



**Karolinska  
Institutet**

# **Alzheimers sjukdom; behandling med fokus på framtiden**

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Dept NVS

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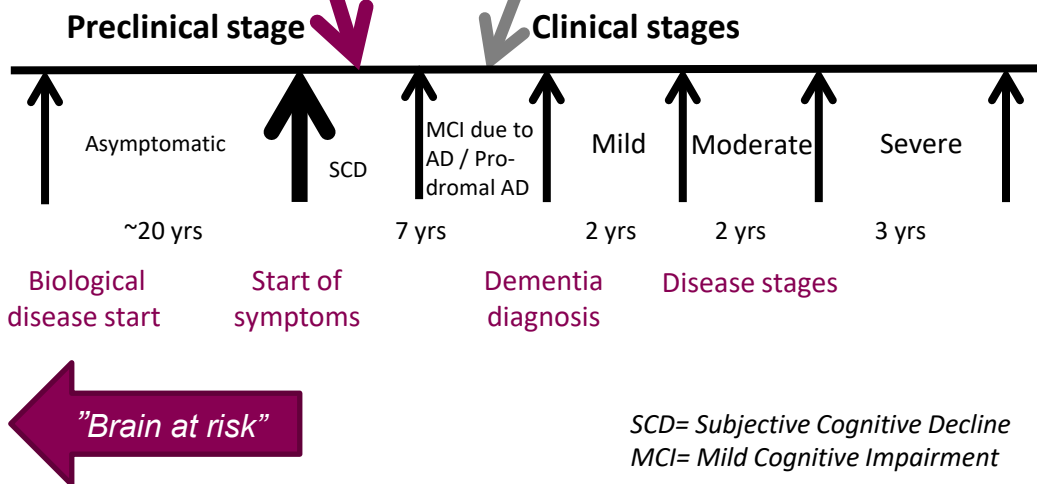
## Redovisning av jäv

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



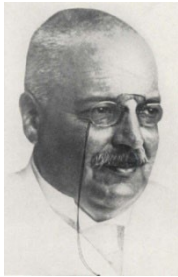
A stadium most often recognized by the patient, but not by the doctor using traditional assessment!

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

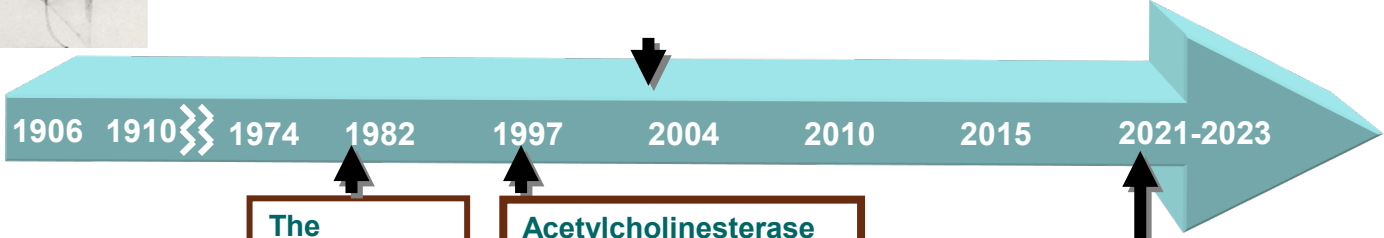
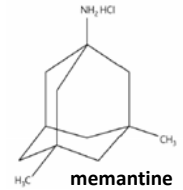


SCD= Subjective Cognitive Decline  
MCI= Mild Cognitive Impairment

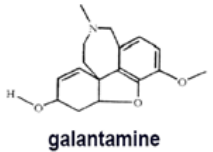
# Therapy in AD: The first hundred years and looking forward.....



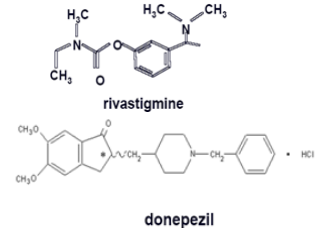
**NMDA,  
uncompetitive  
receptor  
antagonist**



**The  
cholinergic  
hypothesis**



**Acetylcholinesterase  
inhibitors**



**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

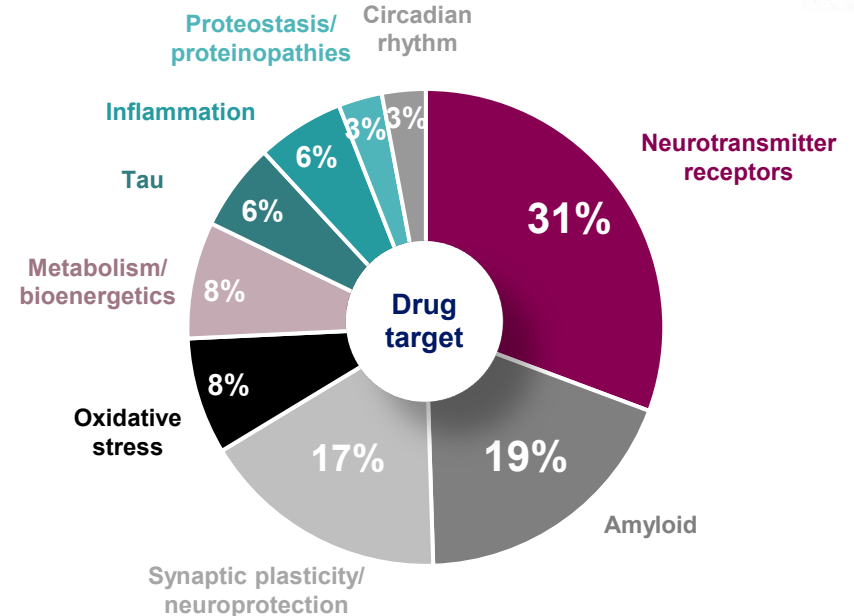
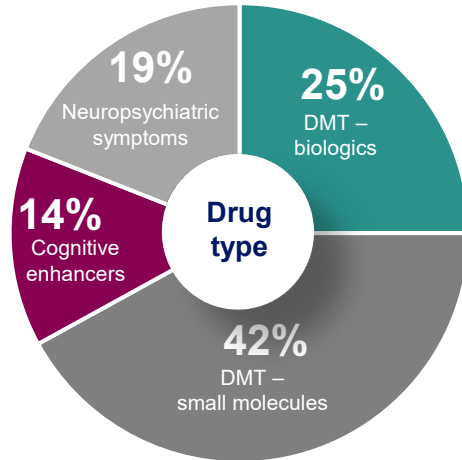


## Overview of drugs in phase 3

**Phase 1:**  
31 agents

**Phase 2:**  
87 agents

**Phase 3:**  
36 agents



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

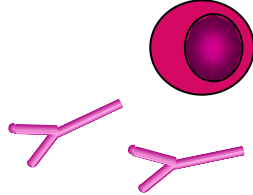
# Active & Passive Immunotherapy against A $\beta$



## Active immunotherapy ("vaccination")

$\beta$ -amyloid

Immunisation with  $\beta$ -amyloid +  
immune stimulating adjuvans



The immune system forms antibodies  
against  $\beta$ -amyloid



The antibodies bind to oligomers and plaques

## Passive immunotherapy



$\beta$ -amyloid

Mice are immunized with  $\beta$ -amyloid



The mice form antibodies  
against  $\beta$ -amyloid

Mice antibodies  
are being humanized



After injection of antibodies, they bind to  
oligomers and plaques



# Tau Vaccine (AADvac1, active immunotherapy)

- phase 1 study

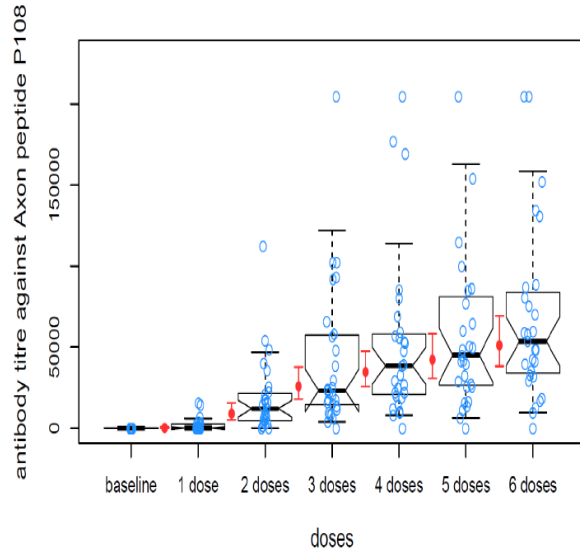


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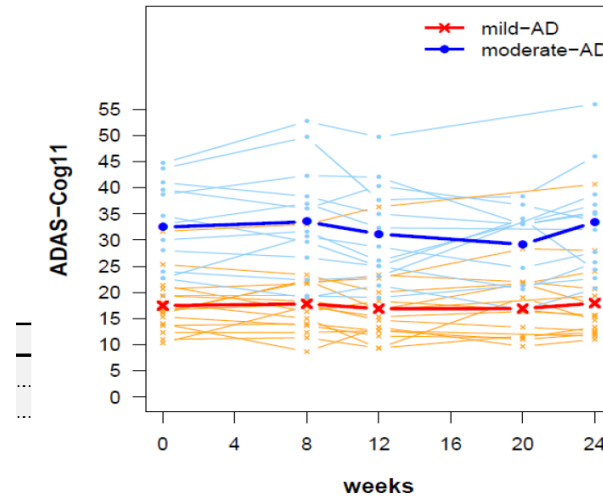
## Immunogenicity

Robust immune response



## Cognition

Mean ADAS-Cog score stable over 6 months

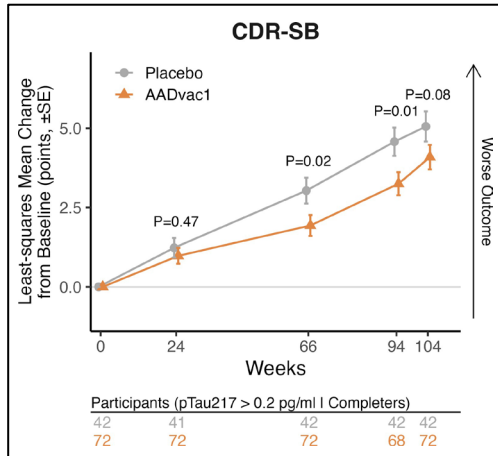


Novak P et al, Lancet Neurol 2016

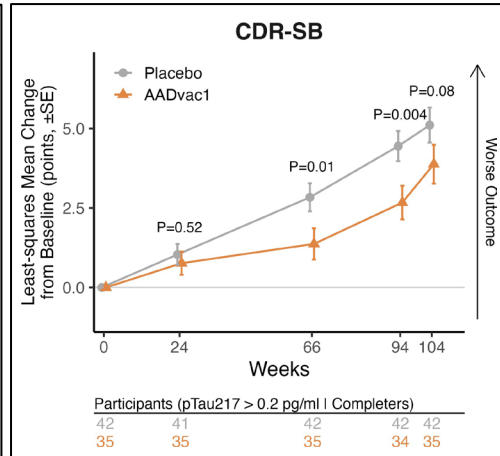
# AADvac1 THERAPEUTIC EFFECT IS MORE PRONOUNCED IN PATIENTS WITH HIGHER ANTIBODY RESPONSE



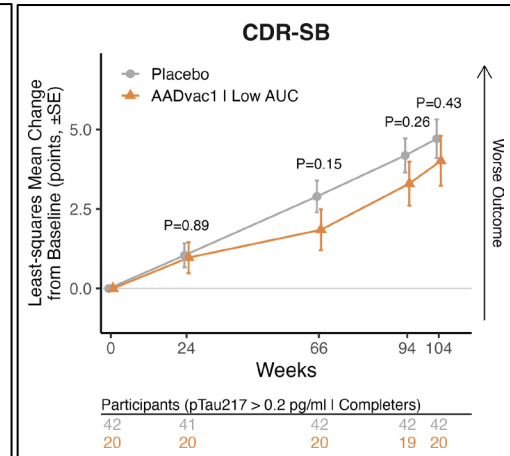
Cognition: CDR-SB  
(ALL COMPLETERS)



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



# Aducanumab (BIIB037) – passive immunotherapy against amyloid- $\beta$

## 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)

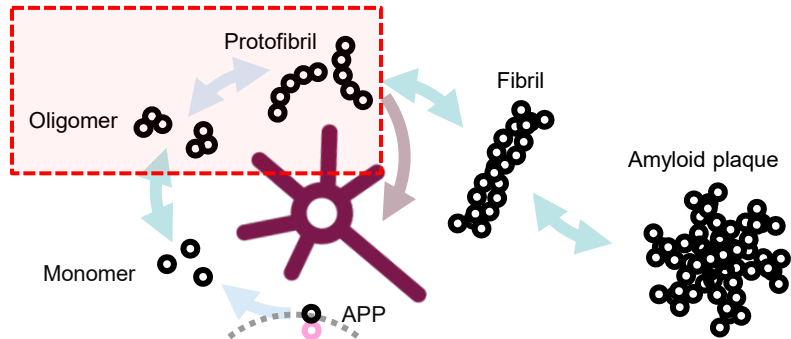


## Lecanemab:

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



## Lecanemab MoA



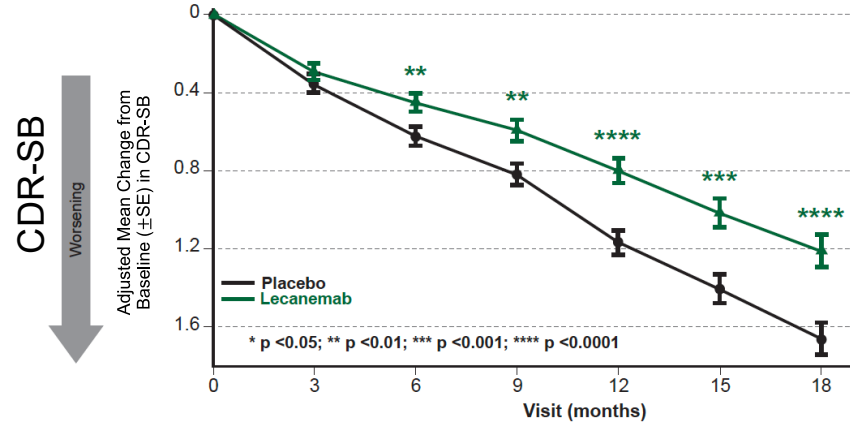
1. Hampel H et al. Mol Psychiatry 2021;26:5481–503;
2. van Dyck CH et al. N Engl J Med 2023;388:9–21.

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

(Global Measure of Cognition and Function)



## Clarity AD



CDR-SB Domains	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	% Slowing	P Value
		← Favors lecanemab		
Memory	875, 859	-0.077	27.5	0.00117
Orientation	875, 859	-0.081	28.1	0.00044
Judgement/Problem Solving	875, 859	-0.053	23.6	0.01008
Community Affairs	875, 859	-0.070	21.2	0.00524
Home and Hobbies	875, 859	-0.098	28.8	0.00018
Personal Care	875, 859	-0.067	29.9	0.01325

Adjusted Mean Difference versus Placebo (95% CI)

### 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

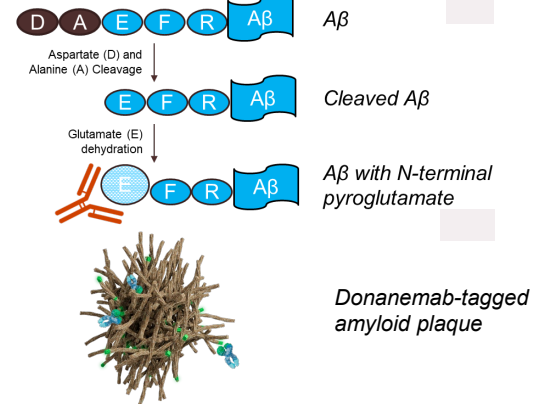


## Donanemab:

- 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



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*

# Pricing and budget impact of lecanemab



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
- Optimisation 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*

# Research – the only way forward to treatment

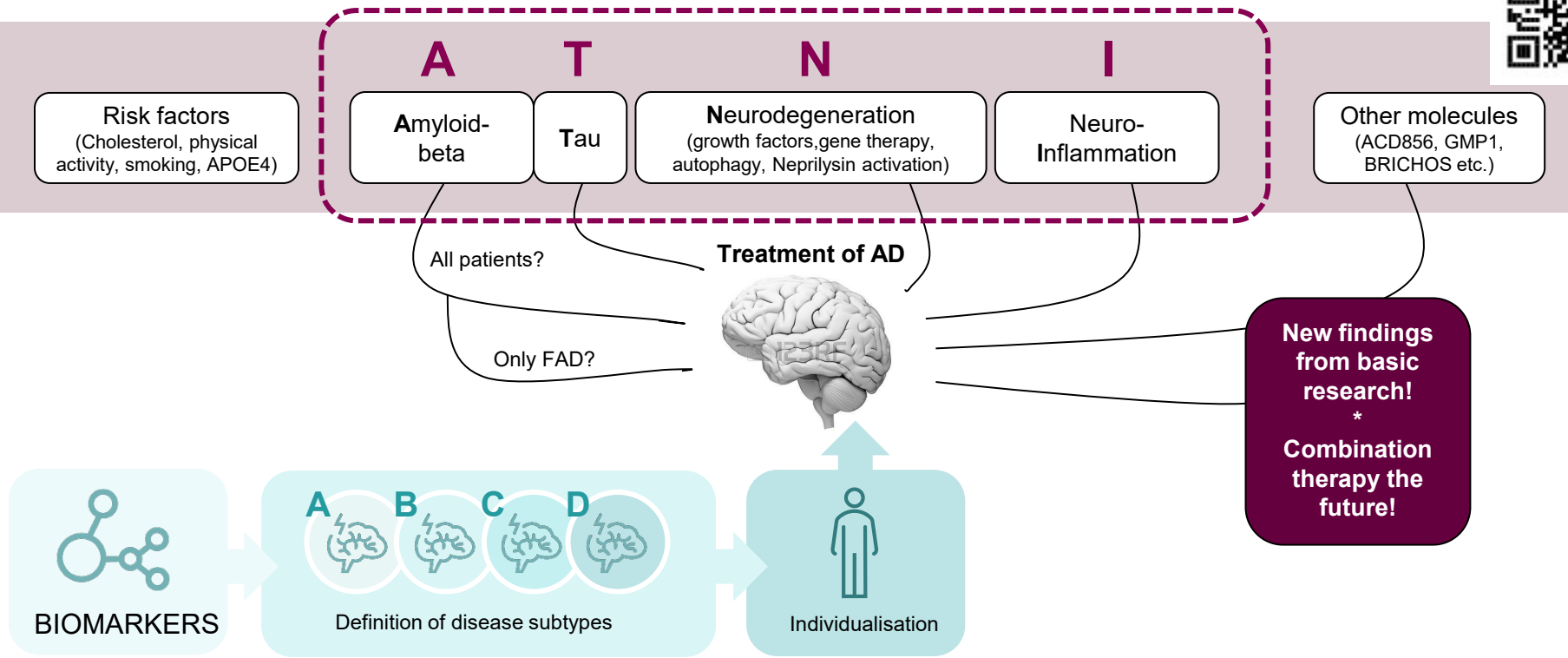


Figure adapted from Cedazo-Minguez A and Winblad B 2010;45:5–14.



## Acknowledgements

- Angel Cedazo-Minguez
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- Linus Jönsson
- Anders Wimo
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