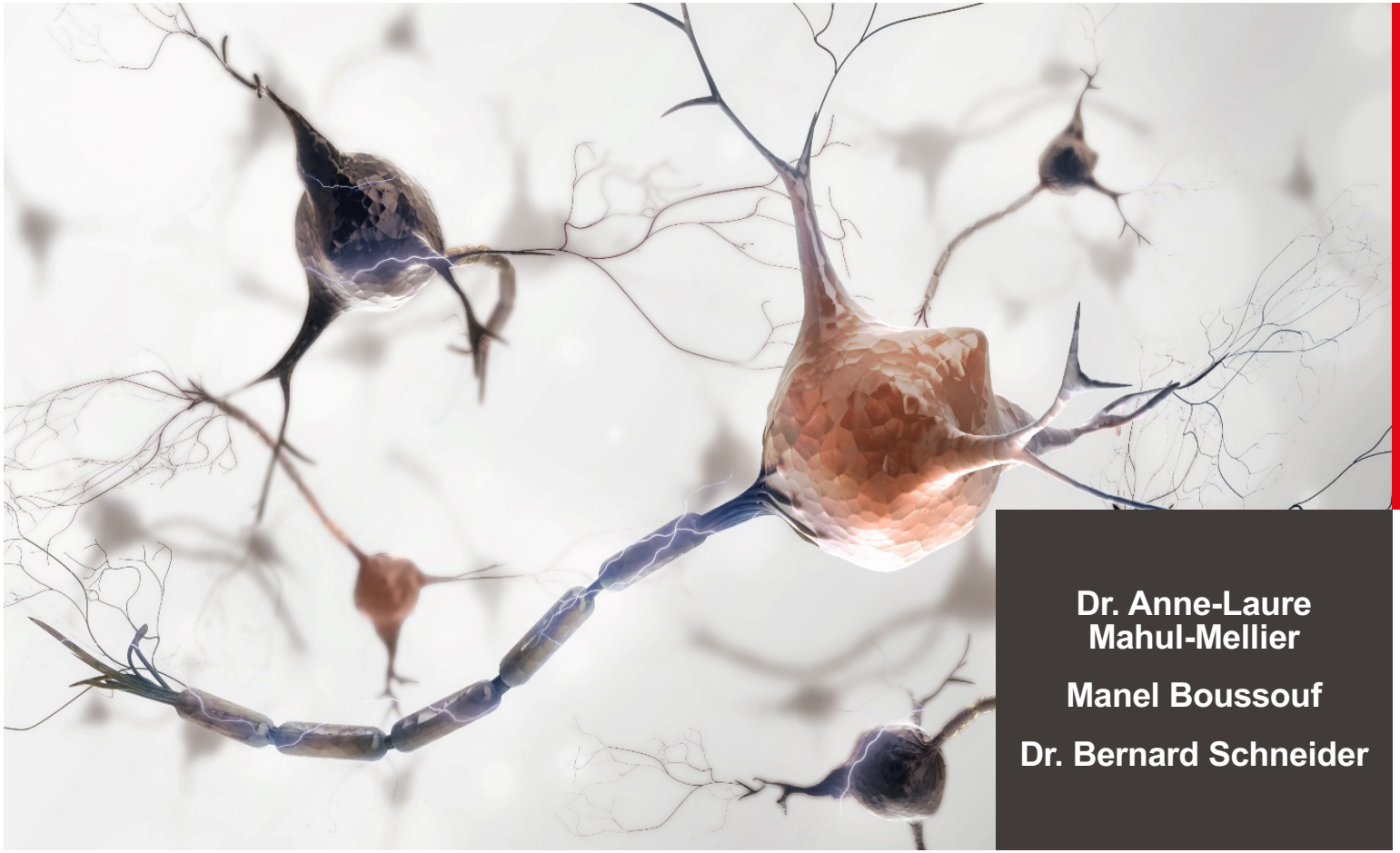
EPFL



Welcome To BIO480 NDDs lectures

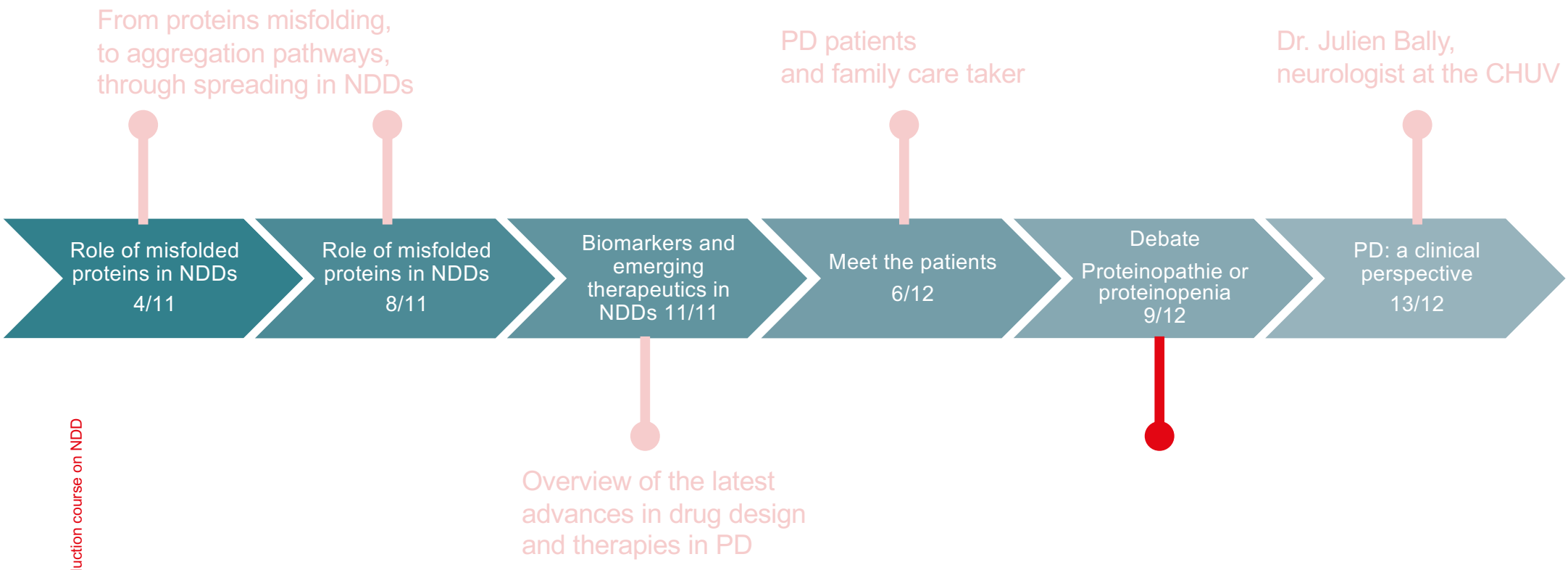
2024-2025

Dr. Anne-Laure Mahul-Mellier

Manel Boussouf

Dr. Bernard Schneider

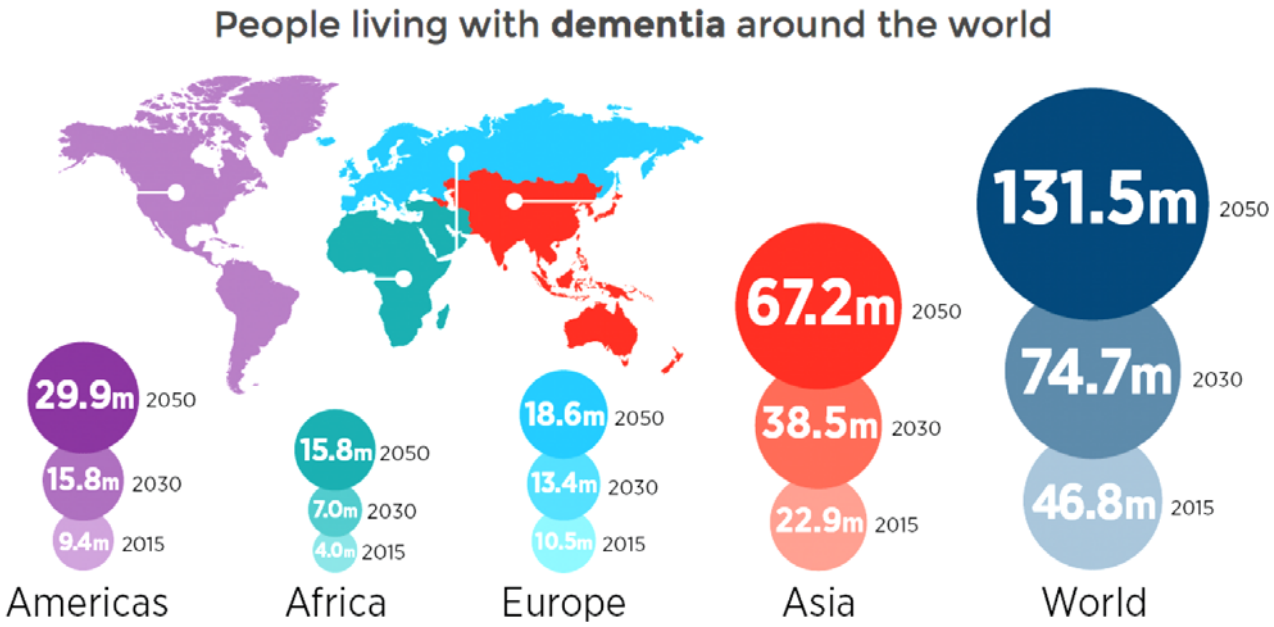
Course organization:

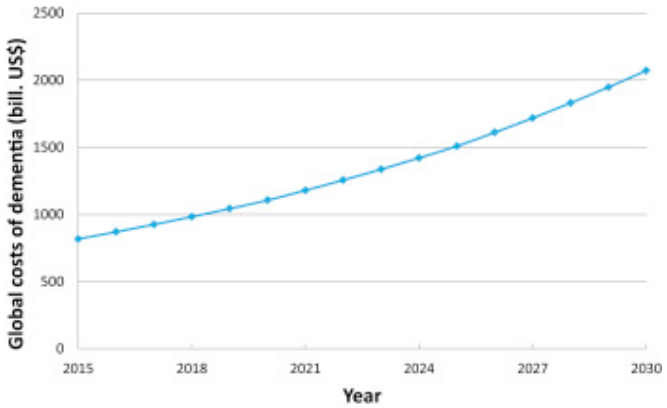


Amyloid aggregation and immunotherapy:

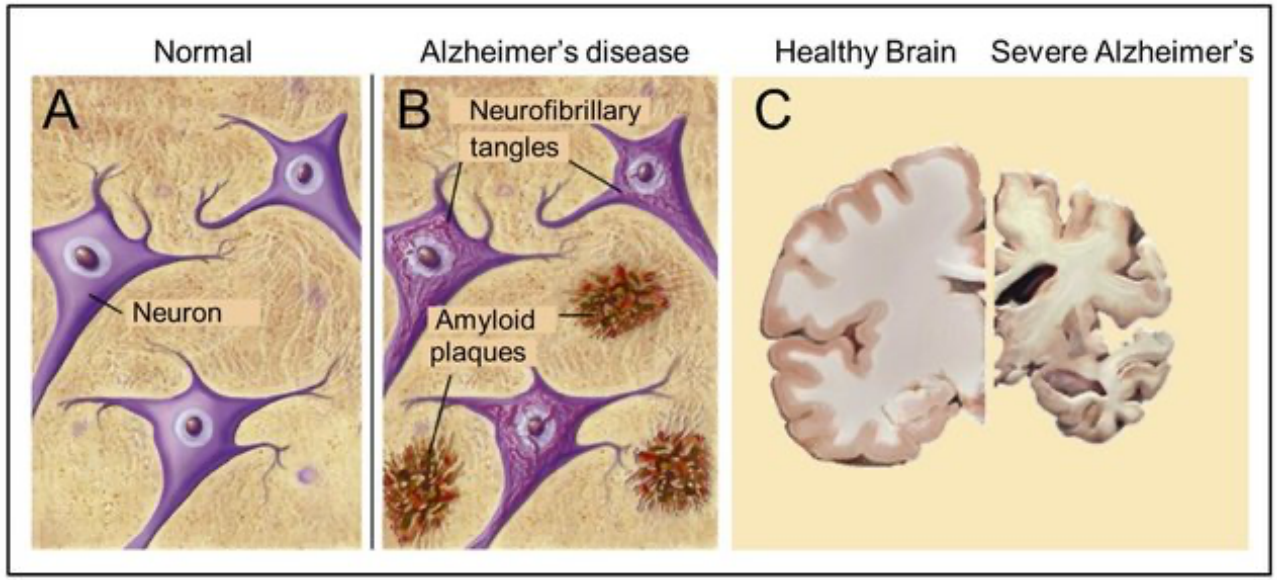
Progress, challenges, and controversies in Alzheimer's treatment

The economic burden of AD:
Public health implications and financial impact

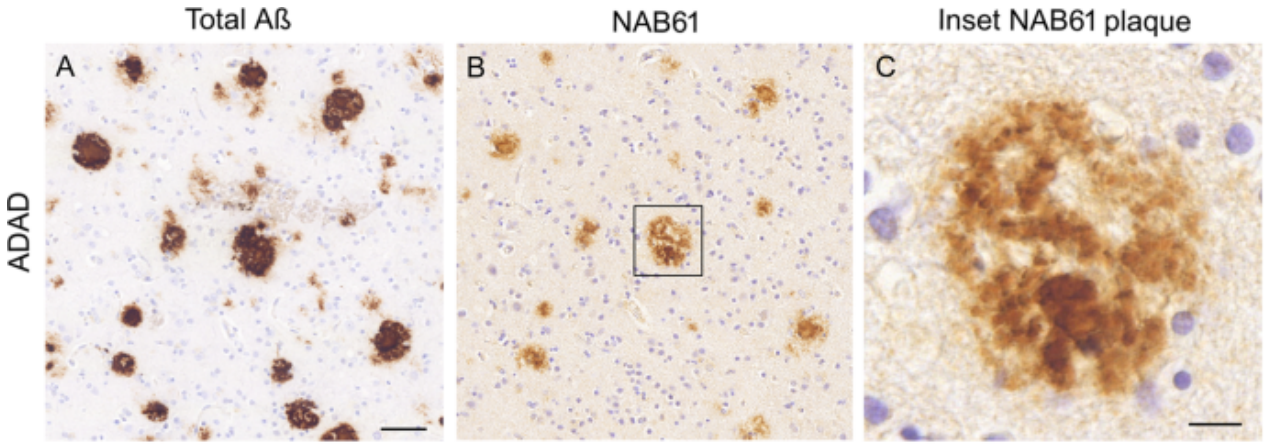




Amyloid hypothesis: the issue is in the tissue



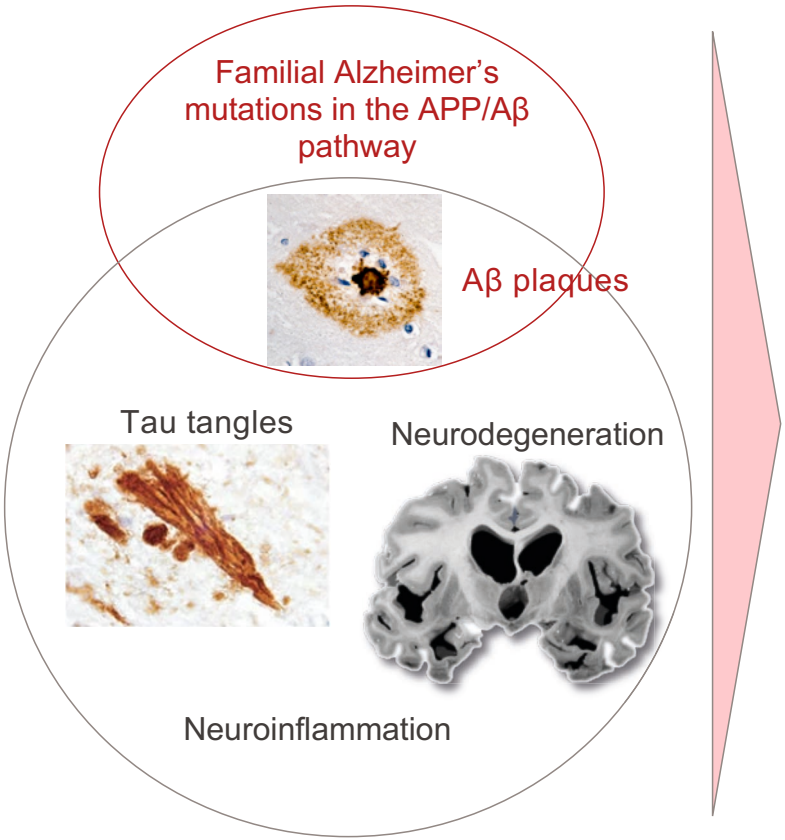
De Loof et al., 2019



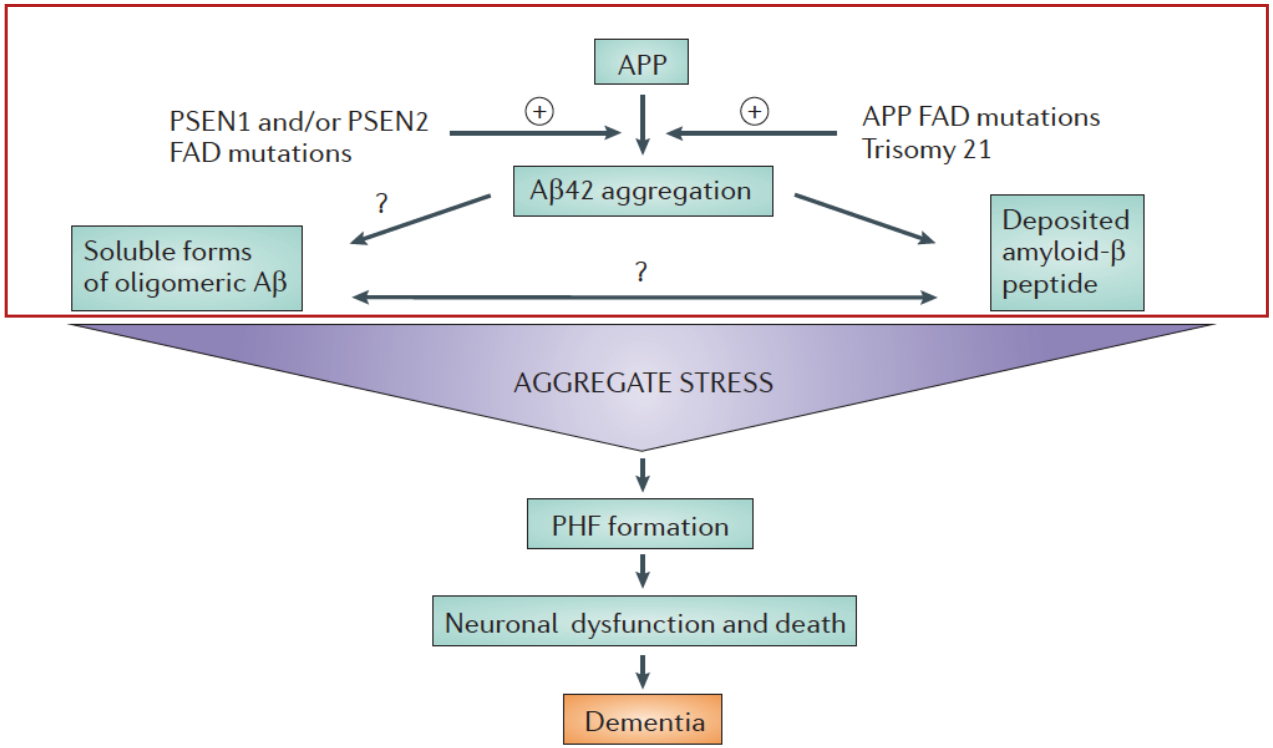
Querol-Vilaseca et al., 2019

Genetic factors for Alzheimer's disease

Genetic causes of AD

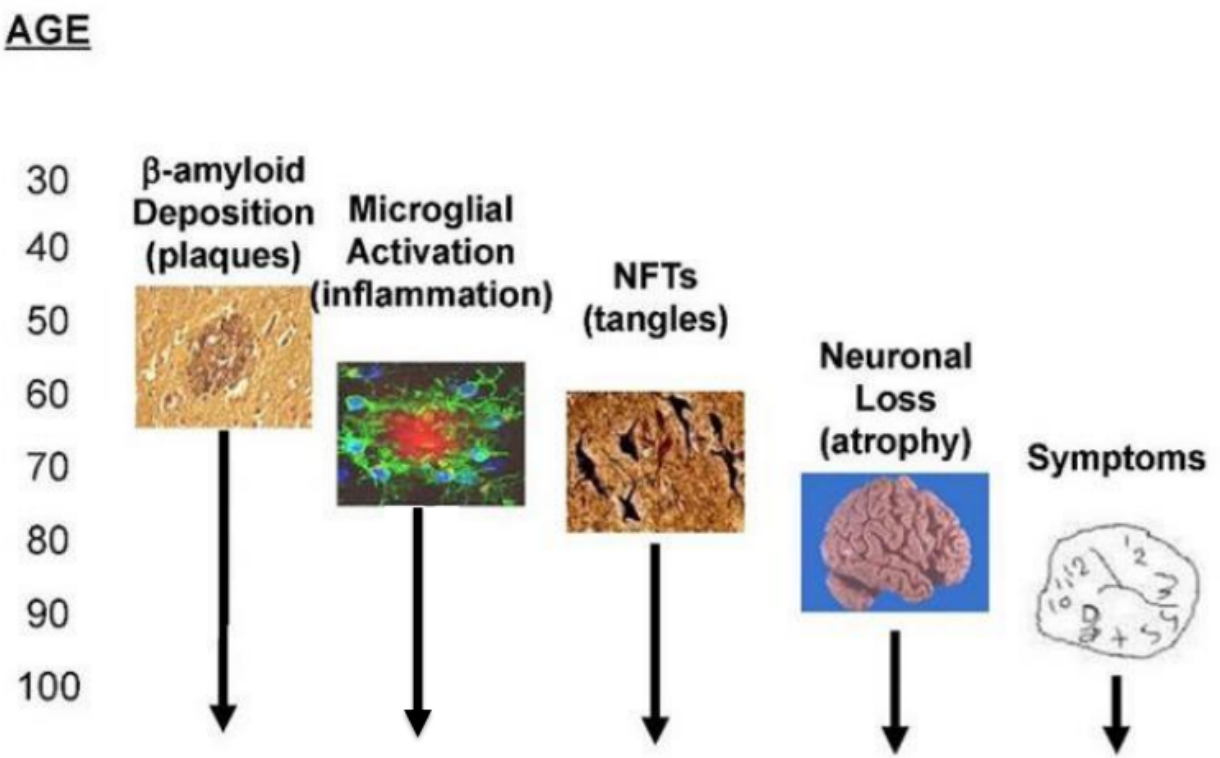


Amyloid β hypothesis

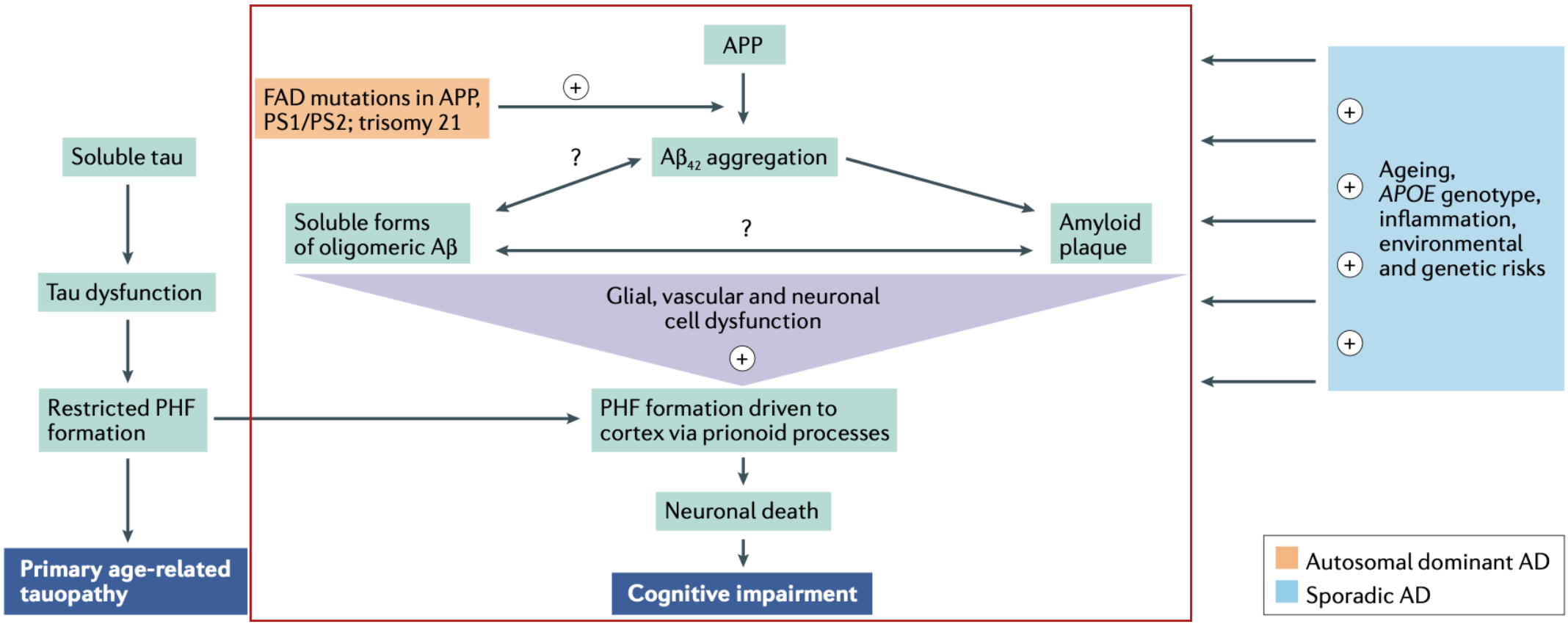


Nature Reviews Drug Discovery 21, pp. 306–318 (2022)

Neuropathological alterations in Alzheimer's disease: the time scale



β-amyloid cascade: a core mechanisms in Alzheimer's disease ?



⇒ based on the Aβ hypothesis, this pathway should be the primary target for therapeutic strategies.

- *Nature Reviews Drug Discovery 21, pp. 306–318 (2022)*

Why did the amyloid hypothesis gain popularity?

Because it is a “Simple” and straightforward explanation.

Rational therapeutic target:
If you block Aβ production or inhibit its aggregation, then you can treat AD.

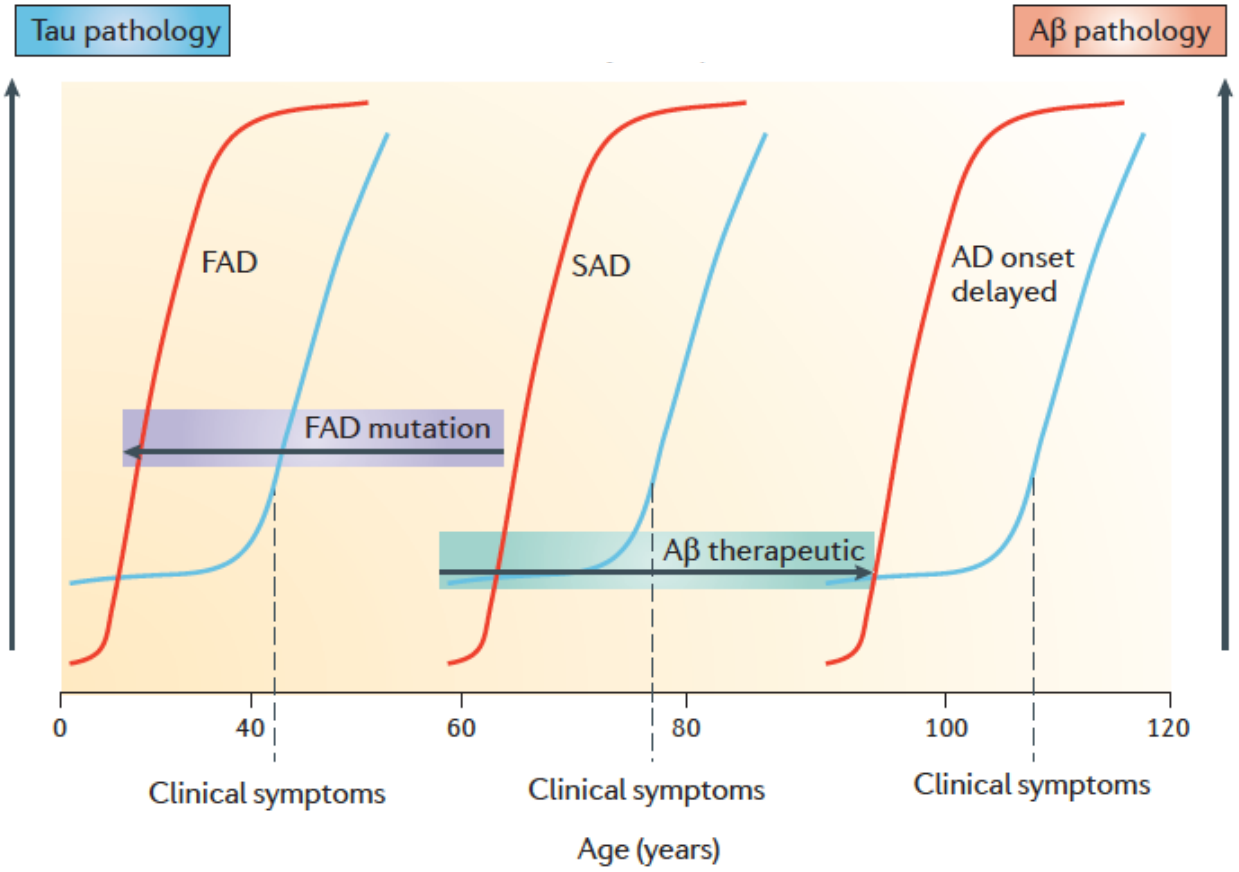
Therapies based on ‘β-amyloid cascade hypothesis’

Assumption:

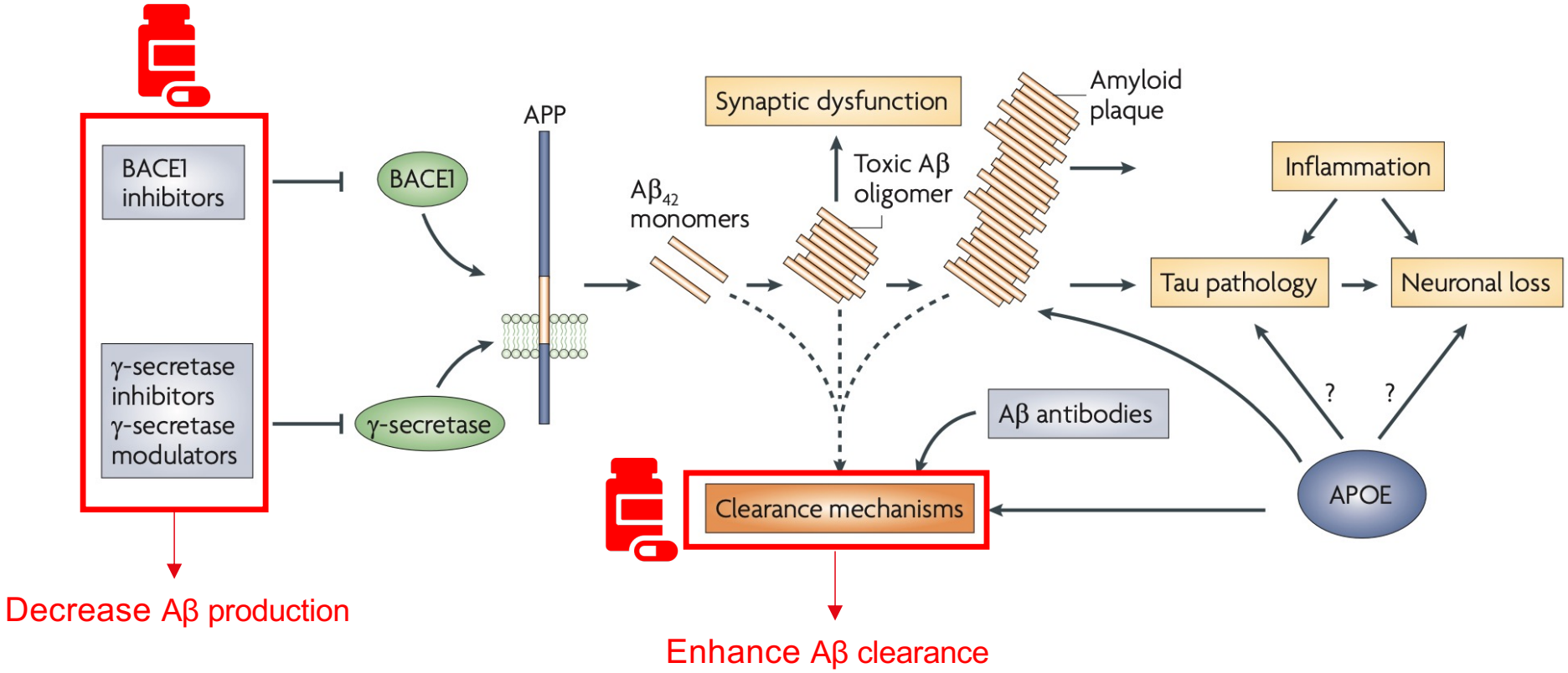
Aβ-related mechanisms leading to familial early-onset Alzheimer’s disease are similar to sporadic late-onset disease:

→ Aβ lowering treatment as an approach to prevent downstream consequences in Alzheimer’s disease?

Rationale for an anti-Aβ treatment:



Current clinical trial in AD – Therapeutics strategies

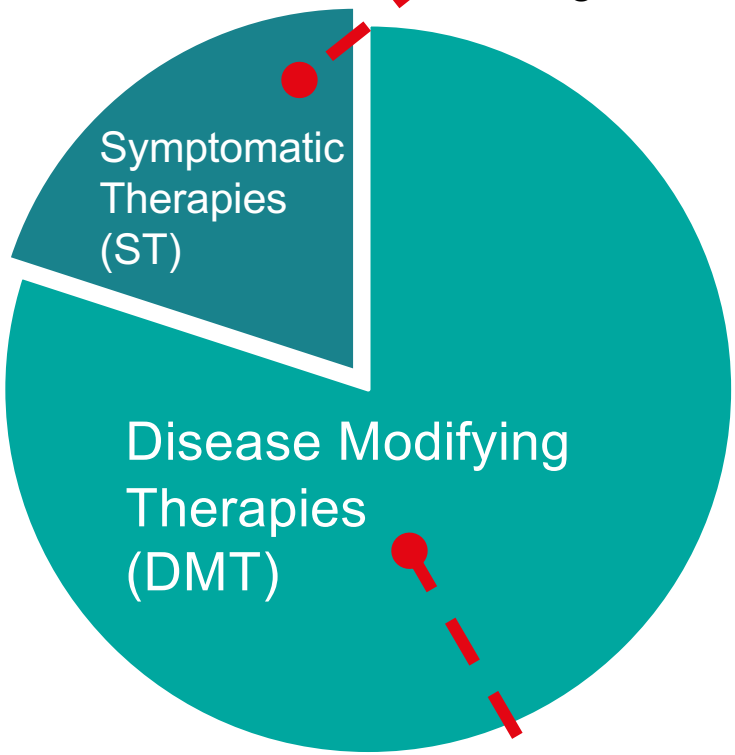


https://www.nature.com/articles/nrd2896

Current clinical trials in Alzheimer's disease

187 Clinical Trials

55'000 Patients Worldwide



20%
Clinical trials to reduce the cognitive symptoms

80%
Clinical trials
to slow or block AD progression

Cummings et al., 2023

2023 AD drug development pipeline

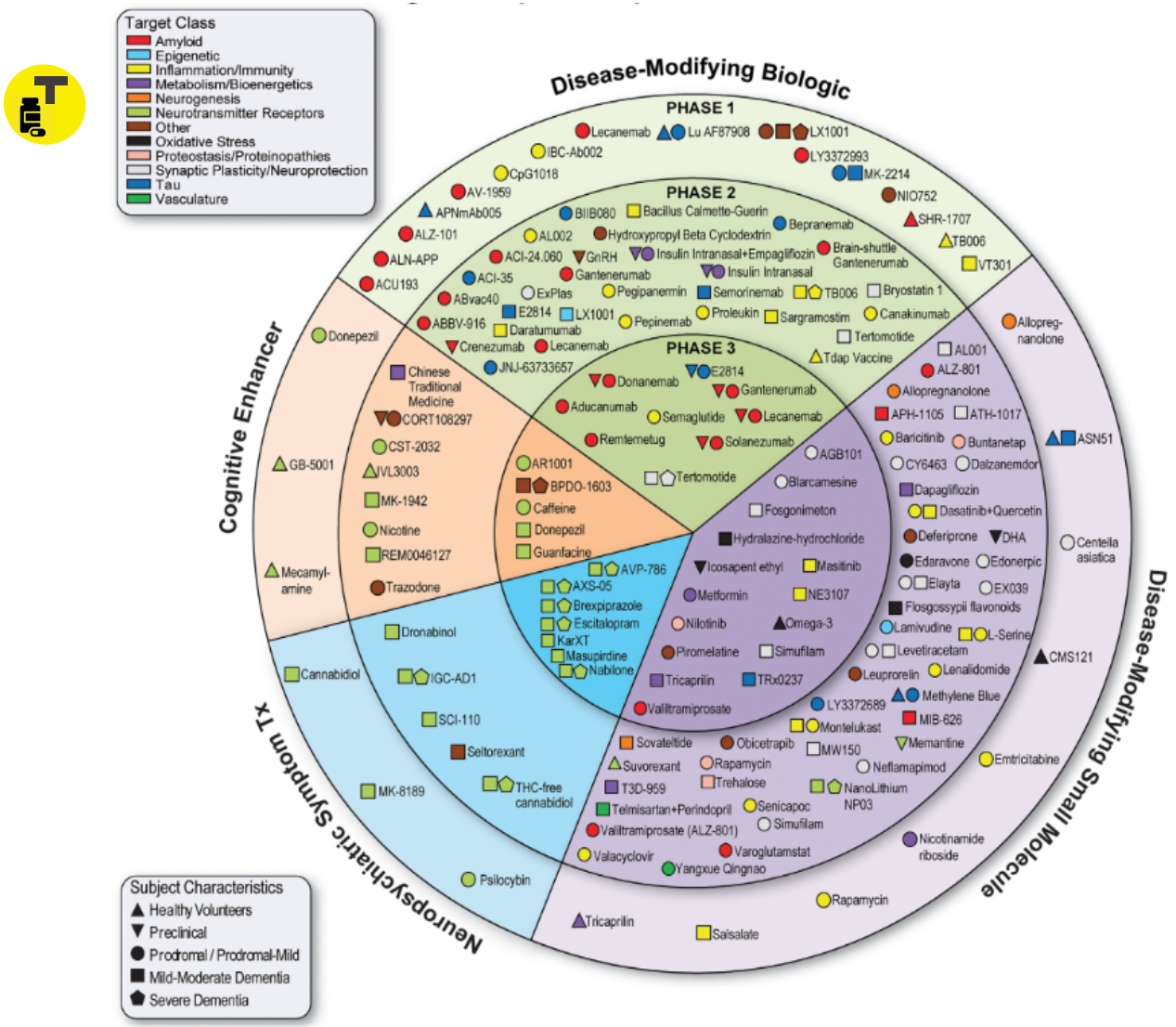
Alzheimer's disease drug development pipeline: 2023

Jeffrey Cummings[1,4] | Yadi Zhou[2] | Garam Lee[3] | Kate Zhong[1,4] | Jorge Fonseca[5]
Feixiong Cheng[2,5,6]

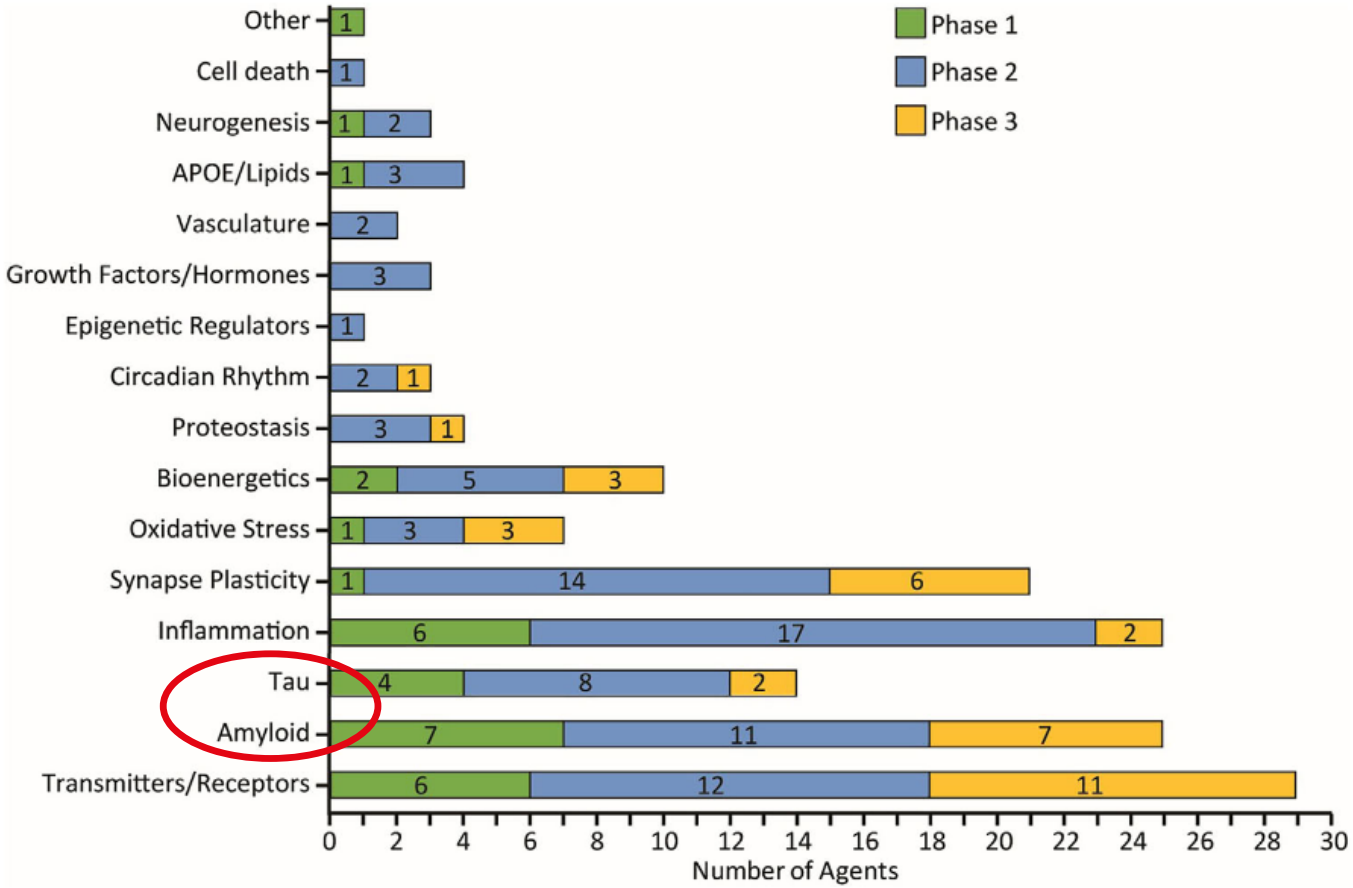
AD/PD™ 2024
ADVANCES IN SCIENCE & THERAPY

International Conference on Alzheimer's and Parkinson's Diseases and related neurological disorders

March 5 - 9, 2024 | Lisbon, Portugal Hybrid



The cellular targets:
Mechanisms of action of the drugs under clinical trial



- Cummings et al., 2023

Therapeutics targeting Aβ

Inhibitors of Presenilin (PSEN2)

Main issue: on-target side effects

(Notch signaling)

Inhibitors of BACE1 (beta secretase, PSEN1)

Main issue: lack of efficacy

and side effects

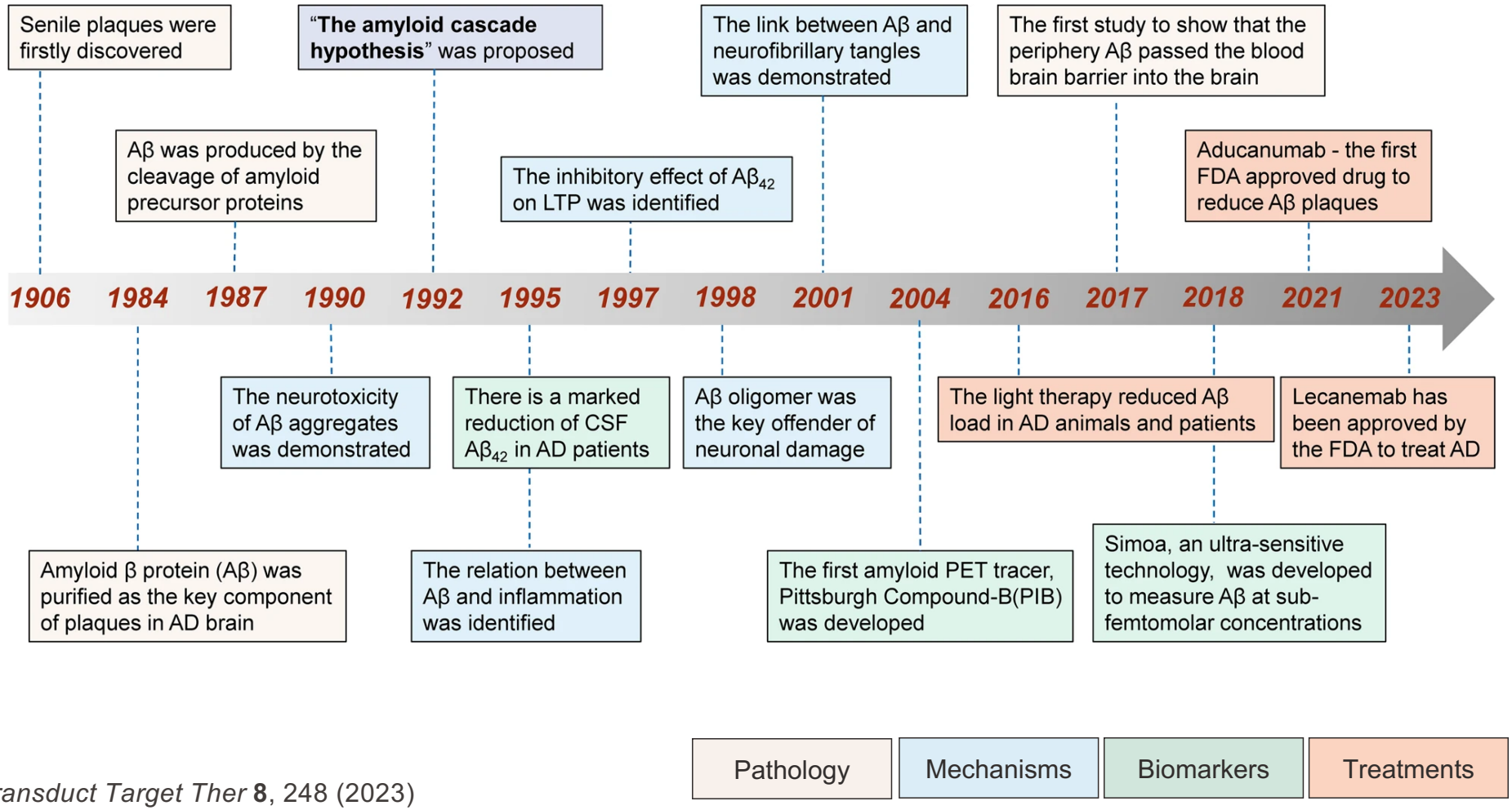
Antibodies against various forms of Aβ

Main issue: lack of efficacy

and side effects (ARIA-E)

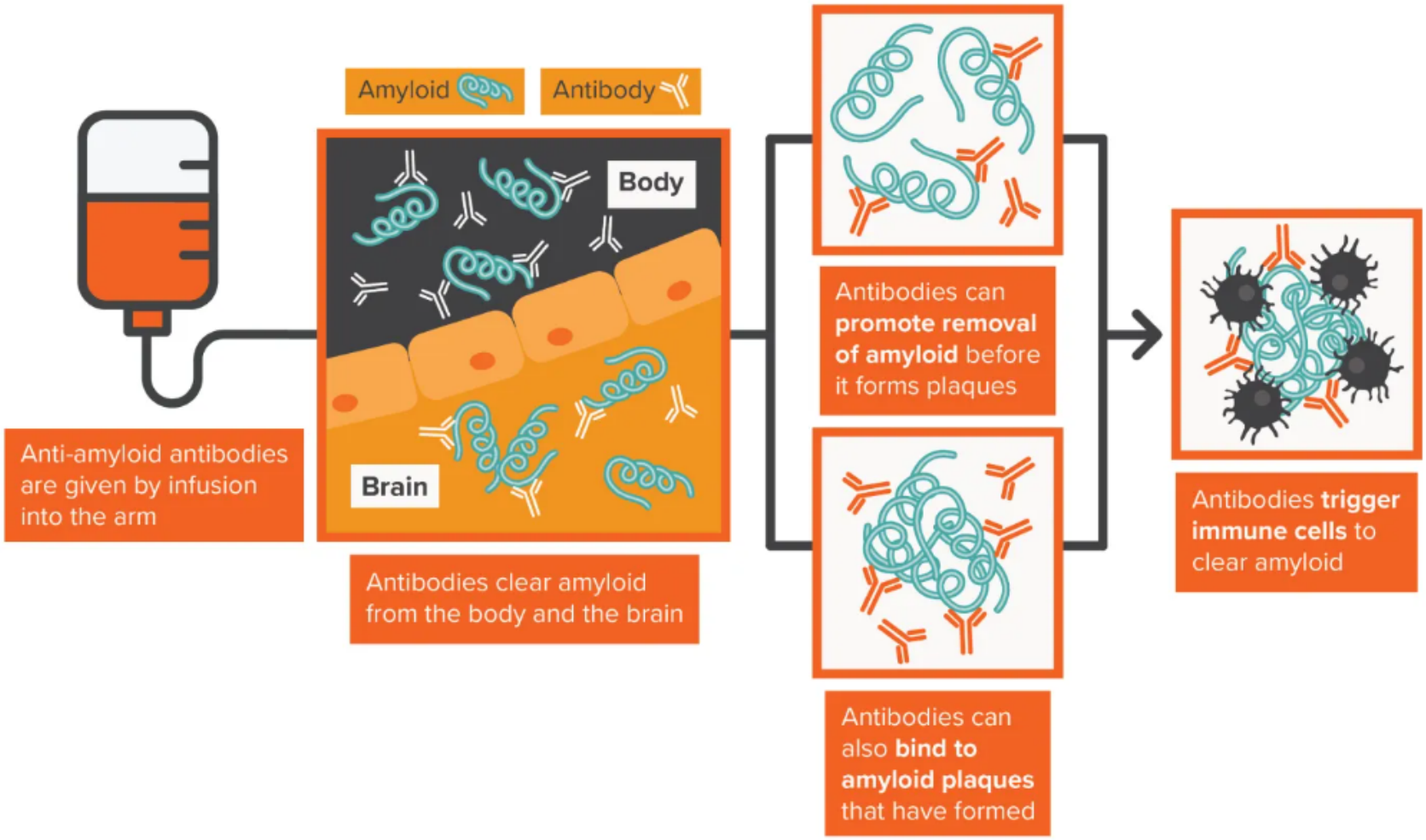
Year	Drug	Company	Mechanism of action	Target	Patient population	Outcome	Observations
2007	Tramiprosate	Neurochem	Unclear; may interact with Aβ oligomers	Soluble Aβ/Aβ oligomers	Mild to moderate AD	Lack of efficacy	–
2009	Tarenflurbil	Myriad Genetics/ Lundbeck	γ-Secretase modulator	Soluble Aβ	Mild AD	Lack of efficacy	Unlikely to have achieved adequate target engagement in the brain
2011	Semagacestat	Eli Lilly	γ-Secretase inhibitor	Soluble Aβ	Mild to moderate AD	Toxicity and lack of efficacy	Increases cognitive decline/no lowering of brain amyloid
2012	Bapineuzumab	Elan/Pfizer/ Johnson & Johnson	Anti-Aβ mAb	Soluble Aβ and plaque	Mild to moderate AD	Lack of efficacy	No significant removal of amyloid
2013	Gammagard	Baxter	Unclear; IVIG may bind soluble Aβ	Soluble Aβ	Mild to moderate AD	Lack of efficacy	–
2013	Solanezumab	Eli Lilly	Anti-Aβ mAb	Soluble Aβ	Mild to moderate AD	Lack of efficacy	No removal of amyloid
2016	Gantenerumab	Hoffman La Roche	Anti-Aβ mAb	Plaque	Mild AD	Lack of efficacy	Converted into an open-label study
2016	Solanezumab	Eli Lilly	Anti-Aβ mAb	Soluble Aβ	Mild AD	Lack of efficacy	No removal of amyloid
2016	Solanezumab	Eli Lilly	Anti-Aβ mAb	Soluble Aβ	Prodromal AD	Trial halted	–
2016	Verubecestat	Merck	BACE inhibitor	Soluble Aβ	Mild to moderate AD	Lack of efficacy	Increases cognitive decline/modest lowering of brain amyloid (~20 CL)
2018	Verubecestat	Merck	BACE inhibitor	Soluble Aβ	Prodromal AD	Lack of efficacy	Increases cognitive decline
2018	Atabecestat	Janssen	BACE inhibitor	Soluble Aβ	Asymptomatic at risk of AD	Toxicity	Increases cognitive decline
2018	Lanabecestat	AstraZeneca/Eli Lilly	BACE inhibitor	Soluble Aβ	Early AD	Lack of efficacy	Increases cognitive decline
2018	Lanabecestat	AstraZeneca/Eli Lilly	BACE inhibitor	Soluble Aβ	Mild AD	Lack of efficacy	Increases cognitive decline
2019	Crenezumab	AC Immune/ Hoffman La Roche	Anti-Aβ mAb	Soluble Aβ	Prodromal to mild AD	Lack of efficacy	–
2019	Elenbecestat	Biogen/Eisai	BACE inhibitor	Soluble Aβ	Prodromal to MCI due to AD	Lack of efficacy	Increases cognitive decline
2019	Umibecestat	Amgen/Novartis	BACE inhibitor	Soluble Aβ	Asymptomatic at risk of AD	Lack of efficacy	Increases cognitive decline
2019	Amilomotide	Novartis	Vaccine	Aβ	Asymptomatic at risk of AD	Trial halted	–
2020	Aducanumab	Biogen/Eisai	Anti-Aβ mAb	Plaque	MCI to early dementia	Evidence of efficacy	BLA given accelerated approval by the FDA but rejected by the CHMP of the EMA

Immunotherapy against Amyloid β pathology: historical perspective



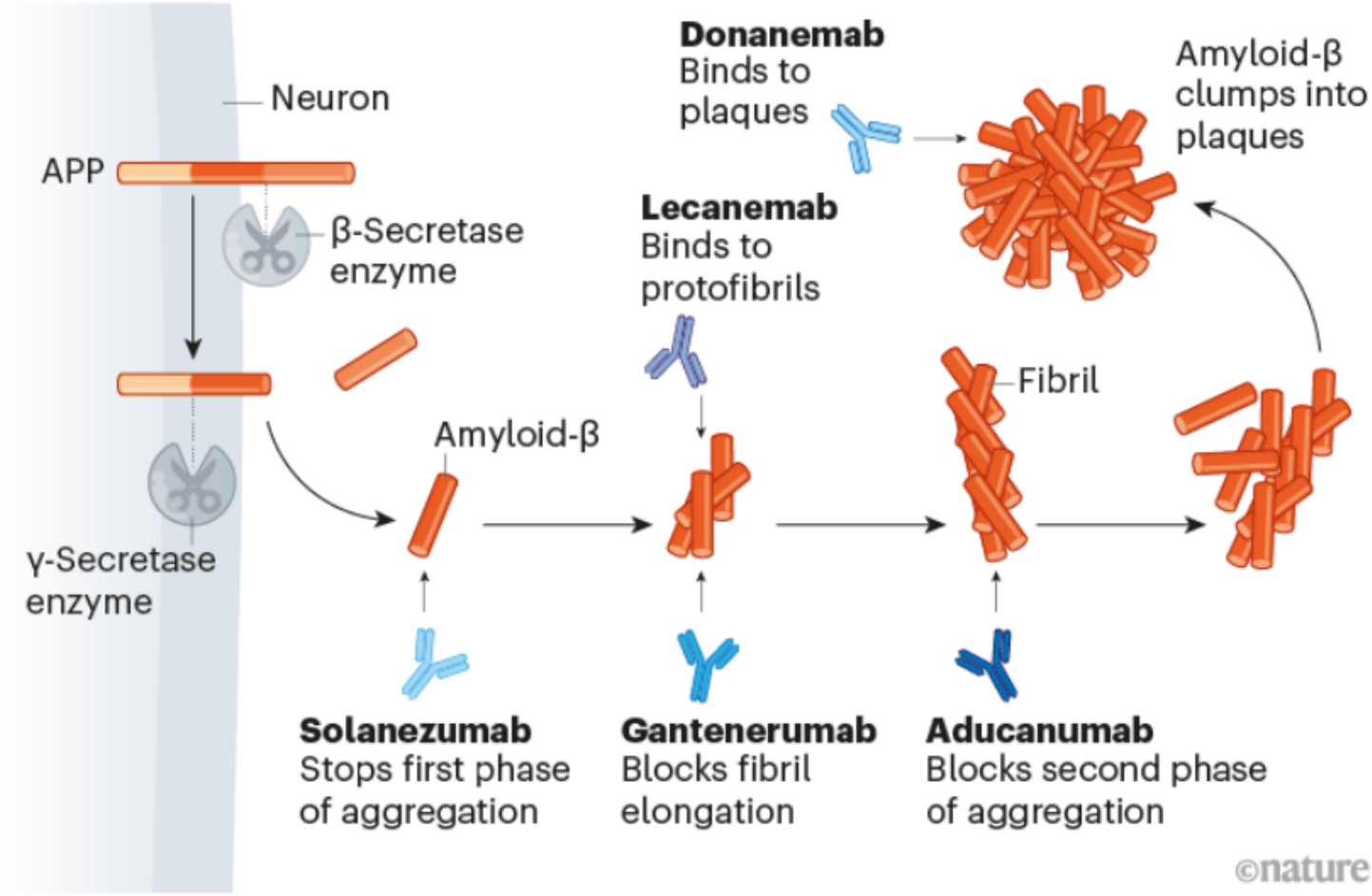
Sig Transduct Target Ther **8**, 248 (2023)

Current clinical trial in AD – The immunotherapy approach



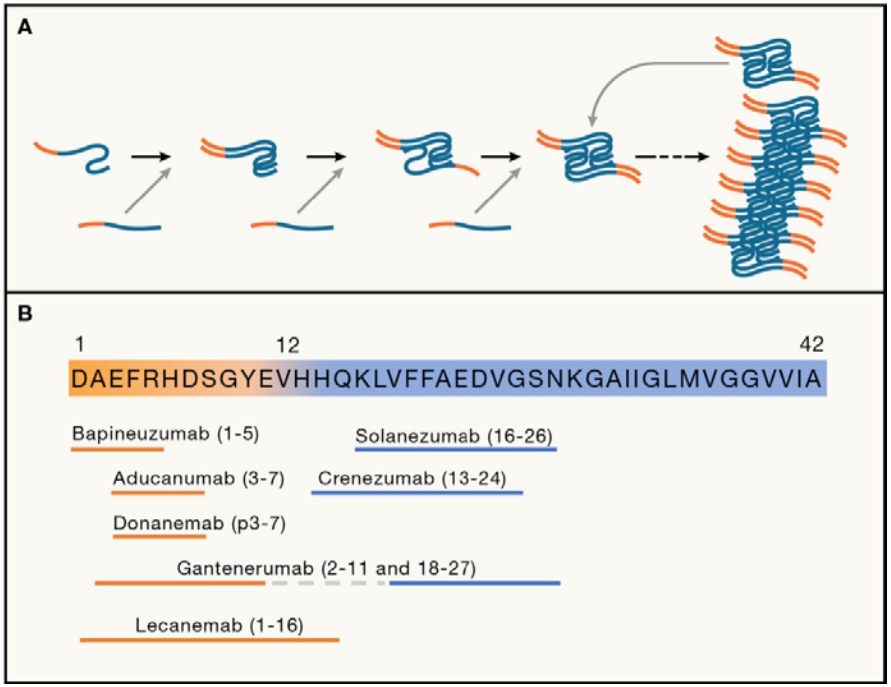
https://www.alzheimersresearchuk.org/news/new-alzheimers-drug-donanemab-what-is-it-and-how-does-it-work/

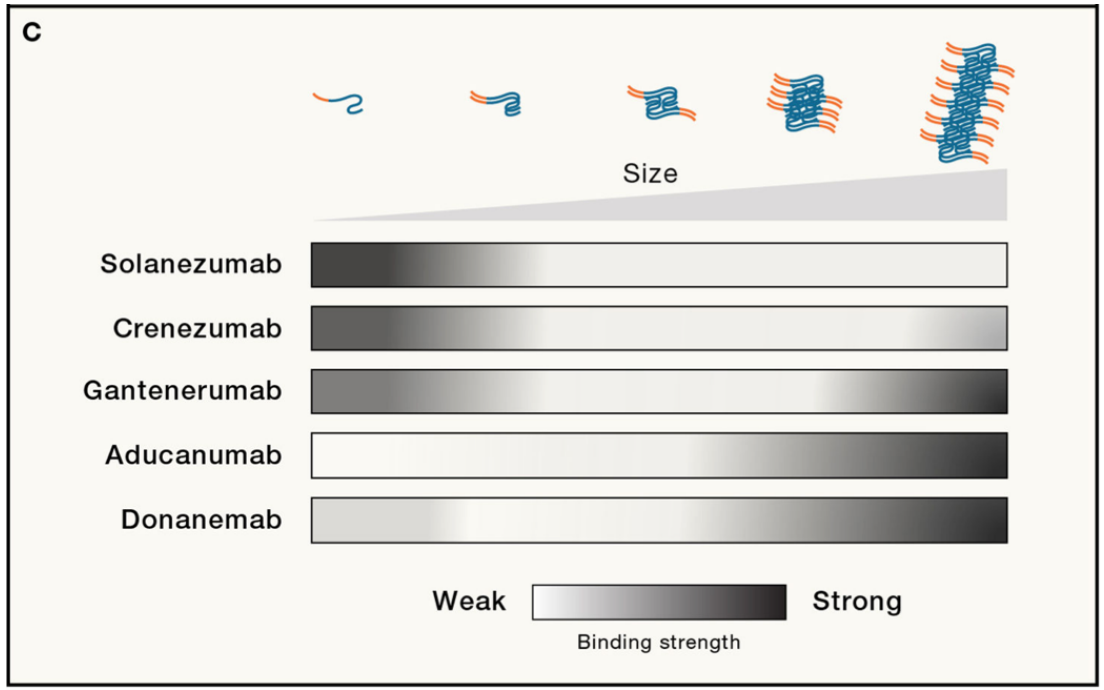
Current clinical trial in AD – The immunotherapy approach



Mullard, Nat Rev Drug Discov. 2023;22:89

Aβ epitopes of antibodies tested in clinical trials for Alzheimer disease



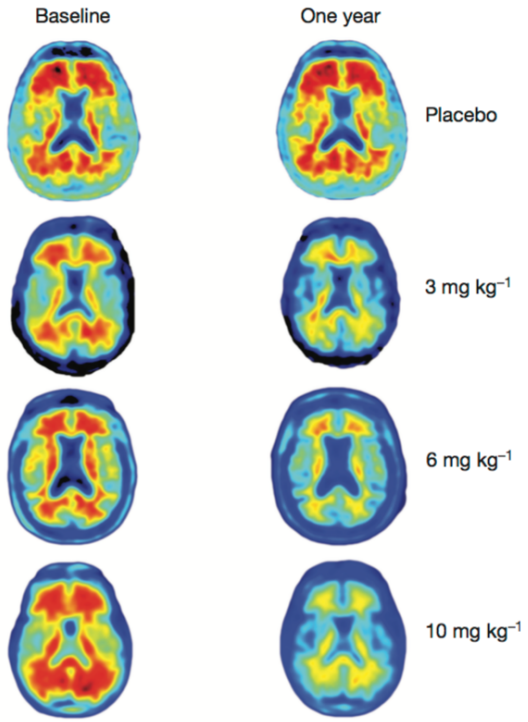


Cell, Vol. 186(20), (2023), pp. 4260-4270
Nature Reviews Drug Discovery volume 21, pages 306–318 (2022)
Nature Structural & Molecular Biology volume 27, pages 1125–1133 (2020)

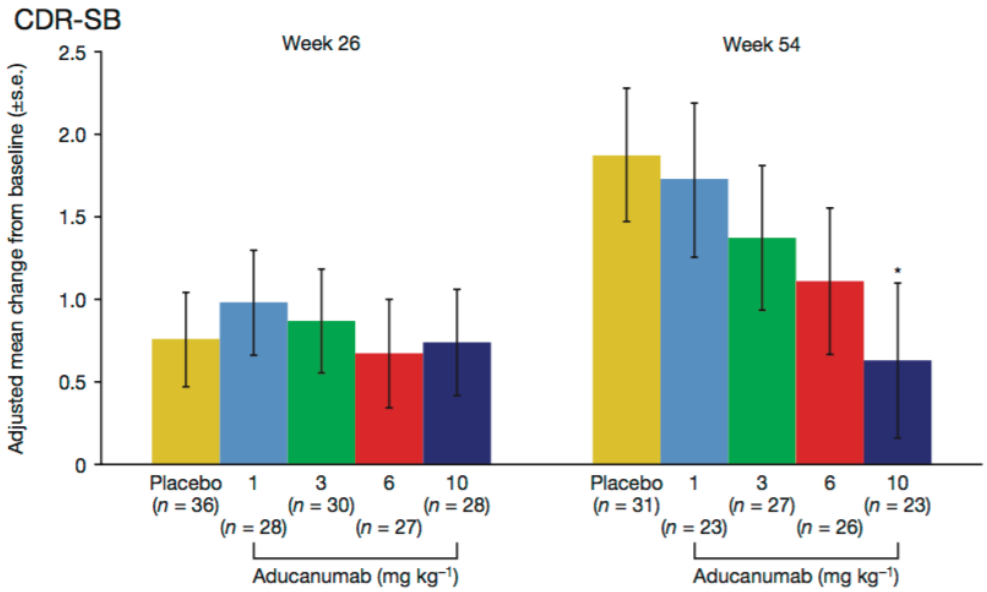
Anti-amyloid β therapy: antibody-mediated clearance

Phase 1b trial with Aducanumab in prodromal or mild AD

Amyloid PET imaging at baseline and week 54



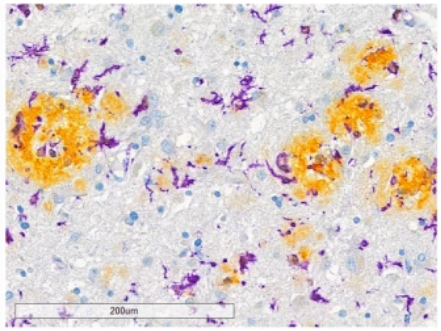
Effect on Clinical Dementia Rating (CDR-SB)

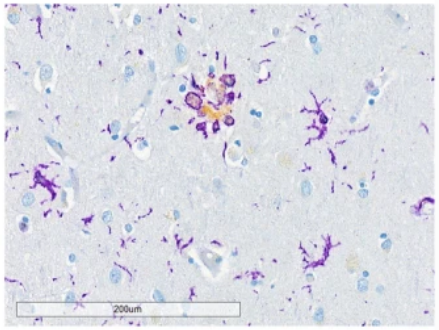


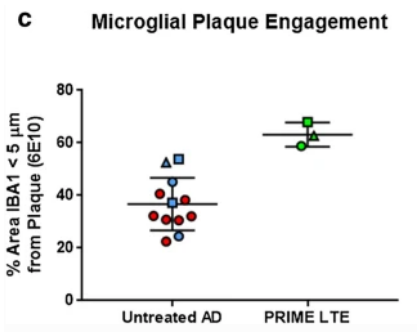
- *Sevigny J et al, Nature 537, 2016*

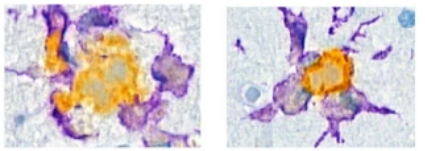
Alzheimer's pathology in a patient treated with Aducanumab (32-months treatment) shows reduction of Aβ plaque pathology

Microglia surrounding amyloid plaques

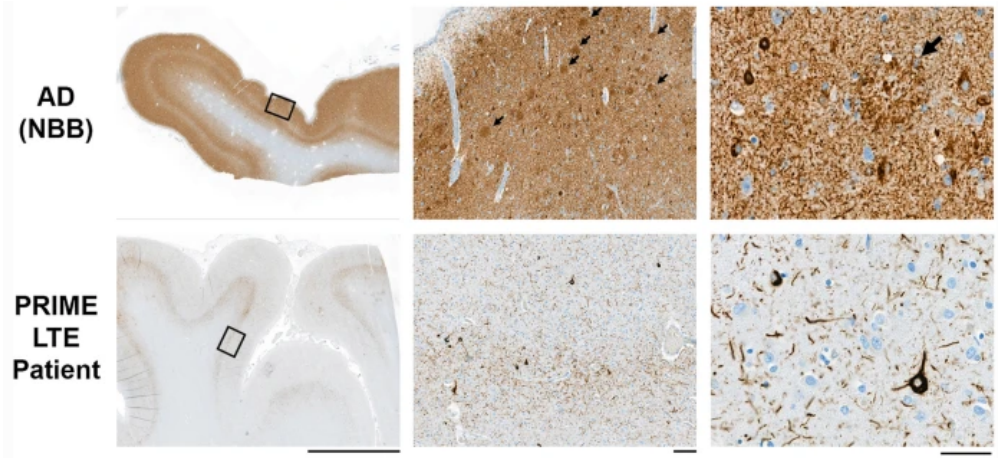


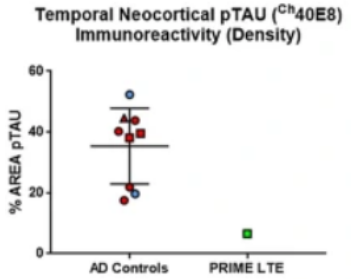






Phospho-tau pathology





Acta Neuropathologica vol 144, pp 143–153 (2022)

The ups and downs of a ‘promising’ anti-Aβ treatment

BIOGEN AND EISAI TO DISCONTINUE PHASE 3 ENGAGE AND EMERGE TRIALS OF ADUCANUMAB IN ALZHEIMER’S DISEASE

March 21 2019

Shock revelation sees Biogen erase its aducanumab losses

Oct 22 2019

Biogen Asks FDA To Approve Aducanumab

July 8 2020

Data for Biogen's Alzheimer's hopeful aducanumab 'highly persuasive': FDA briefing documents

Nov 4 2020

Biogen’s Alzheimer’s drug candidate takes a beating from FDA advisers

Nov 6 2020

Biogen

FDA grants accelerated approval for ADUHELM™ as the first and only Alzheimer’s disease treatment to address a defining pathology of the disease

June 7 2021

Biogen, with sales falling sharply, posts 'obviously disappointing' Aduhelm sales of $300K, CEO Vounatsos says

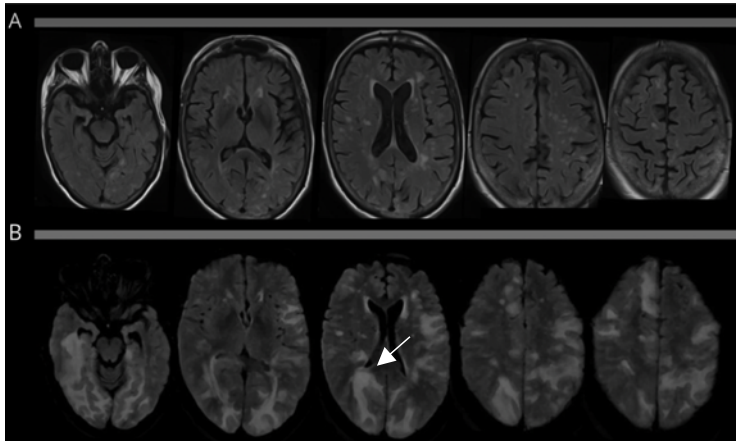
October 20 2021

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Aduhelm: Withdrawal of the marketing authorisation application Share

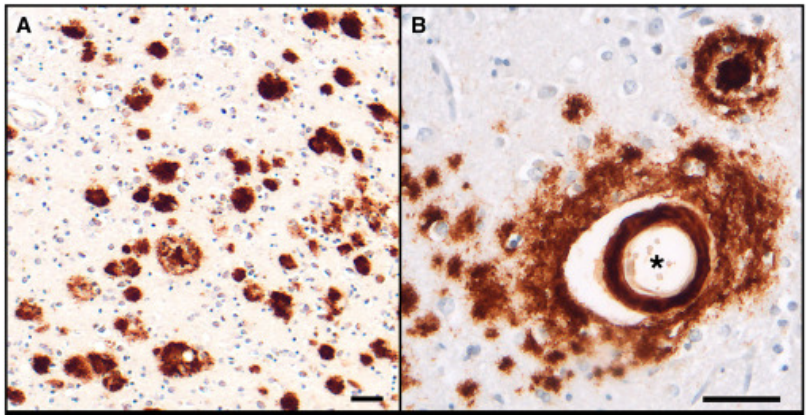
Side-effects associated with anti-Aβ immunotherapy

- Amyloid-related imaging abnormalities (ARIA= edema/effusion) linked to pre-existing Aβ deposition (especially CAA).
- Changes in brain volume.

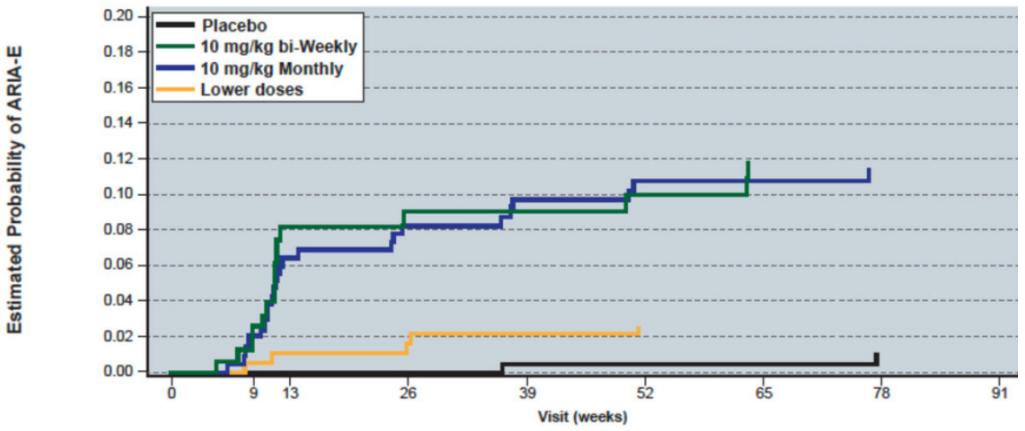


Amyloid plaques in the brain parenchyma

Cerebral β-amyloid angiopathy (CAA)



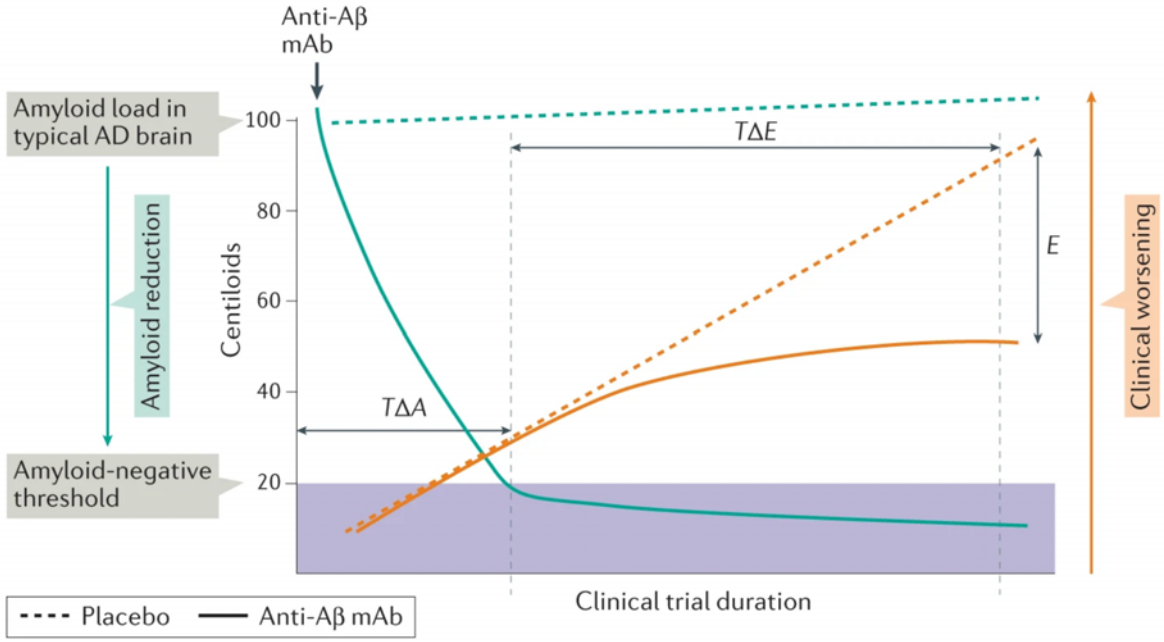
Frequency of ARIA in lecanemab-treated AD patients

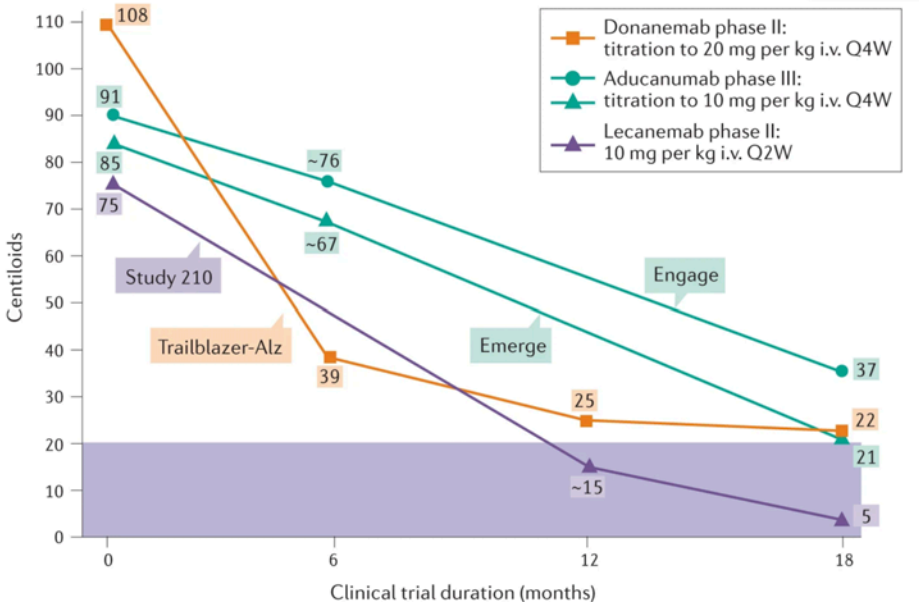


- *Cell, Vol. 186, Issue 20, 2023, pp. 4260-4270*

Aβ immunotherapy: evaluation of efficacy

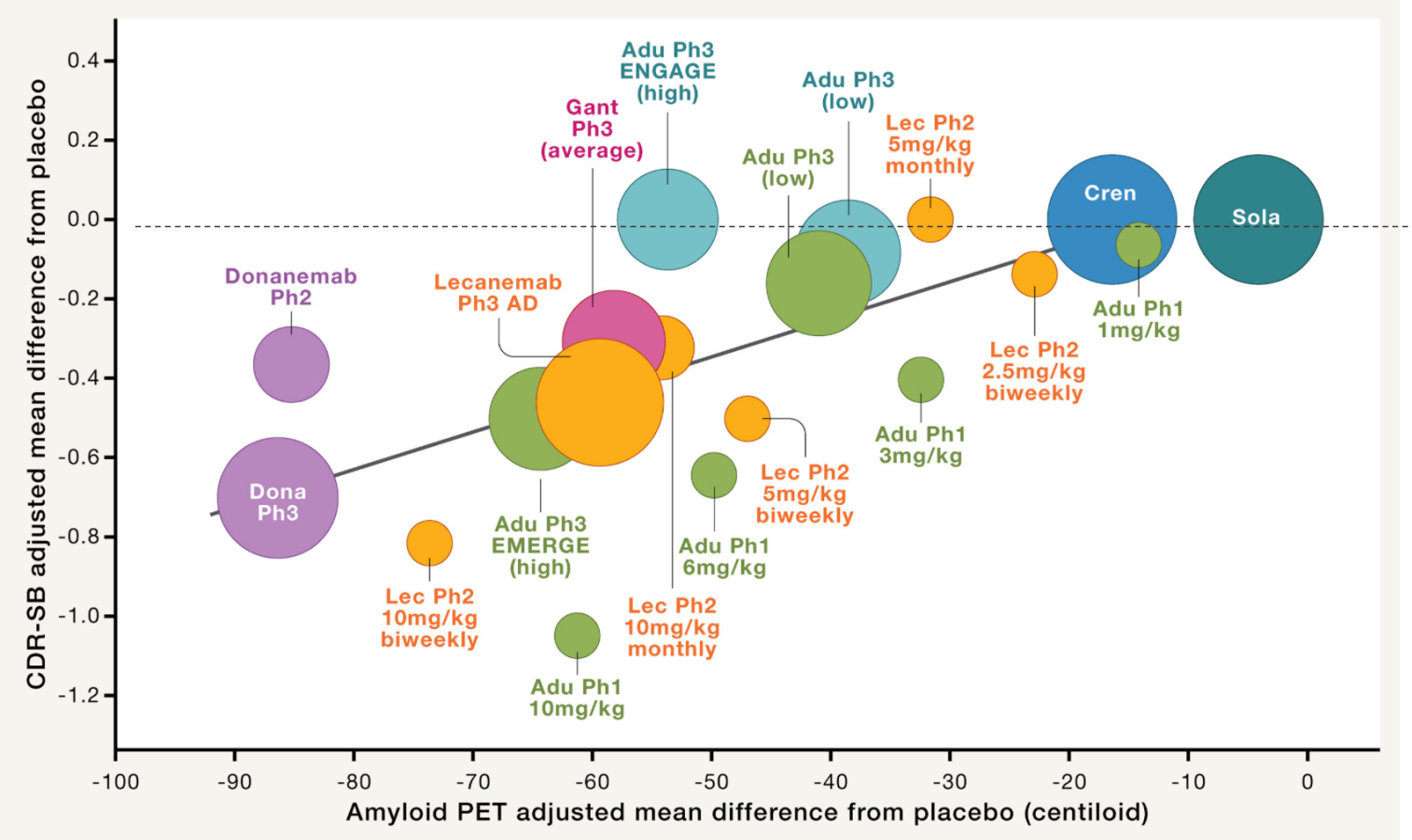
PET imaging of amyloid β load in the brain





- *Nature Reviews Drug Discovery volume 21, pages 306–318 (2022)*

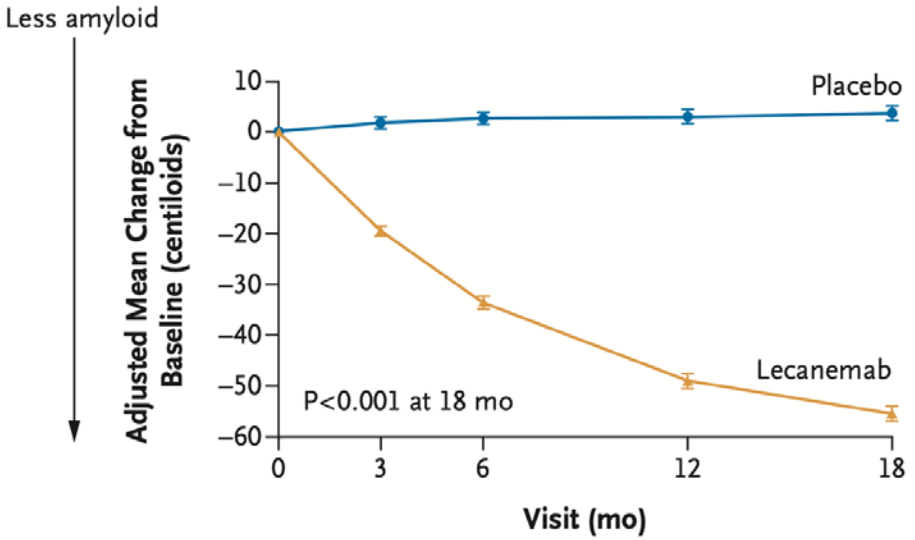
Aβ immunotherapy: evaluation of efficacy of the different antibodies



Cell, Volume 186, Issue 22, 2023, Pages 4757-4772

Aβ immunotherapy: *lecanemab* efficacy

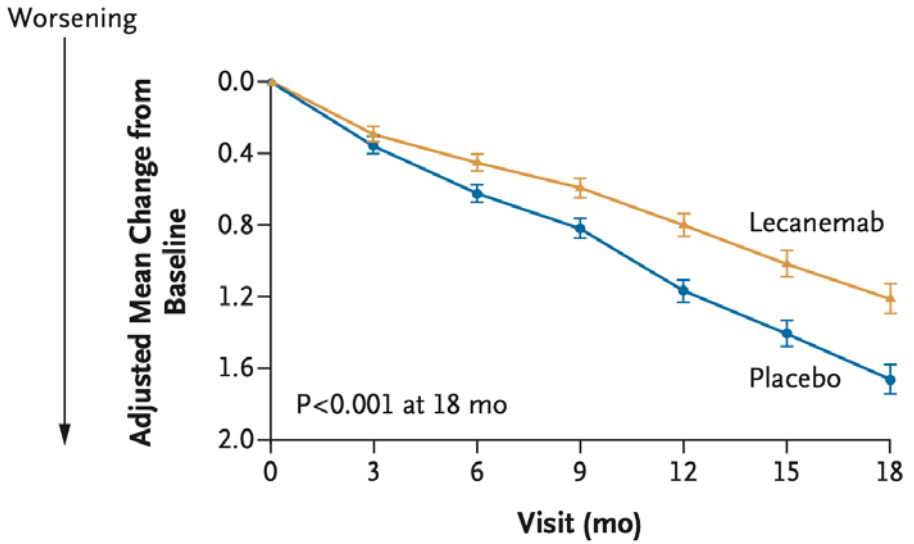
Amyloid Burden on PET



No. of Participants

Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

CDR-SB Score

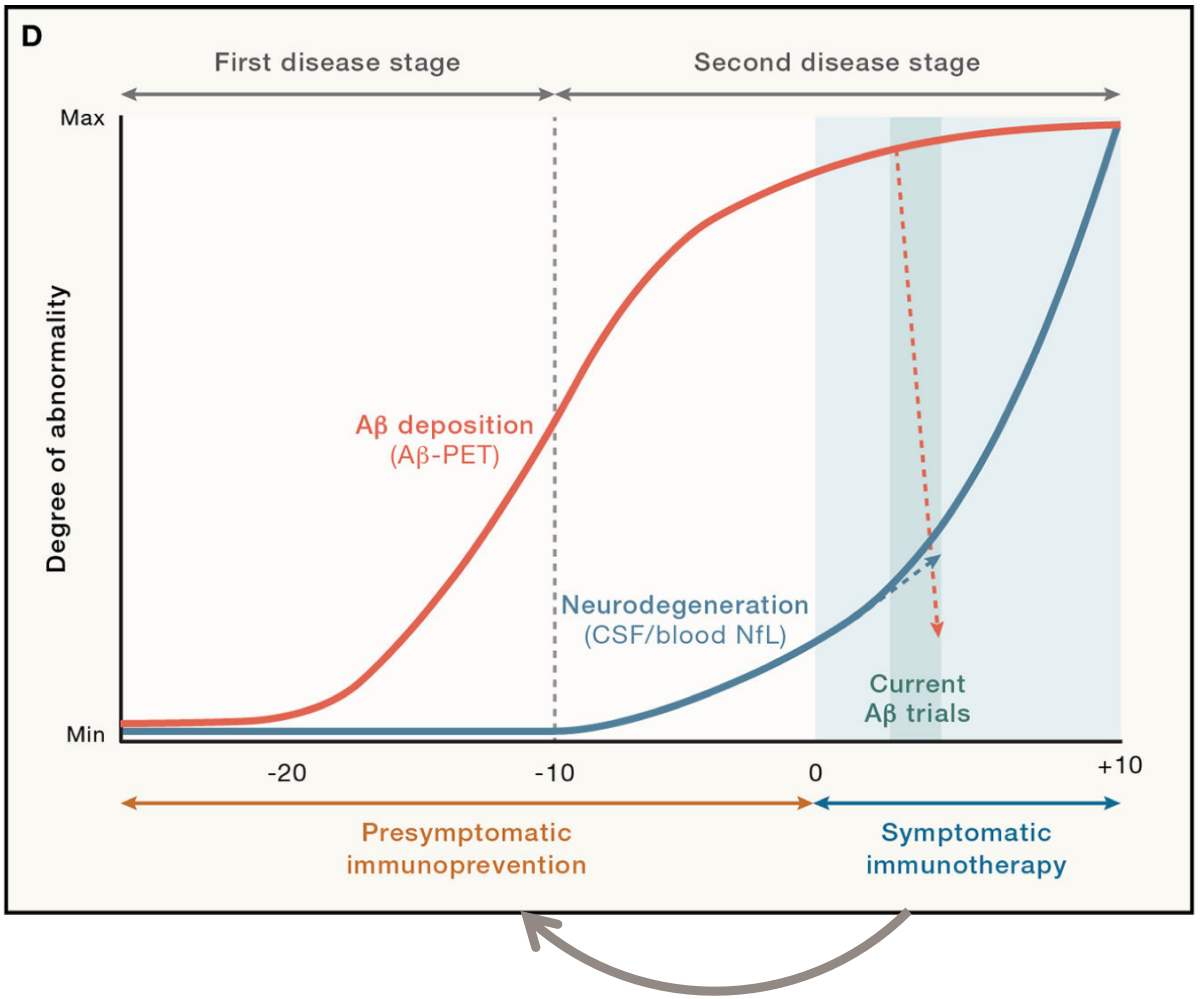


No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

- *N Engl J Med 2023;388:9-21. DOI: 10.1056/NEJMoa2212948*

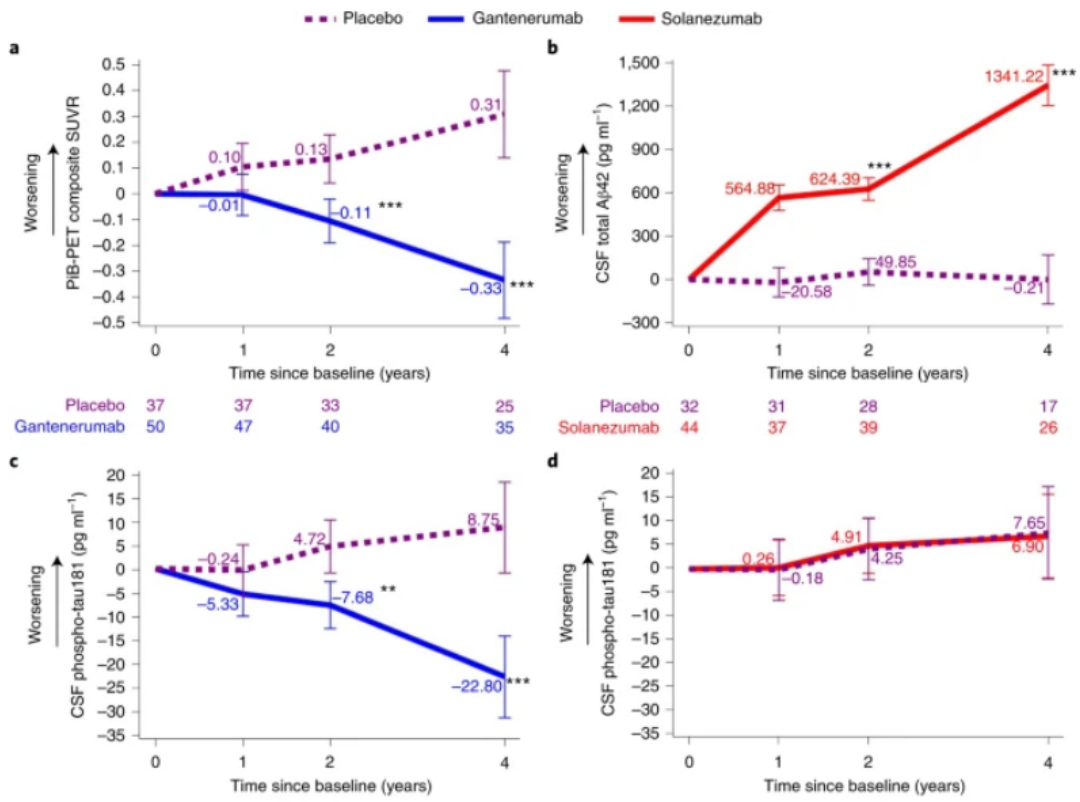
Aβ immunotherapy: the importance of the therapeutic window

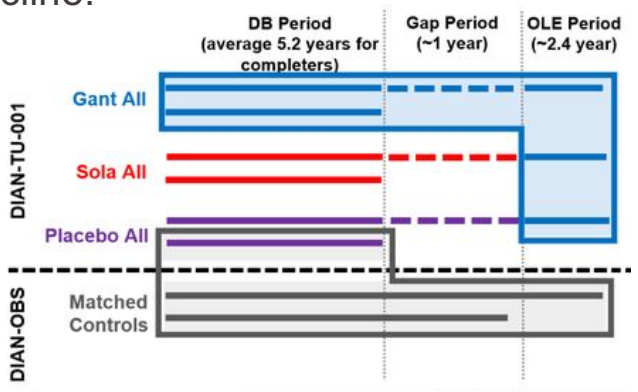


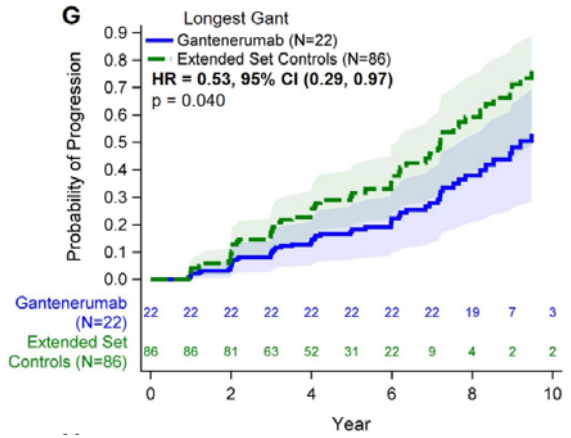
Cell, Vol. 186, Issue 20, 2023, pp. 4260-4270

DIAN-TU preventive trial for Alzheimer's disease

- **Autosomal dominant AD** caused by mutations in APP, Presenilin 1 or Presenilin 2.
- Treatment initiated at **pre-symptomatic and mild symptomatic stages**.
- DIAN–TU-001: testing gantenerumab (anti-fibrillar Aβ) and solanezumab (anti-soluble Aβ).
- 2015: 4-years treatment trial started to slow or prevent cognitive decline.

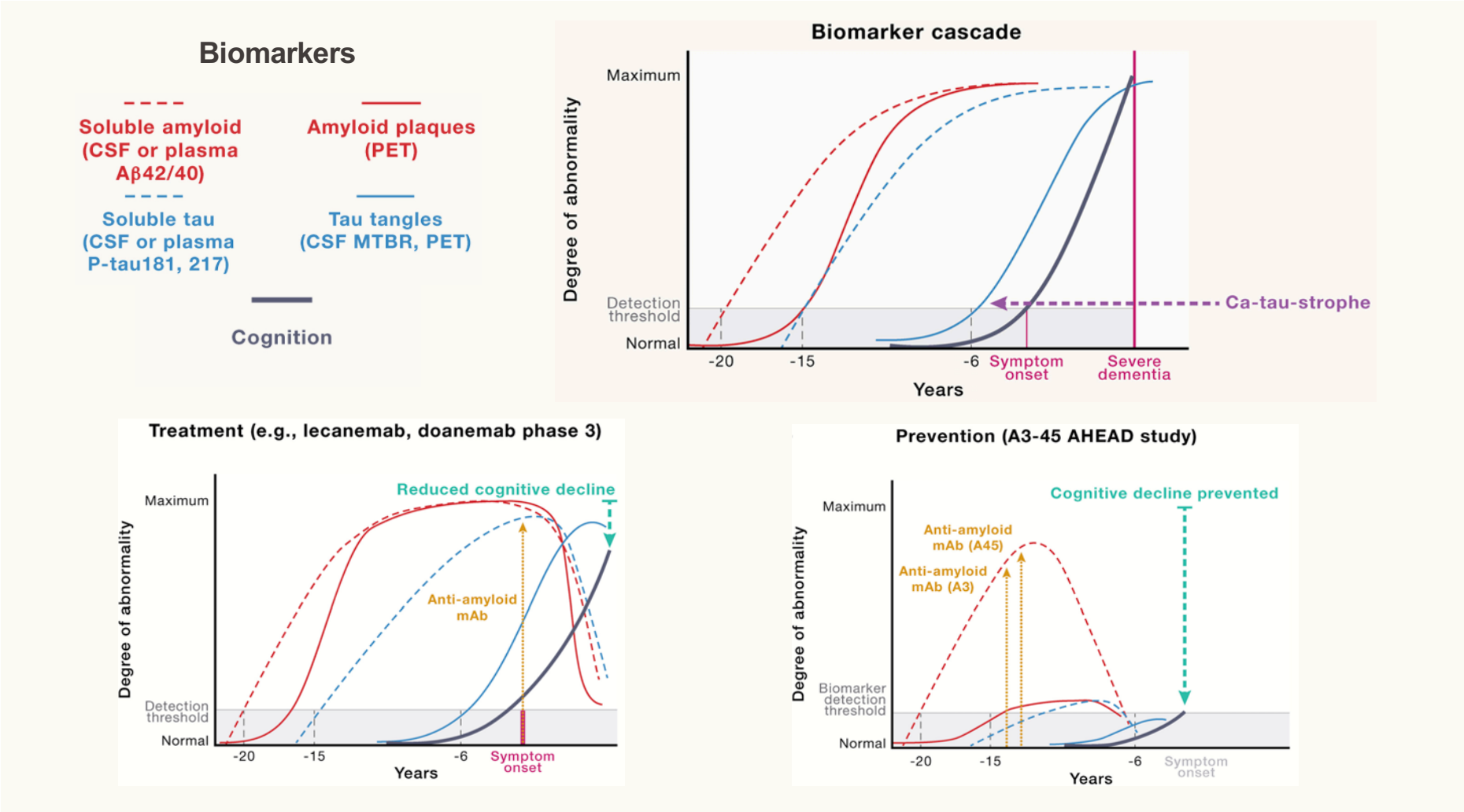






doi: https://doi.org/10.1101/2024.10.29.24316289

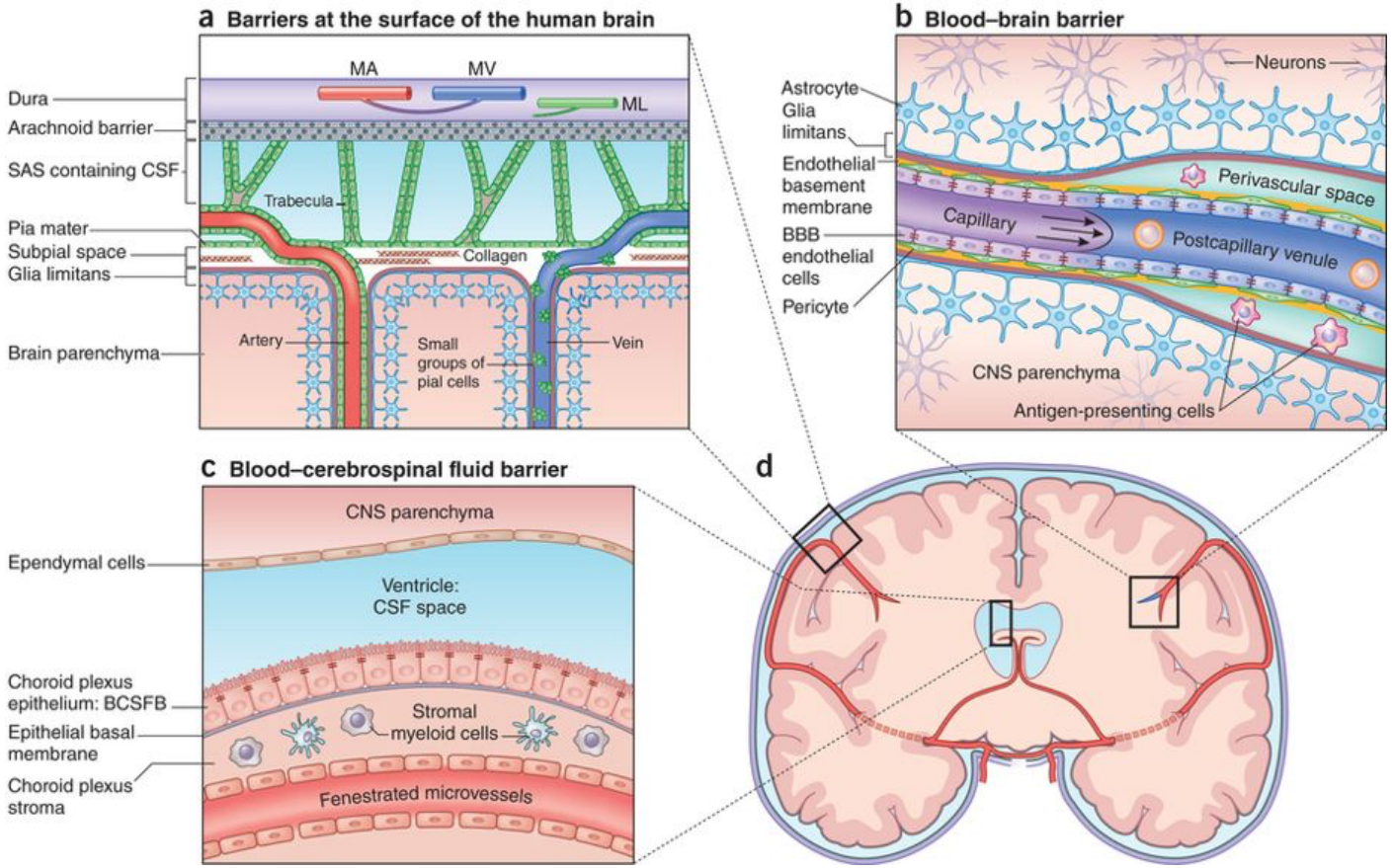
Aβ immunotherapy: towards prevention ?



Cell, Volume 186, Issue 22, 2023, Pages 4757-4772

Barriers to the CNS

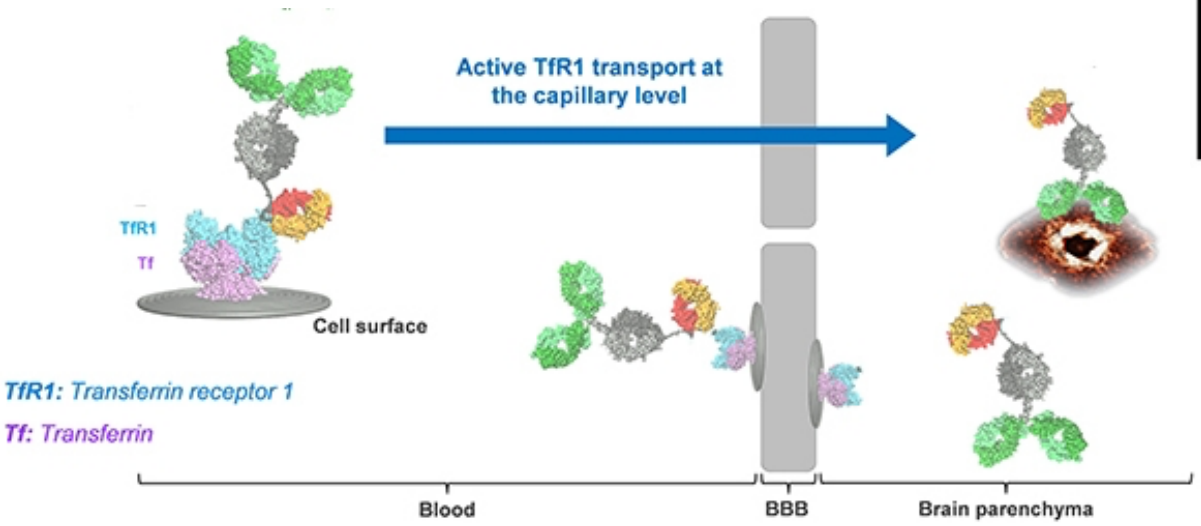
Acellular and cellular brain barriers

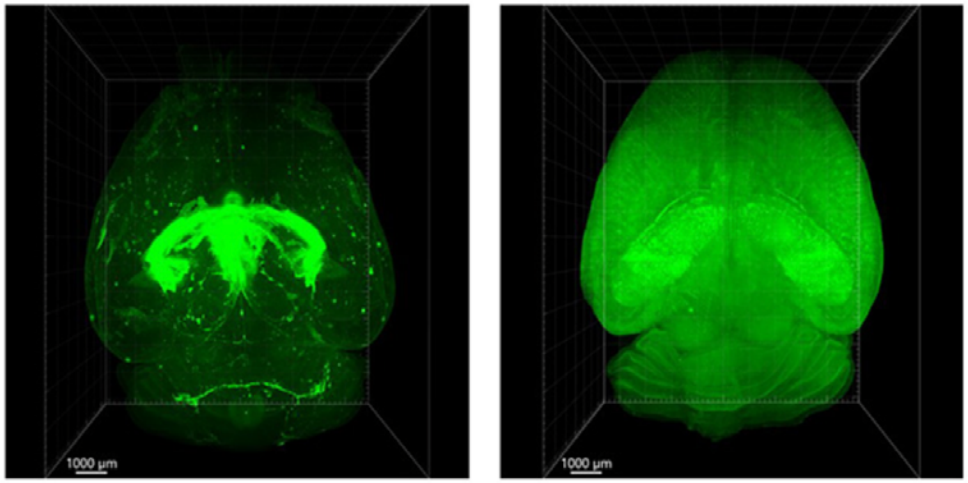


- Engelhardt B, Nature Immunology volume 18, pages 123–131 (2017)

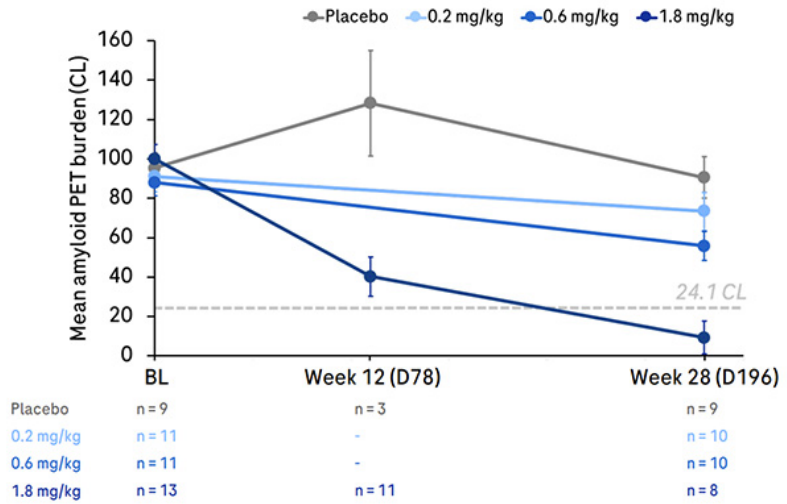
Engineering of anti-Aβ antibodies to cross the blood-brain barrier

- Anti-Aβ antibody designed to bind the transferrin receptor to induce shuttling through the BBB.





Trontinemab phase I clinical trial



- *DOI: 10.1016/j.neuron.2013.10.061*

Paper 1

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Lecanemab in Early Alzheimer's Disease

C.H. van Dyck, C.J. Swanson, P. Aisen, R.J. Bateman, C. Chen, M. Gee, M. Kanekiyo, D. Li, L. Reyderman, S. Cohen, L. Froelich, S. Katayama, M. Sabbagh, B. Vellas, D. Watson, S. Dhadda, M. Irizarry, L.D. Kramer, and T. Iwatsubo

Paper 2

Journal of Alzheimer's Disease 97 (2024) 567–572
DOI 10.3233/JAD-231198
IOS Press

Commentary

Substantial Doubt Remains about the Efficacy of Anti-Amyloid Antibodies

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Paper 3

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PERSPECTIVE

The case for regulatory approval of amyloid-lowering immunotherapies in Alzheimer's disease based on clearcut biomarker evidence