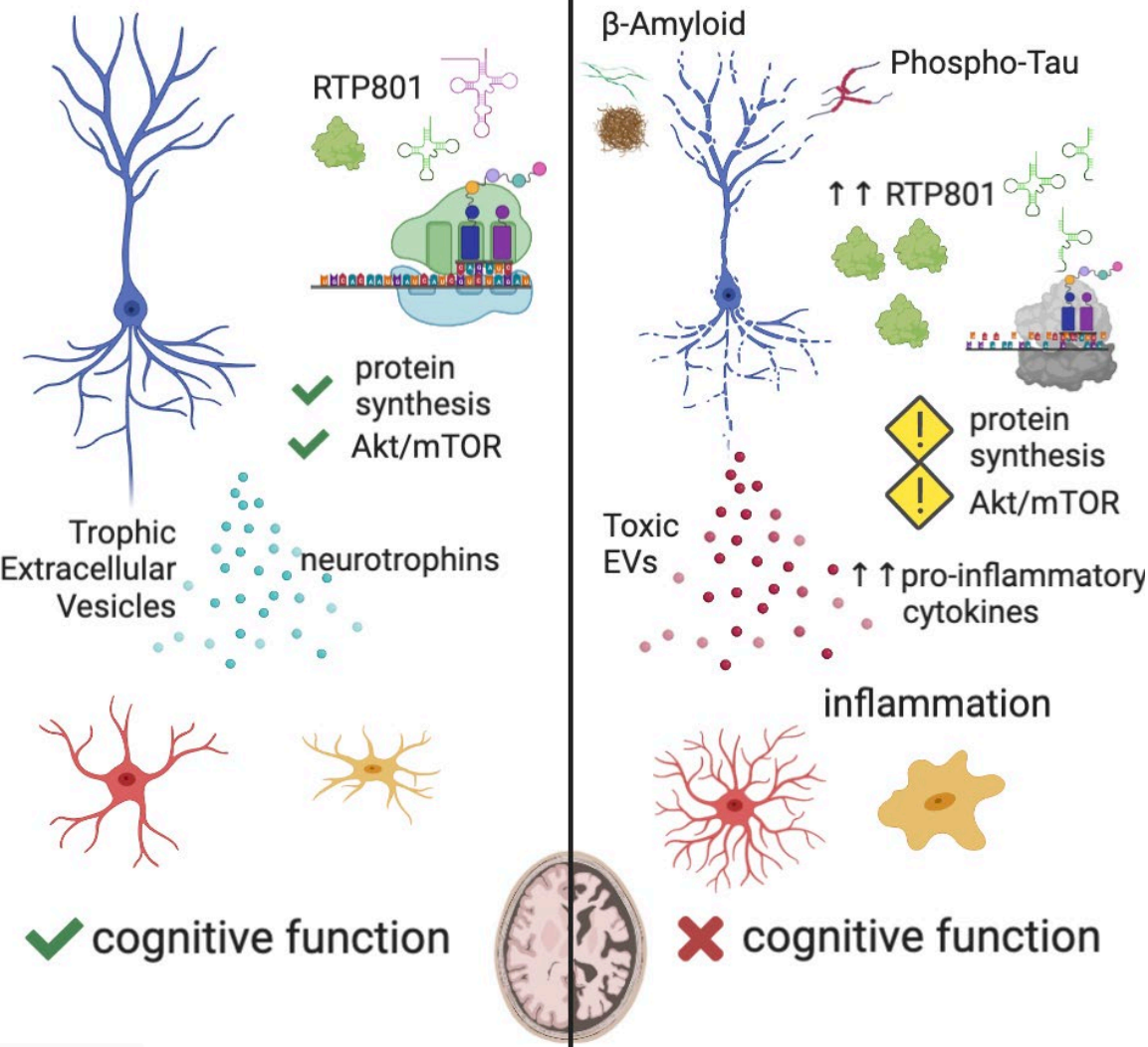
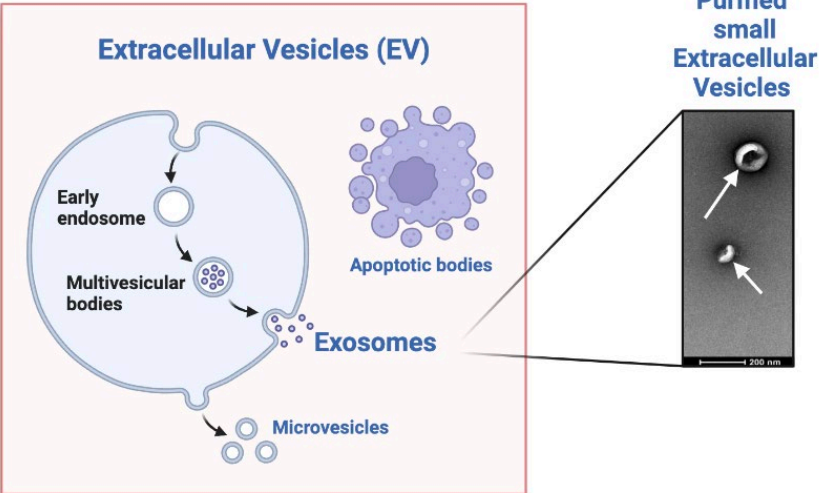


This process requires **NF-κB activation to induce inflammasome assembly and function**

Therefore, it is plausible that **RTP801 atypical activation of NF-κB promotes and worsens HIV-associated NCI**

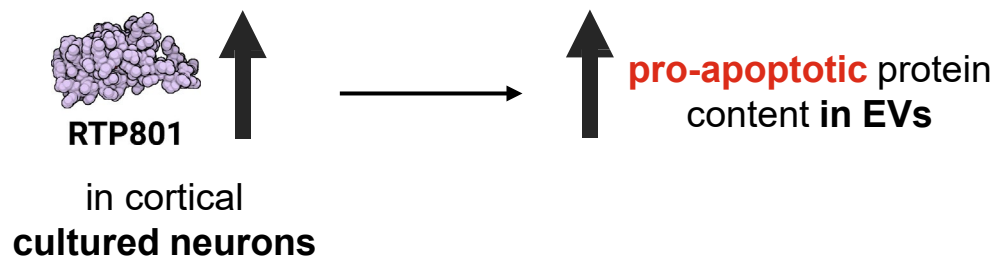
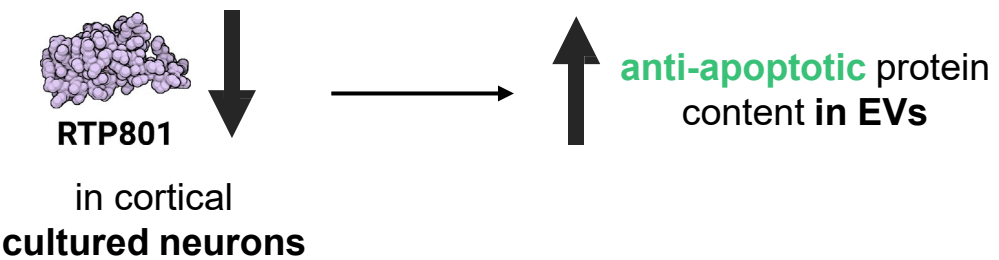
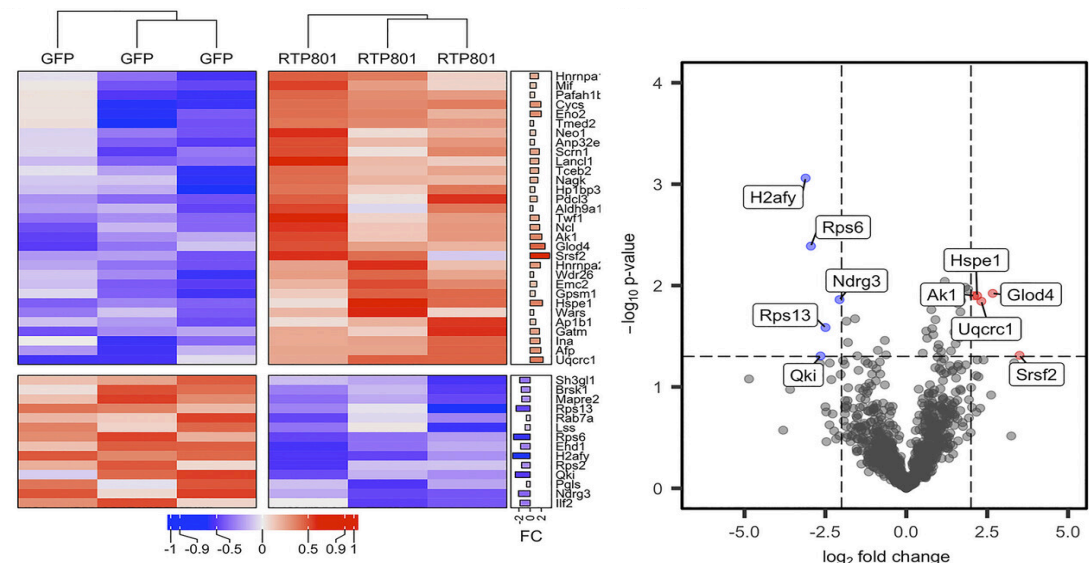
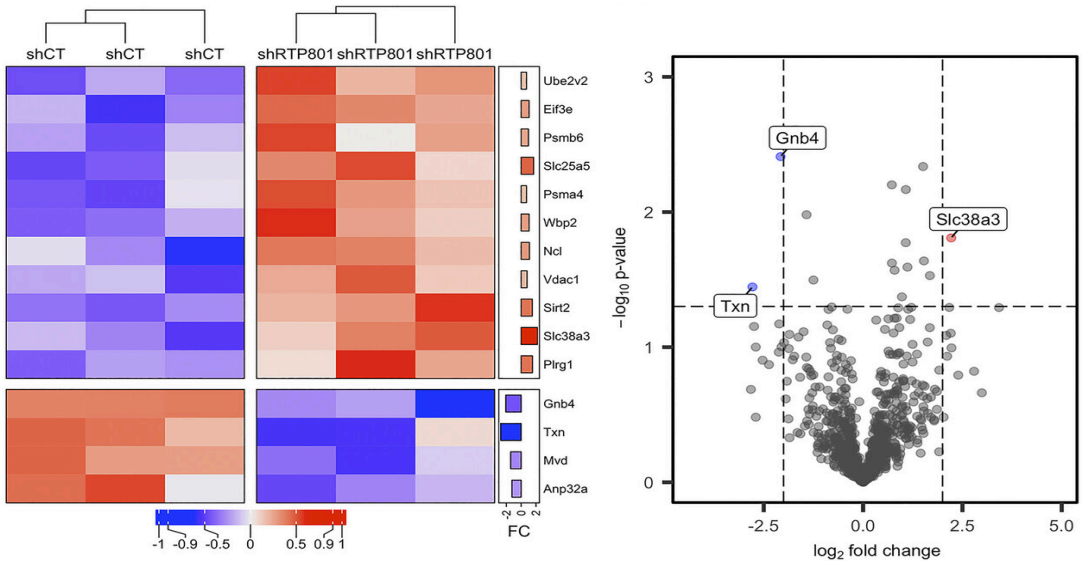


# RTP801 mediates transneuronal toxicity via extracellular vesicles

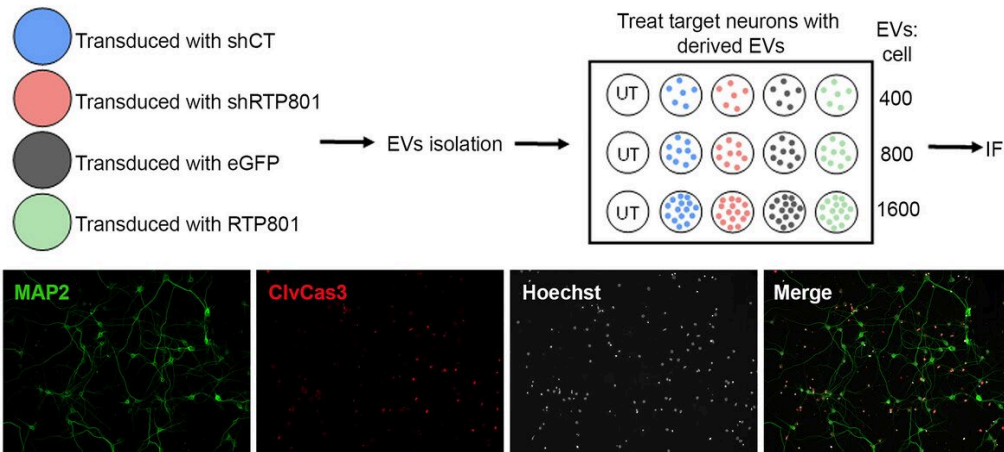




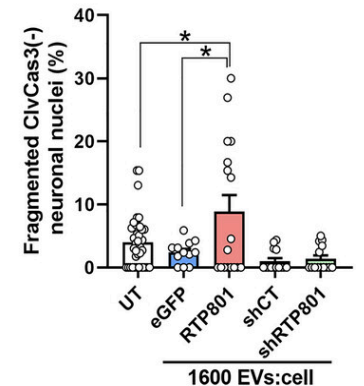
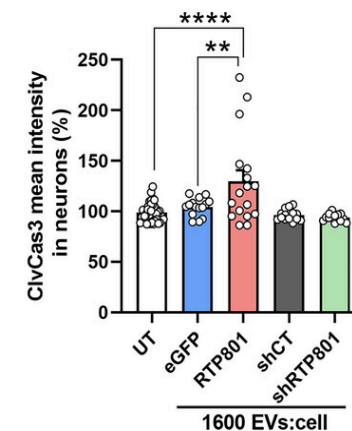
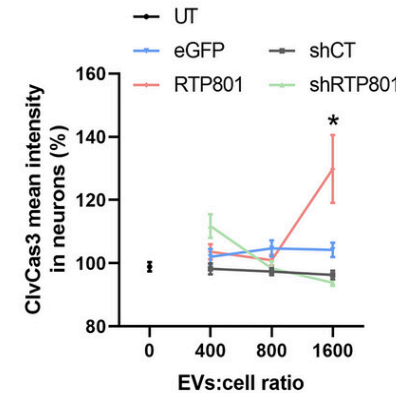
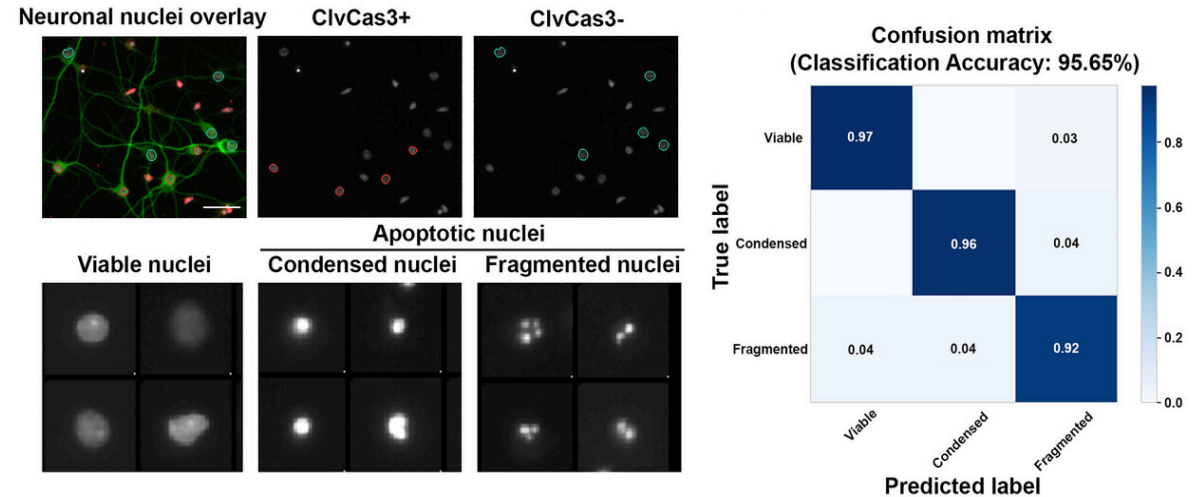
# RTP801 mediates transneuronal toxicity via extracellular vesicles

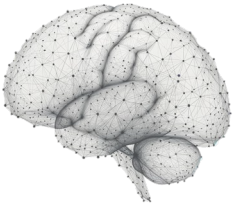


# RTP801 mediates transneuronal toxicity via extracellular vesicles



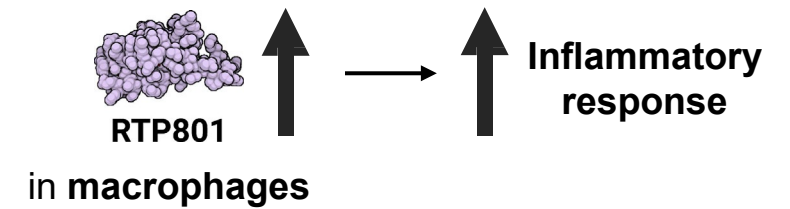
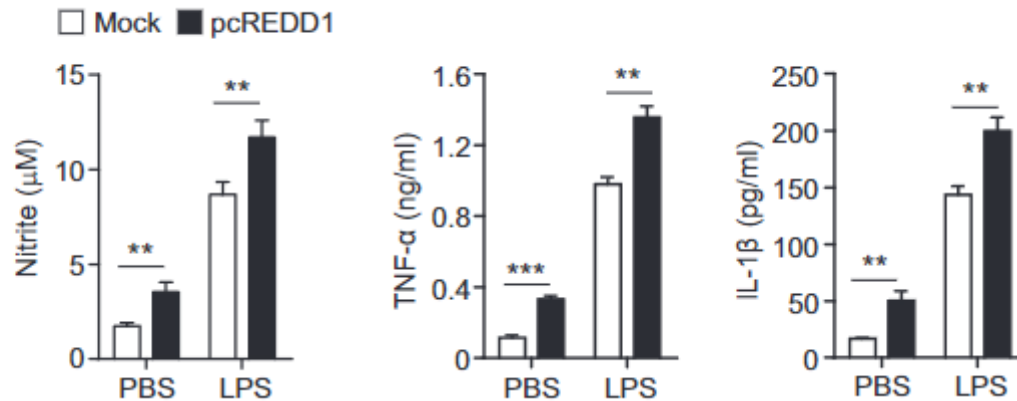
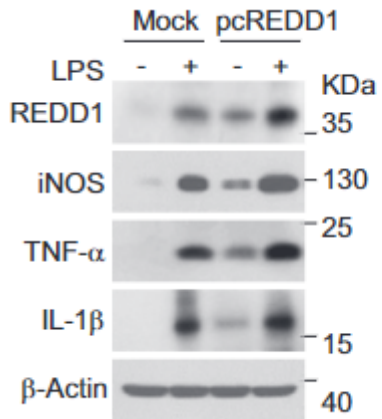
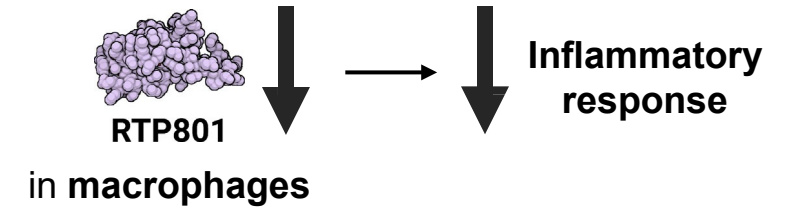
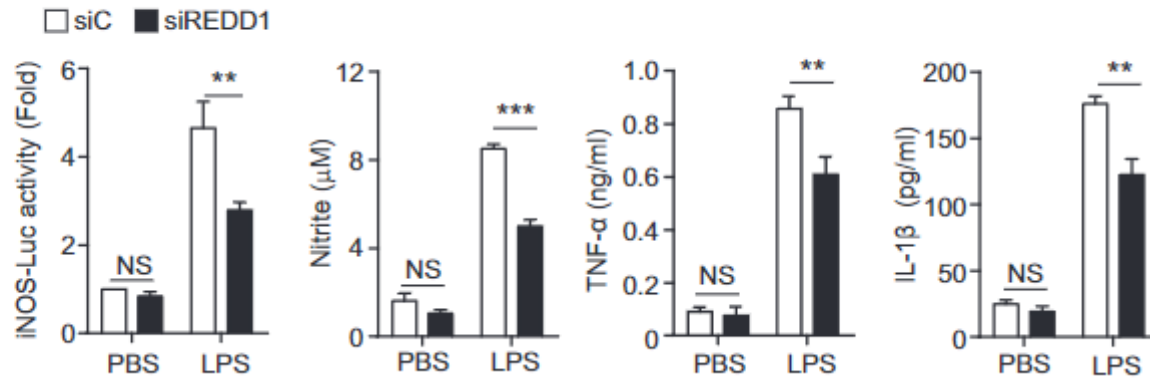
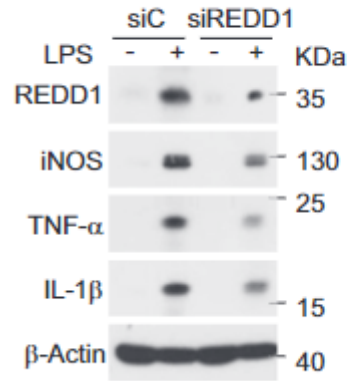
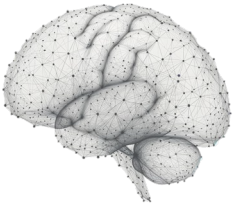
**Overexpression of RTP801 promotes apoptosis and impairs neuron arborization complexity via EVs in cultured cortical neurons**





But, is RTP801 a **cause** or a **consequence** of (neuro)inflammation?

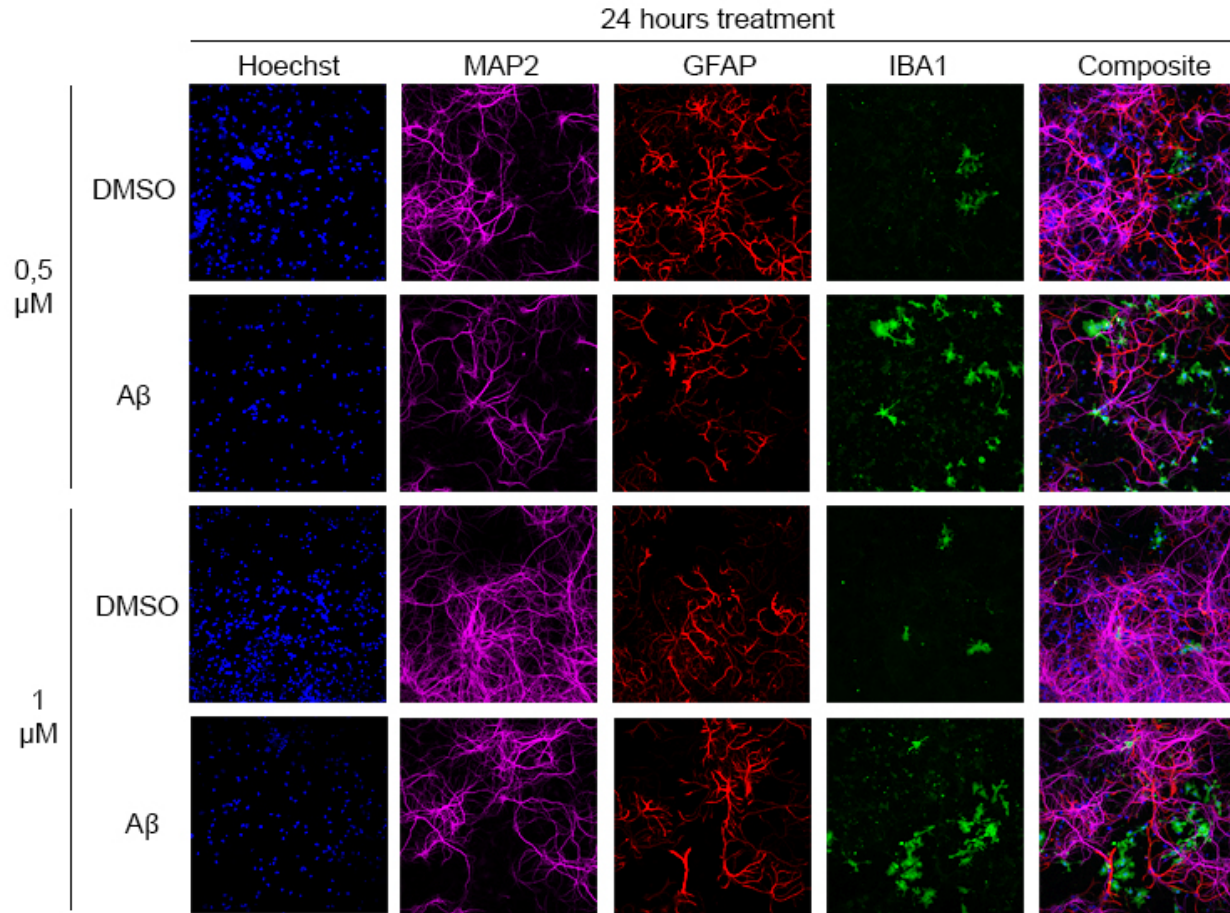
# RTP801 modulates LPS-induced inflammation



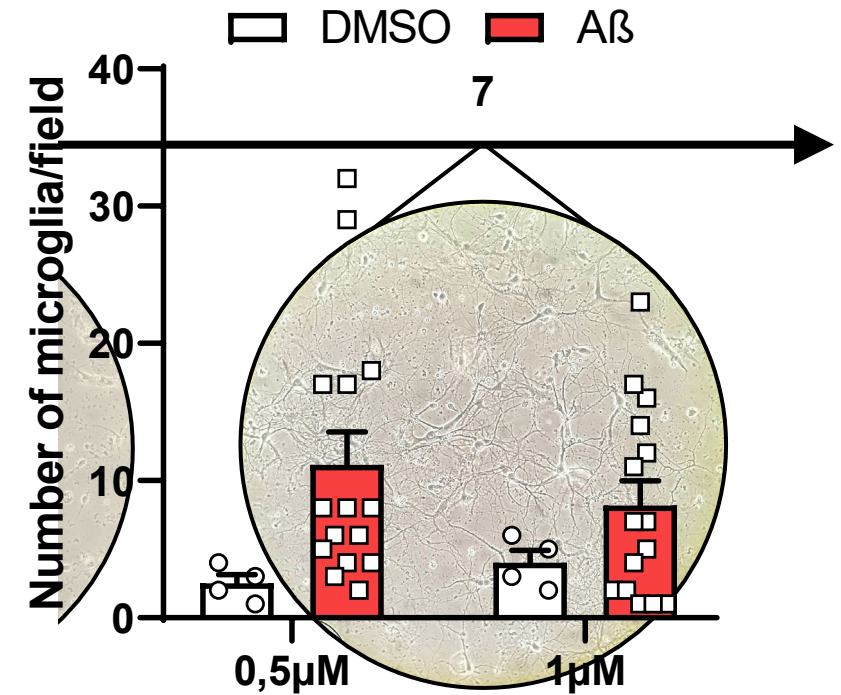
# Does RTP801 modulate LPS-induced neuroinflammation?



An *in vitro* model to evaluate the effect(s) of RTP801 in neuroinflammation



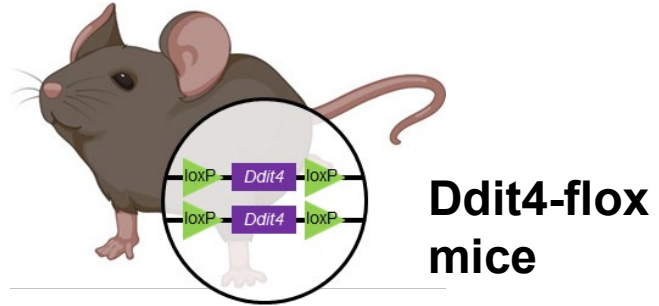
## Preliminary results!



# Does RTP801 modulate LPS-induced neuroinflammation?

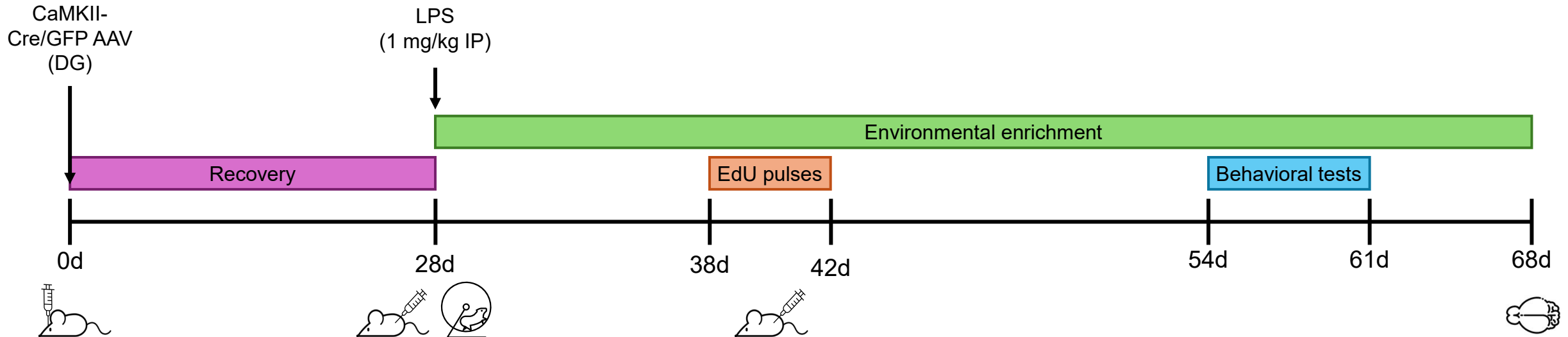


An **in vivo model** to evaluate the effect(s) of RTP801 in neuroinflammation

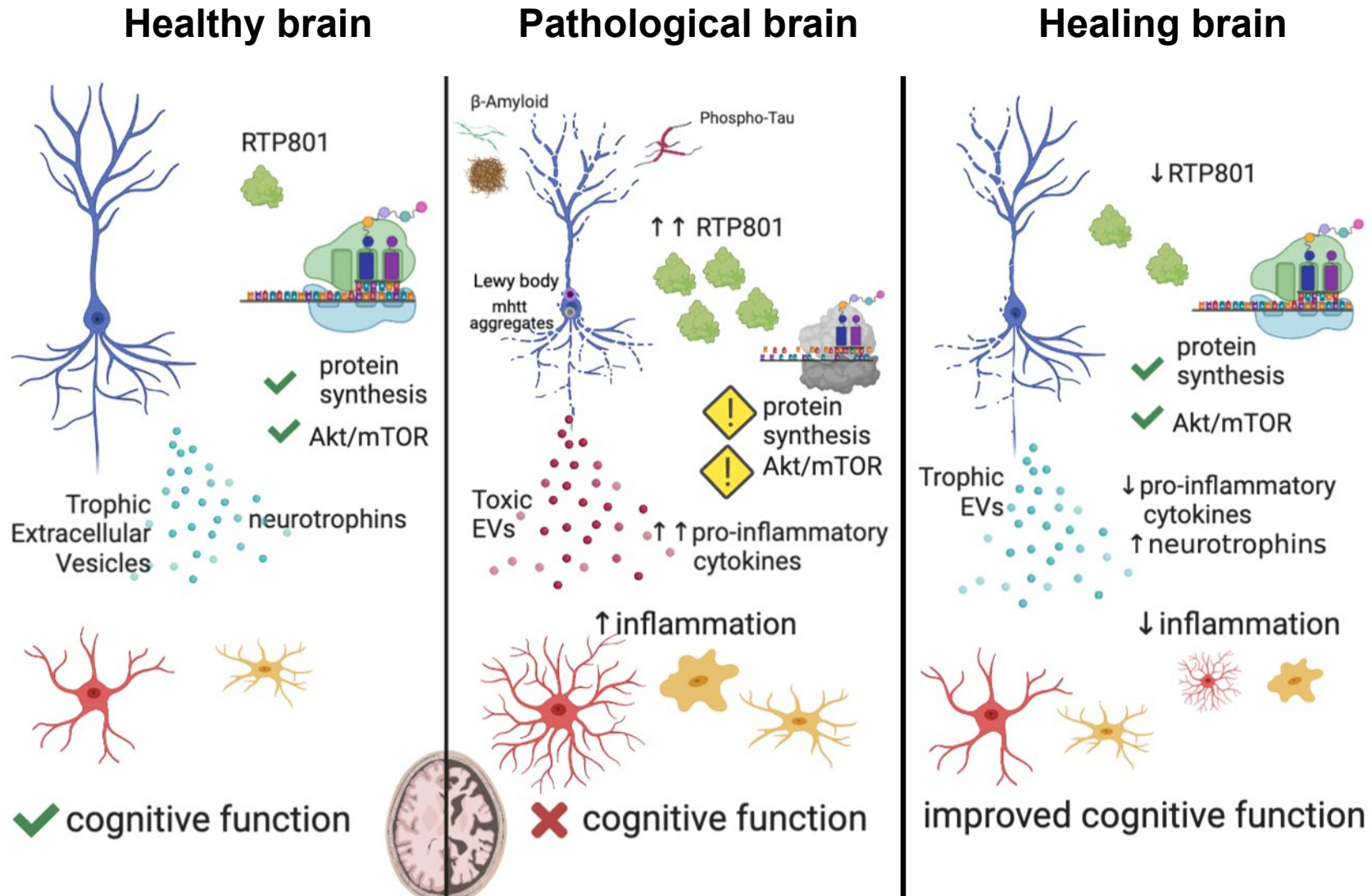
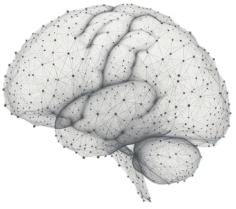


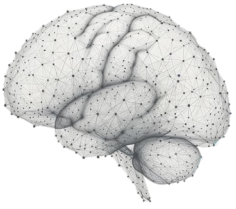
2 months old

## ONGOING EXPERIMENT



# Working hypothesis and summary





**So, since we would like to study this plausible connection in HIV-associated NCI we started an intramural collaboration with:**

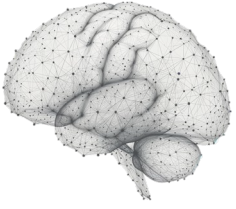


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**Pol Garcia-Segura, PhD student**

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**Leticia Pérez-Sisqués, PhD**  
**Núria Martín-Flores, PhD**

Collaborators:

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**Esther Pérez, PhD**  
**Eulàlia Martí, PhD**  
**Enrique Santamaría, PhD**  
**Joaquín Fernández, PhD**

**Ana Gámez, PhD**  
**Santi Garcia-Vallvé, PhD**  
**Gerard Pujadas, PhD**  
**Guadalupe Soria, PhD**  
**Mercè Massana, PhD**  
**Laura Molina, PhD**