UPDATE ON ALZHEIMER'S DISEASE CLINICAL TRIALS

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National Institute on Aging

Currently FDA Approved Treatments for AD

- The U.S. Food and Drug Administration (FDA) has approved two types of medications to treat cognitive symptoms of AD.

- Provide temporary cognitive improvement and deferred decline in some patients

Currently Approved Treatments for AD

- Cholinesterase Inhibitors*
  - Donepezil (Aricept)
  - Rivastigmine (Exelon)
  - Galantamine (Razadyne)
- Memantine (Namenda)#

*Cholinesterase inhibitors are drugs that block the activity of an enzyme in the brain: cholinesterase. Cholinesterase breaks apart acetylcholine, a neurotransmitter vital for the transmission of nerve impulses. Cholinesterase inhibitors reduce the action of cholinesterase, thus making more acetylcholine available to neurons.

#N-Methyl-D-aspartate (NMDA) antagonist; thought to be a neuroprotective agent that blocks excitotoxicty; May have a potentially disease modifying effect

Failure of AD Candidate Therapeutics in the Clinic

Phase III randomized, placebo controlled , double-blind clinical trials

Agent	Target/Mechanism	Outcome
Atorvastatin	HMG CoA reductase	Negative
Dimebon	Mitochondrial function	Negative
LY450139	Gamma secretase	Negative
NSAIDs	Inflammation	Negative
Phenserine	Cholinesterase/Amyloid	Negative
Rosiglitazone	PPAR gamma agonist	Negative
Simvastatin	HMG CoA reductase	Negative
Tarenflurbil	Gamma secretase	Negative
Xaliproden	Serotonin antagonist	Negative

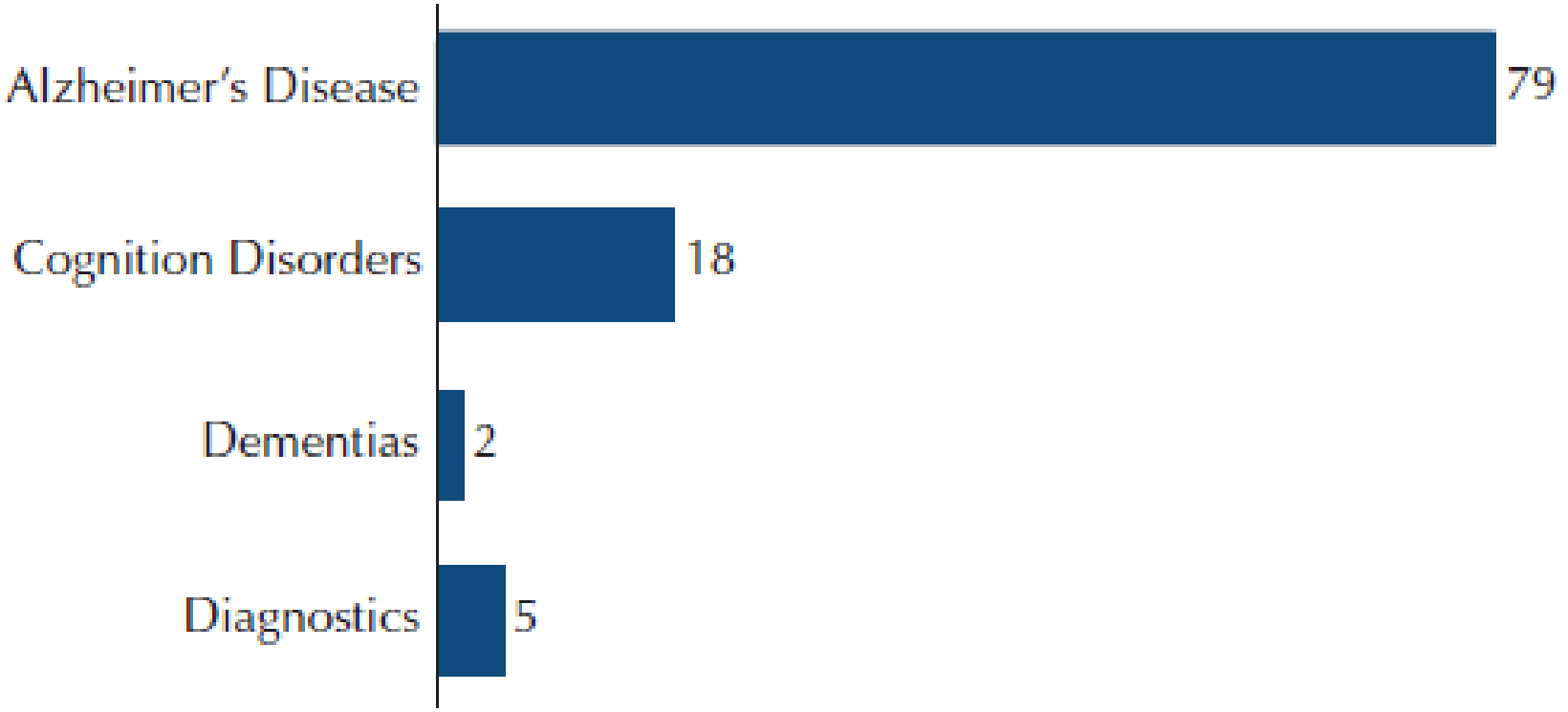
The most common reasons for Phase III failure: *lack of efficacy and toxicity.*

- If no new medicines are found to prevent, delay or stop the progression of Alzheimer's disease, the number of afflicted in America will jump to 13.5 million by 2050 (Alzheimer's Association).

- Costs for care for Alzheimer's patients will increase five-fold to $1.08 trillion a year. That is about 25 times more than the 2010 budget for the Department of Homeland Security.

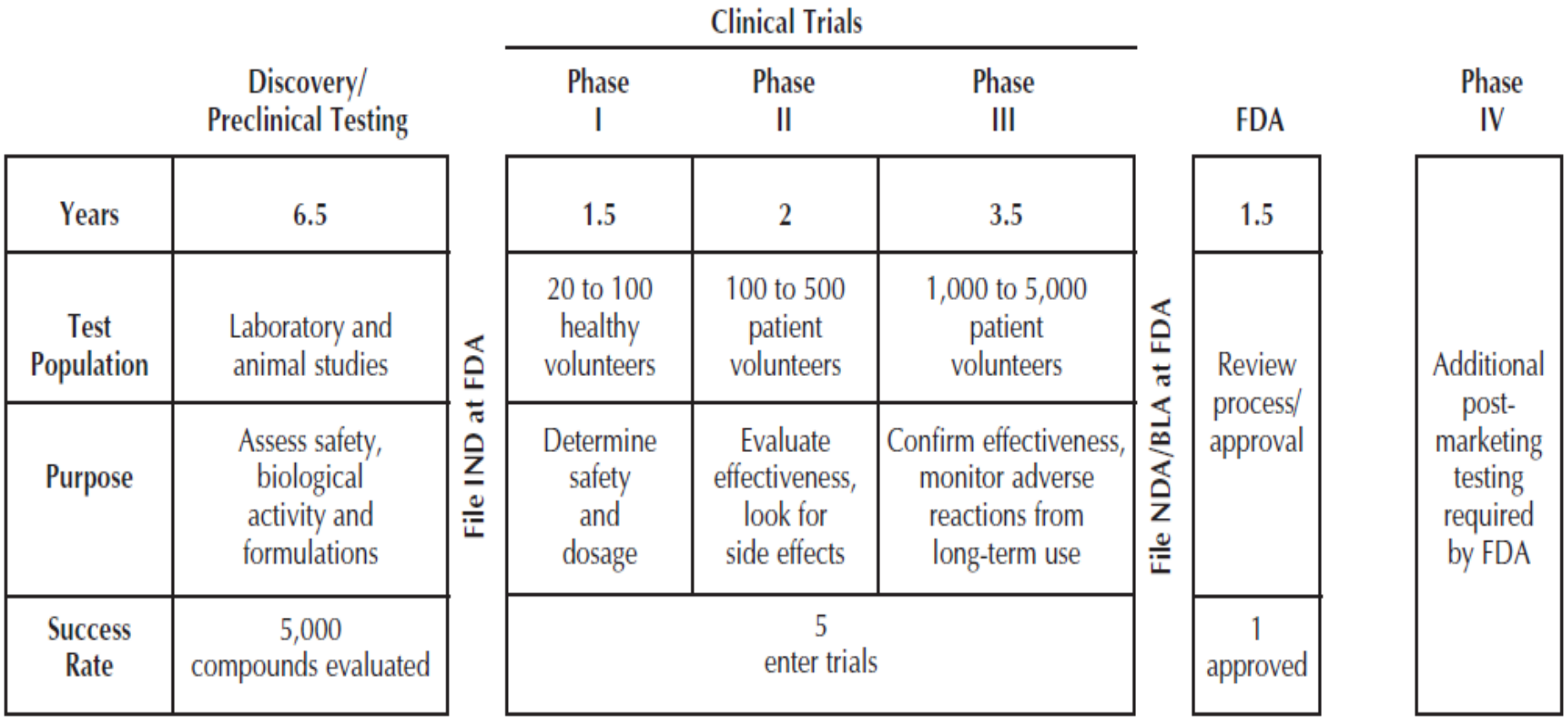
MEDICINES IN DEVELOPMENT FOR **Alzheimer's Disease** 2010

Medicines in Development for Alzheimer's Disease*



* Some medicines are in development for more than one disorder.

The Drug Discovery, Development and Approval Process



It takes 10-15 years on average for an experimental drug to travel from the lab to U.S. patients. Only five in 5,000 compounds that enter preclinical testing make it to human testing. One of these five tested in people is approved.

Disease Modification

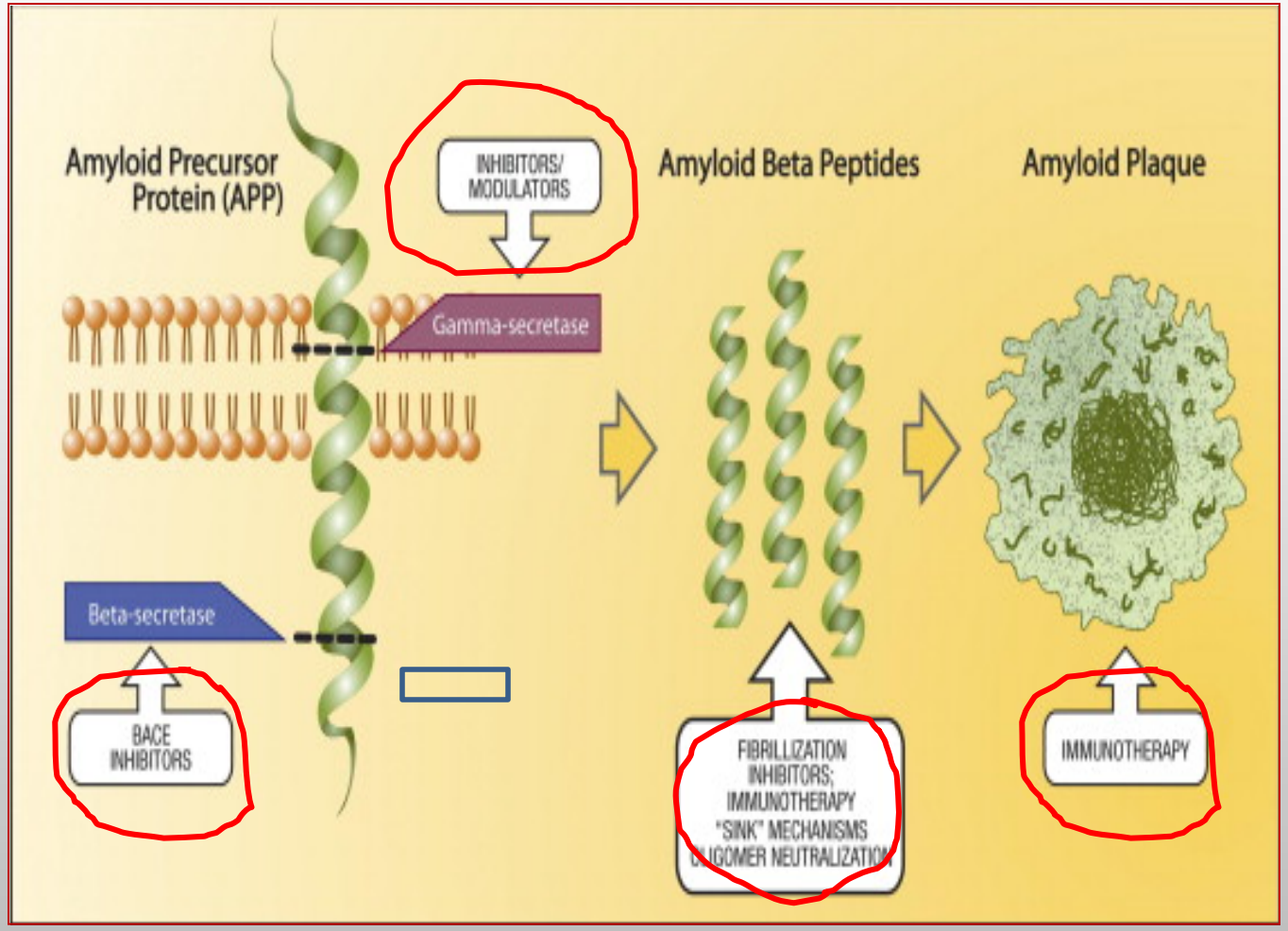
- An improved understanding of the pathogeneses of AD has led to the identification of numerous therapeutic targets

- Many of these targets have been validated in proof of concept studies in preclinical animal models, and a number are being tested in human clinical trials.

Avenues for New AD Therapies

- Prevent build up of plaque (anti-amyloid)
  - slow or prevent amyloid production by inhibiting clipping enzymes or by vaccine therapy
  - slow aggregation into plaques
  - dissolve plaques
  - increase clearance
- Prevent build up of paired helical filaments (tau focused)
  - slow or prevent tau aggregation and dysfunction
  - dissolve paired helical filaments
- Prevent brain cell dysfunction and death
  - slow or prevent oxidative stress, inflammation, reduced blood flow
  - increase levels of protective molecules in brain
  - maintain viable connections between cells

Amyloidogenic Pathways: Possible Therapeutic Targets



Salloway, S. et al. *Alzheimer's and Dementia 2008; 4: 65-79*

Aβ Immunotherapy

- Altering Aβ deposition by inducing a humoral immune response to fibrillar Aβ42 (active) or administering anti-Aβ antibodies (passive)

AN1792: Active Immunization

- Initial human clinical trial was halted due to a meningoencephalitis in 6% of treated subjects.
- Leading hypothesis, supported by some recent experimental data: SAE attributable to an autoreactive T-cell response against Aβ.
- Passive immunization approaches do not initiate this type of response; in human trials
- Alternative active immunization strategies are in human trials

AN1792: Active Immunization

- **AN1792 4½ year follow-up:**
  - After active immunization was D/C'd, researchers continued to follow the participants.
  - Patients who developed antibodies to Aβ continued to show detectable Aβ antibodies and less decline in activities of daily living (ADL) compared to placebo treated patients.

PASSIVE IMMUNIZATION :

IVIg – Intravenous Immunoglobulin (Gammagard)

Purified human immunoglobulin preparation recently found to contain polyclonal anti-Aβ antibodies

PHASE II: 24 patients with mild to moderate AD, one of four doses of IVIg or placebo for 24 mos.

.

RESULTS: Treatment with IVIg over nine months resulted in statistically significant improvements on both cognitive and global clinical measures; FDG-PET: treated groups were observed to show 16% higher brain metabolism (hippocampus, temporal-parietal regions) after treatment compared to placebo

SAFETY: No significant side effects

PHASE III: supported by the NIA through the Alzheimer's Disease Cooperative Study (ADCS), and Baxter, N=390

Aβ Immunotherapies in development.

Drug Name	Sponsor	Characteristics		Phase
Monoclonal Antibodies		*Epitope**	*Isotype*	
Bapineuzumab (AAB-001)	Janssen/Elan/Pfizer	1–5 (free N- terminus)	IgG1	III
Solanezumab (LY2062430)	Eli Lilly	13–28	IgG1	III
PF-04360365	Pfizer	33–40 (free C- terminus)	IgG2	II
MABT5102A	Genentech	NP	NP	I
GSK933776A	GlaxoSmithKline	NP	NP	I
Gantenerumab (R1450/RO4909832)	Hoffmann-La Roche	NP	IgG1	I
Intravenous Immunoglobulin				
Gammagard	Baxter; NIH Alzheimer's Disease Cooperative Study			III
Octagam	Octapharma			II
Active Vaccines		*Fragment**		
CAD106	Novartis	1–6		II
ACC001	Pfizer	1–7		II
UB311	United Biochemical	1–14		I
V950	Merck	NP		I
AD01/AD02	Affiris	**		I

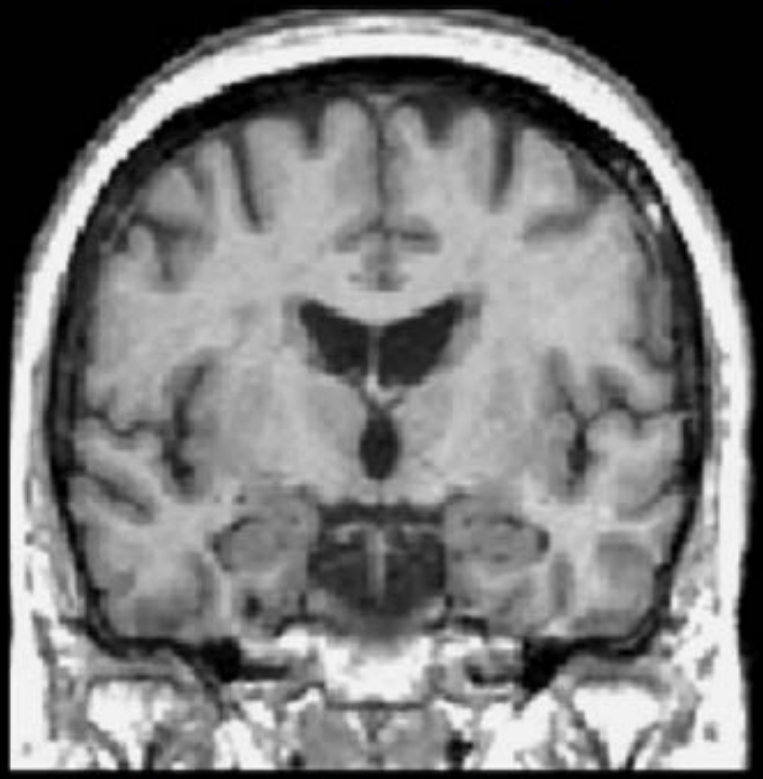
Kerchner & Boxer *Expert Opin Biol Ther.* 2010 July; 10(7): 1121–1130

AD Neuropathology

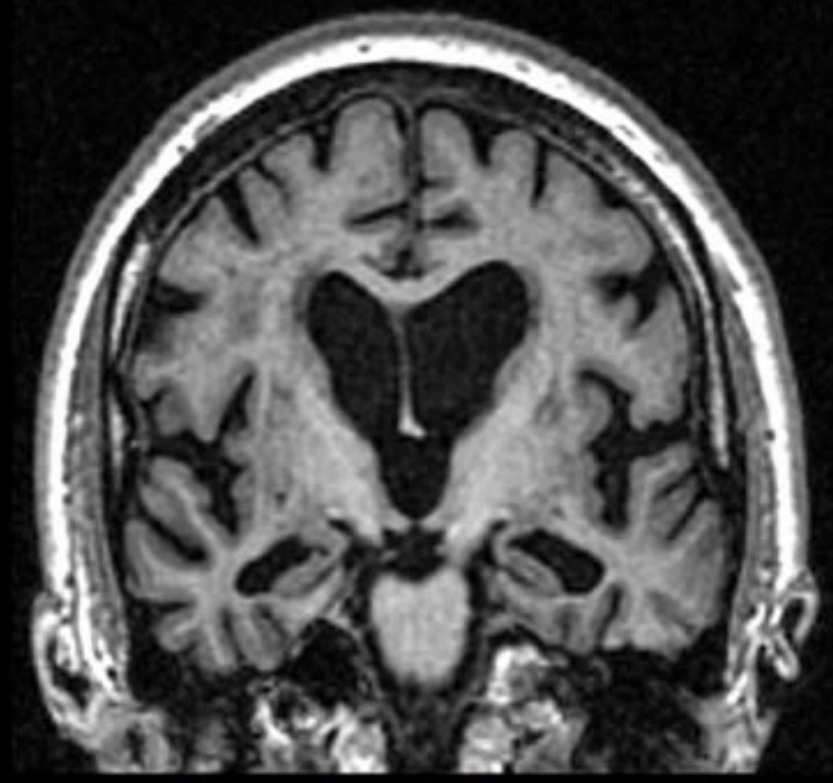
- A growing body of evidence suggests that the underlying pathology precedes the onset of clinically detectable AD by a decade or more

- By the time a patient is diagnosed, there is thought to be massive neuronal loss and widespread pathology

Widespread neuronal loss by the stage of dementia



Cognitively Normal
(age = 77)



Patient with AD Dementia
(age = 77)

From Sperling, ADCS 2012 winter SC meeting, Austin, TX

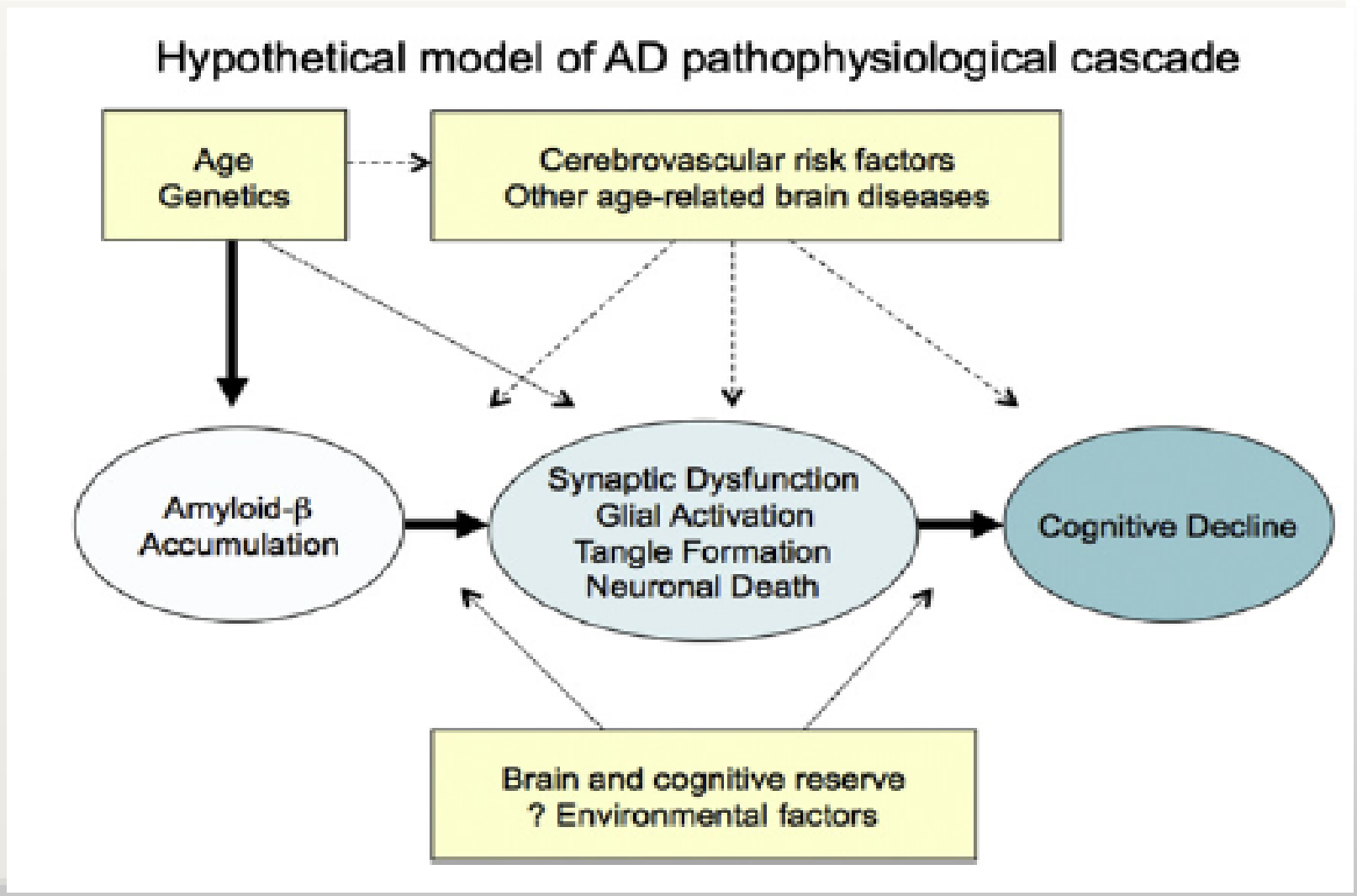


Fig. 2. Hypothetical model of the Alzheimer's disease (AD) pathophysiological sequence leading to cognitive impairment. This model postulates that Aβ accumulation is an "upstream" event in the cascade that is associated with "downstream" synaptic dysfunction, neurodegeneration, and eventual neuronal loss. RA Sperling et al. http://dx.doi.org/10.1016/j.jalz.2011.03.003

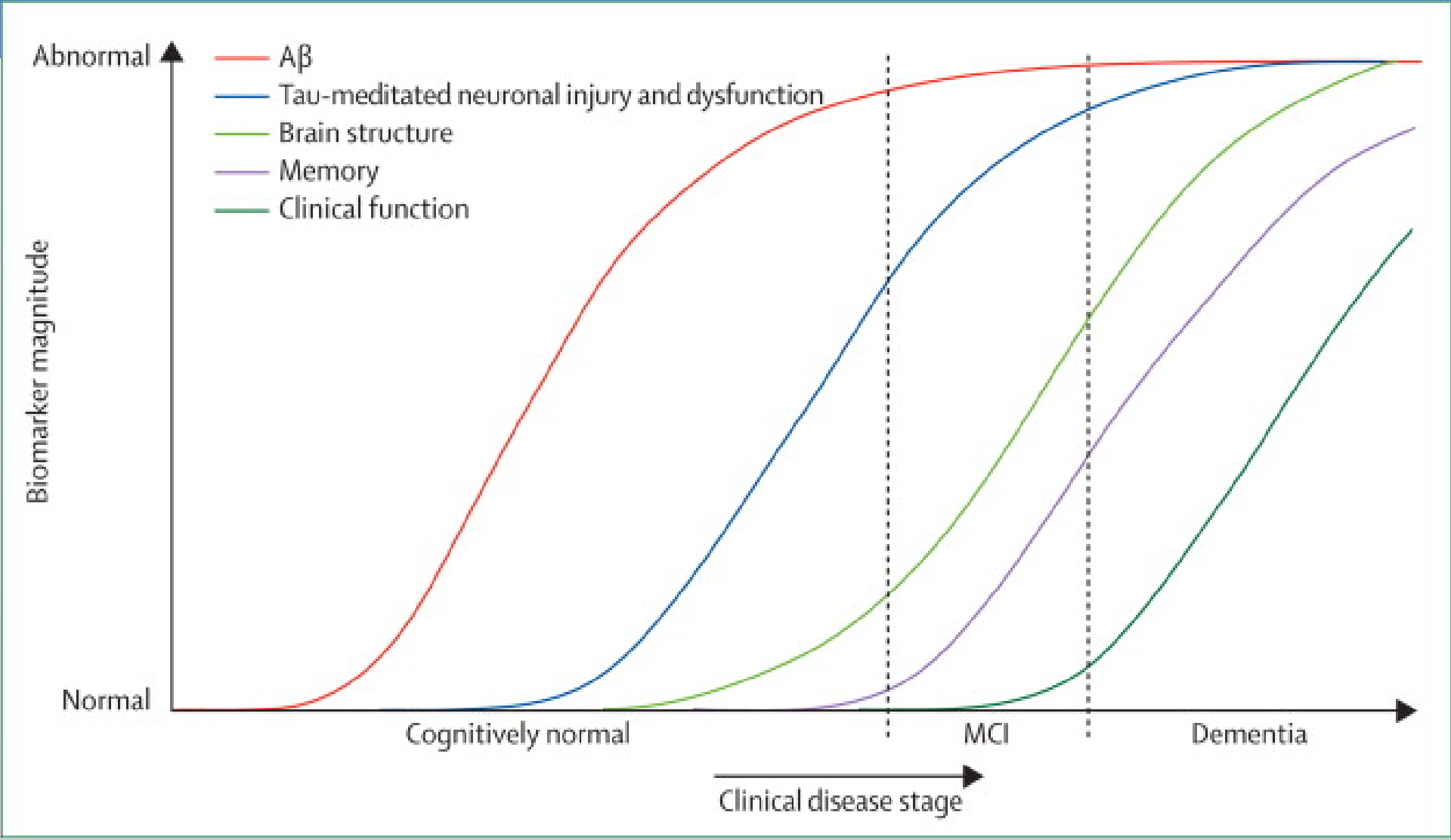
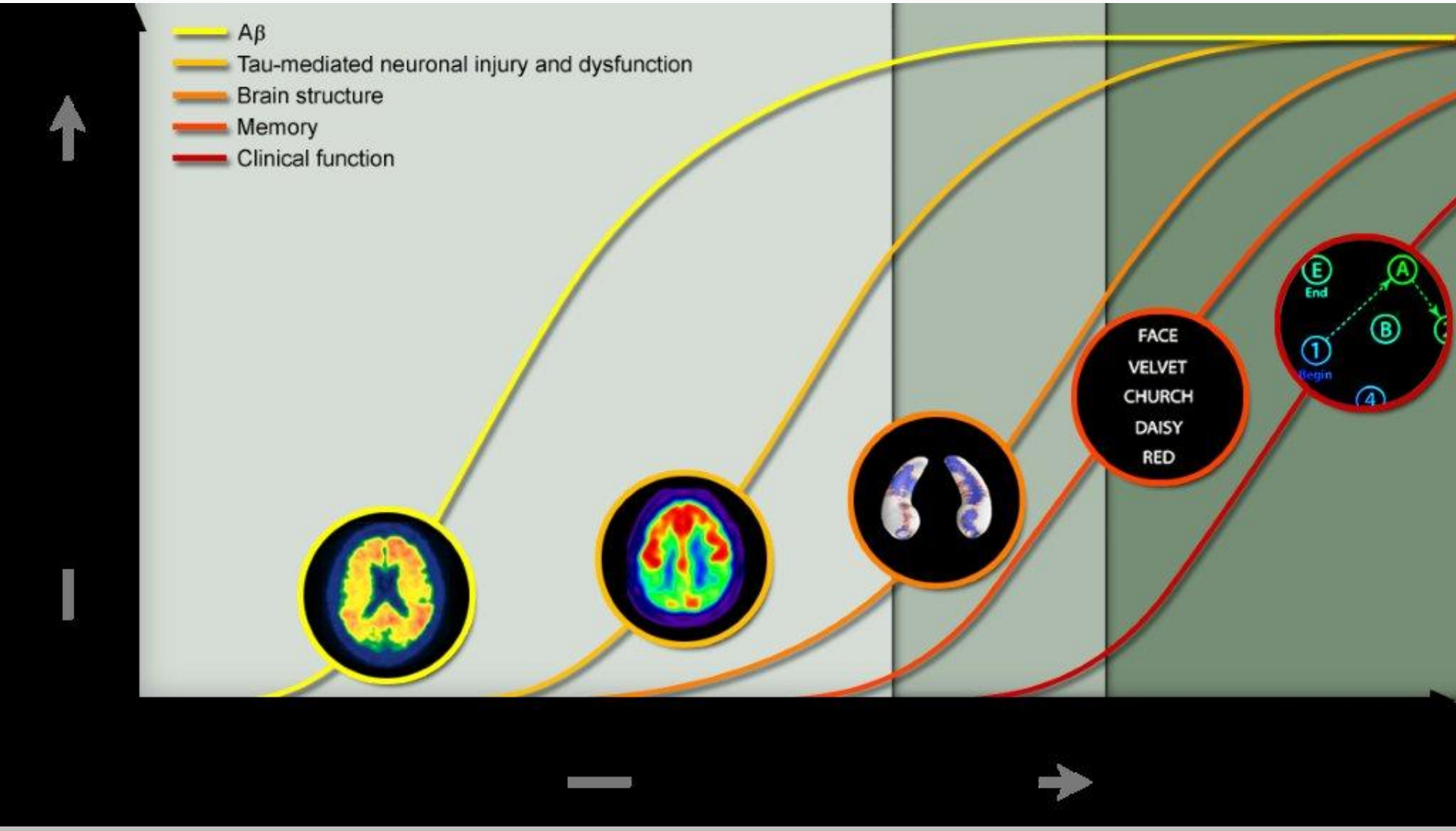


Figure 2. Dynamic biomarkers of the Alzheimer's pathological cascade
Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.


Aβ
Tau-mediated neuronal injury and dysfunction
Brain structure
Memory
Clinical function
FACE
VELVET
CHURCH
DAISY
RED
E
End
A
B
1
Begin
4

ADNI - LONI

The Continuum of Alzheimer's Disease

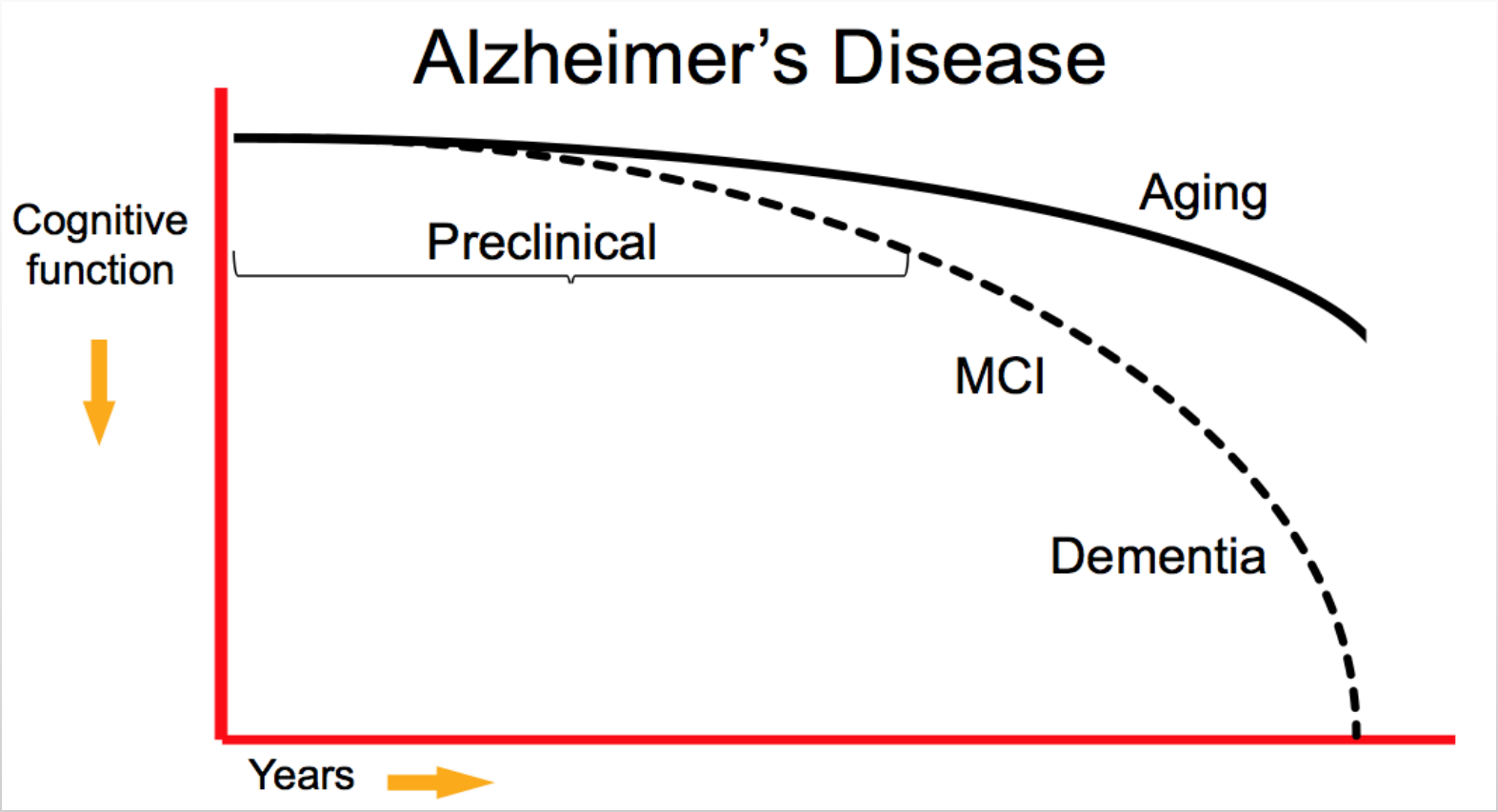


Fig. 1 The stage of preclinical AD precedes mild cognitive impairment (MCI) and encompasses the spectrum of presymptomatic autosomal dominant mutation carriers, asymptomatic biomarker-positive older individuals at risk for progression to MCI due to AD and AD dementia, as well as biomarker-positive ndividuals who have demonstrated subtle decline from their own baseline that exceeds that expected in typical aging, but would not yet meet criteria for MCI.
RA Sperling et al http://download.journals.elsevierhealth.com/pdfs/journals/1552-5260/PIIS1552526011000999.pdf

COMMENTARY

ALZHEIMER'S DISEASE

Testing the Right Target and Right Drug at the Right Stage

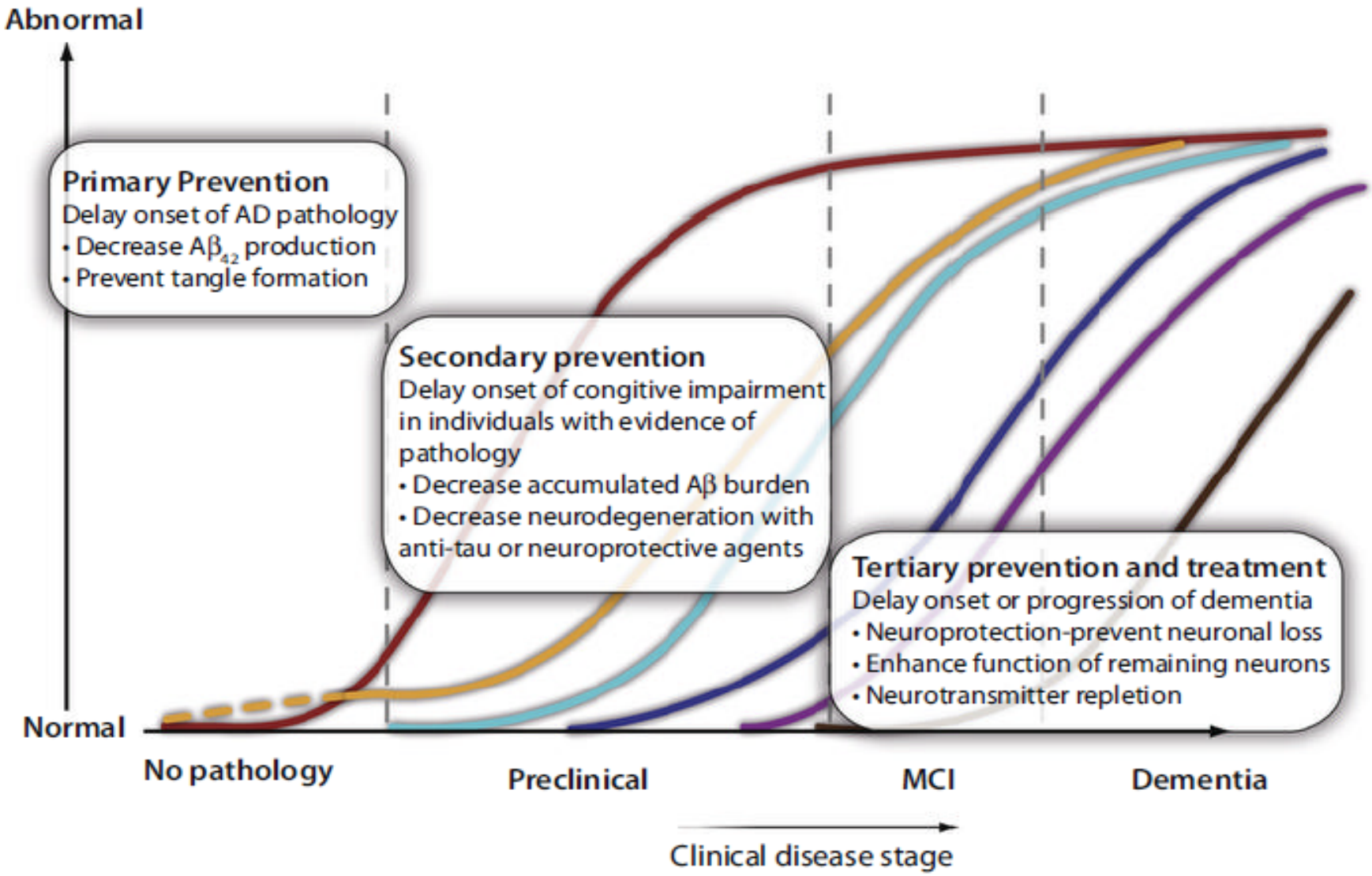
Reisa A. Sperling,[1*] Clifford R. Jack Jr.,[2] Paul S. Aisen[3]

Alzheimer's disease (AD) is the only leading cause of death for which no disease-modifying therapy is currently available. Recent disappointing trial results at the dementia stage of AD have raised multiple questions about our current approaches to the development of disease-modifying agents. Converging evidence suggests that the pathophysiological process of AD begins many years before the onset of dementia. So why do we keep testing drugs aimed at the initial stages of the disease process in patients at the end-stage of the illness?

Implications for the development of effective treatments

- Suggests that researchers should begin to
  - 1) target selected therapies to specific stages of AD and
  - 2) think about the disease in terms of primary, secondary, and tertiary prevention rather than lumping together all disease-modifying treatments across the disease spectrum (see figure 1)

RA Sperling et al www.ScienceTranslationalMedicine.org Nov 2011 Vol 3



www.ScienceTranslationalMedicine.org 30 November 2011 Vol 3 Issue 111 111cm33

Implications for the development of effective treatments

- It is hoped that the advances in pre-clinical detection of AD will enable earlier, more effective treatment,
  - nearly all of therapeutic gains in cancer, cardiovascular disease, osteoporosis, and diabetes involve treatment before significant clinical symptoms are present

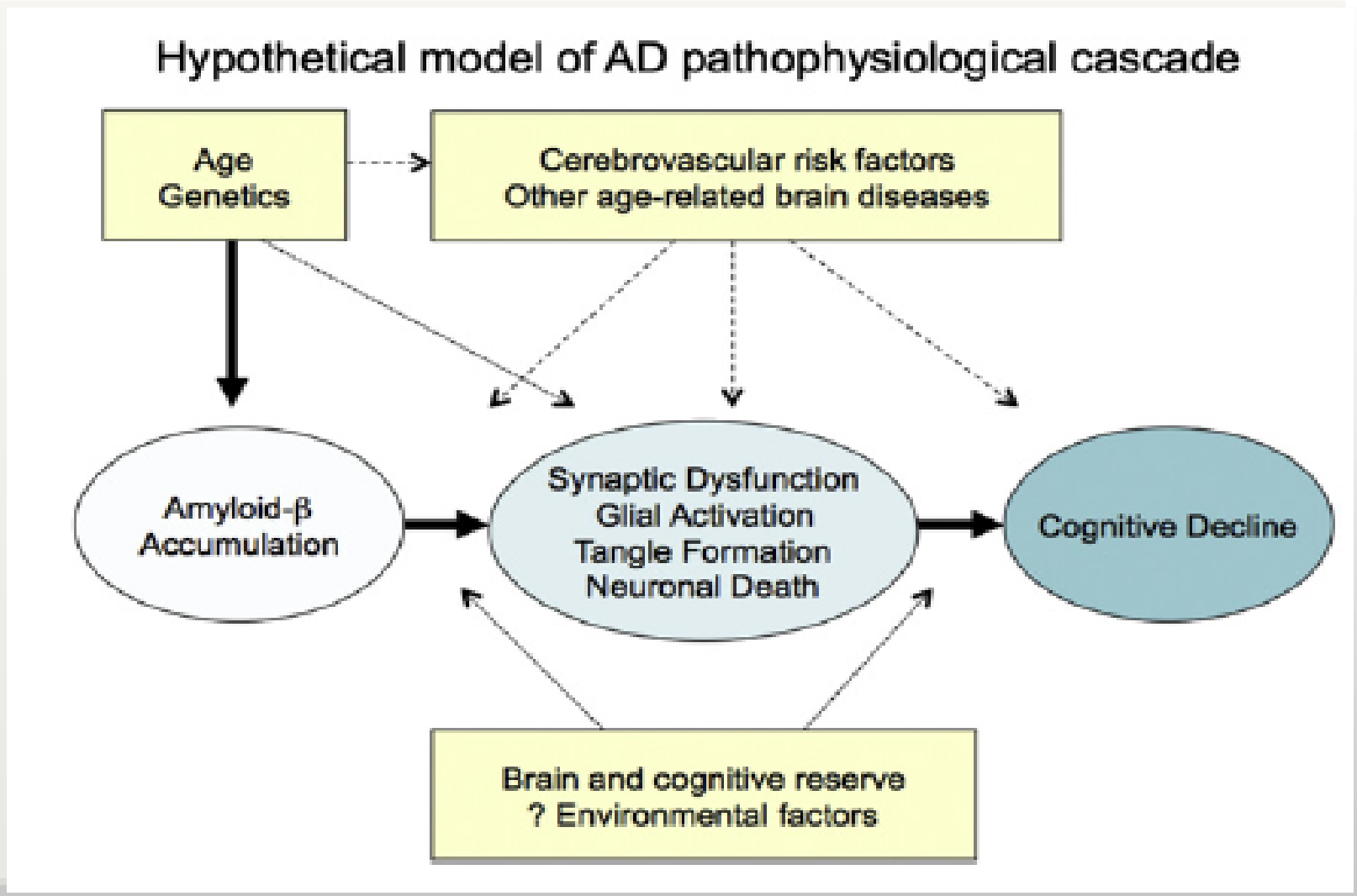
- It is possible that promising drugs, particularly amyloid-modifying agents, may fail to affect the clinical course of AD at the stage of dementia or even MCI, when the neurodegenerative process is well established, but may be beneficial at the earliest stages of the AD, before the onset of symptoms

RA Sperling et al http://download.journals.elsevierhealth.com/pdfs/journals/1552-5260/PIIS1552526011000999.pdf; RA Sperling et al www.ScienceTranslationalMedicine.org Nov 2011 Vol 3

PRESYMTOMATIC

Anti-Amyloid treatment in Asymptomatic AD (A4 Trial)

- ADCS
- Converging evidence from both age and genetic at risk cohorts that the pathophysiological process of AD begins more than a decade before dementia
- Aβ accumulation is thought to be one of the critical factors in the early pathogenesis of AD
- Multiple trial failures at the stage of mild to moderate dementia with anti-Aβ therapies, despite evidence of biological activity
- Need to intervene much earlier to adequately test the amyloid cascade hypothesis



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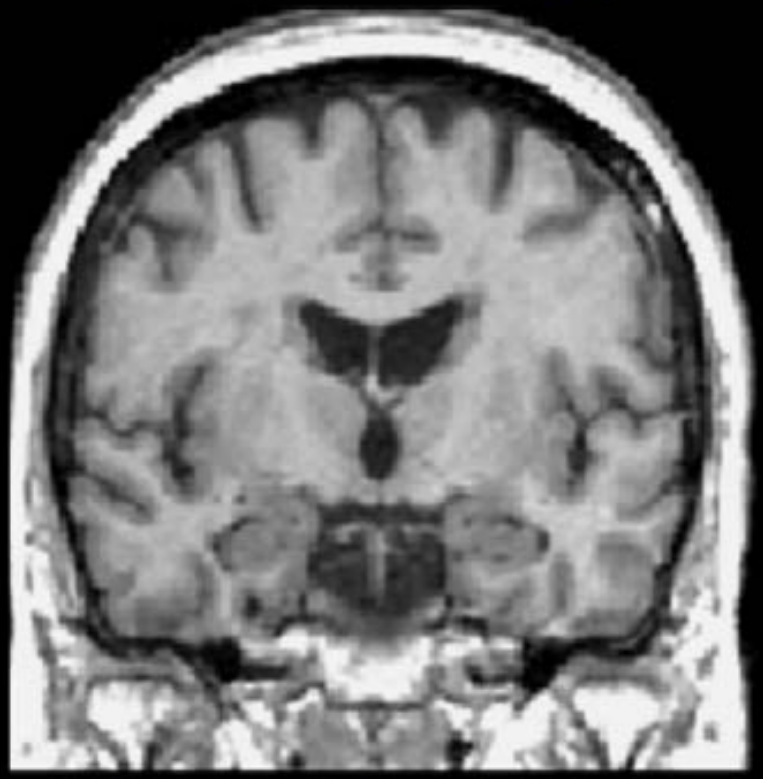
Widespread neuronal loss by the stage of dementia



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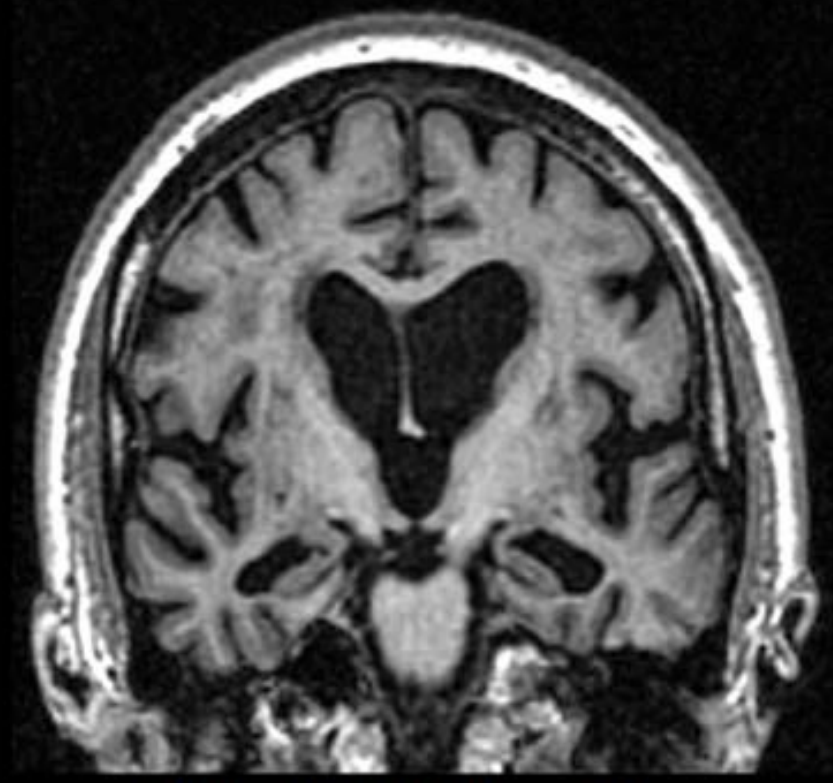

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A4 Trial Aims

- To determine whether decreasing Aβ burden will slow the rate of cognitive decline in clinically normal older Aβ+ individuals at risk for progression to MCI and AD dementia

- To investigate the impact of anti-Aβ treatment on "downstream" markers of neurodegeneration, and explore whether there is a "critical window" for anti-Aβ therapy within the preclinical stages of AD

- To develop more sensitive outcome measures to improve the efficiency of future secondary prevention trials

A4 Trial Design

- Clinically normal older individuals (> age 70) Aβ+ on PET imaging
- Treat with biologically active compound for 3 years in a randomized, double-blind, placebo-controlled trial
- Total N=1000 (N=500 per treatment arm)
- 2 year additional clinical follow-up
- Test the hypothesis that altering “upstream” amyloid accumulation will impact ”downstream” neurodegeneration and cognitive decline
- Include Aβ- arm (N = 500) for natural history study (no treatment) for clinical and novel outcomes

DIAN Coordinating Center at Washington University

DIAN
Dominantly Inherited Alzheimer Network

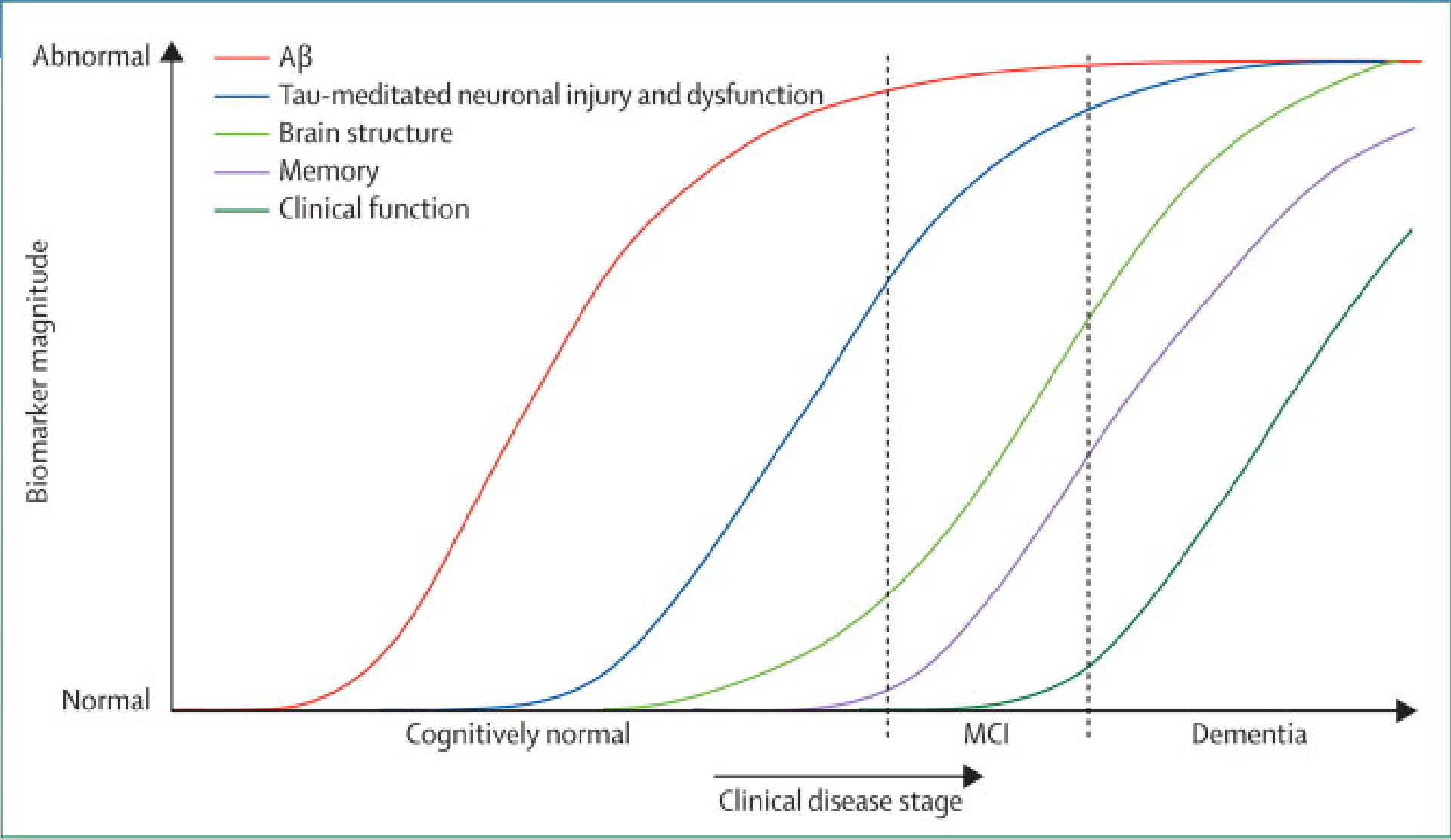
Goals

Enroll 400 individuals from families with a known pathogenic mutation for AD

Longitudinally study carriers in comparison with sibling noncarriers for rate and sequence of AD biomarker changes prior to expected AAO of AD

Performance Sites

- US: Washington Univ (Bateman), MGH/BWH (Sperling), Butler Hosp/Brown Univ (Salloway), Columbia Univ (Mayeux), Indiana Univ (Ghetti), UCLA (Ringman)
- UK: Institute of Neurology, Univ College London (Rossor)
- Australia: Prince of Wales Medical Research Institutes, Sydney (Schofield), Mental Health Research Institute, Melbourne (Masters), Edith Cowan Univ , Perth (Martins)



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DIAN Clinical Trials

- First phase:
  - Compare three different drugs to a shared placebo group.
  - Each drug arm would enroll 80 people, assigning non-carriers to placebo to maintain genetic status blinding, and randomizing mutation carriers to drug versus placebo in a 3 to 1 ratio (a 75 percent chance of receiving drug).
  - Determine whether the drug engages its intended target and whether it affects any downstream biomarkers of neurodegeneration
  - First phase would go on for two years, at which point drugs that met primary aims would be considered for longer-term cognitive endpoint studies.

DIAN Clinical Trials

- Second phase:
  - Drugs that met primary aims would be considered for longer-term cognitive endpoint studies.
  - Those drugs would then be tested in the entire population for three more years. Such a larger, longer trial is necessary for this second phase because its cognitive endpoints are likely to be subtle and change slowly in asymptomatic or very mildly symptomatic family members.
  - If none of the three drug hits its target or a downstream biomarker in the first four-arm phase, then it would also likely fail to provide a cognitive benefit later on. Three new drugs would then be chosen for a second Phase 1 study.

Alzheimer's Prevention Instrument (API)

- Cognitively normal AD-causing *presenilin 1* (PS1) *E280A* mutation carriers, at least 35 years of age (i.e., within 10 years of the carriers' estimated median age at clinical onset), from the world's largest early-onset AD kindred, located in Antioquia, Colombia.

- Kindred includes about 5,000 people with a sufficient number of presymptomatic carriers in the targeted age group to make it possible to relate a treatment's effects on both biomarker and clinical endpoints within 2–5 years.

- *PS1* mutation carriers would be randomized to active treatment or placebo, non-carriers would be assigned to placebo

Reiman et al. *Journal of Alzheimer's Disease* 26 (2011) 321–329

API

- 24 months double-blind, randomized, placebo-controlled trial using amyloid PET, FDG PET, volumetric MRI, CSF, and cognitive endpoints.

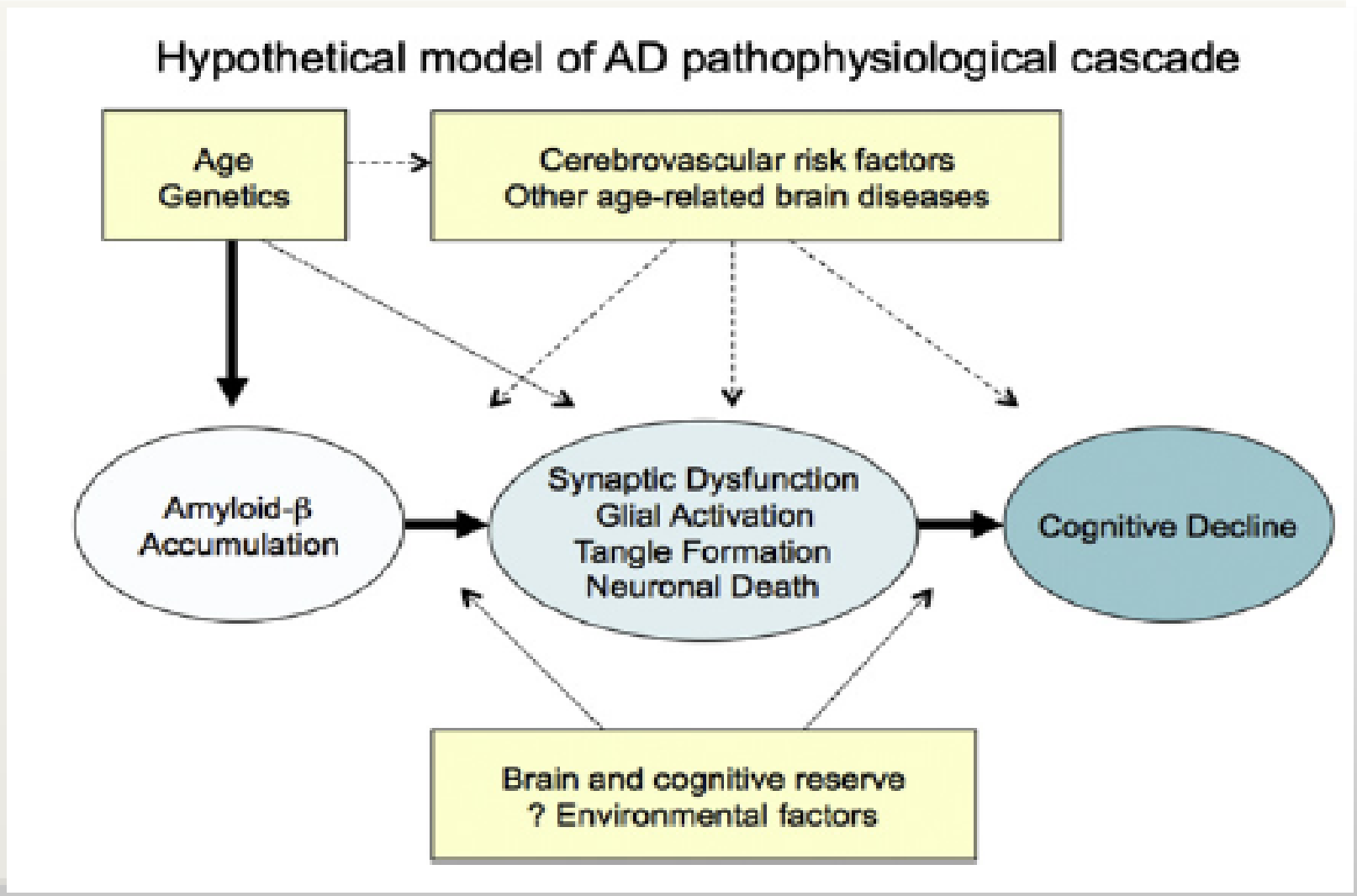
- If after two years, the treatment is not associated with predicted effects on one or more of the biomarkers, the DSMB would declare futility, the trial would be discontinued, and the participants would be eligible to participate in a trial of the next most promising AD-modifying treatment.

- If, however, the treatment is associated with predicted biomarker effects, the trial would be continued to assess effects on a compound cognitive endpoint

Reiman et al. *Journal of Alzheimer's Disease* 26 (2011) 321–329

Targeting Tau

- Increased phosphorylation of the tau protein appears to be a pivotal event in the pathogenesis of AD.
  - Like deposition of Aβ in plaques, accumulation of hyperphsophorylated tau as paired helical filaments within neurofibrillary tangles is a hallmark of AD pathogenesis (Lee and Trojanowski 1992; Selkoe 2001).
  - Hyperphosphorylation of tau is known to interfere with the ability of tau to stabilize and promote the assembly of microtubules (Lee *et al*. 2001; Geschwind 2003).



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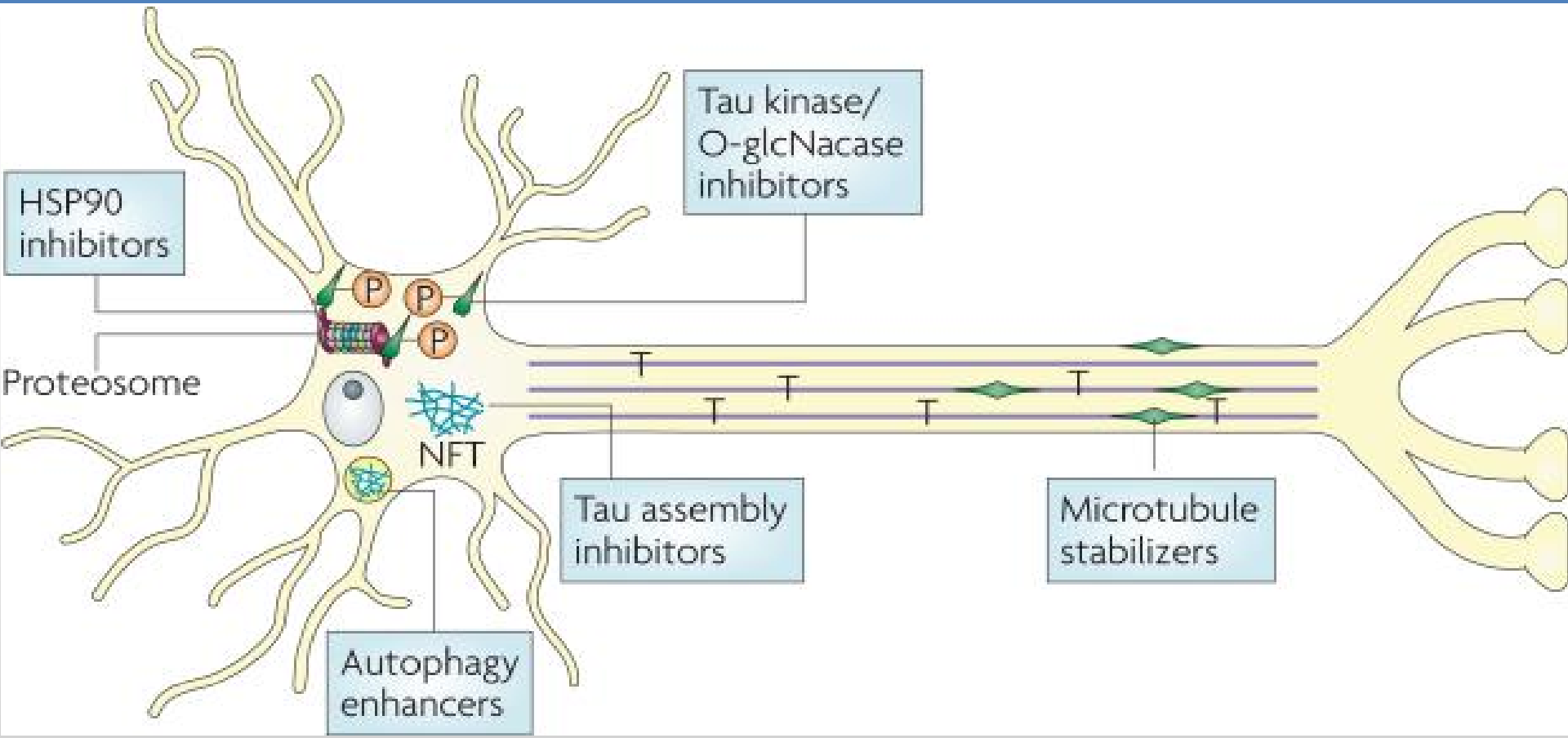
Tau Focused Strategies

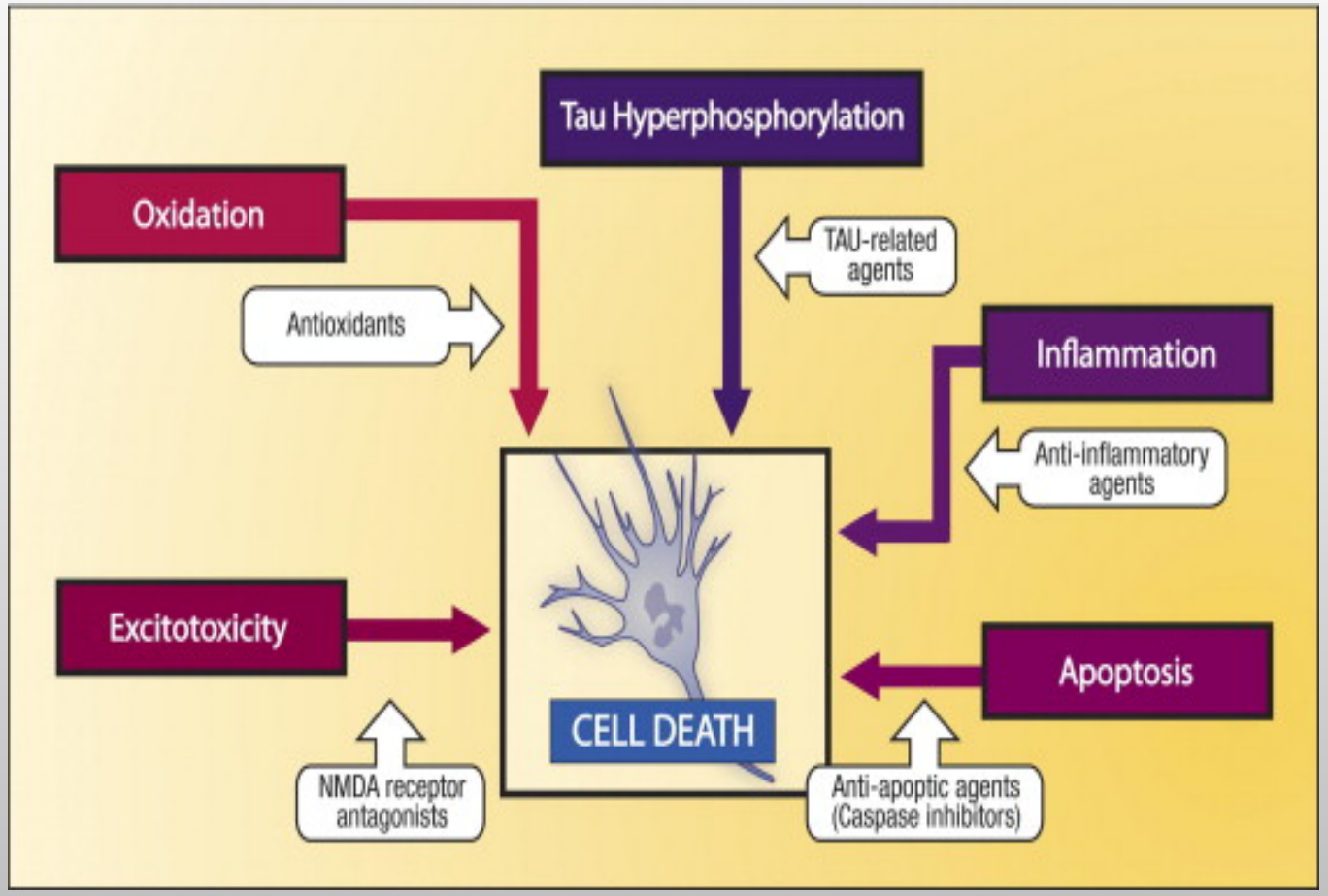
- Although not ignored as a therapeutic target, tau has not received as much attention until recently.

- General strategies for altering tau accumulation include: microtubule stabilizing agents, kinase inhibitors, aggregation inhibitors and methods to enhance clearance of either soluble tau or tau aggregates via chaperones (e.g. HSPs, CHIP) or proteases (e.g. the proteasome).



Bunden, Trojanowski, & Lee. *Rev Drug Discov.* 2009 October ; 8(10): 783–793

Secondary Pathways: Possible Therapeutic Targets



Salloway, S. et al. *Alzheimer's and Dementia 2008; 4: 65-79*

Alternative Strategies Towards Disease Modification

- Both chronic inflammation and oxidative stress are likely to contribute to the degenerative process (Akiyama *et al*. 2000).

- However, to date, treatments targeting these processes (e.g, NSAIDs, Vitamin E, B vitamins, DHA) have not shown efficacy in human trials.

Neuroprotective/Restorative Strategies: Neurotrophins

- Growth factors potently influence neuronal survival and function. They exhibit broad activity against a multitude of toxic mechanisms

- Growth factors offer the potential to treat neurodegenerative disorders

- Gene delivery seems to meet the need for accurately targeted, regionally restricted, safe, and long-term neurotrophin delivery tot he brain.

Tuszynski, *ADAD,* 21, 2007

Neuroprotective/Restorative Strategies: Neurotrophins

- Nerve Growth Factor (NGF): Hypotheses - NGF will protect cholinergic neurons in the pathogenic environment of the AD brain, targeting of the cholinergic system will be sufficient to meaningfully benefit quality of life in patients.

  Tuszynski, *ADAD,* 21, 2007

- <u>NIA Funded Gene Therapy Trial – AAV-NGF:</u>
  - Phase II NGF placebo controlled trial to restore function to degenerating cholinergic neurons; effect on cognition, brain metabolism, safety/tolerability in AD

AD RISK AND INTERVENTIONS

AD Risk Factors

Age

Head Injury

High Blood Pressure

High Cholesterol

High Homocysteine

Diabetes

Diet

Education

Exercise

Social Interaction

Diet and Exercise

- **Mediterranean Diet (MeDi) adherence and physical activity (PA) on AD risk**
  - Prospective multi-ethnic cohort study of 1880 community-dwelling elders without dementia living in New York, New York, with both diet and physical activity information available
  - Results: Risk for incident AD was lower for both higher MeDi adherence and more PA.
  - Adoption of both physical activity and healthy nutrition seem to be independently associated with low risk for AD

Scarmeas, N. et al. *JAMA* 2009;302:627-637

Exercise

- **Home-based Physical Activity**
  - 170 community-dwelling older adults from the Perth Metropolitan area, who were free of dementia, but had subjective memory complaints or Mild Cognitive Impairment
  - Randomized controlled trial of a 24-week physical activity intervention vs. usual care conducted between 2004 and 2007 in metropolitan Perth, Western Australia. Assessors of cognitive function were blinded to group membership.
  - Results: Modest improvement in cognition over 18 months. The effect of exercise was apparent by 6 months and persisted at the 12 and 18-months assessments

Lautenschlager et al *JAMA* 2008

Diabetes Treatment

- Research has suggested that AD and diabetes/insulin resistance are closely related. For example, AD is associated with reduced brain insulin signaling and low levels of insulin in cerebrospinal fluid (CSF). These deficiencies may reduce or eliminate insulin's beneficial roles in the brain.

- **Diabetes Medications:**
  - Postmortem study: 124 older adult diabetic patients and 124 non-diabetic older adult controls

  - Found that those treated with both **insulin and oral diabetic agents** had significantly fewer amyloid plaques (as much as 80 percent) than patients with other medication statuses (none, or only insulin or oral anti-diabetic medication) or non-diabetic controls. Beeri et al., *Neurology*. 2008; 71(10): 750–757

Trials Targeting Diabetes/Insulin Resistance

- Intranasal insulin: Effects on cognition, cerebral glucose metabolism, markers of AD pathology, neuroendocrine functions in AD. Completed

- Insulin Sensitizing Agents:
  - Pioglitazone and Exercise: Effects of the medication or exercise on cognition, inflammation, insulin resistance in individuals with MCI and Metabolic Syndrome. Ongoing
  - Metformin: Effects on cognition, brain metabolism in overweight/obese individuals with MCI. Ongoing

Intranasal Insulin

- Restoring normal insulin function in the brain may provide therapeutic benefits to adults with AD.
- The SNIFF-120 trial was a 4-month, randomized, double-blind trial of placebo vs 2 doses of intranasal insulin (20 or 40 IU).
- 104 patients with AD or amnestic MCI participated; patients with diabetes were excluded.

Craft, et al. *Arch Neurol*. 2012 January ; 69(1): 29–38.

Intranasal Insulin

- Results: 20 IU dose of insulin delayed story recall significantly improved compared to placebo, as did functional status.
- Improvements in delayed memory recall persisted for 2 mos. after treatment ended.

- Improved memory and functional status with insulin were associated with an improved AD biomarker profile as reflected by a lowered CSF Aβ40/42 ratio.

- Also, compared with placebo patients, those in the insulin groups showed preserved glucose metabolism on FDG PET scanning in areas affected by AD pathology.

Craft, et al. *Arch Neurol.* 2012 January ; 69(1): 29–38.

Treatment Approaches For Neuropsychiatric Symptoms In AD

Prevalence of Neuropsychiatric Symptoms in AD

- Behavioral changes/neuropsychiatric symptoms commonly accompany AD, although they are not required for diagnosis
- Prevalence is high, varying from about 60% of individuals in population-based studies , up to 92% in clinical samples

Lykestsos, et al. *Int J Geriatr Psychiatry* 2001;
Fernandez-Martinez, et al. *Curr Alz Res* 2008

- These symptoms are often multiple and simultaneous in dementias
- Contribute to patient distress, add to caregiver burden, increase medical care and costs, and often precipitate institutionalization in nursing homes
- Tend to increase in prevalence and severity as the disease progresses
- Are associated with more rapid cognitive decline

Assal & Cummings, *Curr Opin Neurol* 2002; Beier *Pharmacotherapy* 2007, Bruen, et al *Brain 2008*

Pharmacologic Interventions for Neuropsychiatric Symptoms in AD

- No drugs are specifically approved by the U.S. Food and Drug Administration (FDA) to treat neuropsychiatric dementia symptoms.

- The drugs currently used **“off label”** use, a medical practice in which a physician may prescribe a drug for a different purpose than the ones for which it is approved.

Antipsychotics

- Atypical and conventional antipsychotics have been used to treat agitation, aggression, and psychosis in AD and other dementias
- However these medications are associated with an **increased risk of mortality and cerebrovascular events** in older dementia patients

Gianluca et al *Pharmacol Res* 2008

U.S. Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

Information for Healthcare Professionals
Antipsychotics

FDA ALERT [6/16/2008]: FDA is notifying healthcare professionals that **both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.**

In **April 2005**, FDA notified healthcare professionals that patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. Since issuing that notification, FDA has reviewed additional information that indicates the risk is also associated with conventional antipsychotics.

Antipsychotics are not indicated for the treatment of dementia-related psychosis.

- FDA is requiring the manufacturers of conventional antipsychotic drugs to add a ***Boxed Warning*** **and** ***Warning*** to the drugs' prescribing information about the risk of mortality in elderly patients treated for dementia-related psychosis similar to the *Boxed Warning* and *Warning* added to the prescribing information of the atypical antipsychotic drugs in 2005.*

Serotonergic Antidepressants

- RCTs have demonstrated modest effects in treating depression associated with AD*
- Fairly well tolerated
- One small RCT using citalopram demonstrated reduced agitation in AD patients†
- A large NIA-funded multi-site double-blind RCT of citalopram for agitation in AD began in 2009.

*Beier *Pharmacotherapy* 2007; Sink, Holden, & Yaffe *JAMA* 2005
†Pollock et al. *AJP* 2002

Non-pharmacologic Interventions

- Non-pharmacologic strategies are the cornerstone of the management of AD–related neuropsychiatric symptoms
- However there is a paucity of high quality research, particularly RCTs
- The cumulative research to date suggests these interventions may be efficacious

Ayalon et al. Arch Intern Med 2006; Beier *Pharmacotherapy* 2007

Ongoing NIA Funded Clinical Trials

- Currently support over 30 active clinical trials, including both pilot and large scale trials, of a wide range of interventions to prevent, slow, or treat AD and/or MCI.

- 7 primary and 6 secondary prevention trials. Of the 7 primary prevention trials, 2 are NIA-funded cognitive/AD measure add-ons to large NIH primary prevention trials that address a variety of other primary outcomes.

TABLE 1. Ongoing Alzheimer's Disease/Mild Cognitive Impairment Prevention Trials Funded by NIA

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	TYPE OF TRIAL	ANTICIPATED COMPLETION DATE
		Nutritional			
AREDS2 (Age-Related Eye Disease Study 2)*	John Paul San Giovanni (Study Director), NEI	Macular xanthophylls (lutein and zeaxanthin) and/or omega-3 fatty acids (DHA and EPA)	People age 50-85 with age-related macular degeneration (AMD) in both eyes or advanced AMD in one eye	Primary Prevention	2015
PREADVISE (Prevention of Alzheimer's Disease by Vitamin E and Selenium)†	Frederick Schmitt, University of Kentucky	Vitamin E, selenium, vitamin E + selenium	Men age 60-90	Primary Prevention	2014
Vitamin E in Aging Persons with Down Syndrome	Arthur Dalton, Institute for Basic Research in Developmental Disability	Vitamin E	People age 50+ with Down syndrome, at high risk of developing Alzheimer's disease	Primary Prevention	2012
		Hormones			
ELITE (Early Versus Late Intervention with Estradiol)	Howard Hodis, University of Southern California	17β-estradiol	Healthy early (less than 6 years) or late (10 years +) menopausal women	Primary Prevention	2014
SMART (Somatotrophics, Memory, and Aging Research Trial)	Michael Vitiello, University of Washington	Growth hormone releasing hormone (GHRH)	People with mild cognitive impairment and healthy older adults age 55-80	Secondary Prevention	2011
Testosterone Supplementation in Men with MCI	Monique Cherrier, University of Washington	Testosterone	Older men with MCI and low testosterone	Secondary Prevention	2011
		Cardiovascular			
ASPREE (Aspirin in Reducing Events in the Elderly)	Richard Grimm, Berman Center for Outcomes and Clinical Research; John McNeil, Monash University	Aspirin	Healthy adults age 70+	Primary Prevention	2017

TABLE 1 continued

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	TYPE OF TRIAL	ANTICIPATED COMPLETION DATE
Cardiovascular (Continued)					
SPRINT-MIND (Systolic Blood Pressure Intervention Trial-MIND)†	David Reboussin, Wake Forest University	Blood pressure lowering to <140 mmHg versus <120 mmHg	Adults age 55+ with systolic blood pressure of 130 mmHg or higher, history of cardiovascular disease, high risk for heart disease	Primary Prevention	2017
Metabolic					
Metformin in Amnestic Mild Cognitive Impairment	Jose Luchsinger, Columbia University	Metformin	Overweight/obese older adults with mild cognitive impairment	Secondary Prevention	2012
Pioglitazone and Exercise Effects on Older Adults with Mild Cognitive Impairment and Metabolic Syndrome	Robert Schwartz, University of Colorado, Denver	Pioglitazone	Overweight/obese older adults with mild cognitive impairment	Secondary Prevention	2012
Nonpharmacological					
Exercise Versus Cognitive Interventions for Elders at Risk for Dementia	David Loewenstein, University of Miami	Cognitive training, aerobic exercise training, cognitive training + aerobic exercise training	People with mild cognitive impairment	Secondary Prevention	2012
Memory Training Intervention in Mild Cognitive Impairment	Miriam Mintzer, Johns Hopkins University	Repetition lag training procedure (RLTP)	People with mild cognitive impairment	Secondary Prevention	2014
Preventing Cognitive Decline in African Americans with Mild Cognitive Impairment	Barry Rovner, Thomas Jefferson University	Home-based behavioral treatment	African Americans with mild cognitive impairment	Secondary Prevention	2016

TABLE 2. Ongoing Alzheimer's Disease/ Mild Cognitive Impairment Treatment and Feasibility Clinical Trials Funded by NIA

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	ANTICIPATED COMPLETION DATE
Treatment Trials—Cognition				
Nutritional				
Lipoic Acid and Omega-3 Fatty Acids in Alzheimer's Disease	Lynne Shinto, Oregon Health & Science University	Lipoic acid and/or omega-3 fatty acids (DHA and EPA)	People with Alzheimer's disease	2014
Hormones				
Raloxifene for Women with Alzheimer's Disease	Victor Henderson, Stanford University	Raloxifene (selective estrogen receptor modulator or SERM)	Older women with Alzheimer's disease	2012
Nonpharmacological				
ADMIT (Alzheimer's Disease Multiple Intervention Trial)	Chris Callahan, Indiana University	Home-based occupational therapy	People with Alzheimer's disease	2016
Aerobic Fitness in Slowing the Progression of Alzheimer's Disease	Jeffrey Burns, University of Kansas	Aerobic exercise training	People with Alzheimer's disease	2014
Therapeutic Effects of Cataract Removal in Alzheimer's Disease	Grover Gilmore, Case Western Reserve University	Cataract removal	Adults 65 and older with both Alzheimer's disease and cataracts	2014
Other Interventions				
AAV-NGF Gene Delivery in Alzheimer's Disease	Paul Aisen, University of California, San Diego	Nerve growth factor (NGF) gene delivery	People with Alzheimer's disease	2014
Intravenous Immunoglobulin (IVIg) for Treatment of Alzheimer's Disease (passive immunization)*	Norman Relkin, Weill Medical College of Cornell University	IVIg	People with Alzheimer's disease	2013
Treatment Trials—Neuropsychiatric Comorbidities				
ADMET (Apathy in Alzheimer's Disease Methylphenidate Trial)	Jacobo Mintzer, Medical University of South Carolina; Krista Lanctot; University of Toronto; Paul Rosenberg, Johns Hopkins University	Methylphenidate	People with Alzheimer's disease	2012
Antipsychotic Discontinuation in Alzheimer's Disease	Davangere Devanand, NYSPI/Columbia University	Risperidone	People with Alzheimer's disease	2011

TABLE 2 continued

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	ANTICIPATED COMPLETION DATE
Treatment Trials—Neuropsychiatric Comorbidities (Continued)				
CITAD (Citalopram Treatment for Agitation in Alzheimer Dementia)	Constantino Lykotsos, Johns Hopkins University	Citalopram	People with Alzheimer's disease	2014
Pilot Combination Treatment Trial of Mild Cognitive Impairment with Depression	Davangere Devanand, New York State Psychiatric Institute/ Columbia University	Citalopram and donepezil	People with mild cognitive impairment	2015
Prazosin Treatment for Disruptive Agitation in Alzheimer's Disease	Elaine Peskind, University of Washington	Prazosin	People with Alzheimer's disease	2013
TREA (Treatment Routes for Exploring Agitation)	Jiska Cohen-Mansfield, Hebrew Home of Greater Washington	TREA–systematic approach to individualizing nonpharmacological interventions for persons with dementia	Nursing home residents with Alzheimer's disease	2012
Proof of Concept Trials				
Cardiovascular				
Effects of Simvastatin on CSF Alzheimer's Disease Biomarkers in Cognitively Normal Subjects	Gail Li, University of Washington	Simvastatin	Cognitively normal adults age 45–64	2013
Pilot Trial of Carvedilol in Alzheimer's Disease	Giulio Maria Pasinetti, Mt. Sinai School of Medicine; Paul Rosenberg, Johns Hopkins University	Carvedilol	People with Alzheimer's disease	2015
Statin Effects on Beta-Amyloid and Cerebral Perfusion in Adults at Risk for Alzheimer's Disease	Cynthia Carlsson, University of Wisconsin, Madison	Simvastatin	Adults age 45–65 at high risk of Alzheimer's disease (family history, APOE4)	2013
Hormones				
Estrogen Receptor-beta phytoSERMs for Management	Lon Schneider, University of Southern California	ERβ-selective phytoestrogens (phytoSERMs—selective estrogen receptor modulators)	Postmenopausal women age 50–59	2014
Metabolic				
Glucose Regulation and Memory in Alzheimer's Disease	Suzanne Craft, University of Washington	Improved insulin resistance, 3 studies: diet, triglyceride emulsion, rosiglitazone	People with Alzheimer's disease and age-matched healthy older adults	2016

TABLE 2 continued

TRIAL NAME	PRINCIPAL INVESTIGATOR/ INSTITUTION	INTERVENTION	POPULATION	ANTICIPATED COMPLETION DATE
		Nonpharmacological		
Conversational Engagement As a Means to Delay Alzheimer's Disease Onset	Hiroko Dodge, Oregon Health & Science University	Internet-based conversational engagement	Adults age 75+	2014
Effects of Standardized Aerobic Exercise Training on Neurocognition and Neurodegeneration	Thomas Obisesan, Howard University	Aerobic exercise training	African Americans with Alzheimer's disease	2012
Exercise and Health Promotion for Mild Cognitive Impairment	Linda Teri, University of Washington	Two exercise programs (one for individuals with mild cognitive impairment and the other for cognitively intact older adults)	People with mild cognitive impairment	2012
Lifestyle Interventions and Independence for Elders (LIFE)	Marco Pahor, University of Florida	Aerobic exercise, resistance, and flexibility exercises	Sedentary adults age 70-89	2015
Mild Cognitive Impairment: Cerebrovascular Dysfunction and Exercise Training	Rong Zhang and Hanzhang Lu, University of Texas Southwestern	Endurance exercise training	People with mild cognitive impairment	2014
Neural Effects of Exercise, Cognitive, or Combined Training in Alzheimer's Disease At-Risk Elders	Stephen Rao, Cleveland Clinic	Cognitive training, aerobic exercise training, cognitive training + aerobic exercise training	Healthy adults age 65-85	2012
		Other Interventions		
fMRI Activation in Mild Cognitive Impairment	Michela Gallagher, Johns Hopkins University	Levetiracetam	People with mild cognitive impairment	2012
Thalidomide As BACE1 Inhibitor in Alzheimer's Disease	Yong Shen, Roskamp Institute; Marwan Sabbagh, Banner Sun Health Research Institute	Thalidomide	People with Alzheimer's disease	2012

Thank You!

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