Lecanemab, an Aβ protofibril selective antibody, its mechanism of action and characterization of protofibrils in Alzheimer's disease brain

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Disclaimer: Co-founder of BioArctic with Pär Gellerfors

Overview of lecanemab Clarity AD phase 3 results

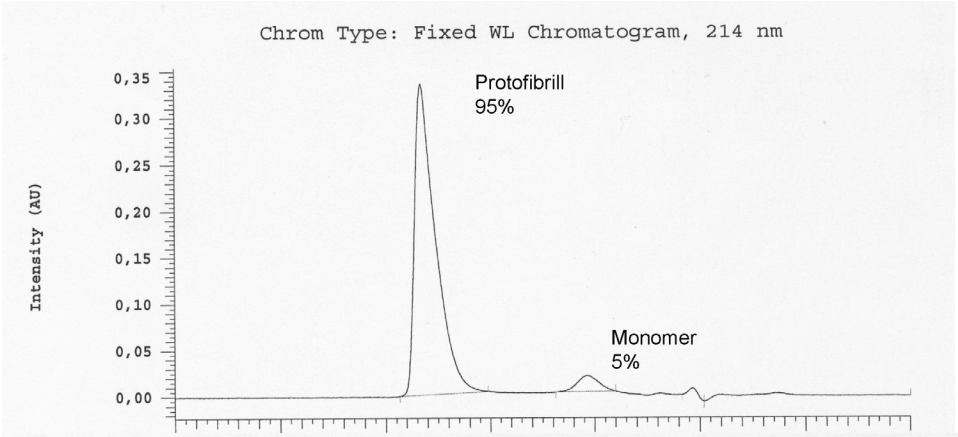
Phase 3 results, a reminder (Van Dyck et al. 2022, New England Journal of Medicine):

- Less clinical decline on primary endpoint CDR-SB (27%) and all secondary end-points were met (ADAS-Cog14, ADCOMS, amyloid PET and ADCS MCI-ADL). Both primary and all key secondary endpoints with high statistical significance
- The effects were seen early and expanded with time which suggests a disease-modifying effect
- Rapid, profound Aβ clearance at an early stage
- Good tolerability, ARIA-E 12.6%, symptomatic ARIA-E 2.8%
- No titration - full dose from first day of treatment
- Effect on down stream biomarkers, in CSF: $A\beta_{1-42}$, $A\beta_{1-40}$, t-tau, p-tau_{181} and neurogranin. In plasma: $A\beta_{42/40}$ ratio, p-tau_{181}, GFAP and NfL
  - Ongoing: sub cutaneous administration, secondary prevention studies AHEAD 3-45 and combination therapy with a tau anitibody
  - Long-term treatment to be expected, with lower maintenance dose

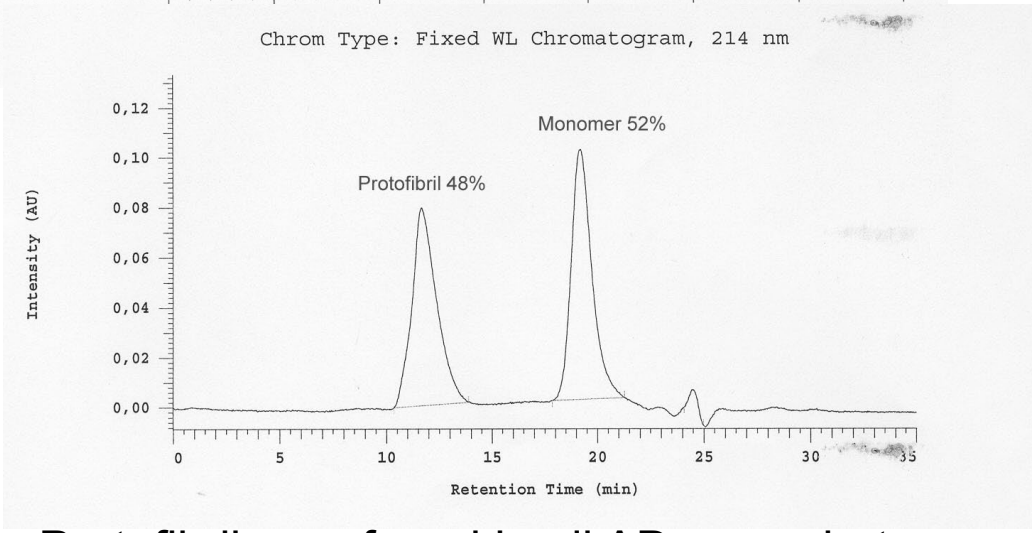
Accelerated protofibril formation with Arctic Aβ (Aβ1-42E22G)

Size Exclusion Chromatography on a Superdex 75 column

Arc



Wt



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

Aβ1-42Arc

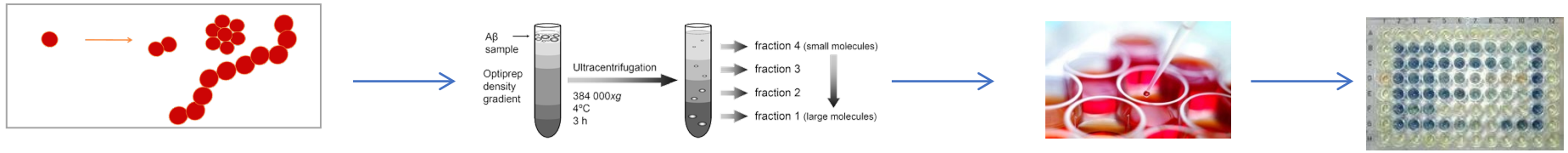
Our definition of protofibrils:
soluble aggregated Aβ eluting in the void volume of a Superdex 75 column, > 75 kDa in size

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

Aβ1-42wt

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

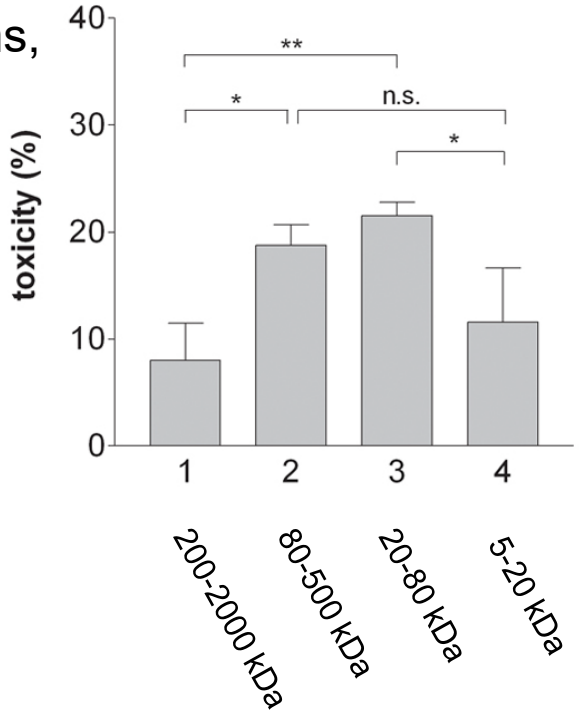
Intermediate sized Aβ42 oligomers/protofibrils: the most toxic species



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:

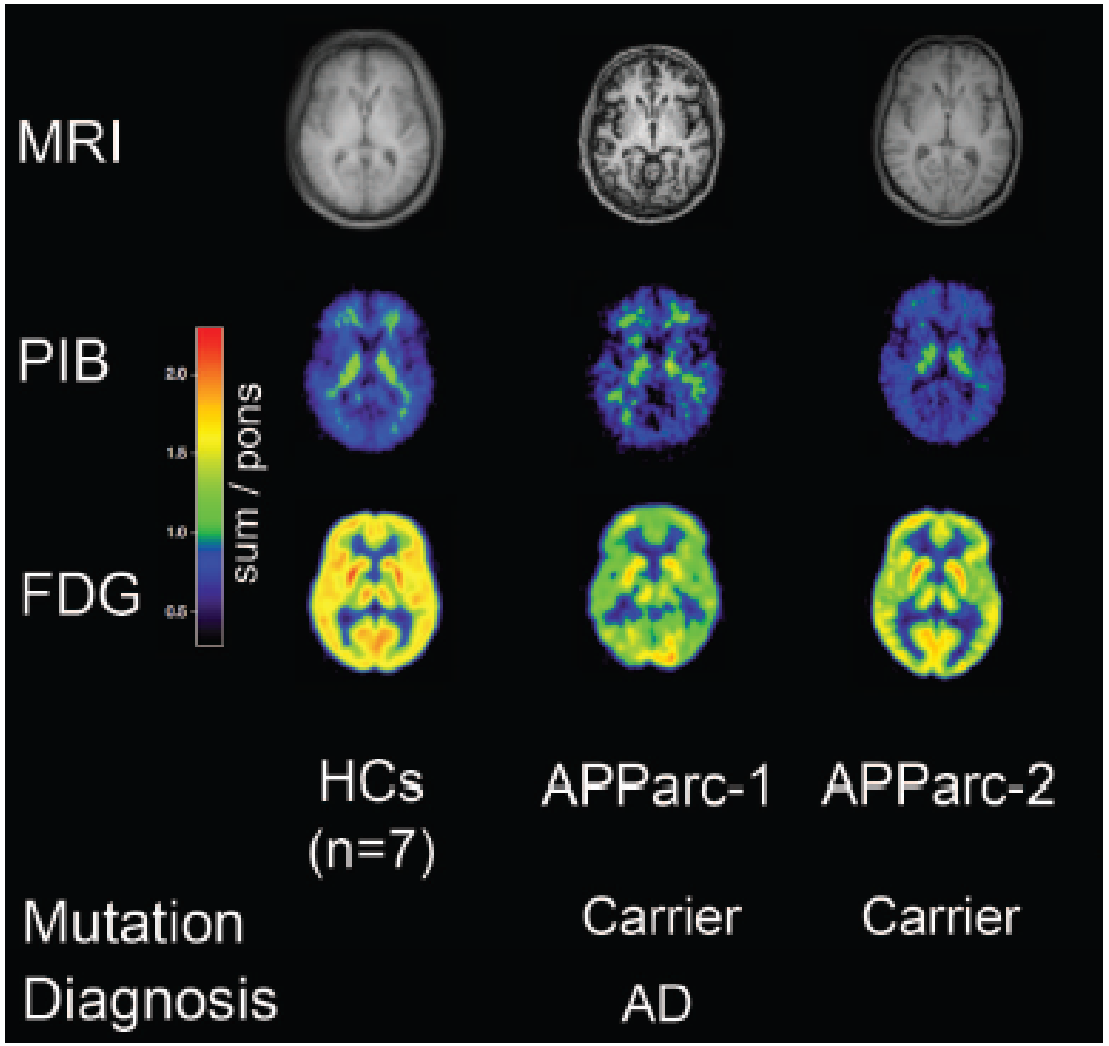
- In fraction 2
- Size of 80-500 kDa

Sehlin et al. 2012 PLoS ONE

No Aβ positive plaques in the Arctic mutation family with PET PIB

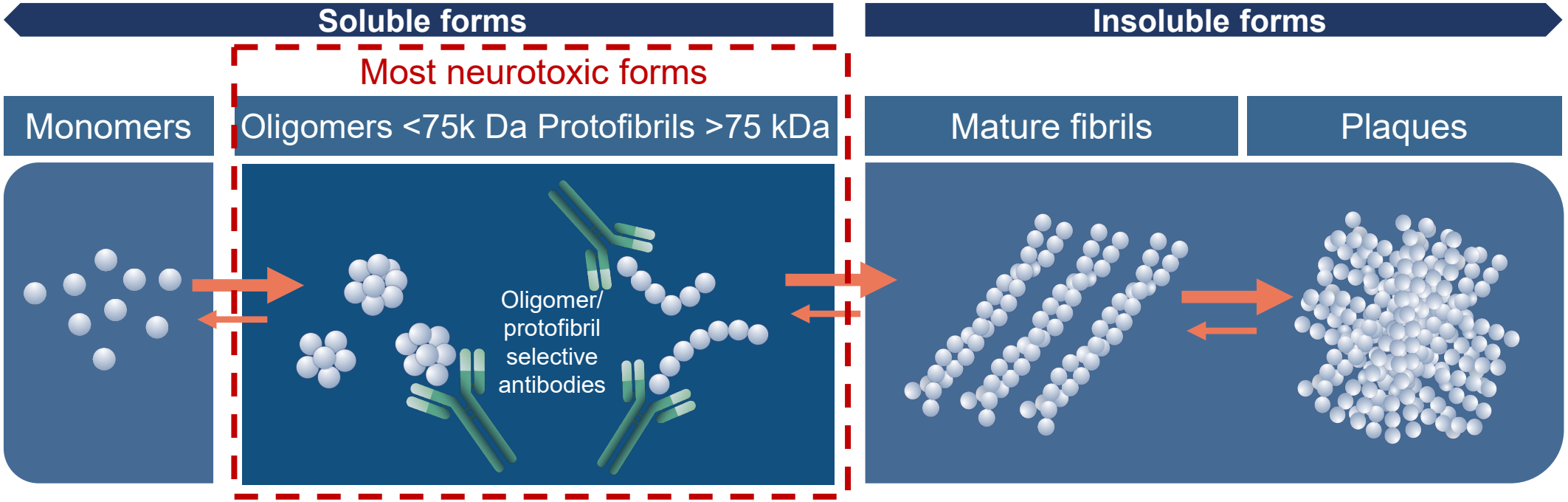
APParc-1 and 2: very low cortical PIB retention, APParc-1 had decreased glucose metabolism and atrophy, and APParc-2 regionally decreased glucose metabolism

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

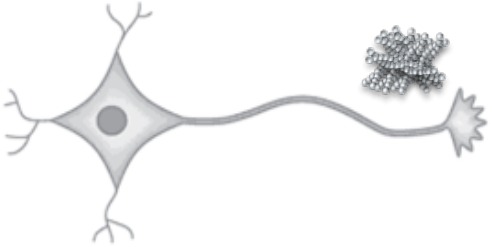


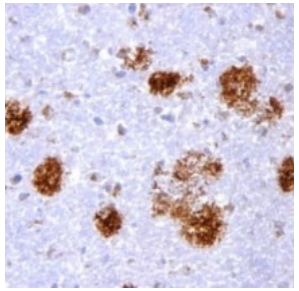
Schöll et al. 2012 Neurology

Targeting most neurotoxic forms of Aβ is important



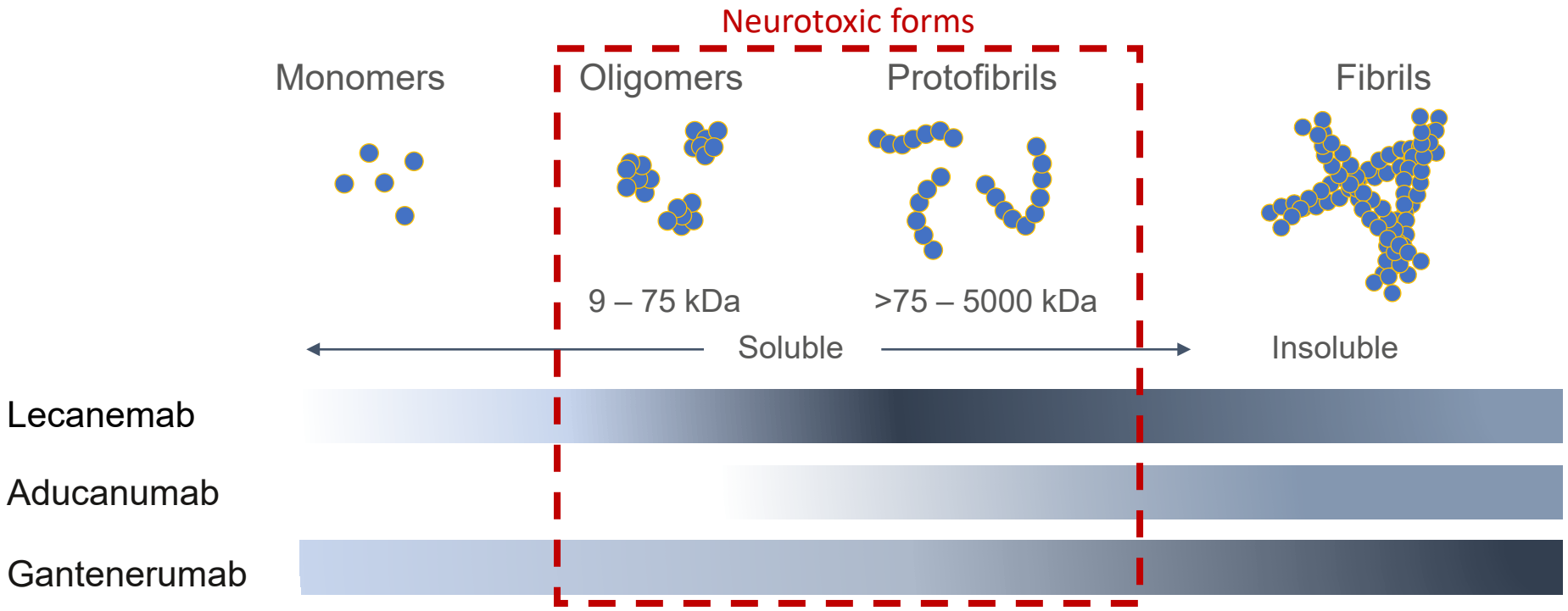
Aggregated Aβ fibrils in amyloid plaques





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

Lecanemab – unique selectivity towards toxic soluble species of Aβ

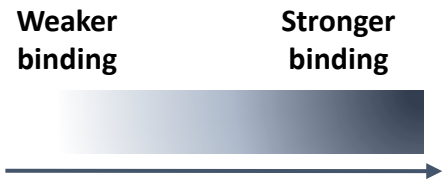


Lecanemab had the highest preference for soluble protofibrils/oligomers versus monomeric and fibrillar forms of Aβ

Aducanumab and gantenerumab had a preferences for the insoluble fibrils

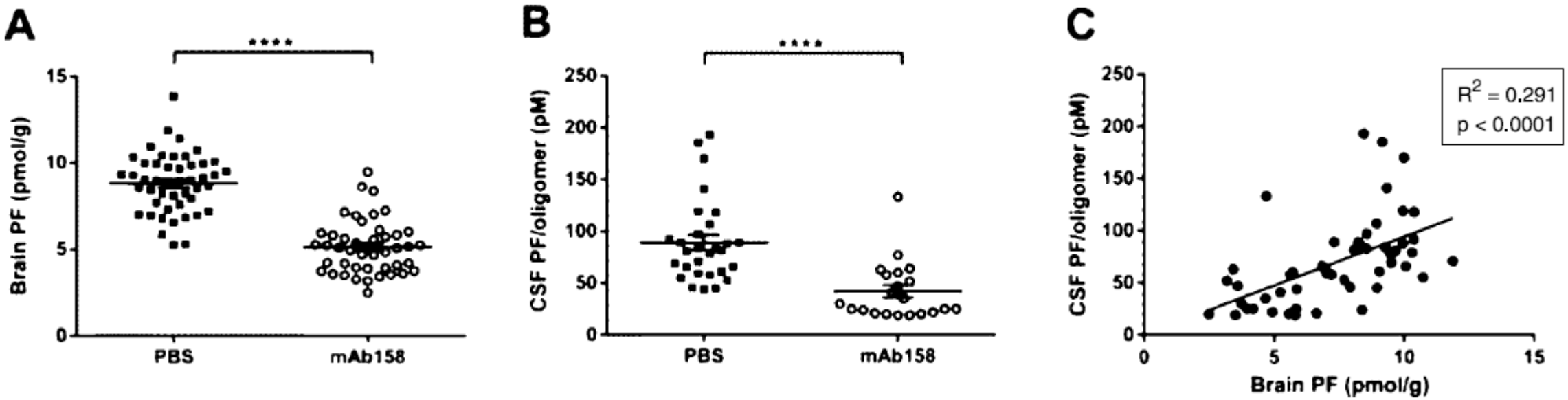
Aducanumab showed a lower binding to all Aβ species

Gantenerumab had somewhat higher binding to monomers



. Söderberg et al. 2022 Neurotherapeutics

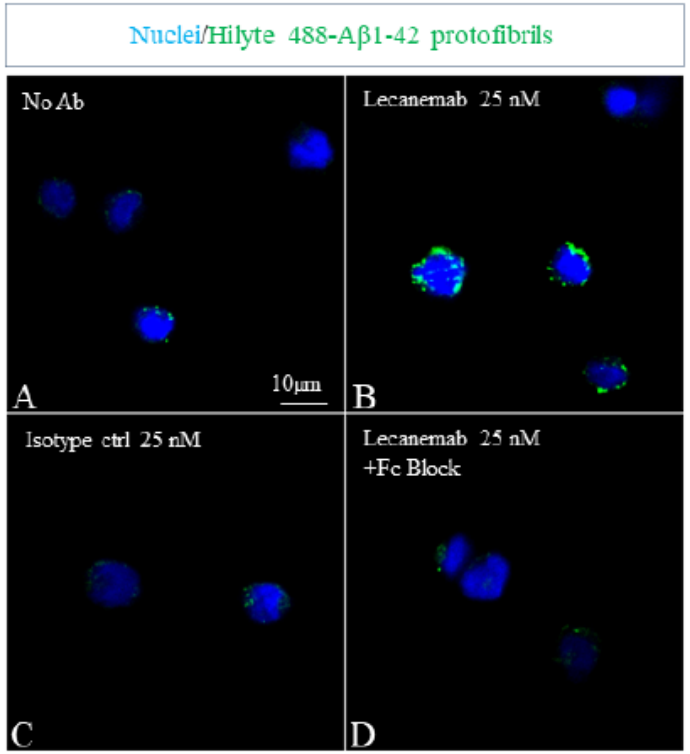
Long-term treatment with mAb158 reduces protofibril levels in brain and CSF of tg-ArcSwe mice

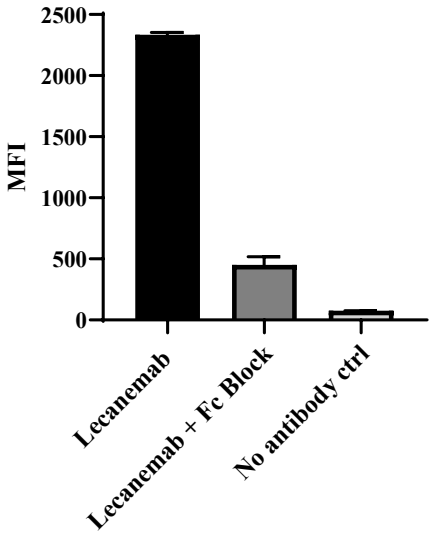


Tucker et al. J Alzheimer's Disease 2015

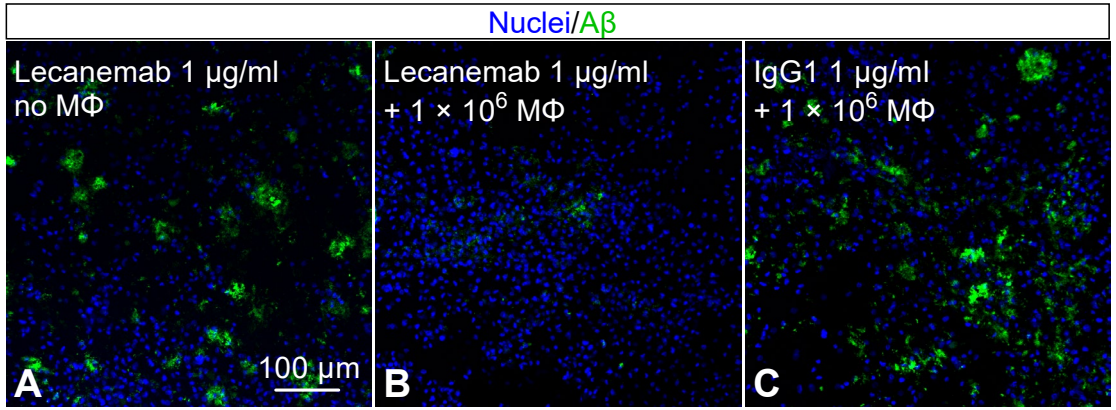
Lecanemab: Mechanism of Action

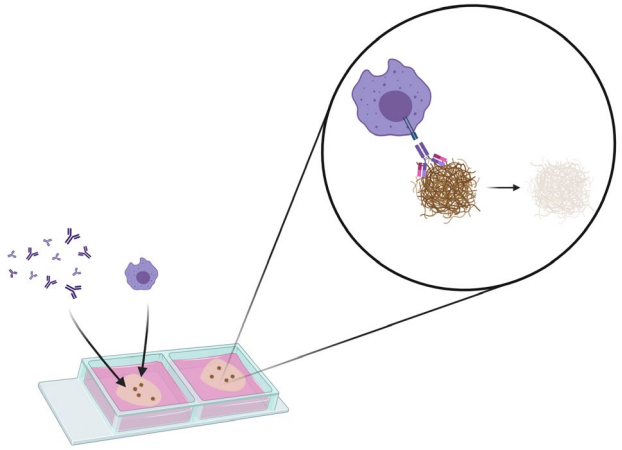
Lecanemab internalizes Aβ protofibrils via a FcγR mediated pathway in THP-1 cells

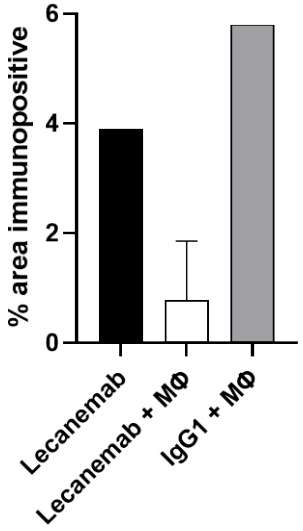




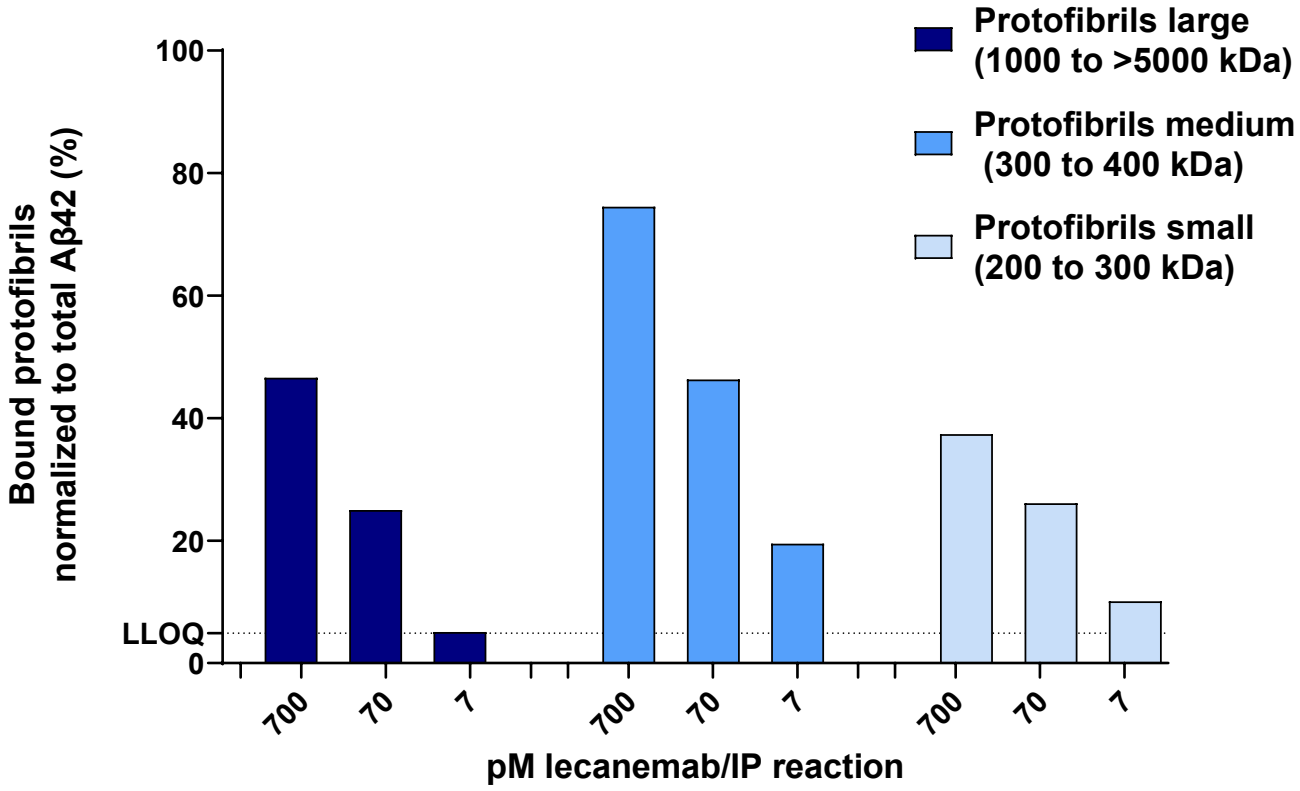
Lecanemab mediates macrophage-induced plaque clearance in AD brain sections





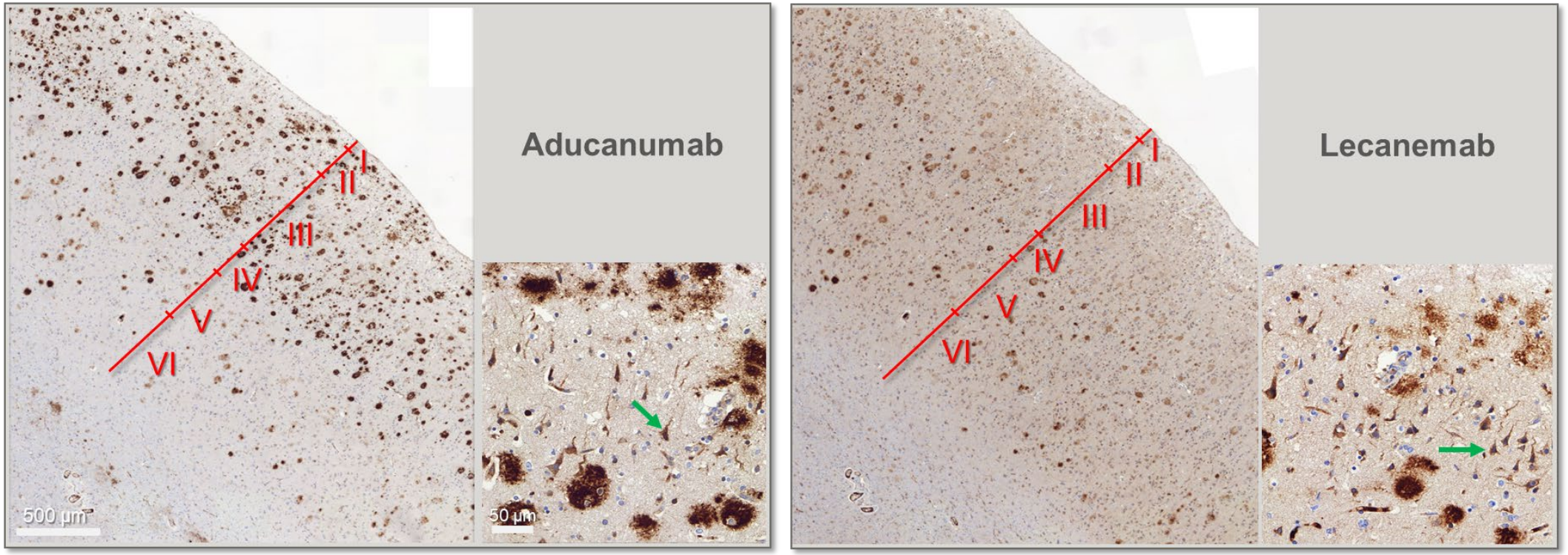


Lecanemab binds similarly to protofibrils of different sizes, isolated from AD brain



- Aβ42 is the major Aβ species in AD protofibrils (shown by MSD and IP-MALDI)
- Method: SEC separation of AD soluble brain extracts followed by immunoprecipitation with lecanemab and then Aβ42 MSD analysis

Binding of aducanumab and lecanemab to AD brain cortex, IHC

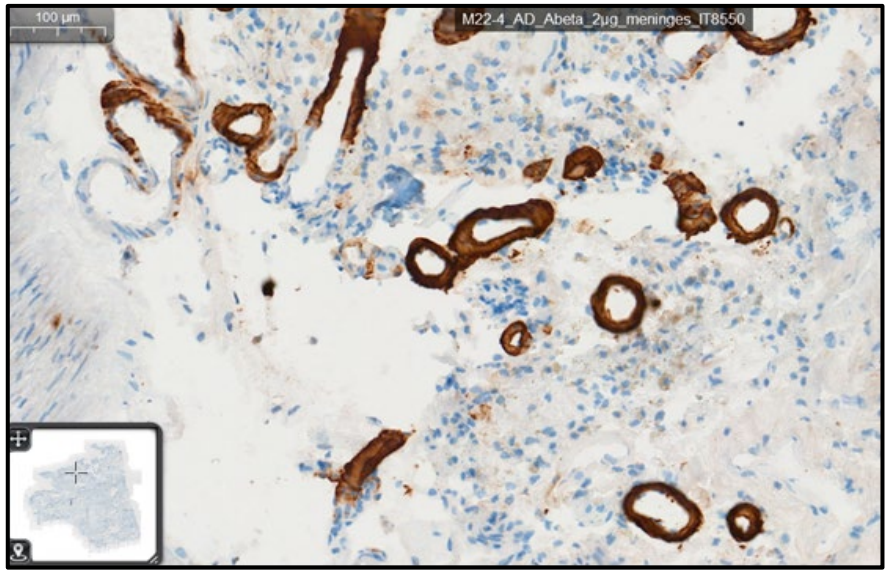


Aducanumab versus lecanemab staining of cortex in an AD case (ApoE3/4)
Aducanumab bound strongly to cored plaques in layers I-IV, whereas lecanemab bound preferentially to diffuse plaques mostly in layers IV-VI and relatively more intraneuronal Aβ (green arrows)
Method: IHC on paraffine embedded AD brain sections (1 µg/ml antibody concentrations)

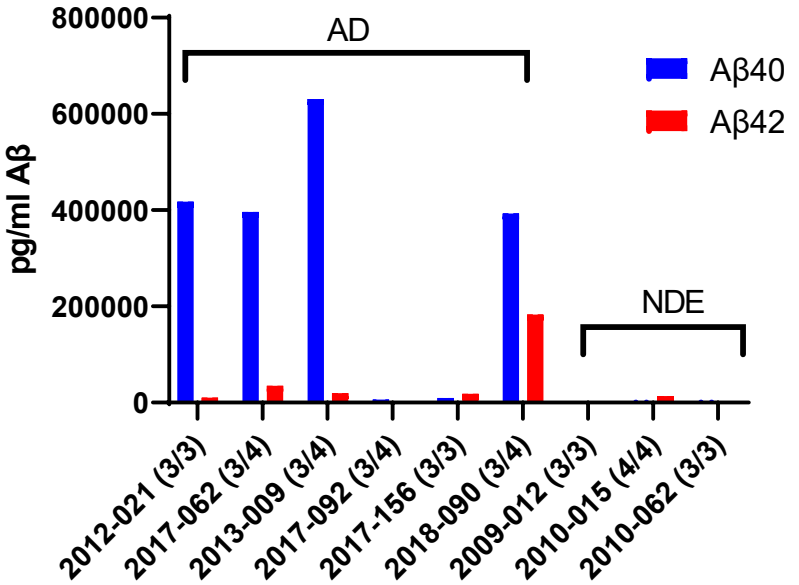
Aducanumab was produced from publicly accessible sequence information, subtle difference to these analogues to the original antibodies could exist

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

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



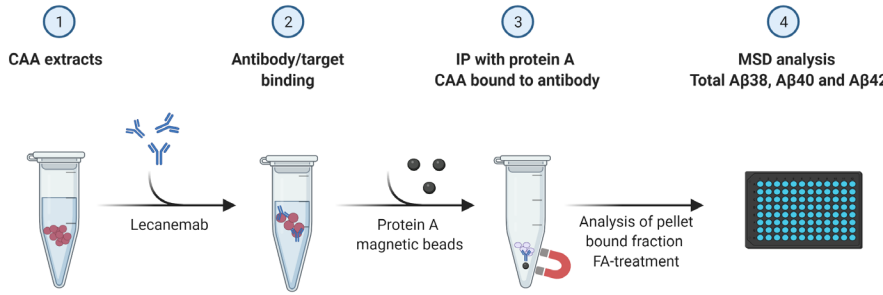
Aβ measurement of CAA extracted from human meningeal tissue

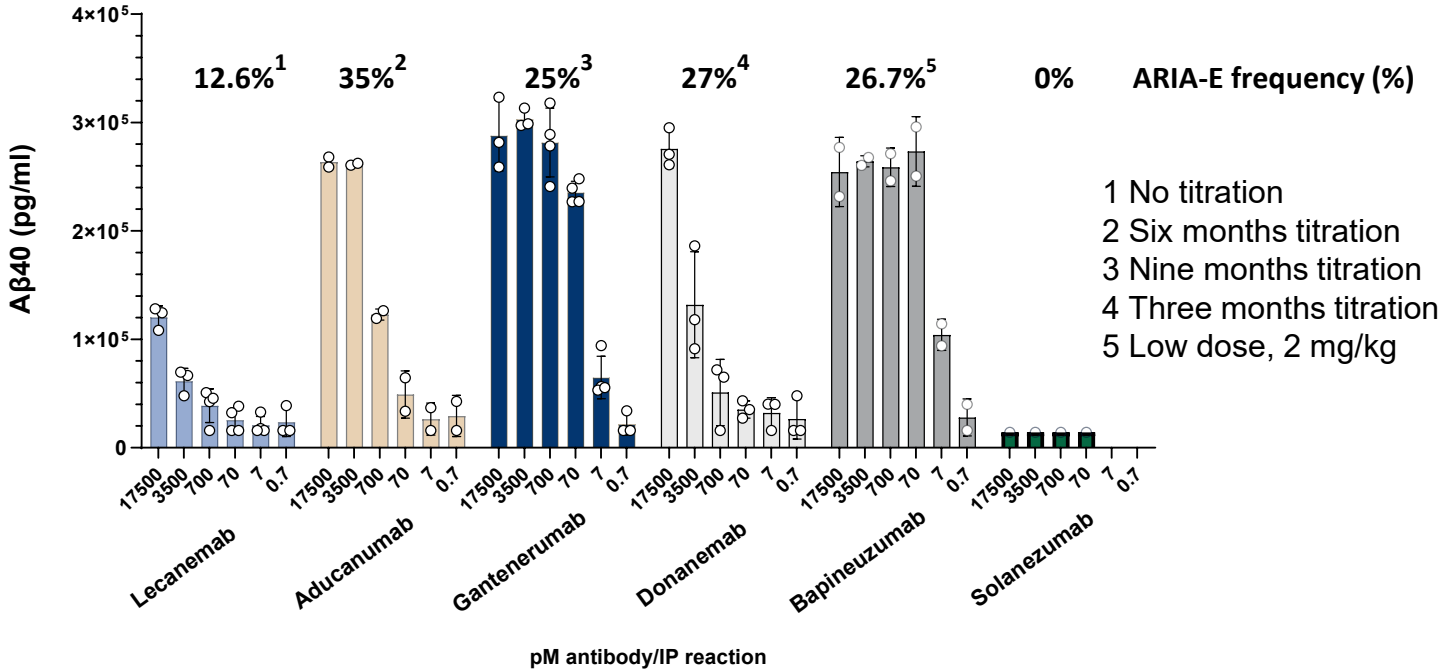


- AD meningeal tissue with CAA confirmed with IHC with 6E10 and 4G8 antibody
- Biochemical extraction of CAA fibrils from meningeal tissue demonstrate that Aβ40 is the major Aβ species in CAA fibrils

Lecanemab: lower binding to CAA fibrils compared to aducanumab, gantenerumab, donanemab and bapineuzumab. Solanezumab: 0 CAA binding

Immunoprecipitation





1 No titration
2 Six months titration
3 Nine months titration
4 Three months titration
5 Low dose, 2 mg/kg

- Lecanemab showed lower binding to CAA fibrils prepared from three different AD cases when compared to aducanumab, gantenerumab, donanemab and bapineuzumab
- Summary of 2-5 independently performed experiments
- Method: Immunoprecipitation of CAA fibrils extracted from AD meningeal tissue followed by Aβ measurement of the pellet by ELISA/MSD

*Christopher H. van Dyck *et al.* Lecanemab in Early Alzheimer's Disease. *N Engl J Med* 2023; 388:9-21 https://www.nejm.org/doi/10.1056/NEJMoa2212948
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Mark A. Mintun *et al*. Donanemab in Early Alzheimer's Disease *N Engl J Med* 2021; 384:1691-1704 https://www.nejm.org/doi/10.1056/NEJMoa2100708
Salloway S *et al*., A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer disease. *Neurology* 2009;73:2061–2070. https://doi.org/10.1212/WNL.0b013e3181c67808
Rachelle S. Doody *et al*. Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease. N Engl J Med 2014; 370:311-321 https://www.nejm.org/doi/10.1056/NEJMoa1312889

Summary: lecanemab

- Lecanemab has a unique binding profile, with strong selectivity for protofibrils over monomers and fibrils
- Lecanemab has relatively low ARIA-E frequency, probably due to less Aβ fibril binding
- Clarity AD: the first phase 3 program with clear conclusive results – implies disease modification
- Effect on down stream biomarkers
- Achieved through combination of utilizing excellent Aβ binding antibody and robust, optimal study design and execution of Alzheimer's disease clinical trial

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