Welcome to the 13th Annual FDA/ACT-AD Allies Meeting!

The program will begin momentarily.

In preparation for the meeting, please:
1. Turn your camera ON
2. MUTE your microphone
3. Rename yourself using the following format: [First Name] [Last Name] – [Org. Name]
13th Annual FDA/ACT-AD Allies Meeting: Common Threads: Learning from the Related Dementias
Agenda

Welcome and Introductions 10:30 AM – 10:40 AM (ET)

The Quest to Develop Biomarkers for Vascular Cognitive Impairment 10:40 AM – 11:00 AM (ET)
Steven Greenberg, M.D., Ph.D., Harvard Medical School/Massachusetts General Hospital

Discussion 11:00 AM – 11:15 AM (ET)

Federal Investment in Alzheimer’s Disease and Related Dementia Clinical Research 11:15 AM – 11:55 PM (ET)
Suzana Petanceska, Ph.D., and Laurie Ryan, Ph.D., National Institute on Aging

Discussion 11:55 PM – 12:15 PM (ET)

Lunch Break 12:15 PM – 12:30 PM (ET)

An Exploration into the Dementia Therapeutic Pipeline 12:30 PM – 12:50 PM (ET)
Jeffrey Cummings, M.D., Sc.D., University of Nevada, Las Vegas

Discussion 12:50 PM – 1:05 PM (ET)

Research into Molecular Underpinning of Dementia 1:05 PM – 1:35 PM (ET)
David Bennett, M.D., Rush Alzheimer’s Disease Center

Discussion 1:35 PM – 1:50 PM (ET)

Dementia Clinical Development Questions and Challenges: Industry Perspective 1:50 PM – 2:25 PM (ET)
Samantha Budd Haebelerin, Ph.D., Biogen, Sanjay Dube, M.D., Avanir, and Eva Kohegyi, M.D., M.S., Otsuka

Closing Remarks 2:25 PM – 2:30 PM (ET)
Housekeeping Rules

At the start of the meeting:
• Turn your camera ON.
• MUTE your microphone
• Rename yourself with the following format: [First Name] [Last Name] – [Org. Name]
  – To rename yourself in Zoon: Click on the “Participants” button (at the bottom of the screen) to open up the Participants Panel.
  – Hover over your name and click on the blue “More” button. Select “Rename.”
  – Enter your name in the format mentioned above. Click the blue “OK” button.
Housekeeping Rules

During Presentations
• Keep your microphone MUTED.
• Submit questions through the Chat feature.
  – To submit a question through the Chat feature: Click the “Chat” button (at the bottom of the screen). The Chat function will pop up.
  – Ensure you are sharing your question with “Everyone” and type your question in the text field.
  – Submit your question by hitting “Enter.”
Housekeeping Rules

During Discussion
• Have your camera ON.
• Your submitted questions will be fielded by the moderators.
• After questions are read, you may UNMUTE your microphone to respond.
• The meeting is a roundtable format, so engagement is encouraged!
Discussion

• Your questions submitted through the Chat feature will be fielded by a moderator.

• After a question is read, you may unmute to respond. Please state your name and affiliation when asking or answering question.

• The meeting is a roundtable format, so engagement is encouraged!
Housekeeping Rules

Technical Issues
• Please reach out to Sarah DiGiovine via email (sdigiovine@agingresearch.org) or the Zoom Chat feature.

Off the Record
• The meeting is off-the-record event. Please do not quote speakers or participants on social media (Twitter, LinkedIn, Facebook, etc.)
ACT-AD Science Advisory Board

Paul Aisen, M.D.
USC Alzheimer’s Therapeutic Research Institute

Phyllis E. Greenberger, MSW
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UNLV School of Allied Health Sciences

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University of Texas, San Antonio

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(Retired) National Institute on Aging

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Brigham and Women’s Hospital
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Thank you for joining us today!

Michael Ward  
Vice President of Public Policy  
Alliance for Aging Research  
mward@agingresearch.org

Ryne Carney  
Manager of Public Policy  
Alliance for Aging Research  
rcarney@agingresearch.org
Taking the shortcut
The quest to develop biomarkers for vascular cognitive impairment

Steven M. Greenberg, MD, PhD
Hemorrhagic Stroke Research Program
Massachusetts General Hospital
& Harvard Medical School

Accelerate Cures/Treatments for All Dementias
FDA/ACT-AD Allies Meeting
February 3, 2021
Disclosure

Work supported by grants from the US National Institutes of Health (R01NS070834, R01AG26484, R01NS096730, U24NS100591)

Safety monitor for AD (DIAN-TU, Roche, Biogen), anticoagulant (Bayer) trials
Thanks to....

MarkVCID
Kristin Schwab  Karl Helmer  Pia Kivisakk-Webb  Herpreet Singh
Rod Corriveau  Hanzhang Lu  Joel Kramer  Gary Rosenberg
Julie Schneider  Sudha Seshadri  Danny Wang  Donna Wilcock

Martinos Center/MGH Radiology
Hemorrhage Research Program  Keith Johnson  Jon Polimeni
Anand Viswanathan  M. Edip Gurol  David Salat  Bruce Fischl
Andreas Charidimou  Elif Gokcal
Kristin Schwab  Vanessa Gonzalez  Zora DiPucchio  Mitchell Horn
Nicholas Raposo  Yael Reijmer  Grégoire Boulouis  Marco Pasi

Center for Human Genetic Research
MassGeneral Institute for NeuroDegeneration  Jon Rosand
Susanne van Veluw  Brian Bacskaï  Chris Anderson
Brad Hyman  Matthew Frosch  Alessandro Biffi
Dementia Burden
The coming storm

Dementia prevalence (US, millions)

Onset delayed 5 yrs

Data from Alzheimer’s Association
Dementia Burden
Role of the AD-related dementias (ADRDs)

Boyle, Schneider Religious Orders/ Rush Memory and Aging
*Ann Neurol* 2018;83:74

<table>
<thead>
<tr>
<th>Path present (n=1079)</th>
<th>Proportion cog decline when present</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>704</td>
</tr>
<tr>
<td>Gross infarcts</td>
<td>388</td>
</tr>
<tr>
<td>Cerebral amyloid angiopathy</td>
<td>386</td>
</tr>
<tr>
<td>TDP-43</td>
<td>377</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>358</td>
</tr>
<tr>
<td>Arteriolosclerosis</td>
<td>338</td>
</tr>
<tr>
<td>Cortical Lewy bodies</td>
<td>143</td>
</tr>
<tr>
<td>Hippocampal sclerosis</td>
<td>112</td>
</tr>
</tbody>
</table>
ADRD Recommendations
Call for biomarkers

Table 1: Topic area 1: Research recommendations for tau

<table>
<thead>
<tr>
<th>Focus area</th>
<th>Priority</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic science</td>
<td>1</td>
<td>Clarify the mechanism of tau pathogenesis and associated neurodegeneration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>using well-defined cohorts with DLB or PSP who have come to autopsy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systematically map disease-specific changes in the brain, spinal cord, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>peripheral autonomic nervous system with state-of-the-art methods, including</td>
</tr>
<tr>
<td></td>
<td></td>
<td>genomics, proteomics, metabolomics, and proteomics to identify underlying</td>
</tr>
<tr>
<td></td>
<td></td>
<td>disease mechanisms that will guide future biomarker and therapeutic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>approaches.</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Develop better FTD in vivo and cell-based model systems</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Determine the molecular basis for C9orf72 expansion-related and GRN-related</td>
</tr>
<tr>
<td></td>
<td></td>
<td>neurodegeneration</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Determine the mechanism of TDP-43 and FUS pathogenesis and toxicity</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Develop imaging approaches to enhance the diagnostic accuracy of DLB and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PSP, detect latent and prodromal DLB and PSP, and monitor disease progress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in natural history and treatment studies by integrating established and new</td>
</tr>
<tr>
<td></td>
<td></td>
<td>imaging tools</td>
</tr>
<tr>
<td>Clinical science</td>
<td>1</td>
<td>Expand efforts to genotype patients with FTD and identify new genes</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Develop FTD biomarkers for diagnosis and disease progression</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Create an international FTD clinical trial network</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Understand phenotypic heterogeneity and natural history</td>
</tr>
</tbody>
</table>

Table 5: Topic area 5: Research recommendations for VaD—Small vessel disease and AD/vascular interactions

<table>
<thead>
<tr>
<th>Focus area</th>
<th>Priority</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic mechanisms and experimental models</td>
<td>1</td>
<td>Develop next-generation experimental models of VCI and VaD</td>
</tr>
</tbody>
</table>
Taking the Shortcut
Biomarkers for vascular cognitive impairment

1. Validating SVD biomarkers: MarkVCID
2. Examples of biomarker applications: CAA
Taking the Shortcut
Biomarkers for vascular cognitive impairment

1. Validating SVD biomarkers: MarkVCID

Biomarker
/biˈoʊˌmɑrkər/
noun: biomarker; plural noun: biomarkers

A measurable substance in an organism whose presence is indicative of some phenomenon.
Taking the Shortcut
Biomarkers for vascular cognitive impairment

“Measurable”
• Accessible
• Reproducible across raters, timepoints, sites

“Indicative of some phenomenon”
• Disease susceptibility/risk
• Diagnosis/subtype
• Prognosis/stratification
• Target engagement
• Mechanism of action
• Disease progression
• (Surrogate efficacy)
FDA Biomarker Qualification Program
BEST Biomarker Category/Drug Development Uses

Biomarker Categories

- Diagnostic
  - Patient Selection
  - Detect a change in the degree or extent of a disease

- Monitoring
  - Indicate toxicity or assess safety
  - Provide evidence of exposure

- Predictive
  - Identify individuals on the basis of effect from a specific intervention or exposure

- Prognostic
  - Stratify patients
  - Enrichment: inclusion/exclusion data

- Pharmacodynamic/Response
  - Efficacy biomarker/surrogate endpoint
  - Show biological response related to an intervention/exposure

- Safety
  - Indicate the presence or extent of toxicity related to an intervention or exposure

- Susceptibility/Risk
  - Indicate the potential for developing a disease or sensitivity to an exposure

Context of Use Examples

www.fda.gov/drugs/biomarker-qualification-program/context-use
MarkVCID Biomarkers Consortium

MarkVCID Consortium to identify and validate biomarkers for small vessel disease-related VCID “to the point of being fully ready for large scale multi-site clinical validation studies...and use in clinical trials.”

Coord Ctr
S Greenberg
K Schwab  K Helmer

Site PIs
J Schneider  K Arfanakis
D Wang  J Ringman
A Kashani
J Kramer, C DeCarli
H Lu, M Albert
G Rosenberg, A Caprihan
S Seshadri, M Fornage, R Tracy
D Wilcock, G Jicha

NINDS
Rod Corriveau

External Advisory Committee
R Gottesman, R Petersen
T Montine, GJ Biessels,
B Dunn
MarkVCID Biomarkers Consortium
Timeline

• Years 1-2 (UH2) Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures

  - Clinical/cognitive data collection protocol
  - MRI and OCTA acquisition protocol
  - Fluid collection and handling best practices protocol
  - Broad IRB/consent language allowing unrestricted sharing and repurposing

Wilcock, Jicha, Blacker, Kivisakk, Greenberg et al *Alzheimers Dement* 2020; in press
Lu, Kashani, Arfanakis, Helmer, Greenberg et al *Alzheimers Dement* 2020; in press
MarkVCID Biomarkers Consortium Timeline

• **Years 1-2 (UH2)** Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures

• **Years 3-5 (UH3)** Validate most promising biomarkers across consortium sites
MarkVCID Biomarkers Consortium
Candidate Kits for Validation

<table>
<thead>
<tr>
<th>MRI</th>
<th>Fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH Volume</td>
<td><strong>Plasma Endothelial Growth Factors</strong></td>
</tr>
<tr>
<td>Lead site: UCSF/UCD/UCLA</td>
<td>(VEGF-D, PlGF, bFGF)</td>
</tr>
<tr>
<td>WMH Growth/Regression</td>
<td>Lead site: UCSF/UCD/UCLA</td>
</tr>
<tr>
<td>Lead site: Univ Kentucky</td>
<td><strong>Exosome Endothelial Inflammatory Factors</strong></td>
</tr>
<tr>
<td></td>
<td>(Complement Bb, C3b)</td>
</tr>
<tr>
<td></td>
<td>Lead site: UCSF/UCLA/UCLA</td>
</tr>
<tr>
<td><strong>Peak Skeletonized Mean Diffusivity</strong></td>
<td><strong>Plasma Neurofilament Light Chain</strong></td>
</tr>
<tr>
<td>Lead site: CHARGE</td>
<td>Lead site: CHARGE</td>
</tr>
<tr>
<td>Free Water</td>
<td><strong>CSF Placental Growth Factor</strong></td>
</tr>
<tr>
<td>Lead site: Univ New Mexico/UCSF</td>
<td>Lead site: Univ Kentucky</td>
</tr>
<tr>
<td>Arteriolosclerosis Score</td>
<td><strong>OCTA</strong></td>
</tr>
<tr>
<td>Lead site: Rush</td>
<td>Retinal Vessel Skeleton Density</td>
</tr>
<tr>
<td></td>
<td>Lead site: USC</td>
</tr>
<tr>
<td>Cerebrovascular Reactivity to CO₂</td>
<td></td>
</tr>
<tr>
<td>Lead site: Johns Hopkins</td>
<td></td>
</tr>
</tbody>
</table>
MarkVCID Biomarkers Consortium Timeline

• **Years 1-2 (UH2)** Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures

• **Years 3-5 (UH3)** Validate most promising biomarkers across consortium sites
  - Instrumental validity
  - Biological validity
MarkVCID Biomarkers Consortium
Timeline

• **Years 1-2 (UH2)**  Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures

• **Years 3-5 (UH3)**  Validate most promising biomarkers across consortium sites

  Instrumental validity: Can the biomarker be accurately measured?
MarkVCID Biomarkers Kits
Instrumental Validation

**Fluid-based kits**
1. Intra- & inter-plate repeatability
2. Inter-site reproducibility
   - 40 plasma, 40 PPP, or 20 CSF samples (stratified by SVD severity)
3. Test-retest reproducibility
   - Repeat blood samples from 10 participants/site (half non-controls) at 3 time points

**Imaging-based kits**
1. Inter-rater reliability
   - 30 MRI/OCTA scans (stratified by SVD severity)
2. Test-retest repeatability
   - Repeat MRI/OCTA on 6 individuals/site at 2 time points
3. Inter-site reproducibility
   - 20 individuals (10 with SVD) traveling to 4 MRI scanner types in Boston & Baltimore
MarkVCID Biomarkers Consortium
Timeline

• **Years 1-2 (UH2)** Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures

• **Years 3-5 (UH3)** Validate most promising biomarkers across consortium sites
  
  **Instrumental validity**

  **Biological validity:** Does the biomarker measure an important aspect of small vessel disease (generally operationalized as cognitive performance)?
MarkVCID Biomarkers Kits
Considerations for biological validation

![Graph showing biomarker changes across different disease stages.](image)

- Vessel pathology & endothelial damage
- ↓ Vascular reactivity & BBB breakdown
- DTI changes, microinfarcts, microbleeds
- ↓ Executive function & processing speed
- ↓ Clinical function

Jack et al *Lancet Neurol* 2010;9:119
### MarkVCID Biomarkers Kits

#### Potential applications to clinical trial

<table>
<thead>
<tr>
<th>Subject selection/stratification</th>
<th>Target engagement/mechanism</th>
<th>Disease progression/treatment effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH</td>
<td>Free Water</td>
<td>WMH growth/regression</td>
</tr>
<tr>
<td>PSMD</td>
<td>CVR</td>
<td>PSMD</td>
</tr>
<tr>
<td>Arteriolar sclerosis score</td>
<td></td>
<td>Free Water</td>
</tr>
<tr>
<td>Free Water</td>
<td></td>
<td>CVR</td>
</tr>
<tr>
<td>CVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelial signaling</td>
<td>Endothelial signaling</td>
<td>NfL</td>
</tr>
<tr>
<td>Endothelial inflammation</td>
<td>Endothelial inflammation</td>
<td></td>
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<tr>
<td>CSF PIGF</td>
<td>CSF PIGF</td>
<td></td>
</tr>
<tr>
<td>OCTA VSD</td>
<td></td>
<td>OCTA VSD</td>
</tr>
</tbody>
</table>
MarkVCID Biomarkers Consortium
Timeline

- **Years 1-2 (UH2)** Refine candidate biomarkers; harmonize clinical, imaging, and fluid procedures
- **Years 3-5 (UH3)** Validate most promising biomarkers across consortium sites
- **Years 6-10** “This program is intended to fully prepare small vessel VCID biomarkers for integration into and widespread use in clinical trials (all phases) including in large-scale late phase clinical trials in general and diverse populations in the United States”

**Funding Opportunity Title**

Small Vessel VCID Biomarker Validation Consortium Sites (U01)
(Clinical Trials Not Allowed)
Taking the Shortcut
Biomarkers for vascular cognitive impairment

1. Validating SVD biomarkers: MarkVCID
2. Examples of biomarker applications: CAA
Cerebral amyloid angiopathy (CAA)
Imaging biomarkers for CAA

Diagnosis
• Cerebral microbleeds
• Cortical superficial siderosis
Imaging biomarkers for CAA

Diagnosis
• Cerebral microbleeds
• Cortical superficial siderosis

Markers of clinical brain injury
• Microinfarcts
• Altered structural connectivity

van Veluw, Reijmer *Neurology* 2019;92:e933

van Veluw *Ann Neurol* 2019;86:279
Imaging biomarkers for CAA

Diagnosis
- Cerebral microbleeds
- Cortical superficial siderosis

Markers of clinical brain injury
- Microinfarcts
- Altered structural connectivity

Markers of pathophysiologic pathways
- Amyloid deposition
- Vascular reactivity

Dumas *Ann Neurol* 2012;72:76
Taking the Shortcut
Biomarkers for cerebral small vessel disease

• Wide range of strong candidate VCID biomarkers addressing different aspects of VCID presence, pathogenesis and progression

• ...but lots of important caveats re instrumental properties, specificity, disease stage, pathophysiologic basis, pathogenic vs bystander role

• A buffet of validated biomarkers will allow marker selection tailored to goals and stage of future trials
MarkVCID Biomarkers Consortium

Open for business!
markvcid.org sgreenberg@partners.org
MarkVCID Biomarkers Consortium
Harmonized MRI Protocol

Common core protocol (<45 mins)
• 3D Multi-echo MPRAGE
• 3D FLAIR
• DTI
• 3D GRE
• T2-w FSE

Optional
• Cerebrovascular reactivity
• 3D pCASL
• Resting-state fMRI
Accelerating Therapy Development for Alzheimer’s and Related Dementias
-Enabling Infrastructure and Initiatives-

Laurie Ryan, PhD
Chief, Clinical Interventions and Diagnostics Branch,
Program Director, Pharmacological Interventions
Precision Medicine Approach

Right Pathway/Target, Therapeutic Agent, and Dose for the Right Patient at the Appropriate Stage of Disease
NIA AD Translational Research Program: Diversifying the Therapeutic Pipeline

A Pipeline of Translational Research Funding Opportunities (R21/R01, U01, SBIR/STTR)

Enabling Infrastructure for Data Driven and Predictive Drug Development

AMP-AD Target Discovery and Affiliated Consortia

TREAT-AD Centers

MODEL-AD Centers AlzPED

ADNI
AMP-AD Biomarkers
ABC-DS
ACTC

OPEN SCIENCE - OPEN SOURCE PRINCIPLES
Alzheimer's Biomarkers Consortium — Down Syndrome (ABC-DS)

Initiated in 2015 by the National Institute on Aging (NIA) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) with the funding of two groups of research collaborators:

- Neurodegeneration in Aging Down Syndrome (NiAD, PIs: Ben Handen, Brad Christian, Bill Klunk U01AG051406)
- Alzheimer's Disease in Down Syndrome (ADDS, PIs: Nicol Schupf, Ira Lott, Wayne Silverman, U01AG051412)
Goals:
• Develop valid assessment procedures for tracking clinical progression in adults with DS
• Determine blood- and CSF-based biomarker profiles associated with clinical profiles
• Identify neuroimaging profiles (MRI & PET) associated with AD progression
• Identify genetic signatures influencing AD risk
• Compare findings with other populations having high and low risk for AD
• Compare findings with studies of sporadic AD to determine common and distinct profiles that can aid in identifying pathways and mechanisms determining risk
• Make data and bio-samples available to the research community
• Employ findings as a foundation to design and implement clinical trials focused on both treatment and prevention

Down syndrome (DS) provides unique platform for understanding the temporal and age-dependent development of AD
• Next iteration of ABC-DS was funded by the NIA, NICHD and the Trans-NIH INCLUDE Project (U19AG068054, PIs: Ben Handen, Brad Christian, Elizabeth Head, Mark Mapstone) in September 2020

• Follow the cohort of people with Down syndrome to conduct three projects:
  • 1. Investigating how Alzheimer’s disease in Down syndrome parallels and differs from sporadic Alzheimer’s within an amyloid, tau, neurodegeneration framework and to identify modifiers of risk of conversion/progression
  • 2. Identifying genetic modifiers of the development of AD in DS
  • 3. Translating outcomes to a precision medicine framework and expedite clinical trials

• Includes an emphasis on the increasing the diversity of individuals in the cohort of adults with DS
  • The Alzheimer’s Disease/Down Syndrome Outreach, Recruitment, and Engagement (ADDORE) Core will rapidly disseminate information to Down syndrome communities and engage underrepresented ethnic groups
Available ABC-DS Data and Biosamples

Data are managed by the University of Southern California Laboratory of Neuro Imaging (LONI)

Biospecimen samples are managed by the National Centralized Repository for Alzheimer’s Disease and Related Dementias (NCRAD)

**Biospecimen**
- Plasma in 0.25 mL (250 uL) aliquots
- Serum in 0.25 mL (250 uL) aliquots
- Buffy coat in 1 mL aliquots
- CSF in 15-20 mL aliquots

**Clinical data**
- Demographic
- Medical and psychiatric history
- Physical and neurological exam results
- Caregiver assessment tools on adaptive functioning (Vineland 3), AD symptoms (DLD and NTG-EDSD), and psychiatric symptoms (Reiss)

**Cognitive data**
- Neuropsychological battery results (DSM5e, Block Design, Timed Gait, Modified Lads & Dogs Task, Cued Recall, Purdue Pegboard, Rivermead)
- Consensus diagnosis

**Neuroimaging data**
- The neuroimaging data are selected to mirror the ADNI protocols
  - PET – amyloid, tau, and FDG
  - MRI – T1-weighted structural, T2 FSE, T2-FLAIR, T2*, ASL, DTI and rs-fMRI.

**Genetic data**
- APOE genotype
- Karyotyping
- GWAS (~760K SNPs)

**Sibling controls**
- Data on over 40 sibling controls of participants with Down syndrome
- Primarily biospecimens and neuroimaging data

https://www.nia.nih.gov/research/abc-ds#data
Volume 12, Issue 1
2020


Abstract | Full text | PDF | References | Request permissions

Proteomic profile of incident mild cognitive impairment and Alzheimer's disease among adults with Down syndrome
Sid E. O'Bryant, Tien Zhang, Wayne Silverman, Joseph H. Lee, Sharon K.闵, Michelle Perlmutter, Deborah Pang, James H. Esiri, Nicole Schupf

Abstract | Full text | PDF | References | Request permissions

Feasibility of dual-task gait to estimate Alzheimer's-related cognitive decline in Down syndrome
Kathy Y. Yau, Paul J. Benoit, Allison Canton-Koltz, Ann Marie Anderson-McKee, Elizabeth Head, Frederick A. Schmitt

Abstract | Full text | PDF | References | Request permissions

Cognitive indicators of transition to preclinical and prodromal stages of Alzheimer's disease in Down syndrome
Samantha J. Kerby, Benjamin Mandel, Jennifer Silverman, Diane Tipton, Shoshana Zeman, Annette Cohen, Brandy T. Christian

Abstract | Full text | PDF | References | Request permissions

Distribution of microglial phenotypes as a function of age and Alzheimer's disease neuropathology in the brains of people with Down syndrome
Alejandro C. Martín, Alan M. Heman, Katie L. McCarthy, Ina T. Lott, Eric O'Bryant, Frederick A. Schmitt, Elizabeth Head

Abstract | Full text | PDF | References | Request permissions

Brain atrophy and the transition to dementia in Down syndrome
David B. Botter, Eric O'Bryant, Lisa Taylor, Michael J. Peen, Christy-Horn, Catherine Dohn, Thea G. M. van Eijden, Steven G. Fidler, Adam M. Bajcak, Michael A. Yassa, Wayne Silverman, Ina T. Lott

Abstract | Full text | PDF | References | Request permissions

Proteomic accumulation in Down syndrome measured with amyloid load

Abstract | Full text | PDF | References | Request permissions

Sex differences in the risk of Alzheimer's disease in adults with Down syndrome
Florencia Li, Paqui G. Minaire, Yuchen Yang, Mei-Cheng Wang, Nicole Schupf, H. Diana Roses

Abstract | Full text | PDF | References | Request permissions

Metabolic correlates of prevalent mild cognitive impairment and Alzheimer's disease in adults with Down syndrome
Mark Magrane, Thomas J. Gross, Fabio Maciel, Arman K. Chornea, Melissa Petersen, Elizabeth Head, Benjamin L. Mandel, William E. Prall, Bradley T. Christian, Wayne Silverman, Iris Lotz, Nicole Schupf

Abstract | Full text | PDF | References | Request permissions

Open Access

Alzheimer-related altered white matter microstructural integrity In Down syndrome: A model for sporadic AD
Hana Noone, Eugene Hou, Katherine G. Mercado, Florencia Li, Margaret Perlmutter, David J. Aronson, Adam M. Bajcak, Julie Price, Michael A. Yassa, Olga Choleva, Sharon K.闵, Wayne Silverman, Iris Lotz, Nicole Schupf

Abstract | Full text | PDF | References | Request permissions

Promising outcome measures of early Alzheimer's dementia in adults with Down syndrome
Sharon K.闵, Warren B. Zinger, Joseph H. Lee, Nicole Schupf, Deborah Pang, Tracy Lockman, Cynthia Rozek, Wayne Silverman

Abstract | Full text | PDF | References | Request permissions

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Diagnosis of prodromal and Alzheimer's disease dementia in adults with Down syndrome using neuropsychological tests
Benjamin J. Basch, Laura Vidal, Eduardo Velez, Isabel Barcenas, Diana Carmona-Argüello, Miren Arzabe, Skila Valdés, Susana Fernández, Sandra Gómez, Florencia Li, Karen Zemski, Alexandra Sejnov, David B. Botter, Susana Vélez, Daniel Alcalde, Rafael Rice, Alberto Lied, Juan Forasté

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Observational study

Enroll 500 amyloid positive APP/PSEN1/PSEN2 mutation negative EOAD and 100 age-matched controls ages 40 to 64 at ~15 sites across US

Collect longitudinal detailed clinical, cognitive, imaging, biomarker and genetics

Imaging and biomarker collection, data sharing aligned with ADNI, Biosamples at NCRAD

Available Data
LEADS uses a standard set of protocols and procedures to collect several types of data. Data is shared for free with authorized investigators through the LONI Image and Data Archive (IDA).

Clinical: Demographic, vitals, general medical and neurologic examinations, past medical history, medications, clinical diagnosis and diagnostic subtype

Biosamples: peripheral blood (plasma, serum, PBMC) and CSF

Cognitive/behavioral: NACC UDS cognitive and FTD batteries, AVLT, Digit symbol, ADAS-Cog, TabCat, FAQ, GDS, NPI-Q, Amsterdam IADL

Genetic: DNA and RNA

Imaging: Magnetic resonance, amyloid (florbetaben) and tau (flortaucipir) PET images, Imaging summary measures
AMP-AD (Biomarkers): Supplement NIA-supported Phase II/III secondary prevention trials testing several anti-amyloid therapies with tau PET imaging (AV1451)

Data sharing under AMP-AD includes making the screening data and biosamples available after enrollment completion and making post-randomization data and biosamples available as soon as possible after completion without compromising trial integrity.

The Anti-Amyloid Treatment in Asymptomatic Alzheimer’s Disease Trial (A4 Trial) has achieved the first milestone:

- Making screening data and biosamples available (via the Laboratory of Neuroimaging, LONI) on 6,763 screened participants
- This is the first registration trial to ever do so and the first paper using the screening data from A4 was published in 2020
- Enrollment complete; open label extension ongoing
- First screening data paper published in *JAMA Neurology*


**Association of Factors With Elevated Amyloid Burden in Clinically Normal Older Individuals**

Reisa A Sperling 1, 2, Michael C Donohue 3, Rema Raman 3, Chung-Kai Sun 3, Roy Yaari 3, Karen Holdridge 4, Eric Siemers 4, 5, Keith A Johnson 1, 2, Paul S Aisen 3, A4 Study Team

Affiliations + expand

PMID: 32250387  PMCID: PMC7136861 (available on 2021-04-06)
DOI: 10.1001/jamaneurol.2020.0387
NINDS Dementia Research Initiatives: Different Forms and Cross-Cutting Themes

- **MarkVCID**, national VCID Biomarkers Consortium
- **Tau Center Without Walls** to study molecular mechanisms that lead to tau toxicity in FTD
- **FTD Sequencing Consortium** to discover FTD-causing gene mutations
- **Lewy Body Center Without Walls** to characterize α-synuclein and β-amyloid subtypes in LBD
- **LBD biomarker discovery research**
- **DetectCID** to develop paradigms to increase detection of cognitive impairment/dementia in primary care settings and in populations that experience health disparities
- **ALLFTD Natural History Study in FTLD**, together with the NIA
- **DISCOVERY** and **Diverse VCID** to determine types of stroke and white matter lesions and comorbidities that cause VCID including in populations that experience health disparities
- **PET Ligand Development Proteinopathy Structural Biology for ADRD Center Without Walls**
- **Establish CARD** with NIA, intramural Center for the Study of Alzheimer’s & Related Dementias

• Center Without Walls (CWOW) for Molecular Mechanisms of Neurodegeneration in FTD – to continue support for interdisciplinary team science on molecular mechanisms of neurodegeneration in FTD, with a focus on tau, TDP-43 or FUS pathogenesis, and specific genetic causes and risks factors. RFA-NS-21-003

• Mechanisms of Selective Vulnerability in LBD and FTD – why certain brain regions are more vulnerable to abnormal protein accumulation and damage. RFA-NS-21-007

• Mechanisms of Pathological Spread of Abnormal Proteins in LBD and FTD – how abnormal proteins spread in the nervous system of LBD and FTD patients. RFA-NS-21-006

• Connecting Pre-mortem Clinical Information with Post-mortem Brain Analysis in LBD – linking comprehensive pre-mortem clinical information with gold standard post-mortem diagnostic analysis in LBD patients. RFA-NS-21-001

• Treatments for LBD-Exploratory Clinical Trial – to encourage exploratory clinical trials (Phase I or II) testing either new or repurposed drugs or devices to treat patients with LBD. RFA-NS-21-008

• Small Vessel VCID Biomarker Validation for Clinical Trials and Coordinating Center – to continue support for a consortium (currently implemented as MarkVCID) to develop and validate high-quality small vessel VCID biomarkers ready for use in clinical trials, and for generating scientific breakthroughs in the understanding and treatment of VCID. RFA-NS-21-004, RFA-NS-21-005
ENABLING INFRASTRUCTURE PROGRAMS FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT

AMP-AD Consortia
- Large scale systems/network biology approach
- Predictive models for novel targets and biomarkers
- Computational methods benchmarking
- Open data, methods and target enabling tools

TREAT-AD Centers

MODEL-AD AlzPED
- Next-gen animal models for late onset AD
- Deep phenotyping and staging relative to human disease
- Methods development for efficacy testing
- Open data and animal models distribution free of IP barriers

ACTC
- Clinical trials infrastructure (Phase I, II, III)
- Methods development for clinical trial design
- New methods for recruitment and retention (emphasis on diversity)
- Sharing of trial design methods, outcomes and analyses strategies
- Sharing of data/biosamples from placebo and treatment arms

OPEN SCIENCE/OPEN SOURCE FROM TARGETS TO TRIALS
Alzheimer's Clinical Trials Consortium

To provide an optimal infrastructure, utilizing centralized resources and shared expertise, to accelerate the development of effective interventions for Alzheimer's disease and related disorders.

actcinfo.org
ACTC

• Initiated in December 2017

• PIs: Paul Aisen, Alzheimer’s Therapeutic Research Institute (ATRI), San Diego; Reisa Sperling, Brigham and Women’s Hospital and Massachusetts General Hospital, Boston; Ronald Petersen, Mayo Clinic, Rochester, Minnesota (U24AG057437)

• Next generation infrastructure - collaboration between NIA and ACTC investigators

• Includes multiple clinical trial sites with dedicated support

• A separate NIA Funding Opportunity Announcement (FOA) is soliciting applications for clinical trials to be managed and supported by the ACTC (PAR-20-309)
ACTC GOALS

• Conduct clinical trials (phase 1b to 3) of promising pharmacological and non-pharmacological interventions for
  • cognitive and neuropsychiatric symptoms in individuals with AD and other age-related dementias
  • across the spectrum from pre-symptomatic to more severe stages of disease

• Provide a state-of-the-art clinical trial infrastructure to facilitate rapid development and implementation of protocols

• Provide leadership in innovative trial design methods, outcomes and analyses as well as recruitment strategies, particularly in diverse/underrepresented populations

• Enable broad sharing of procedures and methods, as well as trial data and biosamples
KEY ELEMENTS OF THE ACTC

• Novel approaches to recruitment and assessment, including innovations in technology:
  • The Minority Outreach and Recruitment Team is developing central and local partnerships with diverse communities to enhance representation of these underrepresented groups in AD/ADRD trials

• Streamlined implementation of trials from start-up to publication, e.g., use of master trial agreements, efficient contracting and centralized IRB

• Track site performance; maximize protocol adherence and data quality

• Centralized tissue banking/sharing for biosamples

• Centralized biostatistics, bioinformatics and data management support

• Meeting and communication coordination among clinical trial sites of ACTC

• Provide guidance to investigators developing interventions for AD/ADRD
THE ACTC INFRASTRUCTURE IS WELCOMING OF:

• Academic and industry applicants; Public-Private Partnerships

• Both pharmacological and non-pharmacological interventions

• Applications are encouraged that propose:
  • Testing candidate therapeutic compounds against novel therapeutic targets
  • Testing repurposed drugs and combination therapies from data driven approaches, including candidates coming from NIA's translational bioinformatics FOA (PAR-20-156)
• Non-AD Dementia Committee (Chairs: Brad Boeve, Adam Boxer)
  • Advises on trial design for studies where the population is non-AD age-related dementia

• Neuropsychiatric Symptoms (NPS, Chair: Jeff Cummings)
  • Advises on trial design for studies of agents, devices, or non-pharmacologic interventions targeting NPS such as agitation, psychosis, depression, apathy, and sleep disorders

• Non-Pharmacological Intervention Committee (Chairs: Laura Baker, Bruno Vellas)
  • Provides expertise and guidance in the development and management of trials involving non-pharmacological approaches in clinical trials

• Inclusion, Diversity, and Education in Alzheimer’s disease Clinical Trials (IDEA-CT) Committee (Chairs: Rema Raman, Reisa Sperling)
  • Developing goals, formulating strategic plan, and providing oversight for ACTC’s core values of inclusion, diversity and training in ADRD clinical trials and the ADRD clinical research community at large

• Research Participant Advisory Board (Chair: Sarah Walter)
  • Provides guidance to the consortium to help ensure that the outcomes of ACTC work are meaningful to the public.
  • Focus on inclusion of individuals from underrepresented populations as well as from across the disease spectrum.
DATA, IMAGES AND BIOSPECIMEN SHARING POLICY

• Primary goal of this policy is to make available project research data, images and biospecimens from ACTC clinical trials to the scientific community in a timely manner, while safeguarding the safety and privacy of trial participants and protecting confidential and proprietary data.

• Follow the Collaboration for Alzheimer’s Prevention (CAP) principles as well as NIA/NIH guidelines and policies

• Data, images and biospecimens will be shared at two time-points for each project:
  1. Pre-randomization data, images and biospecimens will be shared within twelve (12) months of the final participant randomization.
  2. Project data, images and biospecimens will be shared with the scientific community after the earlier of either regulatory approval of the tested treatment, at time of publication of top line results, or nine (9) months after the completion or early termination of the trial.
Alzheimer’s Clinical Trials Consortium (ACTC)

Mission: To provide an optimal infrastructure, utilizing centralized resources and shared expertise, to accelerate the development of effective interventions for Alzheimer’s disease and related disorders.

Apply for an ACTC project

Eligibility: Anyone (academic or industry)

Studies: Phase Ib-Ill, non-pharmacological and novel approaches encouraged

Contact: Sarah Walter waltersa@usc.edu

• We work in collaboration with proposers to develop idea and submit grant to NIA
• Infrastructure includes expertise in study design and conduct, full clinical trial management capability at coordinating center and network of trial sites
• Learn more at: www.actcinfo.org
CURRENT ACTC TRIALS

• Enrolling
  • AHEAD A3-45 (BAN2401)
    • A3: cognitively normal, below threshold amyloid PET, at risk
    • A45: clinically normal, elevated amyloid PET, high risk

• Enrollment Complete – Ongoing
  • A4 Open Label Extension

• Launching in 2021
  • CT1812
    • Phase 2, prodromal or mild AD

  • Life’s End Benefits of Cannabidiol and Tetrahydrocannabinol (LiBBY)
    • Phase 2, severe dementia with agitation
    • Oral combination of tetrahydrocannabinol (THC) and cannabidiol (CBD)
Trial Ready Cohort for the Prevention of Alzheimer’s Dementia

- Establish a trial-ready, AD biomarker positive cohort, i.e., a pool of well-characterized participants, for trials at multiple sites across North America to facilitate recruitment
- Enrolling

Feeder Registries; Media, Community Outreach, etc. → Alzheimer Prevention Trials (APT) Webstudy → ↑Risk

AD Biomarker + → TRC-PAD Cohort
AD Biomarker - → Remain in APT

PIs: Paul Aisen, Reisa Sperling, Jeff Cummings (R01AG053798)
Alzheimer Prevention Trials Webstudy

If you are at least 50 years of age and interested in Alzheimer's research, please join!

www.aptwebstudy.org

Low barriers: 10-15 min per visit, flexible schedule
Engagement: feedback on progress, testing
Education: news and updates on trials
ACTC-DS will leverage the experience and expertise of the ACTC, as well as the NIH-funded Alzheimer’s Biomarker Consortium - Down Syndrome (ABC-DS) groups to build a trial-ready cohort of adults with DS and then design and conduct clinical trials in this cohort.

ACTC-DS will serve as a platform for bringing the latest and most innovative AD therapies to the DS population.

actc-ds.org
Trial Ready Cohort – Down Syndrome

PI: Mike Rafii (AG066543)

- Establish a trial-ready pool of well-characterized adults with Down Syndrome (DS) to participate in AD trials
- Launching in 2021
Pipeline of NIA and Trans-NIH Translational Research Funding Opportunities

DRUG DISCOVERY
- Target ID
  - Early Validation

PRECLINICAL DEVELOPMENT
- Assay Development
- Screening
- Proof of Concept
- Lead Optimization
- Candidate Selection
- IND-enabling toxicology

CLINICAL DEVELOPMENT
- Phase I
- Phase II
- Phase III
- New Drug Approval

AD Drug Development (ADDP)
- Blueprint Neurotherapeutics (BPN)

Drug Discovery for Nervous System Disorders
- Discovery of Cell-Based or in vivo Chemical Probes for Novel Brain Targets
- Advancing Basic Neurobiology Toward Translation Through Assay Development

Small Business Funding Opportunities (SBIR/STTR)

Early and Late-Stage Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline
Clinical Therapy Development

**PAR-18-877:**
Early Stage Clinical Trials for the Spectrum of Alzheimer’s Disease and Age-related Cognitive Decline (R01)

- Phase 1 and Phase 2 Clinical Trials (Pharm and Non-Pharm)
- Studies to enhance trial design and methods

**PAR-18-878:**
Late Stage Clinical Trials for the Spectrum of Alzheimer’s Disease and Age-related Cognitive Decline (R01)

- Phase 2/3 and 3 Clinical Trials (Pharm and Non-Pharm)

*Early and late-stage clinical trials for the spectrum of AD/ADRD and age-related cognitive decline [2021 Re-issue](#): planning to combine these FOAs into a single FOA covering Phases I-III pharm/non-pharm clinical trials, as well as clinical trial design/methods*
Data Sharing Requirements for NIA AD/ADRD Clinical Trials

• Sharing of data and biosamples is expected at the time of publication of the primary results or within 9 months of data lock, whichever comes first

• Pivotal trials are expected to follow Collaboration for Alzheimer's Prevention (CAP) data and sample sharing principles:
  • make screening/pre-randomization baseline data available within 12 months of enrollment completion
  • post-randomization data and biosamples should be made available as soon as possible without compromising trial integrity, i.e., after regulatory approval or trial completion/termination or 18 months whichever comes first

Clinical Therapy Development

**PAS-19-316:**
Advancing Research on Alzheimer’s Disease (AD) and Alzheimer's-Disease-Related Dementias (ADRD) (R43/R44)

- SBIR: Clinical trials allowed

**PAS-19-317:**
Advancing Research on Alzheimer’s Disease (AD) and Alzheimer's-Disease-Related Dementias (ADRD) (R41/R42)

- STTR: Clinical trials allowed
Trends in NIA-funded Early Stage Clinical Trials for AD/ADRD (Phase 1 & 2) 2008-2019 -by therapeutic target/disease mechanism-

# of newly funded projects

**Proportion of Projects**

- a. Amyloid beta
- b. Amyloid Peptides
- c. ApoE, Lipids and Lipoprotein Receptors
- d. Neurotransmitter Receptors
- e. Neurogenesis
- f. Inflammation
- g. Oxidative Stress
- h. Vasculature
- i. Growth Factors and Hormones
- j. Metabolism and Bioenergetics
- k. Synaptic Plasticity/Neuroprotection
- l. Other

**Yearly Distribution**

- 2008: 2 projects
- 2009: 8 projects
- 2010: 6 projects
- 2011: 4 projects
- 2012: 4 projects
- 2013: 6 projects
- 2014: 4 projects
- 2015: 6 projects
- 2016: 10 projects
- 2017: 8 projects
- 2018: 11 projects
- 2019: 10 projects
<table>
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*Vaccine **Gene therapy
Expanding the Alzheimer’s and Related Dementias Clinical Trials Workforce
• With increased federal funding for research in Alzheimer’s Disease and related dementias and a goal of the National Plan to Address Alzheimer’s to identify interventions to treat or cure ADRD by 2025, the number of clinical trials has significantly increased over the last few years.

• There is a critical need to expand the AD/ADRD clinical trials workforce to meet this demand overall and in particular with regards to the inclusion of individuals from diverse backgrounds.

• Clinical trials struggle to recruit individuals from diverse racial, ethnic, socioeconomic backgrounds. One of the potential barriers to participation is the lack of cultural sensitivity and ethic similarity to staff participants.
Alzheimer’s Disease and related disorders (ADRD) course that aims to educate and promote diversity among research professionals and future principal investigators in the field of ADRD research.

Goals of the Course

To provide junior investigators with a unique, comprehensive, and active learning experience in ADRD trials.

This will be accomplished by leveraging the full infrastructure and expertise of the Alzheimer’s Clinical Trials Consortium (ACTC) to enable a diverse range of clinicians, scientists and researchers to receive modern and robust training on ADRD clinical trials.

Supported by:
National Institute on Aging (NIA) U13 AG067696, Alzheimer’s Association
Alzheimer’s Clinical Trials Consortium (ACTC), UCI MIND, USC ATRI
Key Elements

• Provide education and tools to establish a national cohort of qualified investigators to guide the field toward improved therapies

• Focused on diversifying the ADRD trial workforce:
  • Demographic characteristics (age, race, ethnicity, etc.)
  • Specialties (physicians, psychologists, statisticians, etc.)
  • Backgrounds (rural, urban, etc.)
  • Career stage or current position
Course Tracks

Professionals Track

Individuals selected to this track have at least 2 years of experience in ADRD research and/or clinical trials (in a broad variety of roles including, but not limited to clinicians, study coordinators, psychometricians, and other study professionals) and will be trained to further their knowledge and advance their careers in ADRD trials.

Fellowship Track

Individuals selected to this track will be trained to serve as Principal Investigators in ADRD trials and offered mentored training in protocol development.
First Class held online, September 14-17, 2020
• Designed to encourage applications for intensive short courses that will develop, implement, and evaluate creative and innovative short courses to provide education in state-of-the-art clinical research skills in AD/ADRD

• Courses may vary in duration from one-week or less up to a maximum of 12-weeks. Courses will include graduate/medical students, post docs, and/or early career faculty

• Diversify the AD/ADRD clinical trials workforce

• This type of training is necessary to thrive in a team science environment and is rarely provided through the traditional course of medical and graduate education.

• With this proposed concept, we hope to expand AD/ADRD clinical trials training and strengthen the pipeline of promising new trialists
ACKNOWLEDGMENTS

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Deputy Director: Jennie Larkin

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Sharna Tingle
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Office for Strategic Development and Partnerships
Director - Suzana Petanceska
Erika Tarver
Nadezda Radoja
Jean Yuan
Laurie Ryan
Alvin McKelvy
Thank You!

International Alzheimer's and Related Dementias Research Portfolio (IADRP)

Our database brings together funded research supported by public and private organizations both in the US and abroad all categorized using the Common Alzheimer's and Related Dementias Research Ontology or CADRO.

https://iadrp.nia.nih.gov/
Accelerating Therapy Development for Alzheimer’s and Related Dementias -from Open Science to Open Drug Discovery-

Suzana Petanceska PhD  
Director – Strategic Development and Partnerships  
Division of Neuroscience
Outline:

• NIA AD Translational Research Program: New Drug Candidates

• AMP-AD and Affiliated Consortia: Systems-based Approaches to Novel Target and Biomarker Discovery

• TREAT-AD Centers: Advancing Novel Targets into Drug Discovery

• MODEL-AD Consortium: Resources for Rigorous Preclinical Efficacy Testing

• Accelerating Therapy Development through Data-Driven Drug Repurposing

• Understanding the Impact of Sex Differences on AD Risk and Responsiveness to Treatment

• Training the New Translational Workforce
NIA’s Alzheimer’s Translational Research Program provides a pipeline of funding opportunities that support the discovery and development of new drugs for a diverse portfolio of therapeutic targets.
PAR-18-820:
NIA Alzheimer’s Drug Development Program, ADDP (U01)

- Small molecules and biologics
- Two Entry Points: Hits Optimization through IND/Lead Selection through Phase I
- Milestone driven (Go/No-Go decision points)
- Budget capped at $1M Direct Cost per year for up to 5 years

PAR-20-122 and PAR-20-111:
Blueprint Neurotherapeutics Network, BPN (UG3/UH3) (U44)

- Small molecules only
- Two Entry Points: Hits Optimization through IND/Lead Selection through Phase I
- Milestone driven (Go/No-Go decision points)
- Funding up to 5 years
- *Virtual Pharma Model: PIs Collaborate with NIH-funded consultants and NIH CROs*
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***Supported through BPN
NIA Alzheimer’s Translational Research Program: ENABLING INFRASTRUCTURE PROGRAMS FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT

**OPEN SCIENCE/OPEN SOURCE FROM TARGETS TO TRIALS**

**AMP-AD Consortia**
- Large scale systems/network biology approach
- Predictive models for novel targets and biomarkers
- Computational methods benchmarking
  - *Open data, methods and target enabling tools*

**TREAT-AD Centers**
- Next-gen animal models for late onset AD
- Deep phenotyping and staging relative to human disease
- Methods development for efficacy testing
  - *Open data and animal models distribution free of IP barriers*

**MODEL-AD AlzPED**
- Clinical trials infrastructure (Phase I, II, III)
- Methods development for clinical trial design
- New methods for recruitment and retention (emphasis on diversity)
- Sharing of trial design methods, outcomes and analyses strategies
  - *Sharing of data/biosamples from placebo and treatment arms*

**ACTC**
AMP-AD Target Discovery
M²OVE-AD
Resilience –AD
Psych-AD

AMP-AD Biomarkers
ABC-DS
ACTC

MODEL-AD
TREAT-AD

ADRCs/Epi Cohorts/ADNI/ADSP

Research Community

data and biosamples

Research Community

Research Community

ADRCs

participants

Research Community

Research Community

ADRCs/Epi Cohorts/ADNI/ADSP
ACCELERATING MEDICINES PARTNERSHIP FOR ALZHEIMER’S DISEASE (AMP-AD)
TARGET DISCOVERY AND PRECLINICAL VALIDATION PROJECT

Launched in 2014

➢ Systems biology approach to target discovery and validation.
➢ Large-scale, cross-disciplinary, team science.
➢ Open science research model: rapid sharing of data, methods and results through centralized data infrastructure: AD Knowledge Portal
AMP AD 1.0 delivered multi-omic data and analytical resources, mechanistic insights, and a systems-based, data-driven process for target discovery and validation

- Centralized FAIR data repository and knowledgebase - [AD Knowledge Portal](#)
- Rich, human, multi-omic data generated and made available; >3000 users to date (60% academia / 40% industry)
- Molecular network models of disease made available
- Animal models phenotyped and evaluated relative to human molecular networks
- New mechanistic disease insights on role of genome, proteome, metabolome and microbiome
- [Agora](#), open-source platform, featuring AMP-AD nominated targets and verified systems biology analyses for any gene of interest
- 542 unique targets made available through [Agora](#) along with the supporting evidence and extensive druggability information
- Early experimental validation completed for over 20 candidate targets
Meta-Analysis of the Alzheimer's Disease Human Brain Transcriptome and Functional Dissection in Mouse Models


A consensus atlas of the human brain transcriptome in Alzheimer's disease

NIA-supported Grants Provide a Foundation for AMP-AD 2.0

**RFA-AG18-013 (U01) / RFA-AG18-014 (U24)**

- **AMP AD Data Coordinating Center**: Lara Mangravite, Sage Bionetworks
- **Multi-omic network-directed proteoform discovery, dissection and functional validation to prioritize novel AD therapeutic targets**: Phil De Jager, Columbia University
- **AMP AD Brain proteomic network enhancement, validation, and translation into CSF biomarkers**: Allan Levey, Emory University
- **Integrative network biology approaches to identify, characterize and validate molecular subtypes in Alzheimer’s Disease**: Bin Zhang, ISMMS
- **Metabolomic signatures for disease sub-classification and target prioritization in AMP AD**: Rima Kaddurah-Daouk, Duke University
- **A systems approach to targeting innate immunity in AD**: Nilufer Ertekin-Taner, Mayo Clinic
- **Identification of the genetic and transcriptomic networks of cognitive and neuropathological resilience to Alzheimer’s Disease associated viruses**: Ben Readhead, Arizona State University

### Research Scope of Foundational Grants

1. **Sustain and expand the capabilities of the AMP AD Knowledge Portal and the AGORA platform**
2. **Maximize the use of existing data and generate additional molecular profiling data (human and mouse) for use in target and biomarker discovery**
3. **Increase the bandwidth and develop new methods for functional validation of novel targets**
4. **Develop methods for integrative network analyses to discover patient stratification biomarkers and to enable disease sub-classification**

**Opportunity to renew and expand the public private partnership**
FNIH Coordinated the Effort to Develop the Second Phase of AMP-AD

FNIH convened discussions among NIA, existing and potential new private partners (industry and non-profit organizations) to identify key areas for strategic partnering that can leverage the NIA foundational grants investment:

- Expand the multi-omic profiling in samples from diverse cohorts (brain, CSF, plasma)
- Generate longitudinal immunologic profiling data in diverse cohorts
- Expand the existing sn/sc molecular profiling efforts to develop a molecular atlas of AD

Deconstruct Disease Heterogeneity and Enable a Precision Medicine Approach to Target and Biomarker Discovery

FNIH Contact: Eline Appelmans, Scientific Program Manager in Neuroscience, Research Partnerships
eappelmans@fnih.org
Integrated Proteomics Reveals Brain-based Cerebrospinal Fluid biomarkers in Asymptomatic and Symptomatic Alzheimer’s Disease

- Multiplex mass spectrometry of brain (~12,000 proteins) and CSF (~3500 proteins).

- 15 overlapping CSF-Brain protein network modules map to five pathophysiological processes.

- Synaptic, vascular, and metabolic panels demonstrate divergent expression trends in the brain and CSF.

- Replication experiments demonstrate that the CSF signatures are disease specific and reproducible.

Higginbotham et al. Science Advances 2020
https://advances.sciencemag.org/content/6/43/eaaz9360
Recent AMP-AD Manuscripts

Transcriptomic maps of the disease

• Meta-Analysis of the Alzheimer's Disease Human Brain Transcriptome and Functional Dissection in Mouse Models – *Cell Reports*
• Molecular Subtyping of Alzheimer's Disease Using RNA-Sequencing Data Reveals Novel Mechanisms and Targets – *Science Advances*
• Molecular estimation of neurodegeneration pseudotime in older brains – *Nature Communications*

Integrative proteomics

• Integrated proteomics reveals brain-based cerebrospinal fluid biomarkers in asymptomatic and symptomatic Alzheimer’s disease – *Science Advances*
• Large-scale proteomic analysis of Alzheimer's disease brain and cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and astrocyte activation – *Nature Medicine*

Integrative metabolomics/lipidomics

• Sex and APOE €4 genotype modify the Alzheimer’s disease serum metabolome – *Nature Communications*
• Concordant peripheral lipidome signatures in two large clinical studies of Alzheimer's disease – *Nature Communications*
• Metabolic Network Analysis Reveals Altered Bile Acid Synthesis and Metabolism in Alzheimer’s Disease – *Cell Reports*

Cellular resolution modeling

• Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer’s disease – *Nature Communications*
• Deciphering cellular transcriptional alterations in Alzheimer's disease brains - *Molecular Neurodegeneration*

Target ID and Experimental Validation

• Multiscale causal networks identify VGF as a key regulator of Alzheimer’s disease – *Nature Communications*
• Transformative Network Modeling of Multi-Omics Data Reveals Detailed Circuits, Key Regulators, and Potential Therapeutics for AD – *Neuron*
AMP-AD and Affiliated Consortia

Harnessing the Power of Big Data and Open Science to Understand the Complex Biology of Disease Risk and Resilience and Discover New Therapeutic Targets and Biomarkers

Genomic, proteomic, metabolomic data from human brain and peripheral fluid samples

Computational modeling/network biology

Experimental validation in cell-based and animal models

Drug Discovery

AMP-AD Target Discovery

AD Knowledge Portal

Agora

NIA/NINDS

M^OVE-AD

NIA/NIMH

Psych-AD

Resilience-AD

M^OVE-AD – Molecular Mechanisms of the Vascular Etiology of AD
Psych-AD - Molecular Mechanisms of the Neuropsychiatric Symptoms in AD
### Funded projects:

<table>
<thead>
<tr>
<th>Grant ID</th>
<th>Principal Investigator(s)</th>
<th>Project Title</th>
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<tbody>
<tr>
<td>R56AG062302</td>
<td>LUTZ, MICHAEL WILLIAM (contact); CHIBA-FALEK, ORNIT; LUO, SHENG; WILLIAMSON, DOUGLAS E</td>
<td>Shared genetic, epigenetic, and transcriptomic profiles between AD and PTSD: molecular insights into the heterogeneity of neuropsychiatric symptoms in Alzheimer's Disease</td>
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<tr>
<td>R01AG062249</td>
<td>DONG, HONGXIN (contact); WILSON, ROBERT S</td>
<td>Molecular Mechanisms Underlying Behavioral and Psychological Symptoms in Alzheimer's Disease</td>
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<tr>
<td>R01AG062268</td>
<td>HUEY, EDWARD D</td>
<td>Neuroanatomical associations with the factor structure underlying neuropsychiatric symptoms in Alzheimer's disease</td>
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<tr>
<td>R01AG062335</td>
<td>KELLIS, MANOLIS (contact); TSAI, LI-HUEI</td>
<td>Elucidating the Molecular Mechanisms of Neuropsychiatric Symptoms in Alzheimer's Disease</td>
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<td>R01AG062355</td>
<td>SALTON, STEPHEN R (contact); EHRLICH, MICHELLE E; ZHANG, BIN</td>
<td>Systems modeling of shared and distinct molecular mechanisms underlying comorbid Major Depressive Disorder and Alzheimer's disease</td>
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<tr>
<td>R56AG062272</td>
<td>XU, RONG</td>
<td>Construct large-scale phenomes of disease and drugs and develop data-driven systems approaches to understand genetic links between Alzheimer's disease and Neuropsychiatric symptoms</td>
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<td>R01AG067015</td>
<td>LUNNON, KATIE (contact); KOFLER, JULIA K</td>
<td>A multi-omic approach to elucidate novel disease mechanisms and biomarkers for psychosis in Alzheimer's disease</td>
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<tr>
<td>R01AG067025</td>
<td>ROUSSOS, PANAGIOTIS (contact); FINKBEINER, STEVEN M; HAROUTUNIAN, VAHRAM; WANG, DAIFENG</td>
<td>Understanding the molecular mechanisms that contribute to neuropsychiatric symptoms in Alzheimer Disease</td>
</tr>
</tbody>
</table>
Aim 1: Derive additional phenomics data including severity of NPS and cellular features from neuropathological slides by deep learning approaches.

Aim 2: snRNAseq and snATACseq in 1,300 cases from Mount Sinai Brain Bank.

Aim 3: Integrate all data layers with deep learning approaches to identify markers that can predict NPS in AD.

Aim 4: Validate the predictive power of the models using independent genotype and phenomics datasets (ADNI and Million Veteran Program).
Integrate epidemiologic, genomic and mechanistic research to understand the dynamic relationship between NPS and AD/ADRD pathogenesis across diverse populations

Examine the role of the gut-brain axis and the microbiome in the emergence of NPS in AD and as a mediator of responsiveness to interventions targeting NPS

Generate multi-omic data using biosamples from existing as well as legacy clinical trials targeting NPS in AD/ADRD to interrogate disease mechanisms and molecular determinants of responsiveness to treatment

Preclinical validation of novel candidate targets nominated by the AMP-AD Target Discovery Program, to test their utility as therapeutic targets for NPS in AD/ADRD

Academic-industry collaborations are strongly encouraged

Expectations for rapid and broad sharing of data, analytical methods and research tools prior to publication via the NIA-supported AD Knowledge Portal and/or other NIA/NIH designated data repositories
AD Knowledge Portal – an Open Science Discovery Engine

Launched - March 4, 2015

1. Data Reuse
2. Transparency
3. Independent evaluation
4. Attribution

Data
Raw and processed versions of AD Consortia data
open or restricted access based on data type/data source

Algorithms
e.g., RNAseq processing, proteomic analysis, single cell RNA

Analytical results
e.g., eQTL, networks, diff expn

Insights
e.g., targets

AD Knowledge Portal

Agora

SAgE Bionetworks
Welcome to the AD Knowledge Portal

Discover and download Alzheimer's Disease data, analyses, and tools from the National Institute on Aging's Alzheimer's Disease Translational Research Program.

Established by the ACCELERATING MEDICINES PARTNERSHIP

PROGRAMS

AMP-AD
Visit website
Discovering new drug targets for Alzheimer's disease treatment and prevention.

M2OVE-AD
Visit website
Deconstructing the metabolic and vascular etiology of Alzheimer's disease

MODEL-AD
Visit website
Developing new Alzheimer's disease animal models.

Resilience-AD
Visit website
Understanding cognitive resilience under conditions of high risk for Alzheimer's disease.

Psych-AD
Visit website
Understanding the molecular mechanisms of neuropsychiatric symptoms in Alzheimer's disease and Alzheimer's disease-related dementias.

CDCP
Visit website
An AD Knowledge Portal data contribution program

~340TB
17,053 biosamples
15 genomic data types
7,261 human donors

adknowledgeportal.org
New search features to improve data discoverability
Use of AD Knowledge Portal Resources

Active New Users

Data User Requesters Research Affiliations

Academic 59.7%
Industry 40.3%

Users Map

2 7,592
Agora: Sharing Analytical Results and Insights

Open-source platform providing curated, AMP-AD verified, systems biology analyses for any gene of interest.

Enables researchers at large to discover and evaluate the evidence behind the AMP-AD nominated targets as well as to nominate new targets.

542 unique targets currently available, derived from unbiased, computational analyses of high-dimensional human omic data along with supporting evidence and extensive druggability information.

https://agora.ampadportal.org/
Building Confidence in Targets through Independent Converging Lines of Evidence

## Nominated Target List

Researchers have nominated genes that may be good targets for new Alzheimer's Disease treatment or prevention. These targets have been identified using computational analyses of high-dimensional genomic, proteomic and/or metabolomic data derived from human samples.

The initial list of nominated targets was contributed by researchers from the National Institute on Aging's Accelerating Medicines Partnership in Alzheimer's Disease (AMP-AD) consortium.

Search for or select any gene from the nominated target list to view the evidence that led to its nomination

Learn more about Nominated Targets.

Would you like to add to this list?  
Nominate a target

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Nominations</th>
<th>Nominating Teams</th>
<th>Cohort Study</th>
<th>Input Data</th>
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<td>Broad-Rush-Columbia, Emory, Mayo-UFL-ISB, MSSM</td>
<td>ACT, BLSA, Mayo, MSBB, RONAP</td>
<td>Genetics, Protein, RNA</td>
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<td>ADNI, Mayo, MSBB</td>
<td>Genetics, Metabolome, RNA</td>
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Agora Targets – Systems Biology Evidence

VGF
VGF nerve growth factor inducible

**Nomination Details**

**Summary**

**Evidence**

**Druggability**

### RNA

- **UPC2 PROD CHN**: CBE, DUVEC, FP, HFG, HMG, STG, TCK

### Protein

- **UPC2 PROD CHN**: AnHPC, DUVEC, HMG, TCK

### Metabolites

- **PFCH**: AD, DAVMS

**Druggability**

- **Small Molecule Modality**: Unknown: There is no information on ligands or structure in any of the categories above.

- **Antibody Modality**: Secreted protein. Highly accessible to antibody-based therapies.

- **Safety**: Probable safety risks requiring mitigation. More than two of: high off-target gene expression, cancer driver, essential gene, associated deleterious genetic disorder, HPO phenotype associated gene, or black box warning on clinically used drug.
GOAL: Diversify and accelerate therapy development for Alzheimer’s through the development of open source tools, reagents and methods for robust validation of candidate targets delivered by AMP-AD and other target discovery programs, and by integrating enabled targets into drug discovery campaigns.

Two Centers, One Mission

U54AG065187
Alan Levey, Emory University
Lara Mangravite, Sage Bionetworks
Aled Edwards, Structural Genomics Consortium

U54AG065181
Alan Palkowitz and Bruce Lamb
Indiana University School of Medicine
Purdue University
Prioritized Targets

Admin and Data Core
Assay Development and High-Throughput Screening Core
Structural Biology Core
Chemical Biology and Medicinal Chemistry Core

Target Enabling Packages

Assay Development

Preclinical Lead Candidates

Open distribution of knowledge, data and target enabling tools

https://treatad.org
20 Experimental Target Enabling Packages (TEPs)

Antibodies, knockout cell lines

6 Full TE packages
+ expression clones, purified proteins, functional and screening assays, crystal structures

3 Cellular probes

1-2 In vivo probes

Components of a TEP

1. Protein informatics
2. Verified Gene knockout and modifications tools
3. Sequence-characterized knockout cell lines
4. Well-characterized antibodies for research
5. Expression clones for target proteins
6. Purified proteins and production methods
7. Assay protocols
8. Crystal or cryo-EM structures

Supporting the Study of Emerging Therapeutic Hypotheses
Initial Prioritized Targets for Drug Discovery

**INPP5D (SHIP1)**
- AMP-AD nominated target
- AD risk gene preferentially expressed in lymphoid cells including microglia
- Negative modulator of TREM2 function
- MODEL-AD systems biology approach to evaluate and develop animal models for PK/PD and lead optimization
- Target class (phosphatase) druggability challenge

**Phospholipase C gamma 2 (PLCG2)**
- AMP-AD nominated target
- MODEL-AD Animal Model characterization ongoing
- Membrane associated signaling enzyme producing second messenger molecules: diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3)
- Implicated in B-cell activation and proliferation
- PLCG2 mRNA upregulated in cortical tissue of LOAD patients
- PLCG2 P522R variant is protective against AD
- No selective small molecule activators known

**Guiding Principles for Target Selection/Prioritization**
- AMP-AD/MODEL-AD nomination; review of supporting science
- Distribution of portfolio risk
- Opportunity for innovation
- Path to expand functional target validation
- Contributes to systematic study of neuroimmune signaling pathways
- Match to Center capabilities

Hansen, D. V. et al. J Cell Biology 2017 DOI: 10.1083/jcb.201709069
- Prioritize LOAD variants for animal modeling
- Create 50 new mouse models with CRISPR (piloting rat models)
- High-capacity screening of all models, deep phenotyping of the most promising models
- Align mouse and human phenotypes (neuropath, omics, imaging)
- Enable rigorous preclinical efficacy testing of promising candidate therapeutics
- Provide broad, unrestricted distribution of all data and models for use in research and therapy development (https://www.model-ad.org/strain-table).
Legal restrictions for most models

Poor rigor and reproducibility of efficacy testing in mouse models

Models do not develop robust neurodegeneration

Toxic effects of overexpression of transgenes

Difficulties in relating behavioral deficits observed in mouse models to human AD

Largely focused on Early Onset AD vs Late Onset AD

Are mice an appropriate species?

Poor alignment of model pathophysiology with corresponding stages of clinical disease.
Lack of translatable biomarkers.
Transition of mouse modules from red-to-blue indicates higher correlation with human LOAD transcriptomes
Deep Phenotyping of Prioritized Strains

12M/12F per genotype at each time point
Aspects of deep phenotyping are conducted at IU, JAX and UCI for reproducibility

**Metabolic:**
- Weight
- Total Cholesterol, LDL, HDL
- Triglycerides and Non-essential Fatty Acids
- Glucose

**Behavioral Battery:**
- Aging: Frailty index
- Circadian Activity: Homecage wheel running
- Exploratory and locomotor behavior: Open field
- Cognition: Spontaneous Alternation
- Motor Coordination: Rotarod
- Neurophysiology: EEG

**-Omics analyses**
- RNA-seq
- Proteomics
- Metabolomics
- Microbiomics

**Biomarkers in Tissue/CSF/Blood:**
- Neurogranin
- NF-L
- Aβ
- Tau

**Neuropathology**
- Brain morphology: LFB/CV
- Neurons: NeuN/Ctip2
- Amyloid/microglia: X34/22C11/IBA1
- Tau: AT8/H&E
- Astrocyte/microglia: GFAP/IBA1
- Vascular/microglia: CD31/Fibrin/IBA1

**PET/MR imaging**
- Amyloid: AV45
- Tau: AV1451
- Blood flow: PTSM
- Glucose metabolism: FDG
Aligning human and mouse phenotypes

Fluid Biomarkers

Neuropathology

‘Omics

Brain Imaging

LOAD mouse models
<table>
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<th>Currently Available Models</th>
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<td><strong>Allelic Series of APOE</strong></td>
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<td>1. APOE4</td>
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<td>2. APOE3</td>
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<tr>
<td>3. APOE2</td>
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<tr>
<td><strong>Allelic Series of TREM2</strong></td>
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<td>1. Trem2*R47H</td>
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<td>2. Trem2*R47H.HSS</td>
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<tr>
<td>3. Trem2*Y38C</td>
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<tr>
<td>4. Trem2 KO</td>
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<tr>
<td>5. Floxed Trem2</td>
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<tr>
<td><strong>APP and MAPT</strong></td>
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<tr>
<td>1. hAβ</td>
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<tr>
<td>2. App KO</td>
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<tr>
<td>3. MAPT(H2)-GR (Koob)</td>
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<td><strong>LOAD models</strong></td>
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<tr>
<td>1. APOE4/Trem2*R47H</td>
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<tr>
<td>2. APOE4/Trem2*R47H/hAβ</td>
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<tr>
<td>3. APOE4/Trem2*R47H/hAβ/MAPT(H2)-GF</td>
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<tr>
<td><strong>Coding variants</strong></td>
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<td>1. Abca7*A1527G</td>
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<td><strong>Knockouts (to model LOF alleles)</strong></td>
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<td>3. Cd2ap promoter SNP</td>
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<td>4. Epha1 exon 1 SNP</td>
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<td>5. Ptk2b intron SNP</td>
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*APOE4/hAb and APOE3/hAb also available

https://www.model-ad.org/strain-table/
Models Available and Distributed

*2020 metrics as of September 1*

### # models available by type

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<tr>
<th>Year</th>
<th>APOE variants</th>
<th>Trem2 variants</th>
<th>base models</th>
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### # labs ordering mice: academic vs pharma

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### # mice distributed by type

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<thead>
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<th>Year</th>
<th>APOE variants</th>
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<th>APOE4/Trem2</th>
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### # mice distributed: academic vs pharma

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Principle Investigators: Stacey Rizzo, U Pitt and Paul Territo, IU

MODEL-AD Preclinical Testing Core

- Develop a pipeline for rigorous and standardized preclinical efficacy testing.
- Pair promising compounds with the most appropriate LOAD models.
- Make all data, methods and analyses available.

New Model
- genetic model with associated molecular pathology

Pharmacokinetics (PK)
- dose-response
- blood, CSF, and tissue analysis biomarker assays

Pharmacodynamics (PD)
- PET, MRI imaging
- molecular signatures ('Omics)
- histopathology
- functional/behavioral tests
ARRIVE: Highlights

Model Systems
- Construct validity of models
- Face validity of models

Animal Care
- Housing conditions (single vs. multiple)
- Husbandry (food, water, lighting, bedding)

Study Conduct
- Subject randomization/allocation
- Blinding of study personnel (techs, PI)
- Counter balancing for groups, sex, age
- Sample sizes yielding well powered studies (n=10-12 per sex per dose level per tracer)
- Inclusion/Exclusion criteria
Welcome to the STOP-AD Compound Submission Portal

Screening the Optimal Pharmaceutical for Alzheimer’s Disease (STOP-AD) is a program that offers preclinical screening of compounds through the MODEL-AD Preclinical Testing Core.

APPLY FOR COMPOUND TESTING WITH THE MODEL-AD PRECLINICAL TESTING CORE

The Preclinical Testing Core (PTC) of the Model Organism Development for Late Onset Alzheimer’s disease (MODEL-AD) consortium supports preclinical screening of test compounds nominated by the greater research community. The PTC has established a streamlined preclinical drug testing strategy with go/no-go decision points that allow critical and unbiased assessments of potential therapeutic agents.

The PTC is accepting nominations for preclinical screening of compounds to MODEL-AD.

Compounds submitted for testing initiated via an application, USA AG054434, and executed by the MODEL-AD PTC.

Submitters will be reviewed by a Steering Committee to assess the potential therapeutic for the treatment of Alzheimer’s disease.

ABOUT THE PRECLINICAL TESTING CORE

The PTC is a group of researchers under the direction of the PTC to confirm the active pharmacological impact of compounds.

STOP-AD Web Portal
- Required Data
- In Vitro Data
- In Vivo Data
- Pharmacokinetics
- Pharmacodynamics
- Toxicology
- Clinical Data
Welcome to the AD Knowledge Portal

Discover and download Alzheimer’s Disease data, analyses, and tools from the National Institute on Aging’s Alzheimer’s Disease Translational Research Program.

Established by the ACCELERATING MEDICINES PARTNERSHIP

PROGRAMS

- **AMP-AD**
  - Visit website
  - Discovering new drug targets for Alzheimer's disease treatment and prevention.

- **M2OVE-AD**
  - Visit website
  - Deconstructing the metabolic and vascular etiology of Alzheimer’s disease

- **MODEL-AD**
  - Visit website
  - Developing new Alzheimer’s disease animal models.

- **Resilience-AD**
  - Visit website
  - Understanding cognitive resilience under conditions of high risk for Alzheimer’s disease.

- **Psych-AD**
  - Visit website
  - Understanding the molecular mechanisms of neuropsychiatric symptoms in Alzheimer’s disease and Alzheimer’s disease related dementias.

- **CDCP**
  - An AD Knowledge Portal data contribution program

https://news.adknowledgeportal.org/newsletter
Novel uses for existing and failed drugs can save time and cost in bringing new therapeutics to patients.
PAR-20-156  Translational Bioinformatics Approaches to Advance Drug Repositioning and Combination Therapy Development for Alzheimer’s Disease (R01 Clinical Trial Optional)

This funding initiative encourages the use of existing and/or the development of novel computational approaches to identify drugs currently used for other conditions, as well as candidate drugs from failed Phase II/Phase III clinical trials, with potential to be efficacious in AD/ADRD as individual drugs, or as drug combinations.

Launched in 2017 as PAR-17-032; re-issued as PAR-20-156

Active through: May 08, 2023

Program Director: Jean Yuan, MD, PhD
xin.yuan@nih.gov
Purely computational research aimed at using existing or new methodology to identify drugs or drug combinations with favorable efficacy and toxicity profiles as candidates for repositioning.

Research that combines computational and experimental approaches to generate data-driven predictions on the efficacy of repurposed drugs or drug combinations, followed by efficacy testing in proof-of-principle animal studies or in proof-of-principle human trials.

Development of quantitative, mechanistic methods that can assess the synergy of candidate therapeutics, including synergy between candidate drugs and non-pharmacological perturbations (i.e., diet, sleep, cognitive training).

Integration of clinical and phenotypic data with molecular data generated with biosamples from failed AD/ADRD trials, to identify the molecular determinants of responder phenotypes. (academic-industry collaborations)
## Funded Projects:

**R01AG066707**  
CHENG, FEIXIONG  
*Endophenotype Network-based Approaches to Prediction and Population-based Validation of in Silico Drug Repurposing for Alzheimer’s Disease*

**R01AG066749**  
JIANG, XIAOQIAN (contact)  
*Finding combinatorial drug repositioning therapy for Alzheimer’s disease and related dementias*

**R01AG066750**  
SU, ANDREW I  
*Compound repositioning for Alzheimer’s Disease using knowledge graphs, insurance claims data, and gene expression complementarity*

**R01AG068030**  
ZHANG, BIN (contact)  
*Novel Network Biology Approaches to Reposition FDA-approved Drugs for Alzheimer’s Disease*

**R56AG061163**  
CHEN, CHI-HUA  
*Omic analyses for stratifying Alzheimer’s subtypes and identifying novel drug targets*

**R56AG065352**  
LI, FUHAI  
*Combine Genomics and Symptoms Data Driven Models to Discover Synergistic Combinatory Therapies for Alzheimer’s Disease*

**RF1AG059319**  
GANDY, SAMUEL E (contact); XIA, WEIMING (contact)  
*SYSTEMATIC DRUG REPURPOSING TARGETING IMMUNE ACTIVATION NETWORKS IN ALZHEIMER’S DISEASE (AD)*

**R01AG057555**  
XIE, LEI  
*Drug repurposing for Alzheimer’s disease using structural systems pharmacology.*

**R01AG057557**  
XU, RONG  
*An Integrated Reverse Engineering Approach Toward Rapid Drug Repositioning for Alzheimer’s Disease*

**R01AG057635**  
WONG, STEPHEN TC  
*Systematic Alzheimer’s disease drug repositioning (SMART) based on bioinformatics-guided phenotype screening and image-omics*

**R01AG057683**  
HUANG, YADONG (contact); SIROTA, MARINA  
*ApoE Genotype-Directed Drug Repositioning and Combination Therapy for Alzheimer’s Disease*

**R01AG058063**  
ALBERS, MARK W (contact); SORGER, PETER  
*Harnessing Diverse BioInformatic Approaches to Repurpose Drugs for Alzheimer’s Disease*

**R01AG059854**  
TEICH, ANDREW FRANKLIN  
*A Translational Bioinformatics Approach to Rescuing Synaptic and Neurophysiologic Dysfunction in Alzheimer’s Disease*

**R01AG061105**  
LICHTARGE, OLIVIER  
*A knowledge map to find Alzheimer’s disease drugs*

**R01AG062547**  
TANZI, RUDOLPH EMILE (contact)  
*The Alzheimer’s Disease Resiliome: Pathway Analysis and Drug Discovery.*

**R01AG061911**  
WAHLESTEDT, CLAES ROBERT (contact)  
*Leveraging the Human Non-Coding Transcriptome to Identify Therapeutics for Healthy Aging and Alzheimer’s Disease*

**R01AG062620**  
CHANG, RUI (contact)  
*Predictive Networks-based in-silico approach for Precision Medicine-repurposing for Alzheimer’s Disease*
A Precision Medicine Approach to AD Treatment and Prevention
AD Molecular Endophenotypes Show Strong Sex Specificity

- AD Astrocytes
- AD Astrocytes, AD Endothelial, AD Microglia
- AD Neuron
- AD Oligodendrocyte, glial cells
- AD Heat Shock Response
- AD Response to Unfolded Protein

Enrichment for AD DEG Signatures

AMP-AD Consortium - Logsdon et al. – https://doi.org/10.1101/510420

bioRxiv
THE PREPRINT SERVICE FOR BIOLOGY
### Funded Projects:

<table>
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<tr>
<th>Project ID</th>
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<td>NALVARTE, IVAN</td>
<td>Understanding the Role of Menopause and Estrogen Receptor Activation for Alzheimer’s Disease Risk</td>
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<td>RF1AG057884</td>
<td>DONG, HONGXIN</td>
<td>Sex Differences in Central Stress Response and Alzheimer’s Disease Neuropathology</td>
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<td>RF1AG057895</td>
<td>COLTON, CAROL ANNE (contact); BADEA, ALEXANDRA; GOTTSHALK, WILLIAM KIRBY; LUTZ, MICHAEL WILLIAM; THOMPSON, JOSEPH WILBUR; WILLIAMS, CHRISTINA L</td>
<td>Sex and APOE Genotype Interact to Alter Immune Regulated Metabolism in AD</td>
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<td>RF1AG058068</td>
<td>PIKE, CHRISTIAN J (contact); GATZ, MARGARET; LADU, MARY JO</td>
<td>Sex Differences in the Relationship Between APOE and AD: Role of Sexual Differentiation</td>
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<td>KADDURAH-DAOUK, RIMA F (contact); BRINTON, ROBERTA EILEEN; CHANG, RUI; KASTENMULLER, GABI</td>
<td>Metabolic Networks and Pathways Predictive of Sex Differences in AD Risk and Responsiveness to Treatment</td>
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<td>DUBAL, DENA BOU</td>
<td>Mechanisms of X-Chromosome-dependent Sex Difference in Alzheimer’s Disease</td>
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<td>RF1AG057931</td>
<td>BRINTON, ROBERTA EILEEN (contact); CHANG, RUI; MOSCONI, LISA</td>
<td>Sex Differences in the Molecular Determinants of Alzheimer’s Disease Risk: Prodromal Endophenotype</td>
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<tr>
<td>R01AG060393</td>
<td>SIROTA, MARINA</td>
<td>An Integrative Multi-Omics Approach to Elucidate Sex-Specific Differences in Alzheimer’s Disease</td>
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<td>R01AG057307</td>
<td>SCHREURS, BERNARD G (contact); GHRIBI, OTHMAN</td>
<td>Modeling Sex Differences in Alzheimer’s Disease Cognition and Pathology</td>
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<td>*<em>PAR-17-033</em></td>
<td><strong>Integrative Research to Understand the Impact of Sex Differences on the Molecular Determinants of AD Risk and Responsiveness to Treatment (R01)</strong></td>
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*re-issued as RFA-AG-21-029
Develop robust research programs that will explore how genes, environment, and hormonal status (gonadal and brain-derived) interact at various levels of biologic complexity (cell, tissue, organs/organ systems, and populations) to produce heterogeneous phenotypes of disease risk and responsiveness to therapy in AD/ADRD.

A cross-disciplinary team-science approach that brings together experts in neuroscience, physiology, computational biology and data science, and translational and clinical research is strongly encouraged, as is the integrative use of human data and biosamples with cell-based and animal models.

This FOA encourages studies that integrate and analyze multimodal data, such as -omics, imaging, and clinical data, as well as electronic health records and digital health data from biosensors or smart devices.

Of particular interest are projects that use biosamples and/or data collected from prior or ongoing AD/ADRD clinical trials to assess sex differences in response to interventions and to examine the molecular basis of this effect.

Submission Deadline: November 10, 2020
Program Director: Jean Yuan, MD, PhD  xin.yuan@nih.gov
Emphasis on Data Sharing, Scientific Rigor and Reproducibility:

- Applicants are expected to follow open-science, open-source principles for sharing data and research tools.
- The preclinical efficacy studies are expected to follow the general ARRIVE guidelines for animal research and the best practice guidelines for AD preclinical efficacy studies.
Training the New Translational Workforce

Institutional Training Programs to Advance Translational Research on Alzheimer's Disease and AD Related Dementias (T32) PAR-21-112*

Program Director: Yuan Luo, PhD
Yuan.Luo@nih.gov

* re-issue of PAR-18-524
Upcoming Funding Initiatives for Training

https://www.nia.nih.gov/approved-concepts

Fellowship and Career Development Awards to Promote Diversity in Translational Research for AD/ADRD

- Establish a training pipeline for predoc, postdoc and junior faculty from under-represented groups.
- This training initiative will emphasize the development and application of skills in data science and drug discovery disciplines.
- The goal is to develop a diverse translational workforce that can effectively participate in and/or lead a team-science, precision medicine approach to AD/ADRD treatment, prevention, early detection, disease management and care.
Formulate a blueprint for an integrated, translational research agenda that will enable the development of effective therapies (disease modifying and palliative) across the disease continuum for the cognitive as well as neuropsychiatric symptoms of Alzheimer’s disease.

- Recognize the heterogeneity and the multifactorial nature of the disease.
- Understand all aspects of healthy aging and resilience to AD to inform new prevention strategies.
- Support extensive molecular of existing and establish new cohorts to fill the gaps in large-scale human data needed to build predictive models of disease and wellness.
- Employ data-driven research paradigms such as systems biology and systems pharmacology.
- Build new multidisciplinary translational teams and create virtual and real spaces where these teams can operate.
- Engage patients, caregivers and citizens as direct partners in research.
- Enable rapid and extensive sharing of data, disease models, and biological specimens.
- Develop computational tools and infrastructure for storage, integration, and analysis of large-scale biological and other patient-relevant data.
- Support and enable open science.
- Change academic, publishing, and funding incentives to promote collaborative, transparent, and reproducible research.
2021 NIH AD Research Summit: Path to Precision Medicine for Treatment and Prevention

April 19-22, 2021
10:00am -3:30pm EDT
Virtual Event

Program Sessions:

- Deconstructing Disease Complexity: from Populations to Single Cells, from Genes to Multiscale Models
- Enabling Infrastructure and Incentives to Improve Research Rigor, Reproducibility and Translatability
- Accelerating Therapy Development: Open Science from Targets to Trials
- Diversifying the Therapeutic Pipeline to Develop Precision Medicines
- Emerging Biomarkers Landscape
- Advancing Drug Repurposing and Combination Therapy Development
- Understanding the Impact of the Exposome on Brain Health to Advance Disease Prevention

https://www.nia.nih.gov/2021-alzheimers-summit
The coronavirus pandemic has shattered the status quo on drug development. We should build on that.

BY E. RICHARD GOLD
March 26, 2020 7:30 AM EDT

New drugs produce on average either flat or declining additional benefit over their predecessors, according to a 2018 study on cancer drugs. In fact, a recent working paper by Stanford and MIT researchers found that the U.S. must double its investments every 13 years just to stay at the same level or, in some cases, fall behind.

The COVID-19 pandemic shattered this status quo. In the face of this, scientists and governments turned to a new model of drug discovery: open science partnerships. Scientists and governments quickly abandoned proprietary science when faced with the COVID-19 pandemic. They shared data, molecules, and genetic sequences as they were identified and worked together to develop diagnostic kits and repurpose existing drugs.

Open science partnerships play a critical role in drug development by de-risking innovation through cost sharing, leveraging financing, and bringing together actors with diverse skills, tools, materials, and knowledge. All stakeholders have a role in promoting these partnerships.

This requires new forms of research grants targeting open science, increased corporate funding and participation, and changing university promotion and tenure rules to reward data and materials sharing. Researchers should also more actively share data, tools, and materials before publication, such as through e-lab books and regular data uploads.
ACKNOWLEDGEMENTS

DIVISION OF NEUROSCIENCE
Director: Eliezer Masliah
Deputy Director: Jennie Larkin

Office for Strategic Development and Partnerships
Director - Suzana Petanceska
Erika Tarver
Nadezda Radoja
Jean Yuan
Laurie Ryan
Alvin McKelvy

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Cerise Elliot
John Hsiao
Yuan Luo
Akanni Clarke
Grayson Donley
Alvin McKelvy

Neurobiology of Aging and Neurodegeneration
Chief – Bradley Wise
Paul Barrett
Amanda M. DiBattista
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Mack Mackiewicz
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Zane Martin
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Ali Sharma
Jean Yuan

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Dallas Anderson
Jennie Larkin
Marilyn Miller
Damali Martin
Ananya Paria
Sharna Tingle
Alison Yao

Neurobiology of Aging and Neurodegeneration
Chief – Bradley Wise
Paul Barrett
Amanda M. DiBattista
Elizabeth A. Newman
Mack Mackiewicz
Lisa Opanashuk
Austin Yang

Behavioral and Systems Neuroscience
Chief – Molly Wagster
Dave Frankowski
Coryse St. Hillaire-Clarke
Devon Oskvig
Luci Roberts
Matt J Sutterer
Drug Development for Alzheimer’s Disease and Related Disorders (ADRD): Cross-Disease Opportunities

Jeffrey Cummings, MD, ScD
Joy Chambers-Grundy Professor of Brain Science
Director, Chambers-Grundy Center for Transformative Neuroscience
Department of Brain Health
University of Nevada Las Vegas (UNLV)
Dr. Cummings has provided consultation to Acadia, Actinogen, Acumen, Alector, Alkahest, Alzheon, AriBio, Avanir, Axsome, Behren Therapeutics, Biogen, Cassava, Cerecin, Cerevel, Cortexyme, Cytox, EIP Pharma, Eisai, Foresight, GemVax, Genentech, Green Valley, Grifols, Janssen, Jazz, Karuna, Merck, Novo Nordisk, Otsuka, ReMYND, Resverlogix, Roche, Samumed, Samus, Signant Health, Sunovion, Suven, United Neuroscience, and Unlearn AI pharmaceutical and assessment companies. Dr. Cummings has stock options in ADAMAS, AnnovisBio, MedAvante, BiOasis and United Neuroscience. Dr. Cummings owns the copyright of the Neuropsychiatric Inventory. Dr Cummings is supported by NIGMS grant P20GM109025; NINDS grant U01NS093334; NIA grant R01AG053798; and NIA grant P20AG068053.
Drug Development for Alzheimer’s Disease and Related Disorders (ADRD): Cross-Disease Opportunities

Accelerate Cure/Treatments for Alzheimer’s Disease (ACT-AD) Coalition

- ADRD shared biology
- ADRD cross-disease treatments
- ADRD informative trials
- Neurofilament light (NfL) for ADRD trials
- Discussion points
• ADRD are characterized by protein aggregation
  • Proteinopathy is common across ADRD
  • The type of protein differs among ADRD
  • The location of protein aggregation and neuronal loss differs among ADRD

• Protein aggregation initiates processes leading to cell death that have shared features across ADRD

• Shared features suggest that there may be opportunities for
  • Cross ADRD learnings
  • Cross ADRD therapies
Alzheimer
Amyloid

FTD
Pick

PD/DLB/MSA
Lewy body

CTE/PART
Tau

ALS/FTD/LATE
TDP-43
Generalizable Model of ADRD

Protein Aggregation in Vulnerable Cell Population

Regional cell Death; Transmitter Deficits

Clinical Phenotype: AD, PD, DLB, FTD, etc

Cell processes:
• Synaptic loss
• Metabolic effects
• Inflammation
• Epigenetic changes
Generalizable Model of ADRD

Opportunities for shared proteostasis effects

Opportunities for shared cell/disease process effects

Protein Aggregation in Vulnerable Cell Population

Regional cell Death; Transmitter Deficits

Clinical Phenotype: AD, PD, DLB, FTD, etc

Cell processes:
• Synaptic loss
• Metabolic effects
• Inflammation
• Epigenetic changes
### Disease-Specific and Non-specific Targets

#### Protein-specific
- Monoclonal antibodies
- Protein-specific treatment

#### Protein-nonspecific
- Aggregation inhibitors
- Could apply cross-disease

#### Disease-preferential
- ApoE/Alzheimer
- Vascular/VaD
- Epigenetic
- Neurogenesis
- Growth factors
- Gut-brain axis

#### Disease-nonpreferential
- Inflammation
- Synaptic plasticity
- Oxidative stress
- Cell death

---

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<th>Protein of Interest</th>
<th>Disease-Mapping</th>
<th>Disease-Related Targets</th>
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<td>ApoE/lipids</td>
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<td>a-Synuclein</td>
<td>PD; DLB; MSA</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td></td>
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<td>Cell death</td>
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<td></td>
<td>Metabolism/bioenergetics</td>
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<tr>
<td></td>
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<td>Vasculature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Growth factors/hormones</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Synaptic plasticity</td>
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<tr>
<td></td>
<td></td>
<td>Epigenetic regulators</td>
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<tr>
<td></td>
<td></td>
<td>Neurogenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gut-brain axis</td>
</tr>
</tbody>
</table>

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https://iadrp.nia.nih.gov/about/cadro
Current Alzheimer Trials by CADRO
Mechanism of Action/Target

CADRO – Common Alzheimer’s Disease Research Ontology (iadrp.nia.nih.gov)
## Cross-Disease Trials in Progress
*(from clinicaltrials.gov accessed 12/27/2020)*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>AD</th>
<th>PD/PDD</th>
<th>DLB</th>
<th>FTD</th>
<th>ALS</th>
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<tr>
<td>Ambroxol</td>
<td>B-glucocerebrosidase chaperone</td>
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<td>Nalfamapimod</td>
<td>P38δ inhibitor</td>
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<td>Nilotinib</td>
<td>Tyrosine kinase inhibitor</td>
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<td>Intranasal insulin</td>
<td>Glucose metabolism</td>
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<td>Metformin</td>
<td>Insulin sensitizer</td>
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<tr>
<td>PU-AD</td>
<td>Epichaperome inhibitor</td>
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<td>ALZ-OP1a</td>
<td>Anti-aggregation + anti-inflammatory</td>
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<tr>
<td>Masitinib</td>
<td>Kinase inhibitor; microglial modulator</td>
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<tr>
<td>L-serine</td>
<td>Amino acid supplement</td>
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<tr>
<td>Posiphen</td>
<td>Protein production inhibitor</td>
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</table>
Rivastigmine is an Example of a Successful/Approved Cross-ADRD Therapeutic

**Shared biology across several ADRD**
- Cholinergic deficit
- PDD – (-)20%
- DLB – (-)20.3%
- PD w/o dementia – (-)19.9%
- AD – (-) 15% (temporal)


AD – Alzheimer’s disease; DLB – dementia with Lewy bodies; PD – Parkinson’s disease; PDD – Parkinson’s disease dementia
Tau Basket Trial: Alzheimer, Progressive Supranuclear Palsy, Corticobasal Degeneration


Tsai R, et al. JAMA Neurol 2020; 77: 215-224
Pimavanserin for Dementia-Related Psychosis (DRP)

Harmony Trial
- Randomized withdrawal
- Open label initial phase
- DB withdrawal period
- 5 types of dementia
- No biomarker confirmation
- Significant d-p difference in relapse of psychosis
- Currently undergoing FDA review

Pimavanserin (Nuplazid™)
5-HT$_{2A}$ inverse agonist

Final common circuit hypothesis

Alzheimer’s Disease
Dementia w Lewy Bodies
Parkinson’s Dis Dementia
FTLD w Dementia
Vascular Dementia
Dopaminergic Agents May Produce Cognitive Enhancement in Alzheimer’s Disease and Parkinson’s Disease

- Rasagiline produced cognitive enhancement in PD\(^1\)
- Rasagiline produced cognitive and brain metabolism benefit compared to placebo in AD\(^2\)
- Rotigotine improved executive function and decreased decline in ADLs in AD\(^3\)
- DA1 receptor agonists are being considered for apathy in ADRD\(^4\)

\(^1\)Rascol O et al. Lancet Neurol 2011; 10: 425-423;  
\(^2\)Matthews D ewt al. Alz Dem: TRCI 2021 in press;  
\(^3\)Koch G et al, JAMA Neurol Network Open 2020;  
\(^4\)Chong T, Husain M. Prog Brain Res 2016; 229-389
Neurofilament Light (NfL) is Positioned to Assist ADRD Drug Development

NfL is elevated across ADRD. (Olsson B et al. JAMA Neurol 2019; 76: 318-325)

Biomarkers

- Disease-specific $\text{AB}42/40$
- ADRD - NfL

Toferson reduced plasma and CSF NfL in an ALS clinical trial (BIIB Earnings Call 22OCT2019.pdf)
Summary

- Exciting time in treatment development for ADRD
- ADRD share many biological features
- AD drug development includes target relevant to ADRD
- Cross disease therapy has occurred (rivastigmine); trials include > 1 ADRD focusing shared mechanisms
- Novel trial designs for ADRD are promising
- Biomarkers relevant to ADRD trials are emerging
Discussion Points with the FDA

- Would orphan disease strategies (e.g., historical controls) be acceptable in support of an indication for a rare neurodegenerative disorder such as progranulin mutation carriers with FTD?
- Could a positive outcome of a prespecified group in a basket trial constitute 1 of 2 trials for a regulatory package?
- Could a smaller trial with a positive outcome on a biomarker reasonably likely to predict clinical benefit with a larger trial demonstrating a positive clinical outcome constitute the 2 trials of a regulatory package?
Discussion Points with the FDA

- Many non-Alzheimer neurodegenerative disorders do not have diagnostic biomarkers. Is the FDA comfortable with an “indication” based on the clinical phenotype?

- Given the shared biological features, would the FDA view PD dementia and DLB as the same disorder? Could trials of an approvable package include both disorders in the same trials?

- When drugs are being developed to treat neuropsychiatric symptoms in Alzheimer’s disease, will the FDA require biomarker confirmation of the diagnosis of Alzheimer’s disease?

- If a drug were being developed for a process such as inflammation that is present across many ADRD, would the FDA allow an indication such as “for the treatment of Alzheimer’s disease and related disorders”?
Thank you; stay safe; get vaccinated
Research into Molecular Underpinning of Dementia

David A. Bennett, M.D.
Director, Rush Alzheimer’s Disease Center
Robert C. Borwell Professor of Neurological Sciences
Rush University Medical Center
Chicago, IL

13th Annual FDA/ACT-AD Allies Meeting
Common Threads: Learning from the Related Dementias
February 3, 2021
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Study Participants:
Religious Orders Study
Rush Memory and Aging Project

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Alzheimer’s Association
Rush University Medical Center

Disclosures
I have no relevant disclosures.
Objectives

• Motivating questions
• Risk factors, pathology, cognitive decline and Alzheimer’s dementia
• Identifying the molecular basis of dementia
Motivating Questions

➢ Why do older people lose cognition as they age?
Motivating Questions

- Why do older people lose cognition as they age?

We need to study older persons without dementia who agree to:

- Tell us all kinds of things about their lifestyles that possibly could be related to the development of ADRD
- Detailed clinical evaluations every year for ADRD
- Donate blood every year
- Brain donation
- Wait….. for the omic revolution!
- It’s here!
The Religious Orders Study

- Began in 1993
- > 1,500 older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual clinical evaluation
- All agreed to brain donation
- > 375 have developed dementia
- > 600 have developed MCI
- > 750 brain autopsies
Religious Orders Study: Participating Sites

[Map showing participating sites across the United States, with major cities marked.]
The Memory and Aging Project
... because memories should last a lifetime

- Began in 1997
- > 2,100 residents from across the Chicago area
- All agreed to annual clinical evaluation
- All agreed to donate brain, spinal cord, muscle, and nerve at the time of death
- > 375 have developed dementia
- > 625 have developed MCI
- > 800 autopsies
Objectives

- Motivating questions
- Risk factors, pathology, cognitive decline and Alzheimer’s dementia
- Identifying the molecular basis of dementia
Risk Factors → Alzheimer’s Dementia
<table>
<thead>
<tr>
<th>Genes/Proteins</th>
<th>Experiential</th>
<th>Psychological</th>
<th>Medical</th>
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<tbody>
<tr>
<td>APOE, CR1, CD33, ABCA7, CD2AP, CETP, SORL1, APP, ANK1, TREM1, TREM2, ANK1, BIN1, RHBDF2, FADD, PTPRD, SRCAP, UNC5C, ABCC9, EPHA1, TOMM40, T2DM, CDKN2A/B, rs7578326, rs12779790, IGF2BP2, HMGCR, CELSR2, ATP2B1, LOC728723, CELF1, NMD3, MED13, CELF1, PICALM, KLOTHO, BDNF, FOXF2, MS4A, PINX1, CD2AP, CLDN</td>
<td>Education, Late life Cognitive, Physical, &amp; Social Activity, Social Networks, Early life foreign language or music lessons, Physical activity, Life space</td>
<td>Harm avoidance, Emotional neglect, Purpose in life, Depressive symptoms, Conscientiousness, Neuroticism, Loneliness, Risk aversion, Temporal discounting</td>
<td>Sex, CMV, Monocyte CD33, Anemia, Surgical menopause, Gama tocopheral, Cancer, Seafood, Sleep, Circadian phase, Fractal regulation. Head trauma, Chronic kidney disease, MEDI diet, DASH diet, MIND diet</td>
</tr>
<tr>
<td>IGFBP5, AK4, ITPK1, HSBP2,</td>
<td>Health/financial decision making &amp; Literacy, Susceptibility to Scams</td>
<td>Parkinsonian signs, Physical frailty, BMI, Grip strength Odor identification</td>
<td></td>
</tr>
</tbody>
</table>
PSYCHOSOCIAL FACTORS IN RELATION TO AGE AT ONSET OF DEMENTIA IN OLDER PERSONS


<table>
<thead>
<tr>
<th>Depression ADO</th>
<th>No depression ADO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADO=87.1</td>
<td>ADO=92.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Highest tertial ADO</th>
<th>Lowest tertial ADO</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADO=89</td>
<td>ADO=93.5</td>
</tr>
</tbody>
</table>
Building a pipeline to discover and validate novel therapeutic targets and lead compounds for Alzheimer’s disease

Much of Late Life Cognitive Decline Is Not due to Common Neurodegenerative Pathologies

Much of Late Life Cognitive Decline Is Not due to Common Neurodegenerative Pathologies

Much of Late Life Cognitive Decline Is Not due to Common Neurodegenerative Pathologies

What else contributes to cognitive decline?

Person-Specific Contribution of Neuropathologies to Cognitive Loss in Old Age

Person-Specific Contribution of Neuropathologies to Cognitive Loss in Old Age

Demographics
And Pathologic AD
And 7 other pathologies
And an indicator for unaccounted AD dementia cases

67.5% AD dementia cases attributable all eight neuropathologic indices

Much of Late Life Cognitive Decline Is Not due to Common Neurodegenerative Pathologies

Neural reserve, neuronal density in the locus coeruleus, and cognitive decline

Alzheimer’s Dementia

Risk Factors
Religious Orders Study and Rush Memory and Aging Project

APOE, MAPT, CCDC62, MED13, SREBF1, GAK, IRS1, FTO, MAPT H2, urinary incontinence, TBI
APOE/TOMM40, CR1, CD33, ABCA7, CD2AP, CEP5, SORL1, APP, ANK1, TREM1, TREM2, ANK1, BIN1, RHBDF2, FADD, UNC5C, PTPRD, CMV, monocyte CD33, surgical menopause, gamma tocopheral, cancer, literacy, olfaction
APOE, ABCC9, EPBA1, ZCWPW1, SORL1
APOE/TOMM40, T2DM, CDKN2A/B, rs7578326, rs12779790, IGF2BP2, HMGCR, CELSR2, ATP2B1, LOC728723, CELF1, CD33, harm avoidance, emotional neglect, hemoglobin, diabetes, purpose in life, sleep
TMEM106B, GRN
APOE, NMD3, MED13, CELF1, TBI
depressive symptoms
education, sex, late life cognitive, physical, & social activity, social networks, conscientiousness, neuroticism, PICALM, KLOTHO, BDNF, ENC1, UNC5C, early life foreign language/music lessons, loneliness, physical activity, sleep fragmentation, circadian phase, well-being, life space, chronic kidney disease, risk aversion, temporal discounting.
systemic inflammation, cognitive activity
APOE, Internet use

Parkinsonian signs. Physical frailty, BMI, Grip strength. Odor identification

AD pathology
Hippocam sclerosis
CVD
TDP-43
PD/LBD pathology

Brainstem Aminergic neurons
Pre-synaptic proteins
REST, BDNF

Macro/micro structure

Health/financial decision making & Literacy, Susceptibility to Scams

Cognitive Decline, AD MCI & AD Dementia
Relation of genomic variants for Alzheimer disease dementia to common neuropathologies

The Molecular and Neuropathological Consequences of Genetic Risk for Alzheimer’s Dementia

Summary

• Loss of cognition with age is a complex function of multiple brain pathologies adding to and interacting with multiple resilience markers
• Numerous genomic, experiential, psychological, and medical factors are associated with cognitive decline that are not associated with any pathology or biology measured to date
• Risk factors for Alzheimer’s dementia are often NOT risk factors for Alzheimer’s disease (defined biologically in new Framework)
Objectives

• Motivating questions
• Risk factors, pathology, cognitive decline and Alzheimer’s dementia
• Identifying the molecular basis of dementia
Religious Orders Study and Rush Memory and Aging Project

Risk Factors: Medical, Psychological, Experiential, genome-wide genotyping

Epigenome

Transcriptome

Proteome and metabolome

Quantitative neurobiology

Structural & function MRI

Quantitative clinical phenotype

Syndromic phenotype

Affy 6.0/Illumina Quad Whole Genome Sequencing

5mC Methylation 5hmC Methylation H3K9Ac; H3K27Ac, ATACseq

miRNA, RNAseq

SRM, top down proteomics, TMT, LC/MS

Neuropathology AD, CVD, LBD, HS, TDP, microglia

Ante-mortem MCI Flair, MP rage, DTI, SWI, rsfMRI

Cognitive function 21 tests

AD, stroke, PD, depression

Resilience Markers Pre-synaptic proteins, LC neurons

Post-mortem MRI DTI, MP Rage, T2

Motor function, disability, BMI, actigraphy, dynaport, sleep, behavioral economics, decision making, olfaction, nutrition

A molecular network of the aging human brain provides insights into the pathology and cognitive decline of Alzheimer's disease.

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47 co-expression networks
53 ADRD phenotypes

A molecular network of the aging human brain provides insights into the pathology and cognitive decline of Alzheimer's disease.

Knockdown experiments
Effect of construct on Aβ 42 secretion.

Targeted proteomics of human neocortex uncover multiple paths to Alzheimer's dementia

Adjusted for:
Demographics + Aβ + PHFtau

Summary

• Found mRNA coexpression networks related to AD
• Nominated genes in m109 as drivers of amyloid-beta
• Knockdown experiments ex vivo illustrates altered amyloid-beta production as predicted
• SRM proteomics quantified protein and showed its effect mediated by AD pathology as predicted
Residual Decline in Cognition After Adjustment for Common Neuropathologic Conditions

A molecular network of the aging human brain provides insights into the pathology and cognitive decline of Alzheimer's disease.

47 co-expression networks
53 ADRD phenotypes

Targeted proteomics of human neocortex uncover multiple paths to Alzheimer’s dementia

Targeted proteomics of human neocortex uncover multiple paths to Alzheimer’s dementia

<table>
<thead>
<tr>
<th>Protein</th>
<th>Cog Decline Est</th>
<th>P value</th>
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<tbody>
<tr>
<td>AK4</td>
<td>-0.090</td>
<td>7.3×10^{-6}</td>
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<td>ANKRD40</td>
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<td>BCL2L1</td>
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<td>FBXO2</td>
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<td>HSPB2</td>
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<td>IGFBP5</td>
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<td>ITPK1</td>
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<td>SLC6A12</td>
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<td>0.017</td>
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</table>

Targeted proteomics of human neocortex uncover multiple paths to Alzheimer’s dementia

Black is positive and white is negative association

Targeted proteomics of human neocortex uncover multiple paths to Alzheimer's dementia

Cortical Proteins Associated With Cognitive Resilience in Community-Dwelling Older Persons

Cortical Proteins Associated With Cognitive Resilience in Community-Dwelling Older Persons

Cortical Proteins Associated With Cognitive Resilience in Community-Dwelling Older Persons

Summary

• Using residual cognitive decline as a continuous measure of high and low resilience to common brain pathologies, we can use the same pipeline aimed at
  – identifying molecular genomic indices related to common dementing neuropathologies,
  – to identify molecular genomic indices related to high and low resilience