Massachusetts ADRC *

A brief history

30 years of research and discovery

* UMass, MIT and Harvard-affiliated units including MGH, B&W, Beth Israel & McLean.

Seminal events for AD research in the 1970s

- Robert Katzman's stunning article in 1976 equating pre-senile and senile dementia, and calling attention to the gathering silent epidemic of dementia.
- The discovery in 1976 that indices of acetylcholine were reduced in brains of AD patients.
- Jerry Stone established the Alzheimer's Association in 1979 (a private foundation initially known as ADRDA) to promote education and research.
- US Congress established the National Institute on Aging, with a focus on AD. The NIA then took the lead in establishing University-based Alzheimer Disease Research Centers in 1984.

Five Alzheimer's Research Centers Designated

Dr. John Growdon to Direct Massachusetts Center

Sec'y Heckler, Dr. Growdon

Secretary of Health and Human Services Margaret Heckler came to Harvard Medical School this week to announce a new, multi-million dollar federal research initiative on Alzheimer's disease. One of five national Alzheimer's Disease Research Centers funded by Congress this year will be a consortium of Massachusetts institutions led by Harvard Medical School and the Massachusetts General Hospital. Dr. John Growdon, Associate Professor of Neurology at HMS and head of the Memory Disorders Unit at the MGH, is the Program Director; Dr. David Drachman, Professor and Chairman of Neurology at the University of Massachusetts Medical Center, is the Co-director. Other participating institutions are Harvard's Division on Aging and Beth Israel and McLean Hospitals; University of Massachusetts Medical Center; and the Massachusetts Institute of Technology. The Center is funded for five years with a grant of nearly $4 million from the National Institutes on Aging of the National Institutes of Health. The other centers are in Baltimore, San Diego, New York City, and Los Angeles.

Continued on page 4

Clinical Core

- John Growdon – MGH
  - Emeritus Director, but still standing
- David Drachman – UMass
  - Emeritus Chair, still active in patient care
- Marsel Mesulam - BIH
  - Director, Northwestern ADC

Neuropathology Core

- Tessa Hedley-Whyte
- Training program for neuropathologists. The first 5 trainees are all professors : Suzanne de la Monte, Ann McKee, David Louis, Jack Lee, & Jeff Golden.

Information, Education and Training Core

Jack Rowe

- President of Mt. Sinai Medical Center. CEO of Aetna. Professor at Columbia.

Lew Lipsitz

- Professor at HMS & Chief of Geriatrics, BIDMC and Hebrew Senior Life

Year 01-05 Projects

Joseph Martin

Dean, then Chancellor at UCSF. Dean, HMS.

Neurochemistry & neuropeptides in AD

Joseph Rogers

Director, SRI International

Neuron & neurite loss in dementia

Year 01-05 Projects

Marsel Mesulam — Director, Northwestern ADC. Potamkin Prize

Cholinergic pathology in AD

Ralph Nixon — Professor, NYU

Immunchemical study of proteolysis in AD

Neil Kowall — Director, Boston U. ADC

Histochemistry of the cytocskeleton in AD

Year 01-05 Projects

Dennis Landis — Professor, Georgetown

Immunocytochemical studies of neuronal loss in AD

Charles Marotta — Scientific Director, International Corp.

Regulation of RNA levels in AD

Pilot Projects, year 01

Dennis Selkoe	Director, B&W Center for Neurologic Diseases; Potamkin Awardee
Structural analysis of APP protein	
Jim Gusella	Bullard Professor, HMS
Chromosomal localization of the FAD gene	
Rudy Tanzi	Potamkin Awardee
Peter St. George-Hyslop	Potamkin Awardee

Year 05 of the MADRC

Bradley T. Hyman, MD, PhD
Director of the ADRC since 2006

Legacies of the Initial ADRC Years

Personal Friendships – competitive yet collegial; recurring Director's meetings

Expanded ADCs - regional centers of excellence in clinical care and research

Collaborative Networks – the basis of NACC and our other joint ADC projects

International Impact – European and Asian consortia modeled on the US

Joseph and Kathleen Bryan Alzheimer's Disease Research Center

Genetics discovery, translation to delay of onset and treatment clinical trials

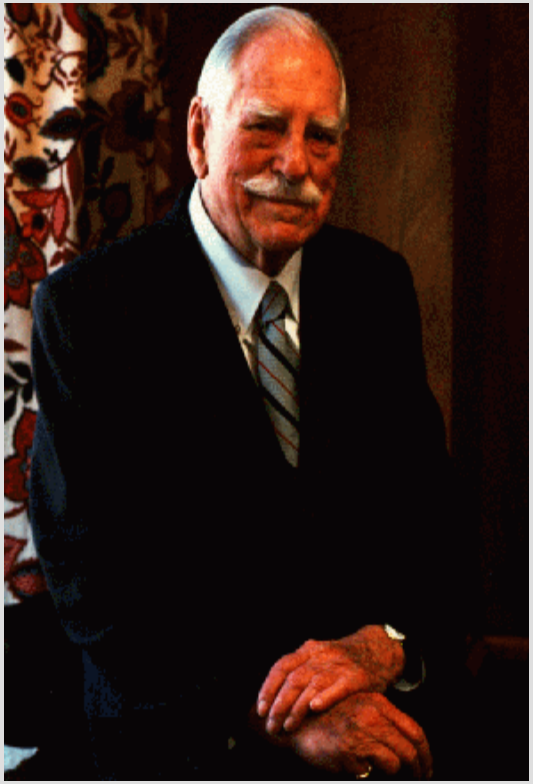
ADC Meeting, October 2014

Baltimore, Maryland

Allen D. Roses, MD, Founding Director
Bryan ADRC at Duke University
Kathleen A. Welsh-Bohmer PhD
Professor & Current Director

History of the Bryan ADRC

- The Joseph & Kathleen Bryan Alzheimer's Disease Research Center (Bryan ADRC) began in 1984 with the generous donation of Joseph McKinley Bryan Sr. to then Director Allen Roses to establish a Rapid Autopsy Program for brain mRNA and protein studies.
- Genetics of LOAD



History of Bryan ADRC

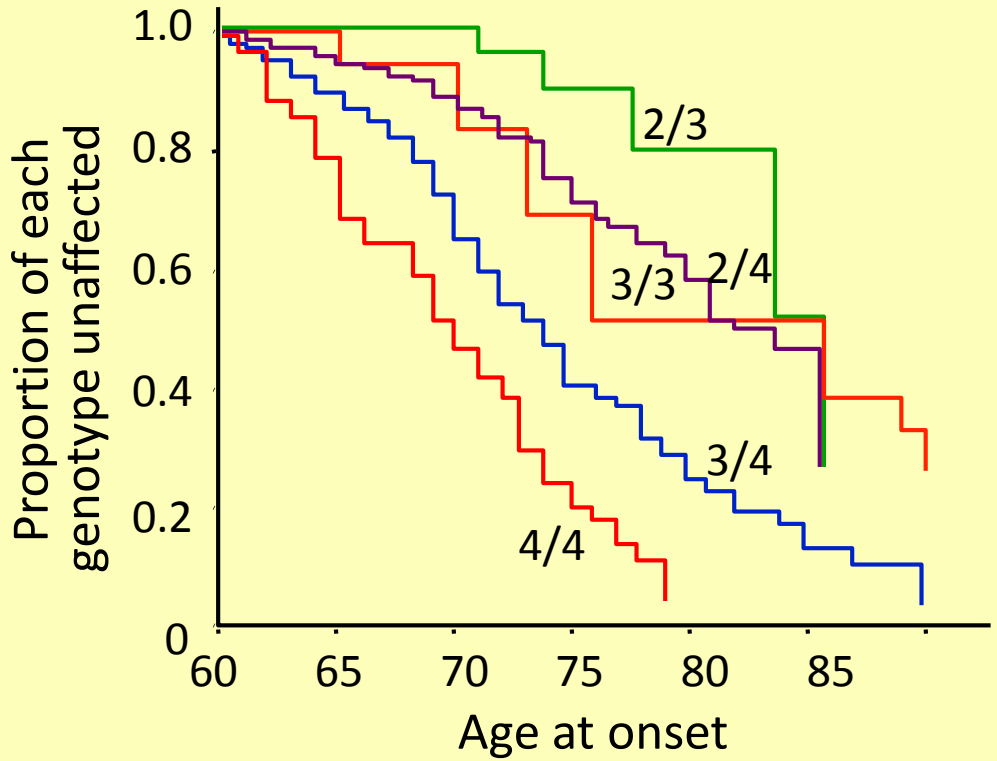
- With granting of the ADC, a subsequent gift led to the construction of our research labs &
  - The establishment of a world renown Brain Bank which bears the name of his wife, Kathleen Price Bryan.
- NIA Funding ADRC P50 AG05128 (1985-2006)
  - Roses (1985-1998)
  - Schmechel (1998-2006)

Joseph and Kathleen Bryan Research Building

History of Bryan ADRC-Genetics

- Started collection of familial DNA – **1981 -** [Heyman]
- LOAD linkage to chromosome 19 [**1988-1990**]
- APOE4>APOE3>APOE2 Locus-**1993**
- APOE GWAS simulation finds *cis* genes **1998**
- **2009** - TOMM40'523 SSR polymorphism is *cis* to APOE and 100% informative for AOO
- **2011** - TOMMORROW delay of onset trial to test genetic algorithm
- **2015** - Treatment trials with a rational treatment [low dose pioglitazone] of

APOE ε4 – A Susceptibility Gene Variant Associated With Alzheimer's Disease – 1993



Mean age of onset of Alzheimer's disease as a function of the inheritance of the five common *APOE* genotypes

In 1998 we reported the biological importance of a *cis*-acting elements independent of APOE Isoforms

Neurobiology of Aging, Vol. 19, No. 1S, pp. S53–S58, 1998

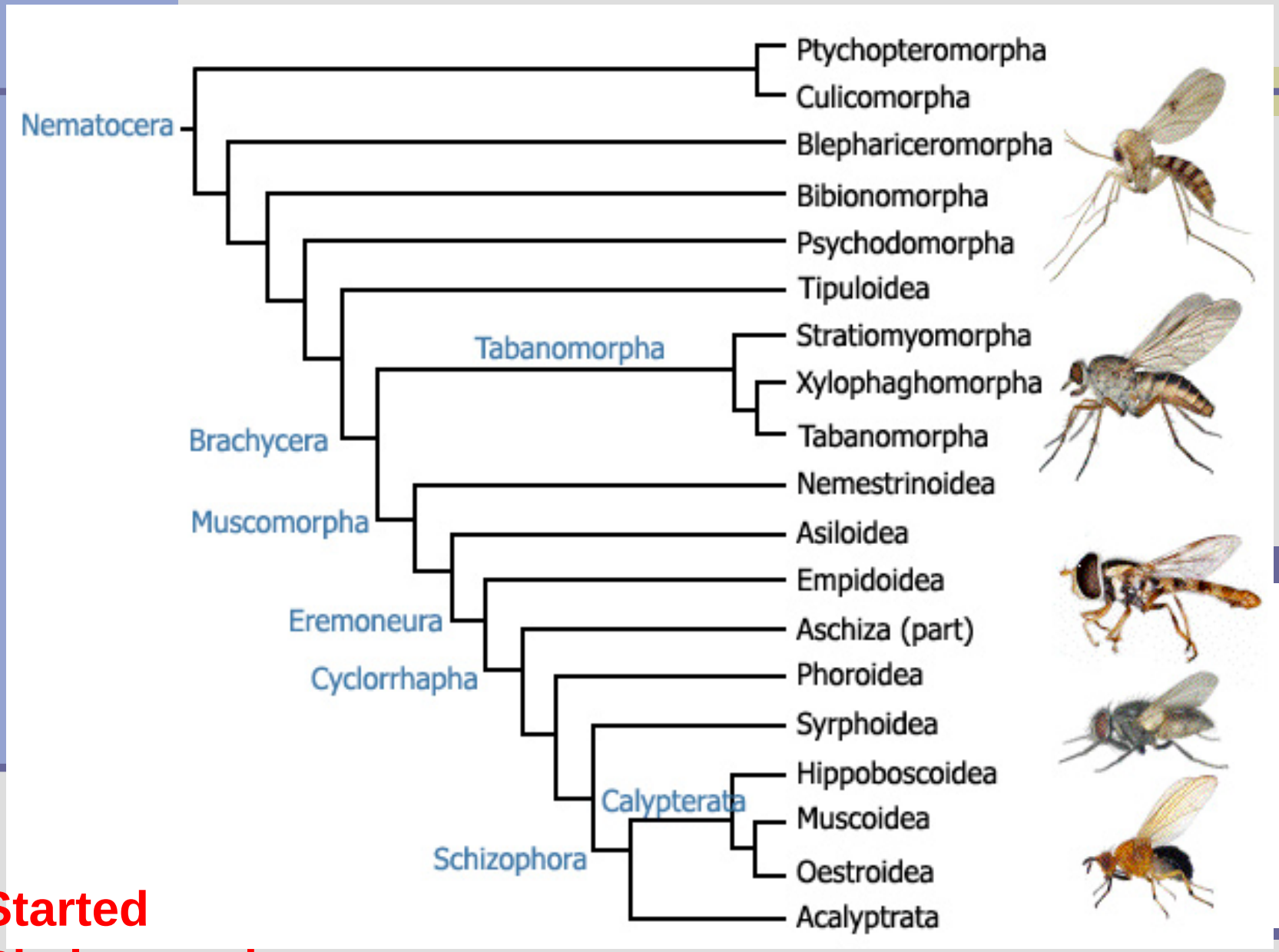
0197-4580/98 $19.00 + .00

PII:S0197-4580(98)00030-X

Cis-Acting Human ApoE Tissue Expression Element is Associated with Human Pattern of Intraneuronal ApoE in Transgenic Mice

A. D. ROSES,[1]* J. GILBERT,† P. T. XU,† P. SULLIVAN,‡ B. POPKO,‡ D. S. BURKHART,†
T. CHRISTIAN-ROTHROCK,† A. M. SAUNDERS,† N. MAEDA,‡ AND D. E. SCHMECHEL§

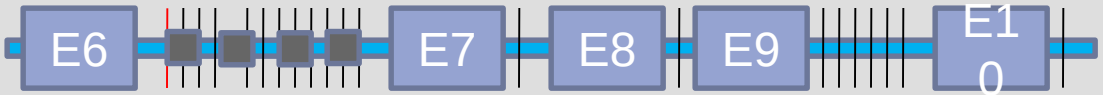
Thereafter we have focused on
what else is within the APOE LD region?



Started Phylogenetic mapping 2005

Figure 1. The Diptera

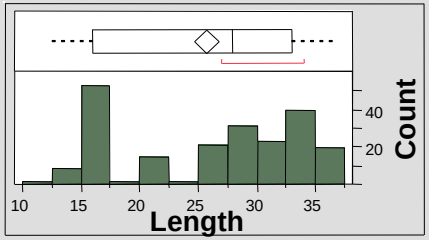
SNP and structural variants are prevalent in regions of the *TOMM40* gene - 2009



rs8106922 SNP

95% "A" allele in clade A

97% "G" allele in clade B



rs10524523 poly-T polymorphism

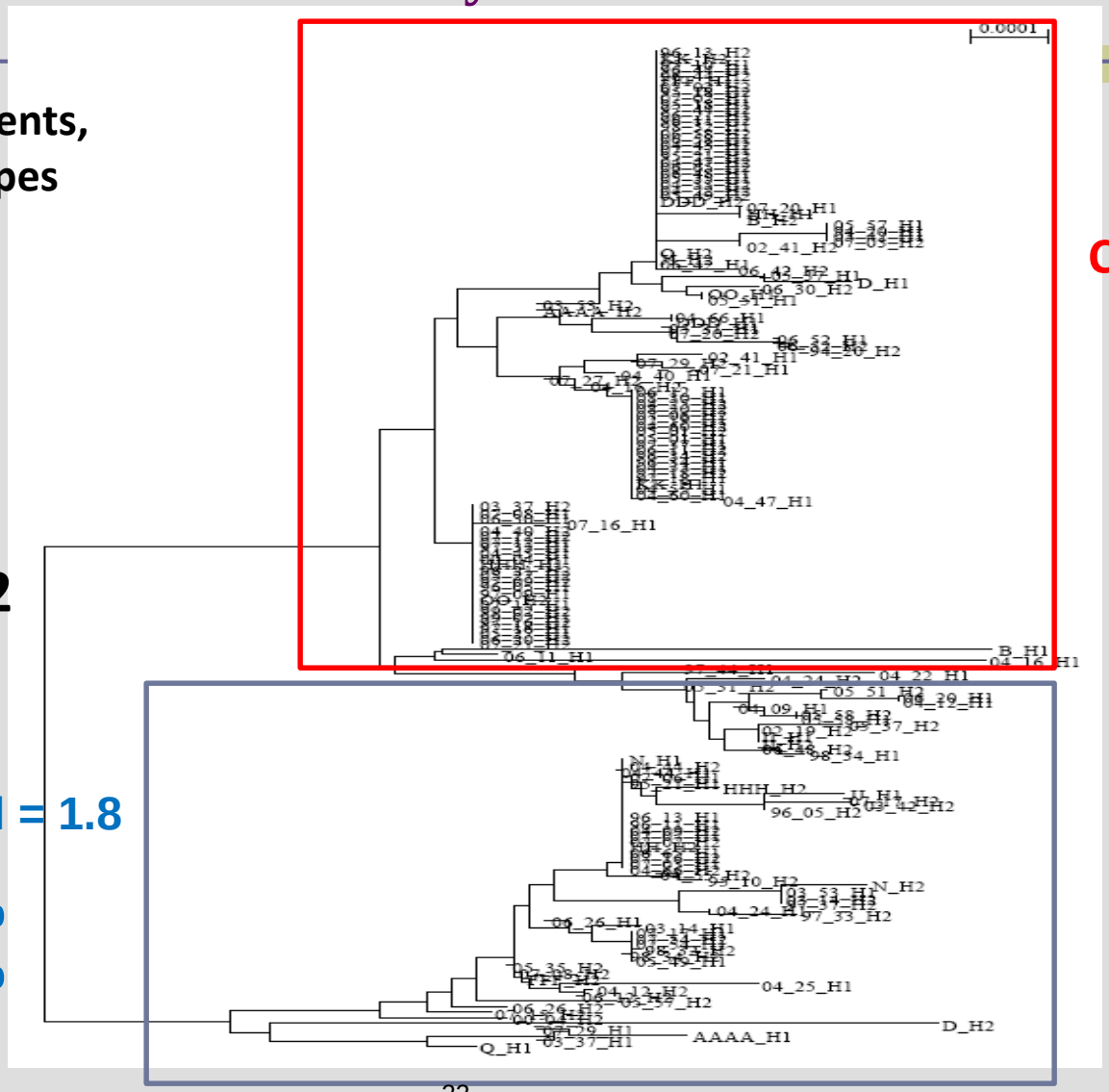
poly-T

SNP

TOMM40 polyTs seggregate out in repetitive clades within a small LD region between APOE and TOMM40.

The discovery data are all Caucasians

N = 105 patients,
210 haplotypes



A

Case/Control = 2.7

ε3/ε3 38%
ε3/ε4 38%
ε4/ε4 24%

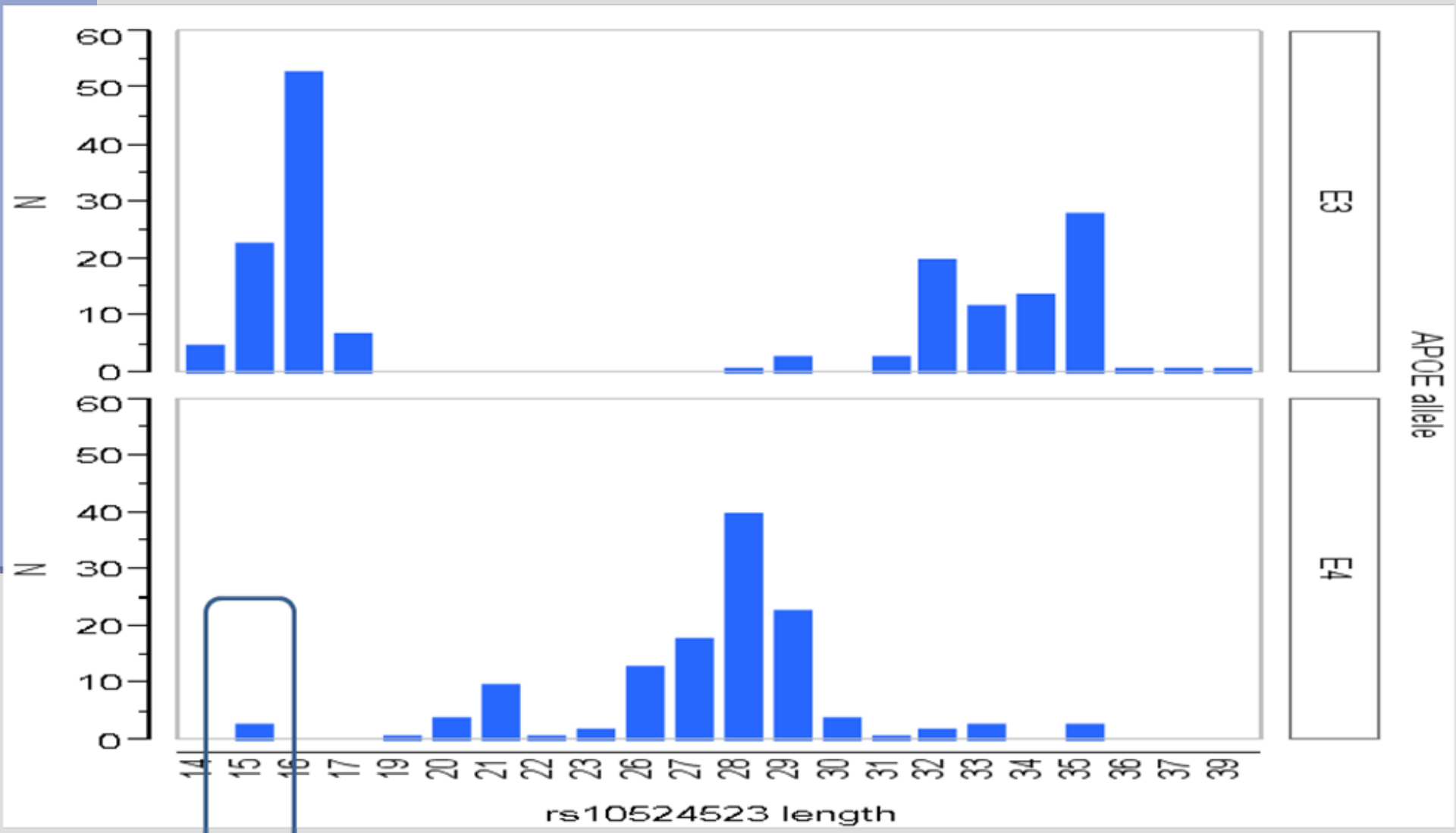
rs8106922

B

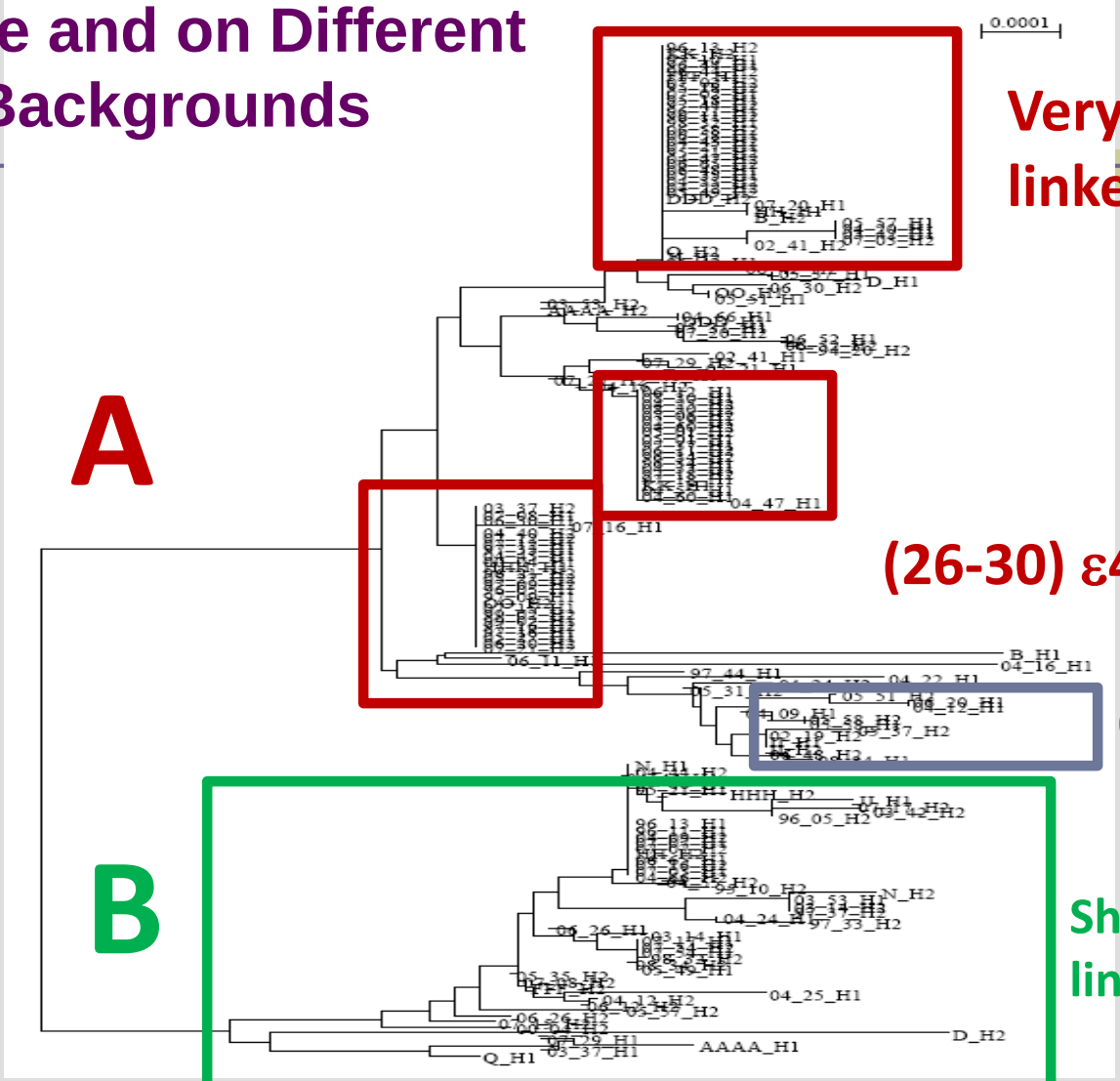
Case/Control = 1.8

ε3/ε3 65%
ε3/ε4 35%
ε4/ε4 0%

Frequency of TOMM40 poly-T repeats associated with APOE3 and APOE4 in AD patients and controls on the same DNA strand [Canadian series]

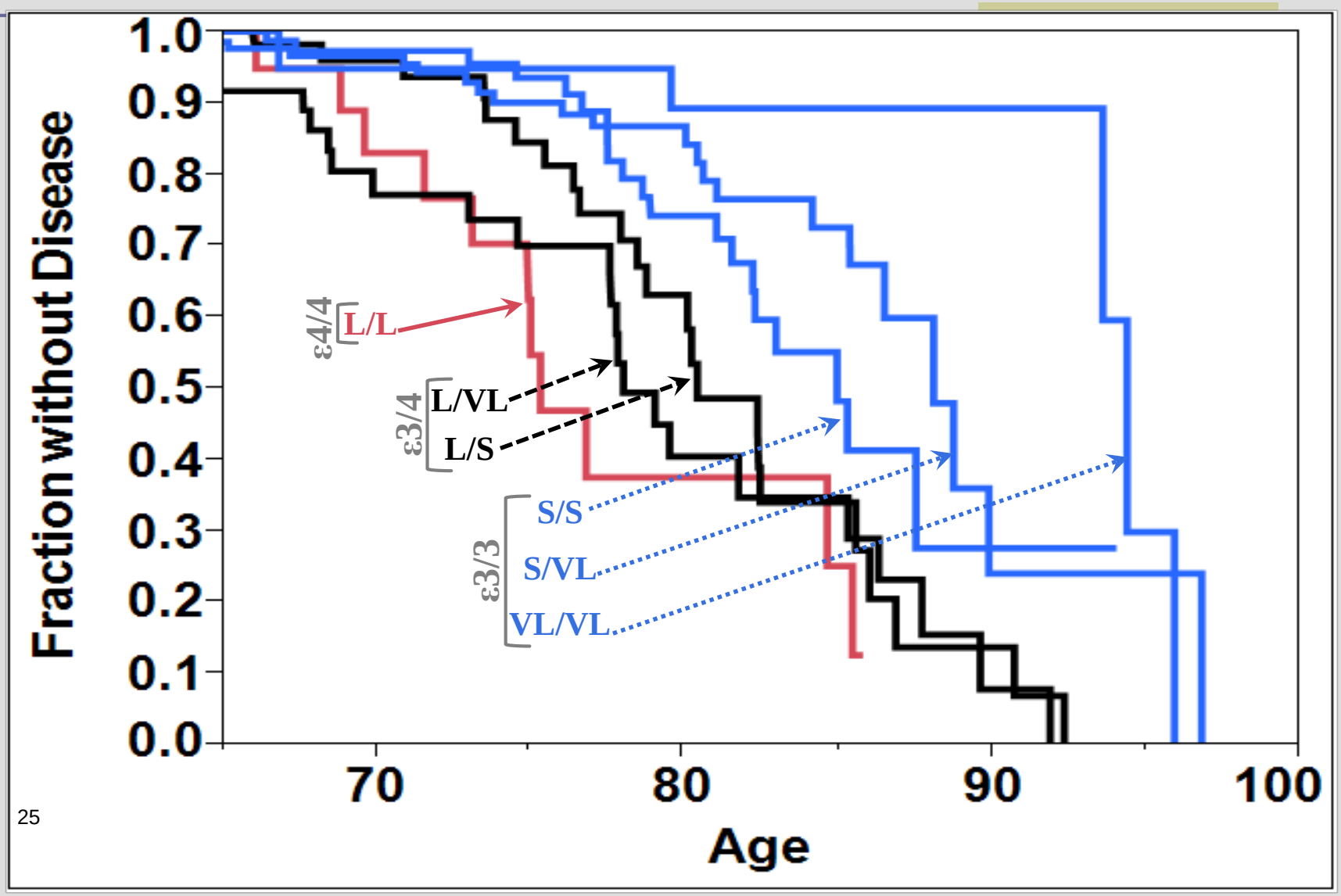


Rs10524523 Poly-T Polymorphisms Evolved Independently Over Time and on Different Genetic Backgrounds



TOMM40’523-APOE cis-Haplotype Curves Colored by APOE Genotype - 2013

Note that APOE ε3/4 and APOE ε3/3 are now also as informative as APOE ε4/4



Overview of the Biomarker Risk Algorithm

TOMM40 523 or APOE Genotype	Risk for the Study
APOE ε2/2	Low risk
APOE ε2/3	Low risk
APOE ε2/4	High risk for trial
APOE ε4/4	High risk
Risks for *APOE ε3/3 and ε3/4 Subjects*	
523 L/L	High risk
523 VL/L	High risk
523 S/L	≥74 yr = High risk
523 S/S	≥77 yr = High risk
523 S/VL	≥76 = High risk
523 VL/VL	Low risk

Zinfandel-Takeda TOMMORROW delay of onset trial based on TOMM40 algorithm

- TOMMORROW will simultaneously qualify a genetic algorithm for assigning 5-year risk for developing MCI due to AD, and evaluate the efficacy of low-dose pioglitazone to delay onset of MCI due to AD in cognitively normal, high-risk individuals. The study will enroll approximately 5800 subjects (ages 65- 83) and will apply operationalized criteria for MCI due to AD, a primary endpoint event. Along with the Clinical Dementia Rating scale, key assessments that enable the diagnosis are 12 neuropsychological measures representing 5 key cognitive domains affected in early AD. A separate neuropsychological instrument validation strategy will ensure that the test measures perform consistently across cultures and languages.

Zinfandel-Takeda TOMMORROW delay of onset trial – LSI April 2016

- **Current status:** TOMMORROW was launched in summer 2013 and is currently recruiting in the US, UK and Australia. To date, over 9,000 subjects have been screened and over 1,000 subjects randomized. Additional sites in Germany, Switzerland, Italy and Russia are expected to begin recruitment in early 2015. **The anticipated treatment period is 4 years, ending when a target number (410 in the high-risk group) with primary endpoint diagnoses have been reached.**

Bryan ADRC- AD Discovery, Prevention, Treatment

- 2009-2011 Registry build for prevention studies requiring healthy subjects (Zinfandel Pharmaceutical support)
- 2011-2016 Study design for Delay of MCI-AD Onset Study (Takeda)
- 2011 PREPARE Study funded by Duke-CTSA & industry (Zinfandel & Takeda companies) to prescreen for prevention studies across three sites (Russia, Kannapolis, and Durham)
- 2013 TOMMORROW study launch

Duke University-
Bryan Neurobiology Building

JOSEPH & KATHLEEN BRYAN
Alzheimer's Disease Research Center

30th Anniversary, NIA Alzheimer's Disease Centers
Baltimore, MD, October 11, 2014

The University of Washington ADRC

George M. Martin, MD
Professor of Pathology Emeritus (Active)
Adjunct Professor of Genome Sciences (Retired)
Visiting Scholar, UCLA

Jim Gusella Maps the Huntington Locus to 4p

Nature. 1983 Nov 17-23;306(5940):234-8.

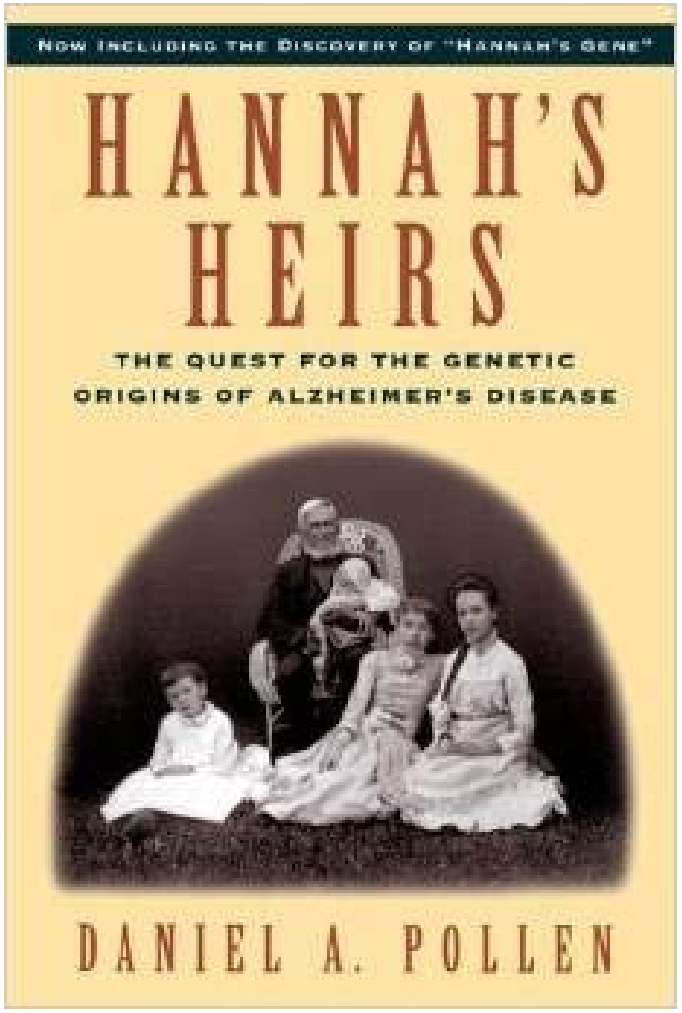
A polymorphic DNA marker genetically linked to Huntington's disease.

Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE, Watkins PC, Ottina K, Wallace MR, Sakaguchi AY, et al.

Abstract

Family studies show that the Huntington's disease gene is linked to a polymorphic DNA marker that maps to human chromosome 4. The chromosomal localization of the Huntington's disease gene is the first step in using recombinant DNA technology to identify the primary genetic defect in this disorder

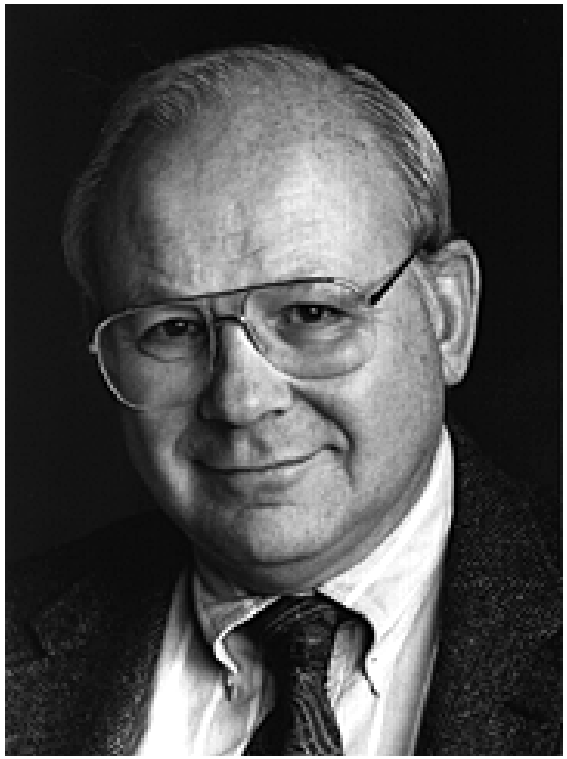
A Fellow Pathologist Writes a Letter About His Autosomal Dominant AD Pedigree



Tom Bird's Large Collection of Autosomal Dominant Dementias, Including a Group Displaying a Founder Effect

Ben Hall Recommends Gerry Schellenberg for The ADRC Molecular Genetics Lab, with Early Mentoring by Samir Deeb

Phil Fialkow, our Dean, Provides Funding for the Recruitment of a Statistical Geneticist from Stanford, Ellen Wijsman



The PS1 Mutation is Mapped at UW to Chromosome 14 & latter cloned by Peter St. George Hyslop & Colleagues

Science. 1992 Oct 23;258(5082):668-71.

Genetic linkage evidence for a familial Alzheimer's disease locus on chromosome 14.

Schellenberg GD, Bird TD, Wijsman EM, Orr HT, Anderson L, Nemens E, White JA, Bonnycastle L, Weber JL, Alonso ME, et al.

Abstract

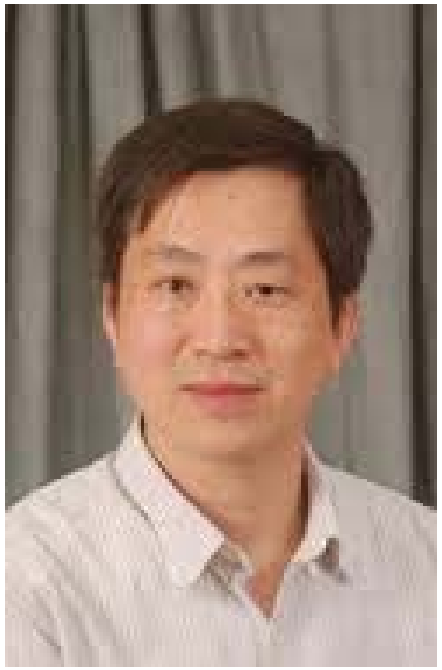
Linkage analysis was used to search the genome for chromosomal regions harboring familial Alzheimer's disease genes. Markers on chromosome 14 gave highly significant positive lod scores in early-onset non-Volga German kindreds; a Zmax of 9.15 (theta = 0.01) was obtained with the marker D14S43 at 14q24.3. One early-onset family yielded a lod score of 4.89 (theta

The PS2 Mutation is Mapped & Cloned

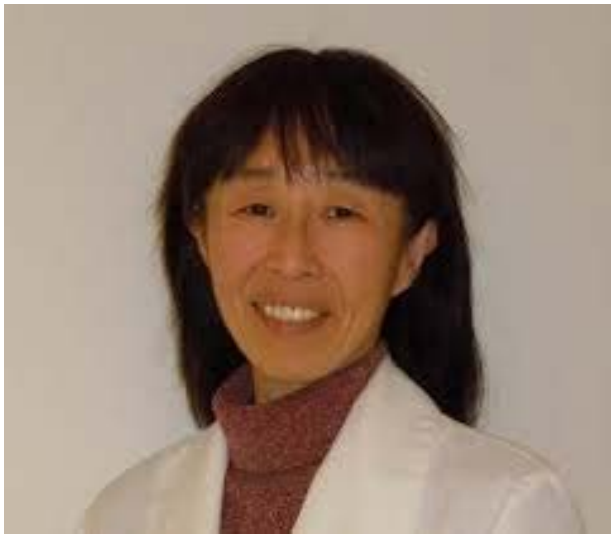
Science. 1995 Aug 18;269(5226):970-3.
A familial Alzheimer's disease locus on chromosome 1.
Levy-Lahad E[1], Wijsman EM, Nemens E, Anderson L, Goddard KA, Weber JL, Bird TD, Schellenberg GD.

Genomics. 1996 Jun 1;34(2):198-204.
Genomic structure and expression of STM2, the chromosome 1 familial Alzheimer disease gene.
Levy-Lahad E[1], Poorkaj P, Wang K, Fu YH, Oshima J, Mulligan J, Schellenberg GD
.

1996: Cloning of the Werner Syndrome Gene, a member of the RecQ family of Helicases



Chang-en Yu



Junko Oshima

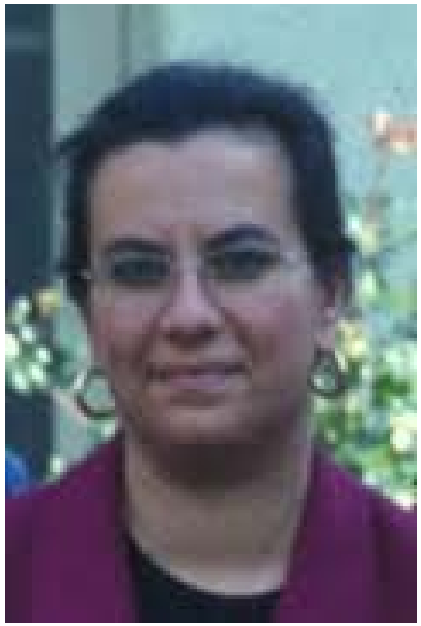
Gerry Schellenberg

The Co-Discovery of Tau Mutations as the First Genetic Cause of Frontotemporal Dementia

Ann Neurol. 1998 Jun;43(6):815-25.

Tau is a candidate gene for chromosome 17 frontotemporal dementia.

Poorkaj P[1], Bird TD, Wijsman E, Nemens E, Garruto RM, Anderson L, Andreadis A, Wiederholt WC, Raskind M, Schellenberg GD



PARVONEH POORKAJ NAVAS

UW ADRC Synthesizes the First PS1 Knock-in Mouse Model & Begins Collaboration with Mark Mattson Lab

Nat Med. 1999 Jan;5(1):101-6.

Increased vulnerability of hippocampal neurons to excitotoxic necrosis in presenilin-1 mutant knock-in mice.

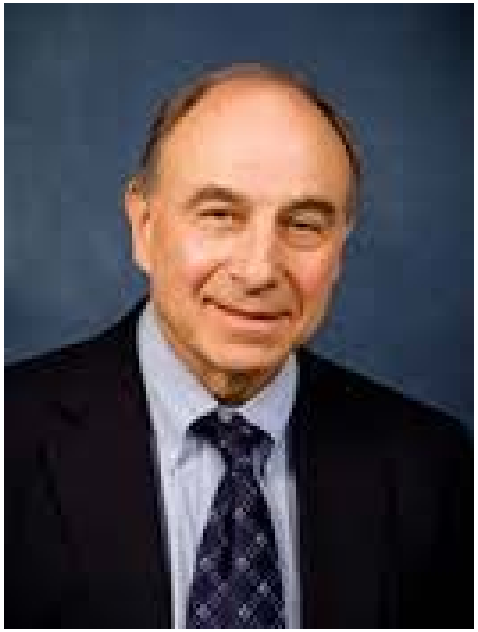
Guo Q[1], Fu W, Sopher BL, Miller MW, Ware CB, Martin GM, Mattson MP.

Author information

Abstract

Excitotoxicity, a form of neuronal injury in which excessive activation of glutamate receptors results in cellular calcium overload, has been implicated in the pathogenesis of Alzheimer disease (AD), although direct evidence is lacking. Mutations in the presenilin-1 (PS1) gene on chromosome 14 are causally linked to many cases of early-onset inherited AD (refs. 5,6). We generated PS1 mutant mice (PS1M146VKI) that express the PS1 M146V targeted allele at normal physiological levels. Although

Murray Raskind Becomes the Second UW ADRC Director
Elaine Peskind, Associate Director
Elaine initiates large scale collection of spinal fluids.
Noradrenergic physiology; AD Aggression & Agitation



Interventions in Caregiver Stress; Community Outreach Program; Research Consortium on Agitation in AD

Eric Larson & Bud Kukull: Growth of Epidemiological Research; The Group Health Registry; The National Alzheimer's Coordinating Center

Thomas J. Montine, MD, PhD
UW Alvord Chair of Pathology
the Third UW ADRC Director
~200 AD publications on AD

C.E. Finch,
PI, 1984-2004

H.C. Chui,
PI, 2004-

The University of Southern California Alzheimer Disease Research Center

The First Decade, 1984-1994

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE

LEAVE BLANK

PROJECT NUMBER

ABSTRACT OF RESEARCH PLAN

NAME AND ADDRESS OF APPLICANT ORGANIZATION (Same as Item 11, page 1)
University of Southern California
University Park, Los Angeles, CA 90089-0191

TITLE OF APPLICATION (Same as Item 1, page 1)
Alzheimer's Disease Research Center of the Consortium of Southern California

Name, Title and Department of all professional personnel engaged on project, beginning with Principal Investigator/Program Director

Finch, Caleb E., Professor, Biological Sciences and Gerontology

Miller, Carol A., Associate Professor, Pathology

submitted March 1984

This ADRC is a consortium of basic and clinical investigators in Los Angeles and Orange Counties who are associated with the University of Southern California, the California Institute of Technology, Beckman Research Institute of the City of Hope, and the University of California at Irvine. Most of these investigators are funded for research on Alzheimer's disease and related neurobiological topics by the NIA. Their independent outside funding totals $2,500,000 per year.

The intent is to provide support for studying Alzheimer's disease and relevant aging processes at a basic level with the tools of modern biology. Brain tissue of Alzheimer's and control brain tissue will be obtained from individuals with detailed psychosocial history and clinical records. Core modules will provide services for DNA and protein sequencing, for immunocytochemistry, for cell quantimetrics at USC, and for microscopic image analysis at UCI. Human brain tissue will be obtained through an Autopsy Module and a Human Material Research Support Module. The proposal includes a new grant "Gene Activity and Alzheimer's Disease," in which neuronal messenger RNA levels will be measured in Alzheimer's brains by *in situ* hybridization and autoradiography. The Human Material Research Module also provide opportunities to study the psycho-social dynamics of Alzheimer's disease.

Consortium Key Investigators

- **USC**: W Bondareff, HC Chui, CE Finch, M Gatz, V Henderson, C Miller, LS Schneider, V Regnier, J Shih, S Zarit
- **UCIrvine**: C Cotman, T Johnson, G Lynch, J Marshall
- **City of Hope**: E Roberts, P Salvaterra
- **CalTech**: E Lazarides, M Simon

2 Southland Centers Will Study Alzheimer's Disease

By KEAY DAVIDSON, *Times Staff Writer*

The University of California at San Diego and a medical consortium run by USC were selected Monday by the federal government as two of five national centers for the study of Alzheimer's disease, a leading cause of senility.

Johns Hopkins University, Harvard University and Mt. Sinai Medical Center in Manhattan also were designated as centers Monday by Margaret Heckler, secretary of Health and Human Services.

Twenty-two institutions across the United States had sought the designation. Heckler is expected to designate an additional five centers soon.

USC gerontologist Caleb E. Finch and pathologist Carol A. Miller will co-direct the Alzheimer's Disease Research Center Consortium of Southern California, which will receive about $2.8 million over five years from the National Institute on Aging. The consortium will include researchers from USC, the Beckman Research Institute of the City of Hope, Caltech and UC Irvine.

The USC-centered consortium "will foster collaboration among multidisciplinary groups of investigators, thus making possible achievements that could not be realized by individual researchers working alone," T. Franklin Williams, director of the National Institute on Aging, said.

Over the next five years, UC San Diego will receive $4.3 million for Alzheimer's research from the National Institute on Aging. UCSD will coordinate research, using scientists from its medical school and from Scripps Clinic and Research Foundation and Salk Institute, both in La Jolla.

UCSD scientists said they will use the money to study causes of and seek treatments for the incurable condition, which afflicts more than 2 million Americans and causes victims to become forgetful and inarticulate; they typically die within 15 years. A few contract the disease in their 20s.

Treatment Is Costly

Alzheimer's afflicts about 10% of Americans older than age 65 and is the major cause of nursing-home admissions, a UCSD statement said. The nation spent $27 billion in 1983 caring for Alzheimer's victims, Dr. Robert Katzman, the director of the UCSD Alzheimer's program, said.

He added that UCSD researchers plan to explore such areas as physical and chemical changes in victims' brains; links between Alzheimer's and Down's syndrome, a major cause of childhood retardation; psychological changes in patients with Alzheimer's, and whether chromosome damage contributes to Alzheimer's disease.

A new state law should help relatives of victims of Alzheimer's disease. Part V, Page 1.

LA Times Oct 23, 1984

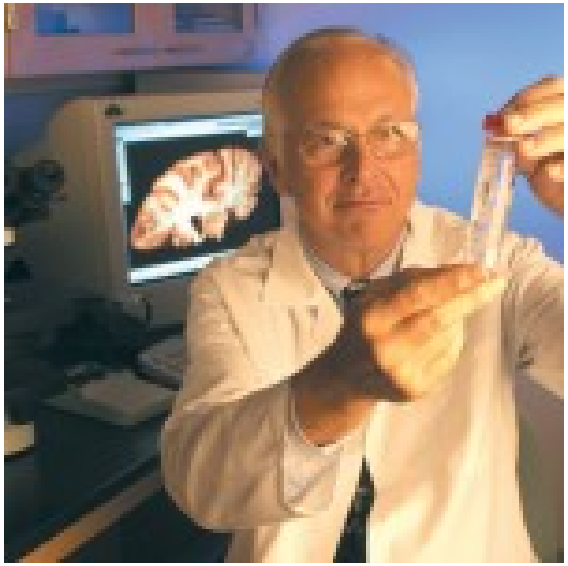
MARTHA HARTNETT / Los Angeles Times

Updating Alzheimer's disease: Drs. Carol Miller, Steven H. Zarit, Helena Chui and Caleb E. Finch.

UCI

- UCI: Carl Cotman

  CoPI, CoDir



- Downs Brain Core (Ira Lott), 1988
- Separate NIA ADRCs after 1999

Helena Chui

- Chui et al. 1984. Stability of neuronal number in the human nucleus basalis of Meynert with age. Neurobiol Aging.
- Perlmutter et al. 1991. Association between vascular basement membrane components and lesions of Alzheimer's disease. J Neurosci Res
- Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, Katzman R. 1992. Criteria for the diagnosis of ischemic vascular dementia proposed by the California Alzheimer's Disease Diagnostic and Treatment Centers. Neurology.
- P01 The Aging Brain: Vasculature, Ischemia, and Behavior

  1994-present (with UCDavis, UCSF, and UCLA)

Carol Miller, Neuropathology

- Brain Bank-Neuropath Core Director since 1984
- MoABs from Drosophila brains that detected neuronal targets of AD and cell death mechanisms (PNAS 1983, 1987)
- Retinal degeneration in AD (NEJM 1986)

Lon Schneider, Drug development

- Tacrine Trial 1986: USC joined UCSD (Leon Thal) and Ken Davis (MSSM)
- Developed the standard clinicians global outcomes scale for clinical trials: the “ADCS-CGIC, CIBIC+”
- CATIE-AD trial for atypical anti-psychotics for behavior-psychotic symptoms

Finch Lab

- 1987 Clonable human brain mRNA stable >24 hrs postmortem; does not require rapid autopsy.
- 1990 cDNA libraries showed increased inflammatory gene expression in AD and normal aging, e.g. C1q, clusterin.
- 1994-5 toxic Abeta oligomers formed with clusterin

Carl Cotman

- The β-amyloid assembly state influences toxicity (Charles Glabe, Christian Pike).
- Aβ synergizes with NMDA receptor activation to cause neuronal death (Jim Geddes, Helena Chui)
- Aberrant sprouting near senile plaques (Gedes, Selkoe)

Geddes JW, Monaghan DT, Cotman CW, Lott IT, Kim RC, Chui HC.

Science (1985)

Plasticity of hippocampal circuitry in Alzheimer's disease.

Two markers of neuronal plasticity were used to compare the response of the human central nervous system to neuronal loss resulting from Alzheimer's disease with the response of rats to a similar neuronal loss induced by lesions……. These results are evidence that the central nervous system is capable of a plastic response in Alzheimer's disease. Adaptive growth responses occur along with the degenerative events.

UC Irvine

- NMDA and other excitatory amino acid receptors in AD brain, Cotman, Geddes 1989 NBA
- Toxicity of β-amyloid and assembly state, Cotman, Pike, Glabe 1989 J Neurosci
- Aβ synergies with NMDA-R activation in neuronal death, Pike, Glabe 1991 Brain Res; 1993 J Neurosci
- Senile plaques cause aberrant neurite sprouting, Whitson, Selkoe, Cotman 1989 Science
- Ira Lott: Downs Brain Bank

Estrogens and brain aging

- Finch CE. 1986. New questions about steroids. JAGS
  "*Recent studies on lab rodents demonstrate that sex and adrenal steroids can cause irreversible dysfunction on select brain cells….The Alzheimer Centers might consider adding subject groups to evaluate these looming questions.*"
- Paganini-Hill A, Henderson VW. 1994. Estrogen deficiency and risk of Alzheimer's disease in women. Am J Epidemiol
  "(Leisure World)…. estrogen replacement therapy may be useful for preventing or delaying the onset of this dementia."

Betza Zlokovic

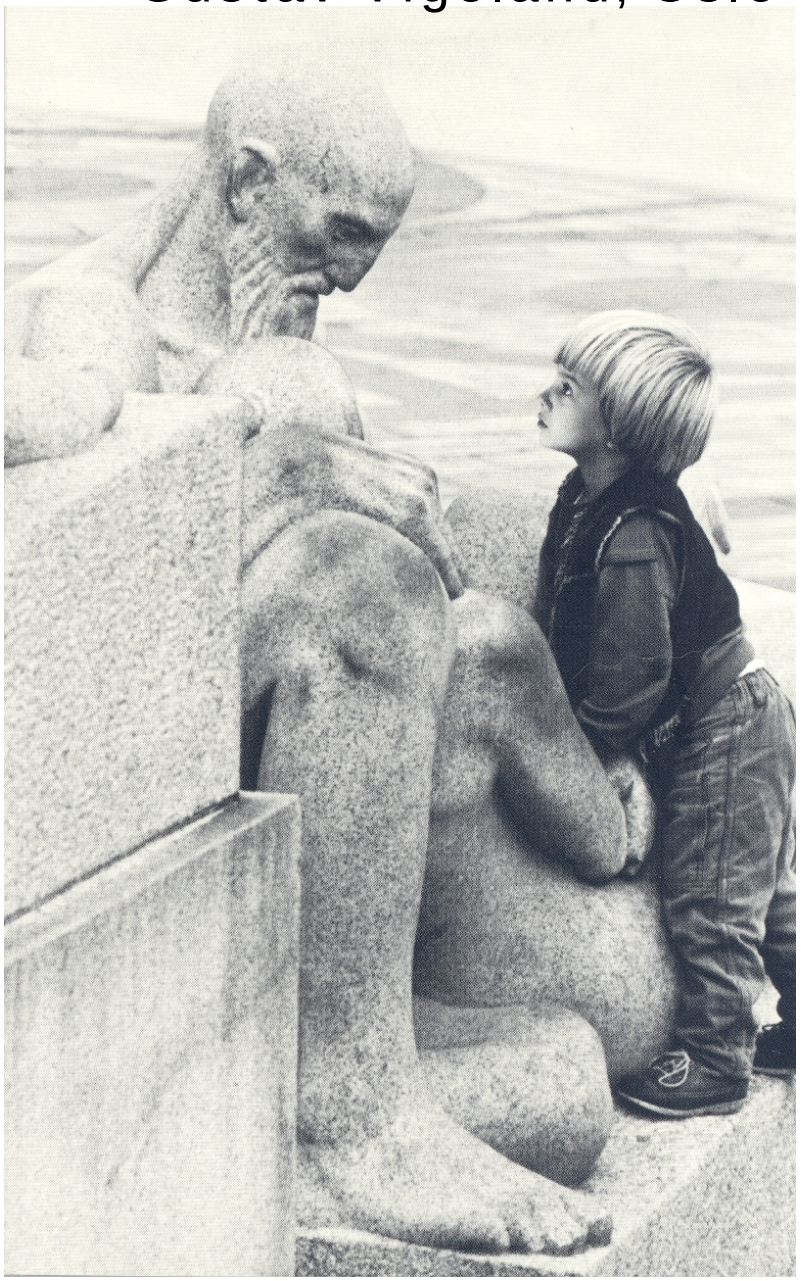
- Recruited to USC 1989; returned 2011

- Zlokovic et al, 1993. BBRC

  Blood-brain barrier transport of circulating Abeta:

  "*BBB has the capability to control the cerebrovascular sequestration of circulating soluble Abeta. Hence, sAbeta can contribute to both cerebrovascular and parenchymal amyloid formation*."

Gustav Vigeland, Oslo



Brain Aging depends on neurovascular neurodegenerative interactions

Fall ADC meeting

October 11th 2014

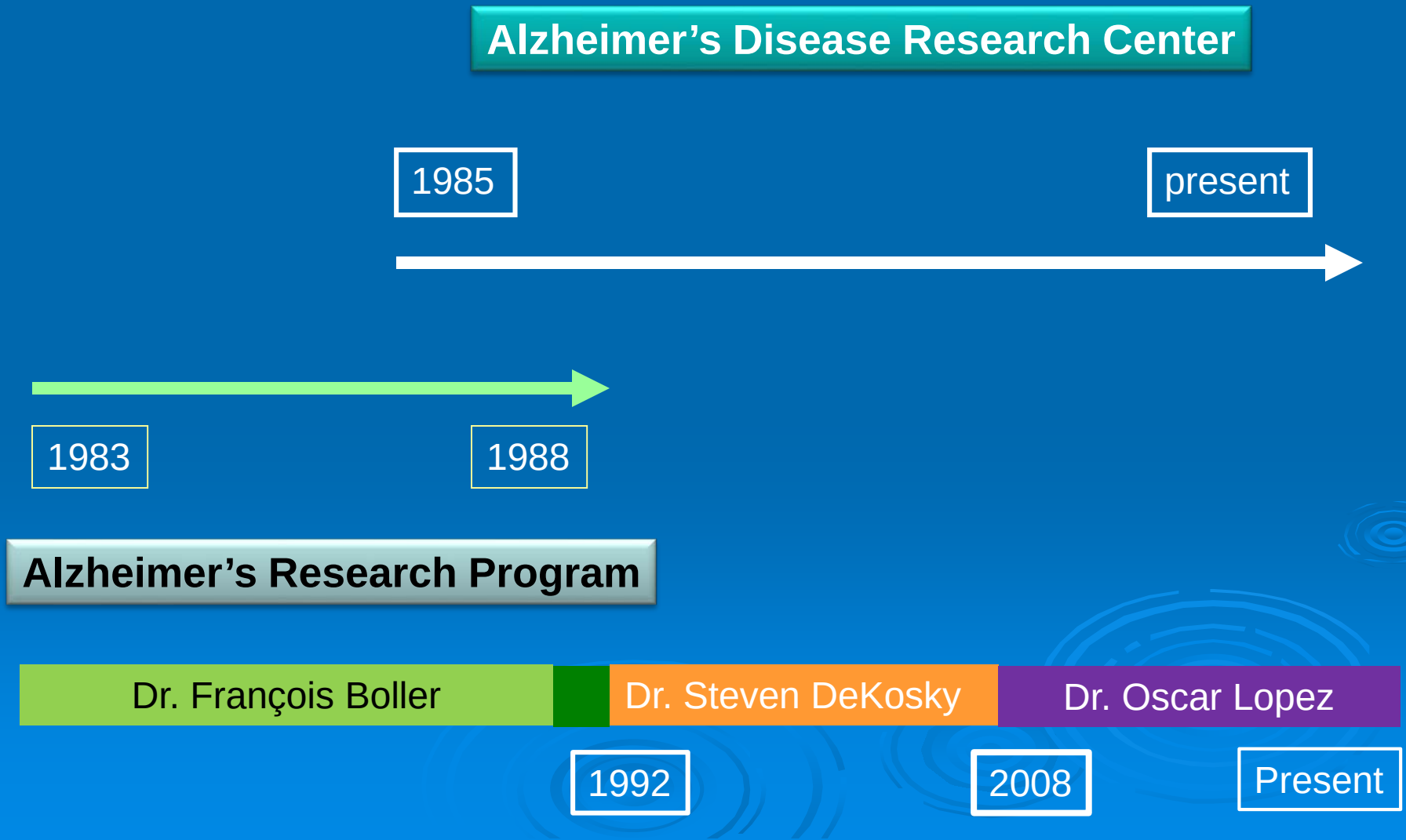
Baltimore, MD

The Pittsburgh ADRC

François Boller, M.D., Ph.D.

fboller@mfa.gwu.edu

The History of the ADRC Registry



Alzheimer's Research Program Overall aims (1983)

- Determine which clinical signs and symptoms best allowed a reliable diagnosis of AD.

- Determine which clinical signs and symptoms could be used to predict the progression of AD

The outcome of the ARP was published in:
Becker JT, Boller F, Lopez, OL, Saxton J, McGonigle K, ARP. The Natural History of Alzheimer's Disease. Archives of Neurology 51:585-594, 1994

Pioneer work at the ADRC of Pittsburgh 1983-1990

Pathological studies

- Moossy J, Zubenko GS, Martinez AJ, Rao GR, Kopp U, Hanin I.Lateralization of brain morphologic and cholinergic abnormalities in Alzheimer's disease.Arch Neurol. 1989 Jun;46(6):639-42.
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- Moossy J, Martinez AJ, Hanin I, Rao G, Yonas H, Boller F. Thalamic and subcortical gliosis with dementia. Arch Neurol. 1987 May;44(5):510-3.
- Grossi D, Lopez OL, Martinez AJ. Mamillary bodies in Alzheimer's disease. Acta Neurol Scand. 1989; 80(1):41-5.

Clinicopathological correlations

- Boller F, Lopez OL, Moossy J. Diagnosis of dementia: clinicopathologic correlations. Neurology. 1989 Jan;39(1):76-9.
- Zubenko GS, Moossy J Major depression in primary dementia. Clinical and neuropathologic correlates. Arch Neurol. 1988 Nov;45(11):1182-6.
- Zubenko GS, Moossy J, Martinez AJ, Rao G, Claassen D, Rosen J, Kopp U. Neuropathologic and neurochemical correlates of psychosis in primary dementia. Arch Neurol. 1991 Jun;48(6):619-24.

Neuroimaging studies

- Jungreis CA, Kanal E, Hirsch WL, Martinez AJ, Moossy J. Normal perivascular spaces mimicking lacunar infarction: MR imaging. Radiology. 1988 Oct;169(1):101-4.
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Pioneer work at the ADRC of Pittsburgh 1983-1990

Neuropsychological studies

- Huff FJ, Becker JT, Belle SH, Nebes RD, Holland AL, Boller F. Cognitive deficits and clinical diagnosis of Alzheimer's disease. Neurology. 1987 Jul;37(7):1119-24.
- Nebes RD, Boller F The use of language structure by demented patients in a visual search task. Cortex. 1987 Mar;23(1):87-98.
- Becker JT, Boller F, Saxton J, McGonigle-Gibson KL. Normal rates of forgetting of verbal and non-verbal material in Alzheimer's disease. Cortex. 1987 Mar;23(1):59-72.
- Becker JT, Huff FJ, Nebes RD, Holland A, Boller F. Neuropsychological function in Alzheimer's disease. Pattern of impairment and rates of progression. Arch Neurol. 1988 Mar;45(3):263-8.
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- Boller F, Becker JT, Holland AL, Forbes MM, Hood PC, McGonigle-Gibson KL.Predictors of decline in Alzheimer's disease. Cortex. 1991 Mar;27(1):9-17.
- Nebes RD, Boller F, Holland A. Use of semantic context by patients with Alzheimer's disease. Psychol Aging. 1986 Sep;1(3):261-9.

Neurological and psychiatric studies

- Brenner RP, Ulrich RF, Spiker DG, Sclabassi RJ, et al. Computerized EEG spectral analysis in elderly normal, demented and depressed subjects. Electroencephalogr Clin Neurophysiol. 1986 Dec;64(6):483-92.
- Huff FJ, Boller F, Lucchelli F, Querriera R, Beyer J, Belle S. The neurologic examination in patients with probable Alzheimer's disease. Arch Neurol. 1987 Sep;44(9):929-32.
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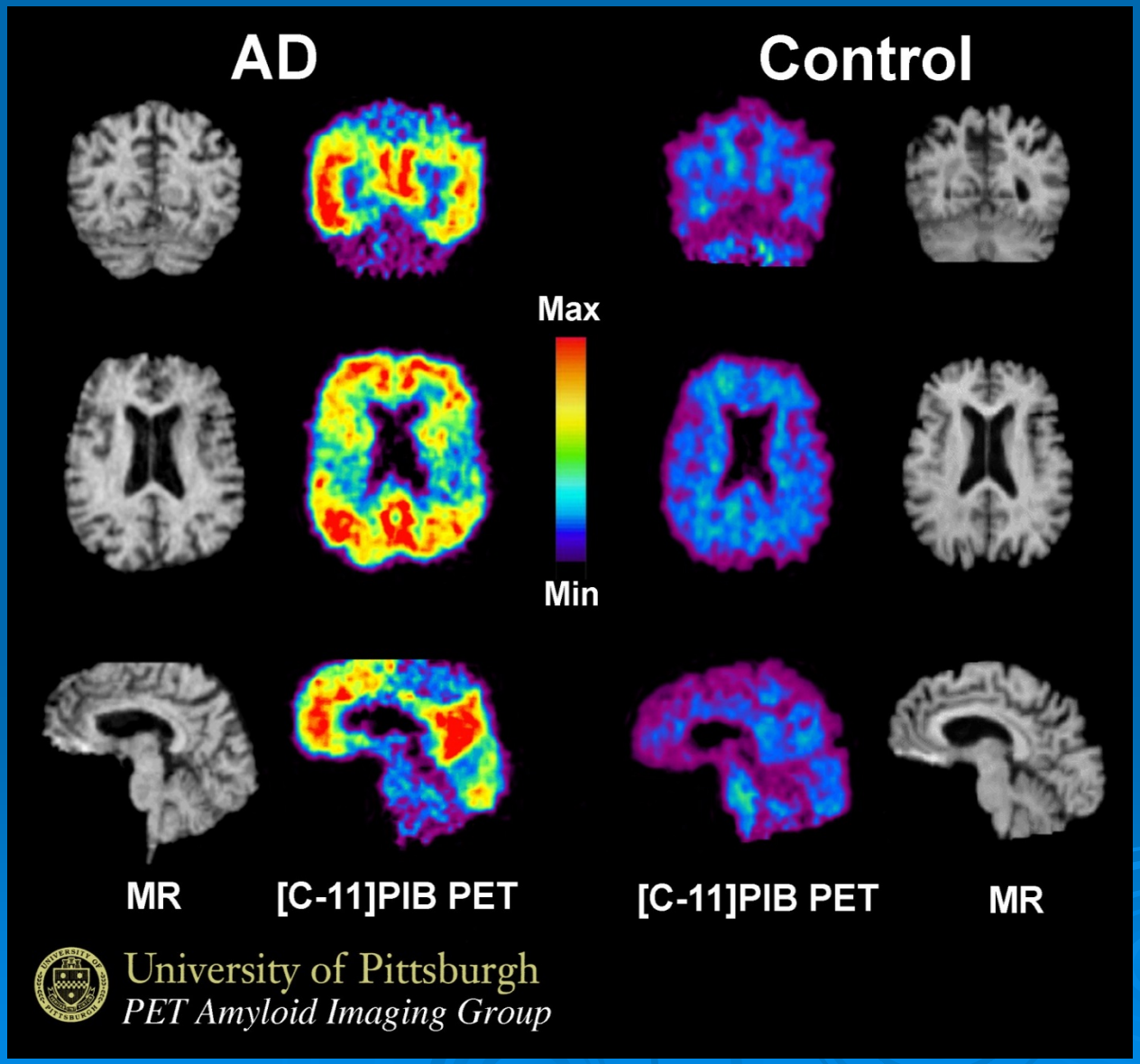
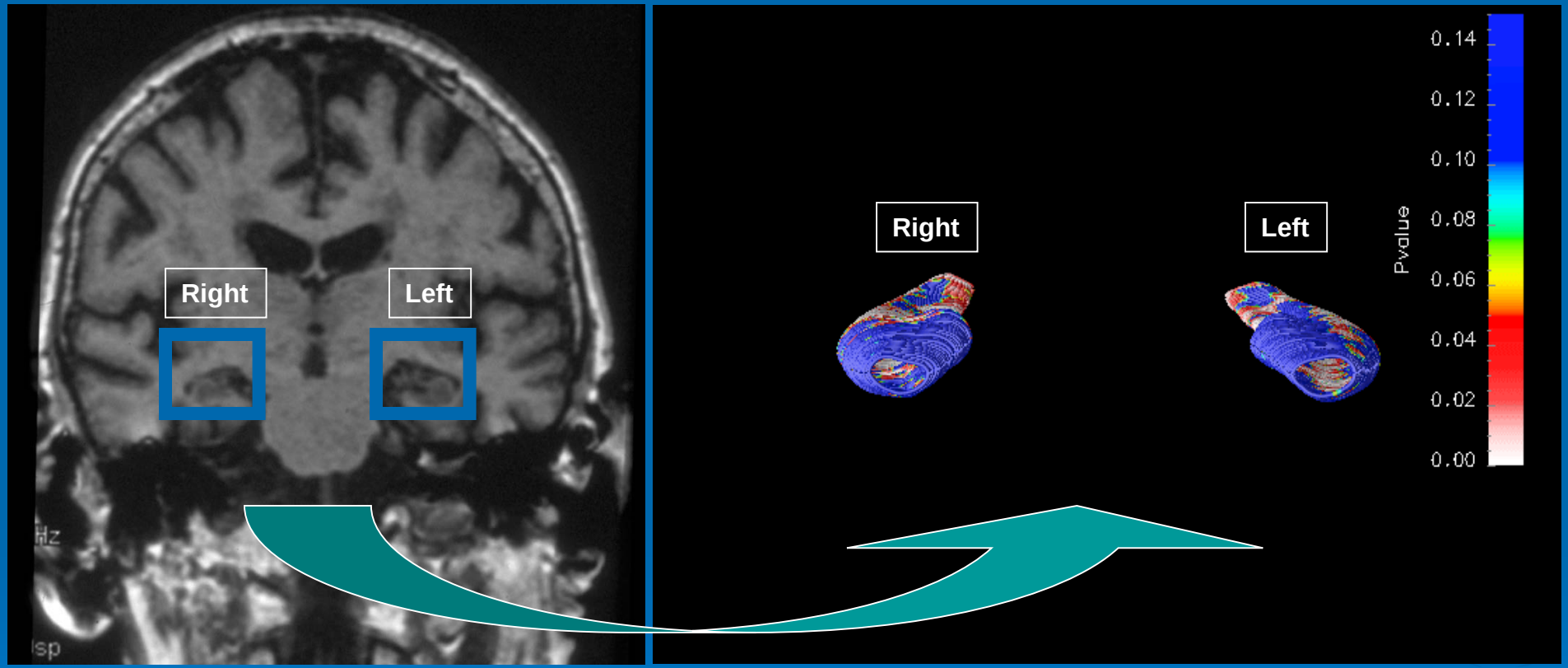
University of Pittsburgh Alzheimer's Disease Research Center

Pioneer work in amyloid ligand technology



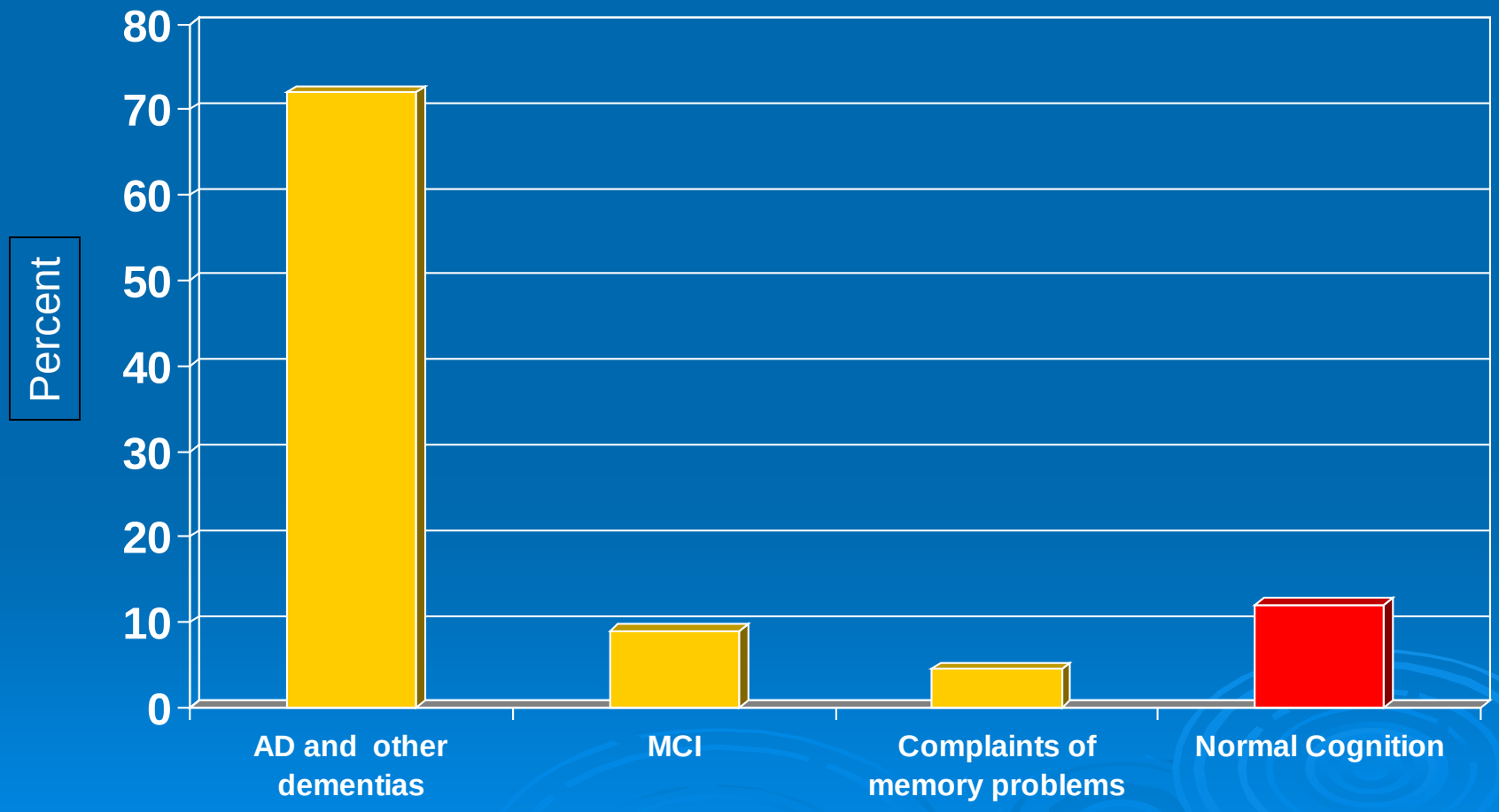
Klunk et al. Annals of Neurology 2004; 55: 306

Neuroimaging studies: Hippocampal volume in AD



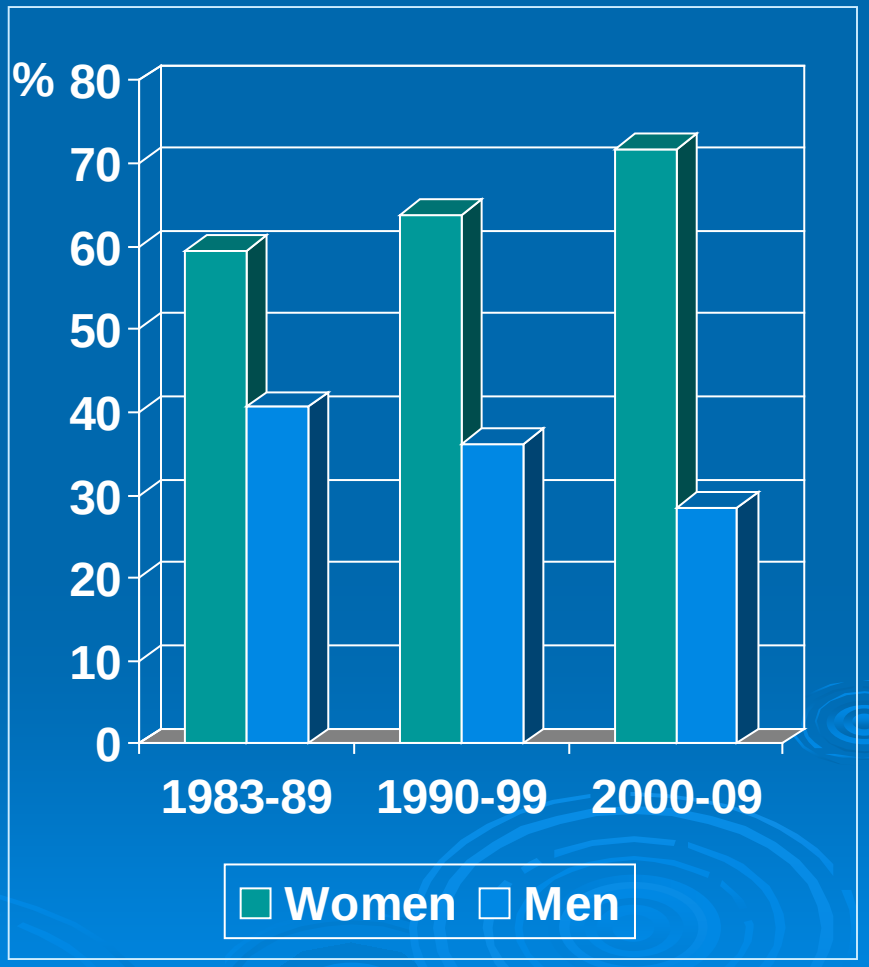
Becker et al. Archives of Neurology 2006: 63: 97

ARP and ADRC Participants from 1983 to 2010 (n= >4,000)

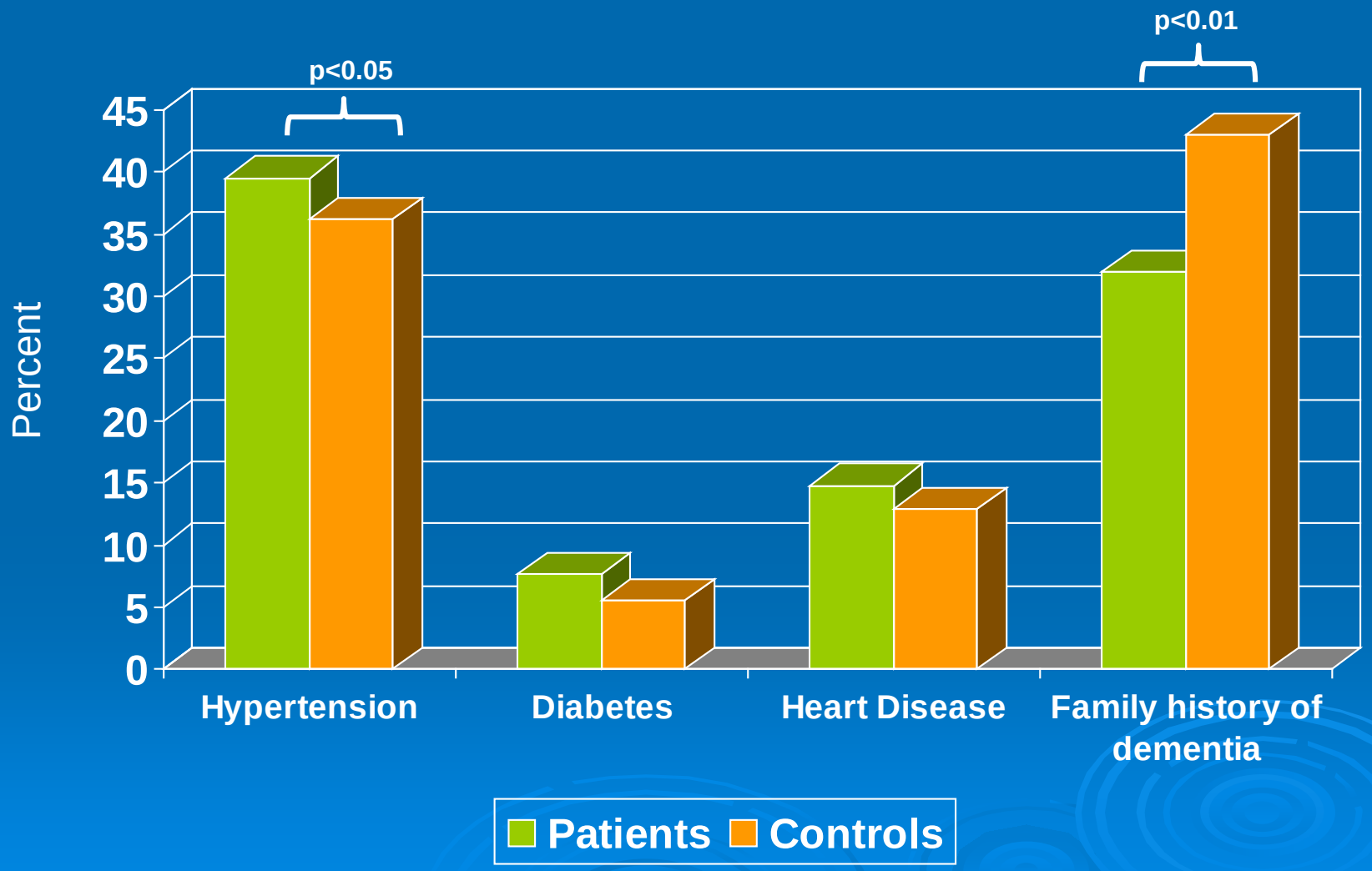


Demographic characteristics of 339 normal control participants from 1983-2009

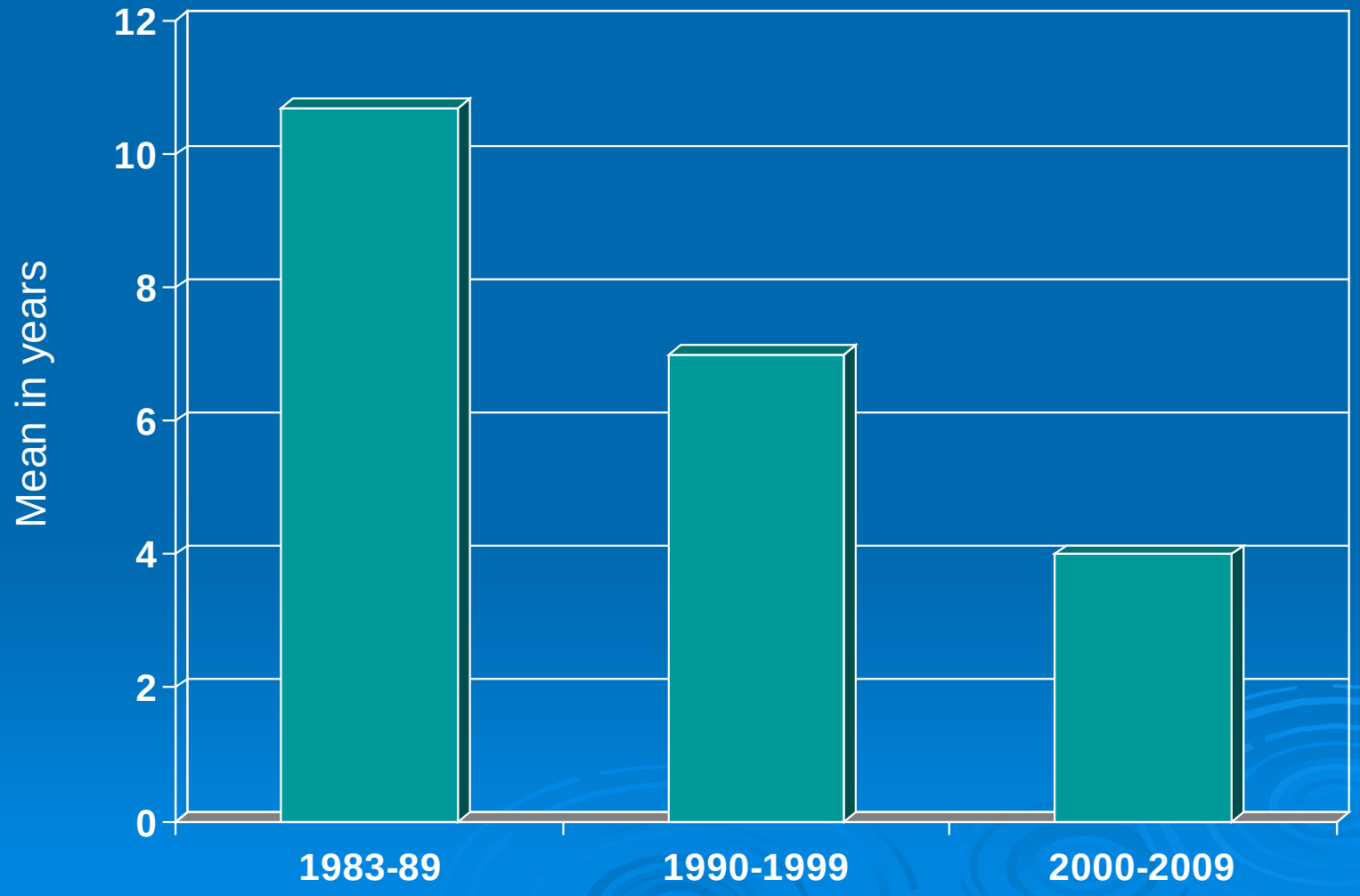
- Mean Age: 65.6
  - <60 26.3%
  - 60-69: 37.5%
  - 70-79: 31.0%
  - >80: 5.31%
- Gender:
  - Men: 36.3%
  - Women: 63.7%
- MMSE: 28.6



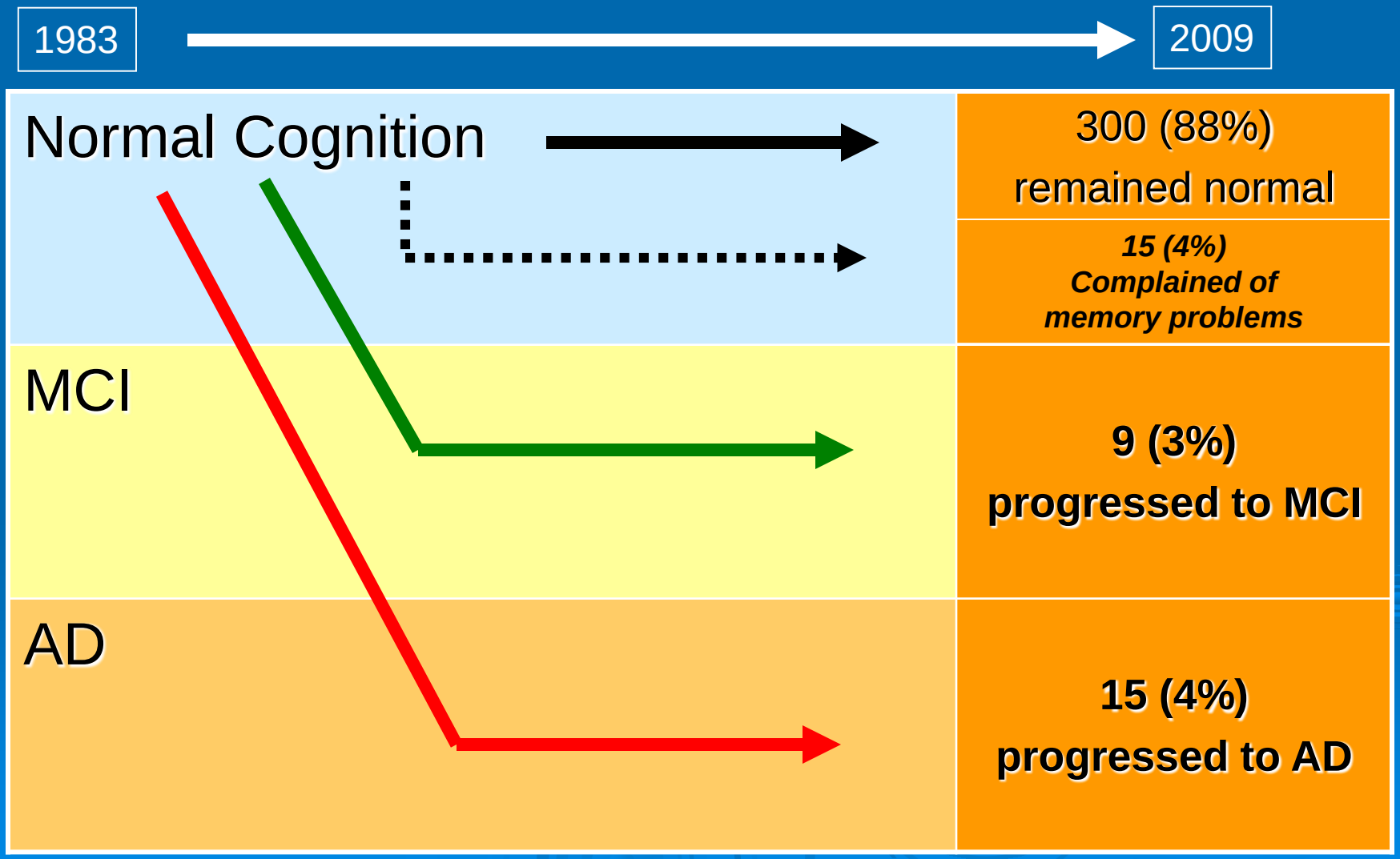
Vascular Factors and Family History of Dementia in Patients with Dementia and Normal Controls



Number of years of follow-up as a function of year of study entry (range 0.8 to 22 years)



Progression to Cognitive Impairment in Normal Controls



Incident Rates

Study	Incidence rates
Cardiovascular Health Study (Fiztpatrick et al., 2004)	25.5 per 1000 person/years
Rotterdam Study (Ott et al., 1998)	10.5 per 1000 person/years
The Canadian Study of Health and Aging (CSHA Working Group, 2000)	21.8 – 19.1 per 1000 person/years
Meta-analysis (Jorm et al. 1998)	9.0 per 1000 person/years at age 65-69. 179 per 1000 person/years at age 90-94

Incidence of dementia in normal controls at the ADRC

The analysis involved 234 participants (*all those* > *65*) enrolled as normal controls in the Pittsburgh ADRC study from 1983 to 2008.

They were followed for an average of 65.3 months (SD 56.8; range 4 to 227.2 months).

Expected incidence: Assuming an average incidence/year of 2% during 5,4 years, we would expect 10.8% of subjects to develop AD, i.e. 25 cases.

Incidence of dementia in normal controls at the ADRC

8.72 **per 1000 subjects after 1147 follow-up years in subjects age 65 or older**

14.7 **per 1000 subjects after 679 follow-up years in subjects age 75 or older.**

Normal controls at the ADRC represent a unique scientific opportunity to study aging and cognition in a healthy group of individuals.

Acknowledgements 1983-2014

- Oscar L. Lopez
- William E. Klunk
- Steven T. DeKosky
- François Boller
- James T. Becker
- Judith Saxton
- Richard Brenner
- Sidney Wolfson
- Ronald L. Hamilton
- Robert A. Sweet
- David Wolk
- Steven Belle
- Ilyas M. Kamboh
- Daniel I. Kaufer
- Donald Rezek
- Jay Huff
- Mark Miller
- Mary Ganguli
- A. Julio Martinez
- John Moossy
- Beth Snitz
- Eric McDade
- Julia Kofler
- Nanci Keefe
- Leslie Dunn
- Heather Eng
- Lori Macedonia
- Carolyn Rickard
- Donna Simpson
- Jennifer Lingler
- Thomas Baumgartner
- Patricia Henderson
- Kendra Greenberg
- Beth Sarles
- Patrick Ketchel
- Mary Ann Oakley
- Timothy Shelley
- Margaret Forbes
- Kathie Savage
- Marlene Paytas
- Shirley Portis
- Audrey Woods
- Kathleen Douglas

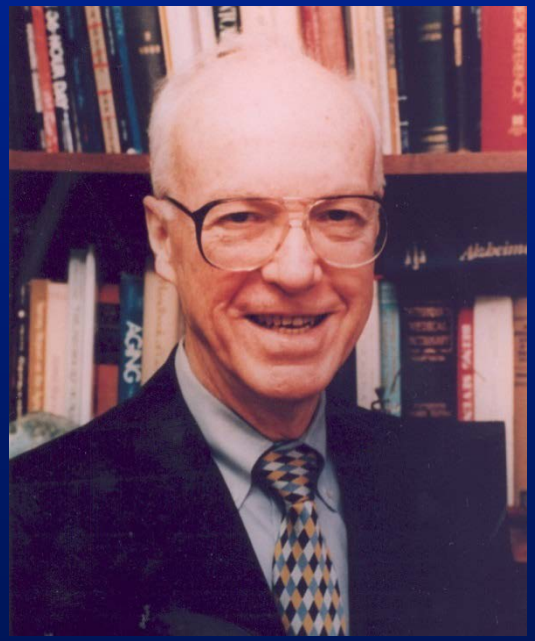
And many more, too numerous to mention.

Washington University Knight Alzheimer's Disease Research Center

Leonard Berg, MD

Founding Director

1927-2007



KnightADRC Alzheimer's Disease Research Center | WASHINGTON UNIVERSITY ST. LOUIS

Leonard Berg, MD

- Precocious; graduated WUSM at age 22
  - Earned money playing clarinet in big bands; “Benny Goodman of St. Louis”
- Neurology residency at The Neurological Institute of New York (Columbia University); he and Bud Rowland were the first postdoctoral fellows at the NIH Clinical Center
- Went into private practice after return to St. Louis in 1955; “wouldn’t be successful” in research

Origin of the CDR

- In the 1970s, his demented patients with suspected NPH did not improve post-shunt; Berg convened a multidisciplinary group to meet weekly to review what then was known about dementia
- The group finally decided that longitudinal studies were needed; the first 2 NIH applications to start a study were unsuccessful
- After adding colleagues from the Department of Psychology, their third application was funded by NIMH from 1979-1982 as “Mental Health in the Aged: Biomedical Factors”
- To avoid circularity in using cognitive tests both to classify individuals and to track cognitive performance, the psychologists recommended classifying patients as “healthy” or “demented” using clinical means only; Berg and close colleague Charles Hughes thus developed the Clinical Dementia Rating

Unexpected Events

- Renewal application to NIMH in 1982 was not funded; Zaven Khachaturian asked Berg to submit it as a PPG to NIA where it was funded January 1st, 1984; the “Healthy Aging and Senile Dementia” PPG is now in Years 31-35
- When call for ADRC applications came in 1983, Berg was engrossed in the PPG application and elected to defer an ADRC application to the following year; the ADRC was formally inaugurated September 30th, 1985
- Charles Hughes left Washington University for private practice; Berg recruited a postdoctoral fellow in neuropharmacology to join him

Unexpected Events

On To Retirement

- Berg remained in full-time private practice until 1989
- Stepped down as ADRC Director in 1997, succeeded by Gene Johnson and John Morris; Morris became PI of HASD in 1997 and of the ADRC in 2003
- First Berg Symposium in 1997: Robert Katzman, Zaven Khachaturian, William Markesbery, Don Price, and Dennis Selkoe were speakers
- Emeritus status July 1998; September 1998, right parieto-occipital cerebral hemorrhage, self-diagnoses CAA

Final Years

- Eventually recovered sufficiently to make public appearances, including at the 2003 Berg Symposium

Final Years

- At the 2005 Berg Symposium, also marking the 20th anniversary of the ADRC, Berg spoke from the audience to his many close colleagues, friends, and family
- Died January 2007, at age 79 after another stroke
- Leonard Berg was an outstanding physician, esteemed mentor, team builder, and pioneer in AD research. He set exacting standards and provided both wise counsel and supportive collegiality. Above all, he was a true gentleman. He bequeathed our ADRC with a legacy of excellence.

Knight ADRC's Evolution

- 1985-1989: clinical, cognitive, and behavioral distinction of early-stage symptomatic AD from cognitively normal aging
  - Storandt and Hill, Arch Neurol 1989; 46: 383-386
- 1990-2000: neuropathological and neuroanatomical characterization of preclinical AD
  - Price and Morris, Ann Neurol 1999;45:358-368
- 2000-2010: molecular biomarker (CSF; amyloid imaging) characterization of preclinical AD
  - Fagan et al., Ann Neurol 2009; 65:176-183
  - Morris et al., Ann Neurol 2010; 66:1469-1475

Knight ADRC's Evolution

- 2010-present:
  1) Temporal ordering of biomarkers in preclinical AD
     - Bateman et al., NEJM 2012; 367:795-804
  2) Risk of conversion from preclinical to symptomatic AD
     - Vos et al., Lancet Neurol 2013; 12:957-965
  3) Secondary prevention trials in ADAD
     - Moulder et al., Alzheimers Res Ther 2013; 5:48
- October 30th, 2015: 9th Leonard Berg Symposium: "Sleep and Neurodegeneration: A Bidirectional Relationship"

Knight ADRC and Affiliated Grants

Healthy Aging and Senile Dementia
JC Morris, PI (P01 AG03991)
8-15-14 to 4-30-19 (since 1984)

- **Project 1: Cognitive and Functional Indicators of Transition to Symptomatic AD**
  Morris
- **Project 2: Potential Prognostic and Theranostic Marker for Preclinical AD**
  Holtzman
- **Project 3: Identification of genetic variants associated with rate of disease progression**
  Cruchaga/Goate

Antecedent Biomarkers for AD: The Adult Children Study
JC Morris, PI (P01 AG026276)
9-30-11 to 5-31-16 (since 2005)

- **Project 1: The natural history of Aβ accumulation in preclinical AD**
  Morris
- **Project 2: CSF Biomarkers of Antecedent AD**
  Fagan
- **Project 3: Behavioral and Neural Markers of Mental Control: Modeling, Imaging, & Enrichment**
  Balota
- **Project 4: Antecedent Imaging Biomarkers**
  Benzinger
- **Project 5: Aerobic Glycolysis in the Pathophysiology of AD**
  Vlassenko

Cores & Satellites

- Administration — Morris
- Clinical — Morris/Bateman
- AA Outreach Core — Carr
- Biostatistics — Xiong
- Neuropathology — Cairns
- Imaging — Benzinger
- Genetics — Goate
- Outreach, Recruitment & Education Core — Denny
- Rural Outreach Core — Denny
- Biomarker — Fagan
- Informatics — Marcus

Knight Alzheimer's Disease Research Center
JC Morris, PI (P50 AG05681)
5-1-15 to 4-30-20 (since 1985)

- **Project 1: Correlation of Tau PET Imaging with CSF AD Biomarkers**
  A Fagan/J McConathy
- **Project 2: Synergy of Aβ clearance mechanisms in vivo**
  J Cirrito
- **Project 3: Circadian rhythms in regulation of Aβ pathology and brain oxidative stress**
  E Musiek

Other affiliations: NACC, NCRAD, LOAD, ADCS, ADNI, GWAS, Alzheimer's Assn, AAA Board, NIH & Industry Clinical Trials, affiliated R01 & other grants

Dominantly Inherited Alzheimer Network (DIAN)
JC Morris, PI (U19 AG032438)
7-15-14 to 12-31-19 (since 2008)

Clinical Performance Sites:

USA
Brigham &Women's Hospital/MGH
Butler H/Brown U
Columbia U
Indiana U
U Pittsburgh
Mayo Clinic – Jacksonville
UCLA
Washington U
UC San Diego

United Kingdom
ION-UC London

Australia
Edith Cowan U-Perth
U Melbourne
U New South Wales-Sydney

Germany
University of Tübingen
Ludwig-Maximillians-Unverstät-Munich

The Knight ADRC Now Studies the Lifespan

Courtesy of
Mary Ganguli


30 years of the UCSD ADRC

The ADRC fosters efforts across:

UCSD Departments of Neurosciences, Neuropathology, Psychiatry, Radiology, Medicine, and Divison of Biostatistics, the VA Medical Center,

and also the Salk Institute, Scripps Research Institute, Sanford-Burnham Medical Research Institute, San Diego State University

Robert Katzman

1925 - 2008

The Prevalence and Malignancy of Alzheimer Disease

A Major Killer

An accompanying letter to the editor (p 304) provides another illustration of the malignancy of Alzheimer disease, a phenomenon well known to neurologists. Katzman and Karasu[1] estimate that the senile form of Alzheimer disease may rank as the fourth or fifth most common cause of death in the United States. Yet the US vital statistics tables do not list "Alzheimer disease," "senile dementia," or "senility" as a cause of death, even in the extended list of 263 causes of death.

The argument that Alzheimer disease is a major killer rests on the assumption that Alzheimer disease and senile dementia are a single process and should, therefore, be considered a single disease. Both Alzheimer disease and senile dementia are progressive dementias with similar changes in mental and neurological status that are indistinguishable by careful clinical analyses.[2,3] The pathological findings are identical—atrophy of the brain, marked loss of neurons, neurofibrillary tangles, granulovacuolar changes, and neuritic (senile) plaques. Ultrastructural studies have established the identity of the neurofibrillary tangle with its twisted tubule and the senile plaque with its amyloid core and degenerating neurites in the brains of patients with Alzheimer disease (under age 65) and senile dementia (over age 65). Most recent ultrastructural and neurochemical studies indicate that the neurofibrillary tangle in both disorders is characterized by the twisted tubule that represents two neurofilaments joined together in a helical fashion with a period of 800 Angstroms. The studies of Tomlinson et al[4] and Blessed et al[5] have established a quantitative correlation between the degree of dementia and the number of neurofibrillary tangles and senile plaques in the cerebral cortex. The evidence on which a distinction between senile dementia and Alzheimer disease can still be argued is the genetic analysis of Larsson et al.[6] In their analysis of the kindred of patients with senile dementia, numerous relatives were found with senile dementia, but none with a diagnosis of Alzheimer disease. However, the incidence of the Alzheimer senile dementia complex is strongly age-related, even among the elderly. Larsson et al[6] had suggested a predisposing, autosomal dominant gene with age-related penetrance, reaching a penetrance of 40% at age 90. Therefore, the absence of any relative with "Alzheimer disease" might be related to its relative infrequency in patients under 65. Moreover, in a genetic study carried out in Switzerland, Constantinidis et al[7] encountered the two diseases in the same family. Although further studies are clearly indicated, the fact remains that neither the clinician, the neuropathologist, nor the electron microscopist can distinguish between the two disorders, except by the age of the patient. Today, the majority of workers in the field accept the identity of the two disease.[8] We believe that it is time to drop the arbitrary age distinction and adopt the single designation, Alzheimer disease.

Precise epidemiological information is not available concerning the prevalence of Alzheimer disease in the United States. However, several excellent community surveys of the prevalence of organic dementias in persons over age 65 have been carried out in northern Europe.[9-15] In these series, care has been taken to include persons living at home as well as those receiving institutional care. The prevalence of "severe dementia" or organic "psychosis," terms used to describe patients in whom, in addition to intellectual deterioration, there was evidence of disorganization of the personality and inability to carry out the normal tasks of daily living, averaged 4.1%. The prevalence of "mild dementia" and "mild mental deterioration" or "chronic brain syndrome without psychosis," terms used to describe individuals with intellectual impairment who are still able to carry out activities of daily living, averaged 10.8%. Estimates of the incidence of Alzheimer disease (senile dementia) among patients over age 65 with organic dementia vary between 40%[16] and 58%.[4] Applying these figures to the United States, the prevalence of Alzheimer disease in persons

In the beginning …

Robert Katzman moved to UCSD in 1983

Chair of Dept of Neurosciences

- an opportunity to recruit faculty, and to build and integrate clinical and neuroscience research

ADRC P50 Grant Application:

“ … to develop the investigators and resources necessary to enable us to move forward in a significant way in the understanding of the pathogenesis and pathophysiology of Alzheimer’s Disease, with the ultimate goal of understanding the etiology of the disease sufficiently to prevent it.”

Original focus of the ADRC

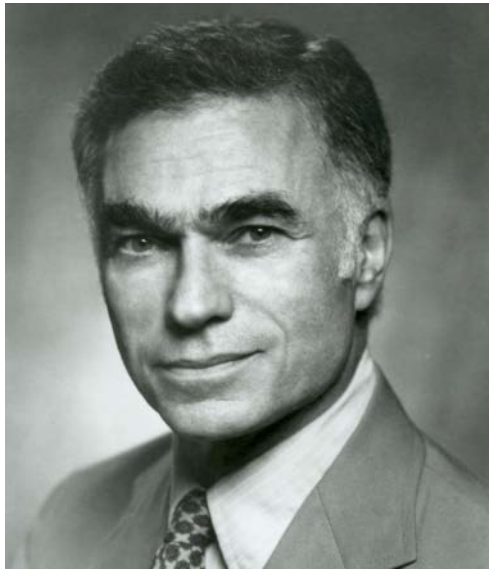
Clinical-pathological correlation

Clinical features, progression

Molecules and mechanisms

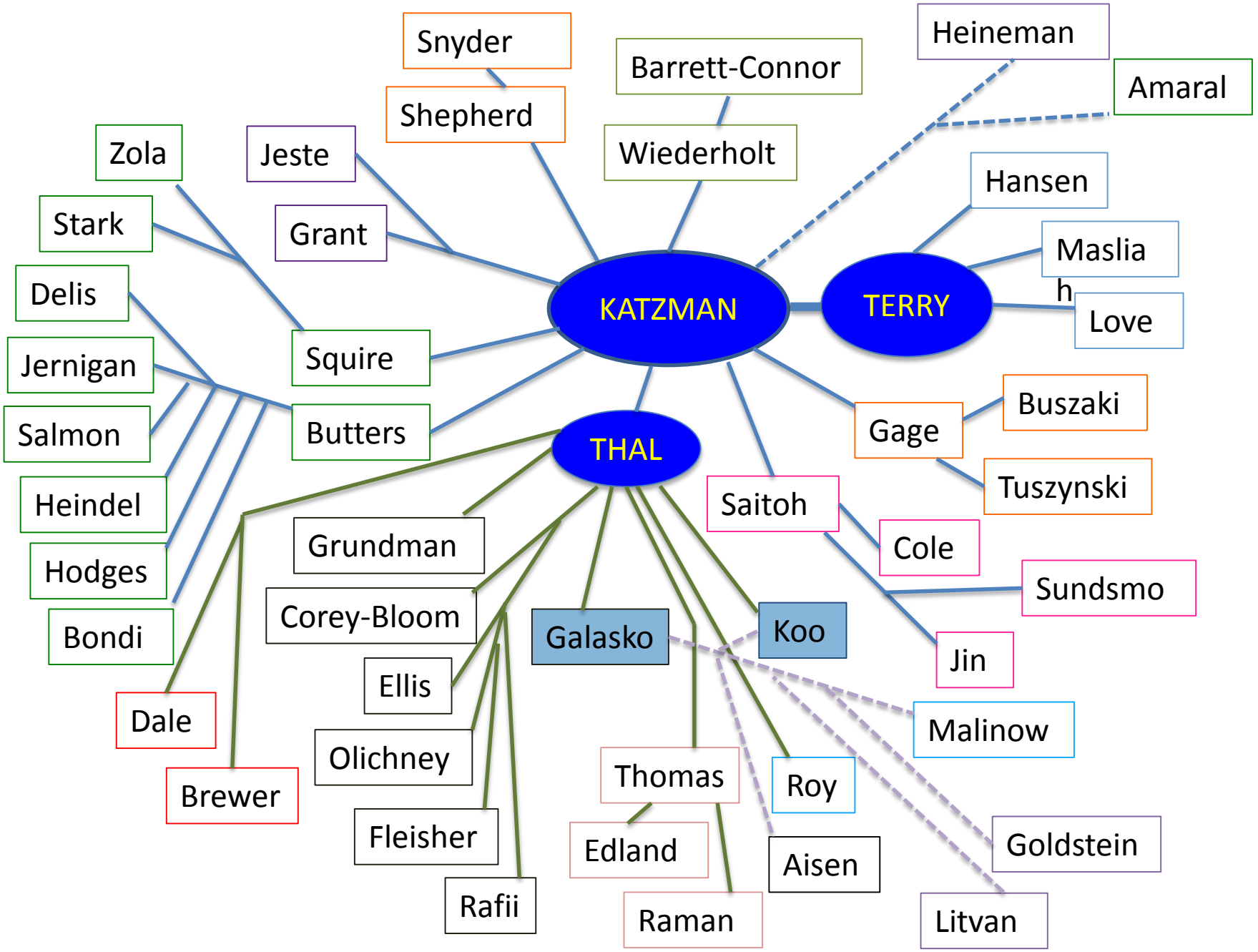
Training and education

Caregiver stress



Leaders: The Bobs: Katzman and Terry

Nelson Butters, Larry Squire, Igor Grant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Ellis
Malinow
Dale
Olichney
Thomas
Roy
Brewer
Goldstein
Fleisher
Edland
Aisen
Rafii
Raman
Litvan

Early ADRC contributions

Katzman

- Rate of clinical progression
- Epidemiology of AD in China
- Testing diagnostic criteria

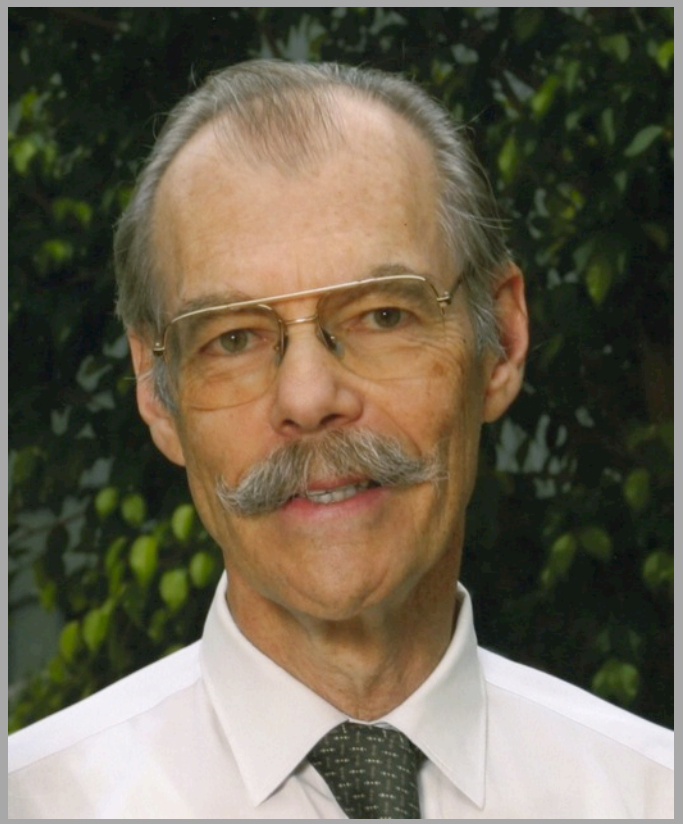
+ Terry / Masliah / Hansen

- Synapse loss correlates with cognition in AD
- Cognitive reserve
- Dementia with Lewy Bodies

+ Butters/ Squire / Salmon

- Episodic memory loss defines AD
- Neuropsychological profiles in differential diagnosis

Leon J. Thal



1944 - 2007

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2005 VOL. 352 NO. 23

Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment

Ronald C. Petersen, Ph.D., M.D., Ronald G. Thomas, Ph.D., Michael Grundman, M.D., M.P.H., David Bennett, M.D., Rachelle Doody, M.D., Ph.D., Steven Ferris, Ph.D., Douglas Galasko, M.D., Shelia Jin, M.D., M.P.H., Jeffrey Kaye, M.D., Allan Levey, M.D., Ph.D., Eric Pfeiffer, M.D., Mary Sano, Ph.D., Christopher H. van Dyck, M.D., and Leon J. Thal, M.D., for the Alzheimer's Disease Cooperative Study Group*

ABSTRACT

BACKGROUND

Mild cognitive impairment is a transitional state between the cognitive changes of normal aging and early Alzheimer's disease.

METHODS

In a double-blind study, we evaluated subjects with the amnestic subtype of mild cognitive impairment. Subjects were randomly assigned to receive 2000 IU of vitamin E daily, 10 mg of donepezil daily, or placebo for three years. The primary outcome was clinically possible or probable Alzheimer's disease; secondary outcomes were cognition and function.

RESULTS

A total of 769 subjects were enrolled, and possible or probable Alzheimer's disease developed in 212. The overall rate of progression from mild cognitive impairment to Alzheimer's disease was 16 percent per year. As compared with the placebo group, there were no significant differences in the probability of progression to Alzheimer's disease in the vitamin E group (hazard ratio, 1.02; 95 percent confidence interval, 0.74 to 1.41; P=0.91) or the donepezil group (hazard ratio, 0.80; 95 percent confidence interval, 0.57 to 1.13; P=0.42) during the three years of treatment. Prespecified analyses of the treatment effects at 6-month intervals showed that as compared with the placebo group, the donepezil group had a reduced likelihood of progression to Alzheimer's disease during the first 12 months of the study (P=0.04), a finding supported by the secondary outcome measures. Among carriers of one or more apolipoprotein E ε4 alleles, the benefit of donepezil was evident throughout the three-year follow-up. There were no significant differences in the rate of progression to Alzheimer's disease between the vitamin E and placebo groups at any point, either among all patients or among apolipoprotein E ε4 carriers.

CONCLUSIONS

Vitamin E had no benefit in patients with mild cognitive impairment. Although donepezil therapy was associated with a lower rate of progression to Alzheimer's disease during the first 12 months of treatment, the rate of progression to Alzheimer's disease after three years was not lower among patients treated with donepezil than among those given placebo.

From the Mayo Clinic College of Medicine, Rochester, Minn. (R.C.P.); University of California, San Diego, San Diego (R.G.T., D.G., S.J., L.J.T.); Elan Pharmaceuticals, San Diego (M.G.); Rush University Medical School, Chicago (D.B.); Baylor College of Medicine, Houston (R.D.); New York University, New York (S.F.); Oregon Health and Science University, Portland (J.K.); Emory University, Atlanta (A.L.); University of South Florida, Tampa (E.P.); Mt. Sinai School of Medicine, New York (M.S.); and Yale University, New Haven, Conn. (C.H.D.). Address reprint requests to Dr. Petersen at the Alzheimer's Disease Research Center, Mayo Clinic College of Medicine, 200 First St. SW, Rochester, MN 55905, or at peter8@mayo.edu.

*Members of the Alzheimer's Disease Cooperative Study (ADCS) Group are listed in the Appendix.

This article was published at www.nejm.org on April 13, 2005.

N Engl J Med 2005;352:2379-88.

The Shiley Gift: Bringing Discovery and Hope to the ADRC

"We chose to support UCSD's Alzheimer's efforts because of its national leadership in this area"

Donald and Darlene Shiley are no strangers to the University of California, San Diego. Longtime supporters of UCSD healthcare and neuroscience initiatives, the couple has generously given to Leon J. Thal, M.D.'s Alzheimer's disease research, experimental Alzheimer's brain cell therapy research, and to the world-renowned Shiley Eye Center at UCSD. This past fall, the Shileys' benevolence touched UCSD yet again. In November 2004, UCSD announced a $4 million pledge from Donald and Darlene Shiley to support the UCSD Alzheimer's Disease Research Center (ADRC), bringing their commitment to the university to more than $8 million. In recognition of their gift, and in honor of Darlene's mother Dee Marcos, UCSD has renamed the ADRC the Shiley-Marcos Alzheimer's Disease Research Center.

Donald and Darlene Shiley are personally invested in Alzheimer's disease research and treatment. Explaining this commitment, Darlene

Leon Thal

- Cholinesterase inhibitor translation
- Clinical trials
- Established ADCS
- Planned ADNI
- Fellowship training program

+ Doug Galasko

- CSF biomarkers: A-beta42, tau

+ Galasko, Salmon, Corey-Bloom

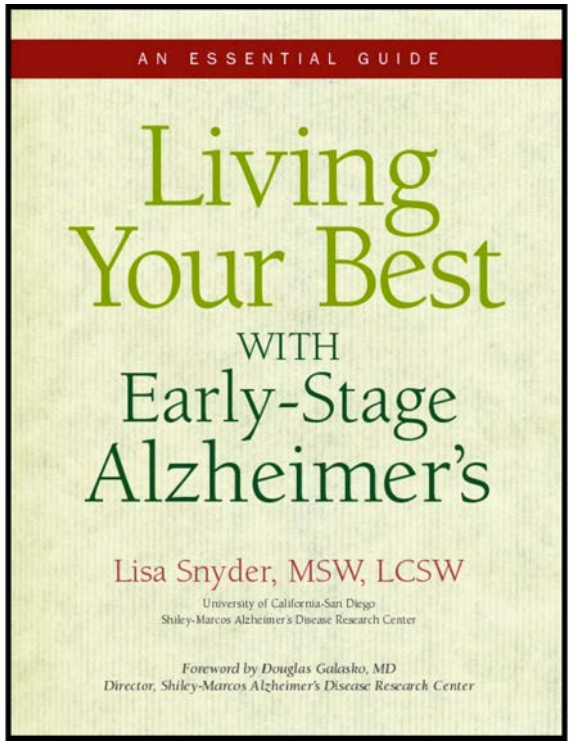
- Dementia with Lewy Bodies

+ Mary Sundsmo

- California law to allow surrogate research consent

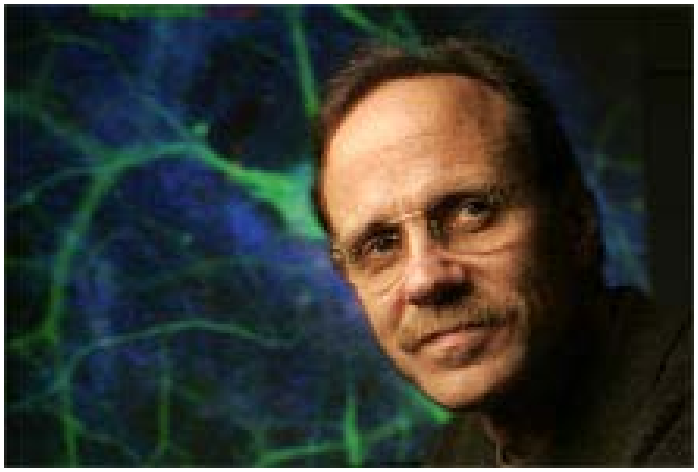
Caregiving and support

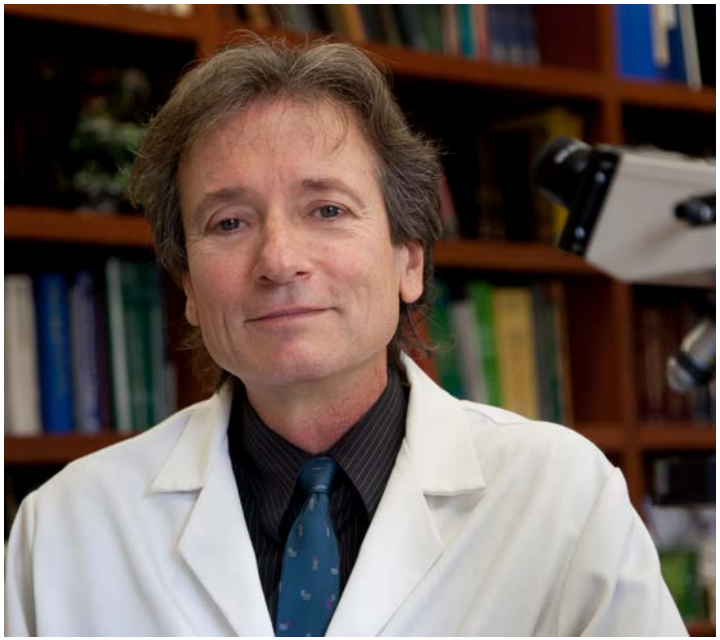
- Effects and mechanisms of caregiver stress (Igor Grant)
- Innovative care programs (Lisa Snyder)
- Early stage support groups



Fred Gage, Mark Tuszynski

- NGF and BDNF in aging and disease models
- Gene therapy for Alzheimer's



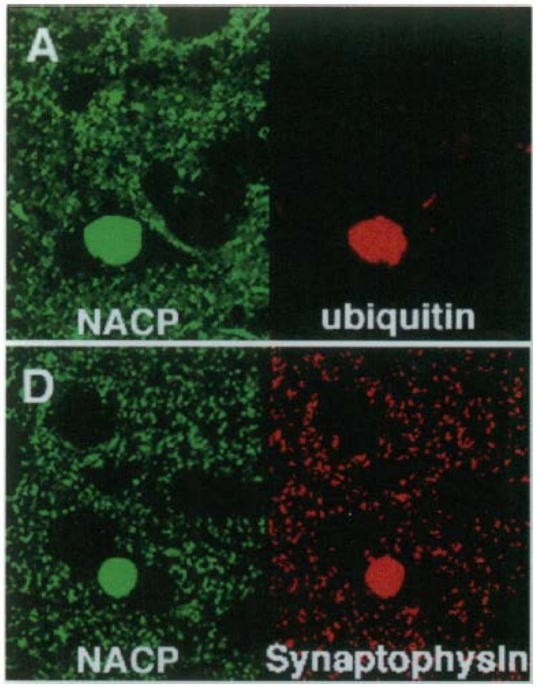


Tsunao Saitoh

- APP trophic function
- Tau haplotype in PSP
- NACP component of alpha-Synuclein

Eliezer Masliah

- Synapse loss correlates with cognition in AD
- α-Synuclein roles in PD pathogenesis
- APP transgenic mice and therapeutics
  - (with Athena / Elan, Inc)



Eddie Koo

- APP biology
- Gamma-secretase modulator mechanism to selectively lower Aβ42

letters to nature

A subset of NSAIDs lower amyloidogenic Aβ42 independently of cyclooxygenase activity

Sascha Weggen*, Jason L. Eriksen†, Pritam Das†, Sarah A. Sagi*, Rong Wang‡, Claus U. Pietrzik*, Kirk A. Findlay†, Tawnya E. Smith†, Michael P. Murphy†, Thomas Bulter§, David E. Kang*, Numa Marquez-Sterling‖, Todd E. Golde† & Edward H. Koo*

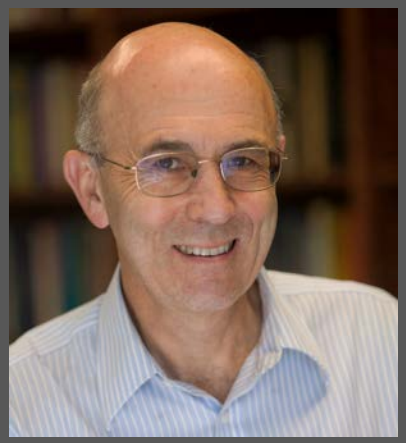
Current ADRC directions

- **Early detection and presymptomatic AD**
  - neuropsychological tests
  - CSF and imaging biomarkers
- **Latino cohort**
  - Risk and protective factors, e.g., genetics, education, bilingualism
- **Mechanisms of disease**
  - APP, A-beta and endosomes
  - C9orf72 and TDP43 pathogenesis
  - α-SYN pathogenesis
  - iPS cell research
- **Therapeutics**
  - Clinical trials
  - Translational research at UCSD, Salk, Scripps, Sanford-Burnham















UC San Diego

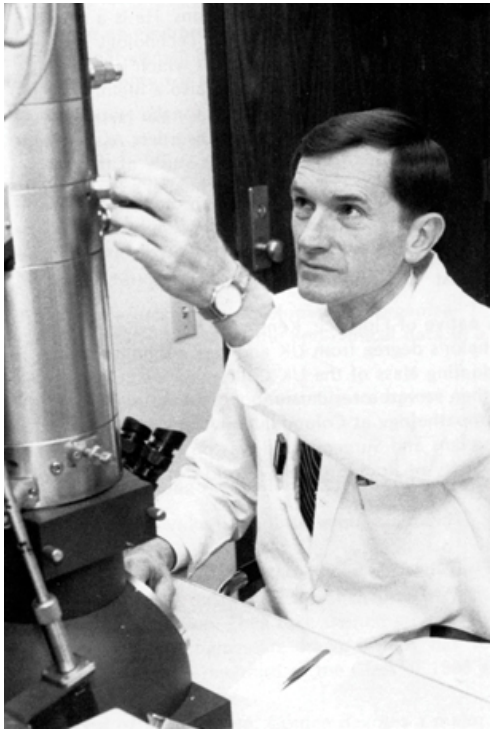

Shiley-Marcos Alzheimer's Disease Research Center
Centro de Investigación de la Enfermedad de Alzheimer
UNIVERSITY of CALIFORNIA
SAN DIEGO
SCHOOL OF MEDICINE

SANDERS-BROWN CENTER ON AGING

UK UNIVERSITY OF KENTUCKY

Sanders-Brown Center on Aging and UK-ADC: A Tribute to William R. Markesbery

www.centeronaging.uky.edu



SANDERS-BROWN CENTER ON AGING

35 YEARS 1979-2014

1972: **$1M grant from the Eleanor and John Y. Brown Jr. Foundation, with matching funds from state of Kentucky and funds from the University of Kentucky, for construction of the Sanders-Brown Research Building.**

1979: **Sanders-Brown building opens; Dr. William Markesbery is named director.**

1985: **NIA awards UK-ADRC.**

WILLIAM R. MARKESBERY, MD (1932-2010)

Founding Director of the Sanders-Brown Center on Aging and Alzheimer's Disease Research Center

Bill Markesbery: Extraordinary researcher and clinician

>430 scientific papers; >40 book chapters

Importance of studying human brain tissue

Internationally recognized in the fields of Neuropathology and Alzheimer's disease. NIA Council, Alz Assoc SAB (chair)

1974: describes a rare form of hereditary muscular dystrophy, now called Finnish-Markesbery Disease

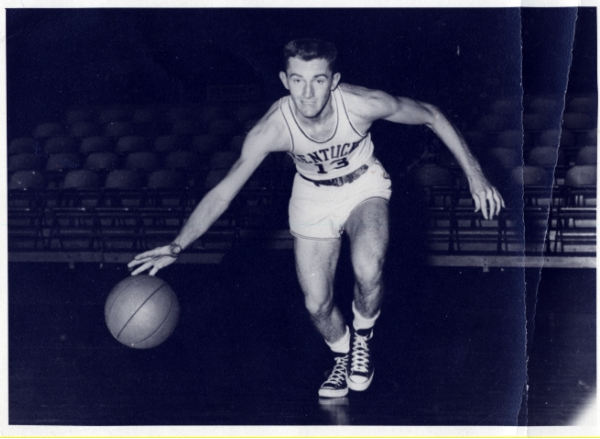
1981: publishes 1st of several studies disproving the once-popular theory that toxic metals, such as aluminum, cause AD.

1984: awarded the 1st P01 at Univ KY; Trace Elements/Oxidative Stress and AD

2009: Alzheimer's Association Khachaturian Award for Outstanding Achievements in Advancing Alzheimer's Science

2009: JAD #23 most prolific AD researcher, #35 most-cited author

Bill Markesbery: Extraordinary individual



BA at Univ KY in Business & Economics

Played basketball as a walk-on for Adolph Rupp

Pitcher for Cincinnati Reds minor league baseball

Member of the first graduating class of UK medical school- AOA

Devoted husband, father, and grandfather

Enjoyed good Chardonnay, classical music, books about the war in the Pacific, driving FAST in his Porsche

SANDERS-BROWN CENTER ON AGING
ALZHEIMER'S DISEASE CENTER
30 YEARS 1985-2015

The Early Years of the UK-ADRC

1985: UK-ADRC awarded

Director: Bill Markesbery

Associate Director: Steve DeKosky

Original Focus:

-- Develop a Center of Excellence devoted to the study of AD and related disorders.

Goals:

-- Conduct multidisciplinary research

-- Train scientists and clinicians

-- Teach and/or transfer new information concerning AD and related disorders

The Early Years of the UK-ADRC

First Project Period:

Clinical Core: to recruit, evaluate and longitudinally follow a pool of AD patients for optimal care and clinical investigation and to serve potentially as subjects for autopsy.

Tissue Specimen Core: to provide a coordinated neuropathological/neurochemical assessment facility on autopsy tissues for verification of AD for clinical-biochemical-morphological research studies.

Training & Information Core: to provide research training to health professional students, postdoctoral fellows and faculty and continuing education to practitioners in the communities and state.

First Year, 1985-1986:

--212 subjects followed

--33 brains from dementia subjects evaluated

The Early Years of the UK-ADRC

1 Research Project:

Calmodulin & CaM binding proteins in AD brain, erythrocytes & leukocytes

5 pilot projects:

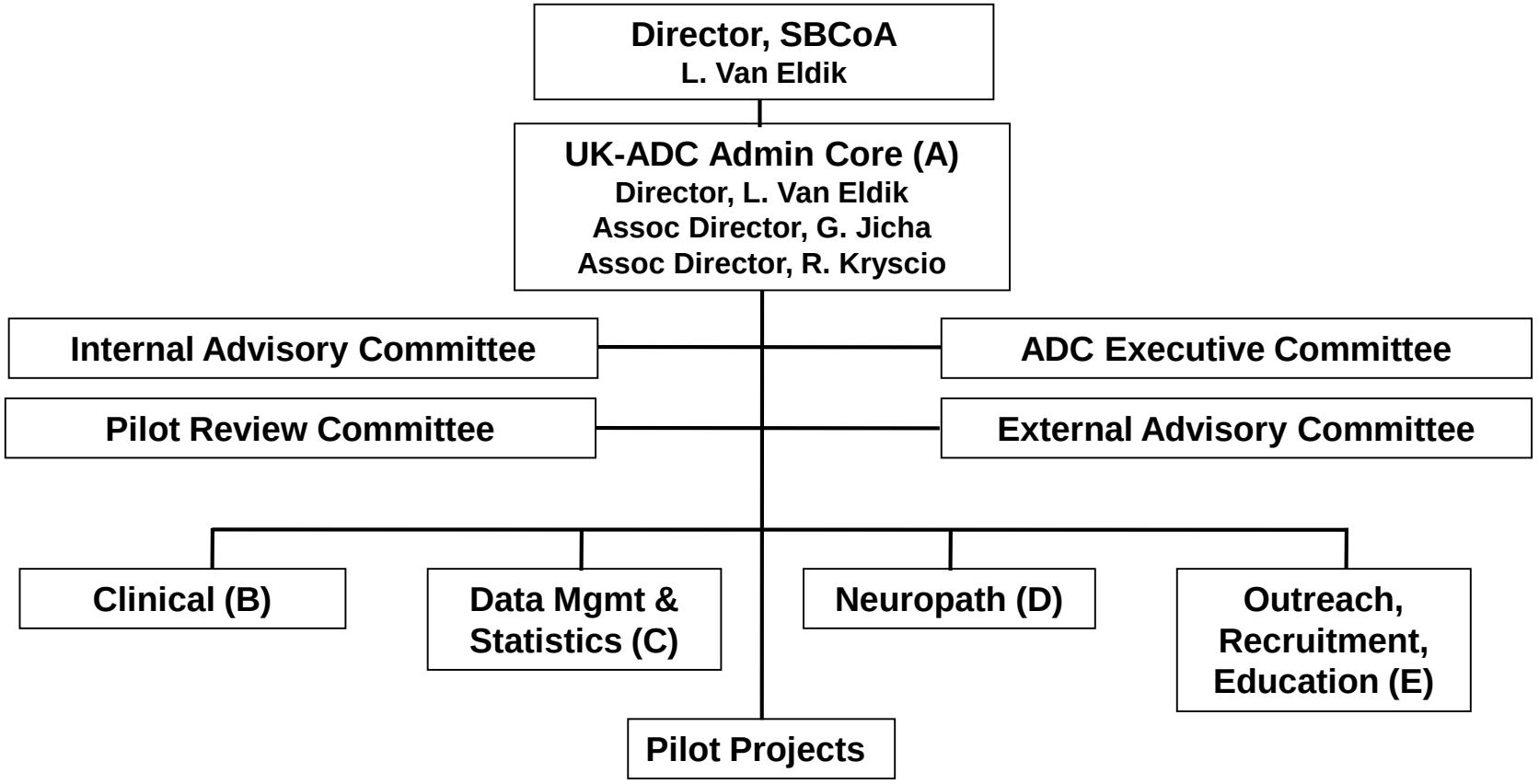
1) **Biochemical nature of neurofibrillary tangles**
2) **Alterations in genes on chromosome 21 in AD brains, lymphocytes**
3) **Morphometric studies of synaptic density correlated with plaque number**
4) **Studies of astrocyte ability to express Ia antigen, produce IL-1 and present antigen**
5) **Studies of coping capacities of families over time**

1989

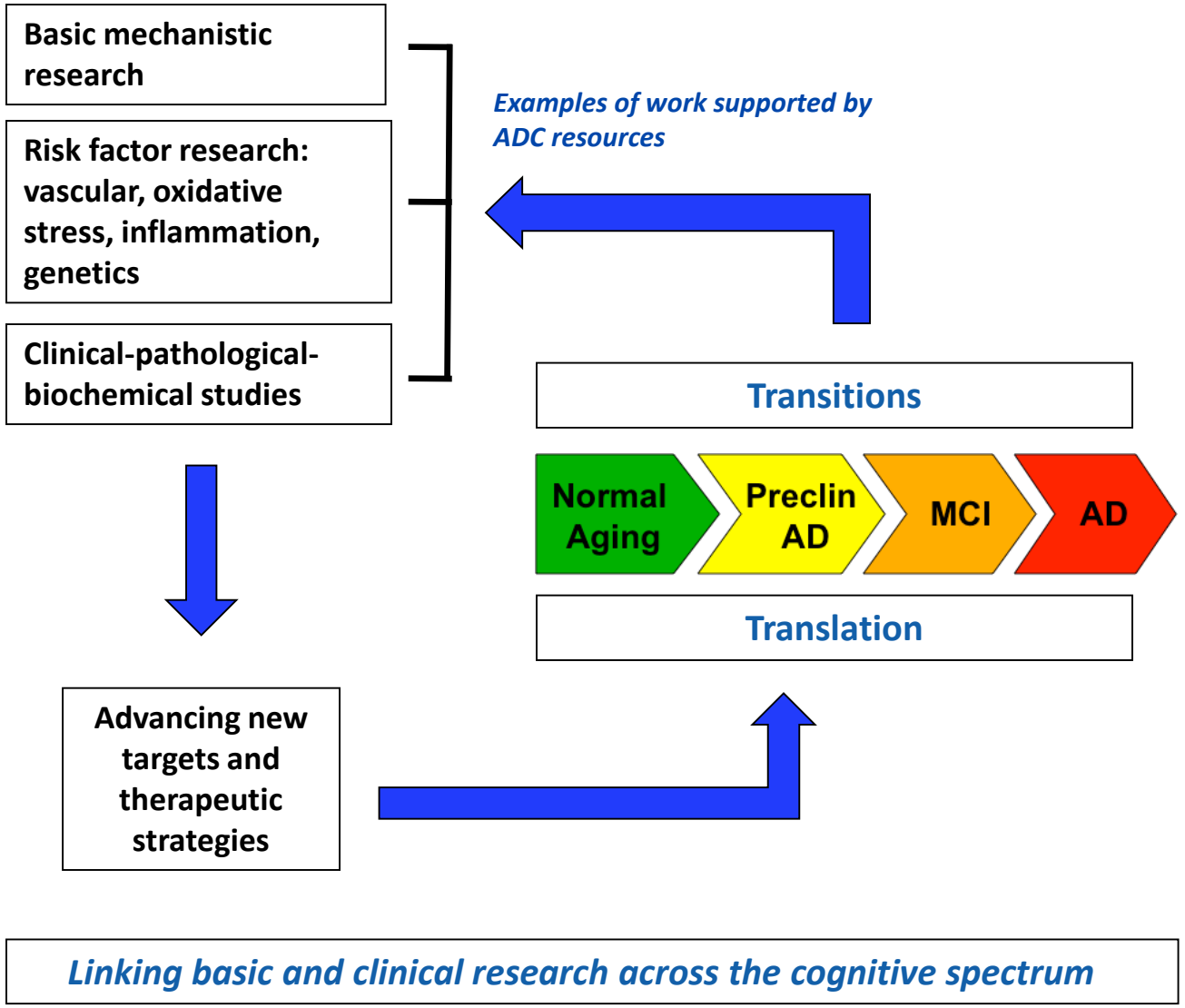
Initiated normal longitudinal control study with subjects followed yearly and agreeing to brain autopsy.

How the UK-ADC has Evolved: Organizational Framework

UK-ADRC: 09/30/1985 - 06/30/2006; UK-ADCC: 07/15/2006 - 06/30/2016



UK-ADC Themes: *Transitions and Translation*



Linking basic and clinical research across the cognitive spectrum

Major Accomplishments of the UK-ADC

- **Strong autopsy program providing clinical-NP correlation and short PMI research material. >1500 brain autopsies, >22,000 biospecimens distributed worldwide 2004-2014. Quantitative digital neuropathology.**

- **Large normal volunteer cohort followed longitudinally, with brain autopsy. ~500 cognitively normal, ~200 impaired**

- **Strong contributor to the national database and collaborative projects. Centralized data warehouse, innovative statistical models.**

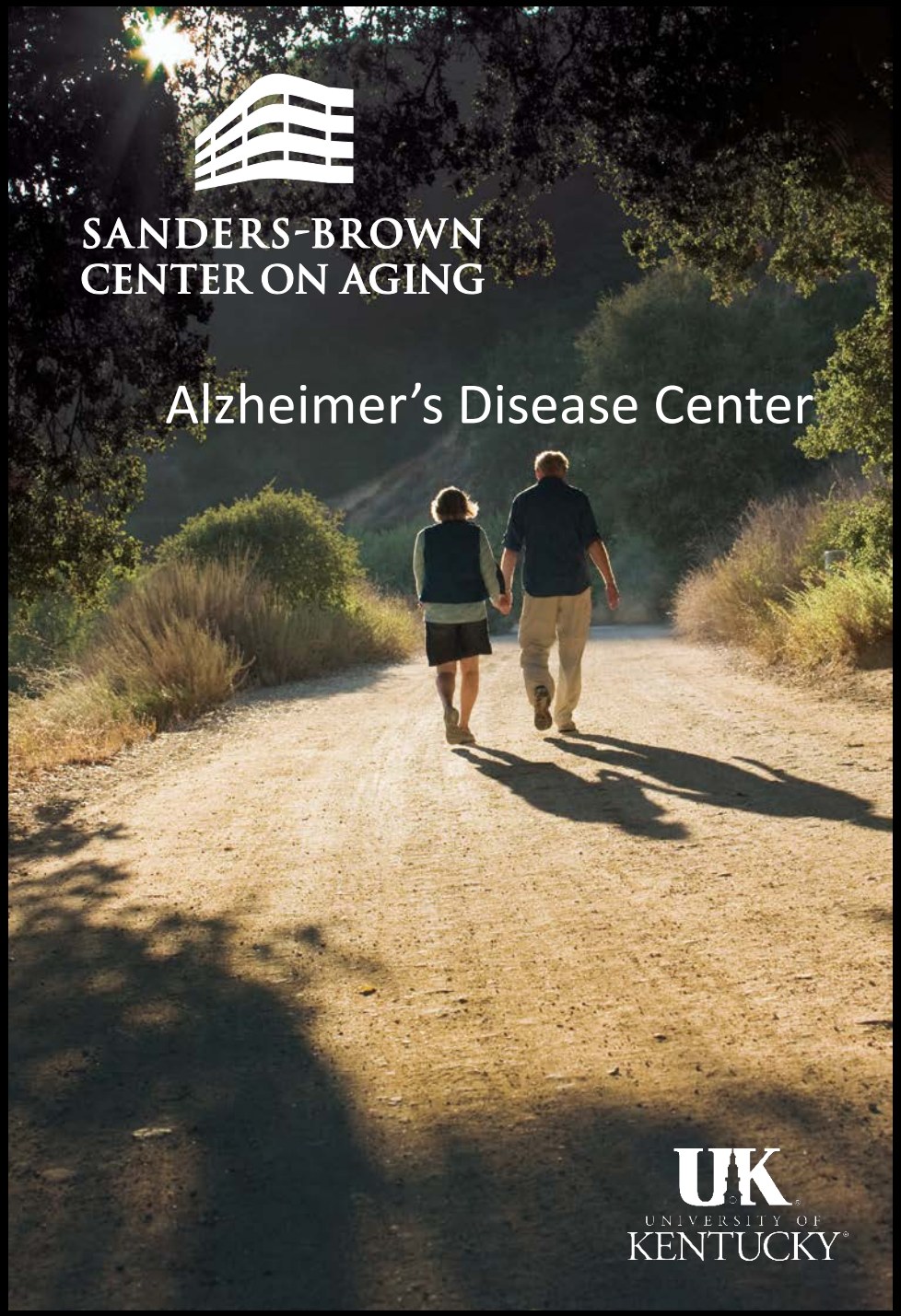
- **Effective in supporting AD research: basic, translational, clinical. Active clinical trials program.**

- **Outreach & education in our community and rural Appalachia.**

- **Well-integrated within a larger, highly collaborative Center of Excellence.**

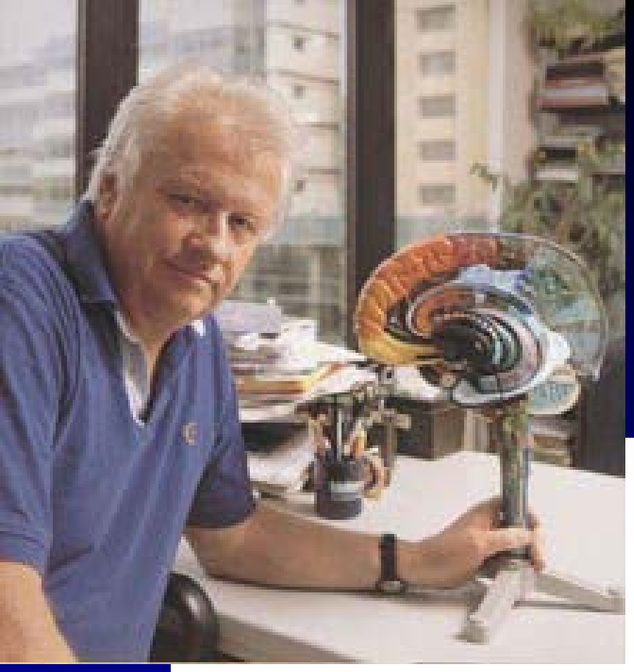
Markesbery's Rules

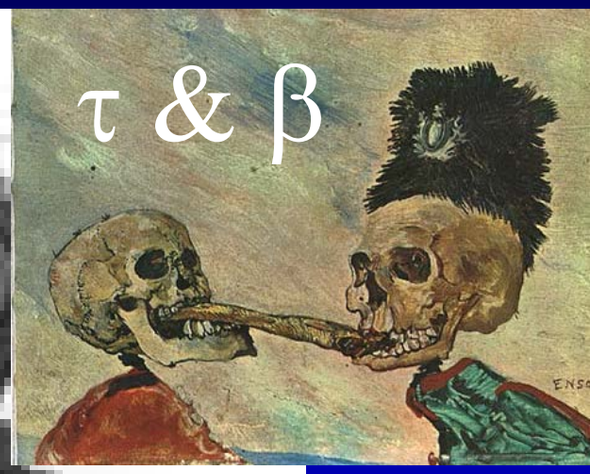
- It's better to be the grand duke than the king
- Save your bullets
- Don't fight over the broom closet
- Don't waste emotional energy on fights you can't win
- Stay focused
- Bow your neck, bite the bullet
- Publish once a month
- Holidays are a great time to work
- Don't work for committees
- Polish your character every day


SANDERS-BROWN
CENTER ON AGING
Alzheimer's Disease Center
UK
UNIVERSITY OF
KENTUCKY

Johns Hopkins ADRC
History of the First 30+ Years

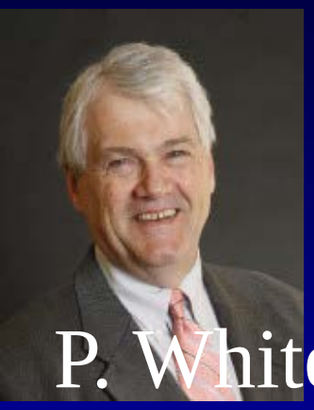
You can’t do it alone; you need colleagues



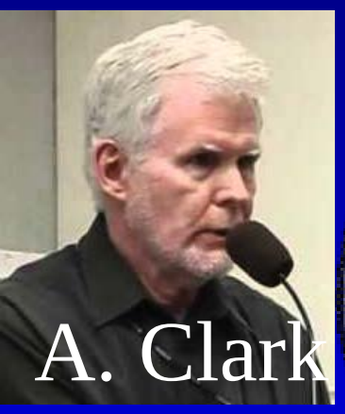


The Seven Samurai

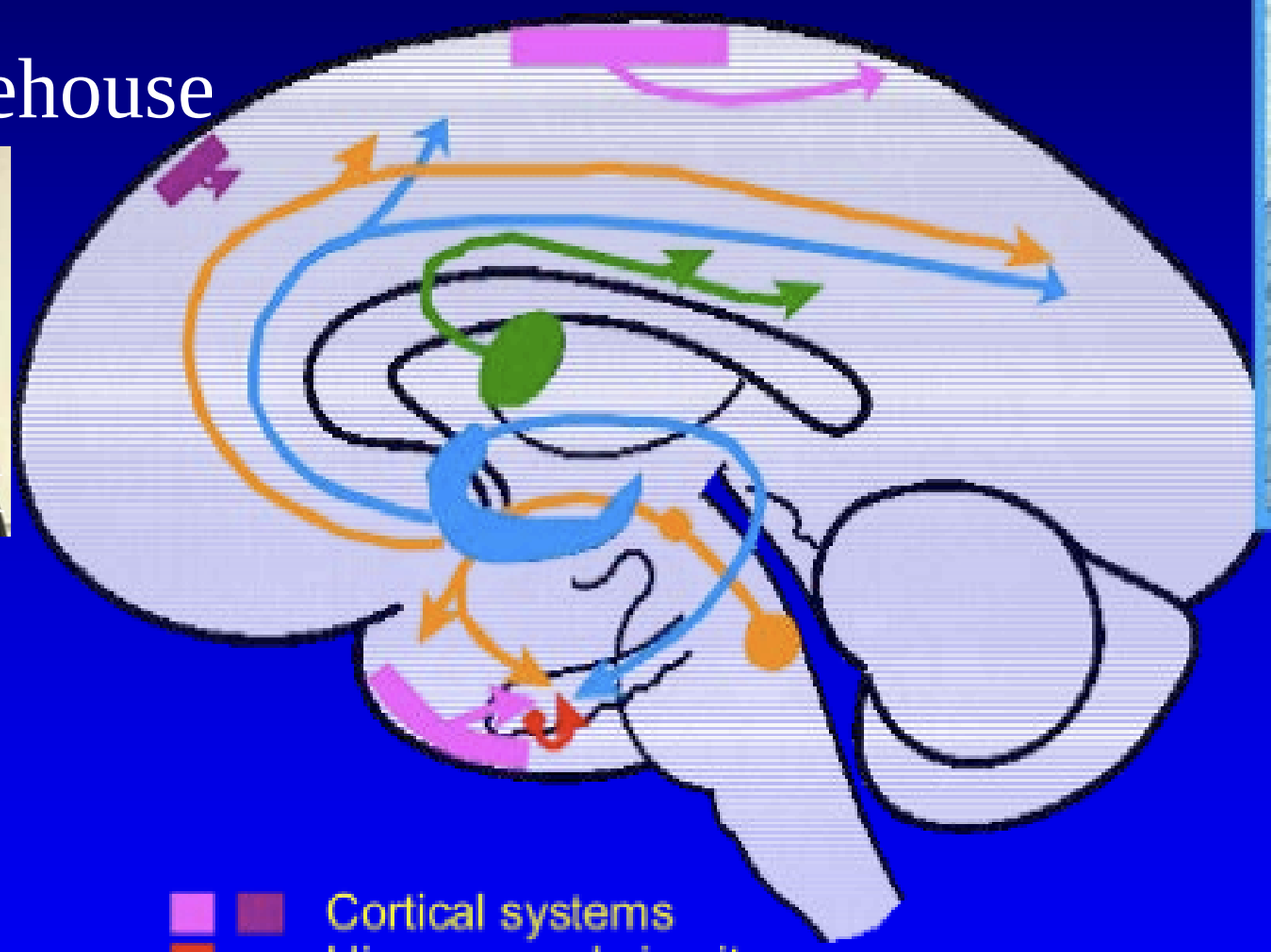
Cholinergic Abnormalities in AD

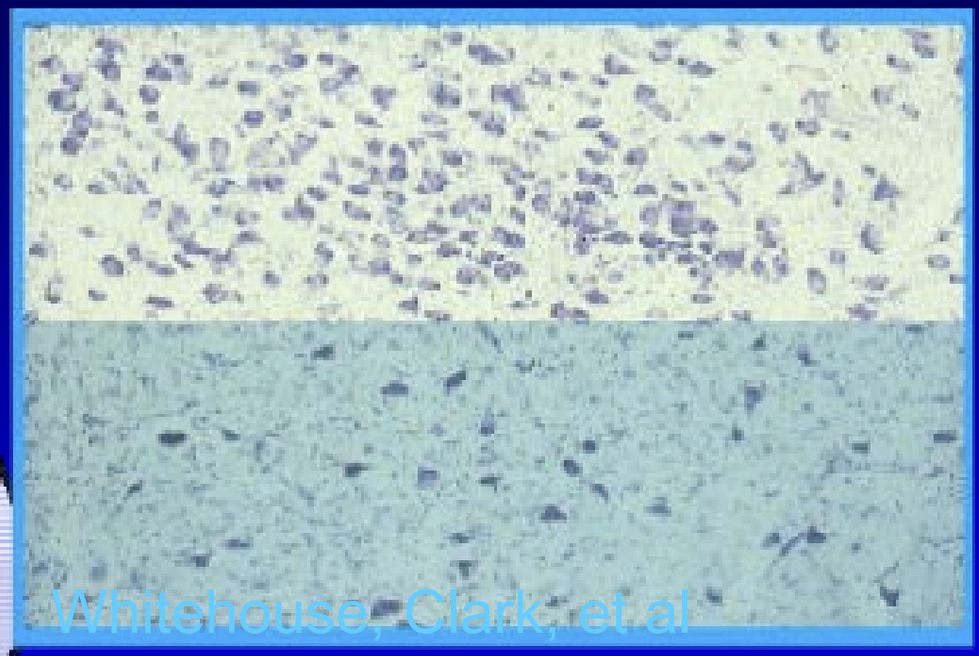


P. Whitehouse

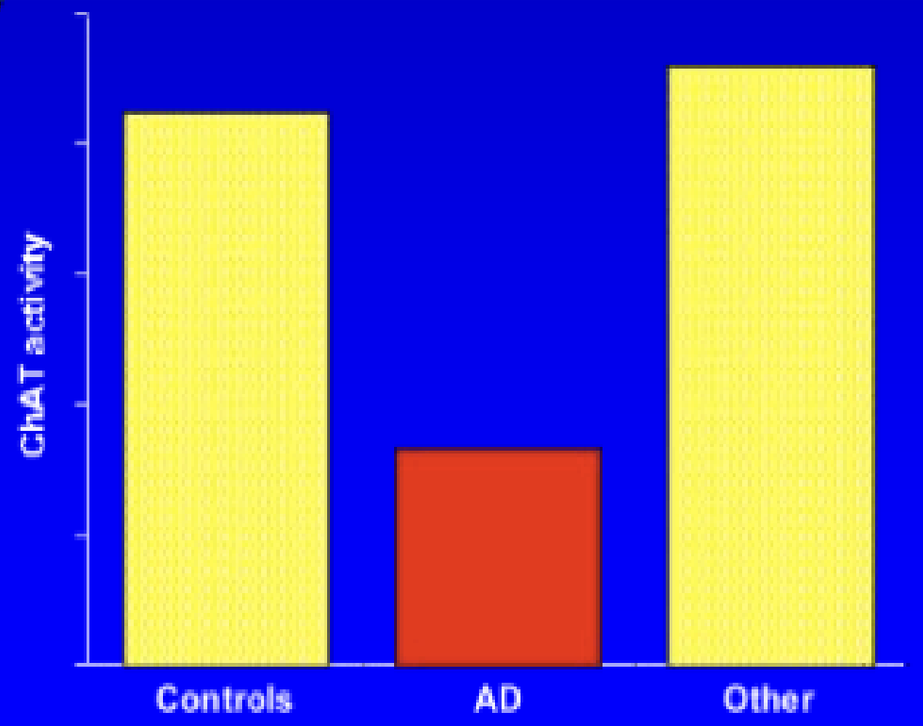


A. Clark



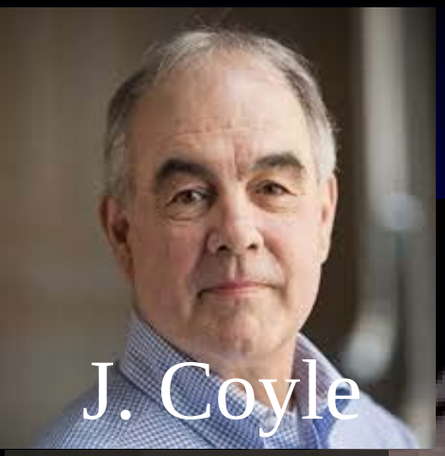


Whitehouse, Clark, et al

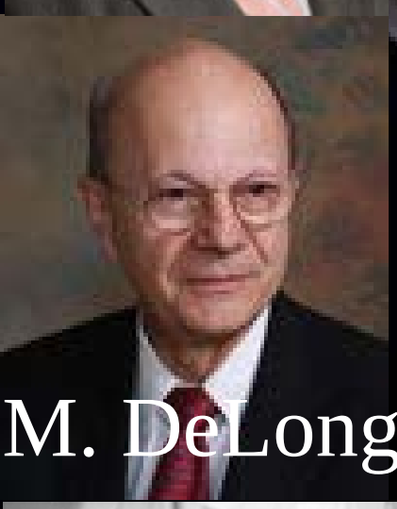


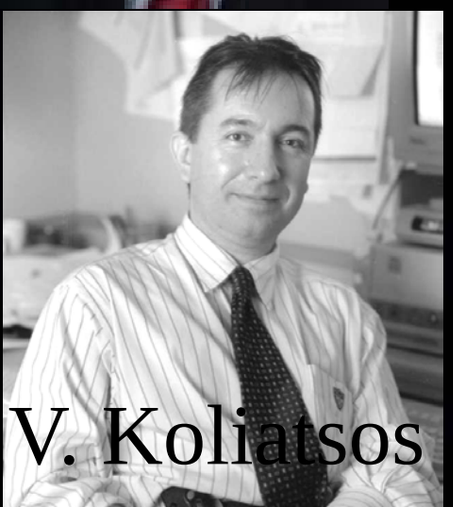
Bowen, et al

Cholinergic System


J. Coyle


P. Whitehouse


M. DeLong


V. Koliatsos

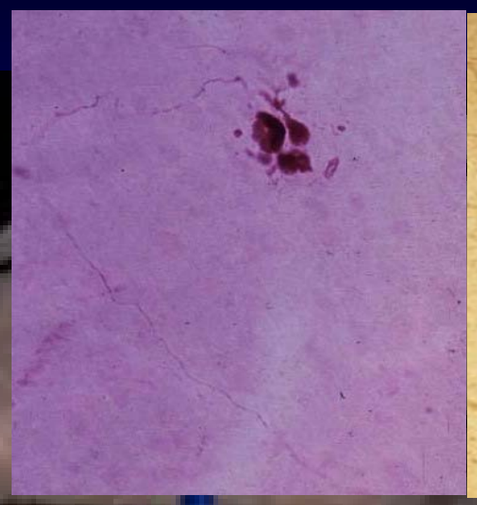
Monkey Brain

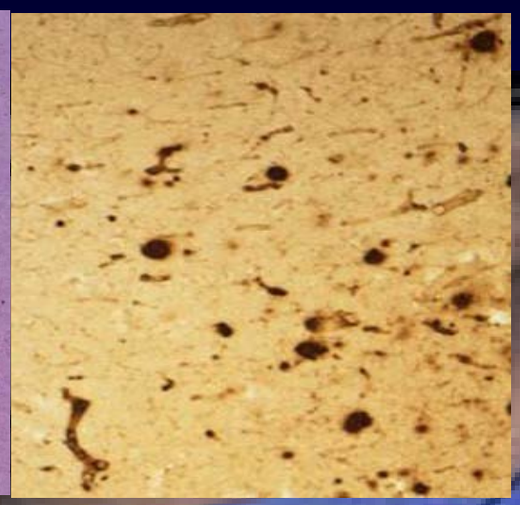
- Scoplamine effects
- Properties of BFCS
- Effects of lesions on cells & behavior in Models (rats and Rhesus)
- Pathology in disease
- Transection of fornix – influence of NGF on BFCS

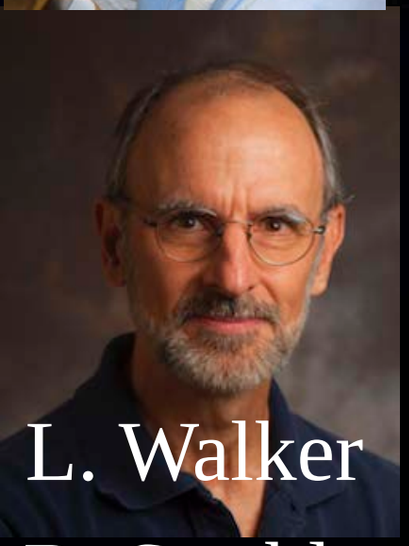
Aβ Model: Aged Rhesus

L. Cork

L.Martin







L. Walker

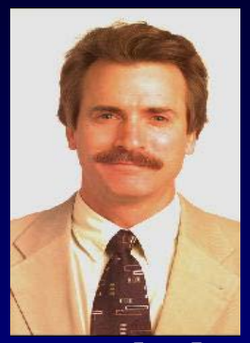
R. Struble

C. Kitt

M. Wagster

M. Mishkin

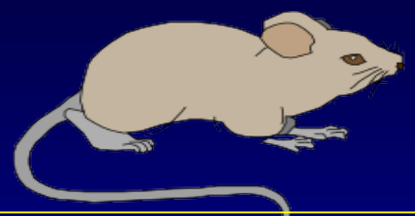
Summary of Mouse Model Systems



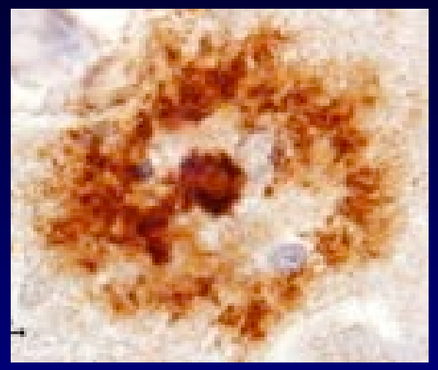
Borchelt

Savonenko

β-amyloidosis model



APPswe/PS1ΔE9

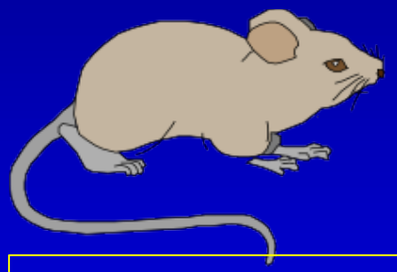


Savonenko et al, '04, 05 and 06; Laird et al '06

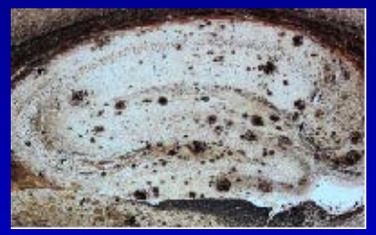
Cai

Laird

Target validation models:



***BACE1* KO**

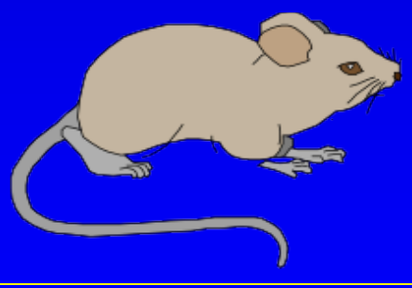


Cai et al '01
Laird et al '05

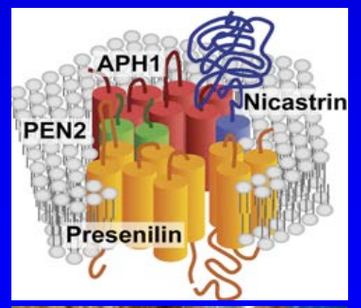
Wong

Li

Chow



γ component KO

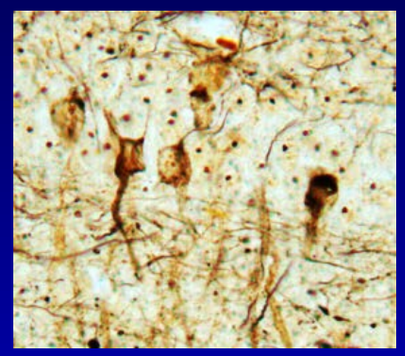


Li et al '07
Chow et al '10

Summary of Mouse Model Systems (con't)

Tauopathy model

TauΔK280



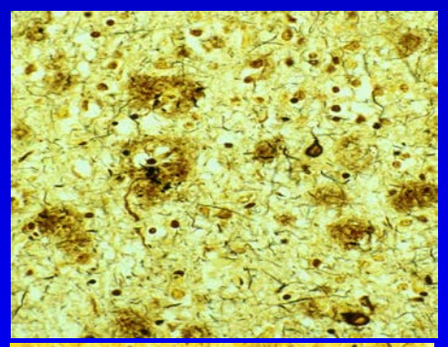
Li et al, submitted

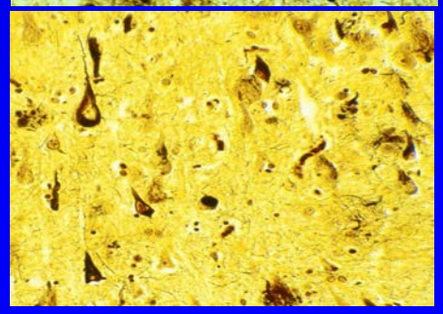
Li

Wong

Alzheimer's model

TauΔK280;APPswe/PS1ΔE9





Li et al, submitted

Troncoso

Clinical Research at JHADRC

Early Days

P. Rabins - Established Hopkins approach to patient care
Co-authored *'36 Hour Day'* in 1984
Now in 5th Edition, with > 2 ½ million copies sold

M. Folstein - First leader of ADRC Clinical Core
Focused on screening for dementia
MMSE among most widely used screening tools in the world

J. Brandt - Continued focus on development of assessment tools
Among the most widely used are the TICS (for telephone screening) &
the Hopkins Verbal Learning Test (HVLT) (for learning and memory)

C. Kawas - Second leader of ADRC Clinical Core
Established collaboration with Baltimore Longitudinal Study on Aging (BLSA)
Goal to examine clinical-pathological correlations and predictors of dementia

Clinical Research at JHADRC

R. O'Brien - Collaboration with BLSA has led to ~100 publications on MRI & PET reports across AD spectrum, predictors of cognitive decline in normals and clinical-pathological correlations (with Neuropath Core). Rich recently moved to Duke University to become first Chair of Neurology

S. Resnick - Chief, Laboratory of Behavioral Neuroscience at NIA
PI of Imaging substudy of BLSA. Currently focused on imaging and cognitive changes during Preclinical AD

M. Albert - Director of ADRC and PI of BIOCARD study
Collaborates closely with BLSA colleagues on studies of Preclinical AD
Focus on clinical, cognitive, brain imaging and CSF analyses

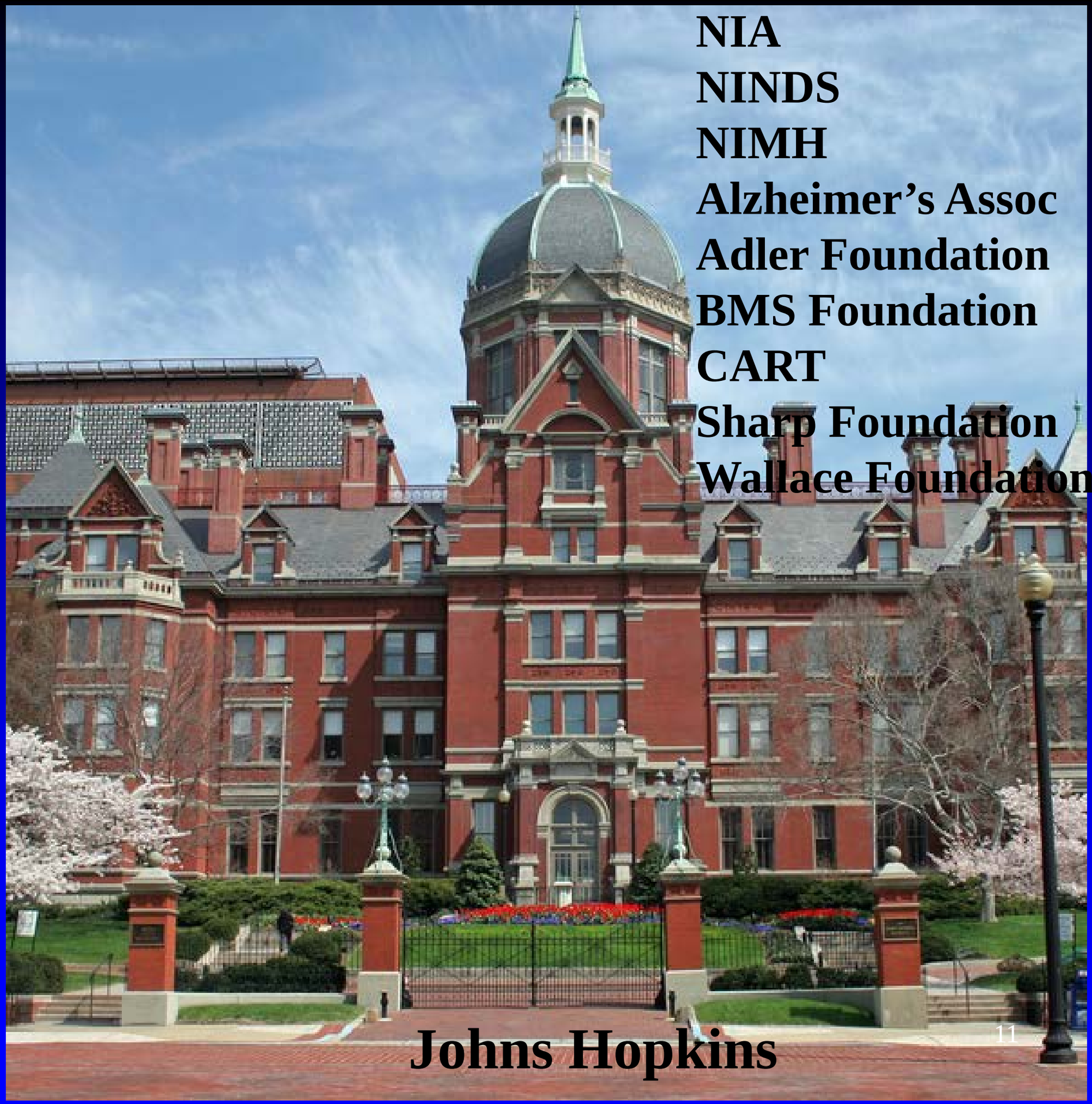
C. Lyketsos - Current leader of ADRC Clinical Core
Expanded expertise in investigator-initiated clinical trials in AD
Recent findings demonstrated positive outcome in treatment of agitation in AD

JHADRC Team

Past and Present

Albert M, Bakker A, Bandeen-Roche K, Black B, Borchelt D, Brandt J, Brookmeyer R, Cai T, Chow V, Crain B, Cork L, Coyle J, DeLong M, Ferrucci L, Folstein M, Gallagher M, Gitlin L, Griffin J, Huganir R, Kawas C, Laird F, Li T, Oh E, Moghekar A, Jankowsky J, Kitt C, Koliatsos V, Koo E, Li T, Lyketsos C, Martin L, O'Brien R, Pletnikova A, Price D, Savonenko A, Sisodia S, Rabins P, Resnick S, Rosenberg P, Rudow G, Samus Q, Thinakaran G, Troncoso J, Walker L, Wagster M, Wang, M-C, Whitehouse P, Wong P, Worley P, Zonderman A.

priced@jhmi.edu



NIA
NINDS
NIMH
Alzheimer’s Assoc
Adler Foundation
BMS Foundation
CART
Sharp Foundation
Wallace Foundation

Johns Hopkins

PAD2020

The Campaign to Prevent Alzheimer's Disease by 2020

Prevention of Alzheimer

May 23, 2014

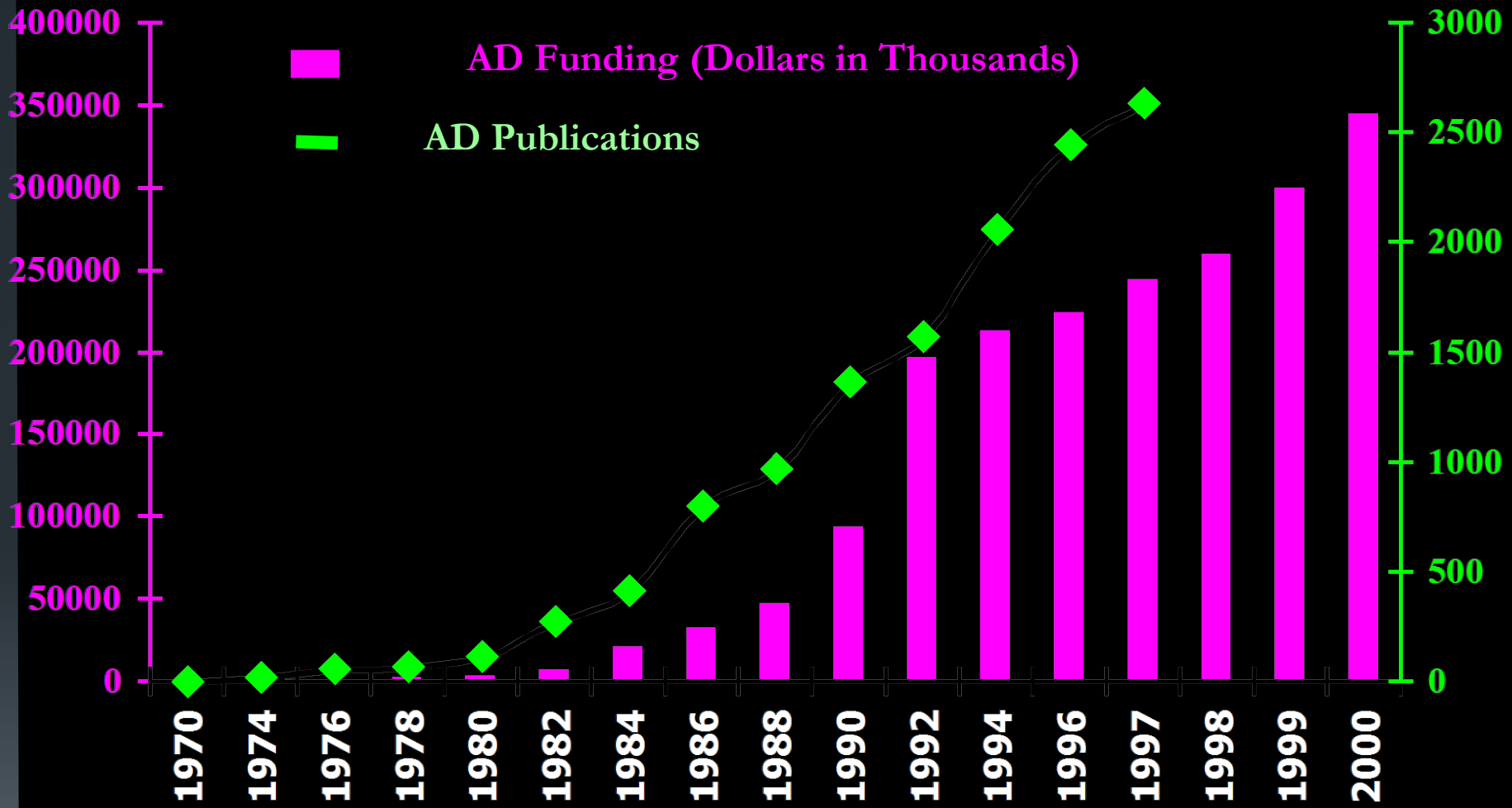
Zaven S. Khachaturian, Ph.D.

Chair and President, PAD2020

zaven@pad2020.org

www.pad2020.org

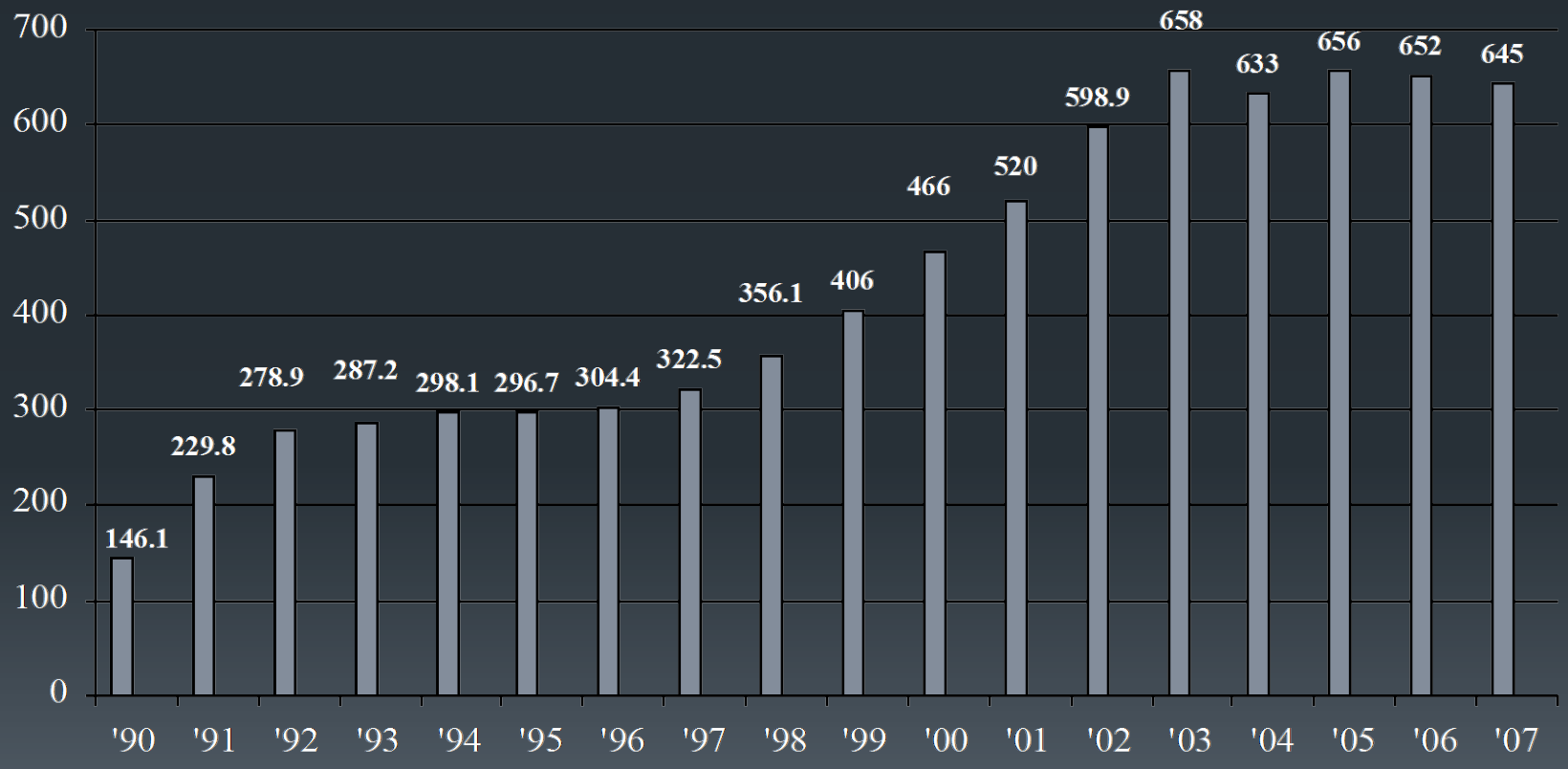
National Institute on Aging
Alzheimer's Disease Funding and Publications



Federal Funding - Alzheimer Research

Fiscal Years 1990-2006

(in millions of dollars)



2006 estimate based on FY 2006 appropriation. 2007 estimate based on President's Budget submitted Feb. 6, 2006.

History of R & D Capacity Building: 1978-Present

- *1978 – Beginnings of Alzheimer's & Brain Aging* research programs at National Institute on Aging/NIH – promoting:
  - formulation of diagnostic criteria
  - development- validation of clinical assessment tools and
  - creation of research *infrastructure to support longitudinal clinical studies*

- *1984-2004 – Evolution of the concept of 'shared-resource'/collaborative research:*

  ADRC – CERAD – ADCS – NACC – ADNI and other

History of R & D Capacity Building: 1978-Present – [continue]

- *Early efforts [1984-2004] focused* on the creation of *infrastructures* and building c*apabilities for clinical studies-trials* on *people with the disease*.

- *2004- Present* - The focus of the field shifted towards research on *people without the symptoms of the disease*

  - Current-Future challenge is to build the appropriate infrastructure to address the newly *emerging needs of the field regarding R & D on disease progression and prevention.*

Major Scientific Challenges

- ***Early Detection*** *– of asymptomatic people at elevated risk for Alzheimer's*
- ***New Therapeutic Target*** *– to maintain synaptic function or prevent synapse loss/dendrite pruning*

Critical Scientific Question

The challenge for a multi-national R&D initiative on *'Prevention'* is:

- The discover-validate of the *earliest* and *smallest* measurable cluster or combination of changes in performance-biomarkers-imaging in asymptomatic population – measures that can serve as *accurate prognostic* indicators of pending chronic brain impairment or dementia.

- The availability of such technologies will drastically reduce the *cost* and *duration* of 'disease modifying' or 'prevention' trial

Aim of the Presentation

Propose:

- A *'Global Strategic Goal – an action plan'* for a multi-national collaborative *R&D* initiative.

Specific Aims:

- Accelerate innovations re: *Dx* and *Rx* for *chronic brain disorders* such as Alzheimer's disease and dementia
- Reduce *prevalence* and *cost* of chronic impairments

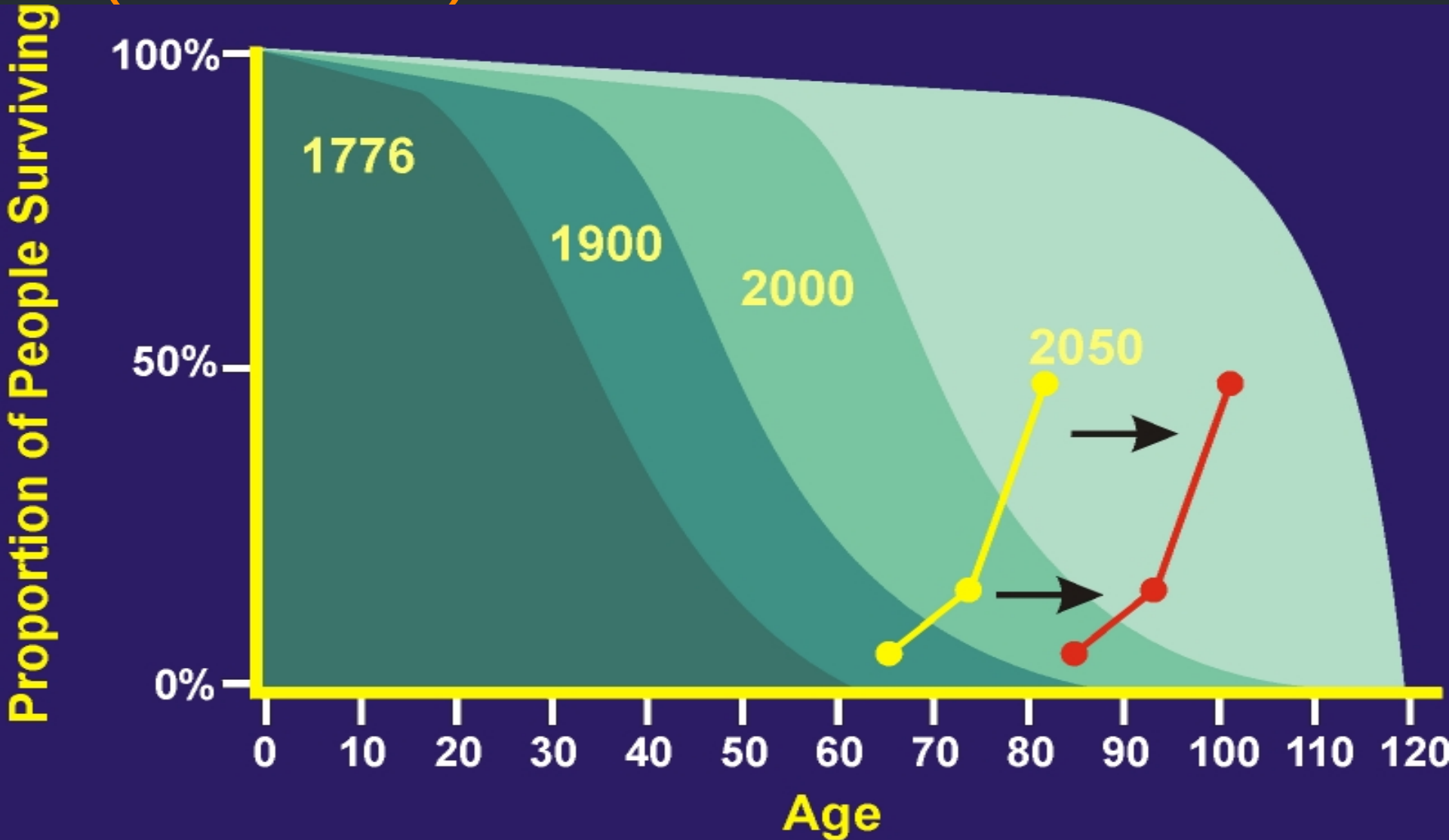
Rationale

- *The Grand Global Challenge of 21st Century* - The *'Mega Problem'* for healthcare systems globally stems from the: ♦ *economic,* ♦ *social,* ♦ *health* cost-burdens of prolonged *chronic disorders*

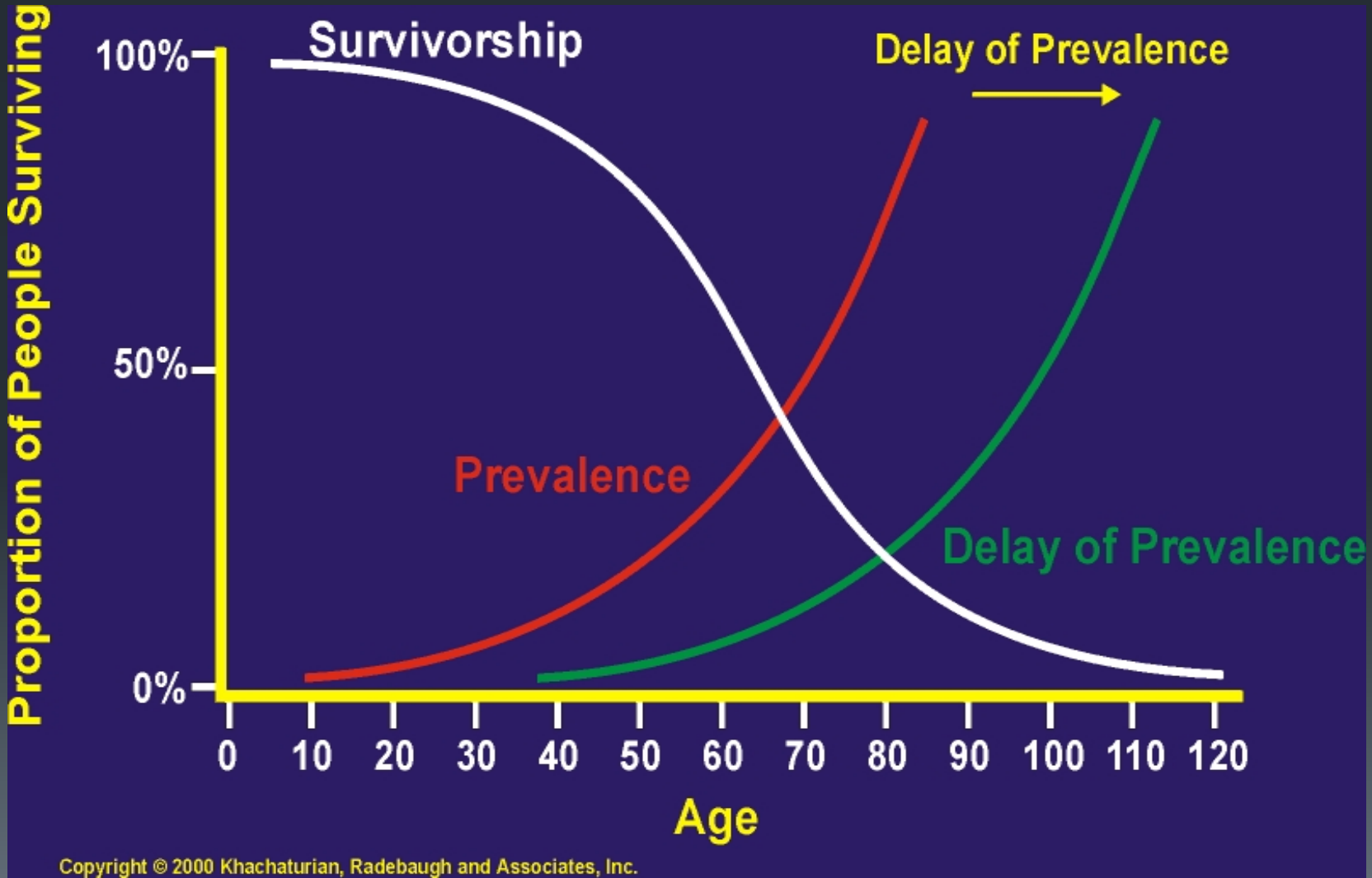
- A modest *delay of five years* in the onset of brain disability *will reduce the cost and prevalence* of these chronic conditions *by half*

- There is urgency for developing R&D capacity for innovations that will *reduce the prevalence of chronic brain disorders* e.g., AD by *50% within five years* and by *75% within ten-years*

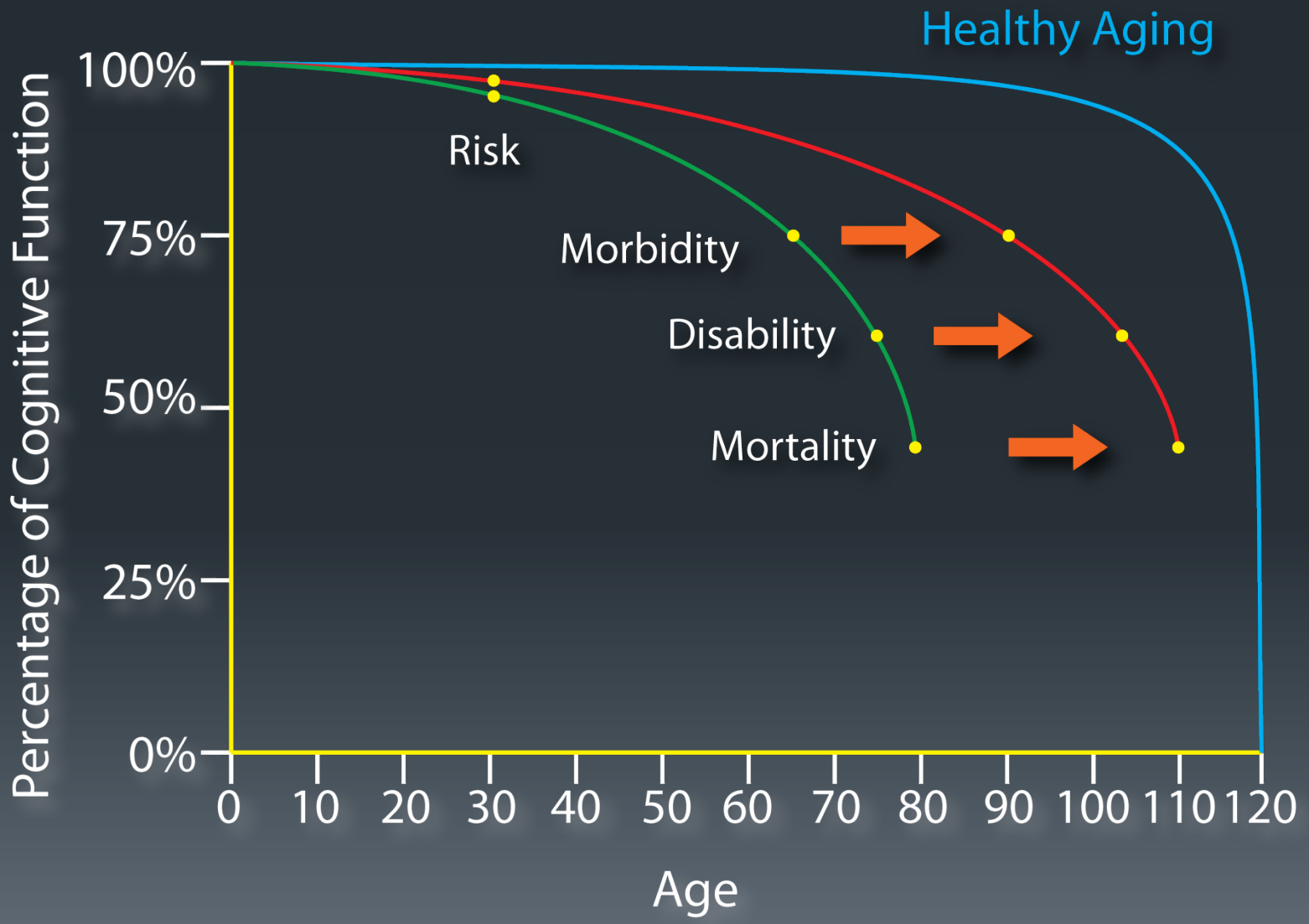
Extension of Life Expectancy (*Simulated*)



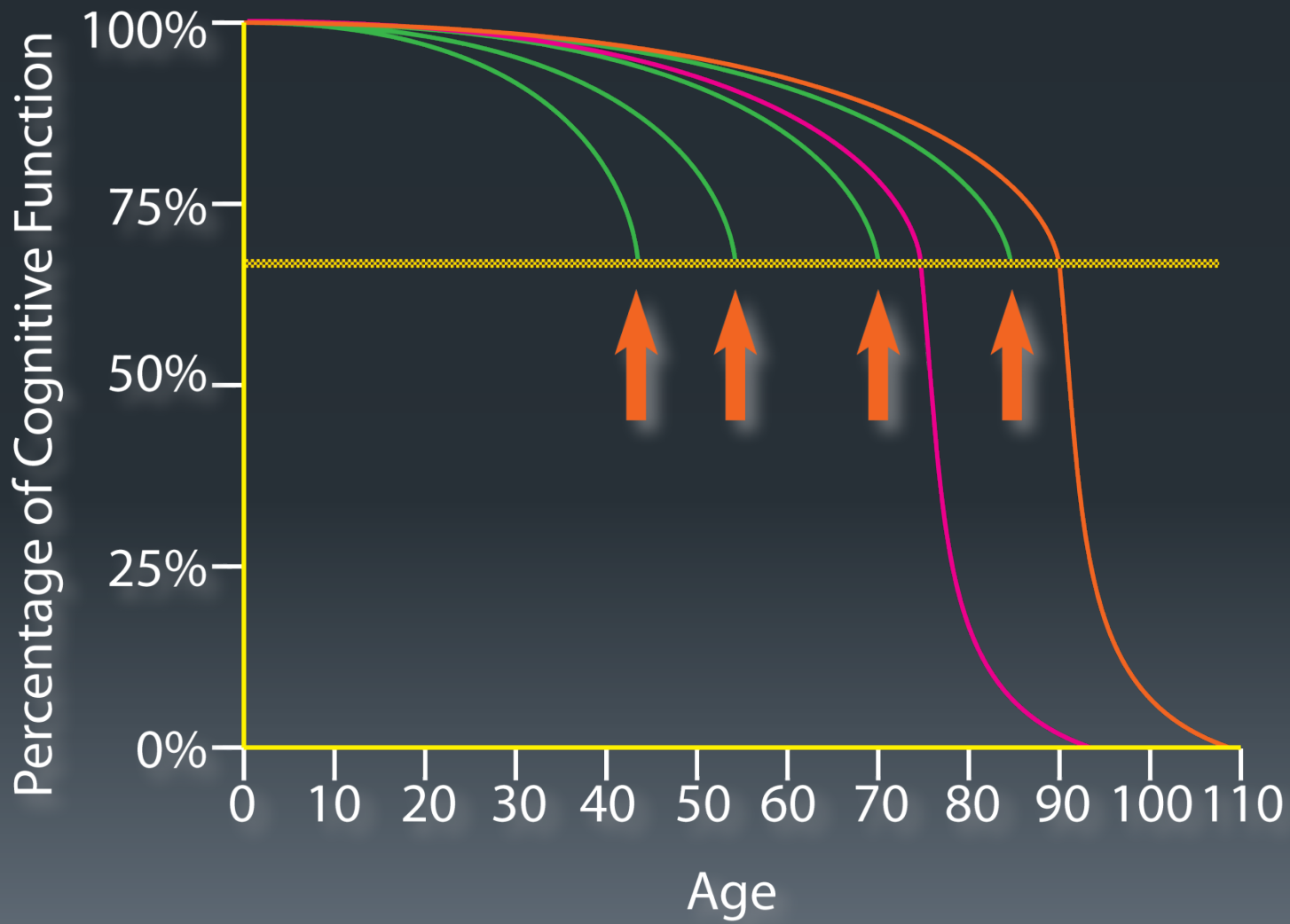
Delaying the Prevalence



stages of degenerative process



heterogeneity of dementia



Challenges for 'Prevention' Initiative

- *Very large population-based, genetically diverse, comprehensive database on well-characterized cohorts with multiple longitudinal data from several different domains –*
  - *An* essential resources for validating new technologies for accurate identification of asymptomatic people [pre-clinical stages] at elevate risk for AD

- *An International Database for Longitudinal Studies on Healthy Aging & Pre-Clinical Dementia [IDAD]* is needed for:
  - *prospective validation studies*,
  - developing new computational algorithms/models,
  - large measurements from varied sources-domains [e.g., biomarkers, genetic, behavioral, imaging and other information on co-morbid conditions], in order to discover/establish probability profiles for predicting the relative risks for memory disorders/dementia in asymptomatic populations and
  - furthering the fundamental understanding of the heterogeneity in the prevalence-incidence of AD as well as the knowledge about people at greatest risk for developing AD

Challenges for Global Strategic Goals:

The G-8 Dementia Summit December 11, 2013

- *Formulate the framework* for harmonizing global 'public policies' - to enable or accelerate multi-national collaborative R & D on early detection [Dx] and prevention [Rx] of chronic brain disorders e.g., AD

- Plan the *launch of a decade-long initiative* is to mobilize multinational efforts to:
  - acceleration of innovation – by building-up R & D infrastructure/ resources/technical capabilities
  - develop new knowledge - by expanding/supporting international collaborative projects
  - facilitating technology transfer – by supporting/harmonizing global data-sharing rules-approaches-algorithms

- Create a *governance* structure and a mechanism or model for *financing* a decade-long multi-national R & D Initiative

History of ‘Prevention’ Initiative

1992: Editorial, *‘The Five-Five, Ten-Ten Plan for Alzheimer’s Disease’;* a call to arms intended to mobilize the federal government, academia, the pharmaceutical industry, the general public, and family support groups behind a concerted and integrated effort aimed at discovering treatments for AD. (Khachaturian ZS. Neurobiol Aging 1992;13:197–8).

History of ‘Prevention’ Initiatives

1997: The Ronald and Nancy Reagan Research Institute’s strategic plan ***‘Prospects for Preventing Alzheimer’s Disease’.*** Testimony by Khachaturian ZS at a hearing on Alzheimer’s disease research. *Senate Committee on Labor and Human Resources*. Washington, DC. June 5, 1997.