Cerebro e Inflamación:
Diferentes Vías, un Mismo Destino

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Fundación Lucha contra las Infecciones

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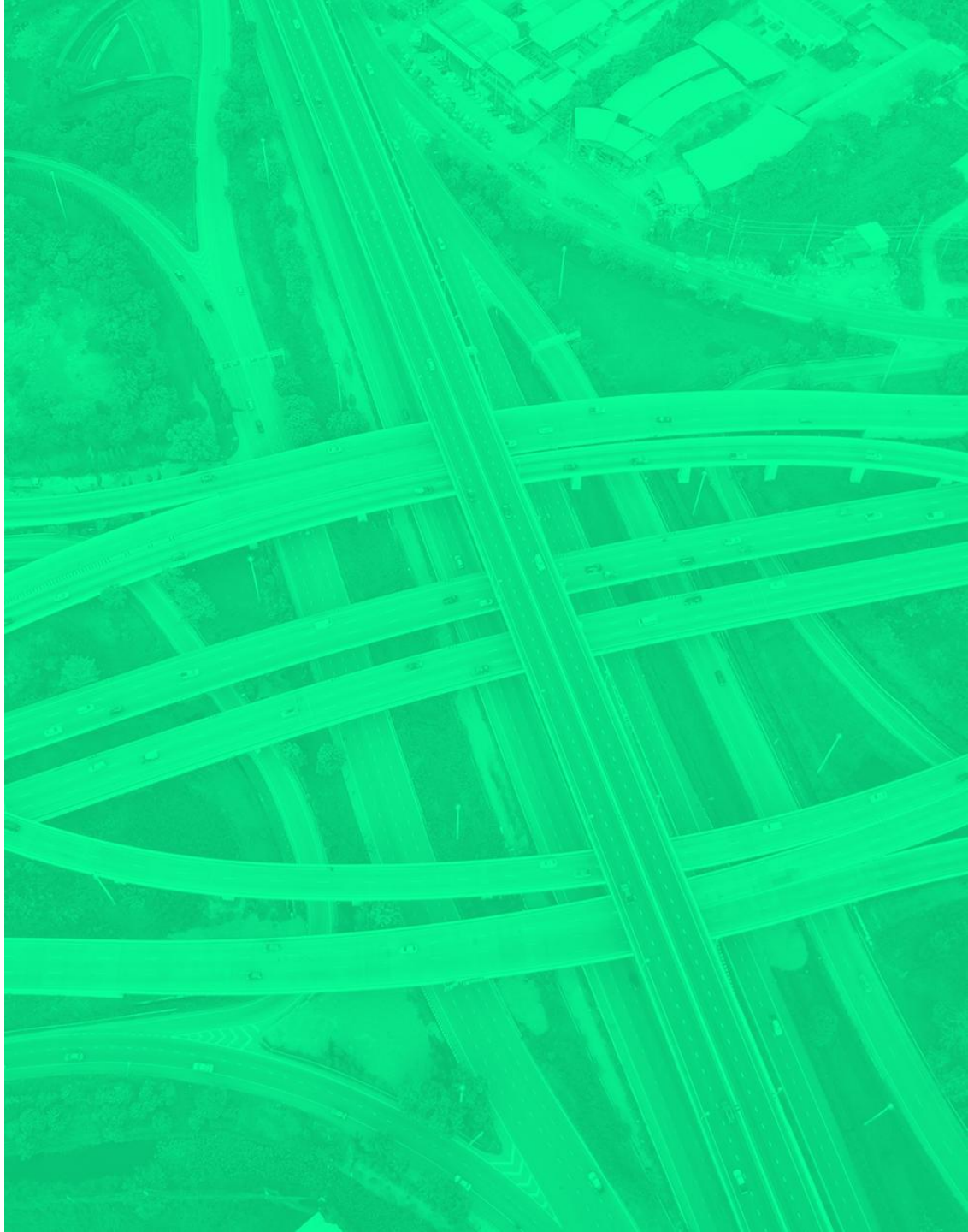

20/02/2025

Inflamación y Enfermedad de Alzheimer

Mecanismos patológicos, principales implicaciones en la enfermedad de Alzheimer y futuras terapias dirigidas.

Dra. Amanda Cano

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Unidad de Investigación – Ace Alzheimer Center Barcelona

Disclosures

The author has any commercial or financial relationships that could be construed as a potential conflict of interest.

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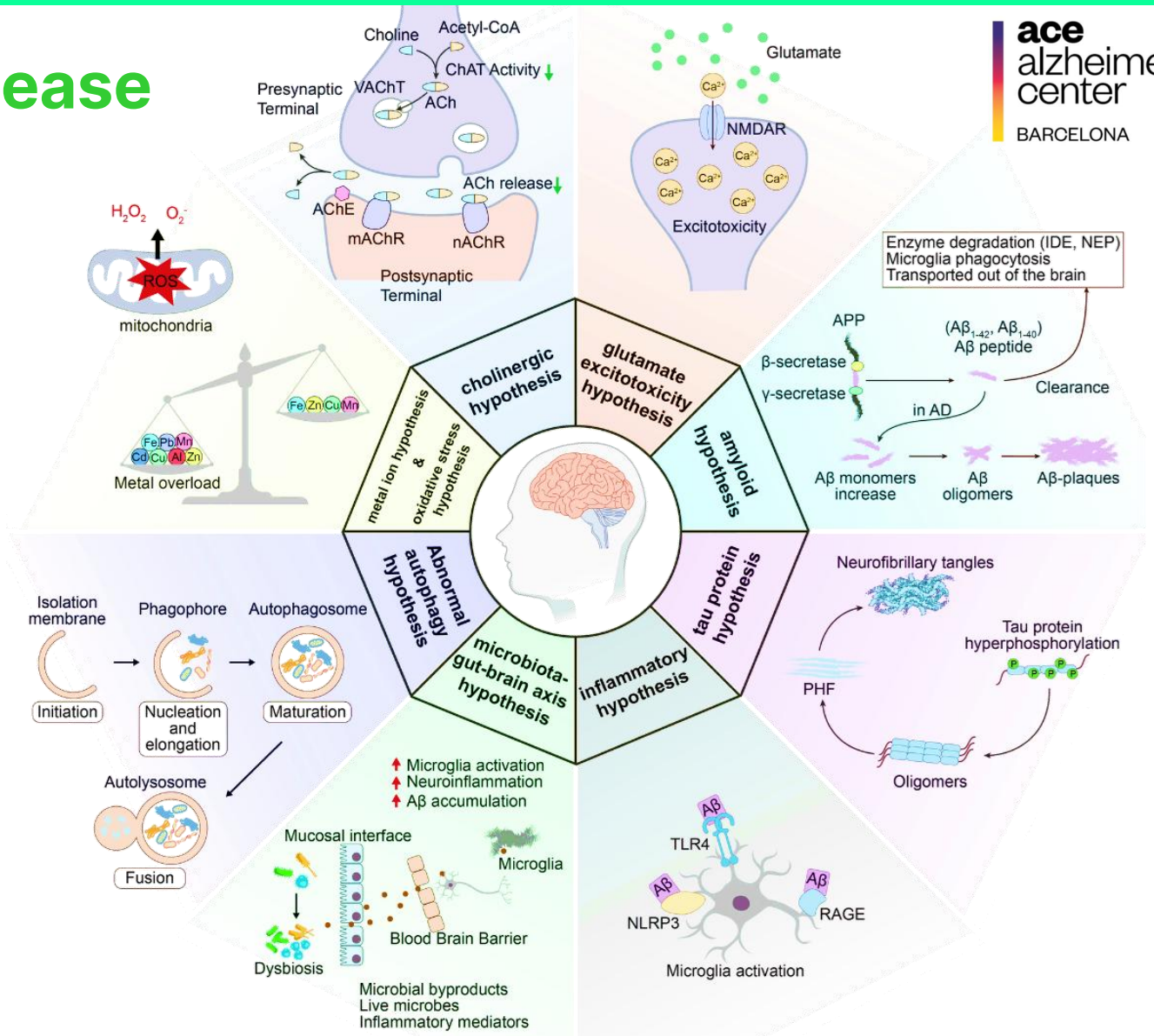
The etiology of Alzheimer's disease

AD is a **multifactorial disease**, and its etiology is still unknown.

Its **origin is intricate and diverse**, stemming from a combination of factors such as aging, genetics, and environment.

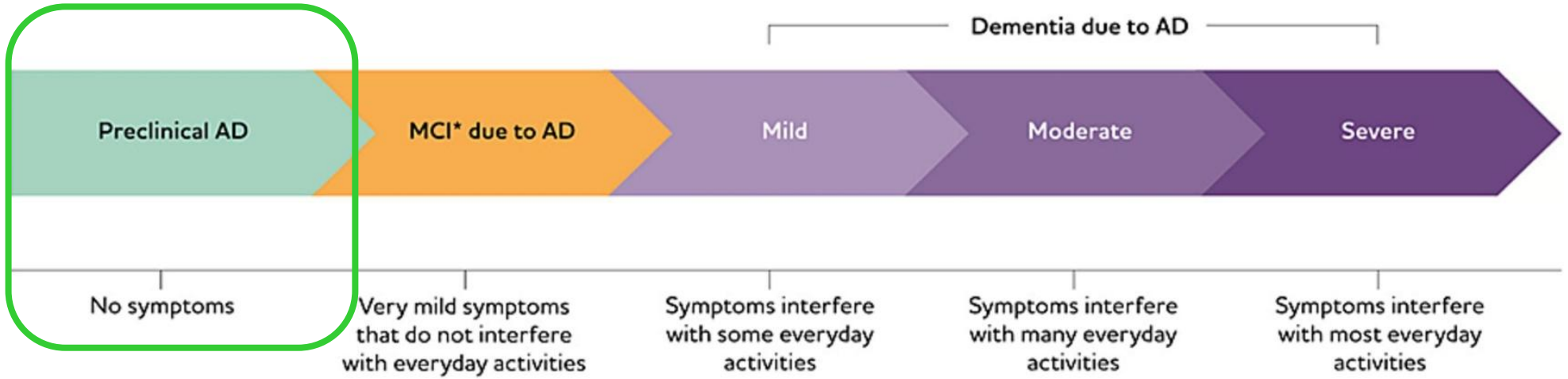
Our current understanding of AD pathologies involves **various molecular hypotheses**, such as the cholinergic, amyloid, tau protein, **neuroinflammation**, oxidative stress, metal ion, glutamate excitotoxicity, microbiota-gut-brain axis, and abnormal autophagy.



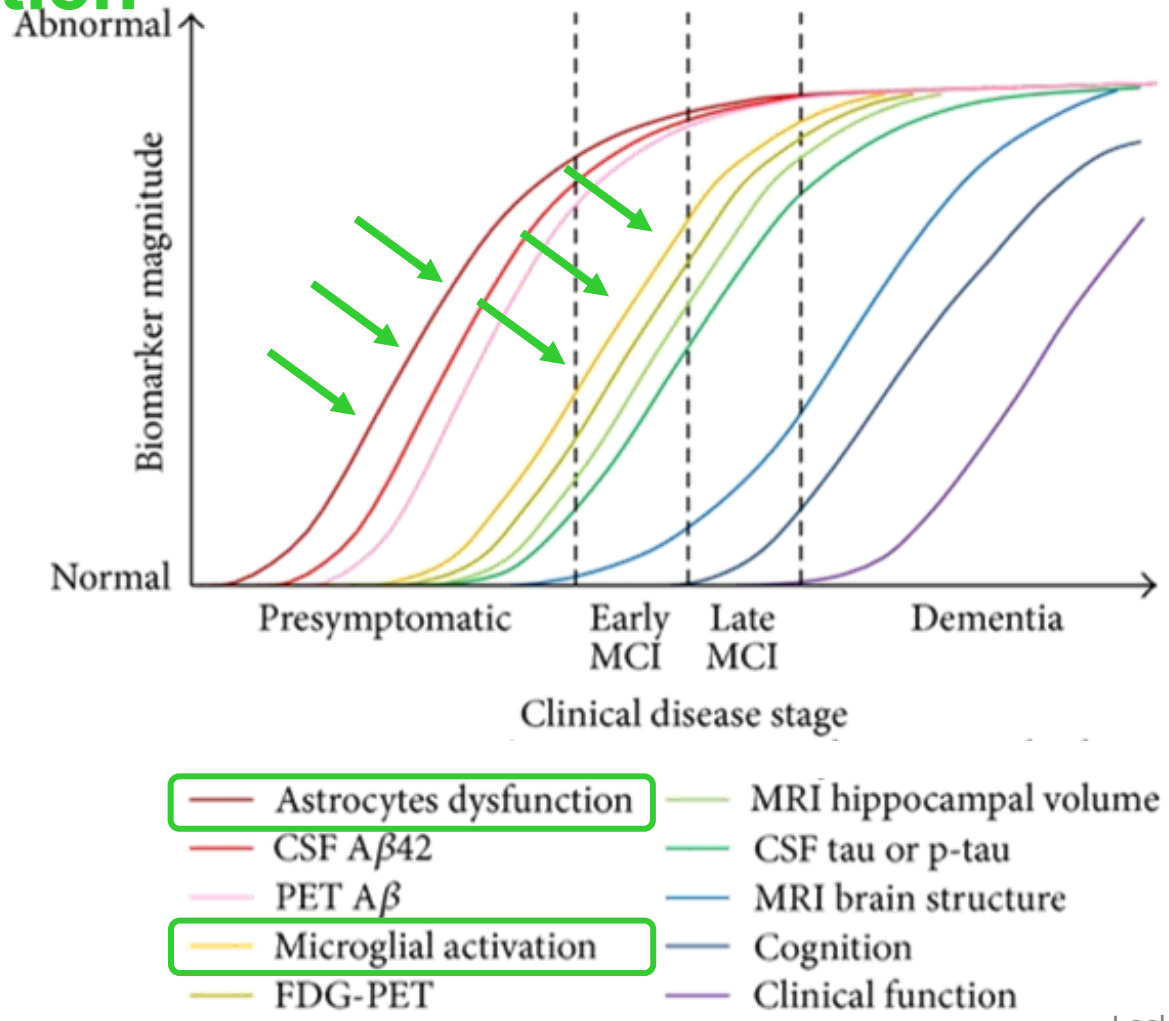
Zhang et al. *Signal Transduct Target Ther (Nature).* 2024 ;9(1):211

The appearance of molecular alterations

First molecular' alterations occurs even **15 years before** the appearance of the first symptoms !

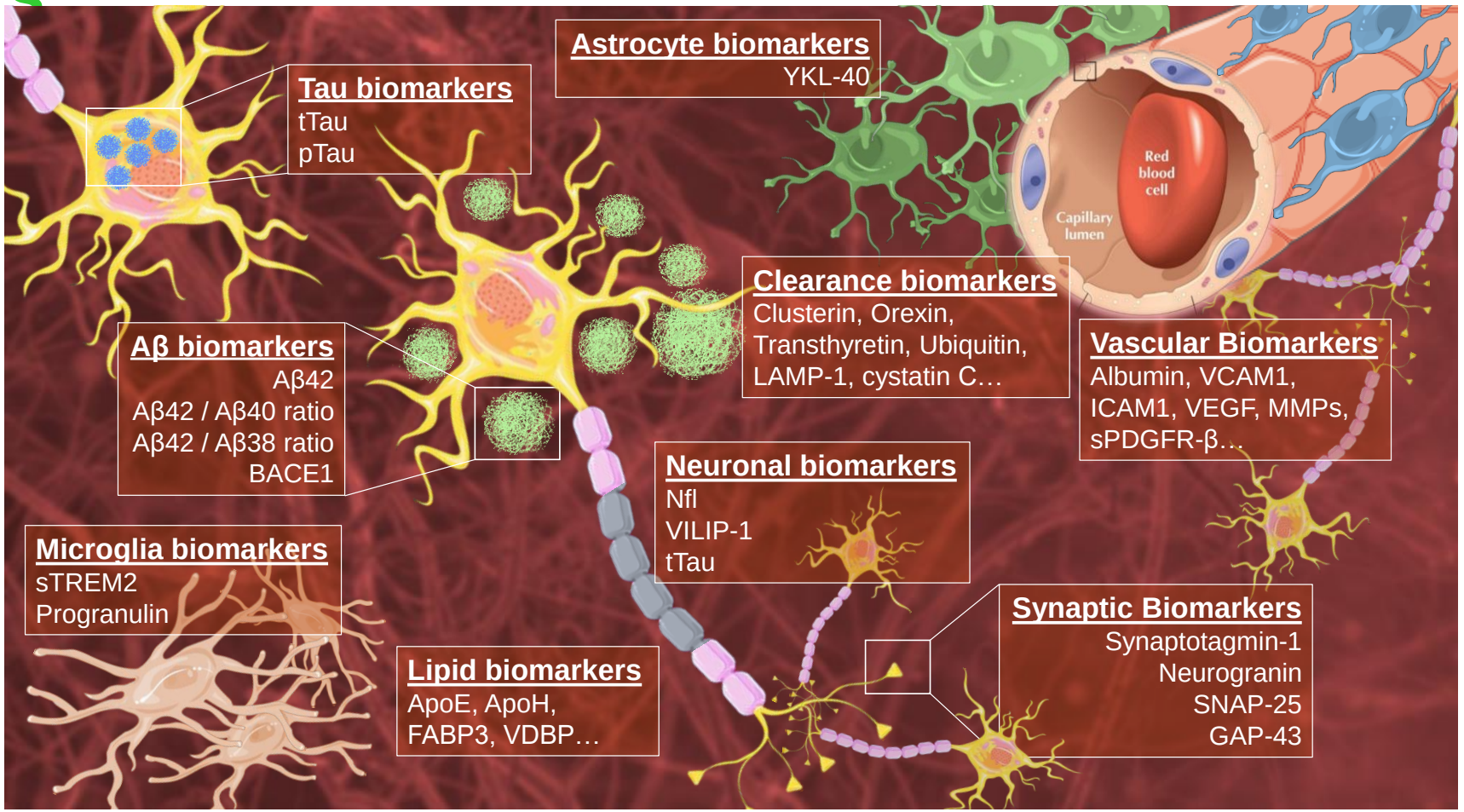


The appearance of molecular alterations - neuroinflammation



Leclerc *et al.* 2013. *The Scientific World Journal.* 2013, 589308

Alzheimer's disease molecular pathways and their biomarkers



Cano *et al.* 2021. *Journal of Nanobiotechnology.* 19(1):122

The biological course of neuroinflammation

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nature › molecular psychiatry › articles › article

Article | Open access | Published: 06 December 2022

Neuroinflammation is independently associated with brain network dysfunction in Alzheimer's disease

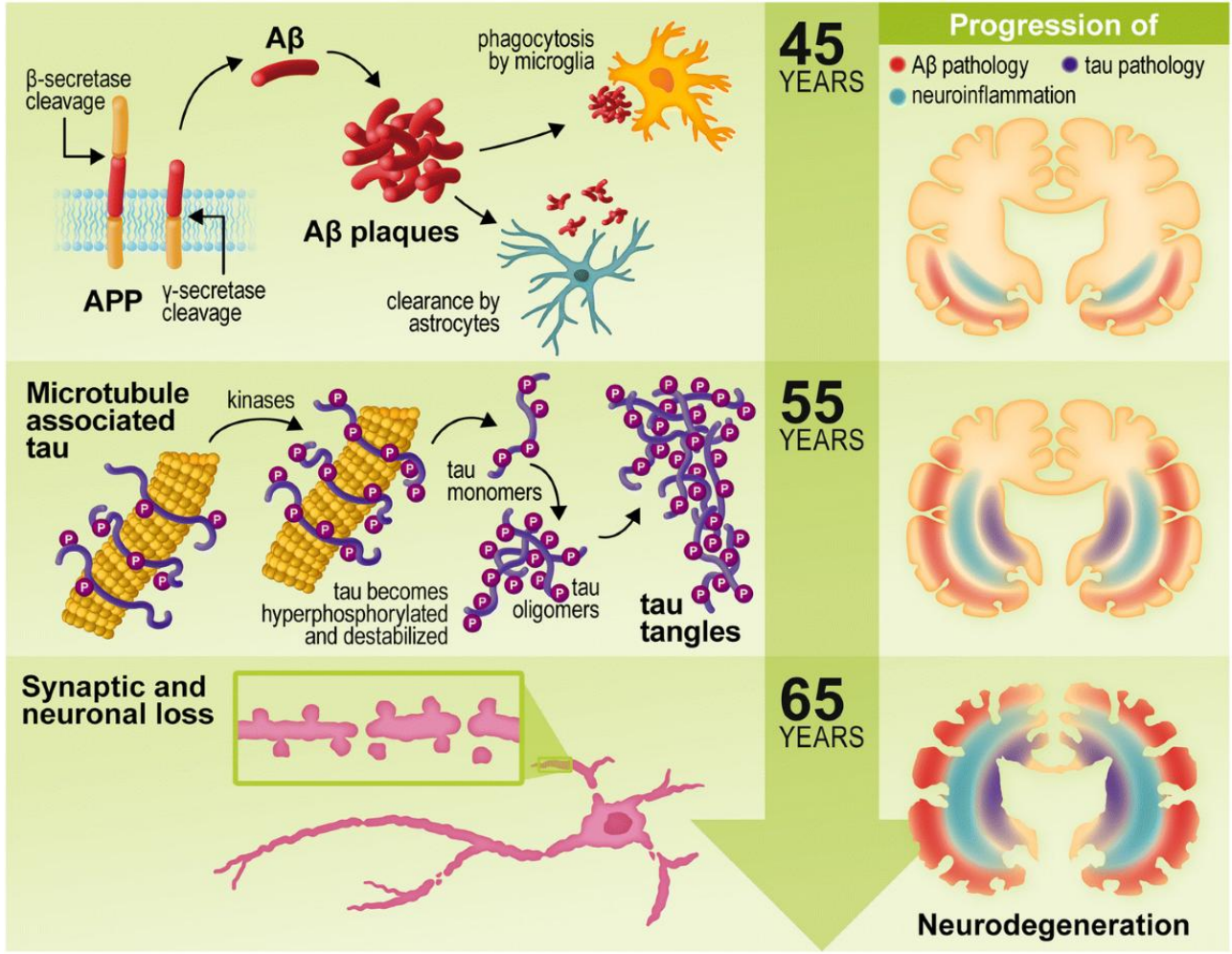
Fangda Leng, Rainer Hinz, Steve Gentleman, Adam Hampshire, Melanie Dani, David J. Brooks & Paul Edison

Molecular Psychiatry **28**, 1303–1311 (2023) | Cite this article

Prof. Paul Edison

Imperial College London

Neuroinflammation in Alzheimer disease disrupts brain networks **independently of Aβ deposition** !



Newcombe et al. *J Neuroinflammation*. 2018; 15(1):276

Evidence for an inflammatory component in Alzheimer's disease

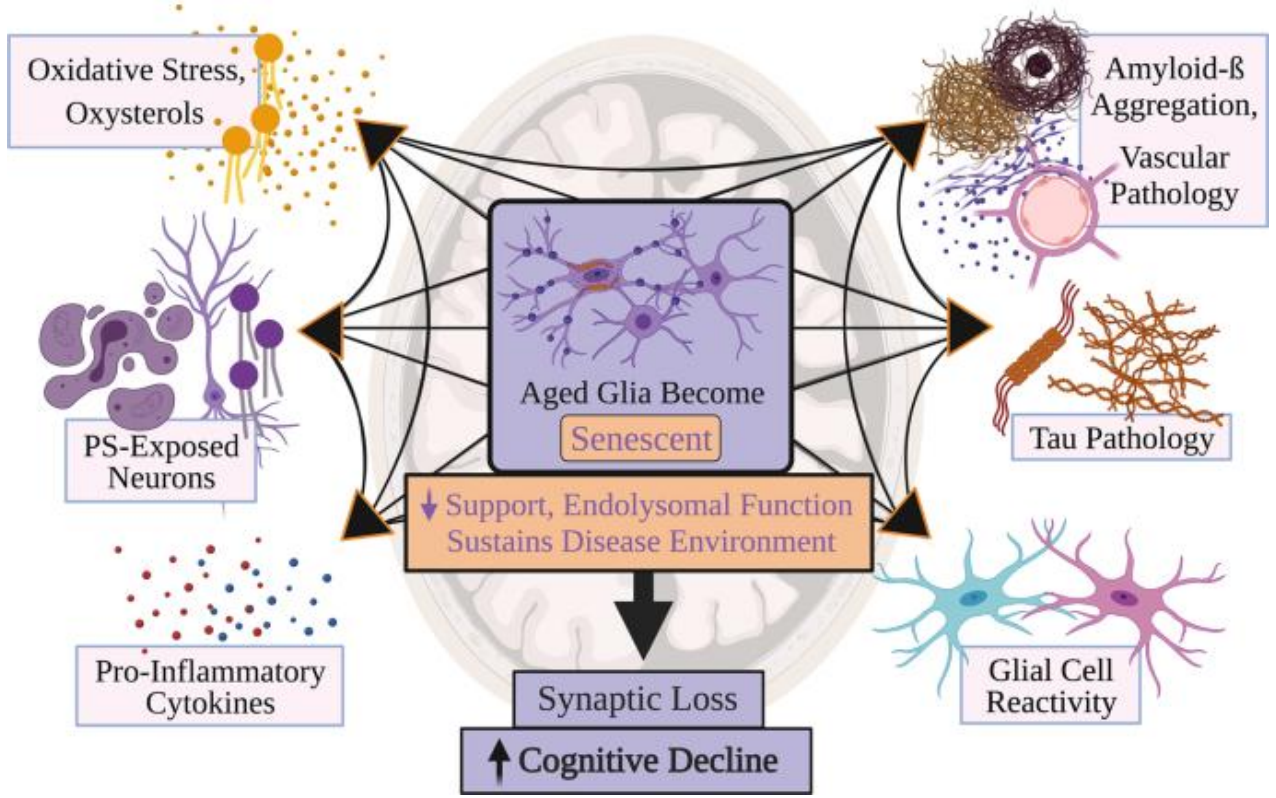
It is well know that **glial cells are reactive** and **increased in AD** brain as well as being associated with Aβ plaques, neurofibrillary tangles and complement factors.

These **glial cells generate immune mediators**, such as cytokines, chemokines, inflammasomes and reactive oxygen species (ROS), and contribute to both the asymptomatic and symptomatic disease stages.

Glial activation is an early event in AD that is instrumental for the **morphology of Aβ deposits, the spreading of pathology** and the clinical presentation of patients with AD.

In CSF, a few proteins have been indentified as robust biomarkers to monitor neuroinflammation in AD:

- **TREM2** → microglial activation
- **YKL-40** → astroglial inflammation marker
- **GFAP** →astrocyte reactivity



Lau et al. *Nat Commun*. 2023;14(1):1670

Which cells drive neuroinflammation in Alzheimer's disease?

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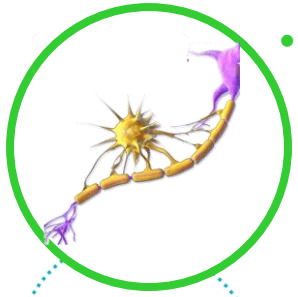
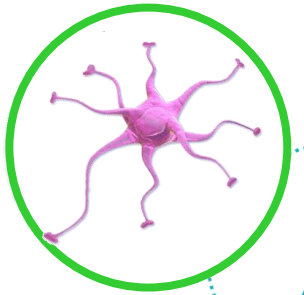
Oligodendroglia

- Associated with axonal perturbation, myelin degeneration and secondary inflammation
- May have immunomodulatory functions
- Undergo marked transcriptional changes
- Our understanding of their role in AD remains limited



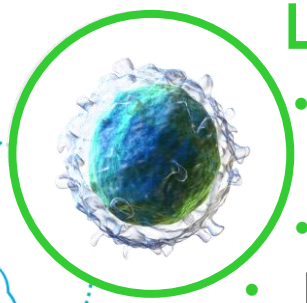
Microglia

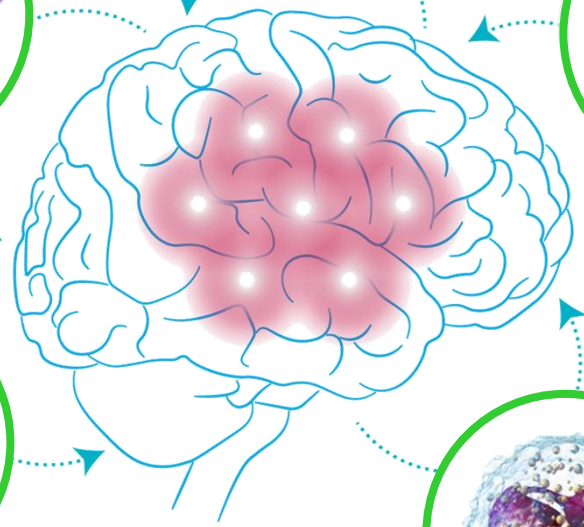
- Main glial cells involved in neuroinflammation
- Generate inflammatory mediators and ROS
- Metabolically flexible (glycolysis → amino acids or fatty acid)
- Surround Aβ plaques and reactive against them
- Dual role in AD development
- Microglial lipid metabolism
- Senescent microglia
- Phagocytic activity



Lymphocytes

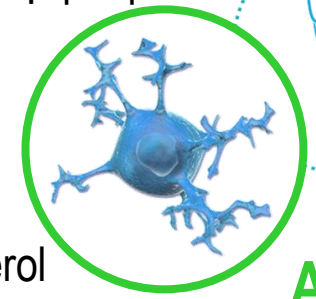
- Disruption of BBB → lymphocytes penetrate into brain parenchyma
- Lymphocytes B → ↑ Aβ burden
- Lymphocytes T → neuroinflammation, pTau neurodeg, and cognitive deficits





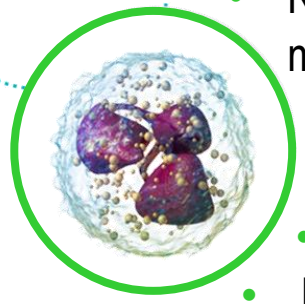
Astrocytes

- In AD, linked to microglia inflammatory responses.
- Reactive astrocytes associated with Aβ plaques.
- Altered function: ↓phagocytosis, ↓glutamate uptake, secretion of neurotoxic compounds (synapsis alteration), loss of homeostatic support, ↓astrocyte-derived cholesterol
- Astrocyte response to Aβ deposits remains unclear



Peripheral myeloid cells

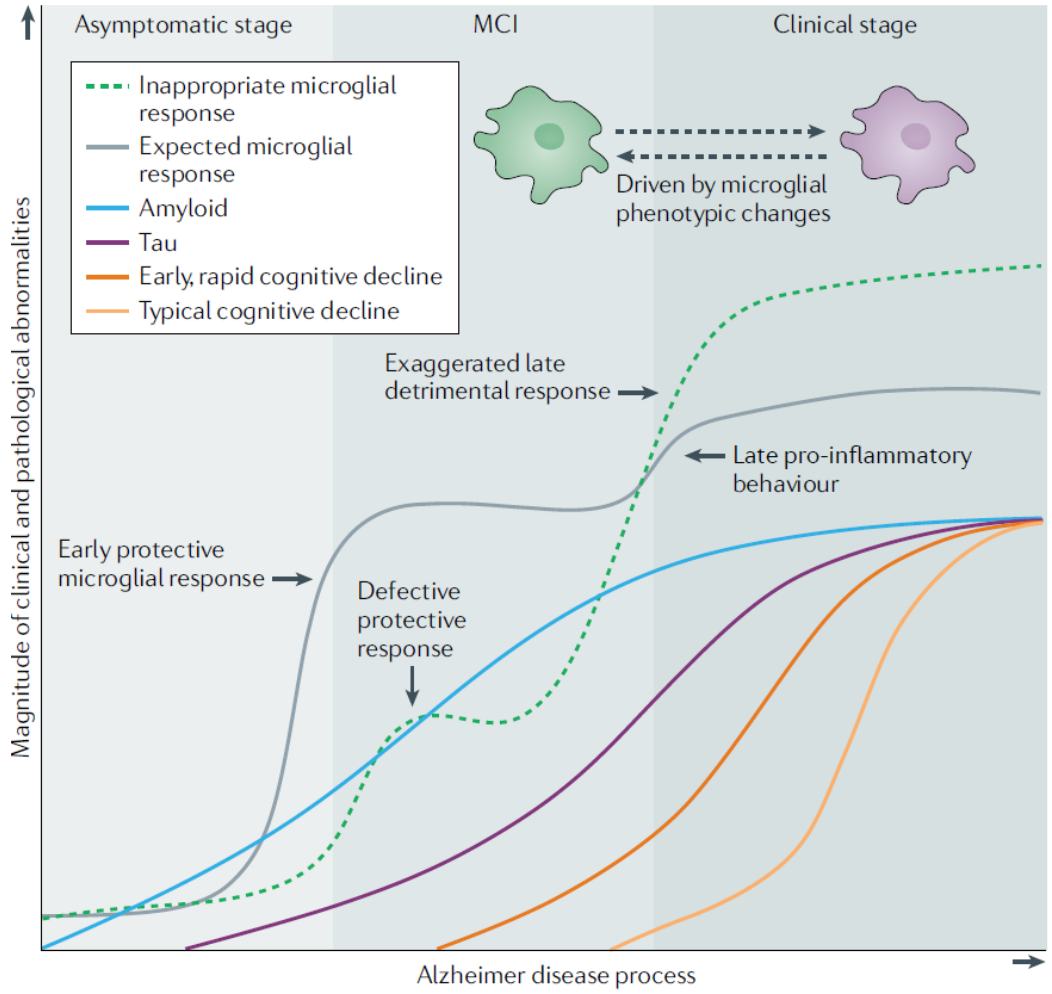
- Neutrophils highly reactive in AD and release multiple cytotoxic molecules
  - Aβ ↑ neutrophil deposition in vessels → BBB dysfunction and neuronal damage
- Monocytes contribute to Aβ clearance
- Dysfunctional monocytes in patients with AD



Dual rol of Microglia in Alzheimer's disease

Early step → Oligomeric or fibrillar Aβ acts as a danger-associated molecular pattern to activate surrounding microglial cells. The microglia release immune mediators, including complement factors, chemokines and cytokines, as well as reactive oxygen species (ROS) and nitric oxide. **Microglia attempt to phagocytose Aβ** to attenuate plaque growth and its neurotoxic effects

Late step → When neurodegenerative processes reach their peak and become irreversible, microglia undergo cell death at sites of Aβ deposition. Activation of different domains of the inflammasome can drive an **inflammatory form of cell death**, namely pyroptosis, which is associated with the release of apoptosis-associated speck-like protein containing a CARD (ASC) specks that can promote further the whole brain parenchyma inflammation.



Leng & Edison. *Nat Rev Neurol.* 2021;17(3):157-172

The rol of the Immune System in Alzheimer's disease

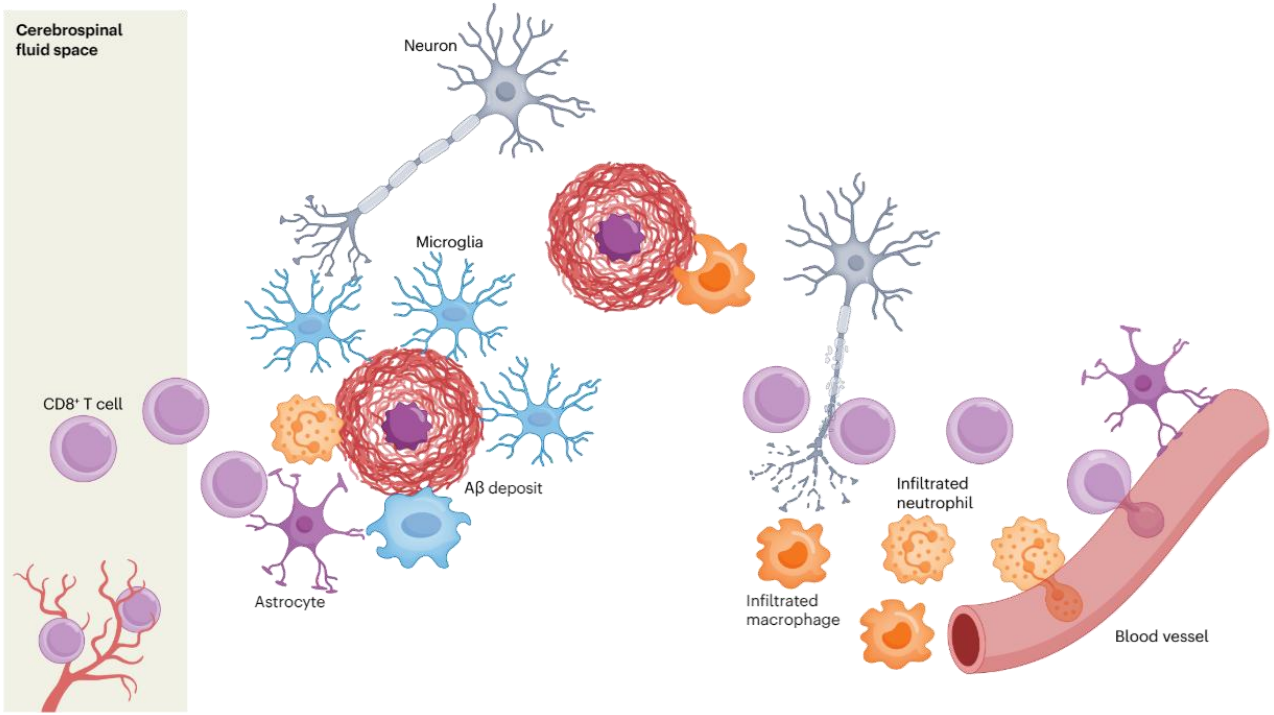
Among the **innate immune cells, microglia** are the primary players in neuroinflammation.

Recent genome-wide association studies have shown that most **polymorphisms recently found in AD** patients are **involved in the immune response and microglial function**.

Contribution of peripheral immune cells to Alzheimer disease: **Neutrophils** and **CD8+ T cells** infiltrate the brain parenchyma. T cells can proliferate and promote neuronal damage through:

1) the **release of inflammatory/cytotoxic molecules**
2) restriction and **block axonal transport**.

Key immune mediators and receptors that have been linked to neuroinflammation in the context of AD: Damage-associated molecular patterns, TREM2 and APOE, complement factors, cytokines, cyclooxygenases and prostanoids, iNOS and NO.



Heneka et al. *Nat Rev Immunol*. 2024; Online ahead of print.

The role of peripheral inflammation in Alzheimer's disease

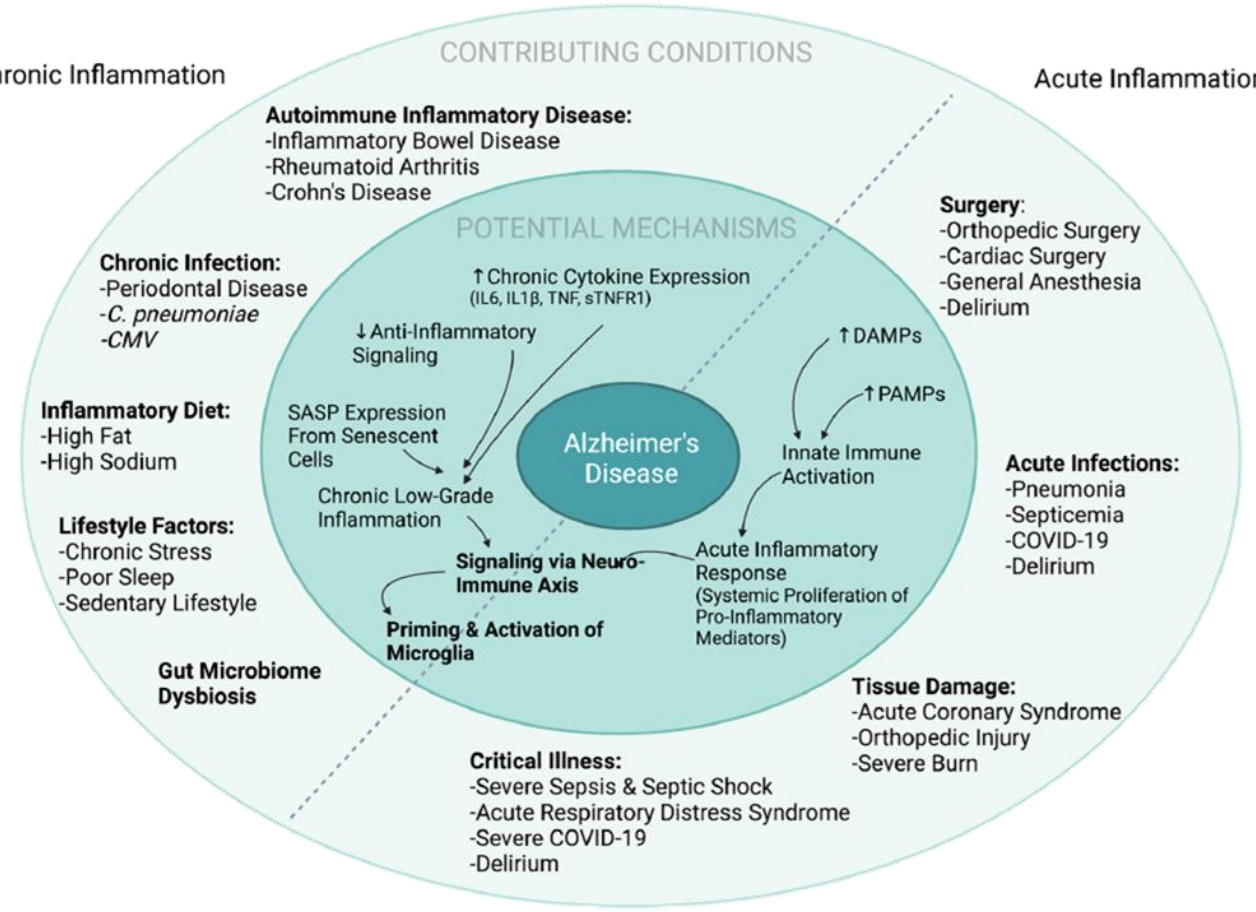
Peripheral inflammation is an **age-related phenomenon** that has been identified as a **risk factor for AD.**

Recent meta-analyses found that **inflammatory proteins** such as IL-1β, IL-6, IL-18, sTNFR1 or IFN-γ, are **elevated in the blood of AD patients**, compared to that of neurologically normal individuals.

Important role of the BBB and other components of the neuro-immune axis in AD.

Acute inflammatory insults and AD: acute infection, critical illness, and surgery (important consideration: biological heterogeneity of acute inflammatory insults)

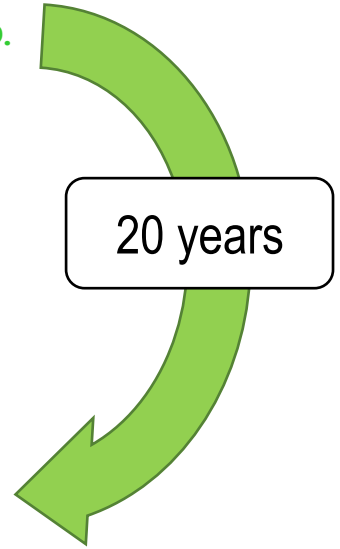
Peripheral inflammatory events may be **targeted pharmacologically** to prevent or reduce risk of AD



Walker et al. *Mol Neurodegener*. 2023;18(1):37

The evolution of Alzheimer's disease knowledge & treatment

1906: Alois Alzheimer first described an unusual set of symptoms, including behavioral disturbances and memory loss, in a relatively young patient
1975; Early brain imaging detects atrophy and reduced perfusión in AD
1976: Cholinergic hypothesis of AD
1982: report from Eikelenboom and Stam of complement components decorating Aβ plaques
1985: Tau identified as main component of tangles
1986: Tau is abnormally phosphorylated in AD
1991: First mutation found to causa autosomal dominant AD (APP)
1991: Amyloid hypothesis
1993: AD signature found in CSF (reduced AB42 and increased pTau)
1993: ApoE risk factor for AD
1995: Oligomer detected as bioactive AB species
1995: Tacrine is the first drug approved for AD.
1996: Donepezil approved
1997: Rivastigmine approved
1999: First AB active immunotherapy in mice
2000: Galantamine approved
2002: Memantine approved for AD.
2002: "Formal" hypothesis was published describing the role of Inflammation in AD.
2002: First results of AB vaccine in humans; Fails in Ph due to encephalitis.
2006: FIH Solanezumab
2007: First Amyloid PET reports
2009: Solanezumab enters Ph 3
2010: Gantenerumab enters Ph 2/3
2010: Prevalence of plaques precedes 15 years AD Dementia
2010: First Ph 1 with Lecanemab (BAN2401)
2011: First Ph 1 with Aducanumab (BIIB037)
2012: First FDA PET tracer approved: Florbetapir
2012: Bapineuzumab fails in Ph 3
2012: Ponezumab fails in Ph 2
2013: Tau PET tracer enters trials.
2013: Inflamasome implicated in AD
2020: Primary results of the AMBAR Study
2021: Aducanumab approved for AD under accelerated approval pathway
2023: Lecanemab approved by traditional approval for AD.
2023: PE-Alb included in the ASFA Guidelines
2024: Donanemab approved by traditional approval for AD



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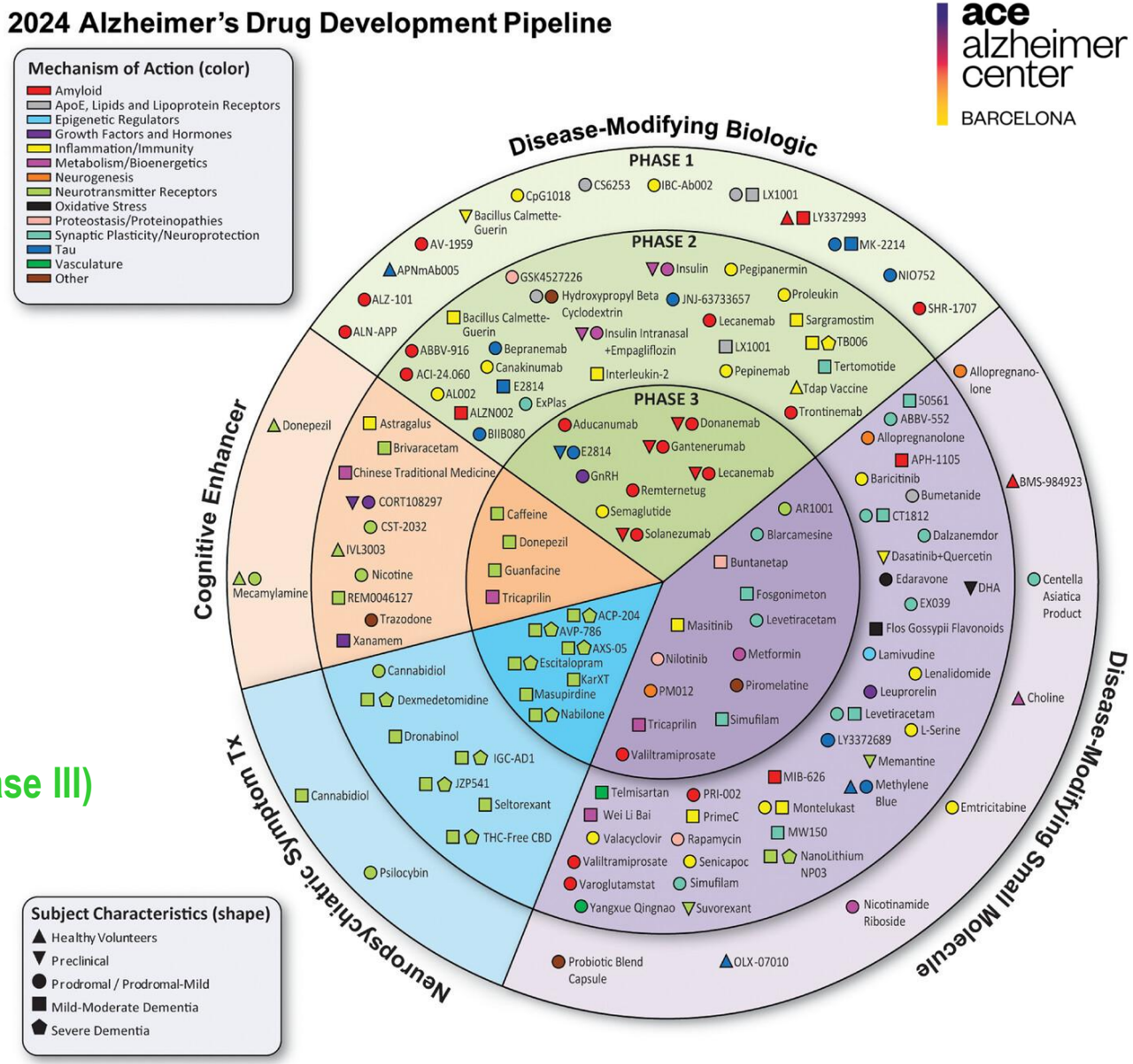
Current Clinical Trials

The **Alzheimer's disease drug development** pipeline target a wide array of targets; **the most common processes** targeted include neurotransmitter receptors, **inflammation**, amyloid, and synaptic plasticity.

Top five agents in the pipeline along Common Alzheimer's Disease Research Ontology (CADRO) classification:

1º) 28 drugs (22%) target neurotransmitter receptors;
2º) 25 agents (20%) target neuroinflammation (19 Phase II / 2 Phase III)
3º) 23 therapies (18%) target amyloid beta protein (Aβ) processes
4º) 15 drugs (12%) address synaptic plasticity/ neuroprotection
5º) 11 agents (9%) target tau-related processes



Cummings et al. *Alzheimers Dement (N Y).* 2024;10(2):e12465

Current Clinical Trials – Phase III

Received: 29 July 2024 | Revised: 10 September 2024 | Accepted: 12 September 2024

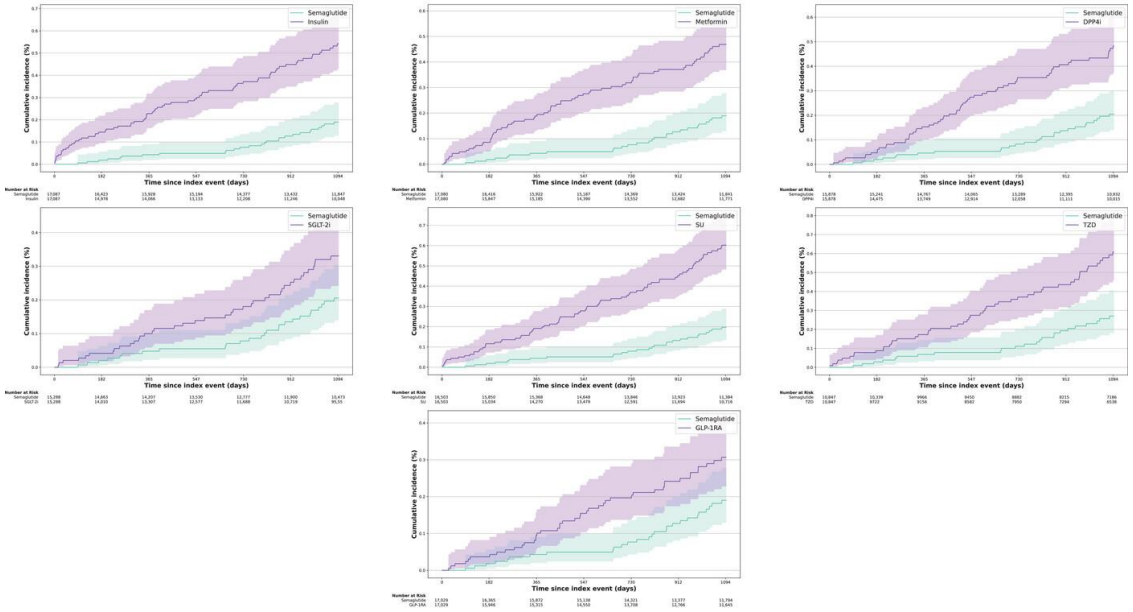
DOI: 10.1002/alz.14313

RESEARCH ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: Target trial emulation using nationwide real-world data in the US

William Wang[1] | QuangQiu Wang[2] | Xin Qi[3] | Mark Gurney[2] | George Perry[2,4] | Nora D. Volkow[5] | Pamela B. Davis[6] | David C. Kaelber[7] | Rong Xu[2]



Neurodegenerative ...

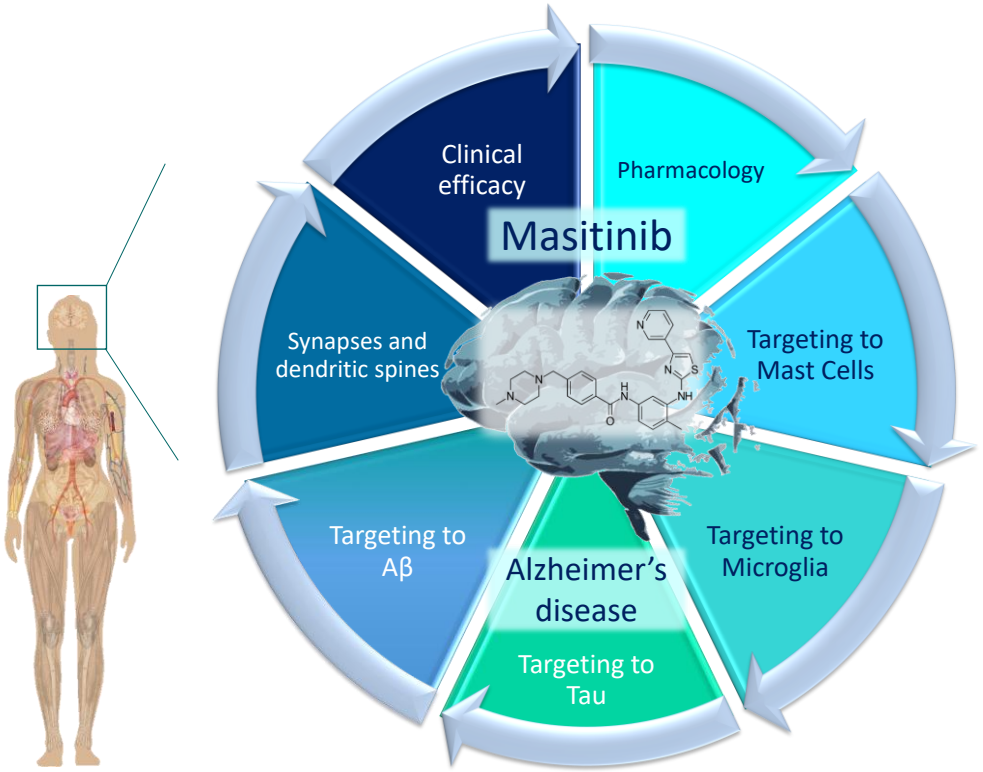
Neurodegenerative Disease Management

Drug Evaluation

Masitinib for the Treatment of Alzheimer's Disease

Miren Ettcheto, Amanda Cano, Elena Sanchez-López, Ester Verdaguer, Carme Auladell & Antoni Camins ...show less

Pages 263-276 | Received 03 May 2021, Accepted 08 Aug 2021, Published online: 20 Aug 2021



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Current Clinical Trials – Phase III

NIH National Library of Medicine
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NCT05891496 Active, not recruiting

A Research Study Looking at the Effect of Semaglutide on the Immune System and Other Biological Processes in People With **Alzheimer's Disease**

NCT04777396 Active, not recruiting

A Research Study Investigating Semaglutide in People With Early **Alzheimer's Disease** (EVOKE)

NCT04777409 Active, not recruiting

A Research Study Investigating Semaglutide in People With Early **Alzheimer's Disease** (EVOKE Plus)

NCT01872598 Completed

Masitinib in Patients With Mild to Moderate **Alzheimer's Disease**

NCT05564169 Not yet recruiting

Masitinib in Patients With Mild to Moderate **Alzheimer's Disease**

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Complejo Asistencial de Zamora. Hospital Provincial de Zamora

Take home messages

- In AD, neuroinflammation occurs even **15 years before** the appearance of the first clinical manifestations.
- **Glial cells are reactive** and **increased in AD** brain as well as associated with Aβ plaques and neurofibrillary tangles
- Neuroinflammation disrupts brain networks **independently of Aβ deposition** .
- **Microglia** are main glial cells involved in neuroinflammation and has a **dual rol** in the AD development.
- **Diverse cell types in the brain parenchyma** contribute to neuroinflammation in the setting of AD.
- Contribution of **peripheral immune cells** and **peripheral inflammation.**
- The **AD drug development** pipeline: neuroinflammation is the **second most common** processes targeted.
- Importance of **pharmacological targeting** of both **neuro and peripheral inflammation** to prevent or reduce risk of AD.

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Thank you!