UPPSALA UNIVERSITET

Genetics, diagnosis and future treatment of Alzheimer's Disease

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Disclaimer: Co-founder of BioArctic AB

Causes of dementia

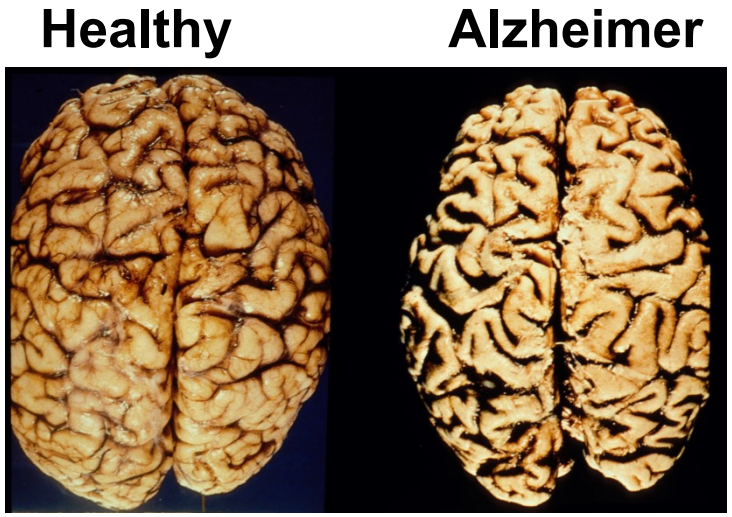
Neurodegenerative
Alzheimer's disease
Frontotemporal dementia
Parkinsons disease
Amyotrofisk lateralscleros(ALS)
Down's syndrom
Prion disease

Vascular dementia
Artheriosclerosis

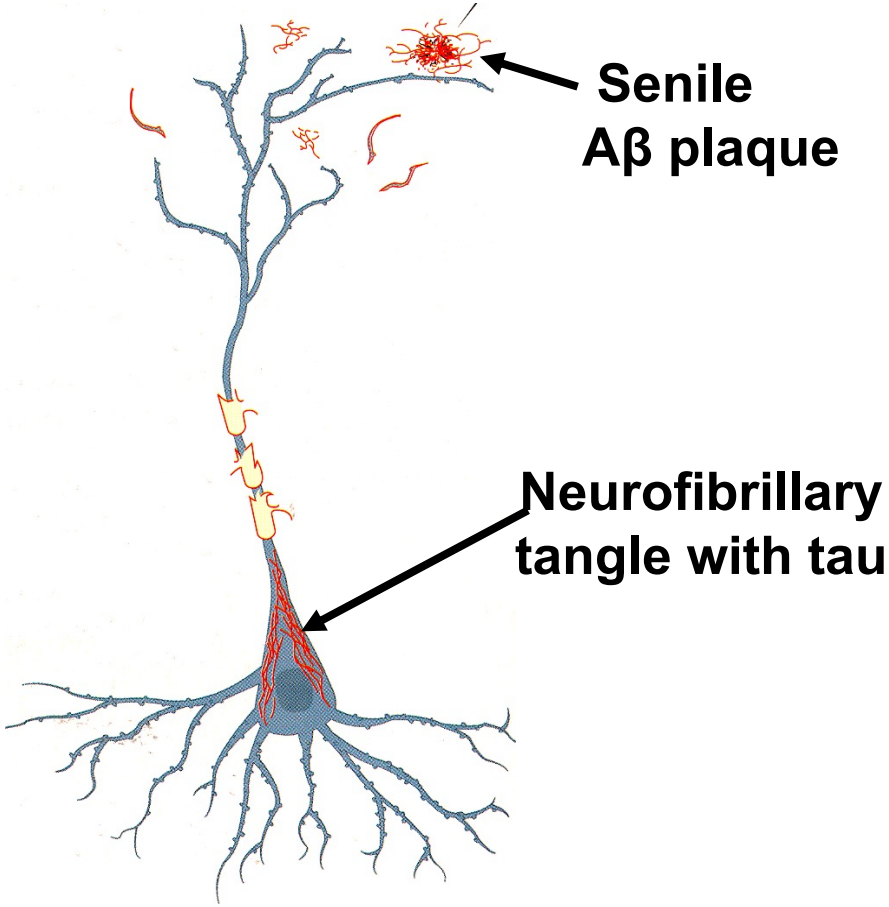
Other causes
Head trauma
Infektions: borelia, syfilis, aids
Brain tumors
Hydrocephalus
B-vitamin deficiency
Metabolic diseases
Depression

Alzheimer's disease 50-60% of all dementia

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

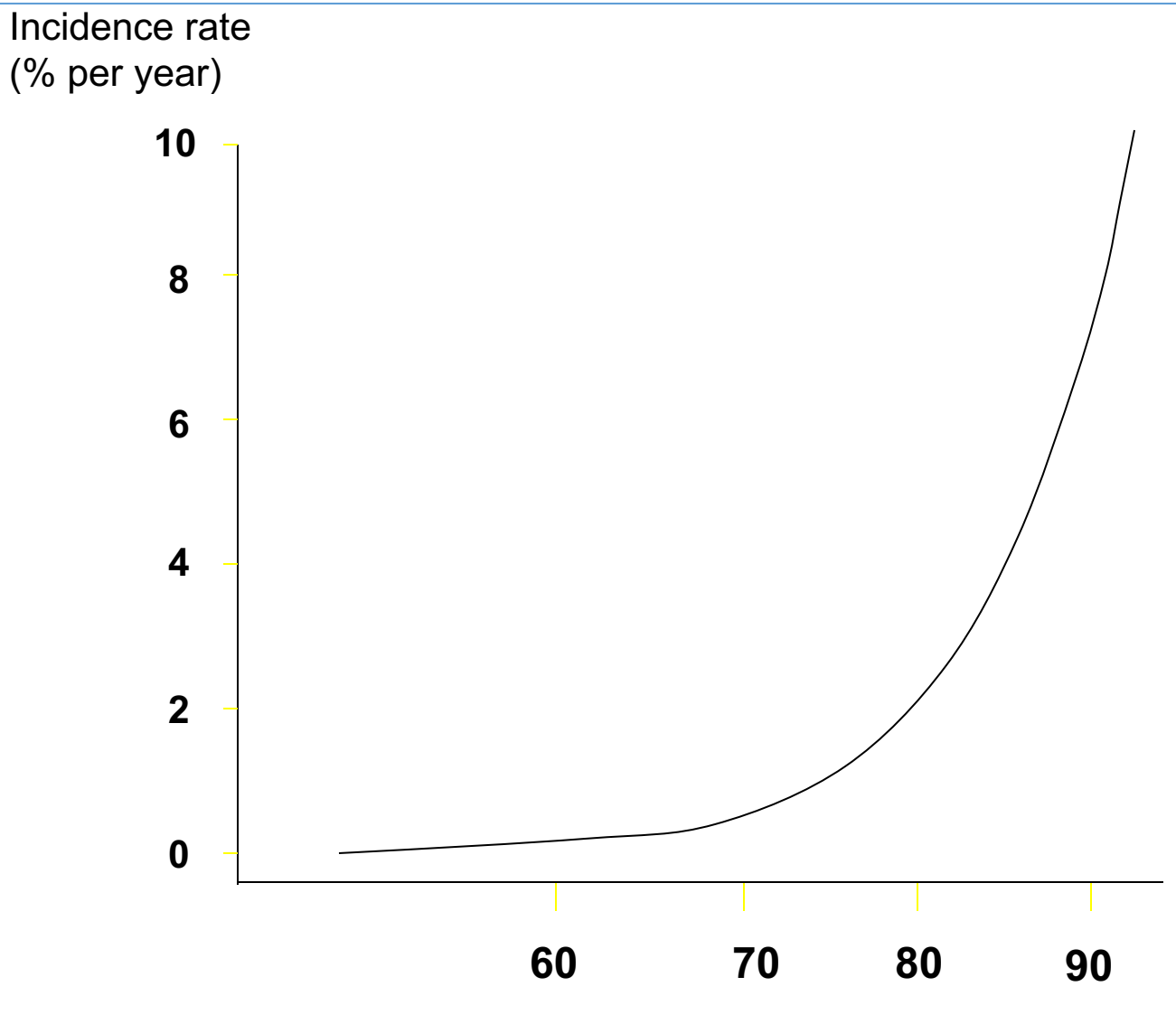


Alzheimer brain: atrophy



Abnormal protein deposition and decline in brain function

Age specific increase of Alzheimer's disease



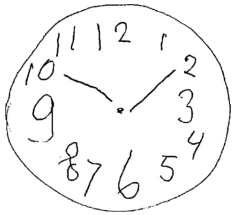
Prevalence in poulation above 65: approx. 5%

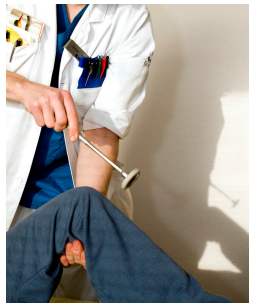
Prevalence in poulation above 80: approx. 20%

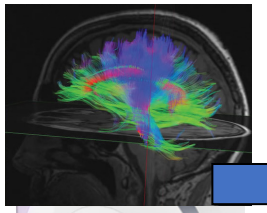
At age 130 all individuals might have AD!

Alzheimer diagnostics – a multidisciplinary approach

Clinical assessments
- Cognitive tests
- Psychiatric & neurological assessments
- ADL function

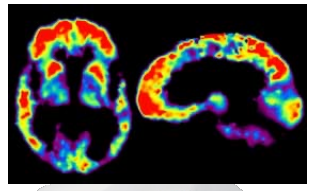






MRI or CT
- Exclude other pathologies
- Regional atrophy patterns
- Cerebrovascular disease
- (Microbleeds)

PET
- Aβ
- Tau



CSF
- Aβ
- T-tau
- P-tau
- NfL

Courtesy Oskar Hansson

Aβ biomarkers

Accumulation of Aβ fibrils can be detected *in vivo* using:

- Amyloid-β PET
- CSF Aβ42/Aβ40 ratio (or CSF Aβ42/P-tau ratio)
- Very high concordance between CSF and PET

Plasma Aβ42/ Aβ40 ratio is a promising blood-based biomarker

- Clinical robustness might be an issue

Courtesy Oskar Hansson

Tau biomarkers

- Tau PET can be used to quantify tau aggregates *in vivo* in AD

- CSF tau levels change during the preclinical stages of AD, before Tau PET, and are associated with **both** amyloid and tau aggregates

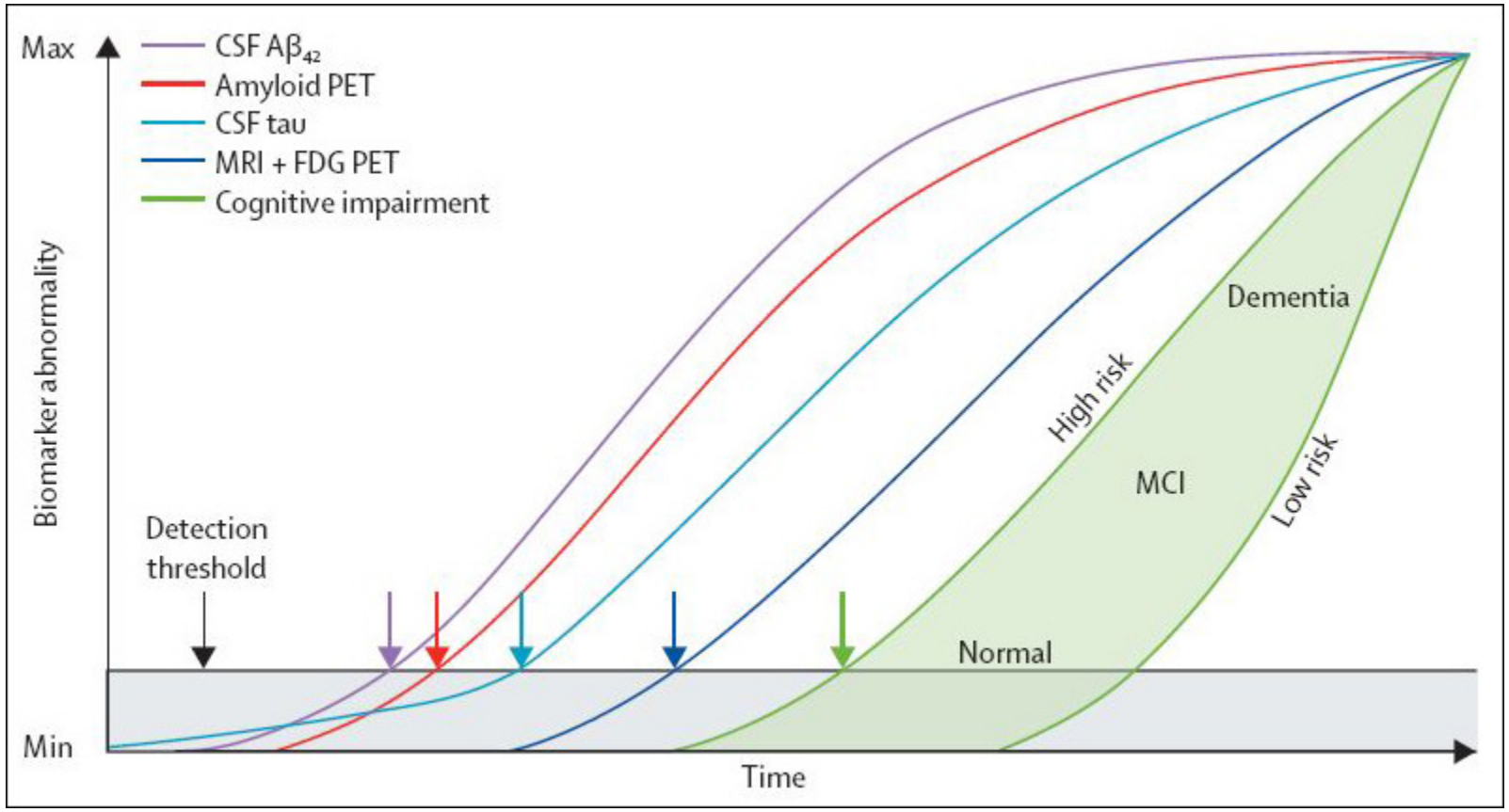
Courtesy Oskar Hansson

Plasma p-tau

- Correlates with tau pathology in AD, but *not* in other tauopathies
- Differentiates between AD dementia and other dementia disorders (similar to CSF AD biomarkers and tau-PET)
- With plasma Aβ42/Aβ40 detects preclinical AD

Courtesy Oskar Hansson

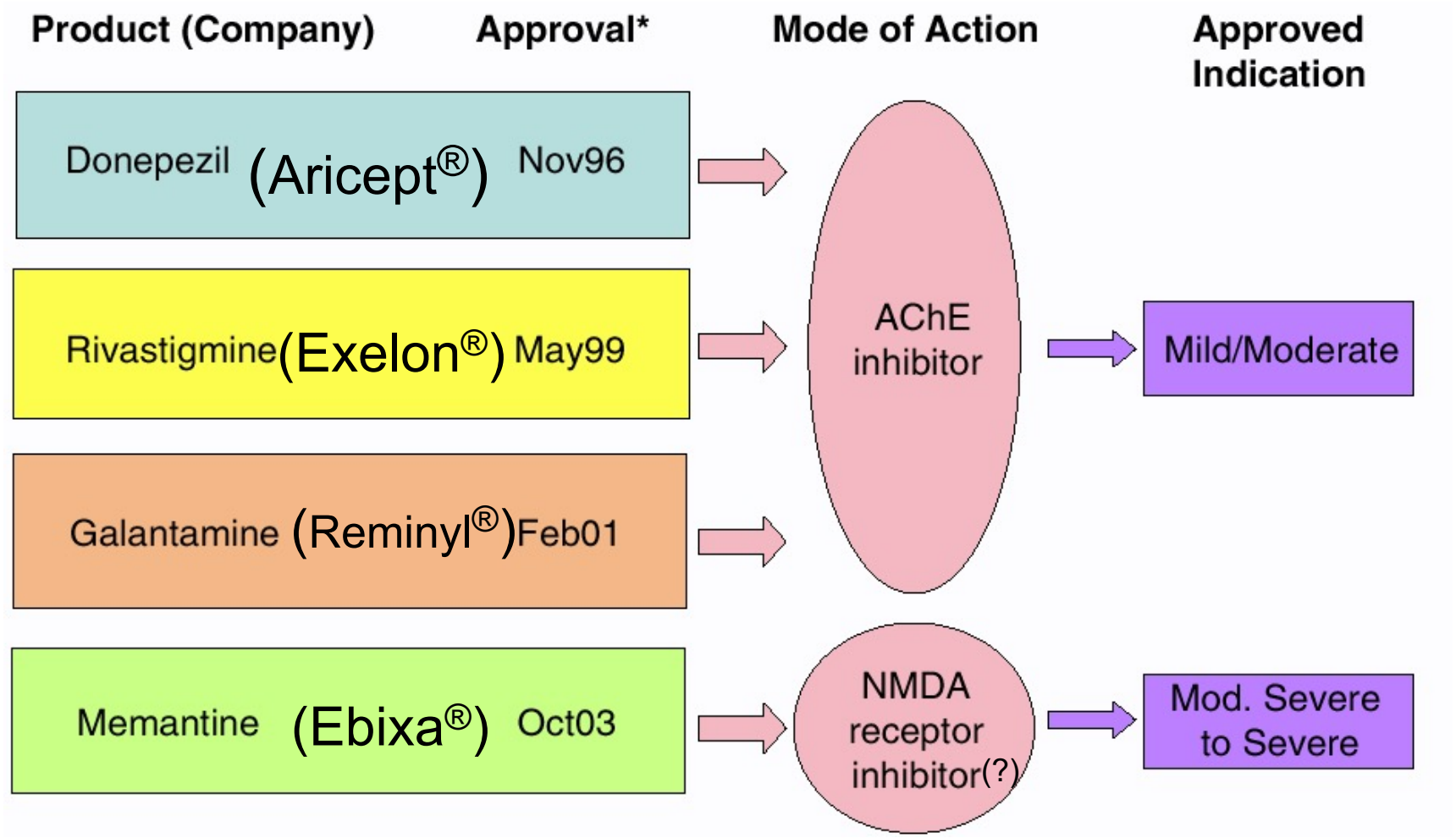
Biomarkers: 15-20 years before clinical symptoms of Alzheimer's disease



High Risk	Preclinical	MCI	Mild	Moderate	Severe

Modified from Hardy and Selkoe, EMBO Mol Med 2016

Todays treatment (symptomatic)



These drugs at best give more activity to the patient for 6-12 months

The usefulness of genetics

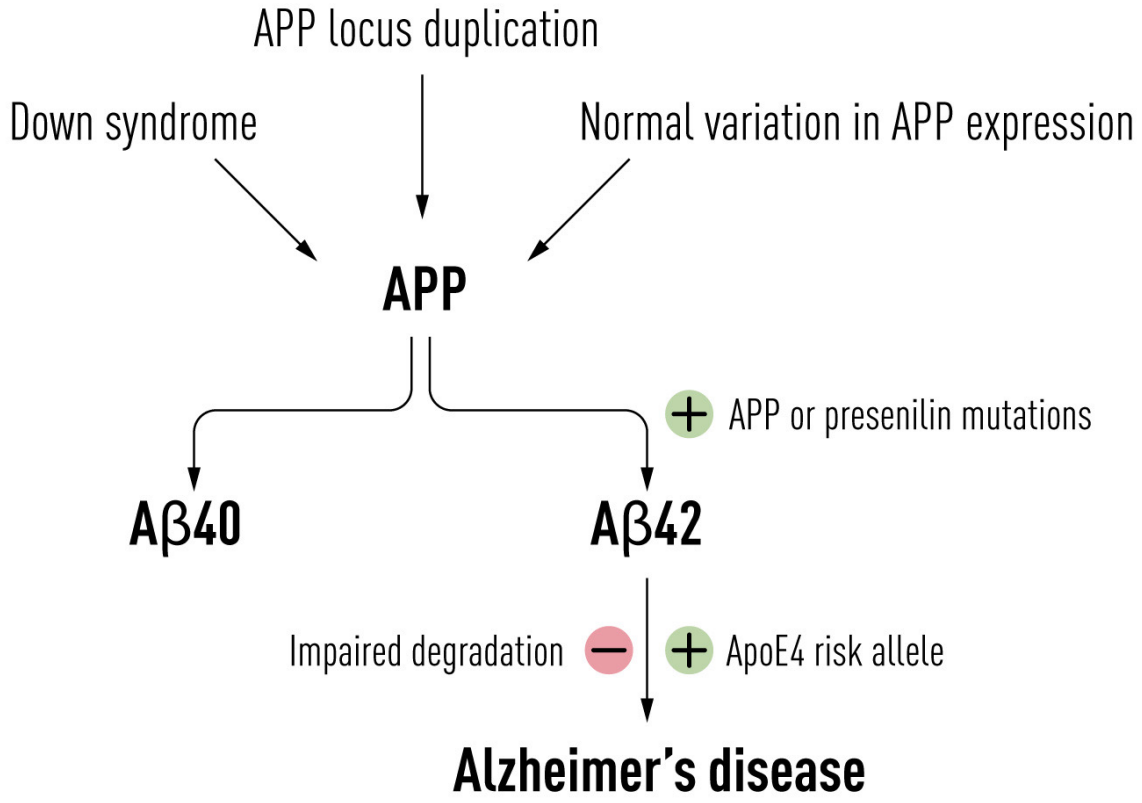
- Puts order into pathology. Genetics shows the start and indicate a pathway where to intervene

- Pathology shows you the endpoint of disease, but does not answer how it started

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

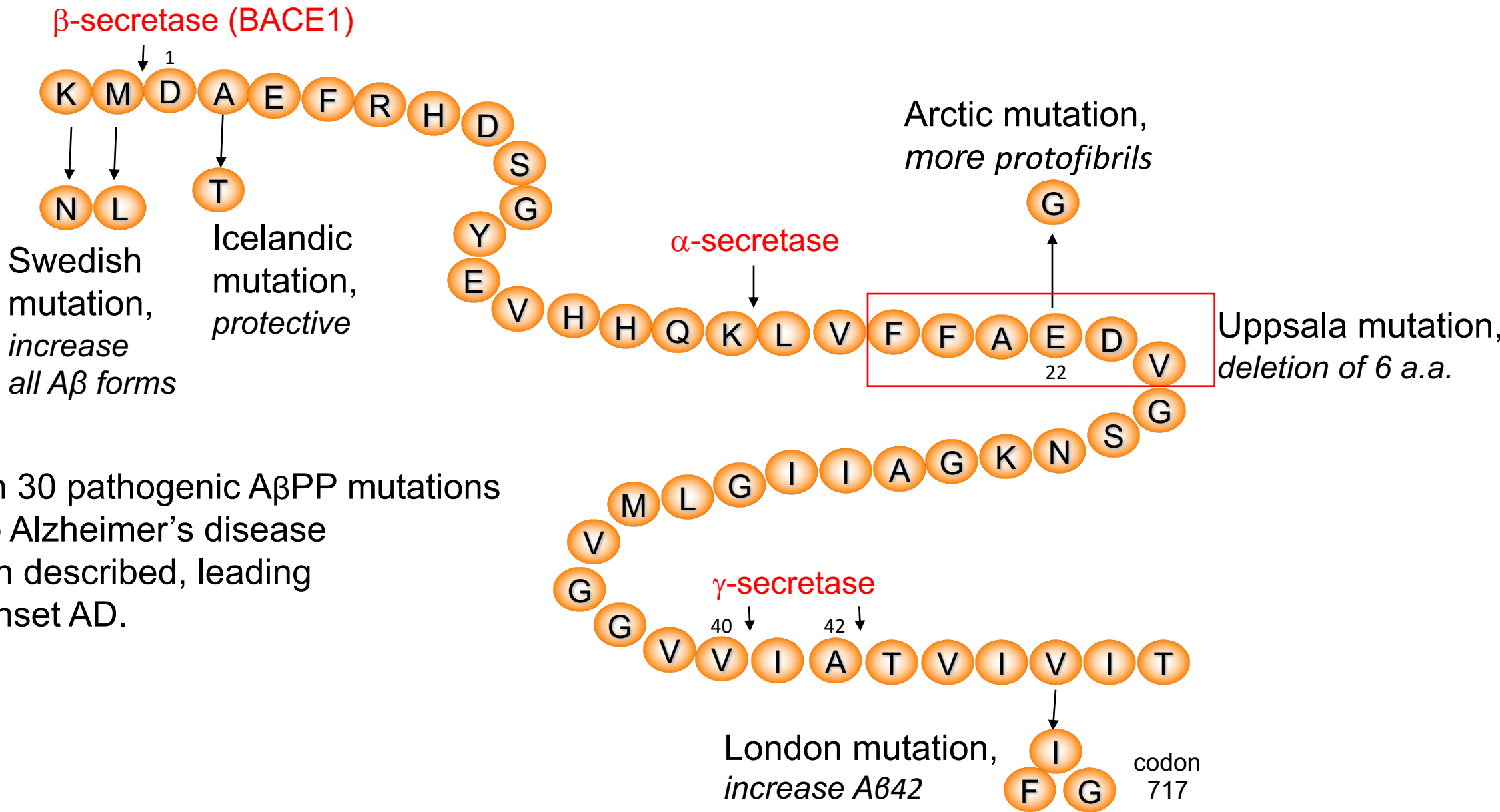
Swedish mutation
(Nature Genet 1992)
'Aβ starts the disease'

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



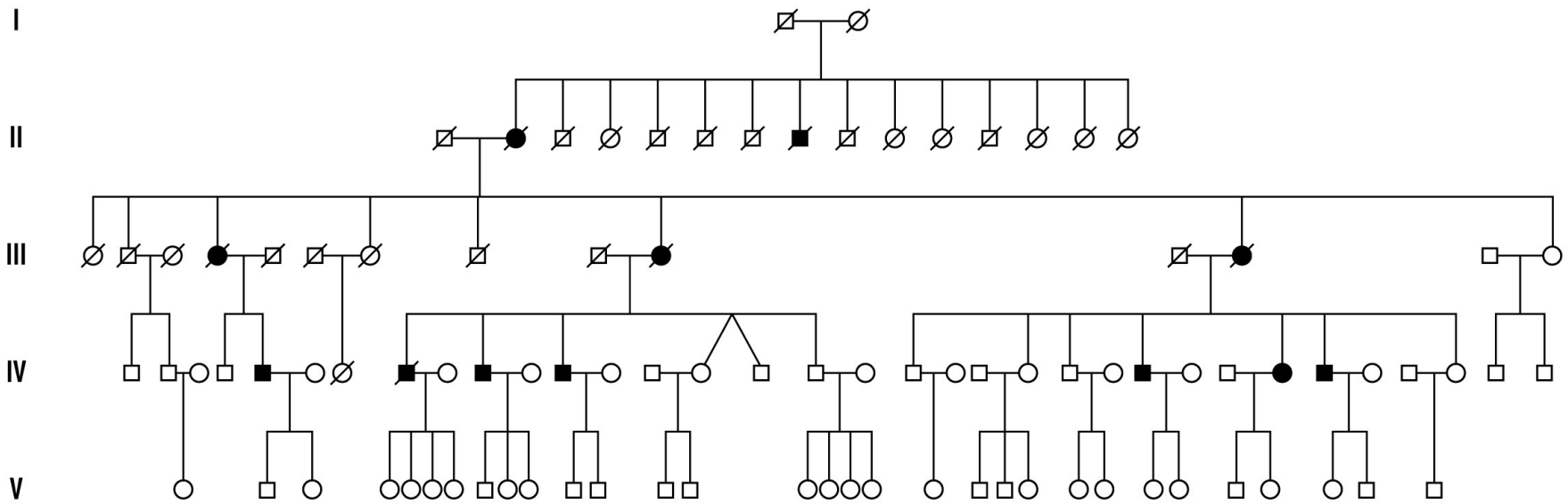
Modified from J. Hardy, J Neurochem 2009

Effects on Aβ by AβPP mutations



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

The Arctic mutation family



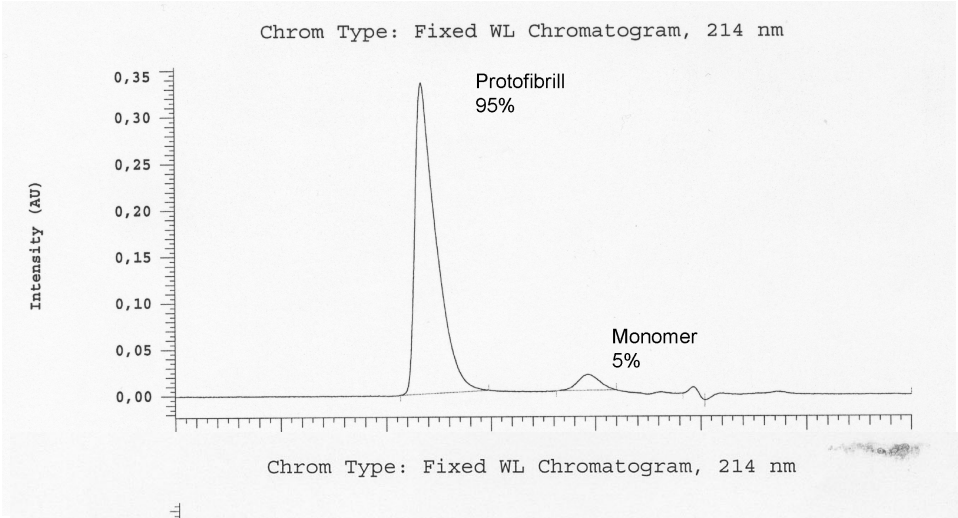
Originates from northern Sweden
Autosomal dominant Alzheimer's disease
No signs of cerebral haemorrhage
Age of onset: 57±3 years
A lod score of 3.66

(Nilsberth et al. Nature Neurosci 2001)

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

Sixe Exclusion Chromatography on a Superdex 75 column

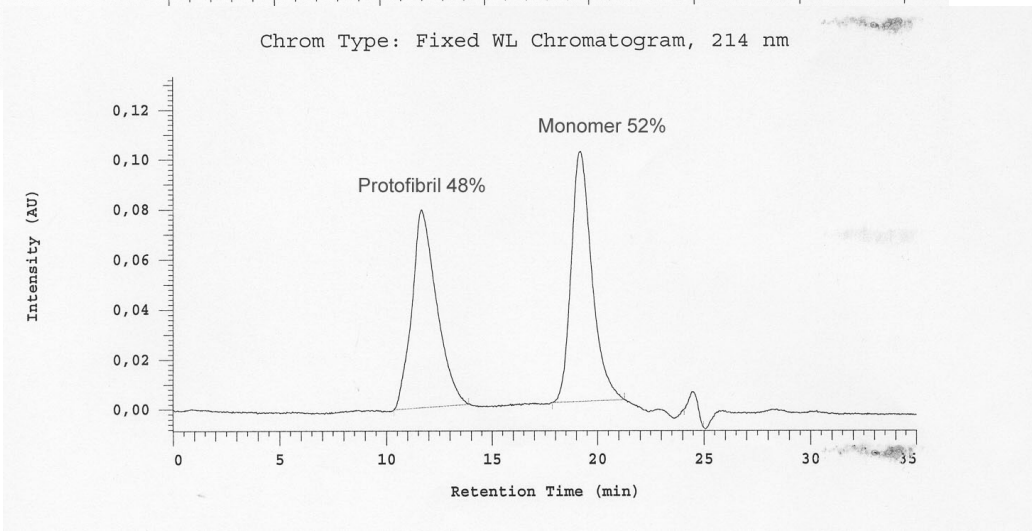
Arc



Aβ1-42Arc

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

Wt

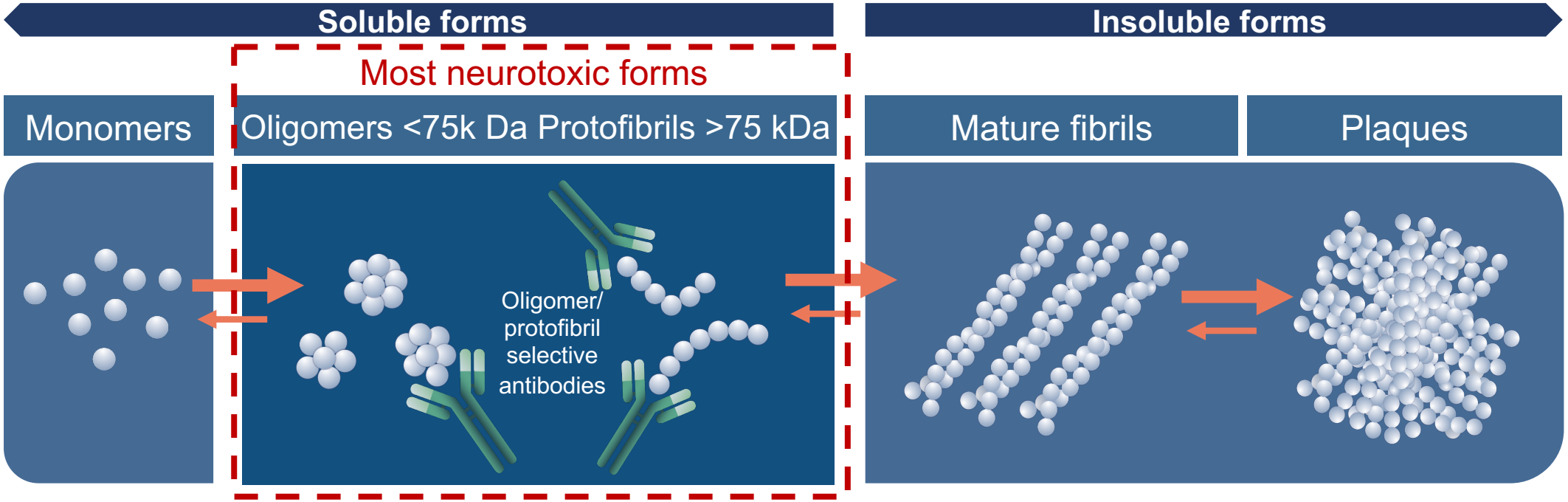


Aβ1-42wt

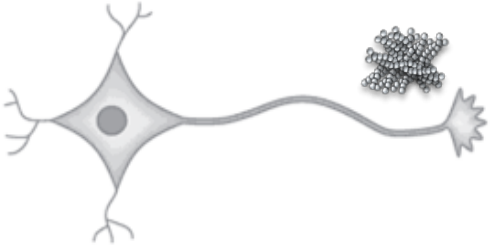
Protofibrils are found in all AD cases but are more prominent with the Arctic mutation

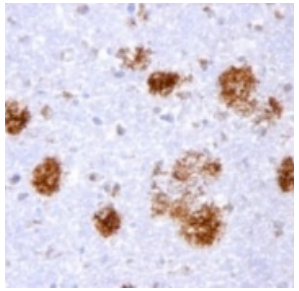
Nilsberth et al. 2001 Nat Neurosci
Johansson et al. 2006 FEBS J

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



Aggregated Aβ fibrils in amyloid plaques



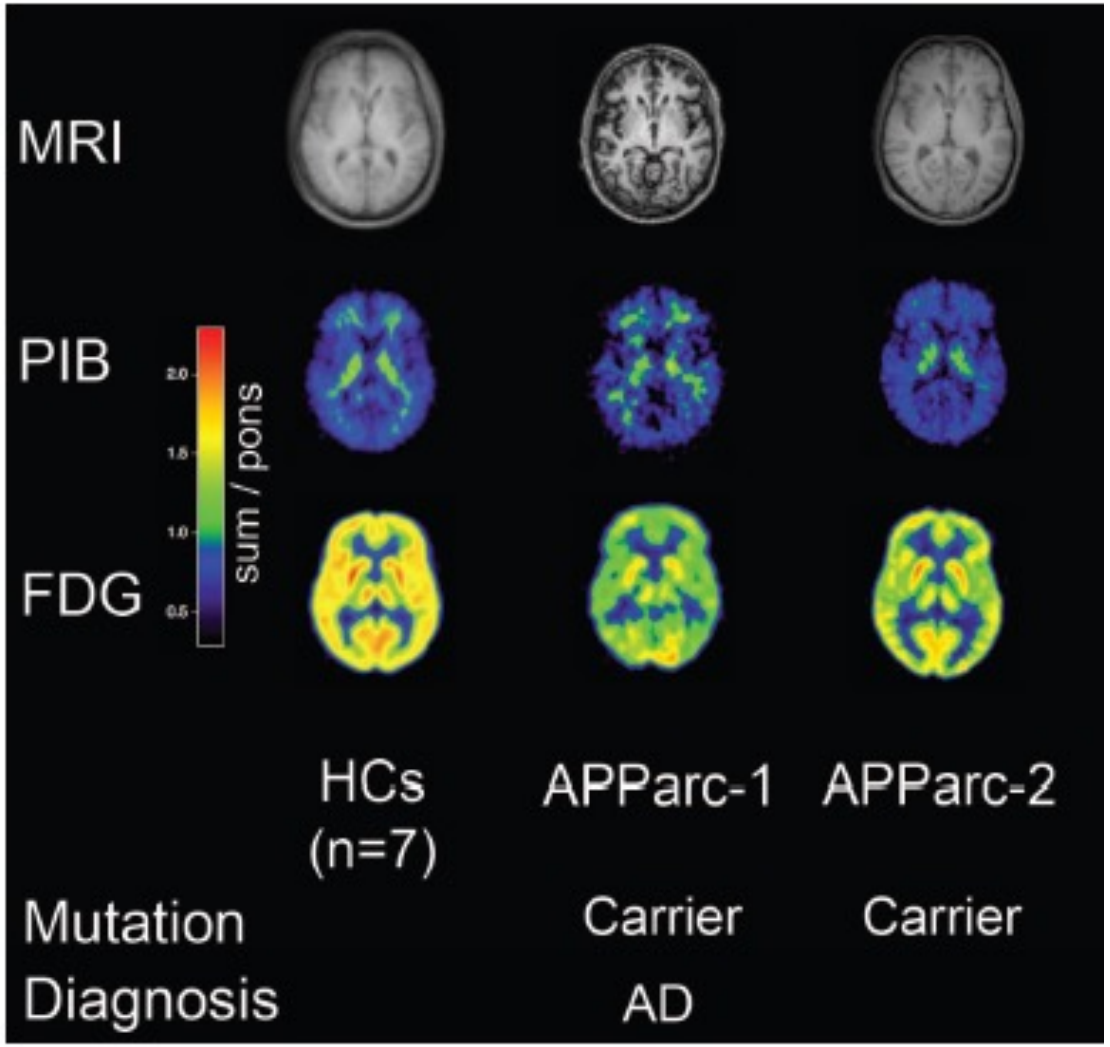


Walsh et al. 1997 J Biol Chem; Harper et al. 1997 Chem Biol; Nilsberth et al. 2001 Nat Genet; O'Nuallain et al. 2010 J Neurosci; Lannfelt et al. 2013 J Intern Med; Lannfelt et al. 2014 Alz Res Ther

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

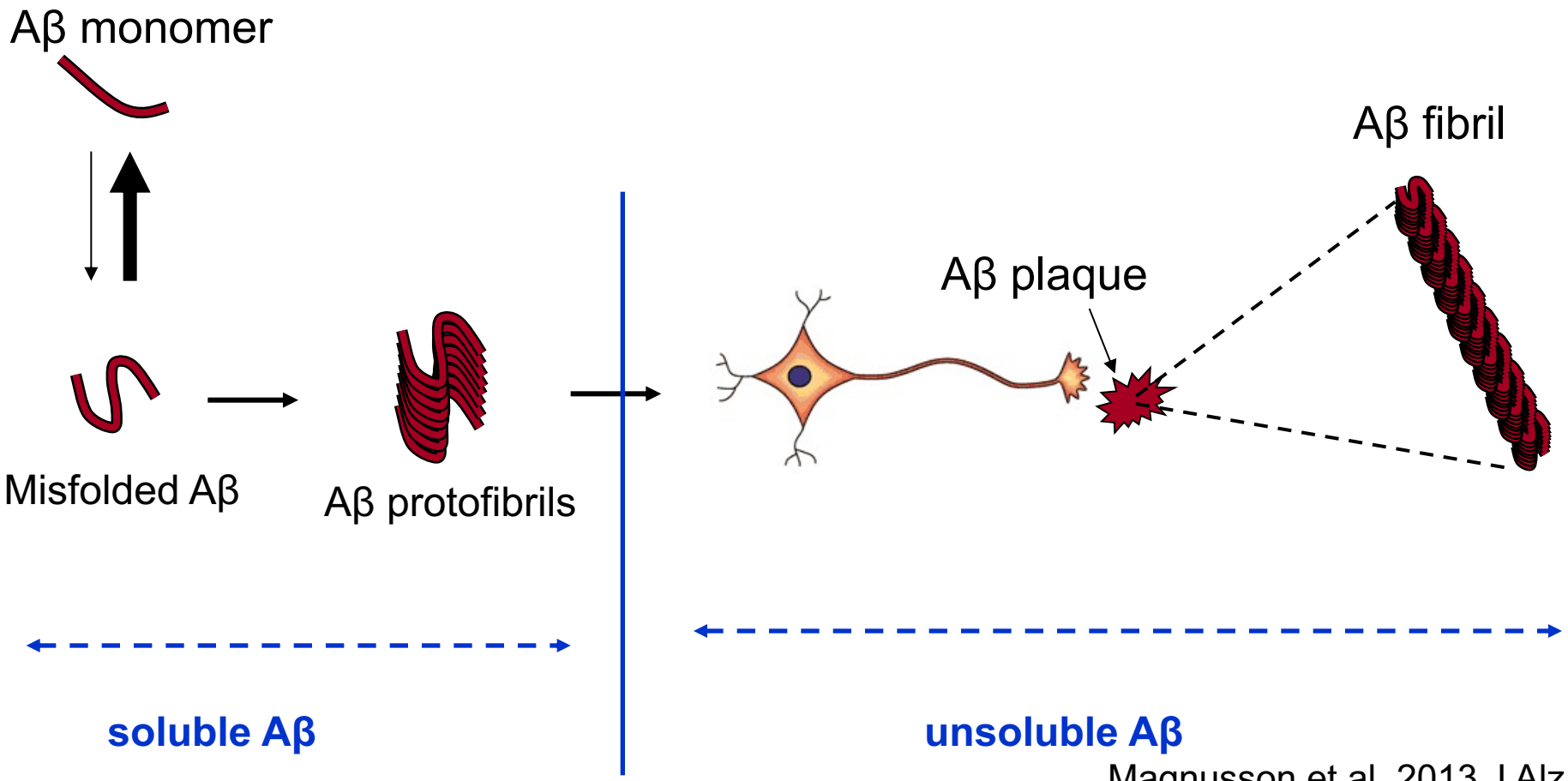
Conclusion: toxicity in the AD brain is mediated by Aβ species not detected by amyloid PET



Schöll et al. 2012 Neurology

The target for mAb158, the mouse precursor to BAN2401/lecanemab: Aβ protofibrils

mAb158: lower binding strength to both
Aβ monomers and to Aβ fibrils



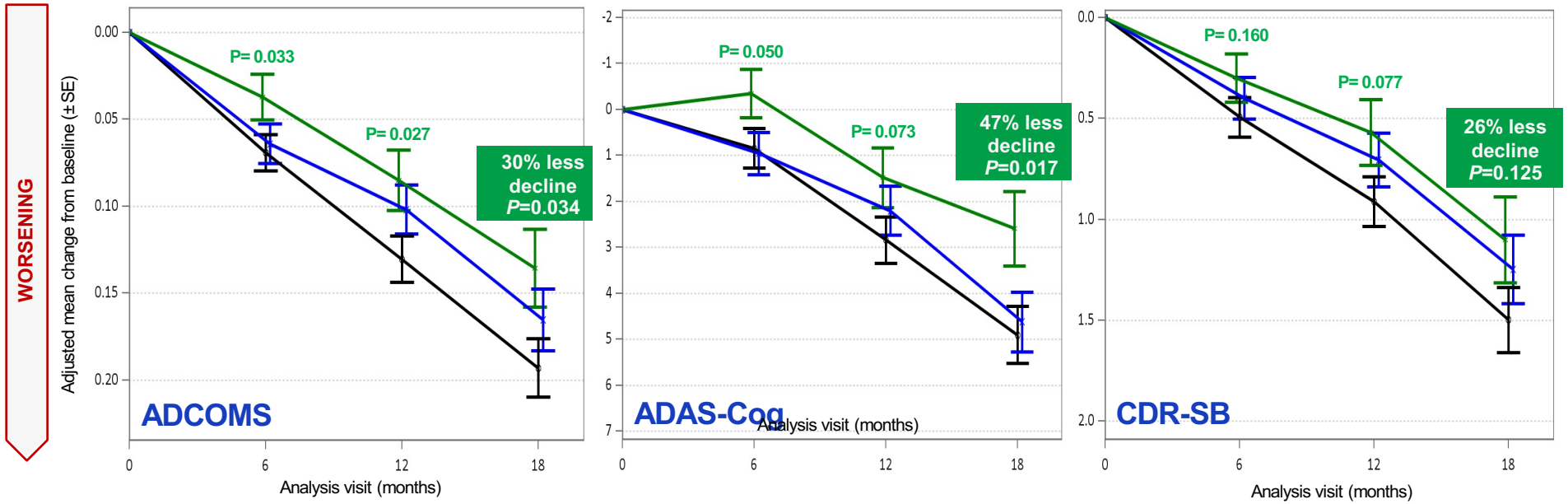
Magnusson et al. 2013 J Alz Dis

BioArctic: collaboration with Eisai on antibody for Alzheimer's disease

2005-2007	Research collaboration: Develop an Aβ protofibril specific antibody, prove efficacy in a transgenic mouse model, humanize mouse mAb158 to BAN2401
2007	License agreement: Bring BAN2401 to the world-market for AD
2010	Clinical development, phase 1 started, Phase 2b started 2013
2018	positive 18 month results from phase 2 in 856 early AD patients
2019	Phase 3 started, read-out expected in September 2022

BAN2401/lecanemab slows disease progression on clinical outcome measures over 18 months

The effect is seen early and is increasing over time

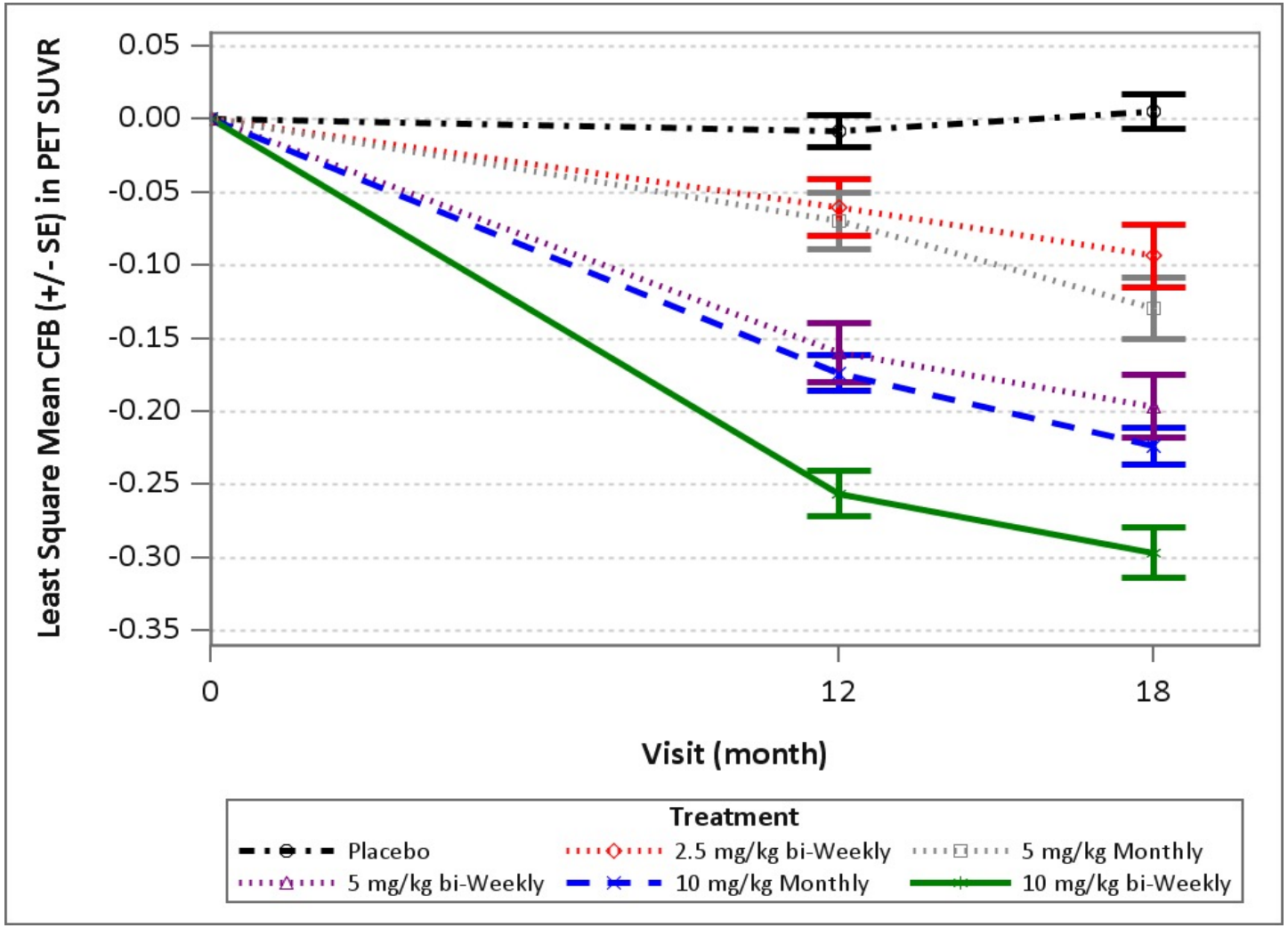


N with data	0 mo.	6 mo.	12 mo.	18 mo.
Placebo	238	216	187	160
10 mg/kg monthly	246	208	165	146
10 mg/kg bi-weekly	152	130	93	79

Presented by Eisai at CTAD Oct 2018

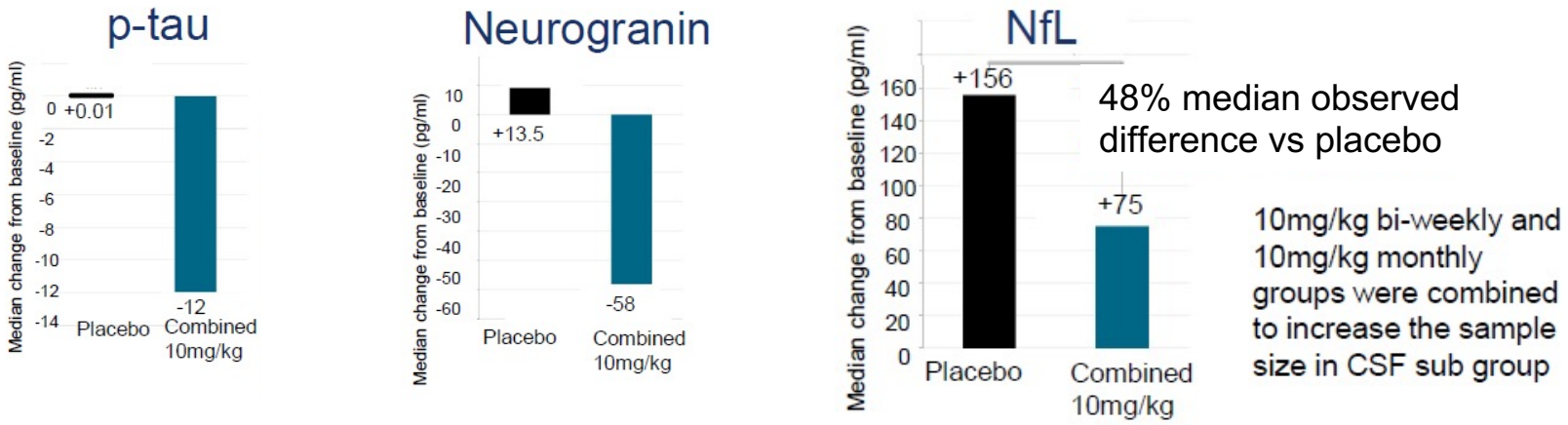
93% of patients in the highest dose group: amyloid negative (SUVr)

Reduction of amyloid levels with all doses, independent of reference region



Lecanemab showed effects on CSF biomarkers – interference in the disease pathophysiology

- Reduction in t-tau (neuron loss)
- Reduction in p-tau (neuronal damage)
- Reduction in neurogranin (synaptic damage)
- Deminished increase of Neurofilament Light (NfL) (axonal degeneration)



Presented at AAIC July 2018 and CTAD Oct 2018 by Eisai

Amyloid-related imaging abnormalities-edema (ARIA-E) in phase 2 study of lecanemab

- Generally well-tolerated with ARIA-E incidence <10% at highest dose, <15% in APOE4 group with highest dose
- Only 5/48 (approx. 10%) cases symptomatic, with headache, visual disturbances or confusion
- Most ARIA-E occurred within first 3 months of treatment
- Mostly mild to moderate in severity (radiographic)
- MRI findings typically resolved within 4-12 weeks

Presented by Eisai at AAIC July 2018

Lecanemab – Phase 3 study designed to confirm the Phase 2b results, read-out Sept. 2022

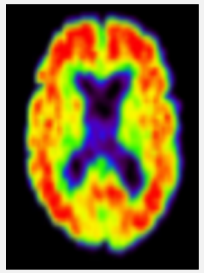
Patient inclusion

Global recruitment

1795 Early Alzheimer patients

Inclusion criteria:

- MCI due to AD or mild AD
- Positive amyloid PET/CSF



Treatment 18 months

Randomized, double-blind study

- Lecanemab 10 mg/kg twice a month (50%)
- Placebo (50%)

Read-out Sept 2022

Primary analysis:
Change from baseline in CDR-SB

Key analyses:

- Change from baseline in ADCOMS, ADAS-cog
- Change from baseline in brain amyloid measured by amyloid PET
- Change from baseline in CSF biomarkers: t-tau, p-tau, neurogranin, Neurofilament light
- Safety and tolerability

AHEAD 3-45, Phase 3 program also ongoing

- A total of 1,400 participants to be enrolled in the study
- A45: no or limited cognitive decline, elevated amyloid in brain
- A3: cognitively normal, intermediate amyloid in brain

ADCOMS = Alzheimer's Disease Composite Score, an evaluation tool developed by Eisai

Selectivity to different Aβ species for lecanemab, aducanumab and gantenerumab

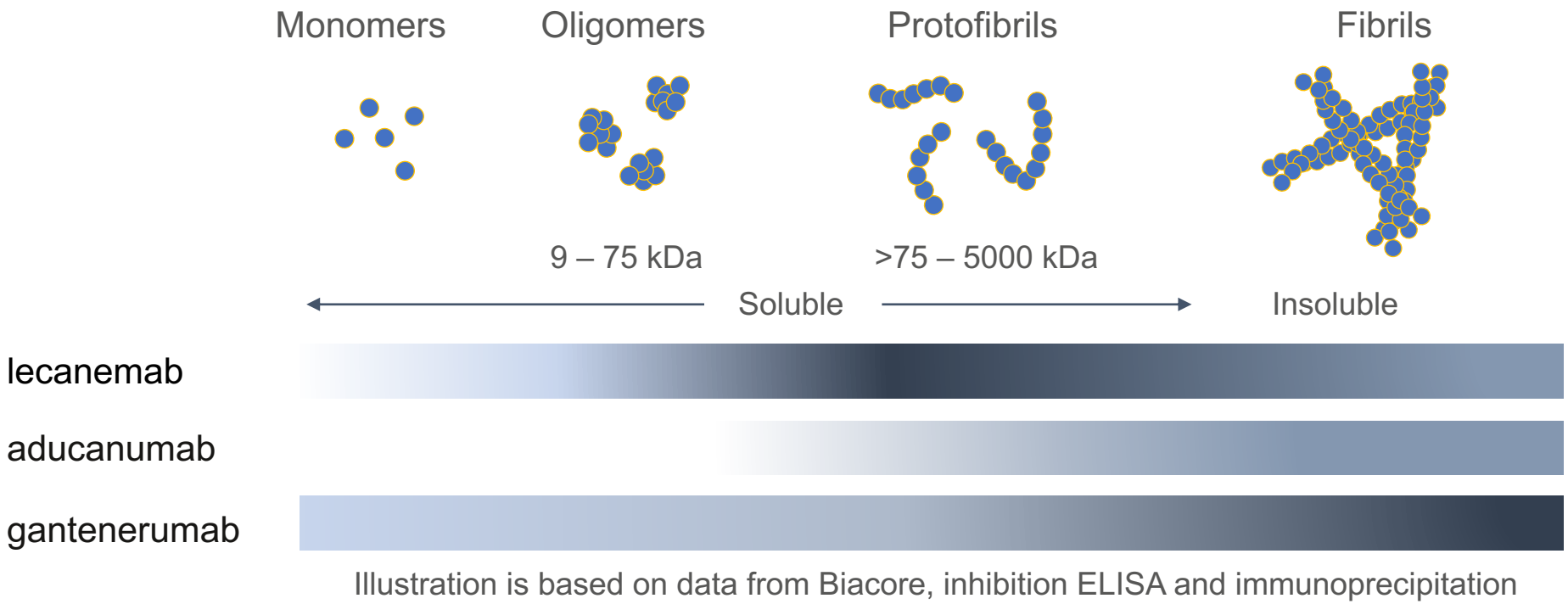


Illustration is based on data from Biacore, inhibition ELISA and immunoprecipitation

- 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

FDA's "Accelerated Approval" of aducanumab (Aduhelm™)

- FDA's "Accelerated Approval" of aducanumab (Aduhelm™) June 7, 2021, was a surprise. One interpretation: it shows FDAs willingness to help the AD population with large unmet medical need
- FDA granted "Breakthrough Therapy Designation" for lecanemab in Alzheimer's disease, a program intended to facilitate and accelerate the development and regulatory review

Thanks to:

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