Alzheimers sjukdom;
behandling med fokus på framtiden

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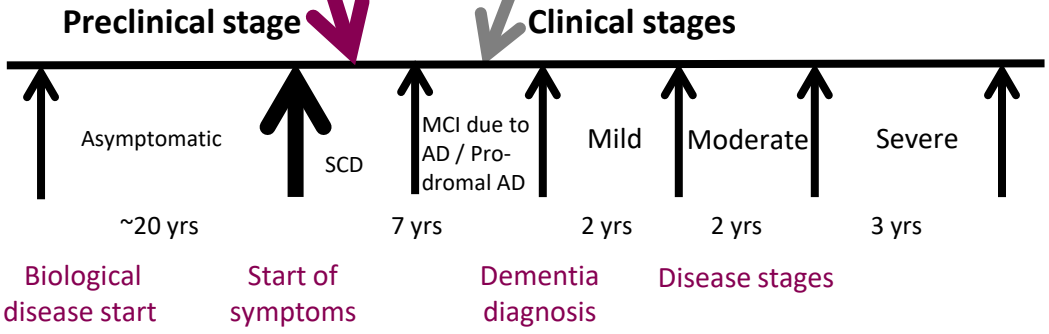
Redovisning av jäv

- Har deltagit i medicinskt rådgivarmöte: BioArtic (2022), Artery Therapeutics (senaste 5 åren), Axon Neuroscience (senaste 5 åren)

A stadium most often recognized by the patient, but not by the doctor using traditional assessment!

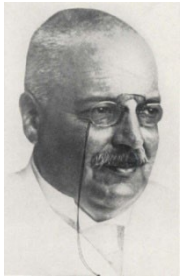
Objective impairment but not enough for dementia diagnosis.
Still, biomarkers give high significance for neurodegenerative etiology.



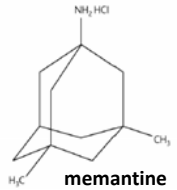
”Brain at risk”

SCD= Subjective Cognitive Decline
MCI= Mild Cognitive Impairment

Therapy in AD: The first hundred years and looking forward…….



NMDA, uncompetitive receptor antagonist

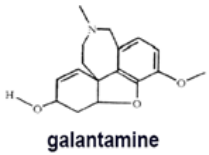


memantine

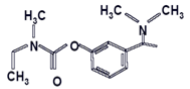
1906 1910 1974 1982 1997 2004 2010 2015 2021-2023

The cholinergic hypothesis

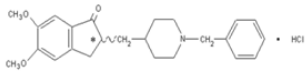
Acetylcholinesterase inhibitors



galantamine



rivastigmine



donepezil

First Disease Modifying Rx aducanumab and lecanemab fully approved by FDA in US (amyloid-beta & tau).

Donanemab got accelerated approval by FDA June 2023

Current treatment recommendations

	AD	LBD	Mixed Dementia	VaD	FTD	MCI
Donepezil	X	X	X			?
Rivastigmine	X	X	X			?
Galantamine	X		X			?
Memantine	X	x	x			
Combination therapy	X					

None of the above recommended for treatment of VaD, FTD or MCI.
Weak recommendation for treatment of LBD and/or Mixed Dementia with memantine.

Huge potential in early AD – DMTs (Disease Modifying Treatments)

CLINICAL BENEFIT

- ✓ **Slow the progression of cognitive and functional decline** of AD
- ✓ Provide enduring **clinical benefits that are not lost when treatment is withdrawn (?)**
- × Symptom improvement not expected

MODE of ACTION (MoA)

- ✓ Drugs **target underlying causes of disease,** interrupting pathways of neuronal damage or death (neurodegeneration)
- ✓ Effect can be measured via biomarkers including amyloid, tau, neurodegeneration and potentially neuroinflammation*

TREATMENTS

- ✓ **Currently, DMTs for patients are only available in the USA (under EMA decision)**
- ✓ **Anti-amyloid Abs** (aducanumab, lecanemab, donanemab)**:** FDA-approved or under assessment

SIDE EFFECTS

- ✓ Anti-amyloid mAbs: **amyloid-related imaging abnormalities** (ARIA)
- ✓ Awaiting adverse events for other DMTs

DMTs target underlying causes of AD and are expected to have enduring clinical benefits over time

Cummings J, Fox N. J Prev Alzheimers Dis 2017;4:109–15.

There are currently 36 DMTs in phase 3 development

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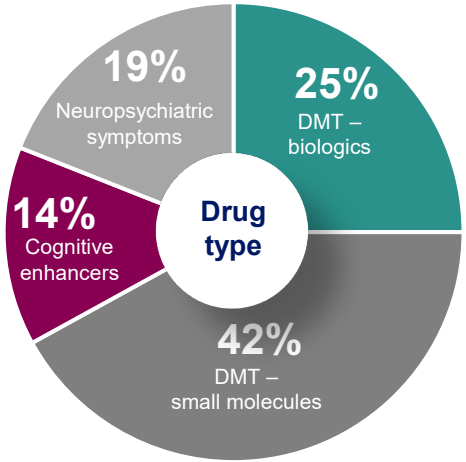
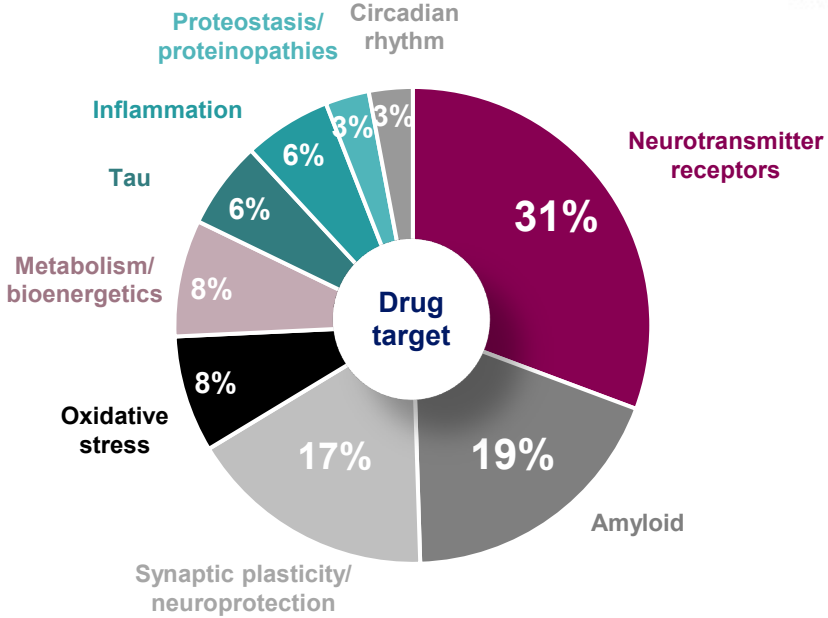
Overview of drugs in phase 3

Phase 1: 31 agents

Phase 2: 87 agents

Phase 3: **36** agents





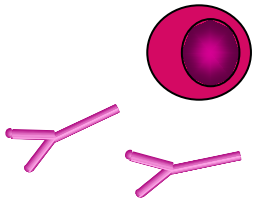
Cummings J et al. Alzheimers Dement (N Y) 2023;9:e12385.

Active & Passive Immunotherapy against Aβ

Active immunotherapy ("vaccination")

β-amyloid

Immunisation with β-amyloid + immune stimulating adjuvans



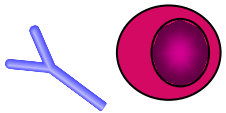
The immune system forms antibodies against β-amyloid

The antibodies bind to oligomers and plaques

Passive immunotherapy

β-amyloid

Mice are immunized with β-amyloid



The mice form antibodies against β-amyloid

Mice antibodies are being humanized

After injection of antibodies, they bind to oligomers and plaques

Tau Vaccine (AADvac1, active immunotherapy)

- phase 1 study

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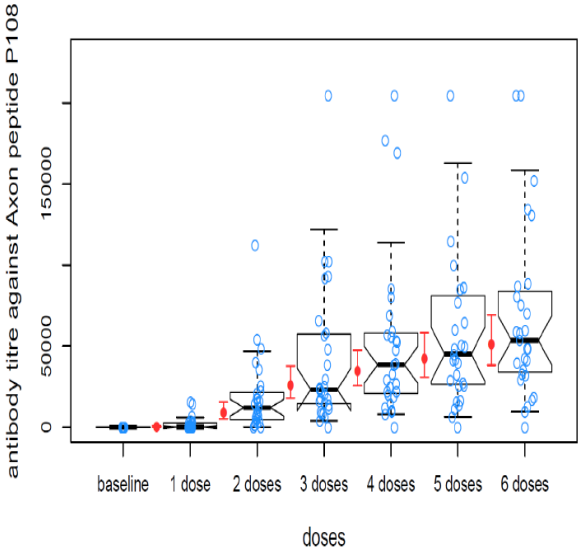
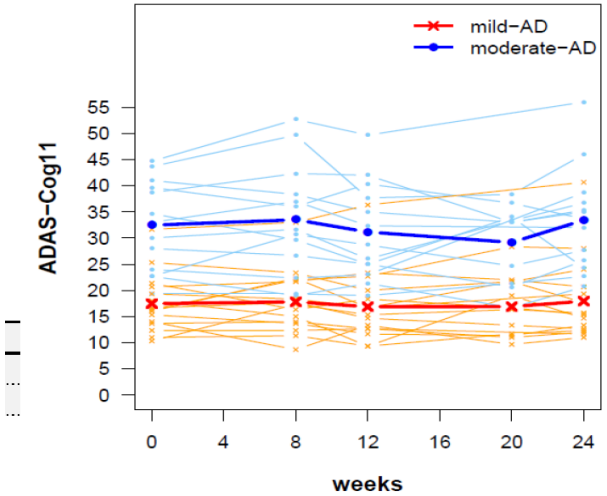
Immunogenicity

Robust immune response



Cognition

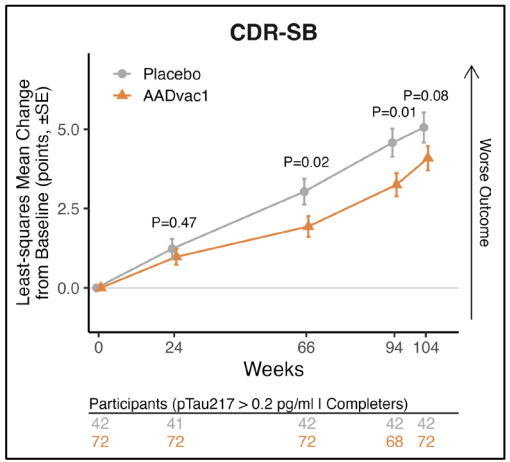
Mean ADAS-Cog score stable over 6 months



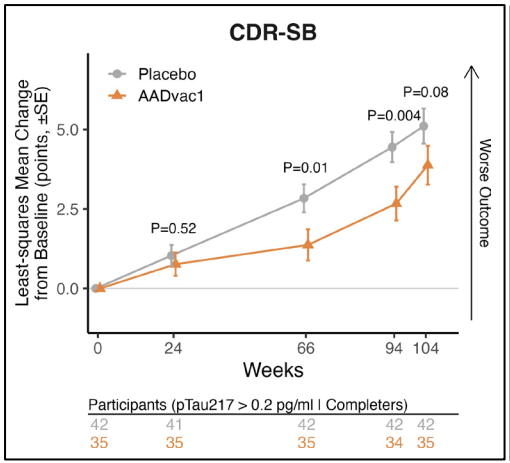
Novak P et al, Lancet Neurol 2016

AADvac1 THERAPEUTIC EFFECT IS MORE PRONOUNCED IN PATIENTS WITH HIGHER ANTIBODY RESPONSE

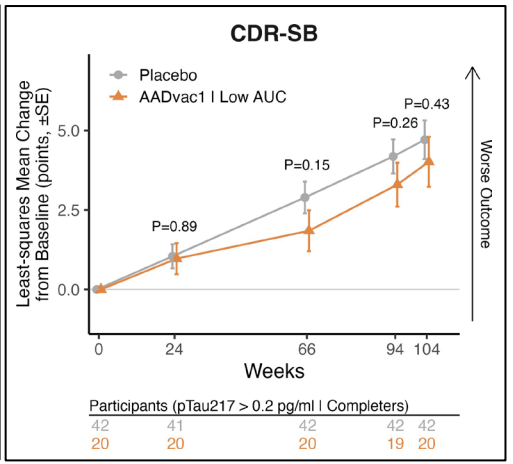
Cognition: CDR-SB (*ALL COMPLETERS*)



Cognition: CDR-SB (*HIGH ANTIBODY RESPONDERS*)



Cognition: CDR-SB (*LOW ANTIBODY RESPONDERS*)



MMRM analysis for given endpoint.
All models were adjusted for the baseline and time-interaction effects of age, sex, geographical region, baseline MMSE, baseline plasma NF-L, years of education, memantine use and APOE status.

The patients were divided into quantiles according to the level of antibody response. High antibody responders represent Q1-Q2, low antibody responders represent Q4

Novak et al, Nature Aging 2021

Aducanumab (BIIB037) –
passive immunotherapy against amyloid-β

Two phase III trials: EMERGE and ENGAGE

- March 2019 – both studies discontinued due to no effect
- October 2019 – Additional data, larger dataset phase III
  → Dose-dependent effect (higher dose effective) in reducing brain amyloid and clinical decline (assessed by CDR-SB, MMSE, ADAS-Cog13 and ADCS-ADL)
- June 2021 – (accelerated) approval by FDA
- Dec 2021 – rejected by EMA due to too low clinical effect plus side effects

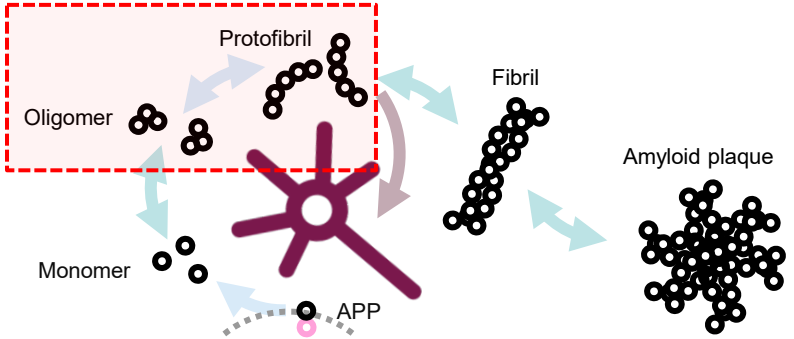
Lecanemab drug profile – Mode of Action (MoA)

(developed by Lars Lannfelt, BioArctic, Sweden)

Lecanemab:

- A humanized IgG1 monoclonal antibody
- Targets amyloid species
- >1,000-fold selectivity for neurotoxic forms of soluble oligomers and protofibrils over monomers[1,2]
- FDA approval January 2023

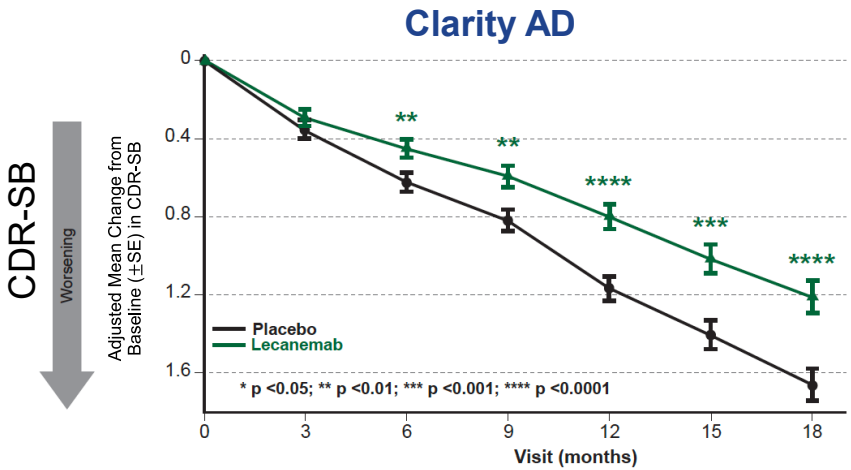
Lecanemab MoA

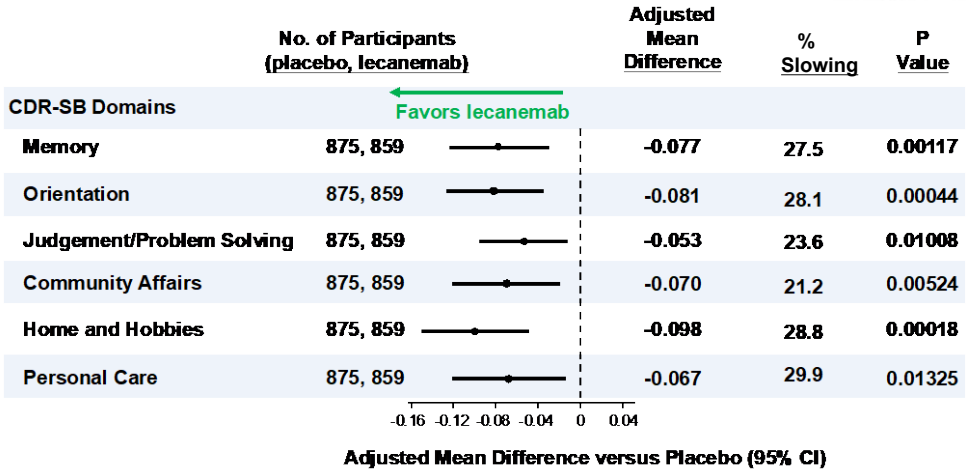


1. Hampel H et al. Mol Psychiatry 2021;26:5481–503;
2. van Dyck CH et al. N Engl J Med 2023;388:9–21.

Clarity AD (phase 3) Treatment Effect: CDR-SB

(*Global Measure of Cognition and Function*)





CDR-SB Scale

- Patient and caregiver interview
- Rates 6 cognitive and functional domains
- Each domain scored from 0, 0.5, 1, 2 for range of 0-18
- MCI and mild AD tend to score 0.5 or 1 in each domain
- Baseline CDR-SB was 3.2

Lecanemab Effect

- 27% slowing on CDR-SB
- Increased magnitude of separation over time (0.45 at 18 months)
- Effect seen across all CDR-SB domains

From press release BioArctic October 25, 2023 - subcutaneous administration

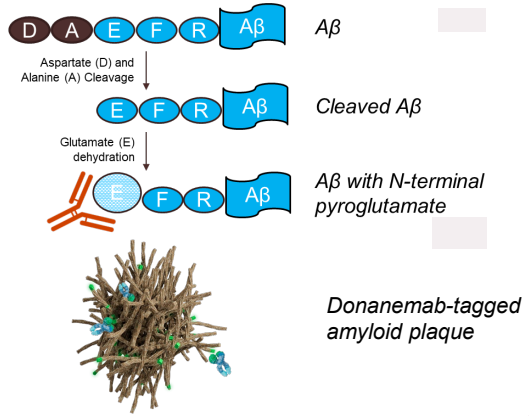
- New data for lecanemab from phase 3 Clarity AD with subcutaneous administration presented at CTAD October 2023
- Subcutaneous treatment with lecanemab gives 14% higher reduction of amyloid plaques as measured by PET, compared to intravenous administration.
- Pharmacokinetics shows 11% higher exposition but similar frequency of ARIA.
- For the tau-PET subpopulation the effects of lecanemab were particularly clear regarding cognition and function in the early stages of AD.

Donanemab drug profile – MoA

Donanemab:

- A humanized IgG1 monoclonal antibody
- Directed against an insoluble, modified N3pG, present only in brain amyloid plaques
- New drug application submitted to both the FDA and EMA

Donanemab MoA



Donanemab (Trailblazer) – latest reported positive immunotherapy study

- Eli-Lilly, USA reported in a press release May 3, 2023 positive top-line results for donanemab from the phase 3 TRAILBLAZER-ALZ2 study.
- Antibody treatment during 18 months targeting amyloid beta aggregates (plaques) in the brain
- 1,736 persons with mild cognitive impairment due to AD or mild dementia due to AD
- Result: 35% less cognitive and functional decline (iADRS)
- 31.4% reported side effects such as brain microbleeds (ARIAs), (13.6% on placebo). Two cases of deaths related to treatment

Comparison:
Phase 3 studies with DMTs lecanemab and donanemab

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Difference in study populations

Different cognitive and ADL scales

CDR-SB is a common scale, but its outcome is also influenced by the different study populations

In summary

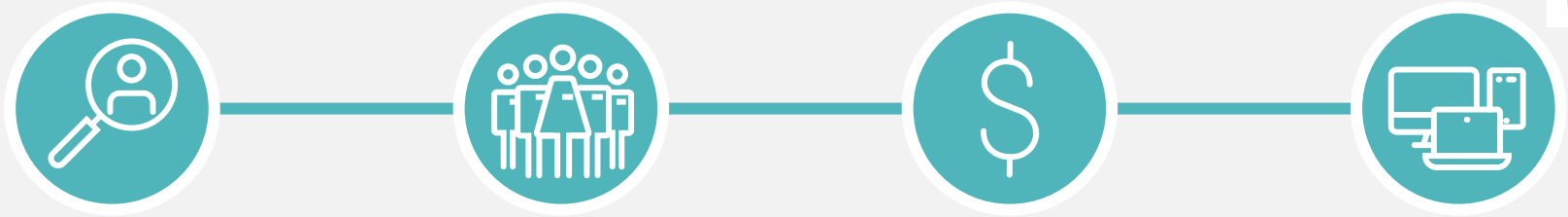
These differences make it **difficult to properly compare** the results from these two studies

Side effects

Owing to their differences, it is also difficult to properly evaluate the reported side effects from these two studies

However, these two studies represent very positive findings, giving hope for future treatment of AD.

Early diagnosis and capacity challenges in an era of DMTs



If DMTs become widely available, more patients with cognitive decline will **seek cognitive testing**

A **lack of AD specialists** might mean that **demand** for cognitive tests **outstrips supply**

Substantial investments will be needed to keep patients' waiting times low

Digital cognitive assessments, blood tests and other **future diagnostic technologies** could help manage the increase in demand

Capacity challenges could have a negative impact on early diagnosis, as a lack of AD specialists might lead to long waiting lists for cognitive testing and diagnosis

AD, Alzheimer's disease; DMT, disease-modifying treatment.
Mattke S et al. J Prev Alzheimer Dis 2023. https://doi.org/10.14283/jpad.2023.94.

Pricing and budget impact of lecanemab

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Estimated 5.4 million individuals in 27 EU countries in 2023

Potential eligible patient population

Prodromal AD/MCI due to AD or mild dementia due to AD

Unsustainable cost of 133 billion EUR per year

Price estimation based on US pricing

26,500 USD (24,766 EUR) per patient

Challenges and extra costs associated with treatment strategy

- Treatment administration and monitoring cost
- Optimalisation diagnostic process
- Identification of eligible patients
- Impact of adverse events

If a treatment is not demonstrated to be cost-effective, healthcare systems may not be willing to invest in diagnostic services

Jönsson L et al. Lancet Reg Health Eur 2023;29:100657.

Research – the only way forward to treatment

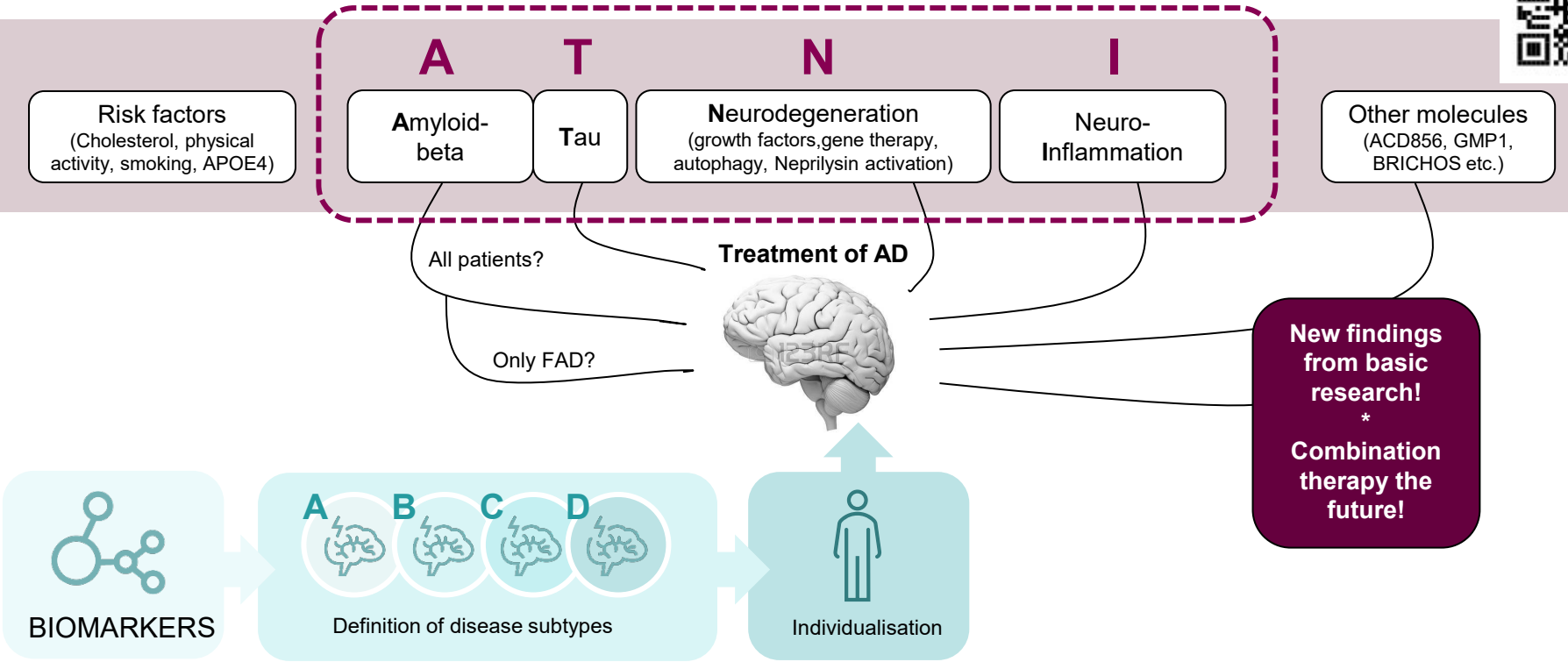

Figure adapted from Cedazo-Minguez A and Winblad B 2010;45:5–14.

Acknowledgements

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