Progress Towards the Goal: Update on the AD/ADRD Clinical Trial Pipeline

Laurie Ryan, PhD
Chief, Dementias of Aging Branch &
Program Director AD/ADRD Clinical Trials (Pharm)
Division of Neuroscience, National Institute on Aging/National Institutes of Health
A Pipeline of NIA and Trans-NIH Translational Research Funding Initiatives (R21, R01, U01, R43/R44)

Target ID
Early Validation
Assay Development
Screening
Proof of Concept
Lead Optimization
Candidate Selection
IND-enabling toxicology
Phase I
Phase II
Phase III
Drug Approval

ADSP
AMP-AD Target Discovery
M²OVE-AD
Resilience-AD
NPS-AD

AD Translational Centers for New Medicines*

MODEL-AD
AlzPED

ACTC
ADCs
ADNI
AMP-AD Biomarkers
ABC-DS

ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE THERAPY DEVELOPMENT

*just launched Oct 2019
Understanding the biology of targets/disease

External Drug Discovery Campaigns

Researchers at Large

Academic Labs
Biotech
Pharma

AD Centers for Discovery of New Medicines

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

Late Stage Preclinical Drug Development through First in Human

ADDP
BPN

MODEL-AD

First in Human through Phase III

ACTC

Early/Late Stage Clinical Trials

ADDP
BPN

ACTC – AD Clinical Trials Consortium
Early/Late-Stage Clinical Trials – PAR-18-877 and 878
ADDP – AD Drug Development PAR 18-174
BPN – Blueprint Neurotherapeutics PAR 18-546
NIA Supported Clinical Trials
Ongoing NIA AD/ADRD and Related Intervention and Prevention Trials (~200)

35 Early-stage Clinical Drug Development (Phase I and Phase II Clinical Trials)

8 Late-stage Clinical Drug Development (Phase II/III and Phase III Clinical Trials)

86 Non-Pharmacological Interventions

8 Clinical Therapy Development for the Neuropsychiatric Symptoms of AD/ADRD

61 Care and Caregiver Interventions

5 Delirium/Post-Operative Cognitive Decline Trials
2018 and 2019 New NIA AD/ADRD Clinical Trials – International Alzheimer’s and Related Dementias Research Portfolio (IADRP)

*(1 Pharm, 2 Non-Pharm)*
Clinical Drug Development
**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

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

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

**Metabolism and Bioenergetics:**
- Insulin Receptor
- Mitochondria

**ApoE4**
- ApoE-antibodies
- Antisense oligonucleotides

**Heat Shock Proteins:**
- HSP 90

**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/Neuroprotection:**
- Calcineurin
- Ryanodine Receptor
- Excitotoxic Amino Acid Transporter
- Somatostatin Receptor subtype-4

**Cell therapies:**
- Neural Stem Cell transplantation

**Cell Death:**
- CDK4/6
- OMA1
Figures represent 28 of 32 funded AD drug development projects between 2006 and 2019

- anti-amyloid therapy
- non amyloid therapy

Alzheimer's Drug Development Program (ADDP)

- anti-amyloid therapy
- non amyloid therapy

HIV/AIDS Hastings CBE (CA)

Gene Therapy (AAV2-BCGF)

Modulator (GM3-776890)

Ohio State University (OH)

Activator (AV-1959)

GABA A and B--Nicotinic Receptors

UC Santa Barbara

Inhibitors (Cdk5)

Gladstone Institute (CA)

Structural Enhancers (ApB4)

UT Houston (TX)

Catalytic Antibodies (Bab-A d5)

AgeneBio Inc (NJ)

Allotopic Modulators (GABA-A d5)

U Penn (PA)

Microtubule Stabilizers (Microtubules)

7. Early-stage Clinical Drug Development (Phase I and II Clinical Trials)

8. Late-stage Clinical Drug Development (Phase II/III and III Clinical Trials)

- a. Amyloid beta
- d. Neurotransmitter Receptors
- f. Inflammation
- j. Metabolism and Bioenergetics
- l. Growth Factors and Hormones
- m. Synaptic Plasticity/Neuroprotection
- o. Circadian Rhythm
Novel Therapeutic Approaches

Non-Amyloid and Tau
Phase 1: NNI-362 – Neuronascent lead candidate - “Neuron Regenerative Therapies”

- Aim to reverse the cognitive deficit in AD patients, by stimulating new neurons and protecting these “nascent” neurons from further neurodegeneration

- In vivo studies demonstrated that NNI-362 significantly increased the number of neurons in a key memory region of the brain, which was associated with the actual reversal of memory impairment in elderly mice

- A similar reversal of both cognitive impairment and neuron formation in the brain, back to wild type or normal animal levels was observed using a well established Down syndrome transgenic mouse model

- Currently in first-in-human phase 1a trial assessing the safety, tolerability and PK in a healthy-volunteers aged 50-72

- In the trial, male and female volunteers will be administered a single dose of NNI-362 orally at one of three ascending doses (SAD). This will be followed by a 14-day daily multiple ascending dose (MAD) test
Phase 1: MW151 – Neuroinflammation

• MW151 is a novel, CNS-penetrant, orally bioavailable, small molecule candidate that selectively suppresses stressor-induced proinflammatory cytokine overproduction

• Ameliorates synaptic damage and cognitive impairment at low doses in diverse animal models where proinflammatory cytokine dysregulation is established as a contributor to disease progression

• Currently in first-in-human phase 1a single ascending dose (SAD) study to determine safety and tolerability, maximum tolerated dose, and pharmacokinetics (PK) in healthy adult volunteers
  • Plasma cytokine levels will be measured to provide baseline data for a future exploratory pharmacodynamic (PD) endpoint in phase 2a clinical trials.

• The SAD will be followed by a phase 1b multiple ascending dose (MAD) study of MW151. This study will determine safety and tolerability, maximum tolerated dose, and PK of MW151 in healthy adult volunteers
  • In addition, a cohort of elderly healthy subjects and exploratory PD inflammatory cytokine endpoints in CSF will be included
LM11A-31 - first in class, small molecule modulator of the P75 Neurotrophin Receptor (growth factor)

The drug may prevent the activation of degenerative processes and protect nerve cells and their connections

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 AD/ADRD early-stage clinical trials program
Phase 2a: LM11A-31 in patients with mild to moderate AD

• 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
Phase 2: VALAD study - Anti-Viral Therapy

- Phase 2 proof of concept trial of valacyclovir in mild Alzheimer’s

- First trial to directly address the long-standing viral etiology hypothesis of AD which posits that viruses, particularly the very common HSV1 and HSV2, may be etiologic or contribute to the pathology of AD

- In patients with mild AD who test positive for serum antibodies to HSV1 or HSV2, the generic valacyclovir will be compared at oral doses of 2 to 4 g per day to matching placebo in the treatment of 130 patients (65 valacyclovir, 65 placebo) in a randomized, double-blind, 78-week Phase 2 trial

- Patients treated with valacyclovir are hypothesized to show smaller decline in cognition and functioning compared to placebo, and, less amyloid and tau accumulation on PET during the trial

- Apolipoprotein E genotype as well as changes in cortical thinning on structural MRI, olfactory identification deficits, and antiviral antibody titers from baseline to 78 weeks, will be evaluated in exploratory analyses

- In patients who agree to lumbar puncture, the degree of CNS penetration of valacyclovir will be assessed as well as AD biomarkers (Aβ42, tau, p-tau)
AGB101 - AgeneBio low-dose formulation levetiracetam - SV2a (synaptic vesicle protein A) antagonist

• Extensive clinical and preclinical data support the hypothesis that neural overactivity is a critical driver of neuropathology leading to neuronal death in early AD and strongly support the hypothesis that hippocampal overactivity is a driver of the spread of tau pathology

• This overactivity is most prominent in patients with clinical MCI and deposited amyloid

• Extensive preclinical data also show that anti-epileptic levetiracetam given in low, but not at the much higher doses used to treat epilepsy, restores hippocampal activity to normal levels and prevents neurodegeneration; other antiepileptic drugs that are not SV2a antagonists do not have this neurobiological effect

• A Phase 2 study measuring hippocampal activity during a pattern separation memory test in patients with aMCI found that AGB101 normalized hippocampal activity and improved performance on this memory test for assessment of hippocampal function
• 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
Non-Pharmacological Interventions
Modalities in NIA’s Non-Pharmacological Clinical Trials Portfolio

- Exercise
- Diet
- Cognitive Training
- Combination
- Technology
- Care Management
2018 and 2019 New NIA AD/ADRD Clinical Trials – International Alzheimer’s and Related Dementias Research Portfolio (IADRP)

Category C - 9. Non-Pharmacological Interventions

- Exercise: 28.57% (8)
- Diet: 21.43% (6)
- Cognitive Training: 14.29% (4)
- Sleep-related: 10.71% (3)
- Neurostimulation: 7.14% (2)
- Other: 3.57% (1)
- Combination therapy: 14.29% (4)

Colors:
- Exercise: Blue
- Diet: Light Blue
- Cognitive Training: Orange
- Sleep-related: Pink
- Neurostimulation: Purple
- Other: Pink
- Combination therapy: Green
Systolic Blood Pressure Intervention Trial (SPRINT) Memory and Cognition in Decreased Hypertension (SPRINT MIND)

Success Story!

NIA, NINDS, NHLBI, NIDDK
• Participants were adults 50 years and older at high risk for cardiovascular disease

• SPRINT trial ended early after 3.3 years of treatment when the major beneficial effects of intensive blood pressure management on mortality and cardiovascular disease were discovered:

  • intensive blood pressure control, i.e., a systolic blood pressure target of less than 120 mmHg (<120 mmHg), compared to a standard target of less than 140 mmHg (<140 mmHg), reduced cardiovascular events and overall mortality

• Between November 2010 and March 2013 more than 9,300 participants were randomized to the two target groups with nearly 4,700 in each group

• SPRINT MIND aimed to address whether intensive blood pressure control would also reduce the risk of developing dementia and cognitive impairment - assessment for development of dementia and MCI continued for the full planned 5 years

• Participants were classified into one of three categories: no cognitive impairment, MCI, or probable dementia
The systolic blood pressure (SBP) target was <120 mmHg in the Intensive Treatment group, and <140 mmHg in the Standard Treatment group. Trial phase includes follow-up through the decision to stop the SPRINT intervention on 8/20/2015, while cohort phase denotes visits that occurred after that date. Points indicate means with error bars denoting 95% Confidence Intervals.
Primary results found no statistically significant difference in the proportion of participants that were diagnosed with dementia.

Secondary results suggested that the intensive treatment reduced the risk of MCI and the combined risk of MCI and dementia.

Because the study intervention was stopped early, participants were treated for a shorter period than originally planned. The investigators concluded that the shorter time and the unexpected fewer cases of dementia may have made it difficult to determine the role of intensive blood pressure control on dementia.
• Testing whether supervised aerobic exercise (YMCA) can slow cognitive decline, slow brain atrophy, or delay onset of Alzheimer’s dementia in MCI

• Recruiting sedentary older volunteers (N = 300, ages 65 – 89) with MCI to participate in a year-long program in which one group will do high-intensity aerobic exercise and the other stretching
Study Design

Medical & Cognitive Screening

Aerobic vs. Stretching/Balance Exercise
- Supervised
- Unsupervised

0
- Walk Test
- Brain s/fMRI
- CSF Collection

6
- Blood Cog Testing
- Actigraphy

Month 12
- Walk Test
- Brain s/fMRI
- CSF Collection

Month 18
- Blood Cog Testing
- Walk Test
- Actigraphy

Slide Courtesy of Laura Baker
Intervention

Aerobic Exercise
4 times per week,
70-85% maximum heart rate

Stretching & Balance
4 times per week,
<35% maximum heart rate

Slide Courtesy of Laura Baker
Enrollment

N = 300 Enrollment Goal across 14 sites
N = 239 Current Enrollment:
  • 20% underrepresented

Adherence

78% Aerobic Trainer-Supervised Sessions Completed
79% Stretching/Balance Trainer-Supervised Sessions Completed

Attrition

10%
MIND Study

- Testing the effects of 3-year intervention of MIND diet (hybrid of the Mediterranean and DASH diets) on:
  
  - Cognitive decline, brain imaging, blood biomarkers for dementia, inflammation & oxidation, other conditions (diabetes, HTN, BMI, cholesterol, depression, chronic psychological distress)

- 2 Groups (MIND diet + calorie restriction or Usual diet + calorie restriction)

- 600 older adults (ages 65 – 84) without cognitive impairment, overweight or obese (BMI≥25), suboptimal diet
Interventions for Neuropsychiatric Symptoms
<table>
<thead>
<tr>
<th>Grant Number</th>
<th>Trial Name</th>
<th>Principal Investigator/ Institution</th>
<th>Intervention</th>
<th>Population</th>
<th>Anticipated Completion Date</th>
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<tbody>
<tr>
<td>R01 AG047146</td>
<td>Treatment of psychosis and agitation in Alzheimer’s disease</td>
<td>Davangere Devanand, Columbia University</td>
<td>Lithium</td>
<td>People with Alzheimer’s disease and agitation/aggression</td>
<td>2020</td>
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<td>R01 AG046543</td>
<td>Apathy in Alzheimer’s Disease Methylphenidate Trial II (ADMET II)</td>
<td>Jacobo Mintzer, Krista Lancot, Nathan Herrmann, Paul Rosenberg, Roberta Scherer, Medical University of South Carolina</td>
<td>Methylphenidate</td>
<td>People with Alzheimer’s disease and apathy</td>
<td>2020</td>
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<td>R01 AG052510</td>
<td>Escitalopram for Agitation in Alzheimer’s Disease</td>
<td>Constantine Lyketsos, Johns Hopkins University Anton Porsteinsson, University of Rochester</td>
<td>Escitalopram</td>
<td>People with Alzheimer’s disease and agitation</td>
<td>2022</td>
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<td>R01 AG050515</td>
<td>Pilot Trial of Dronabinol Adjunctive Treatment of Agitation in Alzheimer’s Disease</td>
<td>Paul Rosenberg, Johns Hopkins University Brent Forester, McLean Hospital</td>
<td>Dronabinol</td>
<td>People with Alzheimer’s disease and agitation</td>
<td>2022</td>
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<tr>
<td>U19 AG010483</td>
<td>PEACE-AD (Prazosin for Agitation In Alzheimer's Disease)*</td>
<td>Elaine Peskind and Murray Raskind, University of Washington</td>
<td>Prazosin</td>
<td>People with Alzheimer’s disease and severe agitation</td>
<td>2021</td>
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**Pharmacological**

**Non-Pharmacological**

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<th>Grant Number</th>
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<th>Intervention</th>
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<td>R01 AG041781</td>
<td>Reducing Agitation in Dementia Patients at Home: The Customized Activity Trail</td>
<td>Laura Gitlin, Johns Hopkins University</td>
<td>Patient customized activity</td>
<td>People with dementia and a family caregiver</td>
<td>2019</td>
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<tr>
<td>R01 AG050514</td>
<td>Problem Adaption Therapy for Mild Cognitive Impairment with Depression</td>
<td>Dimitris Kiosses Cornell University Paul Rosenberg, Johns Hopkins University</td>
<td>Psychosocial therapy</td>
<td>People with Mild Cognitive Impairment and depression</td>
<td>2022</td>
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