Science of the amyloid-b cascade and distinct mechanisms of action of lecanemab

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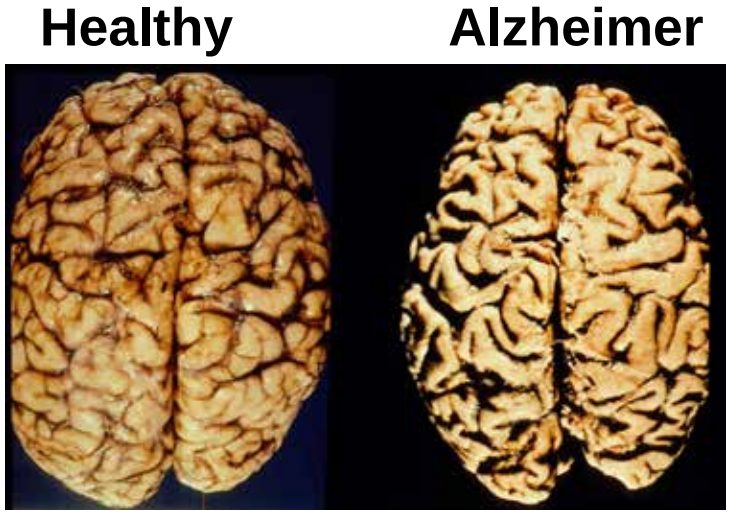
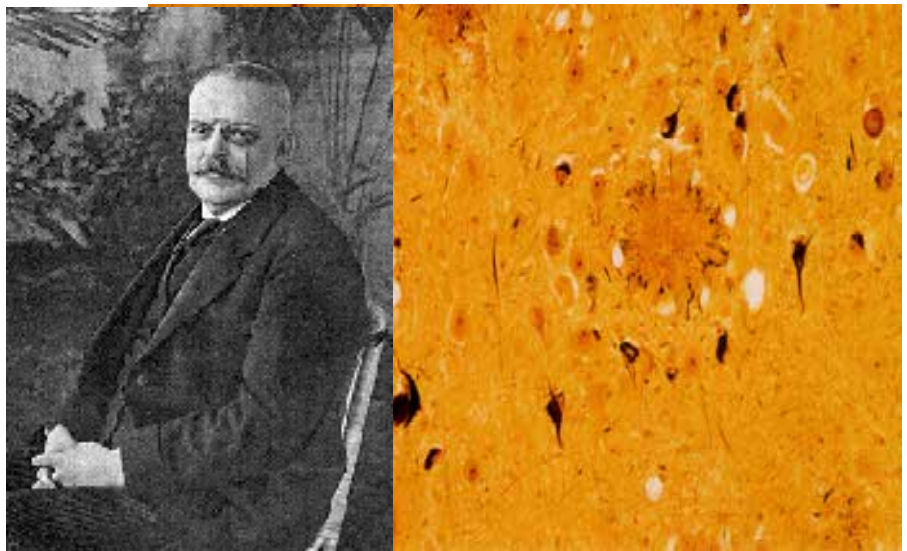
AD/PD, Friday, March 18, 2022

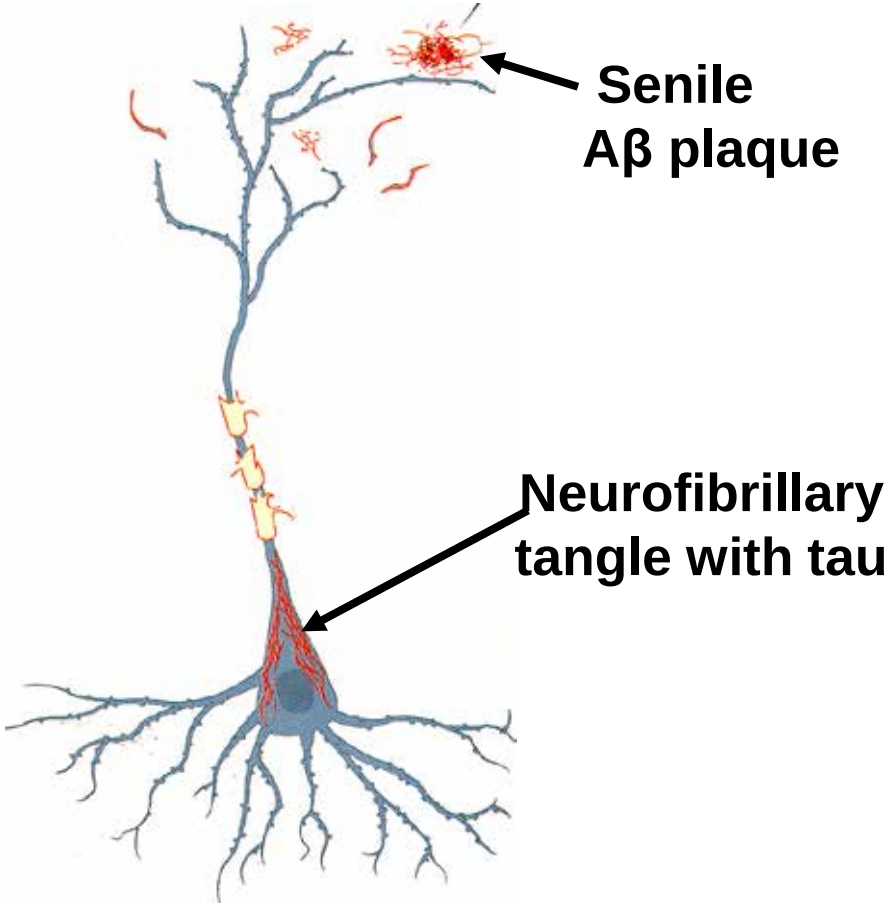
Disclaimer: Co-founder of BioArctic

We have learnt about Alzheimer's disease through studying the affected brain



Alzheimer brain: atrophy



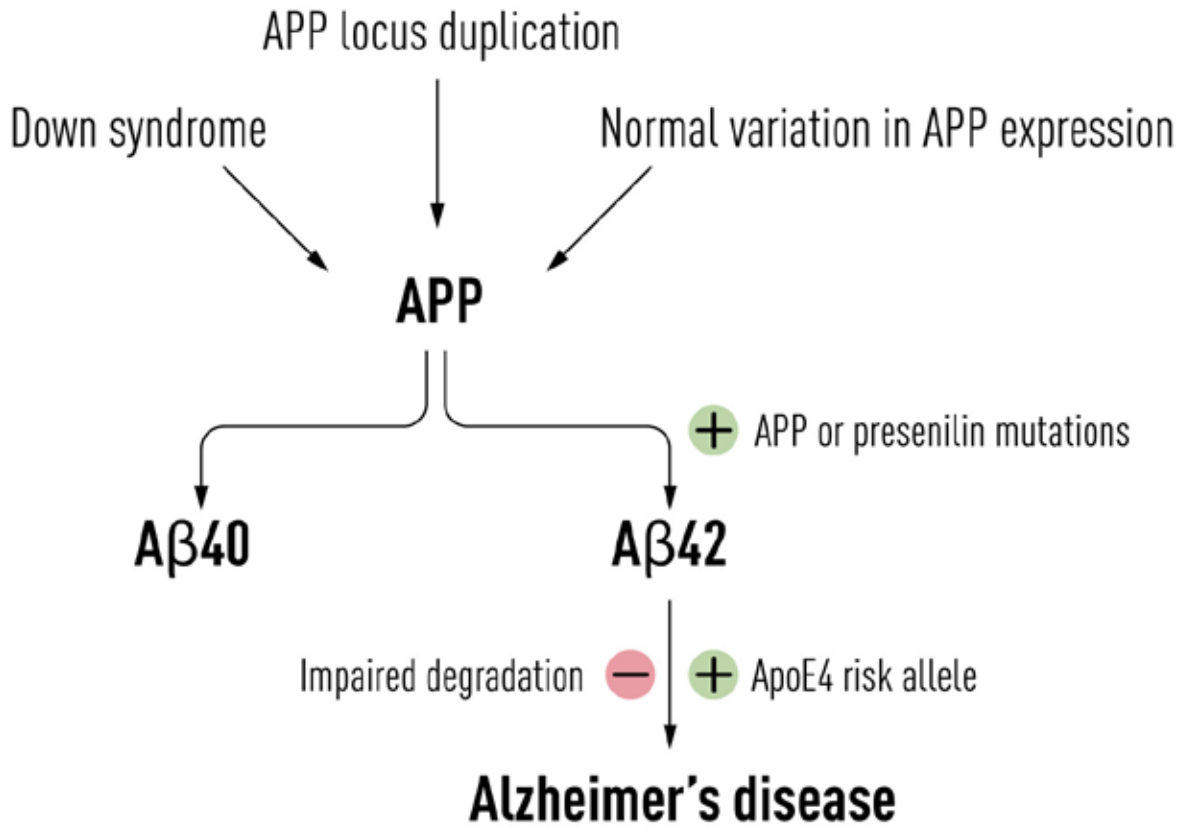


Abnormal protein deposition and decline in brain function

Genetic factors converge on amyloid-β (Aβ), which starts the disease process

Swedish mutation
(Nature Genet 1992)
'Aβ starts the disease'

Arctic mutation
(Nature Neurosci 2001)
'Protofibrils of Aβ are toxic'



Changes in Aβ precedes tau pathology in Alzheimer's disease

Progression of neuropathology, investigations at Harvard brain bank: Aβ pathology precedes tau pathology

(Ingelsson et al. 2004 Neurology)

Aβ levels in CSF are changed, but not tau, 5-10 years before onset of AD

(Buchhave et al. 2012 Arch Gen Psychiatry)

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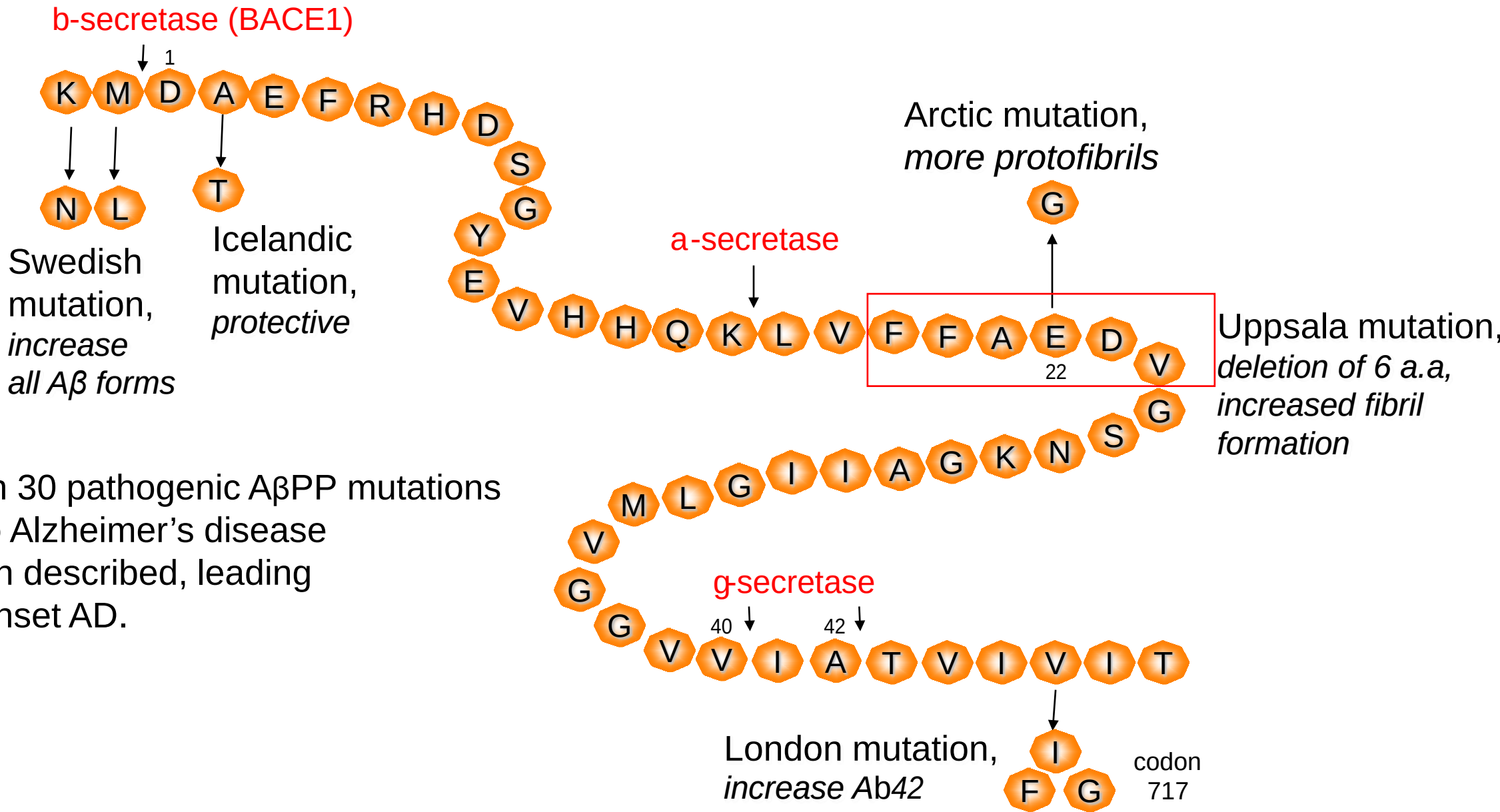
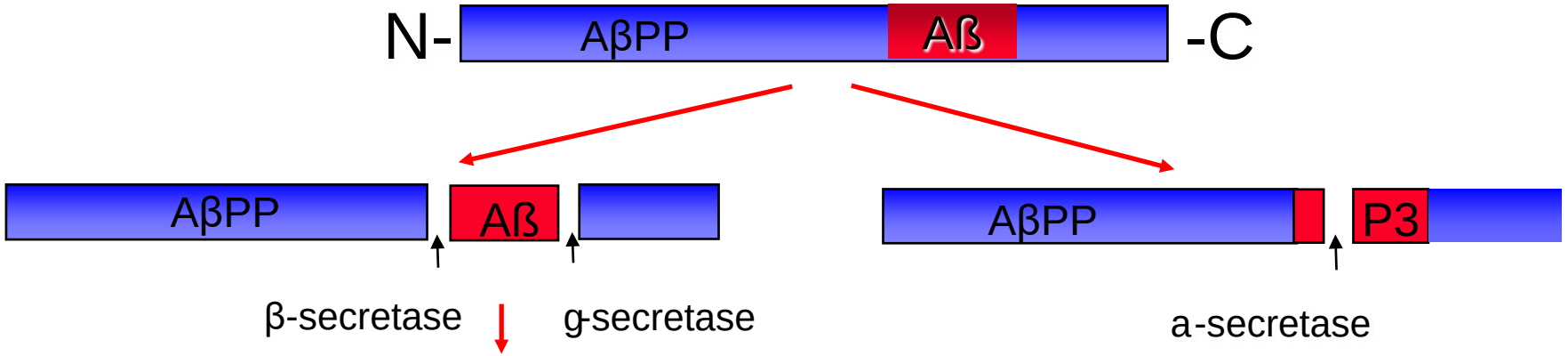
Effects on Aβ by APP gene mutations



More than 30 pathogenic AβPP mutations leading to Alzheimer's disease have been described, leading to early onset AD.

The amyloid cascade hypothesis in Alzheimer's disease – gives ideas for drug targets



soluble Aβ monomers

↓

soluble Aβ oligomers/protofibrils

↓

Aβ deposition in plaques

↓

Microglia activation

↓

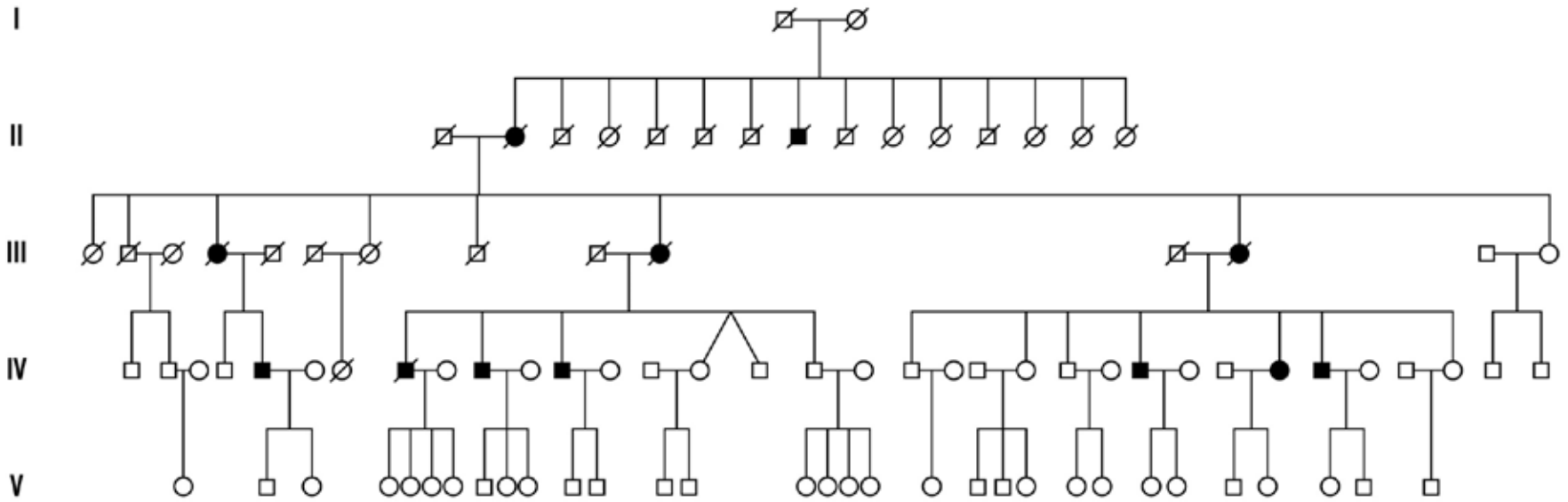
Neurofibrillary Tangles (t-tau, p-tau)
Neurofilament light, Neurogranin
Neuronal Death, Synapse Loss
Neurotransmitter Deficits

→ Dementia

We lack information on mechanisms:

- Why increased risk with ApoE *e*4?
- Why tau pathology?

The Arctic mutation family

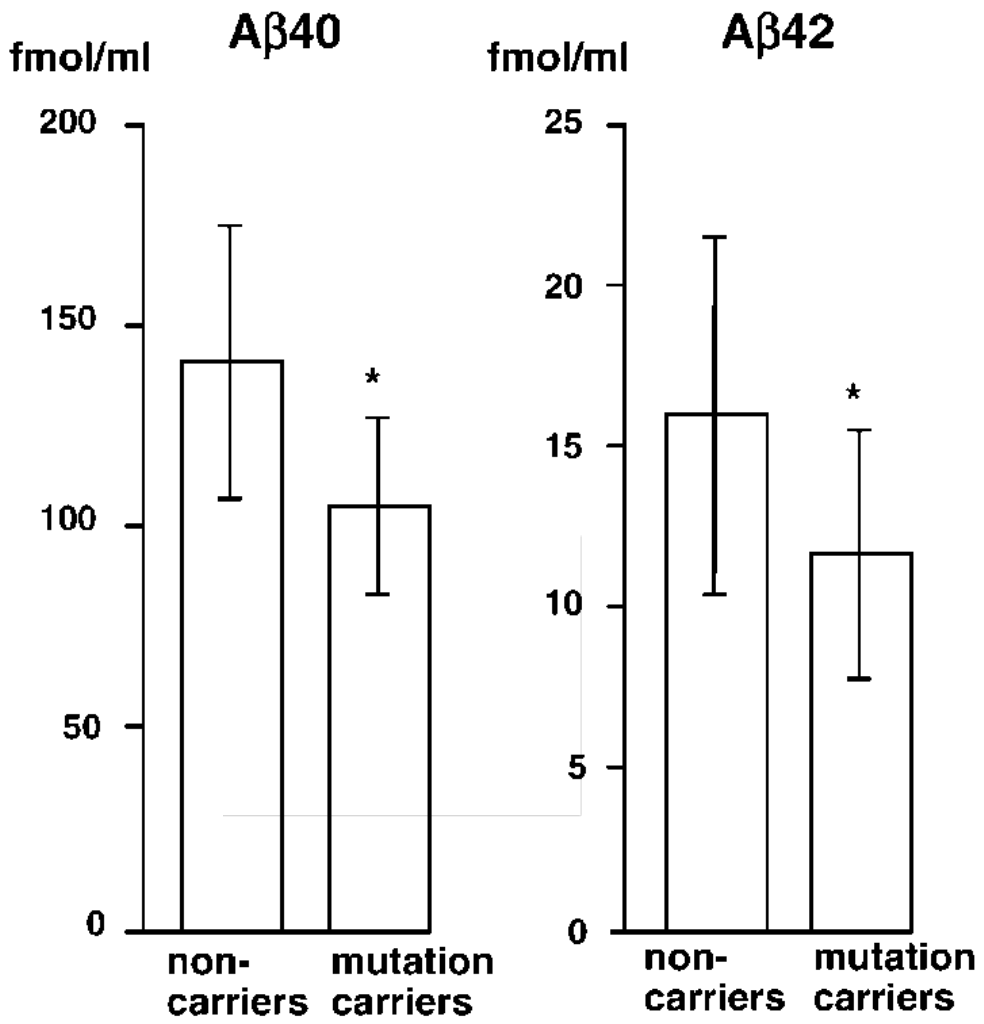


Originates from northern Sweden
Autosomal dominant Alzheimer's disease
No signs of cerebral haemorrhage
Age of onset: 57±3 years
A lod score of 3.66

(Nilsberth et al. Nature Neurosci 2001)

Decreased Ab40 and Ab42 in plasma from mutation-carriers in the Arctic family

Plasma from 9 mutation carriers and 11 non-carriers in the family were analyzed by end-specific ELISAs

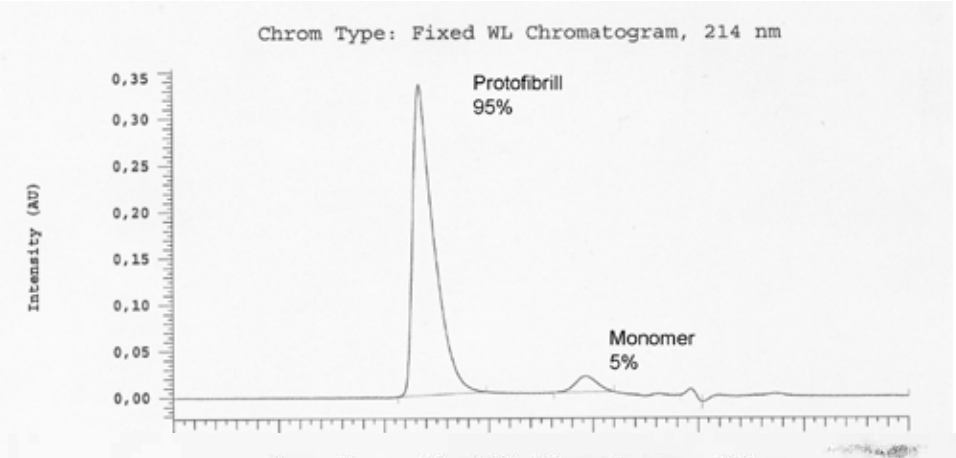


Nilsberth et al. 2001 Nature Neurosci

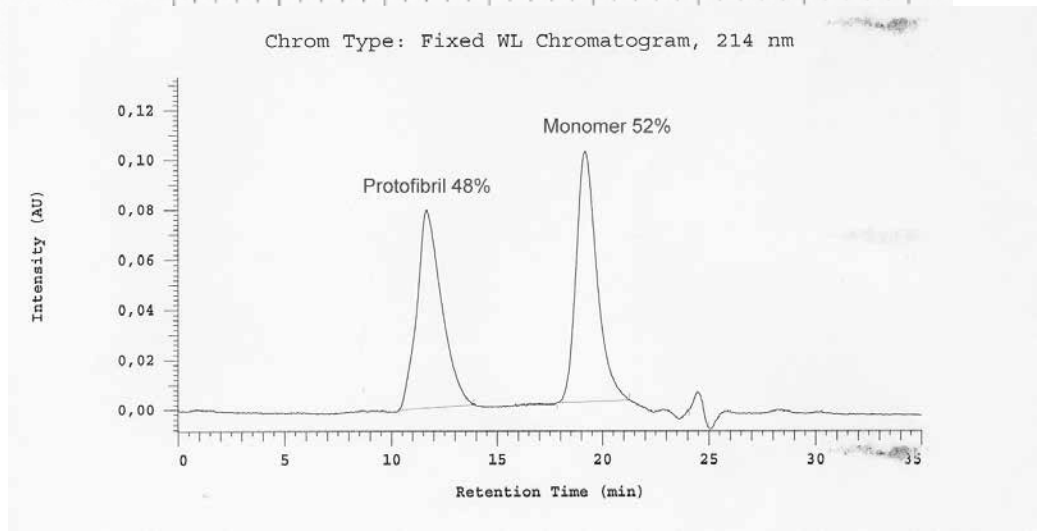
Accelerated protofibril formation of Arctic Aβ (Aβ1-42E22G)

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 Ab eluting in the void volume of a Superdex 75 column, > 75 kDa in size
Oligomers: < 75 kDa

Aβ1-42wt

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

Rationale to target Aβ protofibrils

Aβ protofibrils

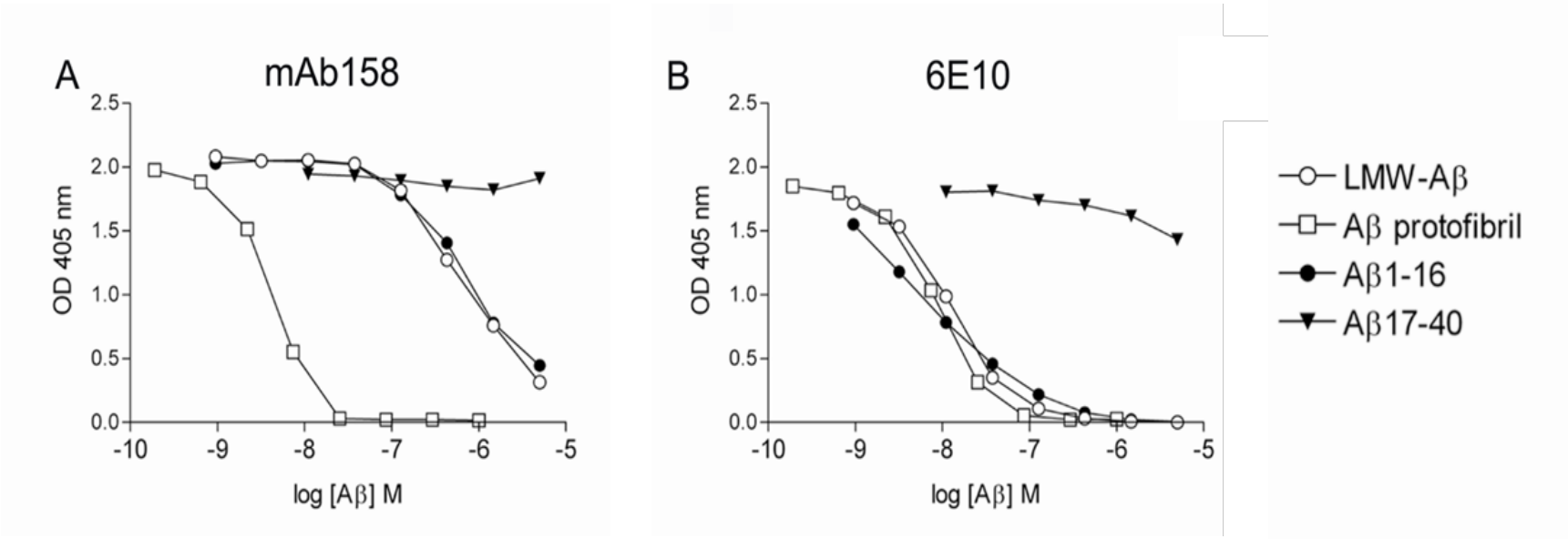
- First observed in 1997, defined by size and structure
- Aβ protofibrils are toxic and detected in the brain
- Increased propensity by the Arctic mutation
- Relevant for all forms of AD

Targeting protofibrils with antibody

- Minimal interference with normally occurring monomeric Aβ
- No sequestering of antibody in the periphery
- Lower binding to Aβ fibrils – lower risk for side-effects, ARIA-E?

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

mAb158, precursor to BAN2401/lecanemab, binds Aβ protofibrils selectively



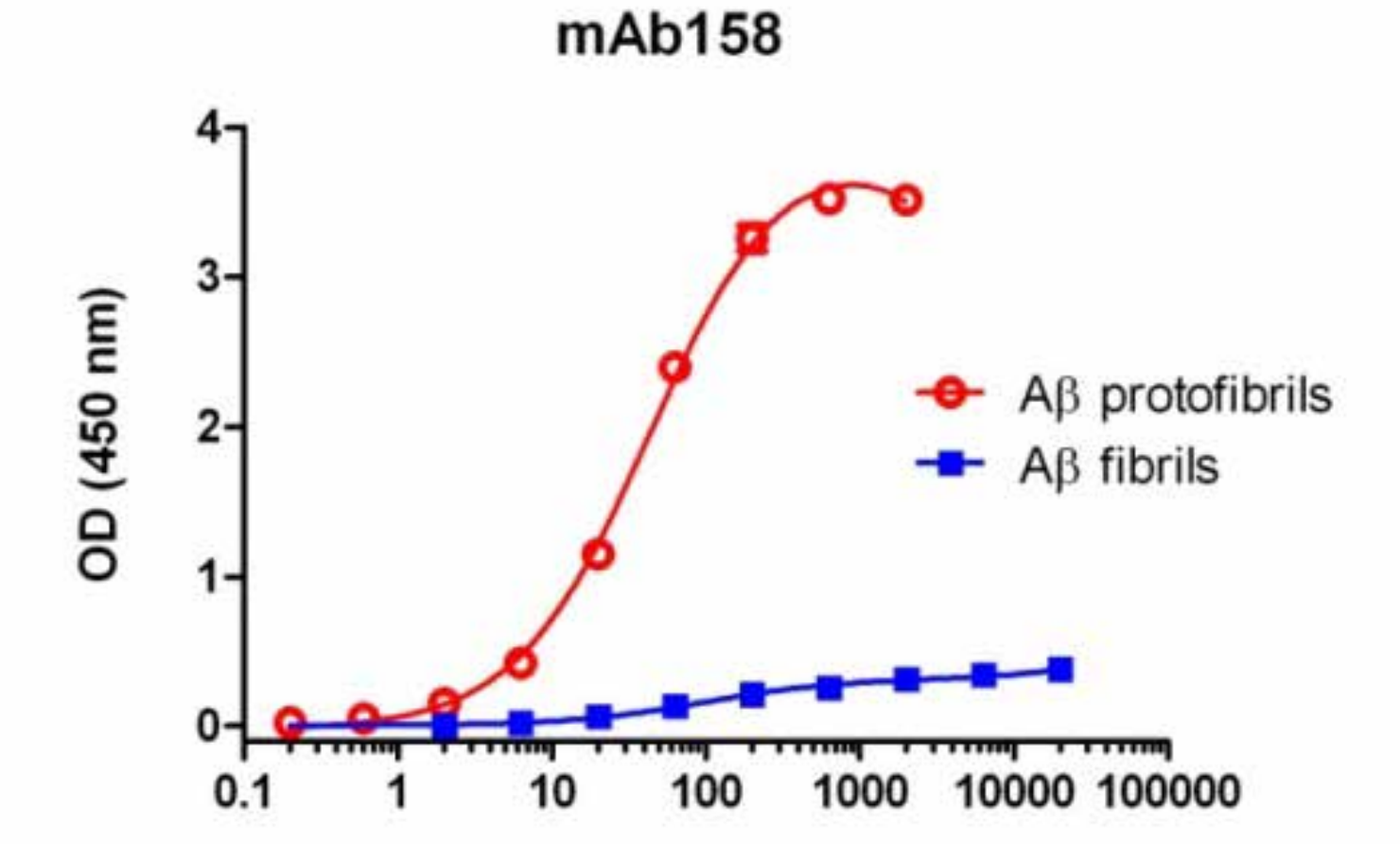
Antibody and antigen were allowed to interact at low concentrations in solution
Reflects a *native* situation

mAb158:

- Strong binding to Ab protofibrils
- Weak binding to Ab monomers

Englund et al. 2007 J Neurochem

mAb158: strong binding to Aβ protofibrils and weaker binding to Aβ fibrils



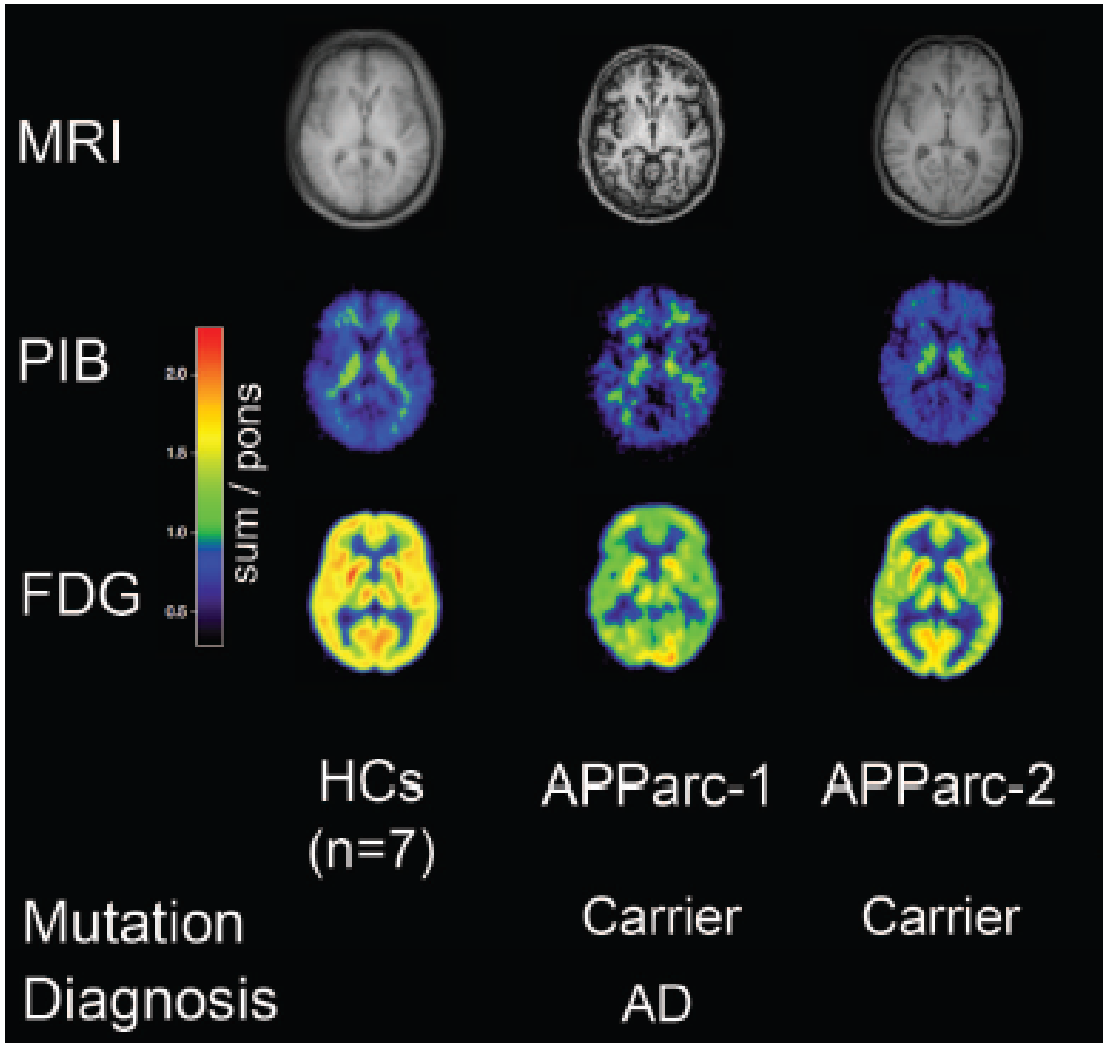
Approx. 10-15 x stronger binding to protofibrils than to fibrils

Magnusson et al. 2013 J Alz Dis

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

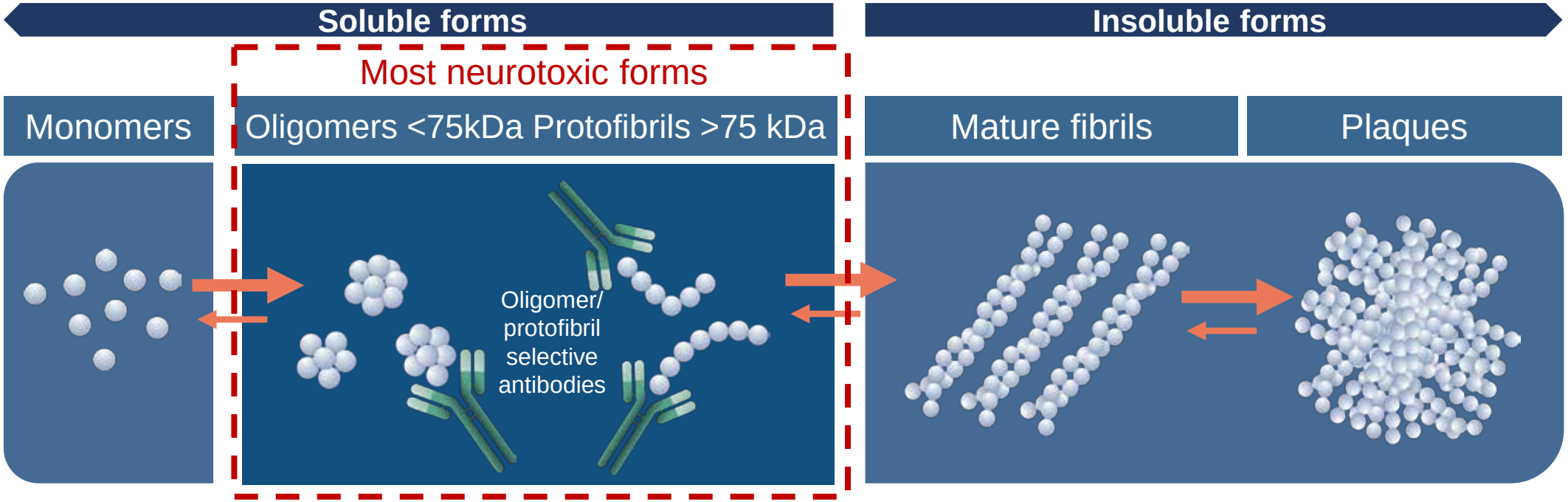
APParc-1 and 2: very low cortical PIB retention, APParc-1 had decreased glucose metabolism and atrophy, and APParc-2 regionally decreased glucose metabolism

Conclusion: toxicity in the AD brain is mediated by Aβ species not detected by amyloid PET

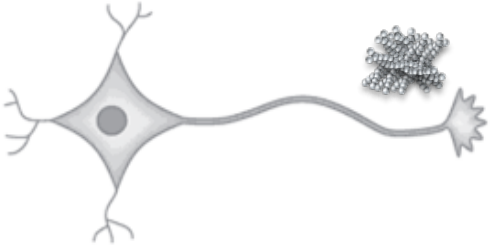


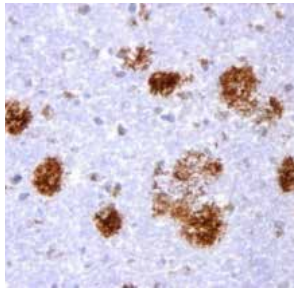
Schöll et al. 2012 Neurology

Targeting most neurotoxic forms of aggregated Aβ is important when designing therapies for Alzheimer's disease



Aggregated Aβ fibrils in amyloid plaques



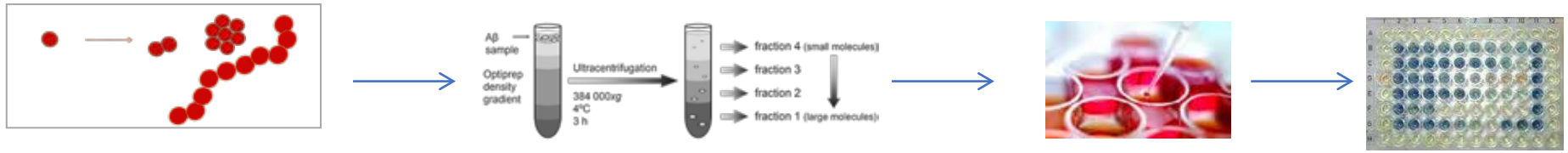


Walsh et al. 1997 J Biol Chem; Harper et al. 1997 Chem Biol; Nilsberth et al. 2001 Nat Genet; O'Nuallain et al. 2010 J Neurosci; Lannfelt et al. 2013 J Intern Med; Lannfelt et al. 2014 Alz Res Ther

Investigations of three anti-Aβ antibodies

- Lecanemab, aducanumab and gantenerumab were investigated using inhibition ELISA, immunodepletion and Surface Plasmon Resonance (SPR, Biacore)
- Affinity and selectivity to different *in vitro* generated species of Aβ such as monomers, oligomers, small and large protofibrils and fibrils, were evaluated side-by-side
- Soluble aggregates (oligomers/protofibrils) of Aβ are considered to be the most toxic forms
- Except for lecanemab, the antibody analogues were produced from publicly available sequences

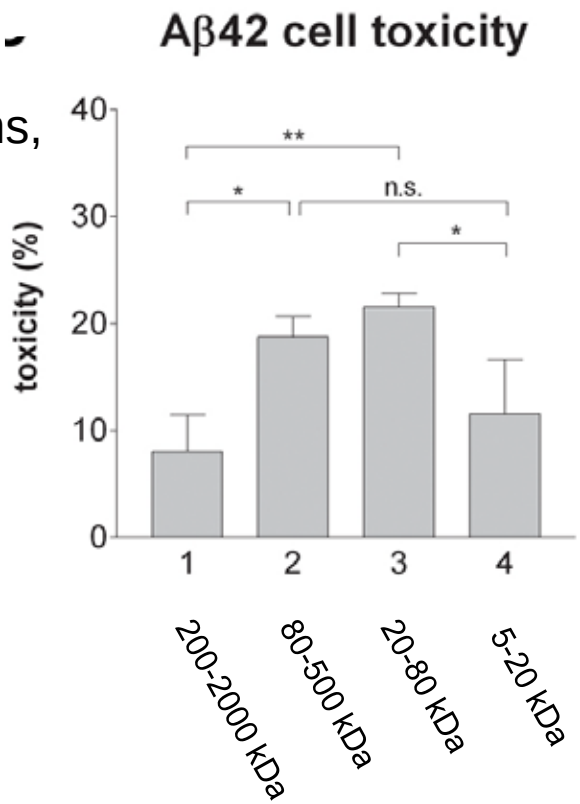
Intermediate sized Aβ42 oligomers/protofibrils: the most toxic species



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 human brain:

- In fraction 2
- Size of 80-500 kDa

Sehlin et al. 2012 PLoS ONE

Definition of Aβ protofibrils and oligomers

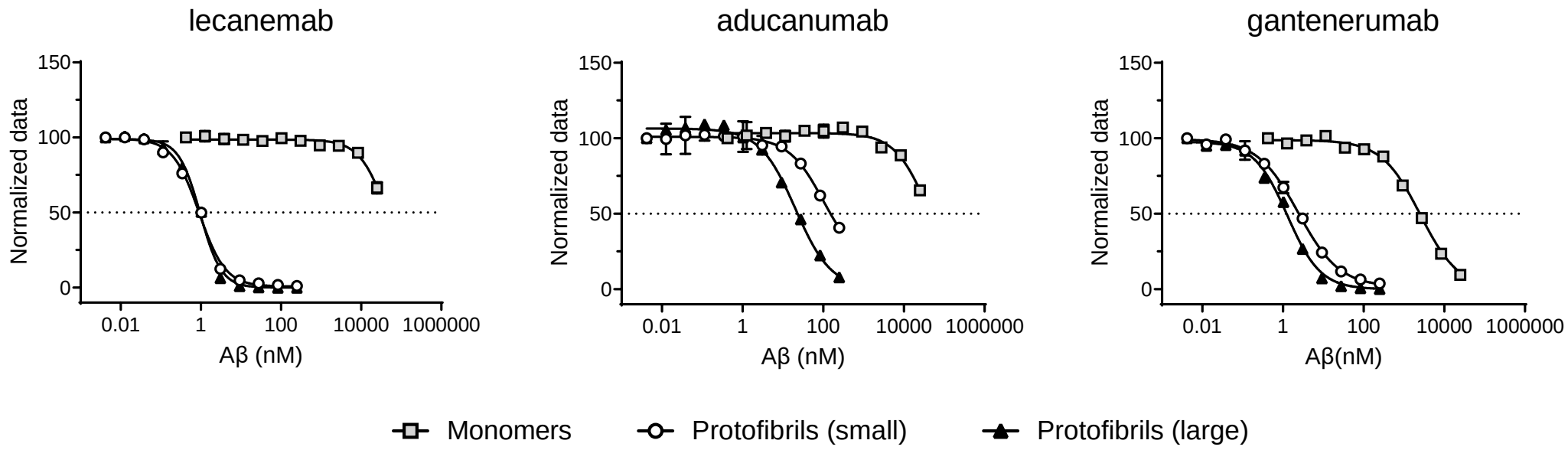
Our definition of protofibrils:

- Soluble aggregated Aβ eluting in the void volume of a Superdex 75 column, >75 kDa in size
- Do not pellet at 16,000 x g centrifugation
- Protofibrils have a beta-sheet structure and do not migrate as globular standard proteins
- Method: incubation of Aβ1-42 and separation of protofibrils from fibrils and monomers by centrifugation and Size-Exclusion Chromatography (SEC)

Our definition of oligomers:

- Less than 75 kDa in size
- Method: photo-induced cross-linking (Bitan et al. 2001 JBC) followed by separation and collection of oligomer fractions of different sizes using a Superdex 75 column

Binding to Aβ protofibrils strongest for lecanemab compared to aducanumab and gantenerumab (inhibition ELISA)

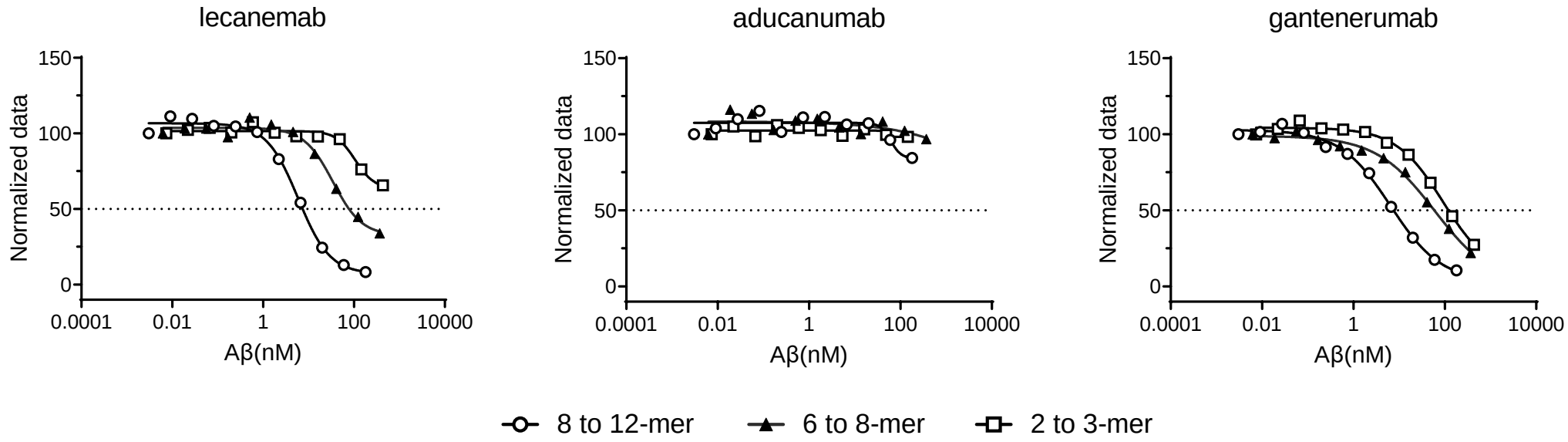


Small protofibrils, approx. 75-300 kDa, large protofibrils, approx. 300-5000 kDa

- Lecanemab binds small protofibrils 100x and large protofibrils 25x stronger than aducanumab
- Gantenerumab is less selective and binds monomers with somewhat higher affinity compared to lecanemab and aducanumab

Söderberg et al. submitted

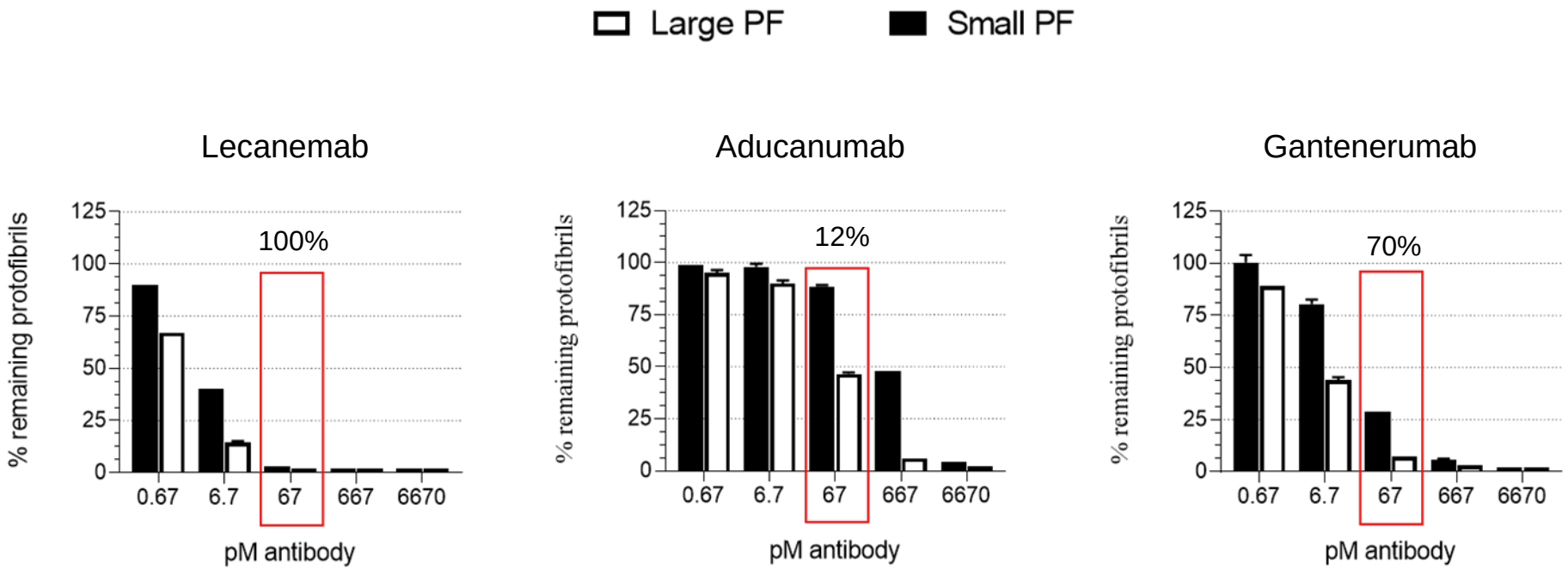
Binding to small Aβ oligomers using inhibition ELISA



- Lecanemab binds 8 to 12-mer oligomers but had reduced binding to smaller species (2 to 3-mer)
- Aducanumab showed very weak binding to small oligomers
- Gantenerumab demonstrated binding to small oligomers

Söderberg et al. submitted

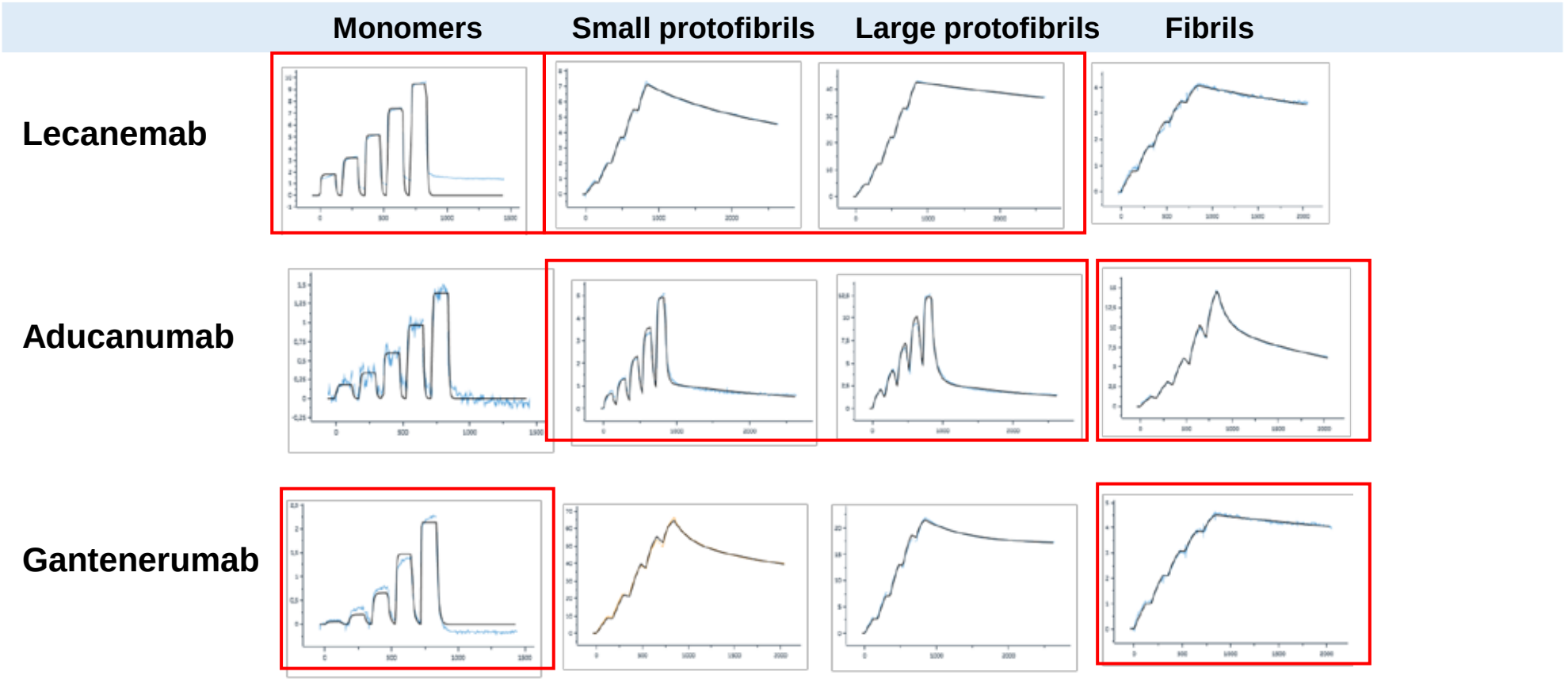
Immunodepletion of protofibrils: lecanemab more potent than aducanumab and gantenerumab



- Lecanemab was most potent in immunodepleting protofibrils in solution
- Full depletion was achieved with 67 pM of lecanemab, with 667 pM of gantenerumab and with 6670 pM aducanumab
- Results in line with inhibition ELISA

Söderberg et al. submitted

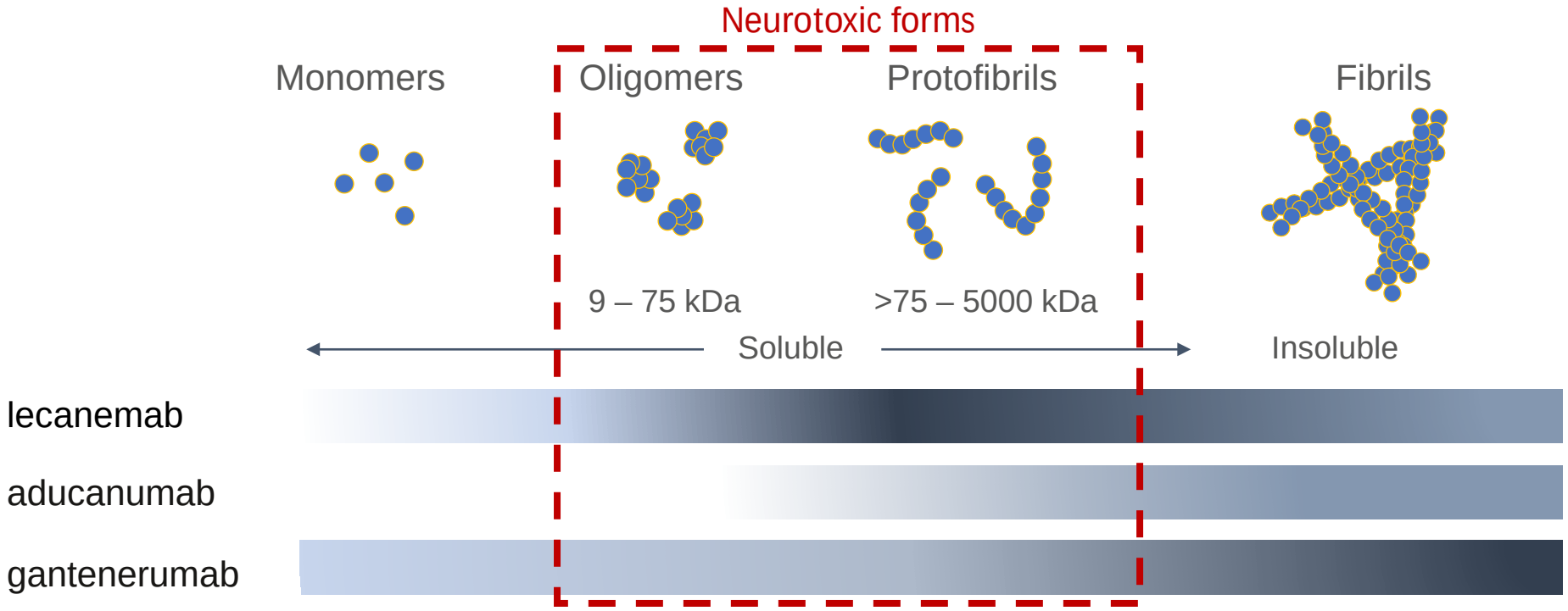
Selectivity for Aβ protofibrils strongest for lecanemab (SPR, Biacore)



- Lecanemab had its strongest binding to protofibrils, very low binding to monomers
- Aducanumab was a weaker Ab binder with a very fast on- and off-rates for protofibrils, very low binding to monomers and prefers fibrils
- Gantenerumab had somewhat higher binding to monomers and prefers fibrils

Söderberg et al. submitted

Lecanemab – unique selectivity towards toxic soluble species of Aβ

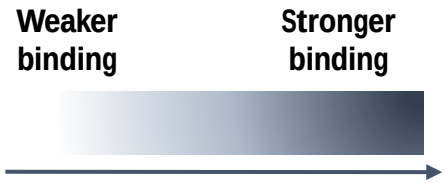


Lecanemab had the highest preference for soluble protofibrils/oligomers versus monomeric and fibrillar forms of Aβ

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 and prefers fibrils



Source: Presented at CTAD 2021. Note: Illustration is based on data from Biacore, inhibition ELISA and immunoprecipitation

Summary

- All genetic, biochemical and clinical data indicate that Aβ starts the disease process
- Changes in Aβ precedes tau pathology
- All three investigated antibodies have low binding strength to monomers
- All three antibodies work through avidity
- The three antibodies have different binding profiles to Aβ
- All three antibodies bind fibrils, but with different selectivity
- Lecanemab was the strongest Aβ binder and prefers protofibrils
- Aducanumab and gantenerumab prefer fibrils
- These binding profiles **might** reflect differences in clinical outcome and also side-effects

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