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Neurodegenerative diseases as a model for other pathologies

Alberto Lleó, MD
Neurology Department
Hospital Sant Pau, Barcelona
November 23, 2023

ciber | NED

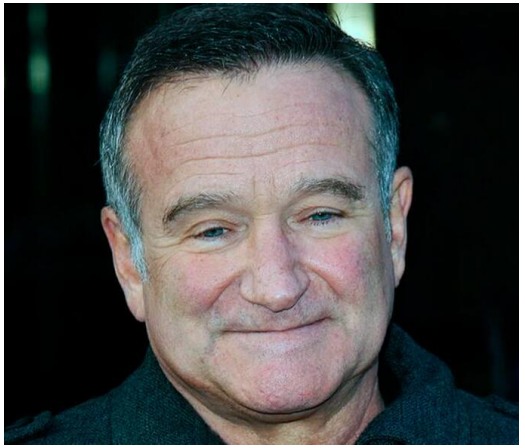
Disclosures

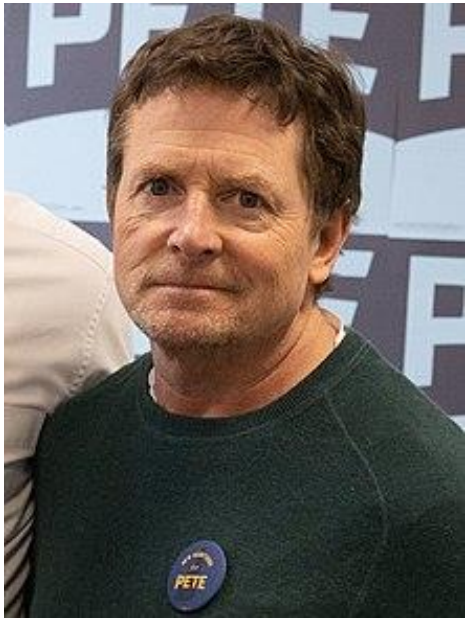
Fees for advisory board meetings from Eisai, Fujirebio-Europe, Grifols, Novartis, Roche Diagnostics, Otsuka Pharmaceutical, Nutricia, NovoNordisk, Zambón and Biogen

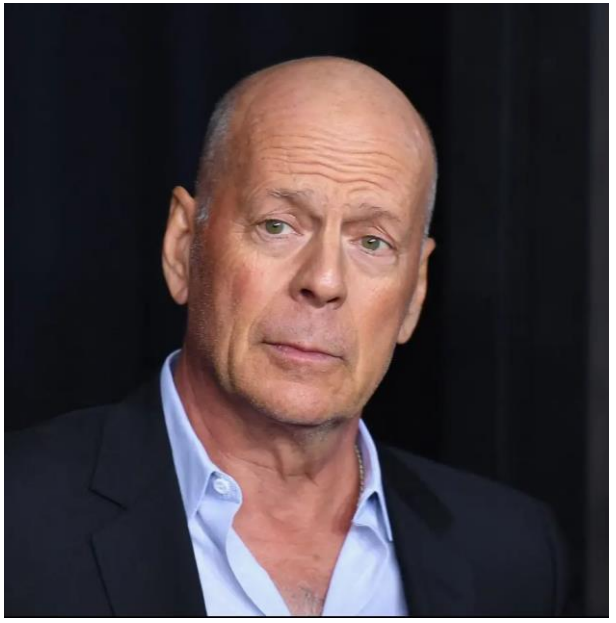
Speaker honoraria from Lilly, Biogen, KRKA, Novartis and Zambon

Co-author of a patent on markers of synaptopathy in neurodegenerative diseases (Nº: EP18382175.0, PCT/EP2019/056535)

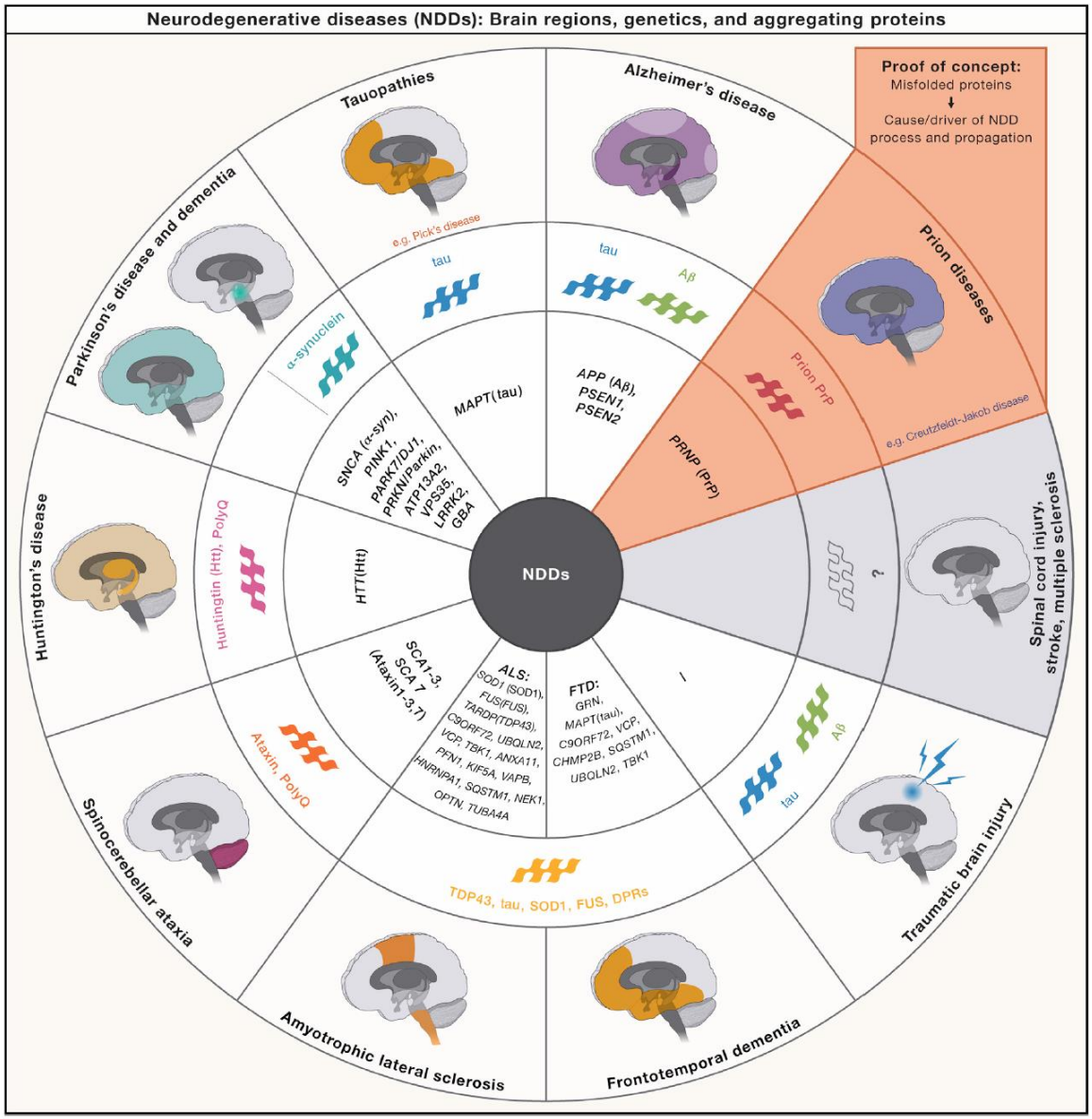
Common diseases with social stigma





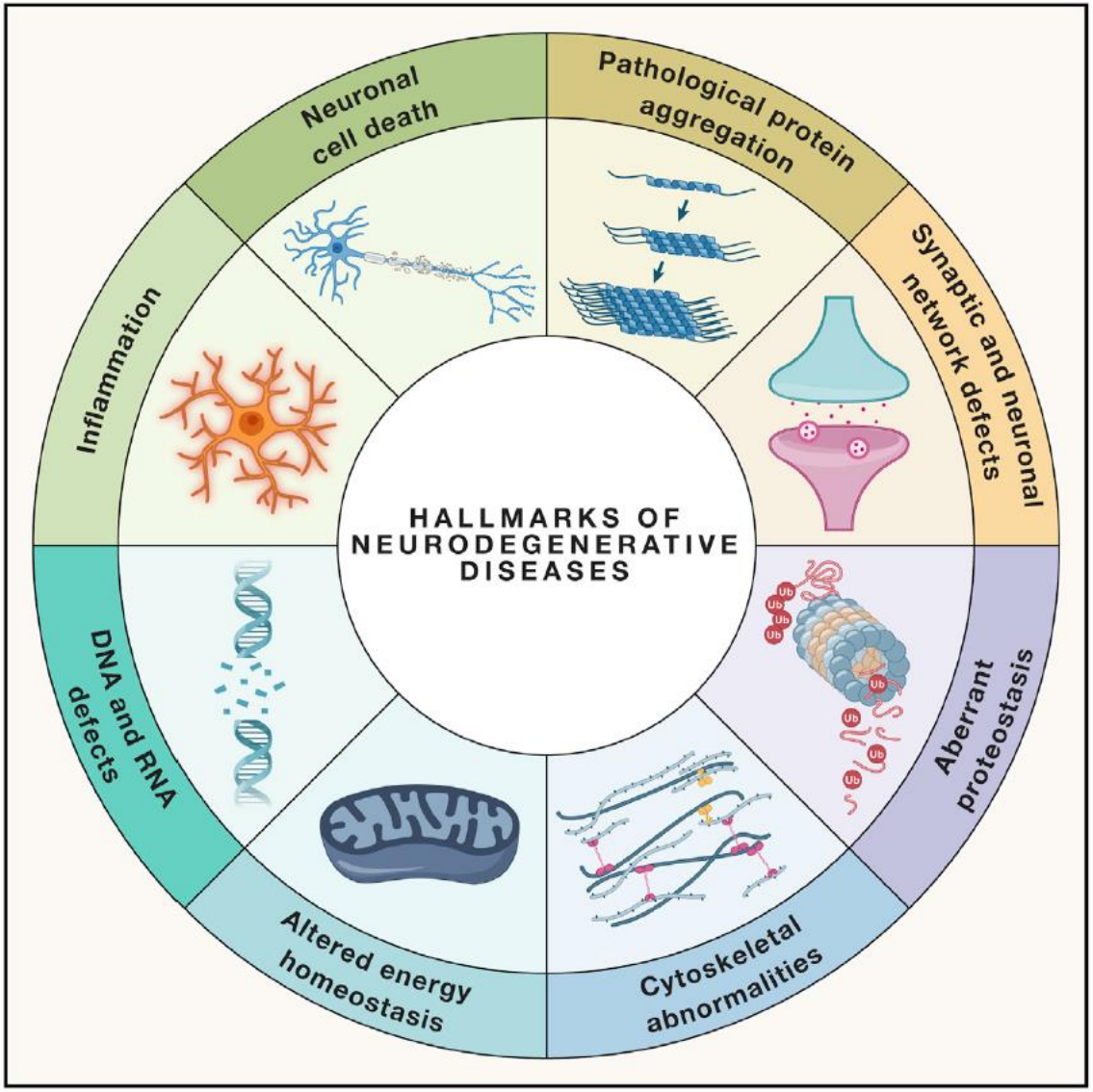


Main neurodegenerative diseases



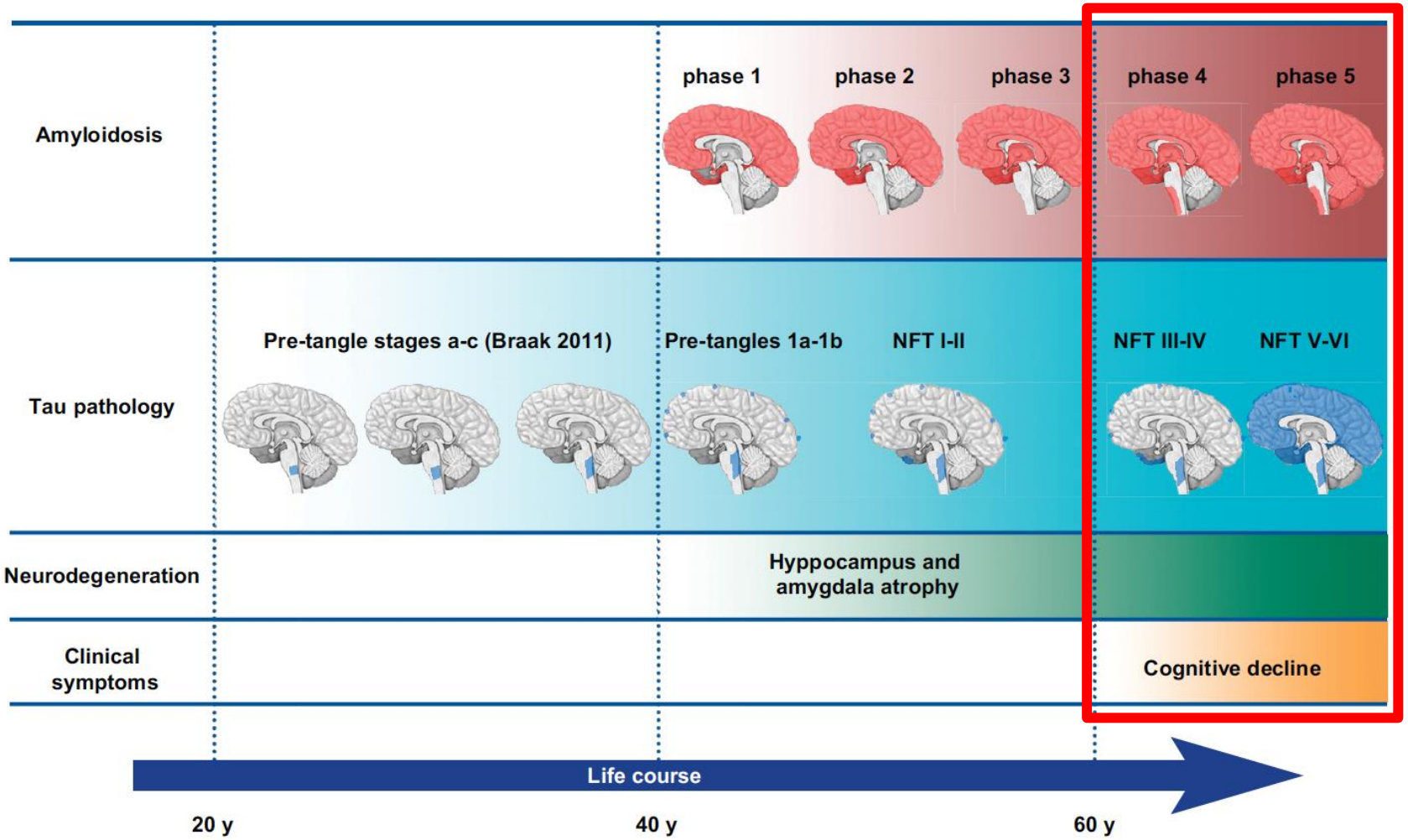
Wilson et al, Cell 2023

Hallmarks of neurodegenerative diseases



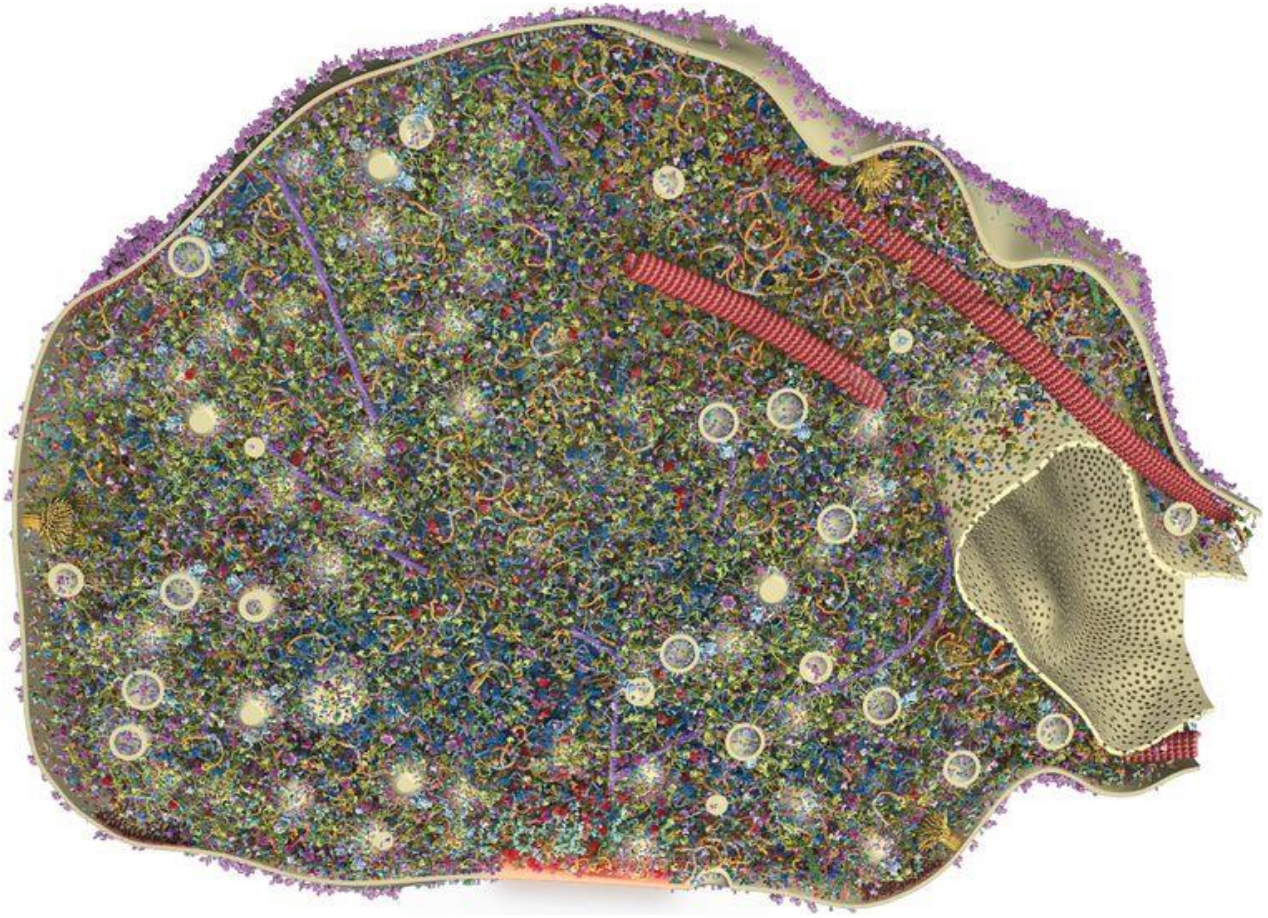
Wilson et al, Cell 2023

Long incubation phase
Alzheimer's disease



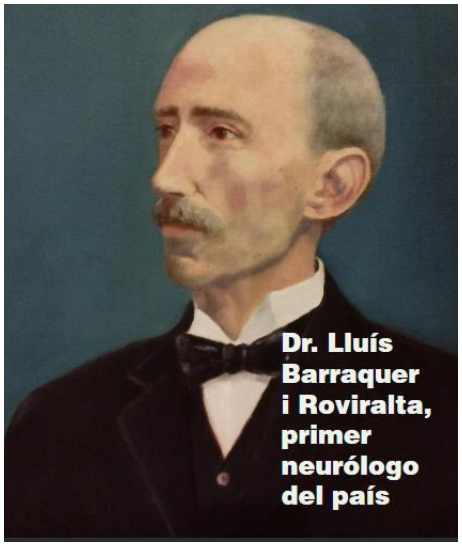
Ferrari & Sorbi, 2021 Physiol Rev 101: 1047–81

Neuronal and synapse loss

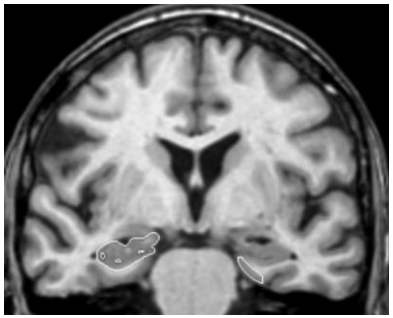


Wilhelm, Science 2014;344:1023-8

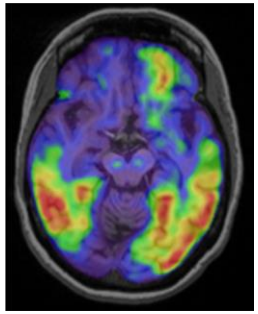
New paradigm in diagnosis

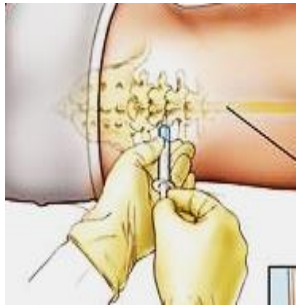


Clinical diagnosis



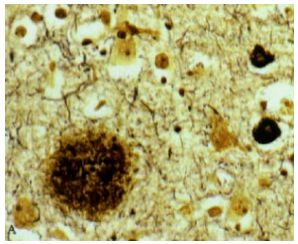
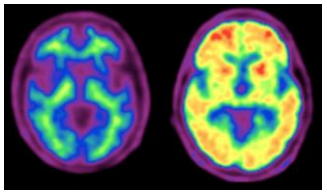
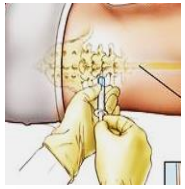
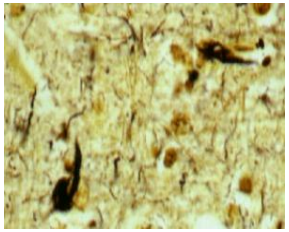
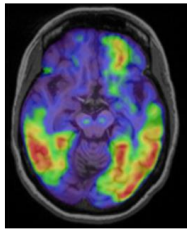
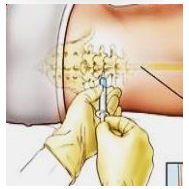
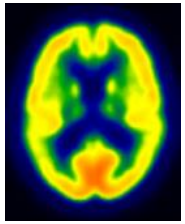
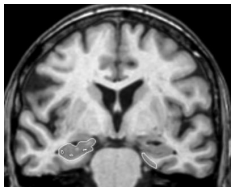
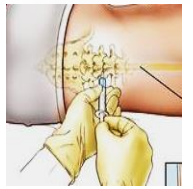
Structural Imaging





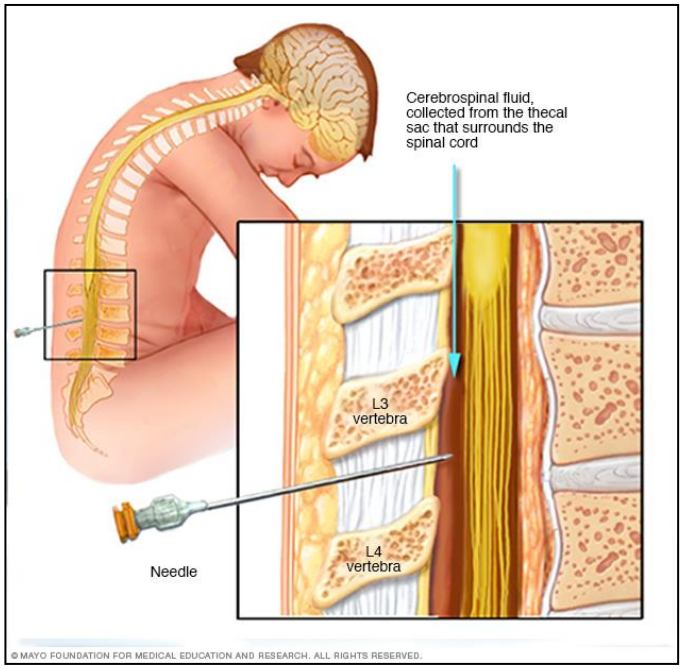
Molecular Imaging
Fluid markers

Main Alzheimer's disease biomarkers
AT (N)

Pathophysiology		Imaging		Fluid
	**A+** **Brain Amyloidosis**	 **Amyloid PET**		 **CSF $A\beta_{42}/A\beta_{40}$ ratio** **Plasma $A\beta_{42}/A\beta_{40}$ ratio**
	**T+** **Tau Pathology**	 **Tau PET**		 **CSF $pTau_{181}$** **Plasma $pTau_{181}$**
	**N+** **Neurodegeneration**	 **FDG PET**	 **Structural MRI**	 **CSF NfL (t-tau)** **Plasma NfL**

Lleo A et al, Nat Rev Neurol 2015

CSF in the diagnosis of Alzheimer's disease



Daniel Alcolesa, M.D.

↓ $A\beta_{42}$
↓ $A\beta_{42/40}$

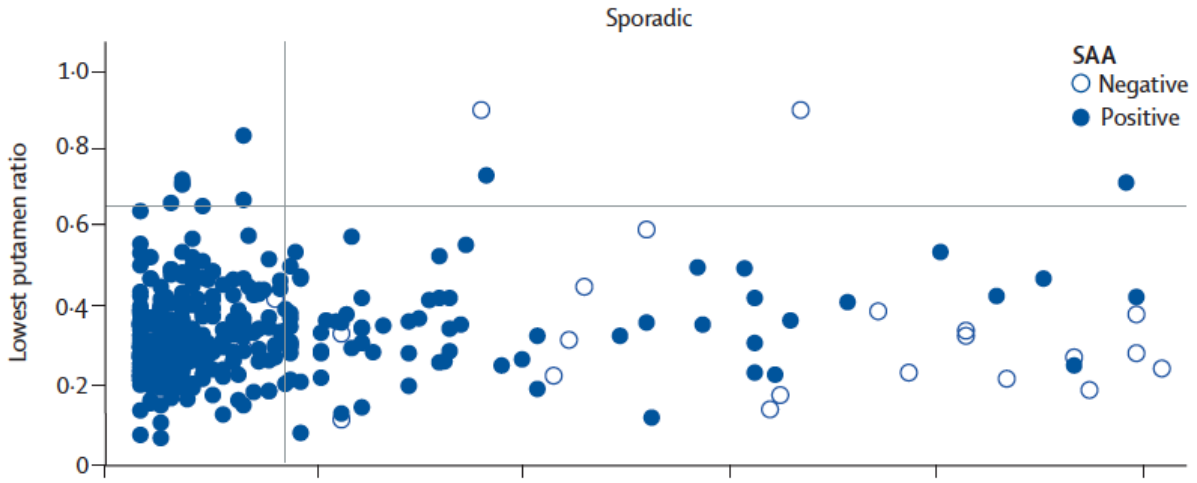
↑ t-tau
↑ p-tau

"AD signature"

Lleo A et al, Nat Rev Neurol 2015;11:41-55
Alcolea D et al, Neurology 2023; 101(4):172-180

CSF markers in the diagnosis of Parkinson disease

α-synuclein Seed Amplification Assay (SAA)



AUC

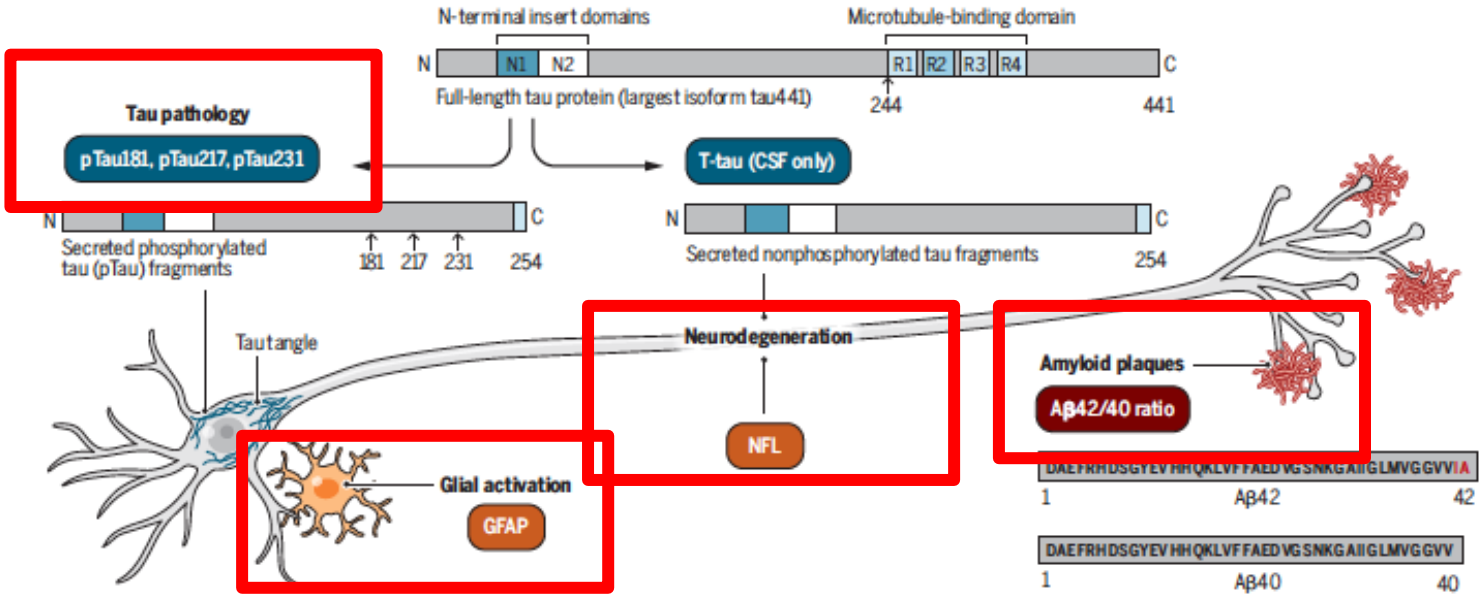
All PD = 87·7% (84·9–90·5)

Sporadic PD = 93·3% (90·8–95·8)

n=1123

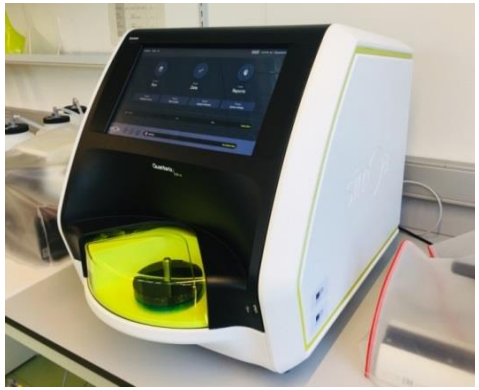
Siderowf et al, Lancet Neurol 2023

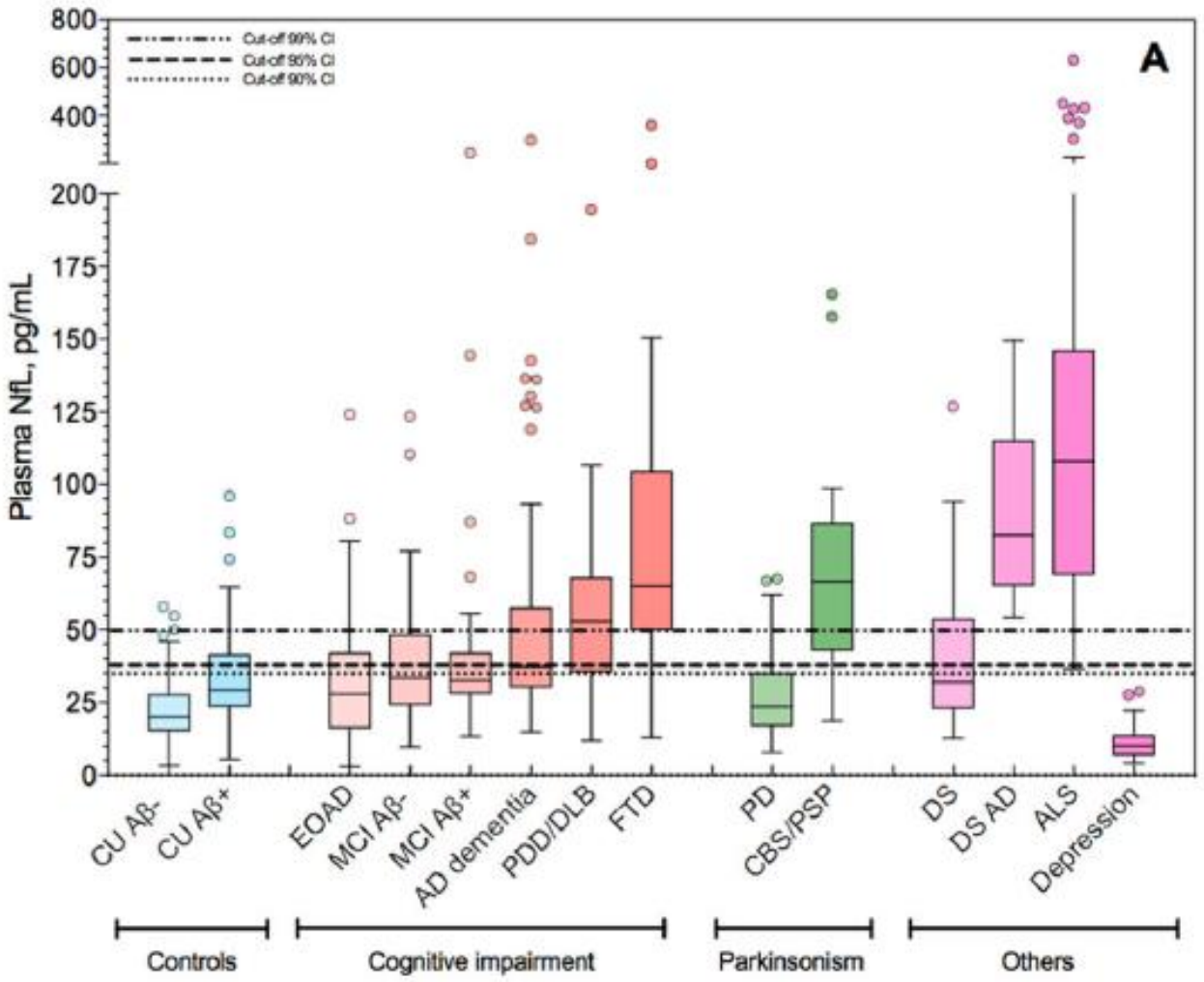
Plasma markers in the diagnosis of Alzheimer's disease



Blennow K. Science 2021;373;626-8
Alcolea D, et al. Neurology 2023;101:172-80

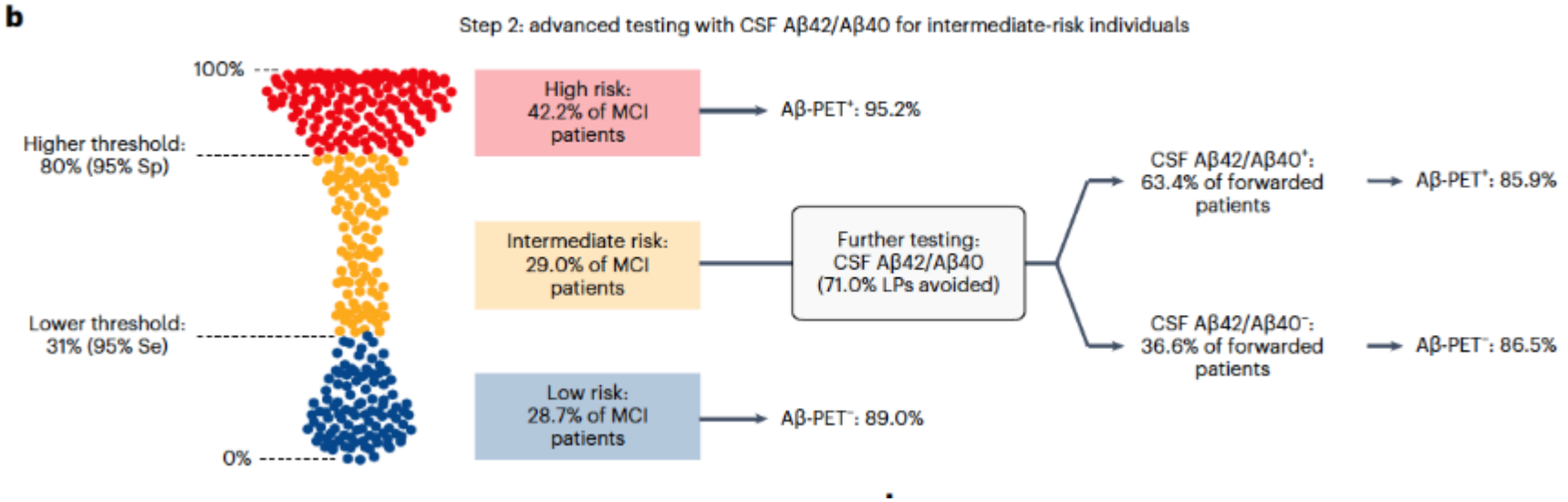
Plasma markers in the diagnosis of Alzheimer's disease





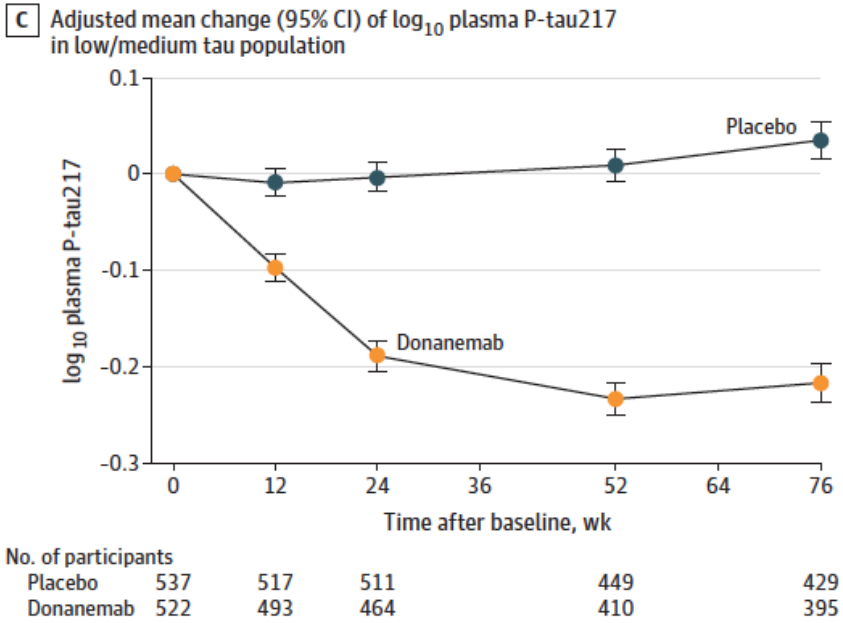
Ashton N, et al. Nat Comm 2021;12 (1):3400

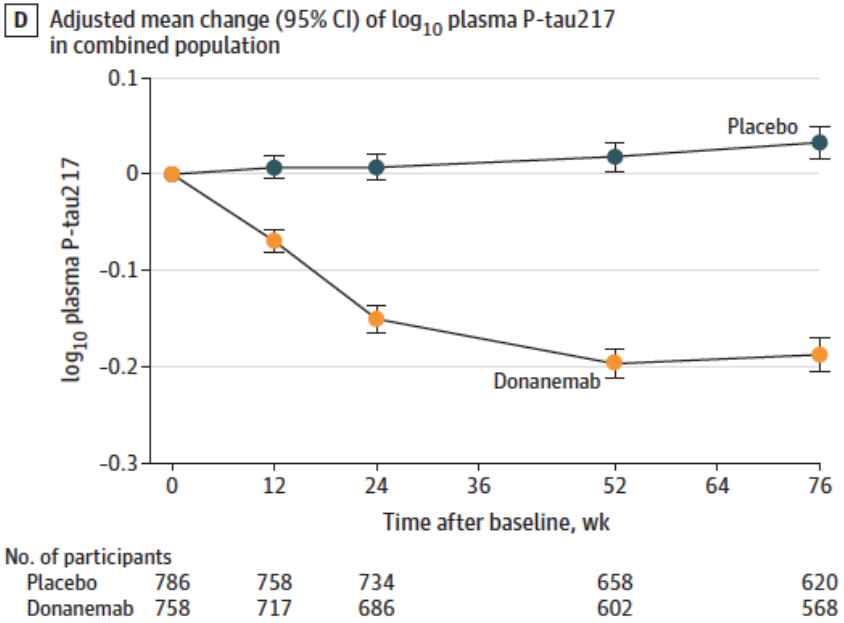
P-tau217 in plasma in the diagnosis of Alzheimer's disease



Hansson O et al. Nat Aging 2023

P-tau217 in plasma in Alzheimer's disease trials





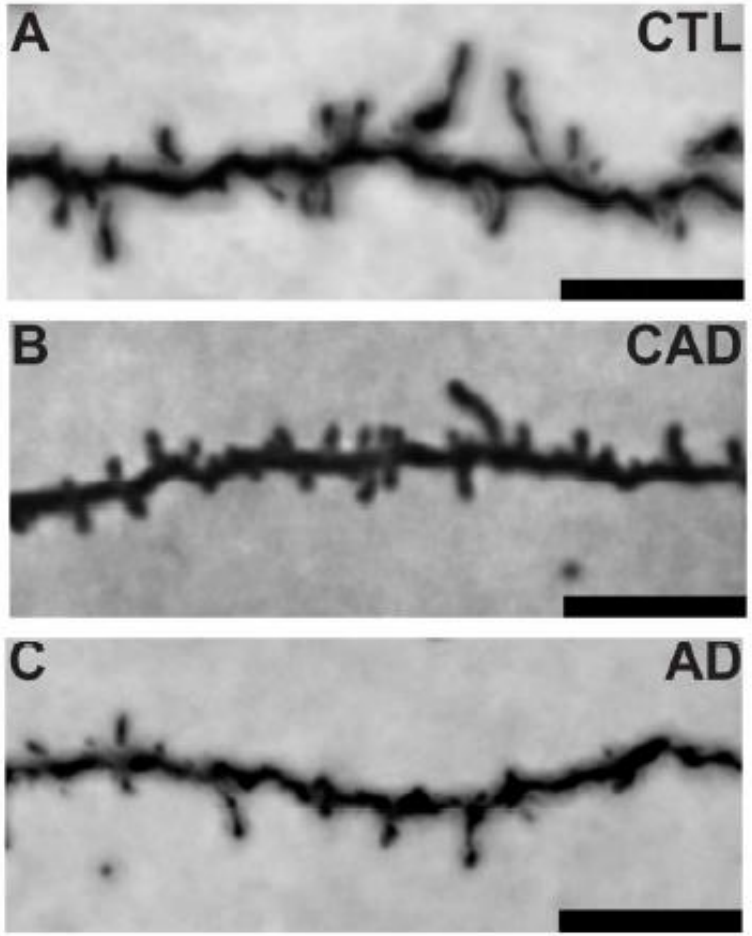
Sims et al. JAMA 2023

Loss of synapses in Alzheimer’s disease

Controls
n=12

Controls with AD pathology
n=8

AD
N=21



Golgi-Cox
BA46
Layer II-III

Boros BD, Ann Neurol 2017

Neuron

CellPress
OPEN ACCESS

COEN Pathfinder

Article

Synaptic oligomeric tau in Alzheimer's disease — A potential culprit in the spread of tau pathology through the brain

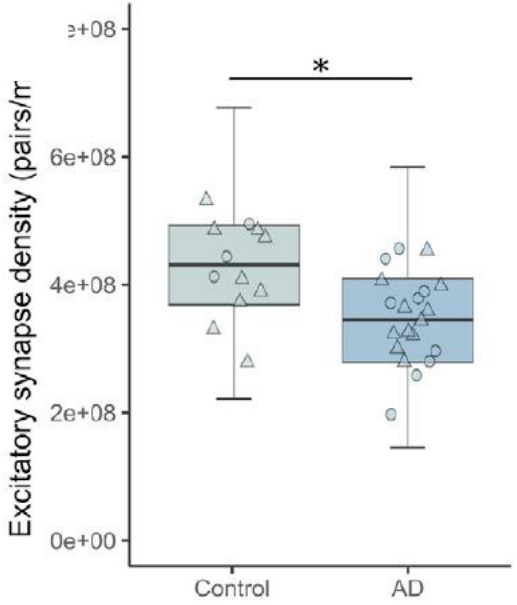
Martí Colom-Cadena,[1,8] Caitlin Davies,[1,8] Sònia Sirisi,[2,3] Ji-Eun Lee,[4] Elizabeth M. Simzer,[1] Makis Tzioras,[1] Marta Querol-Vilaseca,[2,3] Érika Sánchez-Aced,[2,3] Ya Yin Chang,[1] Kristjan Holt,[1] Robert I. McGeachan,[1] Jamie Rose,[1] Jane Tulloch,[1] Lewis Wilkins,[1] Colin Smith,[5] Teodora Andrian,[6] Olivia Belbin,[2,3] Sílvia Pujals,[7] Mathew H. Horrocks,[4] Alberto Lleó,[2,3,*] and Tara L. Spires-Jones[1,9,*]

Sonia Sirisi, PhD

Erika Sánchez, MSC

1.315.583 individual synapses
24 AD cases
19 Controls

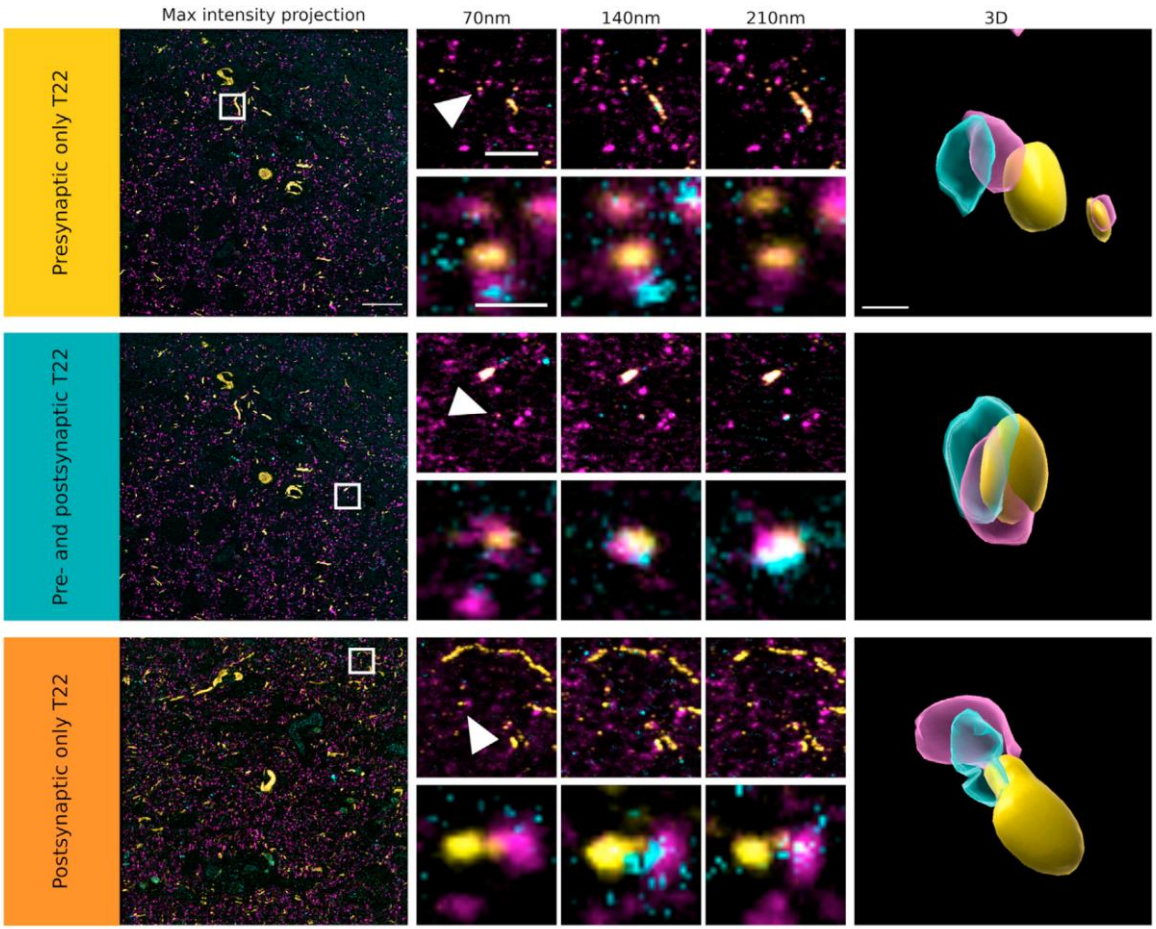
BA 20/21 (Inf Temporal cortex)
BA17 (Visual cortex)

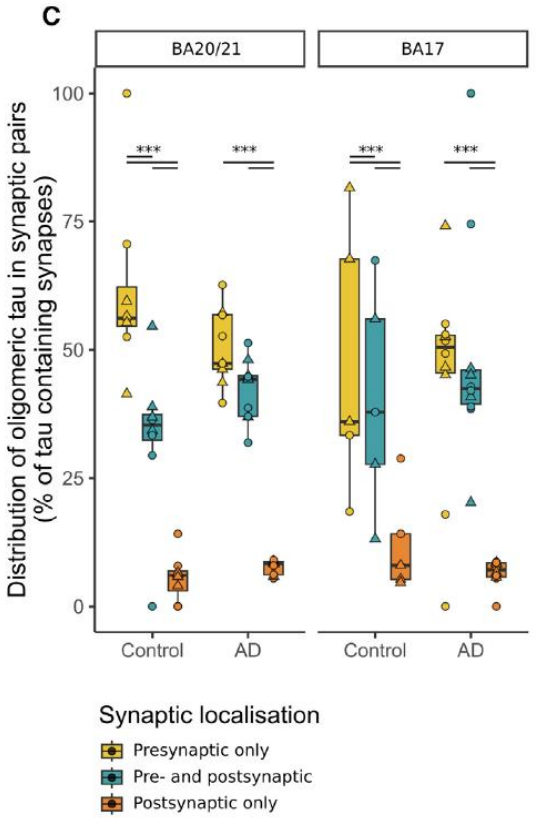


1.2 Fold decrease

Colom-Cadena M et al, Neuron 2023

Synaptic tau localization in Alzheimer's disease

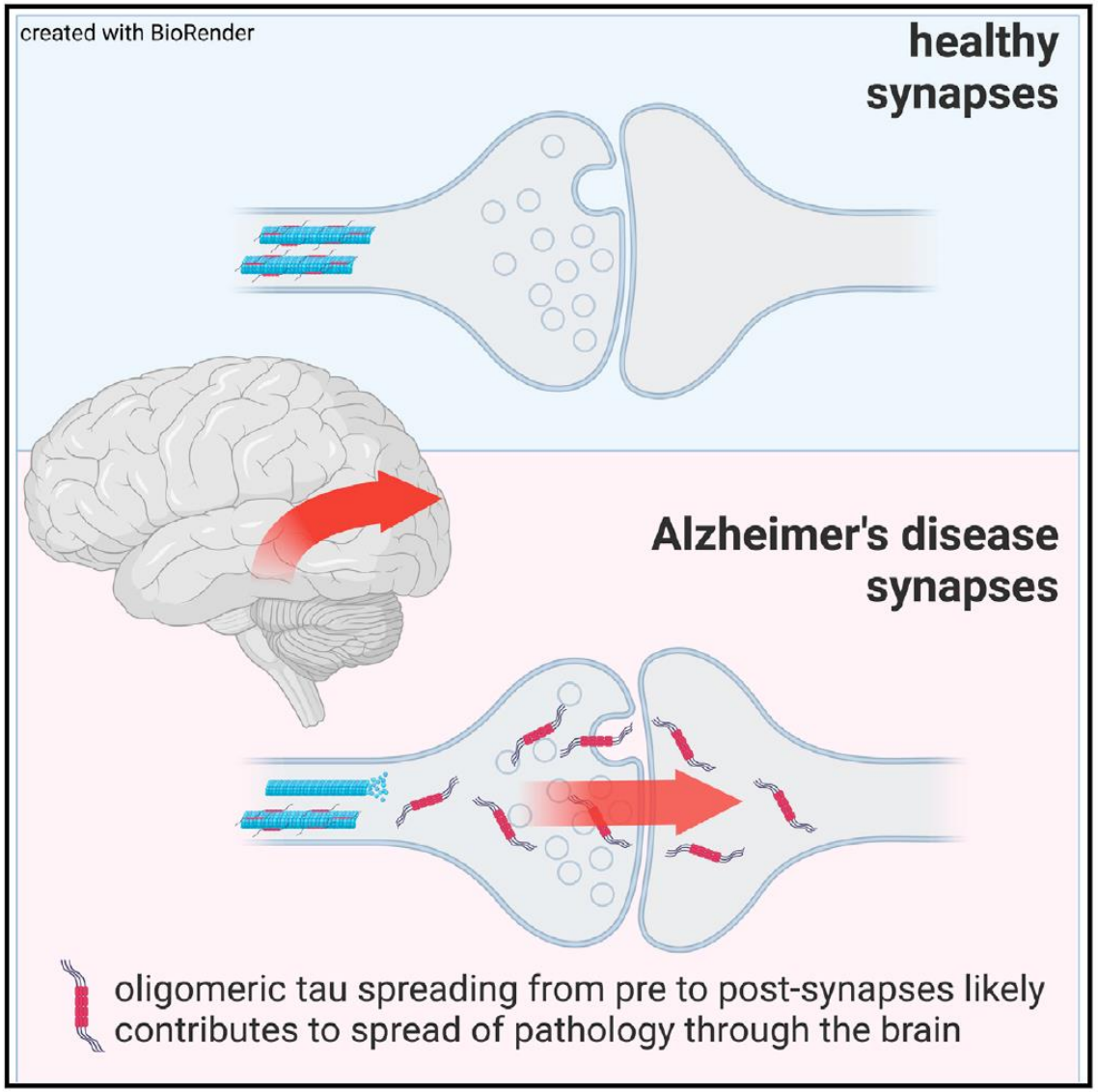




1.315.583 individual synapses

Colom-Cadena M et al, Neuron 2023

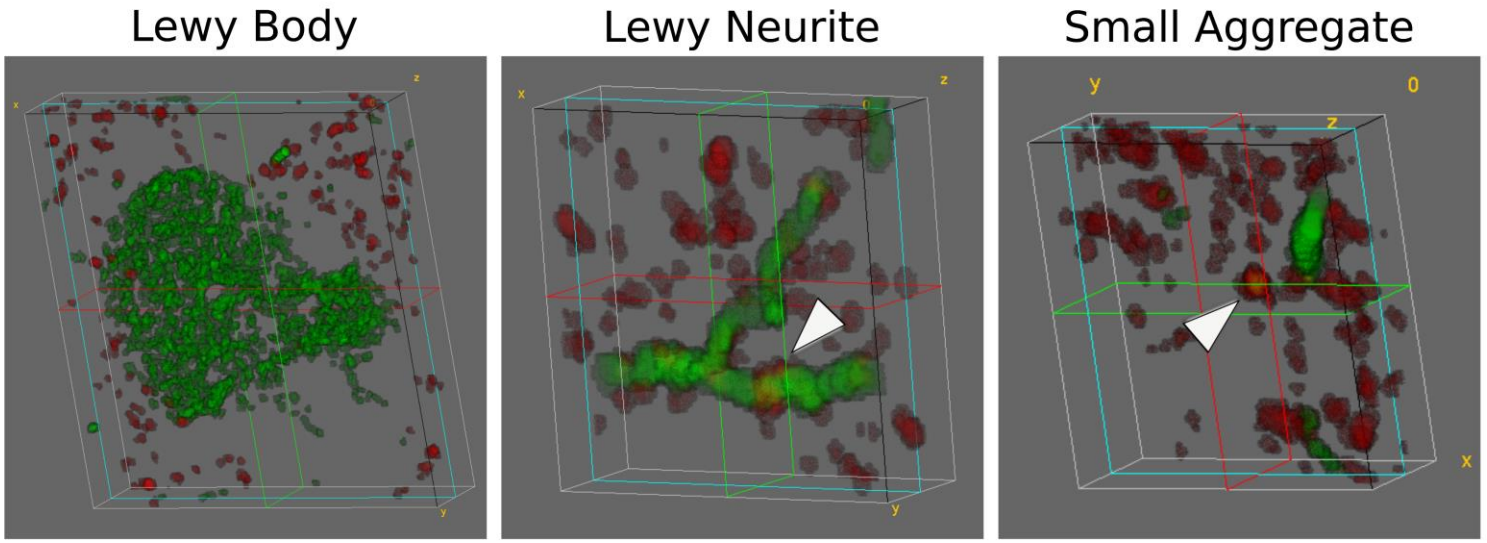
Synaptic oligomeric tau in Alzheimer’s disease



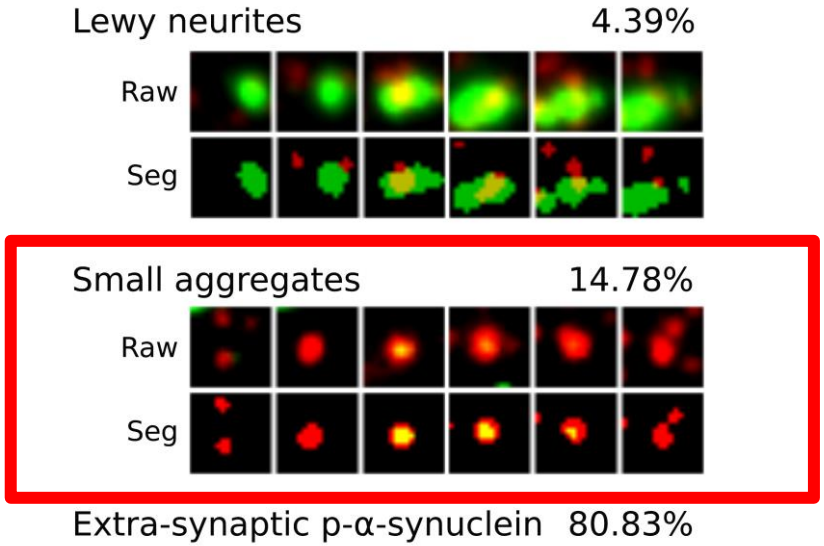
1.315.583 individual synapses

Colom-Cadena M et al, Neuron 2023

P-α-synuclein is found at pre-synaptic terminals in dementia with Lewy bodies



Synaptophysin
P-α-synuclein



Colom-Cadena et al, Brain 2017

Emerging therapies: Antisense oligonucleotides in Spinal Muscular Atrophy

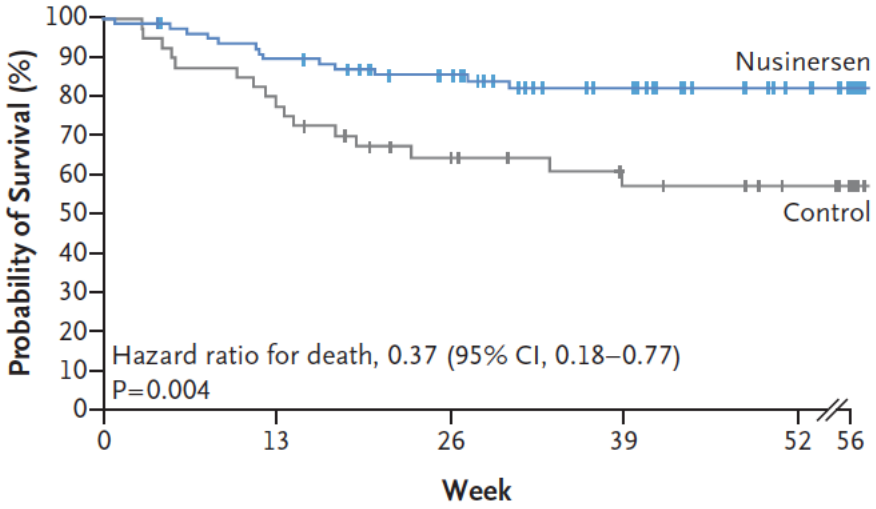
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, J. Montes, A.M. Glanzman, K. Bishop, Z.J. Zhong, S. Gheuens, C.F. Bennett, E. Schneider, W. Farwell, and D.C. De Vivo, for the ENDEAR Study Group*

B **Overall Survival**

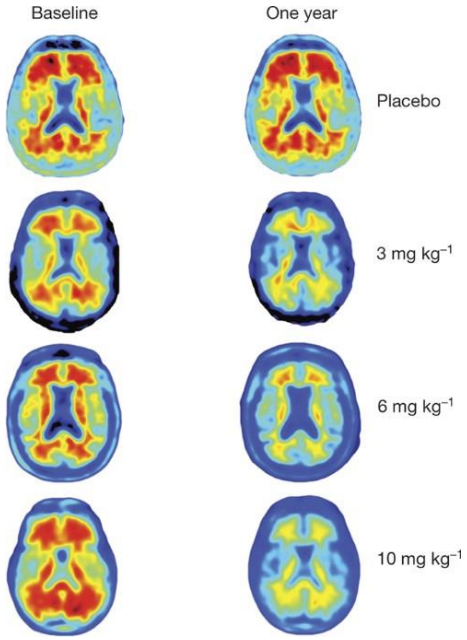


No. at Risk

Nusinersen	80	71	58	41	28	23
Control	41	33	23	17	12	10

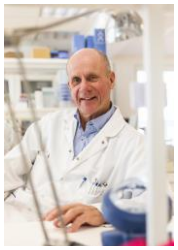
A new era in Alzheimer's disease

Aducanumab

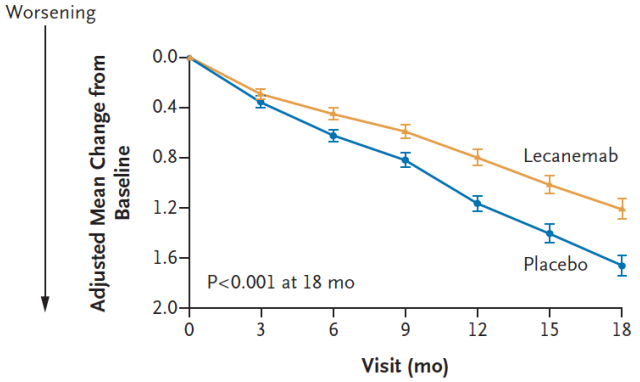


Sevigny J et al. Nature 2016

Lecanemab



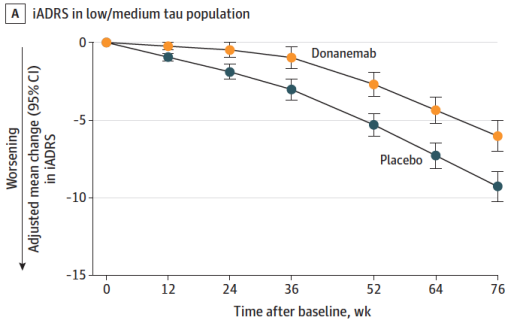
Lars Lannfelt
mAb158



No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

Van Dick et al. N Eng J Med 2022

Donanemab



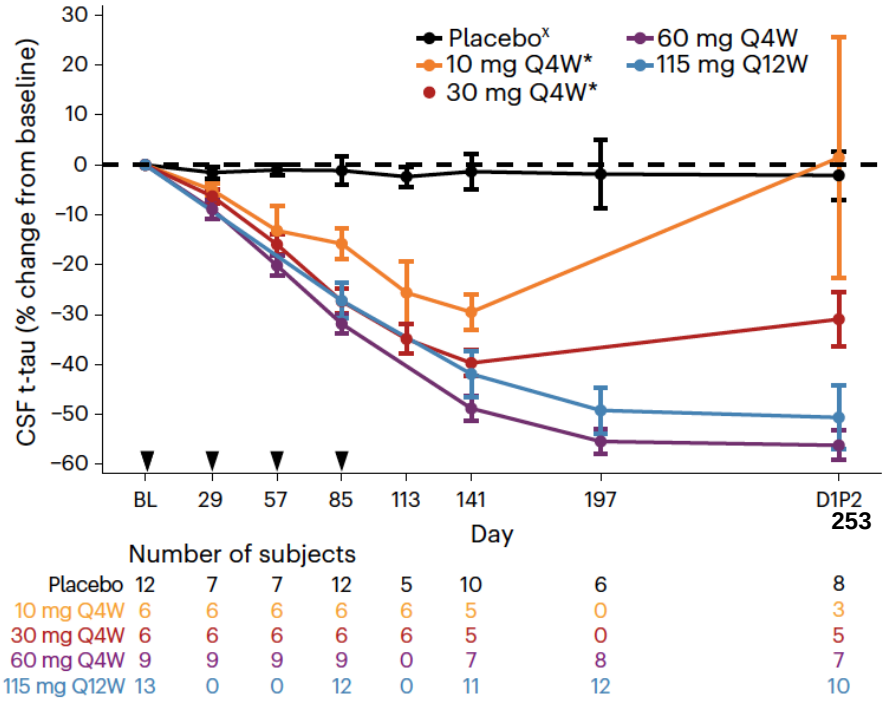
No. of participants							
Placebo	560	549	526	506	474	447	444
Donanemab	533	517	487	459	441	406	418

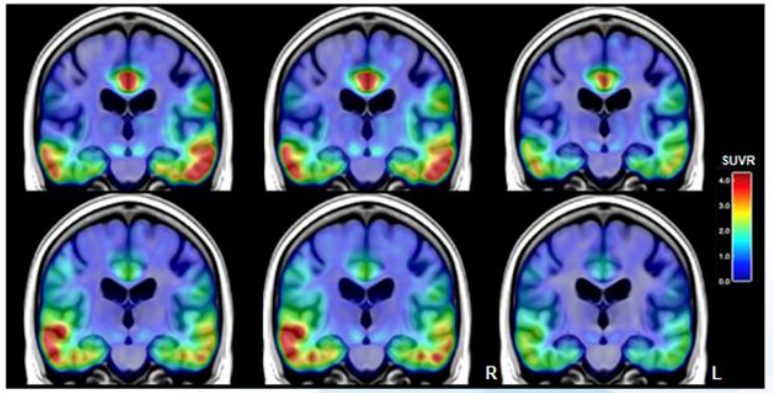
Sims et al. JAMA 2023

BIIB080: Antisense-oligonucleotide in Alzheimer's disease

Article https://doi.org/10.1038/s41591-023-02326-3

Tau-targeting antisense oligonucleotide $MAPT_{Rx}$ in mild Alzheimer's disease: a phase 1b, randomized, placebo-controlled trial





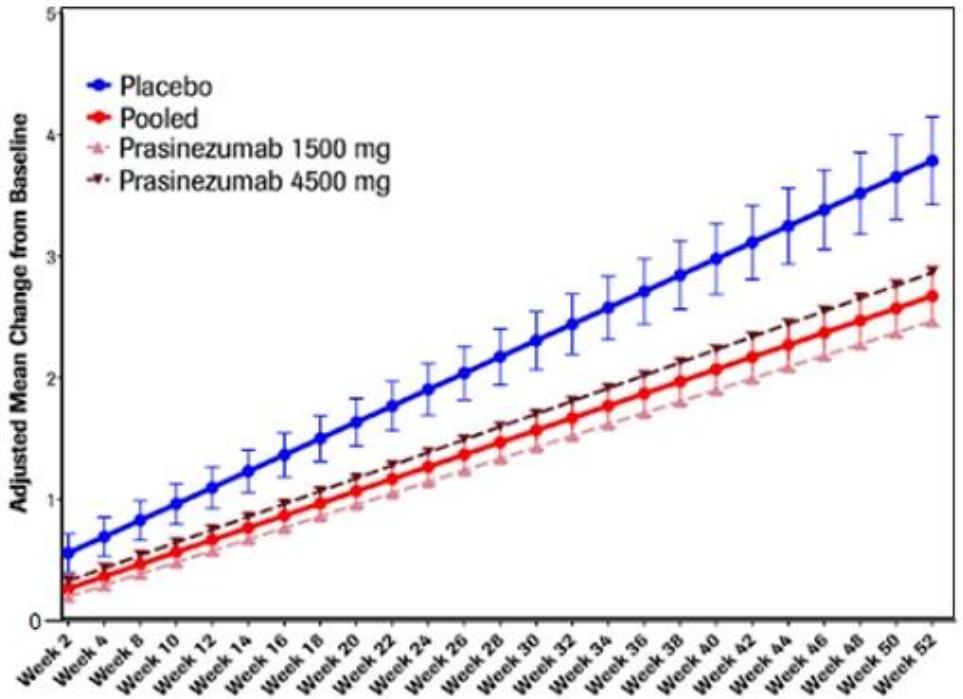
Placebo **Placebo** **Tau ASO**

Mummery CJ et al, Nat Med 2023

Emerging data of efficacy of immunotherapy in Parkinson disease

Prasinezumab (α-synuclein monoclonal antibody)

Digital PASADENA Motor scores



Pooled: –0.030, 80% CI=(–0.050, –0.010); **–25.0%**
Prasinezumab 1500 mg: –0.040, 80% CI=(–0.063, –0.017); **–30.3%**
Prasinezumab 4500 mg: –0.029, 80% CI= (–0.052, –0.006); **–21.5%**

Alzforum, Accessed Nov 18 2023

Conclusions

- Neurodegenerative diseases have entered a new era
- Novel fluid diagnostic biomarkers (CSF and plasma) have been instrumental
- Synaptic pathology is an early and key event
- Immunotherapy will be mainstay
- Antisense oligonucleotide and genetic therapy for genetic cases
- Many other drug targets in the horizon

Thank you!
Gracias!

alleo@santpau.es

Collaborators:

- Raquel Sánchez, Iban Aldecoa, Laura Molina. Hospital Clínic. Barcelona
- Tara Spires-Jones. Univ. Edimburg.
- Bradley Hyman. MGH. Boston.
- Silvia Pujals. IQAC. Barcelona.