Alzheimer's Therapy – Lecanemab is NOT for everyone What are my options in Hawaii?

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Disclosure: Kore Liow, MD

Research Funding received from:

– NIH, NINDS, CDC, T3D, Athira, Takeda, UCB, NovoNordisk, Ipsen, Avanir, Ra Pharma, Sanofi, Novartis, Praxis, Annovis, Merck, NeuroDerm, Cerevel, Acadia, Biogen, Idorsia, Eisai, Xenon, SK Lifescience, Axsome, Engage, Livanova, Neurelis, Longboard, Jazz, NLS, Cyclerion, Takeda, Engrail Therapeutic, Longboard, Prothena, Athira, Eli Lilly, NLS, Sage Therapeutics

Editorial:

Guest Editor -Neurology International, ACP Smart Medicine

Reviewer -Neurology, Clinical Practice, Epilepsia etc

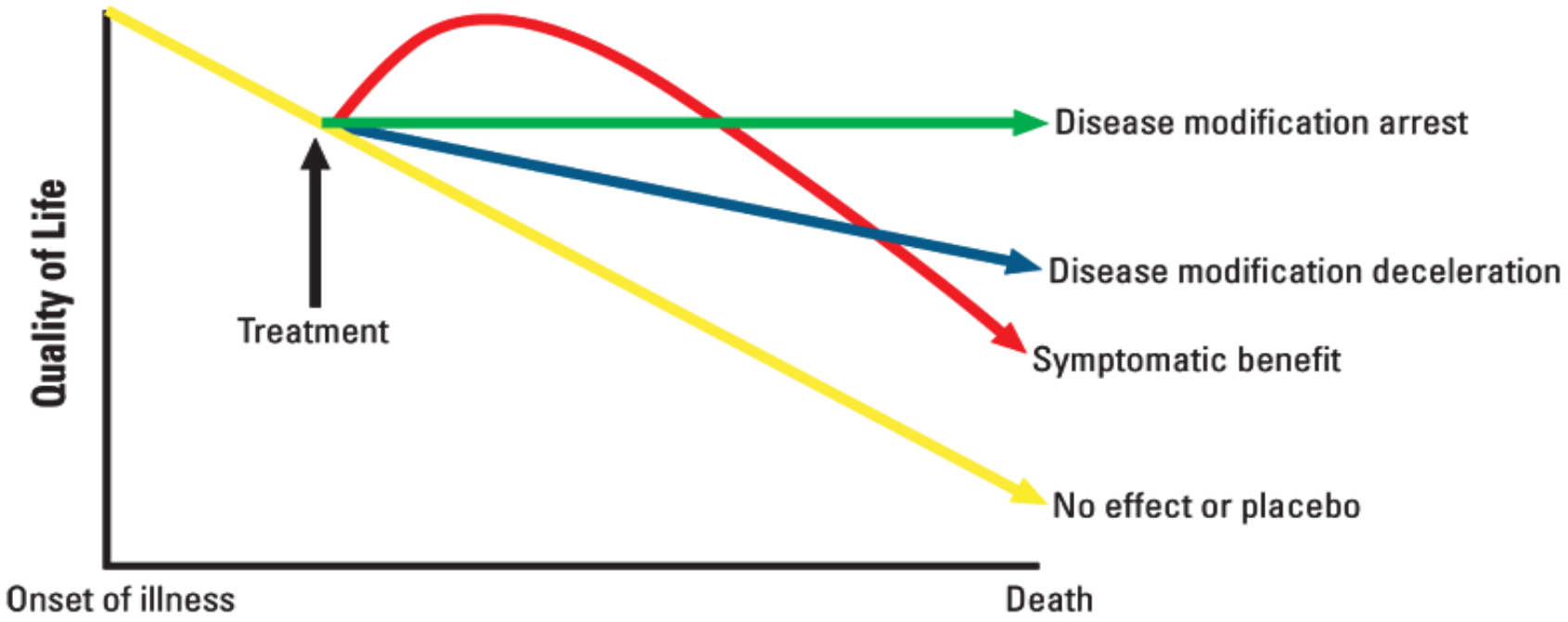
NIH - Review Study Section, Grant Review Panel Member for NINDS

CDC - Advisory & Review Panel

Why all the excitement? How are they different?

FIGURE

DISEASE MODIFICATION VERSUS SYMPTOMATIC BENEFIT IN THE TREATMENT OF ALZHEIMER'S DISEASE

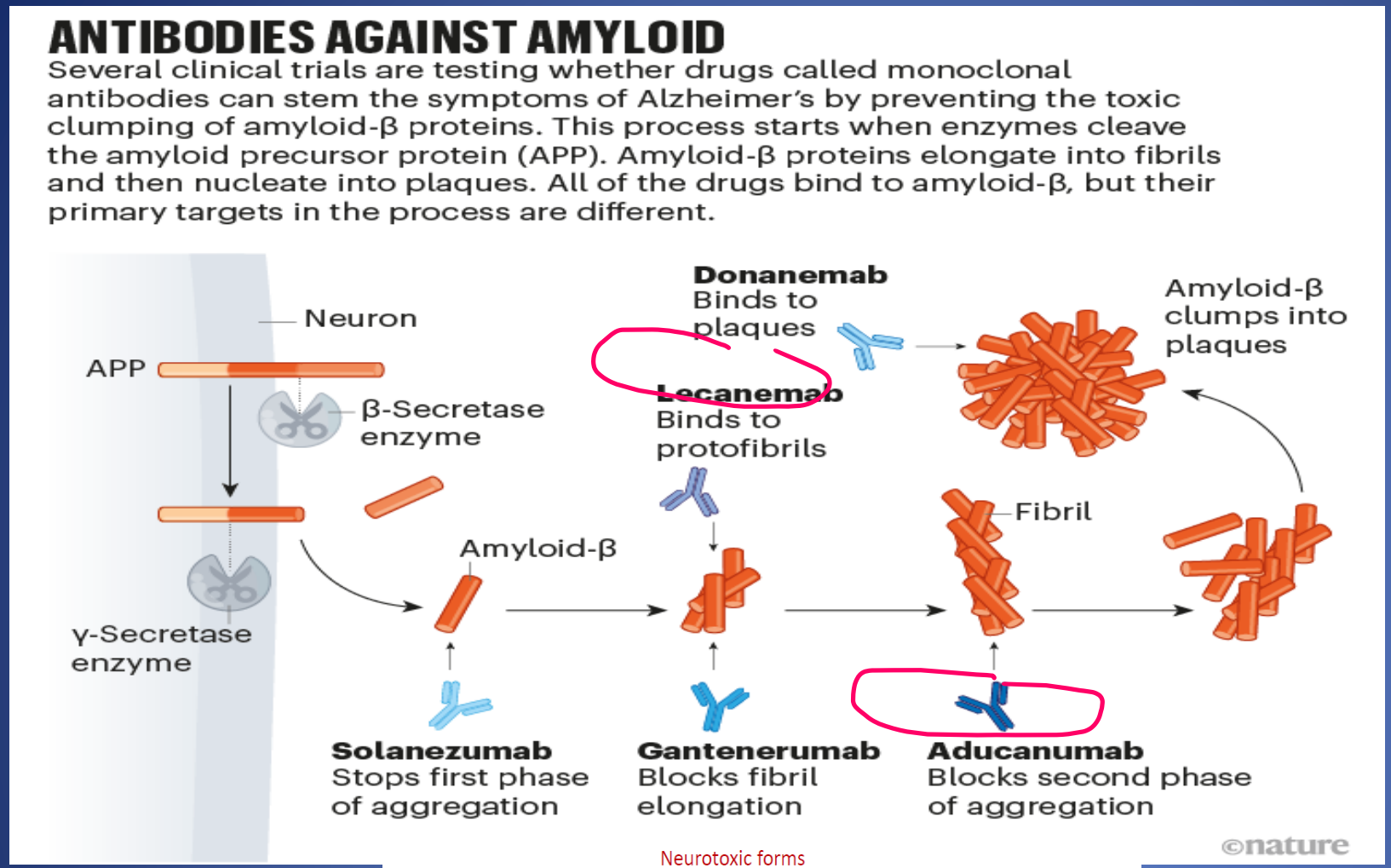


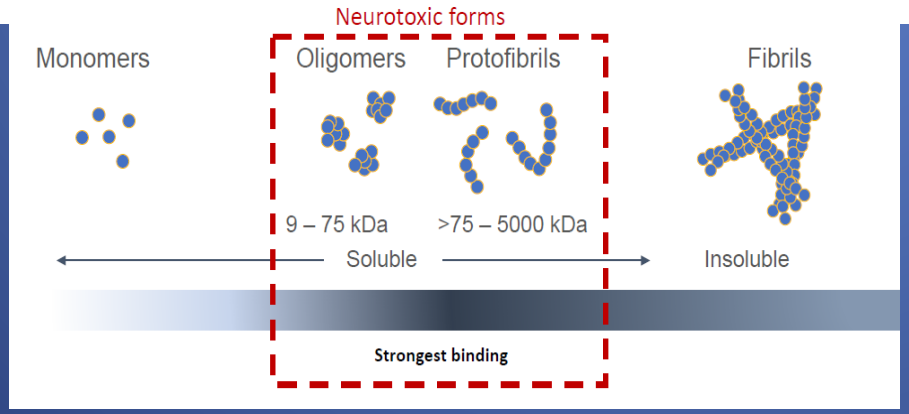
Kennedy GJ. *Primary Psychiatry*. Vol 14, No 11. 2007.

Disease Modifying Treatments (Targeting Biology)

vs

Symptomatic Treatments (Treat Symptoms)
Donepezil (Aricpet)
Rivastigmine (Exelon)
Galantamine (Razadyne)
Memantine (Namenda)
Namzaric (Combo)





Monoclonal Antibody

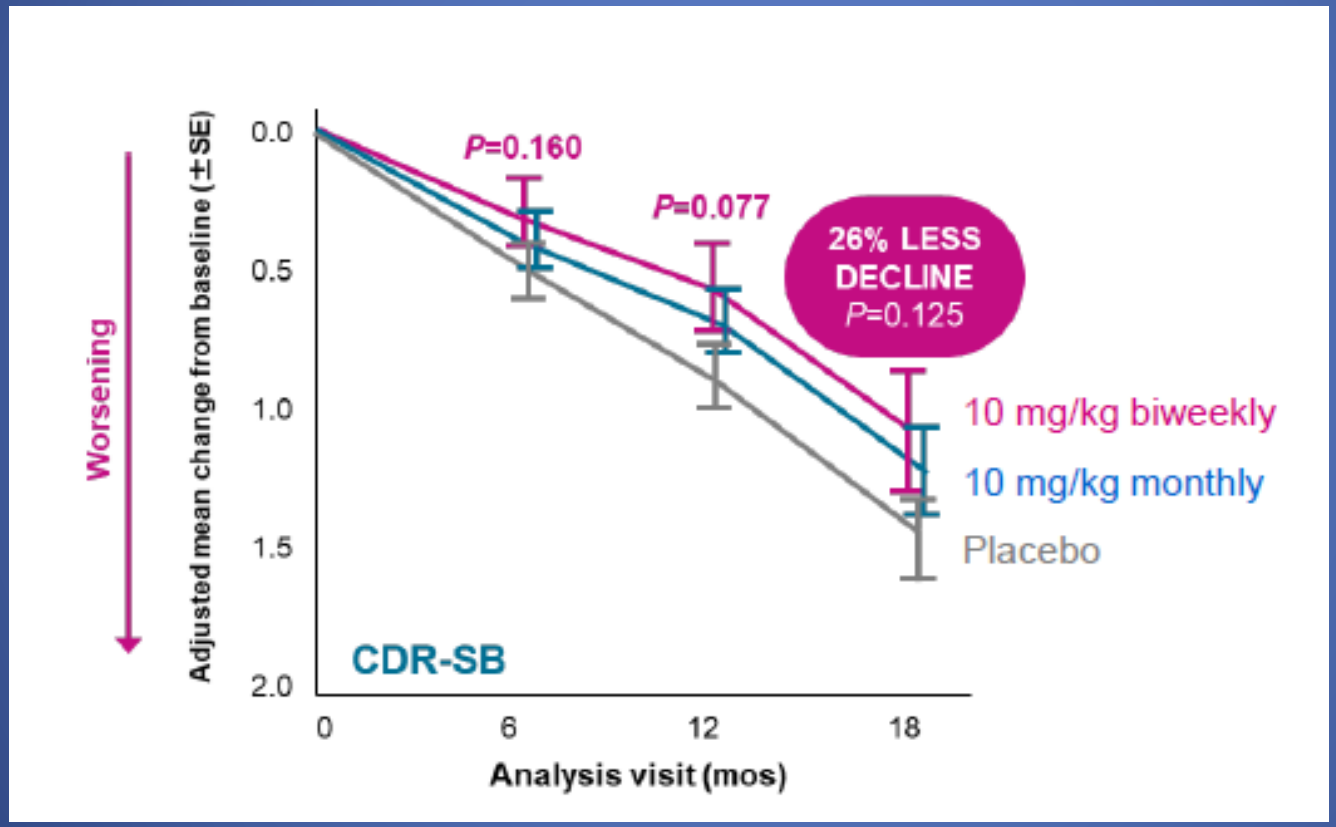
Aducanumab (Aduhelm) 2021

Lecanemab (Leqembi) 2023

Credit: Nik Spencer/*Nature*

What are the Results? Memory Improved?

CDR-SB : Lecanemab 26%



CDR Sum-of-Boxes score (CDR-SB), an 18-point scale measuring cognition (memory, orientation, judgment, and problem solving) and function (community affairs, home and hobbies, personal care)

17% has ARIA
Amyloid Related Imaging Abnormality

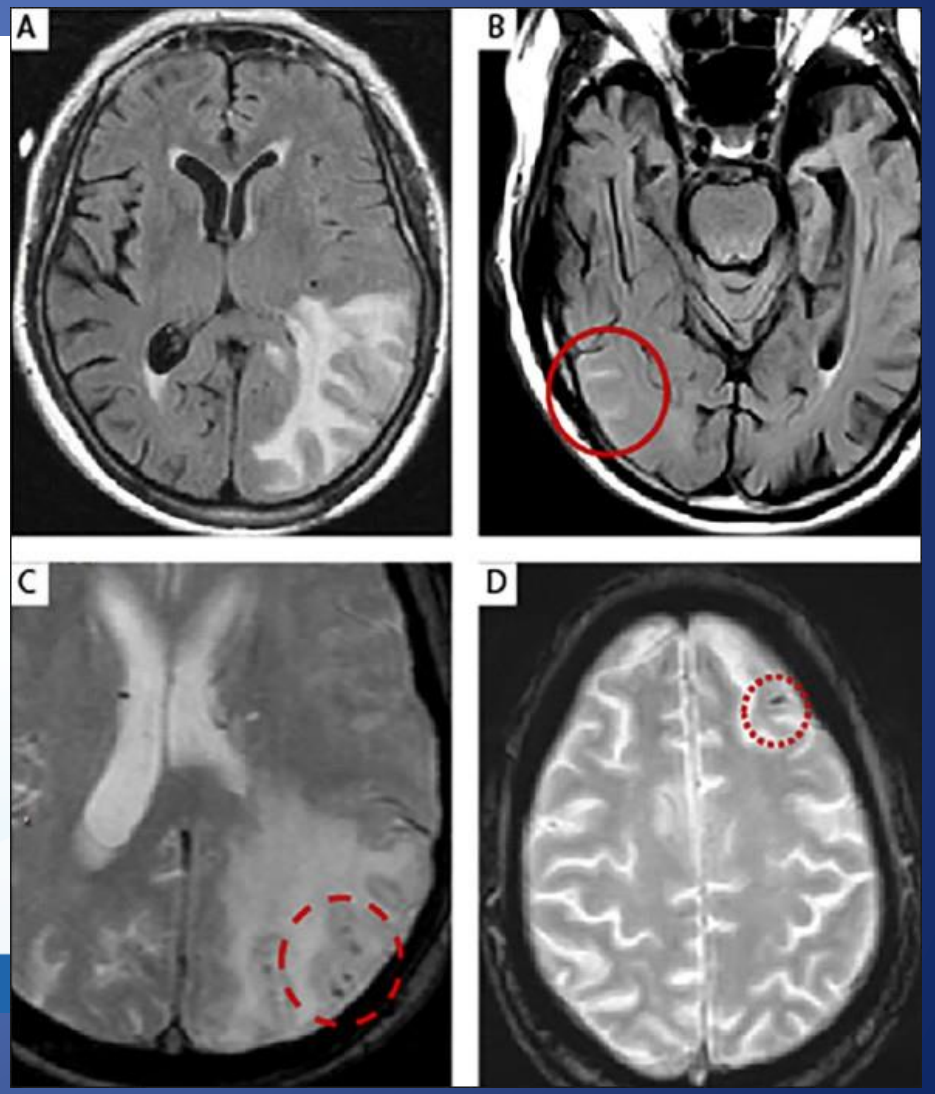
Amyloid-related imaging abnormalities (ARIA)

ARIA refers to radiographic abnormalities observed with anti-Aβ antibodies

- ARIA-Edema (ARIA-E) refers to brain vasogenic edema or sulcal effusion
- ARIA-Hemorrhage (ARIA-H) refers to brain microhemorrhages or localized superficial siderosis

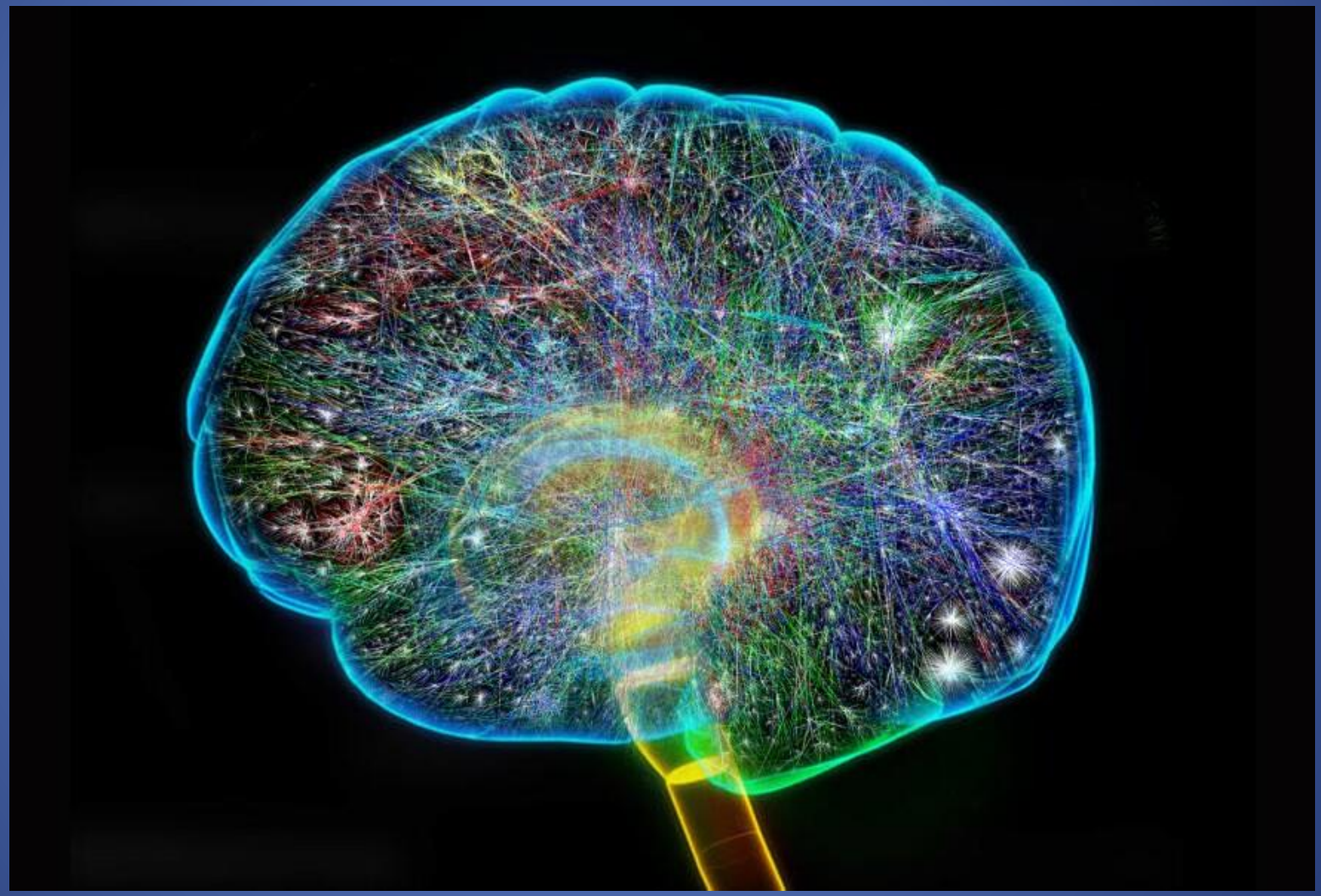
ARIA may result from increased cerebrovascular permeability as a consequence of antibody binding to deposited Aβ

Greenberg SM, et al. *Nature Rev Neurol* 2020;16:30–42.
Aβ, amyloid beta.



Barakos, J., Purcell, D., Suhy, J. et al. Detection and Management of Amyloid-Related Imaging Abnormalities in Patients with Alzheimer's Disease Treated with Anti-Amyloid Beta Therapy. J Prev Alzheimers Dis 9, 211–220 (2022). https://doi.org/10.14283/jpad.2022.21

Case Studies



Mr Vascular

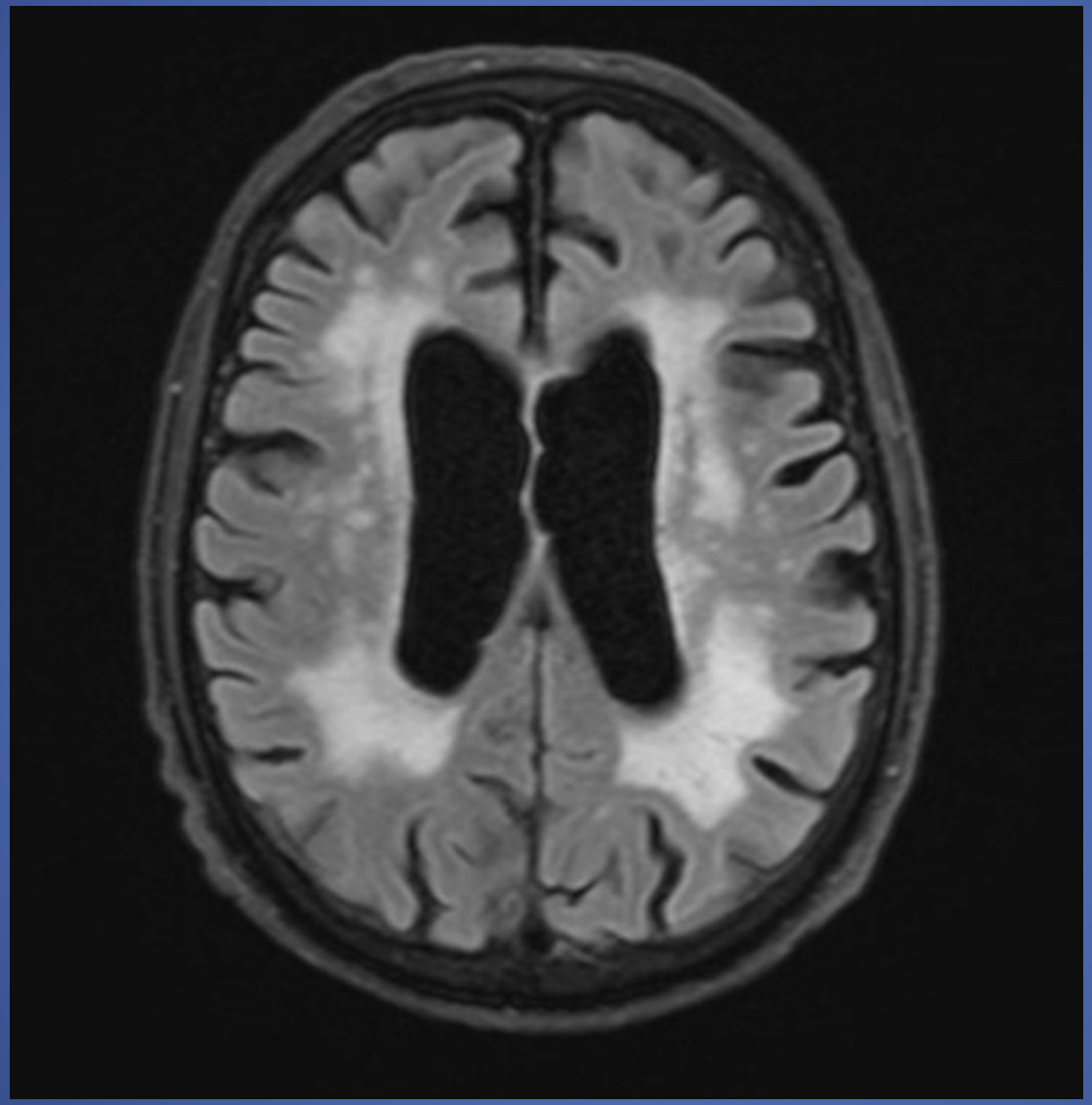
- 71 retired engineer
- Hypertension
- Prediabetic

MMSE 23

E4/E4

MRI noted

- Significant small vessel disease
- Chronic small lacunar infarcts cerebellar
- Cerebral amyloid angiopathy



ARIA – Dose, E4 Risk, Asymptomatic - headache

Anti-amyloid antibody	ApoE genotype	Incidence of ARIA-E (%)	Incidence of ARIA-H/siderosis (%)
Aducanumab (35)	ε4/ε4	64	41/33
	ε4/–	36	17/14
	–/–	20	12/6
Lecanemab (3)	ε4 positive	14.3	13.1
	ε4 negative	8.0	4.6
Donanemab (5)	ε4/ε4	44.0	
	ε4/–	30.0	19.8/17.6 (all genotypes)
	–/–	11.1	
Gantenerumab (105 mg) (6)	ε4/ε4	10.7	32.0
	ε4/-	5.4	19.8
	–/–	1.8	12.3
Gantenerumab (225 mg) (6)	ε4/ε4	?	?
	ε4/-	15.0	19.4
	–/–	11.0	11.0

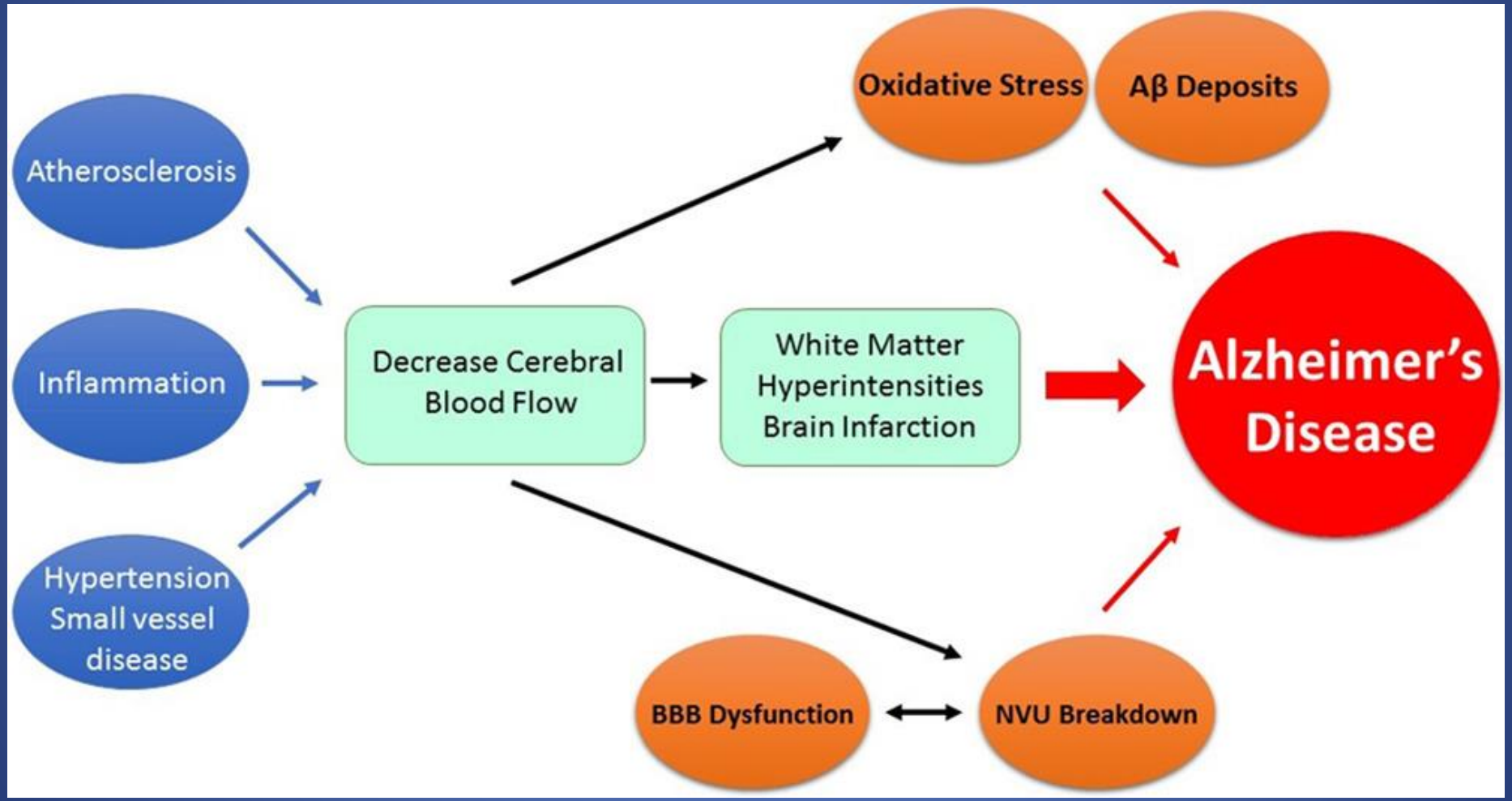
Incidence of ARIA-E and -H by ApoE genotype. ARIA-E and -H may have occurred concurrently in some individuals. [?] indicates data not available.

Sign/Symptom	Aducanumab (2)	Lecanemab (4)	Donanemab (5)	Gantenerumab (6)
Headache (%)	13	12.5	7.6	9.6–12.5
Dizziness (%)	4	8.3	8.4	7.7–10.4
Confusion/altered mental status (%)	5	?	?	?
Visual disturbance/eye disorders (%)	2	?	?	5.9–8.8
Nausea (%)	2	8.3	10.7	?
New onset seizure(s) (%)	?	?	?	?

Signs/symptoms of ARIA by antibody ranked by incidence. Incidence is presented as a percentage of symptomatic patients within the total number of patients with the observation of ARIA. [?] indicates data not available.

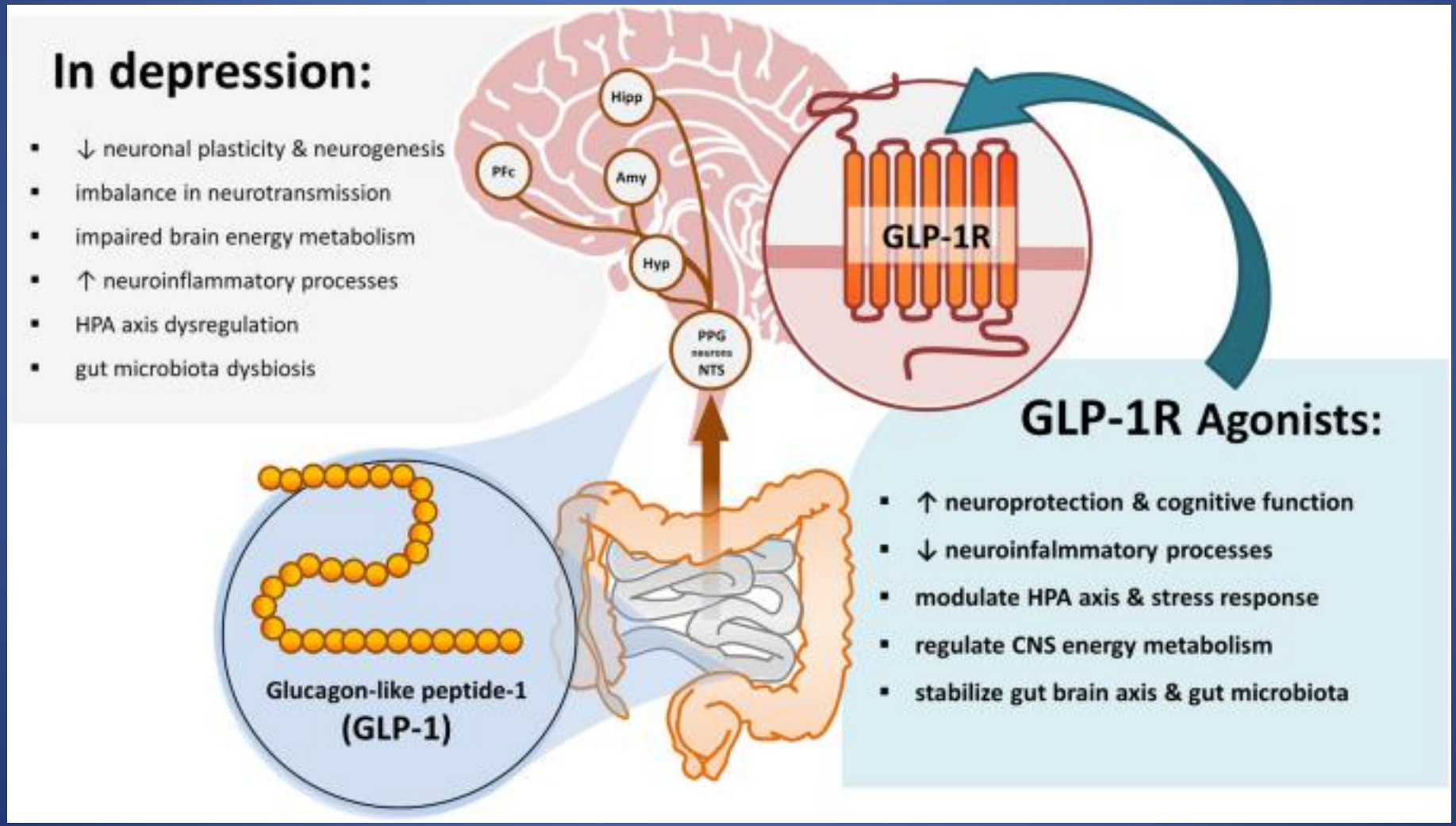
Withington CG, Turner RS. Amyloid-Related Imaging Abnormalities With Anti-amyloid Antibodies for the Treatment of Dementia Due to Alzheimer's Disease. Front Neurol. 2022 Mar 23;13:862369. doi: 10.3389/fneur.2022.862369. PMID: 35401412; PMCID: PMC8985815.

Glucose metabolism, Inflammation, oxidative stress results in Vascular Dysfunction plays a role in AD



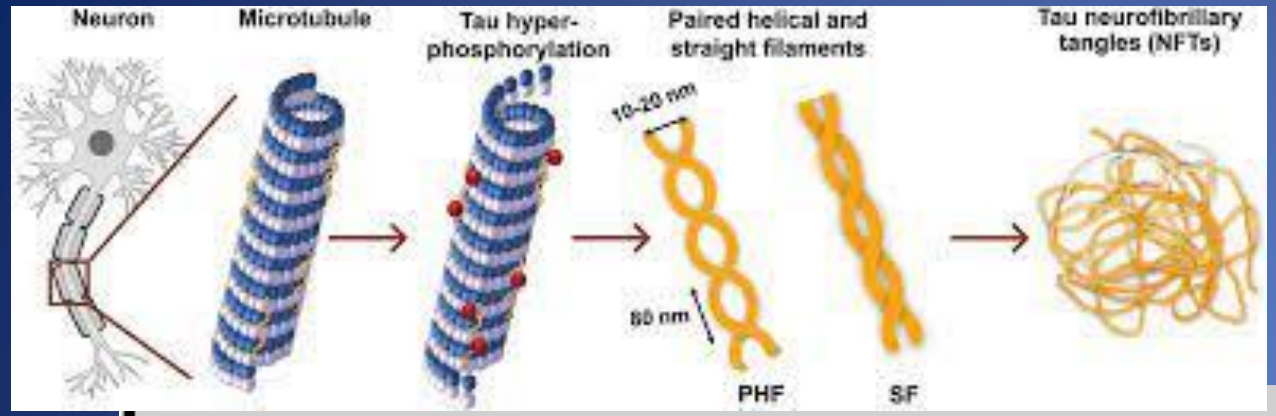
Getting to the Heart of Alzheimer Disease Joshua M. Tublin*, Jeremy M. Adelstein*, Federica del Monte, Colin K. Combs, and Loren E. Wold **Circulation Research** Volume 124, Issue 1, 4 January 2019; Pages 142-149

EVOKE Study NIH NCT 04777396
GLP-1R (Glucagon-like Peptide-1 Receptor) Agonists

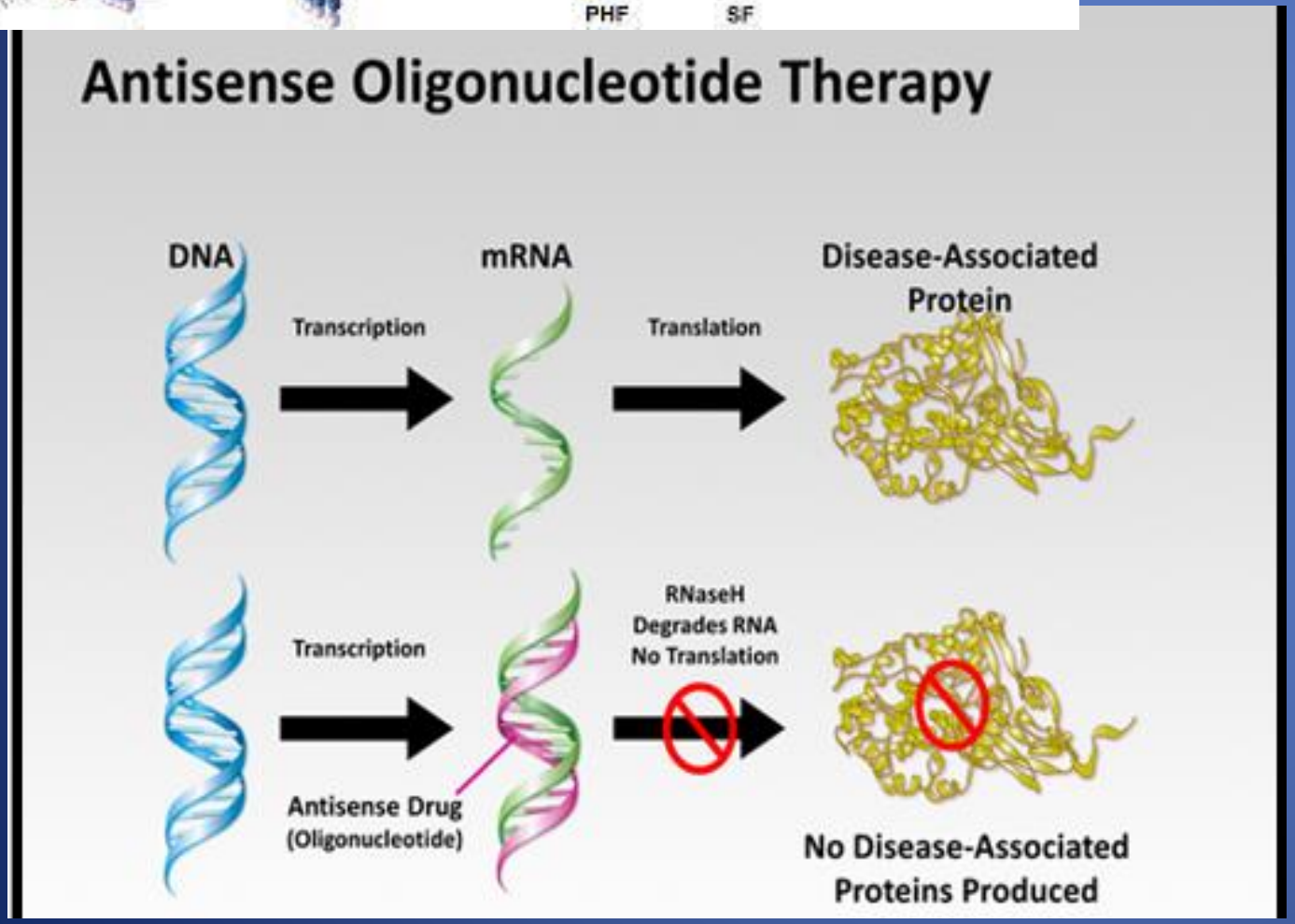


Mrs. Blood Thinner

- 66 yo retired reporter
- History of DVT while flying
- Takes Xarelto when travelling
- MMSE 25
- E2/E3
- MRI disproportional atrophy



Phase 1b/2 BII080- CELIA 247 AD201
Site 1030 – HI Mem Ctr
MMSE > 22



TAU ASO (Antisense Oligonucleotide) Therapy

-binds to & reduce MAPT (Microtubule associated protein Tau) mRNA

(-) Translation of Tau Proteins expression

Intrathecal Q 3 months

Mr Moderate Dementia

- 83 yo retired Japanese Teacher
- Forgetful since age 77
- E2/E2
- MRI: Significant diffuse cortical atrophy - medial temporal
- MMSE 13

NIH Funded Phase 2 ATH 1017 Synaptic Plasticity

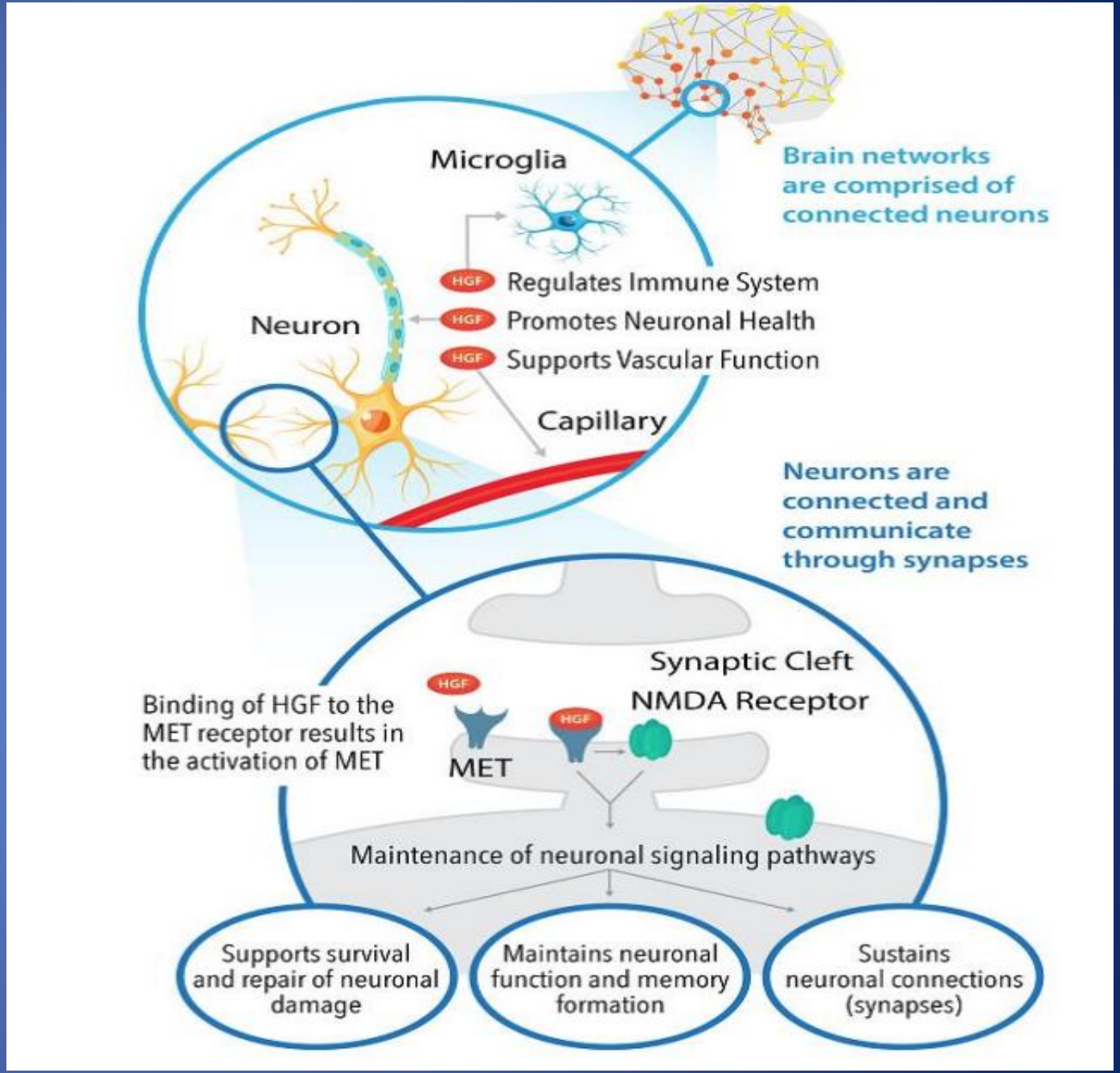
Site 151 – Hawaii Memory Ctr
MMSE 14-24

Regulates Neural Immunity and Inflammation

- ATH 1017 enhance HGF/MET (Hepatic Growth factor/ Receptor Tyrosine Kinase)

SQ Daily

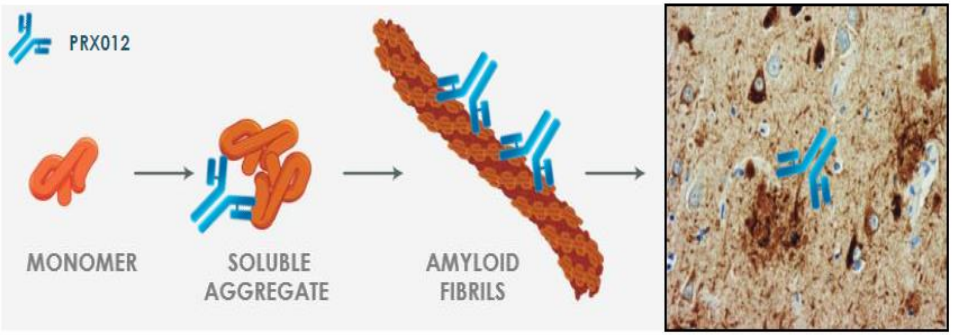
https://investors.athira.com/static-files/efb2f854-d09c-4fa0-9b49-a2ab56fe0585



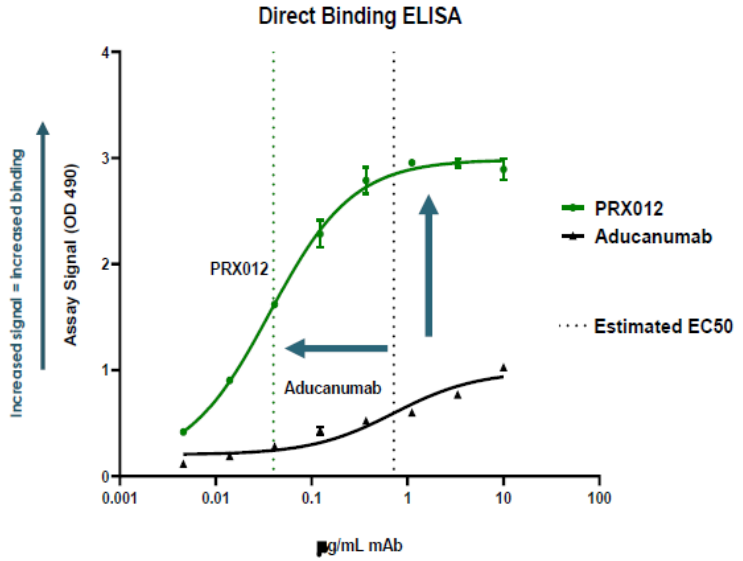
Ms Outer Island

- 67 yo Scientist working in Kona
- Do not want to Travel to Oahu every other week
- MMSE 27
- E3/E4
- MRI disproportional parietotemporal atrophy
- Biomarker: Amyloid + CSF

Phase 1-Next Generation Amyloid Target?
PRX 0012 -SQ Delivery , Site 01 – Hawaii Mem Ctr



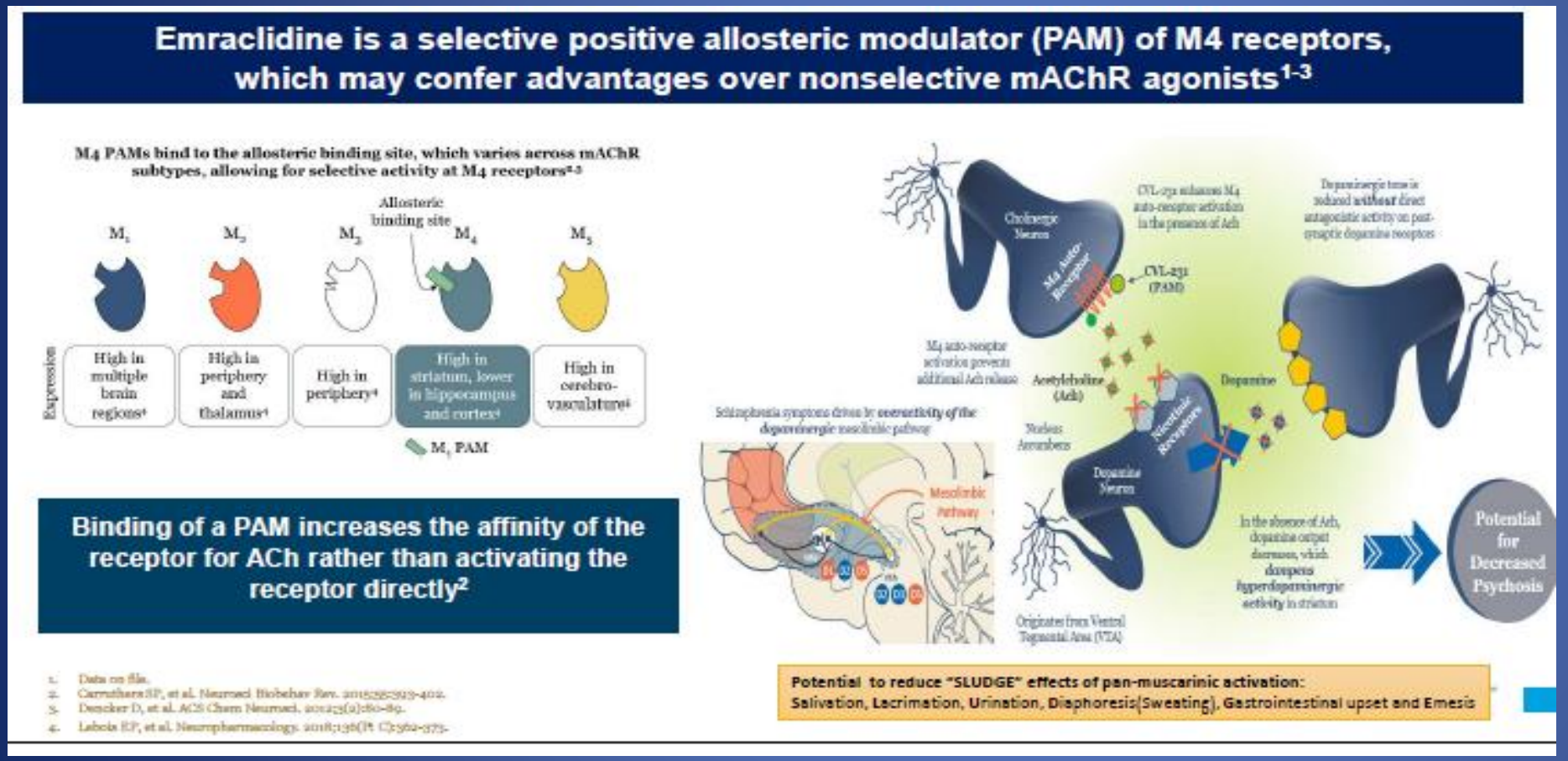
- PRX012 is a novel high affinity humanized immunoglobulin class G1 (IgG1) monoclonal antibody targetin at the N-terminus
- Evidence indicates that clearance of Aβ plaques is necessary to slow clinical decline in AD
- Neutralization of soluble aggregates might provide incremental efficacy, but is not sufficient (e.g., solanezumab, crenezumab)



Mr. Agitated

- 88 yo
- MMSE 15
- Prominent agitation symptoms
- Currently on Memantine

Phase 1, Randomized, Placebo-controlled Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of Emraclidine Following Multiple Oral Doses in Participants With Dementia Due to Alzheimer's Disease



Age 50-90

MMSE 8-26

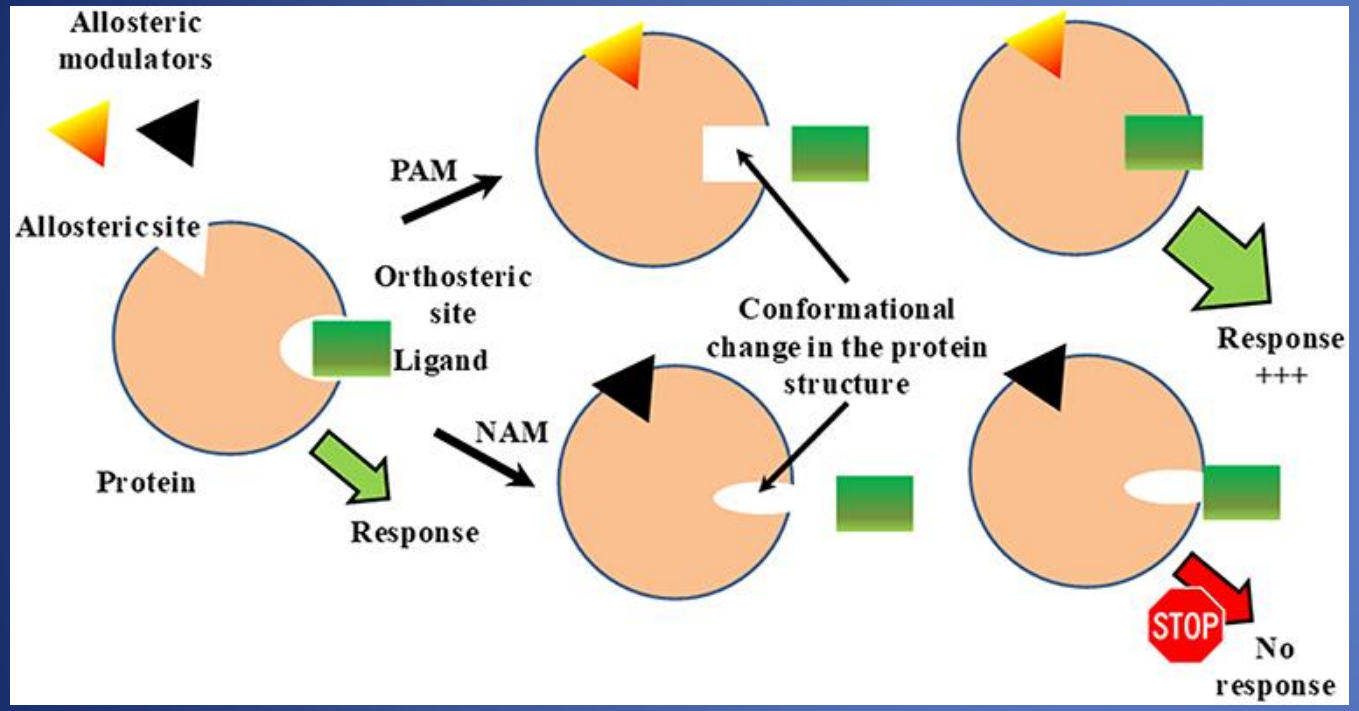
On Treatment with Cholinesterase inhibitor or memantine

Mrs Sleepy, Disinterested

- 77 yo female
- Lives at care facility
- Diagnosed with Alzheimer’s

- MMSE 20
- Disinterested
- Sleepy

Randomized, Double-Blinded Study to Evaluate the Efficacy and Safety of Mevidalen in Patients with Alzheimer's Disease



- Dopaminergic drug for PD, LBD & Sleepiness, Depression
- Positive Allosteric Modulator of D1 receptor
- Crosses Blood brain barrier
- Wake promoting

- Age 50-80
- MMSE 13-24

Summary

1. Lecanemab approved for MCI, Mild AD, MMSE > 22, Biomarker positive
2. Some patients may not be suitable and at higher risk for ARIA
    1. On anticoagulants,
    2. ApoE4E4
    3. MRI findings of Cerebral amyloid angiopathy
3. Consider other options
    1. Bioenergetics or Glucose metabolism
    2. Tau Targeting Therapies like ASO Therapies
    3. Synaptic Plasticity Therapies
    4. Next generation Amyloid Therapies
    5. Geared towards symptoms - agitation, sleepiness

MEMORY CTR

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Received: 14 March 2023 | Revised: 23 March 2023 | Accepted: 23 March 2023

DOI: 10.1002/trc2.12385

Alzheimer's & Dementia
Translational Research & Clinical Interventions

REVIEW ARTICLE

Alzheimer's disease drug development pipeline: 2023

Jeffrey Cummings[1,4] | Yadi Zhou[2] | Garam Lee[3] | Kate Zhong[1,4] | Jorge Fonseca[5] | Feixiong Cheng[2,5,6]

Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2023. Alzheimers Dement (N Y). 2023 May 25;9(2):e12385. doi: 10.1002/trc2.12385.

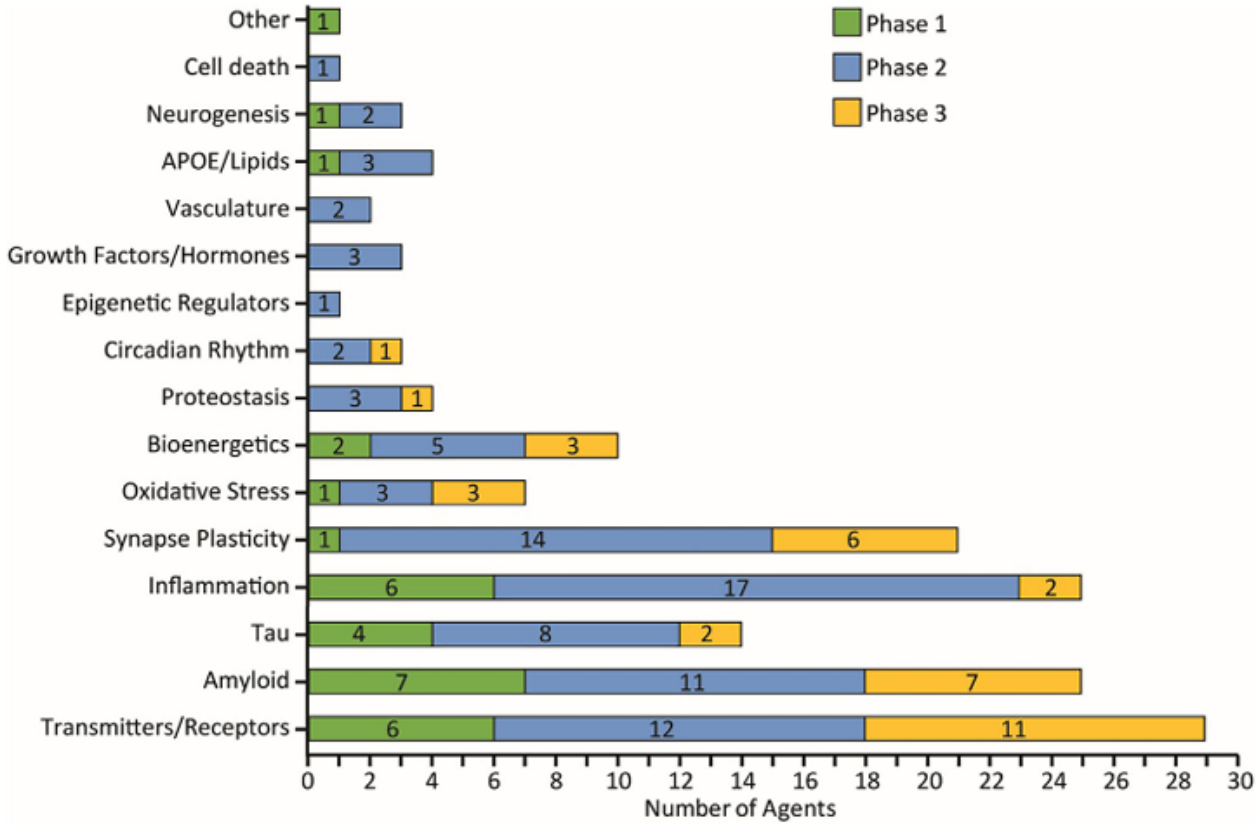

FIGURE 4 Mechanisms of action of all agents in all phases of clinical trials grouped according to the Common Alzheimer's Disease Research Ontology (CADRO). *APOE*, apolipoproein E. (Figure © J Cummings; M de la Flor, PhD, Illustrator).

Acknowledgements

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Clinical & Research Faculty

Kore Liow, MD, Neurology (Director)
Nicholas Anderson, MD, Sleep Medicine
Paul Smith, MD, Lifestyle Med. & Wellness
Darren Dugas, MD, Neurology
Natalia Gonzalez, MD, Neurology
Angeline Kim, MD, Neurology
Janette Abramowitz, MD, Neurology
Chris Larrinaga, MSN, ARNP-BC, Neurology
Nicole Evans, PA-C, Neurology
Qi Zhi, MPH, DNP, Neurology
Alice Smith, MD, Neuroradiology
Young Kim, MD, Neuroradiology
Shephard Kosut, MD, Radiology

BRITL (Brain Research, Innovation and Translation Lab) Research Students