Sorting out Myths & Facts
Alzheimer's New Treatments

Kore Liow, MD, FACP, FAAN

Director, Memory Disorders Center

Principal Investigator, Alzheimer's Research Unit

Neuroscience Chair, Hawaii Pacific Neuroscience

Clinical Professor of Medicine (Neurology),

Graduate Faculty, Clinical & Translational Research

University of Hawaii John Burns School of Medicine

kliow@hawaii.edu

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Editorial:

Guest Editor -Neurology International
Reviewer -Neurology, Clinical Practice,
American College of Physicians, etc

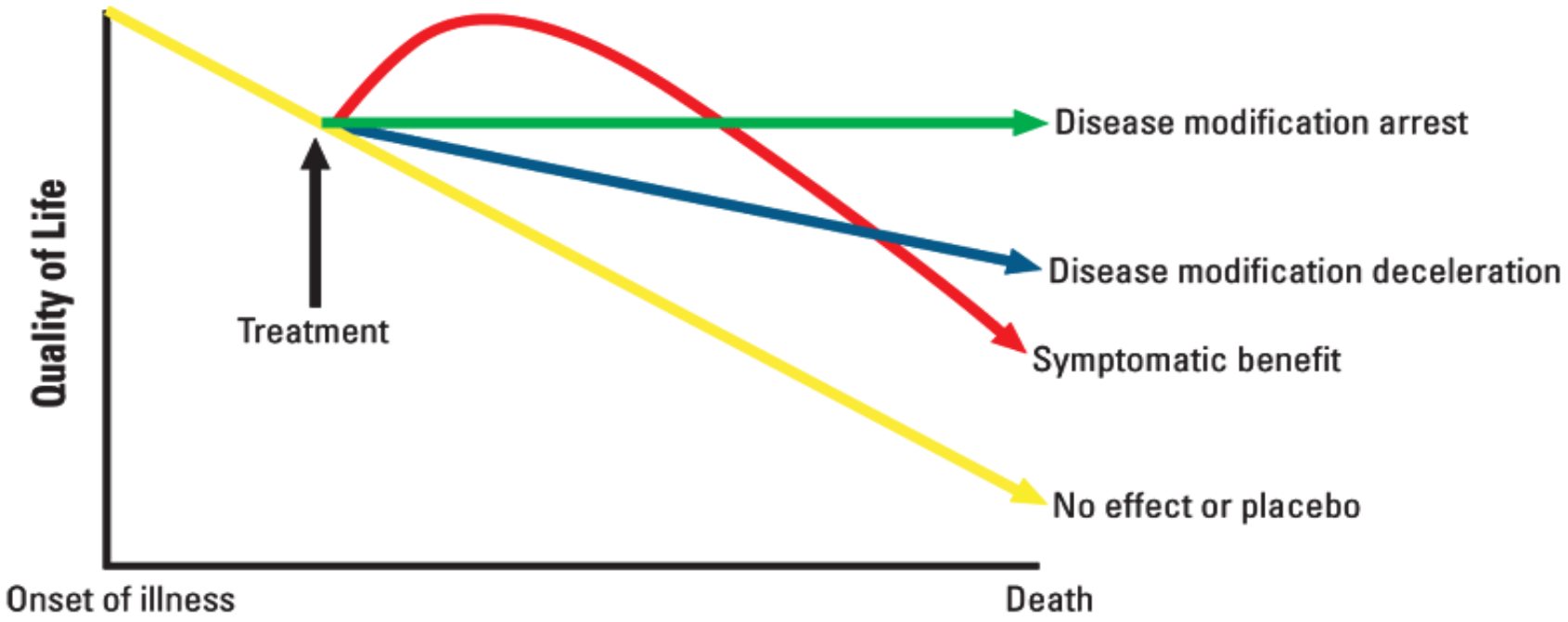
Objectives

1. What is Leqembi and how is it different from Aduhelm?
2. What do I need to know about ARIA?
3. Who is Leqembi indicated for and Who would NOT be suitable?
4. What are the barriers and challenges for developing better AD treatment?
5. What does the future look like?

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)

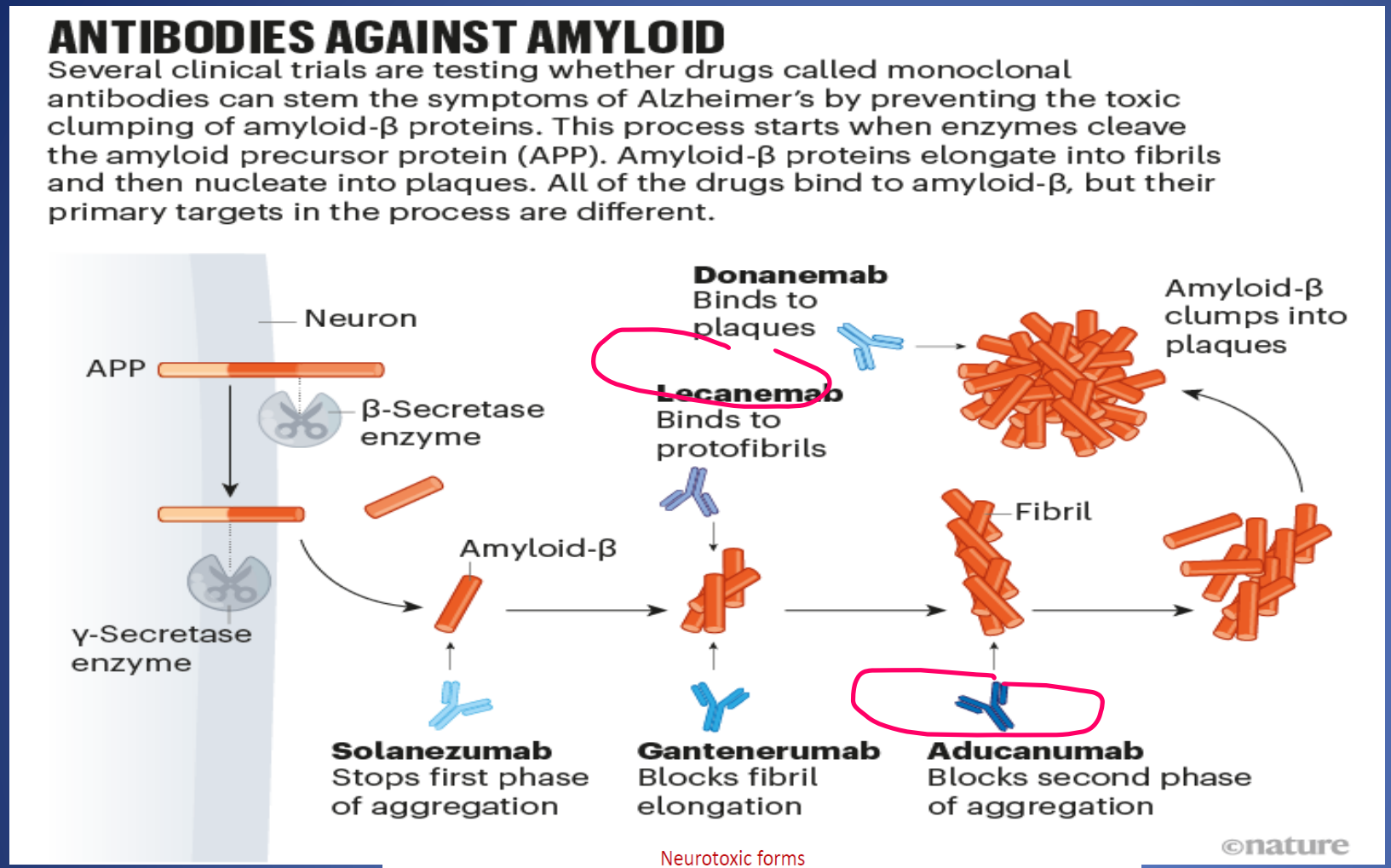
vs

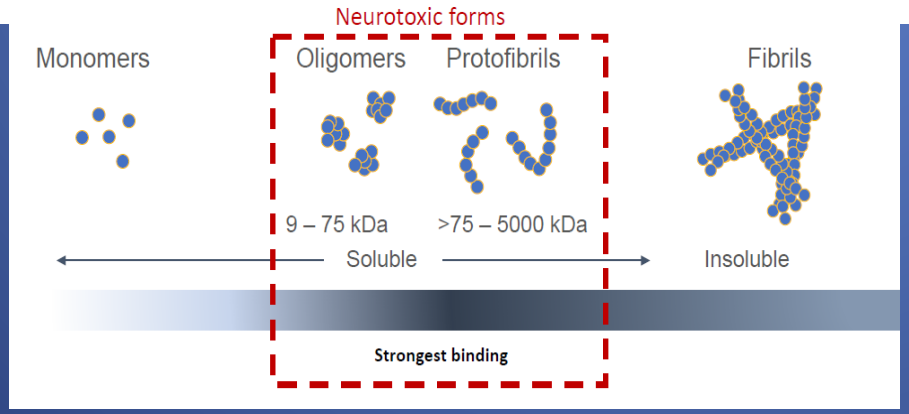
Symptomatic Treatments (Treat Symptoms)
Donepezil (Aricpet)
Rivastigmine (Exelon)
Galantamine (Razadyne)
Memantine (Namenda)
Namzaric (Combo)

FDA full approval July 6

What is Lecanemab?

How is it different from Aducanumab?





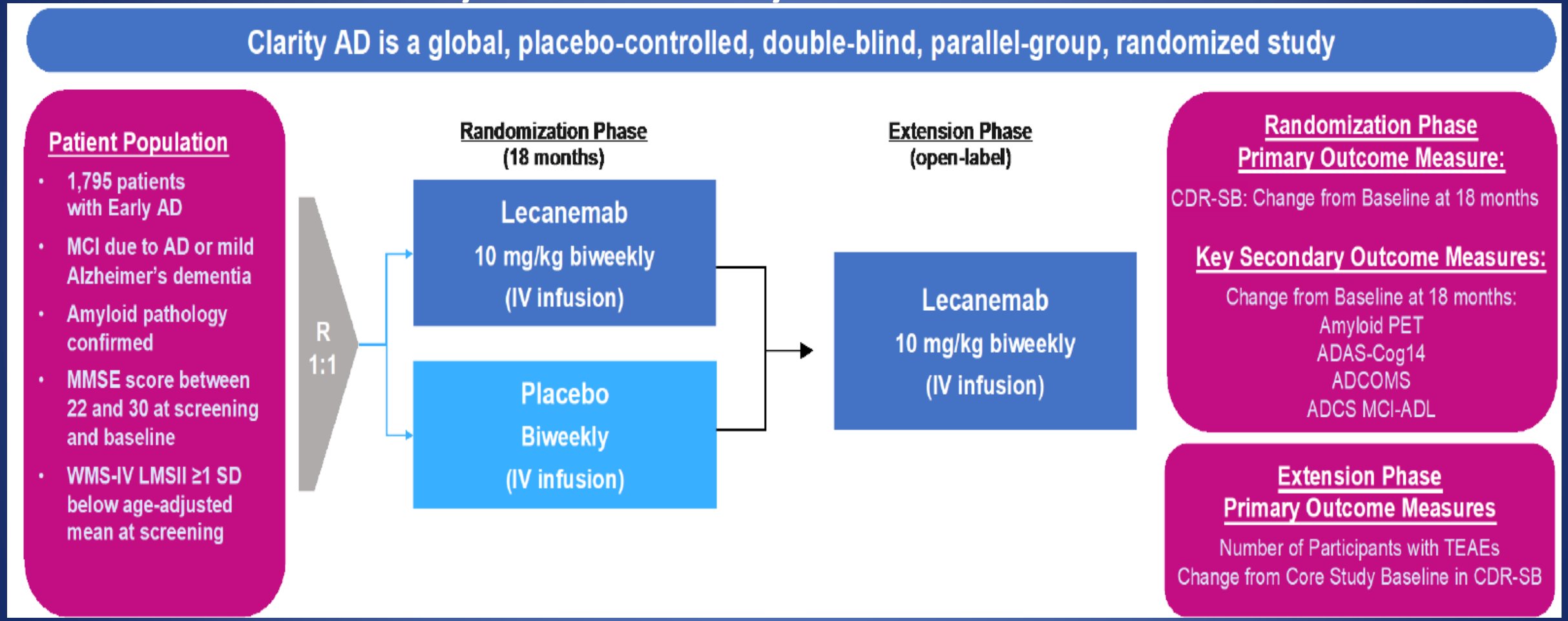
Monoclonal Antibody

Aducanumab (Aduhelm) 2021

Lecanemab (Leqembi) 2023

Credit: Nik Spencer/*Nature*

Lecanemab (Leqembi)
Phase 3 Clarity BAN Study - Site 2109 – HI Mem Ctr



Aducanumab (Aduhelm)
Phase 4 ENVISION Trial–Site 1005 – Hawaii Mem Ctr

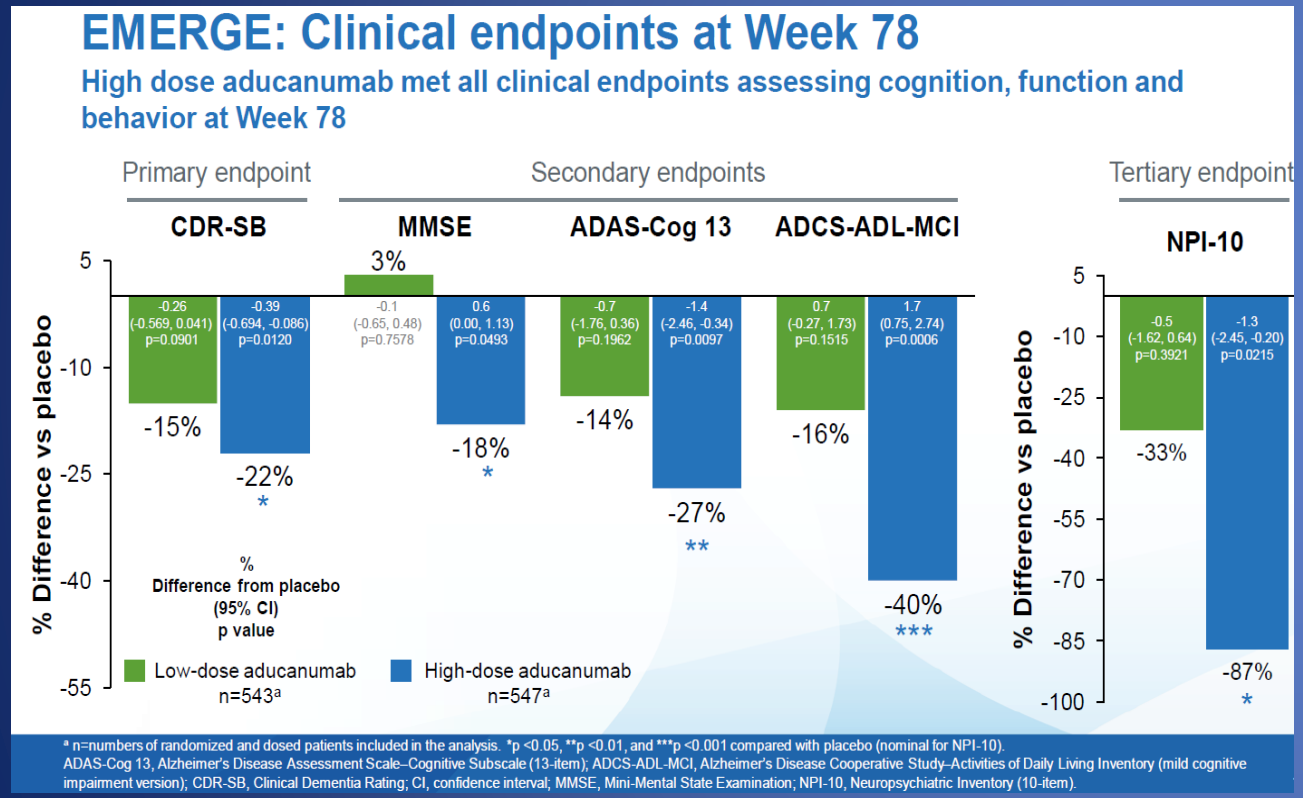
Aducanumab Phase 3 studies EMERGE and ENGAGE

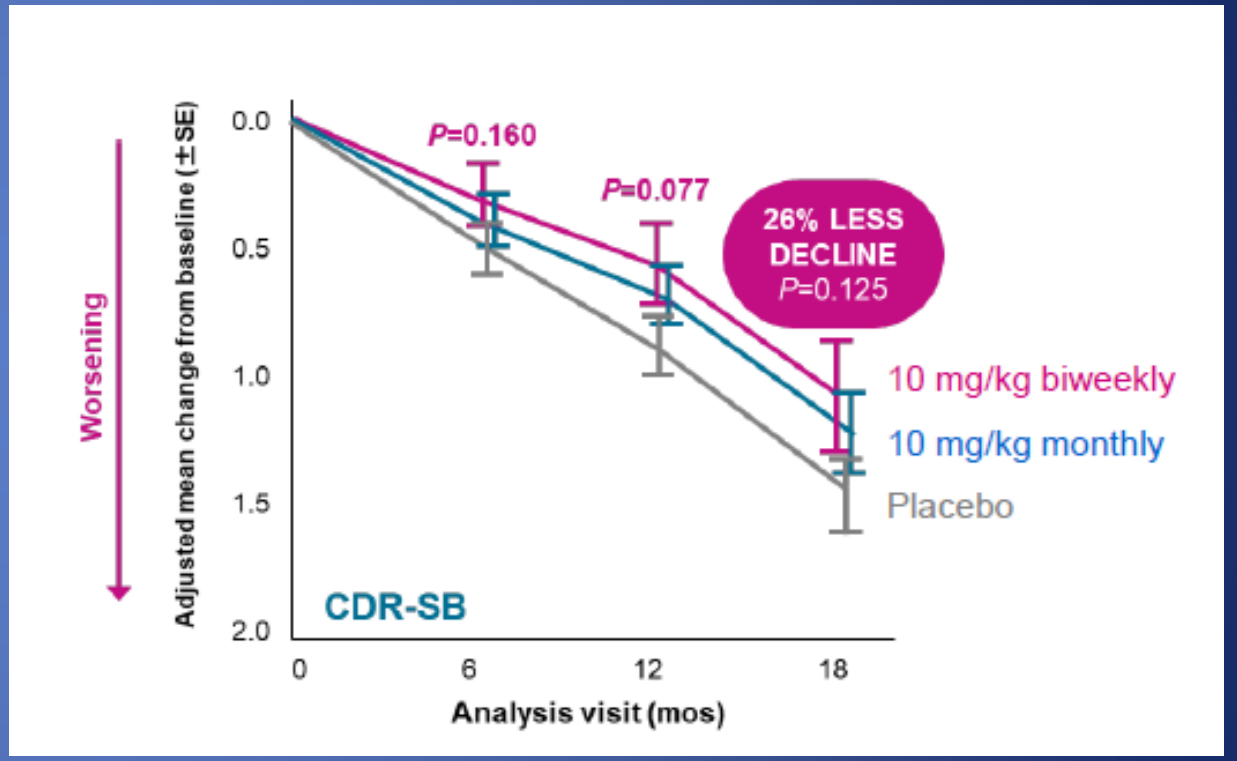
Studies	Two 18-month, randomized, double-blind, placebo-controlled, Phase 3 studies
Geography/ sample size	3285 patients at 348 sites in 20 countries
Population	▪ Early Alzheimer's disease (MCI due to Alzheimer's disease + mild Alzheimer's disease dementia) • MMSE 24-30, CDR-GS 0.5, RBANS DMI score ≤ 85 • Confirmed amyloid pathology
Doses	▪ Two dosing regimens (low and high dose) and placebo; randomized 1:1:1
Primary endpoint	▪ Change from baseline in CDR-SB score at 18 months
Other endpoints	▪ Secondary: MMSE, ADAS-Cog 13, ADCS-ADL-MCI ▪ Tertiary (efficacy): NPI-10 ▪ Sub-studies: amyloid PET, tau PET, CSF disease-related biomarkers

Countries with active sites included:
Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Japan, the Netherlands, Poland, Portugal, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States

What are the Results? Memory Improved?

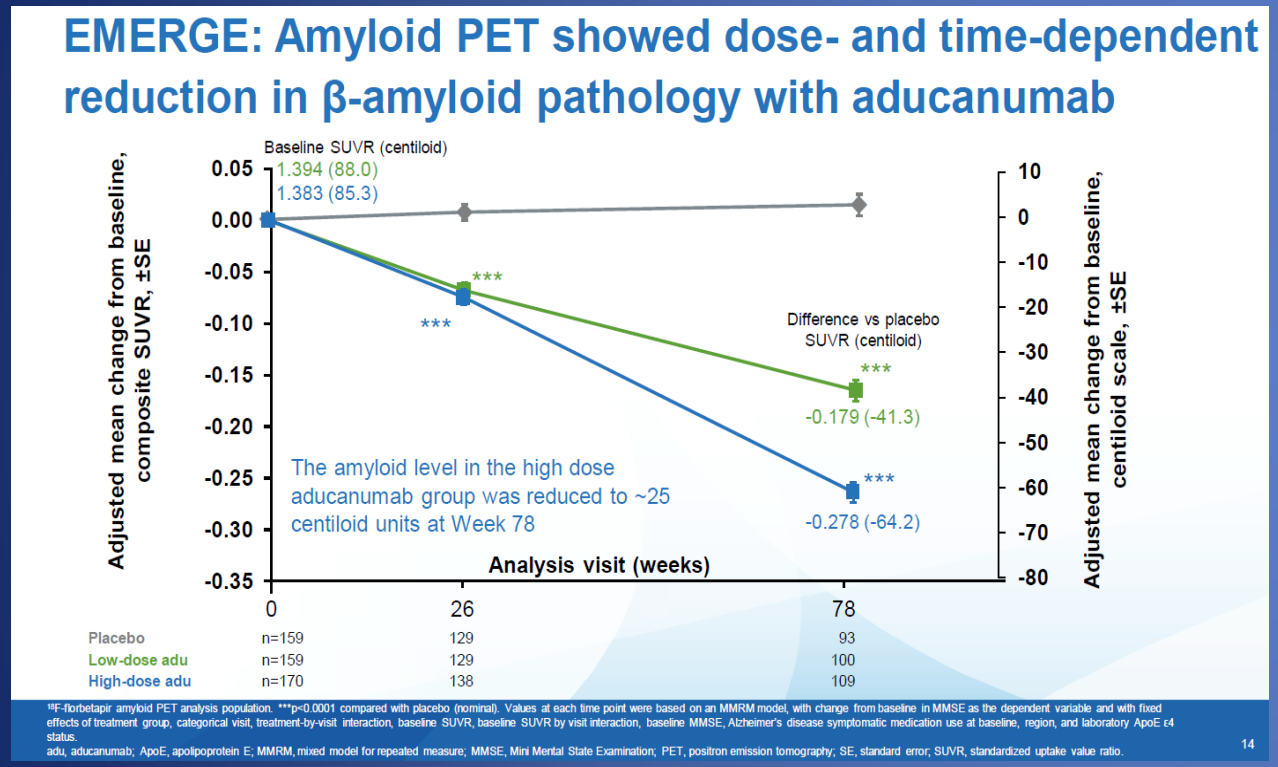
CDR-SB : Aducanumab 22%, Lecanemab 26%

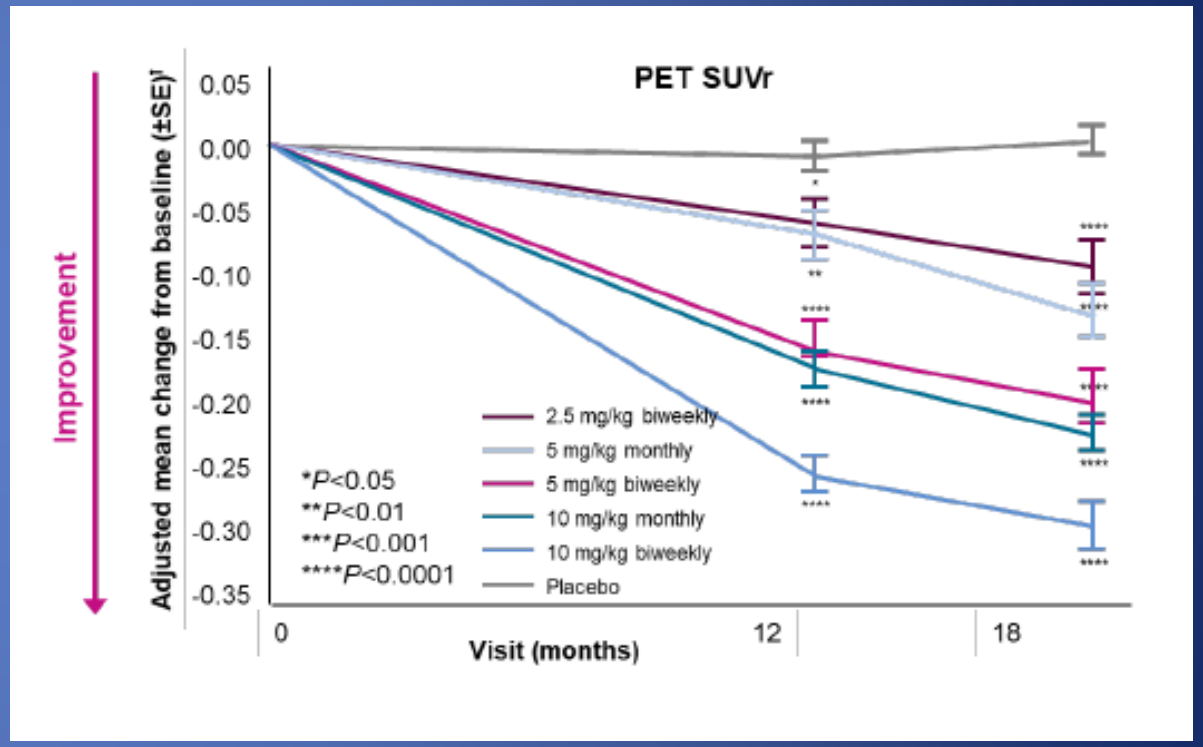




CDR Sum-of-Boxes score (CDR-SB), an 18-point scale measuring cognition (memory, orientation, judgment, and problem solving) and function (community affairs, home and hobbies, personal care)

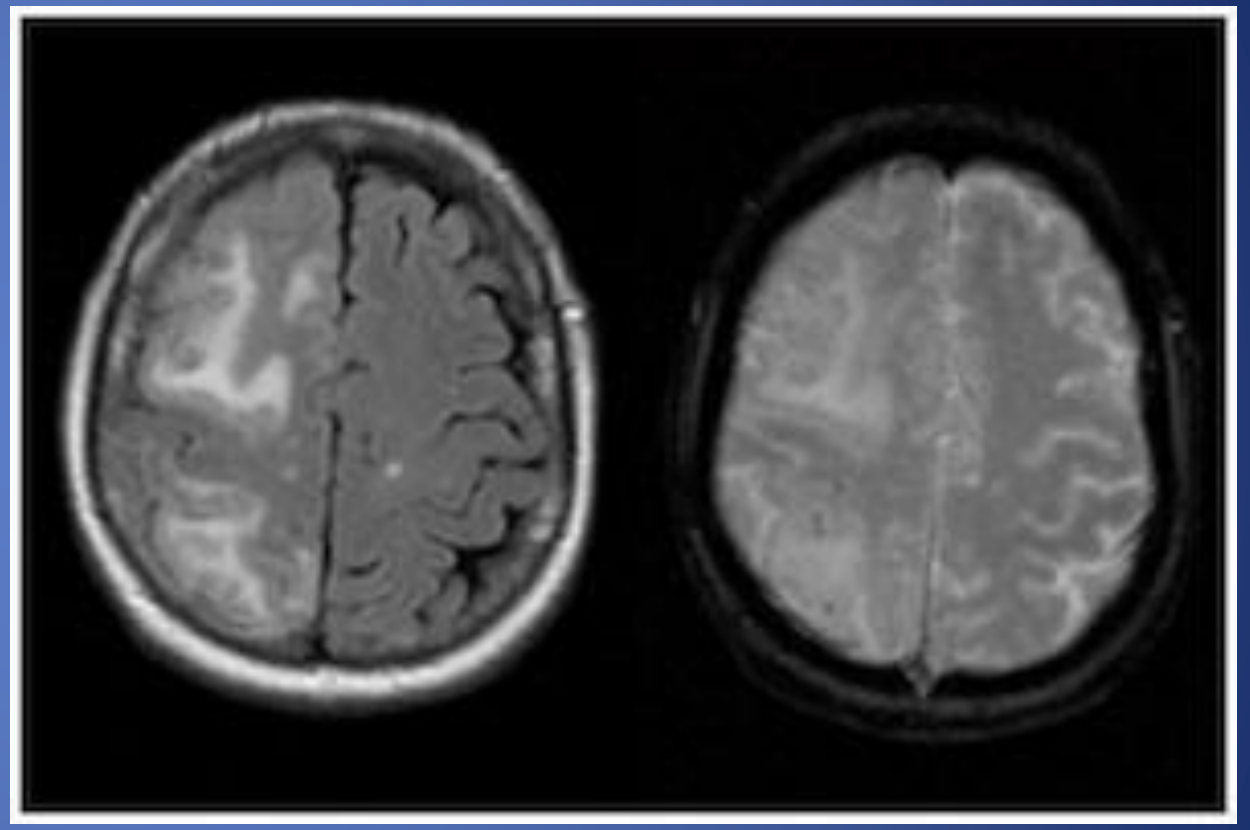
Does it work? Reduction in Amyloid Load Aducanumab 75%; Lecanemab 93%





ARIA

What do I need to know about ARIA (Amyloid Related Imaging Abnormality)?



Is it Safe? What are the Side Effects - ARIA Aducanumab 28% vs Lecanemab 17%

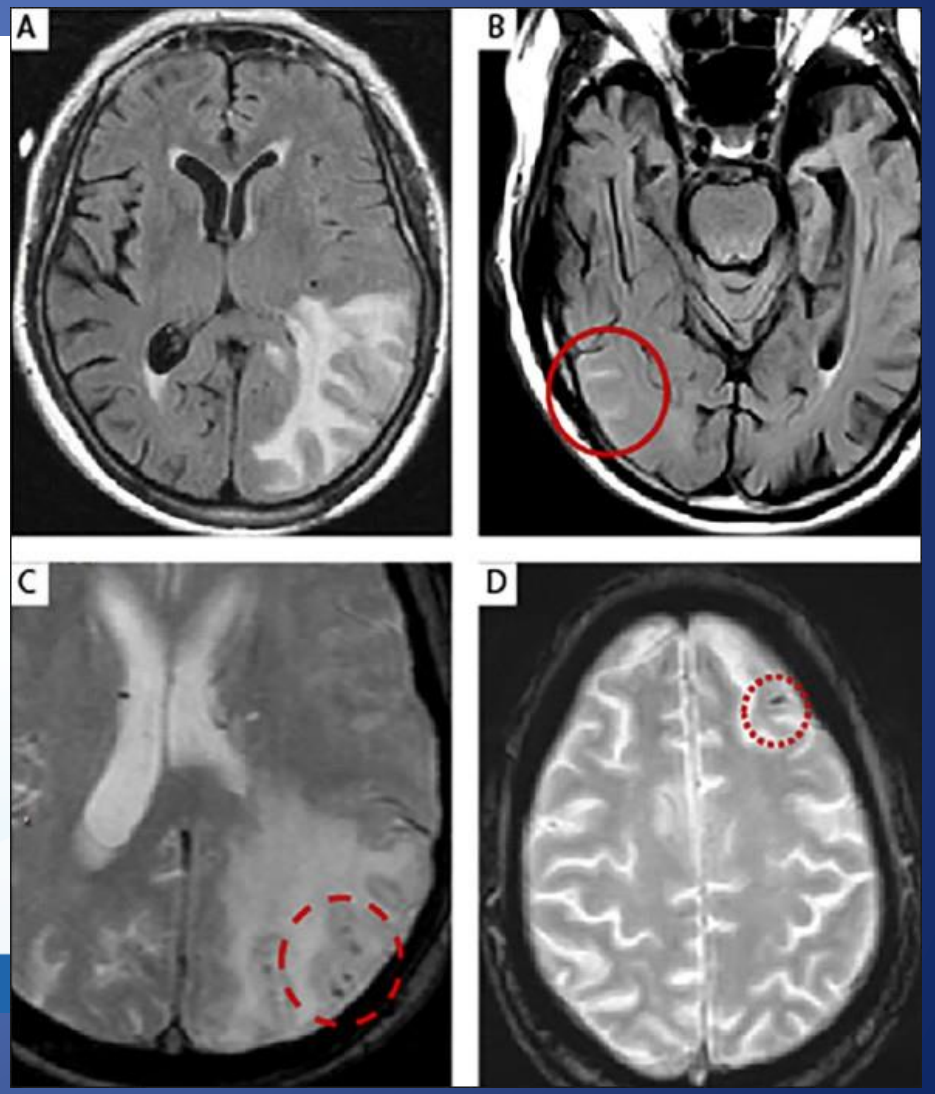
Amyloid-related imaging abnormalities (ARIA)

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

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) (%)	?	?	?	?

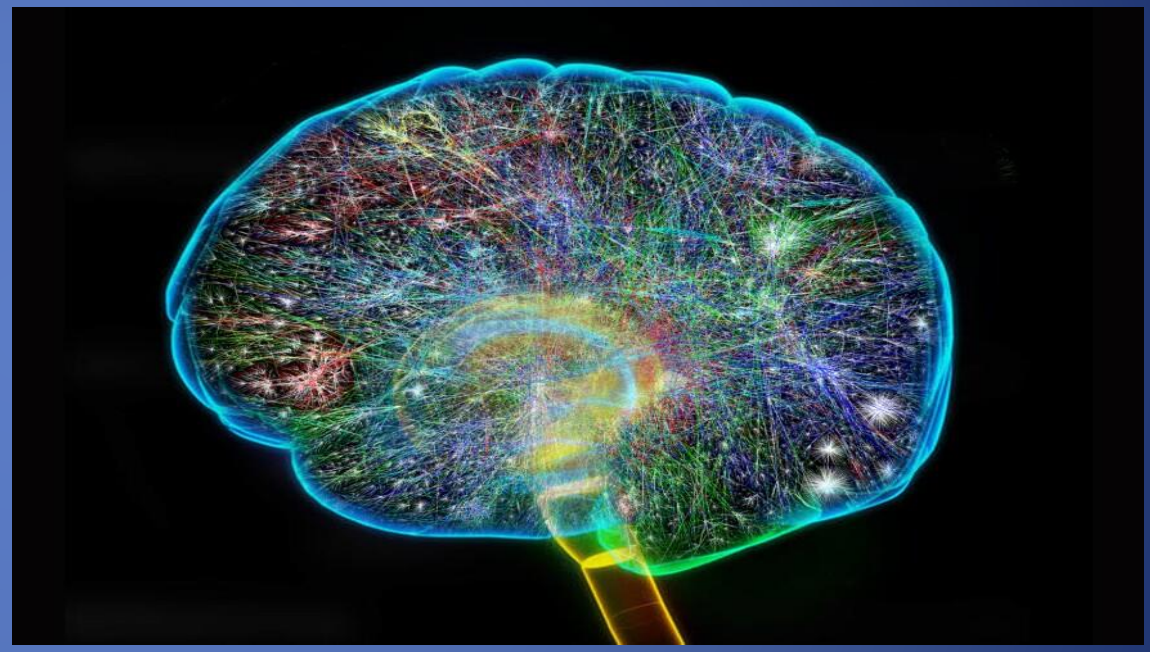
Signs/symptoms of ARIA by antibody ranked by incidence. Incidence is presented as a percentage of symptomatic patients within the total number of patients with the observation of ARIA. [?] indicates data not available.

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.

Case Studies

Who is Lecanemab indicated for

Who would NOT be suitable?



INDICATION

- LEQEMBI is indicated for the treatment of Alzheimer's disease. Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. (MMSE 22 and above)

Uncle Waikiki

- 71 retired Chinese engineer
- Hypertension
- Prediabetic

- Memory Loss since age 68
- Still active and travels
- Family history of AD in mother & older brother

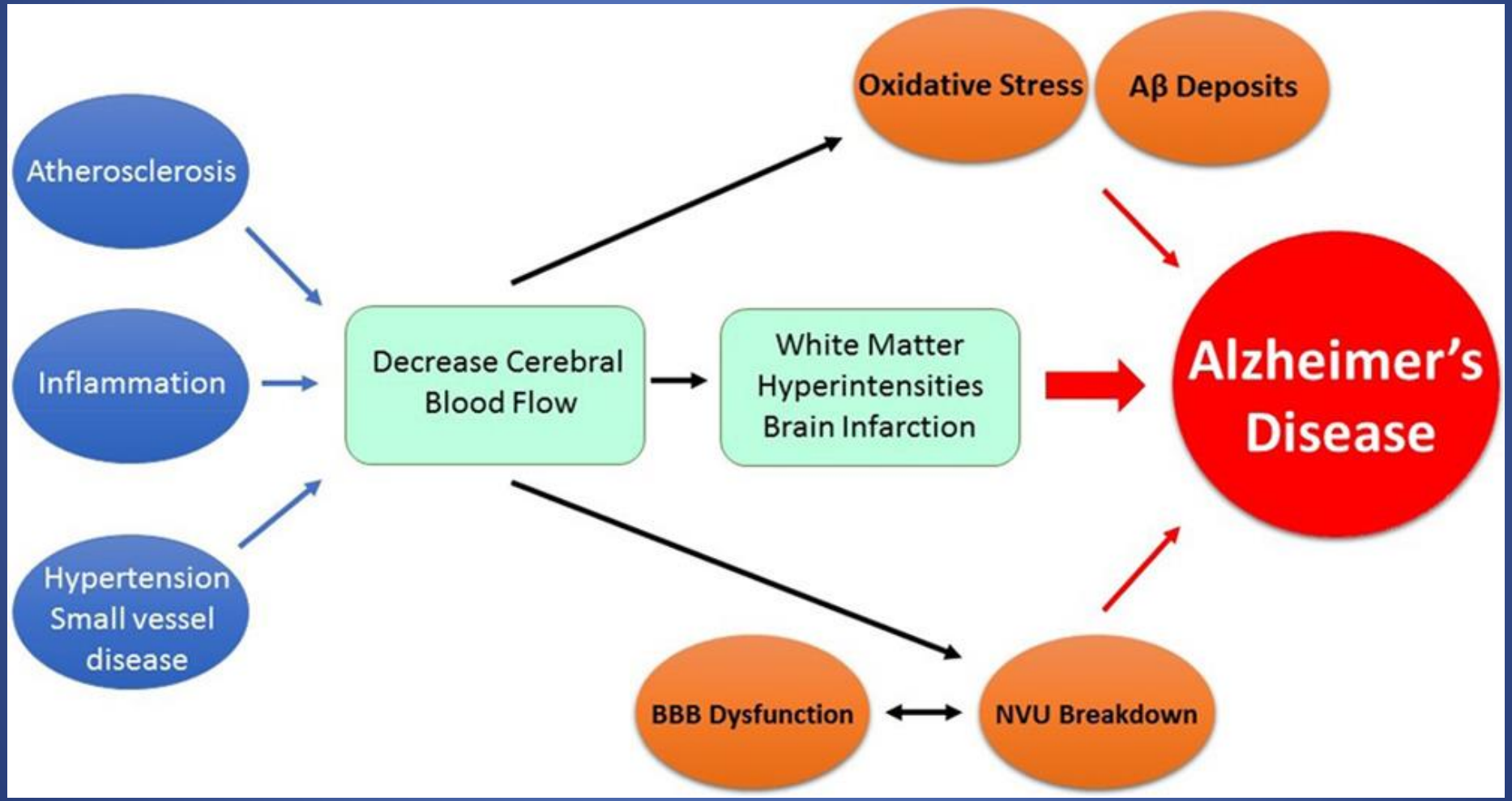
MMSE 23

E4/E4

MRI noted

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

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

Metabolism - Bioenergetics Pathway

Glucose Metabolism – Link with Cognitive Function

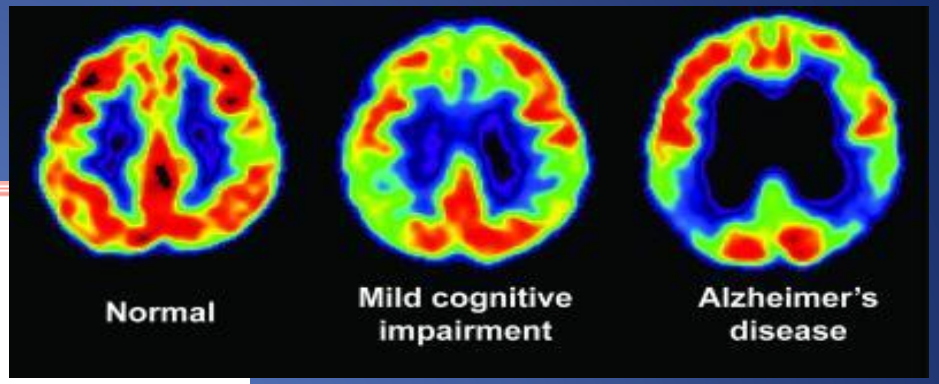
- Diabetics Have 2-Fold Increased Risk of Getting AD
- Almost 70% of diabetics ultimately develop AD
- 37% of AD Patients are Diabetic (vs. 9.4% General Population)

- Multiple Similarities of AD & Type 2 Diabetes: The Common Theme is Insulin Resistance
  - Cognitive Decline
  - Neurodegeneration
  - Amyloid Aggregation and Deposition
  - Inflammation

- Clinical Symptoms of AD Do Not Occur Without Decrea

- Association: Elevated Blood Sugar > Memory Problems

Nguyen TKO, Nguyen TTD, Giau VV. Type 3 Diabetes and Its Role Implications in Alz
30;21(9):3165



NIH Funded Phase 2 T3D (Type 3 Diabetes) PIONEER Study Site 164 – Hawaii Memory Ctr

T3D-959: A Unique Dual PPAR Agonist to Restore Brain Metabolism

Primary Target is PPARδ (delta), (peroxisome proliferator-activated receptor)
Secondary Target is PPARγ (gamma)

- PPARδ (energy expenditure) and PPARγ (energy storage) are master regulators of metabolic homeostasis
- Unique PPAR selectivity > distinctive activity profile > central regulator of both glucose and lipid metabolism
- Only drug in development for AD with PPARδ as a primary target, a target found throughout the brain
- Optimal dosing: Orally delivered as a once-a-day capsule
- Accesses the brain – penetrating the blood brain barrier
- Excellent safety profile

Mr. Kona

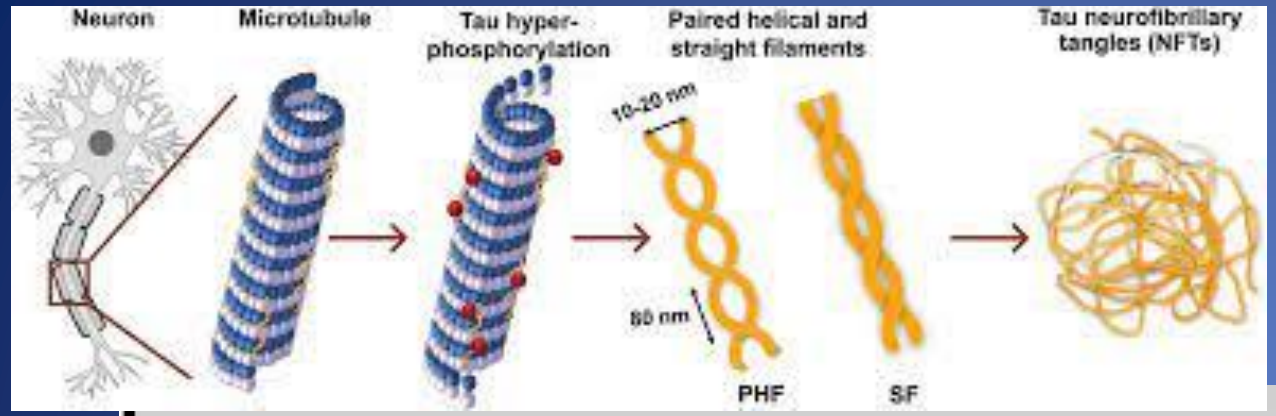
- 66 yo retired reporter from Oregon now lives in Kona
- Travels quite a bit and just got back from a cruise with wife

- History of DVT while flying
- Takes Xarelto when travelling
- Family history: None

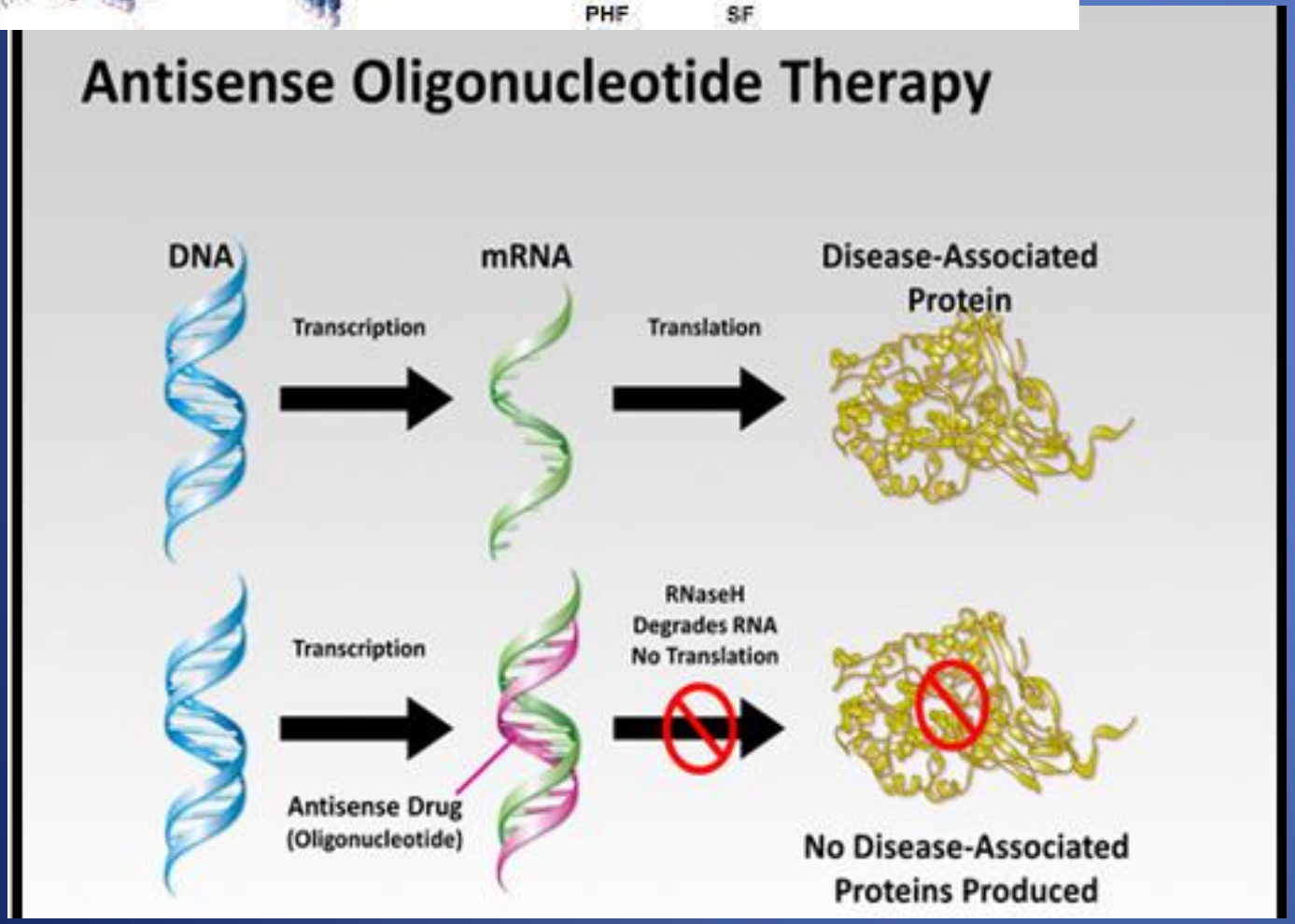
- MMSE 25
- E2/E3

- MRI disproportional atrophy

- Does not want to have IV Infusion every 2 weeks



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

Auntie Kapolei

- 83 yo retired Japanese Teacher
- Forgetful since age 77
- Asking same questions again and again
- Brought in by family
- Denies any issues

- FH: AD in mother and father

- MMSE 18
- E2/E2
- MRI: Significant diffuse cortical atrophy - medial temporal

NIH Funded Phase 2 ATH 1017 Synaptic Plasticity

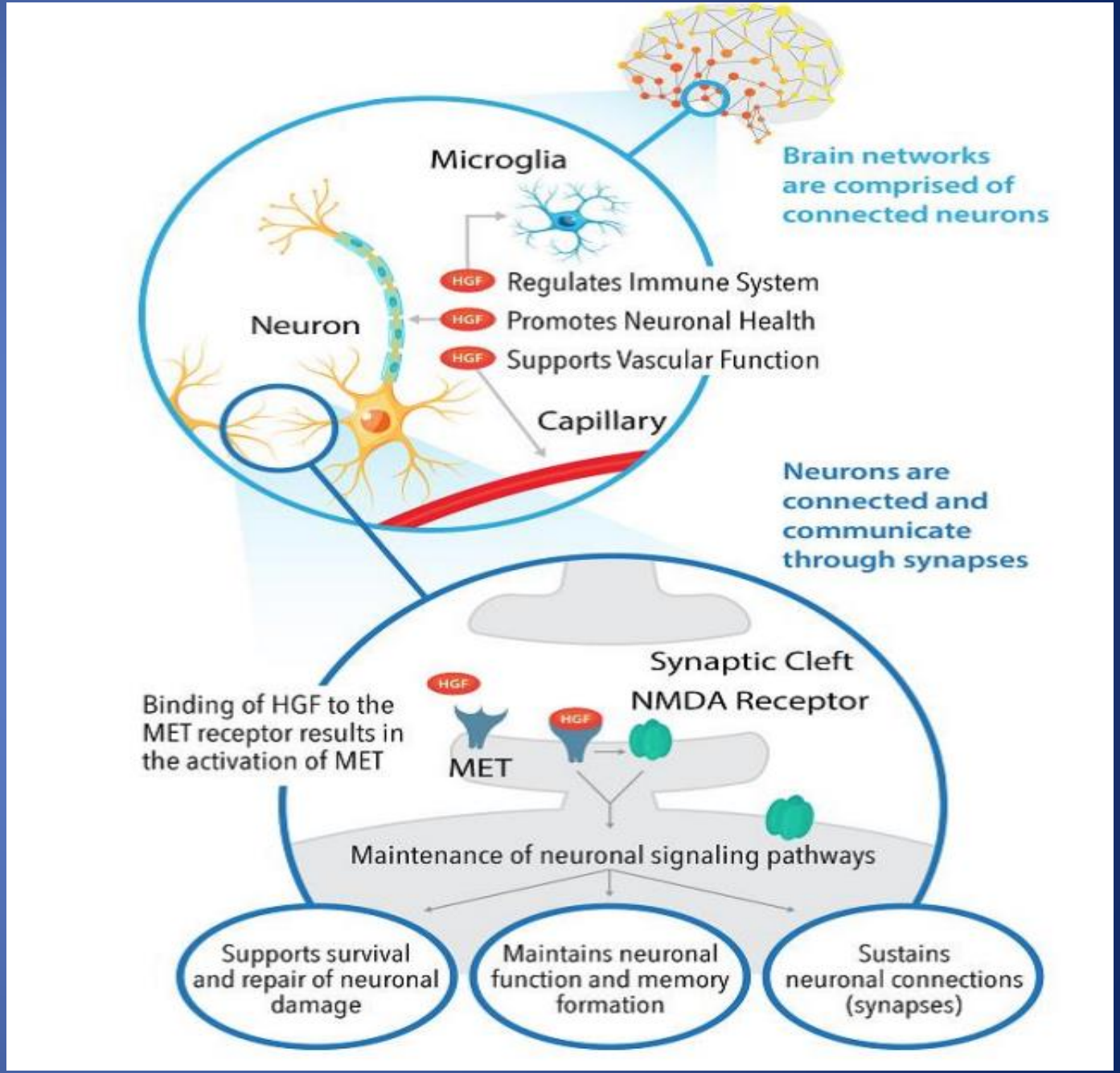
Site 151 – Hawaii Memory Ctr
MMSE 14-24

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



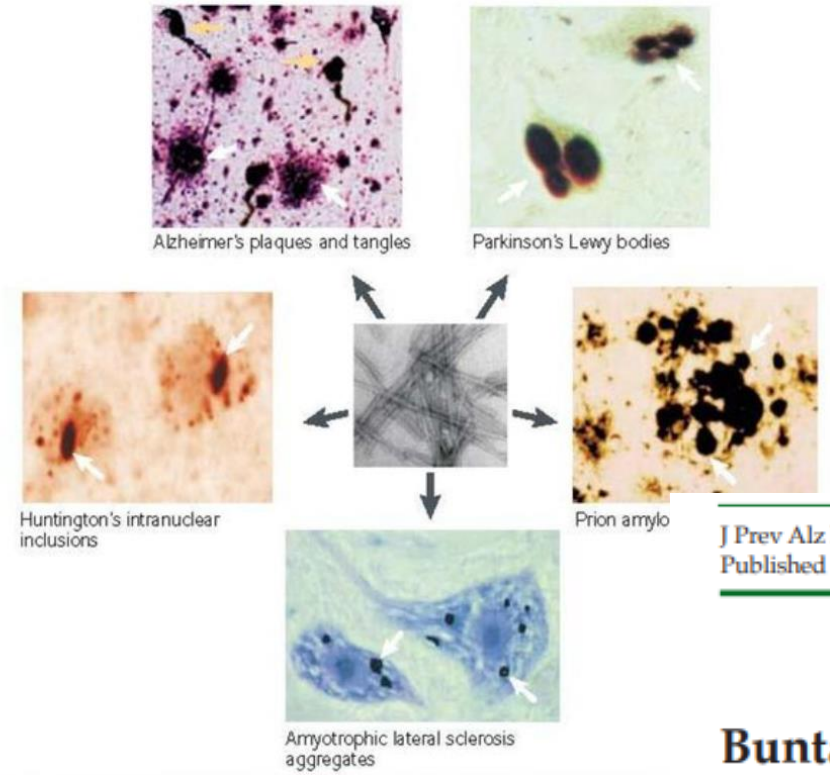
Uncle Waimanalo

- 75 Hawaiian retired Farmer
- Forgetful since age 73
- Cannot recall recent events or conversations
- Brought in by 2 sons and 2 daughters

- MMSE 23
- E3/E3
- MRI: Significant hippocampal and temporal atrophy

- Not interested in
  - anything invasive or “needles” and
  - “would rather go fishing & surfing than see me every 2 weeks”

Common Behavior of Neurotoxic Aggregating Proteins



AD: plaques and tangles

PD: Lewy bodies

HD: Huntingtin inclusions

TSE: prion amyloid plaque

Annovis Phase 2 Buntanetap
Site 124 – Hawaii Memory Ctr
Mild to Mod AD
MMSE 14-24
PO Daily

J Prev Alz Dis 2022;
Published online October 11, 2022, http://dx.doi.org/10.14283/jpad.2022.84

Original Research

Buntanetap, a Novel Translational Inhibitor of Multiple Neurotoxic Proteins, Proves to Be Safe and Promising in Both Alzheimer's and Parkinson's Patients

C. Fang[1], P. Hernandez[2], K. Liow[3], E. Damiano[1], H. Zetterberg[4,5], K. Blennow[4,5], D. Feng[6], M. Chen[6], M. Maccecchini[1]

1. Annovis Bio, Berwyn, PA, USA; 2. EZY Medical Research, Miami, FL, USA; 3. University of Hawaii, HI, USA; 4. University of Gothenburg, Sweden; 5. Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden; 6. TCM, NJ, USA

Corresponding Author: Cheng Fang, 1055 Westlakes Dr #300, Annovis Bio, Berwyn, PA, USA fang@annovisbio.com phone # 610-727-3987

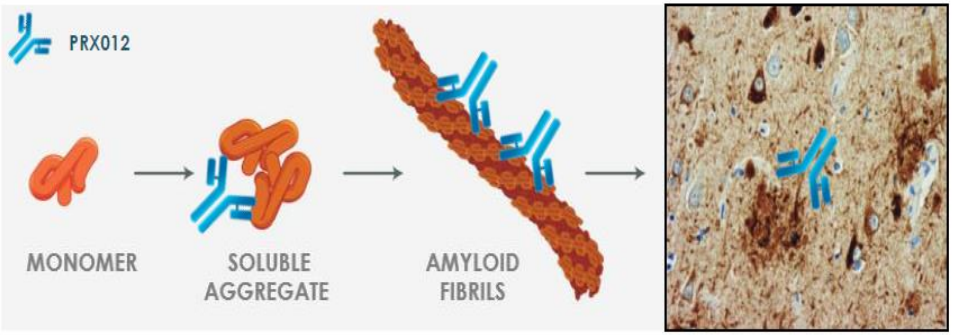
Ms Marhsall Island

- 67 yo Scientist working on Marshall island
- Lives on island 2-3 months at a time
- Cognitive decline since age 60
- Strong Family history of AD

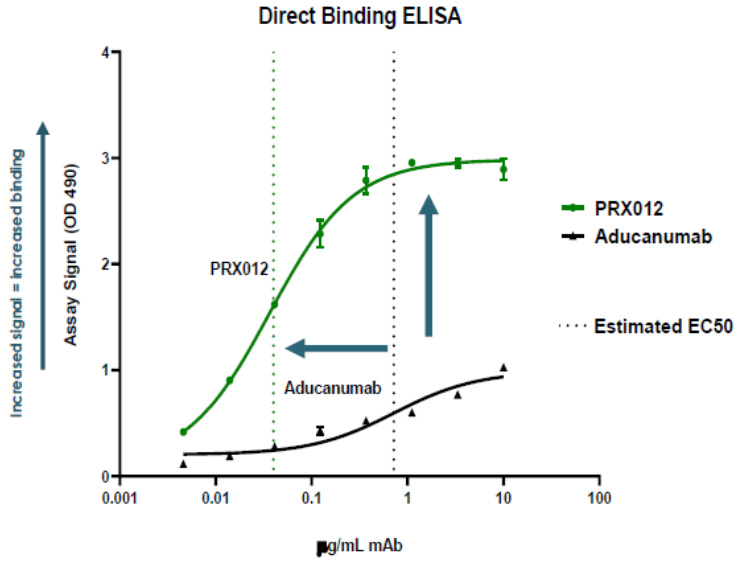
- MMSE 27
- E3/E4

- MRI disproportional parietotemporal atrophy
- Biomarker: Amyloid + CSF

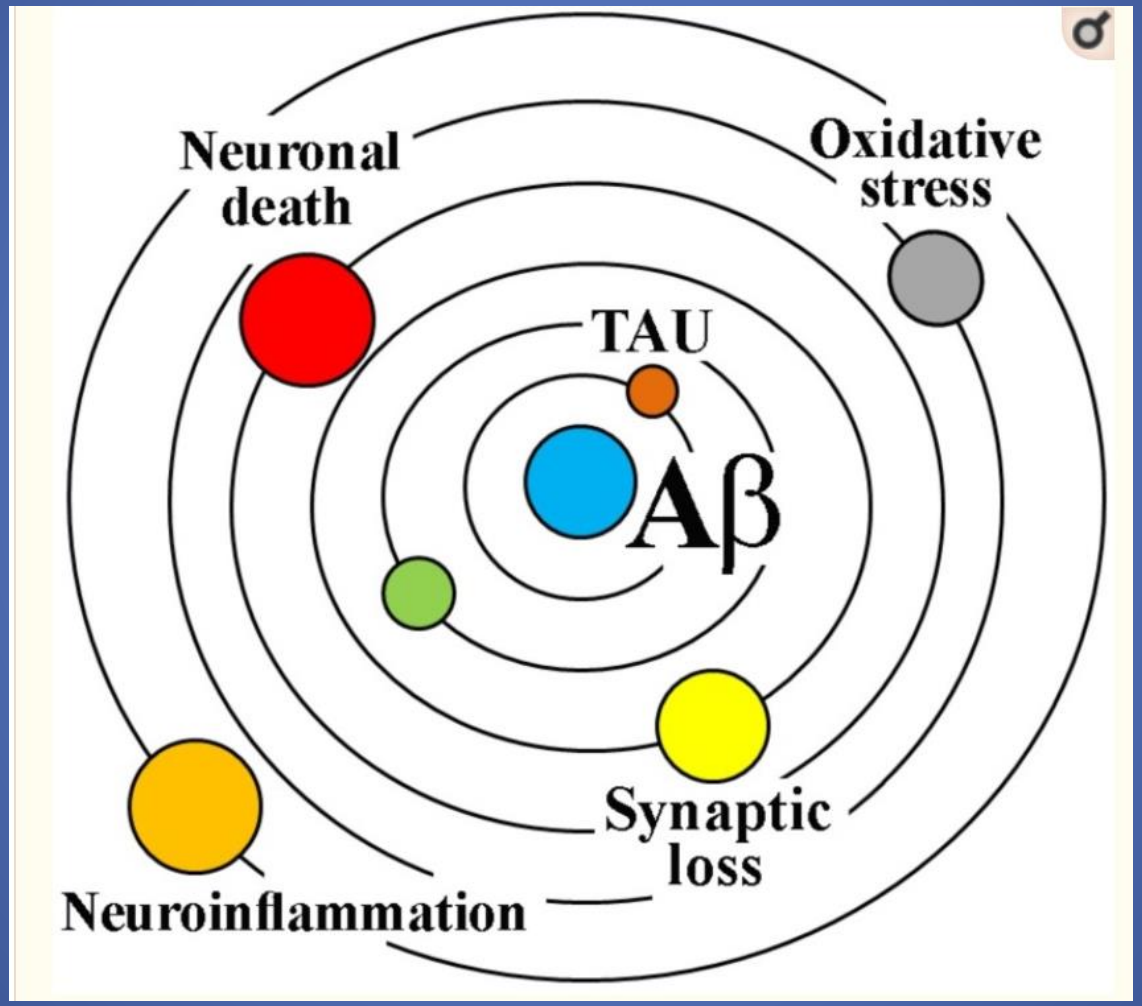
Phase 1-Next Generation Amyloid Target?
PRX 0012 -SQ Delivery , Site 01 – Hawaii Mem Ctr



- 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)



Amyloidocentric Theory of AD?



Ricciarelli R, Fedele E. The Amyloid Cascade Hypothesis in Alzheimer's Disease: It's Time to Change Our Mind. *Curr Neuropharmacol*. 2017;15(6):926-935.

alzheimer's association | Alzheimer's & Dementia Translational Research & Clinical Interventions

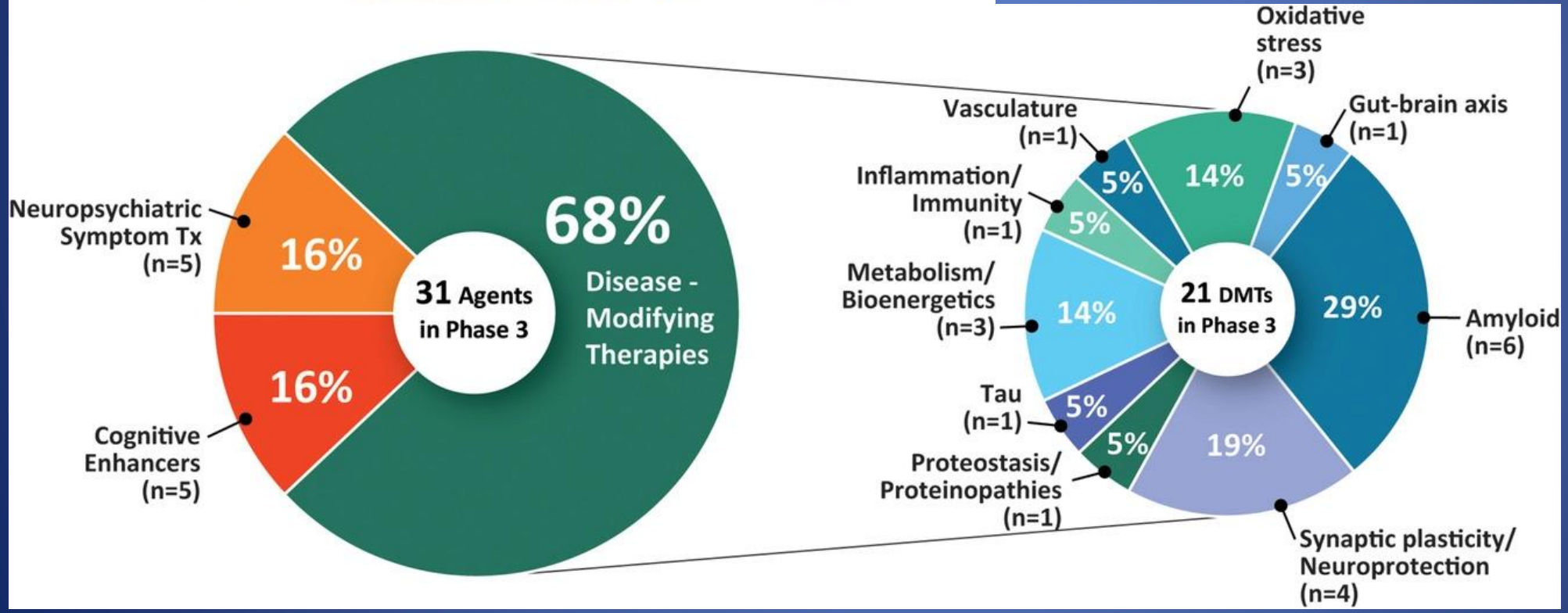
REVIEW ARTICLE | Open Access

Alzheimer's disease drug development pipeline: 2022

Jeffrey Cummings, Garam Lee, Pouyan Nahed, Mina Esmail Zadeh Nojoo Kambar, Kate Zhong, Jorge Fonseca, Kazem Taghva

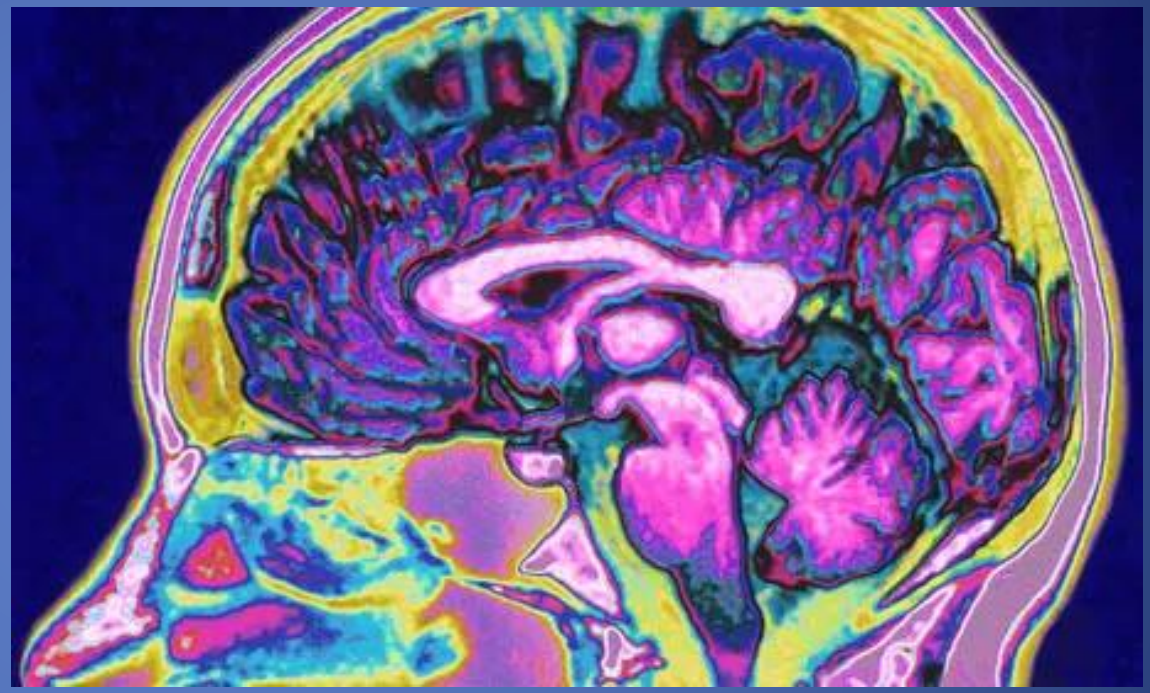
First published: 04 May 2022 | https://doi.org/10.1002/trc2.12295 | Citations: 3

- What are my Options?
- What's in the Pipeline?



Discussion & Local Research

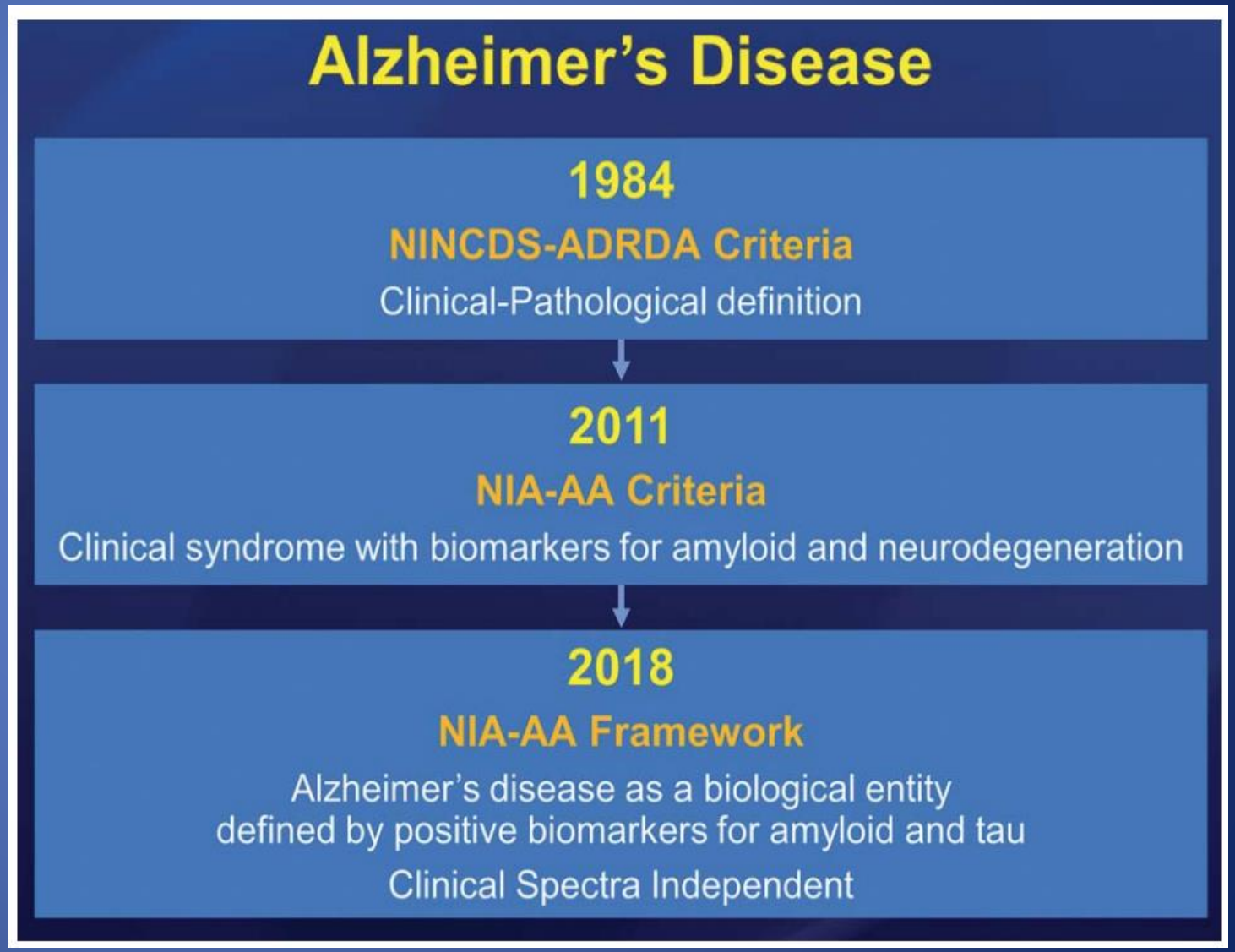
What are the barriers and challenges for developing better AD treatment?



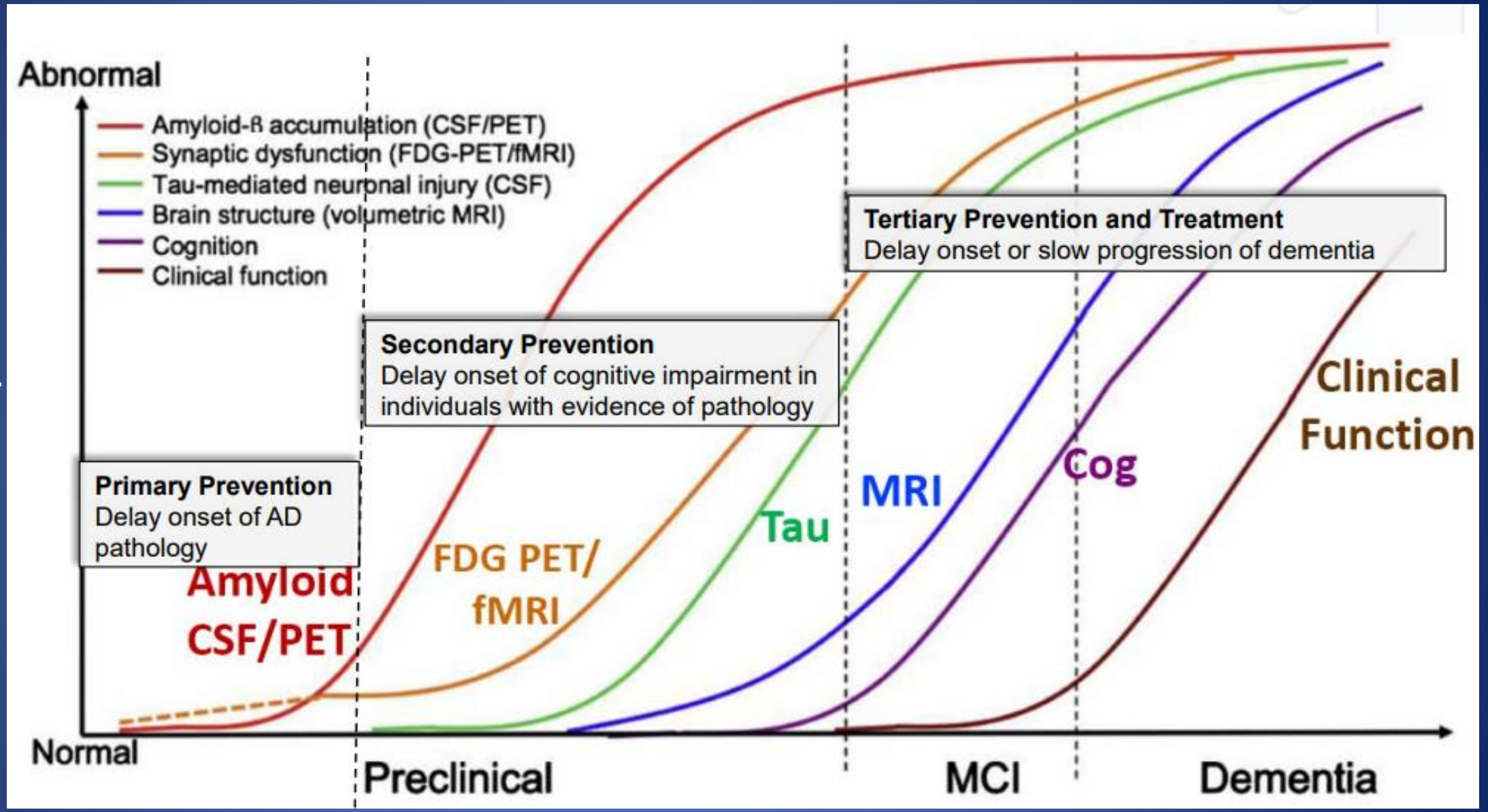
Paradigm Shift in AD Approach

In the last decade, the research definition of AD has moved from a clinical to a more biological Paradigm using biomarkers,

…… independent of clinical spectra



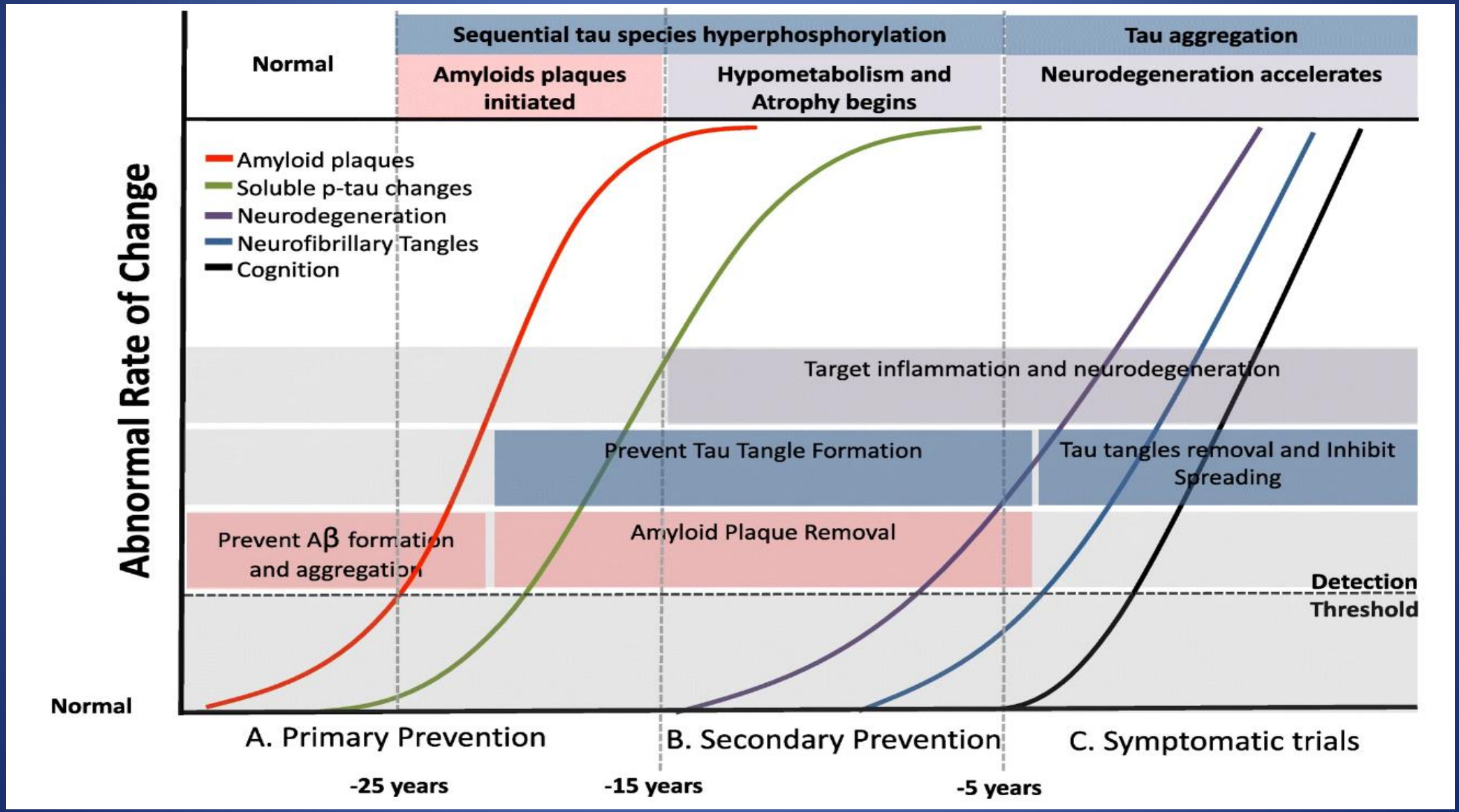
Biomarker - Game changer



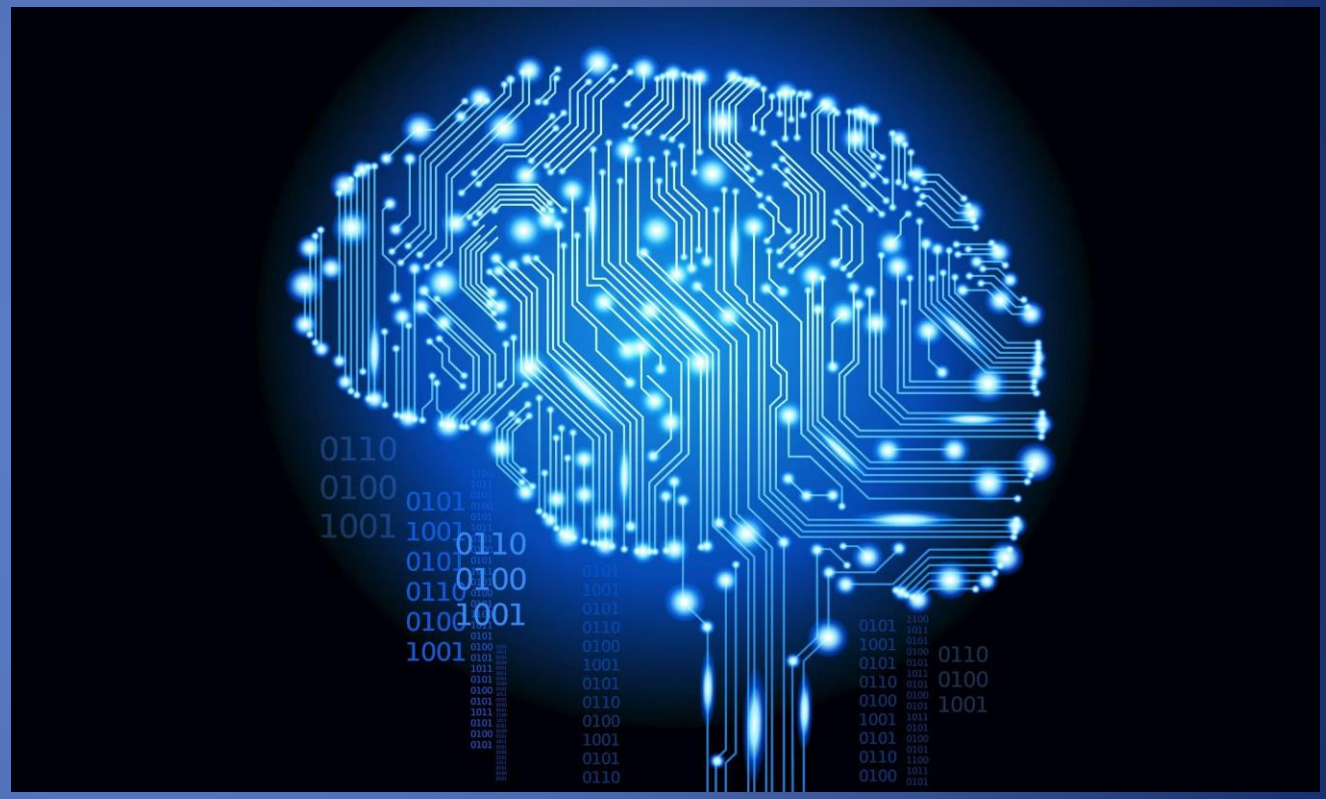
Spatial Patterns of Neuroimaging Biomarker Change in ADAD in DIAN
Brian Gordon. Lancet Neurology Jan 2018

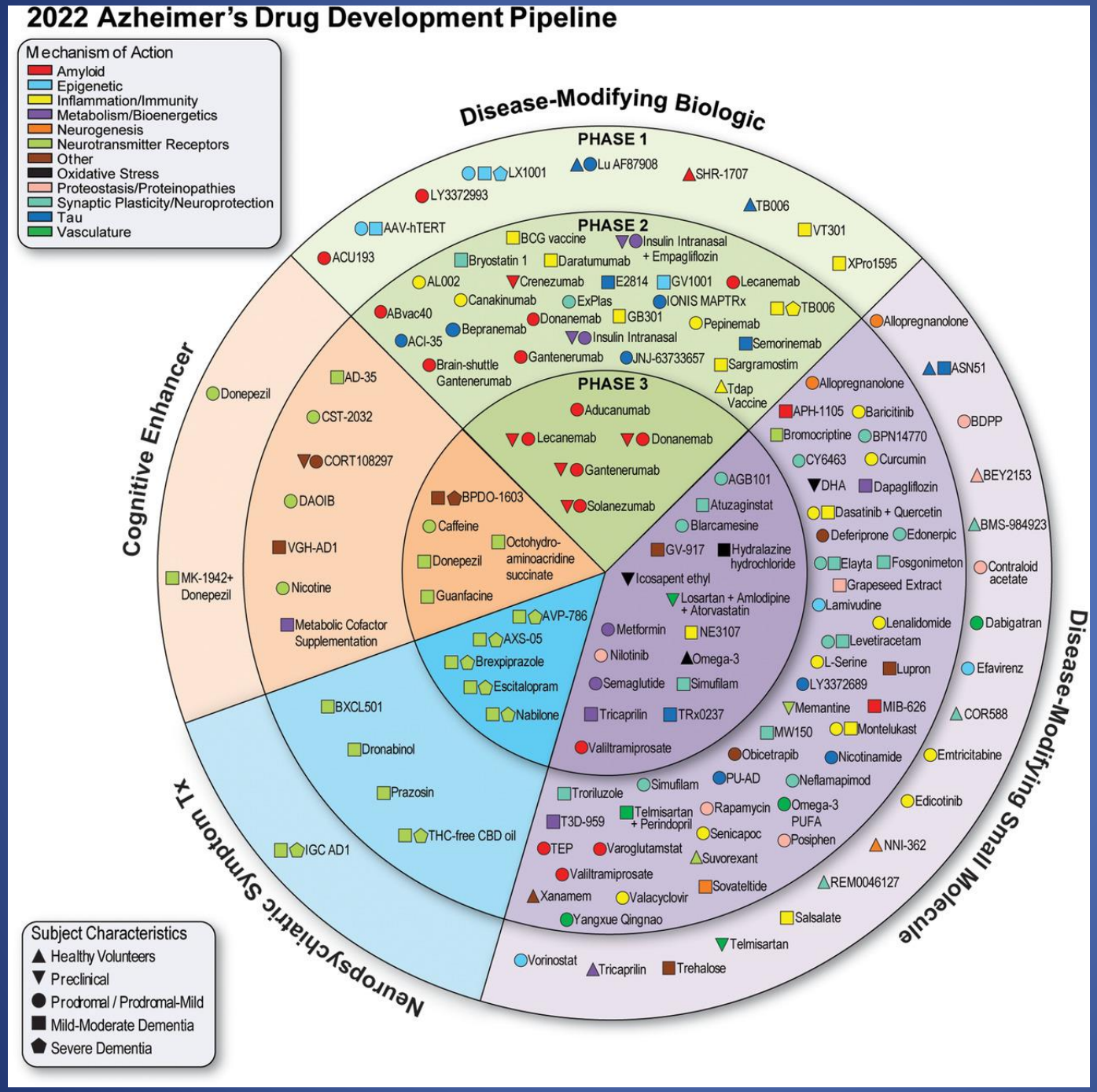
Road Map To Prevention of Alzheimer Disease: A Call To Arms.

Mol Neurodegeneration 16, 49 (2021). McDade, E., Llibre-Guerra, J.J., Holtzman, D.M. et al. (Wash U)



What does the future look like?





What does the Future look like?

143 Drugs in pipeline

83% DMT

50,575 participants

Cummings, J, Lee, G, Nahed, P,et al. Alzheimer's disease drug development pipeline: 2022. Alzheimer's Dement. 2022; 8:e12295

HPN MEMORY DISORDERS CENTER
ALZHEIMER'S RESEARCH UNIT

Summary

MEMORY CTR

INFUSION CTR

1. Since 2019, Hawaii Memory Ctr & Alzheimer's Research Unit collecting efficacy and safety data on Lecanemab & Aducanumab as part of global research effort
2. Although Lecanemab approved for MCI Mild AD, some patients at higher risk for ARIA
3. Although we still have lots of works to do, the future is bright
    1. Besides amyloid, consider tau, immunity, inflammation, metabolism & even lifestyle changes - Combination or "cocktail" therapies
    2. Early detection & prevention is needed
    3. Better biomarkers are needed - Hawaii is leading the research on using widely available, noninvasive and cost-effective EEG Neural Network

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Nicole Evans, PA-C	Neurology
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Ricardo Burgos, MD,	Neuroradiology
Qing Li, PhD	Neuroscience

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Brain Mapping Neural Network EEG Lab

Acknowledgements

Dedicated to our patients, their families & caretakers whom we get to Humbly Serve & Learn from Everyday & who continue to Inspire us to do what we do Today!

Active Alzheimer's Research in Hawaii

Research Hotline (808) 564-6141

MEMORY CTR

CLINICAL TRIALS

Preclinical to MCI (MMSE > 22)

(Spinal Tap needed)

Phase 4 Amyloid

IV monthly ENVISION (Aducanumab)

Phase 3 Metabolism EVOKE

PO Daily

Phase 2 Tau (ASO) CELIA

Antisense Oligonucleotide

IT Q12 weeks

MCI (MMSE > 18)

(Amyloid PET in California)

Phase 1 -ASCENT

Next Generation Amyloid

PK Overnight First in Human Study

SQ 1x PRX012

Mild to Mod AD (MMSE 14-24)

Buntanetap

Phase 2 mRNA (-) Translation Aggregating Toxic Proteins

PO Daily

LIFT AD (NIH Funded)

Phase 2 Synaptic Plasticity Neuroprotection

SQ Daily Injections