ASCPT QSP Preconference
March 13, Washington DC

FROM MOLECULE TO PATIENT

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

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NIH National Institute on Aging

QSP at NIH

NIGMS WORKSHOPS: Quantitative and Systems Pharmacology (2008 and 2010)

NIH QSP White Paper: "Quantitative and Systems Pharmacology in the Post-genomic Era: New Approaches to Discovering Drugs and Understanding Therapeutic Mechanisms," October 2011

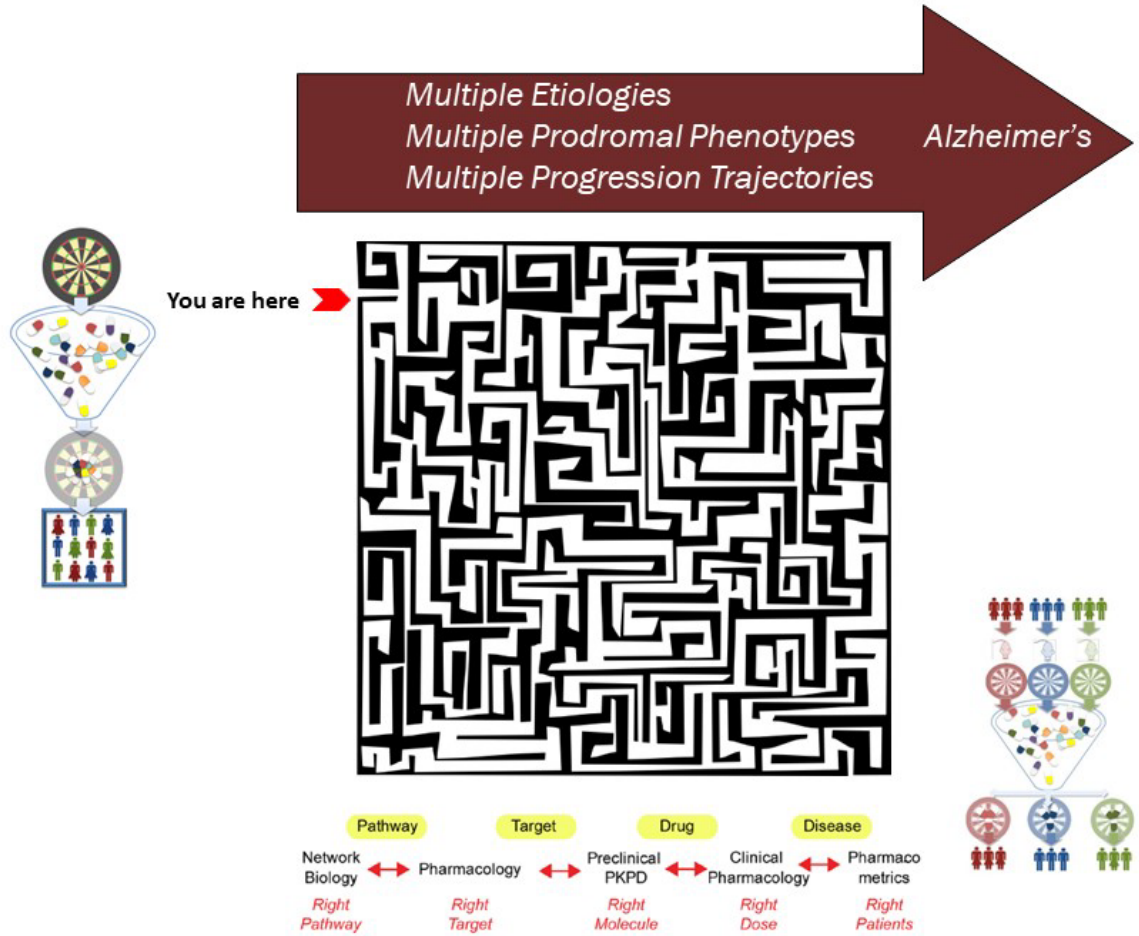
Quantitative Systems Pharmacology and Drug Discovery: Filling the Gaps in Current Models of the R&D July 2017

Organized and sponsored by: NINDS
in collaboration with NIA, NIMH, NIDA and NCATS

Phase III Randomized, Double-blind, Placebo Controlled, Clinical Trials for AD

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
JNJ-54861911	BACE	Negative
Lanabecestat	BACE	Negative
Verubecestat	BACE	Negative

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.

https://www.nia.nih.gov/research/milestones

Overarching Recommendations

- ❑ 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

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

FROM MOLECULE TO PATIENT

ENABLING A SYSTEMS-BASED APPROACH TO TARGET DISCOVERY AND VALIDATION

ACCELERATING MEDICINES PARTNERSHIP (AMP)

ALZHEIMER'S DISEASE - Target Discovery and Preclinical Validation Project

RFA AG13-013

Academic Teams	Broad-Rush	Mt Sinai	UFL/ISB /Mayo	Emory	Duke	Harvard/ MIT
Principal Investigators	De Jager, Bennett	Schadt, Zhang	Golde, Price, Taner	Levey	Kaddurah-Daouk	Yankner, Tsai
Human Data source	ROSMAP	Mt Sinai Brain Bank	Mayo Brain Bank	All	ADNI	ROSMAP
Molecular Data Types	RNAseq	RNAseq Whole exome seq	RNAseq	All Proteomics	Metabolomic	Txpn Factors
Target Identification	Bayesian networks	Bayesian networks	Innate Immunity Networks	Bayesian Networks	Systems analysis	*REST*
Preclinical Validation	iPSCs Cell lines	iPSC, drosophila, mouse	mouse	Mouse, cell culture, drosophila	NA	mouse

Data Coordination and Integrated Analysis
Sage Bionetworks (Mangravite)

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.

7043 human samples | 15 human studies | 15 genomic data types | 22 model system studies

60,000 files contributed by **42 investigators** across
22 institutions representing samples from **36 research studies**

AMP-AD Knowledge Portal

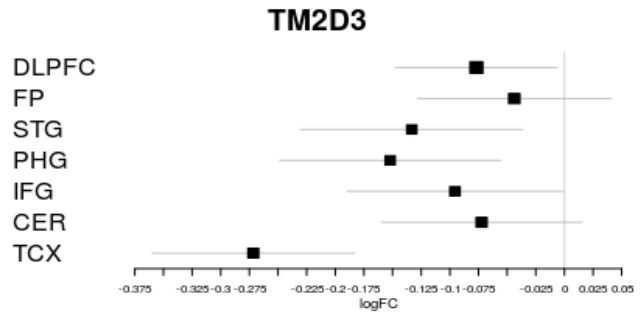
www.ampadportal.org

Over 2000 users* with **~55 new users** per month

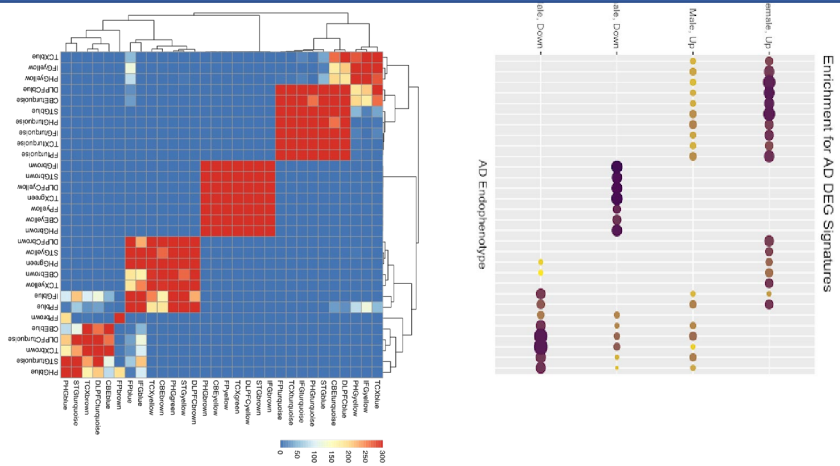
(*users from academia, biotech, pharma)

ACCELERATING MEDICINES PARTNERSHIP (AMP)

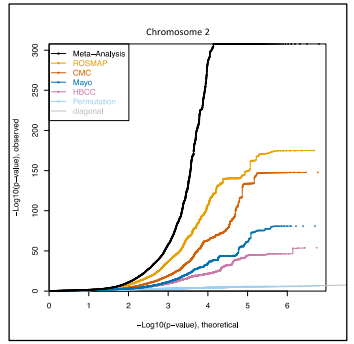
ALZHEIMER'S DISEASE - **Target Discovery and Preclinical Validation Project**



RNAseq Working Group

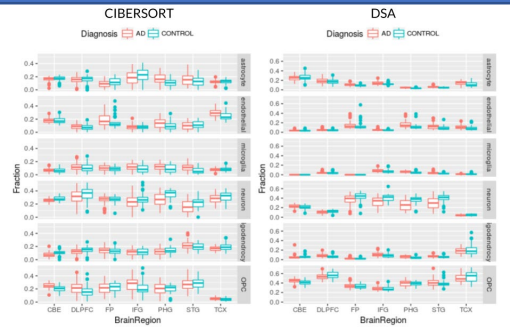


Network Working Group

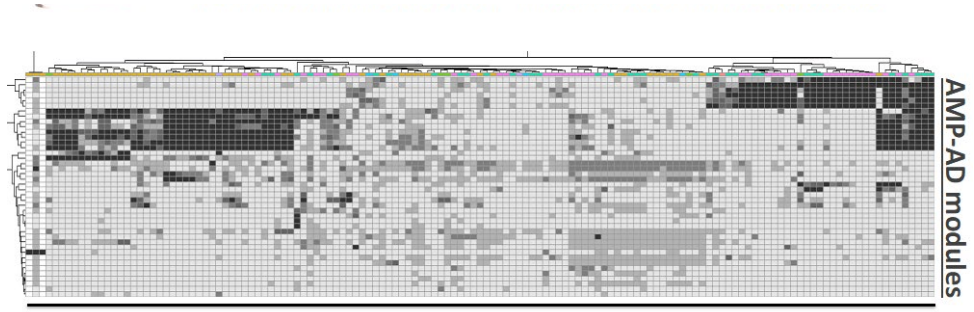


eQTL Working Group

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



Deconvolution Working Group



139 mouse model Differentially Expressed Genes (DEGs) in Brain

Cross-Species Working Group

SageBionetworks

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

Agora

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

~1800 Cases (MSSM, Mayo, Banner, UPenn, BLSA, ACT and Emory)

~3,000 proteins
n=1,000 tissues

~11-12,000 proteins
n=80 tissues

QE-Orbitrap
Label-free
"single shot"

Fusion-Orbitrap
Multiplex (TMT)

2. Validation Proteomics

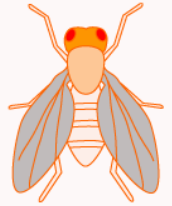
400 Cases (ROS/MAP)

TMT
Multi-Plex

3. Therapeutic Feasibility

Model Systems

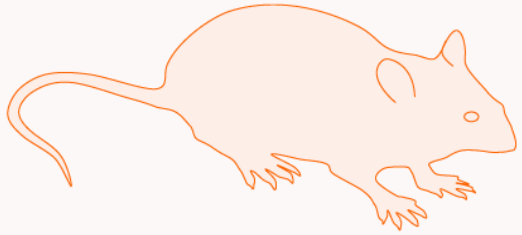
Cell Culture



Transgenic Flies

~50 hub proteins in key modules

~ 5 targets in mouse models



Systems Biology and Predictive Modeling

Protein Networks Associated with Key Traits

Novel Targets

FROM MOLECULE TO PATIENT

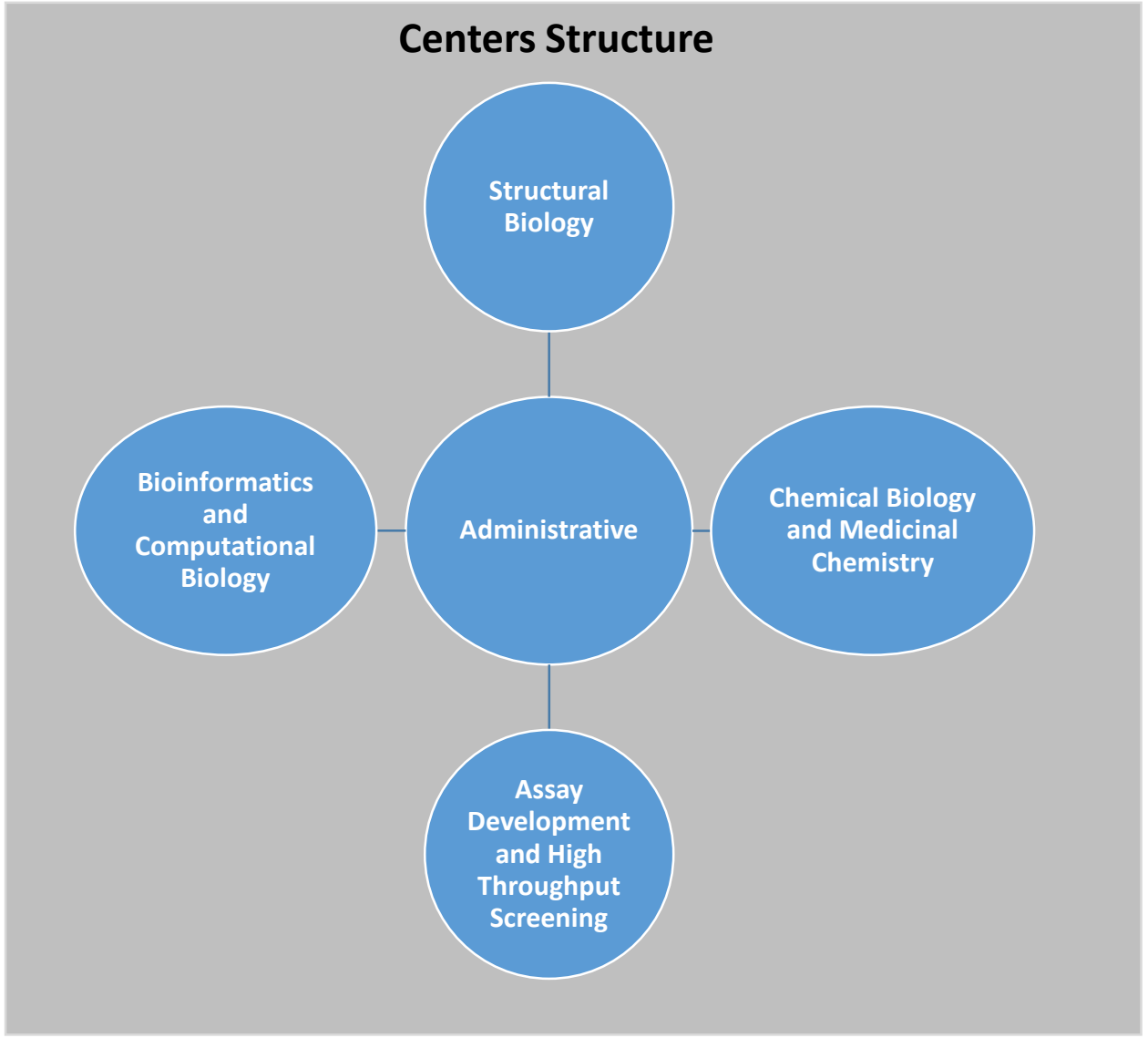
DE-RISKING NOVEL TARGETS THROUGH OPEN SCIENCE

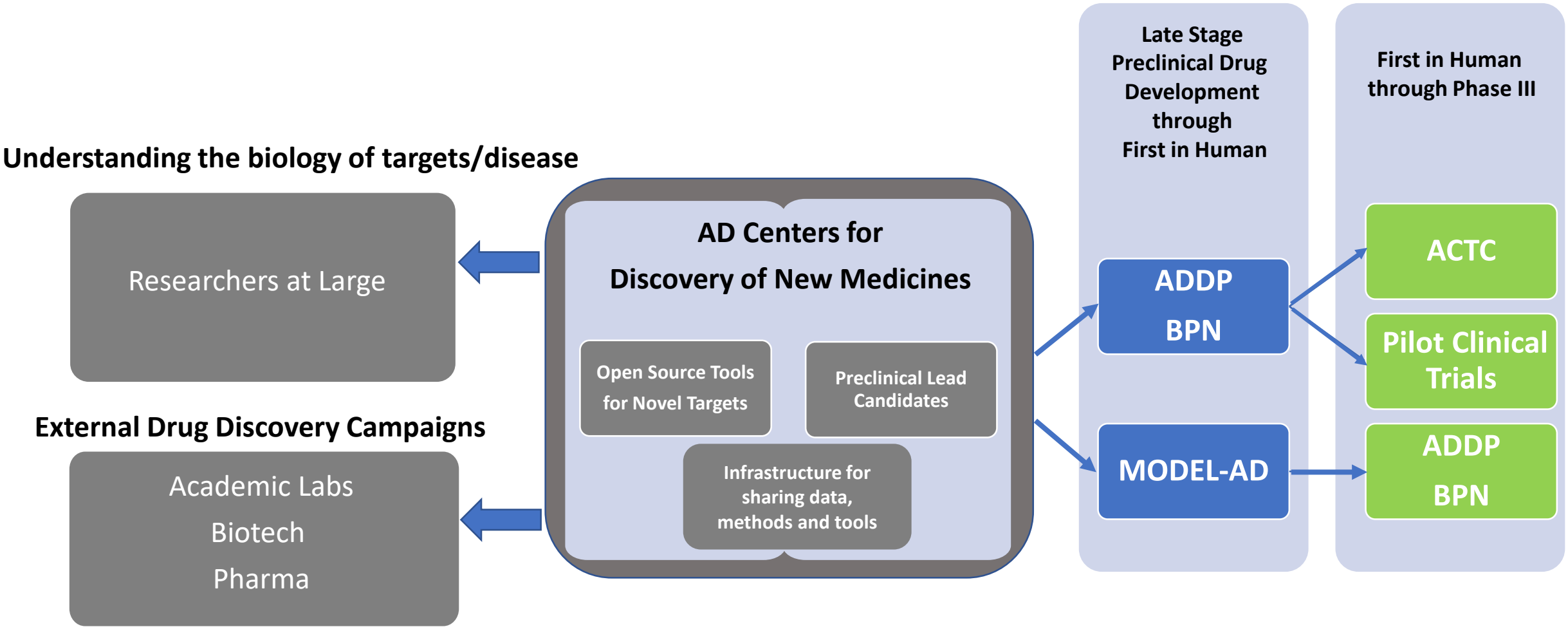
AD Centers for Discovery of New Medicines - RFA AG 19-010

-Applications submitted Feb 2, 2019-

-NIA plans to commit ~$75M over 5 years to support 2 Centers-

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.





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

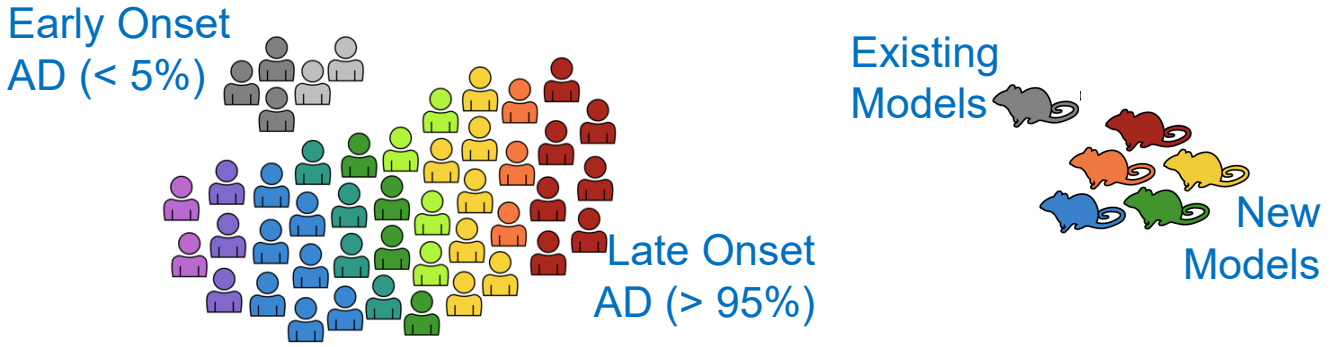
FROM MOLECULE TO PATIENT

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

U Pitt

UCI University of California, Irvine

INTEGRATE

Clinical, Genomic, Mechanistic and Translational Research

INTEGRATE

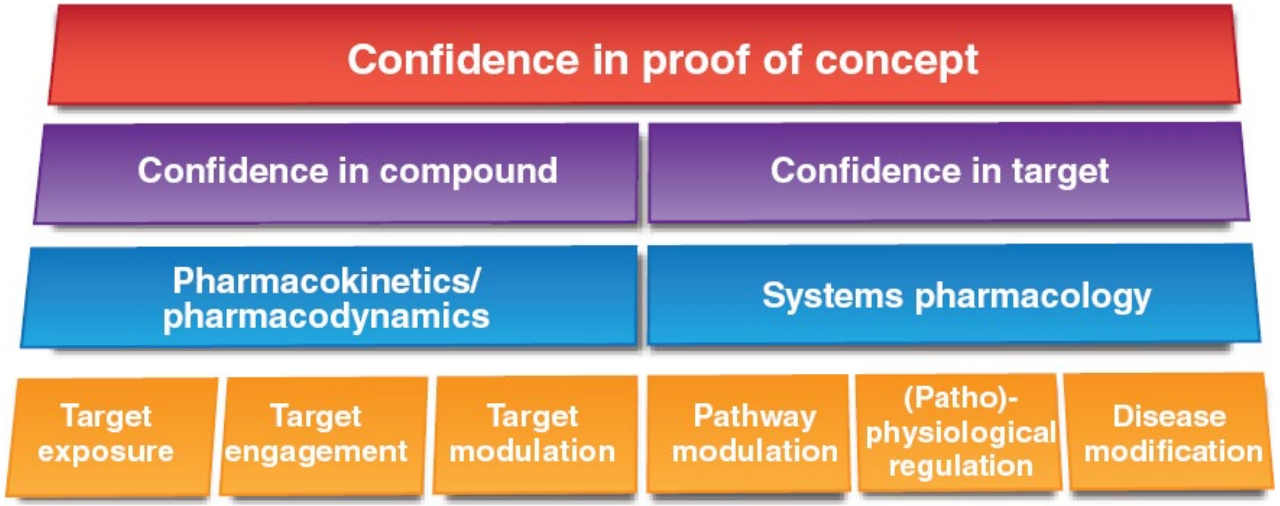
Computational and Experimental Methods

INTEGRATE

Data from Animal Models and Humans

INTEGRATE

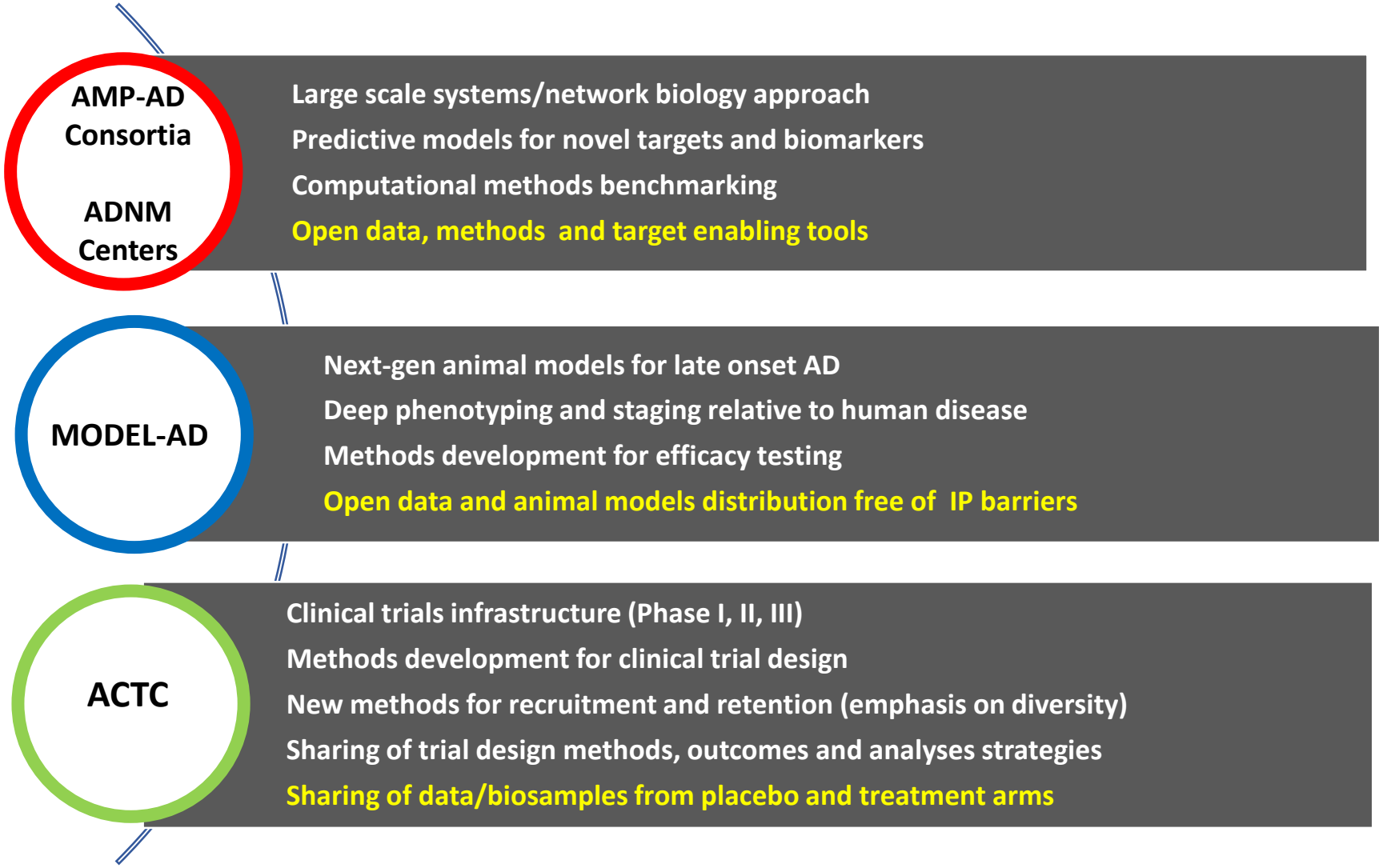
Academic and Industry Expertise

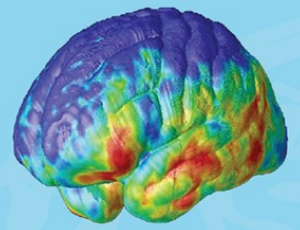


Clinical Pharmacology & Therapeutics, Volume: 93, Issue: 5, Pages: 379-381, First published: 20 February 2013, DOI: (10.1038/clpt.2013.40)

DEPLOYING OPEN SCIENCE/OPEN SOURCE PRINCIPLES: FROM TARGETS TO TRIALS

ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT





2018 NIH Alzheimer's Disease Research Summit

Path to Treatment and Prevention

National Institute on Aging

#ADSummit18

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

2018 NIH AD Research Summit Recommendations

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

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****.*

Data/Methods/Infrastructure/Training
Precompetitive Partnerships

ACKNOWLEDGMENTS:

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Mary Pelleymounter – NINDS

Sage Bionetworks

Lara Mangravite
Ben Logsdon
Larsson Omberg
Mette Peters
Anna Greenwood

FNIH

Rosa Canet–Aviles and David Wholley

AMP-AD Private Partners

Abbvie
Biogen
Eli Lilly
GSK
Alzheimer's Association

AMP-AD and MODEL-AD Academic Teams