Fall ADRC Directors Meeting
National Institute on Aging
Chicago, ILL
October 20, 2022

“Division of Neuroscience Update”

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National Institute on Aging, NIH
NIA Approach to AD/ADRD research

Aging Genetics
- Proteostasis defects
- Mitochondria dysfunction
- Oxidative stress
- Epigenetic alterations
- DNA damage
- Senescent cells
- Immune surveillance

Aging
- Toxins, Pollution, Heavy metals, Trauma, Infectious agents

Genetics
- APP/Abeta
- APOE4
- Presenilin
- Inflammation genes
- Endosomal genes
- Synaptic genes
- Lipid metabolism genes

Environment
- Neurodegeneration
  - Synapse damage
  - Neuronal loss
  - Vascular damage
  - Inflammation

Proteinopathy
- Abeta
- Tau
- Synuclein
- TDP43

Accounts for 70% of the variance

Diagnosis → MCI/Dementia ← Therapeutics
Progress in AD/ADRD research at a time of increased funding

- **NIA funded over 400 clinical trials**
- **PET imaging, CSF biomarkers**
- **NAPA and increased NIH funding for AD/ADRD**
- **Plasma biomarkers**
- **COVID19**
- **Lecanemab and other Mabs**

**Inclusion of DIVERSITY in research**

**NIA supported data sharing and harmonization**

**Immune, endosome, Synaptic, Lipid metabolism, APP, Signaling pathways**

**2025**

**Precision Medicine**
Division of Neuroscience NIA Diversity awards

Total number of all applications (competing, non-competing, supplements, centers, training and research) = **598**
Total number of all new applications (Types 1,2,3) = **291**

DN Awards by Fiscal Year

<table>
<thead>
<tr>
<th>Year</th>
<th>AD/ADRD</th>
<th>Non AD/ADRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>15</td>
<td>3</td>
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<tr>
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<td>3</td>
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<tr>
<td>2021</td>
<td>13</td>
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% of Awards by area of research FY17-21

- **POPULATION STUDIES & GENETICS**: 45.4%
- **CLINICAL INTERVENTIONS & DIAGNOSTICS**: 35.1%
- **BEHAVIORAL & SYSTEMS NEUROSCIENCE**: 12.7%
- **NEUROBIOLOGY OF AGING & NEURODEGENERATION**: 6.8%
- **TRANSLATIONAL RESEARCH**: 0.2%

Total number of all applications (competing, non-competing, supplements, centers, training and research) = **598**
Total number of all new applications (Types 1,2,3) = **291**
NIA released the National Strategy for Recruitment and Participation in AD/ADRD Clinical Research and expanded efforts to include diverse populations in NIA-funded research.
ADNI-4 Increasing Generalizability by Enrollment of a Diverse Population

PI: Mike Wiener, UCSF
NIA Program Directors: John Hsiao, Laurie Ryan

Goal: 500 rollover participants and 500 new participants” 40% MCI, 40% CN, 20% Dem (50-60% diverse populations)

- > 59 sites
- Clinical, blood, LP
- Cognitive Tests
- MRI: all types
- FDG/amyloid/tau PET
- LP: CSF Ab/tau
- Genetics
- Neuropathology

All data in public database: USC/LONI/ADNI: No embargo of data

- NEW Engagement Core- Drs Rivera-Mindt and Okonkwo PI’s
- Enroll 50-60 % of new participants from URPs (African-American, Latino, Asian)
- Facilitate “Community Engaged Research” expanded Community Science Partnership Board
- At least 15 ”hub sites” with full time recruiters
- Digital marketing-social media enroll 20,000 into an on-line screener.
  4000 of these will have blood drawn at local Quest Centers for blood testing
  “Telephone help desk” to facilitate URP participation

http://adni.loni.usc.edu/
Plasma biomarkers in ADNI

- Combined clinical information, plasma p-tau 181 and Nfl and an MRI-score identify Abeta cognitively unimpaired and impaired (area under curve, 0.80–0.90)
- Plasma Abeta improves with age and APOE

CSF Synaptic biomarkers

- CSF synaptic biomarkers, particularly NPTX2, relate to cognition and predict progression in AD beyond Ab1-42 and Tau.

Tosun et al in Brain Comm 2021

Galasko et al in Alz Dem 2019
Health Disparities

PI’, Sid O’Bryant, UNTHSC
NIA Program Directors: Damali Martin

- Total= 3500 participants
- 1,500 Mexican Americans (>1,000 enrolled)
- 1,500 Blacks/African Americans (>700 enrolled)
- 1,500 non-Hispanic whites (>1,000 enrolled)
- 24-month follow-up intervals (>1,000 V2 completed)
- Community-based research approach.
- Engage community leaders, organizations
- “Give Back” to the community
- Be part of the community, always present

Data sharing via LONI
https://apps.unthsc.edu/itr/request/hd

- Functional exam
- Clinical labs
- Sociocultural, environmental and behavioral factors
- Item-level data entry
- Neuropsychological assessment
- Biorepository (n>500,000 aliquots available)
- Multi-level “omics”
- Amyloid and Tau PET Scans
- 3T MRI

A. Admin
B. Neuro Imaging
C. Clinical
D. Omics
E. Disparities
F. Stats
G. Development
Health Disparities

<table>
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<tr>
<th>Visit 1</th>
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<tr>
<td>Mexican American</td>
<td>1122</td>
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<tr>
<td>White</td>
<td>1094</td>
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<tr>
<td>African American</td>
<td>634</td>
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<tr>
<td>White</td>
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<td>African American</td>
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<th>Visit 3</th>
<th>Total</th>
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<td>Mexican American</td>
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<tr>
<td>White</td>
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<td>African American</td>
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<table>
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<tr>
<th>Amyloid PET</th>
<th>Tau PET</th>
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<tbody>
<tr>
<td>White</td>
<td>654</td>
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<tr>
<td>Mexican American</td>
<td>489</td>
</tr>
<tr>
<td>African American</td>
<td>548</td>
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<table>
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<tr>
<th>AT(N) Positivity By Race/Ethnicity</th>
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<tbody>
<tr>
<td>AA</td>
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<tr>
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<tr>
<td>A</td>
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<tr>
<td>T</td>
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<tr>
<td>N</td>
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</tbody>
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- ATN-biomarkers are differentially prevalent among diverse pop
- ATN-biomarkers are differentially related to clinical outcomes
- Clinical, demographic and sociocultural factors are differentially related to ATN-defined and cognitive outcomes
- Precision medicine requires inclusion of diverse communities

O'Bryant et al in preparation
Main objective: What are the determinants and mechanisms of AD/ADRD among persons with PreD and T2D?

- 25 clinical sites and core functions across > 30 institutions in the US
- NACC UDS clinical measures
- Legacy DPPOS measures
- MRI and Abeta PET in a third of participants (one wave in 650 of 1900 participants)
- Plasma AD biomarkers in all participants
  - Amyloid beta 40 and 42
  - ptau-231
  - GFAP
  - NFL

Data sharing via NACC and NIDDK
PreD and T2D clinical AD/ADRD Studies in a diverse US population

Excellent retention 48% underrepresented minorities

<table>
<thead>
<tr>
<th>Ethnic and racial group (%)</th>
<th>DPDP</th>
<th>DPPOS</th>
<th>DPPOS</th>
<th>DPPOS</th>
<th>DPPOS</th>
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<tbody>
<tr>
<td>Hispanic</td>
<td>508 (16%)</td>
<td>424 (15%)</td>
<td>368 (14%)</td>
<td>347 (15%)</td>
<td>312 (15%)</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>1768 (54%)</td>
<td>1506 (54%)</td>
<td>1360 (54%)</td>
<td>1194 (52%)</td>
<td>1030 (52%)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>645 (20%)</td>
<td>558 (20%)</td>
<td>511 (20%)</td>
<td>472 (20%)</td>
<td>406 (20%)</td>
</tr>
<tr>
<td>American-Indian</td>
<td>171 (6)</td>
<td>153 (5)</td>
<td>148 (5)</td>
<td>144 (6)</td>
<td>132 (6)</td>
</tr>
<tr>
<td>Asian American/Pacific Islander</td>
<td>142 (5)</td>
<td>124 (4)</td>
<td>116 (4)</td>
<td>104 (5)</td>
<td>96 (5)</td>
</tr>
</tbody>
</table>

APOE 4 genotype strongly related to higher amyloid burden in vivo (amyloid PET), despite controversy on whether APOE genotype predicts AD in Hispanics

• In a multiethnic urban cohort of 252 persons with a mean age of 64 years with MRI, amyloid PET, and Tau PET, females had higher amyloid and tau burden compared with men, despite better memory and thicker cortices.
Alzheimer’s Disease Sequencing Project

100,000 WG by 2025 includes diverse population

- Over 75 risk loci and 20 genes (from the 75 loci) for AD identified

- Examples: BIN1, TREM2, CR1, PCALM, ADAM10, ABCD4, PLGC2, ANAX5, MEF2

- Involved in immune, neuronal/synaptic, endocytosis, lysosome and lipid metabolism

- Common polygenic variation increases risk prediction (APOE+others)

Work Groups across consortia

Scientific collaboration and resource sharing
ADSP Follow-Up Study (FUS) 2.0: Diversity Initiative (PAR21-212) (FY2023-2028)

- WGS 18,500 cases and 18,500 controls African, Hispanic, and Asian ancestry
- Estimate assembling 130,000~150,000 genomes by 2027-2028
- Case control, epidemiologic, and family-based
- International collaborators: India, Africa, Mexico, Central and South America, Korea, Australia

Release 3, 16,906 WGS, 2021
Release 4, 36,361 WGS, 2022

- Sample acquisition
- Genotyping
- Whole genome sequencing
- Quality control
- Variant calling
- Data calling
- Data sharing
- Data harmonization
- Analysis
- Functional genomics
- Machine Learning
Recruitment and Retention for AD Diversity Genetic Cohorts in the ADSP (REAAD-ADSP)

**University of Miami**
Margaret Pericak-Vance
Brian Kunkle
Jeffery Vance

**Wake Forest University**
Goldie Byrd

**Columbia University**
Giuseppe Tosto
Christiane Reitz

**University of Ibadan**
Rufus Akinyemi
Adesola Ogunniyi

**Case Western Reserve University**
Jonathan Haines
Will Bush

- DNA, RNA, Plasma Biomarkers and CVD markers
- Whole Genome Sequencing
- Social Determinants of Health (SDOH)
- Provide the basis for integrated studies of biological and social risks of AD.

*AfDC; African Dementia Consortium*
Examples of ADSP Foreign Cohorts in Asia

Gwangju Alzheimer’s & Related Dementias (GARD) Study – Korea

PI: Lindsay Farrer (Boston University)
Korea site PI: Kunho Lee (Chosun University)

KBASE2: Korean Brain Aging Study, Longitudinal Endophenotypes and Systems Biology

PI: Andrew Saykin (Indiana University)
Korea site PI: Don Young Lee (Seoul National University)

Aspirin in Reducing Events in the Elderly (ASPREE) Trial cohort – Australia

PI: Paul Lacaze (Monash University)

Longitudinal Aging Study in India – Diagnostic Assessment of Dementia (LASI-DAD) – India

PI: Jinkook Li (University of Southern California)

Association Between Episodic Memory and Genetic Risk Factors for Alzheimer’s Disease in South Asians from the Longitudinal Aging Study in India–Diagnostic Assessment of Dementia (LASI-DAD)

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>$\beta$</th>
<th>$P$ value</th>
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<tbody>
<tr>
<td>rs2830500</td>
<td>ADAMTS1</td>
<td>-.38</td>
<td>.003</td>
</tr>
<tr>
<td>rs10948363</td>
<td>CD2AP</td>
<td>.35</td>
<td>.004</td>
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<tr>
<td>rs9473117</td>
<td>CD2AP</td>
<td>.36</td>
<td>.009</td>
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<tr>
<td>rs4147929</td>
<td>ABCA7</td>
<td>.29</td>
<td>.03</td>
</tr>
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Examples of Latin American and Hispanic Cohorts

**WHICAP** - Washington Heights, Hamilton Heights and Inwood
PI: Richard Mayeux et al (Columbia U)

**EFIGA** - Estudio Familiar de Influencia Genetica en Alzheimer
Only PINX1 and TREM2 survived replication rom IGAP and EFIGA
PI: Richard Mayeux et al (Columbia U)

**Studies of Amerindian populations in South America – Peru and Bolivia**
1,700 dementia cases and 1,850 healthy controls
PI: Giuseppe Tosto (Columbia U), Margaret Pericak-Vance, Eden R (U. Miami). Martin, Mario Cornejo-Olivas (Bolivia), Nilton Custodio (Peru)
ADSP Follow-Up Sequencing (FUS) 2.0: Diversity Initiative

- Twice as frequent in AA as in Non-Hispanic Whites (NHW)
- ABCA7 protein is involved in APP processing (endosomal compartment)
- Frame shift deletion was found in AA, but was absent in NHW
- This deletion is a common ethnic specific variant

Position of rare coding mutations identified in SORL1 in relation to common SNPs (Vardarajan, Annals of Neurology, Feb 2015)

Ancestral origin of ApoE ε4 Alzheimer disease risk in Puerto Rican and African American populations

Compared with individuals with European APOE-ε4 local ancestry
- those with African local ancestry have lower risk of AD
- those with Amerindian local ancestry have higher risk
Study to Expand Registry Participation of Underrepresented Populations (STEP-UP)

MPIs: Jessica Langbaum, (Banner Alzheimer’s Institute) & Amy Bleakley, (University of Delaware)
Co-Investigators: Rachel Nosheny, (UCSF) and Jason Karlawish, (Univ Pennsylvania)
NIA program director: Cerise Elliott

COVID-19 Supplement
Aim 1: COVID-19 news coverage and willingness to participate in AD-related research
Conducted cross-sectional national surveys stratified by racial and ethnic groups over 12mo to monitor how changes in the pandemic and news coverage may be related to attitude shifts

Aim 2: Identify determinants of COVID-19 related health behaviors
Bleakley et al., Ann Behav Med, 2022
Study to understand Black, Hispanic and older adults willingness to participate in AD Registries

Interviews in 60 adults (20 White, 20 Hispanic, 20 Black; equal numbers of men and women) (Bleakley et al JAD 2022)
• Few differences between racial, ethnic or sex groups some differences in behavioral beliefs

National survey in 1500 adults ages 50-80, oversampling for Black & Hispanic respondents (in preparation for submission to Alz & Dementia)
• No differences in intention to join a registry by race, ethnicity or sex

• White women were more likely than White men to take memory & thinking tests every 6mo;

• White women were more likely than Hispanic men to provide family member contact info;

Bleakley et al JAD 2022
Translating AD/ADRD studies in diverse populations to personalized medicine


Data Harmonization*

Genetic and Genomic Data
Multi-OMICS Data
Clinical Data
Biomarkers Data
Neuropath Data

ADSP/NEW COHORTS
ADRC's, DIVERSE DPPOS, COHORTS
AMP-AD DIVERSITY
ADNI4, HABS-HD, ACTC

NIAGADS
NACC
AD Knowledge Portal
LONI

Personalized Medicine
Concept Approvals:  
https://www.nia.nih.gov/approved-concepts

General FOAs:  
https://www.nia.nih.gov/research/funding

Alzheimer’s Disease and Related Dementias FOAs:  
http://www.nia.nih.gov/AD-FOAs

NIA- Division of Neuroscience  
https://www.nia.nih.gov/research/dn