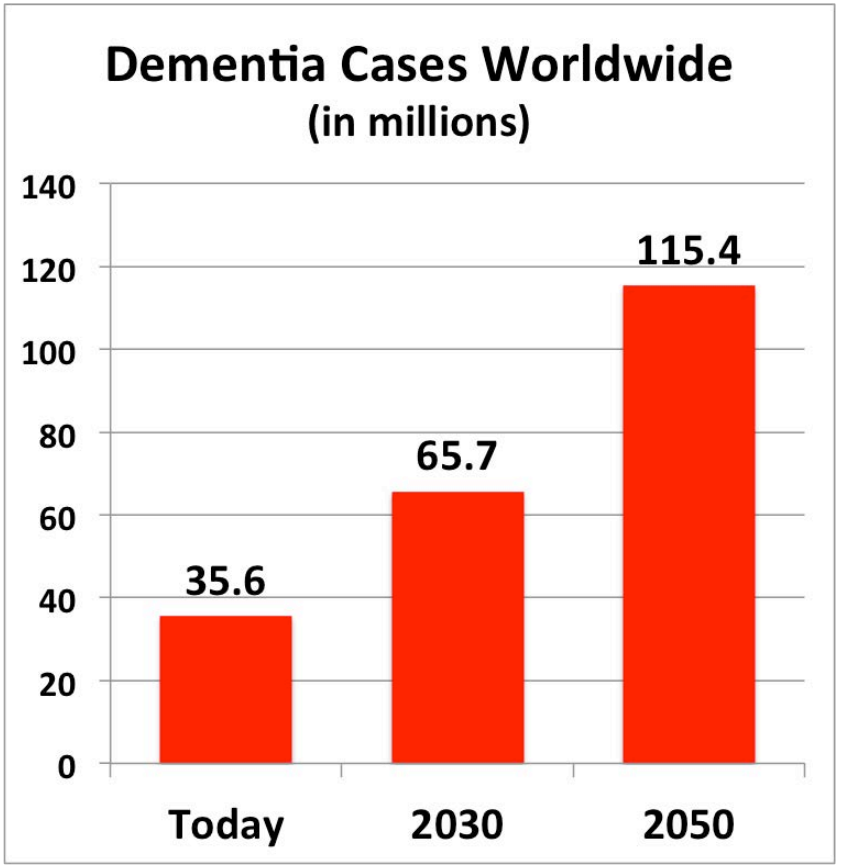
Progress in Treatment and Prevention of Alzheimer's Disease

SNUCMAA 2016 Annual Meeting

June 4, 2016

James J. Lah, MD, PhD

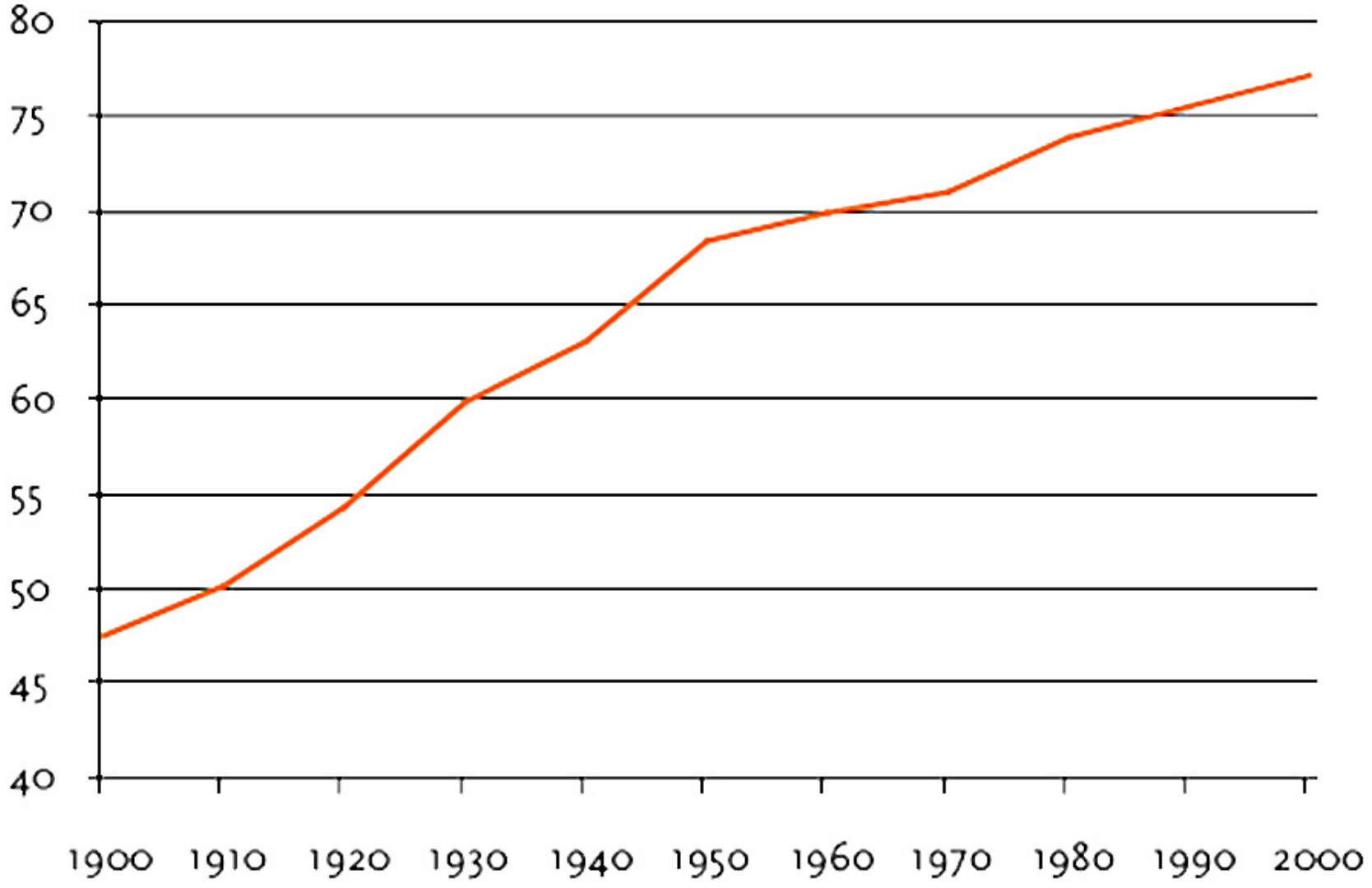
The Dementia Epidemic - A Global Crisis



$315 billion annual costs worldwide
More expensive than heart disease, cancer, and stroke combined

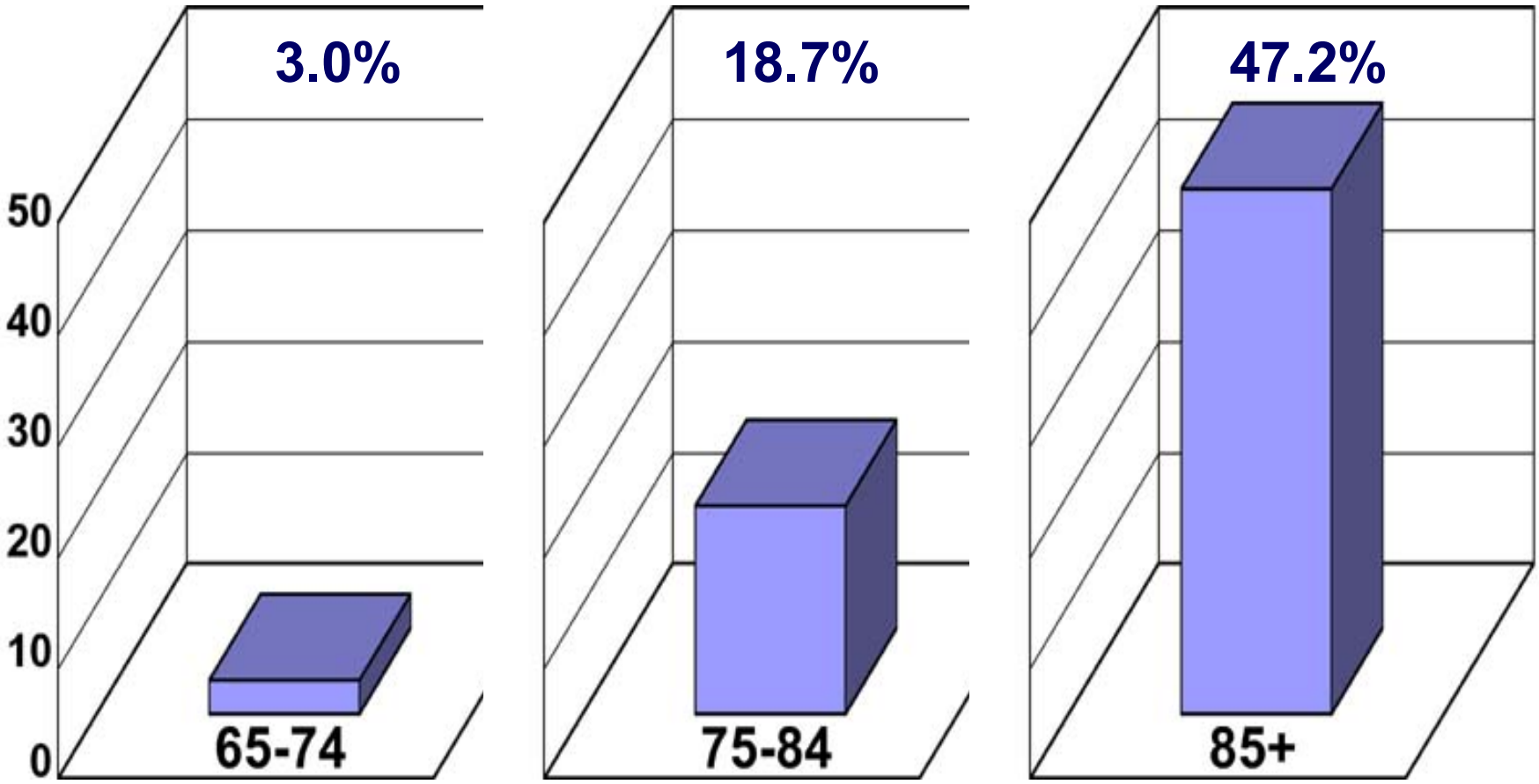
2009 World Alzheimer's Report from Alzheimer's Disease International (ADI)

The Alzheimer's Epidemic



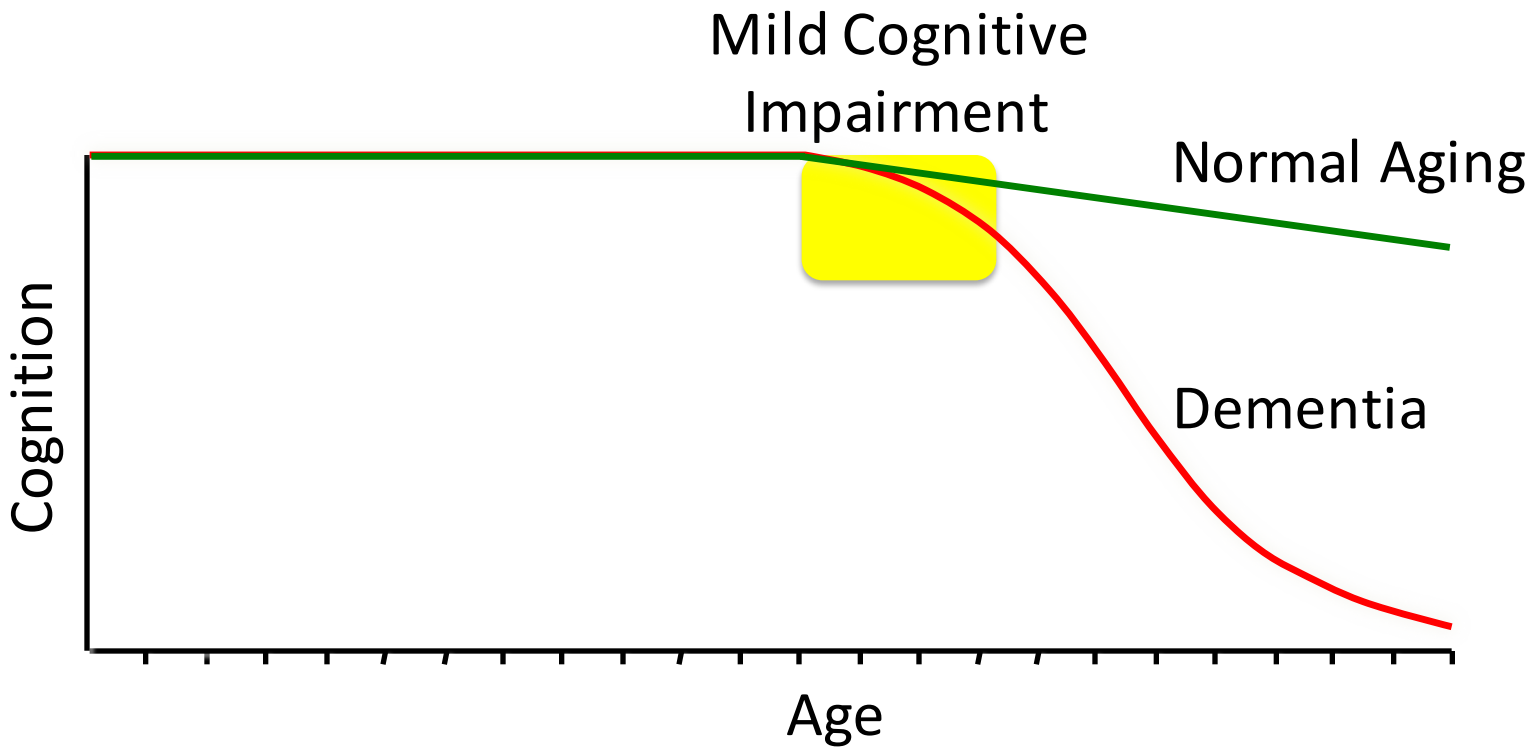
Arias, US Life Tables 2001

Aging and Alzheimer's Disease

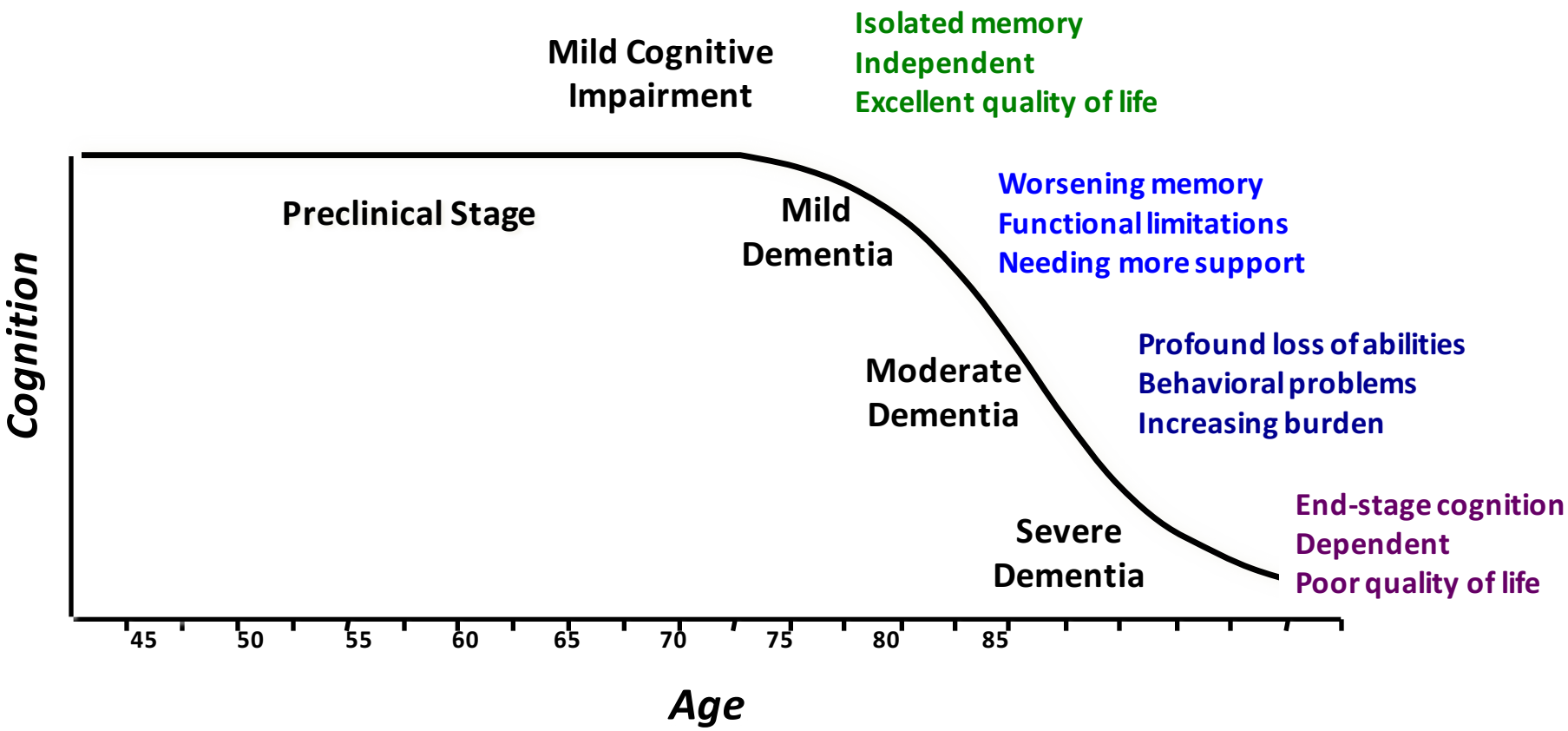


Evans et al. JAMA (1989)

Patterns of Cognitive Aging



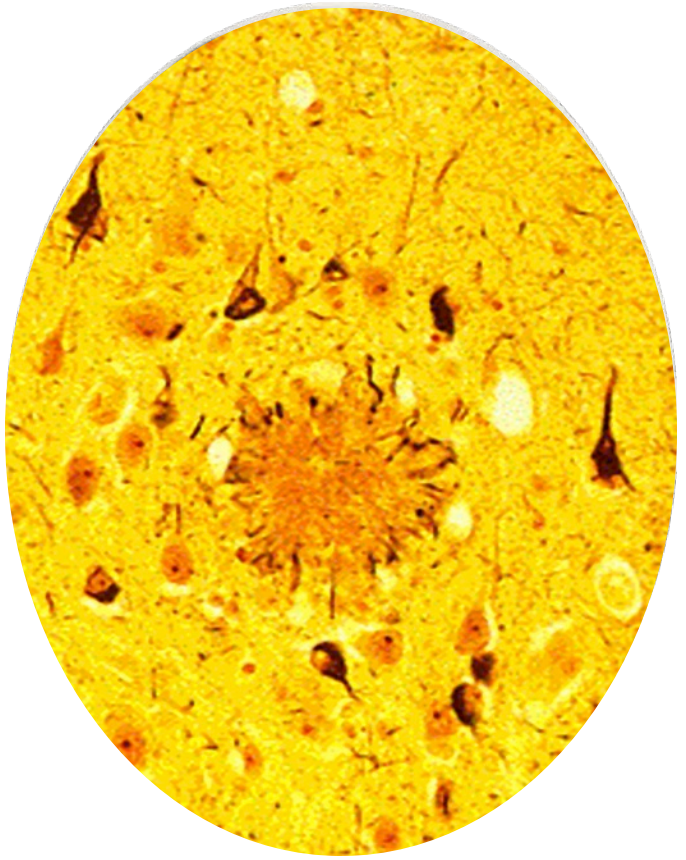
Stages of Dementia



Auguste D. and Alois Alzheimer

- Admitted 1901, age 51
- Frankfurt am Main
- Memory loss
- Language deficits
- Persecutory delusions
- Progressive decline

- Died 1906, age 55



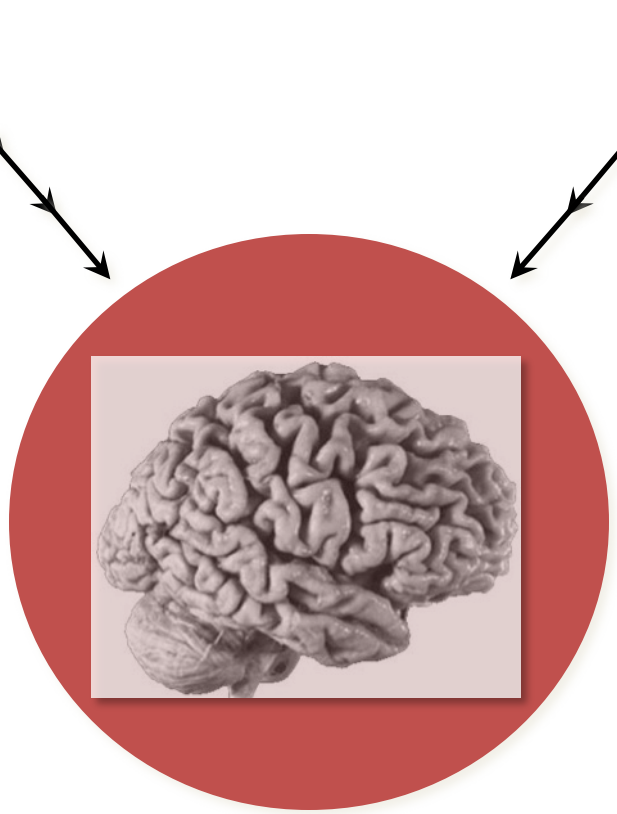
- *Pathophysiological underpinnings of AD*

PROGRESS IN UNDERSTANDING ALZHEIMER'S DISEASE

Multiple Genetic and Environmental Factors Contribute to Alzheimer's Risk

Genes

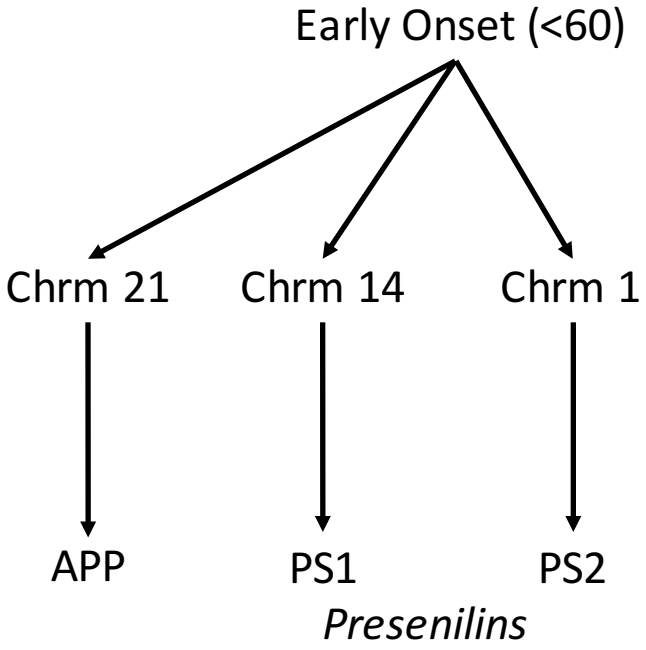
Environment

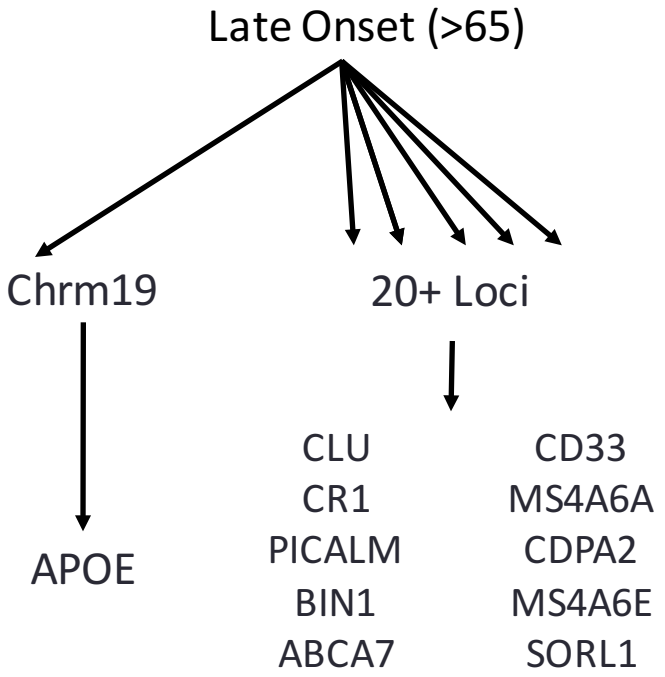


Risk or Protective Factors

- **AGE**
- Head trauma
- Depression
- Hypertension
- Cholesterol
- Homocysteine
- **Ethnic differences**
- Education
- Exercise
- Mediterranean Diet
- NSAIDS
- Statins

Genetics of Alzheimer's Disease





Familial Alzheimer's Disease

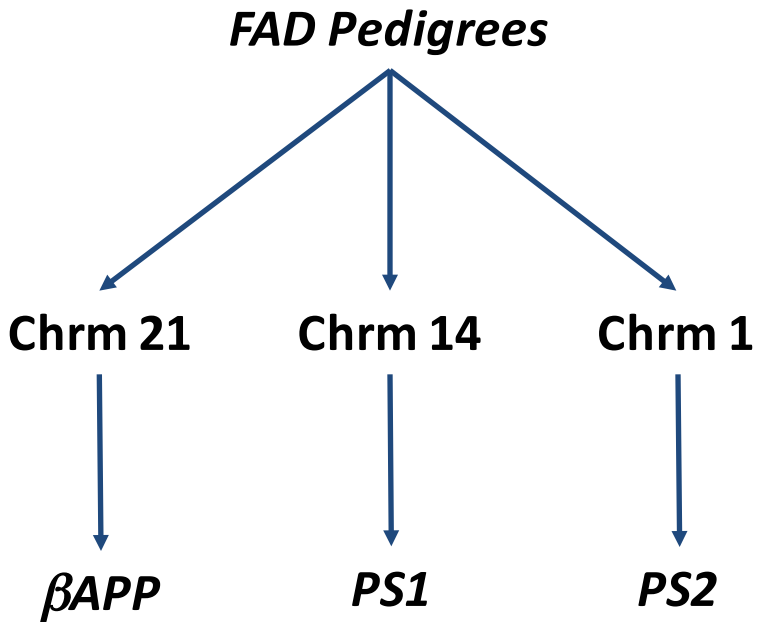
Mutations, Rare
Autosomal Dominant Genes
Large Effects (i.e, causative genes)

Sporadic Alzheimer's Disease

SNPs, Common
Risk Factor Genes
Small Effects

Familial Alzheimer's Disease

- Early-onset (<60 y.o.)
- Autosomal-dominant inheritance with 100% penetrance
- Small percentage of total cases (<1%)
- Pathology and symptoms similar to sporadic, late-onset cases
- Identify molecular mechanisms and therapeutic targets

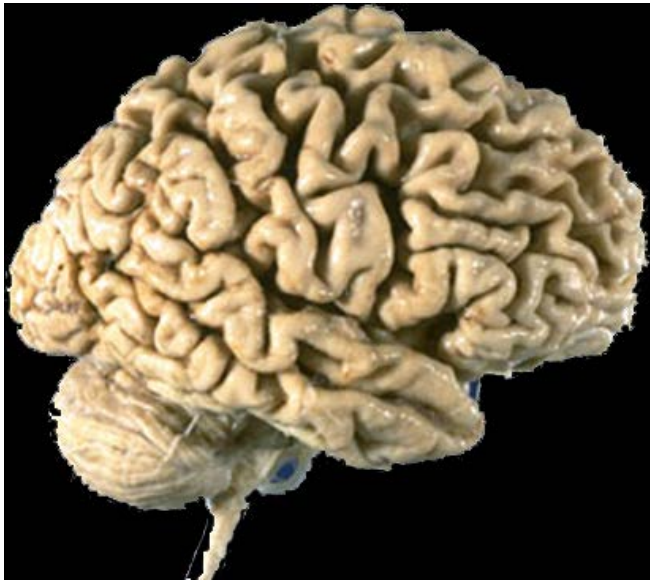


All known pathogenic FAD mutations alter production of Aβ peptide from βAPP.

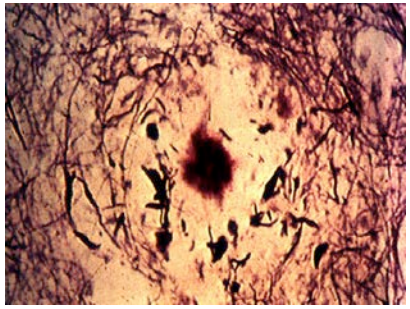
Amyloid Cascade Hypothesis

Hypothesis:

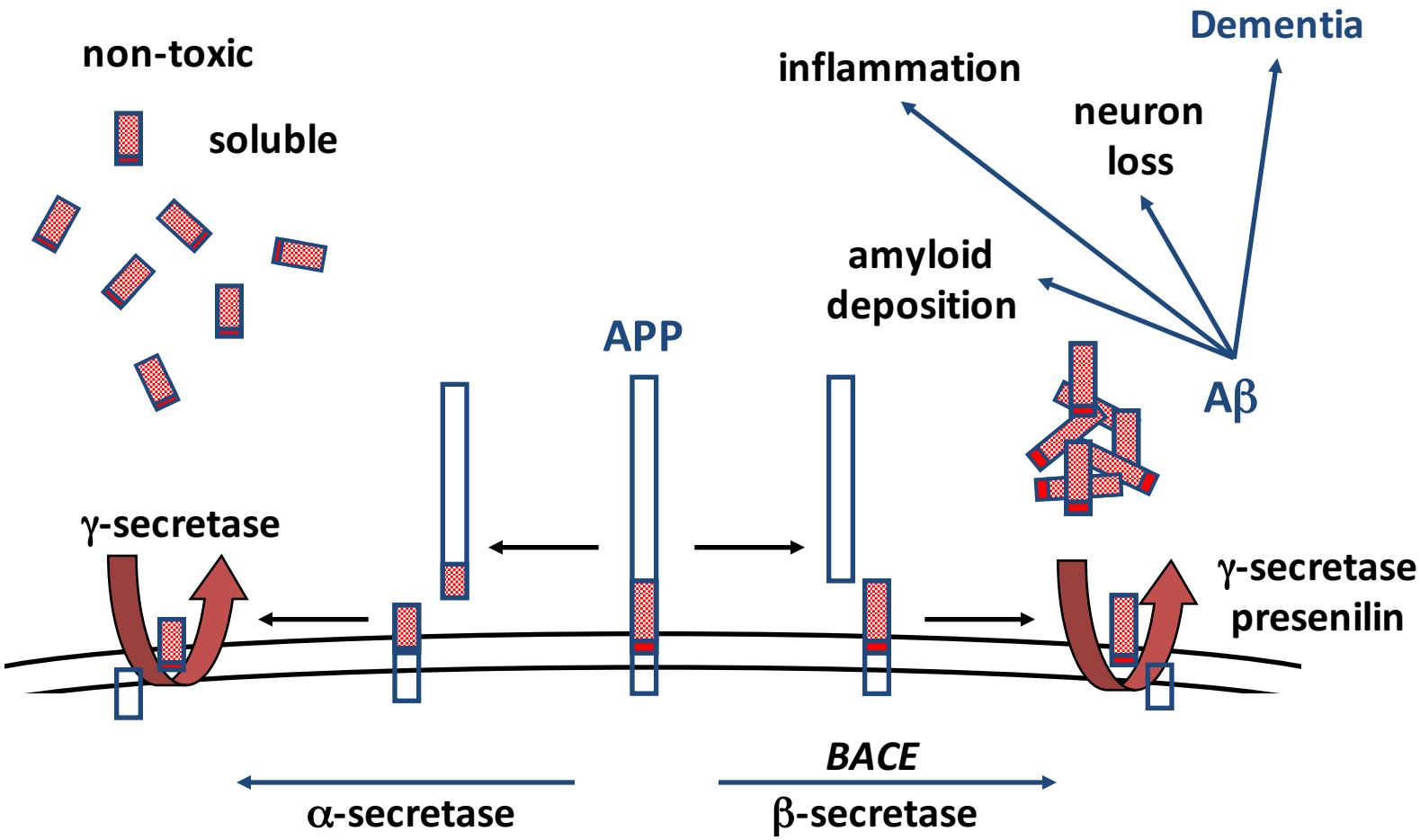
The accumulation of extracellular amyloid initiates a cascade of events leading to neurotoxicity and clinical symptoms in AD.



Beta-amyloid accumulation →

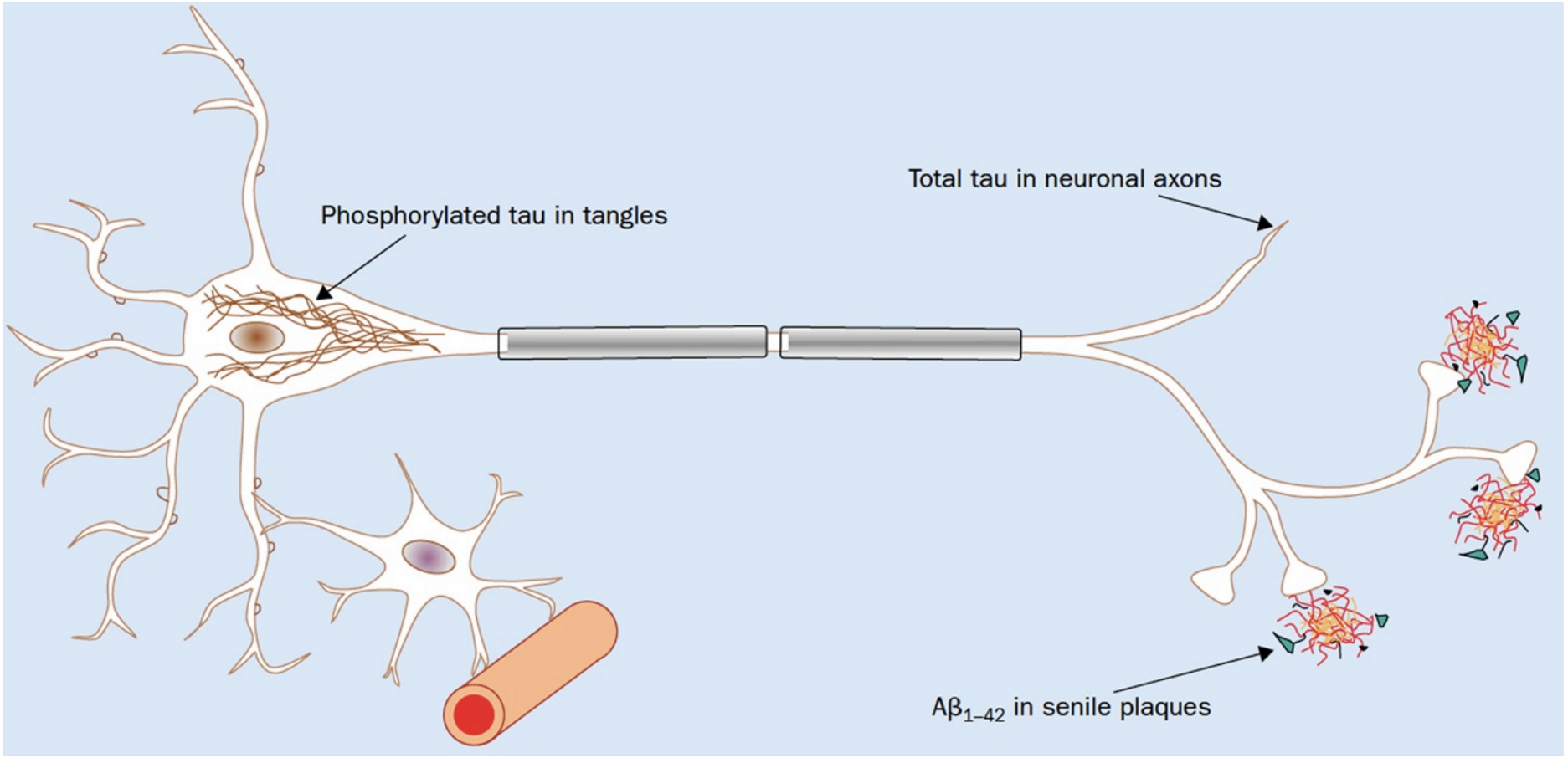


Beta-Amyloid Peptide Production



- *Accuracy of CSF assays*
- *In vivo amyloid imaging*

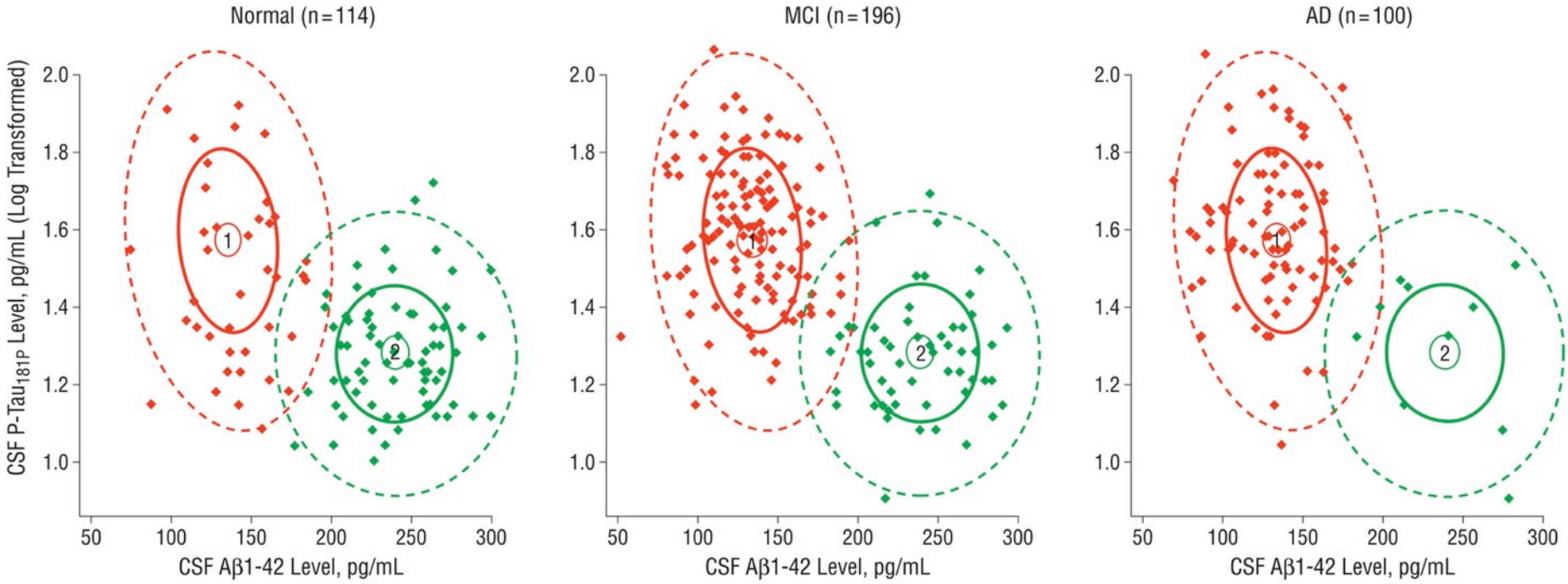
ROLE OF BIOMARKERS IN ALZHEIMER'S DIAGNOSIS



CSF Biomarkers of Alzheimer's Disease

- Beta-amyloid (1-42)
- Total Tau protein
- Phospho-Tau

Blennow and Hampel, Lancet Neurol (2003)

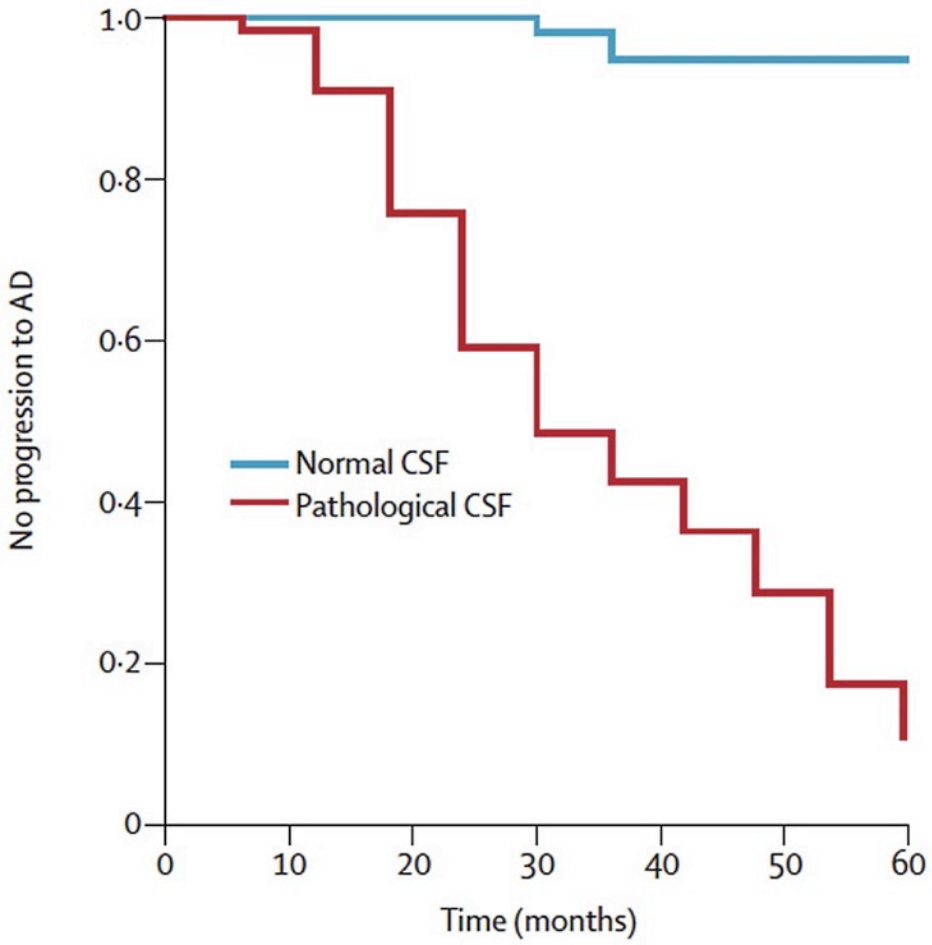


CSF in Clinically Diagnosed Individuals

- **Sensitivity 90%** (90/100 positive AD)
- **Specificity 64%** (41/114 positive Normal)
- **MCI: 72%** (142/196 positive)

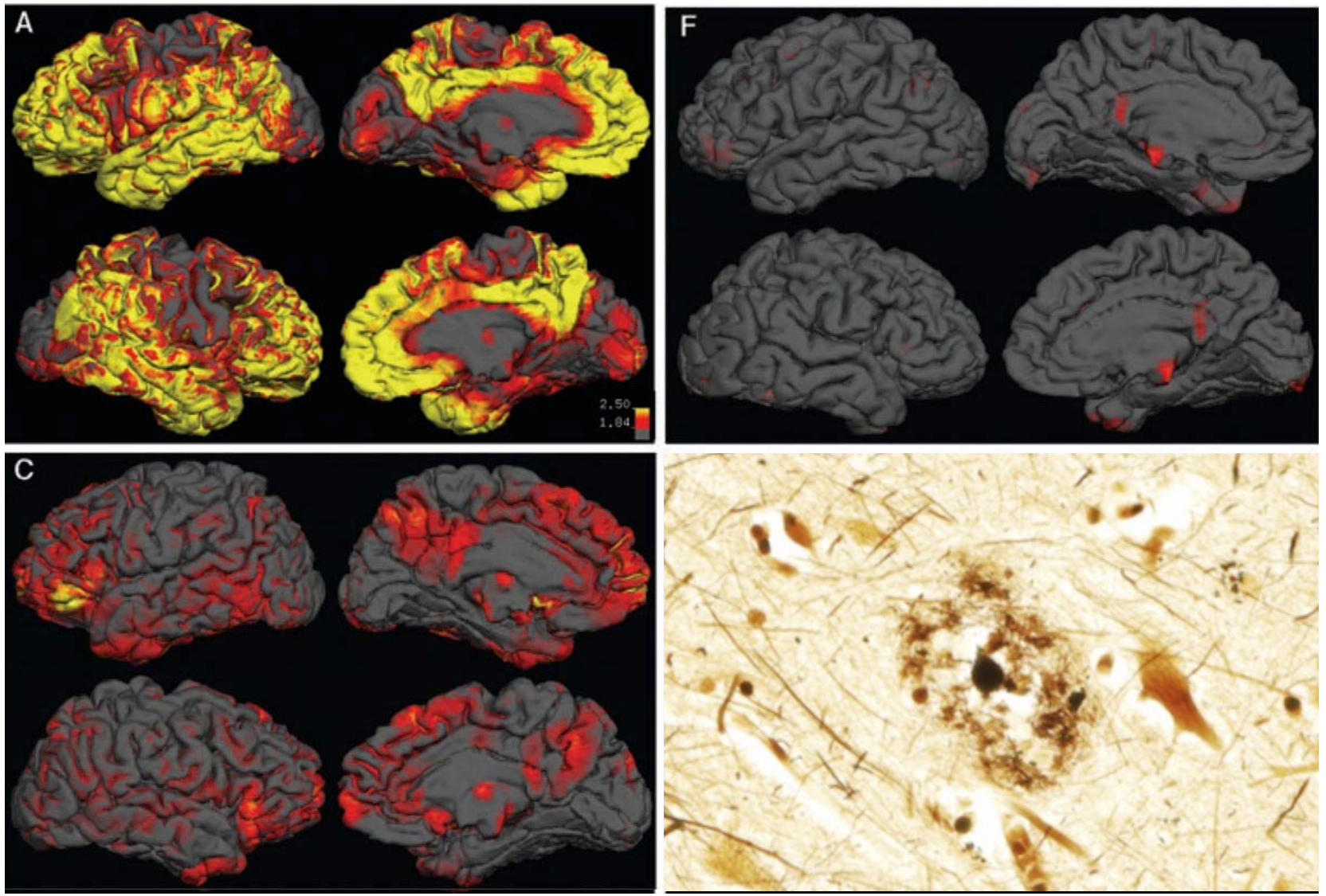
ADNI; De Meyer et al., Arch Neurol (2010)

Cerebrospinal Fluid Results Predicts Progression from MCI to Alzheimer's Disease



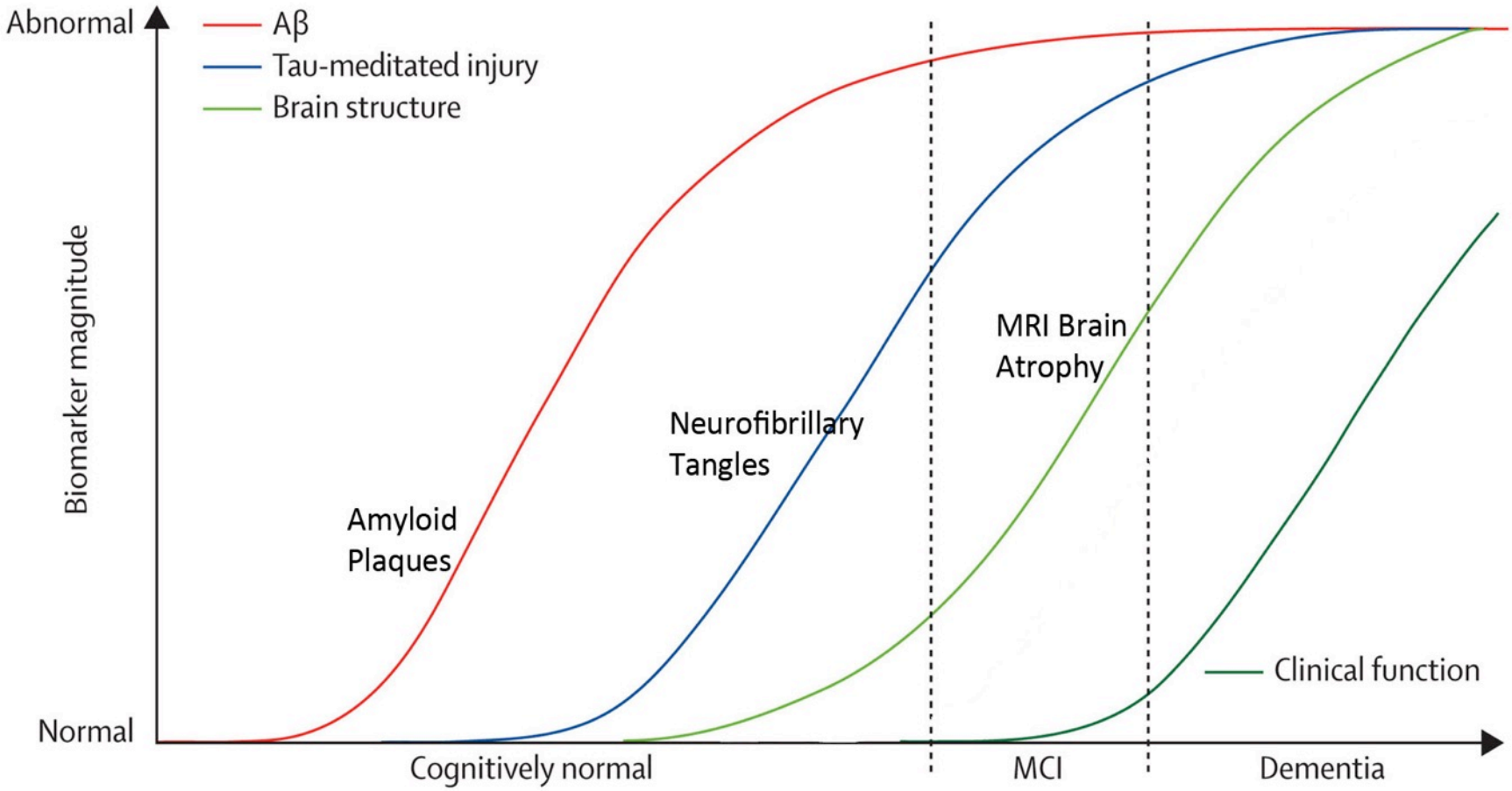
Hansson et al., Lancet Neurol (2006)

Visualizing AD Pathology in Living People



Mormino, et al., Brain (2009)

Biomarkers and Stages of AD



Modified from Jack et al., Lancet Neurol (2009)

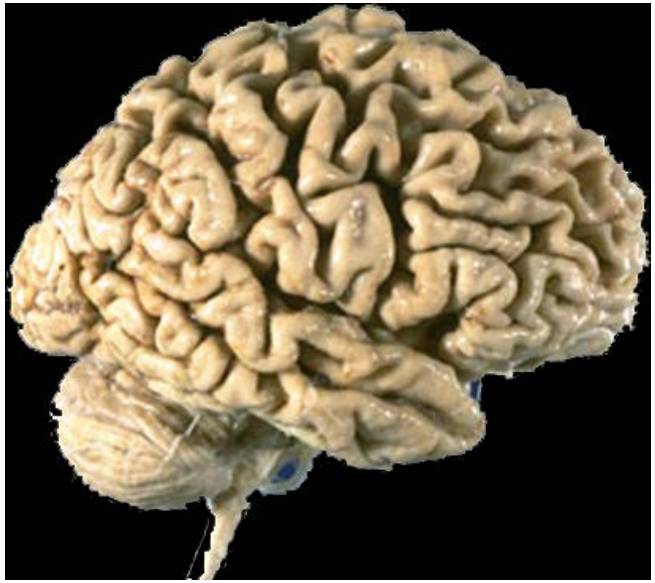
- *Emergence of the amyloid hypothesis*
- *The first wave of rational anti-amyloid therapeutics*

FROM UNDERSTANDING TO TREATMENTS

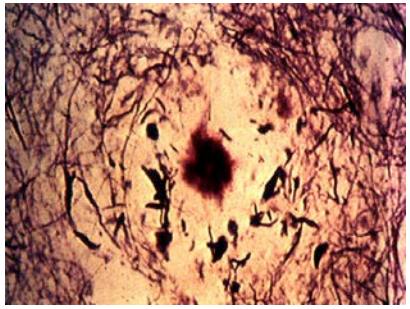
Amyloid Cascade Hypothesis

Hypothesis:
The accumulation of extracellular amyloid initiates a cascade of events leading to neurotoxicity and clinical symptoms in AD.

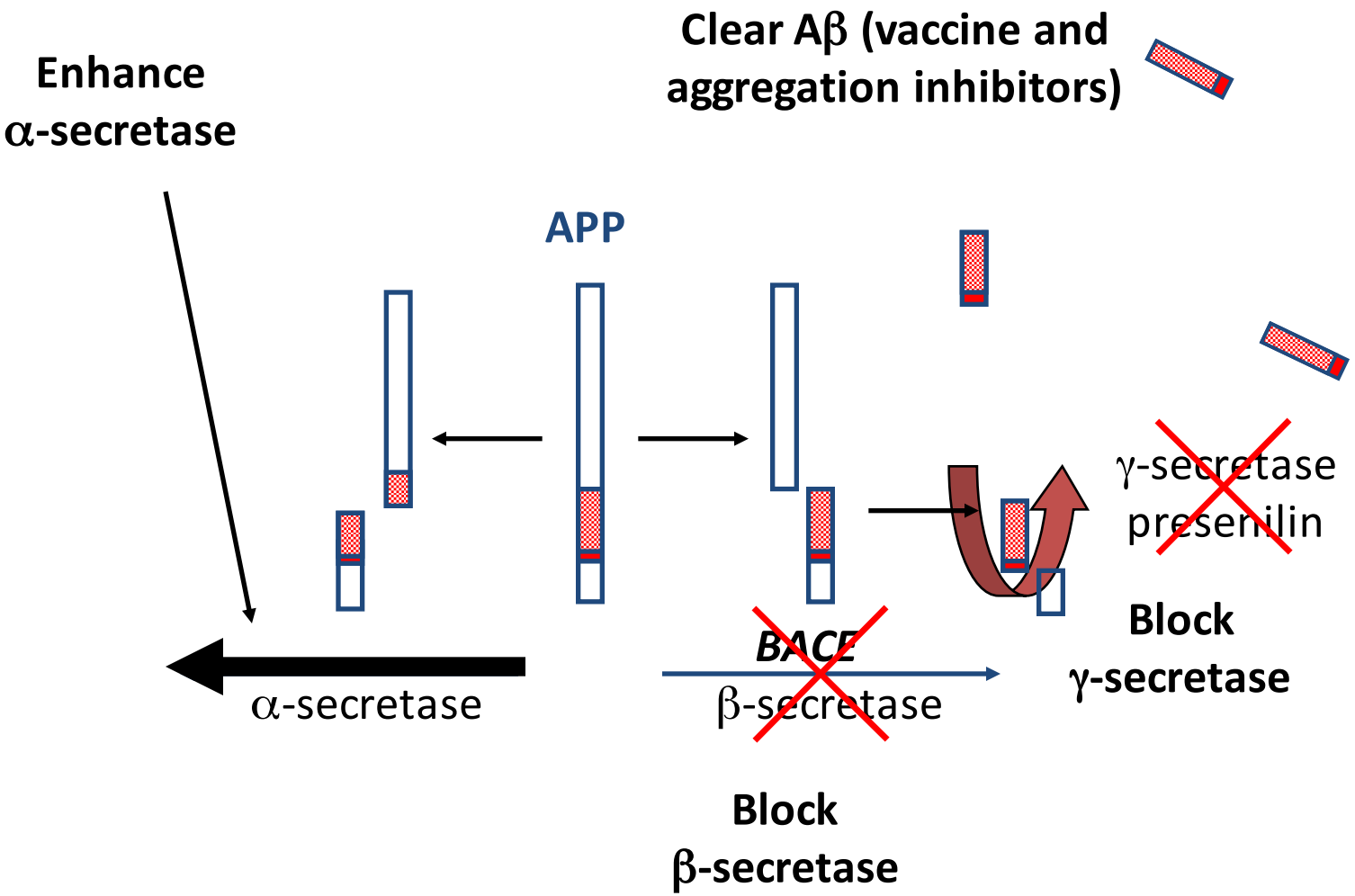
Corollary:
Prevention of amyloid accumulation will slow or prevent the development of symptoms.



Beta-amyloid accumulation →



Amyloid Based Therapeutic Targets



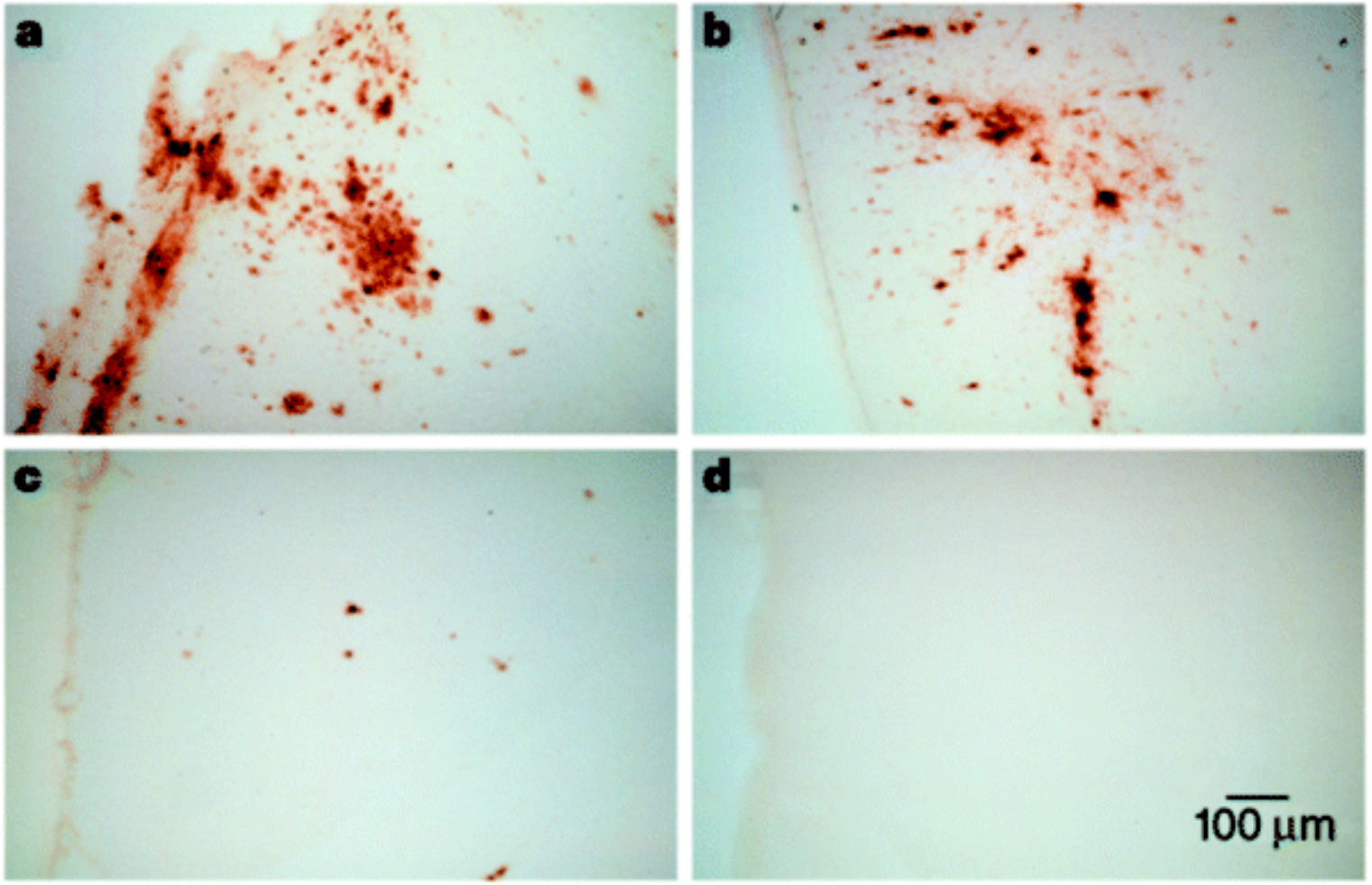
Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse

Dale Schenk, Robin Barbour, Whitney Dunn, Grace Gordon, Henry Grajeda, Teresa Guido, Kang Hu, Jiping Huang, Kelly Johnson-Wood, Karen Khan, Dora Kholodenko, Mike Lee, Zhenmei Liao, Ivan Lieberburg, Ruth Motter, Linda Mutter, Ferdie Soriano, George Shopp, Nicki Vasquez, Christopher Vandevert, Shannan Walker, Mark Wogulis, Ted Yednock, Dora Games & Peter Seubert

Elan Pharmaceuticals, 800 Gateway Boulevard, South San Francisco, California 94080, USA

Schenk et al., Nature (1999)

Prevention of Amyloid Pathology



Schenk et al., Nature (1999)

Alzheimer's drug fails late-stage clinical trial

by Bill Berkrot, Last updated August 07, 2012

NEW YORK (Reuters) - Pfizer Inc and Johnson & Johnson said they were scrapping further studies of one of the most anticipated experimental Alzheimer's disease treatments after the drug failed to help patients with the memory-robbing condition in a second high-profile late-stage clinical trial.

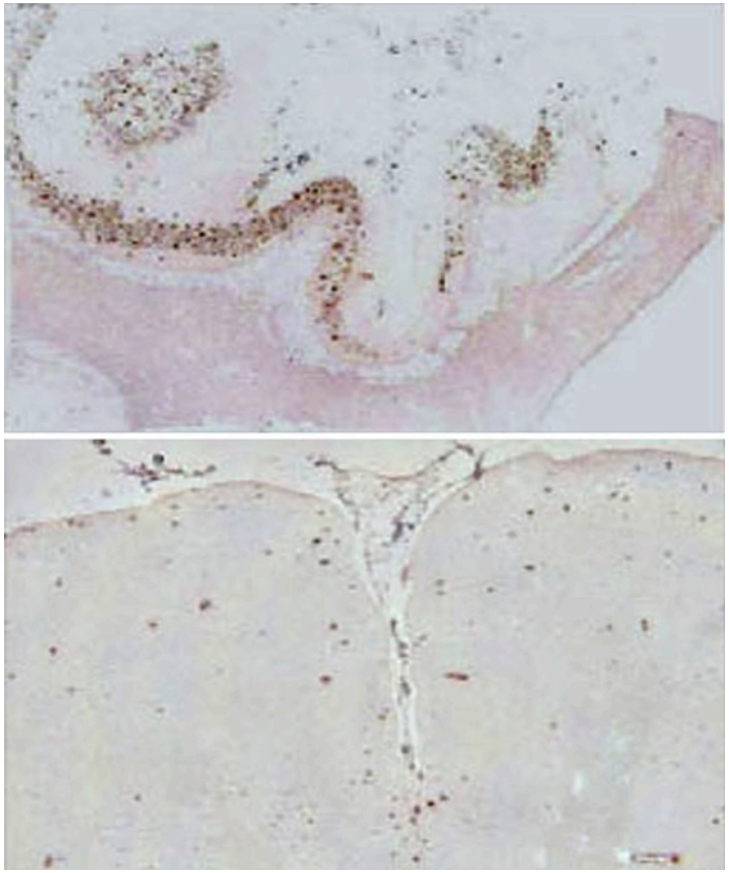
The companies said they would discontinue all other studies of the drug bapineuzumab in its intravenous (IV) form, including two more late stage trials and follow-up extension studies, in patients with mild to moderate Alzheimer's.

The result marked the second such failure announced in recent weeks and was especially disappointing as bapineuzumab had been given a better chance of success in the patients studied in the second trial.

Attention will now turn to solanezumab, a similar drug being developed by Eli Lilly & Co that is also considered a long-

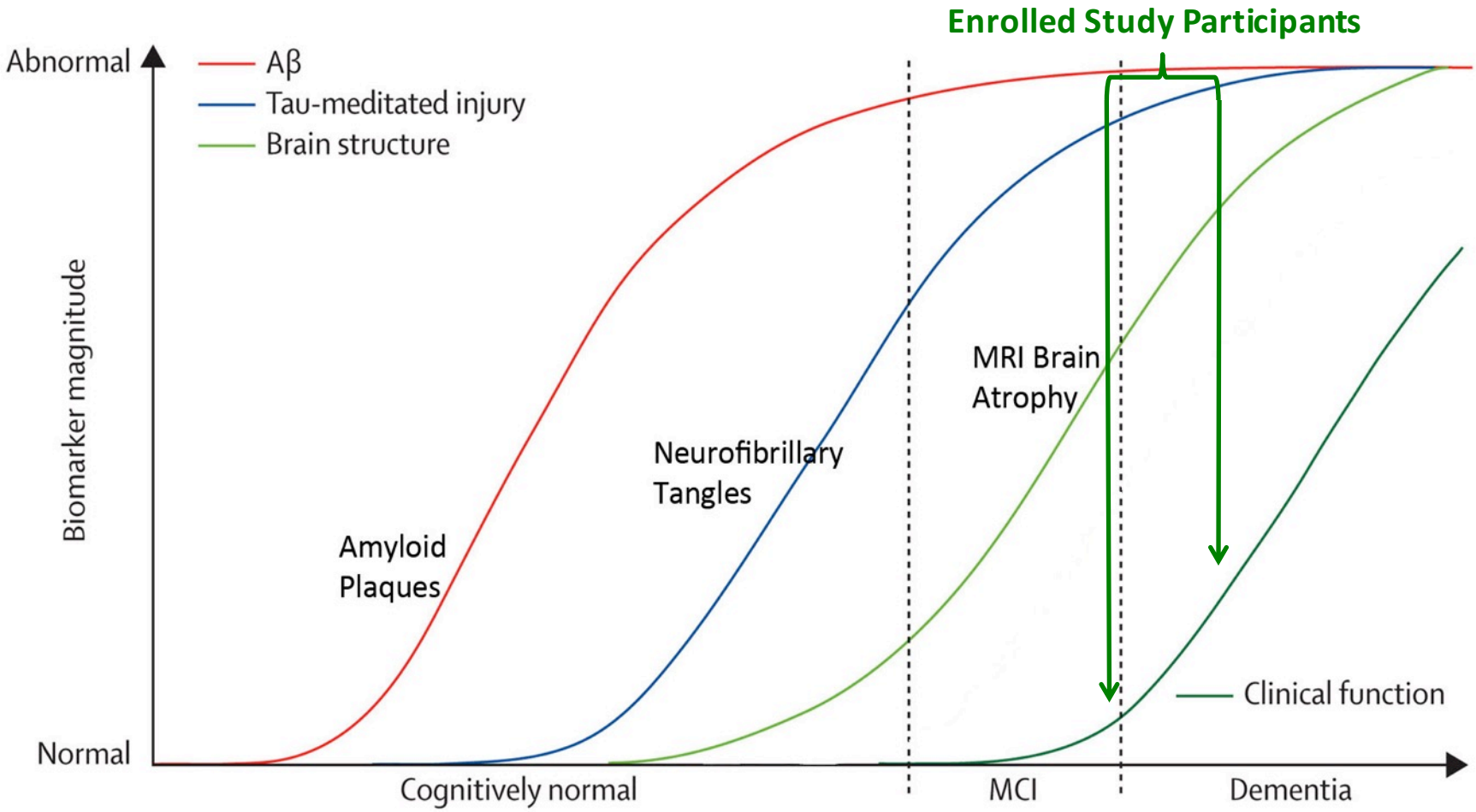
AN1792 Case Report

- AN-1792 (A-beta vaccine)
  - Halted due to encephalitis in ~6%
- Case Report
  - 72 yo woman with 5 year h/o AD
  - Received 5 doses AN-1792
  - Six weeks after last dose confused, unsteady
  - No response to steroids, eventually died from PE
  - Patchy resolution of amyloid



Nicoll et al, Nat Med (2003)

Biomarkers and Stages of AD in Clinical Trials



Modified from Jack et al., Lancet Neurol (2009)

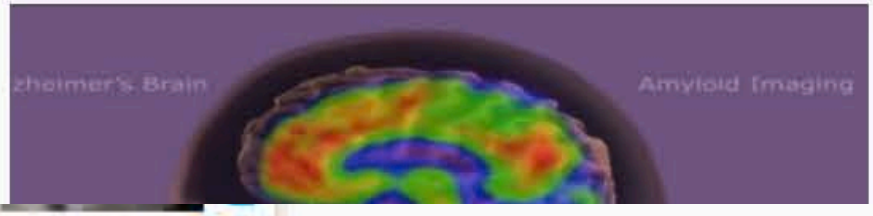
NAPA and the National Plan to Address AD

- National Alzheimer's Plan Act – January 2011
  - "*an aggressive and coordinated national plan to attack Alzheimer's disease and improve care and services*"
- National Plan to Address Alzheimer's Disease
  - US Department of Health and Human Services
    - May 2012, updated June 2013
  - Goal 1:

"prevent or effectively treat Alzheimer's disease by 2025"

Eli Lilly: Alzheimer's drug may slow disease's progress

Jeff Swiatek, The Indianapolis Star 6:43 p.m. EDT July 22, 2015



(Photo: Robert Scheer/The Star 2013 file photo)

Results from the first of the studies Lilly is using to try to breathe new life into solanezumab suggest that the drug seems to delay the progress of Alzheimer's disease in its early stages by 34%.

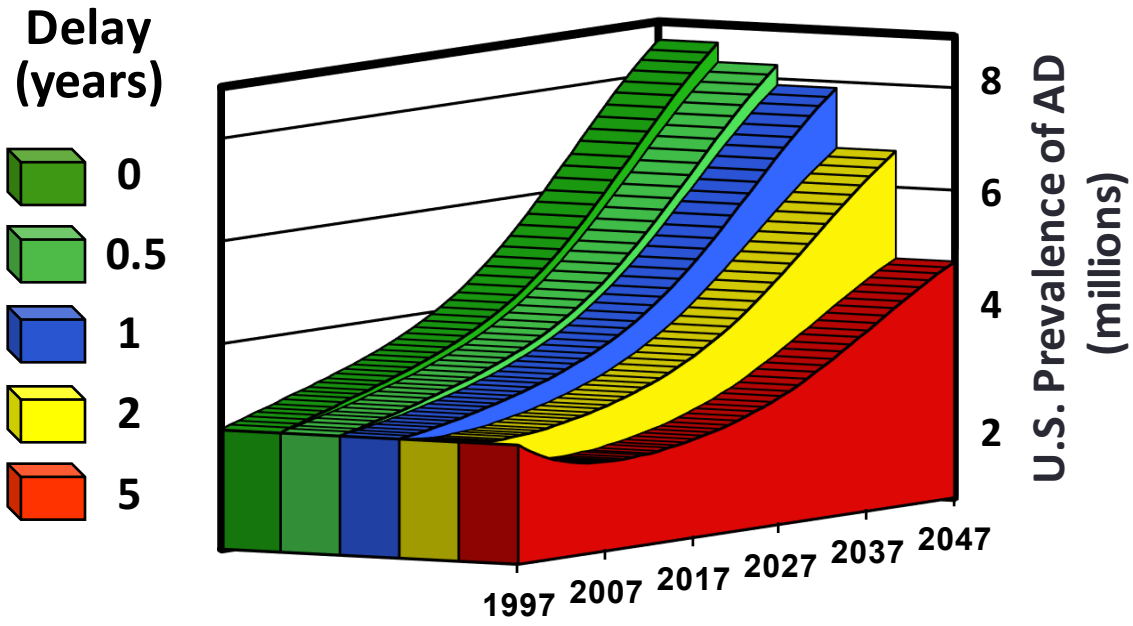
(Photo: Robert Scheer/The Star 2013 file photo)

INDIANAPOLIS — Eli Lilly and Co. hoped to salvage its Alzheimer's drug solanezumab with new studies.

Those hopes are still alive.

Results from the first of the studies Lilly is using to try to breathe new life into solanezumab suggest that the drug seems to delay the progress of Alzheimer's disease in its early stages by 34%.

Potential Impact of Interventions: 5 Year Delay Reduces Prevalence & Cost ~50%

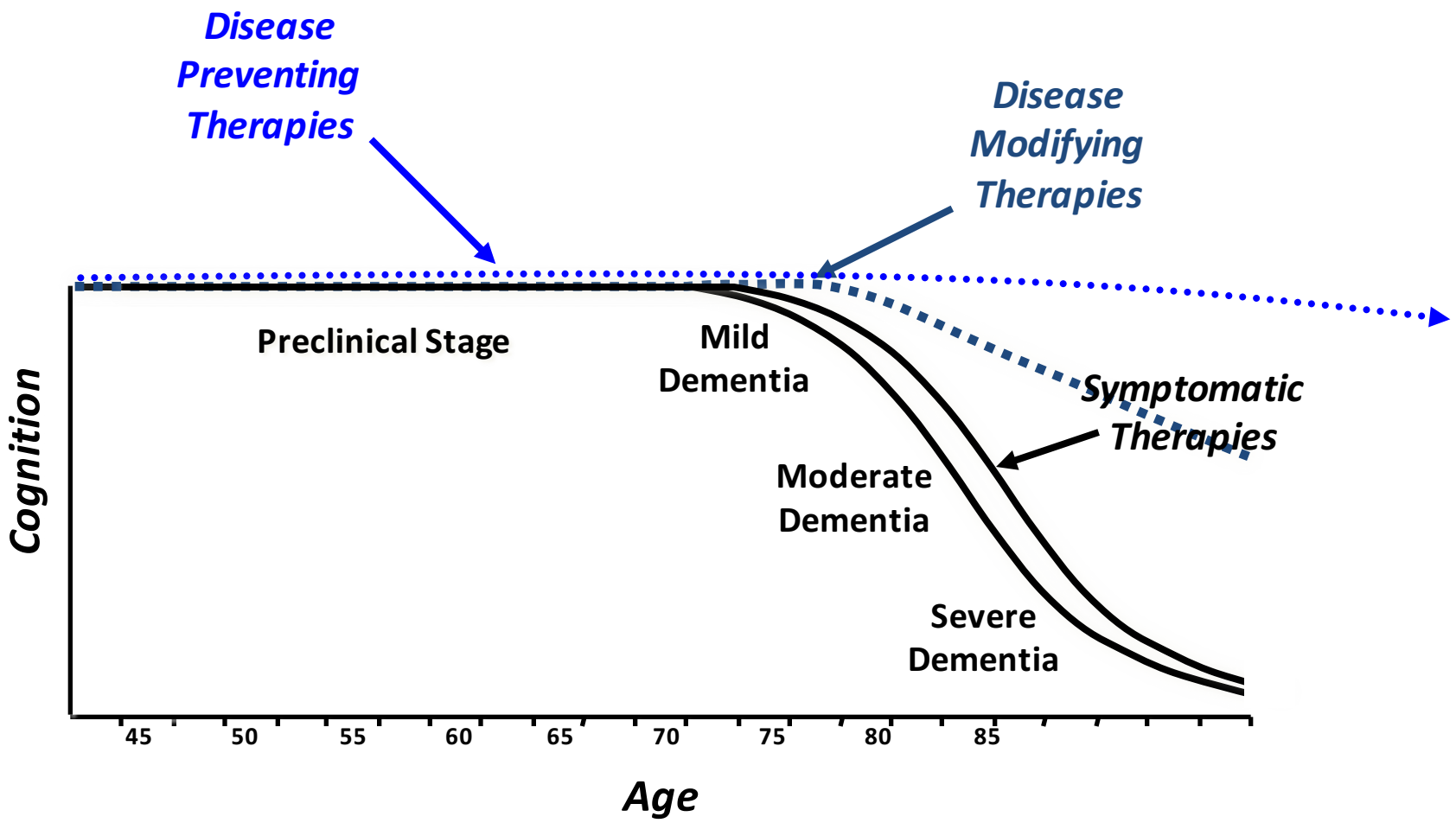


- Projected to increase to 106.2 million by 2050
- Delaying onset by 1 year will save 12 million people
- Delaying onset by 2 years will save 18 million people
- Most dramatic reduction in late stage disease (16 million)

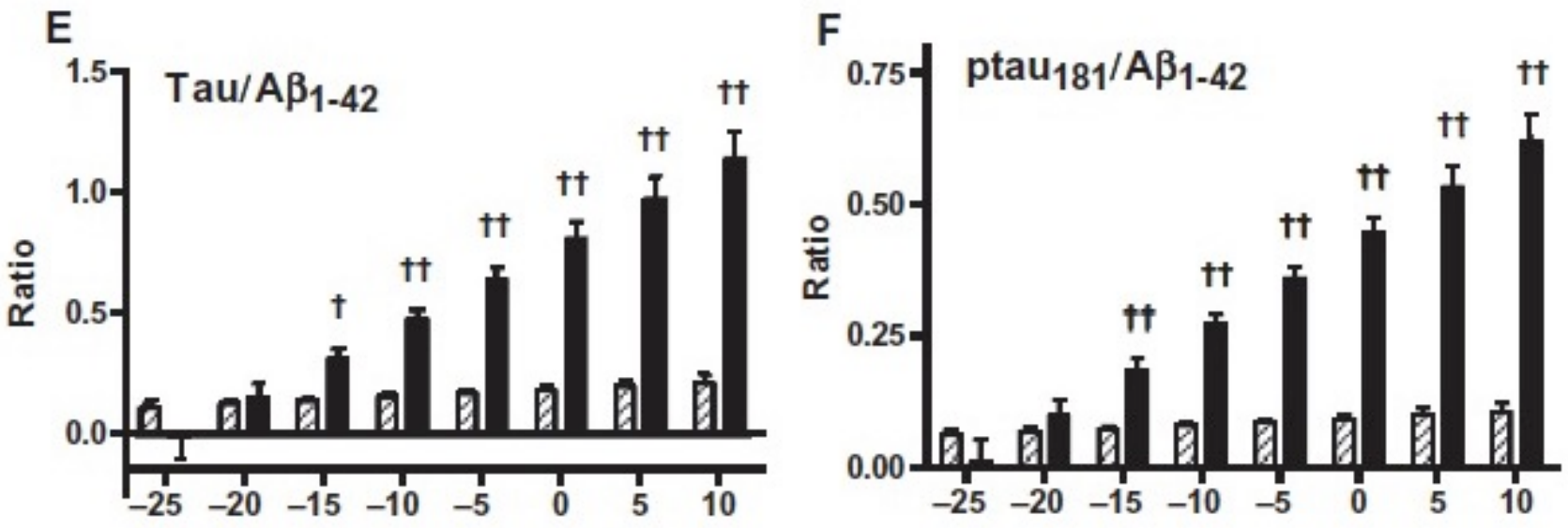
Brookmeyer et al., Am J of Public Health (1998)

Brookmeyer, International Conference on Alzheimer's Disease (2007)

Current Challenges: Early Detection and Treatment



Detection of Preclinical CSF Changes



Fagan et al., Science Trans Med (2014)

What We Are Doing...

Autosomal Dominant Alzheimer's Disease (ADAD) is a rare form of Alzheimer's that causes memory loss and dementia in people in their **30s** *to* **50s.**

The Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) at Washington University has launched the first prevention trial for ADAD families. The DIAN-TU trial focuses on drugs that could potentially change the course of the disease. The trial's goal is to determine the safety, tolerability, and effectiveness of these drugs. The DIAN-TU trial will determine if these medications can prevent, delay, or possibly even reverse Alzheimer's disease changes in the brain.

Although there are differences between ADAD and the more common age-associated, sporadic Alzheimer's disease, the results of this study will have implications for future studies and treatments in sporadic Alzheimer's disease.

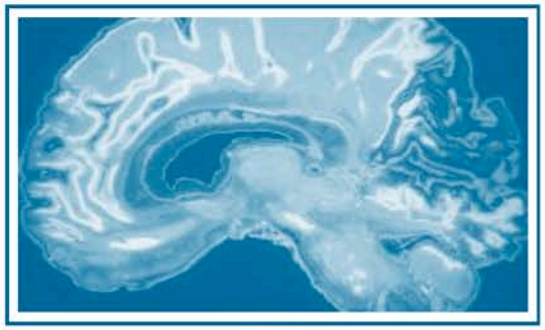
How You Can Help

Are you or someone you know affected by ADAD? We are currently looking for participants that have a parent or sibling who has been affected by an ADAD mutation.

If you or someone you know fits this description, contact us toll-free at:

1-844-342-6297 or **www.DIANexr.org**

to find out more!



DIAN-TU
Dominantly Inherited Alzheimer's Network Trials Unit

Please consider registering on our Expanded Registry Website at:
www.DIANexr.org

Phone: 844-DIAN-EXR (342-6297)
Fax: 314-747-7060
E-mail: dianexr@wustl.edu

Study: DIAN-TU-001
www.clinicaltrials.gov/ct2/show/NCT01760005

Washington University in St. Louis
School of Medicine
Department of Neurology
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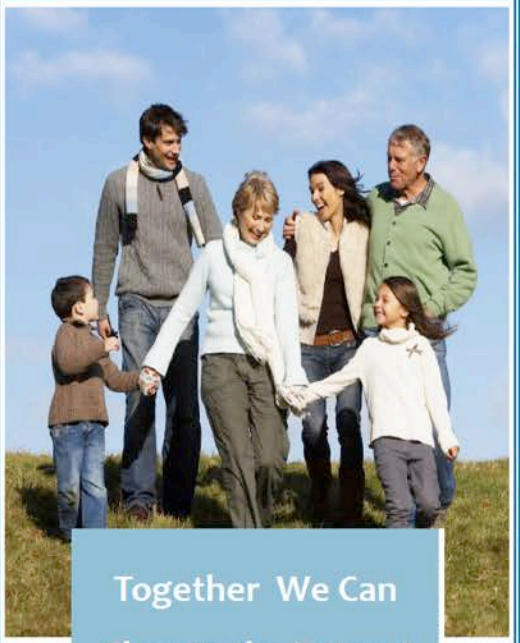
St. Louis, MO 63110

DIAN TU
Dominantly Inherited Alzheimer Network Trials Unit

Washington University in St.Louis
School of Medicine

Autosomal Dominant Alzheimer's Disease



Together We Can Change the Future!

DIAN TU
Dominantly Inherited Alzheimer Network Trials Unit

Washington University in St.Louis
School of Medicine

Tel: 844-342-6297

Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease

- NORMAL 65-85 year old adults
- Evidence of AD pathology in brain scans
- Goal to prevent or slow AD

EMORY | Healthy Aging Study

HealthyAging.emory.edu

Welcome to the **Emory Healthy Aging Study**, your opportunity to partner with leading physicians at Emory University and help make discoveries that will change our understanding of aging and age-related diseases for generations to come. It's easy. It's historic. It's one for the ages.

Please join us.

If you had the opportunity to change the world for the better, would you?

Preventing Age-Related Diseases

Emory Healthy Aging Study: 100,000+ participants

- Online consent and information; anyone over 18 eligible
- Periodic surveys, cognitive games, mobile data collection

Emory Healthy Brain Study: 3,500+ participants

- Face to face evaluation, blood, CSF, and other biospecimens, and brain MRI
- Longitudinal assessment of individuals 50-70 years old

Intensive Data and Biospecimen Analysis (1,000)

- The most comprehensive "omics" data set in existence for Alzheimer's disease
- Goal: identify accurate and predictive biomarker for AD

Earlier Detection and Prevention of Age-Related Diseases

- Target ALL diseases: brain, heart, endocrine, cancer, musculoskeletal, etc.
- http://**healthyaging.emory.edu/**

THANK YOU!