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

Drug Discovery and Preclinical Drug Development

- Target ID
- Assay Development
- Screening
- Proof of Concept
- Lead Optimization
- Candidate Selection
- IND-enabling toxicology
- IND

Clinical Drug Development

- IND
- Phase I
- Phase II
- Phase III
- Drug Approval

Industry & VC partners
U01 Preclinical Drug Development Program PAR 174
-2007-present-

-Supported with set-aside funding

-Applications reviewed at NIA by a Special Emphasis Panel
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
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 - first in class, small molecule modulator of the P75 Neurotrophin Receptor

PI – Frank Longo MD and NeurotrophiX
In vitro models

Pre-IND formal PK/tox

Phase 1 safety/PK

Phase 2a safety
-ex endpoint
-biomarkers

Phase 2/3 efficacy

2000

Academic labs (UCSF/UNC/Stanford)

2005

Virtual company (PharmatrophiX)
-networking/advisors/CROs

now!

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

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

Pharma NIH
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

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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

- **GENETICS**
  - ADGC/NIAGADS
  - ADSP

- **SYSTEMS AND NETWORK BIOLOGY**
  - OPTOGENETICS
  - Human iPSC
  - Next generation animal models

- **DISCOVERY AND VALIDATION OF NOVEL TARGETS**
  - SECONDDARY PREVENTION TRIALS
  - AD BIOMARKERS in DOWN SYNDROME
  - AD Clinical Trials Consortium*

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

- **NEW TRANSLATIONAL CAPABILITIES**
  - INFLAMMATION
  - VASCULAR ETIOLOGY
  - COMPLEX BIOLOGY OF COGNITIVE RESILIENCE*

- **RESEARCH TOOLS AND DISEASE MODELS**

- **BIOLOGY OF DISEASE**

- **ENABLING CLINICAL DRUG DEVELOPMENT**

* 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
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.
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/R01 grants –

Data
Network models
Code

AMP-AD
Knowledge Portal

www.synapse.org.ampad

6 Academic Teams
– NIA U01/R01 grants –
<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>
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<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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<th>Human Data source</th>
<th>ROSMAP</th>
<th>Mt Sinai Brain Bank</th>
<th>Mayo Brain Bank</th>
<th>All</th>
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<th>ROSMAP</th>
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<th>RNAseq</th>
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<th>RNAseq</th>
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<th>Txpn Factors</th>
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<th>Innate Immunity Networks</th>
<th>Bayesian Networks</th>
<th>Systems analysis</th>
<th>REST</th>
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| 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

1. **Data Generation**
   - Brain Bank Cohorts
     - Harvard Medical School
     - Mt. Sinai Medical School
     - Clinical traits
     - DNA
     - RNA in 4 brain regions
     - Moderate-to-severe cases
     - Mild AD including MCI and CDR 0~5

2. **Model Building**
   - Machine Learning
   - Bayesian Algorithms
   - WINA

3. **Data Mining for Causal Regulators**
   - Causal Networks
   - Co-expr Networks
   - Key Driver Analysis
   - Pair-wise Causality Models
   - Classifiers

4. **Hit Prioritization**
   - Highly penetrant, rare, genetic mutations
   - Regulate genes enriched for AD GWAS
   - Regulate genes known to associate with AD
   - Top of rank-ordered causal regulator list

5. **Experimental Validation**
   - Higher-throughput experimental validation
   - Brain Slices
   - Fly Model
   - Human iPSCs
   - Pharmacologic

AMP-AD Mt.Sinai team: Project Workflow
How Are We Doing This Together?

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

**Industry teams**

**Target Nomination**

<table>
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<tr>
<th>Team 1</th>
<th>Team 2</th>
<th>Cross Analysis</th>
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<td>Target 1</td>
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AMP-AD Collaborative Workspace
- Data
- Analyses
- Network models
- Code

Consortium Space

AMP-AD* Knowledge Portal

Quarterly Data Depositions
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

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<tr>
<th>HUMAN TISSUE</th>
<th>Diagnosis</th>
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<td>Prefrontal Cortex</td>
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<td>• Parkinson’s Disease</td>
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<td>• SH-SY5</td>
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<td>• AE4</td>
<td>• ChIPseq</td>
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<tr>
<td></td>
<td>• ELISA (Aβ)</td>
<td>• Proteomics</td>
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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
Quantitative neurobiology

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

DNA methylation, histone acetylation

Next generation RNAseq, miRNA

MS Proteomic and metabolomic

Quantitative neurobiology

Structural and functional MRI

Quantitative clinical phenotype

Syndromic phenotype

Genotypes
Affy 6.0/Illumina Quad
1000G imputation

DNA Methylation Illumina
450K
Histone H3K9Ac
ChIP-Seq

RNA profile
miRNA & RNAseq

LC/MS profile
Lipids, proteins

Neuropathology
AD, CVD, LBD, HS, TDP

Resilience Markers
Synaptic proteins, LC

Flair, MP Rage, DTI, SWI, rsfMRI

post-mortem MRI
DTI, MP Rage, T2

Cognitive Function
19 tests annually

Motor Function
Disability BMI, Actigraphy

Clinical Diagnoses
AD, Stroke, PD,

Genotypes
Whole Exome Sequencing

Dynaport – Gait, Sleep, circadian rhythms, Behavioral Economics, Olfaction,
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
RNAsseq
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
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NOT JUST TARGETS
Discovery of Novel Proteomic Targets for Treatment of Alzheimer's Disease

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

1. Discovery Proteomics
   - Control, AsymAD, non-AD, MCI, AD
   - ~800 Cases (MSSM, Mayo, Banner, UPenn, BLSA, ACT and Emory)

2. Validation Proteomics
   - ~1200 Cases (ROS/MAP)
   - Fusion-Orbitrap Multiplex (TMT)

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

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

- 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)
Non Targeted lipidomics (400)
Highly informative compounds (40)

Data being vetted
 Deposited LONI
 Deposited LONI

- Neurotransmitters
- Methylation

Broad biochemical coverage, high level of standardization!
Partial Correlation Network Analysis Suggests Evolution of Metabolic Changes in AD

Toledo et al. 2017
~$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.
Define the effects of sex and apoE isoforms on the pathological distribution and severity of CAA and parenchymal amyloid plaques

- Postmortem cohort
- Neuropathology
- Biochemistry (sex hormones, Aβ)

Identify novel pathways that contribute to the development of CAA and AD.

- 400 TCX and 200 CER from AD brains subjects with CAA scores.
- RNAseq
- Methylation by RRBS
- GWAS

Discover impact of novel pathways on vascular risk in aging and dementia.

- 400 subjects from MCSA
- RNASeq
- GWAS

Investigate the molecular mechanisms mediating the impact of apoE isoforms and estrogen on brain Aβ clearance and the formation of CAA and amyloid plaques

- Mouse primary cultures
- iPSC-derived cells
- Ovariectomy/estrogen replacement

M2OVE-AD Mayo Team
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

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
-Organization and Workflow-

**BDMC**
- Variant identification and prioritization
  - JAX Carter & IU Saykin

**DMP**
- Model creation
  - JAX Sasner
- High capacity in vivo screening
  - JAX Howell & IU Lamb
- Deep phenotyping
  - JAX Howell & IU Lamb

**BDMC**
- Human-mouse phenotype matching
  - JAX Carter & SAGE Mangravite

**PTC**
- Model reproducibility and compound testing
  - IU Territo & JAX Rizzo

**BDMC**
- Data dissemination
  - SAGE Mangravite

**DMP**
- Model distribution
  - JAX Sasner

**KEY**
- Bioinformatics and Data Management Core
- Mouse Models
- Disease Modeling Project
- Data and Protocols
- Preclinical Testing Core
AlzPED is a publically 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.

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/
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 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*
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
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 M2OVE-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
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.


4. Enhance public awareness and engagement.

5. Track progress and drive improvement.
<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>Xaliproden</td>
<td>Serotonin antagonist</td>
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<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>
</tbody>
</table>

Failures due to lack of efficacy or unforeseen toxicity.
Alzheimer’s Disease

Laying the Foundation for Precision Medicine for AD
NIA ALZHEIMER’S TRANSLATIONAL RESEARCH PROGRAM
LEADERSHIP:

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