Texas Alzheimer’s Research Consortium:
Research Update

Stephen C. Waring, DVM, PhD
Research Epidemiologist and Scientific Coordinator
Texas Alzheimer’s Research Consortium

Assistant Professor of Epidemiology, Biological Sciences, and Environmental Science
University of Texas School of Public Health
Healthy Aging
## Alzheimer’s Disease:  
Public Health Impact – Prevalence in 2007

### 5.1 million people in US with Alzheimer’s disease

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Percent</th>
<th>People</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>&lt;1 %</td>
<td>200,000</td>
</tr>
<tr>
<td>65 - 74</td>
<td>2%</td>
<td>300,000</td>
</tr>
<tr>
<td>75 – 84</td>
<td>19 %</td>
<td>2,400,000</td>
</tr>
<tr>
<td>85+</td>
<td>42 %</td>
<td>2,200,000</td>
</tr>
</tbody>
</table>

Every 72 seconds, someone in America develops Alzheimer’s disease; by 2050, it will be every 33 seconds

There are no formal studies to estimate the true occurrence of Alzheimer’s disease in Texas.

Estimated that over 300,000 people in Texas currently have Alzheimer’s disease.

Expected to be over 700,000 by the year 2030.

A number of factors need to be taken into account such as the demographic makeup (age, sex, race/ethnicity) of the population.

Why AD, Why Now?:
Trends in life expectancy, 1900 - 2003
Alzheimer’s Disease
Neuropathologic Course over Time

- Genetic risk factors
  - Misfolding & aggregation of AB & Tau, followed by plaques & tangles
  - Oxidative, nitrosative, & inflammatory damage
    - Cell death

CLINICAL DIAGNOSIS
- MCI
- Probable AD

Autopsy

Treatment Options
- PREVENTATIVE
- MODIFYING
- SYMPTOMATIC

NIA-ADNI, 2005
Alzheimer’s Disease
Risk/Protective Factor Timeline

- Risk factors
  - Genetic risk factors
  - SES-related factors
  - Life habits (e.g., smoking)
  - Hypertension and other vascular risk factors
  - Occupational exposure
  - Vascular risk factors
  - Vascular diseases
  - Depression
  - Head trauma
  - HRT(?)

- Protective factors
  - High education
  - Antihypertensive drugs
  - Rich social network
  - Mental activities
  - Physical activities
  - Diet: fish, vegetables, moderate alcohol
  - Antihypertensive drugs, statins, NSAIDs, HRT(?)

Fratigioni et al. Lancet Neurology 2004
Texas Alzheimer’s Research Consortium:
Overview of Current Research

Established in 1999 by the 76th Texas Legislature

2007 Population*
Overall: 23,523,700
60+ YRS: 3,354,600

* From US Census Bureau
Texas Alzheimer’s Research Consortium:  
*Timeline*

June 2005 - 79th Texas Legislature appropriated funds to support Consortium research

All activity presented to the Texas Council on Alzheimer’s Disease and Related Disorders for approval based on recommendations of the TARC Steering Committee*

<table>
<thead>
<tr>
<th>Consortium research initiated; creation of minimum database (MDS)</th>
<th>Longitudinal study (LDS) proposals solicited, reviewed, and selected by Oct</th>
<th>Protocols, IRB approvals finalized; recruitment begins</th>
<th>80th legislature appropriated additional funding for next biennium</th>
<th>Plans for research activity for the next biennium finalized</th>
</tr>
</thead>
</table>

*TARC Steering Committee:*
- Dr. Rachelle Doody (Baylor College of Medicine)
- Dr. Randall Schiffer (Texas Tech University Health Science Center)
- Dr. Thomas Fairchild (University of North Texas Health Science Center)
- Dr. Perrie Adams (University of Texas Southwestern Medical Center)
Texas Alzheimer’s Research Consortium:
Goals of the Consortium

- Establish a scientific focus that puts us at the forefront of Alzheimer’s disease research
- Attract collaborations with researchers throughout the Consortium member institutions as well as outside
- Compete for external funding from government and non-government entities in crucial areas of Alzheimer’s disease research such as genetic, molecular, clinical epidemiology, pharmacogenomics, treatment/prevention trials
Texas Alzheimer’s Research Consortium: Research Database Structure and Flow

1. standardized clinical exam
2. data acquisition
3. data forms completed and verified
4. sent to data management system

DNA Serum

Clinical Data

Tissue Handling/Storage System at UTSW

Genetic Analysis

Biomarker Analysis

Data Management System at UTSW

Investigator-initiated research projects
Administrative reporting Planning
Texas Alzheimer’s Research Consortium:
Overview of Current Research

Research Personnel

At each member Institution

- Investigators
  - Director, Neurologists, Clinicians, Nurses, Psychometricians, Neuropsychologists, Neurogeneticists, Epidemiologists, Neuroscientists, Neurobehavioral Scientists, Research Support

- Project Coordinator

- Data Management Team

Consortium Data Coordination and Management

- Statisticians, Data Analysts, Programmers, Data Entry, Bioinformatics, Epidemiologists, Website development/Management

Analysis

- Statisticians, statistical genetics, geneticists, molecular scientists, bioinformatics
Minimum Database (MDS)

- To provide cross-sectional demographic and limited clinical information on individuals recruited for studies of aging and dementia at all member sites
- Similar format and content to the National Alzheimer’s Coordinating Center (NACC) Minimum Data Set (MDS)
- Provides a ‘gateway’ to information useful for planning studies or analyses
## MDS Baseline Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Overall</th>
<th>Initial Visit 2001 – 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2067</td>
<td>1002</td>
</tr>
<tr>
<td>Female</td>
<td>3494</td>
<td>1852</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>4521</td>
<td>2362</td>
</tr>
<tr>
<td>Black</td>
<td>438</td>
<td>174</td>
</tr>
<tr>
<td>Hispanic</td>
<td>489</td>
<td>221</td>
</tr>
<tr>
<td>Other</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>2790</td>
<td>1238</td>
</tr>
<tr>
<td>Non-AD dementia</td>
<td>672</td>
<td>264</td>
</tr>
<tr>
<td>MCI or CDR=0.5</td>
<td>322</td>
<td>220</td>
</tr>
<tr>
<td>Non-demented control</td>
<td>1230</td>
<td>742</td>
</tr>
</tbody>
</table>

Data lock: 10/01/06
Texas Alzheimer’s Research Consortium: Overview of Current Research

MDS Presentation/Publication

**Staging Dementia Severity with CDR Sum of Box Scores: An investigation by the Texas Alzheimer’s Disease Research Consortium (TARC)**

Sid E. O’Bryant, Stephen Waring, Munro Cullum, James Hall, Laura Lacritz, Paul Massman, Rachelle Doody, Philip Lupo, Joan Reisch, and the Texas Alzheimer’s Research Consortium

Abstract in press: *Archives of Clinical Neuropsychology*

- MDS allowed a study of Clinical Dementia Rating (CDR) scale to be presented at the annual conference of the National Academy of Neuropsychology, November 11-14, 2007 in Scottsdale, AZ
- Manuscript to be submitted to peer-review journal
Texas Alzheimer’s Research Consortium: Overview of Current Research

**Longitudinal Database Study (LDS)**

**Research Objectives:**

- To identify potential genetic factors associated with earlier age at onset among patients with AD
- To examine the association between inflammation and AD and determine whether inflammation mediates the effect of cardiovascular risk factors on development of AD
Texas Alzheimer’s Research Consortium:  
Overview of Current Research

**Longitudinal Database Study (LDS):**

Specific Aim 1

To identify novel genes associated with earlier age of onset among patients with AD.

Employing sophisticated bioinformatic and statistical genetic tools to perform a genome-wide association analyses on 500 well characterized AD patients
Texas Alzheimer’s Research Consortium: 
*Overview of Current Research*

**Longitudinal Database Study (LDS):**

Specific Aim 2.

To identify polymorphisms in genes related to inflammatory function that are associated with earlier age of onset of AD

Utilizing the same tools and methods applied in Specific Aim 1, genome-wide association analyses will be performed on 100 well characterized cognitively normal controls and compared to results generated for the 500 AD patients.
Texas Alzheimer’s Research Consortium:
Overview of Current Research

**Longitudinal Database Study (LDS):**

Specific Aim 3

To test the hypothesis that patients diagnosed with Alzheimer’s disease (AD) will demonstrate a significantly different inflammatory profile relative to healthy controls.

Inflammatory markers (α1-antichymotrypsin, IL-1ra, IL-1β, IL-4, IL-6, IL-8, IL-10, INFγ, CRP, and TNFα) will be analyzed from serum samples collected on all participants and subjected to a multivariate analysis of variance profile analysis.
Specific Aim 4

To test the hypothesis that inflammation mediates the relation between cardiovascular disease and Alzheimer’s disease.

Markers of cardiovascular disease and cardiovascular risk factors (hypertension, hyperlipidemia, and diabetes) will be examined to first replicate the previously established relation between cardiovascular disease and AD and then to determine whether inflammatory markers mediate this relationship.
Texas Alzheimer’s Research Consortium:
Overview of Current Research

**Longitudinal Database Study (LDS): Methods**

- **Study population**
  - 500 Individuals with Probable AD
    - All participating in genetic study
    - 100 participating in biomarker pilot study
  - 100 Cognitively normal individuals
    - All participating in both genetics and biomarker study

- **Eligibility**
  - Must be at least 55 years of age and meet criteria for Probable AD or normal control
  - Must have requisite study information and provide DNA (genetics study) and serum (biomarker study participants only)
  - Excluded if have preexisting conditions that would influence findings

- **IRB approved consent obtained on all participants**
Texas Alzheimer’s Research Consortium:  
Overview of Current Research

**Longitudinal Database Study (LDS): Methods**

- **Examination procedures**
  - Clinical evaluation - clinical, neurological examination, establish age at onset, document cardiovascular disease and risk factors
  - Neuropsychological Core Battery
    - Global cognitive functioning/status (MMSE and CDR)
    - Attention (Digit Span and Trails A)
    - Executive function (Trails B and Clock Drawing)
    - Memory (WMS Logical Memory I and WMS Logical Memory II)
    - Language (Boston Naming and FAS Verbal Fluency)
    - Premorbid IQ (AMNART)
    - Depression (Geriatric Depression Scale (GDS))
Texas Alzheimer’s Research Consortium: Overview of Current Research

Methods: Laboratory analysis

Genome-wide association study

- involves rapidly scanning large samples for markers (SNPs) across complete sets of DNA to find genetic variations associated with a particular disease or trait
- new genetic associations identified lead to development of better strategies to detect, treat and prevent disease
- particularly useful in finding genetic variations that contribute to common, complex diseases, such as AD among others (diabetes, cardiovascular, etc)
- Association of genetic variations with disease (or trait) in these markers serve to point to the region of the human genome where the disease-causing problem resides and ultimately identification of the actual gene involved
- TARC will be using the Affymetrix 6.0 GeneChip®
  - allows interrogation of ~1,000,000 SNPs
  - In use by several large studies of diabetes, cardiovascular disease, and others
- Genotyping of first samples to begin in September, expected to be completed by end of year (500 cases, 100 controls)
Biomarker study

- Serum samples on 100 cases and 100 controls will be shipped to Rules Based Medicine in Austin, Texas for analysis
- multiplex assays of α1-antichymotrypsin (ACT), interleukin-1 receptor antagonist (IL-1ra), IL-1β, IL-4, IL-6, IL-8, IL-10, interferon gamma (INFγ), C - reactive protein (CRP), and tumor necrosis factor alpha (TNFα)
- takes advantage of emerging technology offered by RBM called Multi-Analyte Profiles (MAPs), a large panel of tests that provide accurate and precise measurement of numerous biological markers of cancer, infectious disease, autoimmunity, cardiovascular risk, as well as hormones, growth factors, and numerous other proteins in the blood
To date, three genes identified (familial AD)

- younger age at onset (< 55 yrs of age)
- rare, fully penetrant autosomal dominant mutations
- cause abnormal amyloid precursor protein (APP) processing, overproduction of A-β_{1-42}
  - amyloid precursor protein (APP) gene - CH21
  - presenilin 1 (PSEN1) gene - CH14
  - presenilin 2 (PSEN2) gene - CH1
- account for <5% of all AD (majority due to PSEN1)
Apolipoprotein E - Chromosome 19

- Best characterized polymorphism
- accounts for up to 50% of late onset AD
- ε-4 allele associated with increased risk of developing AD
  - heterozygous (2/4, 3/4) - 2-5 fold increase
  - homozygous (4/4) - 10-15 fold increase
- earlier age at onset
  - heterozygous (2/4, 3/4) - 5-10 yrs
  - homozygous genotype (4/4) - 10-20 yrs
- also risk factor for atherosclerosis, myocardial infarction, and stroke
TARC Study of the Genetics of AD
Background: Genetic Risk Factors

Recent findings

**SORL1** (Chromosome 11; Rogaeva et al. Nature Genetics 2007)
- SORL1 levels are reduced in brains of individuals with AD
- SORL1 binds to APP; overexpression reduces Aβ production
- SORL = sortilin-related receptor lipoprotein

**DAPK1** (Chromosome 9; Li et al. Hum Mol Genetics 2006)
- DAPK1 plays a pro-apoptotic role in the programmed cell death cascade, including neuronal apoptosis
- Predominantly expressed in the brain (hippocampus, cortex most severely affected regions)
- DAPK = death associated protein kinase
TARC Study of biomarkers in AD
Background: Biomarker Basics

Definition

- characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (NIH Working Group, 2001)

Types (Vasan Circulation 2006)

- marker of the natural history of a disease and correlates longitudinally with known clinical indices
- marker that captures the effects of a therapeutic intervention in accordance with its mechanism of action
- marker intended to be a surrogate end point expected to predict clinical benefit/lack of benefit/harm based on scientific evidence (clinical, epidemiological, treatment trials, etc)
Candidate markers fall under four main biological rationales:

- specific markers of AD neuropathology
- non-specific markers of neurodegeneration
- markers of oxidative stress
- markers of neural inflammation
Consensus panel on molecular and biochemical markers of AD, ideal biomarker should:

- detect a feature of underlying pathology of AD
- have high sensitivity and specificity
- be reliable, non-invasive, easy to perform, and inexpensive
- be validated in peer-reviewed publications

TARC Study of biomarkers in AD

Background: Ideal Candidates for AD

Growdon JH Arch Neurol 1999
TARC Study of biomarkers in AD
Background: Best Candidates to Date

<table>
<thead>
<tr>
<th>Source</th>
<th>Biomarker</th>
<th>Associated Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>low Aβ 1-42</td>
<td>amyloid plaques</td>
</tr>
<tr>
<td>CSF</td>
<td>elevated p-tau</td>
<td>neurofibrillary tangles</td>
</tr>
<tr>
<td>MRI</td>
<td>medial temporal atrophy</td>
<td>neuronal cell/synaptic loss</td>
</tr>
</tbody>
</table>
Several reports of inflammatory proteins involved in AD
- both anti- and pro-inflammatory mechanisms
  - α1-antichymotrypsin
  - Interleukins (IL-6, IL-1β, IL-1ra)
  - C-reactive protein (CRP)
  - Tumor necrosis factor-α (TNFα)
  - others

No studies have simultaneously evaluated a range of inflammatory markers to compare inflammatory profiles of AD patients to that of non-AD control participants.
Numerous reports linking cardiovascular disease and AD

- midlife hypertension as a risk factor for development of AD
- diabetes, hyperlipidemia, smoking, and obesity have been linked with AD in several studies
- presence of multiple CVD factors puts an individual at increased risk over and above any one marker
- possible role of inflammation on the associations between CVD and AD remains largely uninvestigated
- Only two studies have reported on this but only assessed a very limited group of markers (CRP, TNF-alpha / IL-10 ratio)

We will examine the role of inflammation as a mediating variable between CVD and AD and will have the significant advantage of including multiple inflammatory markers.
What we need to know:
Clinical utility of genetic/biomarker discovery

- Improved understanding of pathophysiology
- Potential for rational drug development
- Potential for pharmacogenomic effects, targeted treatments and preventive strategies
- Potential role in early detection and early intervention
- Potential role in risk assessment and prophylaxis
Alzheimer’s disease likely results from genetic variants that alter either the production or processing of β-amyloid and other proteins.

**Large scale initiatives**
- Texas Alzheimer’s Research Consortium to identify genes and biomarkers
- NIA LOAD Genetics Initiative to identify genes with large and small effects and gene-gene, gene-environment interactions
- NIA ADNI (Neuroimaging Initiative) to assess role of clinical, imaging, biomarkers over time

**Coordinated efforts with cardiovascular and other studies not only efficient but may improve ‘the fit’ in determinant models**

**Impact of disease on caregiver health**
What we need to know:
Goals of AD Research

**Slowing progression**
- enhance quality of life for patient and family

**Delaying onset**
- lower prevalence; reduce burden on health care

**Prevention**
- any reduction in incidence is a significant impact
Public health impact of delaying effect

- Onset 3-5 yrs later
- Institutionalized 5-10 yrs later
- Significant reduction in PH burden of disease
Impact of Healthy Aging
Combined Effects of Age and Age-Related Disease

Theoretical effect of preventing age-related diseases
(Hekimi Nature Genetics 2006)

Morbidity profiles of centenarians
(Evert et al, J Gerontol 2003)
Texas Alzheimer’s Research Consortium:  
*Summary*

- Research focus is centered on novel genetic and biomarker studies to address questions that take advantage of the collective expertise and research interest at each member site.

- Multidisciplinary study will provide a robust dataset of prospectively collected clinical, genetic, and biological data from subjects with sufficient follow-up to address an unlimited number of research questions now and into the future.

- This study population is not currently available at individual sites and would be difficult to assemble at a single site due to inherent budget, resource, and recruitment constraints.
Texas Alzheimer’s Research Consortium: 
Acknowledgements

- **BCM**
  - Dr. Rachelle Doody
  - Dr. Kinga Szigeti
  - Dr. Paul Massman
  - Dr. Norma Cooke
  - Violetta Capriles
  - Eveleen Darby

- **TTU-HSC**
  - Dr. Randall Schiffer
  - Dr. Sid O’Bryant
  - Dr. Parastoo Momeni
  - Dr. Y Xhang
  - Merena Tindall
  - Larry Hill

- **UNT-HSC**
  - Dr. Thomas Fairchild
  - Dr. Janice Knebl
  - Dr. James Hall
  - Dr. Doug Mains
  - Dr. Neeraj Agarwal
  - Jessica Alexander
  - Debbie Hanna
  - Jim Hinds
  - James Crowson
  - Janis Monger
  - Texas Council on Alzheimer’s Disease and Related Disorders

- **UTSW**
  - Dr. Perrie Adams
  - Dr. Ramon Diaz-Arrastia
  - Dr. Roger Rosenberg
  - Dr. Joan Reisch
  - Dr. Munro Cullum
  - Dr. Laura Lacritz
  - Doris Svetlik
  - Keverly Williams
  - Joe Webster
  - Joey Naylor
We don't stop playing because we grow old;
we grow old because we stop playing

George Bernard Shaw
Where to find additional information

- ADEAR (AD Education and Referral):  www.alzheimers.org
- Alzheimer’s Association:  www.alz.org
- Alzheimer’s Research Forum:  www.alzforum.org