Developing a Knowledge Base and Infrastructure to Enable QSP for Alzheimer’s Disease Research and Drug Development

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QSP at NIH


Organized and sponsored by: NINDS in collaboration with NIA, NIMH, NIDA and NCATS
## Phase III Randomized, Double-blind, Placebo Controlled, Clinical Trials for AD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target/Mechanism</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>HMG CoA reductase</td>
<td>Negative</td>
</tr>
<tr>
<td>Dimebon</td>
<td>Mitochondrial function</td>
<td>Negative</td>
</tr>
<tr>
<td>Semagacestat</td>
<td>Gamma secretase</td>
<td>Negative</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Inflammation</td>
<td>Negative</td>
</tr>
<tr>
<td>Phenserine</td>
<td>Cholinesterase/Amyloid</td>
<td>Negative</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>PPAR gamma agonist</td>
<td>Negative</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>HMG CoA reductase</td>
<td>Negative</td>
</tr>
<tr>
<td>Tarenflurbil</td>
<td>Gamma secretase</td>
<td>Negative</td>
</tr>
<tr>
<td>Xaliprofen</td>
<td>Serotonin antagonist</td>
<td>Negative</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>amyloid beta (passive immunization)</td>
<td>Negative</td>
</tr>
<tr>
<td>Solanezumab</td>
<td>amyloid beta (passive immunization)</td>
<td>Negative*</td>
</tr>
<tr>
<td>IVIG</td>
<td>amyloid beta (passive immunization)</td>
<td>Negative</td>
</tr>
<tr>
<td>JNJ-54861911</td>
<td>BACE</td>
<td>Negative</td>
</tr>
<tr>
<td>Lanabecestat</td>
<td>BACE</td>
<td>Negative</td>
</tr>
<tr>
<td>Verubecestat</td>
<td>BACE</td>
<td>Negative</td>
</tr>
</tbody>
</table>

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.
- Support extensive 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.
- 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.
- Develop new precompetitive public-private partnerships.
- Change academic, publishing, and funding incentives to promote collaborative, transparent, and reproducible research.
- Engage patients, caregivers and citizens as direct partners in research.
QSP at NIA

NIH AD Research Summits: Path to Treatment and Prevention

May 14-15, 2012
Feb 9-10, 2015
March 1-2, 2018

Building a Foundation for QSP in Alzheimer’s Research and Drug Development
- 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

QSP to the Rescue?

- Complexity of disease
- Complexity of the physiologic response to therapeutic intervention
ENABLING A SYSTEMS-BASED APPROACH TO TARGET DISCOVERY AND VALIDATION
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>
<th>Harvard/MIT</th>
</tr>
</thead>
<tbody>
<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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<tr>
<td>Human Data Source</td>
<td>ROSMAP</td>
<td>Mt Sinai Brain Bank</td>
<td>Mayo Brain Bank</td>
<td>All</td>
<td>ADNI</td>
<td>ROSMAP</td>
</tr>
<tr>
<td>Molecular Data Types</td>
<td>RNAseq</td>
<td>Whole exome seq</td>
<td>RNAseq</td>
<td>All Proteomics</td>
<td>Metabolomic</td>
<td>Txn Factors</td>
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<tr>
<td>Target Identification</td>
<td>Bayesian networks</td>
<td>Bayesian networks</td>
<td>Innate Immunity Networks</td>
<td>Bayesian Networks</td>
<td>Systems analysis</td>
<td>REST</td>
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<tr>
<td>Preclinical Validation</td>
<td>iPSCs, Cell lines</td>
<td>IPSC, drosophila, mouse</td>
<td>mouse</td>
<td>Mouse, cell culture, drosophila</td>
<td>NA</td>
<td>mouse</td>
</tr>
</tbody>
</table>

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

- Generate multi-omic 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.

Data Coordination and Integrated Analysis
Sage Bionetworks (Mangravite)
60,000 files contributed by 42 investigators across 22 institutions representing samples from 36 research studies.

AMP-AD Knowledge Portal
www.ampadportal.org

Over 2000 users* with ~55 new users per month

(*users from academia, biotech, pharma)
ACCELERATING MEDICINES PARTNERSHIP (AMP)

ALZHEIMER’S DISEASE - Target Discovery and Preclinical Validation Project

Analytical working groups (academic and industry participation): developing new data and analytical resources for AD research

RNAseq Working Group
Network Working Group
eQTL Working Group
Deconvolution Working Group
Cross-Species Working Group

139 mouse model Differentially Expressed Genes (DEGs) in Brain
Agora

An open source, interactive platform to discover and evaluate the results from the AMP-AD consortium.

agora.ampadportal.org

- Broadcast AMP-AD target predictions

- Establish confidence in target predictions through unbiased, consistent assessment across multiple types of evaluations

- Disseminate tools to encourage independent evaluation
PLANNED ADDITIONAL FEATURES

• New widgets to incorporate additional lines of evidence:
  — genome explorer (eQTLs, GWAS, transcription factor networks)
  — proteomic data: differential expression and networks
  — metabolomic data: differential expression and networks
  — integrative ranking across multiple types of evidence
  — single cell RNA-seq
  — druggability widget

• New widgets to highlight available tools and resources:
  — model systems and other experimental models

• Enabling users to follow, favorite, and give feedback on gene targets of interest
AMP-AD: Integrative Proteomics for Novel Target and Biomarker Discovery

1. Discovery Proteomics
   - Control
   - AsymAD
   - non-AD
   - MCI
   - AD
   ~3,000 proteins
   n=1,000 tissues

2. Validation Proteomics
   - 400 Cases (ROS/MAP)
   ~11-12,000 proteins
   n=80 tissues
   TMT Multi-Plex
   ~50 hub proteins in key modules
   ~5 targets in mouse models
   Novel Targets

3. Therapeutic Feasibility
   - Model Systems
     - Cell Culture
     - Transgenic Flies
   Protein Networks Associated with Key Traits

Label-free "single shot"
DE-RISKING NOVEL TARGETS THROUGH OPEN SCIENCE
Accelerate the characterization and validation of candidate targets delivered by AMP-AD and other target discovery programs, through the development of open source tools, reagents and methods and by integrating the enabled targets into drug discovery campaigns.
Open Source Tools for Novel Targets Preclinical Lead Candidates

ADDP – AD Drug Development PAR-18-174
BPN – Blueprint Neurotherapeutics PAR 18-546
ACTC – AD Clinical Trials Consortium

Understanding the biology of targets/disease

Researchers at Large

External Drug Discovery Campaigns

Academic Labs
Biotech
Pharma

AD Centers for Discovery of New Medicines

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

Late Stage Preclinical Drug Development through First in Human

MODEL-AD

First in Human through Phase III

ADDP
BPN

BPN
Pilot Clinical Trials
ADDP
BPN

ADDP – AD Drug Development PAR-18-174
BPN – Blueprint Neurotherapeutics PAR 18-546
ACTC – AD Clinical Trials Consortium
INCREASING THE PREDICTIVE POWER OF ANIMAL MODEL EFFICACY TESTING
MODEL-AD
Model Organism Development & Evaluation for Late-Onset Alzheimer’s Disease

https://model-ad.org

- Prioritize LOAD variants for animal modeling
- Create 50 new mouse models with CRISPR (piloting rat models)
- High-capacity screening of all models, deep phenotyping of promising models
- Align mouse and human phenotypes (neuropath, omics, imaging)
- Rigorous preclinical testing of the most promising models and therapeutics
- Broad, unrestricted distribution of all data and models for use in research and therapy development.

Bioinformatics and Data Management Core (BDMC)

Disease Modeling Project (DMP)

Preclinical Testing Core (PTC)

Indiana University

The Jackson Laboratory

Sage BioNetworks

University of Pittsburgh

University of California, Irvine
INTEGRATE Clinical, Genomic, Mechanistic and Translational Research

INTEGRATE Computational and Experimental Methods

INTEGRATE Data from Animal Models and Humans

INTEGRATE Academic and Industry Expertise

Confidence in proof of concept

Confidence in compound

Confidence in target

Pharmacokinetics/pharmacodynamics

Systems pharmacology

Target exposure
Target engagement
Target modulation
Pathway modulation
(Patho)-physiological regulation
Disease modification
DEPLOYING 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 and target enabling tools

ADNM Centers

MODEL-AD
- Next-gen animal models for late onset AD
- Deep phenotyping and staging relative to human disease
- Methods development for efficacy testing
- Open data 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/biosamples from placebo and treatment arms
2018 NIH AD Research Summit Recommendations

https://www.nia.nih.gov/research/administration/recommendations-nih-ad-research-summit-2018

**AGENDA**

- 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

**Expand support for quantitative systems pharmacology approaches** that couple biological network and pathway analyses with mechanistic systems models, and integrate data from disparate sources (e.g., preclinical and clinical; in vitro, ex vivo, and in vivo; acute and chronic intervention) to enable predictive drug development.

These efforts should **ensure full transparency of data and analytical methods development** and encourage **precompetitive academic-industry collaborations**.
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Biogen
Eli Lilly
GSK
Alzheimer’s Association

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