Overview of the NIA portfolio in AD clinical trials: Which new targets could be explored?

Eliezer Masliah
Division of Neuroscience, National Institute on Aging, NIH
The world in the year is 2025

• Earth population reaches 8 billion

• Next generation AI and (super-intelligent AI) augmented virtual reality developed

• World largest telescope opens (European Extremely Large Telescope Atacama Chile)

• *New treatments to prevent and treat Alzheimer’s Disease developed*
US National Plan to Address AD
https://aspe.hhs.gov/national-alzheimers-project-act

- The **National Alzheimer’s Project Act (NAPA)** signed 2011.

- The primary research goal of the NAPA is to prevent the onset of and develop effective treatments for AD by 2025.

- The plan also covers other dementias- **DLB, FTD and VCID**
Catching up……

The Alzheimer’s gamble: NIH tries to turn billions in new funding into treatment for deadly brain disease

By Jocelyn Kaiser | Aug. 30, 2018, 9:00 AM

The National Institutes of Health (NIH) has dramatically ramped up funding for only three specific disease priorities: cancer, AIDS, and, most recently, Alzheimer’s.

$39 Billion for the NIH in FY19

$500M for HEAL (opioids)

$169M for BRAIN

$149M for All of US

$400M for Cancer moonshot

$425M to NIA for AD/ADRD

Comparison of # of clinical trials by disease

Source: ClinicalTrials.gov
Cancer and Neurological clinical trials bird’s eye view (AERO DATA LAB)

- **Color** company
- **Shape** trial’s status — completed ○, recruiting △ terminated “x” through them
- **Size** number of patients enrolled.

Spencer Phillips Hey STAT 2019
NIA-AD Research Priorities

- Greater integration among basic, preclinical and clinical AD programs
- Early detection and diagnosis
- Research Framework
  - Biomarkers
  - National Strategy to enhance recruitment for AD clinical studies
  - Enhance clinical trials Pipeline
  - "More shots on goal"

DATA SHARING
NIA resources for data sharing in support of 2025

NIA Program Directors: Nina Silverberg, Cerise Elliott, Laurie Ryan, Suzana Petanceska, Larry Refolo, Marilyn Miller, Dallas Anderson, Kristina McLinden

- **ACTC** - Alz Dis Clinical trials consortium
- **ADSP** - Alz Dis sequencing program
- **ADGC** - Alz Dis Genomic Center
- **ADNI** - Alz Dis Neuroimaging initiative
- **ADCs** - Alz Dis Centers
- **AMP-AD** - Accelerating medicines partnership
- **MODEL-AD** - Model Organism Develop and Evaluation for Late-onset AD
- **NACC** - National AD coordinating center
- **NCRAD** - Natl Centralized Repository AD

[Diagram showing various resources and their relationships, including AMP-AD, MODEL-AD, ADC New Medicines, GWAS, WES, WGS, Biomarkers, Clinical Trials, LONI/ADNI, NIAGADS, NACC, and NCRAD.]
NIA-AD programs from “bench to bedside”

Core principles: data sharing, transparency, rigor in science
Pipeline of NIA and Trans-NIH Translational Research Funding Initiatives

Provides support for each step of the drug development process to accelerate and diversify AD therapy development.

Chemical Probes and Novel Target Identification and Validation (R21/R01)
Assay Development (R01)
AD Drug Discovery (R21/R01)
AD Drug Development (U01, R01)
Blueprint Neurotherapeutics (UH2/UH3)
Clinical Trials (R01)

SBIR (R43/44)/ STTR (R41/42)
Training and Career Development (T32) (K18)
NIA sponsors over 200 AD trials and interventions

- **35 Early-stage Pharmacologic (Phase I and II Clinical Trials)**
  - Amyloid (10)
  - Receptors (4)
  - Neuroprotection (4)
  - Metabolism and Bioenergetics (2)
  - Vasculature (2)
  - Growth Factors and Hormones (2)
  - Multi-target (2)
  - Inflammation (2)
  - Oxidative Stress (2)
  - Other (5)

- **8 Late-stage Pharmacologic (Phase II and III Clinical Trials)**
  - Amyloid (6) - DIAN-TU, A4, API-ADAD, API-E4, others
  - Vasculature (2) - SPRINT-MIND, ASPREE

- **86 Non-Pharmacological Interventions**
  - Exercise (19)
  - Diet (6)
  - Cognitive Training (21)
  - Assistive Tech. (8)
  - Sleep (5)
  - Combination Therapy (10)
  - Other (17)

- **8 Clinical Therapy Development for the Neuropsychiatric Symptoms of AD/ADRD**
  - Pharmacological (5) - lithium, methylphenidate, escitalopram, dronabinol, others
  - Non-Pharmacological (3) - CAP, PATH

- **61 Care and Caregiver Interventions**
  - PWD (35) for family (36)

- **5 Delirium/pot-operative cognitive decline**
  - Anesthesia (1), Sleep (1), Device (1), Combination (1), Cognitive training (1)
NIA AD Pharmacologic Therapeutics Portfolio in 2019 (n=138)

- **Preclinical Drug Development**
  - N=48
  - Amyloid
  - Tau
  - Neurotransmitters
  - Inflammation
  - Growth factors/hormones
  - Neurogenesis
  - Metabolism/bioenergetics
  - Synaptic plasticity/neuroprotection
  - ApoE/lipids
  - Proteostasis/proteinopathies
  - Cell Death

- **Early-Stage Clinical Trials**
  - N=35
  - Amyloid
  - Tau
  - Neurotransmitters
  - Inflammation
  - Growth factors/hormones
  - Neurogenesis
  - Metabolism/bioenergetics
  - Synaptic plasticity/neuroprotection
  - ApoE/lipids
  - Proteostasis/proteinopathies
  - Cell Death

- **Late-Stage Clinical Trials**
  - N=8
  - Amyloid
  - Tau
  - Neurotransmitters
  - Inflammation
  - Growth factors/hormones
  - Neurogenesis
  - Metabolism/bioenergetics
  - Synaptic plasticity/neuroprotection
  - ApoE/lipids
  - Proteostasis/proteinopathies
  - Cell Death
Changes in NIA-AD clinical drug development portfolio from 2014 to 2018

Source: https://iadrp.nia.nih.gov
Comparison of NIA Projects funded by year (2014-2019) in the area of Molecular Pathogenesis of AD/ADRD

Source: https://iadrp.nia.nih.gov
NIA Alzheimer’s Translational Research Program – since 2006
Diversifying the Therapeutic Pipeline

**Next-gen anti-Aβ therapeutics:**
Sigma receptor – anti Aβ oligomer therapy
Gamma secretase modulators
Anti-Aβ oligomer immunotherapy
Aβ immunotherapy – DNA vaccine
Aβ aggregation inhibitors
Aβ catalytic antibodies

**Cytoskeleton/Tau:**
Microtubule stabilizers
CDK5-tau phosphorylation
Calpain Inhibitors
Tau aggregation inhibitors
DYRK1A

**Oxidative Stress:**
Nrf2
γ-ketoaldehyde
Glutathione S-transferase

**Vasculature:**
Angiotensin II receptor
Mas receptor

**αSyn**
Heavy chain αSyn antibodies
αSyn aggregation inhibitors

**Multi-target therapeutics:**
 p38αMAPK
GABA Receptor and NO production
Neurogenesis
Proteostasis

**Metabolism and Bioenergetics:**
Insulin Receptor
Mitochondria

**ApoE4**
ApoE-antibodies
Antisense oligonucleotides

**Neuroinflammation**
EP2 receptor
P38 MAPK
CRAC Channel
NLRP3
Inflammasome
TNFα

**Neurotransmitter Receptors and Growth Factors:**
mGluR5 Receptor
GABA Receptor A alpha5
TrkB
P75 Neurotrophin Receptor

**Synaptic Plasticity**
Calcineurin
Ryanodine Receptor
Excitotoxic Amino Acid Transporter
Somatostatin Receptor subtype-4

**Cell therapies:**
Neural Stem Cell transplantation

**Cell Death:**
CDK4/6
OMA1
Examples of Therapeutic Projects Supported through our NIA AD Translational Programs

<table>
<thead>
<tr>
<th>Therapeutic Agent and Target/Mechanism</th>
<th>Drug Discovery</th>
<th>Drug Development</th>
<th>Phase 1 Trial</th>
<th>Phase 2 Trial</th>
<th>Phase 3 Trial</th>
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<tbody>
<tr>
<td>AGB101 (SV2a, synapse vesicle)</td>
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<tr>
<td>LM11A-31 (Nerve Growth Factors)</td>
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<tr>
<td>CT1812 (Amyloid)</td>
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<td>BPN14770 (Synaptic Plasticity)</td>
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<td>Allopregnanolone (Neurogenesis)</td>
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<td>MW151 (Neuroinflammation)</td>
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<td>MW150 (Neuroinflammation)</td>
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<td>PU-AD (Proteostasis)</td>
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<td>NNI-362 (Neurogenesis)</td>
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<td>AV-1959 (Amyloid)</td>
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<td>AAV2-BDNF (Growth Factors)</td>
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<td>GSM-776890 (Amyloid)</td>
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<td>EAAT Activator (Synaptic Plasticity/Neuroprotection)</td>
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<td>ACU193 (Amyloid)</td>
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<td>Neural Stem Cells (Neurogenesis)</td>
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<td>Triazolopyrimidines (Tau)</td>
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<td>AV1980R/A (Tau)</td>
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<td>BPN-27473 (Neurotransmitter Receptor)</td>
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<td>E64 and BDA-410 (Synaptic Plasticity/Neuroprotection)</td>
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<tr>
<td>EP2 receptor inhibitor (Neuroinflammation)</td>
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<tr>
<td>BMS984932 (Neurotransmitter receptor)</td>
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</table>

Therapeutic agents targeting amyloid
Phase 2a: LM11A-31 in patients with mild to moderate AD

AG051596

- Double-blind, placebo-controlled, randomized trial to evaluate proof-of-concept, safety and exploratory end-points for LM11A-31 in mild-moderate AD

- 3 arms each consisting of 80 patients including placebo and two doses treated twice daily for 26 weeks

- FDG-PET key biomarker and proof-of-mechanism, testing the hypothesis that a p75 ligand can modulate p75 signaling and restore synaptic mechanisms in AD

- Additional measures: Cognition (Neuropsychological Test Battery including ADAS-Cog-14, NPI), CSF (Aβ, tau, p-tau, acetylcholinesterase activity) and structural MRI
Hippocampal network dysfunction is a driver of the spread of tau pathology (*Palop and Mucke Nat Rev Neurosci 2016*).

The anti-epileptic levetiracetam given in low dose restores hippocampal activity to normal; other antiepileptic drugs that are not SV2a antagonists do not have this neurobiological effect (*Sanchez, Mucke et al PNAS 2012*).

A Phase 2 study in patients with aMCI found that AGB101 normalized hippocampal activity and improved memory.

**Pivotal Phase 3**

Testing the efficacy of a low-dose formulation levetiracetam (AGB101) to slow disease progression in patients with amnestic Mild Cognitive Impairment (aMCI) due to Alzheimer’s disease (AD).

830 patients randomly assigned to either AGB101 or placebo and followed for 78 weeks.

Subset of 160 will have tau PET imaging at baseline and endpoint to assess the effect of AGB101 on the spread of tau pathology.
Understanding AD in the context of Aging

Proteinopathy

Aging

HIV-1, HHV, other pathogens

Trauma, chemicals, radiation, radicals, stress, metabolic, viruses

DNA damage

Transposable elements

senescence/immune surveillance

Proteostasis
Mitochondria
Inflammation
Endosomes
Growth Factors
Epigenetics

DNA damage

Senescent cells
Immune surveillance

Synapse damage

Neurodegeneration

Abeta
Tau
Synuclein
TDP43
Others

HIV-1, HHV, other pathogens

DNA damage

Senescence initiation
Early senescence

T cells
Mac's
NK's

senescence-inducing signals, e.g., oncogene activation, DNA damage
Progressive chromatin remodeling, implementation of senescence program

Senescence

Cell cycle exit

Mitochondrial oxidative metabolism, apoptosis resistance
G1/S transformation, p16
Tumor suppressor

Loss of Lamin B1

Mitochondrial network remodeling

G1/S checkpoint

Vacuole

p53/p21 activation

SASP

Lysoosomal activity, autophagy

Cell cycle exit
Aging mechanisms related targets relevant to AD/ADRD

**Pathway**
- AMPK
- P16/p21
- ATM/p53
- mTor

**Target**
- Insulin R, OCT1/mitochondria
- Cell senescence
- DNA damage
- Autophagy

**Drug**
- Metformin
- Dasatinib + Quercetin; Navitoclax
- ARV
- Rapamycin

**Human trials**
- Campbell et al., J Alzheimers Dis 2018; 65:1225-36
- Alzheimer’s disease n=5 NCT04063124
- ?
- ?
Targeting senescence cells ameliorates AD/ADRD neuropathology in animal models

Dasatinib + Quercetin

5XAPP tg

PS19 Tau tg
Young blood rescues neurodegenerative pathology in mice

**PLASMA trial** (Plasma for Alzheimer’s Symptom Amelioration)
- Stanford Clinical Trials group
- N=18 AD participants, caregiver reporting
- 2 stages over 6 months
- 4 weekly infusion plasma (18-30 y/o) vs saline
- 6 weeks washout period
- Safe
- Improvement on tests of functional ability to perform tasks of daily life
- Larger studies underway

*Middeldorp, Wyss-Coray, et al JAMA Neurology 2016*
Approaches towards discovering and developing new targets to treat AD/ADRD

Strategies for target discovery
- Small molecule library
- Genetics
- Multi-OMICS approach

Tractability
- Target qualification: Mechanistic understanding from model organisms
- Other proximal targets
- Assay, translational cellular and animal models, and SM, antibody or new modality druggability; tool molecules
- Biomarker: target engagement, pharmacodynamic, efficacy
- Path to Proof-of-concept
- Patient benefit and trial outcome measures
- Competitive landscape

Safety
- On target toxicity
- Mechanistic toxicity
- Therapeutic window

AD is an heterogeneous disorder
A systems biology approach to discover and validate the next generation therapeutic targets using an open science research model.

Genomic, proteomic, metabolomic data from human brain and plasma samples

Computational modeling

Experimental validation in cell-based and animal models

Drug Discovery

AMP-AD Data Coordinating Center (U24):
Sage Bionetworks

U01 Grants:
Duke U-Helmholtz U-Indiana University
Icahn Institute at Mount Sinai
Arizona State University
Columbia-Rush
Emory-Baylor
UFL-Mayo-ISB

Launched in 2014
AMP-AD Knowledge Portal and AMP-AD accomplishments

- **Centralized data resources** for sharing raw and processed data, analytical results and target nominations: AMP-AD Knowledge Portal and AGORA platform.
- **Rich, high quality, multi-omic, human data** and network models of disease pathways/targets made available via the Portal.
- **Datasets being widely used**: ~3000 users to date - 60% academia, 40% biotech/pharma.
- **Over 500 novel candidate targets** identified and made available via the AGORA platform along with druggability information developed by AMP-AD industry partners.
AMP-AD nomination of over 500 novel targets for AD in the Agora platform

TARGET DEVELOPMENT LEVEL

Tclin: Proteins annotated as drug targets
Tchem: Proteins for which potent small molecules are known
Tbio: Proteins for which some biology is known
Tdark: These proteins lack antibodies, publications or Gene RIFs
AMP-AD Pharma partners rate targets across 6 dimensions

- Small Molecule Druggability
- Antibody feasibility
- Safety
- Tissue Engagement
- Feasibility
- New Modality

### AMP-AD/Agora Targets – Small Molecule and Antibody Druggability Rankings

<table>
<thead>
<tr>
<th>SM Druggability</th>
<th>Description</th>
<th>Number of Targets</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Small molecule druggable</td>
<td>113</td>
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<tr>
<td>2</td>
<td>Targetable by homology</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>Targetable by structure</td>
<td>139</td>
</tr>
<tr>
<td>4</td>
<td>Targetable by homologous structure</td>
<td>11</td>
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<tr>
<td>5</td>
<td>Probably small molecule druggable</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Probably small molecule druggable by homology</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>Potentially small molecule druggable by family (active ligand)</td>
<td>137</td>
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<tr>
<td>8</td>
<td>Potentially small molecule druggable by family (low activity ligand)</td>
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<tr>
<td>9</td>
<td>Potentially targetable by protein family structure</td>
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<tr>
<td>10</td>
<td>Endogenous ligand</td>
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<tr>
<td>11</td>
<td>Druggable protein class, no other information</td>
<td>0</td>
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<tr>
<td>12</td>
<td>Potentially low ligandiability</td>
<td>25</td>
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<tr>
<td>13</td>
<td>Unknown</td>
<td>65</td>
</tr>
<tr>
<td><strong>Not found</strong></td>
<td></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>
RNA
- Expressed in a subpopulation of neuroendocrine cells, and is upregulated by nerve growth factor.
- Similarities with the secretogranin/chromogranin family, however, its exact function is not known.
- Multiple VGF peptides decreased in MCI and AD Spellman et al. 2015

Protein

Metabolites

Druggability
- Small Molecule Modality: 13 (Unknown: There is no information on ligands or structure in any of the categories above.)
- Antibody Modality: 1 (Secreted protein. Highly accessible to antibody-based therapies.)
- Safety: 4 (Probable safety risks requiring mitigation. More than two or: high off-target gene expression, cancer driver, essential gene, associated deleterious genetic disorder, HPO phenotype associated gene, or black box warning on clinically used drug.)

VGF

TLQP-62

TLQP-21

AQEE-30
Molecular Networks as novel therapeutic targets for AD/ADRD

- **CLU**- (Clusterin, ApoJ) apoptosis, inflammation
- **NLRC5**- innate immunity to virus, regulate IFN
- **RUFY3**- neuronal polarity, axon growth
- **BIN1**- adaptor protein, endocytosis
- **MEF2C**- transcription activator, synapse activity
- **INPP5D**- phosphatase, adaptive immunity, cell proliferation, survival
- **EPHA1**- ephrin tyrosine kinase, neurodevelopment

Viral signal Abundance Associates with AD Clinical and Neuropathology Traits

- RNA sequencing indicating abundance of HHV-6A and HHV-7 nucleotides and pathways in AD

- Regulatory relationship linking viral abundance and modulators of APP metabolism – APBB2, APPBP2, PSEN1, BACE1, CLU, PICAL and PSEN1
Valacyclovir clinical trial in AD

PI: Devanand, Davangere P
Institution: Columbia University/ New York State Psychiatric Institute

Rationale: Infections from herpes virus including HSV1 (oral herpes) and HSV2 (genital herpes) have been implicated in etiology for AD.

Anti-HSV drugs reduce Aβ and p-tau accumulation in infected mouse brains.

Study Design (groups, doses): Oral Valacyclovir at 2 g to 4 g per day, randomized, double-blind, 18-month Phase II, will involve 130 mild AD patients (65 valacyclovir, 65 placebo) who test positive for herpes simplex virus-1 (HSV1) or HSV2

Outcome measures include:
- Change in Alzheimer's Disease Assessment Scale - Cognition (ADAS-COG11, modified version) scores from baseline to 78 weeks
- Pet amyloid scan with 18F-Florbetapir and with 18F-MK-6240[ Time Frame: Week 0, Week 78 ]
- Change in Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)

Study duration: 78 weeks study
Study start date to estimated end date: Feb 2018 – Aug 2022
MISSION: Diversify and accelerate therapy development for AD through open source tools, reagents and methods for robust validation of candidate targets delivered by AMP-AD and other discovery programs, and by integrating enabled targets into drug discovery campaigns. $73M commitment over the next 5 years.
AMP-AD and affiliated consortia
Advancing drug discovery through Open Science

M²OVE-AD – Molecular Mechanisms of the Vascular Etiology of AD
NPS-AD – Molecular Mechanisms of the Neuropsychiatric Symptoms in AD
Active NIA-AD Phase II/III clinical trials in AD

- Pharm
- Exercise
- Multidomain Lifestyle
- Diet
- Exercise + Cog Training
- Pharm + non-Pharm

Diagrams showing timelines and interventions like DHA, intranasal insulin, CITALOPRAM, ADMET (RITALIN), IVIG, Intraparenchymal Insulin, and others.
Thoughts for the Future of AD/ADRD Trials

• Need for open science and data sharing to develop new biomarkers and targets

• Amyloid remains a target for early intervention therapy

• The heterogeneous nature of the disease highlights the need for combination therapies

• Multi-omics approaches (eg- AMP-AD) for new drug discovery

• Aging mechanisms as a target for new drugs for AD/ADRD

• Precision medicine for AD/ADRDs is the goal
Concept Approvals:  
https://www.nia.nih.gov/approved-concepts

General FOAs:  
https://www.nia.nih.gov/research/funding

Alzheimer’s Disease and Related Dementias FOAs:  
http://www.nia.nih.gov/AD-FOAs

Follow our “Inside NIA” blog:  
https://www.nia.nih.gov/research/blog