ACCELERATING MEDICINES PARTNERSHIP®
ALZHEIMER’S DISEASE (AMP AD)

Accelerating Medicines Partnership® Program Symposium
Bethesda, February 5-6, 2024

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ACCELERATING MEDICINES PARTNERSHIP® ALZHEIMER’S DISEASE (AMP AD)

Suzana Petanceska, PhD
National Institute on Aging
co-chair AMP AD 2.0

Accelerating Medicines Partnership® Program Symposium
Bethesda, February 5-6, 2024
Accelerating Medicines Partnership for Alzheimer’s disease (AMP AD)  
Launched 2014

**Biomarkers in Clinical Trials**

- Enrich anti-amyloid AD secondary prevention trials (A4 and DIAN-TU) with Tau PET imaging to test its utility as a marker of disease progression and treatment response.

- Make pre-randomization and post-randomization data and biospecimens broadly available.

**Target Discovery and Preclinical Validation**

- Apply a systems biology approach to discover and validate the next generation of therapeutic targets using an open science research model.

- Develop centralized data infrastructure/portal for rapid sharing of all data and analytical results.
Accelerating Medicines Partnership for Alzheimer’s disease (AMP AD) Target Discovery and Preclinical Validation Project

Large-scale, cross-disciplinary, team science: 6 multi-institutional academic teams and a data coordinating team

- Generate high quality multiomic data from postmortem brain tissue and plasma samples from well phenotyped cohorts and AD brain banks.
- Build network models of targets/pathways
- Carry out early target validation in cell-based and animal models.

Rapid sharing of data, analyses, methods and nominated targets through centralized data infrastructure
AMP AD 1.0
Systems-based, multi-omic approach to target discovery and validation

AMP AD 2.0
Precision medicine approach to target and biomarker discovery
AMP AD 2.0: Enabling a Precision Medicine Approach to Target and Biomarker Discovery

- Expand multi-omic profiling in samples (brain, CSF, blood) from diverse cohorts (African American and Latino American)
- Generate longitudinal immunologic profiling data across diverse cohorts (Caucasian, African American, and Latino American)
- Expand the existing sn/sc molecular profiling efforts to multiple brain regions and in samples from diverse cohorts
AMP AD 2.0: Research Teams
ACKNOWLEDGMENTS

AMP AD PUBLIC SECTOR PARTNERS

AMP AD 1.0 PRIVATE SECTOR PARTNERS

AMP AD 2.0 PRIVATE SECTOR PARTNERS
ACKNOWLEDGMENTS

National Institute on Aging
Suzana Petanceska
Nandini Arunkumar
Erika Tarver
Laurie Ryan
Neil Buckholtz
Eliezer Masliah
Richard Hodes

Industry Co-chairs*
Michael Nagle, Eisai
Maria Quinton, Takeda
David Collier, Eli Lilly
Michael Decker, AbbVie

*Co-chairs affiliations at the time of service

AMP AD Data Coordinating Center
Sage Bionetworks
Anna Greenwood
Christine Suver
Lara Mangravite
Ben Logsdon
Mette Peters
Stephen Friend

Foundation for the NIH
Francesca Cignarella
Eline Appelmans
Rosa-Canet-Aviles
David Wholley

All Members of the AMP AD 1.0 and AMP AD 2.0 Steering Committees and the Academic Research Teams!
AMP Symposium: AMP AD Session

1. AMP AD 1.0 Highlight: Impact of sharing clinical trials data on understanding disease progression in diverse populations and patient selection - Laurie Ryan, NIA

2. AMP AD 2.0 Enabling Data Infrastructure for Systems Biology Research and Target Prioritization - Anna Greenwood, Sage Bionetworks

3. AMP AD 2.0 Precision Medicine Approach to Deconstructing Disease Complexity and Identifying Novel Targets and Biomarkers
   - Insights from Integration of Multiscale Data for Subtyping Persons with Alzheimer’s Dementia - David Bennett, Rush University
   - Integrative Proteomics Approach to Deconstructing Disease Complexity and Biomarker Discovery - Nick Seyfried, Emory University
   - Developing a Multiomics Atlas of Alzheimer’s Disease - Matthias Arnold, Helmholtz University/Duke University

4. Alzheimer’s Association Perspective on the Value and Impact of AMP AD - Rebecca Edelmayer, Alzheimer’s Association

5. Industry Perspective on the Value and Impact of AMP AD - Michael Nagle, Eisai
AMP Symposium Poster Reception  5:30-7:15PM, Feb 5
AMP AD Poster Presentations

1. **Brain Multiomics Analysis in Diverse Cohorts** - Joseph Reddy, Mayo Clinic, Jacksonville

2. **Open-Source Tools for Target Discovery and Validation: Agora Results Explorer** - Jessica Britton, Sage Bionetworks


4. **Modeling the Heterogeneity of AD in iPSC cell lines** - Sarah Heuer, Harvard U/BWH

5. **Insights from CSF Proteomics in Diverse Cohorts** - Madison Bangs, Emory University

6. **Integrative Metabolomics and Systems Modeling for Target Discovery and Validation** - Priyanka Baloni, Purdue University

7. **Comparative Brain Metabolomics: AD / PSP** - Richa Bhatra, Cornell University
AMP AD 1.0 Highlight: Impact of sharing clinical trials data on understanding disease progression in diverse populations and patient selection

Laurie Ryan, PhD
Division of Neuroscience
National Institute on Aging (NIA)
National Institutes of Health (NIH)

co-chair AMP AD 1.0

Accelerating Medicines Partnership® Program Symposium
Bethesda, February 5-6, 2024
Enrich anti-amyloid AD secondary prevention trials (A4 and DIAN-TU Trials) with Tau PET imaging to test its utility as a marker of disease progression and treatment response.

Screening/Pre-randomization data/biospecimens made broadly available 12 months after enrollment completion

Post-randomization data/biospecimens 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
Anti-Amyloid Treatment in Asymptomatic AD (A4 Trial)

Trial Design

First of its kind secondary prevention trial in cognitively healthy older adults (age 65-85) who had evidence of amyloid pathology on screening PET imaging

Randomized, double-blind, placebo-controlled Phase 3 trial solanezumab vs. placebo for 240 weeks with an open label extension (2014-2022)

1323 Participants; 6763 screened; 67 sites (US, Canada, Japan, Australia)

Observational cohort of amyloid negative “screen fails” – LEARN study (Alzheimer’s Association)

Data and biosample sharing (NIA/Collaboration for Alzheimer’s Prevention (CAP) Principles):

- screening/pre-randomization data/biospecimens made available within 12 months of enrollment completion
- post-randomization data/biospecimens 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

Public Private Partnership– supported by NIA, Lilly, Alz Assoc, GHR Foundation, FNIH, and other philanthropies
Solanezumab did not slow cognitive decline in preclinical AD or reduce risk of progression to symptomatic AD.

There was not a slowing or stoppage of amyloid accumulation - on amyloid PET imaging, amyloid continued to accumulate over time in both the placebo and treatment groups.

Higher baseline amyloid levels were strongly associated with a greater risk of progression to symptomatic AD and a more rapid decline.

Amyloid-Related Imaging Abnormalities with edema (ARIA-E) were uncommon and similar between treatment and placebo groups.
A4 Screening data – data and image sharing

Data sharing requests to ATRI as of December 2023

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<td>Taiwan (Province of China)</td>
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Apply for access: https://ida.loni.usc.edu/
Investigated whether amyloid PET in cognitively normal (CN) individuals screened for the Anti-Amyloid in Asymptomatic Alzheimer's Disease (A4) study differed across self-identified non-Hispanic White and Black (NHW and NHB) groups.

Examined 3,689 NHW and 144 NHB participants who passed initial screening for the A4 study and underwent amyloid PET.
Proportion of Amyloid Positivity Across APOE Genotypes

Kacie D. Deters et al.
Neurology
2021;96:e1491-e1500
© 2021 American Academy of Neurology
Figure 3 Plot of Continuous Amyloid PET Standardized Uptake Value Ratios (SUVRs) Compared to Percent African Ancestry
Investigated how the associations between tau and cognitive measures differ by sex in the preclinical Alzheimer's disease (AD) stage.

343 cognitively unimpaired, amyloid-positive individuals (205 women, 138 men) who self-identified as non-Hispanic White from the A4 Study were included.

Sex-stratified associations between 18F-flortaucipir positron emission tomography (PET) standardized uptake value ratio (SUVR) in the meta-temporal region and Preclinical Alzheimer's Cognitive Composite (PACC) and Computerized Cognitive Composite (C3) components were analyzed.
Results

• Higher tau level was significantly associated with worse cognitive performance only in women (PACC and its components except for MMSE; C3 components).

• All but one of the cognitive associations were APOE ε4 independent.
• Investigated associations between subjective cognitive decline (SCD), cognition, and amyloid across diverse participants in the A4 study.

• 5150 non-Hispanic White (NHW), 262 non-Hispanic Black (NHB), 179 Hispanic-White (HW), and 225 Asian participants completed the Preclinical Alzheimer Cognitive Composite (PACC), self- and study partner-reported Cognitive Function Index (CFI). A subsample underwent amyloid PET (18F-florbetapir) (N = 4384).

• Examined self-reported CFI, PACC, amyloid, depression (GDS), anxiety (STAI), and study partner-reported CFI by ethnoracial group.
Results

- The associations between SCD and objective cognitive measures and amyloid were moderated by race.

- Lower cognitive performance was significantly associated with higher SCD in NHW and Asian groups but not in HW and NHB groups.

- Amyloid positivity was associated with greater SCD in NHW and Asian groups but not in the NHB and HW groups.

- Depression and anxiety were predictors of SCD in the NHB and HW groups.
RCT Data (treatment and placebo) will be available June 28, 2024
THANK YOU!
AMP AD 2.0 Enabling Data Infrastructure for Systems Biology Research and Target Prioritization

Anna Greenwood, PhD
Sage Bionetworks

AMP AD Data Coordination Center

Accelerating Medicines Partnership® Program Symposium
Bethesda, February 5-6, 2024
AD Knowledge Portal
FAIR Data Infrastructure for Systems Biology Research and Target Prioritization

2/5/2024
Anna Greenwood, PhD
Sage Bionetworks
AMP-AD Data Coordination Center
Overall Goals of AMP-AD 1.0 Target Discovery Project

- shorten the time between the discovery of potential drug targets and the development of new drugs for Alzheimer's disease treatment and prevention
- integrate analyses of large-scale molecular data from human brain and fluid samples with network modeling approaches and experimental validation
- openly and rapidly distribute all outputs to the broader research community
AMP-AD 1.0 approach to target discovery

Samples from multiple human cohorts

Deep multi-omic profiling

Systems biology/network approaches

Target nomination and open distribution
AMP-AD 1.0: Harmonization of Molecular Data

AMP-AD cross-consortium harmonized analyses

- Differential gene expression (bulk RNAseq)
- Transcriptome wide association
- Variant calls
- Expression QTL
- Meta-network analysis

Harmonized results from transcriptomic and genomic variant studies are available in the portal
Brain Multi-omic Data from AMP-AD 1.0 and 2.0

- 1744 individuals (EA, AA, LA) with bulk transcriptomics, proteomics and WGS data
  - 695 EA donors also have metabolomics data; metabolomics profiling ongoing for AA and LA donors
- 859 individuals with bulk RNAseq and single cell/nucleus transcriptomic data (EA, AA, LA)
Current Infrastructure to Support AMP-AD 2.0 and Other Programs

**Data Discoverability**
- AD Knowledge Portal

**Results Exploration**
- Agora
- AD Atlas

**Data Processing and Analysis**
- Cloud workspaces
- Programmatic Clients
- Direct download

**Access Control**

**Data Cataloging and Storage**

**Governance**
- Sage Team

**Data Contribution**
- MODEL-AD
- Resilience-AD
- CDCP
- MARMO-AD
- FunGen-AD
- TREAT-AD
- ACTRDx-AD
- CLEAR-AD
- AGMP

12 NIA programs
103 grants
126 studies
AD Knowledge Portal Resources Encompass More Than 180,000 Data Files

Diverse specimens
- human
- longitudinal cohorts
- brain bank samples
- brain
- iPSCs
- CSF/plasma
- mouse
- Drosophila

Diverse data types
- genomics
- transcriptomics
- proteomics
- epigenetics
- metabolomics
- metagenomics
- electrophysiology
- imaging
- behavior

Diverse level of processing
- raw
- processed
- analytical outputs

Data from 60+ assays and in 50+ different file formats
Commitment to FAIR Principles

Streamlined Data Governance
- All controlled access data available for General Research Use under one umbrella DUC

Data deposition post QC

Data made available to AMP-AD Partner organizations and research community at large at the same time

No publication embargo

Community outreach and education
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<tr>
<th>GO FAIR* Criteria</th>
<th>Feature in Synapse</th>
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<tr>
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<tr>
<td>F2. Data are described with rich metadata (defined by R1 below)</td>
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<tr>
<td>F3. Metadata clearly and explicitly include the identifier of the data they describe</td>
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<tr>
<td>F4. (Meta)data are registered or indexed in a searchable resource</td>
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<tr>
<td>A1. (Meta)data are retrievable by their identifier using a standardised communications protocol</td>
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<tr>
<td>A1.1 The protocol is open, free, and universally implementable</td>
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<tr>
<td>A1.2 The protocol allows for an authentication and authorisation procedure, where necessary</td>
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</tr>
<tr>
<td>A2. Metadata are accessible, even when the data are no longer available</td>
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<tr>
<td>I1. (Meta)data use a formal, accessible, shared, and broadly applicable language for knowledge representation.</td>
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<tr>
<td>I2. (Meta)data use vocabularies that follow FAIR principles</td>
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<tr>
<td>I3. (Meta)data include qualified references to other (meta)data</td>
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<tr>
<td>R1. (Meta)data are richly described with a plurality of accurate and relevant attributes</td>
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<tr>
<td>R1.1. (Meta)data are released with a clear and accessible data usage license</td>
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<tr>
<td>R1.2. (Meta)data are associated with detailed provenance</td>
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<tr>
<td>R1.3. (Meta)data meet domain relevant community standards</td>
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*https://www.go-fair.org/fair-principles/
Streamlined Data Access Requests

Access requirements by data tier

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<th>DATA TIERS</th>
<th>Open</th>
<th>Restricted</th>
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<td>Downloading model system data</td>
<td>Downloading individual level human data</td>
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<td>Viewing study descriptions</td>
<td>Downloading summarized human data</td>
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<td>Viewing help &amp; documentation</td>
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<th>REQUIREMENTS</th>
<th>Synapse account</th>
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Controlled data access request process

1. Register on Synapse
2. Submit Data Use Certificate Request
   - Intended Data Use Statement
   - Institutional Official Signature
   - List Collaborators
3. Sage ACT Review
4. Access Data

Annual Renewal
Multiple User Support Channels

Documentation And Help Site

Monthly Data Release Notes and Newsletter

Discussion Forum

Hands On Workshops
Data Use Metrics: Downloads and Data Access Requests

Number of Unique Users Downloading AD Knowledge Portal Data per 6 month interval

DUC by Institution Type

Non-Academic* (40%)

Academic (60%)

*Includes Pharma/Biotech/Gov/Nonprofit

Over 2800 research teams downloaded data between 2019 and 2023
Data is used by consortium members as well as the broader research community, to study topics ranging from AD, ADRD to research on brain aging, neuroscience and basic and translational research.

653 publications referencing the AD Knowledge Portal (as of March 2023)

- data contributors as authors
- secondary data use

Data Use Metrics: Publications

- 44% (287) for research with data contributors as authors
- 56% (366) for research using secondary data
AD Knowledge Portal
Evolving to Enhance Interoperability and Better Support a Diverse Set of End-users

AMP-AD Portal launch (Synapse)
AD Knowledge Portal relaunch (Javascript)
Download cart
News site
New Study detail pages
New homepage
Technical vignettes
Publication datasets
Redesigned Project pages

2015
2019
2020
2021
2022
2023

Faceted file browser
Keyword search
Access restriction icons
Data access request in Portal
Analytical workspace

Documentation/Help site
Experimental Tools Redesign
Animal Models Redesign

New Improvements

- Cohort builder
- Improved high-level navigation
- Full site search
- Interoperability w ADRD data repositories and other AMP platforms
- Linking to compute platforms
Connectivity to CAVATICA facilitates external data access

- AD Knowledge Portal
- AnVIL
- BioData
- CATALYST
- dbGaP
- NIH
- NATIONAL CANCER INSTITUTE
- Cancer Research Data Commons
- 1000 Genomes Project
- CHS
- TOPMed
- BioLINCC
- INCLUDE
- HTAN
- CPTAC
- TCGA
- HUMAN CELL ATLAS
Agora: community resource for advancing AD targets

Discover Alzheimer's Disease Genes

Agora hosts evidence for whether or not genes are associated with Alzheimer’s disease (AD). Agora also contains a list of over 600 nascent drug targets for AD that were nominated by AD researchers.

Gene Comparison
Explore differential RNA and protein expression results for 20k+ genes. Build custom result sets by sorting, filtering, and searching for genes of particular interest.

Gene Search
Find one of 20k+ genes in the Agora database and get detailed information about Experimental Evidence, Nominations, and Association with Alzheimer’s Disease.

Nominated Targets
Browse genes that research teams have nominated as potential new targets for Alzheimer’s Disease treatment or prevention.

Search for any gene of interest
View list of nominated targets
Compare evidence across genes
View resources and evidence for individual genes

agora.adknowledgeportal.org
Nominated targets are central to Agora

Current targets:
- 1134 nominations
- 947 unique nominated targets
- 144 targets with more than one nomination

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Nominations</th>
<th>Year First Nominated</th>
<th>Nominating Teams</th>
<th>Cohort Study</th>
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Use Agora’s Gene Comparison Tool to compare all nominated genes in this list.
Exploration of curated multi-omics results

One gene at a time

Comparison across all genes
Molecular profiling data
- Differential gene expression
- Correlation with neuropathology
- Differential protein abundance
- Metabolite levels in brain

Target risk score
- ‘Omics score
- Genetics score

Biological domain classification
- Curated list of 19 biological domains
- Associated GO terms

Target nominations
- Number of teams nominating
- Evidence supporting nomination
- Proposed directionality

Experimental Validation Data
- Hypothesis being tested
- Description of results
- Links to publications

Target tractability
- Predicted tractability for small molecule and antibody modalities
Agora has been cited more than 100 times since its launch in 2018.
Acknowledgements: AD Consortia and Centers

NIA grants: U24 AG061340, U24 AG078753, U54 AG065187, U54 AG054345, U54 AG054349; supplements to U19 and U01 (CLEAR-AD, AGMP, AMP-AD)
# Acknowledgements: Sage Team

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<th>Scientific Coordination and Analysis</th>
<th>Infrastructure and Tools</th>
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<tr>
<td>Victor Baham</td>
<td>Jaclyn Beck</td>
<td>Kevin Boske</td>
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<tr>
<td>Amelia Kallaher</td>
<td>Anna Greenwood</td>
<td>Jess Britton*</td>
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<td>Rich Yaxley</td>
<td>Milan Vu*</td>
<td>Lawrence Yi</td>
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NIA grants: U24 AG061340, U24 AG078753, U54 AG065187, U54 AG054345, U54 AG054349; supplements to U19 and U01 (CLEAR-AD, AGMP, AMP-AD)
Insights from Integration of Multiscale Data for Subtyping Persons with Alzheimer’s dementia

David A. Bennett,
Rush Alzheimer’s Disease Center
Rush University Medical Center
Chicago, IL

AMP Alzheimer’s Disease (AMP AD)

Accelerating Medicines Partnership® Program Symposium
Bethesda, February 5-6, 2024
Acknowledgments

National Institutes of Health
State of Illinois
Alzheimer’s Association
Rush University Medical Center

Study Participants:
Religious Orders Study
Rush Memory and Aging Project
Minority Aging Research Study
ADRC African American Core
ADRC Latino Core

No Relevant Disclosures
Multiple Etiologies
Multiple Prodromal Phenotypes
Multiple Progression Trajectories

Genetics

Environment

Healthy State

Disease progression

Disease modifying therapy

Disease State

Genetics

Environment
AMP AD 1.0/AMP AD 2.0
Leveraging Harmonized, Longitudinal Community-based Studies

- Religious Orders Study (ROS)
- Rush Memory and Aging Project (MAP)
- Minority Aging Research Study (MARS)
- ADRC African American Core
- ADRC Latino Core
- Rich antemortem phenotypic data
- Brain, blood, other biosamples, iPSCs
- ~5,300 participants across the USA
- Harmonized clinical and neuropathologic evaluations
- ~2200 brain autopsies
- ~110 iPSC lines

RADC Research Resource Sharing Hub

www.radc.rush.edu

AD Knowledge Portal

www.adknowledgeportal.org
Quantitative neurobiology

Medical, Psychological, Experiential, and genomic risk factors

Epigenomics and Epitranscriptomics

Transcriptomics

Proteomics and metabolomics

Quantitative neurobiology

Structural &function MRI

Blood biomarkers

Quantitative clinical phenotype

Syndromic phenotype

Motor Function
Disability BMI, olfaction, pulmonary function

Biomedical Devices
Actigraphy, Dynaport, WatchPAT, ANNE, digital pen:
Sleep and, circadian rhythms, gait and balance, sleep, cardiovascular function

Health and financial decision making and literacy, susceptibility to fraud and scams

Blood biomarkers

Ptau, cfDNA, 5hmC, proteomics, Metabolon, Biocrates, Monocyte RNAseq, Routine quest labs

Clinical Diagnoses
AD, Stroke, PD,

Post-mortem MRI
DTI, MP Rage, T2

Flair, MP Rage, DTI, SWI, rsfMRI

SRM, TMT, Top-down,
Glycoproteomics, Phosphoproteomics, Eliza, Metabolon, Biocrates

SRM, TMT, Top-down,
Glycoproteomics, Phosphoproteomics, Eliza, Metabolon, Biocrates

Metabolon’s Complex Lipid Panel, Ubiquitination

Whole genome bisulfite sequencing

5mC, 5hmC, m6A, Histone acetylation, snATACseq

Bulk, snRNAseq, ST, miRNA

D, CVD, LBD, HS, TDP, CVD

Clinical Diagnoses
AD, Stroke, PD,

Clinical Diagnoses
AD, Stroke, PD,

21 annual cognitive test
Motivation Questions

➢ The field has long been interested in subtypes of Alzheimer’s disease

Subtypes of Alzheimer’s dementia: a conceptual analysis and critical review

A F Jorm

➢ Can we use molecular brain omics to generate molecular subtypes?
➢ Can we translate the subtypes to living humans?
➢ Can we eventually test the subtypes in ex-vivo human cell systems?
Unified epigenomic, transcriptomic, proteomic, and metabolomic taxonomy of Alzheimer’s disease progression and heterogeneity


ROSMAP Cohort

Multi-omics molecular profiling on dorsolateral prefrontal cortex (DLPFC), of 822 autopsied brains, 168 of whom have matched blood monocyte RNA quantification

Contrastive PCA

mDPS = molecular disease progression score

Brain Multimodal Molecular Information Reveals Distinct AD Subtypes

Translation of Brain Subtypes to \textit{in-vivo} Monocyte RNAseq


110 differentially expressed Blood RNAseq monocyte transcripts for the 3 subtypes
Summary

We integrated epigenomic, transcriptomic, proteomic, glycoproteomic, metabolomic, and neuropathologic data to generate:

- a pseudotime molecular disease progression score (mDPS) from NCI (0) to AD dementia (1)
- 3 pseudotime integrated omic sub-trajectories within multi-dimensional-omic space

We translated the subtrajectories to ptau, blood cell-free DNA, monocyte RNAseq, proteomics, and metabolomics

- Phosho-Tau AUC for all three brain trajectories was chance (0.48)
- Multi-blood omic AUCs ranged from 0.7-0.8 for monocyte RNAseq, proteomics, and metabolomics

Ongoing work integrating:

- single-cell RNA seq and other layers of brain omics as they are generated
- structural and functional MRI, and other layers of blood omics as they are generated
- PRS

Next steps: modeling these results in ex vivo human cell models

- See poster by Sarah Heuer and Tracy Young-Pearse with work on iPSC generated from these same individuals
Integrative Proteomics Approach to Deconstructing Disease Complexity and Biomarker Discovery

Nick Seyfried, PhD
Emory University

AMP Alzheimer’s Disease - AMP AD

Accelerating Medicines Partnership® Program Symposium
Bethesda, February 5-6, 2024

Disclosure: Co-founder Emtherapro
<table>
<thead>
<tr>
<th>Brain Tissue Proteomics</th>
<th>Disease/Pathology</th>
<th>Region(s)</th>
<th>Single-shot LFQ</th>
<th>Deep TMT</th>
<th>PRM/SRM</th>
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<tbody>
<tr>
<td>Emory</td>
<td>Control, AD, PD and mixed pathologies</td>
<td>BA9, BA24</td>
<td>50</td>
<td>80</td>
<td>x</td>
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<tr>
<td>Banner</td>
<td>Control, AD, and AsymAD</td>
<td>BA9</td>
<td>201</td>
<td>198</td>
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<td>BA9, BA6, BA37</td>
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<td>MSSM</td>
<td>Control and AD</td>
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<td>BLSA</td>
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<td>Adult Changes in Thought (ACT)</td>
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<td>x</td>
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<td>355</td>
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<td>Mayo</td>
<td>Control, PSP and AD</td>
<td>BA20</td>
<td>199</td>
<td>286*</td>
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<td>Johns Hopkins Aging</td>
<td>Control</td>
<td>BA9</td>
<td>93</td>
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<tr>
<td>Emory Diverse</td>
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<td>BA9</td>
<td>x</td>
<td>129*</td>
<td>x</td>
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<tr>
<td>ROSMAP + MARS Diverse</td>
<td>Control, AsymAD, and mixed pathologies</td>
<td>BA9</td>
<td>x</td>
<td>269*</td>
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<td>Control and AD</td>
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<td>1326</td>
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<td>1532</td>
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<tr>
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<th>Disease</th>
<th>Fluid</th>
<th>Single-shot TMT</th>
<th>Deep TMT</th>
<th>PRM/SRM</th>
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<tr>
<td>Emory ADRC</td>
<td>Control and AD</td>
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<tr>
<td>Emory ADRC</td>
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<td>Plasma</td>
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<td>36*</td>
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<td>Emory Diverse (50% African American)</td>
<td>Control and AD</td>
<td>CSF</td>
<td>x</td>
<td>300*</td>
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<td>Emory Diverse (50% African American)</td>
<td>Control and AD</td>
<td>Plasma</td>
<td>x</td>
<td>300*</td>
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<tr>
<td>Emory MOVE-AD</td>
<td>Control, AsymAD and AD</td>
<td>CSF</td>
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<td>x</td>
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<td>Emory Multi-Disease</td>
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<td>CSF</td>
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<td>CSF</td>
<td>x</td>
<td>x</td>
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<td>Emory/Mayo ALS</td>
<td>Control, sporadic ALS, C9+ ALS</td>
<td>CSF</td>
<td>x</td>
<td>100*</td>
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<td>NeuroNEXT Multiple Sclerosis</td>
<td>NN102 SPRINT-MS</td>
<td>CSF</td>
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<td>2047*</td>
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<td></td>
<td>1136*</td>
<td>1103*</td>
<td>2047*</td>
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</table>

5000+ brain MS samples
3000+ biofluid MS Samples
A Pipeline for Discovery of Molecular Targets and Biomarkers for AD

1. Collect Samples (Brain, CSF, Blood)
2. Acquire high resolution proteomics data
3. Identify patterns related to biology, structure and function
4. Discover communities (modules) of proteins
5. Integrate GWAS and other omics
6. Integrate gene ontologies and cell-specific expression data
7. Assess and prioritize module-phenotype relationships
Integrated Proteomics to Map Brain-linked CSF Biomarkers

Human Brain Proteome: Unbiased Network Analysis

Human CSF Proteome: Differential Expression Analysis

Brain-Biofluid Integration

~70% overlap

Higginbotham / Ping et al. Science Advances 2020
Resolving Brain-Derived CSF Biomarkers

Reflect Diverse Biology in AD Brain

Correlate with Pathology and Cognition

271 brain-linked proteins with meaningful differential expression in CSF proteome.

Replicated panels in >500 CSF from Four Independent Cohorts

Data-Driven Peptide Selection

SRM Biomarker Validation

Prognostic Protein Panels

Higginbotham, Ping et al. Science Advances 2020

Haque et al. Science Translational Medicine 2023

Johnson et al. Nature Medicine 2023

Watson et al. Scientific Data 2023
Multi-Platform Proteomic Analysis of AD Biofluids For Brain Network Biomarker Translation

- Most measurements correlate well across platforms
- Median correlation is lower in plasma than in CSF
- Correlation in plasma is better for higher S:N proteins

Dammer et al., *Alz Res Therapy* 2022
Evaluating Disease Specificity of High Value Targets: SMOC1

SMOC1 Increased in AD CSF and Plasma

SMOC1 Increases with Age

SMOC1 Not Increased in PD CSF

SMOC1 Not Increased in ALS, FTD PD CSF

Dammer et al., Alz Res Therapy 2022
CSF Proteomics: African Americans with AD Have Lower Levels of Tau Compared to European Americans with AD

- **Caucasian** (n=53) vs. **African American** (n=52)
- **Caucasian** (n=48) vs. **African American** (n=51)

**TMT-MS Tau**
- Log2 abundance/GIS

**Control MCI/AD**

**Discovery TMT-MS**
- ~2000 proteins across 204 individual CSF samples

**Roche Elecsys**

**MAPT (Tau)**

**Cor=0.85 p=2E-54**
CSF Proteomics: African Americans with AD Have Lower Levels of Neuronal Markers Compared to European Americans with AD

Contrary to predictions based on CSF tau levels, African Americans have lower levels of neuronal markers compared to Caucasians with AD

Modeste et al., *Mol. Neurodegeneration* 2023
Proteomic Panels in CSF are Responsive to Drug Treatment

A phase II study repurposing atomoxetine for neuroprotection in mild cognitive impairment
Subtyping of patients by proteomic signature of underlying brain pathophysiology

- Key questions in exploration:
  - Do subtypes differ in AD risk (PRS)?
  - Do subtypes differ by co-morbidities (diabetes, hypertension, etc.)?
  - Do specific subtypes progress faster?
  - Do specific subtypes respond better or worse to treatment?
  - Which patients have higher risk of adverse affects?

Cerebrospinal fluid proteomics in patients with Alzheimer’s disease reveals five molecular subtypes with distinct genetic risk profiles


*Nature Aging*. 4, 33–47 (2024) | [Cite this article](#)
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Caroline Watson
Fatemeh Seifar
Adam Trautwig

AMP-AD Collaborations

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R01AG053960
P50AG025688
R01AG057330
Developing a Multi-Omics Atlas of Alzheimer’s Disease

Matthias Arnold, PhD
AMP Alzheimer’s Disease – AMP AD

Accelerating Medicines Partnership® Program Symposium
Bethesda, February 5-6, 2024
Mapping the AD Metabolome with High-quality Metabolomics/Lipidomics Data Across Different Cohorts

Rapid and broad data sharing, transparent reporting of methods, rigor and reproducibility

AMP-AD Metabolomics Data

The Human Metabolome

Carbohydrate metabolism
Nucleotide metabolism
Cofactors & vitamin metabolism
Amino acid metabolism
Energy metabolism
Biogenic amine metabolism
Lipid metabolism & transport
Catecholamine metabolism
Steroid & bile acid metabolism
Xenobiotics metabolism

AMP-AD Metabolomics Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Ntotal</th>
<th>Blood samples</th>
<th>Brain samples</th>
<th>CSF samples</th>
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<tr>
<td>Blood</td>
<td>46,277</td>
<td>58,894</td>
<td>2,738</td>
<td>710</td>
</tr>
<tr>
<td>Blood: Brain</td>
<td>1,051</td>
<td>778</td>
<td>778</td>
<td>1,051</td>
</tr>
<tr>
<td>Blood: Brain: CSF</td>
<td>74</td>
<td>74</td>
<td>74</td>
<td>74</td>
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</table>
Integrative AD research

Aim: embed single-omics disease associations into the wider context of multi-level molecular changes

- data heterogeneity
- data access restrictions
- missing (bio)informatics resources
The AD Atlas concept

- Collect **large-scale multi-omics data**
- Process/harmonize data and analysis pipelines
- Derive an **integrated data model** to represent all data in one multi-omics network
- Make the data usable through public access
- Develop tools to leverage the collective evidence
Building a multi-omics network of AD

Composite network

Intra-omics links
- co-expression networks
- partial correlation networks (GGMs)

Inter-omics links
- GWAS with molecular traits
- knowledge-based (Ensembl)

Phenotype-specific links
- GWAS with AD phenotypes (e.g. age of onset, CSF Aβ, t-/p-tau)

Woerheide et al., medRxiv (2021)
Integrated datasets

Population- and knowledge-based data
- gene-protein-transcript mapping using Ensembl
- variant annotation using SNiPA
- eQTL associations from GTEx v8 in 48 tissues (13 from the brain) + brain eQTL meta-analysis
- mQTL associations from 6 studies
- metabolite links for metabolites (GGM)
- protein co-expression network

Genetics of AD and associated markers
- traitQTL associations from 6 studies
- 43 unique AD related phenotypes
- cohorts incl. UKBiobank, IGAP, ROS/MAP

Alzheimer’s Disease Metabolomics Consortium / AMP-AD
- metabolite links for metabolites (GGM)
- metabolic associations with AD
- consensus protein co-expression network
- gene co-expression for 7 brain regions
- genetic associations with AD and metabolites
- differentially expressed proteins and genes (brain region specific)

Woerheide et al., medRxiv (2021)
Multi-omics network of AD

Woerheide et al., medRxiv (2021)
Content of the AD Atlas

**Nodes:**
Clinical-pathological traits & biomarkers: 67 (43 unique)
Genes (protein-coding):
- with DEG data: 14,731
- with DEP data: 7,867
Metabolites: 1,328

**Edges:**
979,190 significant associations

---

*Woerheide et al., medRxiv (2021)*
The AD Atlas web interface
The general idea

Augmenting single putative targets with their functional neighborhood at genome scale

Use functional neighborhood for adding information through enrichments

<table>
<thead>
<tr>
<th>Genes:</th>
<th>Metabolites:</th>
<th>Traits:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 1 with trait association(s)</td>
<td>8 - 1 with trait association(s)</td>
<td>36</td>
</tr>
<tr>
<td>Genes:</td>
<td>Metabolites:</td>
<td>Traits:</td>
</tr>
<tr>
<td>176 - 61 with trait association(s)</td>
<td>75 - 19 with trait association(s)</td>
<td>52</td>
</tr>
</tbody>
</table>
Use cases

Drug repositioning

- Lipid metabolism and transport
  Exploring the functional neighborhood of APOE and CLU to identify drug repositioning candidates.

- Global disease network
  Building a global AD associated network to identify promising repositioning candidates.

- Statins in AD
  Evaluating known drug targets in an AD context to prioritize potential drug repositioning candidates.

Explorative analysis

- Contextualization of sphingomyelins
  Providing functional insights into the role of SMs in AD.

- Disease-associated microglia (DAM) transition
  Exploring the transition of homeostatic microglia to disease-associated microglia in AD.
Computational approaches utilizing the AD Atlas towards target discovery and prioritization

(i) Unsupervised identification of disease modules
Deep learning approach for disease module identification

Network
- Brain-specific
- simplified graph (15,310 nodes)
- only gene and metabolite nodes

Embedding
- GeneWalk
- 130 dimensions
- 2-step context window

Exploration
- UMAP {metric: 'cosine'}
- Hierarchical clustering {'Ward.D2'}
- Enrichment
Hierarchical clustering on 130D, Ward.D2, cut h=30

Immune response $p_{adj} = 6.51 \times 10^{-80}$

DEG in TCX $p_{adj} = 5.92 \times 10^{-29}$

Shortest path to AD trait $p_{adj} = 9.44 \times 10^{-41}$
Hierarchical clustering on 130D, Ward.D2, cut h=30

Global structure of the association-based multi-omics network reflects AD-relevant biological information

Ulmer et al., submitted
Computational approaches utilizing the AD Atlas towards target discovery and prioritization

(i) Unsupervised identification of disease modules

(ii) Computational drug repositioning
Computational drug repositioning

Data extraction

Disease nodes

DEGs/DEPs/DEM

Network-based repositioning

Signature Search

Rank aggregation

Compare across brain regions/cell types
Continued development and enrichment with new data

**AMP-AD/AMP-SBI:**
- Newly derived datasets (incl. longitudinal)
- Brain multi-omics data from diverse cohorts
- Multi-scale analysis results
- Genetics of inflammatory/(auto)immune traits
- Single-cell/single-nucleus RNA-seq data
- Epigenetics & gene regulation data

**AGMP:**
- AD-gut microbiome associations
- Gut microbiome-metabolome associations
- Dietary & lifestyle interventions, exposomics
- Neuropsychiatric symptoms
- Data driven microbiome/metabolome networks

**TargetAD:**
- High-confidence PPIs
- Tissue/cell type specificity
- Drug-drug target interactions

**Alzheimer’s Disease Metabolomics Consortium:**
- Metabolomic & lipidomic links from periphery to brain
- (Subgroup-specific) metabolic/lipidomic risk scores
- Modifiable metabolotypes for non-pharmacological interventions
Acknowledgements: AD Metabolomics Consortium (ADMC) + partners

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(ADNI: Genomics Core)
Kwangsik Nho

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University of Texas Health Science Center San Antonio
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Dinesh Barupal

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CalTech
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(Overall PI) & Team

ADMC Posters:

1. Integrative Metabolomics and Systems Modeling for Target Discovery and Validation - Priyanka Baloni
2. Comparative Brain Metabolomics: AD / PSP - Richa Batra
Alzheimer's Association Perspective on the Value and Impact of AMP AD

Rebecca Edelmayer, PhD
Senior Director, Scientific Engagement - Alzheimer’s Association

Accelerating Medicines Partnership® Program Symposium
Bethesda, February 5-6, 2024
Industry Perspective on the Value and Impact of AMP AD

Michael Nagle, PhD
Executive Director, Head of Human Biology Integration Foundation – Eisai
co-chair AMP AD 2.0

Accelerating Medicines Partnership® Program Symposium
Bethesda, February 5-6, 2024
Industry Perspective on the Value and Impact of AMP AD

- **Data:**
  - Expansion of multi-omic profiling from ethnically diverse cohorts allows for better representation of disease and patient diversity
  - Expansion of single-nuclei/ single-cell profiling to different brain regions and across samples allow for deeper investigation of disease biology and mechanisms, as well as new target space to explore

- **Analytics:** New methods and approaches being developed and applied by AMP-AD investigators, industry partners, and the greater scientific community → novel targets and mechanisms (e.g. Contrastive PCA, pseudotime analyses, network representation learning, etc.)

- **Validation:** In-depth exploration of nominated targets in complex model systems (i.e. iPSC-derived neurons, organoids, etc.) allows de-risking of targets, lowering thresholds for new project initiation in industry setting

- **Infrastructure:** Coordinated and centralized storage of and access to data, results, and targets generated by AMP-AD and other AD Systems Biology Consortia democratizes the insights that can be derived from this resource

- **Culture:** Open sharing of ideas and data along with close interactions between key academic leaders and experts generating and evaluating this data and industry partners allows for better, more informed target identification/ validation, and patient stratification strategies
ACCELERATING MEDICINES PARTNERSHIP®
ALZHEIMER’S DISEASE (AMP AD)

Accelerating Medicines Partnership® Program Symposium
Bethesda, February 5-6, 2024
Backup slides
Acknowledgements
AMP AD 1.0 Partners

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PUBLIC SECTOR PARTNERS
AMP AD 2.0 Partners

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AMP Symposium February 5-6, 2024
AMP AD Session: 10:00-11:15 AM - Feb 5th

Overview of the goals and deliverables of AMP AD 1.0 and AMP AD 2.0 – Suzana Petanceska, NIA - 5 min

1. AMP AD 1.0 Highlight: Impact of sharing clinical trials data on understanding disease progression in diverse populations and patient selection - Laurie Ryan, NIA - 10 min

3. AMP AD 2.0 Enabling Data Infrastructure for Systems Biology Research and Target Prioritization - Anna Greenwood, Sage Bionetworks - 10 min

4. AMP AD 2.0 Precision Medicine Approach to Deconstructing Disease Complexity and Identifying Novel Targets and Biomarkers - 10 min each

   - Insights from Integration of Multiscale Data for Subtyping Persons with Alzheimer’s dementia - David Bennett, Rush University
   - Integrative Proteomics Approach to Deconstructing Disease Complexity and Biomarker Discovery - Nick Seyfried, Emory University
   - Developing a Multi-Omics Atlas of Alzheimer’s Disease - Matthias Arnold, Duke University

5. Alzheimer’s Association Perspective on the Value and Impact of AMP AD - Rebecca Edelmayer, Alzheimer’s Association - 5 min

6. Industry Perspective on the Value and Impact of AMP AD - Michael Nagle, Eisai - 5 min
AMP Symposium February 5-6, 2024
Poster Reception: 5:30-7:15PM – Feb 5th

AMP AD Poster Presentations

1. Brain Multiomics Analysis in Diverse Cohorts - Joseph Reddy, Mayo Clinic, Jacksonville

2. Open-Source Tools for Target Discovery and Validation: Agora Results Explorer - Jessica Britton, Sage Bionetworks


4. Modeling the Heterogeneity of AD in iPSC cell lines - Sarah Heuer, Harvard U/BWH

5. Insights from CSF Proteomics in Diverse Cohorts - Madison Bangs - Emory Univ

6. Integrative Metabolomics and Systems Modeling for Target Discovery and Validation - Priyanka Baloni, Purdue Univ

7. Comparative Brain Metabolomics: AD / PSP - Richa Bhatra, Cornell Univ