DEVELOPING A KNOWLEDGE BASE AND INFRASTRUCTURE TO ENABLE PRECISION MEDICINE RESEARCH FOR ALZHEIMER’S DISEASE

Suzana Petanceska PhD
Laurie Ryan PhD
Division of Neuroscience
Multiple Etiologies
Multiple Prodromal Phenotypes
Multiple Progression Trajectories
## Phase III Randomized, Double-blind, Placebo Controlled, Clinical Trials for AD

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**Failures due to lack of efficacy or unforeseen toxicity.**
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.

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.

Build new multidisciplinary translational teams and create virtual and real spaces where these teams can operate.

Support and enable open science.

Change academic, publishing, and funding incentives to promote collaborative, transparent, and reproducible research.

Engage patients, caregivers and citizens as direct partners in research.
Responding to Summit Recommendations
-NIA/NIH Integrated Program Development-

- Enabling Clinical Drug Development
  - Genetics Population Research
  - New, Translational Capabilities
    - For Predictive Drug Development
  - Public Private Partnerships
  - Discovery and Validation of Novel Targets and Biomarkers
  - Systems and Network Biology

- Preclinical Drug Development
  - Preclinical Efficacy Testing Database
  - Preclinical Efficacy Testing Database
  - New, Diverse Cohorts
  - Health Disparities

- Preclinical Drug Development
  - Translational Centers for Next-Gen Animal Models and Efficacy Testing
  - Translation of Bioinformatics and Systems Pharmacology/Drug Repositioning
  - Cross-Disciplinary Training:
    - Basic and Clinical Research/Data Science/Drug Discovery

- New, Diverse Cohorts
  - ADGC/NIAGADS/ADSP
  - AD BIOMARKERS IN DOWN SYNDROME
  - New AD Clinical Trials Infrastructure
  - Digital Technologies
  - Systems and Network Biology

- Optogenetics
  - iPSC Technologies
  - Animal Models

- Inflammation
  - Metabolic/Vascular Etiology
  - Complex Biology of Cognitive Resilience and more...

- Public Private Partnerships
  - Optogenetics
  - iPSC Technologies
  - Animal Models
BASIC RESEARCH PROGRAMS
AREAS OF EMPHASIS

UNDERSTANDING THE COMPLEX BIOLOGY OF AD/ADRD

- Metabolic and Vascular Etiology/Lymphatic System
- Dynamic Interaction Between Peripheral Systems and the Brain in Aging/AD
- Understanding Neurodegeneration in the Context of Aging
- Complex Biology of Resilience
- Proteostasis and Structural Biology
- Inflammation
- Functional Validation of Genetic Risk Factors for AD
- Sex Differences and AD Risk
- Integrative Biology of APOE
- Common Mechanisms of Neurodegeneration

and more – full listing https://www.nia.nih.gov/ad-foas
- We are targeting the wrong pathophysiological mechanisms
- Drugs do not engage with the intended target
- Interventions are started at the wrong stage of the disease
- Lack of translatable pharmacodynamic biomarkers
- Poor predictive power of animal model preclinical efficacy testing

- Complexity of disease
- Complexity of the physiologic response to therapeutic intervention
SYSTEMS APPROACHES FOR NOVEL TARGET AND BIOMARKERS DISCOVERY
Accelerating Medicines Partnership Alzheimer’s Disease Program

https://www.nia.nih.gov/alzheimers/amp-ad
Accelerating Medicines Partnership Alzheimer’s Disease Program

AMP Executive Committee

AMP-AD Steering Committee

NIA

Target Discovery Consortium
-cooperative agreement grants-

CT/Biomarkers Consortium
-cooperative agreement grants-

Private partners

Working Groups

$182.5M (plus $40M in kind contribution by industry) over 5 years
AMP-AD TARGET DISCOVERY AND PRECLINICAL VALIDATION PROJECT

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

- Generate multi-omics human data from postmortem brain tissue and plasma samples (well phenotyped cohorts and brain banks)
- Build network models of targets/pathways
- Carry out early target validation in multiple cell-based and animal models.
- Develop a data portal to enable rapid and broad sharing of data and analytical results.

ACCELERATING MEDICINES PARTNERSHIP (AMP)
# ALZHEIMER’S DISEASE - Target Discovery and Preclinical Validation Project

**RFA AG13-013**

<table>
<thead>
<tr>
<th>Academic Teams</th>
<th>Broad-Rush</th>
<th>Mt Sinai</th>
<th>UFL/ISB/Mayo</th>
<th>Emory</th>
<th>Duke</th>
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<tr>
<td>Principal Investigators</td>
<td>De Jager, Bennett</td>
<td>Schadt, Zhang</td>
<td>Golde, Price, Taner</td>
<td>Levey</td>
<td>Kaddurah-Daouk</td>
<td>Yankner, Tsai</td>
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Data Enablement and Coordination of Collaborative Analyses: Sage Bionetworks, Principal Investigator – Lara Mangravite
AMP-AD Mt.Sinai Team

Project Workflow

Data Generation
- Brain Bank Cohorts
  - Harvard Medical School
    - Clinical traits
    - DNA
    - RNA in 4 brain regions
    - Moderate-to-severe cases
  - Mt. Sinai Medical School
    - Clinical traits
    - DNA
    - RNA in 4 brain regions
    - Mild AD including MCI and CDR 0-5

Model Building
- WINA
- Machine Learning
- Bayesian Algorithms

Data Mining for Causal Regulators
- Causal Networks
- Co-expr Networks
- Key Driver Analysis
- Pair-wise Causality Models
- Classifiers

Experimental Validation
- Brain Slices
- Fly Model
- Human iPSCs
- Pharmacologic
- Validated Hits

Hit Prioritization
- Highly penetrant, rare, genetic mutations
- Regulate genes enriched for AD GWAS
- Regulate genes known to associate with AD
- Top of rank-ordered causal regulator list
How Are We Doing This Together?

Academic teams
1) Centralized data resources
2) Consortium-wide collaborative projects
3) Consortium-wide milestones

Industry teams

Target Nomination

| Team 1 | Team 2 | Cross Analysis | ...
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AMP-AD Collaborative Workspace

- Data
- Analyses
- Network models
- Code

Quarterly Data Depositions

AMP-AD Knowledge Portal

Launched - March 4, 2015

- Data released after QC is completed
- Date available as Open or Controlled Access depending on data type and data source
- No publication embargo imposed on the use of data after they have been made available through the public portal

Centralized Data Resource

www.synapse.org/ampad
60,000 files contributed by 42 investigators across 22 institutions representing samples from 36 research studies

AMP-AD Knowledge Portal

Over 1800 users with ~55 new users per month

www.synapse.org/ampad
Religious Orders Study and Rush Memory and Aging Project

ROS/MAP

Two cohort studies of aging and AD ongoing for 20+ years

>3,000 older persons without [known] dementia from across the USA

All agreed to annual detailed clinical evaluation for common chronic conditions of aging with detailed evaluation of risk factors, and blood donation

All agreed to organ donation at death

> 900 cases incident MCI

> 700 cases incident AD dementia

> 1,200 autopsies
Consortium-wide Analytical Working Groups*
-establishing new data and analytical resources for AD research-

**AMP-AD Cross Network WG:**
Evaluate network biology of dementia across methods and data-sets

- **Methods**
  - Sage Team metanetworks
  - ISB Team TRENa
  - Broad-Rush Team SpeakEasy
  - Emory Team WGCNA
  - MSSM Team Megena

*Sage Bionetworks, Academic and Industry Teams*
ACCELERATING MEDICINES PARTNERSHIP (AMP)

ALZHEIMER’S DISEASE - Target Discovery and Preclinical Validation Project

PROGRESS OVER 4 and 1/2 YEARS

- Centralized data resource established
- Rich genomic, proteomic, metabolomic human data made available and being widely used
- Network models of disease pathways/targets developed
- Over 100 novel candidate targets identified and being prioritized in collaboration with industry partners
- Animal models evaluated relative to human networks
- Web-based interface for sharing target nominations and analytical outputs - AGORA platform, being launched TODAY
- Open source research tools for de-risking dark targets - being developed
- Novel biomarker discovery efforts - initiated
- Single cell RNAseq profiling (human and mouse) - initiated
NIA plans to invest $55M over the next 5 years to:

- sustain and expand the capabilities/functionality of the AMP-AD Knowledge Portal
- maximize the use of existing and generate additional molecular profiling data for use in target and biomarker discovery
- enable robust preclinical validation of pioneer targets
- develop novel analytical methods to discover patient stratification biomarkers and to enable disease sub-classification

opportunity to continue and expand the partnership
TARGETS and BIOMARKERS

OPEN DATA

OPEN METHODS

ALZHEIMER’S DISEASE - Target Discovery and Preclinical Validation Project
• $40 million over 5 years to support 6 multi-institutional and cross-disciplinary research teams. The teams will generate various “omics” data from brain tissue and peripheral fluids from individuals participating in natural history/population studies across diverse cohorts and use network biology approaches to integrate these data with data on neuroimaging, vascular physiology and cognitive measures. Predictions about molecular mechanisms are being explored in various animal models (AD models and models of vascular/metabolic risk factors).

Goals and deliverables:

- rapid and broad sharing of data via the AMP-AD Knowledge Portal
- deeper understanding of the phenotypes of risk and the molecular mechanisms linking vascular and metabolic risk factors, cerebrovascular disease and AD (impact of ApoE and sex-differences)
- new disease-relevant therapeutic targets
- molecular signatures that can be non-invasively measured and used for patient stratification
Generate deeper understanding of the mechanisms by which gene-environment interactions lead to cognitively resilient phenotypes in the presence of high risk for disease and identify new therapeutic targets amenable to pharmacologic and non-pharmacologic treatment/prevention strategies.

Conduct integrative network analysis of high-dimensional data collected from individuals resilient to various type of AD risk:
  - high genetic risk (E4 homozygous, Down Syndrome and FAD mutation carriers)
  - very old age (e.g. 90+, centenarians)
  - presence of disease biomarkers established by neuroimaging or by postmortem neuropathologic assessment

Use various cell-based and/or animal models to interrogate pathways implicated in resilience to high AD risk predicted by the application of network biology approaches.

UNDERSTANDING THE COMPLEX BIOLOGY OF RESILIENCE TO AD RISK (R01)
RFA-AG17-061/RFA-AG18-029

* ~$35 million over 5 years supporting 6 multi-institutional projects; additional investment planned for FY18
Impact of Sex Differences on AD Risk and Treatment Response

*Molecular Mechanisms of Neuropsychiatric Symptoms in AD*
INTEGRATE
Epidemiologic, Genomic and Mechanistic Research

INTEGRATE
Computational and Experimental Research

INTEGRATE
Peripheral Systems and the Brain
Research on Aging and AD
ENABLING REPRODUCIBLE AND TRANSLATABLE PRECLINICAL EFFICACY TESTING
KEY FACTORS CONTRIBUTING TO THE POOR PREDICTIVE POWER OF PRE-CLINICAL EFFICACY TESTING STUDIES IN AD ANIMAL MODELS

- The limitations of transgenic animal models used in AD drug development
- Lack of translatable biomarkers
- Failure to match outcome measures used in clinical studies
- Lack of standard/rigor in study design and analysis of data
- Poor reproducibility of published studies and publication bias due to under-reporting of negative results in the literature

Maximize human datasets to identify putative variants, genes and biomarkers for AD

Generate, characterize and validate the next generation of mouse models of LOAD

Develop a preclinical testing pipeline that implements rigorous study design and data analyses

Make data and animal models available to the research community for use in therapy development free of IP barriers
MODEL-AD
Consortium
AlzPED is a publicly available, searchable, data resource that aims to increase the transparency, reproducibility and translatability of efficacy testing studies for Alzheimer's disease candidate therapeutics performed in animal models.

Current Member Organizations:
- National Institute on Aging
- NIH Library
- Alzheimer's Association
- Alzheimer's Drug Discovery Foundation
- Sage Bionetworks
ADVANCING DATA DRIVEN DRUG REPOSITIONING AND COMBINATION THERAPY DEVELOPMENT
This funding opportunity announcement encourages the use of existing and the development of novel computational approaches to identify drugs or drug combinations currently used for other conditions with potential to be efficacious in AD and AD-related dementias.

This initiative invites purely computational research as well as studies that integrate computational and experimental approaches and encourages cross-disciplinary, team-science approach and academia-industry collaborations.

Launched in FY17 - active through January 8, 2020 - three submission deadlines each year.

Annual direct costs cap - $500K.
TRAINING THE NEW TRANSLATIONAL WORKFORCE
PAR-18-524
Institutional Training Programs to Advance Translational Research on Alzheimer's Disease and AD Related Dementias (T32)

Translational, Team-oriented Scientists
PAR 17-052
Research Career Enhancement Award to Advance Therapy Development for Alzheimer's (K18)

Computational Biologists
Data Scientists

Disease Biology
Clinical Research

Data Science
Drug Discovery

Biologists
Clinical Researchers
ENABLING CLINICAL DRUG DEVELOPMENT
A Pipeline of NIA and Trans-NIH Translational Research Funding Initiatives

Target ID Early Validation
Assay Development
Screening
Proof of Concept
Lead Optimization
Candidate Selection
IND-enabling toxicology
Phase I
Phase II
Phase III
Drug Approval

AMP-AD Targets
M²OVE-AD
Resilience-AD

MODEL-AD
AlzPED

ACTC
ADNI
AMP-AD Biomarkers
ABC-DS

ENABLING INFRASTRUCTURE FOR
DATA DRIVEN AND PREDICTIVE
DRUG DEVELOPMENT
AMP-AD BIOMARKERS PROJECT

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 baseline data from the trials will be made broadly available through the Alzheimer Association’s GAAIN platform (http://gaain.org).

Trial data and biological samples will also be shared after completion of the trials.
Anti-Amyloid treatment in Asymptomatic AD Trial (A4 Trial)

ADCS, Reisa Sperling - Harvard Medical School
THERAPEUTIC: Solanezumab
TARGET POPULATION: Cognitively normal older adults (age 65-85), positive for amyloid

Dominantly Inherited Alzheimer Network (DIAN) Trial
Randall Bateman - Washington University
THERAPEUTIC: Gantenerumab and Solanezumab
TARGET POPULATION: Individuals at risk for and with Dominantly Inherited Alzheimer’s Disease
Alzheimer’s Biomarkers Consortium - Down Syndrome (ABC-DS)

Exploring the Connection Between Down Syndrome and Alzheimer’s Disease

The ABC-DS study is a joint study conducted by two groups of research collaborators—Neurodegeneration in Aging Down Syndrome (NIAD) and Alzheimer’s Disease in Down Syndrome (ADDS)—and is supported by the National Institute on Aging (NIA) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), both part of NIH.

https://www.nia.nih.gov/research/abc-ds
$43M consortium - Two multi-institutional, cross-disciplinary research teams (PIs: Ben Handen, Nicole Schupf) collaborating and harmonizing measures and procedures

Biomarkers to track AD-related changes in the brain and cognition for ~450 adults with Down syndrome (25-85 years old)

Measures include PET (amyloid and Tau), MRI, CSF and blood markers, DNA for GWAS, cognitive/memory tests

Data will be available in a public database, pre-publication; samples will be made available to qualified investigators via the National Centralized Repository for Alzheimer’s Disease and Related Dementias (NCRAD)
Longitudinal Early-Onset AD Study

- R56 AG057195 (Liana Apostolova), Alzheimer Association, Industry
- Enroll 400 amyloid positive APP/PSEN1/PSEN2 mutation negative EOAD and 100 age-matched controls, 15 sites across US
- Collect longitudinal detailed clinical, cognitive, MRI, amyloid and tau PET, CSF, plasma, DNA and RNA
- Imaging and biomarker collection aligned with ADNI
- Establish an EOAD clinical trials network
New AD Clinical Trials Infrastructure: Alzheimer's Clinical Trials Consortium (ACTC) (U24)

• **RFA-AG-17-005** Awarded December 2017; ~$70 M

• 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)

• 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-18-513**)
ACTC Goals:

• Conduct clinical trials (early to late stage) 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, including a centralized Institutional Review Board (IRB).

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

Data Sharing Requirements for ACTC Trials

• Data sharing will be achieved through the ACTC resources

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

• Late-stage pivotal trials are expected to make screening/pre-randomization baseline data available within 12 months of enrollment completion per the **Collaboration for Alzheimer's Prevention** data and sample sharing principles.* Moreover, 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.

Guidelines for ACTC Clinical Trial Applicants

The ACTC infrastructure is welcoming of:
• Academic and industry applicants
• Both pharmacological and non-pharmacological interventions

Applications are encouraged that propose:
• Testing candidate therapeutic compounds against novel therapeutic targets (other than amyloid)
• Testing repurposed drugs derived from data driven approaches, including candidates coming from NIA's translational bioinformatics FOA (PAR-17-032)

Note, the ACTC infrastructure is not appropriate for:
• Single site clinical trials
• Routine Phase I, First-in-human single, or multiple ascending dose studies
Trial-Ready Cohort for Preclinical/Prodromal Alzheimer’s Disease (TRC-PAD)

• PIs: Paul Aisen, Reisa Sperling, Jeff Cummings (R01AG053798); ~$25M

• With collaboration of the Global Alzheimer’s Partnership (GAP) Foundation

• Overarching goal: to accelerate current and future secondary prevention trial enrollment through an innovative, highly efficient approach to identify, evaluate, and enroll appropriate prevention trial candidates

• Will 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
TRC-PAD Approach

• Multiple feeder registries (Brain Health Registry, Alzheimer’s Prevention Registry, etc.) and media/community outreach invite individuals interested in trials to join the Alzheimer Prevention Trials (APT) Webstudy.

• APT Webstudy in turn will utilize demographic, medical, lifestyle and genetic factors, as well as longitudinal web-based cognitive testing, to assess each participant’s risk for AD biomarker positivity (using an adaptive algorithm).

• The highest risk individuals based on the algorithm will have in-person assessments; those who are AD biomarker positive will be eligible for the TRC-PAD Cohort, where they will be followed (in-person and remotely), ready for enrollment in trials.
Low barriers: 10-15 min per visit, flexible schedule
Engagement: feedback on progress, testing
Education: news and updates on trials

Alzheimer Prevention Trials Webstudy
If you are at least 50 years of age and interested in Alzheimer’s research,
www.aptwebstudy.org

Slide courtesy of Gustavo Jimenez-Maggiora, ATRI with modifications
ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT

AMP-AD
M²OVE-AD
Resilience-AD

Large scale systems/network biology approach
Predictive models for novel targets and biomarkers
Computational methods benchmarking
Open data and methods

MODEL-AD
AlzPED

Next-gen animal models for late onset AD
Deep phenotyping and staging relative to human disease
Methods development for efficacy testing/Transparent reporting
Open data and 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
Novel Mechanistic Insights into the Complex Biology and Heterogeneity of AD

Enabling Precision Medicine for AD

Translational Tools and Infrastructure to Enable Predictive Drug Development

Emerging Therapeutics

Understanding the Impact of the Environment to Advance Disease Prevention

Advances in Disease Monitoring, Assessment and Care

Building an Open Science Research Ecosystem to Accelerate AD Therapy Development

NAPA Research Goal #1: Treat and Prevent AD by 2025

2018 NIH AD Research Summit Recommendations
https://www.nia.nih.gov/research/administration/recommendations-nih-ad-research-summit-2018
Laying the Foundation for Precision Medicine for AD

Network Biology → Pharmacology ← Preclinical PKPD → Clinical Pharmacology → Pharmaco metrics

Right Pathway → Right Target ← Right Molecule → Right Dose → Right Patients
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Division of Neuroscience
Dallas Anderson
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Charlene Liggins
Yuan Luo
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AMP-AD Private Partners
Abbvie
Biogen
Eli Lilly
GSK
Alzheimer’s Association

Sage Bionetworks
Lara Mangravite
Ben Logsdon
Mette Peters

AMP-AD and Affiliated Consortia Teams and the growing army of researchers embracing open science!