Accelerating Therapy Development for Alzheimer’s through Open Science

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US National Plan to Address Alzheimer’s: GOAL #1: Prevent and Effectively Treat Alzheimer's Disease by 2025

Multiple Etiologies
Multiple Prodromal Phenotypes
Multiple Progression Trajectories

Pathway  
Network Biology  
Right Pathway

Target  
Pharmacology  
Right Target

Drug  
Preclinical PKPD  
Right Molecule

Disease  
Clinical Pharmacology  
Right Dose

Pharmacometrics  
Right Patients
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.
NIA AD Translational Research Program: Diversifying the Therapeutic Pipeline

A Pipeline of Translational Research Funding Opportunities

OPEN SCIENCE - OPEN SOURCE PRINCIPLES

AMP-AD Target Discovery and Affiliated Consortia
AD Centers for Discovery for New Medicines
MODEL-AD AlzPED
ADNI AMP-AD Biomarkers ABC-DS ACTC

ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE THERAPY DEVELOPMENT

NIH National Institute on Aging
ACCELERATING MEDICINES PARTNERSHIP (AMP-AD)

Target Discovery and Preclinical Validation Project

- **Rapid and Broad Sharing of Data**
  - Human multi-omic data (brain/plasma samples)
  - Experimental Validation (iPSCs/animal models)

- **Predictive Modeling**

- **AMP-AD KNOWLEDGE PORTAL**

- **GOVERNANCE AND/OR FUNDING PARTNERS**
  - NIH National Institute on Aging
  - NIH National Institute of Neurological Disorders and Stroke
  - U.S. Food & Drug Administration
  - abbvie
  - Biogen
  - gsk
  - Lilly
  - FNIH Foundation for the National Institutes of Health
  - alzheimer's association
  - Geoffrey Beene Foundation
  - UsAgainstAlzheimer's

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

- **Launched in 2014; ~$50M over 5 years.**

- **6 academic teams**

- **Sage Bionetworks**
ACCELERATING MEDICINES PARTNERSHIP (AMP-AD)

Target Discovery and Preclinical Validation Project

KEY ACHIEVEMENTS OVER 5 YEARS

- Centralized data resources developed for sharing raw and processed data, analytical results and target nominations: AMP-AD Knowledge Portal and AGORA platform.

- Rich, high quality, multi-omic, human data and network models of disease pathways/targets made available via the Knowledge Portal.

- Datasets being widely used: ~3000 users to date - 60% academia, 40% biotech/pharma.

- Over 500 novel candidate targets identified and made available via the AGORA platform along with supporting evidence and extensive druggability information.
AMP-AD Knowledge Portal

Data
- Raw and processed versions of AD Consortium 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

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

https://agora.ampadportal.org/

542 unique target nominations currently available, along with associated evidence and data, including information on druggability.
AD Centers for Discovery of New Medicines (RFA-AG-19-010)
Bringing Open Science to Drug Discovery

Launched October 1, 2019; $73M over 5 years

**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.

**Open Drug Discovery Center for Alzheimer’s Disease (Open-AD)**
Allan Levey, Emory University
Lara Mangravite, Sage Bionetworks
Aled Edwards, Structural Genomics Consortium

**IUSM Alzheimer’s Disease Drug Discovery Center (IUSM ADDDC)**
Alan Palkowitz and Bruce Lamb, Indiana University and Purdue University
AD Centers for Discovery of New Medicines

- Open Source Tools for Novel Targets
- Preclinical Lead Candidates
- Infrastructure for sharing data, methods and tools

NIA funding programs for preclinical and clinical drug development

Understanding the biology of targets/disease
Biologists/Basic Researchers

External Drug Discovery Campaigns
Academia/Biotech/Pharma
OPEN SCIENCE-OPEN SOURCE PRINCIPLES: FROM TARGETS TO TRIALS

ENABLING INFRASTRUCTURE 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, target enabling tools and preclinical lead candidates for novel targets

AD Centers for New Medicines

MODEL-AD
- Next-gen animal models for late onset AD
- Deep phenotyping and staging relative to human disease
- Methods development for rigorous efficacy testing
- Open data, methods 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 and biosamples from placebo and treatment arms
M²OVE-AD – Molecular Mechanisms of the Vascular Etiology of AD
NPS-AD – Molecular Mechanisms of the Neuropsychiatric Symptoms in AD
INTEGRATE Clinical, Genomic, Mechanistic and Translational Research

INTEGRATE Computational and Experimental Approaches

INTEGRATE Data from Animal Models and Humans

INTEGRATE Academic and Industry Expertise
NIH AD Research Summits: Change academic, publishing, and funding incentives to enable collaborative, transparent and reproducible research
AMP-AD 1.0 Private Partners
Abbvie
Biogen
Eli Lilly
GSK
Alzheimer’s Association

Foundation for the NIH
Rosa Canet–Aviles

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Dallas Anderson
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Ben Logsdon
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Mette Peters
Anna Greenwood
Cristine Suver

All NIA-supported academic teams practicing Open Science!