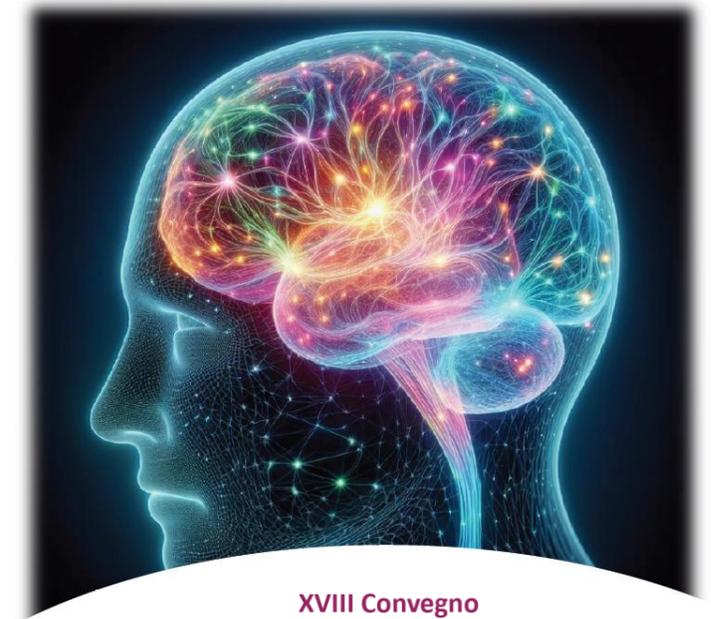


L'intricata e complessa interazione tra cellule gliali e neuroni nella malattia di Alzheimer



XVIII Convegno
I CENTRI PER I DISTURBI COGNITIVI
E LE DEMENZE E LA GESTIONE
INTEGRATA DELLA DEMENZA

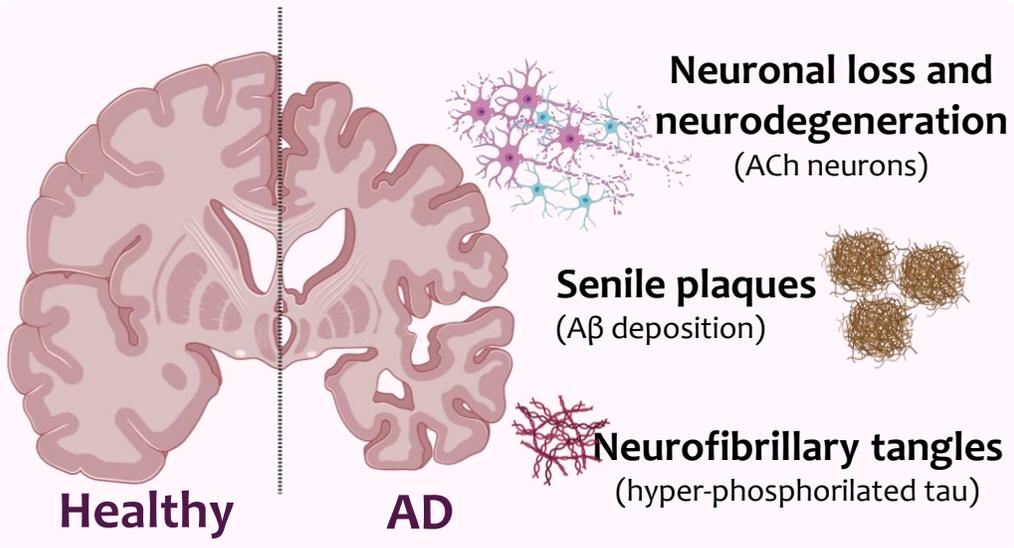
27 – 28 novembre 2025

Ciarla Claudia¹, Facchinetti Roberta^{1,2}, Burla Silvia¹, Valenza Marta¹, Scuderi Caterina¹

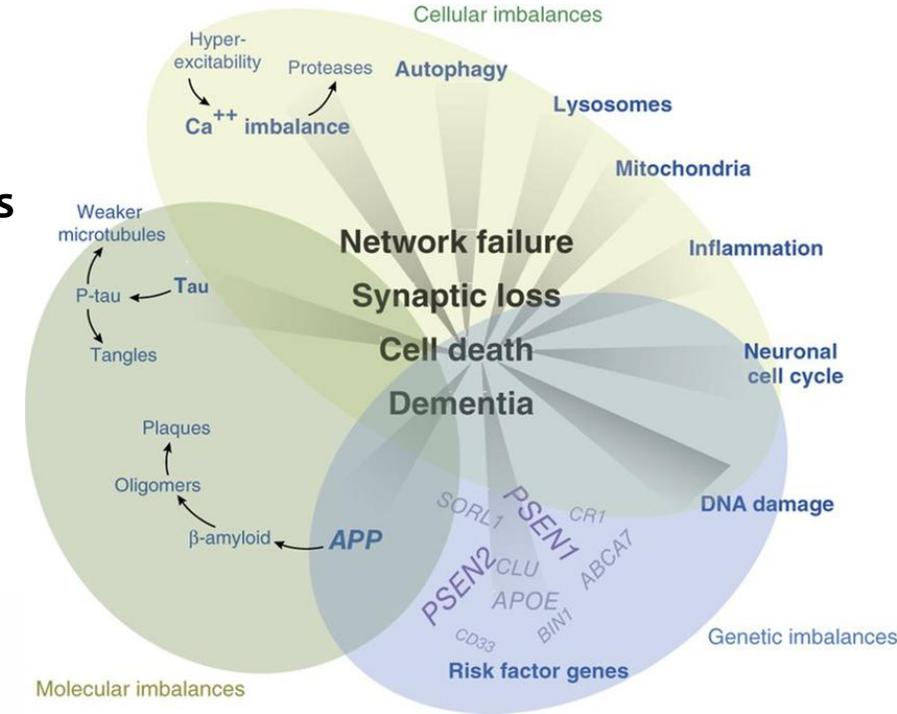
¹Dept. Physiology and Pharmacology «Vittorio Erspamer»

²Department of Life Sciences, Health, and Health Professions, LINK Campus University

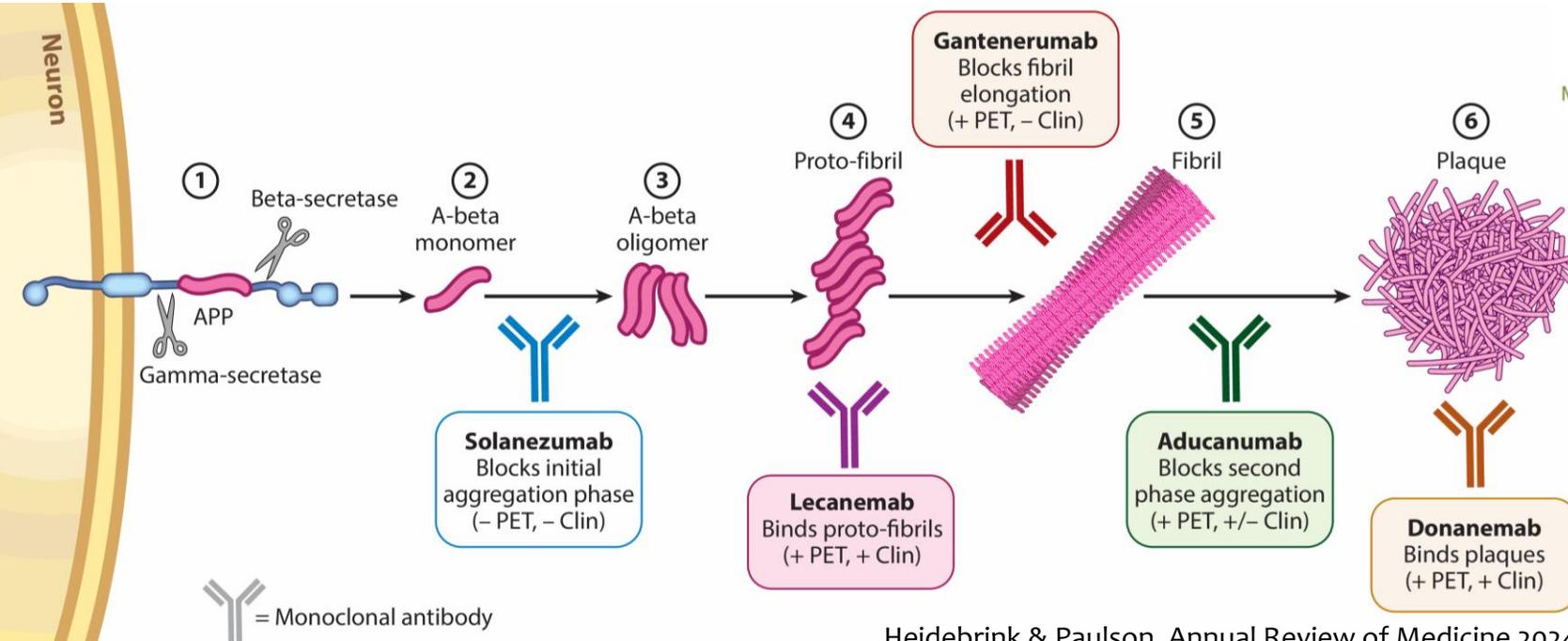
Alzheimer's disease: the hallmarks of the pathology



- Mitochondrial dysfunctions
- Inflammation
- DNA damage
- BBB impairment
- ...



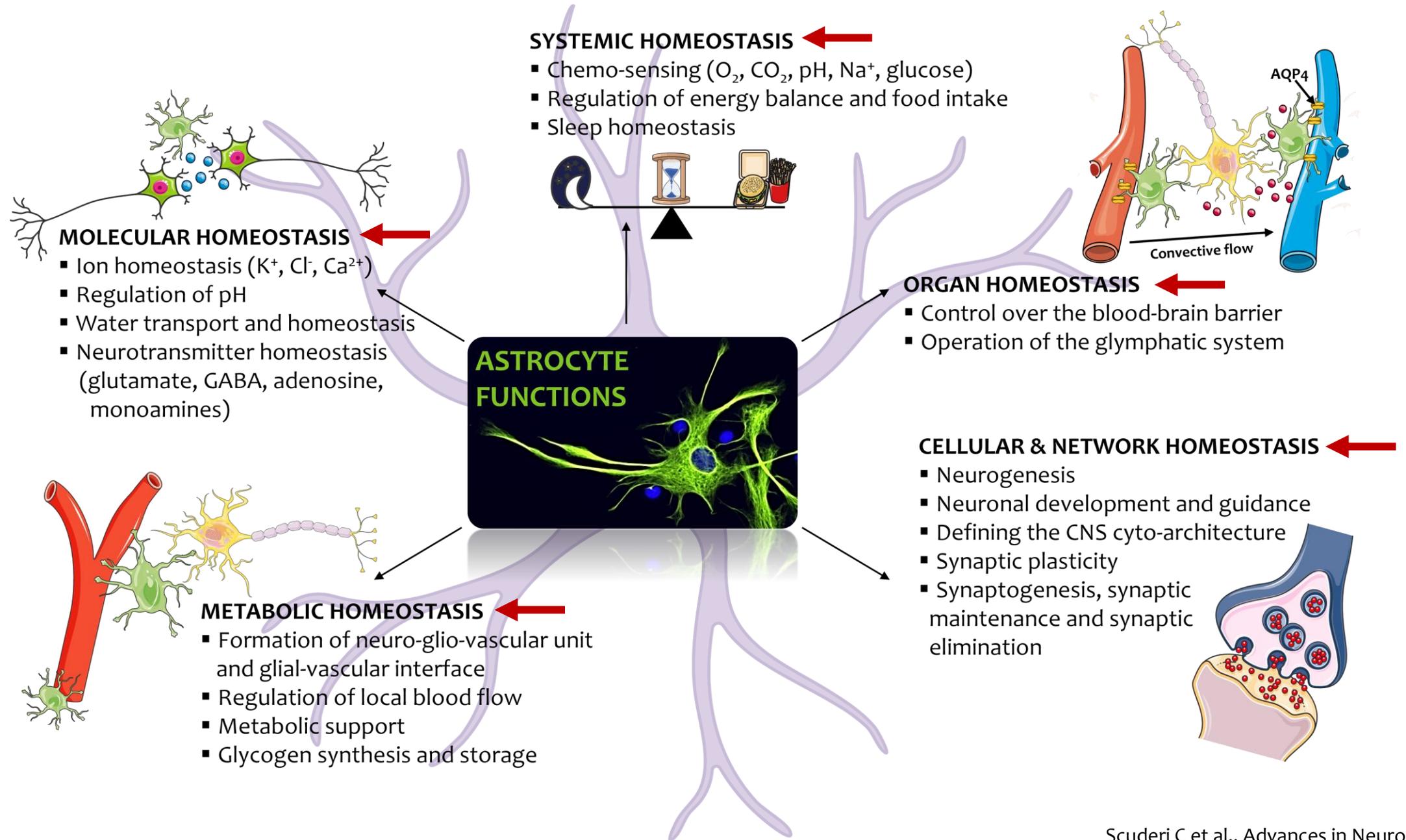
Herrup, Nature Neuro, 2015

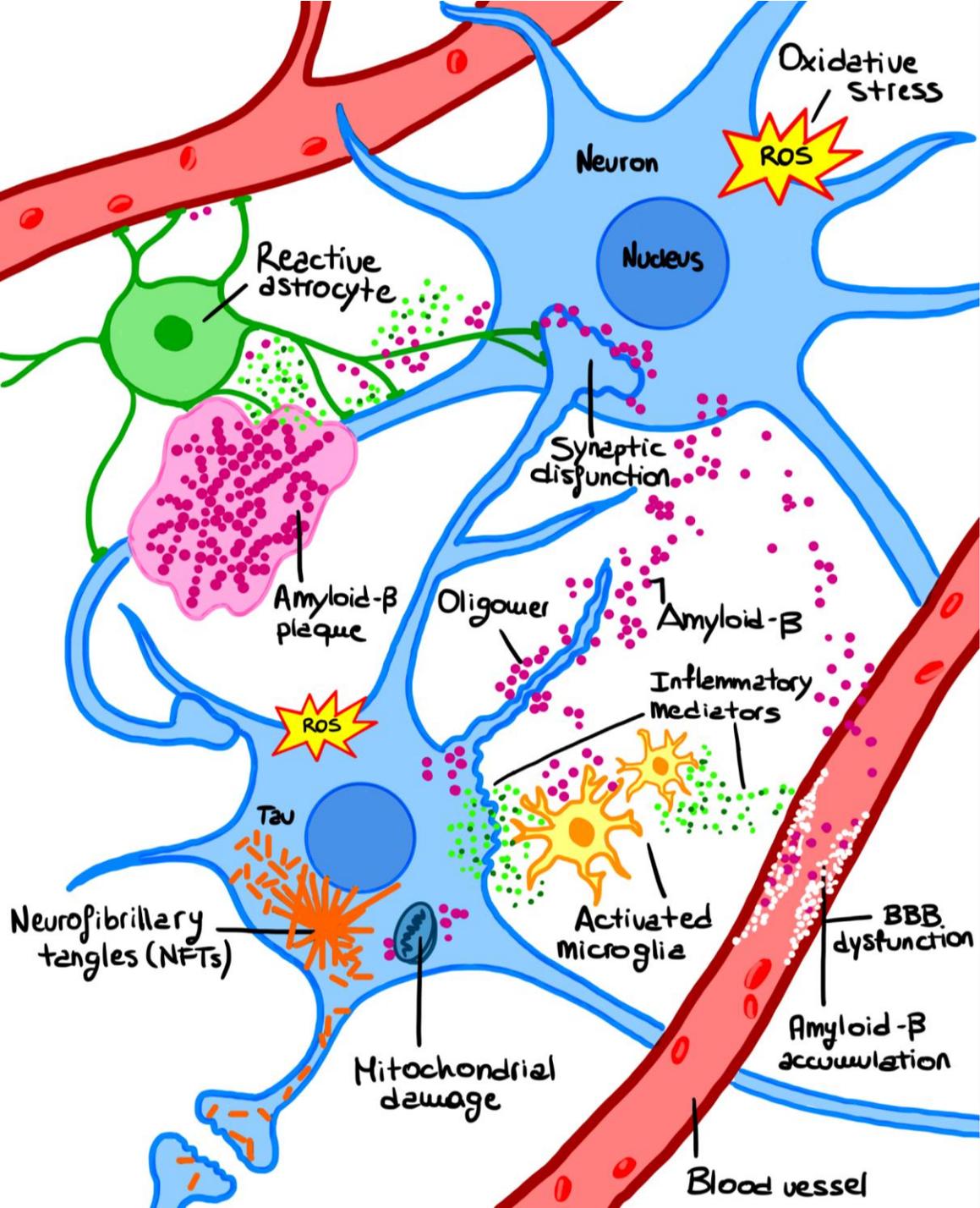


Heidebrink & Paulson, Annual Review of Medicine 2024

Amyloid immunotherapy could be a hit, but not a home run!

Astrocytes are the housekeepers and guardians of the CNS

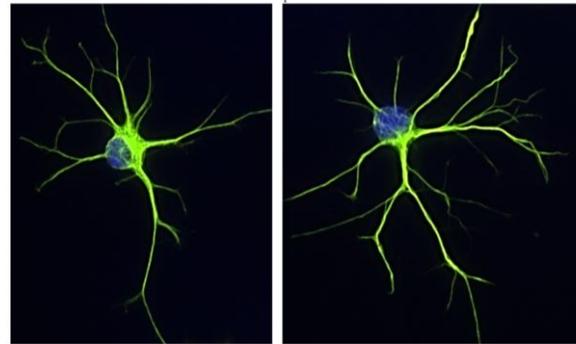




Besides aberrant proteins deposits, **alterations of glia morphology and activities** have been observed...

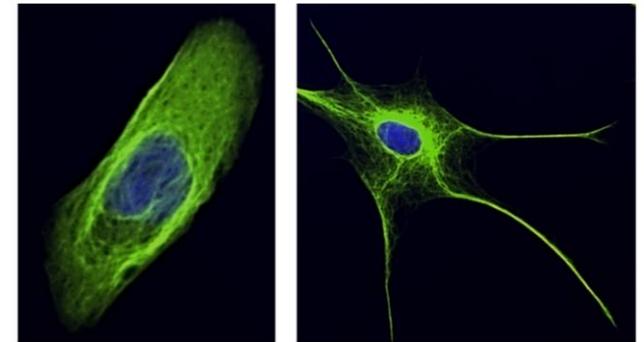
...that seem to occur well in advance of histopathological modifications.

Reactive astrogliosis



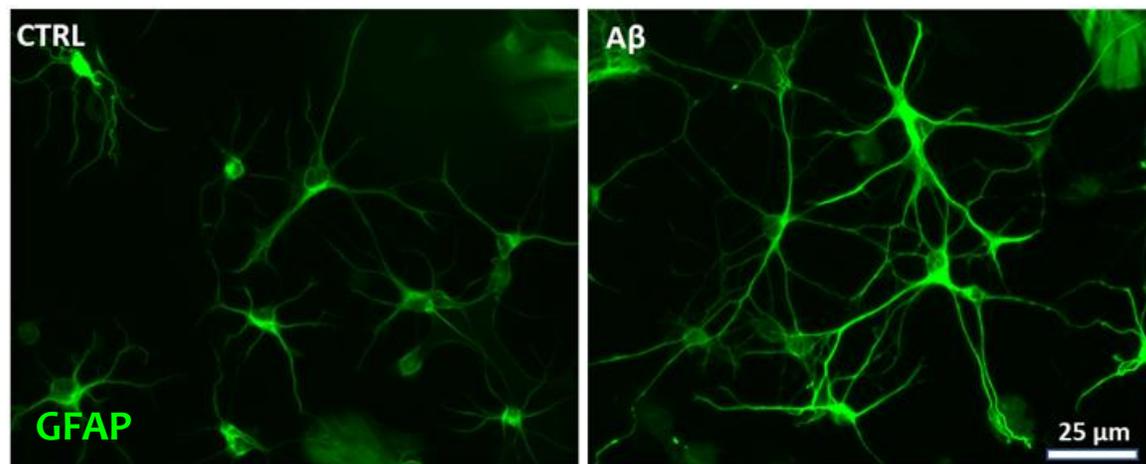
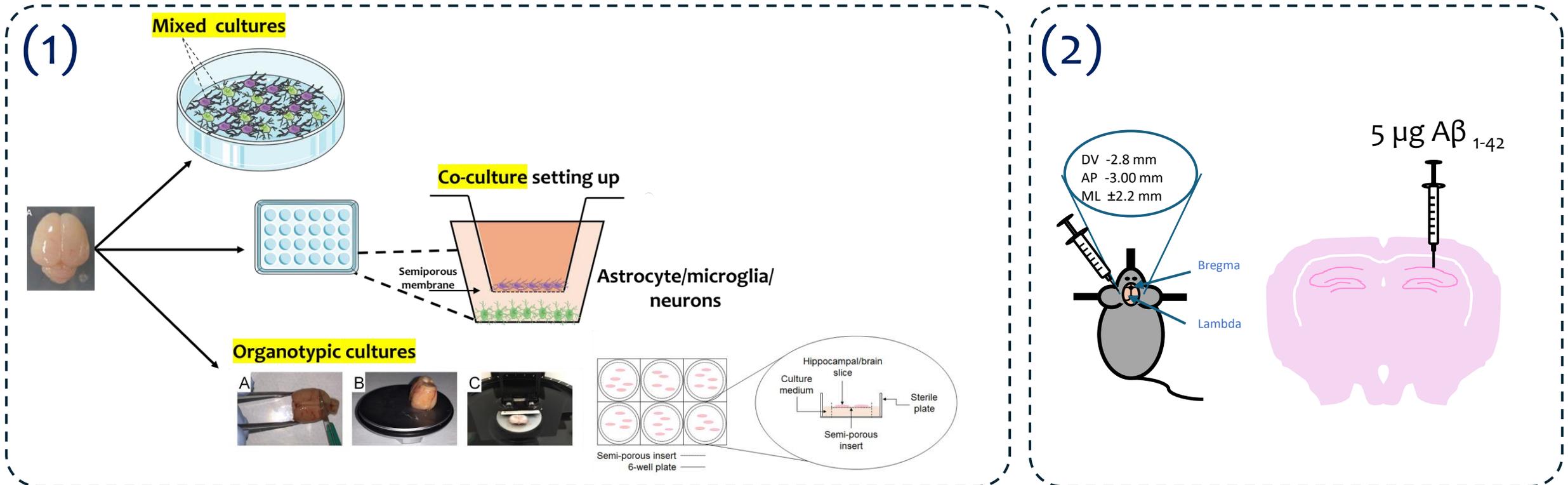
- Huntington disease
- **Alzheimer's disease**
- Frontotemporal dementia

Astrocyte degeneration, atrophy, and loss of function



- Addiction
- Stroke
- Severe trauma
- Schizophrenia
- Major depression
- Amyotrophic lateral sclerosis
- Huntington disease
- Frontotemporal dementia
- **Alzheimer's disease**
- **Aging**

Using *in vitro* (1) and *in vivo* (2) models of β amyloid-induced toxicity

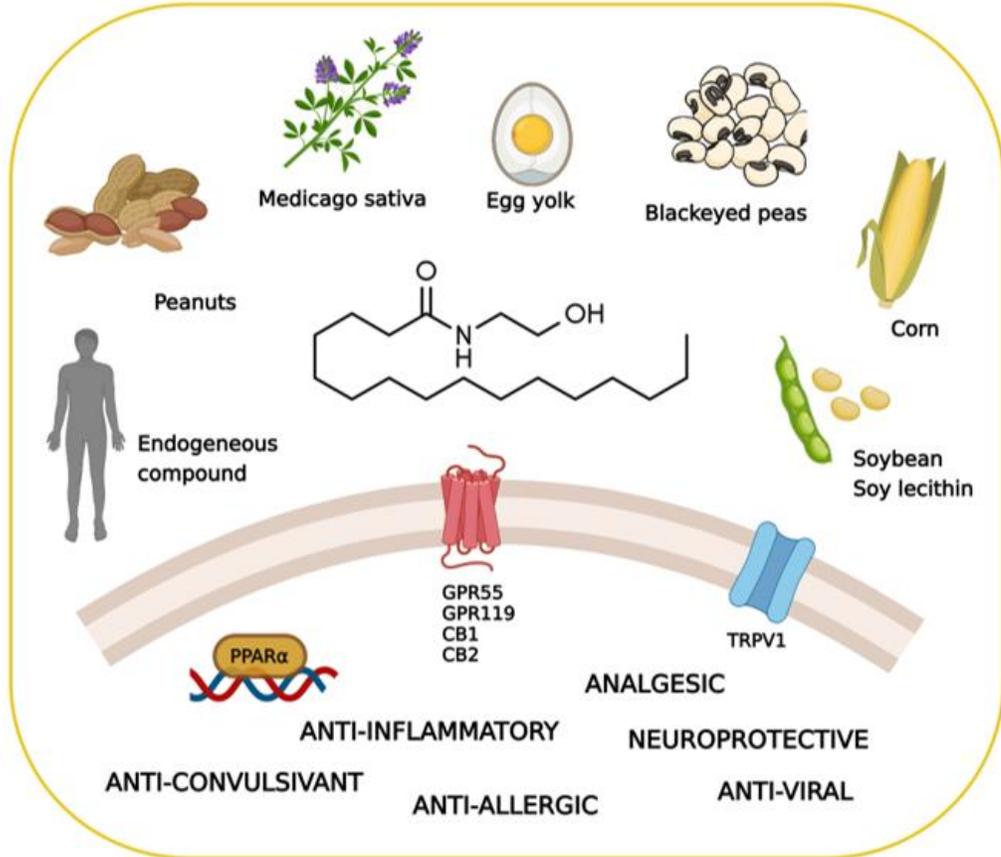


We observed a strong and long-lasting **glial reactivity** as well as **inflammation!**

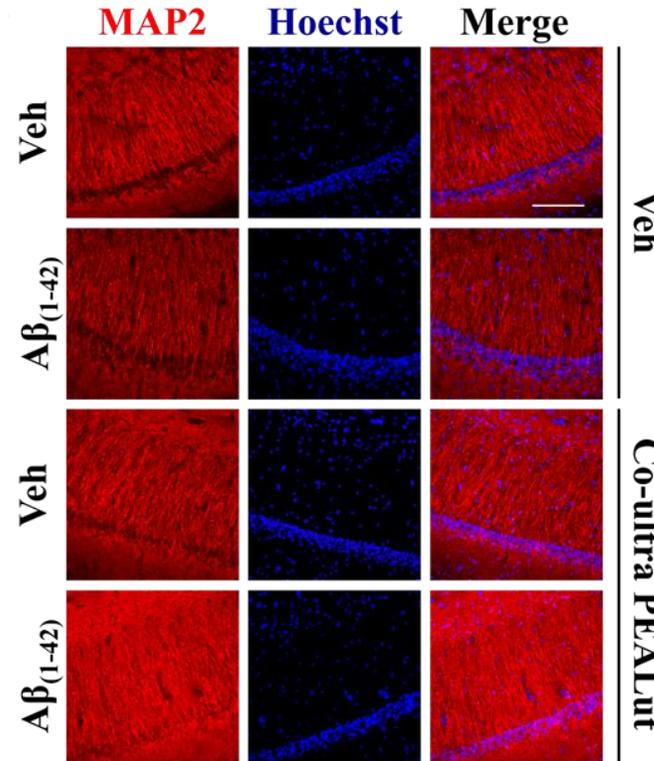
Facchinetti & Valenza et al., Biomedicines 2022
Facchinetti et al., Int J Mol Sci 2020
Scuderi et al., Cell Death Dis 2014
Esposito & Scuderi et al., PLoS One 2011
Esposito et al., Br J Pharmacol 2007
Facchinetti et al., Int J Mol Sci 2020

How can we modulate glial reactivity and inflammation?

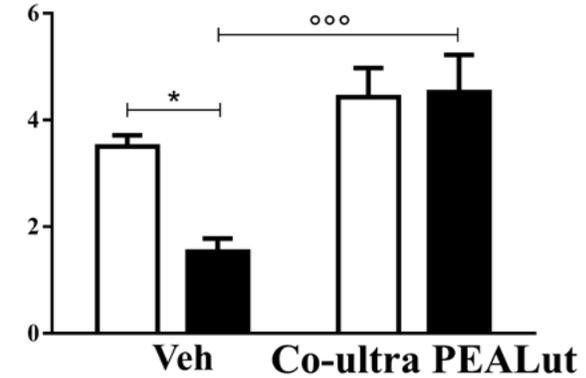
Palmitoylethanolamide (PEA)



as a glial modulator



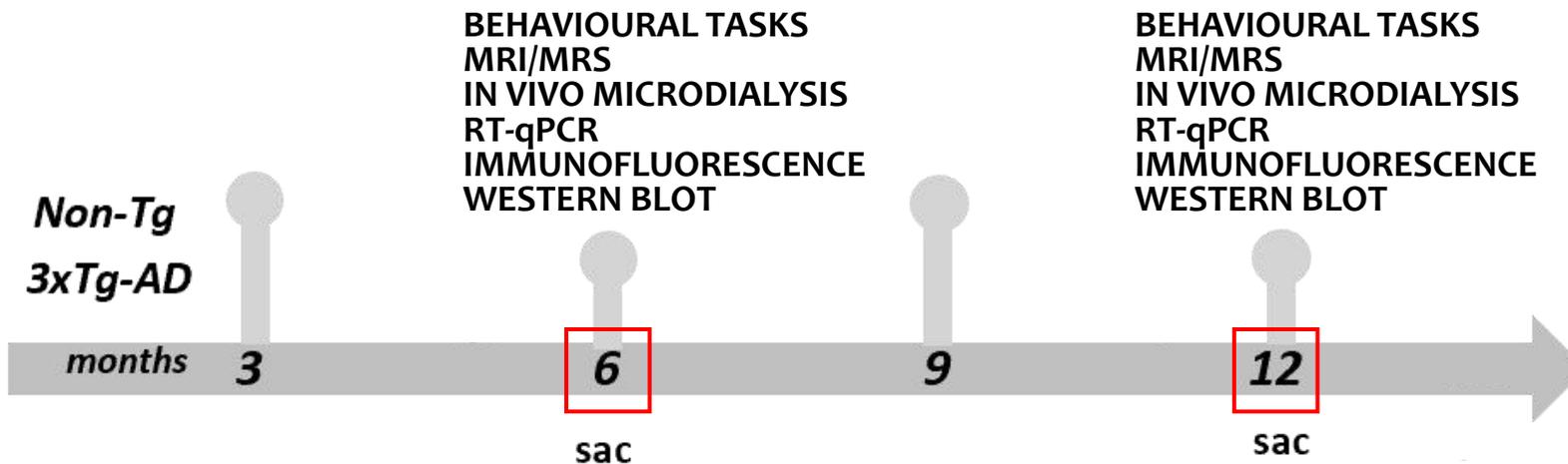
MAP2 protein expression ($\Delta F/F_0$)



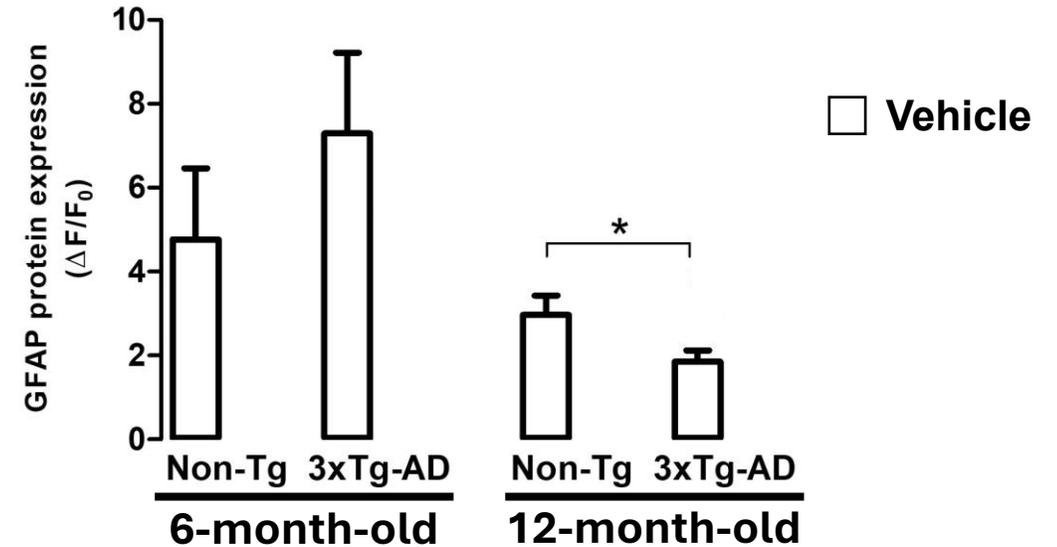
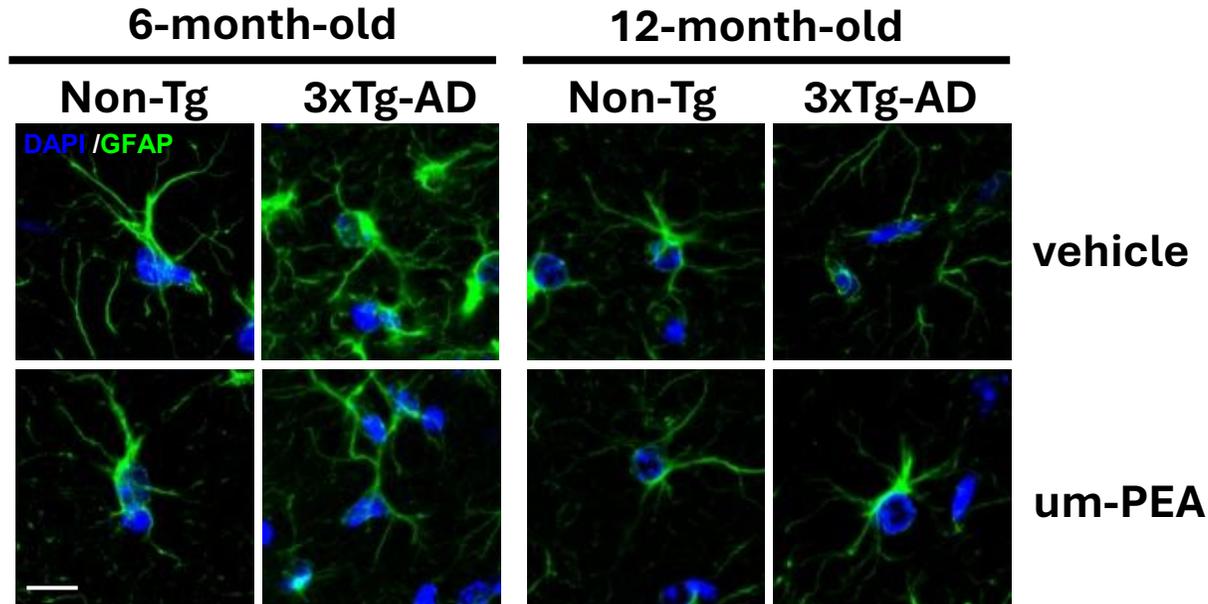


Change the model, change the results...

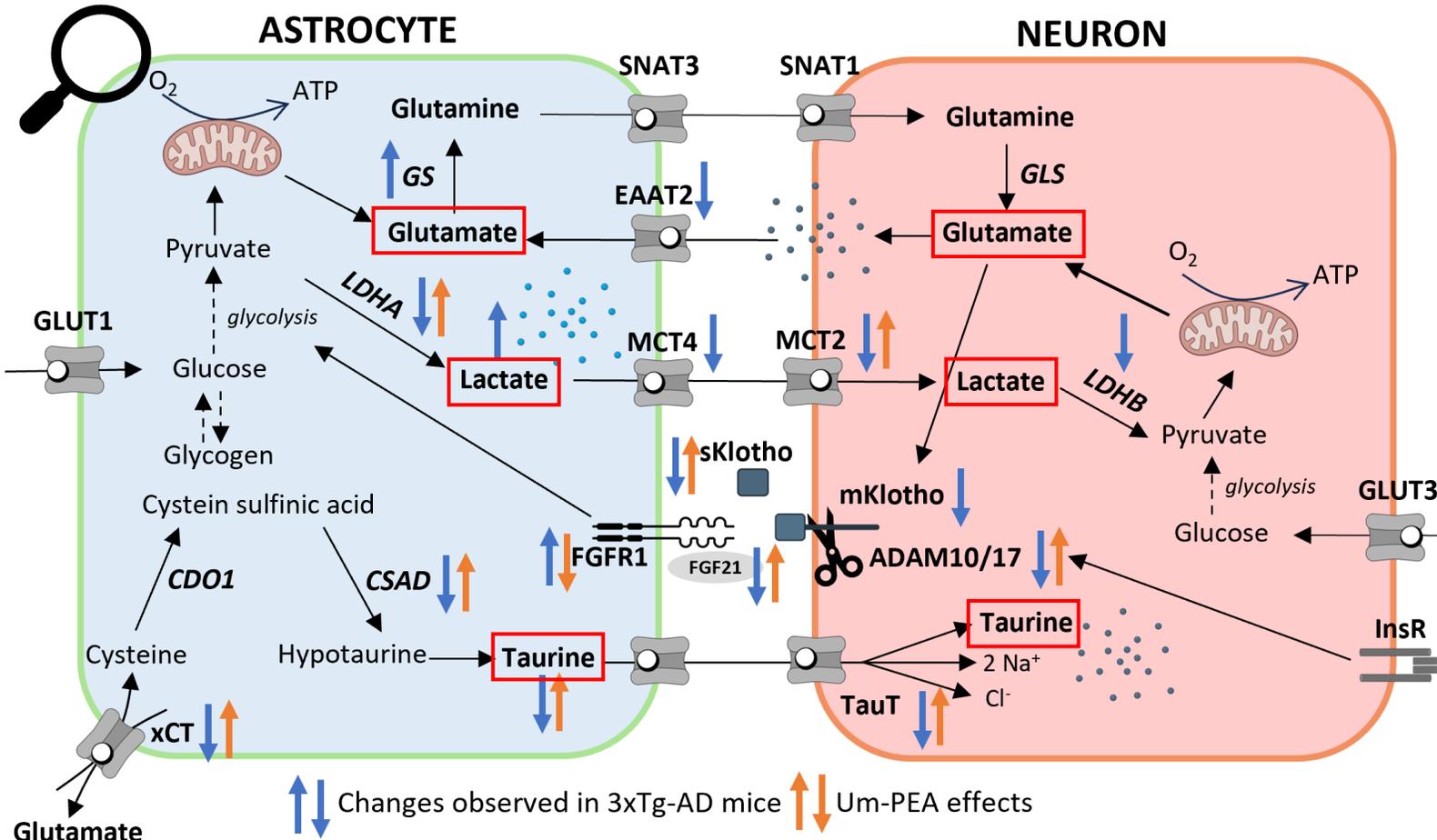
Triple transgenic mouse model of Alzheimer's disease (3xTg-AD mice)



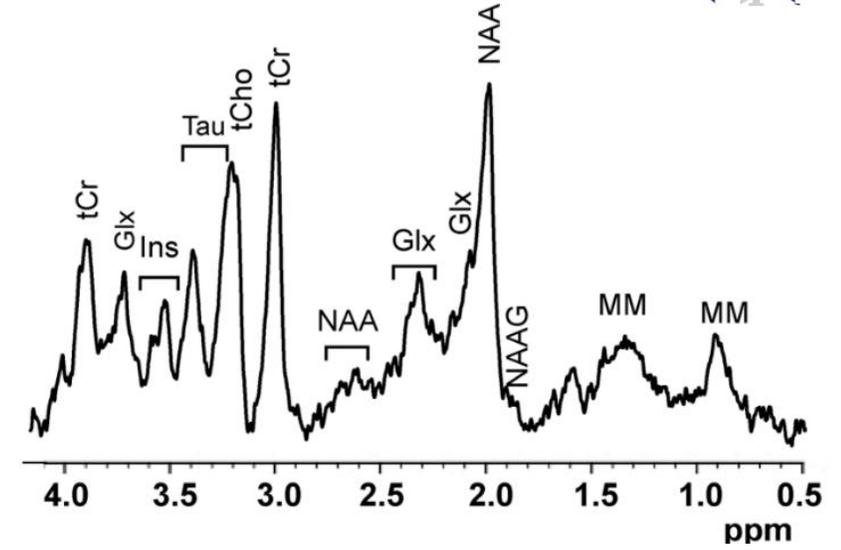
Astrocyte morphology and reactivity in young and aged 3xTg-AD mice



Astrocyte-neuron metabolic coupling as a key player in brain homeostasis



MRI/MRS

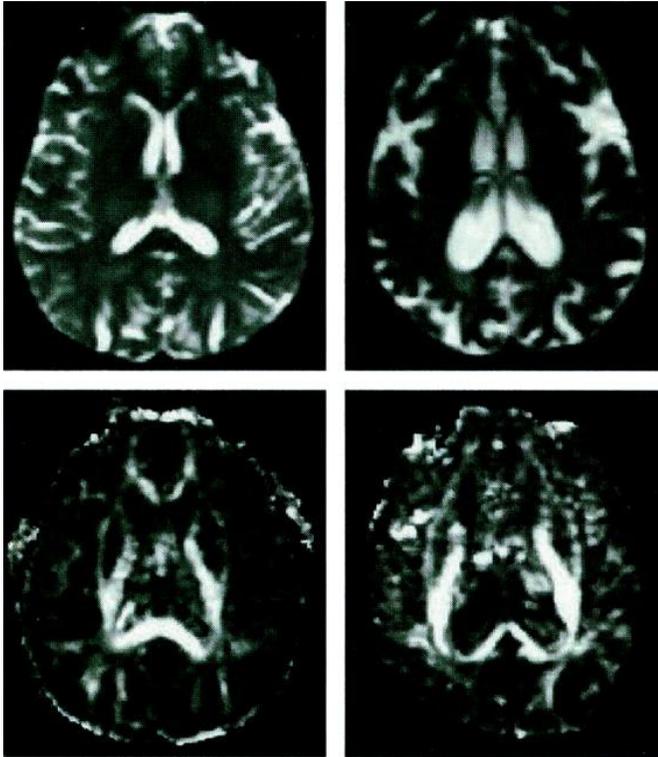


Um-PEA chronic treatment was able to normalize some alterations observed in 3xTg-AD mice related to cerebral metabolism!

Myelin defects even in Alzheimer's disease

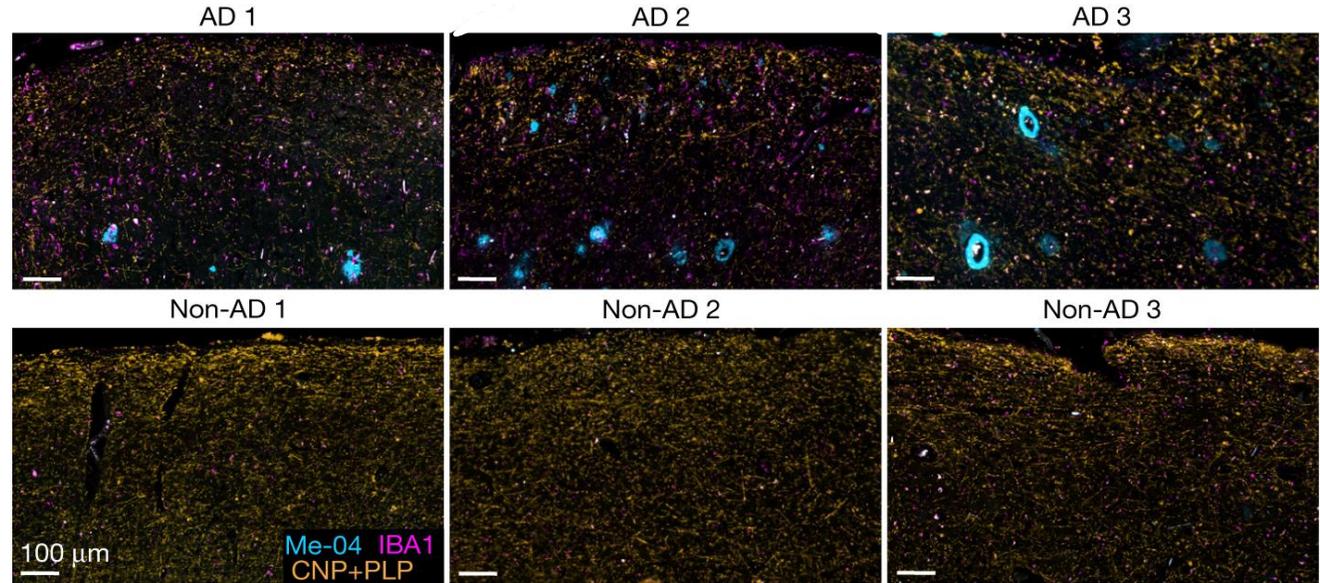
Non-AD

AD



Rose et al., J Neurol Neurosurg Psychiatry, 2000

The medial temporal lobe of patients with AD shows fewer myelinated fibers (CNPase and PLP) and more A β plaques (Me-04 staining) than non-AD individuals.



Depp et al., Nature, 2023

No effects in the maturation and complexity of oligodendrocytes after direct exposure to A β ₁₋₄₂

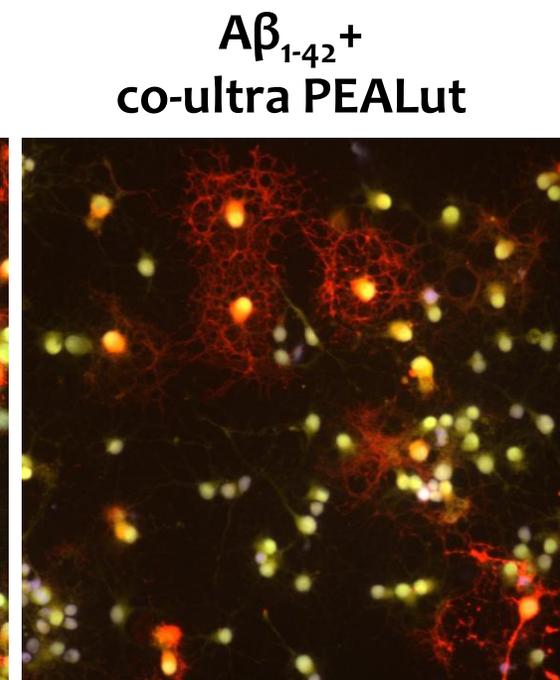
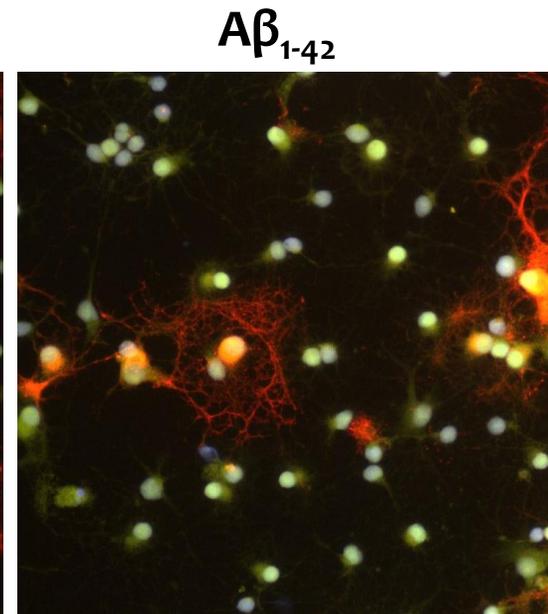
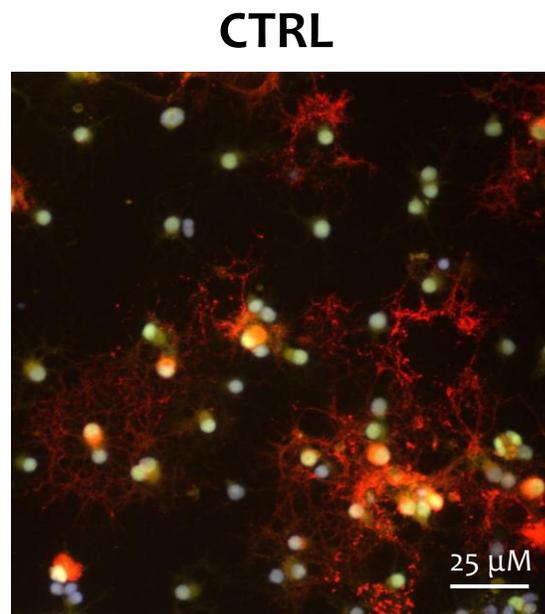
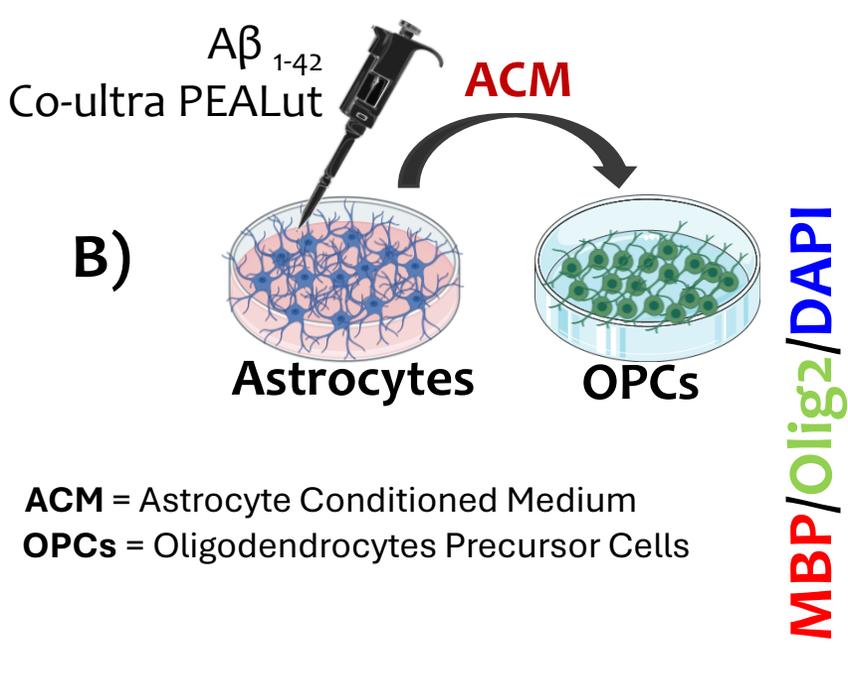
A)

A β ₁₋₄₂
Co-ultra PEALut

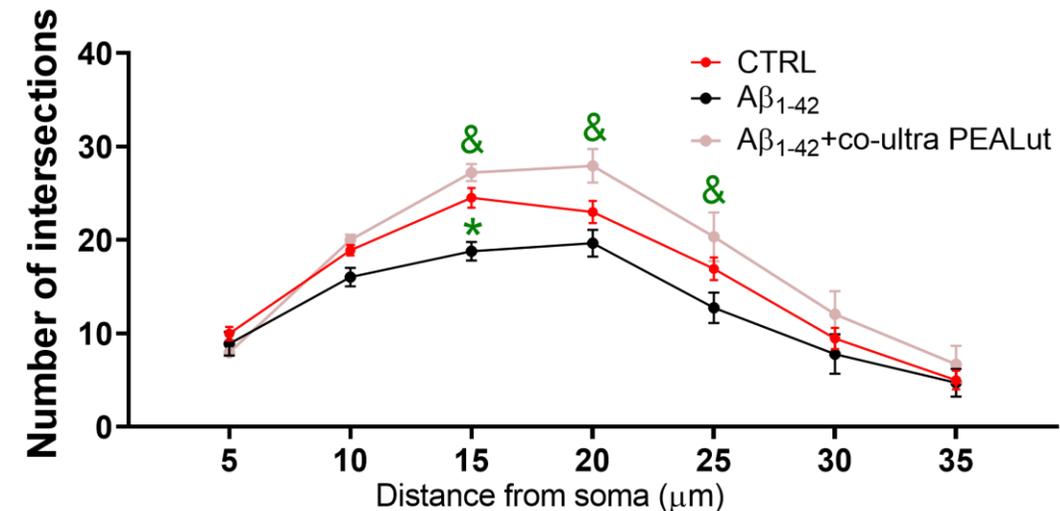
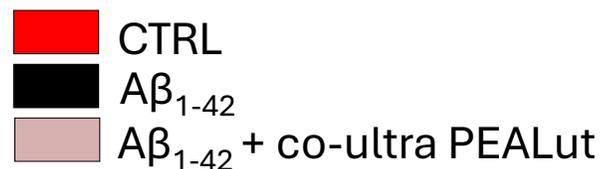
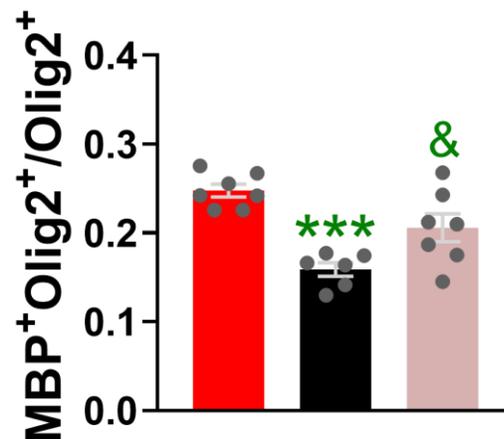


OPCs

OPCs = Oligodendrocytes Precursor Cells

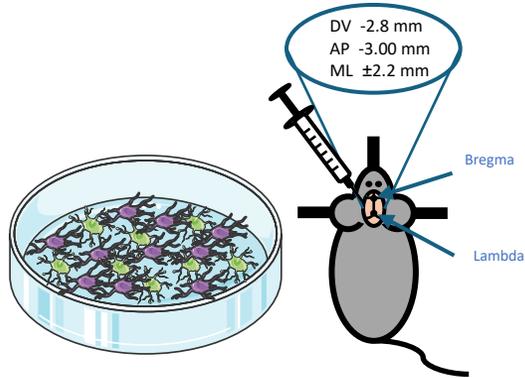


**Co-ultra PEALut normalizes
ACM-induced reduction in
oligodendrocyte
maturation and complexity
in the $A\beta$ group!**



*** vs CTRL
 & vs $A\beta_{1-42}$

To recap



In the models of beta-amyloid toxicity, we observed glia reactivity as well as inflammation

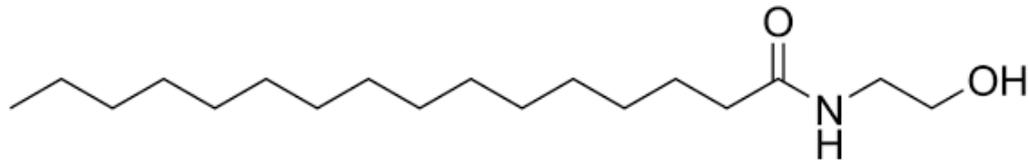
ASTROGLIA
REACTIVITY

ATROPHY/LOSS
OF FUNCTION



3xTg-AD

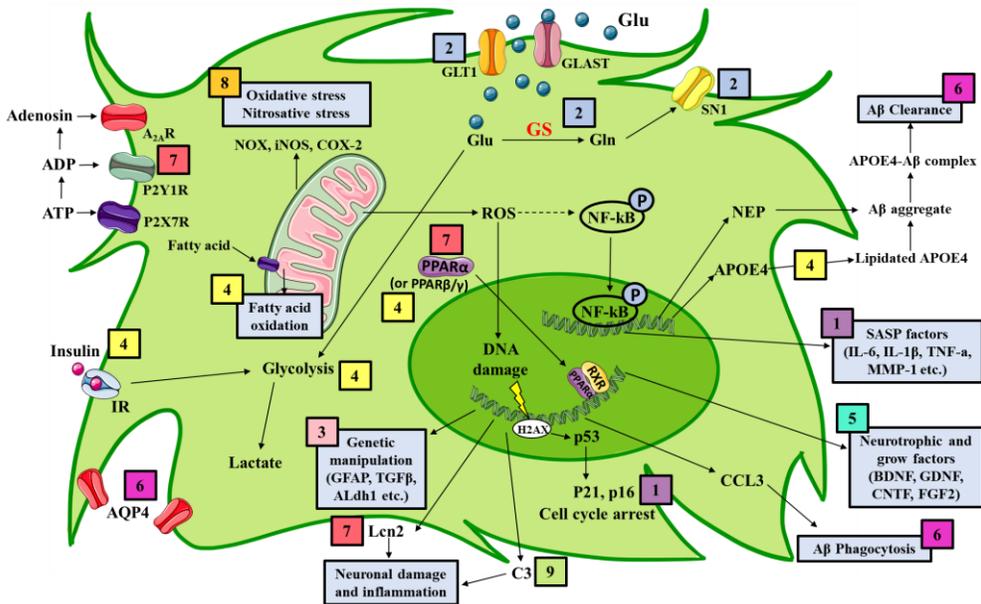
3xTg-AD mice show signs of inflammation and glia reactivity in the early stage of the disease while in the late stages these phenomena decrease (effect of age?)



PEA

Compounds able to modulate glial dysfunctions and dampen inflammation also exert neuroprotective effects, like palmitoylethanolamide!

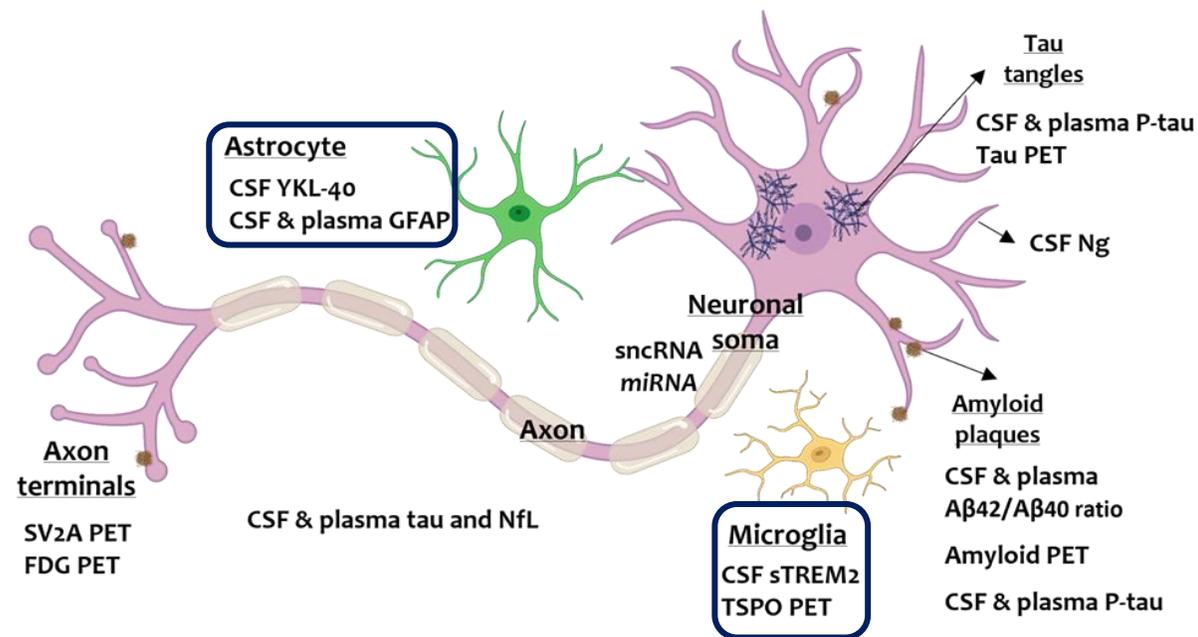
Conclusions



Valenza et al., Biomolecules 2021

Glia reactivity is a complex process and seems **context-, region- and time-dependent.**

A detailed understanding of the molecular alterations occurring in **glial cells** during aging and age-related diseases could offer new **biomarkers** as well as promising **pharmacological targets**



Valenza & Scuderi, Neural Regen Res 2022



SAPIENZA
UNIVERSITÀ DI ROMA

Acknowledgments



The University of Manchester

Alexei Verkhatsky, MD, PhD

Caterina Scuderi, PhD
Marta Valenza, PhD
Roberta Facchinetti, PhD
Silvia Burla, PhD student

Luca Steardo, MD, PhD
Patrizia Campolongo, PhD
Maria Rosanna Bronzuoli, PhD



Vladimir Parpura, MD, PhD

FUNDINGS



Baoman Li, PhD



Tommaso Cassano, MD, PhD



Rossella Canese, PhD
Giulia Carpinelli, PhD



Finanziato
dall'Unione europea
NextGenerationEU



Ministero
dell'Università
e della Ricerca



Italiadomani
PIANO NAZIONALE
DI RIPRESA E RESILIENZA



SAPIENZA
UNIVERSITÀ DI ROMA