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

NAPA Advisory Council Meeting

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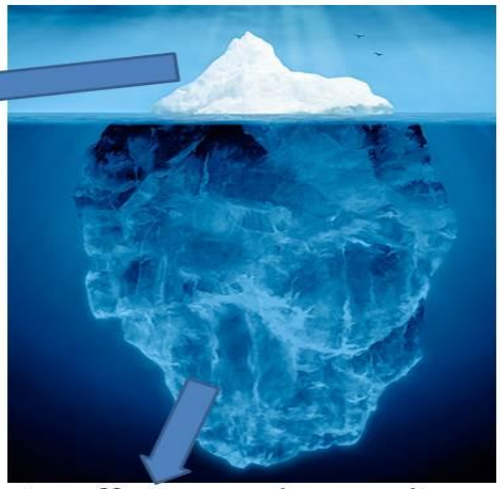
Current AD Clinical Trials "Score Card"

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

Agent	Target/Mechanism	Outcome
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

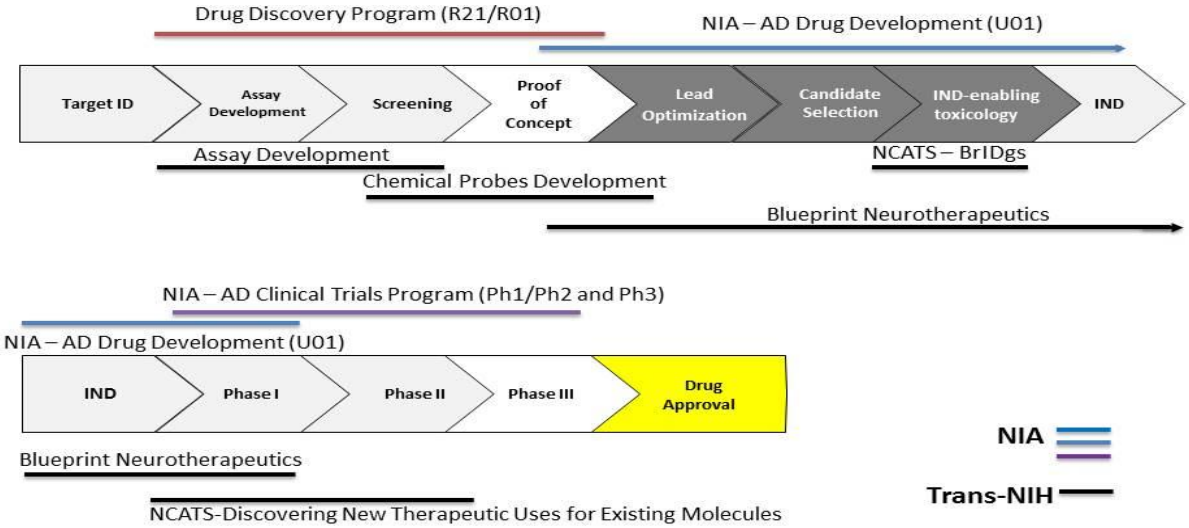
What may have gone wrong? An iceburg analogy

- 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

NIH National Institute on Aging

NIH National Institute of Neurological Disorders and Stroke

FDA

abbvie

Biogen

gsk GlaxoSmithKline

Lilly

alzheimer's association

Alzheimer's Drug Discovery Foundation

GEOFFREY BEENE

US4gainst Alzheimer's

Managing Partner → FNIH Foundation for the National Institutes of Health

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

GAAIN
alzheimer's association

Sage BIONETWORKS Synapse

AMP-AD Partner
AMP-AD Partner
AMP-AD Partner
AMP-AD Partner
Additional Contributors

AMP-AD Collaborative Workspace
- Data
- Analyses
- Network models
- Code

Consortium Space

Quarterly Data Depositions

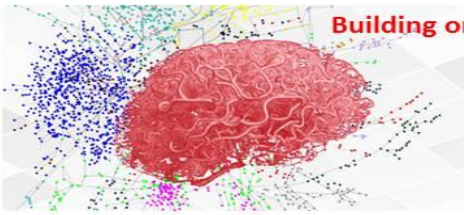
AMP-AD* Knowledge Portal
Public space

Launched - March 4, 2015

-Data released as soon as QC is completed
-Open and Controlled Access

-No publication embargo imposed on the use of data after they have been made available through the public portal

*AMP-AD Knowledge Portal – www.synapse.org.ampad



Building on and expanding the AMP-AD Target Discovery Project

M²OVE-AD

Molecular Mechanisms of the
Vascular Etiology of Alzheimer's Disease

A collaboration between NIA and NINDS

- ~$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

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

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**

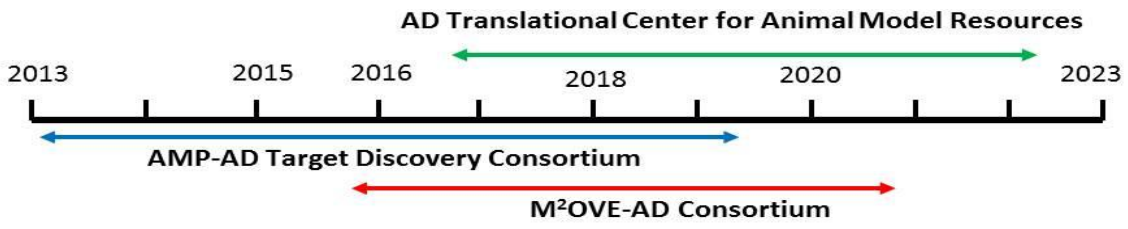
RFA AG16-014 (U54): Indiana University/Jax Labs/Sage Bionetworks

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

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)

- 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)

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.

NIH National Institute on Aging
Turning Discovery Into Health

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^2OVE-AD Consortia (R01)
http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-17-054.html

Newest Alzheimer's FOAs

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

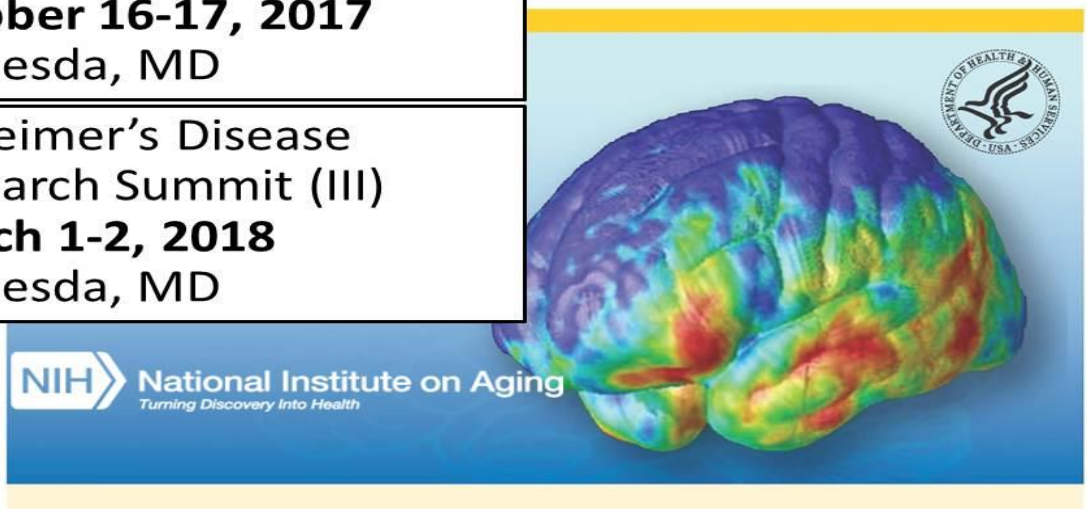
Alzheimer's Disease FOAs:
http://www.nia.nih.gov/AD-FOAs

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