

# Alzheimer's and Related Dementias Research: Transforming AD Therapy Development

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## NAPA Advisory Council Meeting

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National Institute on Aging

February 3, 2017

## Current AD Clinical Trials "Score Card"

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Phase III Randomized, Double-blind, Placebo Controlled, Clinical Trials for AD -  
Failures due to lack of efficacy or unforeseen toxicity.

<u>Agent</u>	<u>Target/Mechanism</u>	<u>Outcome</u>
Atorvastatin	HMG CoA reductase	Negative
Dimebon	Mitochondrial function	Negative
Semagacestat	Gamma secretase	Negative
NSAIDs	Inflammation	Negative
Phenserine	Cholinesterase/Amyloid	Negative
Rosiglitazone	PPAR gamma agonist	Negative
Simvastatin	HMG CoA reductase	Negative
Tarenflurbil	Gamma secretase	Negative
Xaliproden	Serotonin antagonist	Negative
Bapineuzumab	amyloid beta (passive immunization)	Negative
Solanezumab	amyloid beta (passive immunization)	Negative*
IVIg	amyloid beta (passive immunization)	Negative

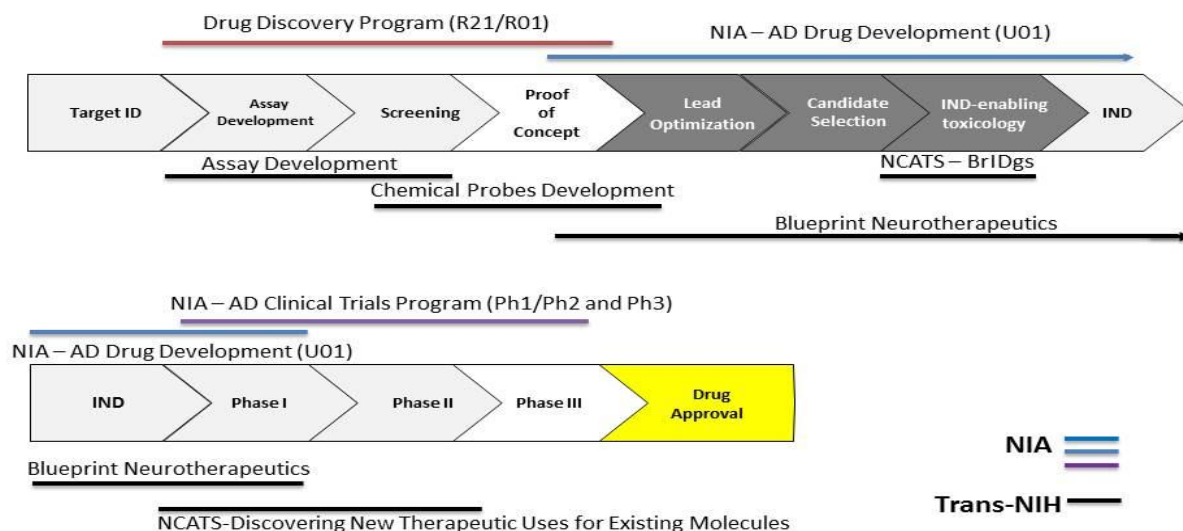
# What may have gone wrong? An iceberg analogy

- 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



- Insufficient understanding of disease complexity and the physiologic response to therapeutic intervention

## Leveraging Trans-NIH Translational Programs



\*SBIR/STTR funding opportunities exist for the full spectrum of drug discovery/development



**LM11A-31** - first in class, small molecule modulator of the P75 Neurotrophin Receptor PI – Frank Longo MD and Neurotrophix

The pre-clinical drug development and part of the IND-enabling studies for **LM11A-31** were supported through NIA's

- AD Translational Program
- IND Toxicology Program

The Phase II trial is being supported through NIA's Pilot Clinical Trials Program

## Accelerating Medicines Partnership



abbvie



GEOFFREY BEENE



Managing Partner



### Alzheimer's Disease Program Partners





# ACCELERATING MEDICINES PARTNERSHIP (AMP)

## ALZHEIMER'S DISEASE – TWO PROJECTS

### Target Discovery and Preclinical Validation to Find New Disease-Relevant Drug Targets

Generate "omic" data on ~2,500 brains

Integrate  
Molecular profiling  
Predictive Modeling  
Experimental validation

Central Portal for Data Sharing

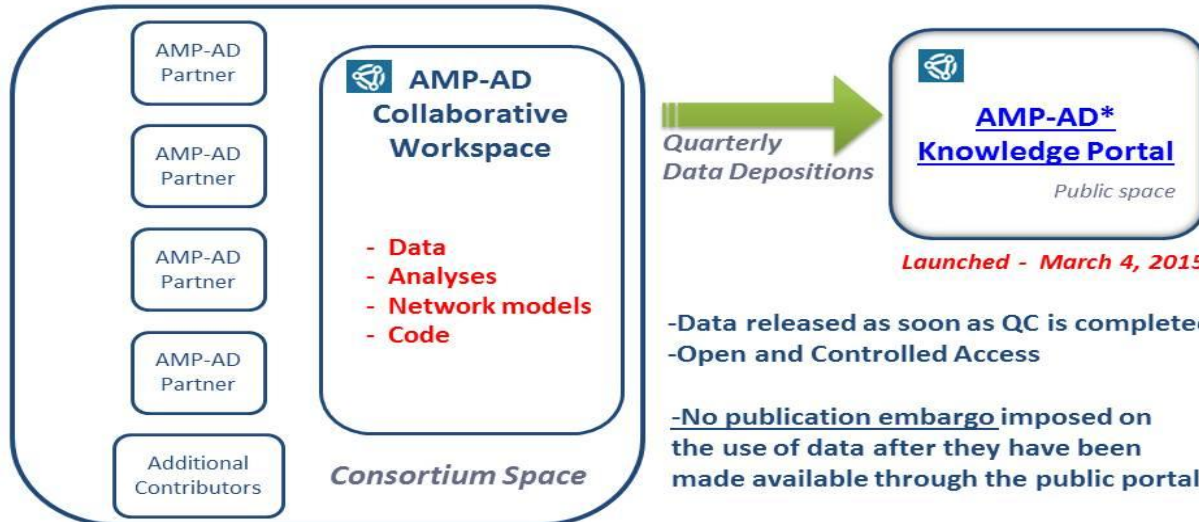
6 Academic Teams – NIA grants –

### Biomarkers to Characterize Existing and New Biomarkers

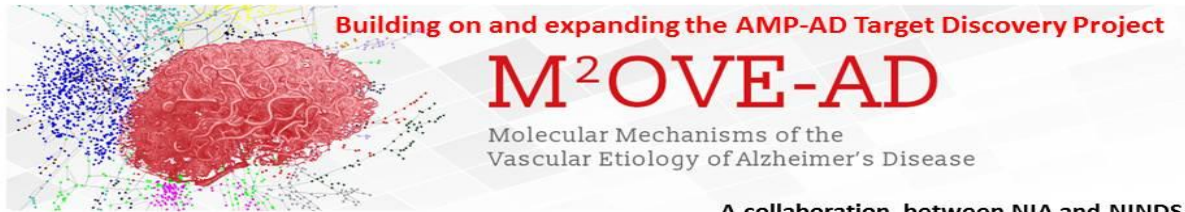
PET TAU and novel biomarkers

ADDED TO THREE ANTI-AMYLOID PREVENTION TRIALS

A4 DIAN API-ApoE4



\*AMP-AD Knowledge Portal – [www.synapse.org.ampad](http://www.synapse.org.ampad)



- ~\$30 million over 5 years to support cross disciplinary research teams:
- 5 research teams will generate various “omics” data from brain and peripheral fluids from individuals participating in several **natural history and population studies** and use network biology approaches to integrate these data with data on neuroimaging, vascular physiology and cognitive measures.
- Predictions about molecular mechanisms will be explored in **animal models** (AD models and models of vascular/metabolic risk factors).
- Goals and deliverables:
  - rapid and broad sharing of data
  - deeper understanding of the phenotypes of risk and the mechanisms linking vascular risk factors, cerebrovascular disease and AD
  - new disease-relevant therapeutic targets for prevention
  - molecular signatures that can be non-invasively measured and used for patient stratification

<https://alzped.nia.nih.gov/>

## Alzheimer’s Disease Preclinical Efficacy Database

HOME LOGIN

ABOUT AlzPED
SEARCH AlzPED
RESOURCES
SUBMIT YOUR DATA

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.

Q
SEARCH

[MORE SEARCH OPTIONS](#)

### GETTING STARTED

- [>](#) How to Enter Data
- [>](#) Frequently Asked Questions
- [>](#) Search Guides
- [>](#) AlzPED Team
- [>](#) Glossary of Terms

### Current AlzPED Members:

**NIA**

**NIH Library**

**ADDF**

**Alzheimer Association**

**Center for Open Science**

## **Alzheimer's Disease Translational Center for Animal Model Resources and Preclinical Efficacy Testing Multi Component Center**

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### **Program Scope and Goals:**

- **Development and characterization of the next generation of AD Tg animal models, ensuring their maximal and rapid availability to researchers engaged in preclinical drug development**
- **Extensive characterization and clinico-pathological staging of existing and new AD Tg mouse models with the corresponding stages of clinical disease**
- **Development of translatable pharmacodynamic biomarkers for novel therapeutic targets**

[RFA AG16-014 \(U54\): Indiana University/Jax Labs/Sage Bionetworks](#)

## **Alzheimer's Disease Translational Center for Animal Model Resources and Preclinical Efficacy Testing Multi Component Center**

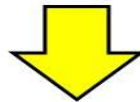
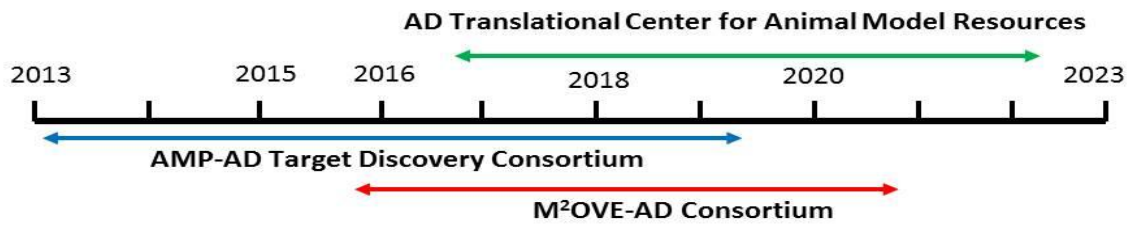
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### **Program Scope and Goals, cont'd:**

- **Establishment and implementation of guidelines for standardized best practices for the rigorous preclinical testing of AD candidate therapeutics in AD Tg models**
- **Preclinical efficacy testing of *selected* candidate AD therapeutics (single or combinations of compounds) using standardized best practices**
- **AD models distribution - rapid and free of legal barriers for use in therapy development.**

[RFA AG16-014 \(U54\): Indiana University/Jax Labs/Sage Bionetworks](#)





- rich human and cell/animal models 'omics' data
- network models of targets and disease pathways
- "omics"- based biomarkers for target engagement and patient stratification biomarkers
- cell and animal models characterized relative to human network

## **ENABLING CLINICAL DRUG DEVELOPMENT**

-new biomarker initiatives and clinical trials infrastructure-

## **Alzheimer's Biomarker Consortium – Down Syndrome (ABC-DS)**

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- Supported by NIA and NICHD
- ~\$37 million over 5 years, for two research teams
- Biomarkers will be explored to track AD-related changes in the brain and cognition for ~500 adults with Down syndrome
- Measures include PET, MRI, CSF and blood markers, DNA for GWAS, cognitive/memory tests
- Research teams are collaborating and harmonizing measures and procedures
- Data and samples will be made available

## **Alzheimer's Clinical Trials Consortium (ACTC)**

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**Purpose:** Establish a consortium to run trials focused on interventions that may prevent, delay, or treat the symptoms of AD and other age-related dementias.

- Include multiple clinical trials sites and trial coordination and management infrastructure.
- Conduct clinical trials (Phase I to III) of promising pharmacological and non-pharmacological interventions for cognitive and neuropsychiatric symptoms.
- Provide a state-of-the-art clinical trial infrastructure to facilitate rapid development and implementation of protocols.



## Related Recent Funding Initiatives

Interdisciplinary Research to Understand the Complex Biology of Resilience to Alzheimer's Disease Risk (R01) <https://grants.nih.gov/grants/guide/rfa-files/RFA-AG-17-061.html>

Phenotypic and Functional Characterization of ApoE2 to Inform Translation Strategies for Aging-Related Conditions (R01/R21)

<http://grants.nih.gov/grants/guide/pa-files/PAR-16-370.html>

<http://grants.nih.gov/grants/guide/pa-files/PAR-16-371.html>

Integrative Research to Understand the Impact of Sex Differences on the Molecular Determinants of AD Risk and Responsiveness to Treatment (R01)

<https://grants.nih.gov/grants/guide/pa-files/PAR-17-033.html>

Translational Bioinformatics Approaches to Advance Drug Repositioning and Combination Therapy Development for Alzheimer's Disease (R01)

<https://grants.nih.gov/grants/guide/pa-files/PAR-17-032.html>

Enhancing the Target and Biomarker Discovery Efforts of the AMP-AD and M<sup>2</sup>OVE-AD Consortia (R01)

<http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-17-054.html>

## Newest Alzheimer's FOAs

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- Resource Leveraging
- Caregiving
- Clinical Care and Trials
- Translational research
- Basic research
- Training

### Alzheimer's Disease FOAs:

<http://www.nia.nih.gov/AD-FOAs>

## NINDS Funding Opportunity Announcements on Alzheimer's Disease-Related Dementias (ADRD) for FY 2017

Two new Funding Opportunity Announcements in partnership with NIA:

- **Leveraging Existing Resources for Research on Lewy Body Dementia (R03) [RFA-NS-17-016](#)**
  - This FOA encourages researchers to take advantage of existing data and biospecimens housed in two large NIH-supported programs (i.e., [ADNI/NACC](#) and [Parkinson's Disease Biomarkers Program](#) databases) for the purpose of answering research questions about LBD and co-occurrence of dementia and parkinsonism.
- **Frontotemporal Degeneration (FTD) Sequencing Consortium: Discovery, Replication, and Validation (UG3/UH3) [RFA-NS-17-017](#)**
  - This FOA supports the genetic discovery, replication and validation of disease-causing mutations, risk variants and genetic modifiers that contribute to FTD.
- Applications are due Feb 10

## Save the Dates!

AD Care and Services  
Research Summit  
**October 16-17, 2017**  
Bethesda, MD

Alzheimer's Disease  
Research Summit (III)  
**March 1-2, 2018**  
Bethesda, MD

 **National Institute on Aging**  
*Turning Discovery Into Health*



## February 3, 2017 -- Advisory Council Meeting #23

The meeting was held on Friday, February 3, 2017, in Washington, DC. The theme of this Advisory Council meeting was clinical trials for Alzheimer's disease and related dementias and recruitment challenges. Additional afternoon presentations included updates on progress towards a Care and Services Summit, federal workgroup updates, and preparation for the Advisory Council's 2017 Recommendations, due in April 2017. Material available from this meeting is listed below and is also available at <https://aspe.hhs.gov/advisory-council-alzheimers-research-care-and-services-meetings#Feb2017>.

Comments and questions, or alerts to broken links, should be sent to [napa@hhs.gov](mailto:napa@hhs.gov).

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### General Information

<b>Agenda</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Meeting Announcement</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Meeting Summary</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Public Comments</b>	<a href="#">[HTML Version]</a>

### Handouts

<b>Panelist Bios</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
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### Presentation Slides

<b>2017 Recommendations</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Alzheimer's Association TrialMatch</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Clinical Services Subcommittee Federal Update</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Clinical Studies Recruitment Strategy</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Development and Use of Registries to Accelerate Enrollment into Alzheimer's Trials</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Long-Term Services and Supports Committee Update</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>National Recruitment Strategy</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>



<b>NINDS Update</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Randomized Controlled Trials for Alzheimer's Disease</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Strategies to Facilitate Recruitment and Screening for Alzheimer's Clinical Trials</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Transforming AD Therapy Development</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>
<b>Update National Research Summit on Care, Services and Supports for Persons with Dementia and Their Caregivers</b>	<a href="#">[HTML Version]</a> <a href="#">[PDF Version]</a>

## **Videos**

<b>Welcome thru Perspectives</b>	<a href="#">[Video]</a>
<b>Rachel, Jessica, George Presentations</b>	<a href="#">[Video]</a>
<b>Keith Presentation and Panel Discussion</b>	<a href="#">[Video]</a>
<b>Public Comments</b>	<a href="#">[Video]</a>
<b>Care Summit and Milestones</b>	<a href="#">[Video]</a>
<b>Federal Workgroups and Adjourn</b>	<a href="#">[Video]</a>

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