Overview Of The ADNI Biomarker Core And The ABCs Of The Integrated NIA Alzheimer's Program

John Q. Trojanowski, M.D., Ph.D.
Institute on Aging, Alzheimer's Disease Center,
Center for Neurodegenerative Disease Research,
Department of Pathology and Laboratory Medicine,
University of Pennsylvania
Philadelphia, PA

NIA Alzheimer's Disease Centers Program

- Initiated in 1984
- Presently 29 ADCs
  - 17 ADRCs [P50]
  - 12 ADCCs [P30]
- NACC [UO1]
- NCRAD [UO1]
- ADCS [UO1]
- ADNI [UO1]

ADCs - Selected Accomplishments

- Genetics
  - Chr 21, 19, 4, 1, 17
- Assessment and Clinico-pathological Correlations
  - Development of ADAS
  - Development of CDR
  - Development of concept of MCI
  - Development of NIA-Reagan Criteria
- Amyloid and Tau Processing Research
- Neurotoxicity, Cell loss, Synapse Loss, and Inflammation Research

ADCs - Selected Accomplishments II

- Minority Studies and Satellites
  - Recruitment and Evaluation of Subjects for Minority Studies such as:
    - Indianapolis-Ibadan (Indiana)
    - Caribbean Hispanics (Columbia)
    - Mexican Hispanics –Salsa (UC-Davis)
    - Native Americans (UT-Southwestern)
- Training and Education Cores
  - Multidisciplinary training for scientists
  - Public outreach

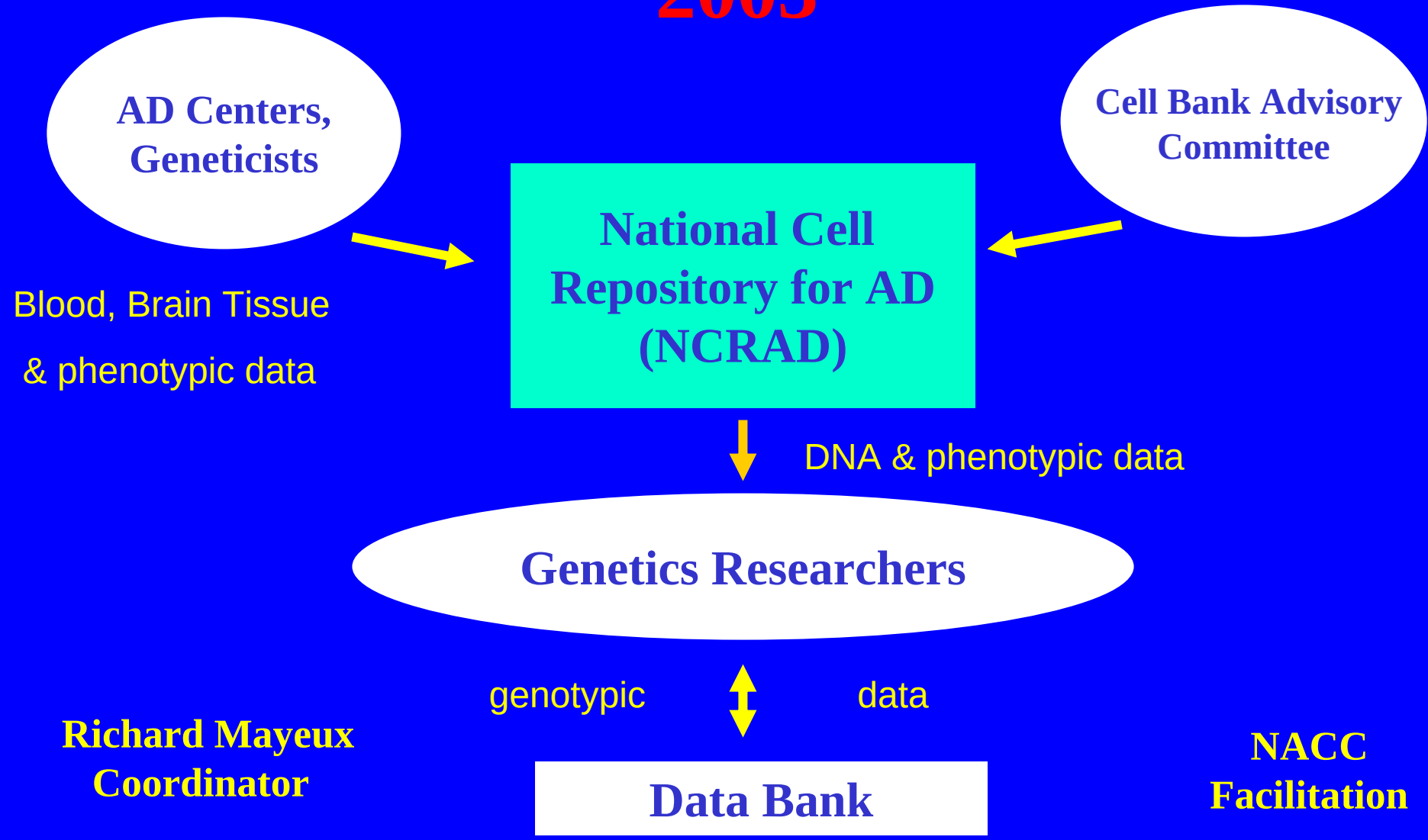
Recommendations from Planning Group for Future of ADCs

- Greater Flexibility
  - Special populations (eg. Religious Orders)
  - Structural options (pathology and education)
- More standardized data collection
- More data and sample sharing (Collaborations)
- Increased emphasis on the transition from normal Aging to MCI to early AD
- More emphasis on “related disorders”

Collaborative Research Among ADCs

- Collaborative Pilot Studies – NACC
- Collaborative Projects RFA (R01s)
- Collaborative Studies Funded by Supplements to ADCs (eg. Genetics Initiative)

NIA LOAD Genetics Initiative 2003



Richard Mayeux
Coordinator

NACC
Facilitation

NATIONAL ALZHEIMER'S COORDINATING CENTER

- Demographic, Clinical, Pathological, Biochemical Data Storage (MDS,UDS)
- MetaData (Site Database)
- Study Design and Statistical Consulting
- Characterization of Specimen Collections
- Collaborative Studies and Coordination of New Data Collection

Brief History Of The ADCS

- ADCS = Alzheimer's Disease Cooperative Study
- First funded by NIA in 1991 as a U01 (cooperative agreement)
- Major goals
  - Instrument development
  - Drug testing

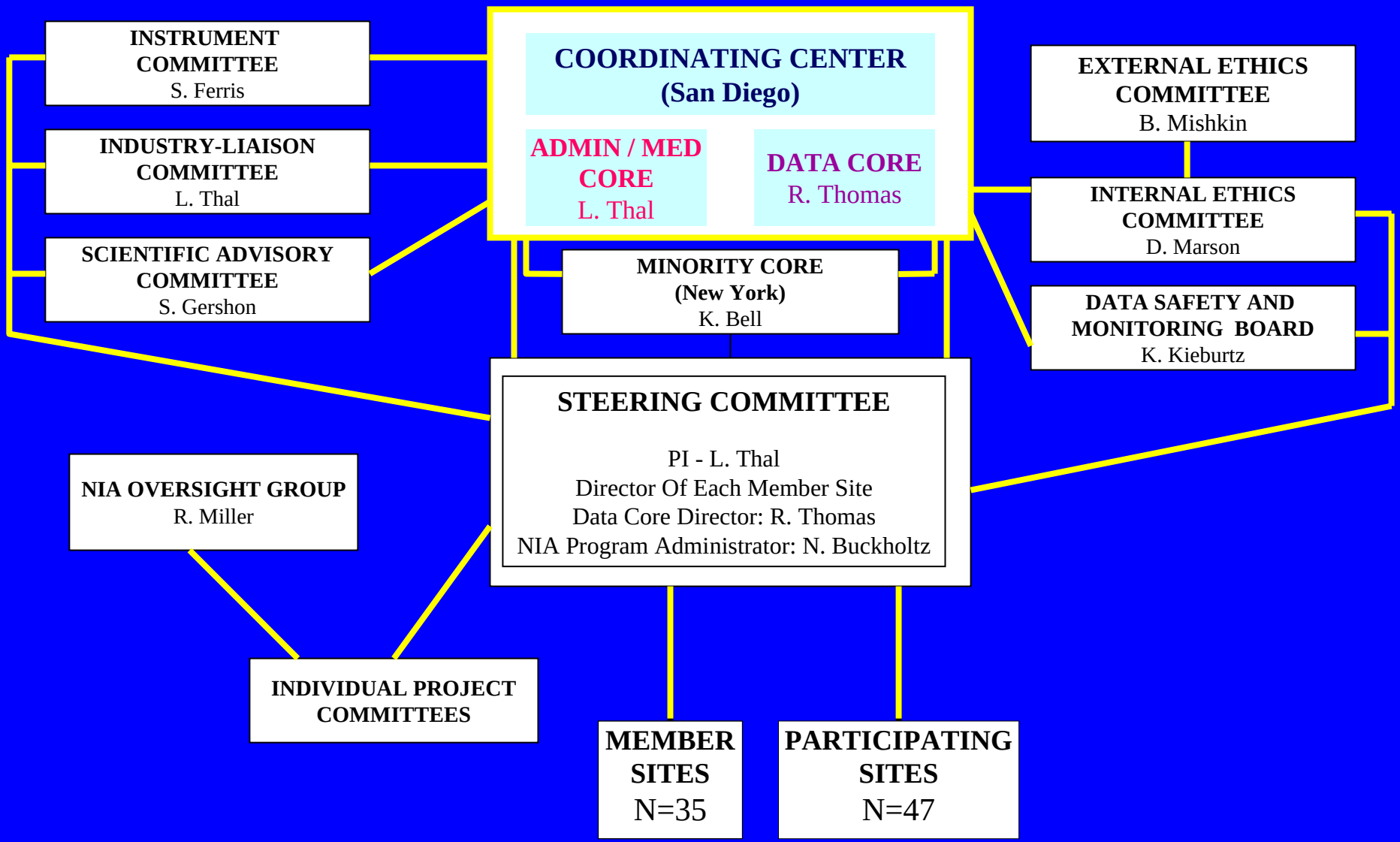
VISION

- Carry out the scientifically best and most important trials in the field of AD for compounds that would not be developed by industry
- Develop innovative ways of collecting data for AD trials

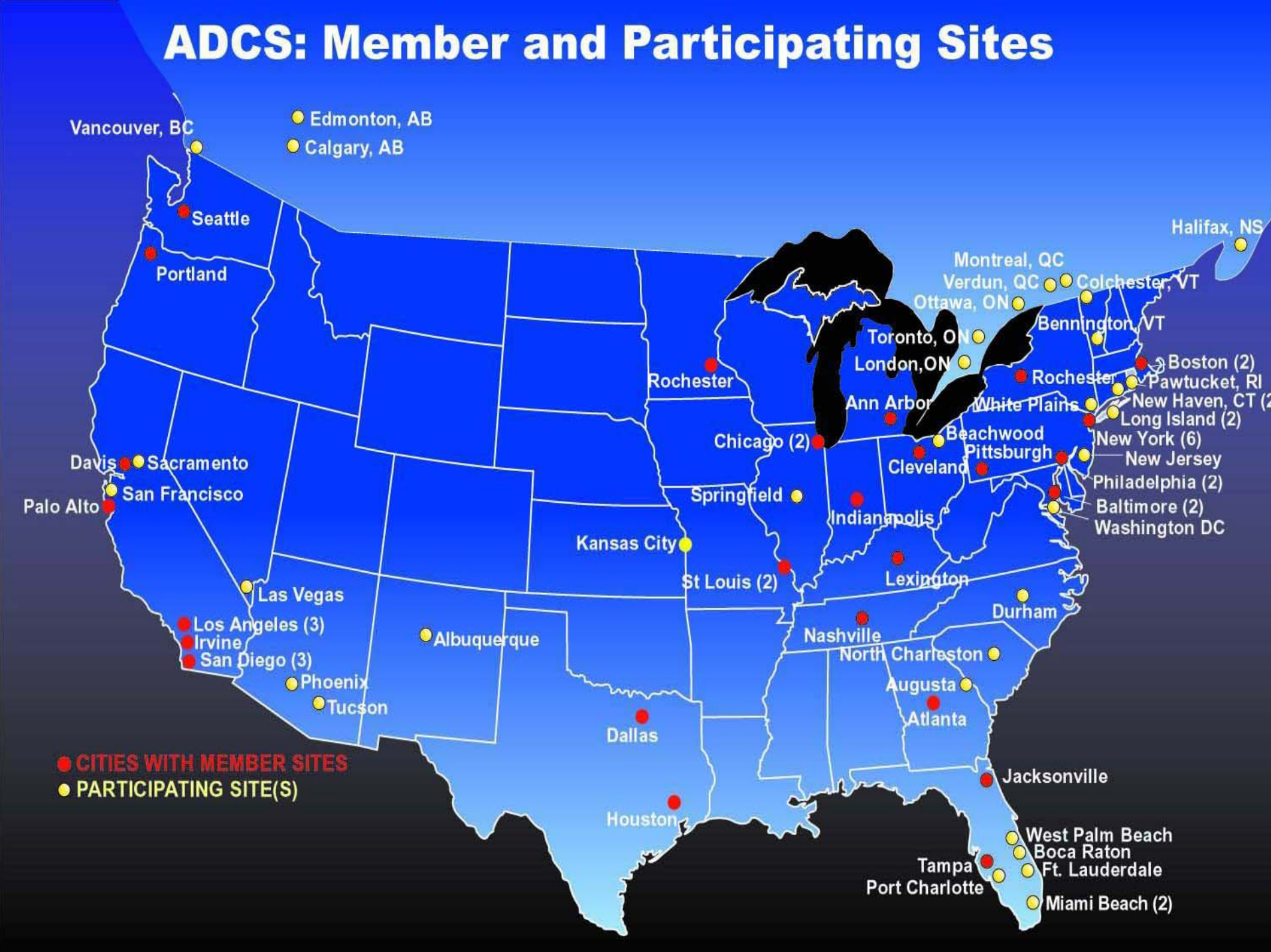
ADCS Mandate For Testing Drugs

- Lacking patent protection
- Marketed for other indications but possibly useful for AD
- Novel compounds
  - Laboratory developed
  - Small biotech company developed
- Scientifically highly promising in answering a hypothesis

ADCS Operational Flow Chart



ADCS: Member and Participating Sites



ADCS Resources

- Skilled clinical trialists
- Biostatistical consultation and study design
- Protocol development/instrument development
- Ability to provide project directors
- Experience in AD drug development
- Network of sites collaborating for over a decade
- Infrastructure including construction of case report forms, data entry, monitoring, regulatory compliance, DSMB
- Data analysis
- Outstanding scientific advisory board
- Excellent relations with: FDA, NIH

NIA ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE (ADNI)

Michael W Weiner

Leon Thal

Ronald Petersen

Clifford Jack

William Jagust

Arthur Toga

John Trojanowski

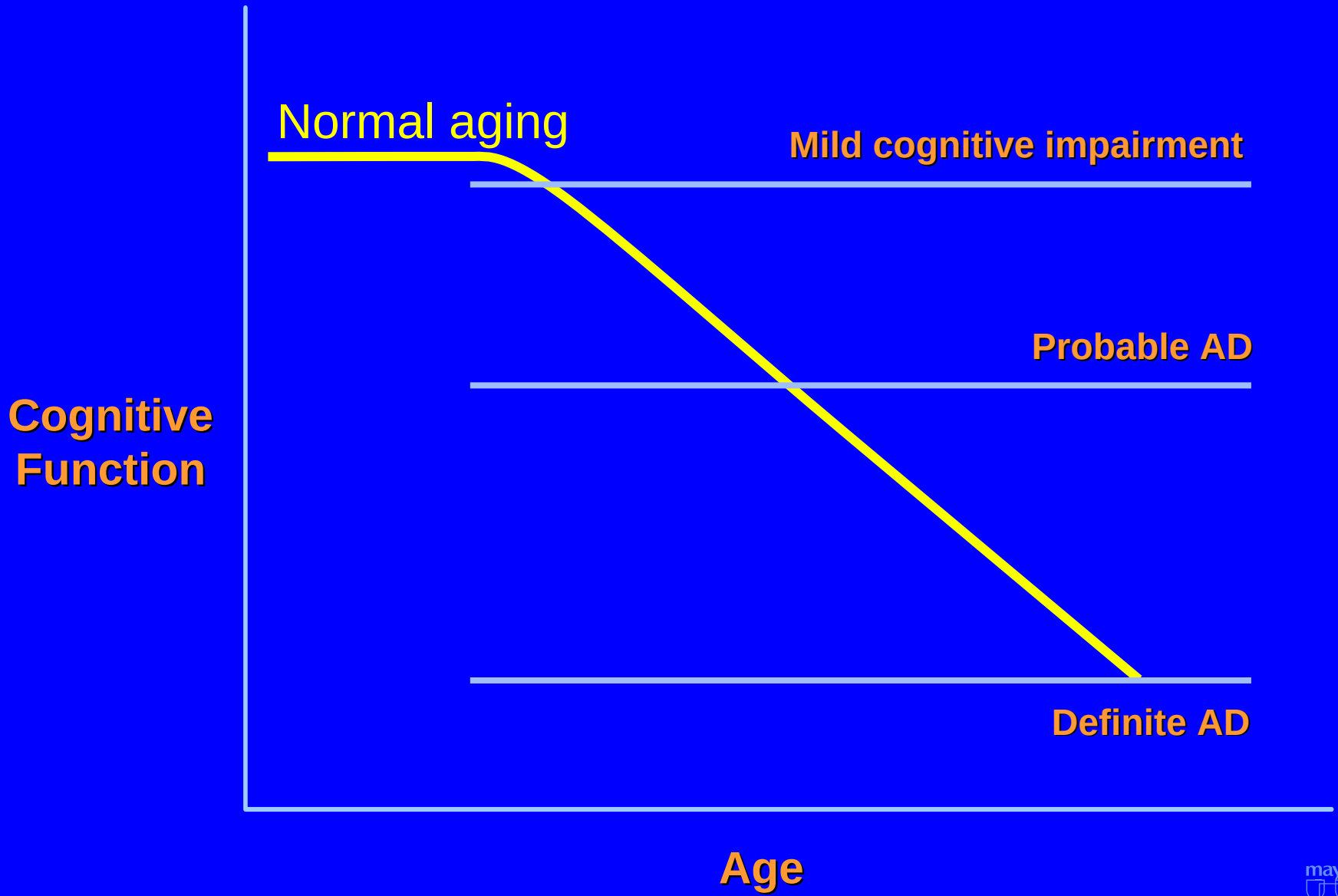
Laurel Beckett

Ronald Thomas

SUMMARY

- **Currently, there are no treatments which slow the progression of Alzheimer's disease (AD)**
- **However, substantial progress has been made towards understanding AD**
- **PHARMA is developing new treatments which are hoped to slow the progression of AD**
- **The ADNI will provide imaging and biomarker data, improved methods, and a network of sites which should greatly facilitate treatment trials, ultimately leading to development of effective therapy**

TRANSITION FROM NORMAL AGING TO ALZHEIMER'S



POTENTIAL TREATMENTS

- **CHOLINESTERASE INHIBITORS**
- **Currently available: symptomatic**
- **AMYLOID: Reduce production, increase removal, immunotherapy**
- **ANTIOXIDANTS**
- **ANTI-INFLAMMATORIES**
- **NEURO-TROPICS**

INCREASING ROLE of IMAGING and BIOMARKERS IN AD TREATMENT TRIALS AND DETECTION

- Many studies have shown changes in the brain of normal aging and in AD
- Structural MRI shows brain shrinkage: hippocampus and cerebral cortex
- FDG PET shows reduced metabolism
- Thus, imaging and biomarkers can improve diagnosis and reflect disease progression
- Great potential for use in clinical trials and for early detection

ROLE of IMAGING in TREATMENT TRIALS

- Current trials using cognitive measures have large sample size
- Cognitive measures do not easily determine disease modifying effects of treatment
- PHARMA has high interest in use of imaging and biomarkers for treatment trials
- Current data (MRI and PET) from many labs, different methods, different subjects

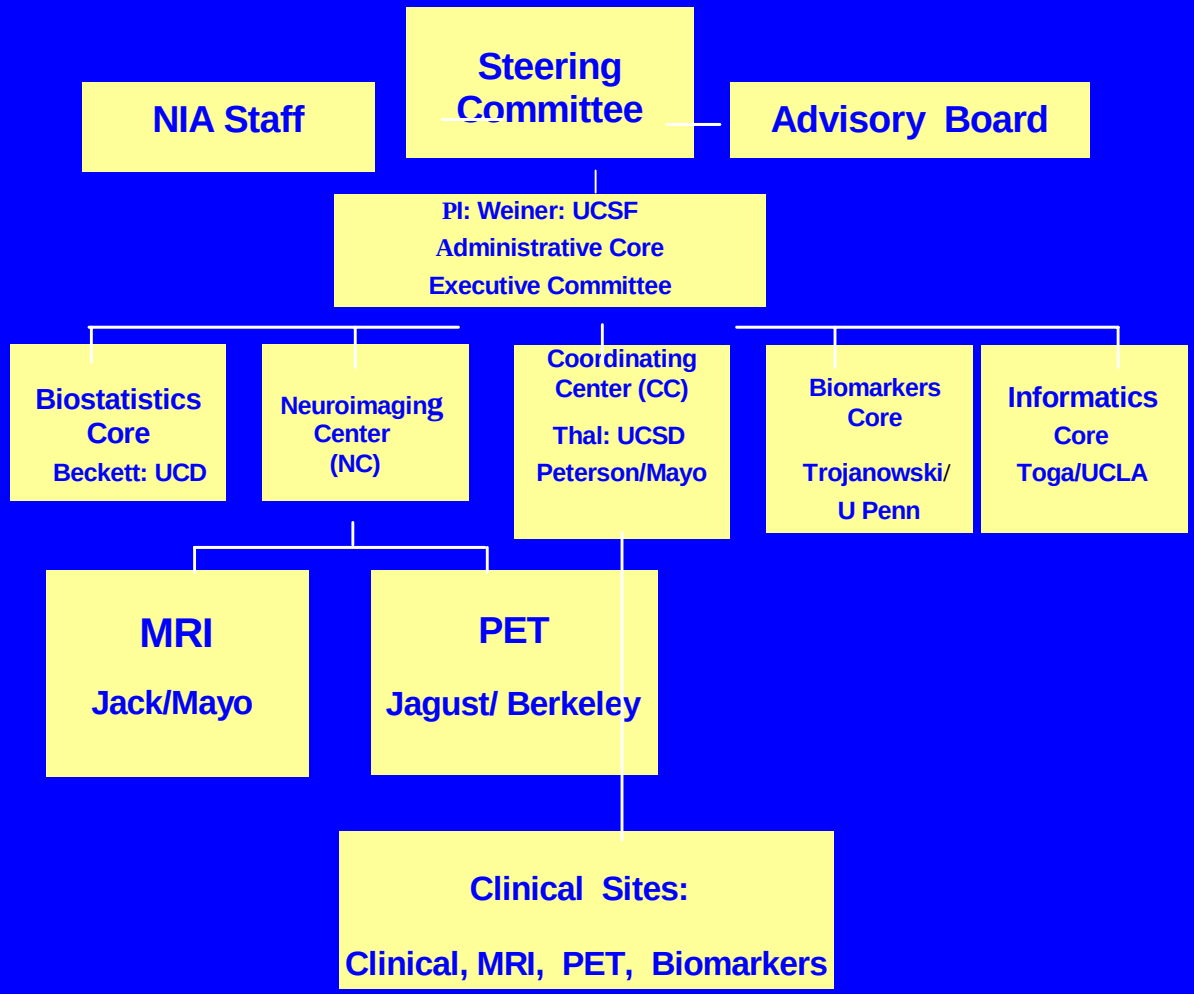
GOALS OF THE ADNI: LONGITUDINAL MULTI-SITE OBSERVATIONAL STUDY

- Major goal is collection of data and to establish a brain imaging and biomarker database
- Determine the optimum methods for acquiring and processing images for clinical trials
- Develop “standards” for imaging, biomarkers
- “Validate” imaging and biomarker data by correlating with neuropsych and behavioral data. Facilitates FDA approval!
- Rapid public access of *all* data

STUDY DESIGN

- **MCI (n= 400):** 0, 6, 12, 18, 24, 36 months
- **AD (n= 200):** 0, 6, 12, 24 months
- **Controls (n= 200):** 0, 6, 12, 24, 36 months
- **All subjects (age 55-90):** Clinical, MRI (1.5 T) at all time points
- **FDG PET** at all time points in 50%
- **3 T MRI** at all time points in 25%
- **Blood and urine** at all time points from all subjects, **CSF** from 20% of subjects less often

ADNI GOVERNANCE

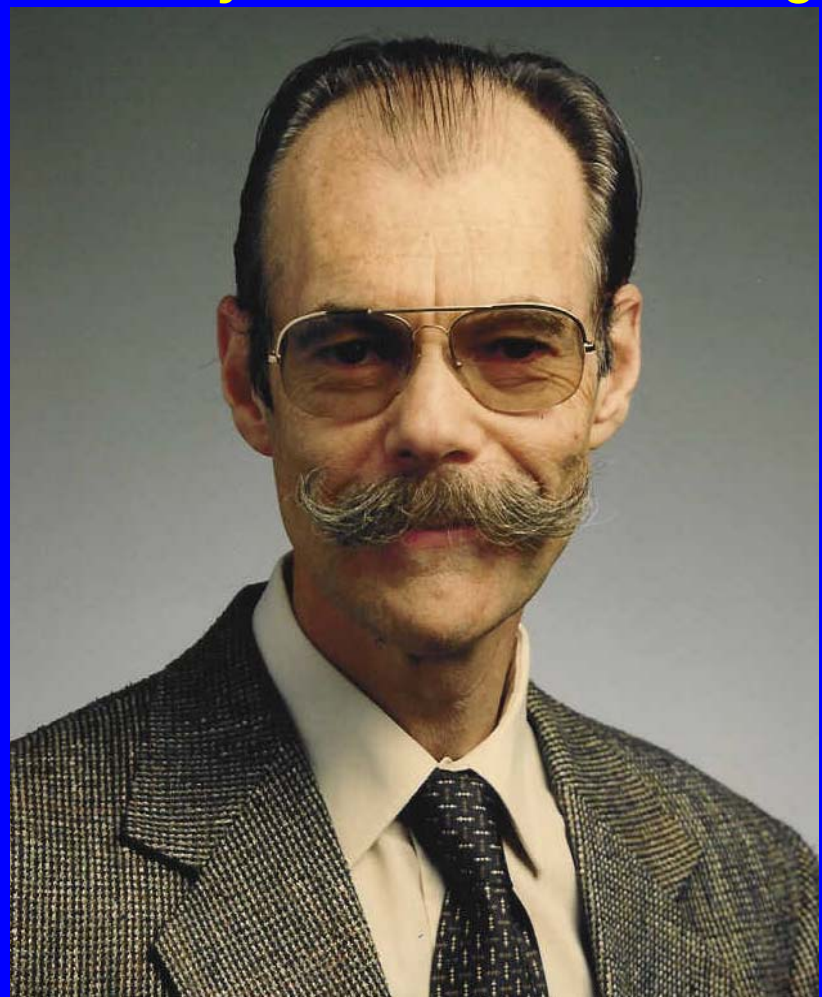


Dr. Michael W. Weiner - PI of the ADNI

Center for Imaging of Neurodegenerative Diseases
University of California, San Francisco

Leon J. Thal, M.D.
PI: Clinical Center

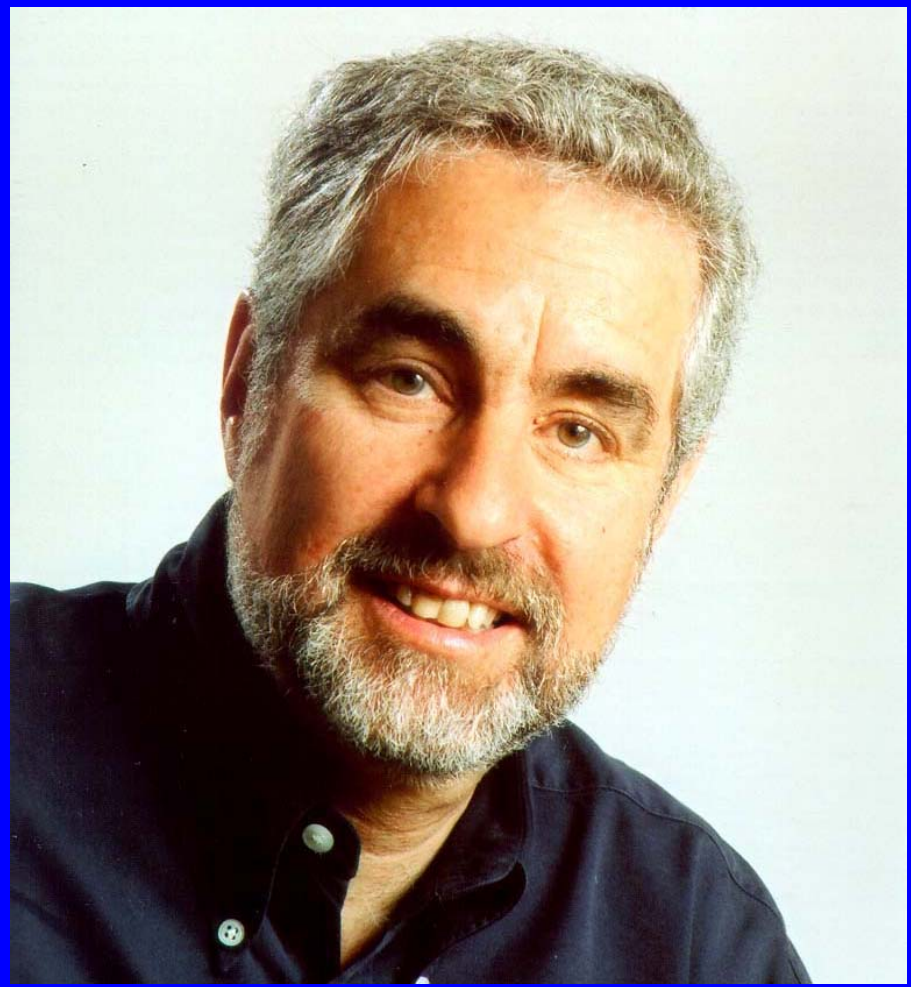
Director: ADCS
Professor and Chairman
Department of Neurosciences
University of California San Diego



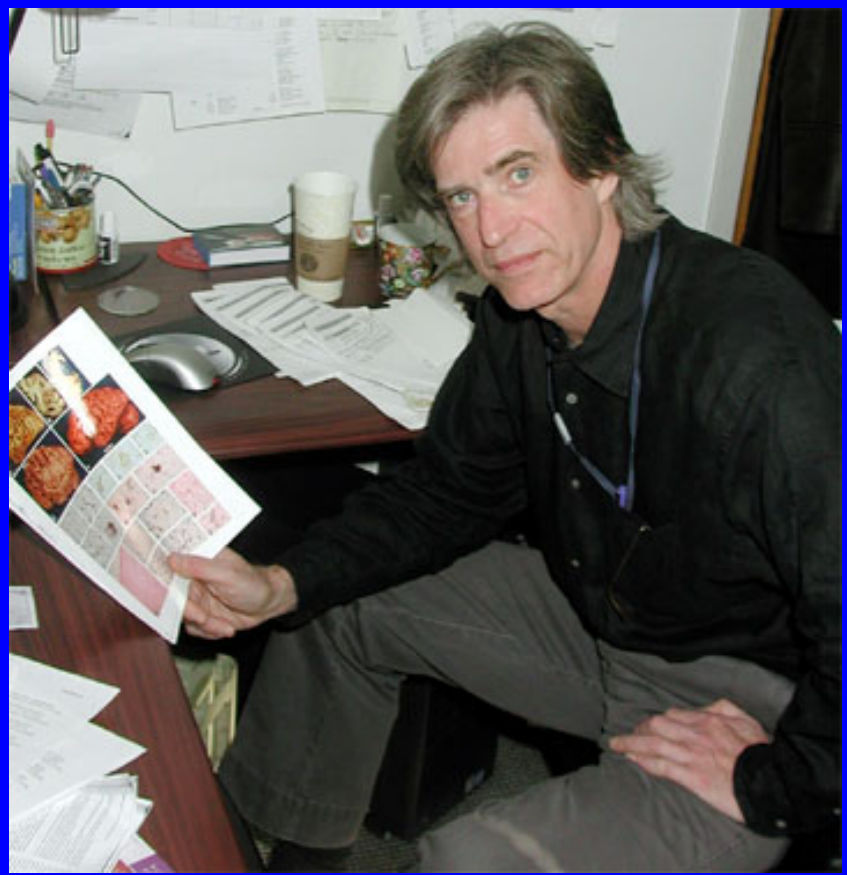
Ronald Petersen, PhD, MD
Co PI Clinical Center
Mayo Clinic Rochester
School of Medicine
Department of Neurology

Clifford Jack, MD
PI MRI Core
Mayo Clinic
Rochester, Minnesota

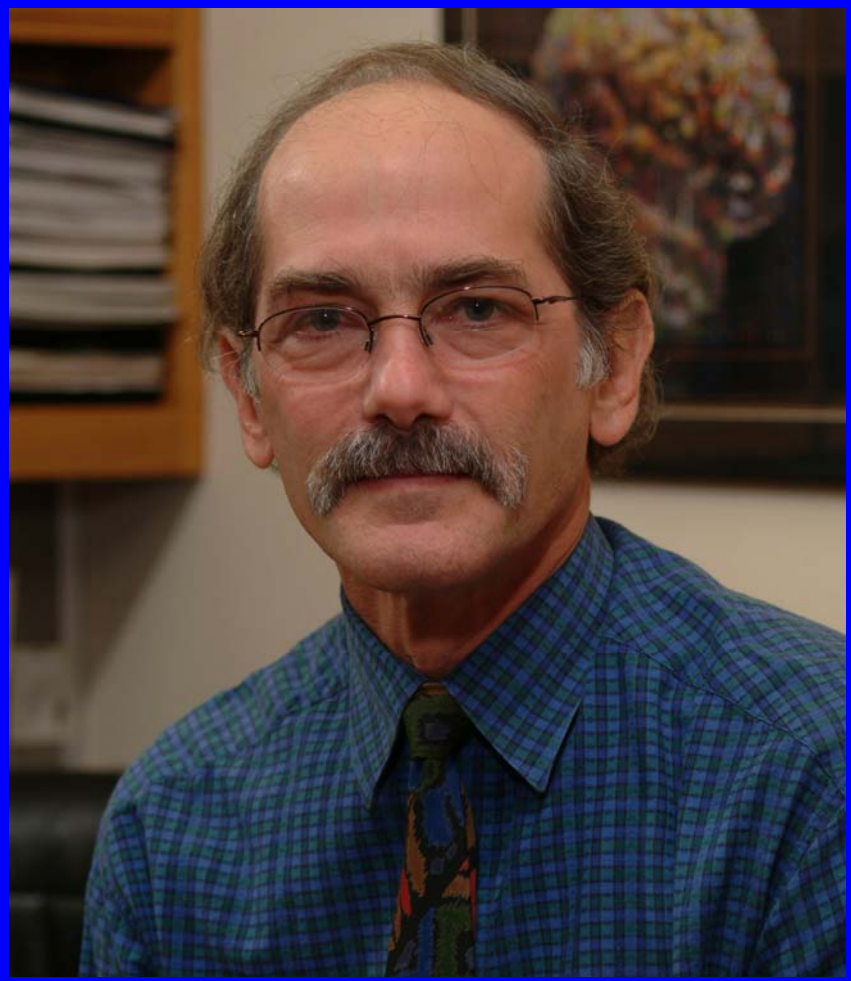
WILLIAM JAGUST M.D.
PI: PET CORE
UNIVERSITY OF CALIFORNIA BERKELEY



John Q Trojanowski, MD, PhD
PI: Biomarker Core
University of Pennsylvania



Arthur Toga, PhD
PI: Informatics Core
Director Laboratory of Neuro Imaging
University of California, Los Angeles,
UCLA School of Medicine



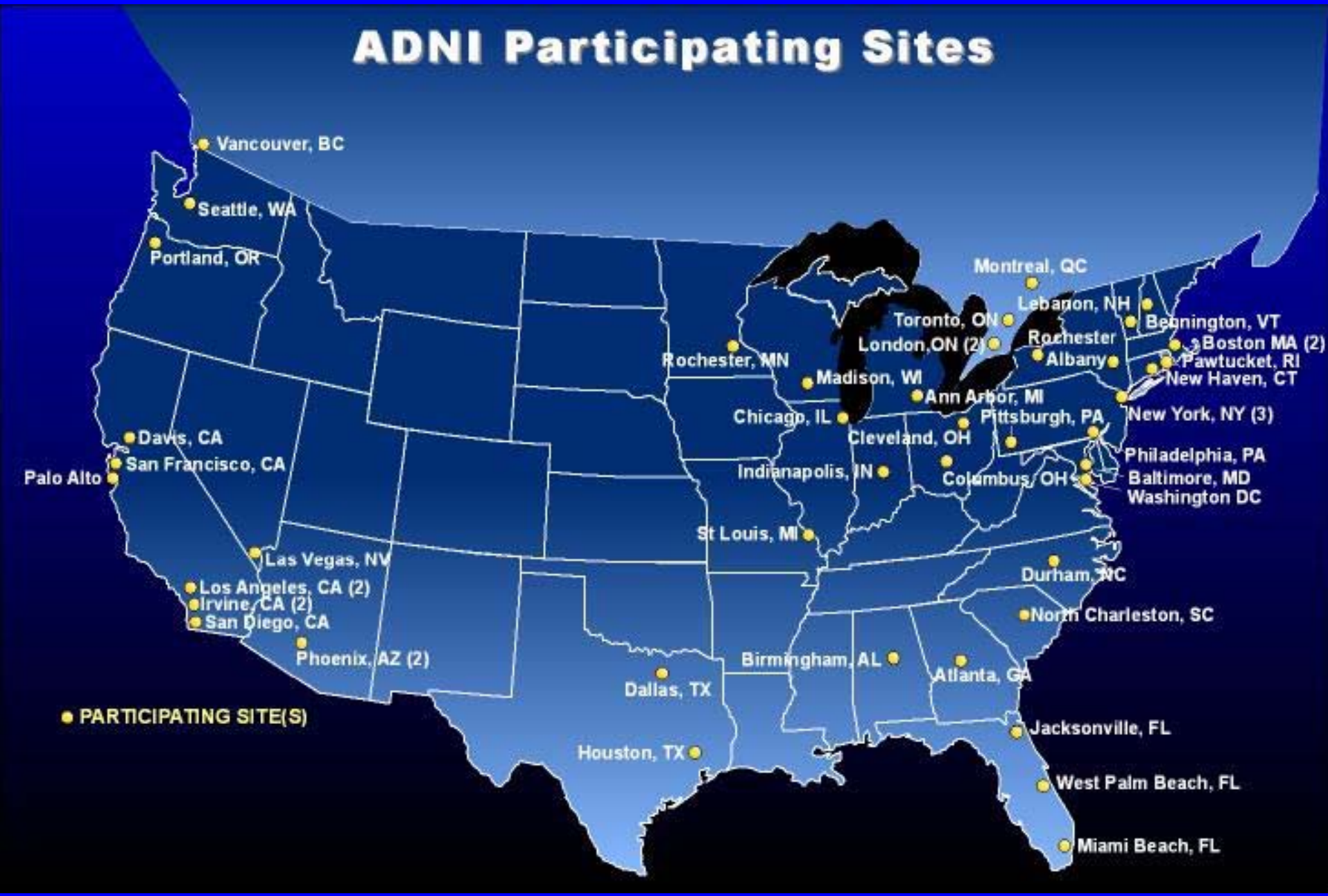
Laurel Beckett, PhD
PI: Biostatistics Core
University of California, Davis
School of Medicine, Department of Epidemiology and Preventive Medicine

INFORMATICS

- Goal is rapid public access of *all raw and processed data*
- ADCS (UCSD) will receive all clinical data
- LONI (UCLA) will receive all MRI and PET scans
- Clinical and imaging data will be linked
- All clinical, imaging and biomarker data will be publicly available

RECRUITMENT SITES: REQUIREMENTS

- 45-50 sites have been selected
- Major requirement: demonstrated ability to recruit MCI, AD and control subjects for trials
- Also need acceptable 1.5 T MRI
- Some sites will provide 3 T and PET


ADNI Participating Sites
Vancouver, BC
Seattle, WA
Portland, OR
Montreal, QC
Lebanon, NH
Toronto, ON
Bennington, VT
London,ON (2)
Rochester
Boston MA (2)
Albany
Pawtucket, RI
Rochester, MN
New Haven, CT
Madison, WI
Ann Arbor, MI
Chicago, IL
Pittsburgh, PA
New York, NY (3)
Davis, CA
Cleveland, OH
San Francisco, CA
Philadelphia, PA
Palo Alto
Indianapolis, IN
Columbus, OH
Baltimore, MD
Washington DC
St Louis, MI
Las Vegas, NV
Durham, NC
Los Angeles, CA (2)
North Charleston, SC
Irvine, CA (2)
San Diego, CA
Phoenix, AZ (2)
Birmingham, AL
Atlanta, GA
Dallas, TX
PARTICIPATING SITE(S)
Jacksonville, FL
Houston, TX
West Palm Beach, FL
Miami Beach, FL

TIME LINE

- Funds awarded October, 2004
- First meeting of Steering Committee October, 2004
- Preparatory Phase Oct –April
- Patient enrollment targeted to begin:
- April-July 2005
- Enrollment ends July 2006.
- Study Completion 2009

Penn Biomarker Core

Core Leader: J.Q. Trojanowski

Co-Investigators: L. Shaw, A. Nanji, V.M.-Y. Lee

The goals of Biomarker Core:

1) Measure these analytes in ADNI subjects:

ApoE genotype **Homocysteine**

Isoprostanes (blood, urine, CSF)

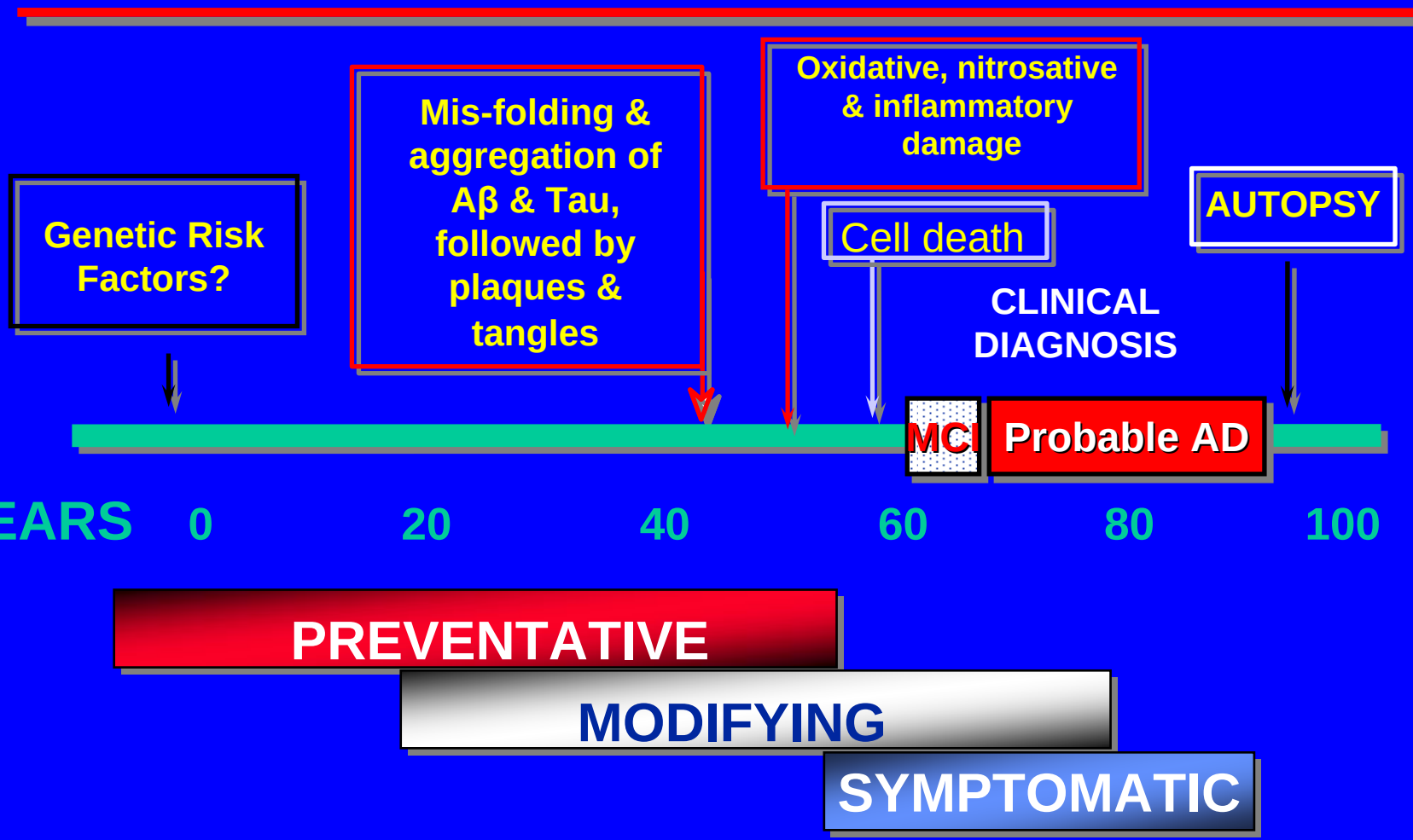
Tau and Aβ (CSF) **Sulfatides (CSF)**

2) Create immortalized cell lines

3) Utilize the Resource Allocation Committee Review Committee to distribute samples for "add on studies"

4) Seek other funding for additional analyses and "add on studies"

ALZHEIMER'S DISEASE Rx
SPECULATIVE TIMELINE



Metrics for AD Biomarkers

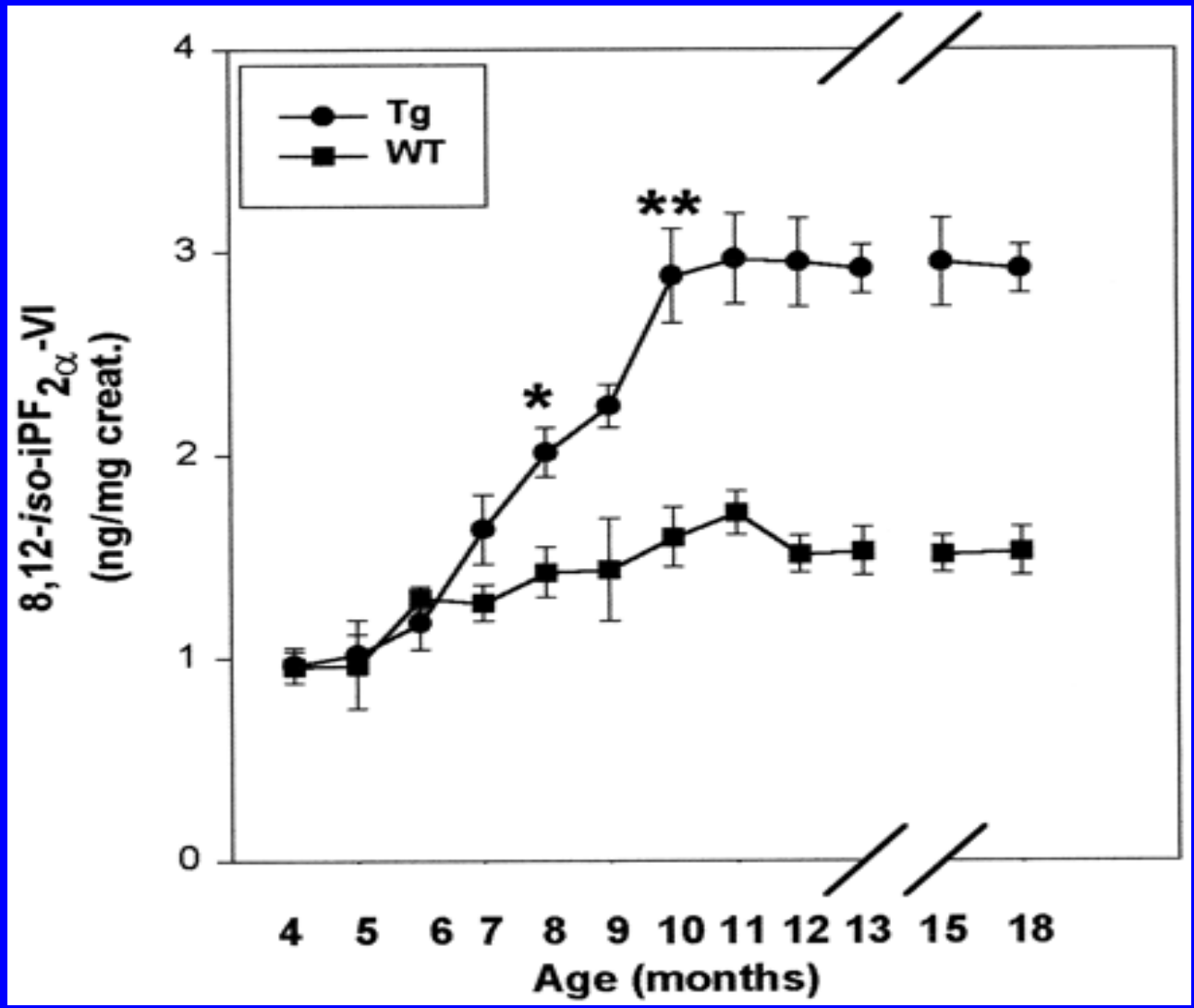
- **Sensitivity - A sensitivity of 100% indicates a marker that can identify 100% of patients with AD. (Biomarker should have a sensitivity of >90%)**
- **Specificity- A test with 100% specificity differentiates AD from other causes of dementia in every case. (Biomarker should have a specificity of >90%)**
- **Prior probability - The frequency of disease occurrence in a particular group. A perfect biomarker would detect only true positives and no false negatives and thus would reflect accurately the prevalence of the disease in the population.**
- **Positive predictive value - The % of people who have a positive test who can be shown at subsequent autopsy examination to have the disease. A positive predictive value of 100% means that all patients with a positive test actually have the disease. For a biomarker to be useful clinically it should have a positive predictive value of >90%.**
- **Negative predictive value - The % of people with a negative test who subsequently at autopsy do not to have the disease. A negative predictive value of 100% indicates that the test completely rules out the possibility that the individual has the disease at the time that the individual is tested. A reliable marker with a high negative predictive value would be useful. A test with low negative predictive value might be useful in some circumstances if it also had a high positive predictive value.**

Plans For First 6 Months Of The ADNI Penn Biomarker Core

- Create a budget for Biomarker Core.
- Select personnel
- Set up Core in new space; purchase/install equipment
- Purchase kits and assay reagents for testing of assays.
- Test assay kits/protocols/methods for measuring homocysteine, isoprostanes, sulphatide, Abeta, tau, as well as DNA extraction from peripheral blood cells for APOE genotyping and DNA storage and immortalizing cell lines.
- Conduct pilot studies using artificial CSF, plasma and urine "doped" with the analytes of interest followed by similar studies using "live" archival samples.
- Train Core staff on sample receipt, log-in, aliquoting, storage, tracking, report generation, database usage, data transfer to UCSD.
- Develop SOPs, QC&QA protocols, and incorporate into lab manuals for use by staff for implementing all Core activities.
- Receive authentic biological fluids from ADNI subjects on ~1 July, 2005 and implement the activities summarized above.

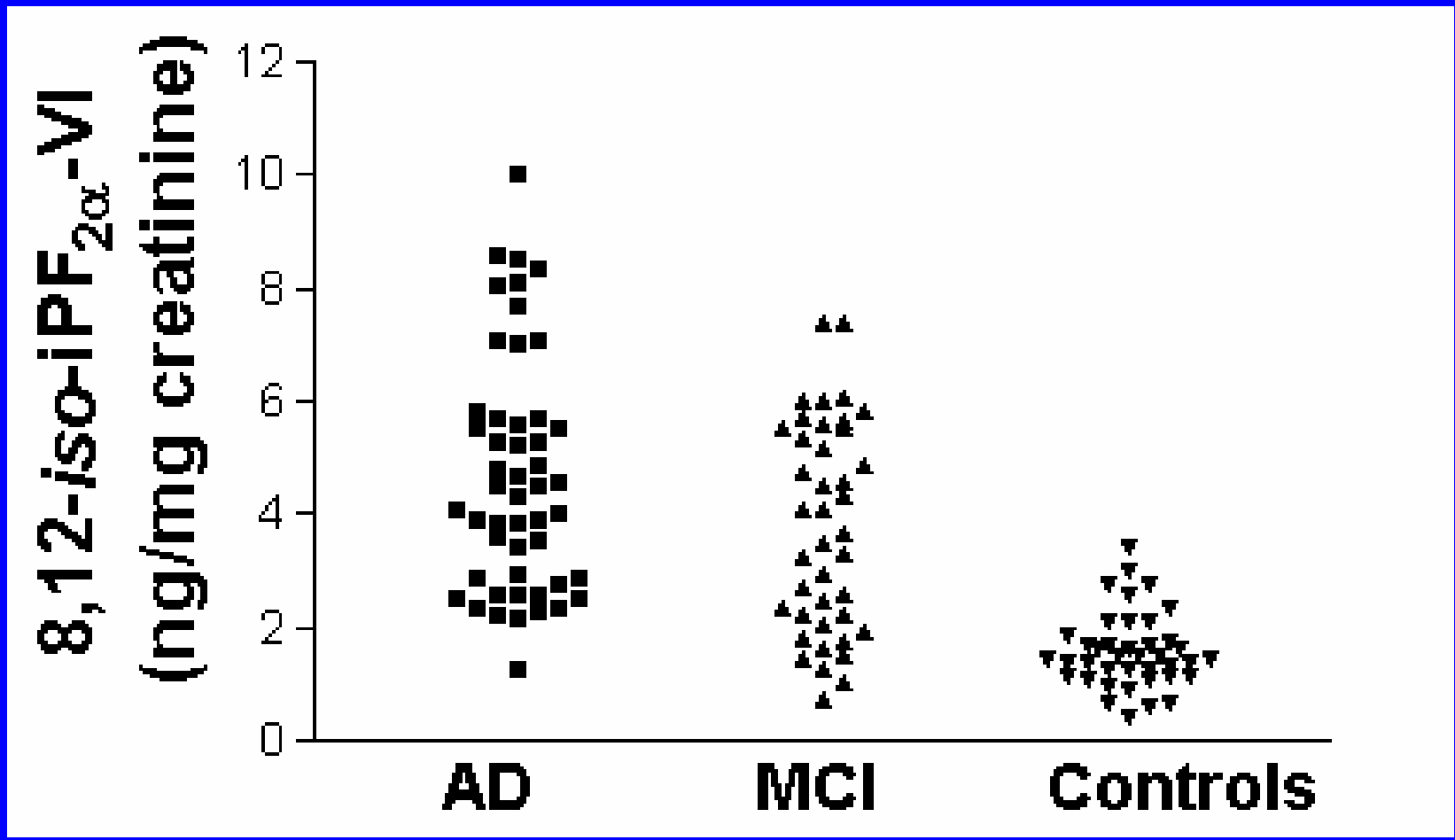
Age-dependent increase in urinary 8,12-iso-iPF$_{2a}$-VI in Tg2576

(Pratico D, Uru K, Leight S, Trojanowski JQ, Lee VM-Y. Increased lipid peroxidation precedes brain deposition of Aβ in a transgenic mouse model of Alzheimer's disease amyloidosis. J. Neurosci., 21:4183-4187, 2001)



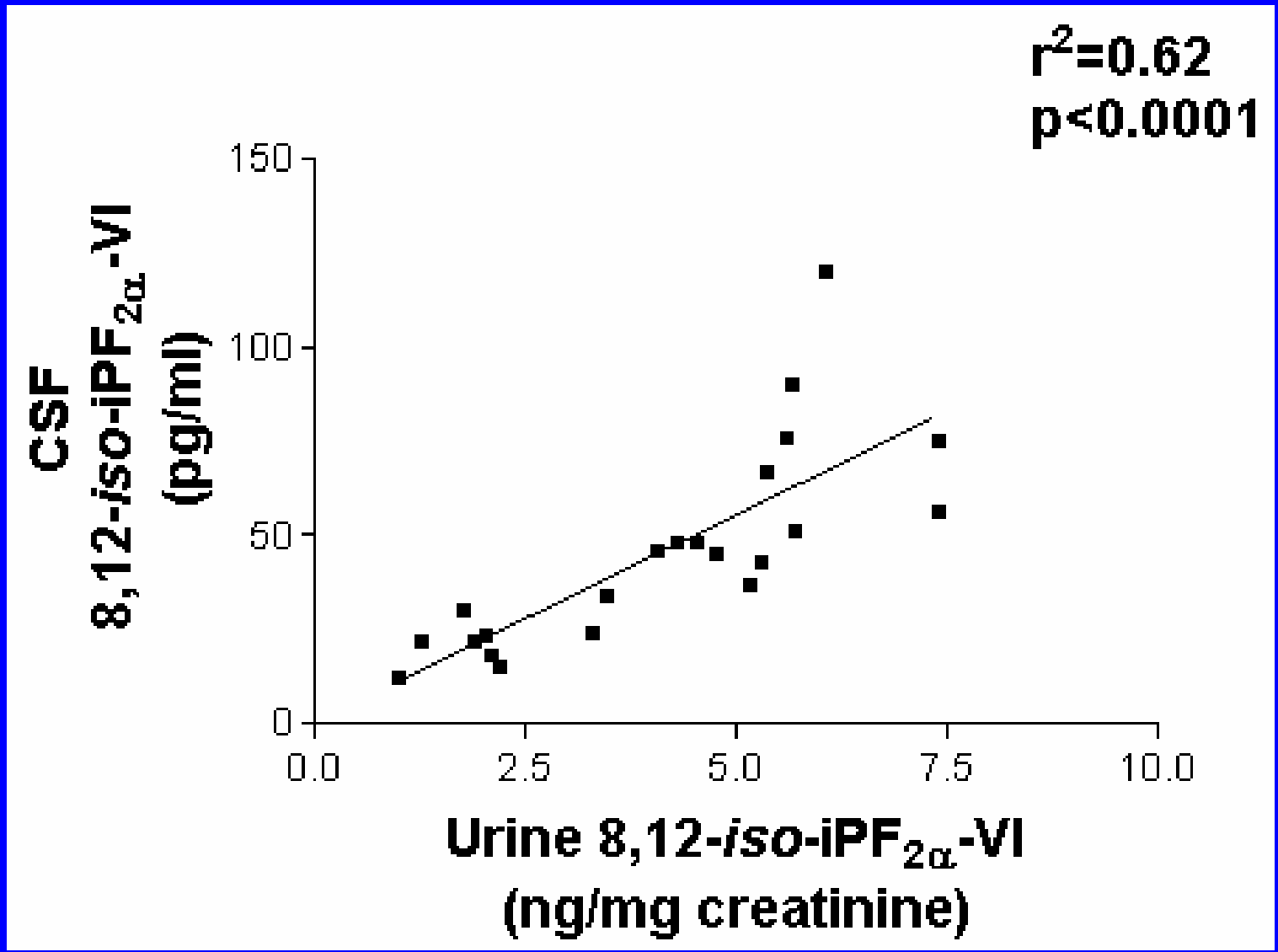
Urinary 8,12-*iso*-iPF$_{2a}$-VI levels are elevated in MCI

(Pratico D, Clark CM, Liun F, Lee VM-Y, Trojanowski JQ. Increase of brain oxidative stress in mild cognitive impaiment: A possible predictor of Alzheimer's disease. Arch. Neurol., 59:972-976, 2002)



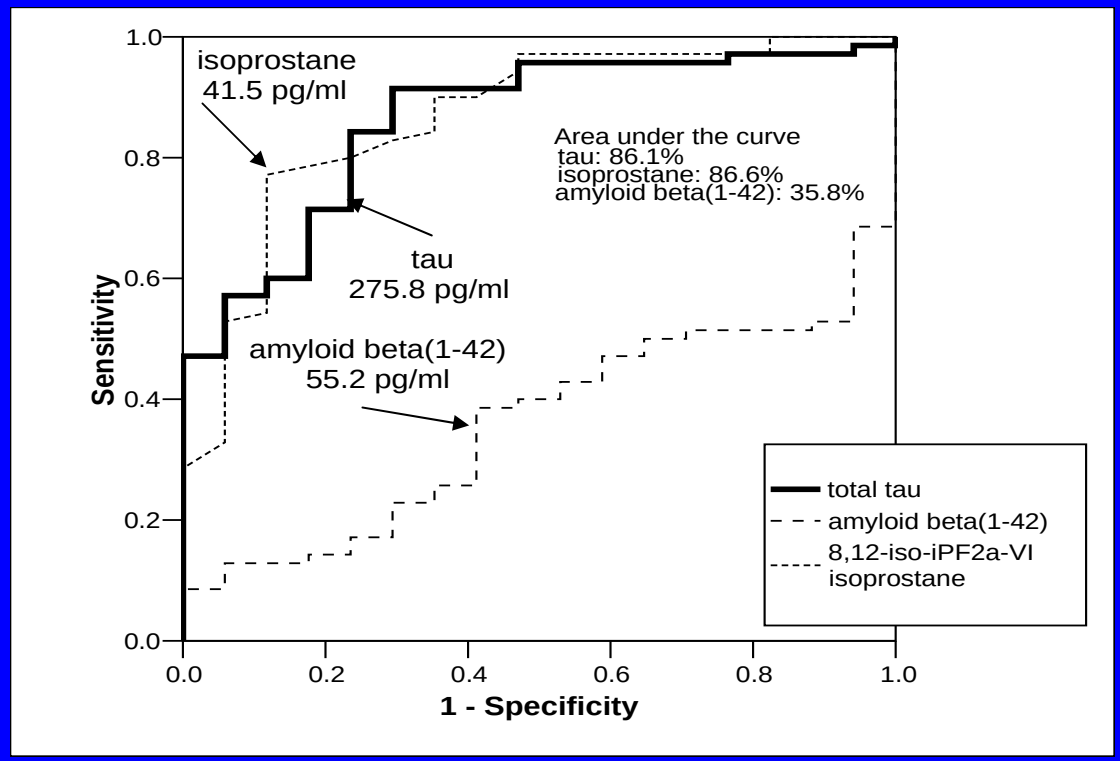
Correlation between CSF and urinary 8,12-*iso*-iPF$_{2a}$-VI levels in MCI subjects

(Pratico D, et al. Arch. Neurol., 59:972-976, 2002)



CSF Profiles Of Tau, A And Isoprostanes To Differentiate FTD From AD

ROC CURVES OF CSF TAU, Aβ (1-42), AND ISOPROSTANES



NOTE

1. CSF tau: At a cutoff of 275.8 pg/ml, sensitivity = 74.0%, specificity = 82.4%, positive predictive value = 94.7% and positive likelihood ratio = 18.0 to distinguish between an FTD-related disorder and AD. CSF iP: At a cutoff of 41.5 pg/ml, sensitivity = 77.1%, specificity = 94.1%, positive predictive value = 98.2%, and positive likelihood ratio = 54.0 to distinguish between an FTD-related disorder and AD. CSF Aβ1-42: At a cutoff of 55.2 pg/ml, sensitivity = 37.0%, specificity = 58.8%, positive predictive value = 79.4%, and positive likelihood ratio = 3.9 to distinguish between an FTD-related disorder and AD.

CONCLUSION

- **Currently, there are no treatments which slow the progression of Alzheimer's disease (AD)**
- **However, substantial progress has been made towards understanding AD**
- **PHARMA is developing new treatments which are hoped to slow the progression of AD**
- **The ADNI will provide imaging and biomarker data, improved methods, and a network of sites which should greatly facilitate treatment trials, ultimately leading to development of effective therapy**