"The landscape for dementia treatment in 2022"

Presentation to BrainXChange,
May 2022

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- Professor of Medicine (Neurology), University of Toronto;
- Scientific Director, CCNA (Canadian Consortium on Neurodegeneration in Aging);

Medicine
UNIVERSITY OF TORONTO

CCNA CCNV
Canadian Consortium on Neurodegeneration in Aging
Consortium canadien en neurodégénérescence associée au vieillissement

Baycrest 100 YEARS 1918-2018

U of T NEUROLOGY

Funding Support for Dr. Chertkow

- Dr. Chertkow is supported by a research chair from Baycrest Health Science and University of Toronto.
- Canadian Institutes for Health Research
  - MOP 10392
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  - CIHR: PI of operating grant for CCNA,plus "BRAIN" big data and dementia operating grant
- Weston Foundation
- The 11 partners of the Canadian Consortium on Neurodegeneration in Aging (CCNA)contribute to the national program. I am Scientific Director of CCNA.

Mitigating Bias: All recommendations for clinical therapy have been suggested by the Canadian Consensus Conference on Diagnosis and Treatment of Dementia

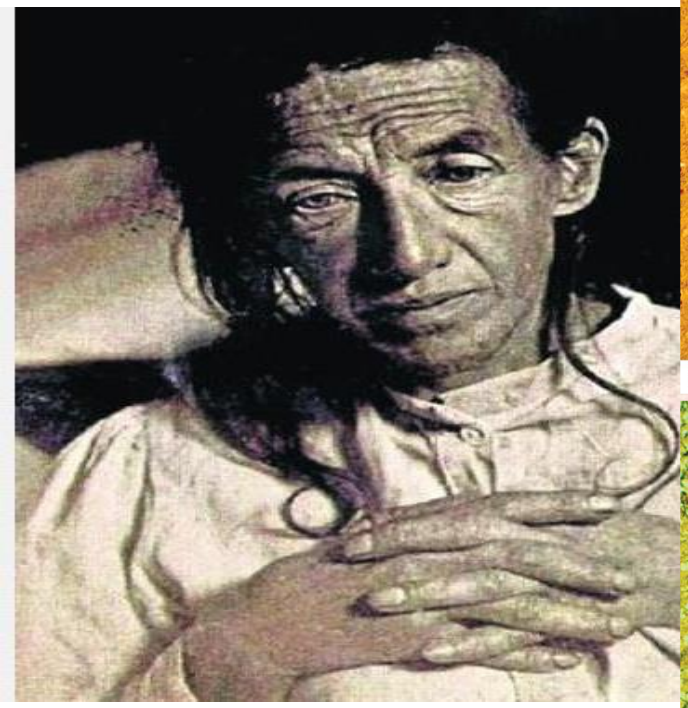
Faculty/Presenter Disclosure

- **Relationships with commercial interests past five years:**
- Dr. Chertkow is co-investigator on pharma-sponsored clinical trials of Roche (Gantenerumab,Graduate), Immunotec, Anavex Life Sciences, Lilly (Donanemab), Alector and Abbvie.
- Previous Industrial Support over five years for clinical trials, research studies, speakers boards, advisory boards, received from:
  - Pfizer Inc.
  - Bristol Myers Squibb
  - TauRx
  - No Funding support has been received for this presentation

Learning Objectives

- To understand where we are in treatment of Alzheimer Disease in 2022.
- To appreciate the major mechanisms being pursued for disease modifying therapy in Alzheimer Disease, and the disease treatments that might emerge from these.

Dementias (such as Alzheimer Disease) are complex diseases



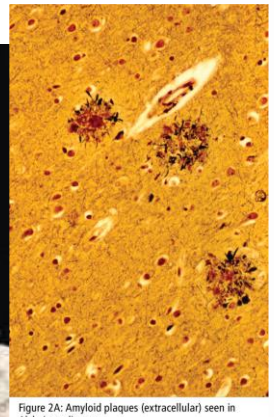


Figure 2A: Amyloid plaques (extracellular) seen in Alzheimer disease

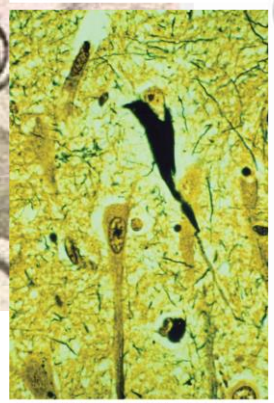
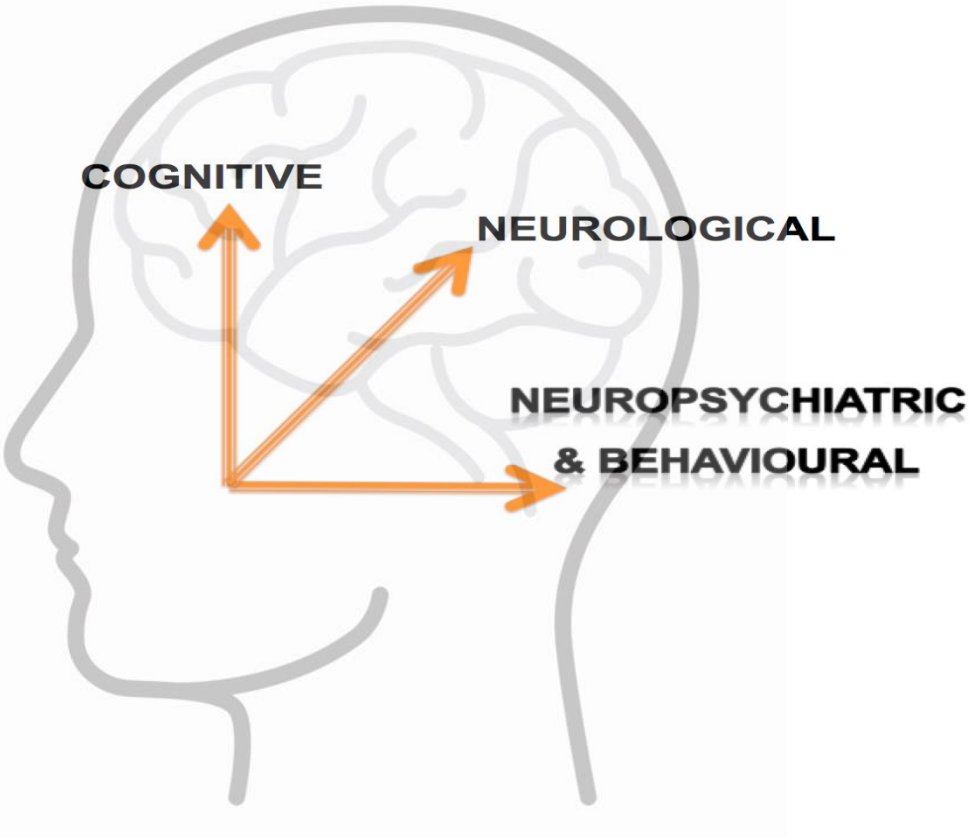


Figure 2B: Neurofibrillary tangle (intraneuronal) seen in Alzheimer disease



Treatments to:

- improve the cognitive symptoms- memory loss, planning, language
- Stop and prevent the neurological brain damage from Alzheimer Disease
- Treat the neuropsychiatric symptoms and behavioural problems encountered

What are the Behavioural and Psychological Symptoms of Dementia (BPSD)?

- Anxiety, Sleeplessness
- Depression
- Agitation and aggression
- Wandering
- Psychosis, hallucinations, delusions
- Paranoia
- Apathy

Treatment approaches = combination of environment, non-pharmacological, and pharmacological approaches

Medications for Neuropsychiatric Symptoms in Dementia

- Risperidone
- Quetiapine
- Olanzapine
- Aripiprazole
- Loxapine
- Clozapine

MajTrq

- Gabapentin
- Carbamazepine
- Oxcarbazepine
- Eslicarbazepine

AED

- Sertraline
- Citalopram
- Escitalopram
- Fluoxetine
- Trazodone
- Mirtazapine
- Clomipramine
- Doxepin

Anti Dep, SSRI

- Lorazepam
- Clonazepam

Relx

- Donepezil
- Galantamine
- Rivastigmine

ChI

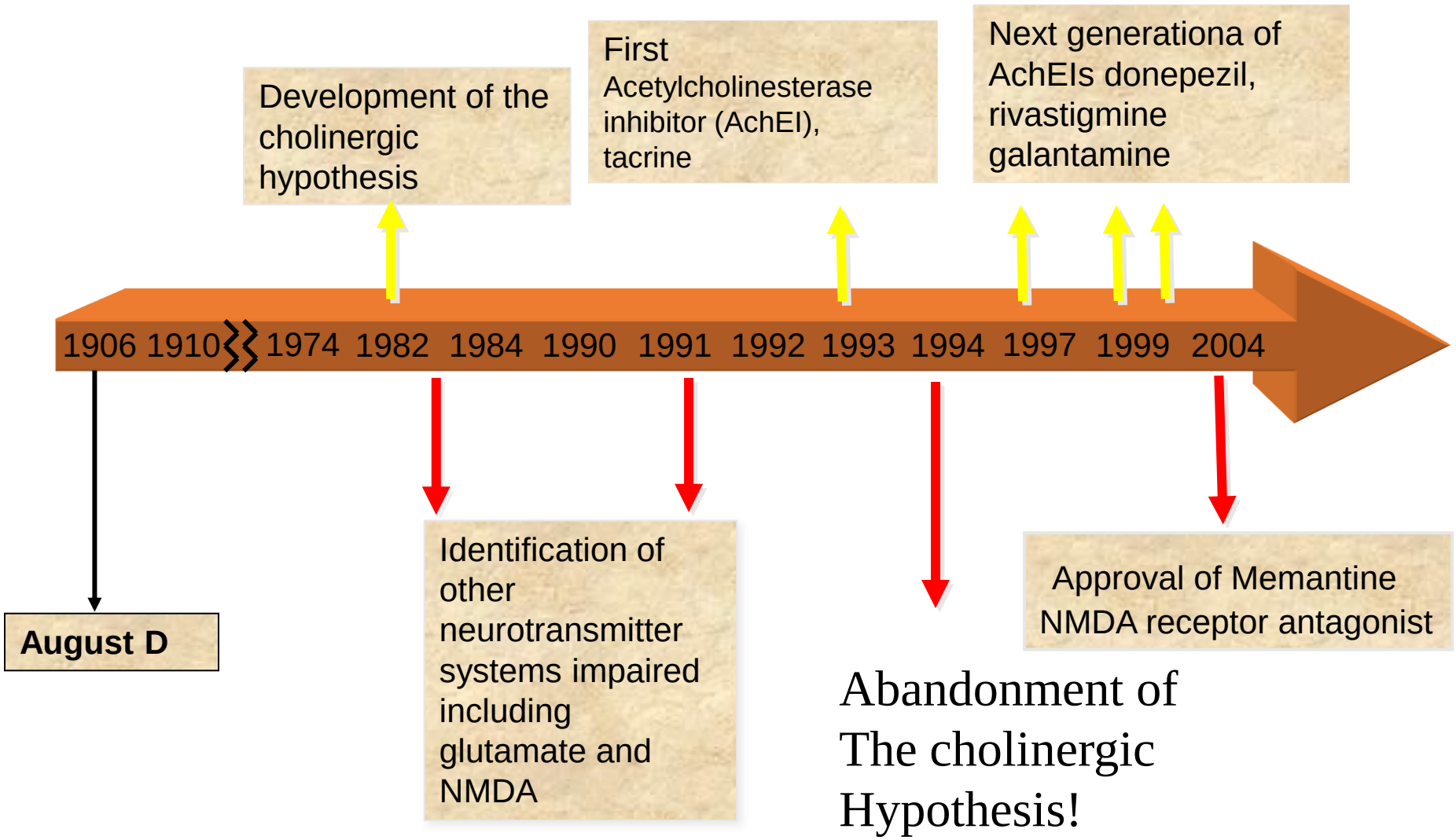
- Prazosin
- Memantine
- Nabilone
- CBD oil

Misc

- Ritalin

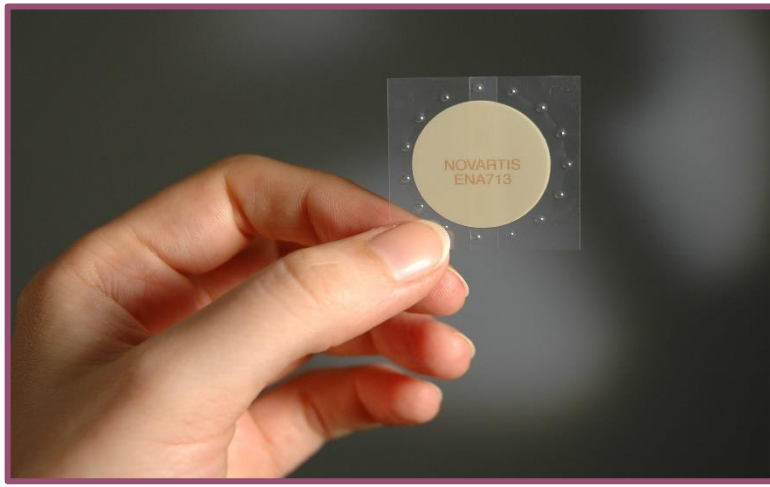
Key thing is to have an interested and accessible and knowledgeable physician able and willing to try and try and try to find solutions

Timeline of therapy for Alzheimer's Disease

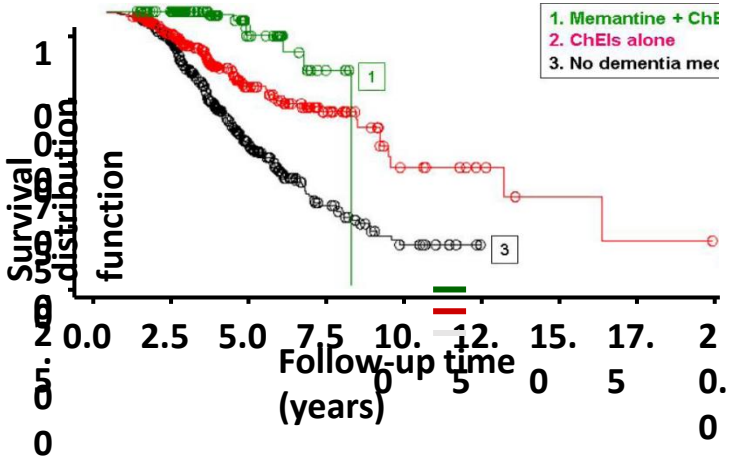


Symptomatic treatment of cognitive symptoms

- Cholinesterase inhibitors:
  Aricept (Donepezil),
  Exelon(Rivastigmine), Reminyl
  (Galantamine), Exelon Patch
- Modest improvement/stabilization
- 25% AD - no benefit
- Best result: "roll back 6-12 months"
- Memantine "Namenda" or "Ebixa"-
  blocking NMDA glutamate receptors.
  - proven in moderate to severe AD.
  Mild benefit-particularly for agitation.
- Combination therapy advantageous

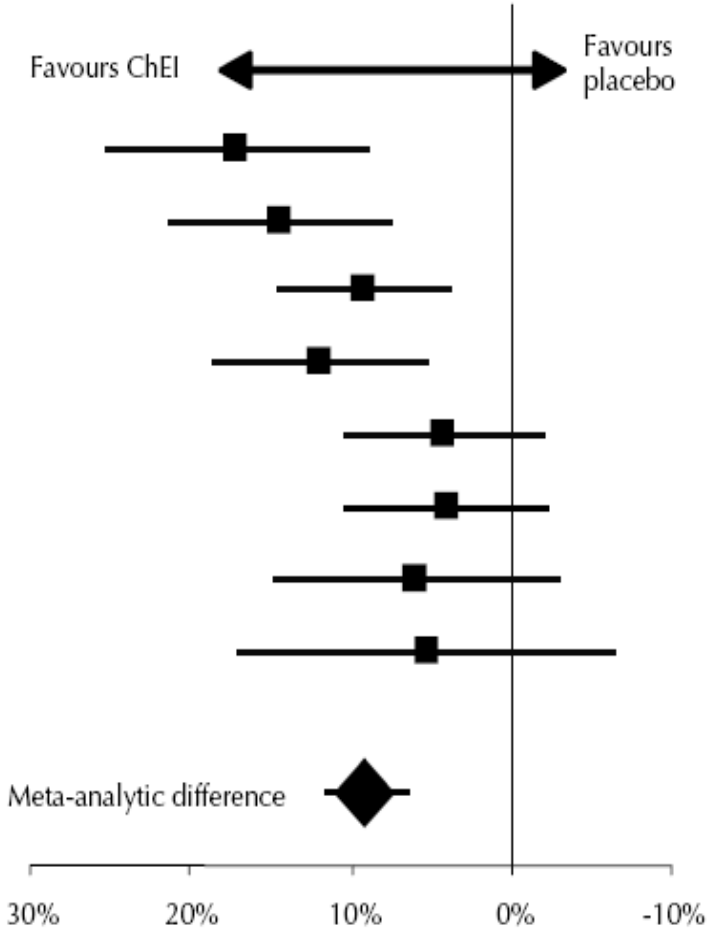


•None new released since 2004
•There is no evidence that one CI is more efficacious than another
äChoosing one- ease of use, side effects profile.
•Many new ones in different stages of research development

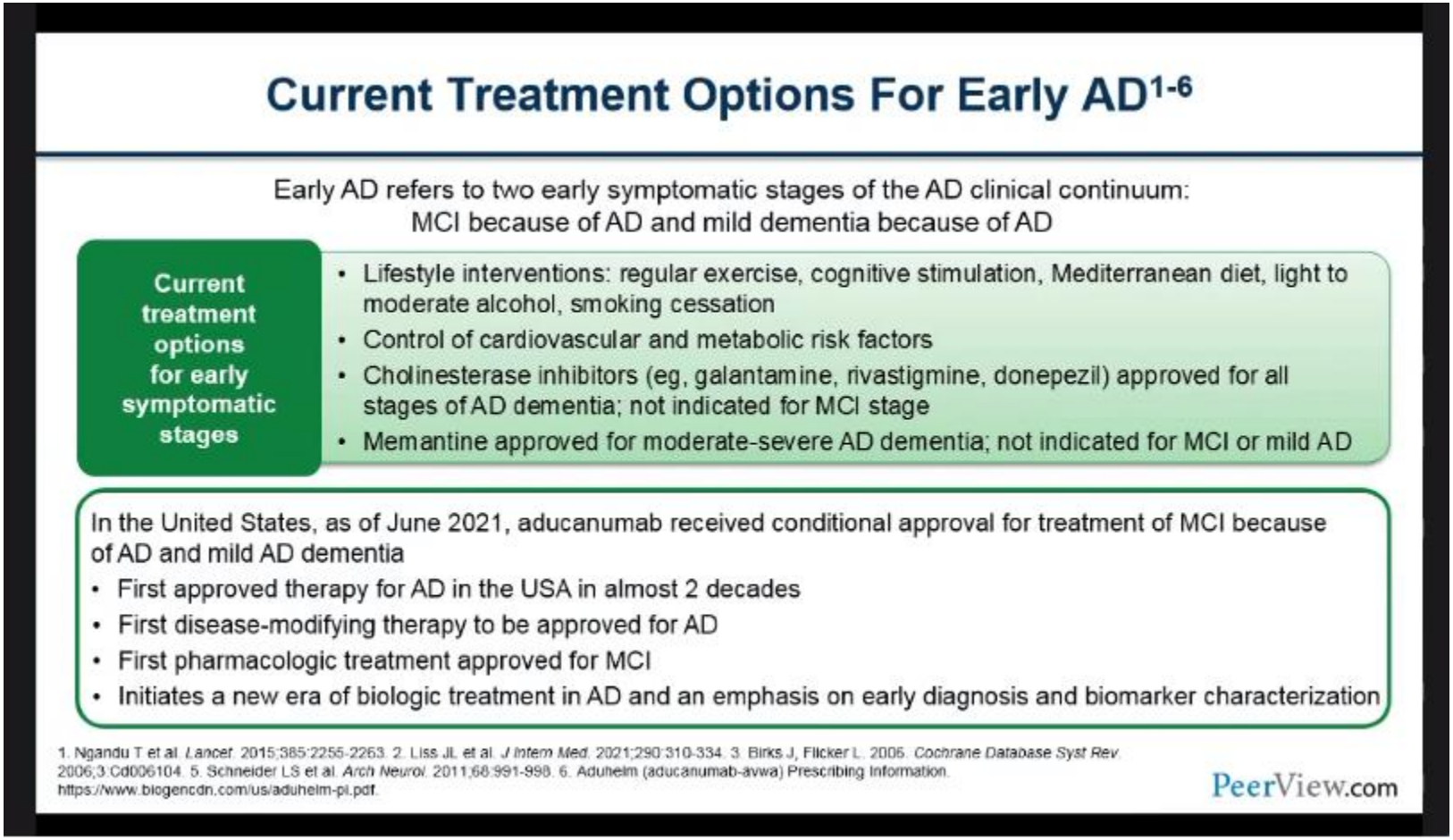


AChEIs: meta-analysis
Lanctôt et al *CMAJ* 2003

Study	Cholinesterase inhibitor	ChEI responders	Placebo responders	Total subjects
Rogers,[11] 1998a	Donepezil	107/305	27/150	455
Rogers,[10] 1998b	Donepezil	76/298	17/152	450
Burns,[12] 1999	Donepezil	125/544	38/274	818
Rösler,[18] 1999	Rivastigmine	149/467	44/220	687
Raskind,[20] 2000	Galantamine	64/357	27/196	553
Wilcock,[21] 2000	Galantamine	84/414	33/203	617
Rockwood,[24] 2001	Galantamine	61/240	24/123	363
Wilkinson,[23] 2001	Galantamine	59/179	23/83	262



Current Treatment for Early AD



Cognitive Continuum

Normal

Can start Subjective Complaints here

No cognitive complaints
And no objective cognitive loss

Mild Cognitive Impairment

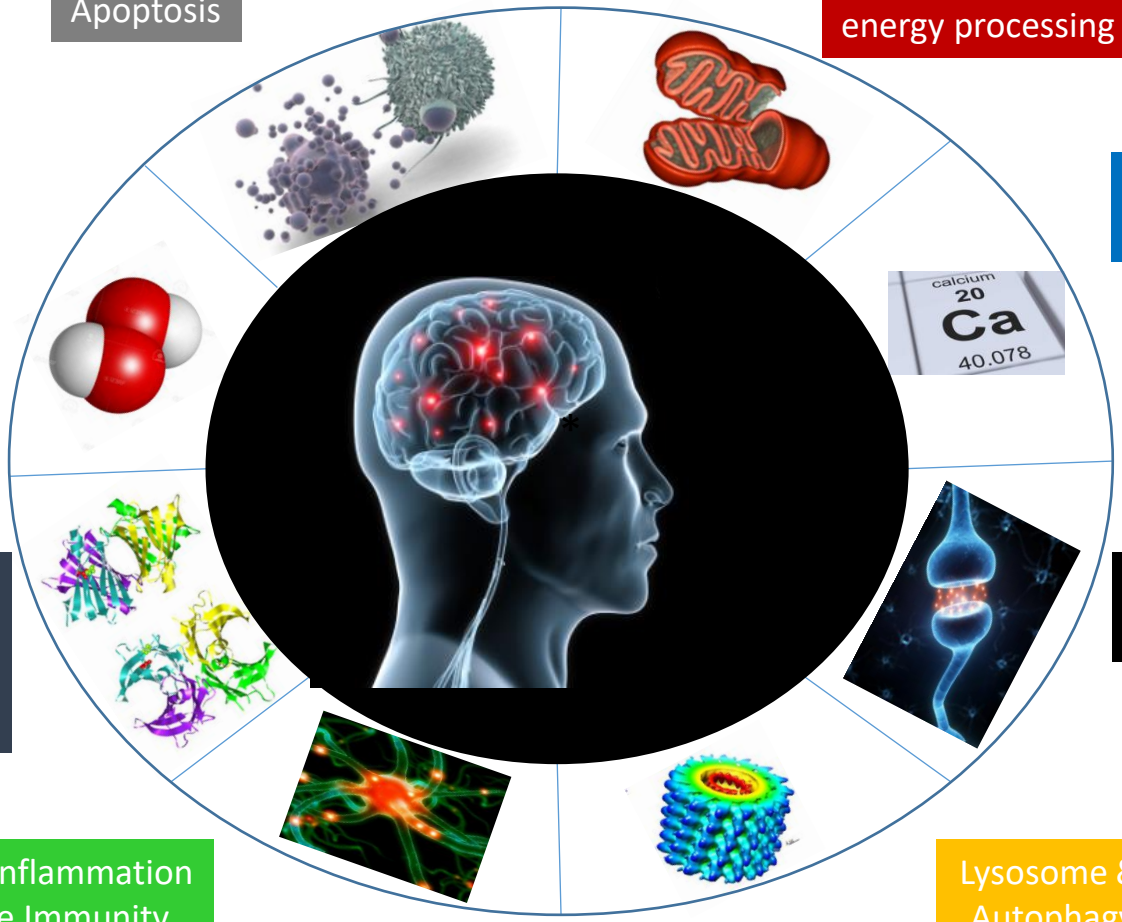
MCI plus biomarker evidence of amyloid = "prodromal AD"

No functional loss

AD Dementia

Significant cognitive impairment,
Functional impairment too

There are many proposed mechanisms involved in Alzheimer's Disease - Are they all present in every patient? Can they be targetted for treatment?

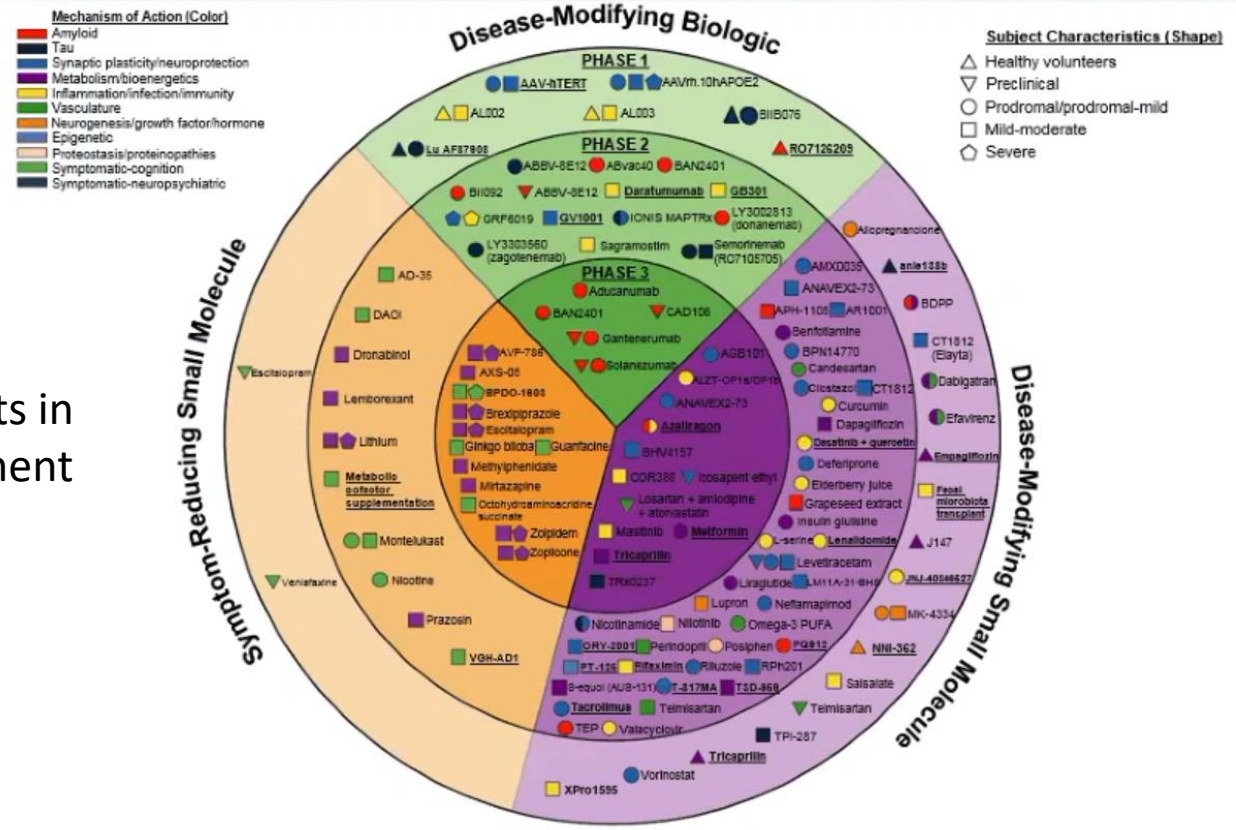


adapted from slide by Ouassila Habi (OIAP)

Agents in Clinical Trials for Treatment of AD in 2021

Agents in Clinical Trials for Treatment of AD in 2021[1]

120 agents in development



1. Cummings J et al. *Alzheimer's Dement.* 2021;7:e12179.

What is being tried to treat AD now?

Cognitive; ApoE, apolipoprotein E; ATRI, Alzheimer's Therapeutic Research Institute; CDR-SB, Clinical Dementia Eating-Sum of Boxes; FCSRT, Free and Cued Selective Reminding Test; HbA1c, hemoglobin A1c; MCI, mild cognitive impairment; NIA, National Institute on Aging; NIH-TB, National Institutes of Health toolbox.

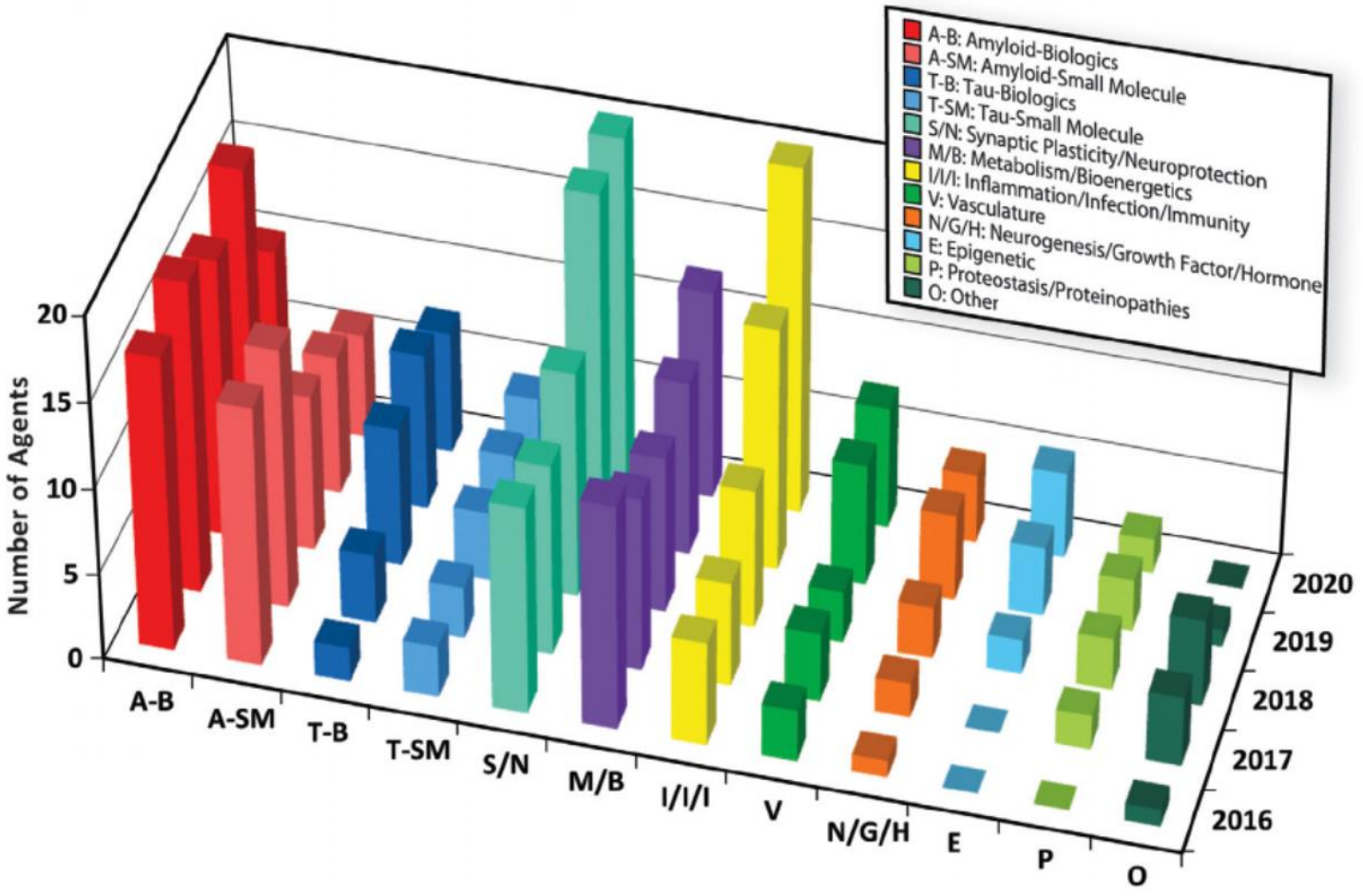


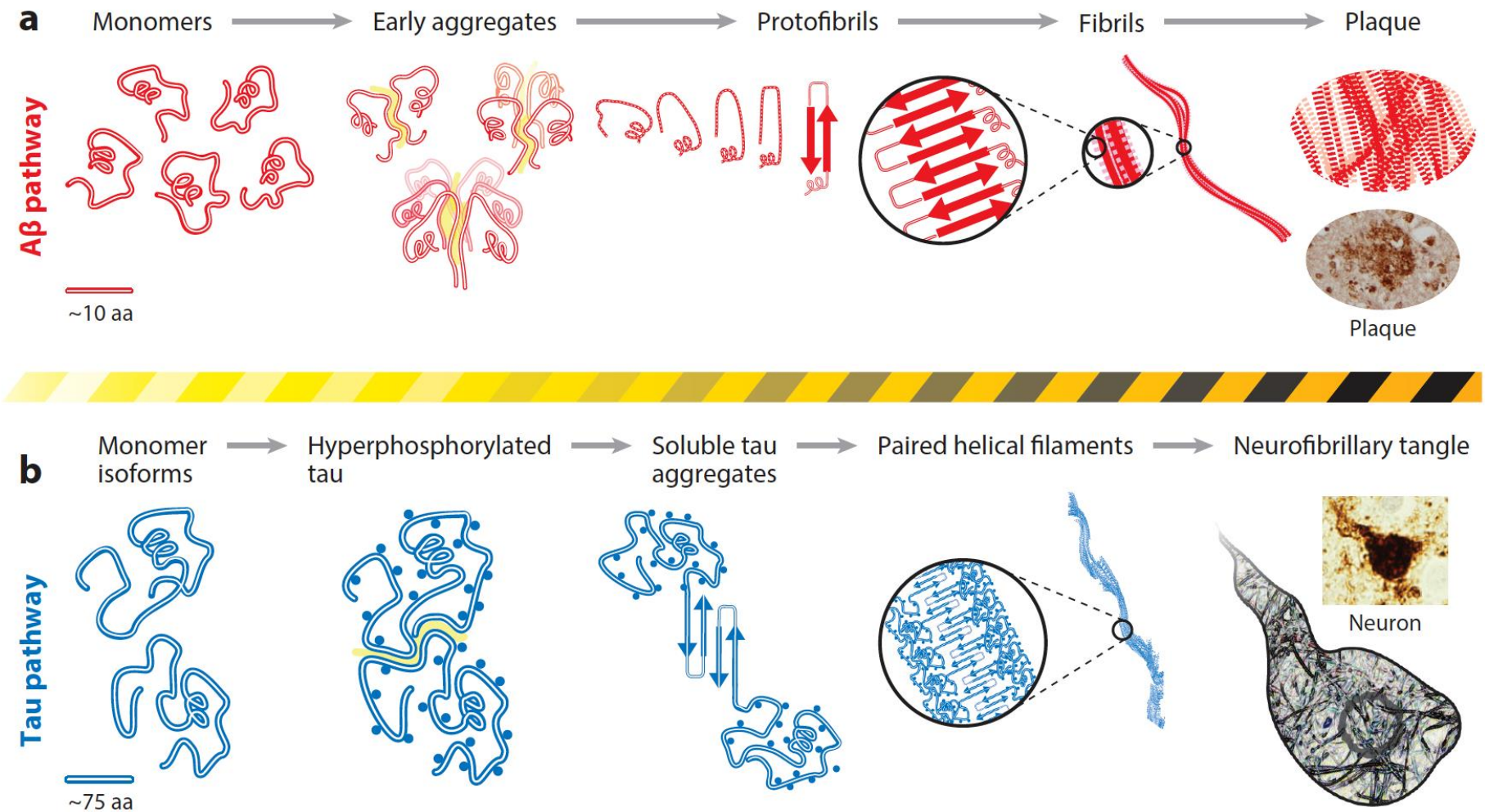
FIGURE 6 Targets of Alzheimer's disease therapeutics by Common Alzheimer's Disease and Related Disorders Research Ontology (CADRO) category: 2016–2020 (ClinicalTrials.gov accessed February 27, 2020) (Figure by Mike de la Flor)

Drug mechanisms and DMT approaches for Alzheimer Disease

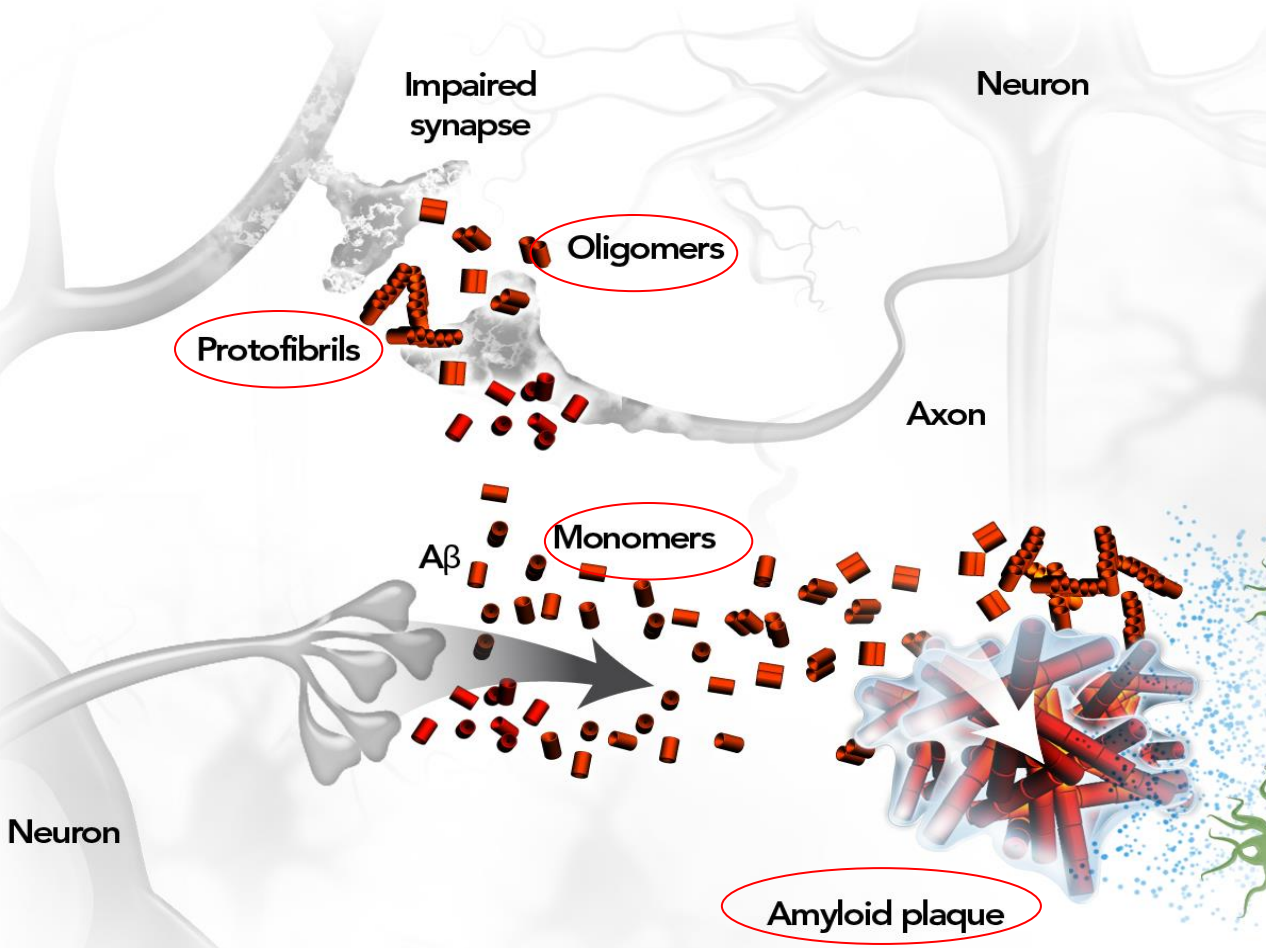
- Reduce Amyloid*
- Reduce Tau Hyperphosphorylation*
- Improve synaptic activity and neurotransmitters
- Neuroprotection, augment synaptic plasticity*
- Mitochondrial and metabolic function*
- Bioenergetics approaches*
- Inflammation and microglial modulators*
- Counteract cell senescence*

- Improve Vascular function
- Growth factors
- Hormones
- Epigenetics
- Proteostasis, proteinopathy approach
- Other novel mechanisms-lipid rafts

Amyloid beta and Tau Protein Misfolding Pathways

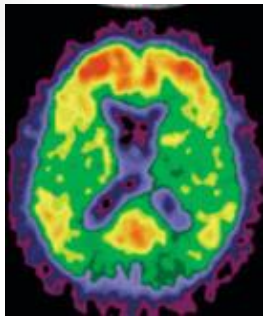


Amyloid Targets: Aβ Aggregates and Plaques



Soluble Species
Monomers
Oligomers

Insoluble Species
Protofibrils
Neuritic Plaques



In-vivo imaging of fibrillar amyloid

Mucke, 2009; LaFerla, 2007

↑ Aβ deposition (familial AD)

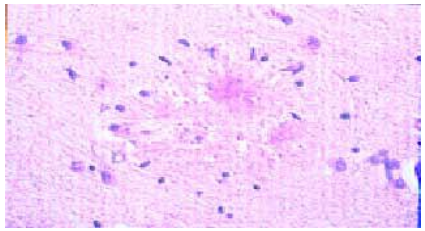
γ secretase too active
β-secretase too active
α-secretase too low

Neurodegeneration

Senile neuritic plaques

Inflammation
Oxidative Stress

Failure of clearance mechanisms,
multiple causes



Decrease in Aβ clearance
Sporadic AD, LOAD

Scarpini et al. *Lancet Neurol.* 2003;2:539-547

Phase 3 failure of anti-amyloid therapies

- Bapineuzamab results:negative 2013
- Tramiprosate , Scyloinossitol failures - 2010
- IVIG Results: Negative
- Solenuzemab: Negative -no individual studies have reached significance- Lilly 2016.
  - Subanalyses and post-hoc analyses of some studies indicate efficacy in removing plaques, without clinical benefit (Holmes et al, 2008, Lancet; Castellani (2011), J. Pathology)
- Low dose Gantenerumab (Roche) 2017: failure
- DIAN (Dominantly Inherited Alzheimer Network): Five year trial of FAD gene positive carriers, with Solenuzemab and Gantenerumab- Failure to delay AD symptoms! (2020 release)

Anti-AB MABs Currently in Phase 3 Clinical Trials

Anti-Aβ MABs Currently in Phase 3 Clinical Trials[1-4]

Antibody	Target	Active Phase 3 trials	Study Population
Aducanumab Human IgG1 anti-Aβ mab	Soluble and insoluble aggregated amyloid	EMBARK; TRAILBLAZER 4	Early to mod AD Early AD
Donanemab Humanized IgG1 anti-Aβ mab	Plaque-bound amyloid (N-terminal pyroglutamate epitope found only in Aβ plaque)	TRAILBLAZER 2; TRAILBLAZER 3; TRAILBLAZER 4	Early AD Preclinical AD Early AD
Gantenerumab Human IgG1 anti-Aβ mab	Soluble and insoluble aggregated amyloid	GRADUATE 1; 2 SKYLINE; DIAN-TU	Early AD Preclinical AD ADAD (primary prevention)
Lecanemab Humanized IgG1 anti-Aβ mab	High affinity for large soluble Aβ protofibrils	Clarity AD; AHEAD 3-45 Study	Early AD Preclinical AD
Solanezumab Humanized IgG1 anti-Aβ mab	Preferentially binds to Aβ monomers	A4	Preclinical AD

1. Bullain S, Doody R. *J Neurochemistry*. 2020;155:120-136. 2. https://clinicaltrials.gov/. 3. https://practicalneurology.com/articles/2021-june/novel-treatments-for-alzheimer-disease-disorders. 4. Arndt JW et al. *Sci Rep*. 2018;8:6412.

ARTICLE

Sevigny,J. (2016) Nature, PMID 27582220

doi:10.1038/nature19323

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

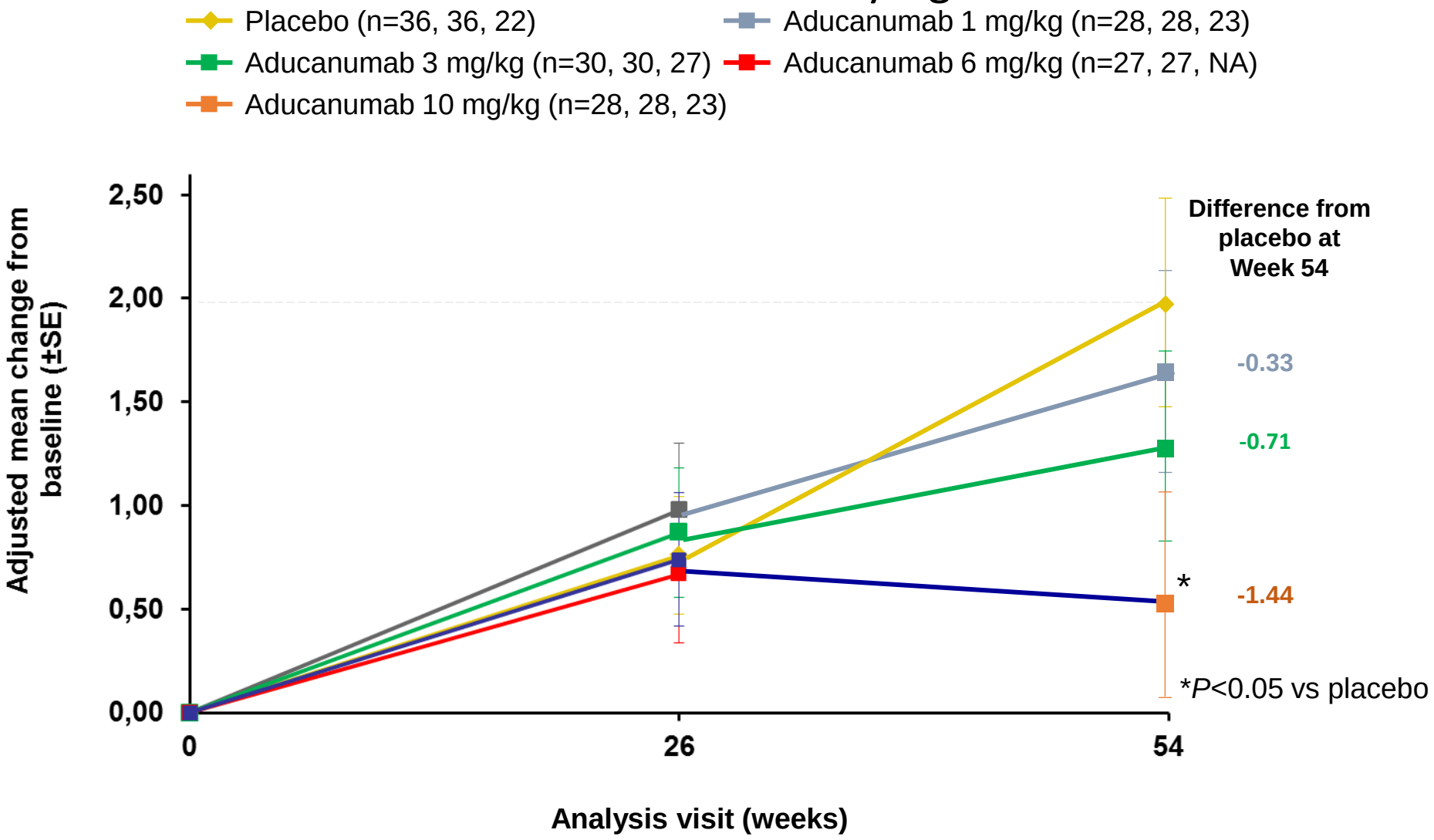
Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§

Alzheimer's disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.

Aducanumab Effect on CDR-sb

18 point scale- MCI range from .5 to 3.5. Higher score = worse

A difference on CDR-sb of >.98 is clinically significant



J Prev Alz Dis 2022;
Published online March 18, 2022, http://dx.doi.org/10.14283/jpad.2022.30

Original Research

Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease

S. Budd Haeberlein[1], P.S. Aisen[2], F. Barkhof[3,4], S. Chalkias[1,], T. Chen[1], S. Cohen[5], G. Dent[1], O. Hansson[6,7], K. Harrison[1], C. von Hehn[1,*], T. Iwatsubo[8], C. Mallinckrodt[1,*], C.J. Mummery[9], K.K. Muralidharan[1], I. Nestorov[1], L. Nisenbaum[1,*], R. Rajagovindan[1,*], L. Skordos[1,*], Y. Tian[1], C.H. van Dyck[10], B. Vellas[11], S. Wu[1], Y. Zhu[1], A. Sandrock[1,*]*

1. Biogen, Cambridge, MA, USA; 2. Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA, USA; 3. Department of Radiology and Nuclear Medicine, Amsterdam UMC, Amsterdam, the Netherlands; 4. UCL Queen Square Institute of Neurology & Centre for Medical Image Computing, London, UK; 5. Toronto Memory Program, Toronto, ON, Canada; 6. Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden; 7. Memory Clinic, Skåne University Hospital, Malmö, Sweden; 8. Department of Neuropathology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; 9. Dementia Research Centre, Queen Square Institute of Neurology, University College London, London, UK; 10. Alzheimer's Disease Research Unit, Yale School of Medicine, New Haven, CT, USA; 11. Toulouse Gerontopole University Hospital, Universite Paul Sabatier, INSERM U 1295, France; *Denotes an author who was an employee of Biogen at the time of this study and who has since left the company.

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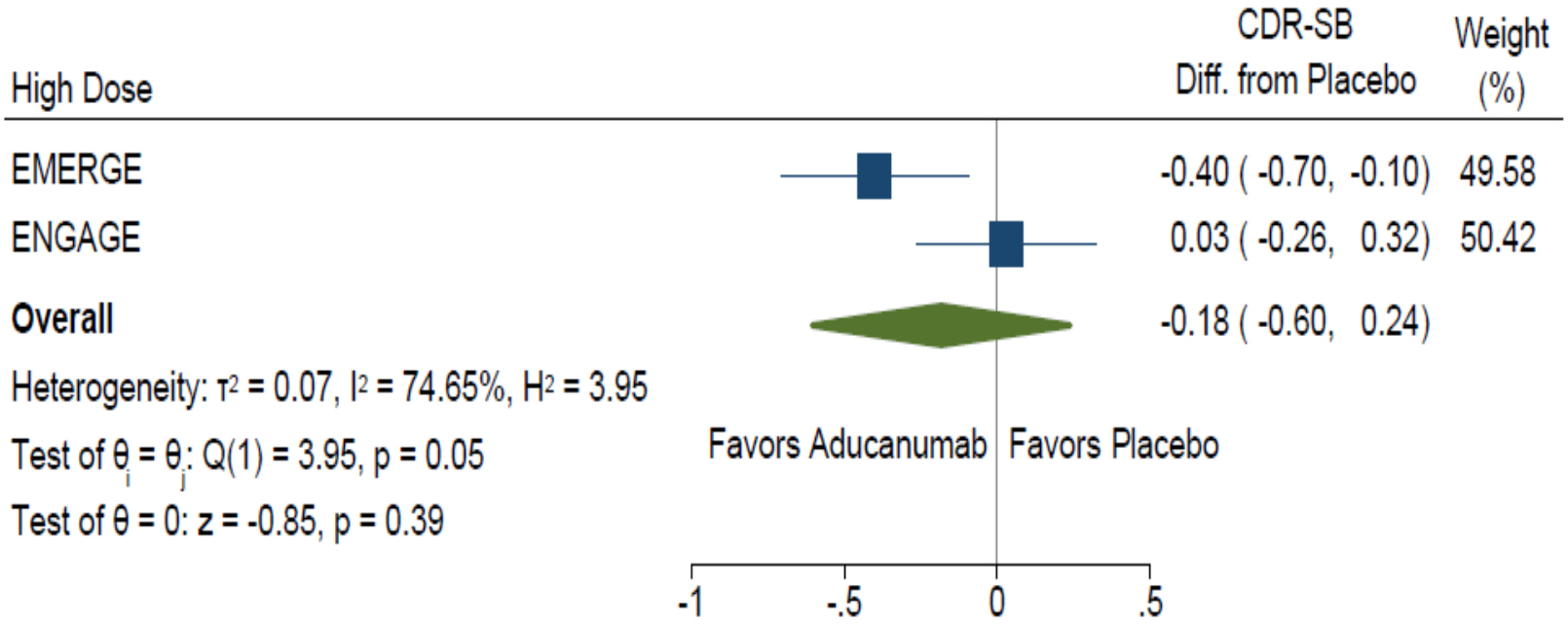
Abstract

abnormalities-edema.

Meta-Analysis of Difference in CDR-SB versus Placebo – High Dose



Thus, one study succeeded, one study failed in meeting planned endpoint at high dose.

- Efficacy (as specified by company beforehand) meant both studies had to meet primary endpoint.

How effective might Aducanumab be?
{Watt et al, CMAJ 2021 , Sept 13. Commentary}

- Concept of "Minimally clinically important difference in outcome" = what effect can be detected clinically.
- On the CDR-SB (Clinical Dementia Rating Scale Sum of Boxes) this =.98 point in subjects with MCI and 1.6 in AD (Andrews et al., Alz & Dementia, 2019).
- In EMERGE trial the difference was only 0.39 points.
- Minimally clinically important difference in outcome scale on the MMSE is noted to be 1 to 3 points (Andrews et al., Alz & Dementia, 2019.. In EMERGE it is 0.6 points.
- These levels cannot be reliably distinguished from chance variations (Jutten et al., Neurology (2021) 96, e2673-e2684.)

COMMENTARIES

Consensus Statement Regarding the Application of Biogen to Health Canada for Approval of Aducanumab

Howard Chertkow, MD,FRCP,FCAHS[1,2,3,4], Kenneth Rockwood, MD, MPA, FRCPC, FRCP[5,6], David Hogan, MD, FACP, FRCP[7,8], Natalie Phillips, PhD[4,9,10], Manuel Montero-Odasso, MD, PhD, FRCPC, AGSF, FGSA[11,12,13], Shabbir Amanullah, DPM, MD, FRCPsysch (UK), CCT (UK), FRCPC, DFCPA, FIIOPM[14], Sandra Black, OC, O.Ont, HON.DSc, MD, FRCP(C), FRSC, FAAN, FAHA, FANA[15,16,17], Christian Bocti, MD, FRCPC[18], Michael Borrie, MB ChB, FRCPC[19], Howard Feldman, MDCM, FRCP(C)[20,21,22], Morris Freedman, MD, FRCPC[23,24,25,26], Robin Hsiung, MD, MHSc, FRCPC, FACP, FAAN[27], Andrew Kirk, MD, FRCPC[28], Mario Masellis, MD, PhD[15,16,29,30], Haakon Nygaard, MD, PhD[31], Tarek Rajji, MD, FRCPC[32,33], Louis Verret, MD, FRCPC[34,35]

[1]Rotman Research Institute, Baycrest Health Sciences, Toronto, ON; [2]Kimel Centre for Brain Health and Baycrest Clinical

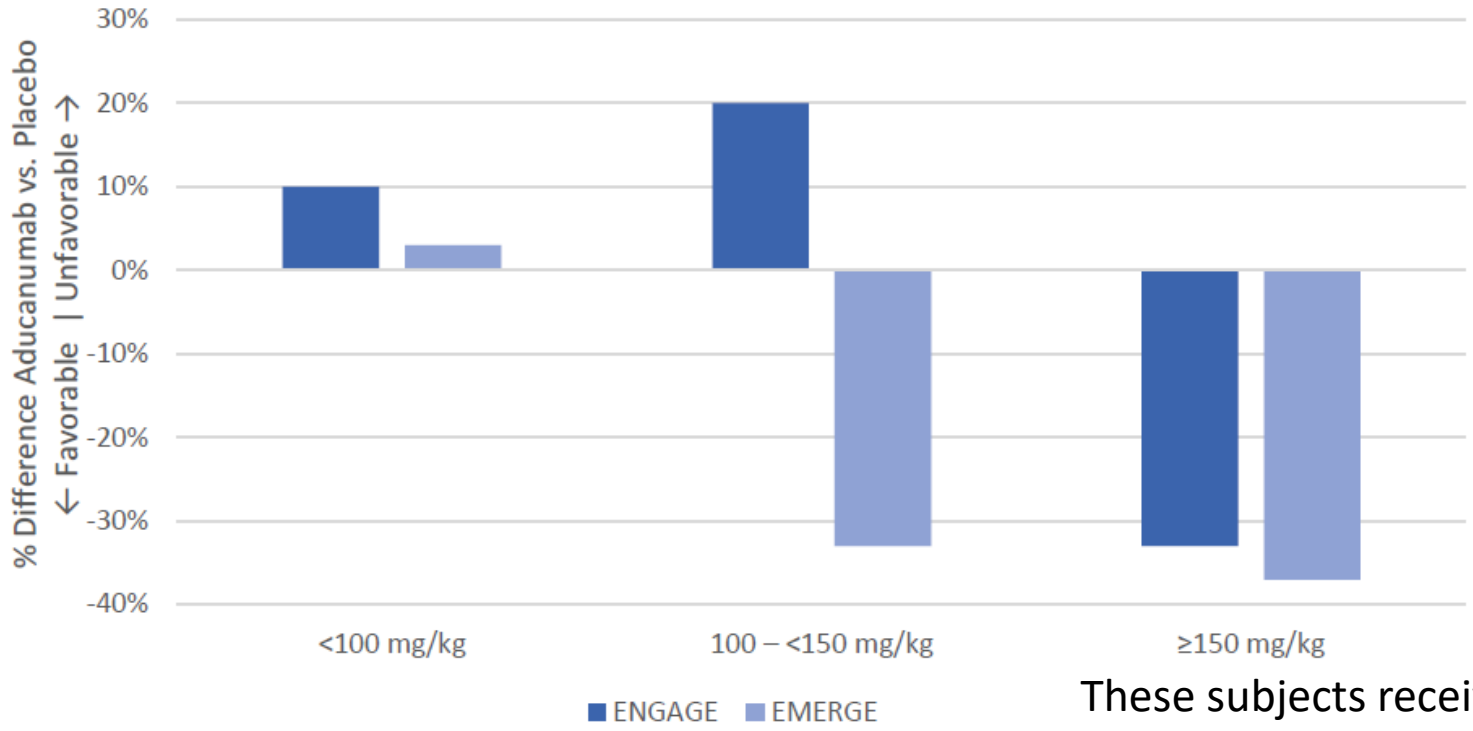
Published in Canadian Geriatrics Journal,vol. 24,no.4, December, 2021

July 2021 – Letter to Health Canada on Aducanumab

(see www.ccna-ccnv.ca/aducanumab);
Chertkow et al.; Canadian Geriatrics Journal, Dec. 2021 (available online)

- Canadian experts were not impressed by the argument that "people should have choices"……in a single payer system, the cost/benefit must be clearly established.
- **"What [evidence] is available suggests aducanumab does not meet accepted criteria for clinical efficacy, safety, and risk benefit of an agent for Alzheimer's disease that would justify Health Canada regulatory approval**.
- Concerns were raised about raising false hope.
- Concerns were raised that aducanumab might in the end prove ineffective.
- A further Phase 3 trial was suggested.
- Health professionals volunteered to form a committee to work with Health Canada to establish criteria for DMT in AD. We must develop a feasible cost-effective trajectory for access to biomarkers and DMT's in the future.
- Finally…concerns over scientific decision-making for non-scientific reasons.

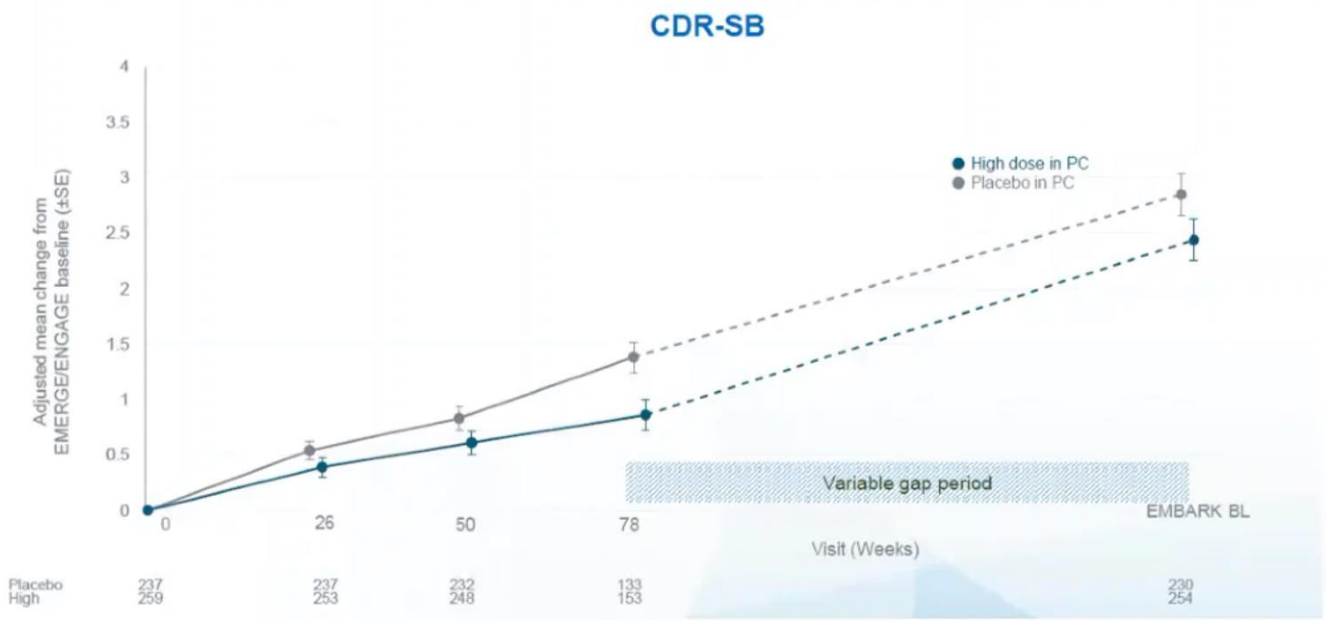
Post-Hoc Analysis of Adjusted Mean Change from Baseline in CDR-SB: % Difference from Propensity-Matched Placebo by Cumulative Dose Received



kg: kilogram, mg: milligram

These subjects received at least 14 high dose injections

Differences for CDR-SB as Maintained During Treatment Gap From End of EMERGE/ENGAGE to EMBARK Baseline[1]

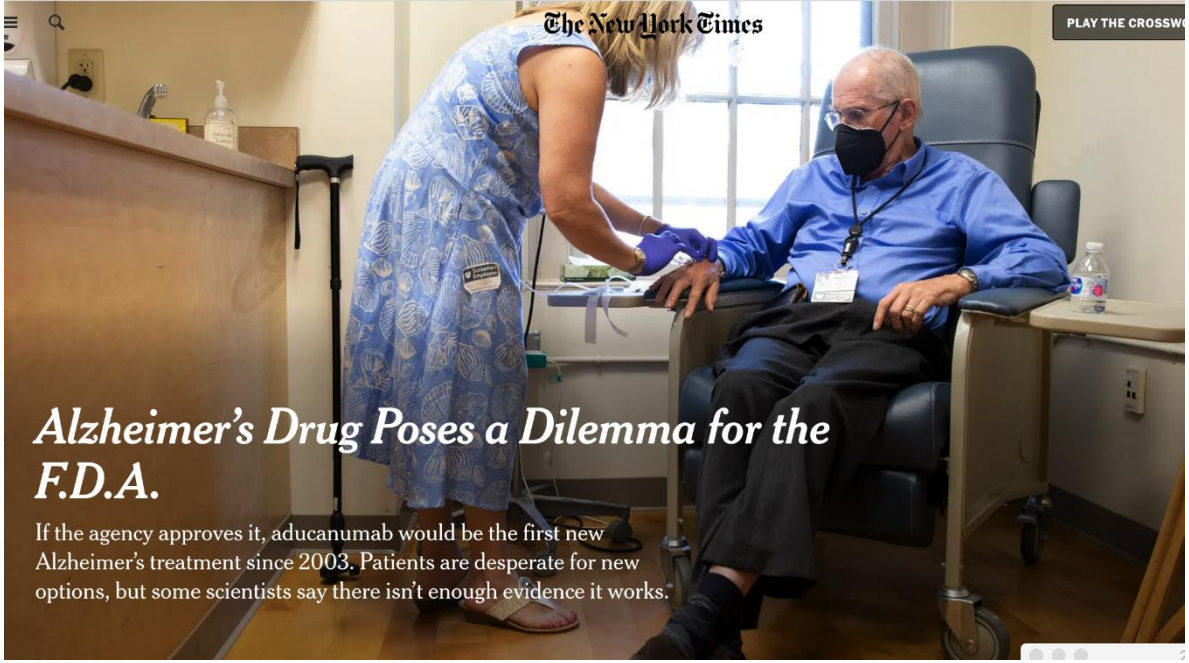


1. Cohen S et al. CTAD 2021.

Some arguments for licensing of aducanumab

- Cummings et al,2021: "We support providing persons with AD, who face a progressive and incurable disease, with the option of making informed choices about their health and lives (with aducanumab)."
- Cavazzoni of FDA, letter June 7th:"we listened to the perspectives of the patient community ….The need for treatments is urgent".

Latest news

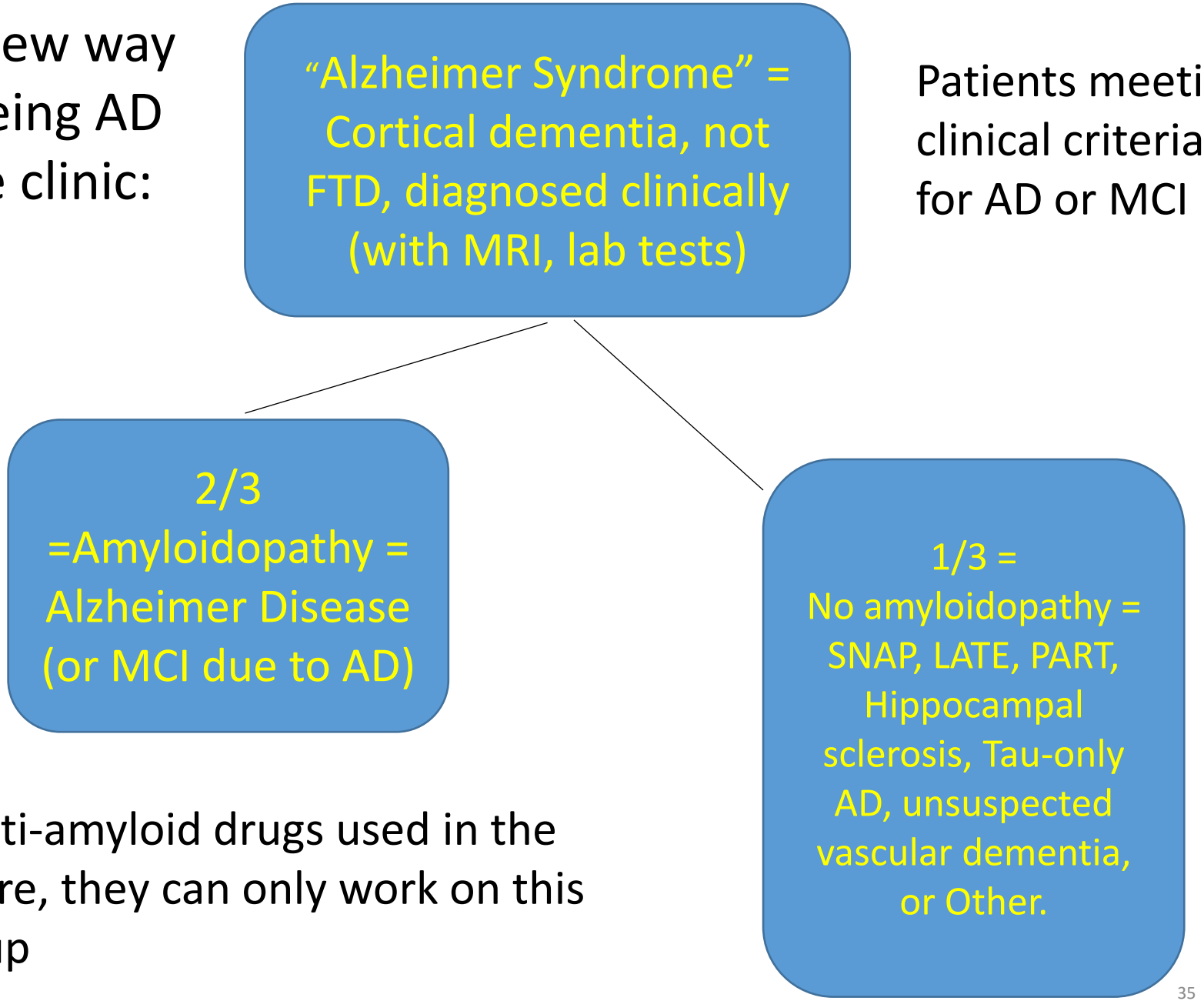


- Dec 2021: Centers for Medicare and Medicaid Services (MS) announces it will only cover aducanumab (or other monoclonal antiobodies directed against amyloid for AD) in the context of CMS-approved randomized controlled trials.
- Dec 2021: Independent group of expert physicians (Whitehouse, Schneider) calls for FDA to recall aducanumab.
- Dec 2021: Biogen slashes annual cost of Aduhelm to $23,000/patient
- May, 2022: Still no response from Health Canada on Biogen's aducanumab application.
- May 2022- CEO of Biogen resigns…fate of Aduhelm?

ARIA (amyloid related imaging abnormalities) , microbleeds, and screening for anti-amyloid therapy

- ARIA occurred in 35% of individuals receiving anti-amyloid therapies, more if ApoE4 positive.
- May need ApoE screening in all subjects.
- ARIA-E = focal edema, ARIA-H = microbleeds.
- Usually within first few months-first year of starting therapy. Reflect drug action.
- 80% asymptomatic. 20% = headache, dizziness, focal findings.
- Rarely (but occasionally) fatal.
- Do not start therapy if >6 microbleeds exist already; microhemorrhages can change to macro. Screen and follow with MRI.

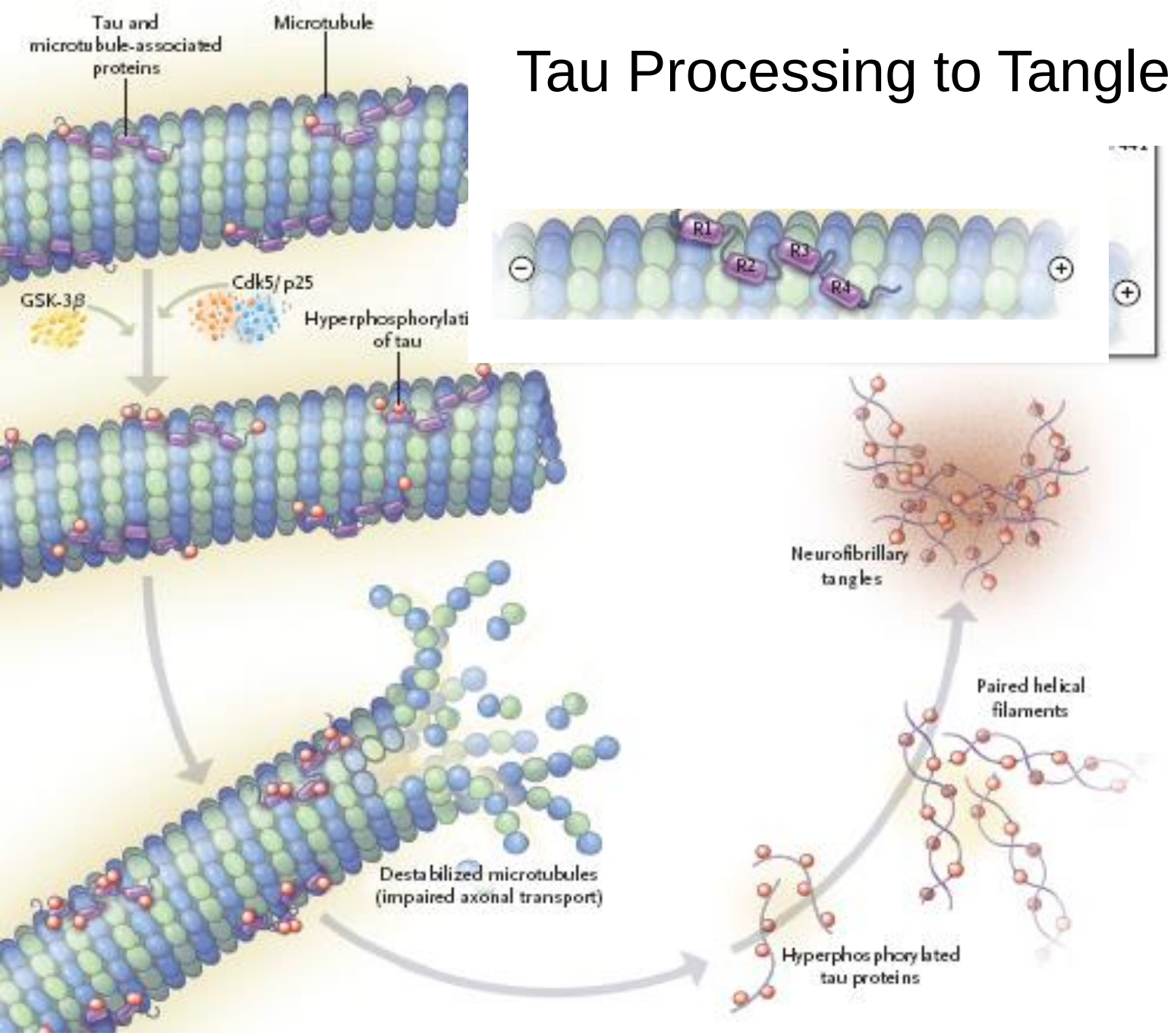
The new way of seeing AD In the clinic:



Patients meeting clinical criteria for AD or MCI

If anti-amyloid drugs used in the future, they can only work on this group

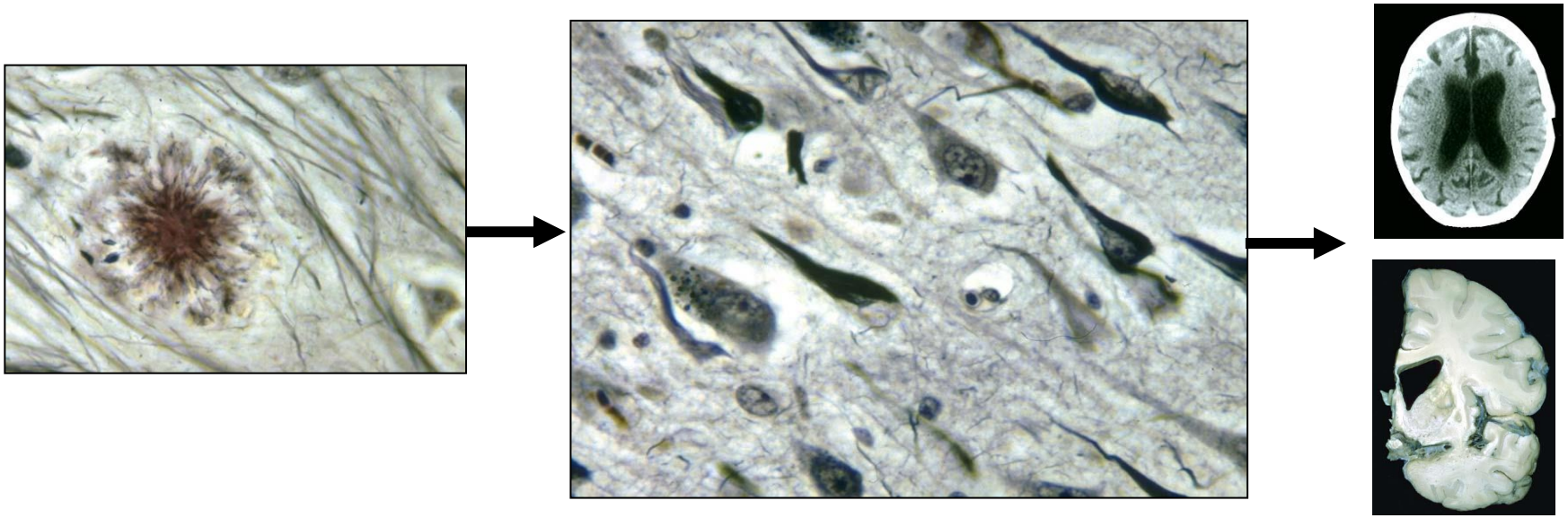
Tau Processing to Tangles



4 repeat sequences (R1-R4) make up the microtubule-binding domain (MBD) of tau

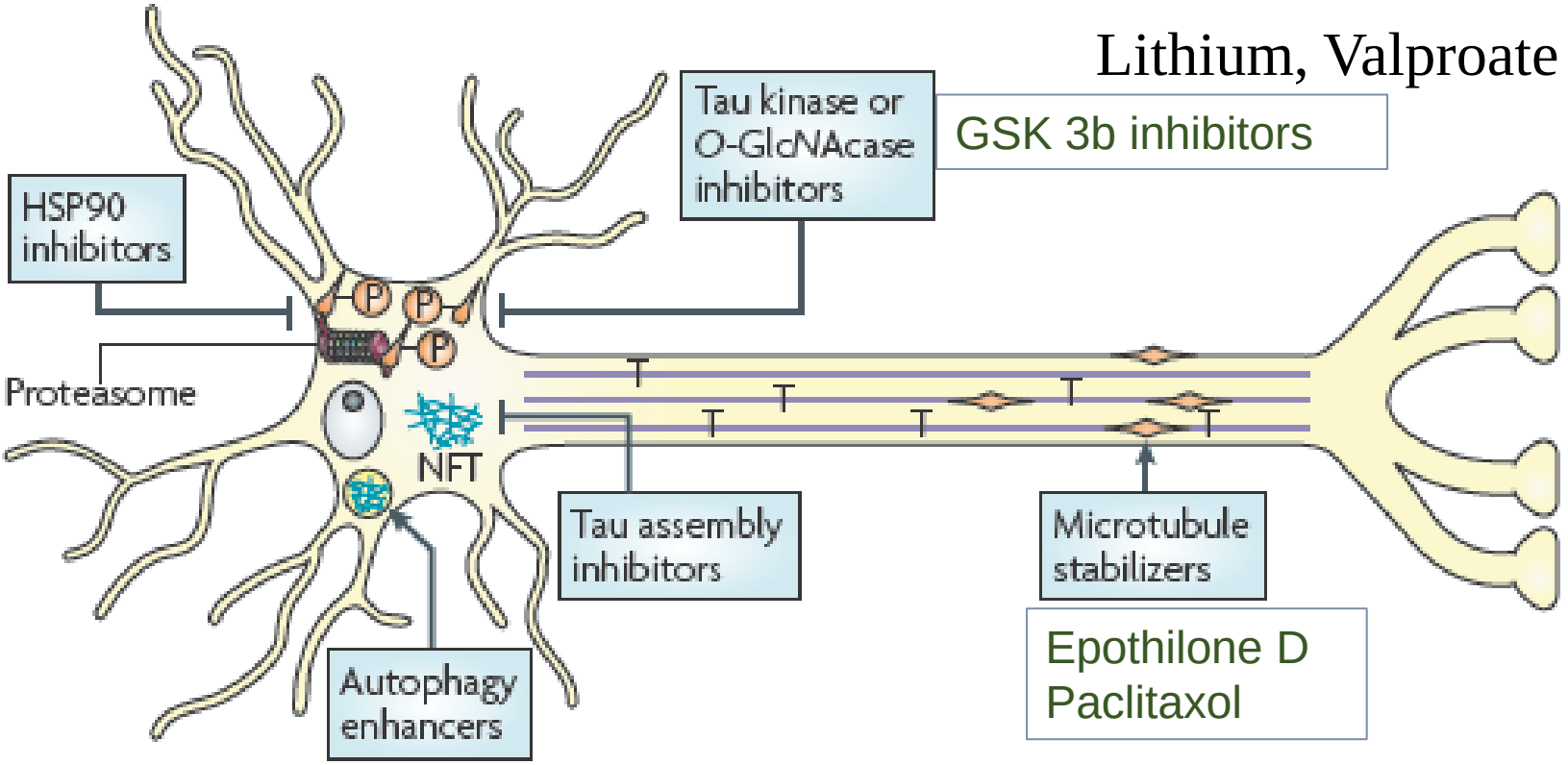
Querfurth HW, LaFerla,FM *N Engl J Med* 2010:362:329-44

Other target: Anti-tau drugs against Neurofibrillary tangles



- **Tangles include intracellular aggregates of microtubule-associated proteins (tau) that are hyper-phosphorylated.**
- **Increase correlates with symptoms, progression, severity.**

Treatments Directed at Microtubules and Tau Pathology



IMMUNOTHERAPY DIRECTED AT TAU OLIGOMERS

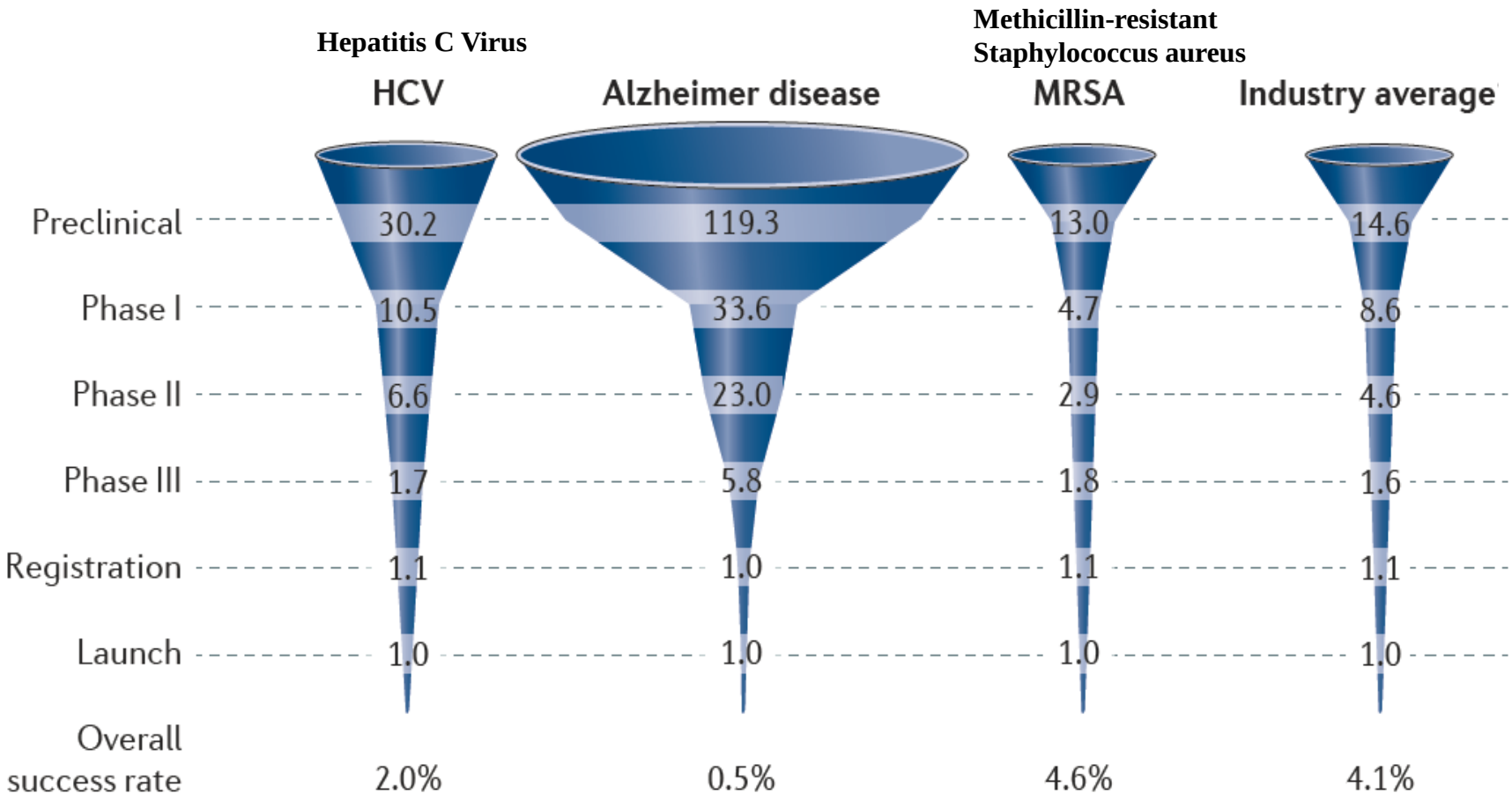
Adapted from Brunden et al *Nature Rev Drug Discovery* 2009; Boutajangout et al *J Neurosci* 2010

Anti NFT approaches

(Knopman (2021), Nature Reviews, Disease Primers, Alzheimer Disease. Vol 7, pp 33.)

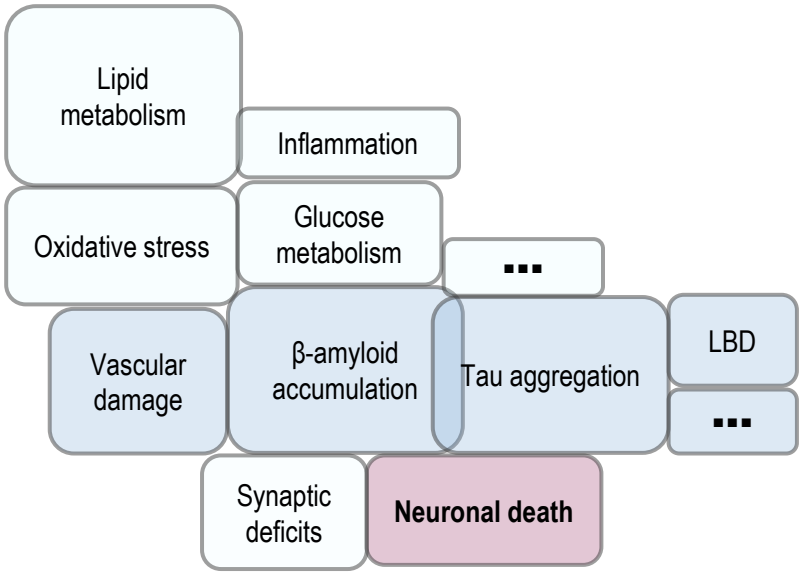
- Genetic targeting: Antisense oligonucleotides to suppress tau gene (MAPT). Current BIIB080 intrathecal ASO against tau mRNA.
- Immunotherapy vs. N-terminal: 4 negative trials of monoclonal antibodies at phase 2 (Gosuranemab, Tilavonemab, Semorinemab, Zagotenemab).
- Immunotherapy vs. C-terminal and MTBR (Microtubule binding region): Current Esai: E2814, UCB 0107, AF87908
- Combining with anti-amyloid therapy (DIAN-TU, presymptomatic FAD subjects).
- Unanswered questions: Primary tauopathy (PSP), vs. secondary tauopathies (AD). 3 repeat vs. 4 repeat tauopathy, etc.

Attrition Profile for Drug Development for Alzheimer's Disease

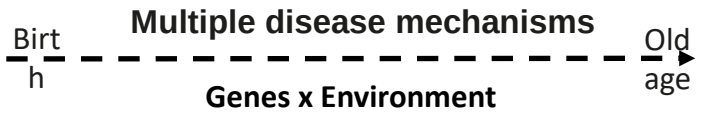


Calcoen, Elias & Yu. Nature Reviews Drug Discovery 14, 161–162 (2015)

How to treat Alzheimer's & Dementia? – Complex & Multifactorial illness



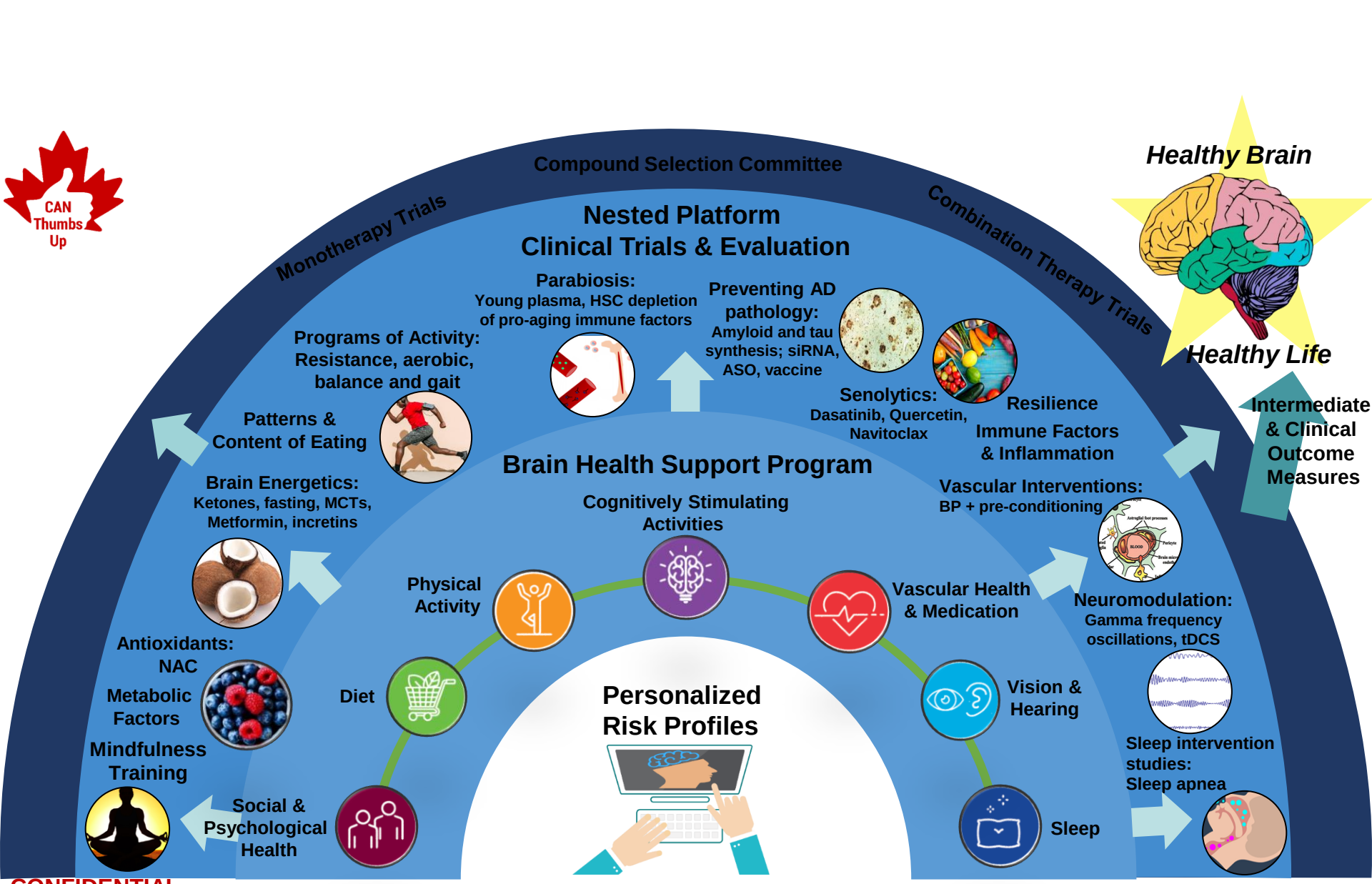
Norton et al, Lancet Neurol 2014
Livingston et al., Lancet 2020



Boyle et al., Ann Neurol 2018
Kivipelto, Ngandu et al., Nature Neurology (in press)

Diabetes	**Depression**
Hypertension	**Smoking**
Obesity	**Low education**
Physical inactivity	**Alcohol, air pollution**

Slide courtesy of Dr. Miia Kivipelto


CAN Thumbs Up
Compound Selection Committee
Monotherapy Trials
Combination Therapy Trials
Nested Platform
Clinical Trials & Evaluation
Healthy Brain
Healthy Life
Parabiosis:
Young plasma, HSC depletion of pro-aging immune factors
Preventing AD pathology:
Amyloid and tau synthesis; siRNA, ASO, vaccine
Programs of Activity:
Resistance, aerobic, balance and gait
Senolytics:
Dasatinib, Quercetin, Navitoclax
Resilience
Immune Factors & Inflammation
Intermediate & Clinical Outcome Measures
Patterns & Content of Eating
Brain Health Support Program
Brain Energetics:
Ketones, fasting, MCTs, Metformin, incretins
Cognitively Stimulating Activities
Vascular Interventions:
BP + pre-conditioning
Physical Activity
Vascular Health & Medication
Neuromodulation:
Gamma frequency oscillations, tDCS
Antioxidants:
NAC
Metabolic Factors
Diet
Personalized
Risk Profiles
Vision & Hearing
Sleep intervention studies:
Sleep apnea
Mindfulness Training
Social & Psychological Health
Sleep
CONFIDENTIAL

The coming Alzheimer Disease prevention / treatment cocktail

Neurotransm modulators

Neuroprotection

Dietary interventions/ Medical food

Amyloid & Tau lowering molecules

Next generation targets

Risk factors intervention

Cocktail vs. Personalized Medicine

Chertkow lab- prior to pandemic

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Thank you! Time for questions