ACT- AD Webinar

New Approaches to Target Discovery for Alzheimer’s Disease

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National Institute on Aging
National Plan Goals:

1. Prevent and effectively treat Alzheimer’s Disease by 2025.

2. Optimize care quality and efficiency.


4. Enhance public awareness and engagement.

5. Track progress and drive improvement.
### Phase III Randomized, Double-blind, Placebo Controlled, Clinical Trials for AD:

<table>
<thead>
<tr>
<th>Agent</th>
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**Failure due to lack of efficacy or unforeseen toxicity.**
A publicly available database developed by the National Institute on Aging/NIH and the Alzheimer’s Association.

Housing the AD portfolios of ~30 funding agencies (over 4,000 projects) classified using a common AD research ontology.

Providing funders, researchers and the public with a detailed picture of the scale of ongoing research on AD in the US and internationally.

Enabling funding agencies to coordinate planning, leverage resources, avoid duplication, and identify opportunities for collaboration.

A tool for developing research milestones and tracking progress.

http://iadrp.nia.nih.gov
Alzheimer’s Disease Research Summit 2012: Path to Treatment and Prevention

May 14-15, 2012

A blueprint for an integrated translational research agenda.

- **Session 1**: Interdisciplinary Approach to Discovering and Validating the Next Generation of Therapeutic Targets for AD
- **Session 2**: Challenges in Preclinical Therapy Development
- **Session 3**: Who to Treat, When to Treat and What Outcomes to Measure
- **Session 4**: Drug Repurposing and Combination Therapy
- **Session 5**: Non-pharmacological Interventions
- **Session 6**: New Models of Public Private Partnerships
Recognize the heterogeneity and the multifactorial nature of the disease.

Employ new research paradigms such as systems biology and systems pharmacology.

Enable rapid and extensive sharing of data, disease models, and biological specimens.

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

Develop strategies to overcome intellectual property barriers to Alzheimer’s disease drug development.

Develop new public-private partnerships.

Establish a National IRB
NIA/NIH Funding Initiatives and Programs
-developed in response to recommendations from the 2012 AD Summit-

- ENABLING CLINICAL DRUG DEVELOPMENT
- NEW TRANSLATIONAL CAPABILITIES
- BIOLGY OF DISEASE
- PUBLIC PRIVATE PARTNERSHIPS
- QUANTITATIVE SYSTEMS PHARMACOLOGY -in development-
- SYSTEMS AND NETWORK BIOLOGY
- DISCOVERY AND VALIDATION OF NOVEL TARGETS
- RESEARCH TOOLS AND DISEASE MODELS
- GENETICS
- ADGC/NIAGADS
- ADSP
- SECONADARY PREVENTION TRIALS
- AD BIOMARKERS in DOWN SYNDROME
- OPTOGENETICS
- Human iPSC
- INFLAMMATION
- VASCULAR ETIOLOGY
- NIA/NIH Funding Initiatives and Programs -developed in response to recommendations from the 2012 AD Summit-
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**Failure due to lack of efficacy or unforeseen toxicity.**
- 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 drug action
Complexity of Disease

Multiple Etiologies
Multiple Prodromal Phenotypes
Multiple Progression Trajectories

Genetics
Environment

Healthy State
Disease State

Disease progression
Disease modifying therapy
Complexity of Drug Action

Idealistic view

Drug affects many targets
Targets interact
Targets lead to multiple physiological responses

Real life scenario

Polypharmacy

Drug is delivered in specific times
Network changes with time

Chronopharmacy
RFA AG13-013: Interdisciplinary Approach to Identification and Validation of Novel Therapeutic Targets for AD

A funding opportunity (multi PD/PI R01 mechanism) inviting interdisciplinary research that integrates identification of novel targets for AD with initial target validation required to make a decision to pursue drug discovery for a specific molecule/pathway. The FOA encourages the use of network-based approaches such as systems biology to enable target prioritization and to gain understanding of the molecular and physiological context within which potential therapeutic targets operate.  [grants.nih.gov/grants/guide/rfa-files/RFA-AG-13-013.html](grants.nih.gov/grants/guide/rfa-files/RFA-AG-13-013.html)
NIA Funding Opportunities
-developed in response to recommendations from the 2012 AD Summit-

**RFA AG13-013:** Interdisciplinary Approach to the Identification and Validation of Novel Therapeutic Targets for AD

**RFA AG15-013:** Alzheimer’s Disease Prevention Trials

Accelerating Medicines Partnership – AD (AMP-AD)

[www.nia.nih.gov/alzheimers/amp-ad](http://www.nia.nih.gov/alzheimers/amp-ad)
GOVERNMENT-INDUSTRY-NON PROFIT

A PRECOMPETITIVE PARTNERSHIP FOR KNOWLEDGE CREATION
Alzheimer’s Disease Program

Target Discovery and Preclinical Validation

- ~2,500 brains
  - Clinical
  - Pathologic
  - Genomic
  - Epigenomic
  - RNAseq
  - Proteomic

Biomarkers

- tau PET imaging
- novel fluid biomarkers

Secondary Prevention Trials
- anti-amyloid treatment

Rapid and Broad Sharing of Data

Data Integration

Experimental Validation

AMP-AD Knowledge Portal

Predictive Modeling

ICahn School of Medicine
- NY Stem Cell Foundation
- Rush University
- Emory University
- U Florida
- ISB
- Mayo Clinic

NIH National Institute on Aging

FNIH Foundation for the National Institutes of Health
Data to be Generated by the AMP-AD Target Discovery Consortium

systems
- human
- mouse
- drosophila
- iPSC

perturbations
- shRNA
- compounds
- RNAi

data types
- RNA-seq
- Whole exome
- WGS
- methylation
- miRNA
- proteomics
- phenotypic measurements
This Knowledge Portal is supported by contributions from all members of the Accelerating Medicines Partnership for Alzheimer’s disease.

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

First public data release: March 4, 2015
Building a pipeline to discover and validate novel therapeutic targets and lead compounds for Alzheimer’s disease

2015 NIH AD Research Summit: Path to Treatment and Prevention

Feb 9-10, 2015

- Understanding the Heterogeneity and Multifactorial Etiology of AD
- Transforming AD Therapy Development: From Targets to Trials
- New Strategies for AD Prevention
- Innovating Disease Monitoring, Assessment and Care
- Empowering Patients, Engaging Citizens
- Enabling Partnerships for Open Innovation
data ➔ information ➔ knowledge ➔ understanding
Laying the Foundation for Precision Medicine for AD

Pathway

Network Biology ↔ Pharmacology

Target

Right Pathway ↔ Right Target

Drug

Preclinical PKPD ↔ Clinical Pharmacology

Disease

Right Molecule ↔ Right Dose ↔ Right Patients

Pharmacometrics

Diagram showing the relationship between network biology, pharmacology, preclinical PKPD, clinical pharmacology, and disease for precision medicine in Alzheimer's Disease.
Some key messages:

- Integrate AD research with research on the fundamental biology of aging.
- Support intense molecular profiling of existing and establish new cohorts to fill the gaps in large-scale human data needed to build predictive models of disease and wellness.
- Expand systems biology and systems pharmacology programs.
- Maximize the availability and usability of data, network models and analytical tools.
- Expand the precompetitive space for target validation through clinical proof of mechanism.
- Build a new translational and data science workforce.
- Change the reward systems in academia, publishing and funding agencies to enable large-scale team science and transparent, reproducible and translatable research.
- Engage patients, caregivers and citizens as direct partners in research.
Update and expand the implementation research milestones for the NAPA Goal: Treat and Prevent AD by 2025

New Funding Opportunities and Public Private Partnerships

2015 AD Summit Recommendations