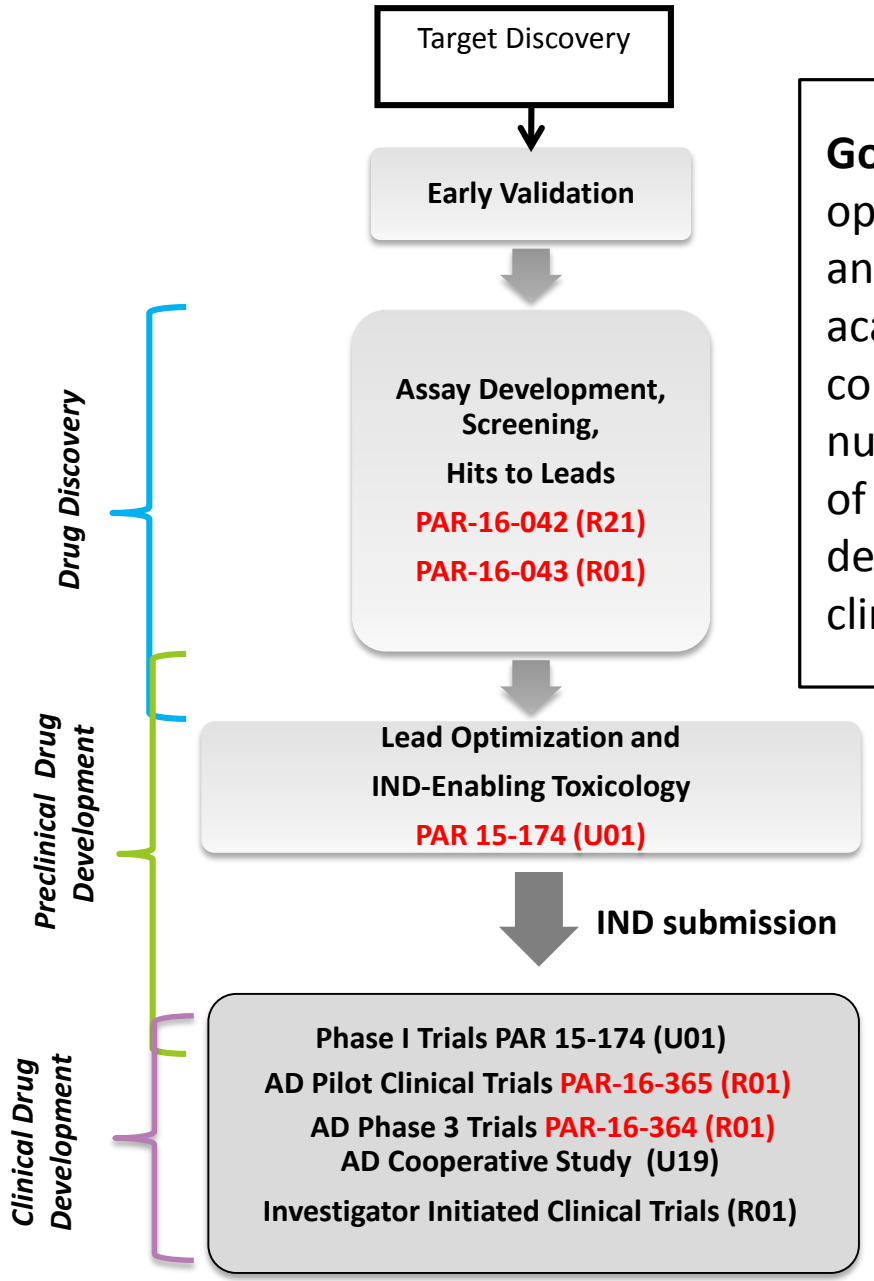
National Institute on Aging

DEVELOPING A KNOWLEDGE BASE AND INFRASTRUCTURE FOR DATA-DRIVEN AND PREDICTIVE DRUG DEVELOPMENT FOR ALZHEIMER'S DISEASE

Suzana Petanceska PhD
Lorenzo Refolo PhD
Laurie Ryan PhD
Division of Neuroscience

NIA's Alzheimer's Disease Translational Research Program

-2005-present

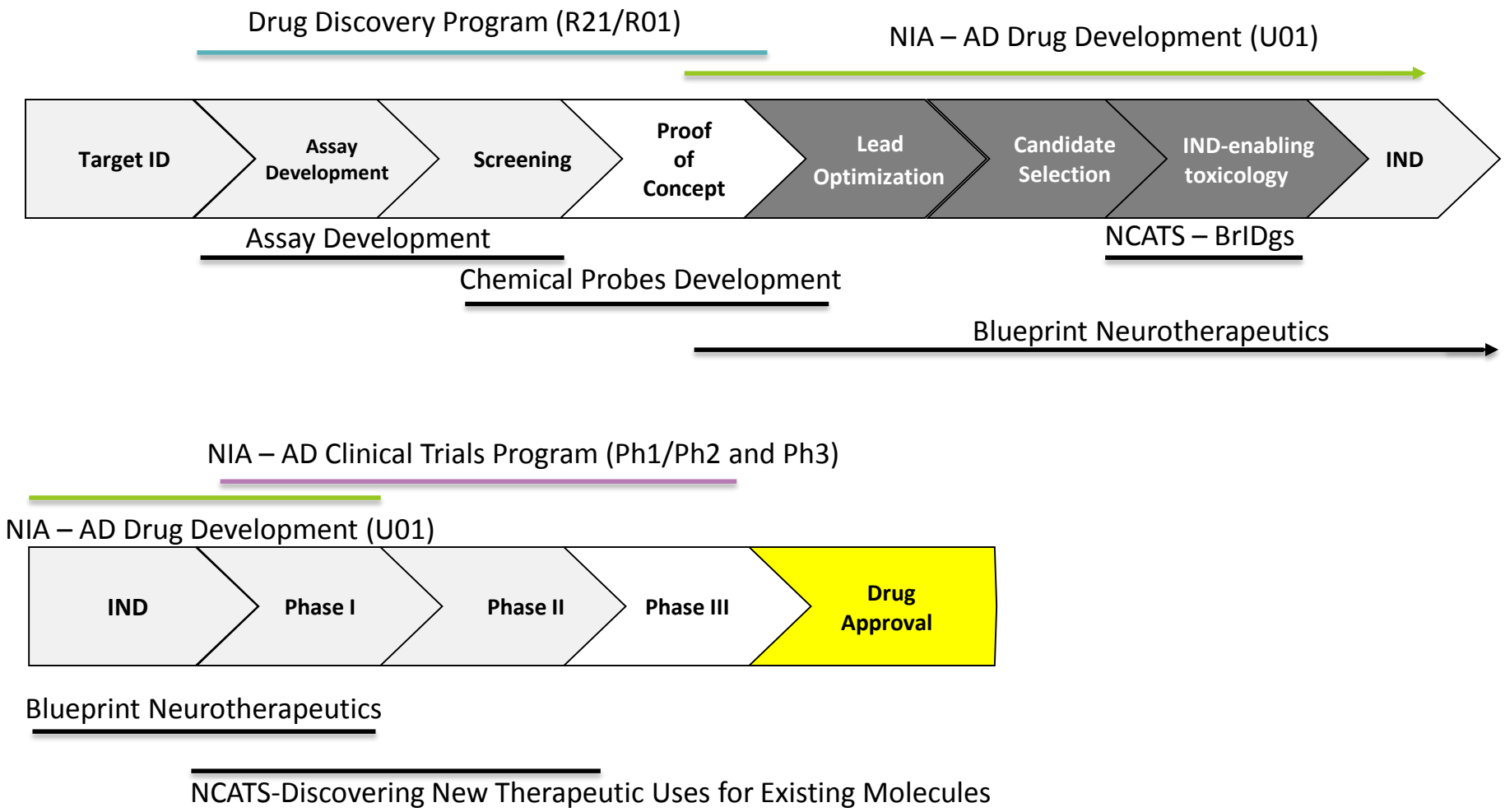


Goal: Develop a pipeline of funding opportunities to seed early drug discovery and preclinical drug development projects in academia and in the small business community and in doing so increase the number of drug candidates against a variety of therapeutic targets that can be clinically developed by industry or through various clinical trial programs at the NIA and NIH.

Educational Components of the AD Translational Research Program

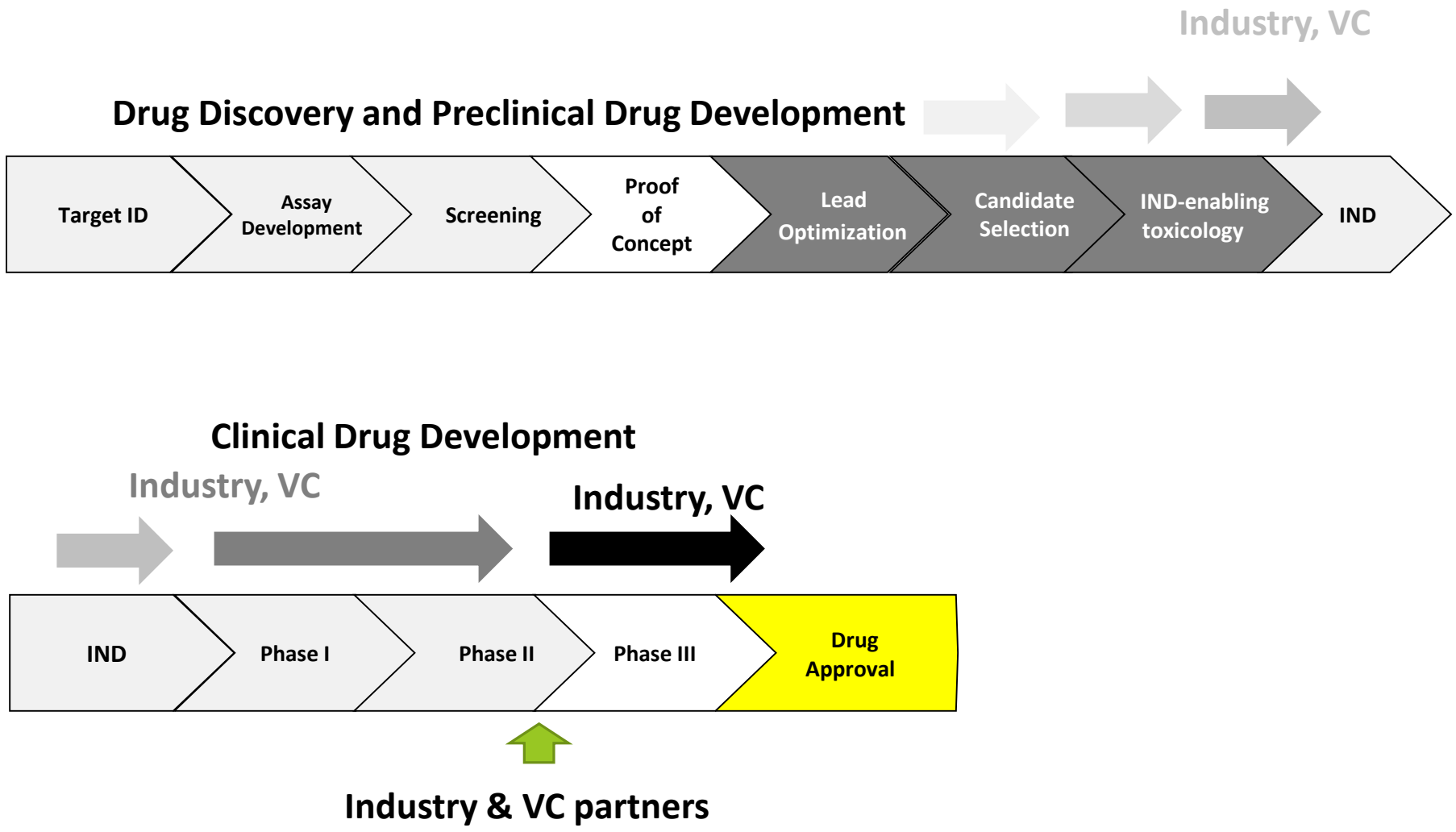
- ❑ **U13 Conference Grant to ADDF (NIA with co-funding from NINDS and ORD) to support a Training Course/Annual Meeting on Drug Discovery for Neurodegeneration**
- ❑ **AD Translational Research Investigators' Meetings**
- ❑ **New training and career development programs in data science and drug discovery**

NIA and Trans - NIH Translational Programs*



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

The Expanding Valley of Death



U01 Preclinical Drug Development Program PAR 174

-2007-present-

- amyloid
- tau
- apoE
- synaptic plasticity
- growth hormone receptors
- proteostasis
- neurotransmitter receptors
- cell death
- vascular factors
- anti-inflammatory
- multi-target

-Supported with set-aside funding

-Applications reviewed at NIA by a Special Emphasis Panel

U01 Preclinical Drug Development Program PAR 174

-2007-present-

Milestone driven program

Allows for 2 entry points and can be used for small molecules and biologics:

-early stage preclinical development through IND
starting point: preclinical lead selection

-late stage preclinical development through Phase I trial
starting point: fully optimized lead compound

Annual Direct Costs Budget Cap: $1.0M

Project Duration: 3-5 years

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 Research Program

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

LM11A-31

p75 mechanisms
-tractable target?
-biomarkers?

Small molec devel
-IP

In vitro models

In vivo models (relevance)

Pre-IND formal PK/tox

Phase 1 safety/PK

Phase 2a
-safety
-ex endpoint
-biomarkers

Phase 2/3 efficacy

2000

2005

now!

Academic labs
(UCSF/UNC/Stanford)

Virtual company
(PharmatrophiX)
networking/advisors/CROs

Pharma
NIH

- **grants (ADDF / AA / NIA – U01 Program)**
- **gifts**

- **grants (NIA Pilot Trial Program/ADDF/AA)**
- **investors**
- **partnerships**

First Blueprint Neurotherapeutics Project to Complete Phase I Trial

Mark Gurney, PhD, Tetra Discovery Partners

Phosphodiesterase 4D (PDE4D) Allosteric Modulators for Treating Cognitive Impairment in AD

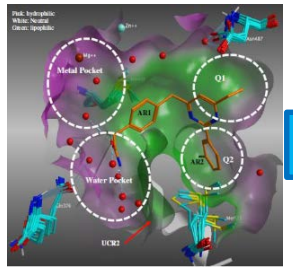
CENTRAL HYPOTHESIS

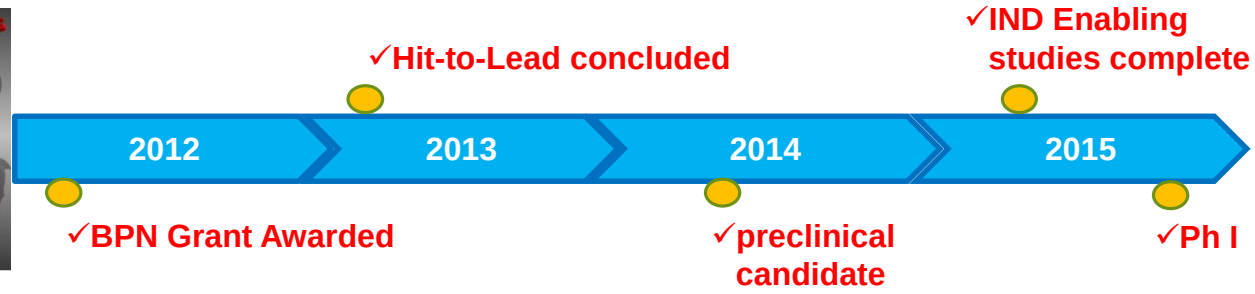
Negative allosteric modulators of PDE4D will improve cognition without the emetic side effects of active-site inhibitors

BPN Achievement

1. Discovery and development of BPN14770, clinical candidate
2. Completion of Phase I clinical trial

TETRA DISCOVERY PARTNERS





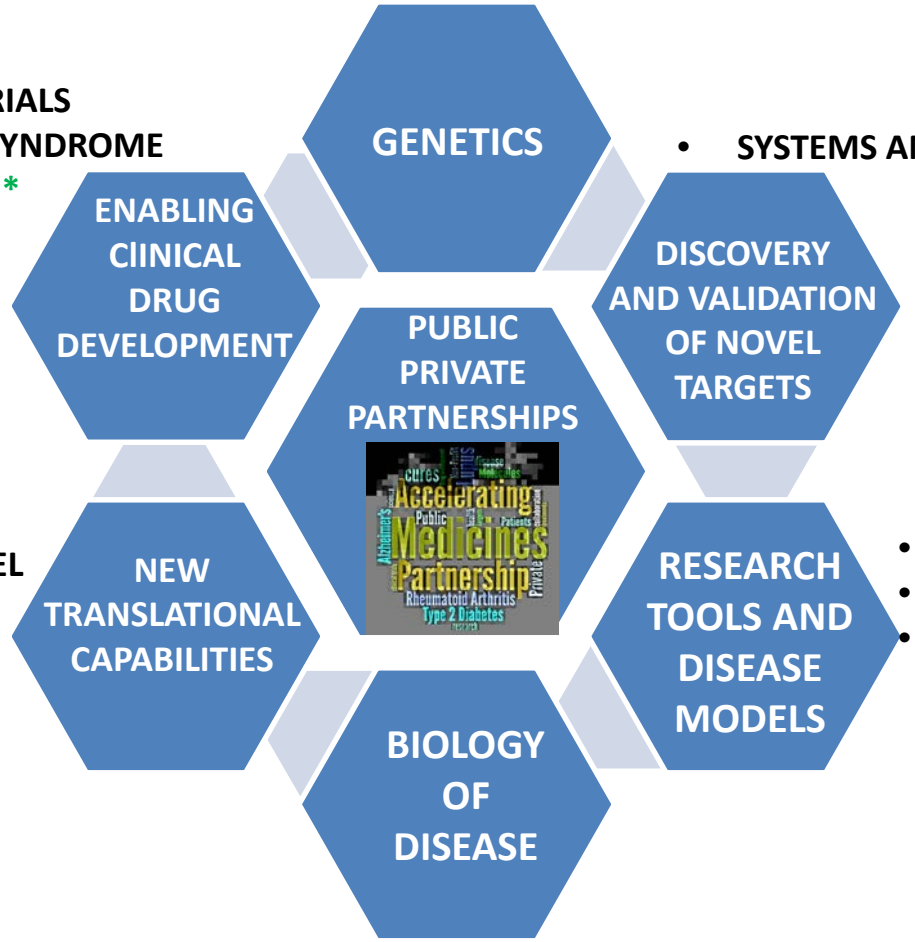
Goal: **To formulate a blueprint for a new integrated, translational research agenda that will enable the development of effective therapies (disease modifying and palliative) across the disease continuum for the cognitive as well as neuropsychiatric symptoms of Alzheimer's disease and to identify the resources, infrastructure and public private partnerships necessary to successfully implement this research agenda.**

New NIA/NIH Funding Initiatives and Programs

- ADGC/NIAGADS
- ADSP

- SECONDARY PREVENTION TRIALS
- AD BIOMARKERS in DOWN SYNDROME
- AD Clinical Trials Consortium*

- SYSTEMS AND NETWORK BIOLOGY



- TRANSLATIONAL CENTER FOR ANIMAL MODEL RESOURCES
- PRECLINICAL EFFICACY TESTING DATABASE
- TRANSLATIONAL BIOINFORMATICS AND SYSTEMS PHARMACOLOGY*

- OPTOGENETICS
- Human iPSC
- Next generation animal models

- INFLAMMATION
- VASCULAR ETIOLOGY
- COMPLEX BIOLOGY OF COGNITIVE RESILIENCE*

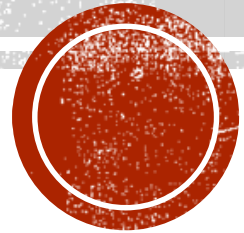
* Programs in development

- 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

- Complexity of disease
- Complexity of the physiologic response to therapeutic intervention

SYSTEMS APPROACHES FOR TARGET DISCOVERY AND VALIDATION

Suzana Petanceska PhD



Accelerating Medicines Partnership Alzheimer's Disease Program

https://www.nia.nih.gov/alzheimers/amp-ad

Government

Industry

Non-profit

AMP-AD Partners

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

US Against Alzheimer's

Managing Partner → FNIH Foundation for the National Institutes of Health

ACCELERATING MEDICINES PARTNERSHIP (AMP)

ALZHEIMER'S DISEASE - Target Discovery and Preclinical Validation Project

- **Discover and carry out preclinical validation of novel disease-relevant therapeutic targets by integrating the analyses of large-scale molecular data from human brain/blood samples with network modeling approaches and experimental validation.**

- **Enable rapid and broad sharing of data.**

ACCELERATING MEDICINES PARTNERSHIP (AMP)

ALZHEIMER'S DISEASE - Target Discovery and Preclinical Validation Project

- **The project is a consortium of 6 multi-institutional, multidisciplinary research teams supported by NIA grants.**

- **The teams are applying cutting-edge systems and network biology approaches to integrate multidimensional human "omic" data (genomic, proteomic, metabolomic) from ~2,500 human brains/~1000 blood samples from all stages of the disease with clinical and pathological data to:**
  - **discover and select novel therapeutic targets for Alzheimer's disease**
  - **gain a systems-level understanding of the gene, protein, and metabolic networks within which these targets operate**
  - **evaluate their druggability in cell-based and animal models**

ACCELERATING MEDICINES PARTNERSHIP (AMP)

ALZHEIMER'S DISEASE - Target Discovery and Preclinical Validation Project

Generate

High-dimensional multi-omic data:
~2,500 human brains;~1000 blood samples

Integrate

Molecular profiling
Predictive Modeling
Experimental validation

6 Academic Teams
– NIA U01/R01grants –

www.synapse.org.ampad

Data
Network models
Code

AMP-AD Knowledge Portal

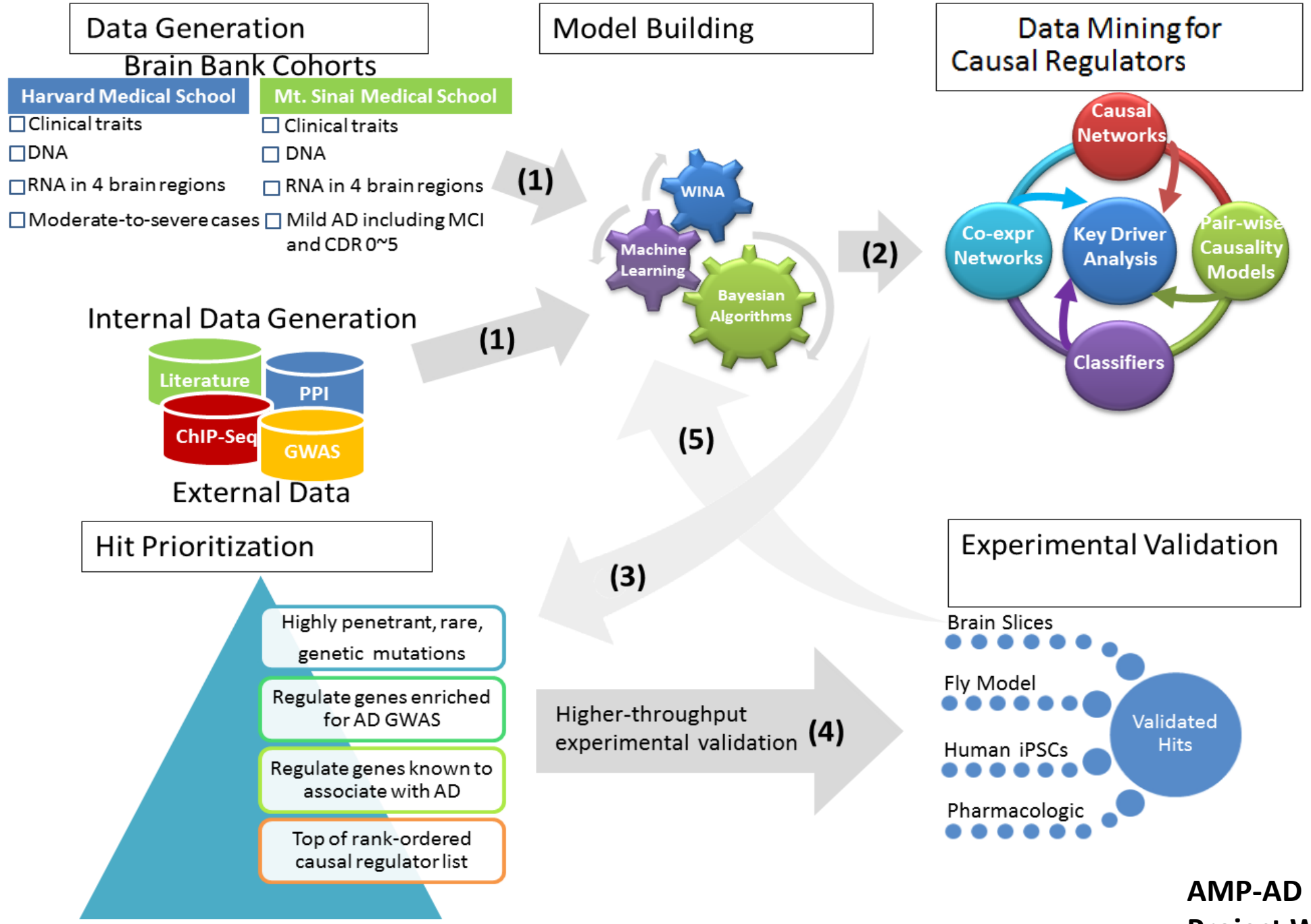
Sage BIONETWORKS Synapse

ACCELERATING MEDICINES PARTNERSHIP (AMP)

ALZHEIMER'S DISEASE - Target Discovery and Preclinical Validation Project

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 Enablement and Coordination of Collaborative Analyses:
Sage Bionetworks, Principal Investigator – Lara Mangravite



AMP-AD Mt.Sinai team: Project Workflow

How Are We Doing This Together?

Academic teams

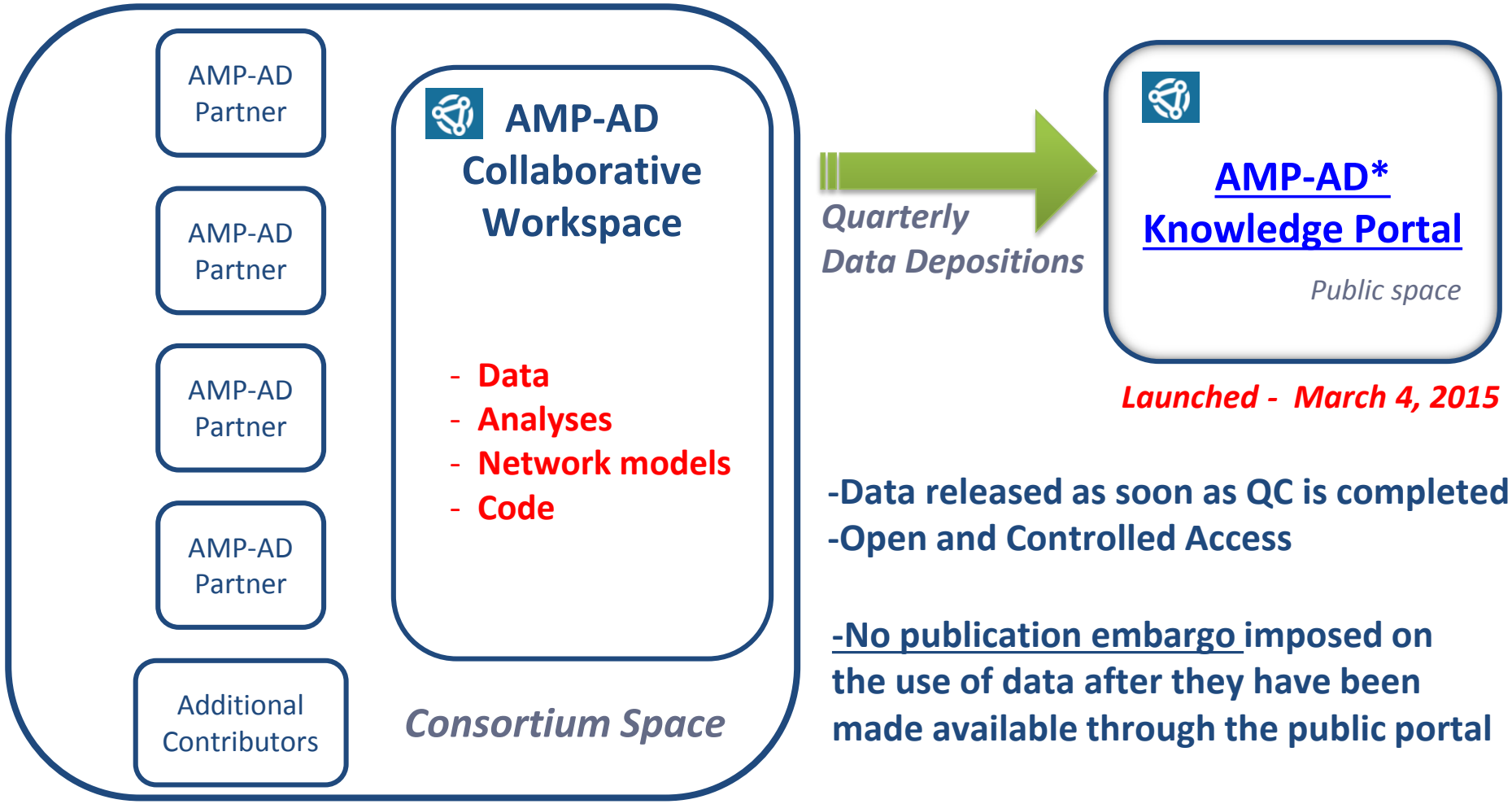
Industry teams

1) Centralized data resources
2) Consortium-wide milestones
3) Consortium-wide collaborative projects

Target Nomination

	Team 1	Team 2	Cross Analysis	…
Target 1				
Target 2				
…..				

Sage BIONETWORKS Synapse



Launched - March 4, 2015

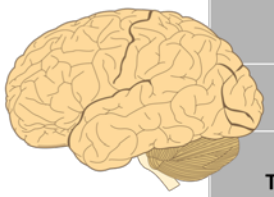
-Data released as soon as QC is completed
-Open and Controlled Access

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

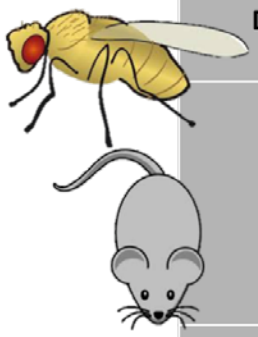
***AMP-AD Knowledge Portal** – https://www.synapse.org/#!Synapse:syn2580853/wiki/409840

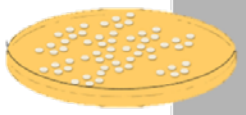
Sage BIONETWORKS Synapse

AMP-AD Knowledge Portal



HUMAN TISSUE	Diagnosis	Assay
Prefrontal Cortex	• Alzheimer's Disease • Mild Cognitive Impairment • Parkinson's Disease • Amyothrophic Lateral Sclerosis • Corticobasal Degeneration • Frontotemporal Dementia • Dementia with Lewy Bodies	• RNAseq • Gene Expression array • miRNA array • ChIPseq • DNA Methylation array • Proteomics • Confocal Imaging • SNP genotypes • Proteomics • Whole Exome Seq
Visual Cortex	• Alzheimer's Disease	• Gene Expression Array • SNP genotypes
Temporal Cortex	• Alzheimer's Disease • Progressive Supranuclear Palsy • Parkinson's Disease	• RNAseq • SNP genotypes
Cerebellum	• Alzheimer's Disease • Progressive Supranuclear Palsy • Parkinson's Disease	• RNAseq
Superiour Temporal Gyrus	• Alzheimer's Disease	• RNAseq • Whole Exome Seq
Parahippocampal Gyrus	• Alzheimer's Disease	• RNAseq
Serum	• Alzheimer's Disease • Mild Cognitive Impairment	• Metabolomics





MODELS	Type	Assay
Drosophila	• TAU • TYROBP • TREM2	• Proteomics • RNAseq
Mouse	• APP • TAU • PSEN1 • HDAC1 • db/db • Stroke	• RNAseq • Gene Expression array • Behavioral analysis • Electrophysiology
CELLULAR MODELS - Human - Rat	• iPSC • iPSC derived organoids • Microglia • Macrophages • Astrocytes • APP/PSEN1, SNRNP70 transduced neurons • SH-SY5Y	• RNAseq • ChIPseq • ELISA (Aβ) • Proteomics

Religious Orders Study and Rush Memory and Aging Project

- Two cohort studies of aging and AD ongoing for 20+ years
- >3,000 older persons without [known] dementia from across the USA
- All agreed to annual detailed clinical evaluation for common chronic conditions of aging with detailed evaluation of risk factors, and blood donation
- All agreed to organ donation at death
- > 900 cases incident MCI
- > 700 cases incident AD dementia
- > 1,200 autopsies

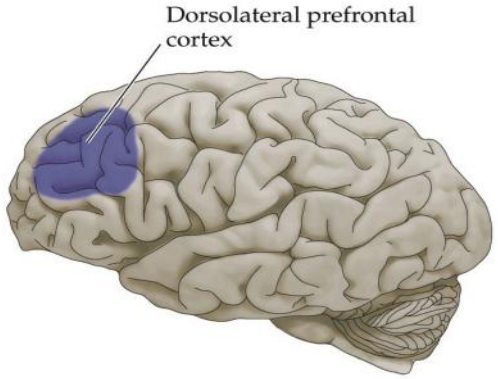
Risk Factors: Medical, Psychological, Experiential, and genome-wide genotyping

Genotypes
Affy 6.0/Illumina Quad
1000G imputation

Genotypes
Whole Exome Sequencing

DNA methylation, histone acetylation

DNA Methylation Illumina 450K
Histone H3K9Ac
ChIP-Seq



Next generation RNAseq, miRNA

RNA profile
mIRNA & RNAseq

MS Proteomic and metabolomic

LC/MS profile
Lipids, proteins

Quantitative neurobiology

Neuropathology
AD, CVD, LBD, HS, TDP

Resilience Markers
Synaptic proteins, LC

Structural and functional MRI

Flair, MP Rage, DTI, SWI, rsfMRI

post-mortem MRI
DTI, MP Rage, T2

Quantitative clinical phenotype

Cognitive Function
19 tests annually

Motor Function
Disability BMI,
Actigraphy

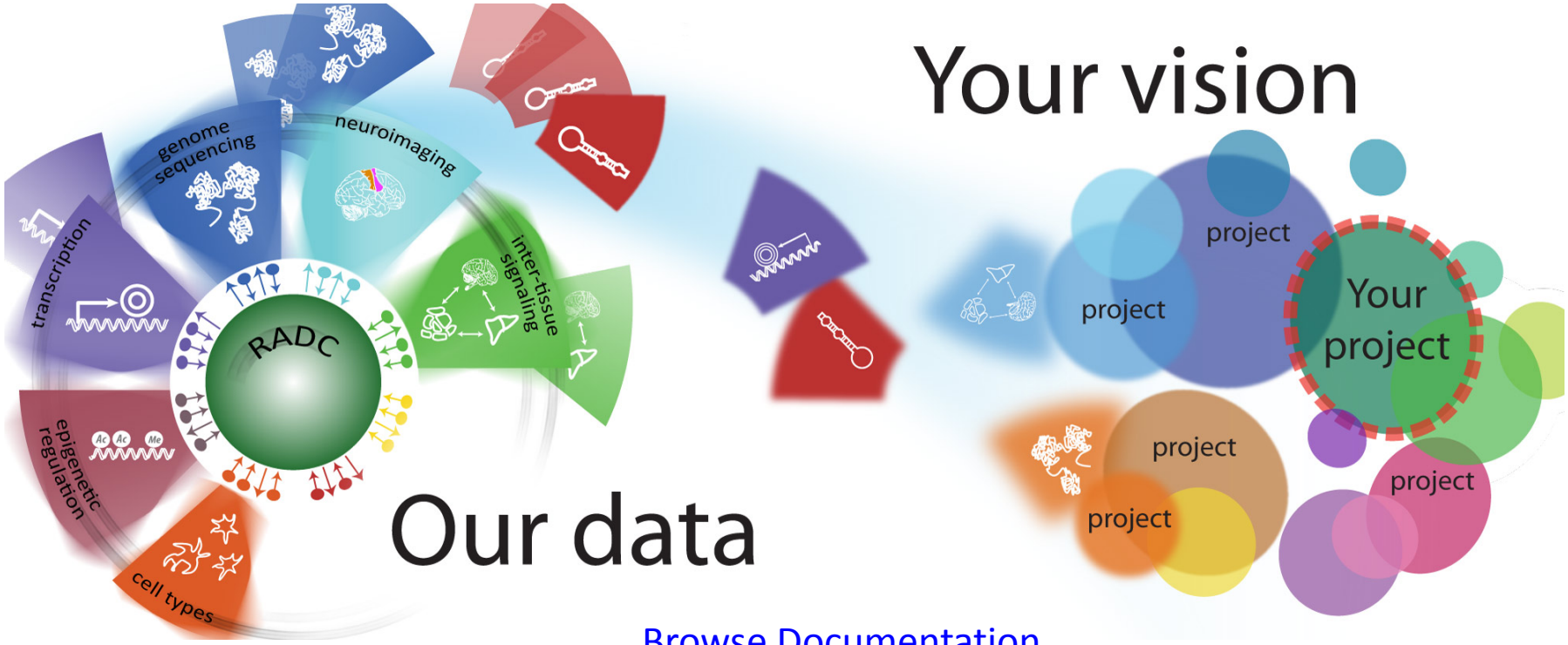
Dynaport – Gait, Sleep, circadian rhythms, Behavioral Economics, Olfaction,

Syndromic phenotype

Clinical Diagnoses
AD, Stroke, PD,

RADC Research Resource Sharing Hub

https://www.radc.rush.edu



Browse Documentation

Query Frequency Reports

Request Data/Specimens

CONSORTIUM-WIDE MILESTONES

M1. Complete multi-omics (genomic, proteomic, metabolomic) data generation from human samples

M2. Develop project specific network models of AD

M3. Carry out comparative analysis across network models

M4. Target Nomination/Selection

M5. Characterize experimental validation models and assess their relevance to human disease through comparative analysis with human network models

M6. Consortium-wide preclinical validation of up to 6 novel targets

Target Discovery and Preclinical Validation Project Working Groups

Bioinformatics

RNAseq

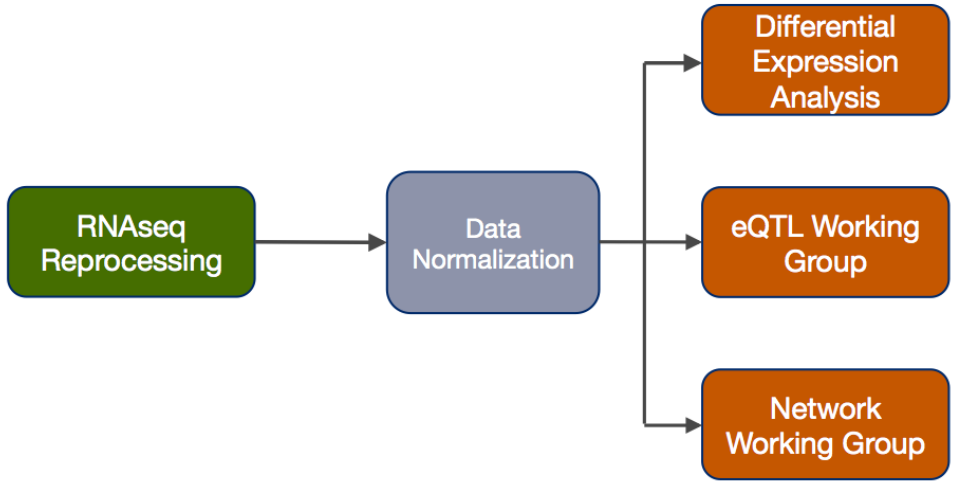
Comparative Network Analysis

eQTL

Experimental Validation

AMP-AD RNASeq Reprocessing WG: Goals and Deliverables

- **Enable joint analysis through uniform reprocessing to reduce technical variation across Human RNAseq datasets**
- **Meta-analysis to inform internal AMP-AD projects and support target selection processes**
- **Development of a standardized resource for external users**



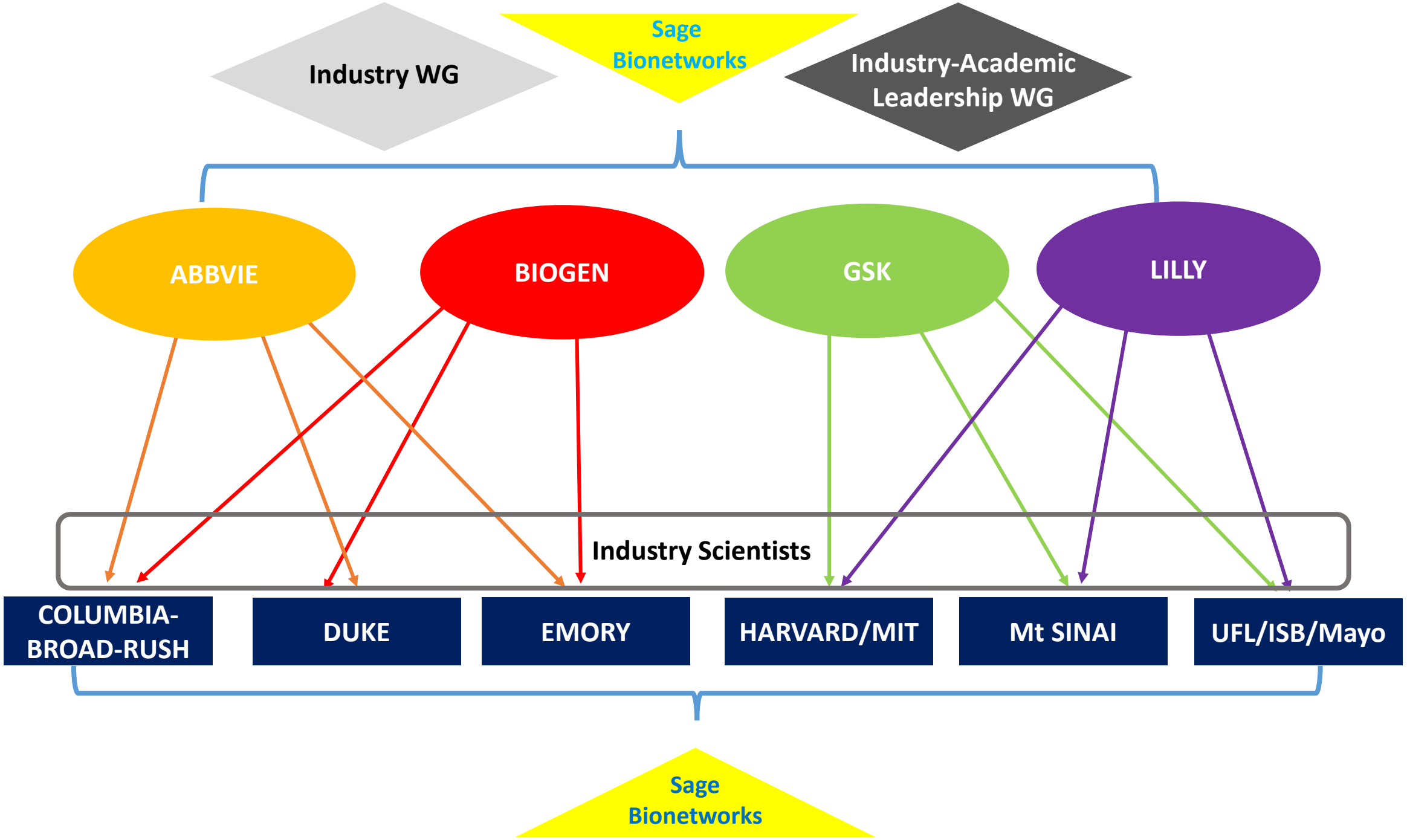
RNAseq reprocessing working group

29 members representing 5 AMPAD academic teams and all 4 industry partners

Contacts: kristen.dang@sagebase.org & thanneer.perumal@sagebase.org

AMP-AD Mount Sinai Team Candidate Targets: preliminary list

1	RGS4
2	SCN2A
3	OLFM3
4	SLC22A10
5	ENAH
6	WWTR1
7	LRP10
8	SYP
9	PCSK1
10	KMO
11	PTTG1IP
12	MLIP
13	PLXNB1
14	DLGAP1
15	MOAP1
16	PRKCB
17	VGF
18	YAP1
19	GNA13
20	TRIM56
21	KCNV1
22	STXBP5L
23	DOCK2
24	GABRG2
25	STAT3
26	SV2B
27	RBFOX1
28	STAT4
29	PAK1
30	RASAL2
31	SYT1
32	NCKAP1L
33	PARD3B
34	TLN1
35	NRXN1
36	TNFRSF1B
37	ARHGEF9
38	DUSP4
39	DTX3L
40	SNAP25
41	PLCB1
42	WDR49
43	NFIA
44	XK
45	NAPB
46	MVP
47	GABRA1
48	CD68
49	LAPTM5
50	ANGPT1


Industry WG
Sage Bionetworks
Industry-Academic Leadership WG
ABBVIE
BIOGEN
GSK
LILLY
Industry Scientists
COLUMBIA-BROAD-RUSH
DUKE
EMORY
HARVARD/MIT
Mt SINAI
UFL/ISB/Mayo
Sage Bionetworks

NOT JUST TARGETS

AMP-AD Emory/UCLA Team – PI: Allan Levey

Discovery of Novel Proteomic Targets for Treatment of Alzheimer's Disease

1. Discovery Proteomics

Control AsymAD

non-AD MCI AD

~800 Cases (MSSM, Mayo, Banner, UPenn, BLSA, ACT and Emory)

QE-Orbitrap
Label-free
"single shot"

Fusion-Orbitrap
Multiplex (TMT)

2. Validation Proteomics

~1200 Cases (ROS/MAP)

SRM

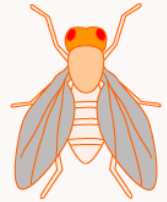
Systems Biology and Predictive Modeling

Protein Networks Associated with Key Traits

3. Therapeutic Feasibility

Model Systems

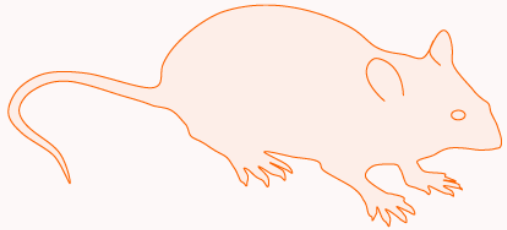
Cell Culture



Transgenic Flies

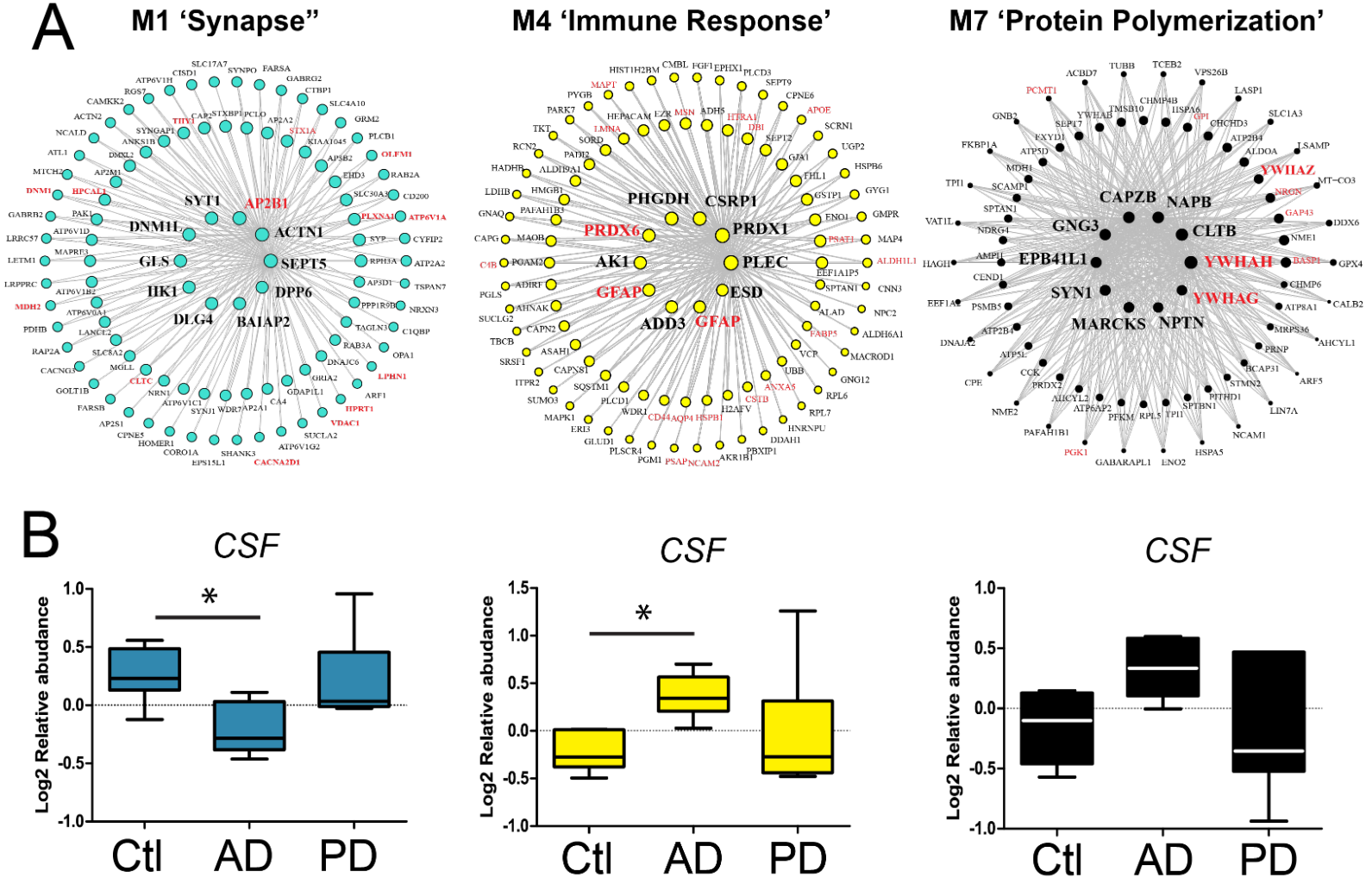
~50 hub proteins in key modules

~ 5 targets in mouse models



Novel Targets

AMP-AD Emory/UCLA Team – PI: Allan Levey



Hub proteins from brain networks are found in human CSF and discriminate AD from control and PD patients. Hub proteins are defined as proteins with the highest intra-modular connectivity (i.e., proteins that are most central within the module) in the M1, M4 and M7 modules. Red symbols are proteins that were also identified in the CSF.

AMP-AD Duke Team/AD Metabolomics Consortium
PI: Rima Kaddurah-Daouk

ADNI I Baseline Datasets - Targeted and Non Targeted Metabolomics and Lipidomics Platforms

P180
Amines, acylcarnitines, PC, SM (180)

Bile Acid
Cholesterol and gut microbiome metabolism (20)

Purine (10)

PE plasmalogen (10)

PC, LPC NESI (30)

PC, LPC PESI (30)

Replication of findings

Rotterdam

Framingham

Indiana

Made public – LONI 2015/2016

Non Targeted Metabolomics (300)

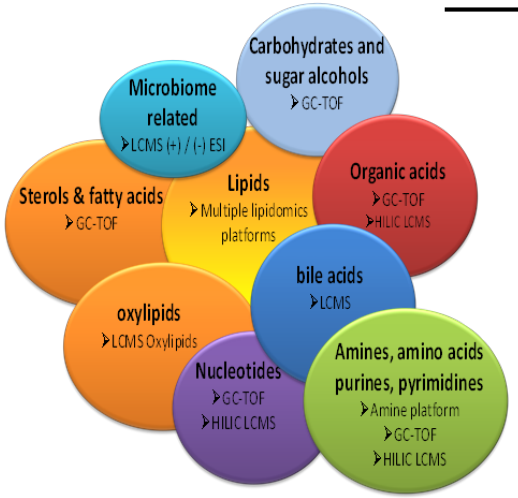
Data being vetted

Non Targeted lipidomics (400)

Deposited LONI

Highly informative compounds (40)

Deposited LONI



Neurotransmitters

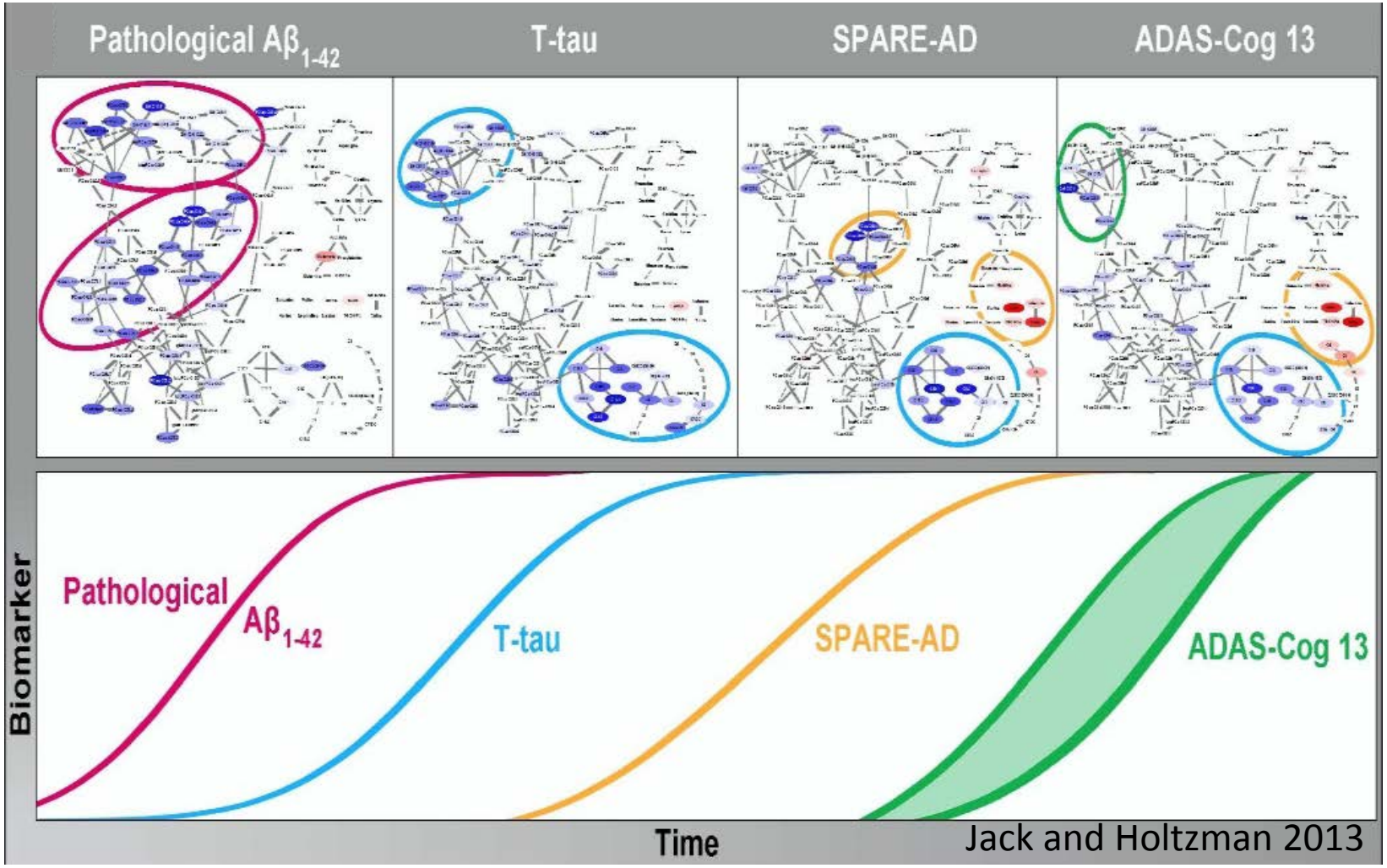
Methylation

Analysis ongoing

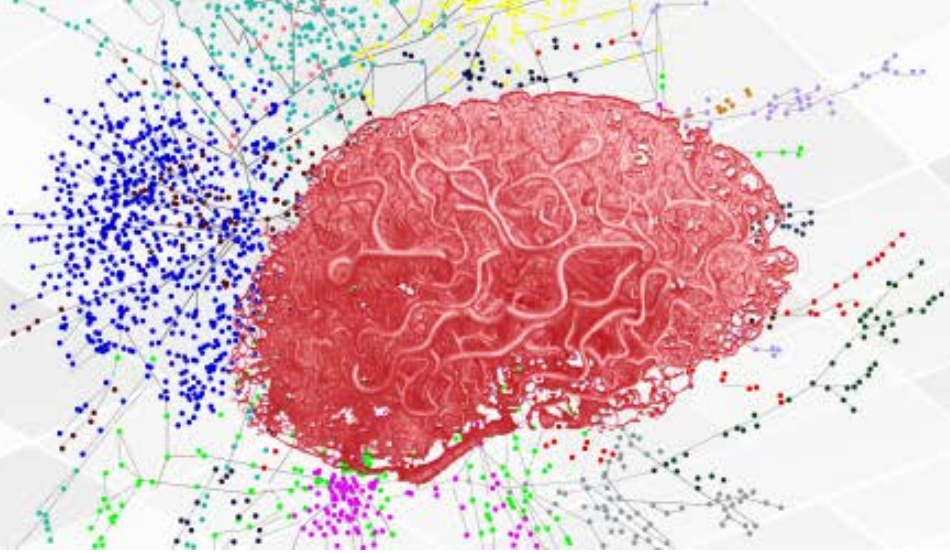
Broad biochemical coverage, high level of standardization!

AMP-AD Duke Team/AD Metabolomics Consortium
PI: Rima Kaddurah-Daouk

Partial Correlation Network Analysis Suggests Evolution of Metabolic Changes in AD



Toledo et al. 2017



A collaboration between NIA and NINDS

M²OVE-AD

Molecular Mechanisms of the
Vascular Etiology of Alzheimer's Disease

- ~$35 million over 5 years to support 6 multi-institutional and cross-disciplinary research teams. The teams will generate various "omics" data from brain tissue and peripheral fluids from individuals participating in natural history or 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 various animal models (AD models and models of vascular/metabolic risk factors).

- Goals and deliverables:

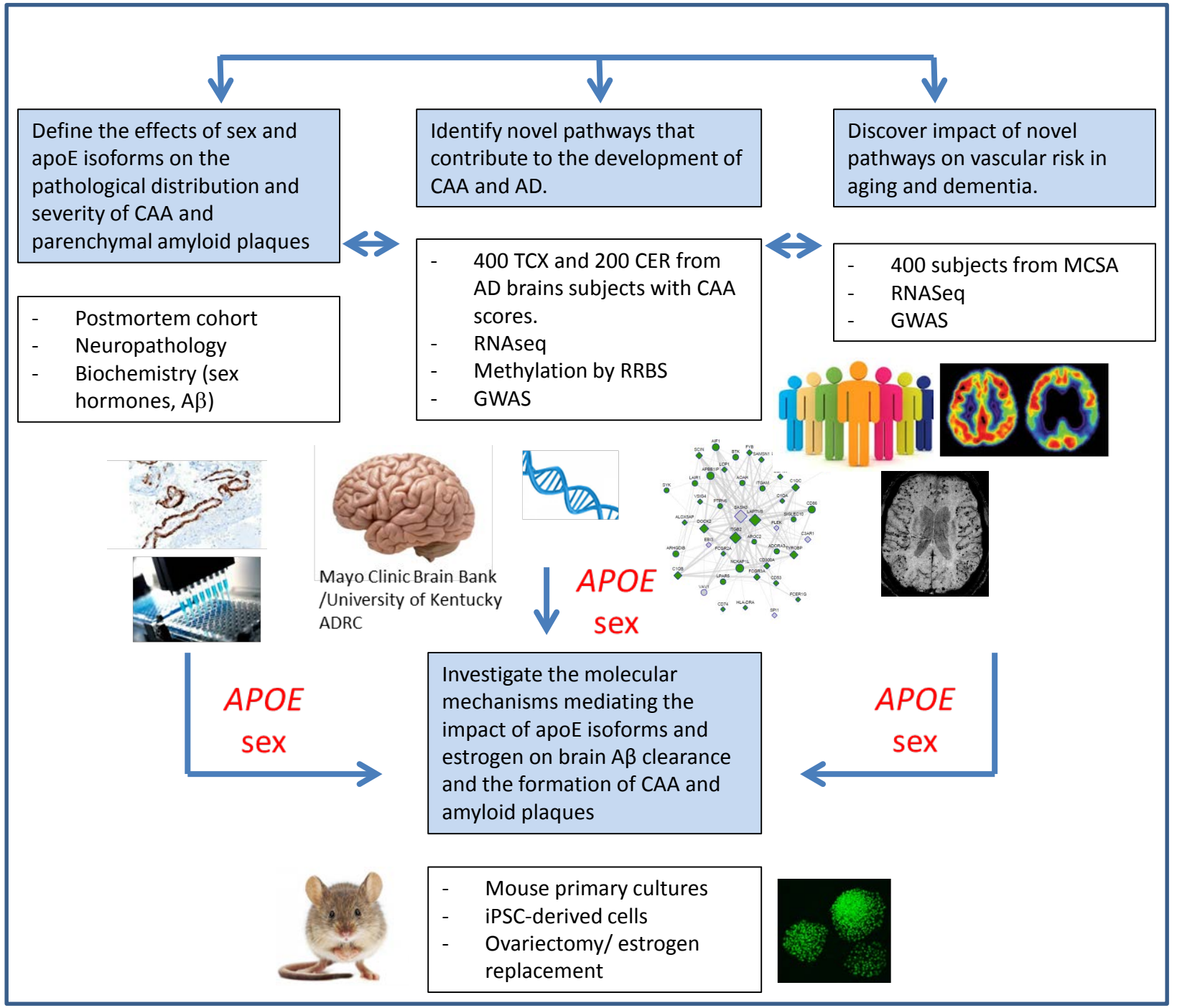
  -rapid and broad sharing of data via the AMP-AD Knowledge Portal

  -deeper understanding of the phenotypes of risk and the molecular mechanisms linking vascular risk factors, cerebrovascular disease and AD (tease out the impact of ApoE and sex-differences)

  -new disease-relevant therapeutic targets for prevention

  -molecular signatures that can be non-invasively measured and used for patient stratification.

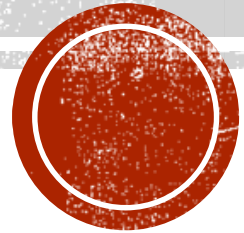
M2OVE-AD Mayo Team Project Workflow



Principal Investigators:
Nilufer Ertiken-Taner
Guojun Bu

ENABLING REPRODUCIBLE AND TRANSLATABLE PRECLINICAL EFFICACY TESTING

Lorenzo Refolo PhD



KEY FACTORS CONTRIBUTING TO THE POOR PREDICTIVE POWER OF PRECLINICAL EFFICACY TESTING STUDIES IN AD ANIMAL MODELS

- **The limitations of transgenic animal models used in AD drug development**
- **Lack of translatable biomarkers**
- **Failure to match outcome measures used in clinical studies**
- **Lack of standard/rigor in study design and analysis of data**
- **Poor reproducibility of published studies and publication bias due to under-reporting of negative results in the literature**

Shineman et. al. 2011; Landis et al. 2012; Snyder et al. 2016

MODEL-AD Translational Center

-$25M over 5 years-

- **Maximize human datasets to identify putative variants, genes and biomarkers for AD**
- **Generate, characterize and validate the next generation of mouse models of AD**
- **Develop a preclinical testing pipeline that implements rigorous study design and data analysis**
- **Make data and animal models available to the research community for use in therapy development**

MODEL-AD
Translational Center

Bruce Lamb - Indiana Univ.
Paul Territo –Indiana Univ.
Gareth Howell – Jax Labs
Greg Carter – Jax Labs
Lara Mangravite – Sage Bionetworks

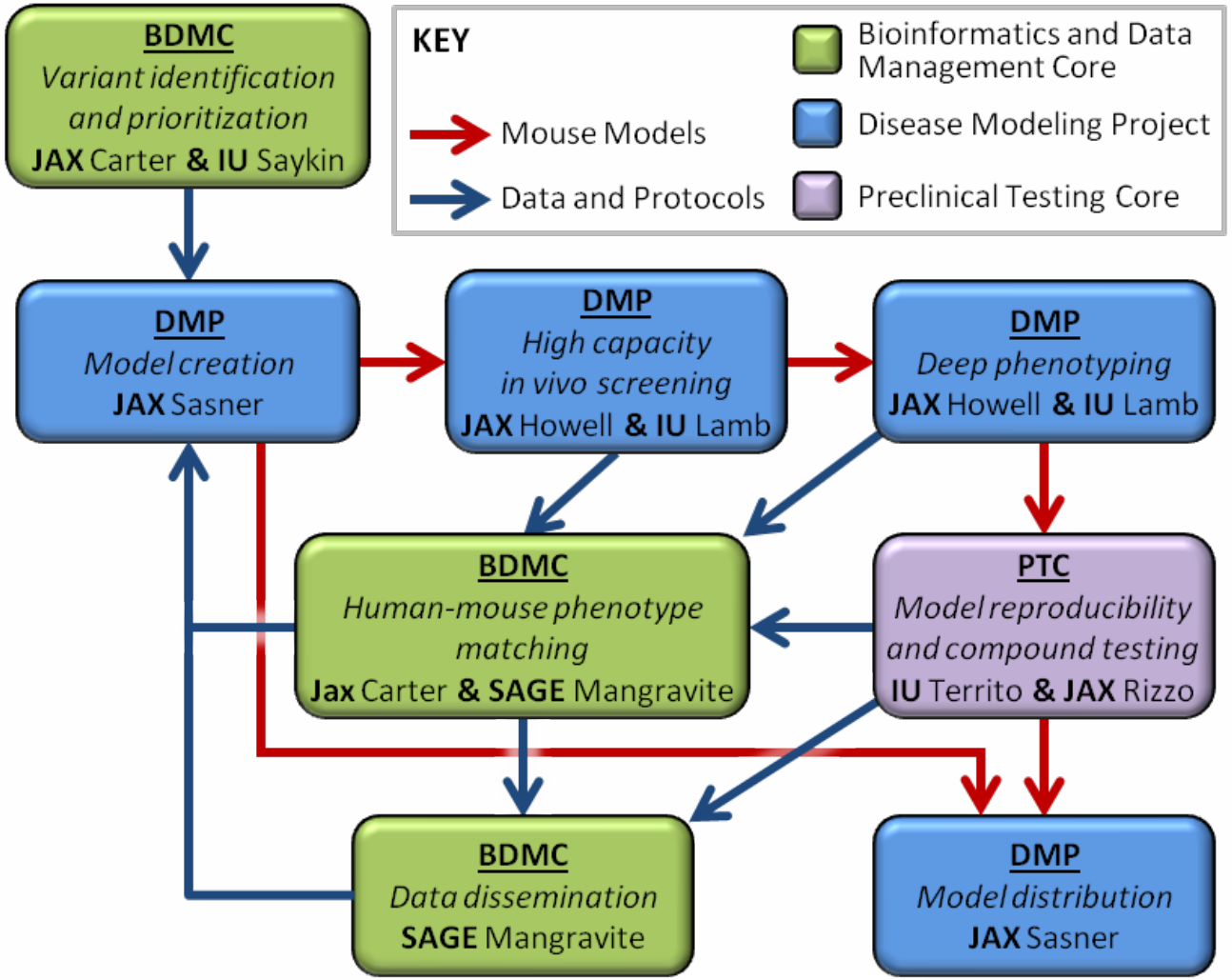
INDIANA UNIVERSITY

The Jackson Laboratory
Leading the search for tomorrow's cures

Sage BIONETWORKS

MODEL-AD Translational Center

-Organization and Workflow-

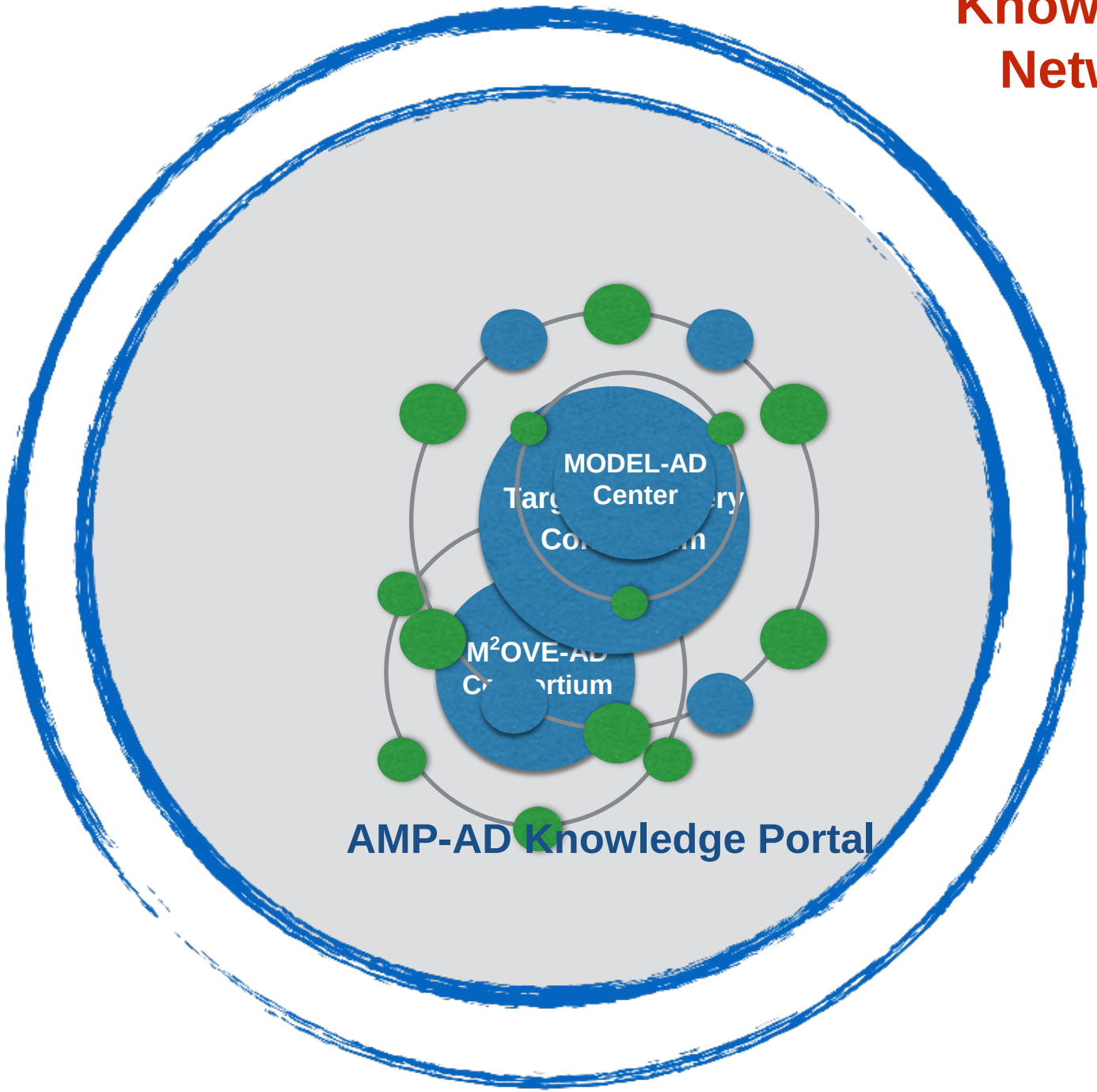


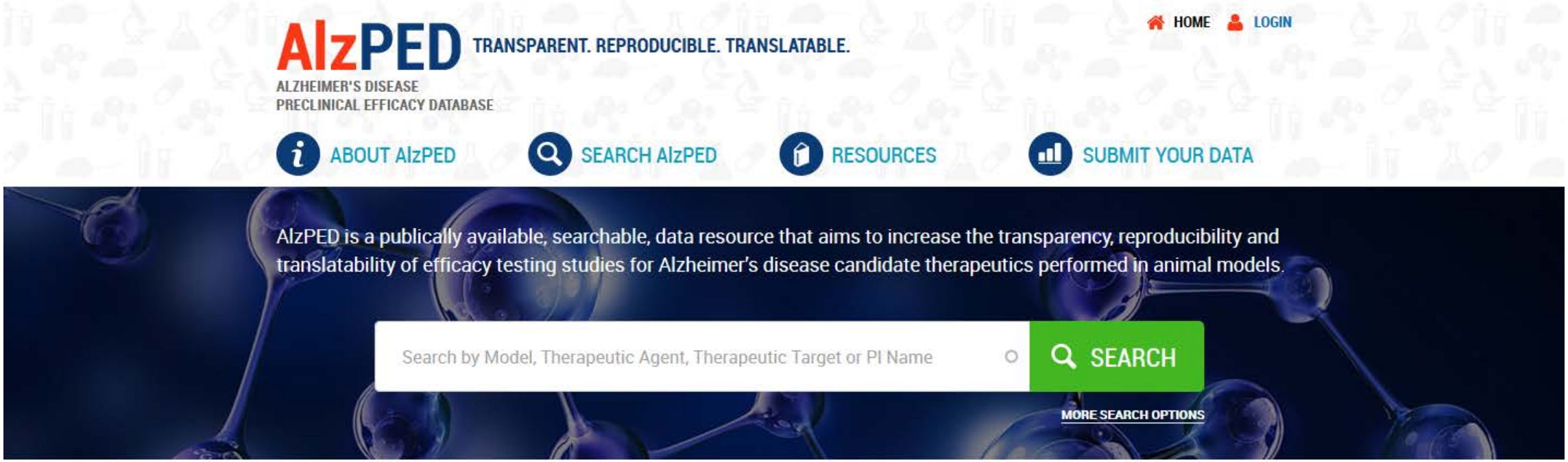
INDIANA UNIVERSITY

The Jackson Laboratory

Sage BIONETWORKS

Knowledge Network





GETTING STARTED

- How to Enter Data
- Frequently Asked Questions
- Search Guides
- AlzPED Team
- Glossary of Terms

Current AlzPED Member Organizations:

National Institute on Aging
NIH Library
Alzheimer's Drug Discovery Foundation
Alzheimer Association

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

AlzPED TRANSPARENT. REPRODUCIBLE. TRANSLATABLE.
ALZHEIMER'S DISEASE
PRECLINICAL EFFICACY DATABASE

PURPOSE AND GOALS:

- **Provide researchers and information scientists with a facile way to survey existing AD preclinical therapy development literature and raise awareness about the elements of rigorous study design and requirements for transparent reporting.**

- **Provide funding agencies with a tool for enforcement of requirements for transparent reporting and rigorous study design.**

AlzPED TRANSPARENT. REPRODUCIBLE. TRANSLATABLE.
ALZHEIMER'S DISEASE
PRECLINICAL EFFICACY DATABASE

AlzPED Features:

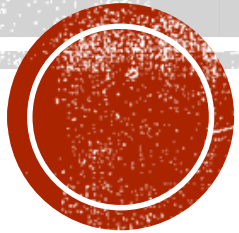
- **Searchable** (by target, therapeutic agent, animal model, investigator) **summaries of the experimental design and findings of published preclinical efficacy testing studies.** ***available***

- **Citable and searchable summary reports of unpublished studies.** ***in development***

- **Pre-registration of the study design for preclinical efficacy testing studies.** ***to be developed***

ENABLING CLINICAL DRUG DEVELOPMENT

Laurie Ryan PhD



ACCELERATING MEDICINES PARTNERSHIP (AMP)

ALZHEIMER'S DISEASE - **Biomarkers Project**

A consortium of NIA-supported Phase II/III secondary prevention trials testing several anti-amyloid therapies. Through the AMP-AD partnership, imaging and fluid biomarker panels already included in these trials will be supplemented with tau PET imaging and novel fluid biomarkers.

The goal is to explore the utility of tau imaging (AV1451) and novel fluid biomarkers for tracking responsiveness to treatment and/or disease progression. Screening/baseline (pre-randomization) data from the trials will be made broadly available through the Alzheimer Association's GAAIN collaborative platform following completion of enrollment and QC.

Trial data (placebo and treatment arms) and biological samples will also be made available to qualified investigators after completion of the trials.

- **Anti-Amyloid treatment in Asymptomatic AD Trial (A4 Trial)**

ADCS, Reisa Sperling - Harvard Medical School

THERAPEUTIC: Solanezumab

TARGET *POPULATION*: Cognitively normal older adults (age 65-85), positive for amyloid

- **Dominantly Inherited Alzheimer Network (DIAN) Trial**

Randall Bateman - *Washington University*

THERAPEUTIC: Gantenerumab and Solanezumab

TARGET POPULATION: Individuals at risk for and with Dominantly Inherited Alzheimer's Disease

National Institute on Aging

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Health research throughout the lifespan

Alzheimer's Biomarker Consortium – Down Syndrome ABC-DS

- **~$37 million over 5 years - two multi-institutional, cross-disciplinary research teams**
- **Biomarkers will be explored to track AD-related changes in the brain and cognition for ~500 adults with Down syndrome (25-80+ years old)**
- **Measures include PET (amyloid and Tau), MRI, CSF and blood markers, DNA for GWAS, cognitive/memory tests**
- **Research teams are collaborating and harmonizing measures and procedures**
- **Data will be available in a public database, pre-publication; samples will be made available to qualified investigators**

ABC-DS Research Teams

Benjamin Handen, Ph.D., Department of Psychiatry, University of Pittsburgh, heads a team that involves investigators and data from:

- **Banner Alzheimer's Institute, Phoenix;**
- **Cambridge University, England;**
- **Laboratory of Neuro Imaging, University of Southern California, Los Angeles.**

Nicole Schupf, Ph.D., Columbia University Medical Center, New York City, leads a team involving investigators at:

- **University of California, Irvine;**
- **Kennedy Krieger Institute/Johns Hopkins University, Baltimore; Massachusetts General Hospital/Harvard University, Boston;**
- **University of North Texas Health Sciences Center, Fort Worth.**

NEW FUNDING OPPORTUNITIES

RFA AG17-054 Enhancing the Target and Biomarker Discovery Efforts of the AMP-AD and M^2OVE-AD Consortia (R01)

Submission deadline Feb 3, 2017

RFA AG17-061 Interdisciplinary Research to Understand the Complex Biology of Resilience to Alzheimer's Disease Risk (R01)

Submission deadline Feb 21, 2017

NEW FUNDING OPPORTUNITIES

PAR 17-032 Translational Bioinformatics Approaches to Advance Drug Repositioning and Combination Therapy Development for Alzheimer's Disease (R01)

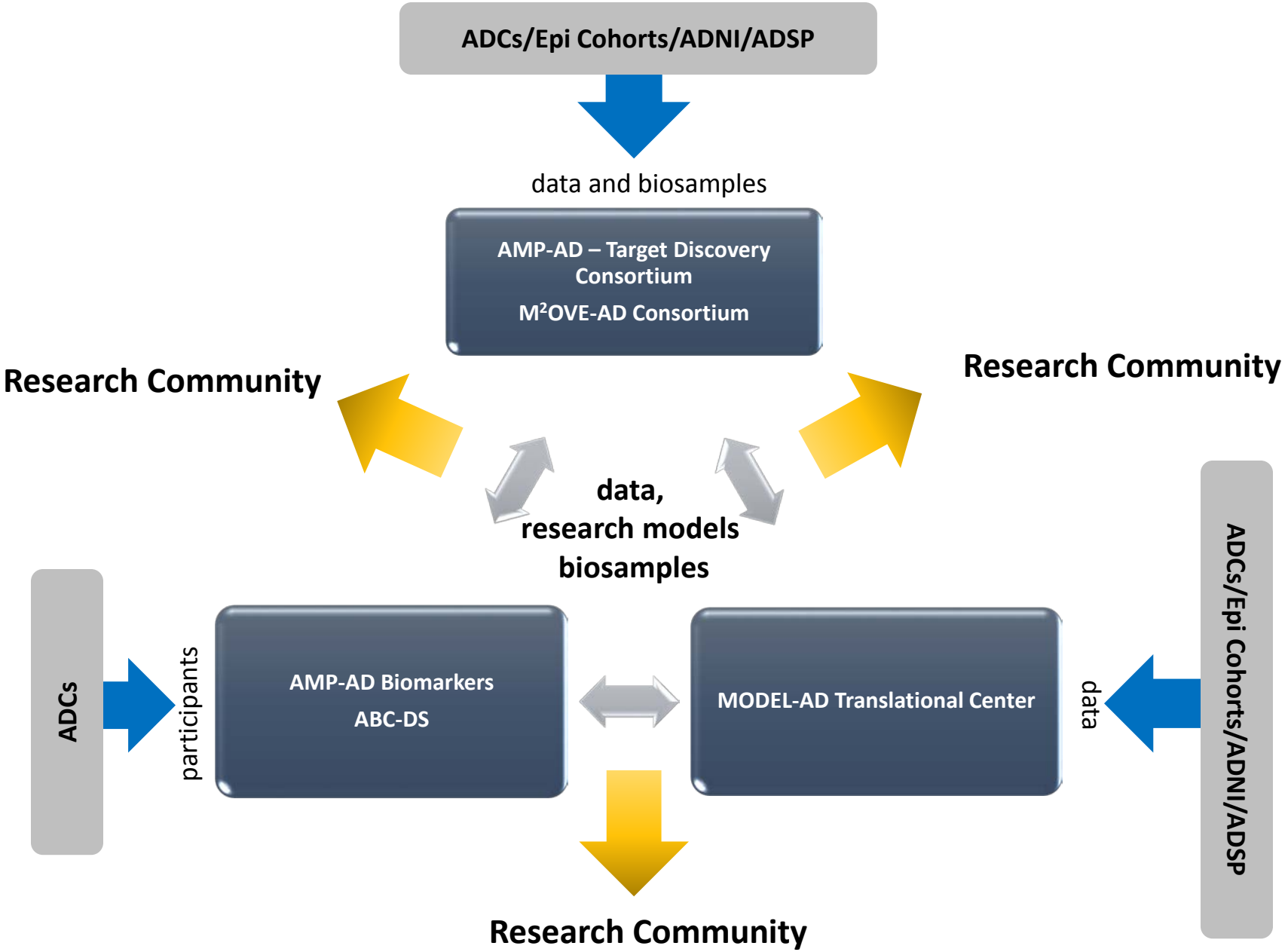
Active through 2020; three submission deadlines each year

PAR 17-033 Integrative Research to Understand the Impact of Sex Differences on the Molecular Determinants of AD Risk and Responsiveness to Treatment (R01)

Active through 2020; three submission deadlines each year

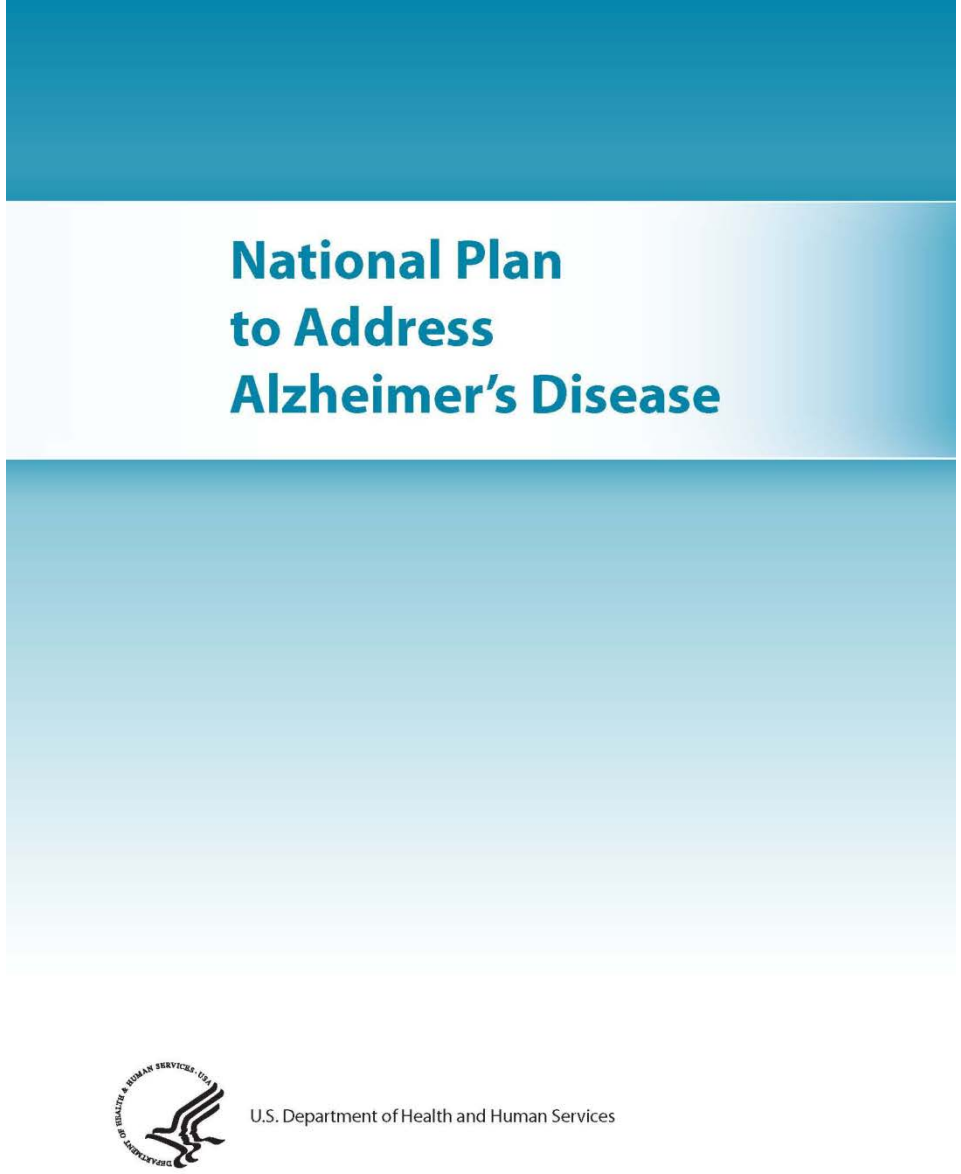
PAR 17-052 Research Career Enhancement Award to Advance Therapy Development for Alzheimer's (K18)

Active through 2020; three submission deadlines each year


ADCs/Epi Cohorts/ADNI/ADSP
data and biosamples
AMP-AD – Target Discovery Consortium
M2OVE-AD Consortium
Research Community
Research Community
data,
research models
biosamples
ADCs
participants
AMP-AD Biomarkers
ABC-DS
MODEL-AD Translational Center
data
ADCs/Epi Cohorts/ADNI/ADSP
Research Community

2012/2015 AD Research Summits: Some Key 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 new 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.



National Plan Goals:

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

2. Optimize care quality and efficiency.

3. Expand supports for people with Alzheimer's disease and their families.

4. Enhance public awareness and engagement.

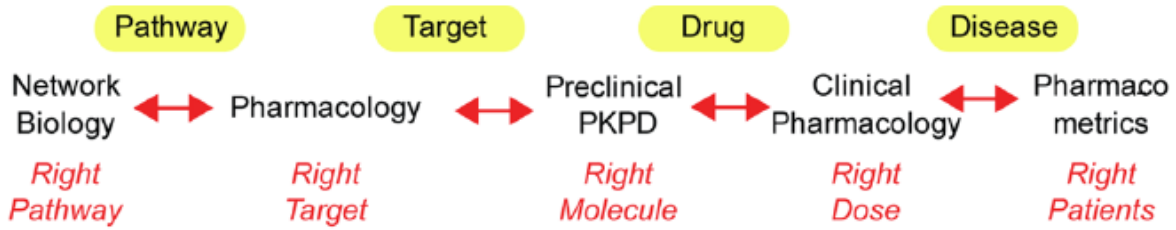
5. Track progress and drive improvement.

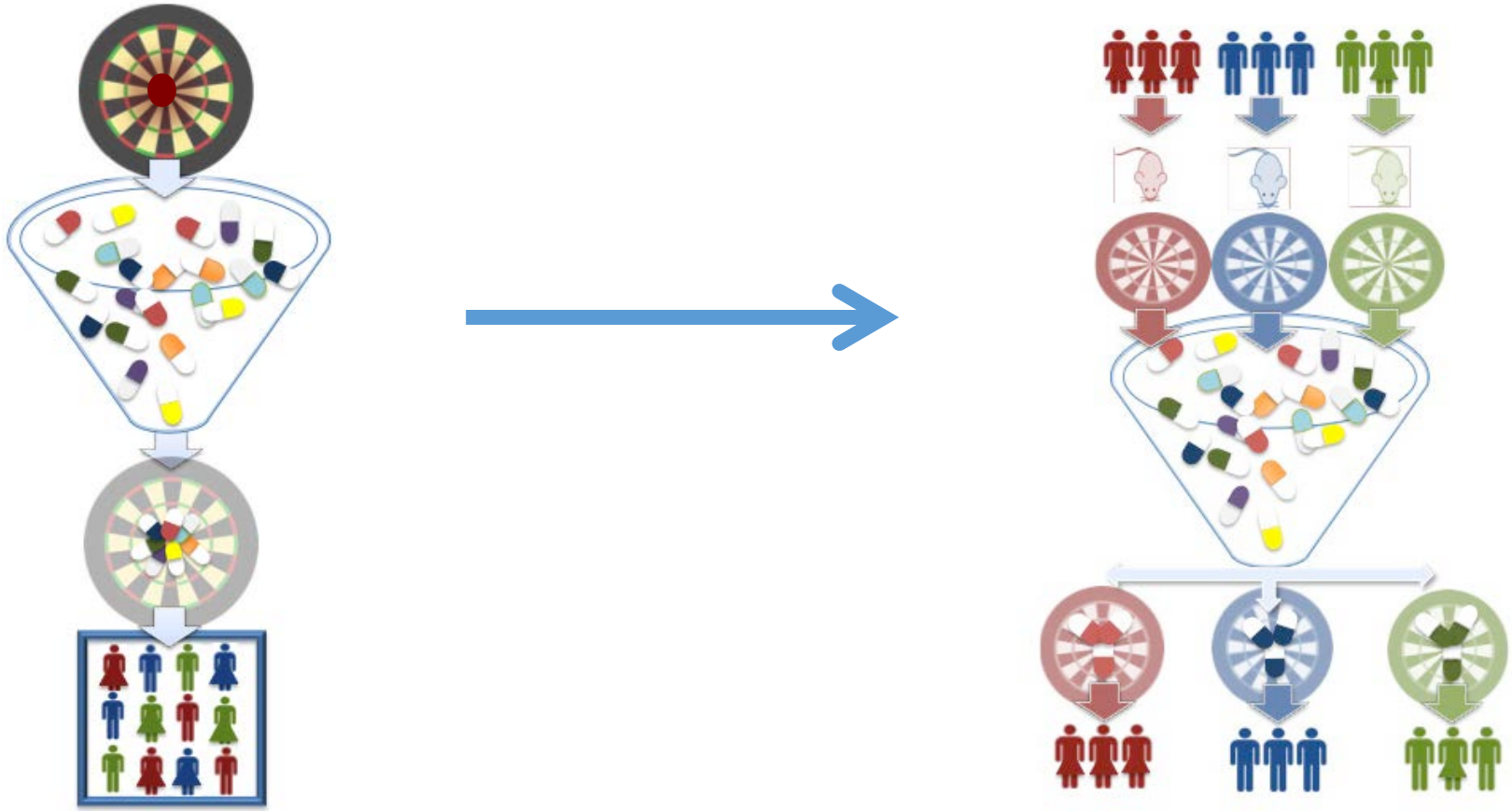
Phase III Randomized, Double-blind, Placebo Controlled, Clinical Trials for AD

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

Failures due to lack of efficacy or unforeseen toxicity.

Laying the Foundation for Precision Medicine for AD





National Institute on Aging

NIA ALZHEIMER'S TRANSLATIONAL RESEARCH PROGRAM LEADERSHIP:

Target Discovery and Validation

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Clinical Drug Development

Laurie Ryan PhD
ryanl@nia.nih.gov