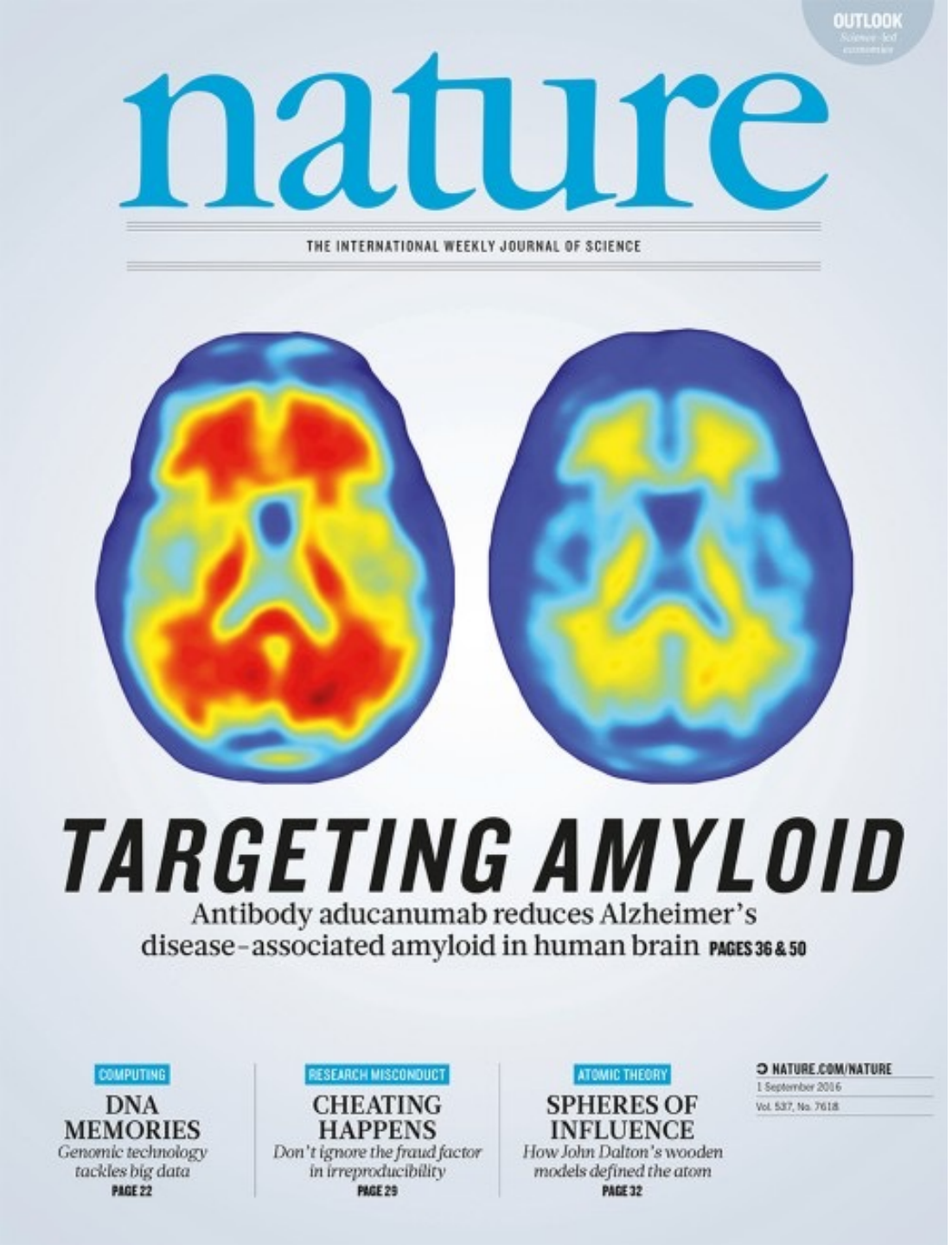


Immunotherapy against Alzheimer's amyloid and tau

연세대학교 의과대학 정신과학교실
세브란스병원

김어수

Contents

- General concept
- Safety issues
- Still survivors in clinical trials
- Discussion

TABLE 1. Principal Failed Clinical Studies on Anti-Aβ Therapies in AD and Related Disorders

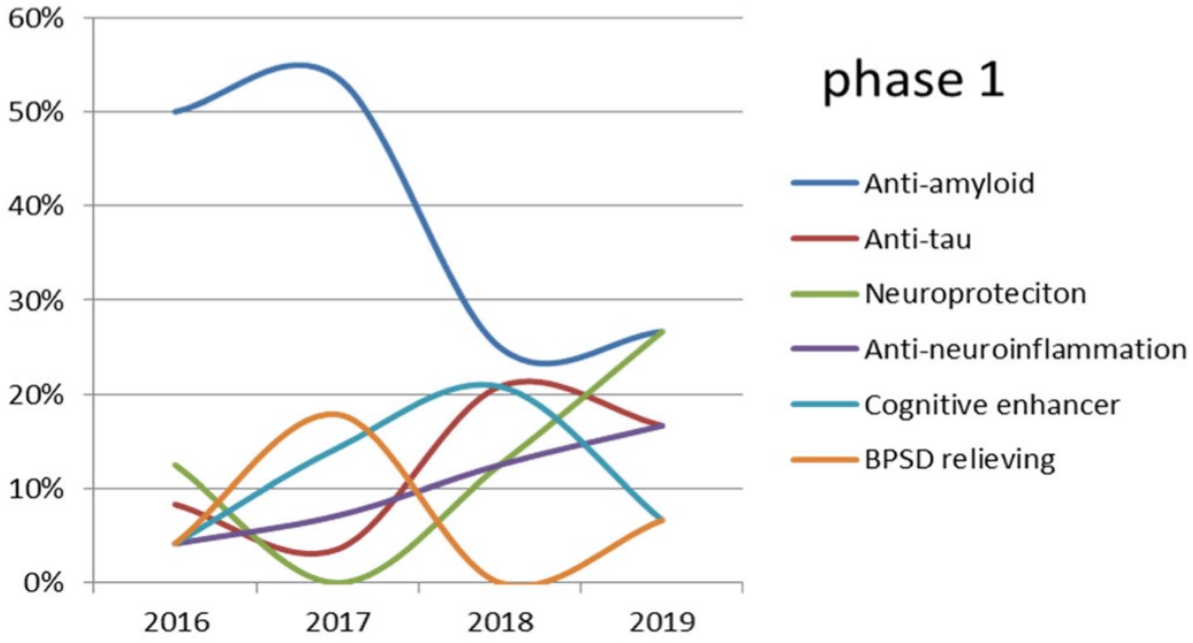
Year (main reference #)	Drug	Mechanism of Action	Subjects	Clinical Phase	Subjects, N	Study Duration, wk	Main Reasons for Failure	Remarks
2002[52]	AN-1792	Aβ antigen	Mild-to-moderate AD	Phase II	372	52	TOX and LOE	
2007[112]	Tramiprosate	Aβ aggregation inhibitor	Mild-to-moderate AD	Phase III	1,052	78	LOE	
2009[39]	Tarenflurbil	γ-Secretase modulator	Mild AD	Phase III	1,684	78	LOE	Worsens global status
2009[42]	Scyllo-inositol	Aβ aggregation inhibitor	Mild-to-moderate AD	Phase II	353	78	TOX and LOE	Increases mortality
2010[113]	Begacestat	γ-Secretase inhibitor	Mild-to-moderate AD	Phase II	17	2	TOX and LOE	
2011[114]	Ponezumab	Anti-Aβ MAb	Mild-to-moderate AD	Phase II	15	24	LOE	
2011[36]	Semagacestat	γ-Secretase inhibitor	Mild-to-moderate AD	Phase III	1,537	76	TOX and LOE	Worsens cognition
2012[115]	Bapineuzumab	Anti-Aβ MAb	Mild-to-moderate AD	Phase III	2,452	78	LOE	
2012[38]	Avagacestat	γ-Secretase inhibitor	Mild-to-moderate AD	Phase II	209	24	TOX and LOE	Worsens cognition
2012[37]	Avagacestat	γ-Secretase inhibitor	Prodromal AD	Phase II	263	104	TOX and LOE	Worsens cognition
2013[57]	Solanezumab	Anti-Aβ IgG1 MAb	Mild-to-moderate AD	Phase II	2,052	78	LOE	
2013[116]	Vanutide	Aβ antigen	Mild-to-moderate AD	Phase II	245	52	LOE	
2013[117]	Immunoglobulin	Anti-Aβ PAb	Mild-to-moderate AD	Phase III	390	78	LOE	
2013[118]	LY2886721	β-Secretase inhibitor	Mild-to-moderate AD	Phase II	70	26	TOX	
2013[119]	AZD3839	β-Secretase inhibitor	Healthy volunteers	Phase I	54	1	TOX	
2014[41]	Affitope AD02	Aβ antigen	Early AD	Phase II	332	78	LOE	Worsens cognition
2014[120]	CAD-106	Aβ antigen	Mild AD	Phase II	121	90	LOE	Worsens cognition
2014[121]	PBT2	Aβ aggregation inhibitor	Prodromal AD	Phase II	42	52	LOE	
2014[61]	Crenezumab	Anti-Aβ MAb	Mild-to-moderate AD	Phase II	433	73	LOE	Binds oligomeric Aβ
2014[58]	Gantenerumab	Anti-Aβ IgG1 MAb	Prodromal AD	Phase II	797	104	LOE	Binds oligomeric Aβ
2014[59]	Gantenerumab	Anti-Aβ IgG1 MAb	Mild AD	Phase II	387	104	LOE	Binds oligomeric Aβ
2016[5]	Solanezumab	Anti-Aβ IgG1 MAb	Mild AD	Phase III	2,129	80	LOE	
2017[122]	Solanezumab	Anti-Aβ IgG1 MAb	Prodromal AD	Phase III	2,450	104	LOE	
2017[123]	Verubecestat	β-Secretase inhibitor	Mild-to-moderate AD	Phase III	1,958	78	LOE	Worsens cognition
2018[34]	Verubecestat	β-Secretase inhibitor	Prodromal AD	Phase III	1,454	104	LOE	Worsens cognition and behavior
2018[124]	Atabecestat	β-Secretase inhibitor	Cognitively healthy subjects at risk of developing AD	Phase III	600	231	TOX and LOE	Worsens cognition
2018[125]	Lanabecestat	β-Secretase inhibitor	MCI and mild AD	Phase III	2,202	104	LOE	Worsens cognition
2018[125]	Lanabecestat	β-Secretase inhibitor	Mild AD	Phase III	1,899	104	LOE	Worsens cognition

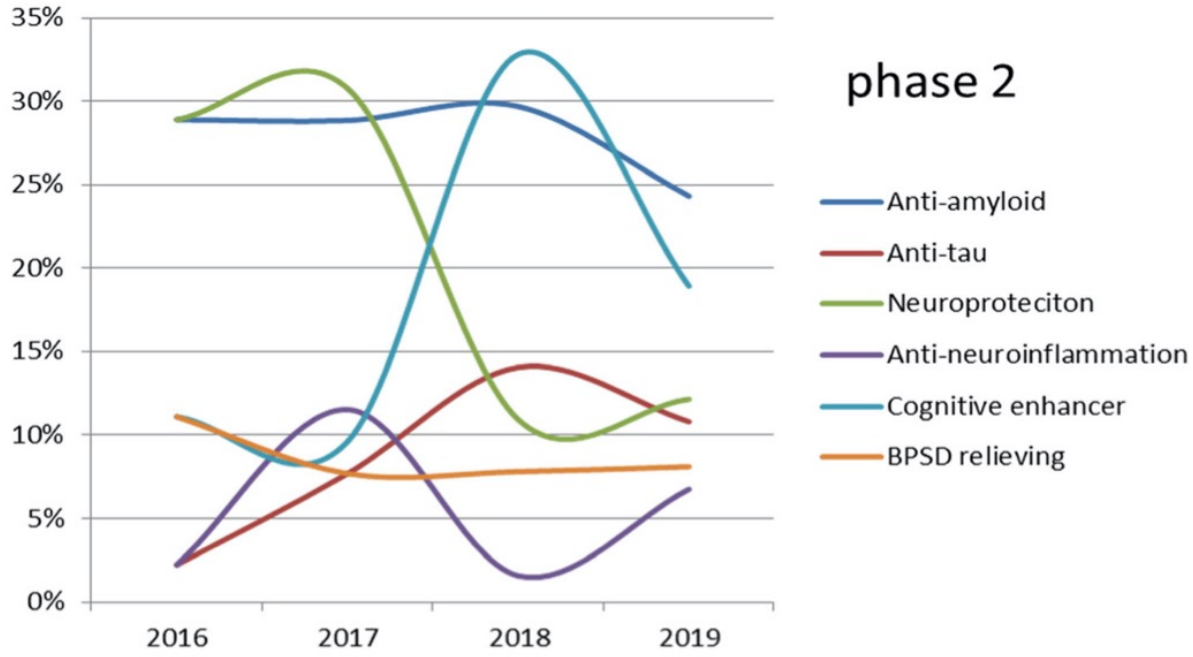
The list is ordered by the year of publication of the main results of the studies.
Aβ = amyloid-β; AD = Alzheimer disease; LOE = lack of efficacy; MAb = monoclonal antibody; MCI = mild cognitive impairment; PAb = polyclonal antibody; TOX = toxicity.

AN-1792 (2002)

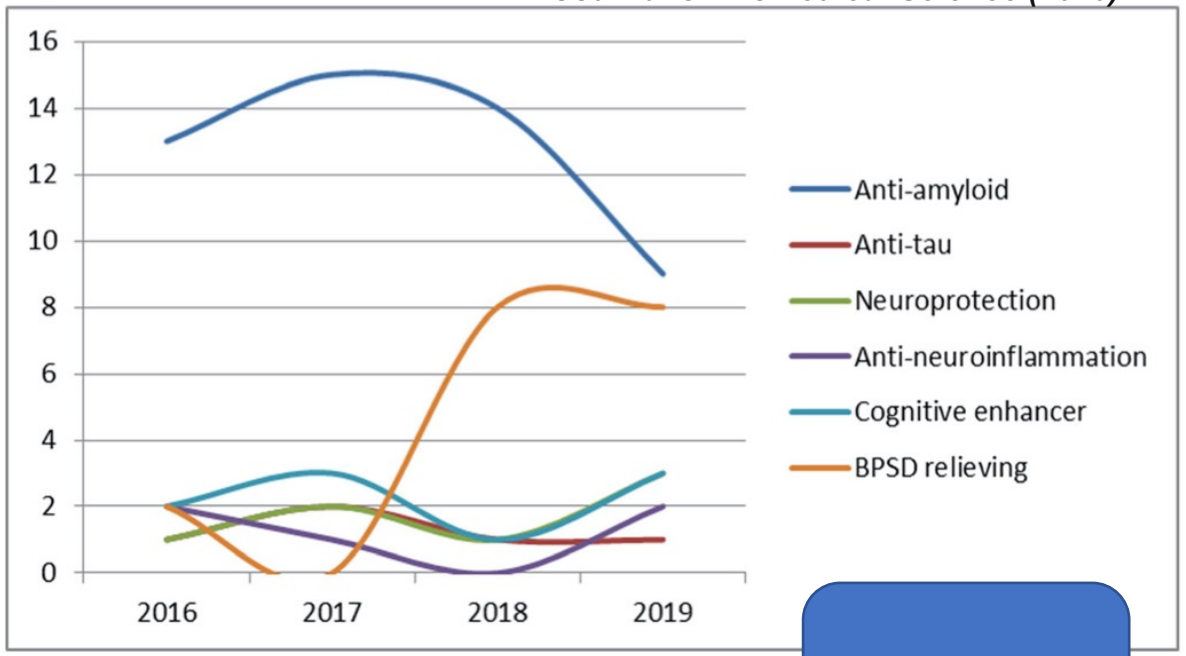
All failied

ANN NEUROL 2019;85:303–315


phase 1
60%
50%
40%
30%
20%
10%
0%
2016
2017
2018
2019
Anti-amyloid
Anti-tau
Neuroproteciton
Anti-neuroinflammation
Cognitive enhancer
BPSD relieving

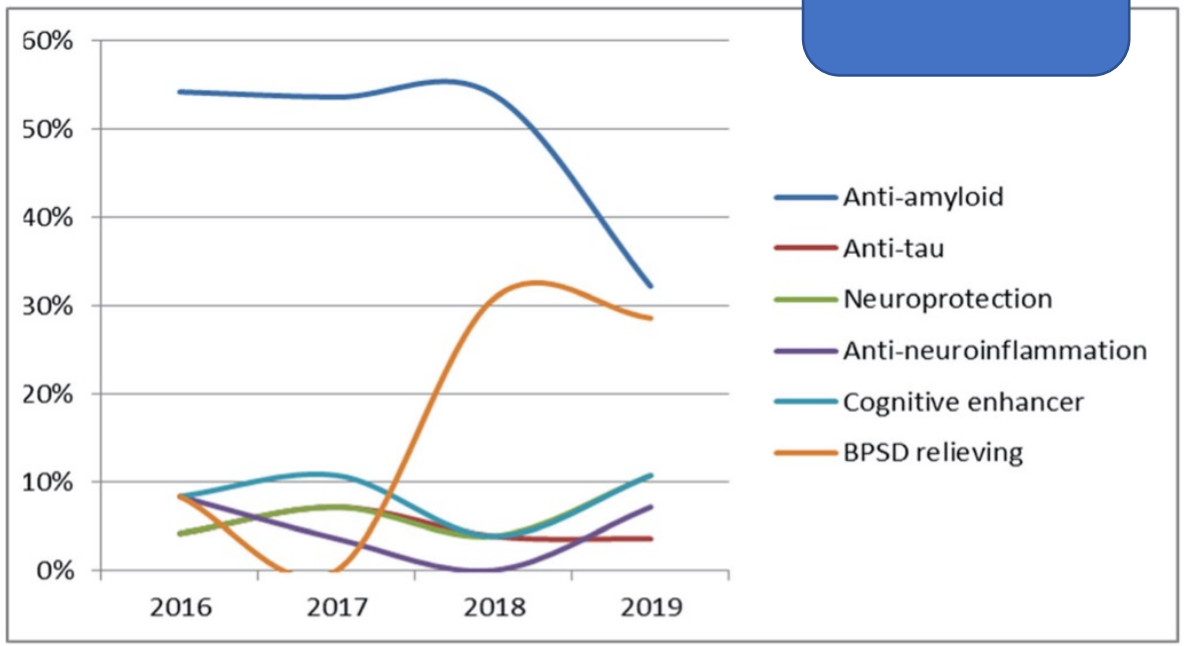

phase 2
35%
30%
25%
20%
15%
10%
5%
0%
2016
2017
2018
2019
Anti-amyloid
Anti-tau
Neuroproteciton
Anti-neuroinflammation
Cognitive enhancer
BPSD relieving

A.

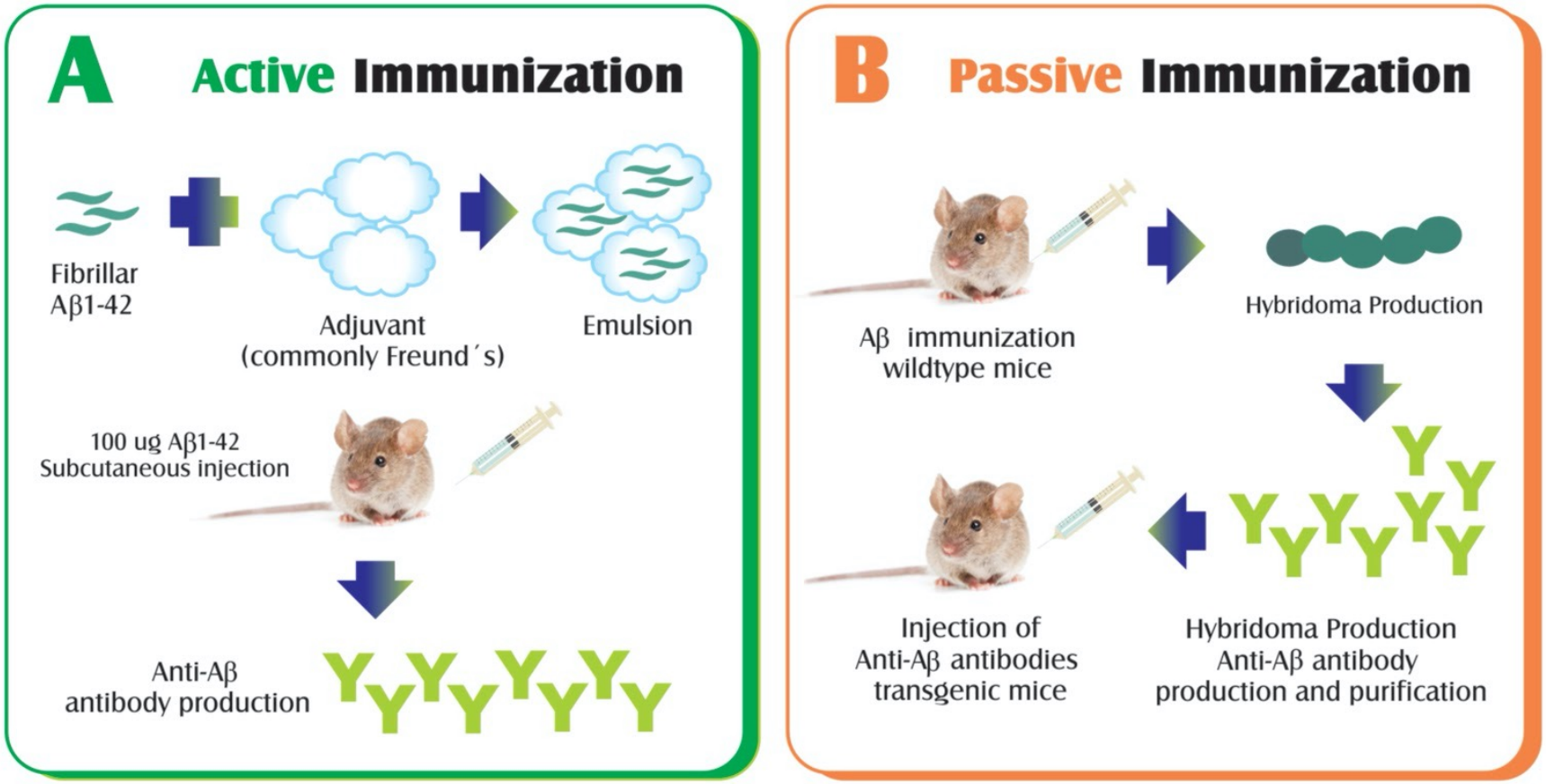

16
14
12
10
8
6
4
2
0
2016
2017
2018
2019
Anti-amyloid
Anti-tau
Neuroprotection
Anti-neuroinflammation
Cognitive enhancer
BPSD relieving

Phase 3

B.

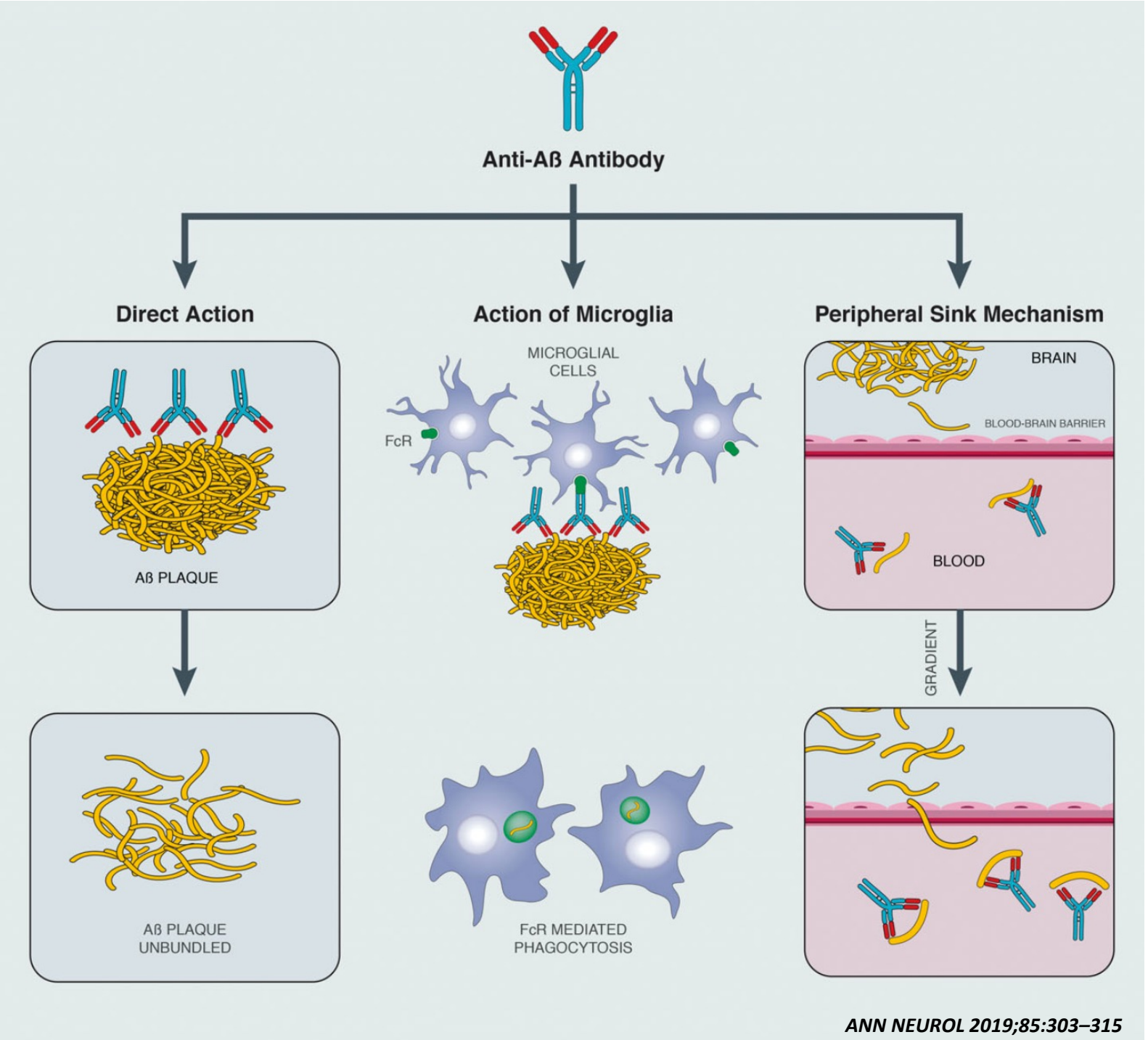

60%
50%
40%
30%
20%
10%
0%
2016
2017
2018
2019
Anti-amyloid
Anti-tau
Neuroprotection
Anti-neuroinflammation
Cognitive enhancer
BPSD relieving

Immunotherapy of AD



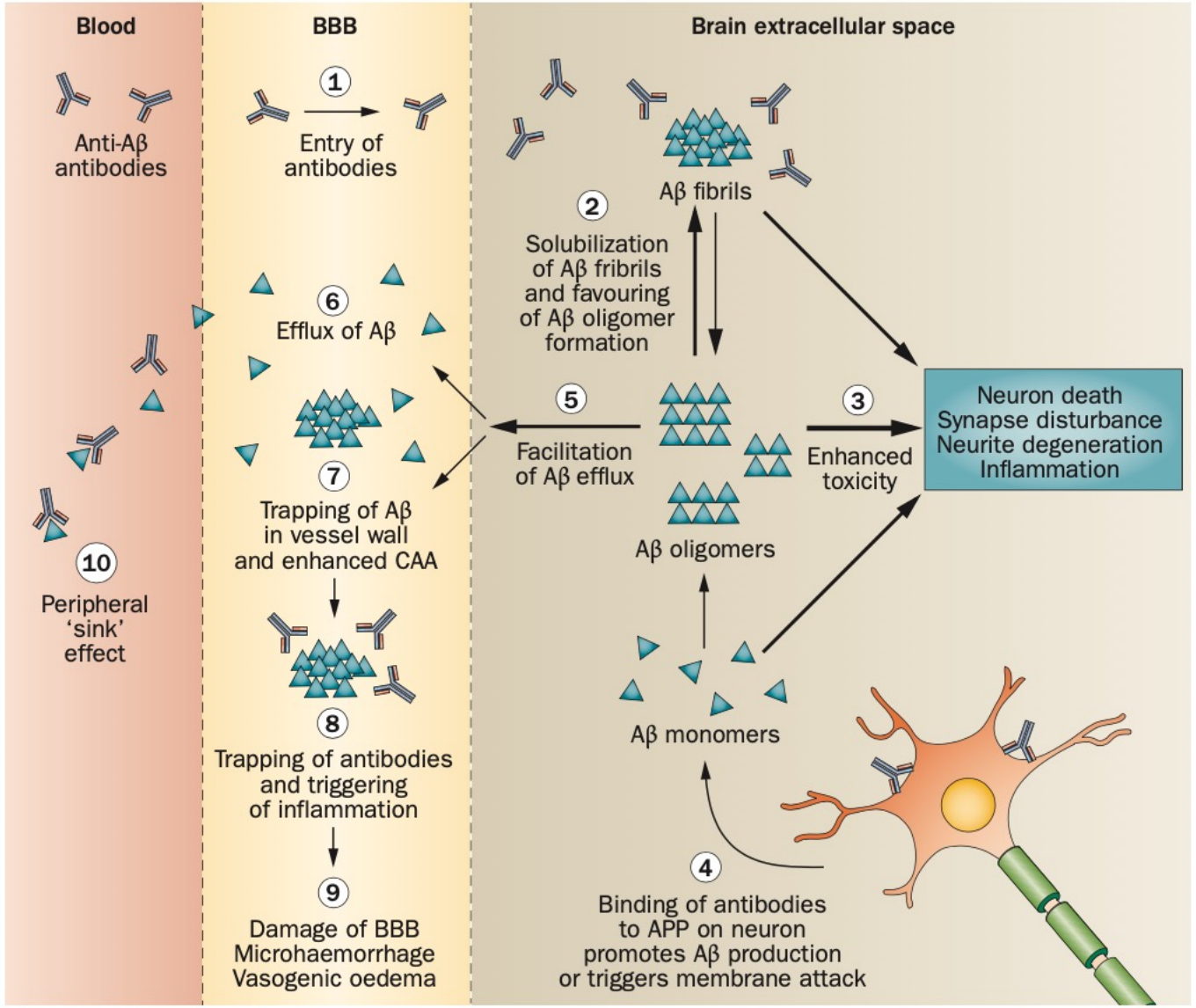
http://neuroimmuno.blogspot.com/

MOA of passive immunization



ANN NEUROL 2019;85:303–315

Adverse effects a/w AD immunotherapy



- Neuroinflammation
- Synaptic dysfunction
  → Cognitive worsening

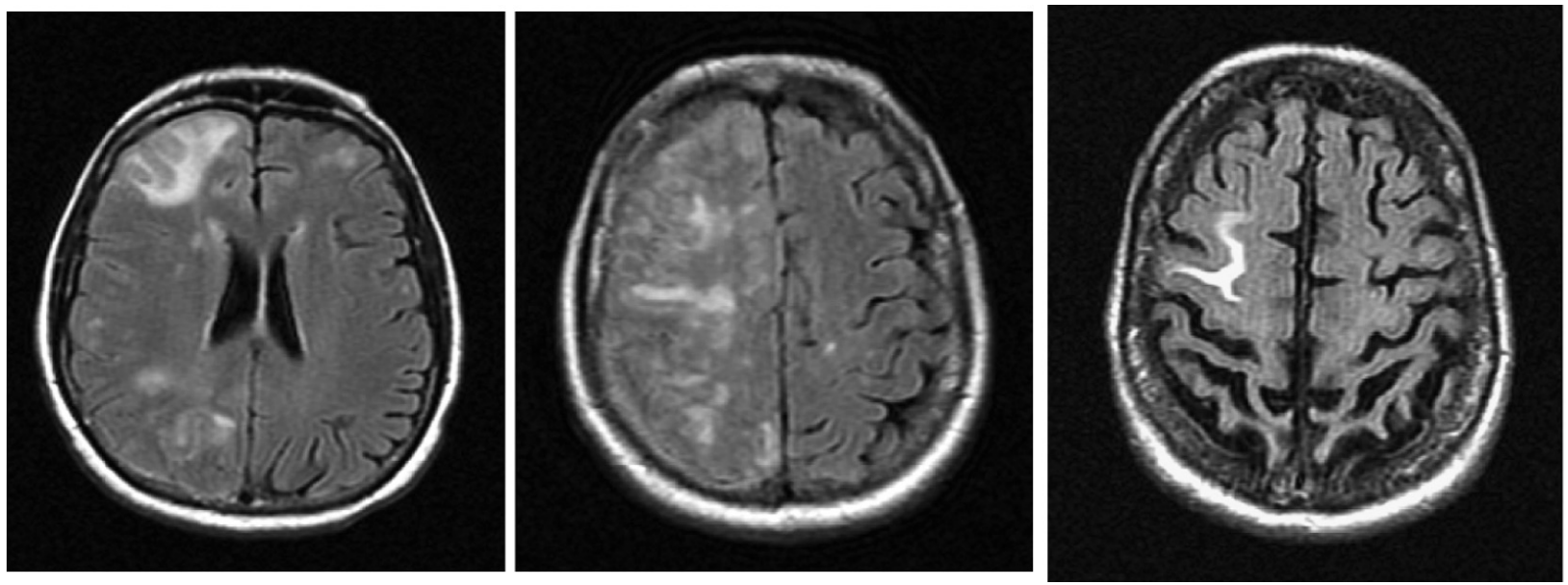
- Neuronal death
  → Brain atrophy?

- Microhemorrhage
- Vasogenic edema
  → ARIA

Liu,Y.-H.*etal.Nat.Rev.Neurol.*8,465–469(2012)

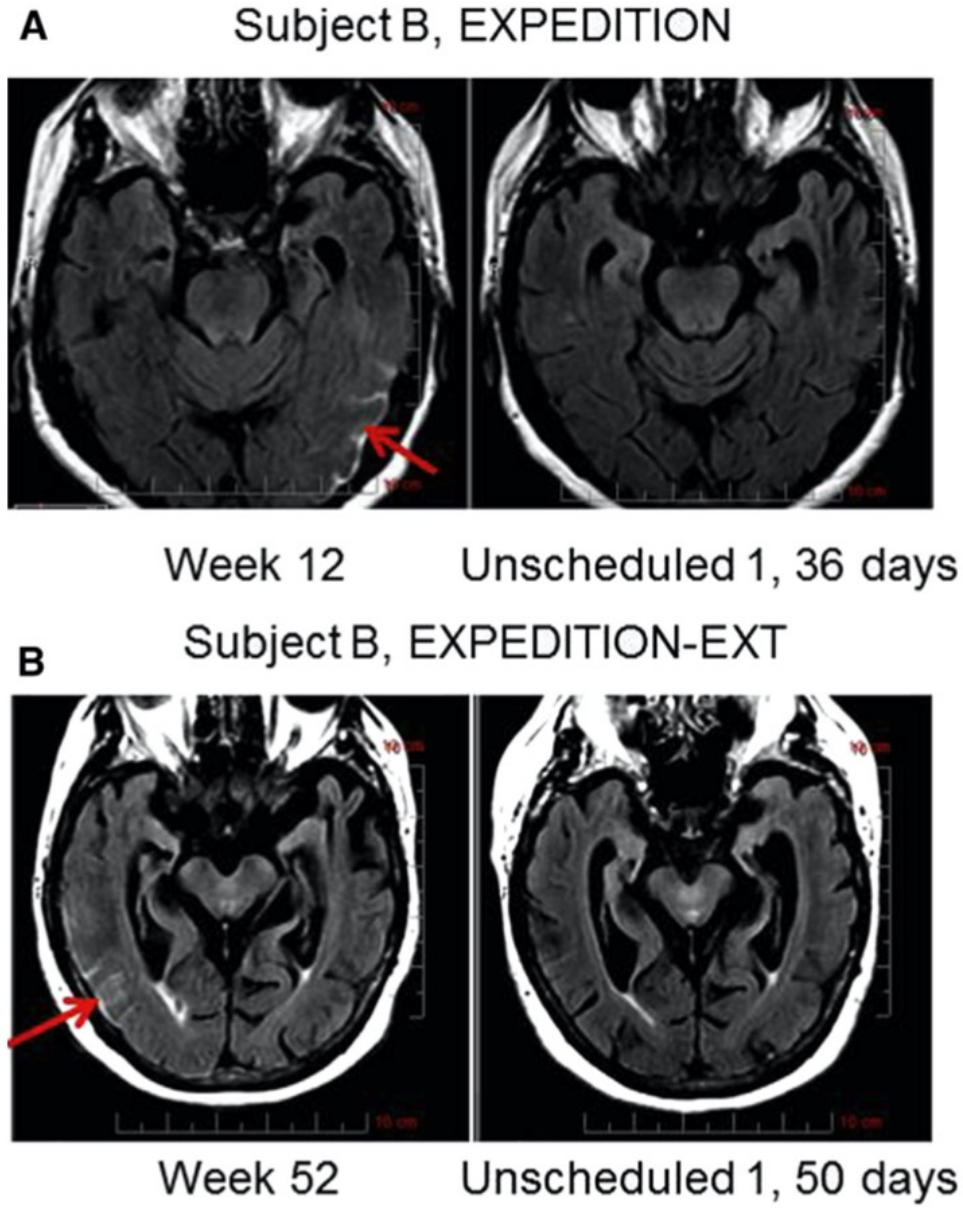
ARIA (Amyloid-related Imaging Abnormality)

- ARIA-E (Edema)



R.A. Sperling et al. / Alzheimer's & Dementia 7 (2011) 367–385

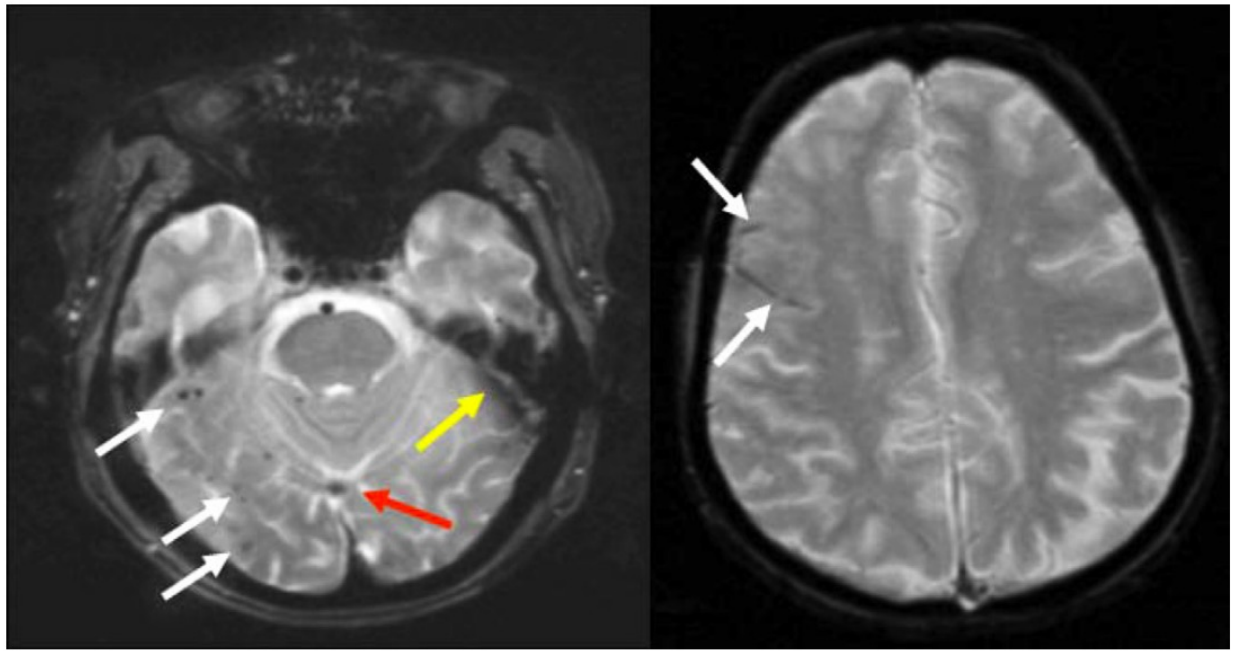
Resolution of ARIA-E



Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring 2 (2016) 75-85

ARIA-H

- Microhemorrhage (microbleed) and superficial siderosis

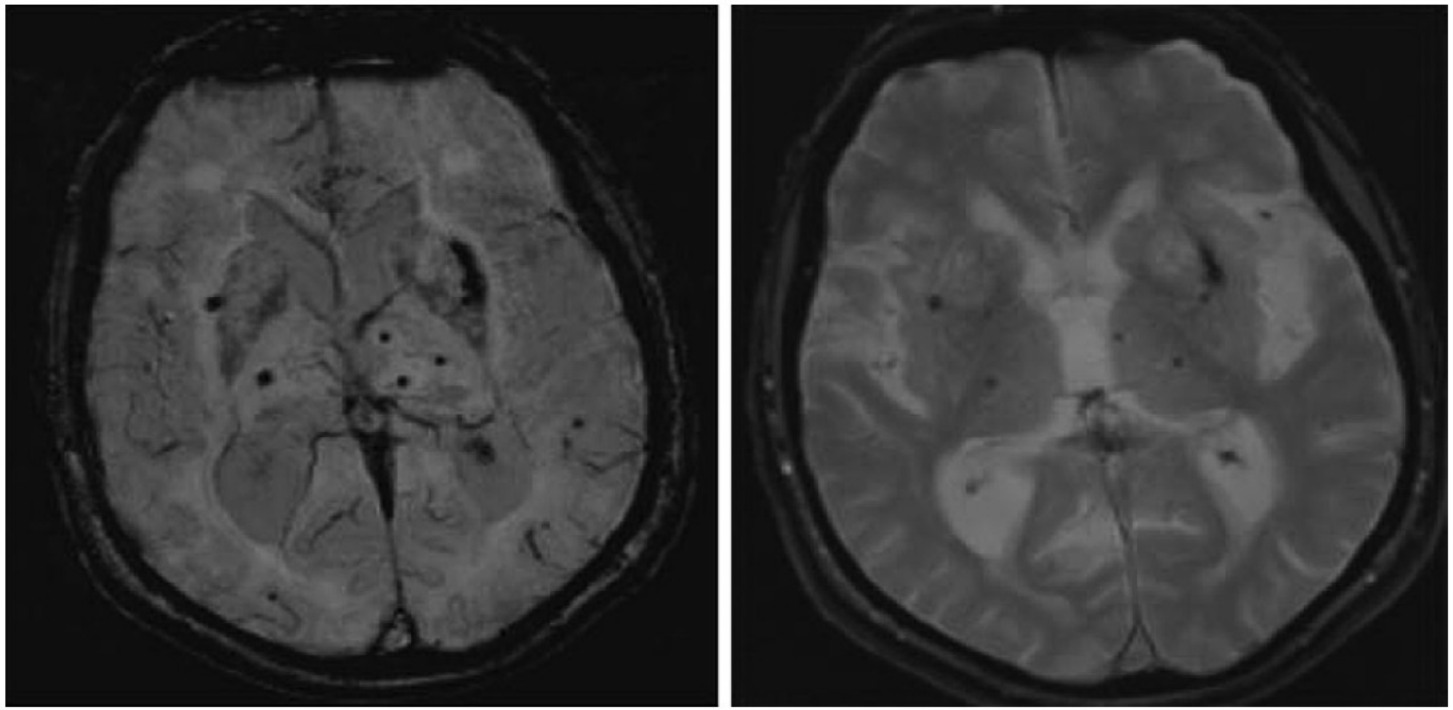


R.A. Sperling et al. / Alzheimer's & Dementia 7 (2011) 367–385

다른 그림 찾기 (SWI vs. GRE)

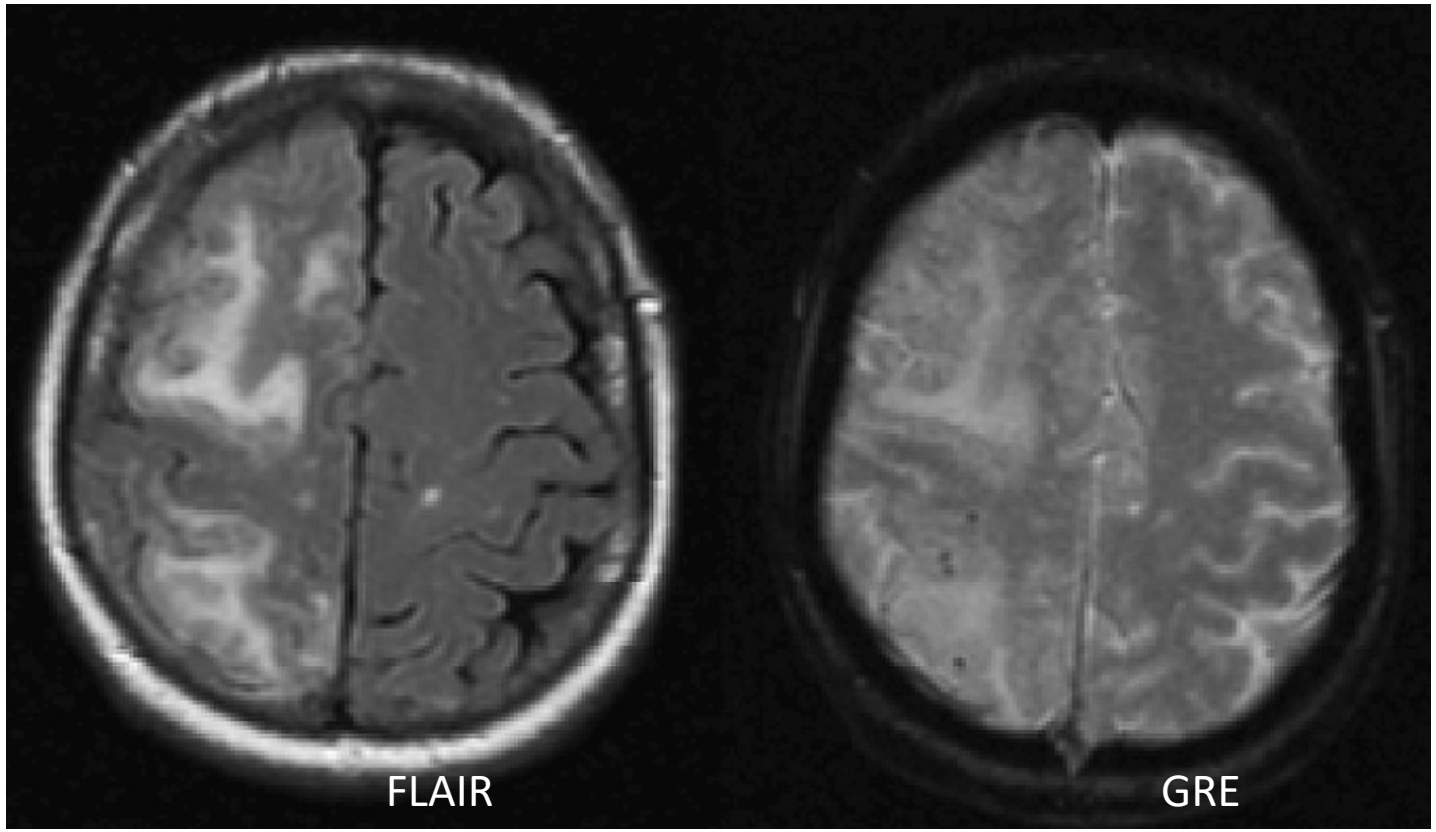
Susceptibility-weighted imaging(SWI) vs. T2-GRE(gradient refocused echo)

- Microbleeds in SWI and GRE



R.A. Sperling et al. / Alzheimer's & Dementia 7 (2011) 367–385

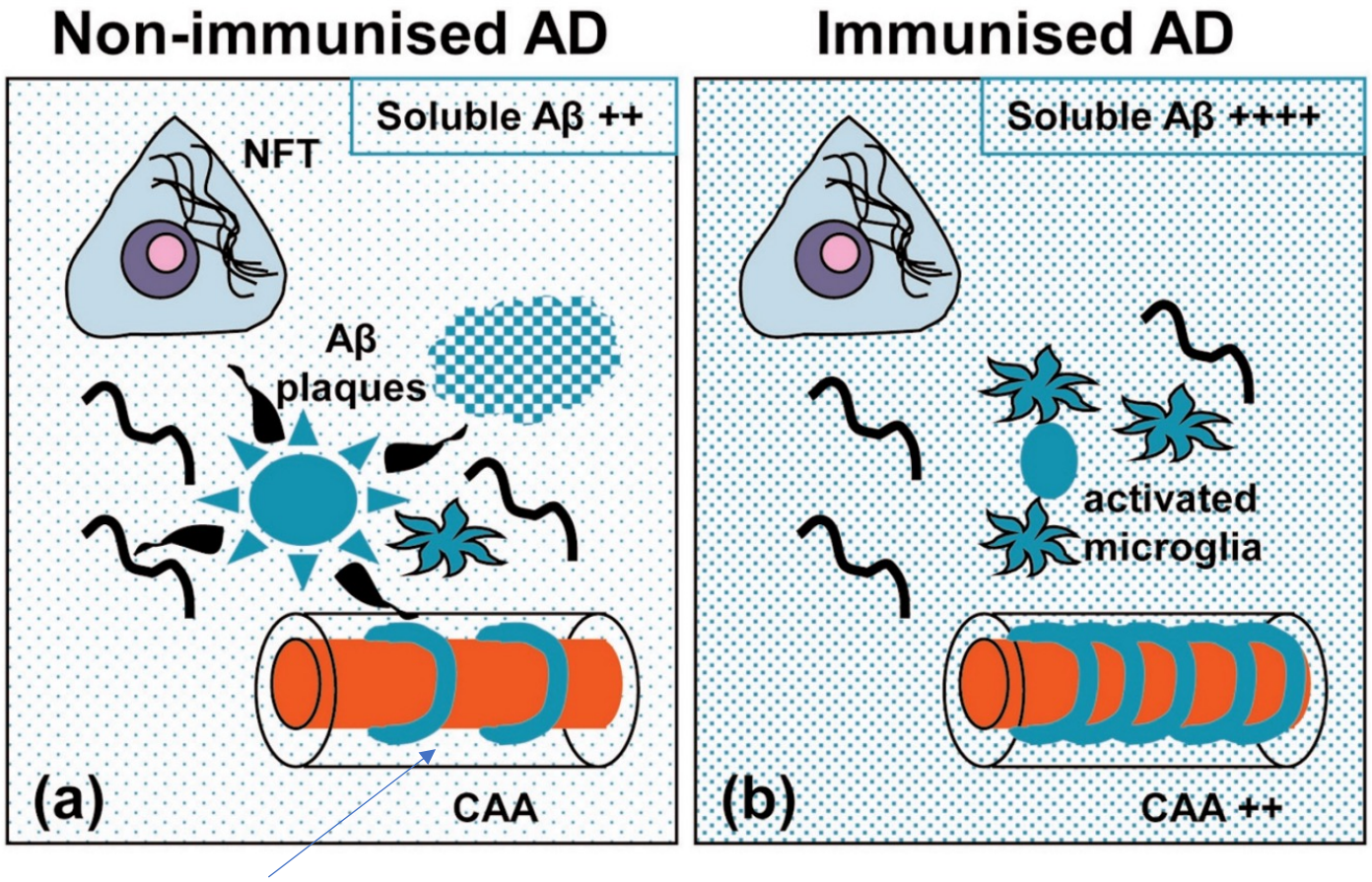
ARIA-E and ARIA-H, coincidental



R.A. Sperling et al. / Alzheimer's & Dementia 7 (2011) 367–385

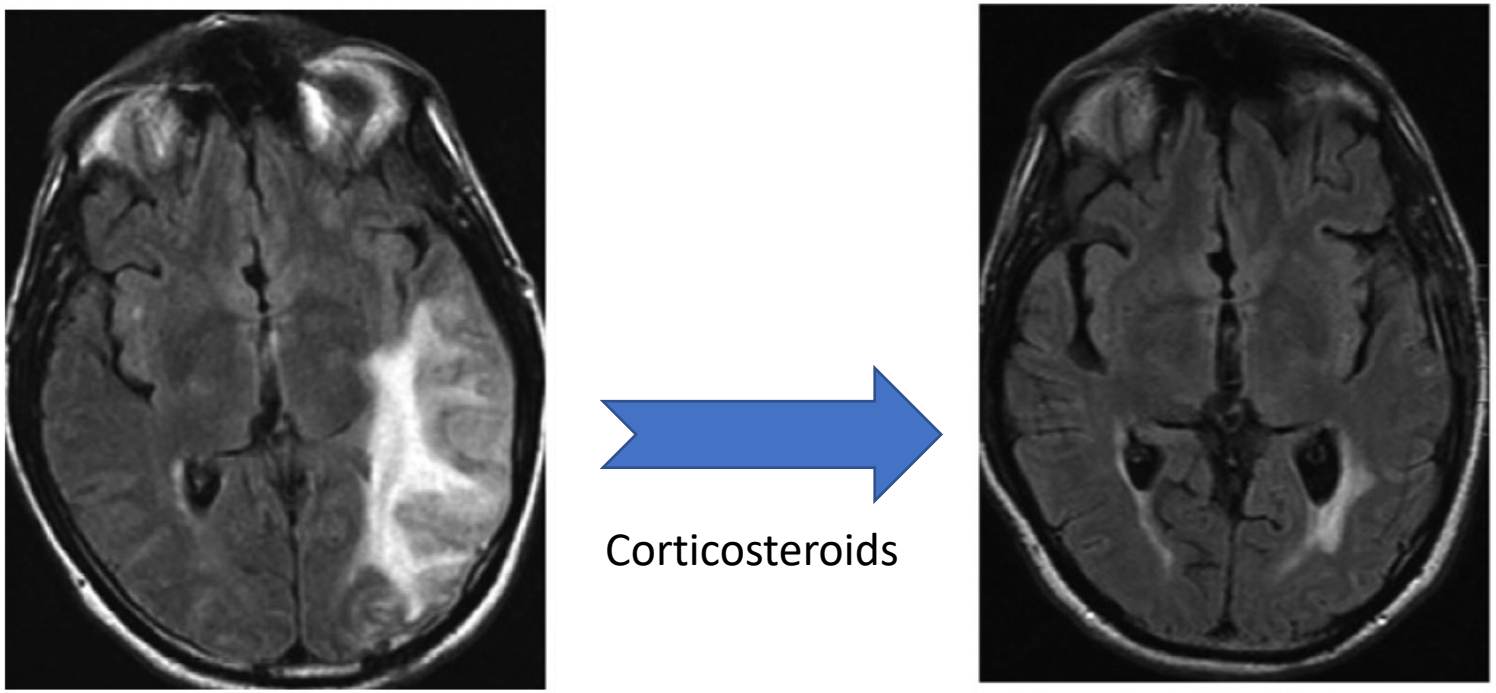
Oops! Oligomers there!

Cerebral Amyloid Angiopathy (CAA)



perivascular lymphatic drainage pathways

Spontaneous cerebral amyloid angiopathy-related inflammation



R.A. Sperling et al. / Alzheimer's & Dementia 7 (2011) 367–385

Did you know?

- Anti-Abeta treatments shrink the brain!

doi:10.1093/brain/awaa332 BRAIN 2020: 143; 3816–3826 | 3816

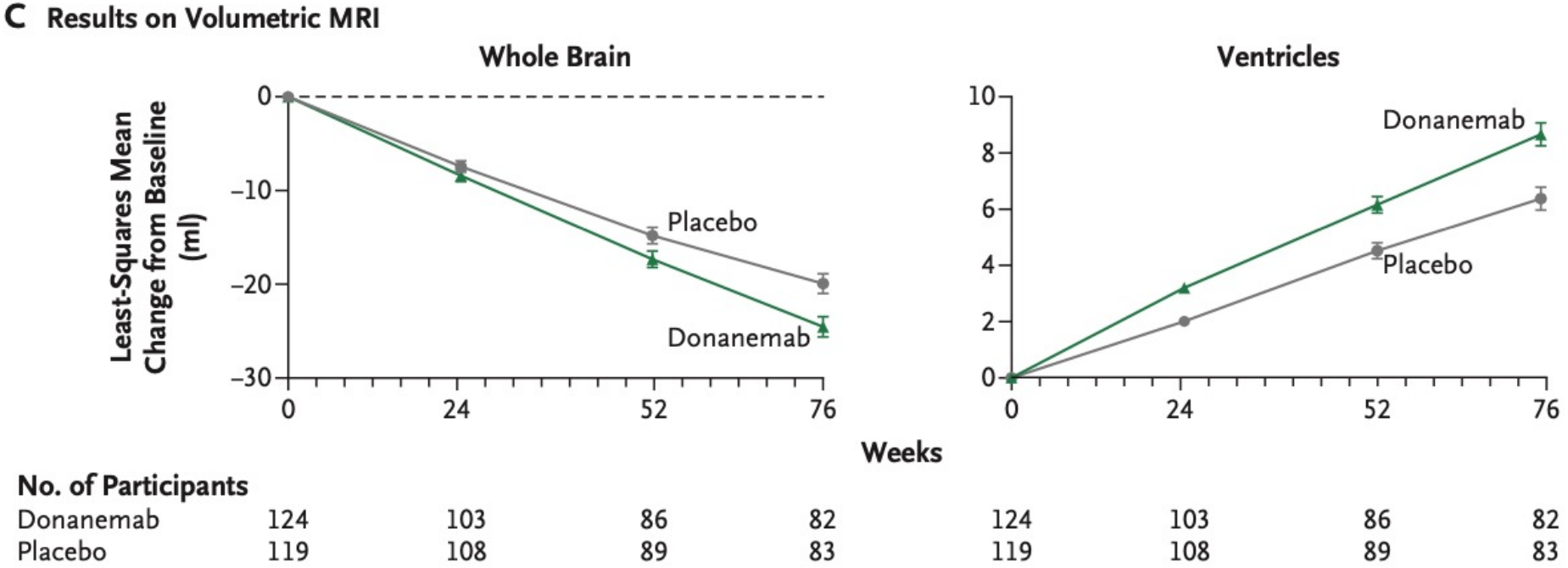
BRAIN
A JOURNAL OF NEUROLOGY

BACE inhibition causes rapid, regional, and non-progressive volume reduction in Alzheimer's disease brain

Cyrille Sur,[1] James Kost,[1] David Scott,[2] Katarzyna Adamczuk,[2] Nick C. Fox,[3] Jeffrey L. Cummings,[4,5,6,7] Pierre N. Tariot,[8] Paul S. Aisen,[9] Bruno Vellas,[10] Tiffini Voss,[1] Erin Mahoney,[1] Yuki Mukai,[1] Matthew E. Kennedy,[1] Christopher Lines,[1] David Michelson[1] and Michael F. Egan[1]

In the phase 3 EPOCH trial (Clinicaltrials.gov; NCT01739348), treatment with the BACE inhibitor verubecestat failed to improve cognition in patients with mild-to-moderate Alzheimer's disease, but was associated with reduced hippocampal volume after 78 weeks as assessed by MRI. The aims of the present exploratory analyses were to: (i) characterize the effect of verubecestat on brain volume by evaluating the time course of volumetric MRI changes for a variety of brain regions; and (ii) understand the mechanism through which verubecestat might cause hippocampal (and other brain region) volume loss by assessing its relationship to measures of amyloid, neurodegeneration, and cognition. Participants were aged 55–85 years with probable Alzheimer's disease dementia and a Mini Mental State Examination score $\geqslant$15 and $\leqslant$26. MRIs were obtained at baseline and at Weeks 13, 26, 52 and 78 of treatment. MRIs were segmented using Freesurfer and analysed using a tensor-based morphometry method. PET amyloid data were

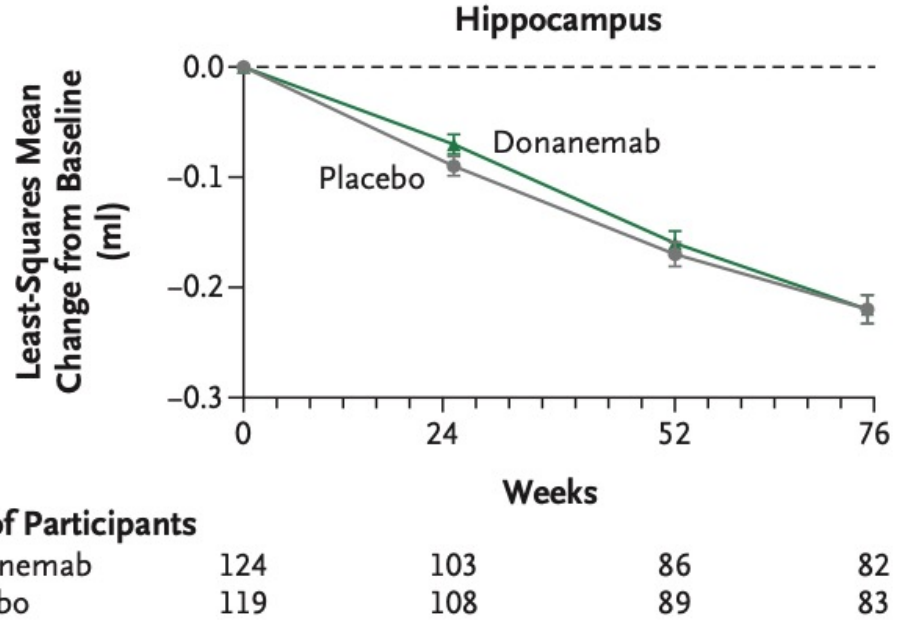
Donanemab Case



"이것은 사라진 Abeta volume 보다 1000배 넘게 더 줄어든 것이다!"

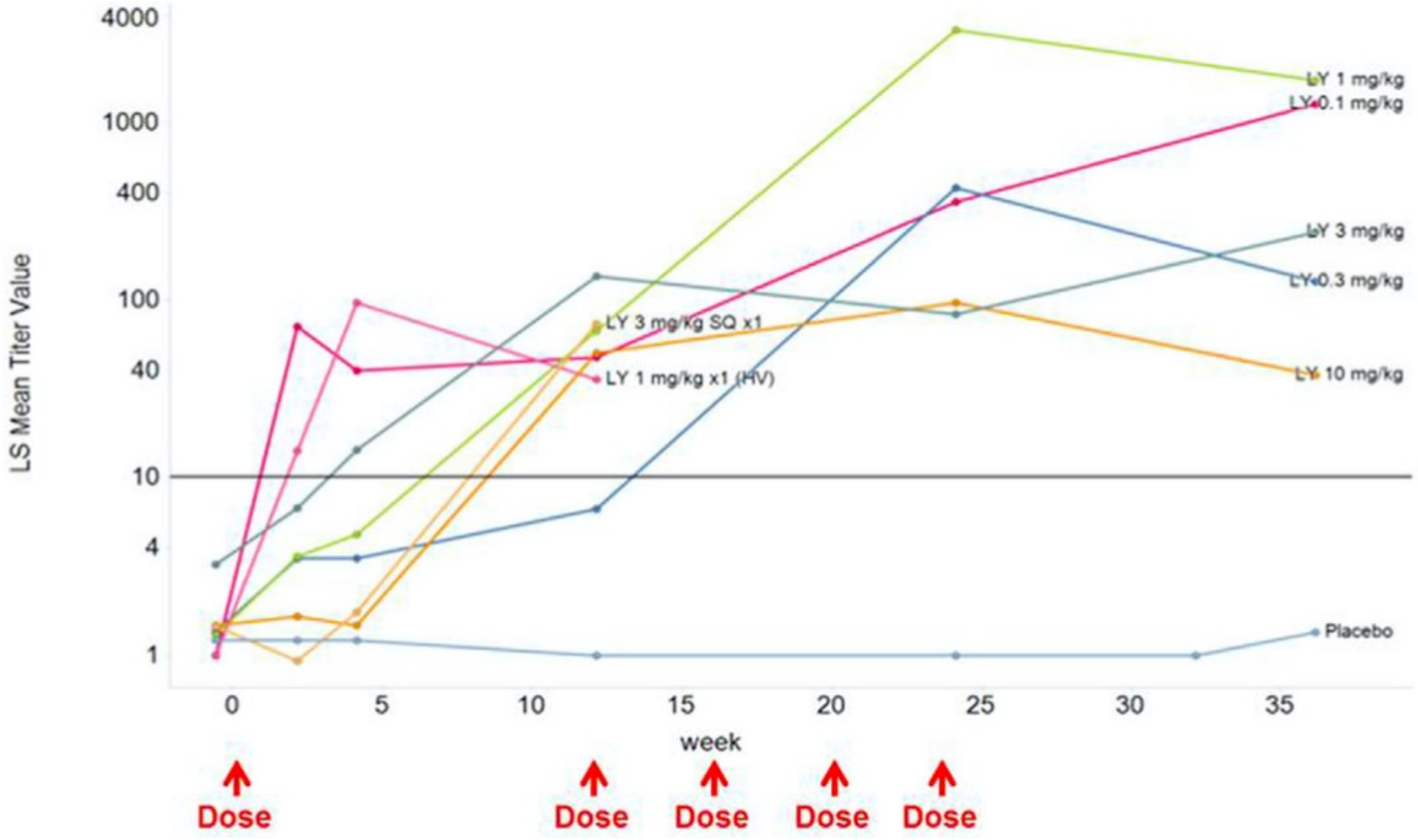
- Scott Ayton
  Melbourne Dementia Research Centre,
  Florey Institute of Neuroscience and Mental Health

Eur J Neurol. 2021;28:e67–e68.



NEJM (2021) 384;18

Immunogencity of Mab (Donanemab)



Donanemab

placebo

FIGURE 5 Mean antidrug antibodies titers by time for dose groups. HV, healthy volunteers; LS, least squares; LY, LY3002813 (donanemab); SC, subcutaneous

Alzheimer's Dement. 2021;7:e12112.

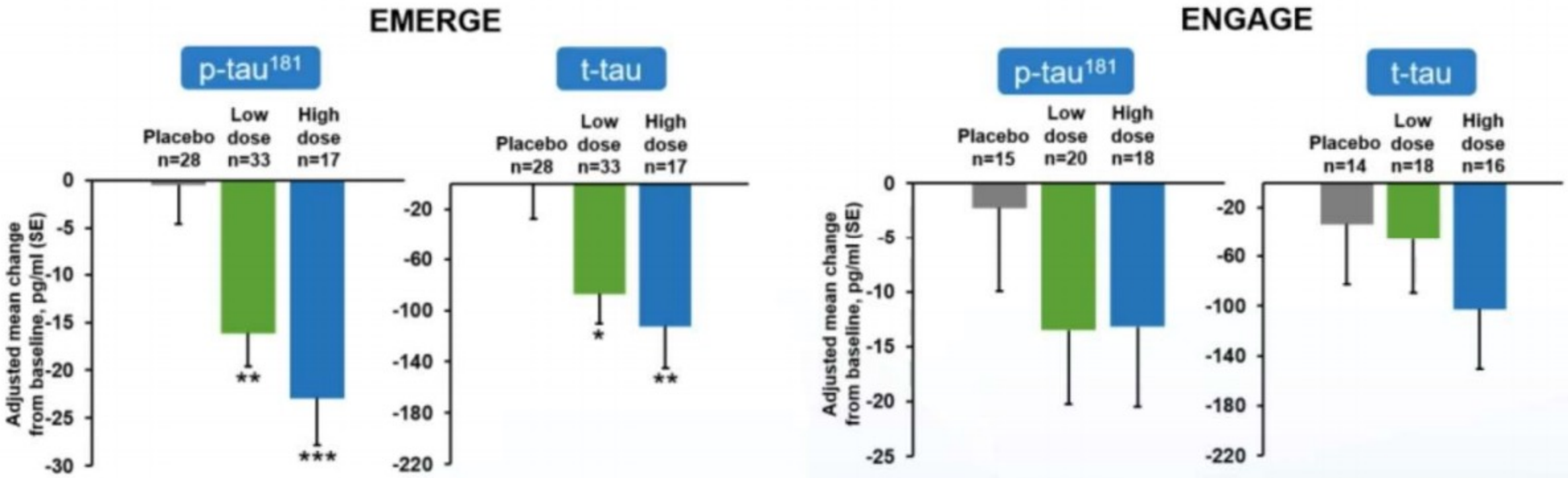
Monoclonal antibodies to Abeta (phase2/3)

Drug	Sponsor	Trial	Phase	Population	Target	Outcome
Aducanumab	Biogen	ENGAGE	3	Early AD	Plaques and oligomeric Aβ	Terminated due to futility[b]
Aducanumab	Biogen	EMERGE	3	Early AD	Plaques and oligomeric Aβ	High dose arm positive on primary outcome[b]
Crenezumab	Genentech /Roche	CREAD 1 & 2	3	Early AD	Monomeric Aβ and oligomeric Aβ	Terminated due to futility
Solanezumab	Eli Lilly	EXPEDITION 3	3	Early AD	Monomeric Aβ	Terminated due to futility
Gantenerumab	Roche	SCarlet/Marguerite RoAD OLE[a]	3 OLE[a]	Early AD	Plaques and oligomeric Aβ	Terminated due to futility
Donanumab	Eli Lilly	TRAILBLAZER-ALZ	2	Early AD	Pyroglutamate Aβ	Met primary clinical outcome
Lecanumab (BAN2401)	Eisai	BAN2401-G000-201	2	Early AD	Plaques and Aβ protofibrils	Did not meet primary outcome Secondary outcomes positive

https://doi.org/10.1007/s00415-021-10790-5

Aducanumab reduced CSF biomarkers of tau pathology and neurodegeneration at Week 78[a]

Previously reported at ADPD 2021



In EMERGE and ENGAGE, **aducanumab also reduced tau levels** in areas of the brain that have tau pathology at early stages of Alzheimer's disease (*tau PET pooled data)*

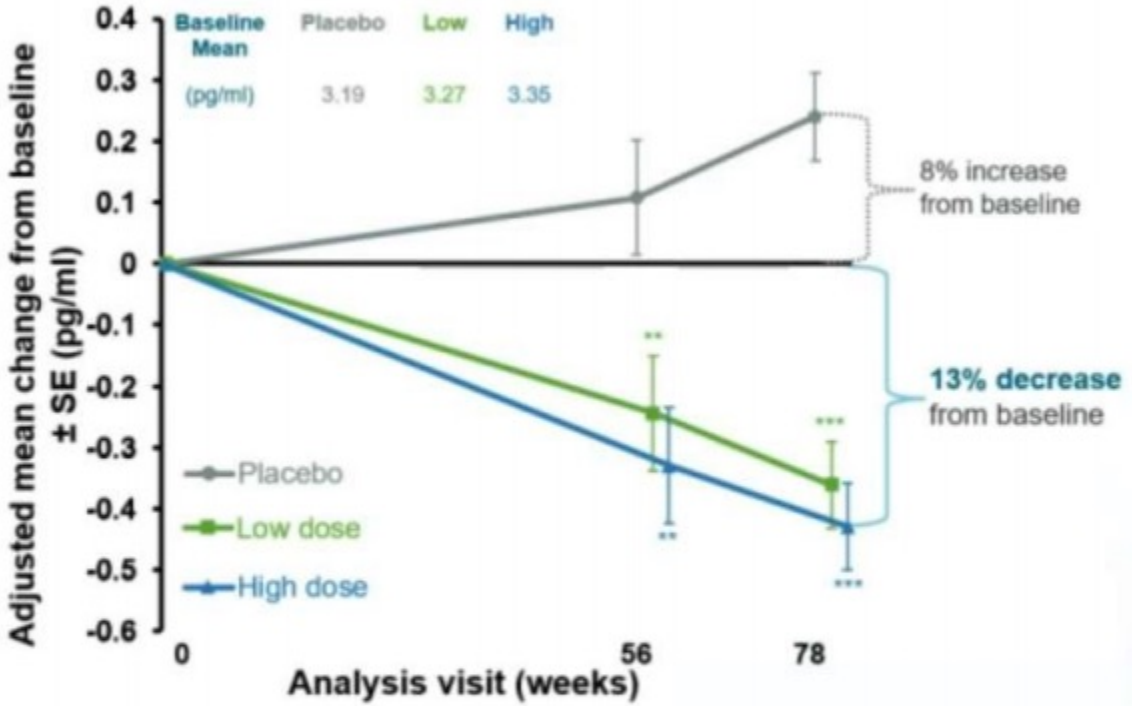
- Dose-dependent reduction in brain tau levels in the frontal, temporal and medial temporal composite brain regions

[a] Significant reduction for EMERGE and numerical for ENGAGE. CSF modified analysis population (patients with both baseline and post-baseline CSF assessments). *p<0.05, **p<0.01, ***p<0.001 compared with placebo (nominal). Values were based on an ANCOVA model at Week 78, fitted with change from baseline as the dependent variable, and with categorical treatment, baseline biomarker value, baseline age, and

Slide from Eisai Korea

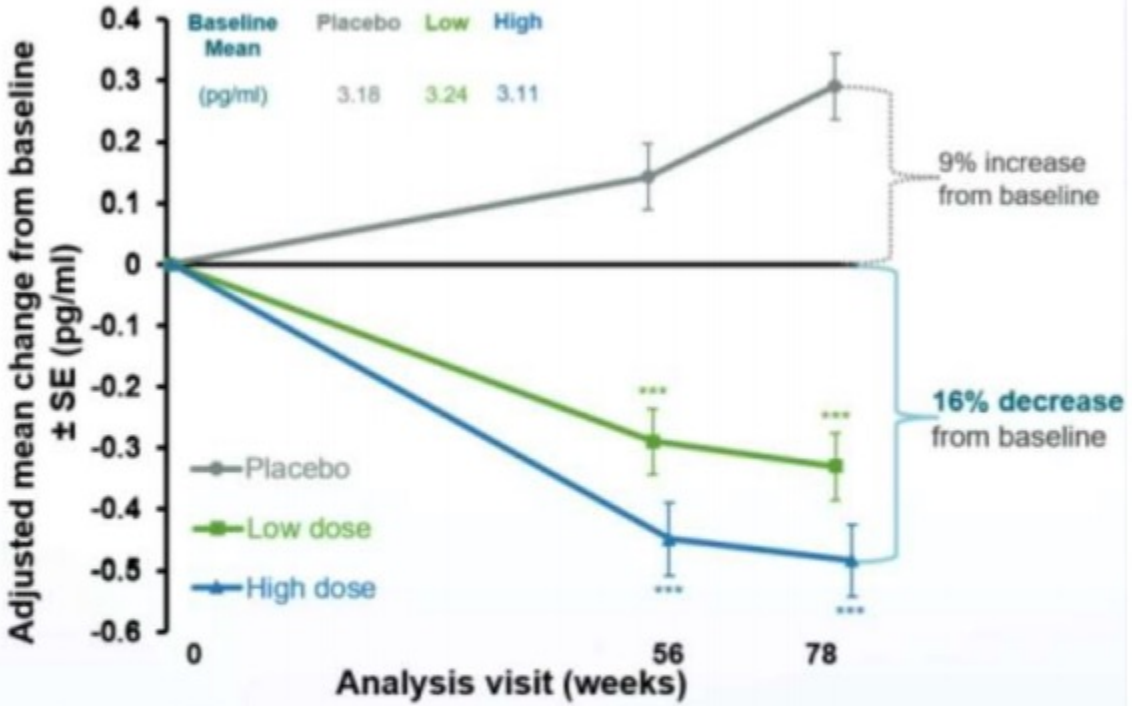
Aducanumab significantly lowers plasma p-tau^{181}

EMERGE



Placebo	287	177	273
Low dose	293	172	269
High dose	290	168	271

ENGAGE



Placebo	333	301	325
Low dose	331	299	322
High dose	281	242	274

*p<0.05, **p<0.01, ***p<0.001 compared with placebo (nominal). **MMRM with change from baseline as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline value, baseline value by visit interaction, baseline age, and ApoE status**. ApoE, apolipoprotein E; MMRM, mixed model for repeated measures; pg/ml, picograms per milliliter; p-tau, phosphorylated tau; SE, standard error.

Slide from Eisai Korea

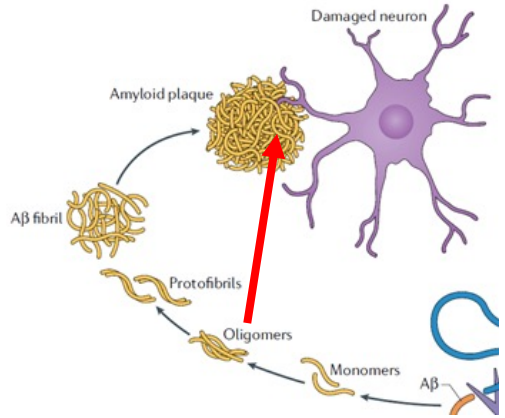
Greater reduction in plasma p-tau^{181} is associated with less clinical decline across all four clinical measures in both studies

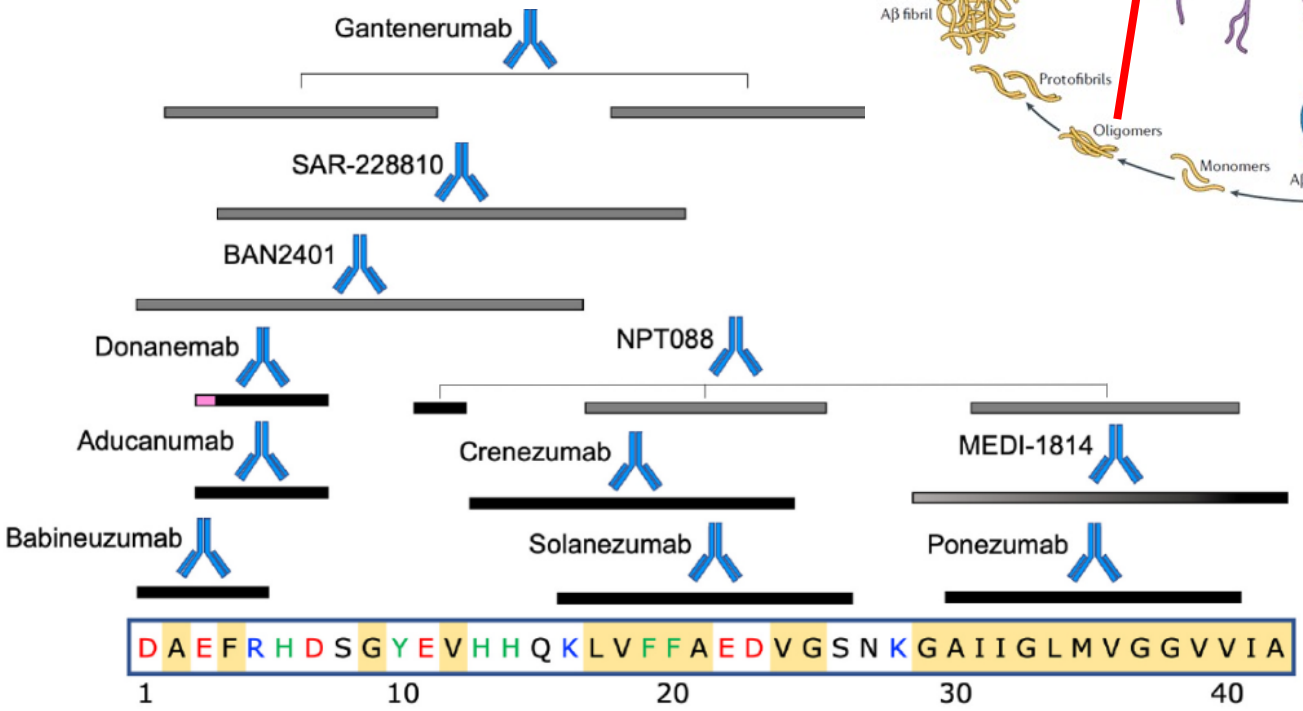
Association between change in p-tau and efficacy at Week 78		Expected correlation	Correlation (p-value)	
			EMERGE (n=514–521)	ENGAGE (n=577–581)
p-tau^{181}	CDR-SB	Positive	**0.11** (0.0166)	**0.14** (0.0005)
	MMSE	Negative	**-0.21** (<0.0001)	**-0.15** (0.0002)
	ADAS-Cog13	Positive	**0.17** (0.0001)	**0.15** (0.0002)
	ADCS-ADL-MCI	Negative	**-0.12** (0.0086)	**-0.14** (0.0010)

Correlations are partial Spearman correlations assessed in pooled low and high dose aducanumab-treated groups, adjusting for baseline p-tau, baseline clinical endpoint, and age. ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; p-tau, phosphorylated tau.

Slide from Eisai Korea

DONANEMAB





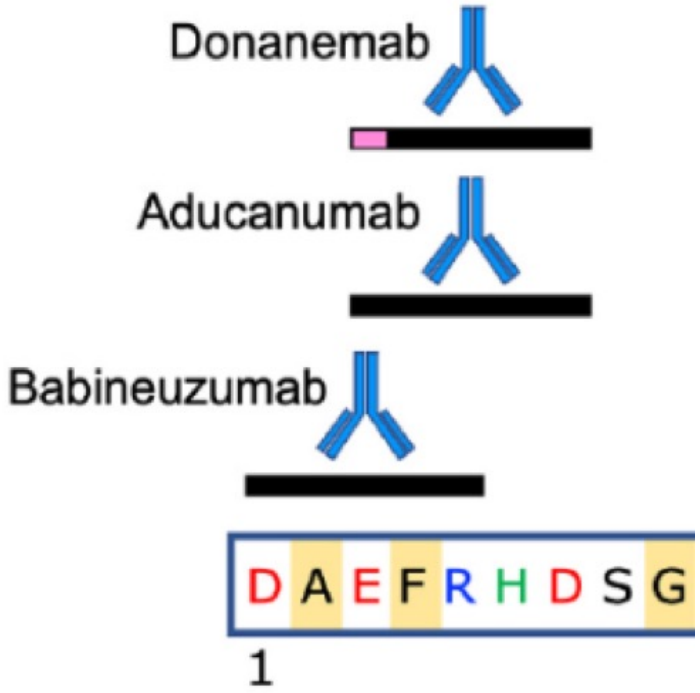
CLINICAL TRIAL TIMELINE

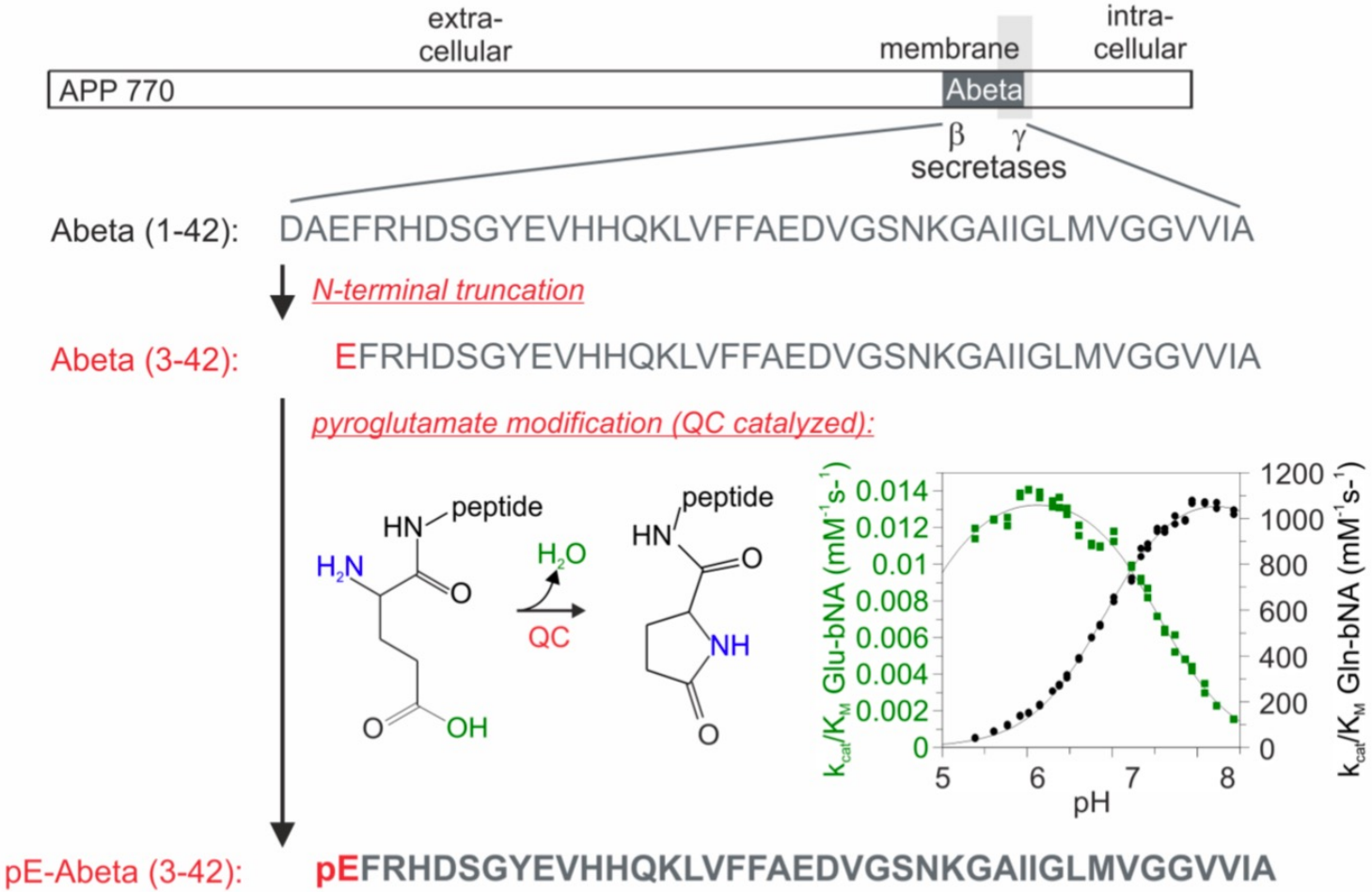
Phase 2 | Study completed / Planned end date | Planned end date unavailable

Sponsor	Clinical Trial	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
Eli Lilly & Co.	NCT03367403				N=266						

Neurobiology of Disease 144 (2020) 105010;
https://www.alzforum.org/therapeutics/donanemab;
Slide from 서승완 교수님 (한림대)

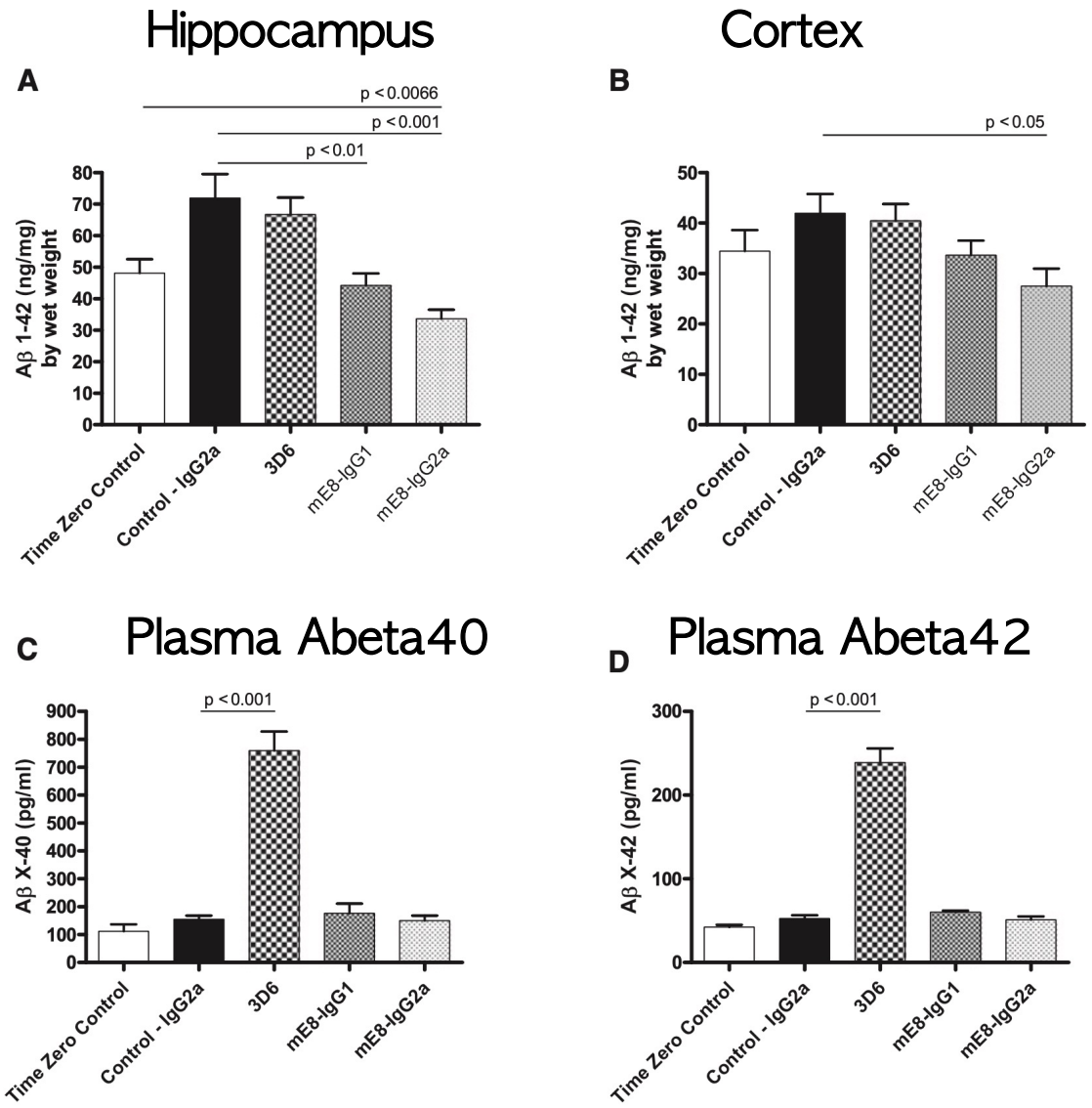
pE Abeta$_{p3-42}$

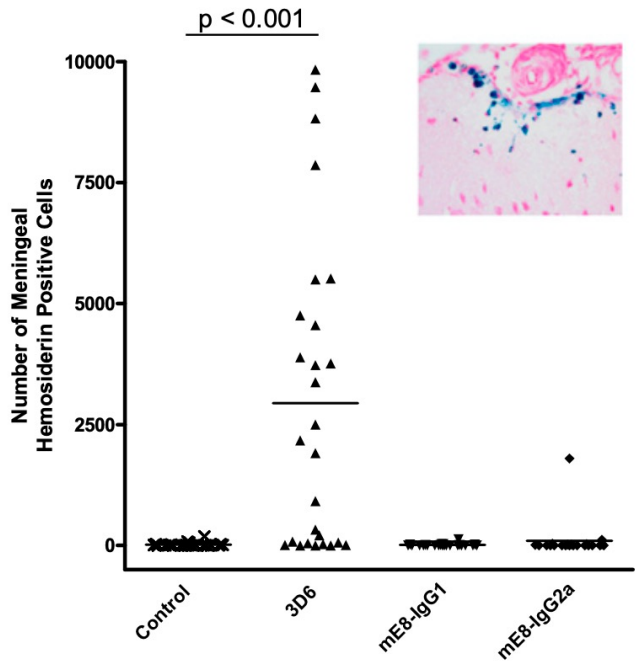




Molecules 2018, 23, 924

No hemorrhage with donanemab's pre-drugs





bapineuzumab

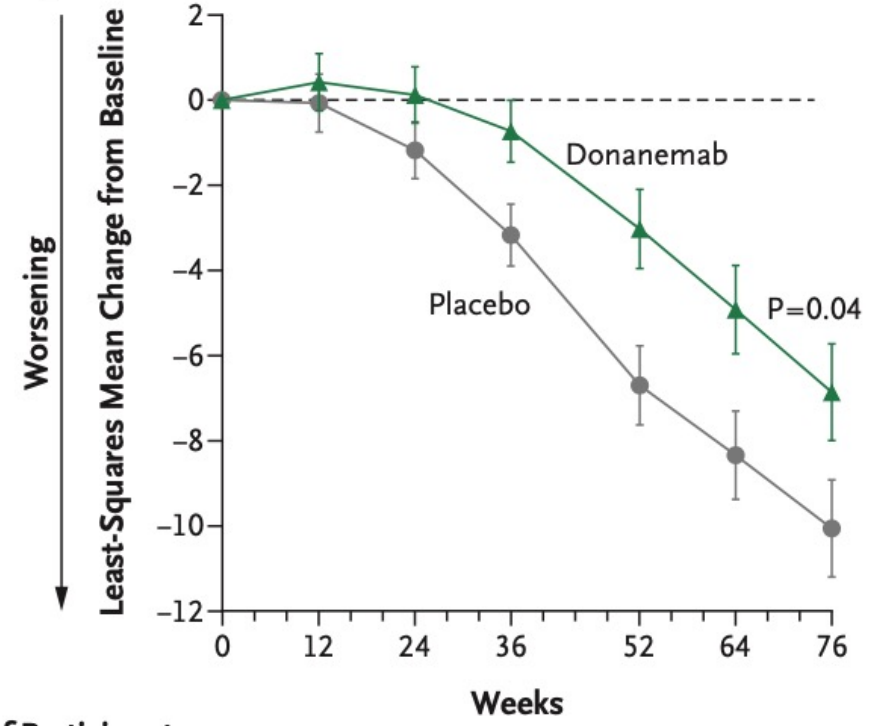
donanemab

Neuron 76, 908–920, December 6, 2012

Donanemab - Cognition

The NEW ENGLAND JOURNAL of MEDICINE

A Primary Outcome: iADRS Score



No. of Participants

Donanemab	125	120	112	102	88	89	93
Placebo	120	113	110	103	90	90	91

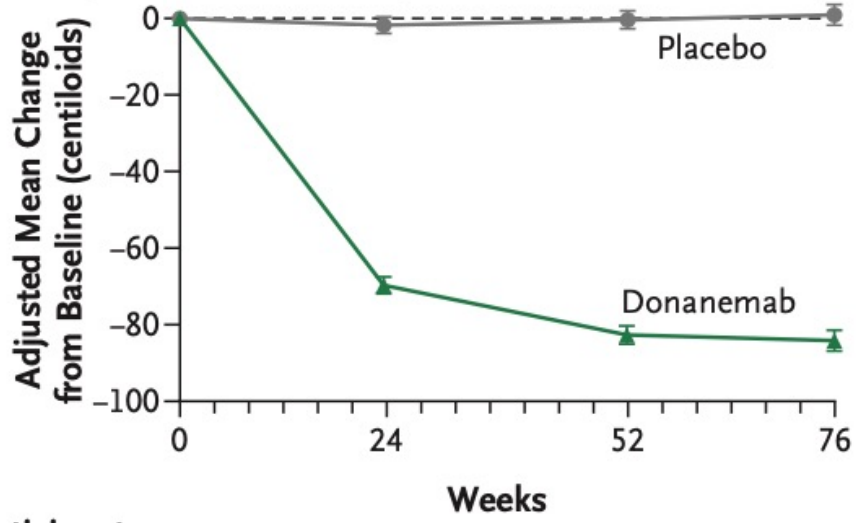
Difference in Least-Squares Mean Change

	Donanemab vs. placebo	95% CI
	points	
Wk 36	2.44±0.96	0.55–4.33
Wk 52	3.67±1.26	1.19–6.15
Wk 64	3.42±1.42	0.63–6.21
Wk 76	3.20±1.56	0.12–6.27

NEJM (2021) 384;18

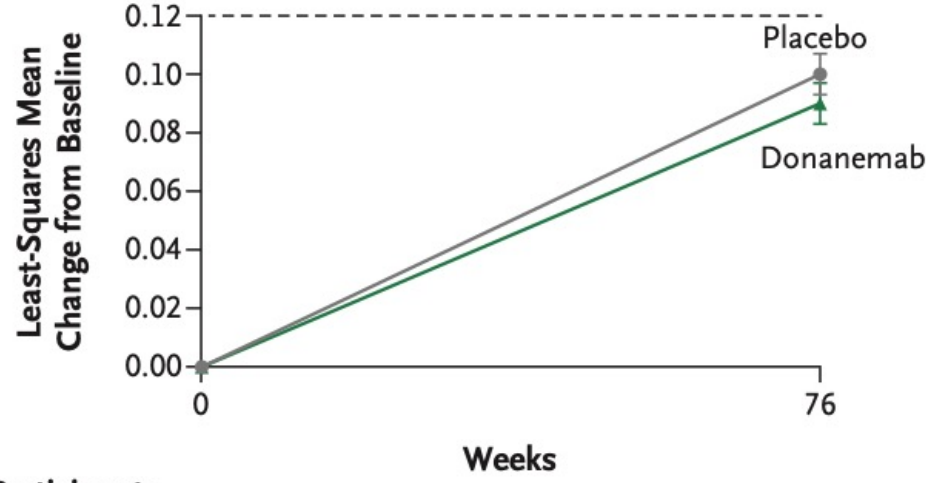
Donanemab – PET (Abeta, tau)

A Amyloid Plaque Level on Florbetapir PET



No. of Participants				
Donanemab	121	115	92	90
Placebo	112	111	91	91

B Global Tau Load on Flortaucipir PET



No. of Participants		
Donanemab	90	90
Placebo	87	87

NEJM (2021) 384;18

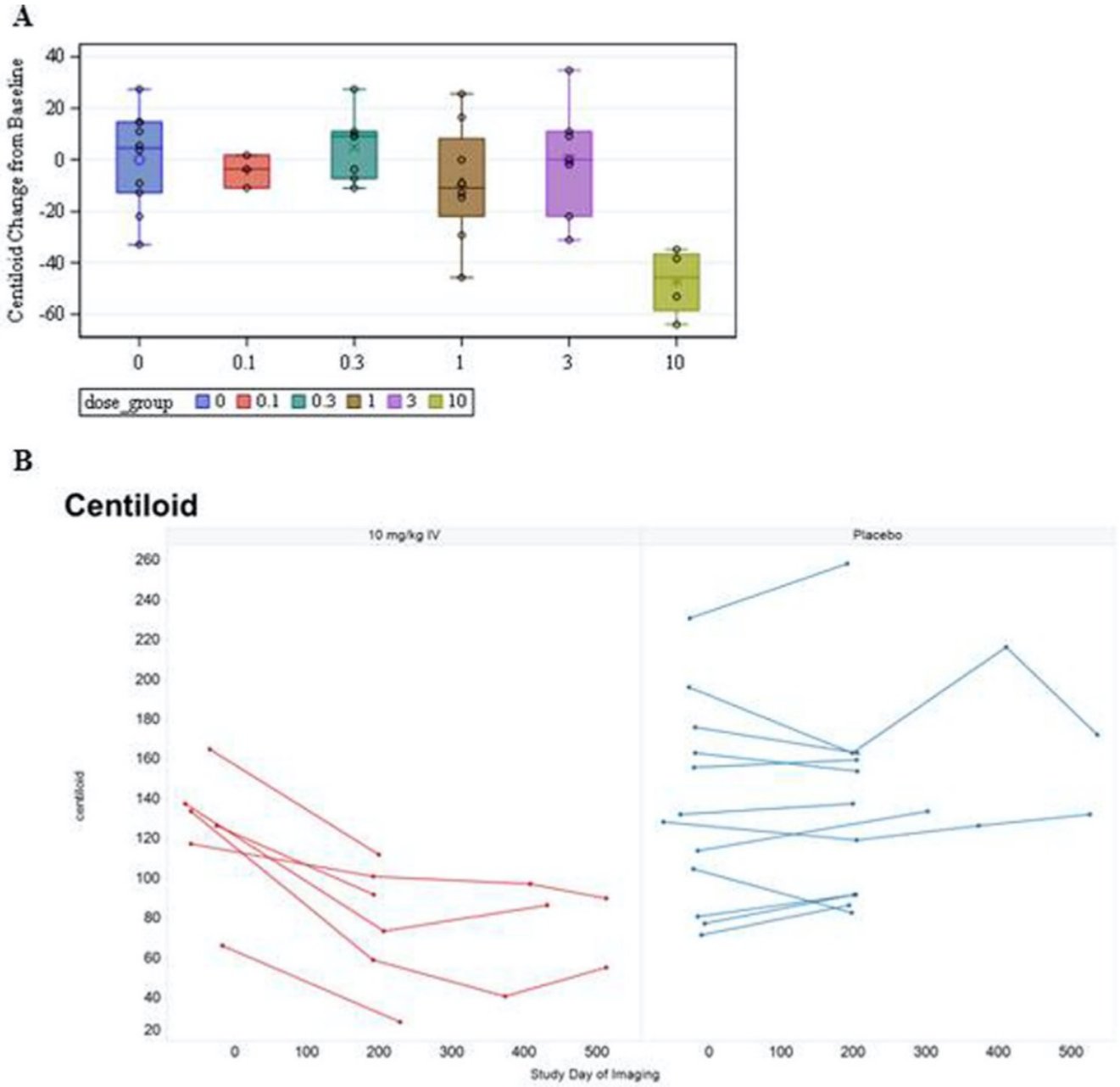
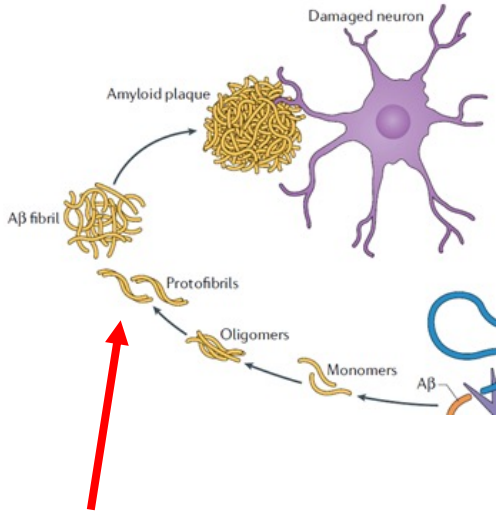


FIGURE 4 Centiloid change of florbetapir scans from baseline at 28 weeks for donanemab (A). Baseline and follow-up centiloid values in 10 mg/kg donanemab and pooled placebo arms (B). IV, intravenous

LECANEMAB (BAN2401)



CLINICAL TRIAL TIMELINE

Phase 1 | Phase 2 | Phase 3 | Study completed / Planned end date | Planned end date unavailable | Study aborted

Sponsor	Clinical Trial	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Eisai Co., Ltd.	NCT01230853			N=80															
Eisai Co., Ltd.	NCT01767311						N=856												
Eisai Co., Ltd.	NCT03887455												N=1566						

https://www.alzforum.org/therapeutics/lecanemab
Slide from 서승완 교수님 (한림대)

LECANEMAB PHASE II (2021)

Swanson *et al. Alzheimer's Research & Therapy* (2021) 13:80
https://doi.org/10.1186/s13195-021-00813-8

Alzheimer's Research & Therapy

RESEARCH

A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody

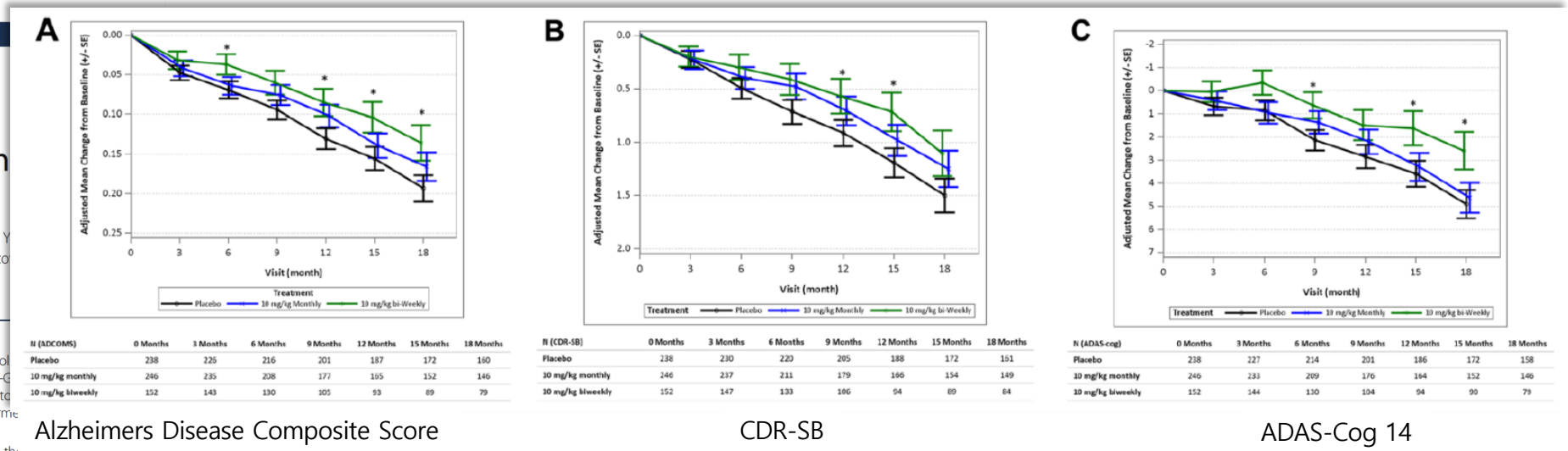
Chad J. Swanson[1], Yong Zhang[1], Shobha Dhadda[1], Jinping Wang[1], June Kaplow[1], Robert Y
Heather Bradley[1], Martin Rabe[1], Akihiko Kovama[1], Larisa Reyderman[1], Donald A. Berry[5], Sco

PRODROMAL/MILD AD

BASELINE Aβ +

72 WEEKS

N = 856



N (ADCOMS)	0 Months	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months
Placebo	238	226	216	201	187	172	160
10 mg/kg monthly	246	235	208	177	165	152	146
10 mg/kg biweekly	152	143	130	105	93	89	79

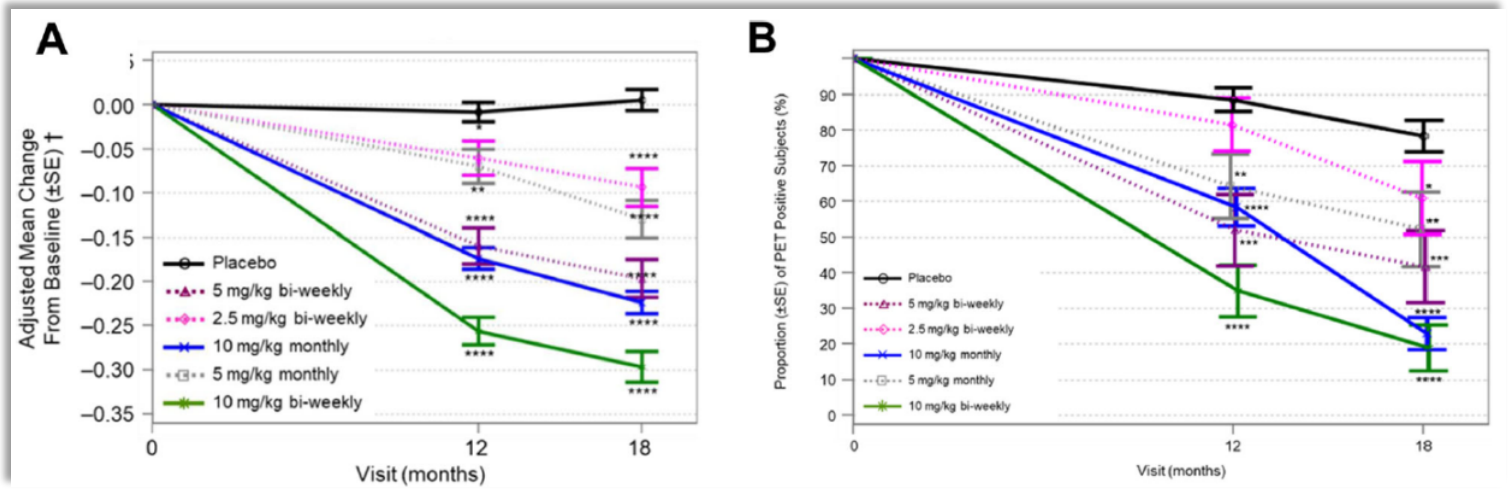
Alzheimers Disease Composite Score

N (CDR-SB)	0 Months	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months
Placebo	238	230	220	205	188	172	161
10 mg/kg monthly	246	237	211	179	166	154	149
10 mg/kg biweekly	152	147	133	106	94	89	84

CDR-SB

N (ADAS-cog)	0 Months	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months
Placebo	238	227	214	201	186	172	158
10 mg/kg monthly	246	233	209	176	164	152	146
10 mg/kg biweekly	152	144	130	104	94	90	79

ADAS-Cog 14



Amyloid PET SUVr

Slide from 서승완 교수님 (한림대)

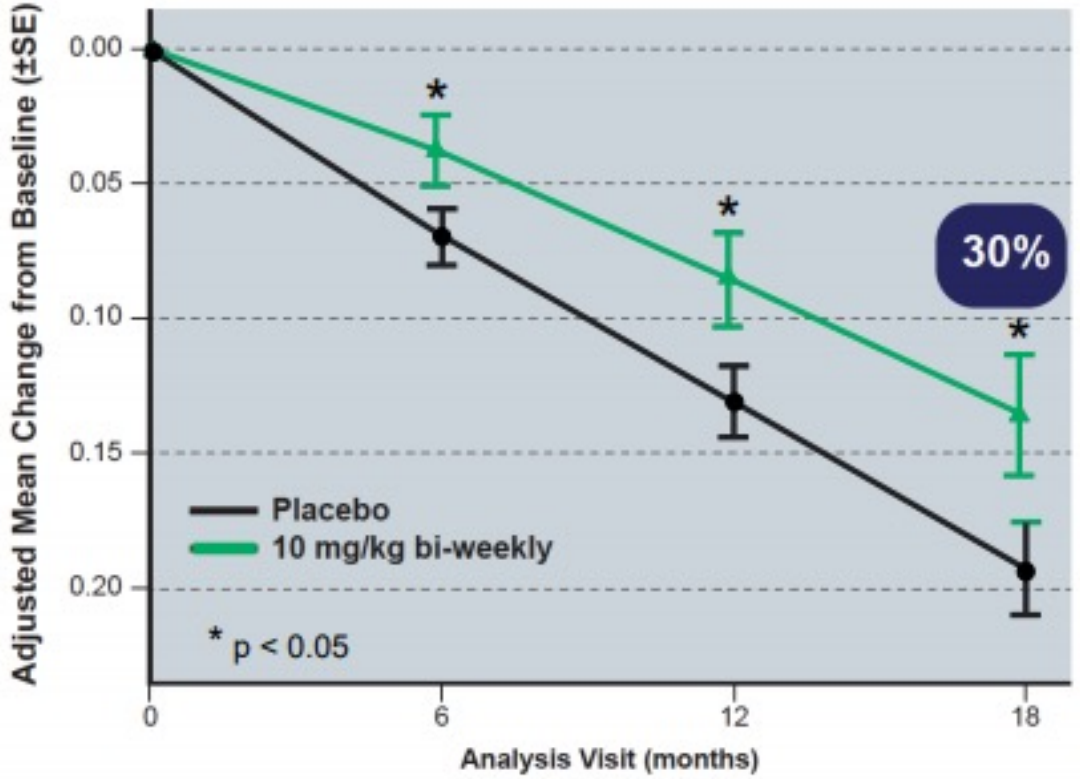
Lecanemab Phase 2 Core Study Results:

Early Clinical Effects: Amyloid Reduction Correlates with Reduction in Clinical Decline

- Clinical decline slowed as early as 6 months in assessments of cognition and function
- Core Phase 2 data suggest that clinical efficacy is correlated with amyloid reduction

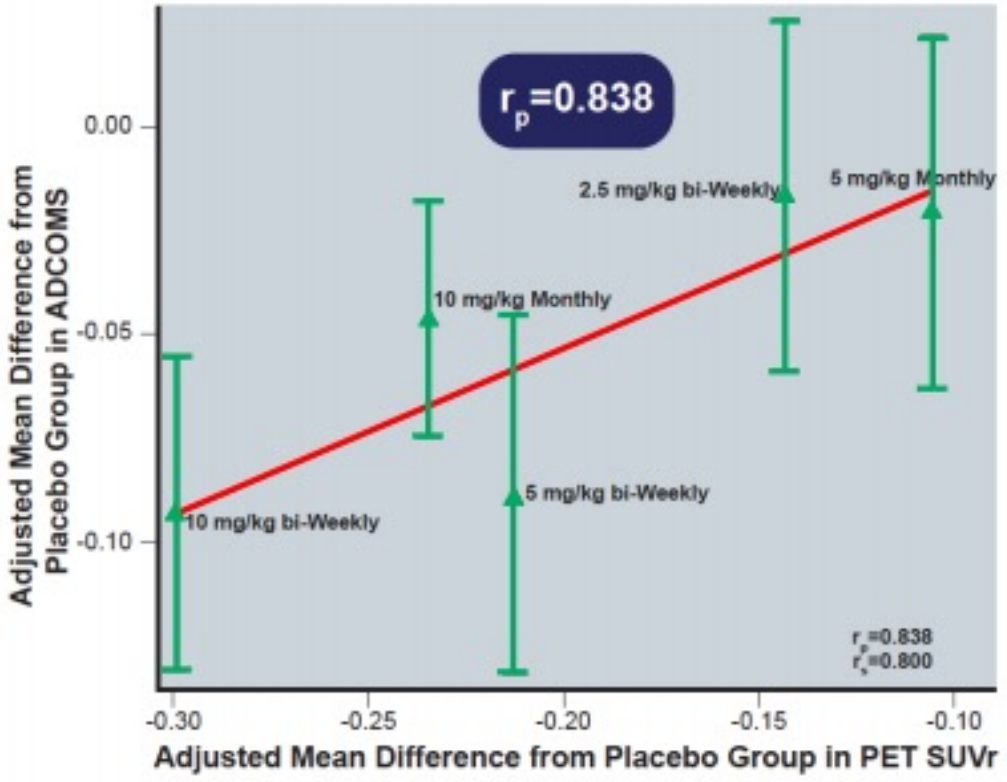
ADCOMS

Similar results for CDR-SB and ADAS-cog



ADCOMS / PET*

Similar results for CDR-SB and ADAS-cog



CDR-SB: Clinical Dementia Rating, sum of boxes. ADCOMS: Alzheimer's Disease Composite Score. ADAS-cog: Alzheimer's Disease Assessment Scale–cognitive subscale. PET SUVr: positron emission topography standardized uptake value ratio. ç
Adjusted mean was based on a protocol-specified mixed model for repeated measures (MMRM). The MMRM included baseline as a covariate, with treatment group, visit, region, randomization stratification variables (clinical stage, concurrent AD medication, APOE4 status), and treatment group-by-visit interaction as fixed effects. Analysis population: FAS. Data shown in right figure are for subjects enrolled in the PET sub-study with PET SUVr and clinical data at 12 or 18 months. *: r_p is Pearsons' correlation coefficient and r_s is Spearman's correlation coefficient.

Adapted from Swanson et. al, 11th Clinical Trials on Alzheimer's Disease (CTAD) Conference October 24-27, 2018 and Swanson et al. Alzheimers Res Ther. 2021;13(1):80.

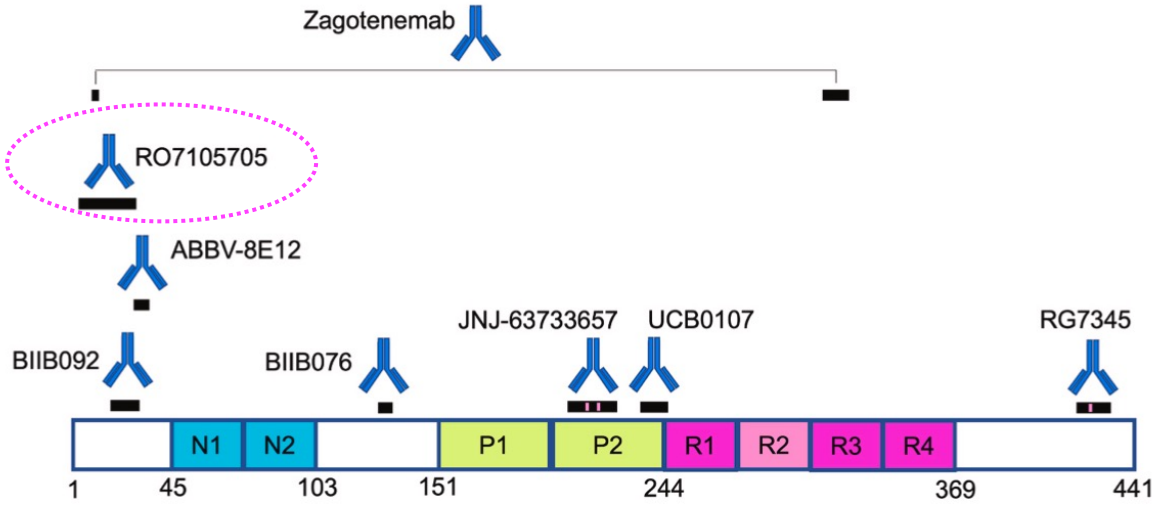
Slide from Eisai Korea

Monoclonal antibodies to Tau (phase2)

Drug	Sponsor	Trial	Population	Target	Phase	Outcome
Gosuranemab (BIIB092)	Biogen	TANGO	Early AD	N-terminal epitope	2	Terminated due to lack of efficacy
Semorinemab (RO7105705)	Roche/AC Immune	TAURIEL	Early AD	N-terminal epitopes	2	Failed phase II
Semorinemab (RO7105705)	Roche/AC Immune	LAURIET	Moderate AD	N-terminal epitopes	2	Completes September 2021
Tilavonemab (ABBV-8E12)	AbbVie/C2N Diagnostics	NCT02880956	Early AD	N-terminal epitope	2	Terminated Jul 2021
Zagotenemab (LY3303560)	Eli Lilly	NCT03518073	Early AD	Mid-region and N-terminal epitope	2	Terminated Oct 2021

https://doi.org/10.1007/s00415-021-10790-5

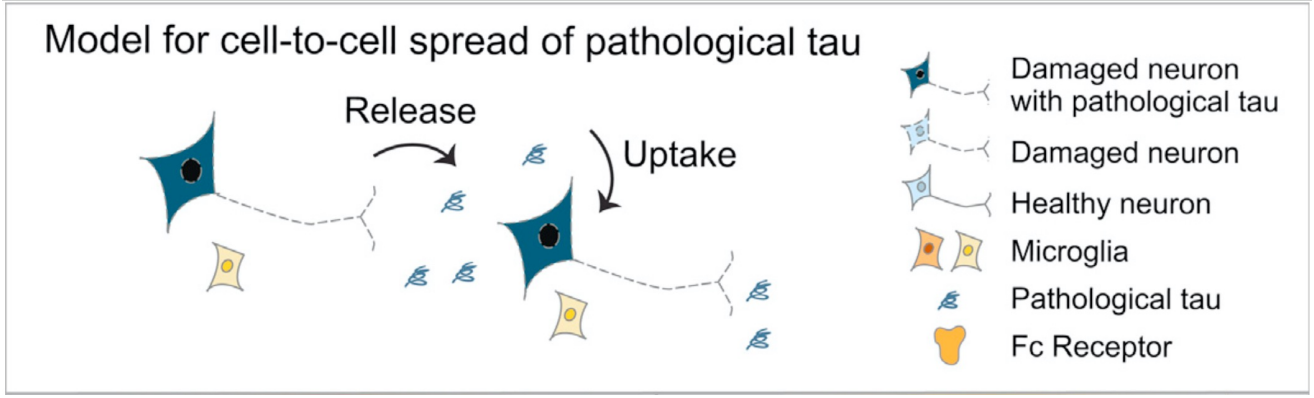
SEMORINEMAB

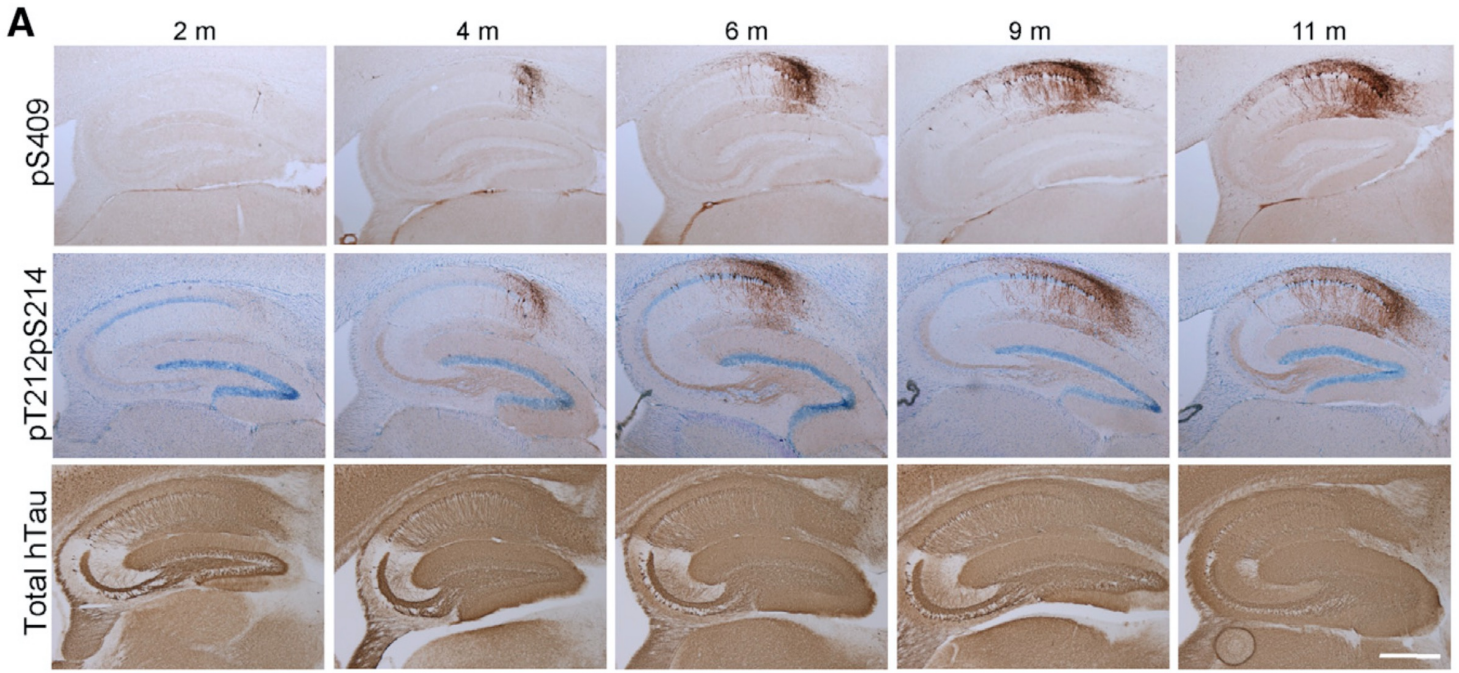


Neurobiology of Disease 144 (2020) 105010;

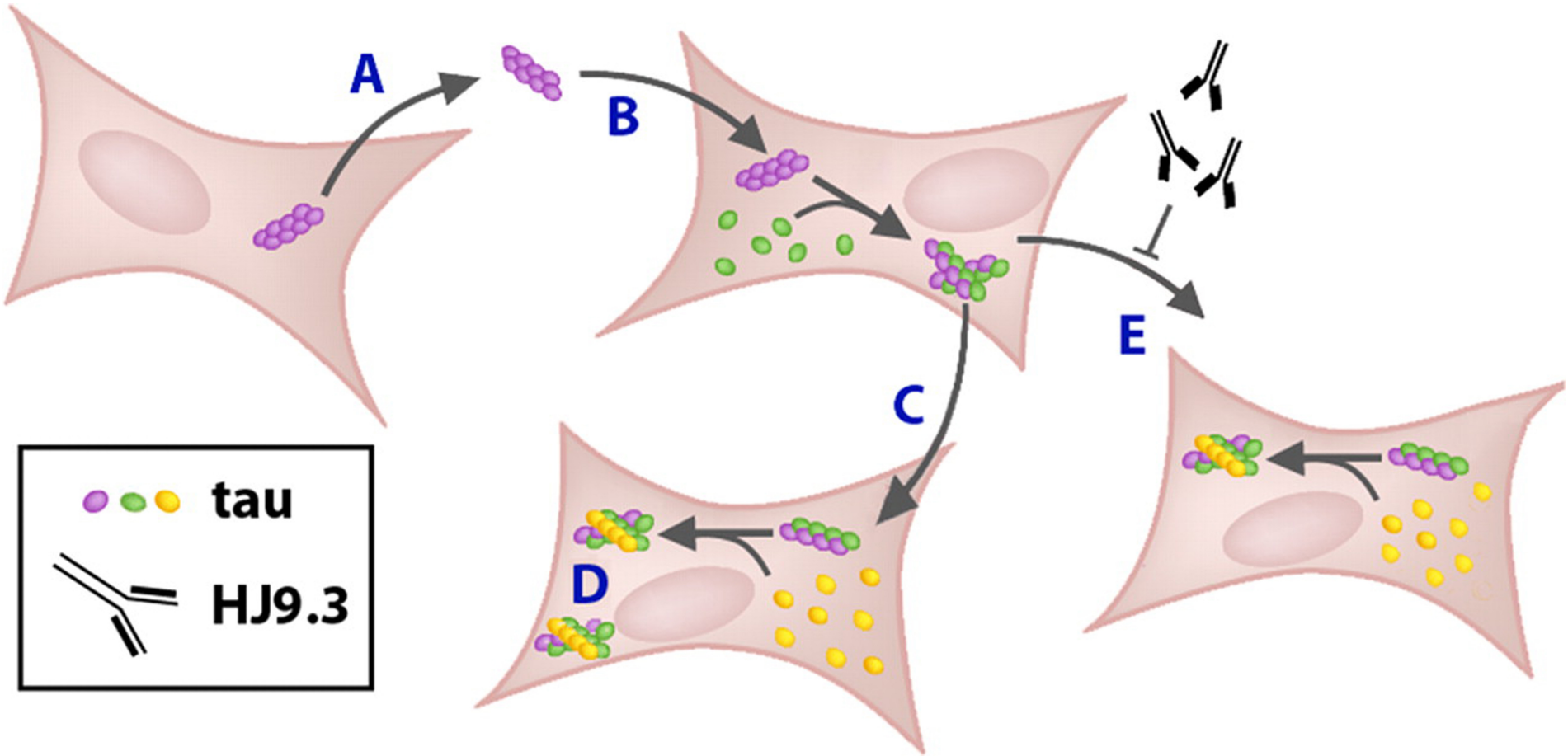
- Anti-tau IgG4 antibody
  - targets extracellular, not intracellular, tau.
  - antibodies with *reduced effector function* in an effort to limit microglial activation leading to inflammatory responses
- In October 2017, Genentech started TAURIEL
  - a Phase 2 study in 457 people with prodromal or probable AD → failed
- In February 2019, Roche started LAURIET,
  - another Phase 2 study in 272 people with a diagnosis of probable AD conirmed by amyloid positivity
  - *43.6% slowing of decline on the ADAS-Cog11*

Reduced effector function



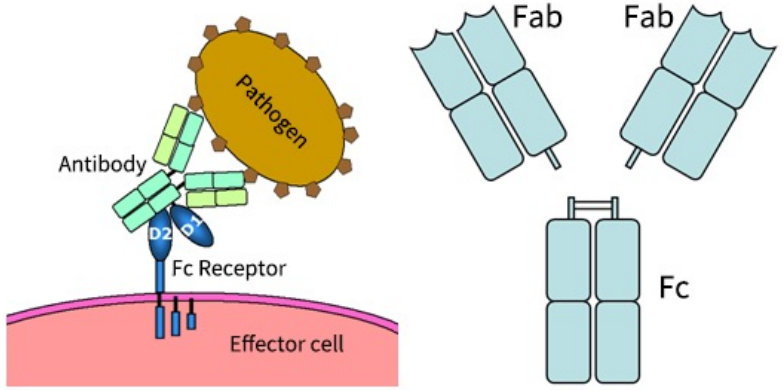


Lee et al., 2016, Cell Reports 16, 1690–1700

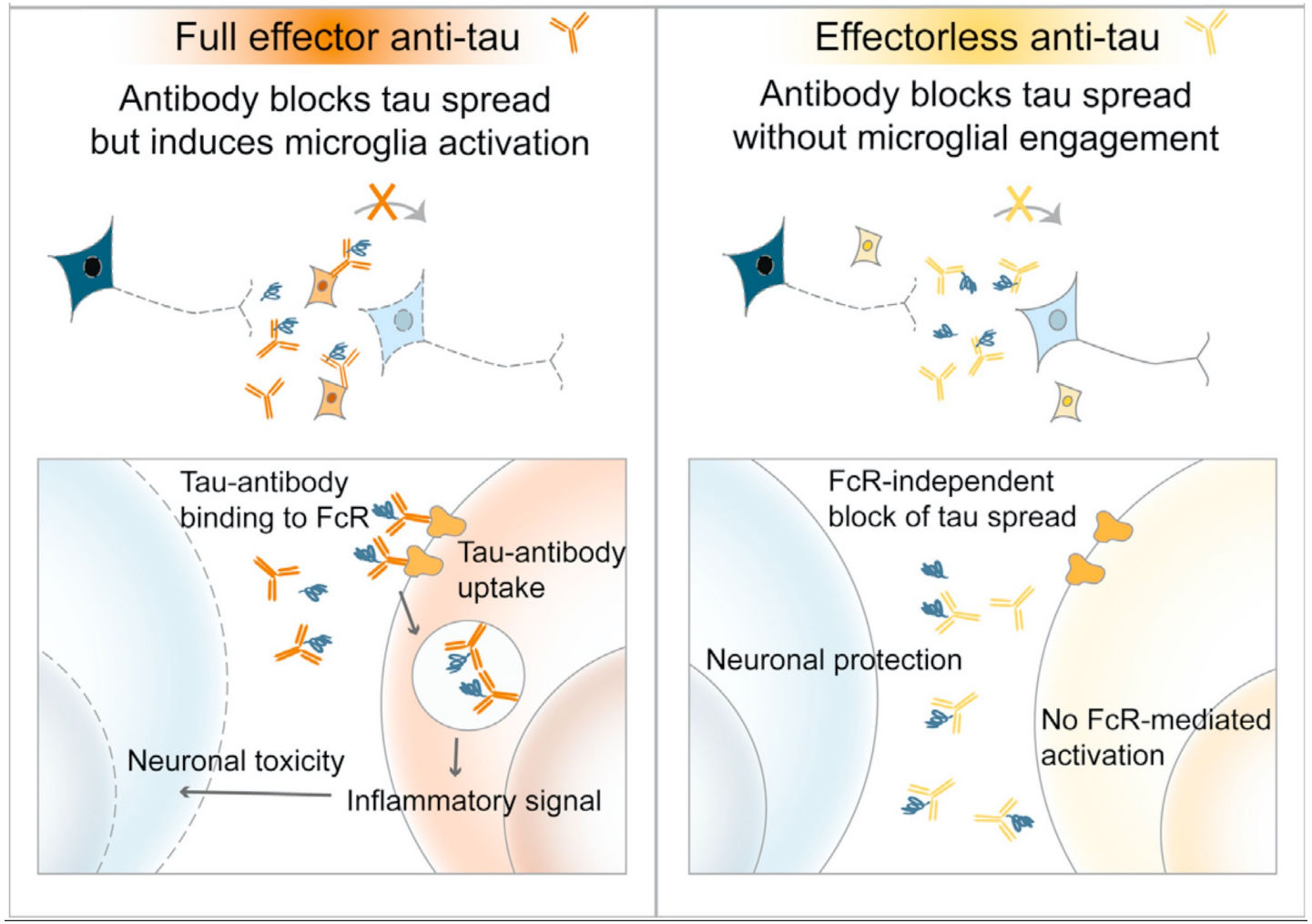


JBC, Volume 287, Issue 23, 1 June 2012, Pages 19440-19451

No effector function could be better

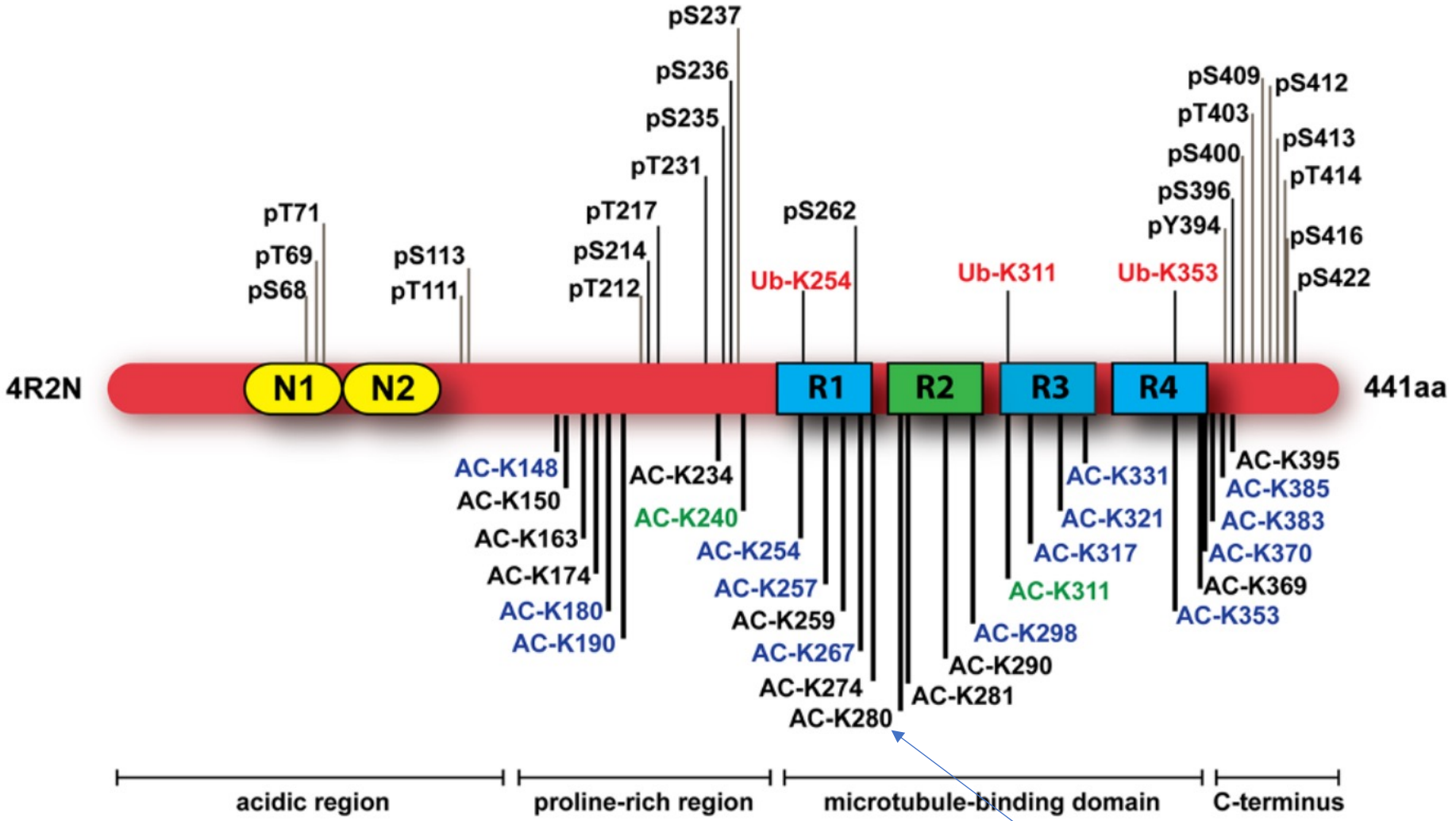


https://www.sinobiological.com/research/receptors/fc-receptor



Lee et al., 2016, Cell Reports 16, 1690–1700

Tau-acetylation



ADEL-Y01 (ADEL©)

Discussion

- Target population
  - Stage of AD
  - Heterogeneity of AD / pure AD?
- Long-term safety issues
  - Brain atrophy
  - ARIA-E/H
  - Anti-drug antibody
- Socioeconomical impact
  - High cost and reimbursement
  - MRI, PET scan availability