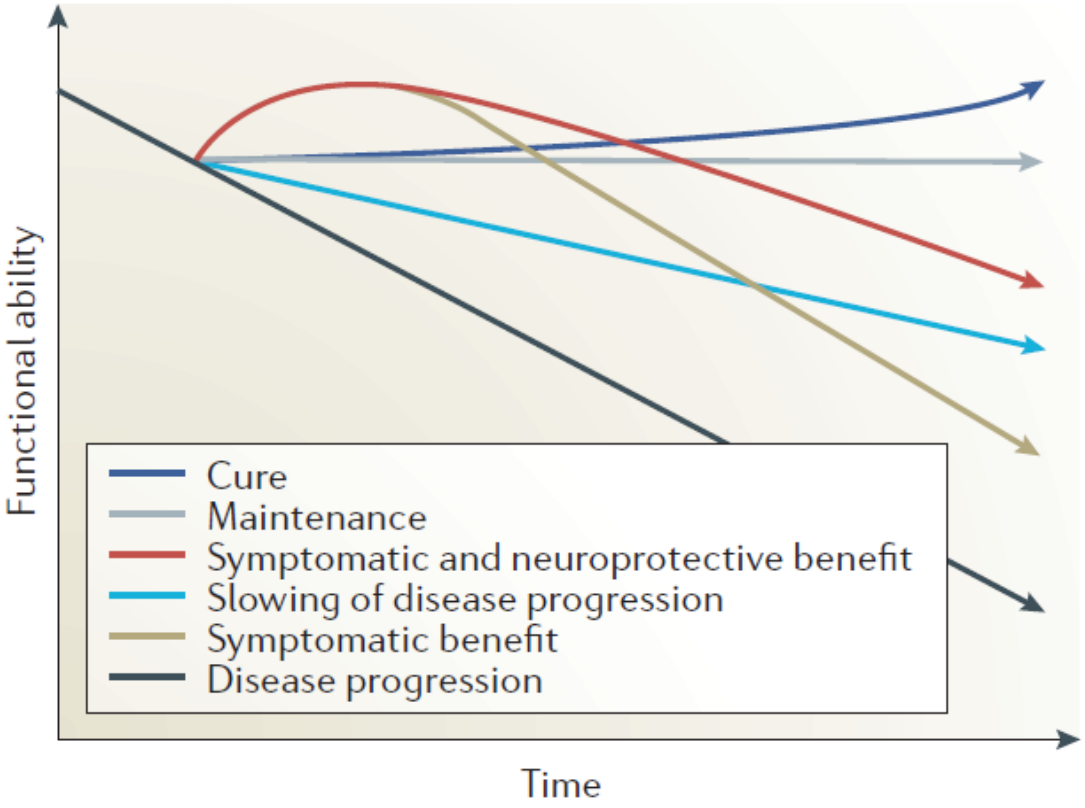
Wanneer een vaccin tegen Alzheimer ?

Peter Paul De Deyn

ziekenhuisnetwerk antwerpen

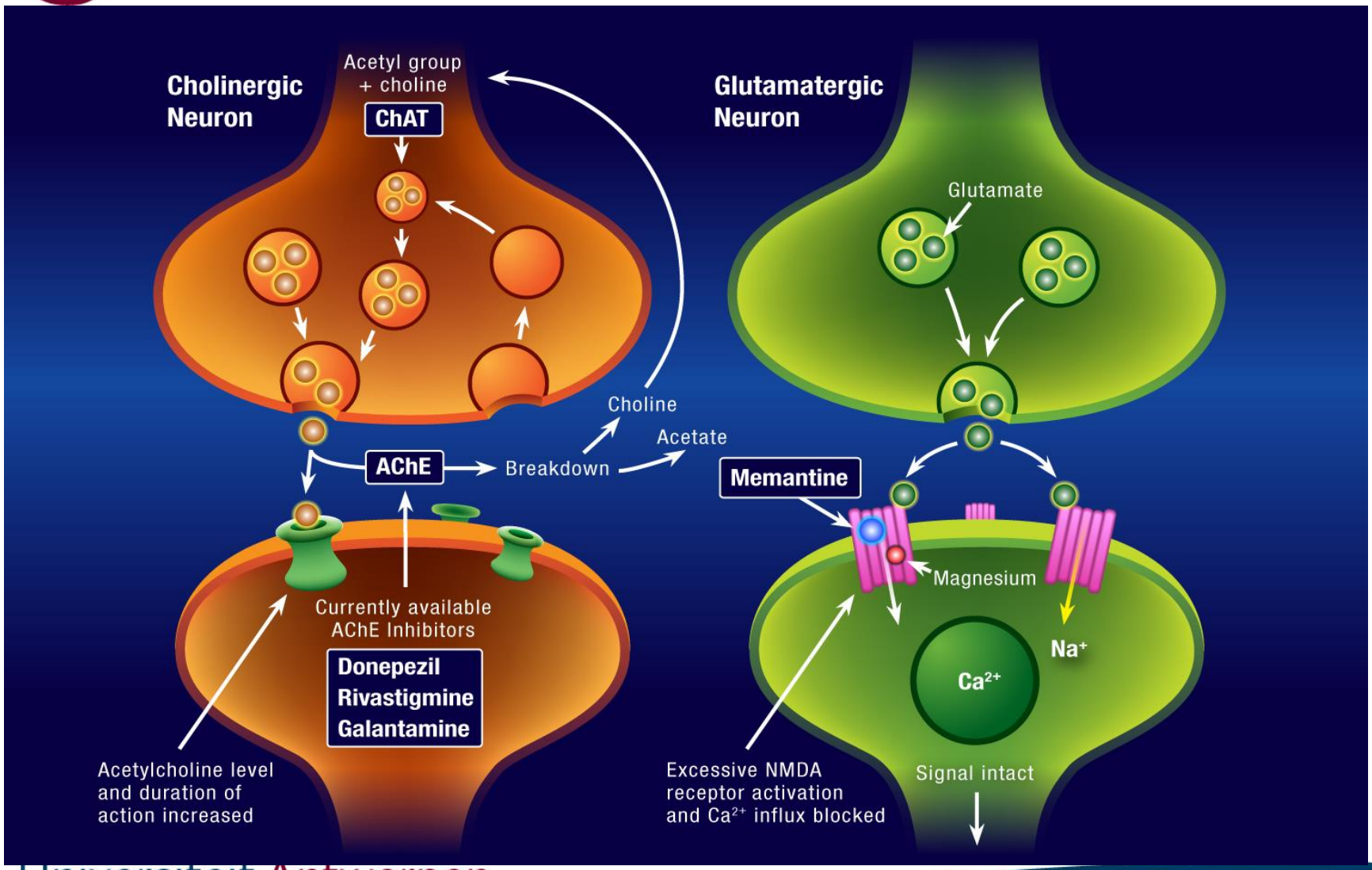
Universiteit Antwerpen

Theoretische mogelijkheden van AD behandeling



Van Dam & De Deyn (2006) Nat. Rev. Drug Discov.

Neurotransmitter-gerichte benadering



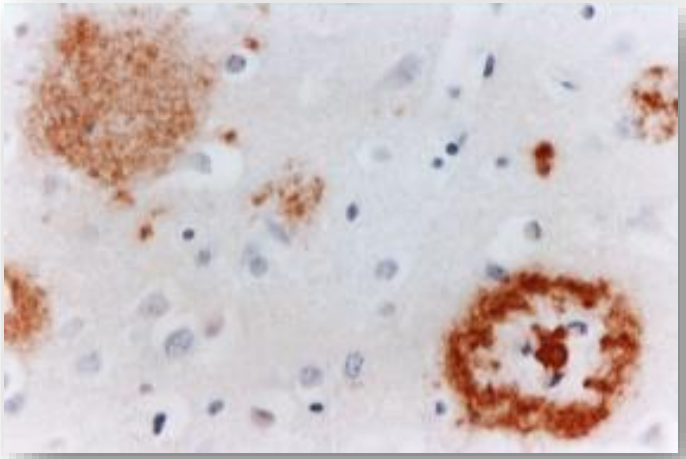
Naar een ziekteproces modificiërende aanpak

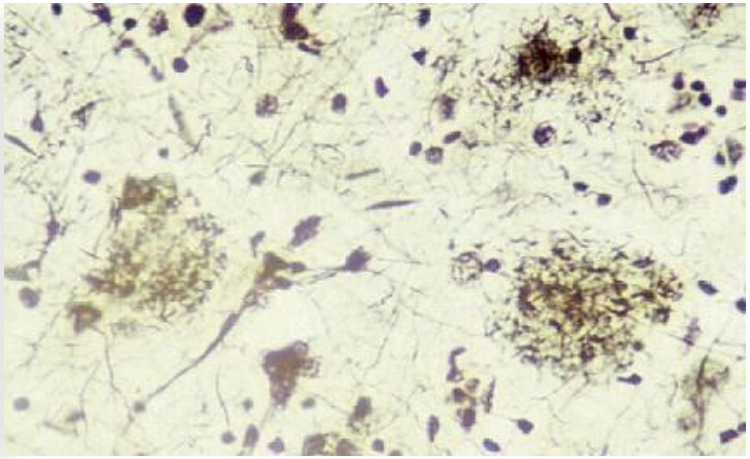
ziekenhuisnetwerk antwerpen

Universiteit Antwerpen

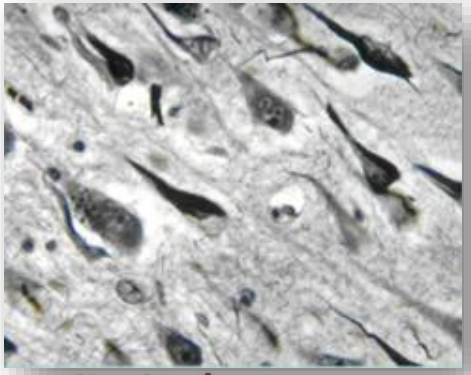
Neuropathologie dementie

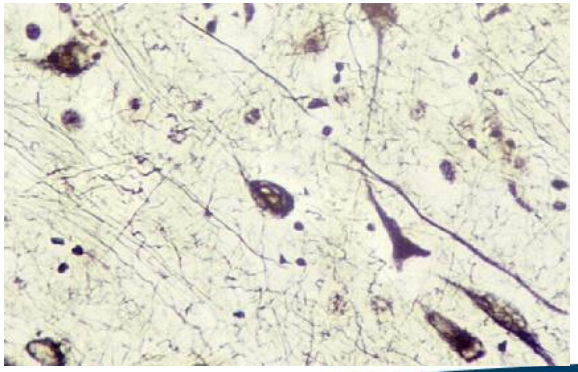
Amyloid plaques





Neurofibrillaire kluwens

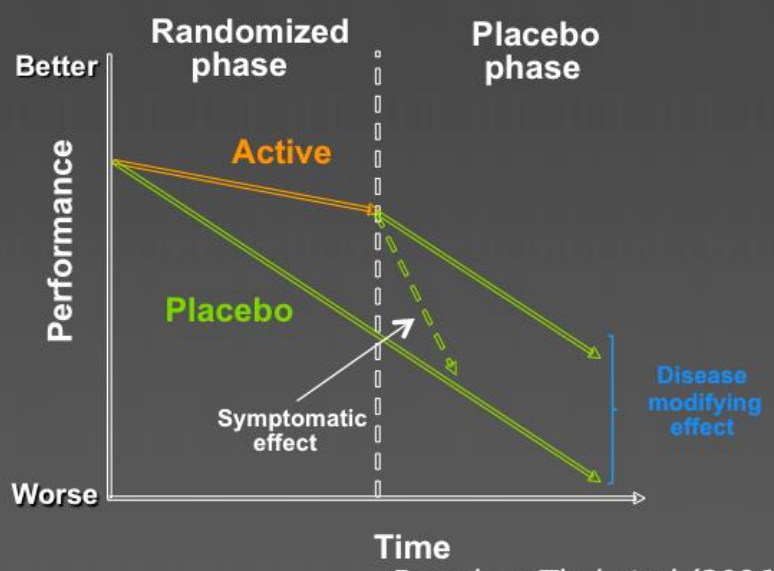




Ziekteproces beïnvloedende trials

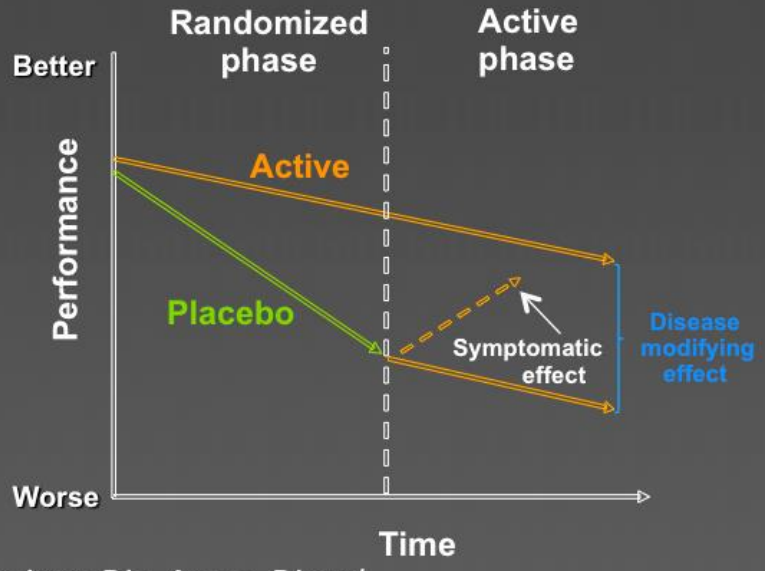
Randomized Withdrawal design

Include a wash-out period and see if any effects are maintained over placebo



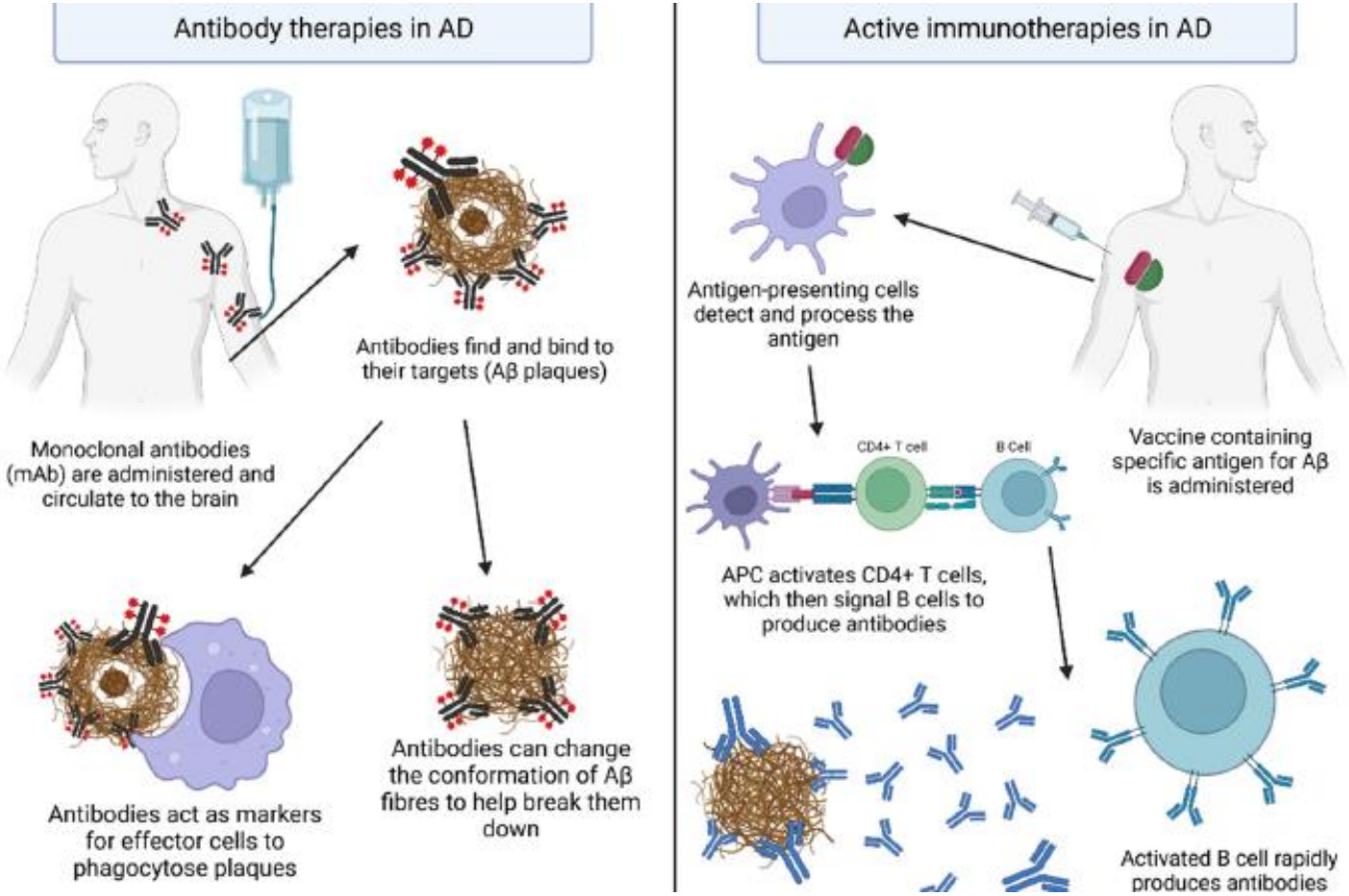
Randomized Start design

Do patients treated for a longer time maintain some benefit over newly treated patients?



Based on Thal et al (2006) Alzheimer Dis. Assoc. Disord.

Vaccinatie versus passive immunotherapy



Vaccins

- **Active Vaccines:**
  - compound AN1792 seemed to have promising effects against β-amyloid and slowing down functional decline
  - however too many potential side effects from the treatment (since it requires the body to produce anti-bodies)
- **Monoclonal Antibodies:** potentially safer since using laboratory or harvested from human blood antibodies
  - **Bapineuzumab** (Salloway et al., 2014) and **Solanezumab** (Doody et al., 2014) = good safety profiles but no significant effect seen.
  - Ongoing trials include patients in very early AD and MCI due to AD stages, while others just include individuals that are at risk to develop AD in the future.
    - **Aducanumab** (By Biogen): All phases completed- On August 2020, granted priority review by the FDA to expedite the approval of the medication
    - Gantenerumab (By Roche)
    - En andere

Passive Immunization

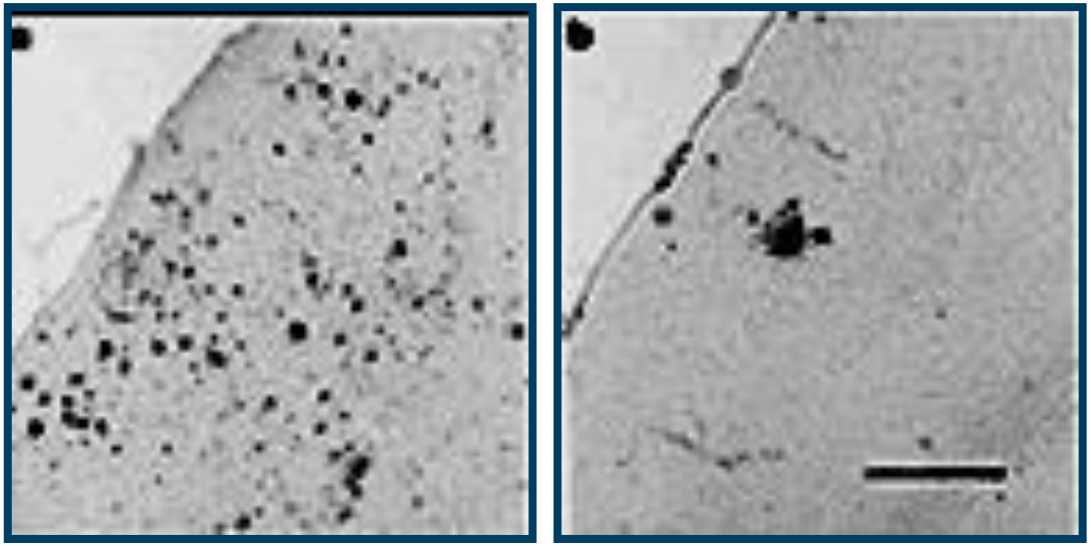
- Monoclonal antibodies in development are designed to target 1 of 3 domains of the Aβ protein: the n-terminus, the middle portion, or the c-terminus.
  - It is possible that efficacy, safety, or both may be substantially different depending on the binding domain.
- Elan/Wyeth, bapineuzumab (AAB-001) is a humanized monoclonal antibody to N-terminus of Aβ in phase III development
- Lilly, LY206430 (a humanized version of m266) targets A β and is in phase II (Bales et al. *Neurobiol Aging. 2004*)
- Others are in development as well

Anti-amyloid Immunotherapy:
Amyloid "Vaccine" Reduces Plaque Burden and Memory Loss in Transgenic Mouse Model of AD

Amyloid Stain (Mouse Brain)

Unvaccinated

Vaccinated



Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse

Dale Schenk, Robin Barbour, Whitney Dunn, Grace Gordon, Henry Grajeda, Teresa Guido, Kang Hu, Jiping Huang, Kelly Johnson-Wood, Karen Khan, Dora Kholodenko, Mike Lee, Zhenmei Liao, Ivan Lieberburg, Ruth Motter, Linda Mutter, Ferdie Soriano, George Shopp, Nicki Vasquez, Christopher Vandevert, Shannan Walker, Mark Wogulis, Ted Yednock, Dora Games & Peter Seubert

Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, California 94080, USA

NATURE | VOL 400 | 8 JULY 1999

Morgan et al. *Nature*. 2000;408:982-985.

Vaccination with AN-1792: First demonstration of reversal of AD neuropathology ?

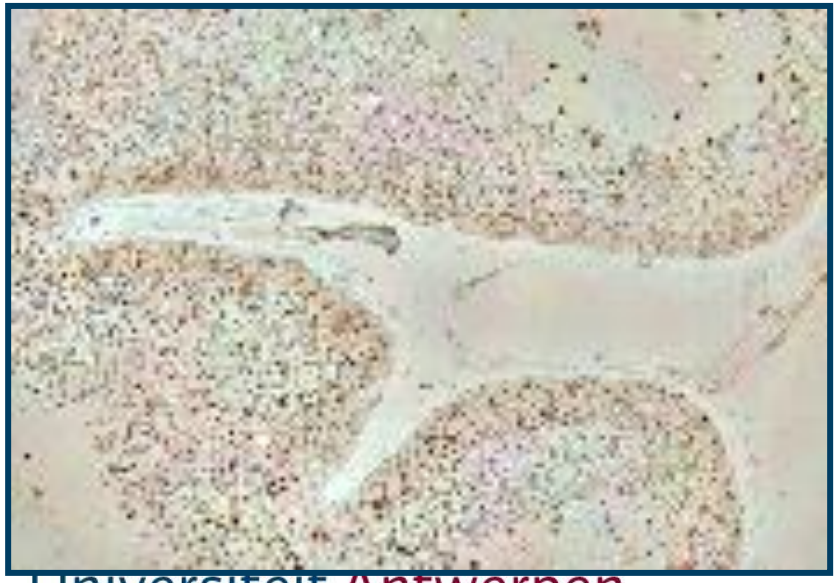
ARTICLES

Neuropathology of human Alzheimer disease after immunization with amyloid-β peptide: a case report

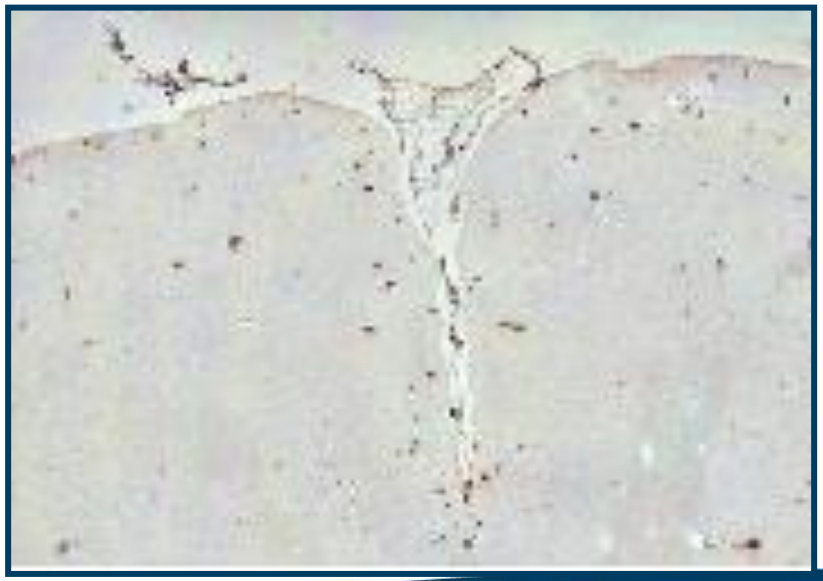
James A.R. Nicoll[1,2], David Wilkinson[1,3], Clive Holmes[1,3], Phil Steart[2], Hannah Markham[1,2] & Roy O. Weller[1,2]

NATURE MEDICINE • VOLUME 9 • NUMBER 4 • APRIL 2003

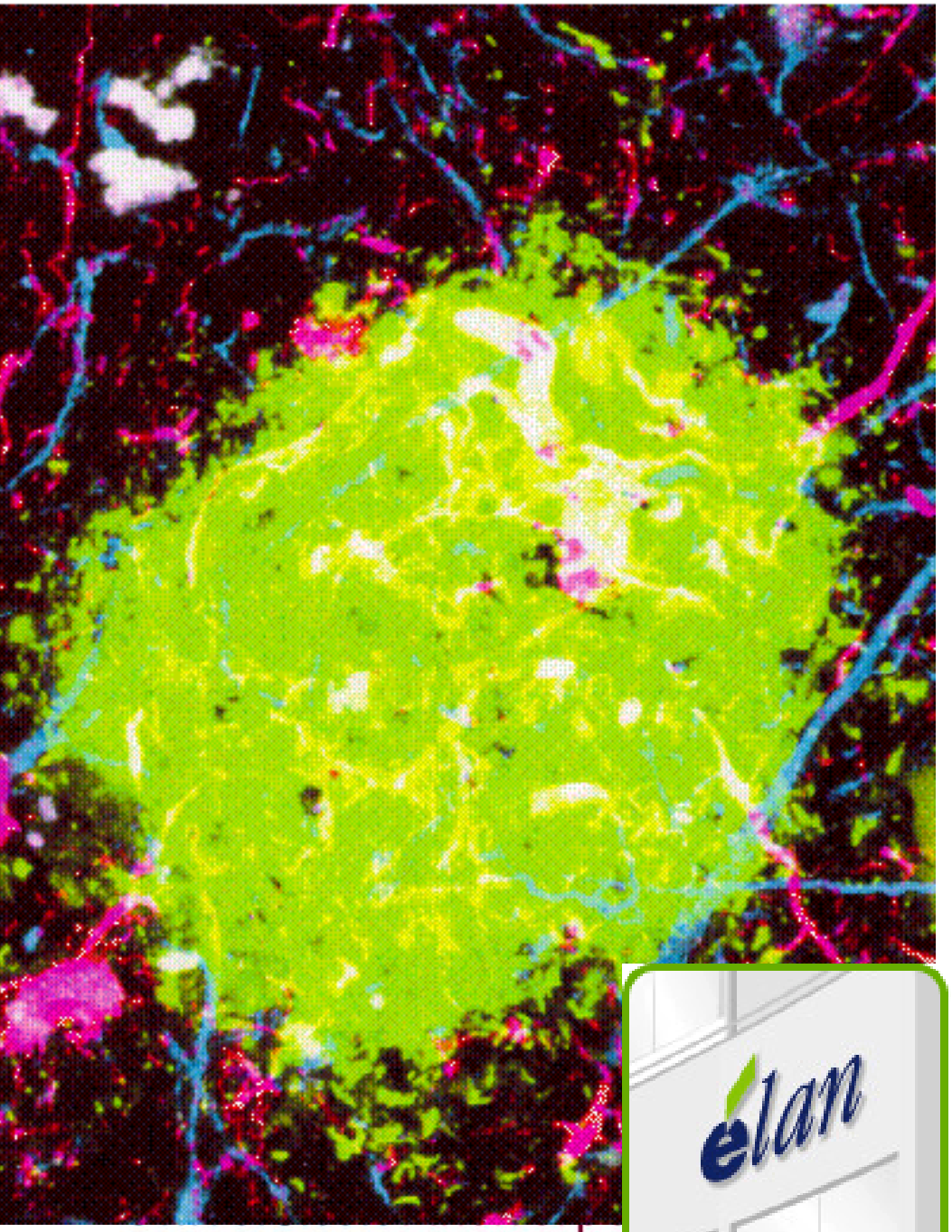
Parietal neocortex, non-immunized patient at comparable stage of AD



Parietal neocortex, immunized AD patient in Elan AN-1792 Trial



Nicoll et al. *Nat Med*. 2003;9:448-452.



Vaccination against Alzheimer's

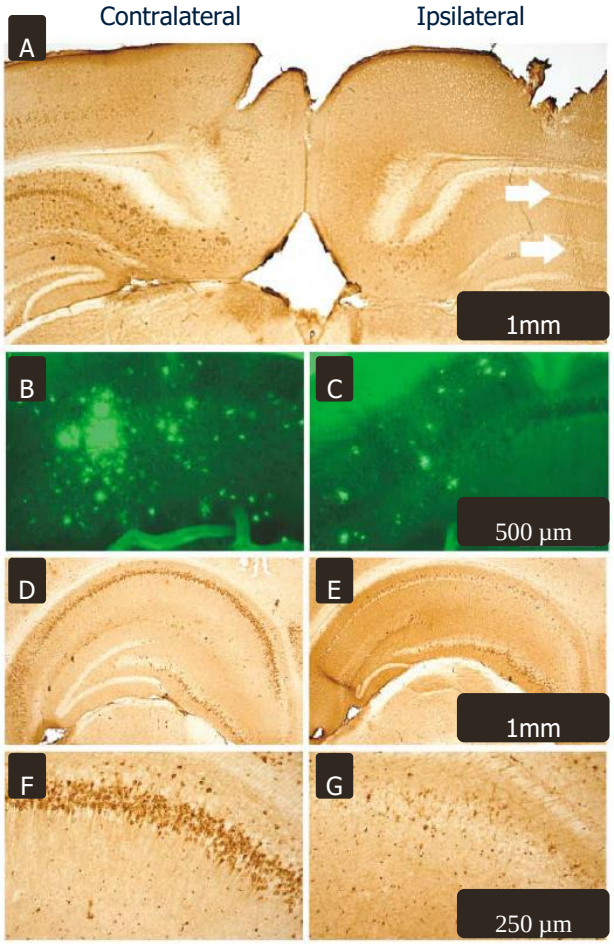
Injecting people with small amounts of β-amyloid protein to raise an immunity to it.

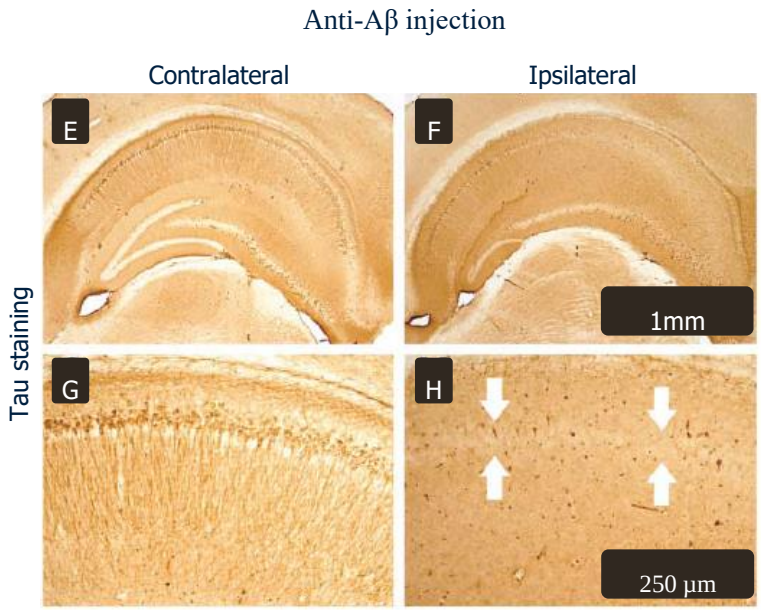
But 6% of test patients got seriously ill.

Vaccins

- **Active Vaccines:**
  - compound AN1792 seemed to have promising effects against β-amyloid and slowing down functional decline
  - however too many potential side effects from the treatment (since it requires the body to produce anti-bodies)
- **Monoclonal Antibodies:** potentially safer since using laboratory or harvested from human blood antibodies
  - **Bapineuzumab** (Salloway et al., 2014) and **Solanezumab** (Doody et al., 2014) = good safety profiles but no significant effect seen.
  - Ongoing trials include patients in very early AD and MCI due to AD stages, while others just include individuals that are at risk to develop AD in the future.
    - **Aducanumab** (By Biogen):
    - Gantenerumab (By Roche)
    - En andere

Preclinische data met AAB-001 (bapineuzumab)





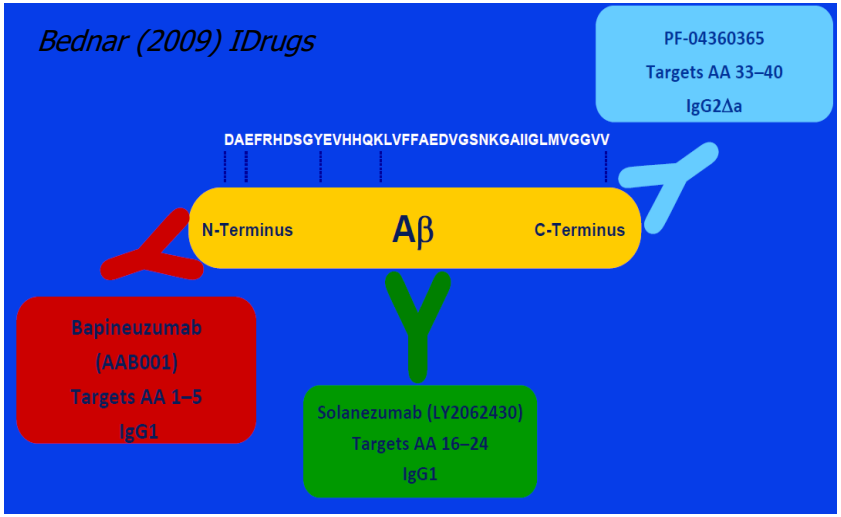
Bapineuzumab
(orig. Elan & Wyeth)

- AAB-001, ELN-115727
- Passive immunization
- Bapi-neu-zu-mab

Neuro(logical)

Humanized

Monoclonal antibody



- Previous results (review: Kerchner & Boxer, 2010; Expert Opin Biol Ther)
  - Reduction CNS amyloid burden
  - Primary efficacy outcomes phase II not sginificant
  - Post-hoc: Efficacy limited to non-ApoE4 carriers?
  - Dose-dependent vasogenic edema (+ link to ApoE4?)

N Engl J Med. 2014 January 23; 370(4): 322–333. doi:10.1056/NEJMoa1304839.

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

CONCLUSIONS—Bapineuzumab did not improve clinical outcomes in patients with Alzheimer's disease, despite treatment differences in biomarkers observed in *APOE ε4* carriers.

tinued)

Drug	Mechanism	Sponsor	Study population	Admin	Phase	Results	Clinical Trial Identifier	Start date	Estir
Aducanumab (BIIB037)	Monoclonal antibody	Biogen	Early AD	IV	III	Terminated	NCT02484547	2015 Sept	2019
			Early AD		III	Terminated	NCT02477800	2015 Aug	2019
			Early AD		III	Active, not recruiting	NCT04241068	2020 Mar	2023
Crenezumab (RG7412)	Monoclonal antibody	Roche/AC Immune SA	Prodromal to mild AD	IV	III	Terminated	NCT02670083	2016 Mar	2019
			Prodromal to mild AD		III	Terminated	NCT03114657	2017 Mar	2019
			Prodromal to mild AD		III	Terminated	NCT03491150	2018 Apr	2019
Lecanemab (BAN2401)	Monoclonal antibody	Biogen /Eisai	Early AD	IV	III	Recruiting	NCT03887455	2019 Mar	2024
			Preclinical AD		III	Recruiting	NCT04468659	2020 Jul	2027
Donanemab (LY3002813)	Monoclonal antibody	Eli Lilly	Early symptomatic AD	IV	III	Recruiting	NCT04437511	2020 Jun	2023
			Preclinical AD		III	Recruiting	NCT05026866	2021 Aug	2027

isease; Admin, Route of administration; SC, subcutaneous; IM, intramuscular; IV, intravenous

Recente data en een FDA approved product

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

Alzheimer's disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.

50 | NATURE | VOL 537 | 1 SEPTEMBER 2016

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

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50 | NATURE | VOL 537 | 1 SEPTEMBER 2016

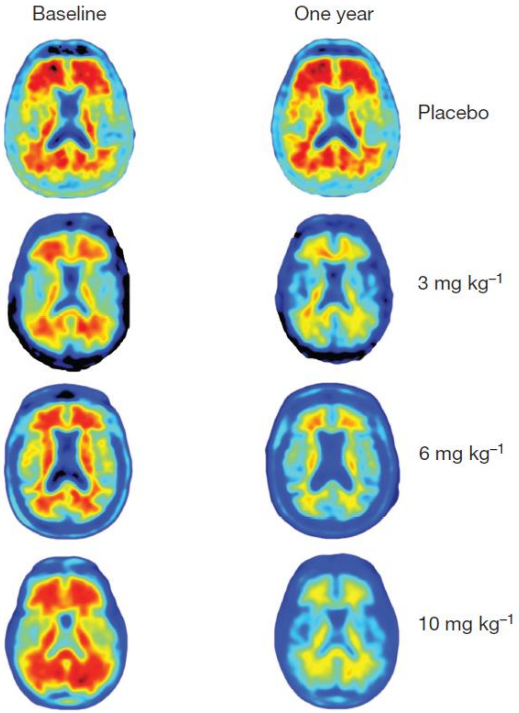


Figure 1 | Amyloid plaque reduction with aducanumab

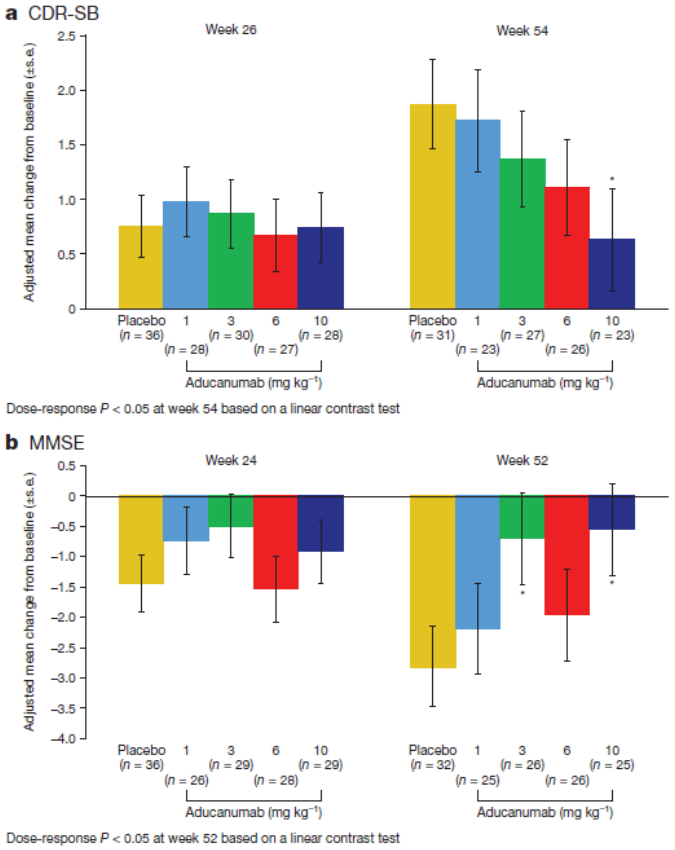


Table 2 | Summary of adverse events and most common adverse events

		Aducanumab			
Adverse event (*n* (%))	Placebo (*n* = 40)	1 mg kg^{-1} (*n* = 31)	3 mg kg^{-1} (*n* = 32)	6 mg kg^{-1} (*n* = 30)	10 mg kg^{-1} (*n* = 32)
Any adverse event	39 (98)	28 (90)	27 (84)	28 (93)	29 (91)
Serious event	15 (38)	3 (10)	4 (13)	4 (13)	12 (38)
Discontinuing treatment due to an adverse event	4 (10)	3 (10)	2 (6)	3 (10)	10 (31)
Common adverse events					
ARIA	2 (5)	2 (6)	4 (13)	11 (37)	15 (47)

pubs.acs.org/chemneuro

Editorial

FDA Approval of Aducanumab Divided the Community but Also Connected and United It

Cite This: *ACS Chem. Neurosci.* 2021, 12, 2716–2717

Read Online

Lecanemab

Swanson *et al. Alzheimer's Research & Therapy* (2021) 13:80
https://doi.org/10.1186/s13195-021-00813-8

Alzheimer's Research & Therapy

RESEARCH Open Access

A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody

LECANEMAB CONFIRMATORY PHASE 3 CLARITY AD STUDY MET PRIMARY ENDPOINT, SHOWING HIGHLY STATISTICALLY SIGNIFICANT REDUCTION OF CLINICAL DECLINE IN LARGE GLOBAL CLINICAL STUDY OF 1,795 PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE

SEPTEMBER 27, 2022 • INVESTOR RELATIONS

- *ALL KEY SECONDARY ENDPOINTS ALSO MET, DEMONSTRATING HIGHLY STATISTICALLY SIGNIFICANT RESULTS*
- *PROFILE OF AMYLOID-RELATED IMAGING ABNORMALITIES (ARIA) INCIDENCE WAS WITHIN EXPECTATIONS*
- *EISAI AIMS TO FILE FOR TRADITIONAL APPROVAL IN THE U.S., AND TO SUBMIT MARKETING AUTHORIZATION APPLICATIONS IN JAPAN AND EUROPE BY THE END OF EISAI FY2022, WHICH ENDS ON MARCH 31, 2023*

Gantenerumab / negatief 14.11.22

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Genentech, a member of the Roche Group (SIX: RO, ROG; OTCQX: RHHBY), today announced results from the Phase III GRADUATE I and II studies evaluating gantenerumab in people with mild cognitive impairment (MCI) due to Alzheimer's and mild Alzheimer's dementia, collectively called early Alzheimer's disease. The studies did not meet their primary endpoints of slowing clinical decline. Gantenerumab was well tolerated including the subcutaneous administration.

"So many of our families have been directly affected by Alzheimer's, so this news is very disappointing to deliver"

Tweet this

"So many of our families have been directly affected by Alzheimer's, so this news is very disappointing to deliver," said Levi Garraway, M.D., Ph.D., chief medical officer and head of Global Product Development. "We are profoundly grateful to the study participants, their care partners and study sites for their contributions to this research. While the GRADUATE results are not what we hoped, we are proud to have delivered a high quality, clear and comprehensive Alzheimer's dataset

New Treatments targeting neurofibrillary tangles are needed

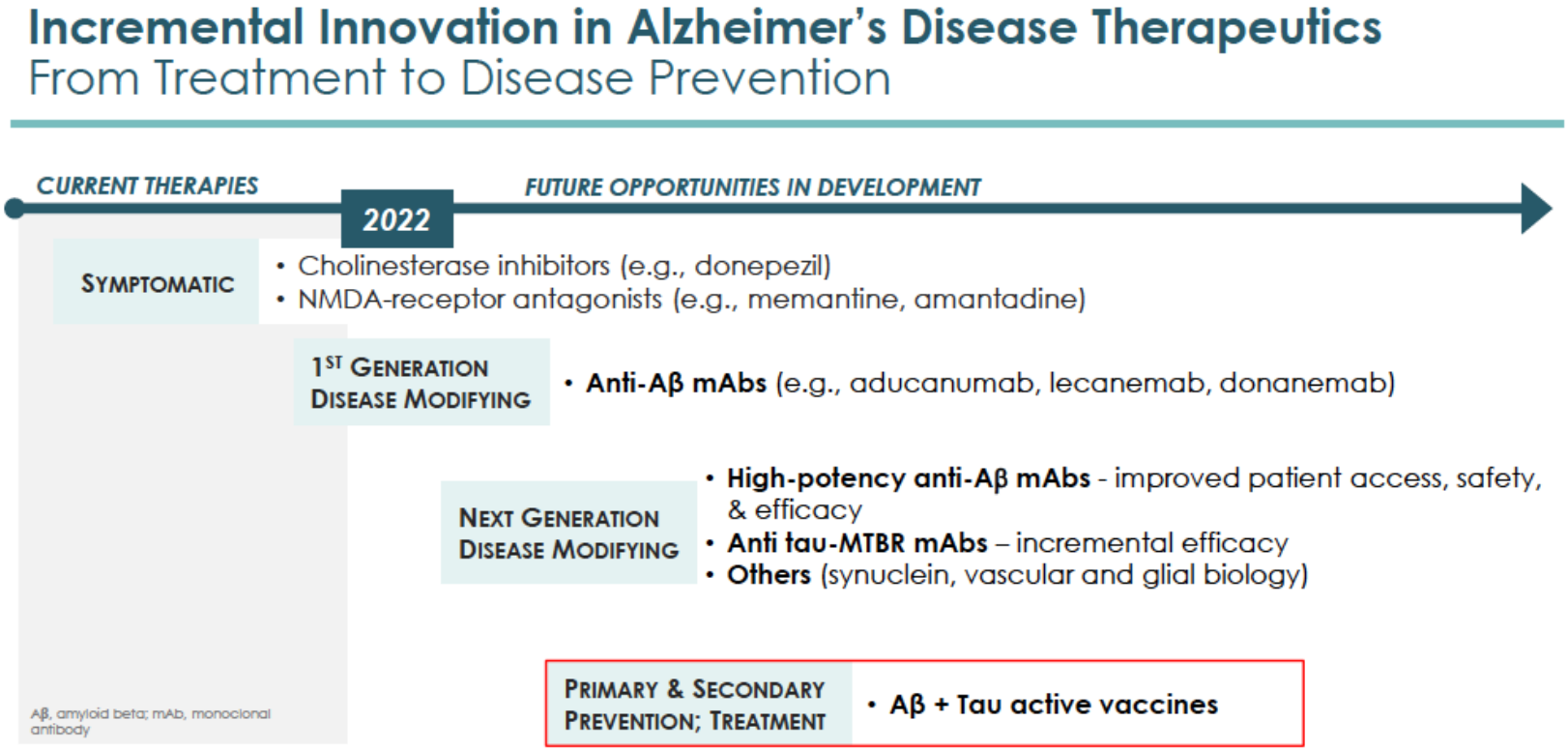
- Anti-Tau treatment is now considered as important as anti-β-amyloid in AD progression.
- Also, tau seems the primary cause of cell death in other related dementias as CTE, and Primary Age-Related Tauopathy (PART)- *no β-amyloid involvement in these dementia types.*
- Anti-tau treatments have become a major focus in the current research to block tau aggregation and block tau spreading from cell to cell (Congdon & Sigurdsson, 2018)

Anti-Tau Treatments in progress:

1. TauRX compound LMTB: Phase III tested in mild to moderate AD with negative results. Currently looking at its effect in early Alzheimer's Disease.
2. New Phase II trials (focus on MCI, and early AD using positive tau and β-amyloid PET scans) –initiated in 2019
    a. Gosuranemab (by Biogen)
    1. Zagotenemab (by Lilly)

- Since these trials started, many other anti-tau studies initiated using both drugs and biologics (Cummings et al., 2019)

Gecombineerd anti amyloid/tau



microorganisms

MDPI

Article

Evaluation of BCG Vaccination and Plasma Amyloid: A Prospective, Pilot Study with Implications for Alzheimer's Disease

Coad Thomas Dow [1,2,*], Charles L. Greenblatt [3], Edward D. Chan [4,5,6] and Jordan F. Dow [7,8]

Microorganisms **2022**, *10*, 424. https://doi.org/10.3390/microorganisms10020424

https://doi.org/10.1093/braincomms/fcac022 BRAIN COMMUNICATIONS 2022: Page 1 of 7 | 1

BRAIN COMMUNICATIONS

An amyloid beta vaccine that safely drives immunity to a key pathological species in Alzheimer's disease: pyroglutamate amyloid beta