Binding characteristics of lecanemab, donanemab and other amyloid-beta antibodies to different forms of amyloid-beta in Alzheimer's disease brains

Lars Lannfelt, MD, PhD
Professor, Uppsala University

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Disclaimer: Co-founder of BioArctic with Pär Gellerfors

Overview of lecanemab Clarity AD phase 3 results

Phase 3 results (Van Dyck et al. N Engl J of Med 2022):

- Lecanemab is a monoclonal antibody mainly targeting soluble protofibrils of Aβ
- Lecanemab slowed cognitive decline as measured by CDR-SB as compared to placebo at 18 months
- Lecanemab reduced amyloid plaque load
- No titration - full dose from first day of treatment
- ARIA-E developed in 13% of treated patients, symptomatic ARIA-E was 3%
- Lecanemab is intended for continuous treatment, potentially at a lower maintenance dose
- The AD population investigated had a MMSE score of 25.5
  - Ongoing: sub cutaneous administration, secondary prevention (AHEAD 3-45) and a tau antibody combination studies

Overview of donanemab AD TRAILBLAZER-ALZ 2 phase 3 results

Phase 3 results (Sims et al. 2023 JAMA):

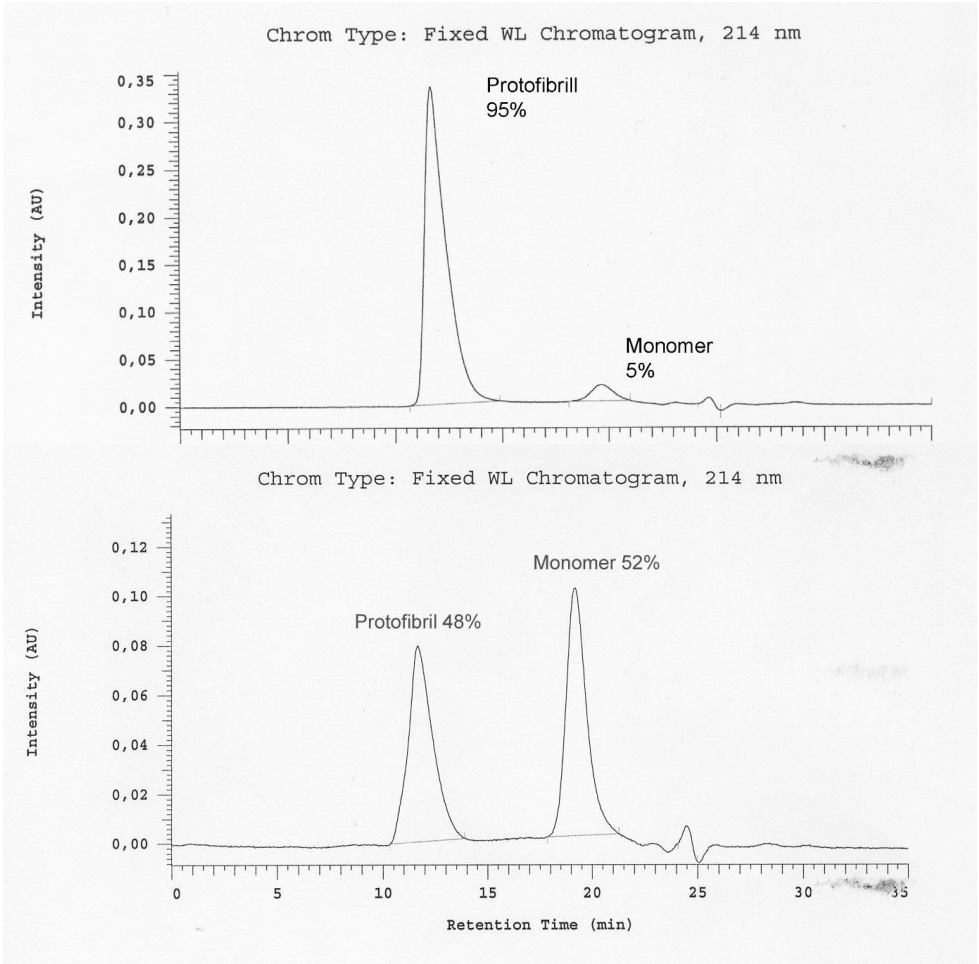
- Donanemab is a monoclonal antibody mainly targeting an N-terminally truncated and pyroglutamate-modified form of Aβ found aggregated in amyloid plaque cores
- Donanemab slowed cognitive decline measured by iADRS as compared to placebo at 18 months
- Donanemab reduced amyloid plaque load
- Titration of the dose was done for 3 months
- ARIA-E developed in 24% of treated patients, symptomatic ARIA-E was 6%
- Donanemab is planned to be dosed until the amyloid plaques have disappeared
- The AD population investigated had a MMSE score of 22
  - Ongoing: secondary prevention (TRAILBLAZER-ALZ 3)
  - Other differences in study populations make comparisons difficult between the two studies

Accelerated protofibril formation with Arctic Aβ (Aβ1-42E22G)

Size Exclusion Chromatography on a Superdex 75 column

Aβ1-42Arc

Aβ1-42wt



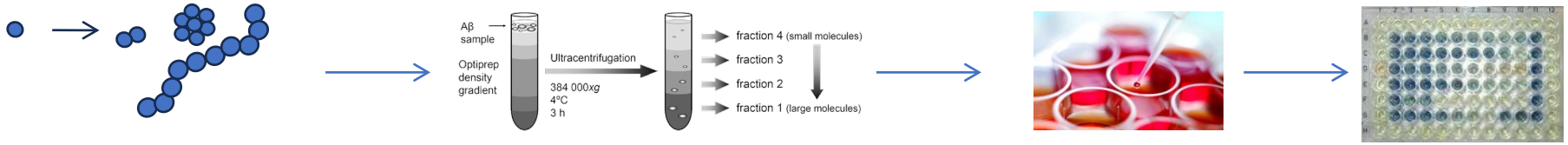
Protofibrils are found in all AD cases but are more prominent with the Arctic mutation

Our definition of protofibrils: soluble aggregated Aβ eluting in the void volume of a Superdex 75 column, > 75 kDa in size

Our definition of oligomers: soluble aggregated Aβ < 75 kDa in size

Nilsberth et al. 2001 Nat Neurosci
Johansson et al. 2006 FEBS J

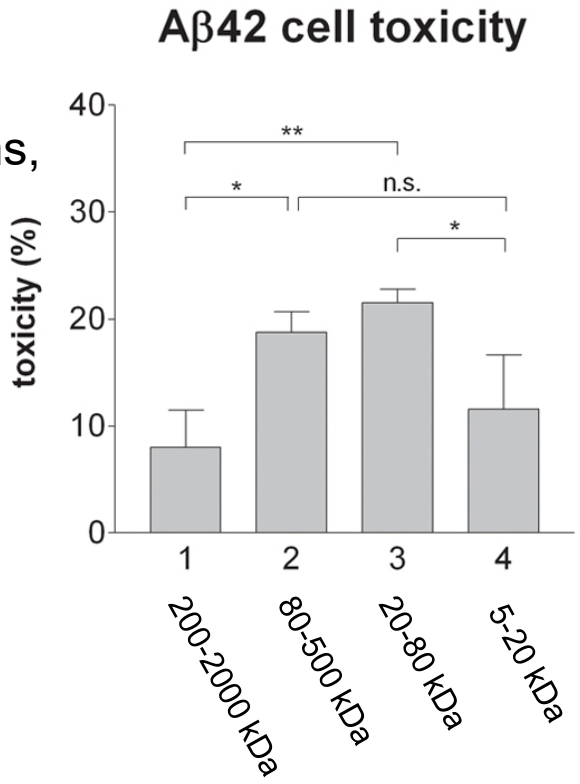
Intermediate sized Aβ42 oligomers/protofibrils: the most toxic species



Ultracentrifugation, of all soluble forms, intermediate sized most toxic

Adjusted for protein (Aβ) and optiprep concentration of each fraction

MTT toxicity assay



Fraction 2 and 3 most toxic

Most Aβ from AD brain:

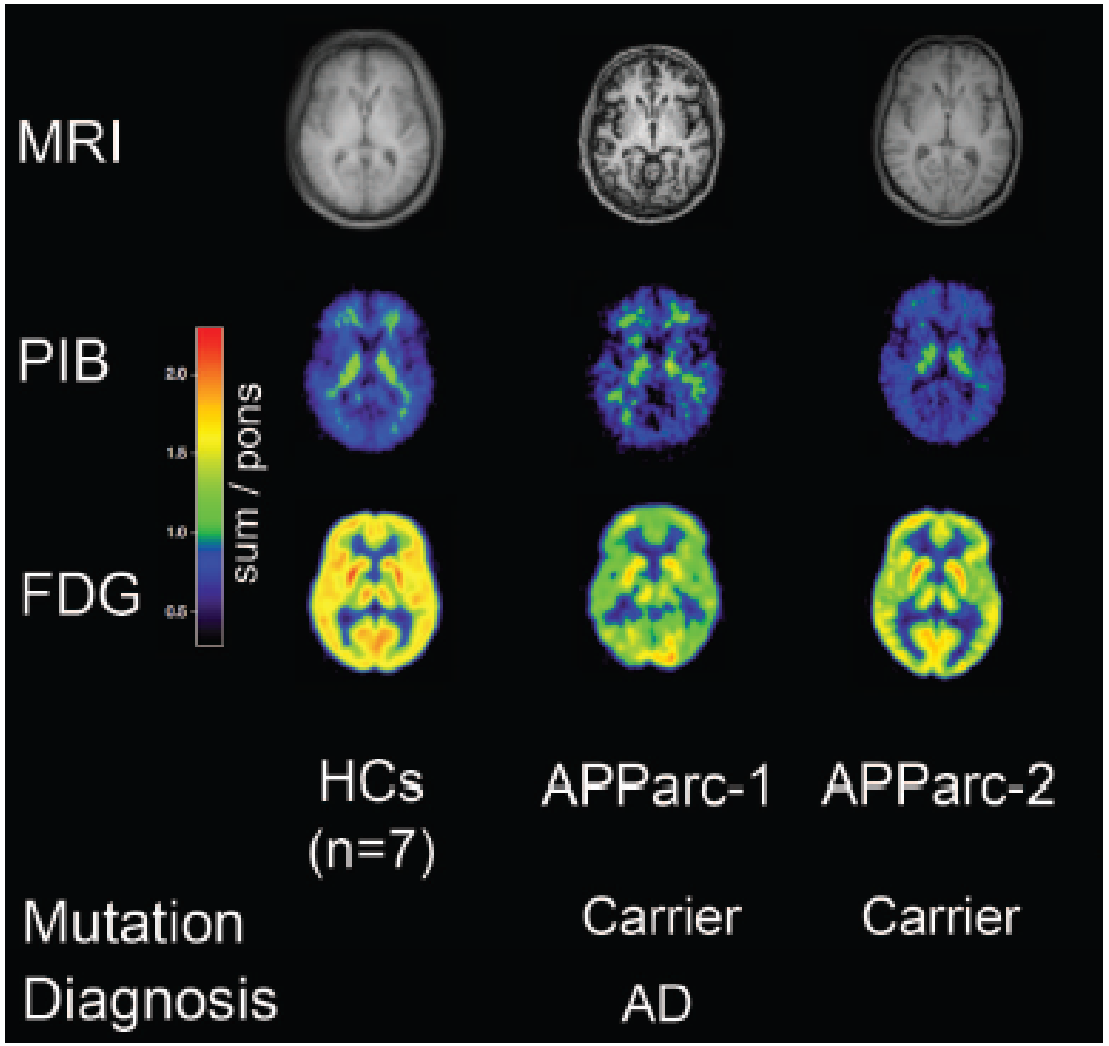
- In fraction 2
- Size of 80-500 kDa

Sehlin et al. 2012 PLoS ONE

No PET Aβ positive plaques in the Arctic mutation family

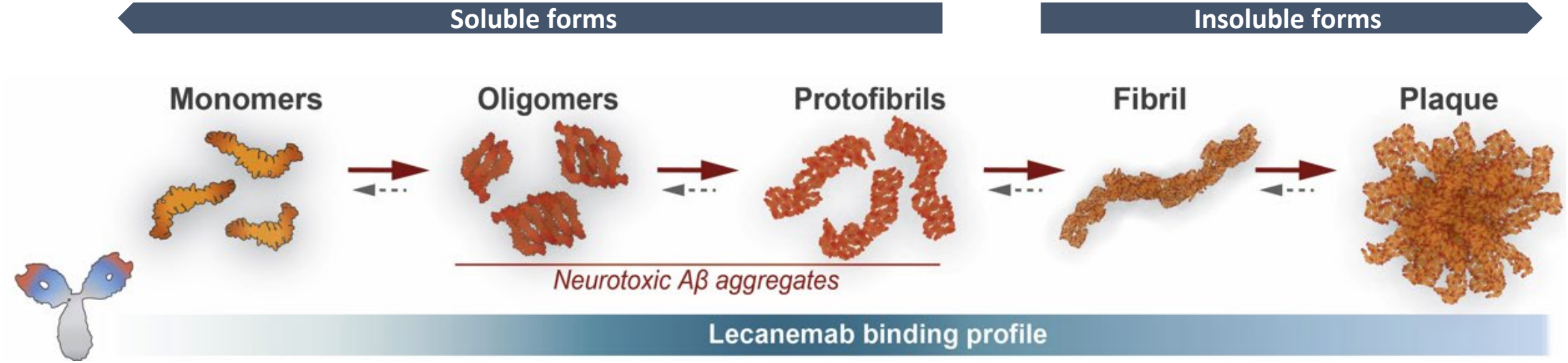
APParc-1 and 2: very low cortical PIB retention, APParc-1 had decreased glucose metabolism and atrophy, and APParc-2 regionally decreased glucose metabolism

Conclusion: AD does not require the presence of abundant PET-detected amyloid

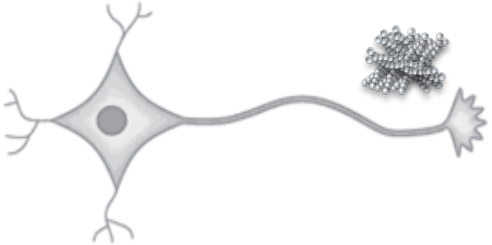


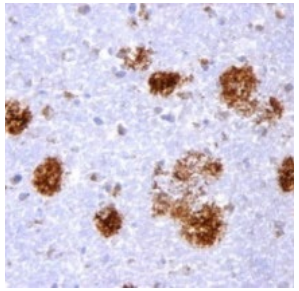
Schöll et al. 2012 Neurology

Targeting most neurotoxic forms of Aβ is important



Aggregated Aβ fibrils in amyloid plaques





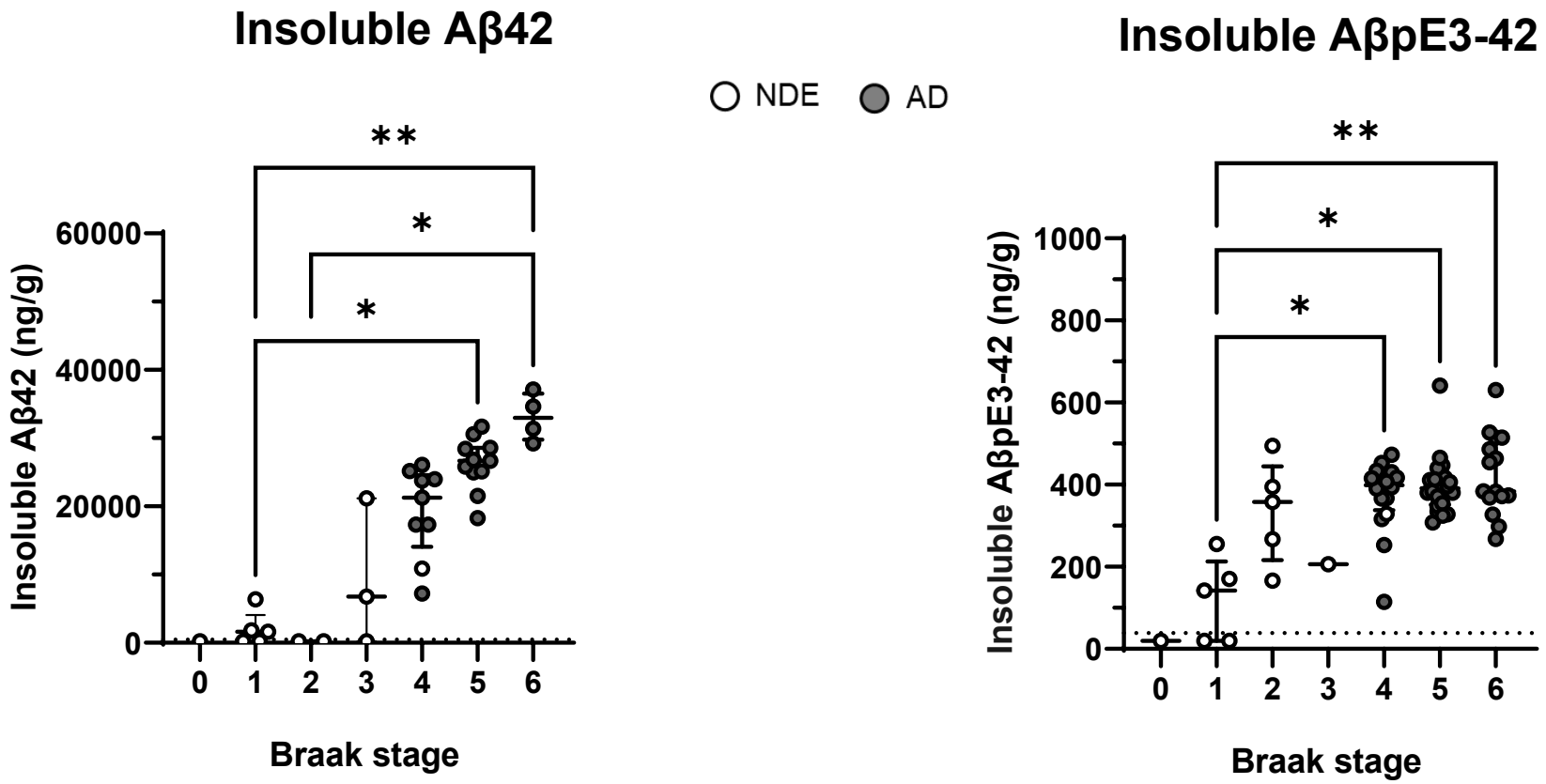
Walsh et al. 1997 J Biol Chem; Harper et al. 1997 Chem Biol
Nilsberth et al. 2001 Nat NeuroSci; O'Nuallain et al. 2010 J Neurosci
Lannfelt et al. 2013 J Intern Med; Lannfelt et al. 2014 Alz Res Ther

The present study

Our aim is to develop biochemical methods to be able to study interaction between different species of Aβ and different antibodies. We might be able to better understand:

- Mode of action
- Efficacy in relation to antibody target binding
- Side-effects in relation to antibody binding properties
- Character of Aβ species in different stages of disease

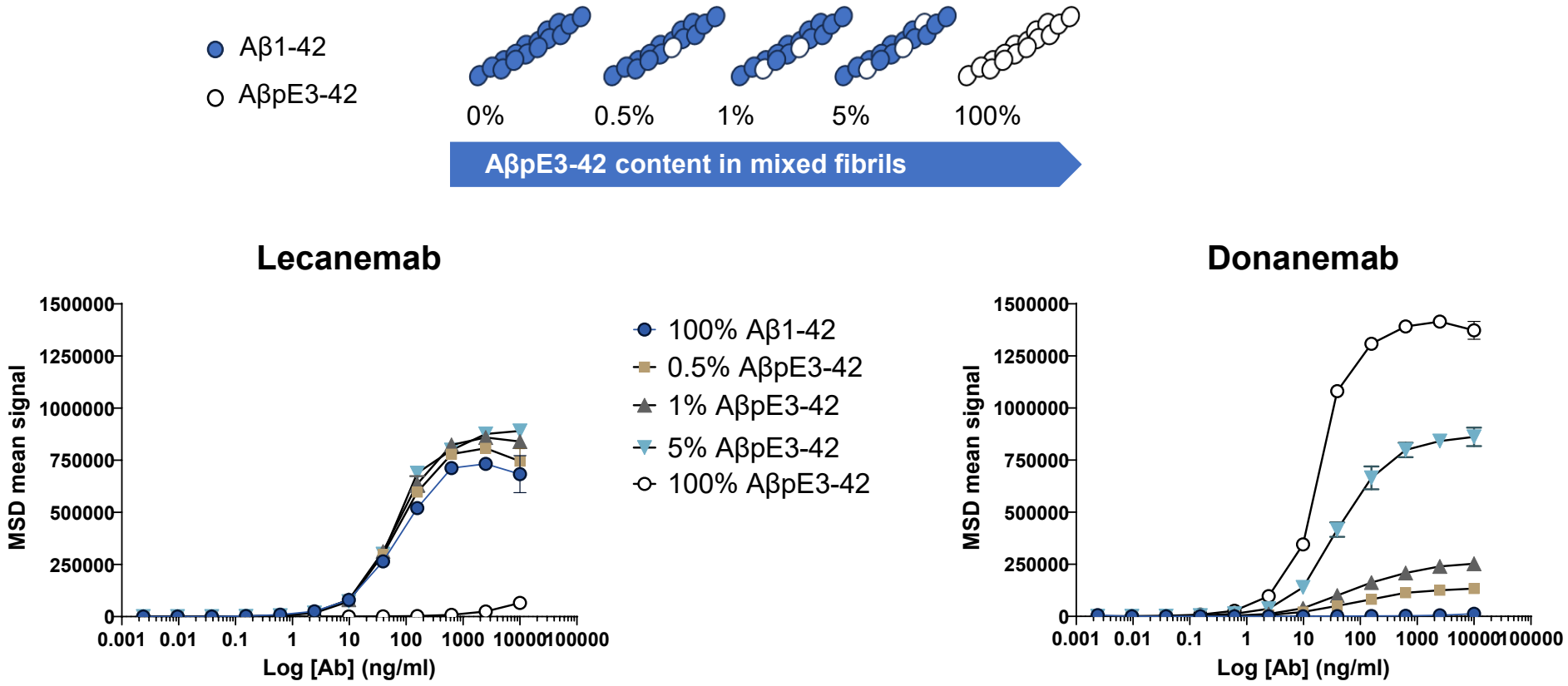
Aβ42 and AβpE3-42 levels increase with higher Braak stages in insoluble brain fractions



AβpE3-42 of total Aβ42 is ~2%

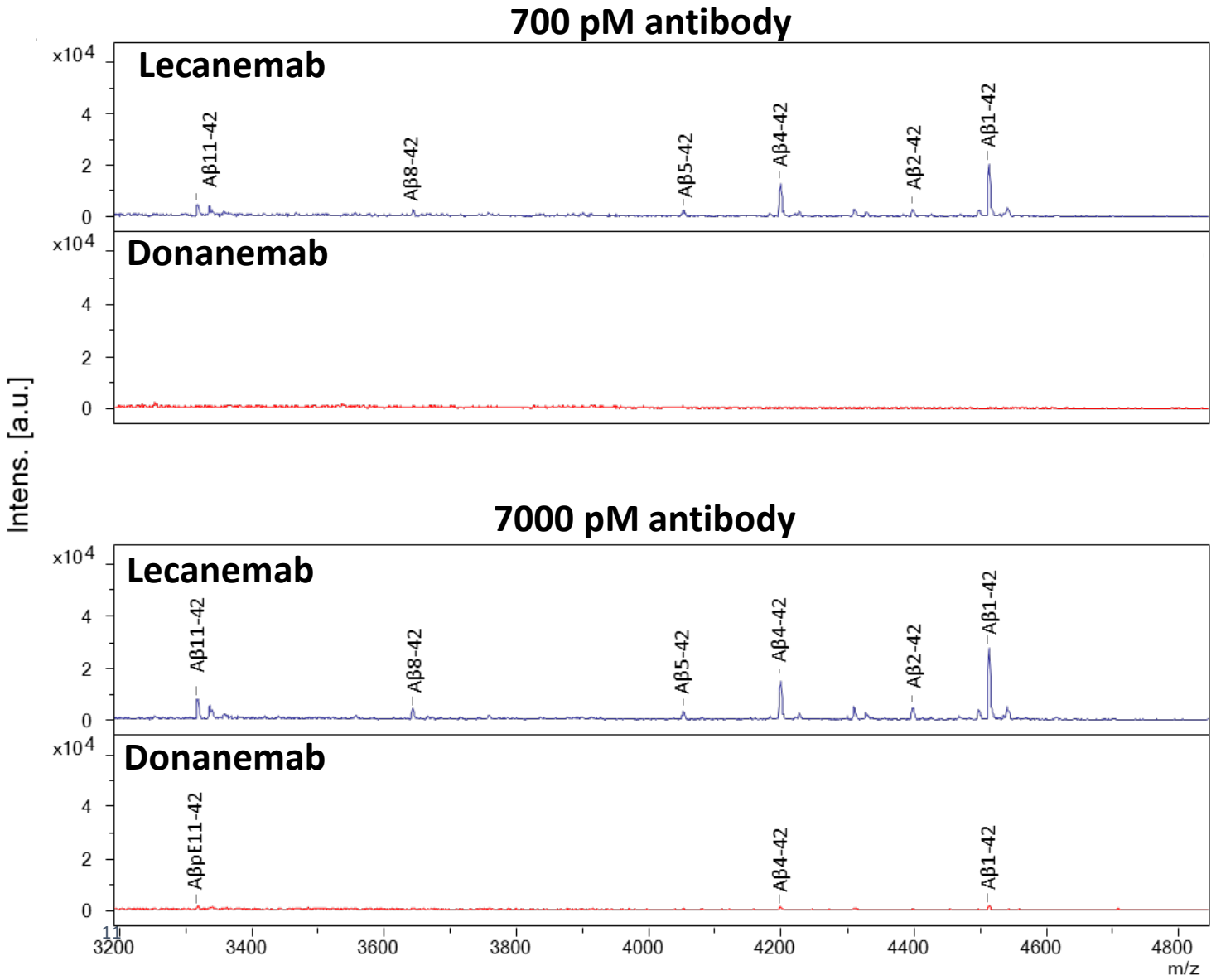
Kruskal-Wallis ANOVA followed by Dunn´s multiple comparisons test

Donanemab displayed lower binding to fibrils with low content of pyroglutamate Aβ compared to lecanemab

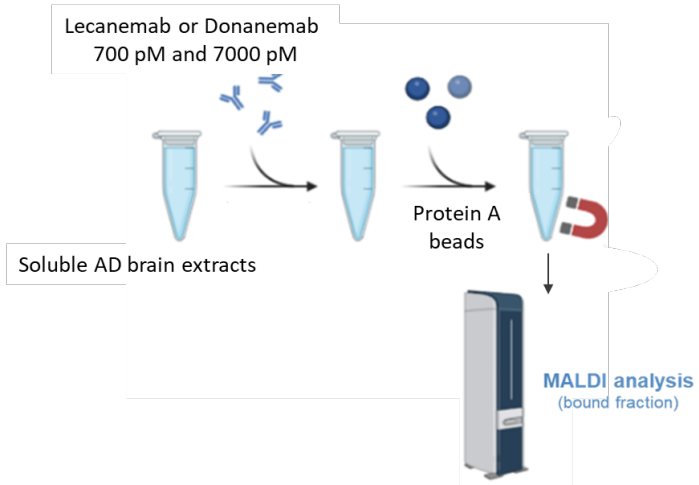


- In AD brains a mixture of Aβ species exist and the content of AβpE3 in fibrils is ~2% of total Aβ
- Lecanemab showed equal binding to mixed synthetic fibrils
- Donanemab displayed weaker binding to mixed synthetic fibrils with low AβpE3 content

Lecanemab efficiently binds soluble Aβ species from AD brain



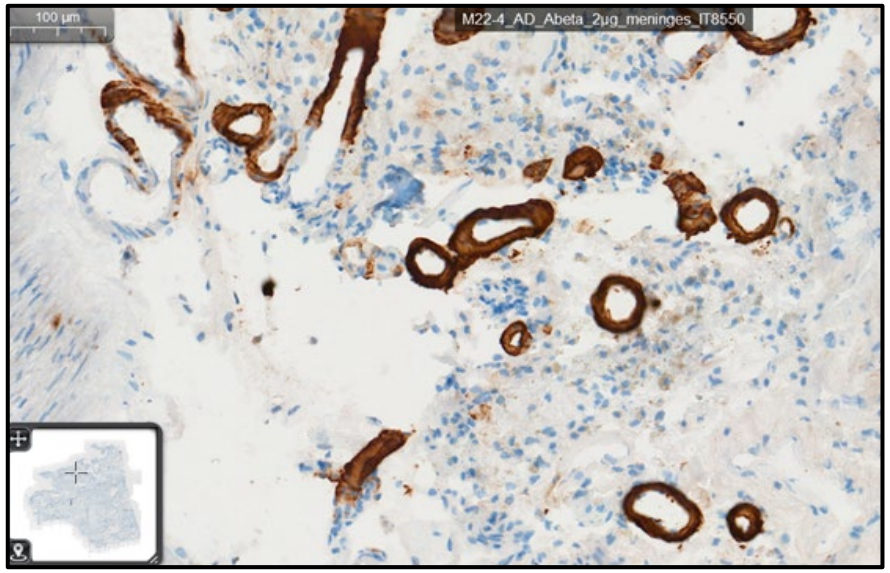
IP-MALDI



MALDI spectra intensities were lower in the bound fraction from donanemab IP compared to lecanemab IP in brains with low AβpE3 levels

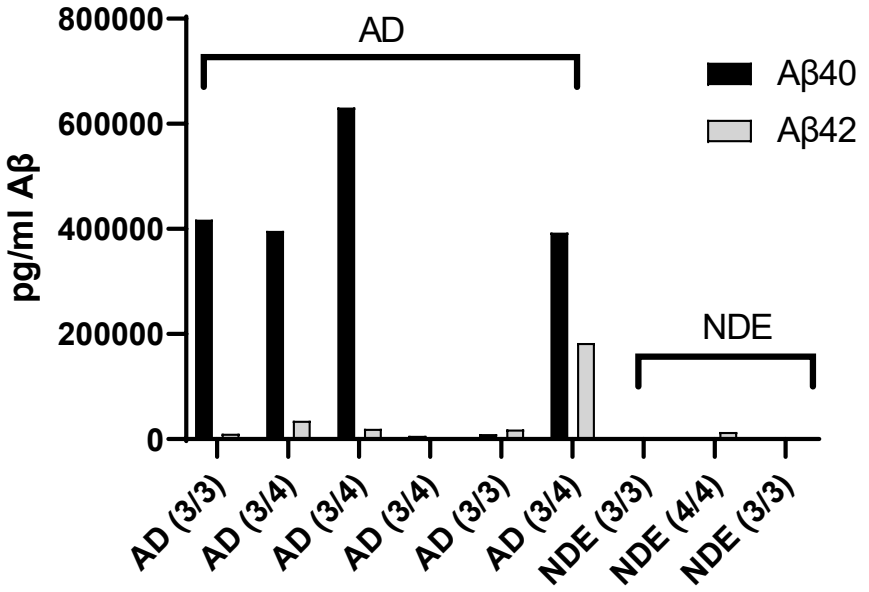
Hypothesis: ARIA-E is caused by antibody binding to CAA

IHC of meningeal tissue from AD (ApoE E3/E4) with 6E10/4G8



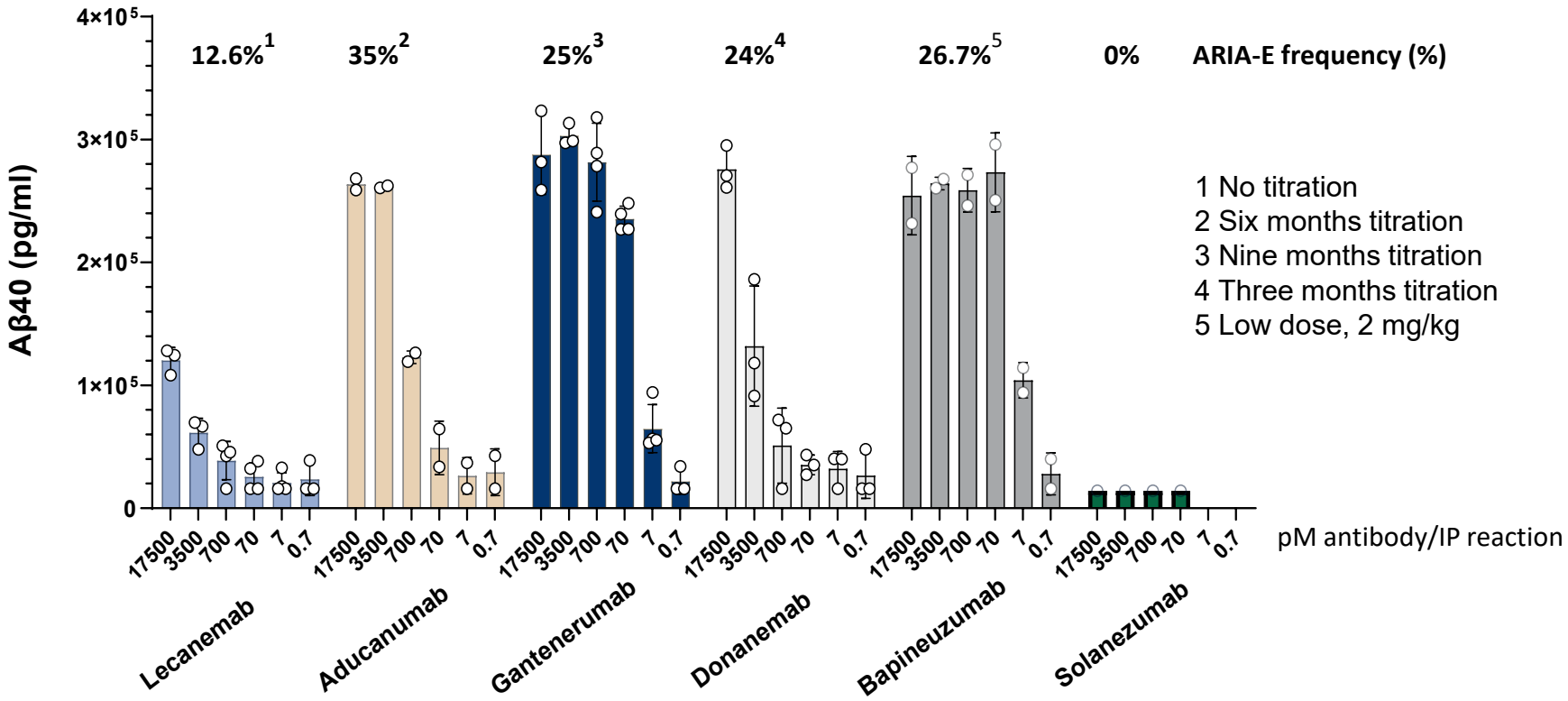
CAA: cerebral amyloid angiopathy

Aβ measurement of CAA extracted from human meningeal tissue



- AD meningeal tissue with CAA confirmed with IHC with 6E10 and 4G8 antibody
- Biochemical extraction of CAA fibrils from meningeal tissue demonstrate that Aβ40 is the major Aβ species in CAA fibrils

Low CAA fibril binding for lecanemab with immunoprecipitation



- Lecanemab showed lower binding to CAA fibrils prepared from AD meningeal tissue when compared to aducanumab, gantenerumab, donanemab and bapineuzumab
- Method: Immunoprecipitation of CAA fibrils extracted from AD meningeal tissue followed by Aβ measurement of the pellet by ELISA/MSD

Schematic illustration of lecanemab's mechanism of action

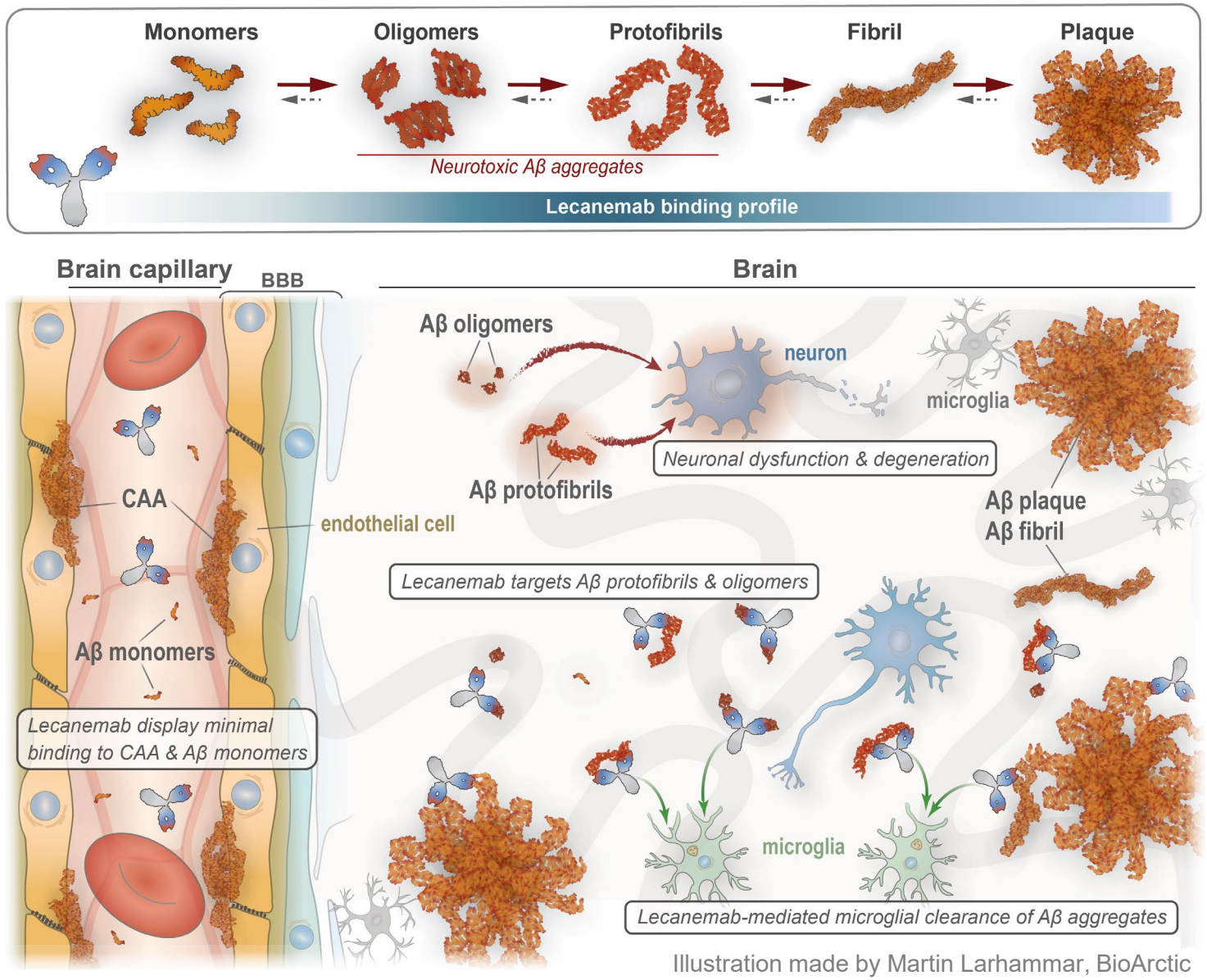


Illustration made by Martin Larhammar, BioArctic

Summary

- Lecanemab is a monoclonal antibody mainly targeting soluble protofibrils of Aβ
- Donanemab is a monoclonal antibody mainly targeting N-terminally truncated and pyroglutamate-modified forms of Aβ (AβpE3-42)
- AβpE3-42 levels increase with higher Braak stages in insoluble brain fractions, more AβpE3-42 later in the disease
- Donanemab displayed lower binding to synthetic fibrils with low content of pyroglutamate Aβ as compared to lecanemab
- Lecanemab bound soluble aggregated Aβ species from AD brain stronger as compared to donanemab
- Antibody binding to CAA is plausibly a key driver of ARIA-E
- With three different methods, immunoprecipitation, MSD and SPR, we could demonstrate weaker binding to Aβ fibrils from CAA for lecanemab than for donanemab

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