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

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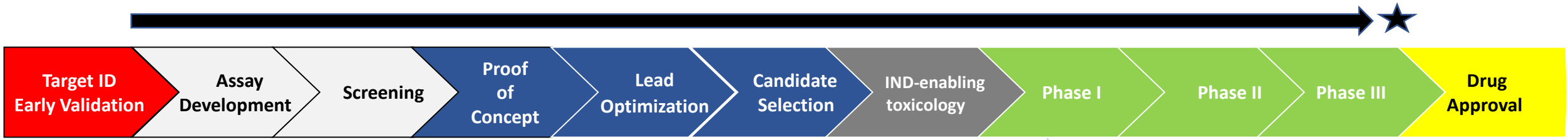
A Pipeline of NIA and Trans-NIH Translational Research Funding Initiatives (R21, R01, U01, R43/R44)



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

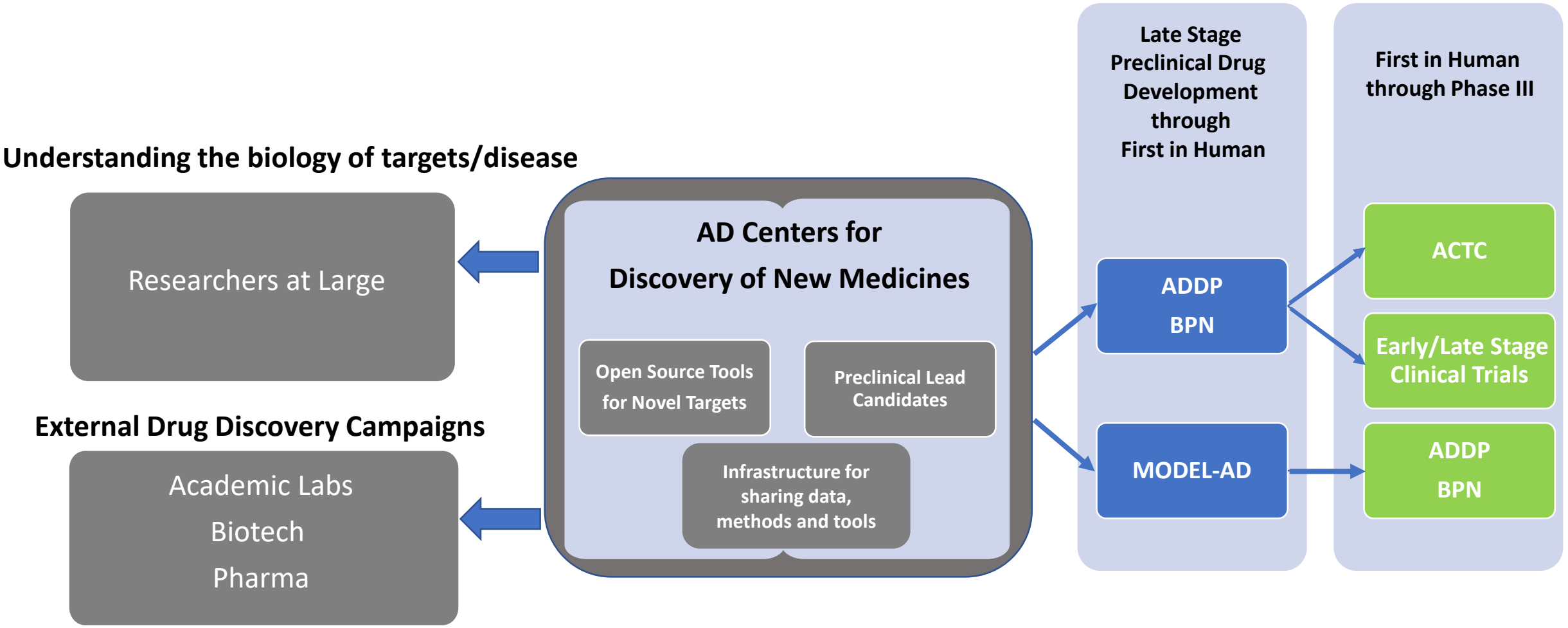
AD Translational Centers for New Medicines*

MODEL-AD
AlzPED

ACTC
ADCs
ADNI
AMP-AD Biomarkers
ABC-DS

ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE THERAPY DEVELOPMENT

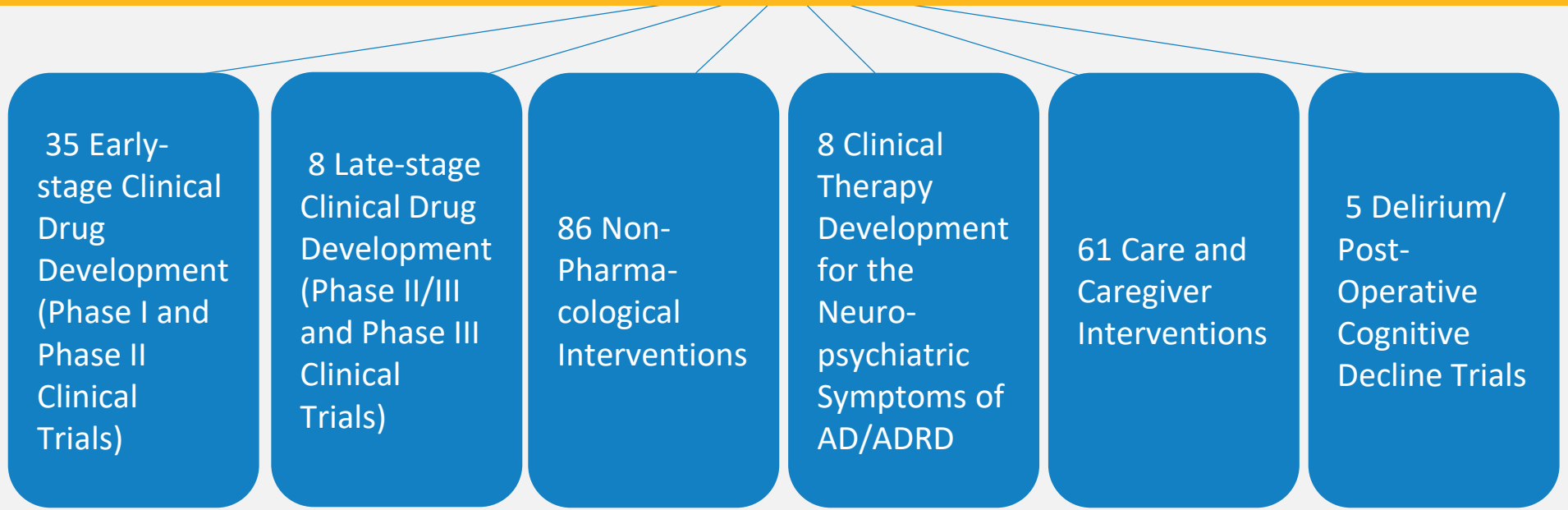
*just launched Oct 2019



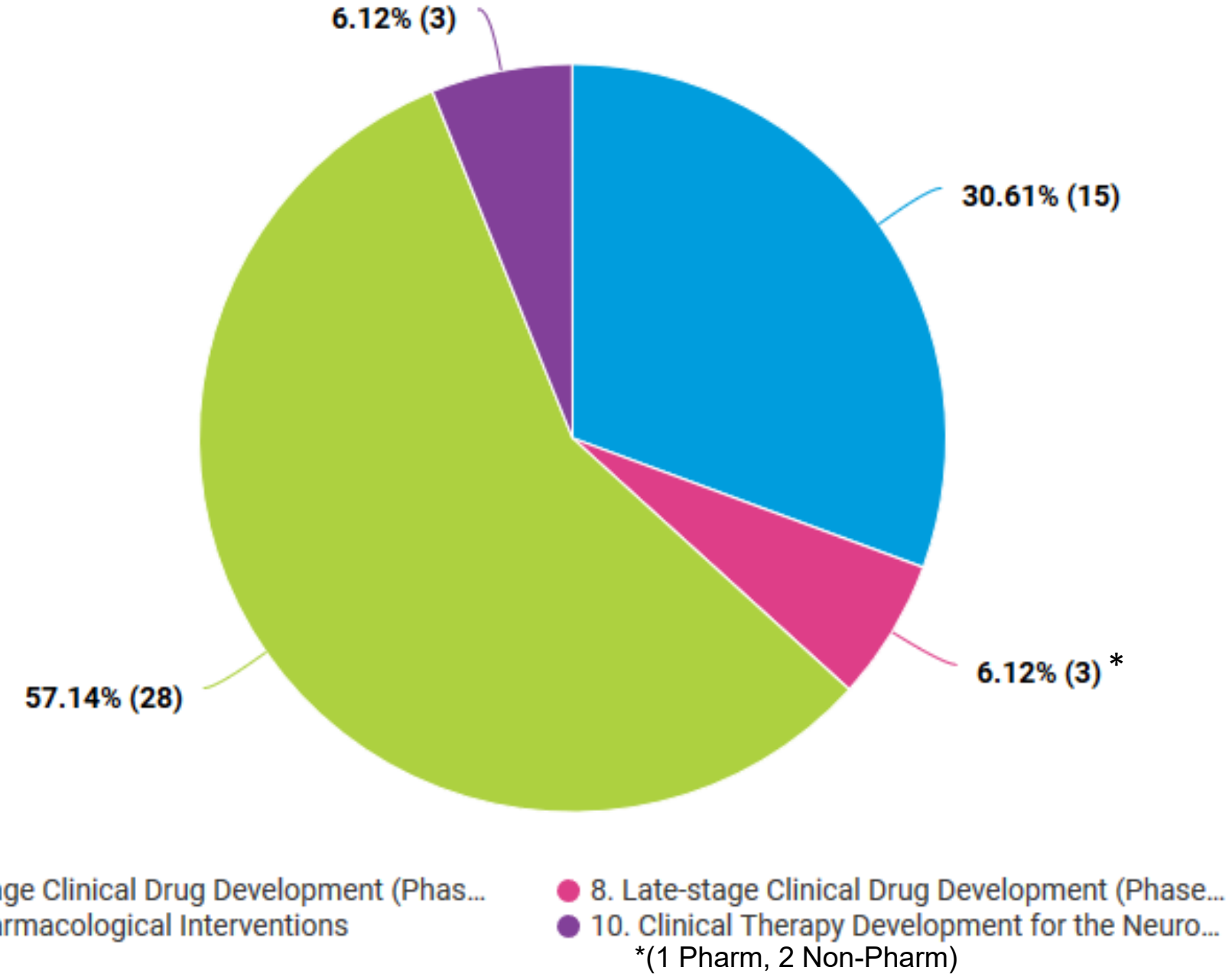
ACTC – AD Clinical Trials Consortium
Early/Late-Stage Clinical Trials – PAR-18-877 and 878
ADDP – AD Drug Development PAR 18-174
BPN – Blueprint Neurotherapeutics PAR 18-546

NIA Supported Clinical Trials

Ongoing NIA AD/ADRD and Related Intervention and Prevention Trials (~200)



2018 and 2019 New NIA AD/ADRD Clinical Trials – International Alzheimer's and Related Dementias Research Portfolio (IADRP)



Clinical Drug Development

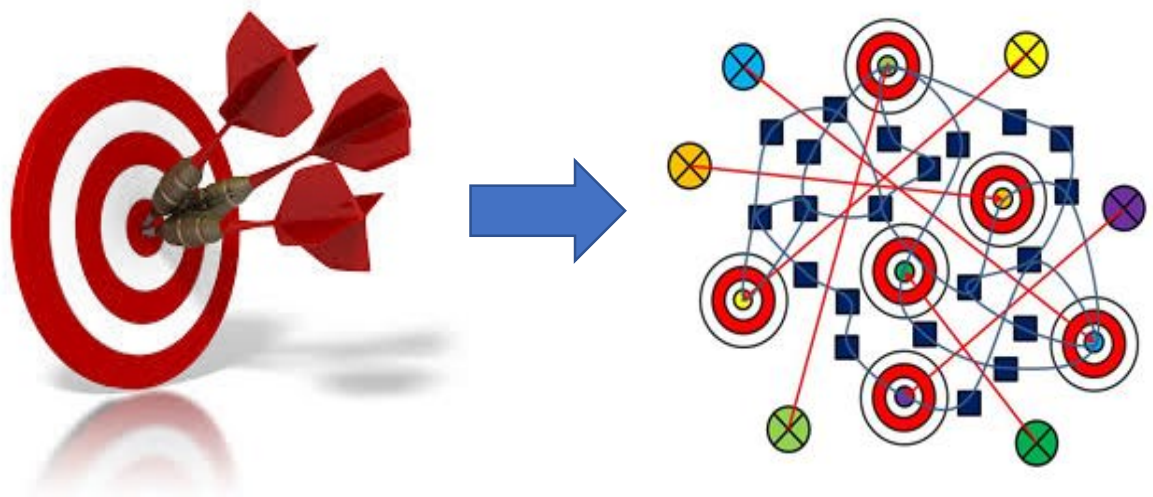
NIA Alzheimer's Translational Research Program – *since 2006*
Diversifying the Therapeutic Pipeline

Next-gen anti-Aβ therapeutics:
Sigma receptor – anti Aβ oligomer therapy
Gamma secretase modulators
Anti-Aβ oligomer immunotherapy
*A*β 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

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

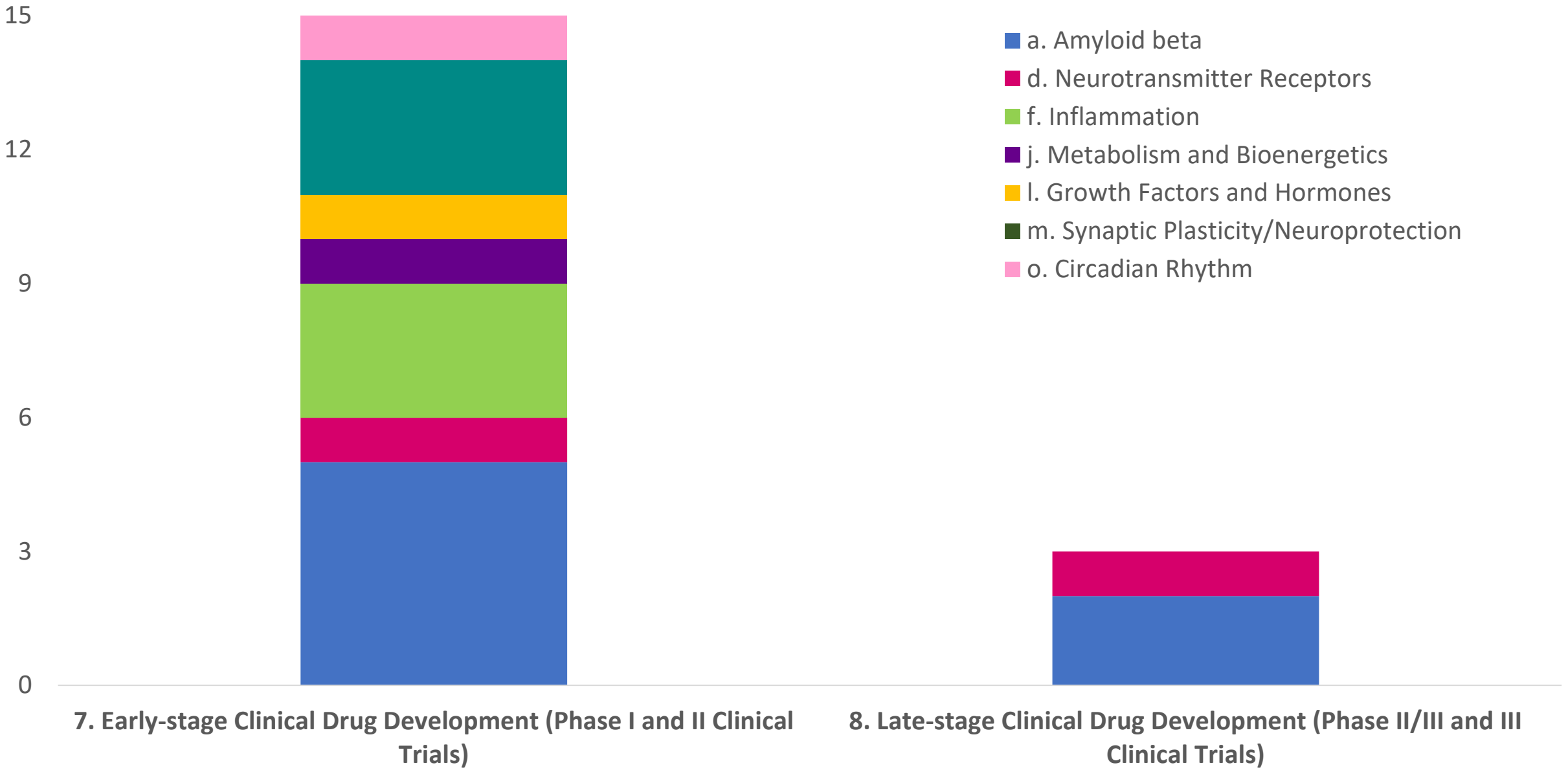
Institution	Therapeutic Agent	Therapeutic Target	Drug Discovery	Preclinical Drug Development	Phase 1 Clinical Trial	Phase 2 Clinical Trial	Phase 3 Clinical Trial
Stanford U Pharmatropix (CA)	Ligand (LM11A-31)	p75NTR Neurotrophin receptor					
Cognition Therapeutics (PA)	Inhibitor (CT1812/Elayta)	Sigma-2 receptor Aβ Oligomers					
University of Arizona (AZ)	Allopregnanolone	Neurogenesis					
University of Kentucky (KY)	Inhibitor (MW151)	Neuroinflammation					
SL Associates (IL)	Inhibitor (MW150)	p38 MAPK					
Sloan-Kettering (NY) Samus Therapeutics (MA)	Inhibitor (PU-AD)	HSP90 Proteostasis					
Neuronascent, Inc. (MD)	Modulator (NNI-362)	p70S6 kinase Neurogenesis					
Institute for Molecular Medicine (CA)	DNA vaccine (AV-1959)	Aβ immunotherapy					
UCSF (CA)	Gene Therapy (AAV2-BDNF)	TrkB BDNF Receptor					
UCSD (CA)	Modulator (GSM-776890)	Gamma secretase					
Ohio State University (OH)	Activator	Excitotoxic Amino Acid Transporter					
Accumen Pharmaceuticals, Inc. (IN)	Aβ Oligomer Antibody (ACU193)	Aβ Oligomers					
University of Michigan (MI)	Human Neural Stem Cells	Neurogenesis					
University of Pennsylvania (PA)	Triazolopyrimidines	Microtubules					
Institute for Molecular Medicine (CA)	Tau Immunotherapy (AV-1980R/A)	Tau					

Institution	Therapeutic Agent	Therapeutic Target	Drug Discovery	Preclinical Drug Development	Phase 1 Clinical Trial	Phase 2 Clinical Trial	Phase 3 Clinical Trial
Columbia University (NY)	Inhibitors (E64 and BDA-410)	Calpain					
Emory University (GA)	Inhibitor	EP2 receptor Neuroinflamation					
Yale University (CT)	BMS-984923	Glutamate Receptor					
Columbia University (NY)	Inhibitors	Calpain					
UCLA (CA)	Curcumin	Multi Target					
U. Pitt (PA)	Aβ Binding Agents	β–amyloid					
Mt Sinai Medical Center (NY)	Carvedilol	beta Adrenergic Receptors					
UCI (CA)	Modulators	GABA-A and α–Nicotinic Receptors					
UC Santa Barbara	Inhibitors	Cdk5					
Gladstone Institute (CA)	Structural Enhancers	ApoE4					
UT Houston (TX)	Catalytic Antibodies	β–amyloid					
AgeneBio Inc (NJ)	Allosteric Modulators	GABA-A α5					
U Penn (PA)	Microtubule Stabilizers	Microtubules					

Figures represent 28 of 32 funded AD drug development projects between 2006 and 2019

- anti-amyloid therapy
- non amyloid therapy

IADRP - Category C. Translational Research and Clinical Interventions – 7. Early-stage and 8. Late-stage Clinical Drug Development – Therapeutic Targets - New NIA Funded Projects – 2018 and 2019



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

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

NeurotrophiX

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 (Aß, 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 (Aß42, tau, p-tau)

AG055422

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

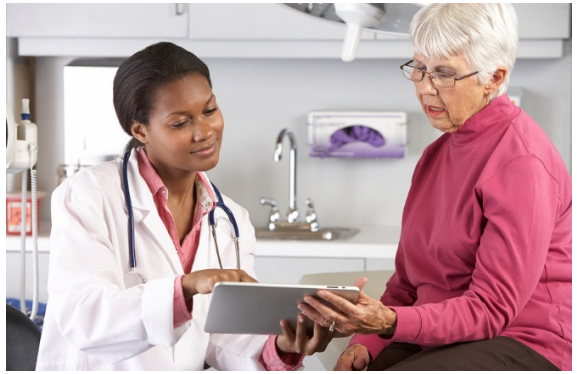
HOPE4MCI

- 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



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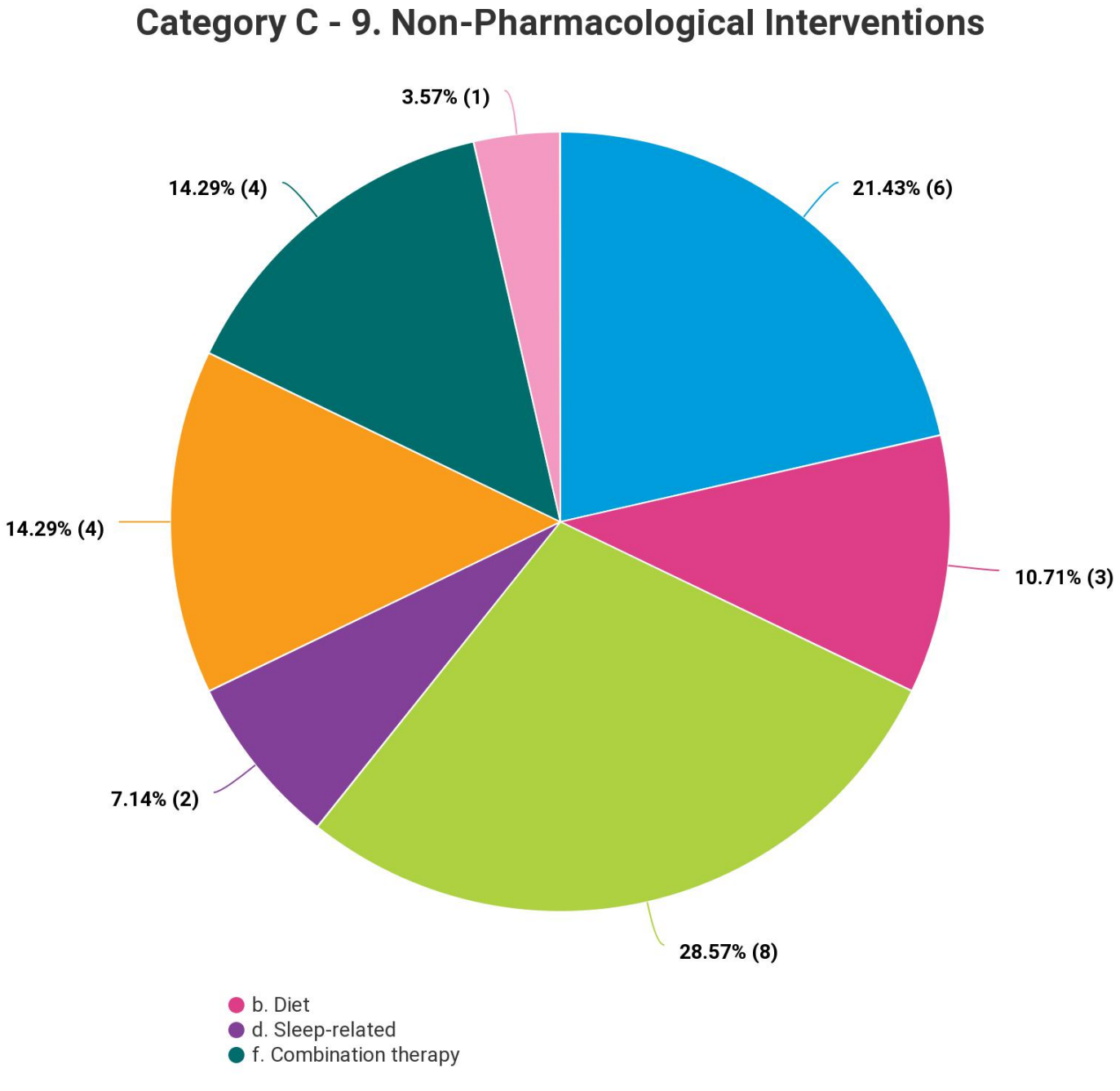


Systolic Blood Pressure Intervention Trial (SPRINT) Memory and Cognition in Decreased Hypertension (SPRINT MIND)

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

eFigure 3. Systolic Blood Pressure in the Two Treatment Groups Over the Course of Follow-up

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.

JAMA. 2019;321(6):553-561. doi:10.1001/jama.2018.21442

Table 2. Incidence of Probable Dementia and Mild Cognitive Impairment by Treatment Group

Outcomes	Treatment Group: Intensive — No. With Outcome/Person-Years	Intensive — Cases per 1000 Person-Years	Standard — No. With Outcome/Person-Years	Standard — Cases per 1000 Person-Years	Hazard Ratio (95% CI)[a]	*P* Value
Probable dementia	149/20 569	7.2	176/20 378	8.6	0.83 (0.67-1.04)	.10
Mild cognitive impairment[b]	287/19 690	14.6	353/19 281	18.3	0.81 (0.69-0.95)	.007
Composite of mild cognitive impairment or probable dementia	402/19 873	20.2	469/19 488	24.1	0.85 (0.74-0.97)	.01

[a] Intensive treatment group vs standard treatment group based on Cox proportional hazards regression.

[b] Participants adjudicated as having probable dementia at the first follow-up visit (year 2) do not contribute to the analyses of mild cognitive impairment.

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

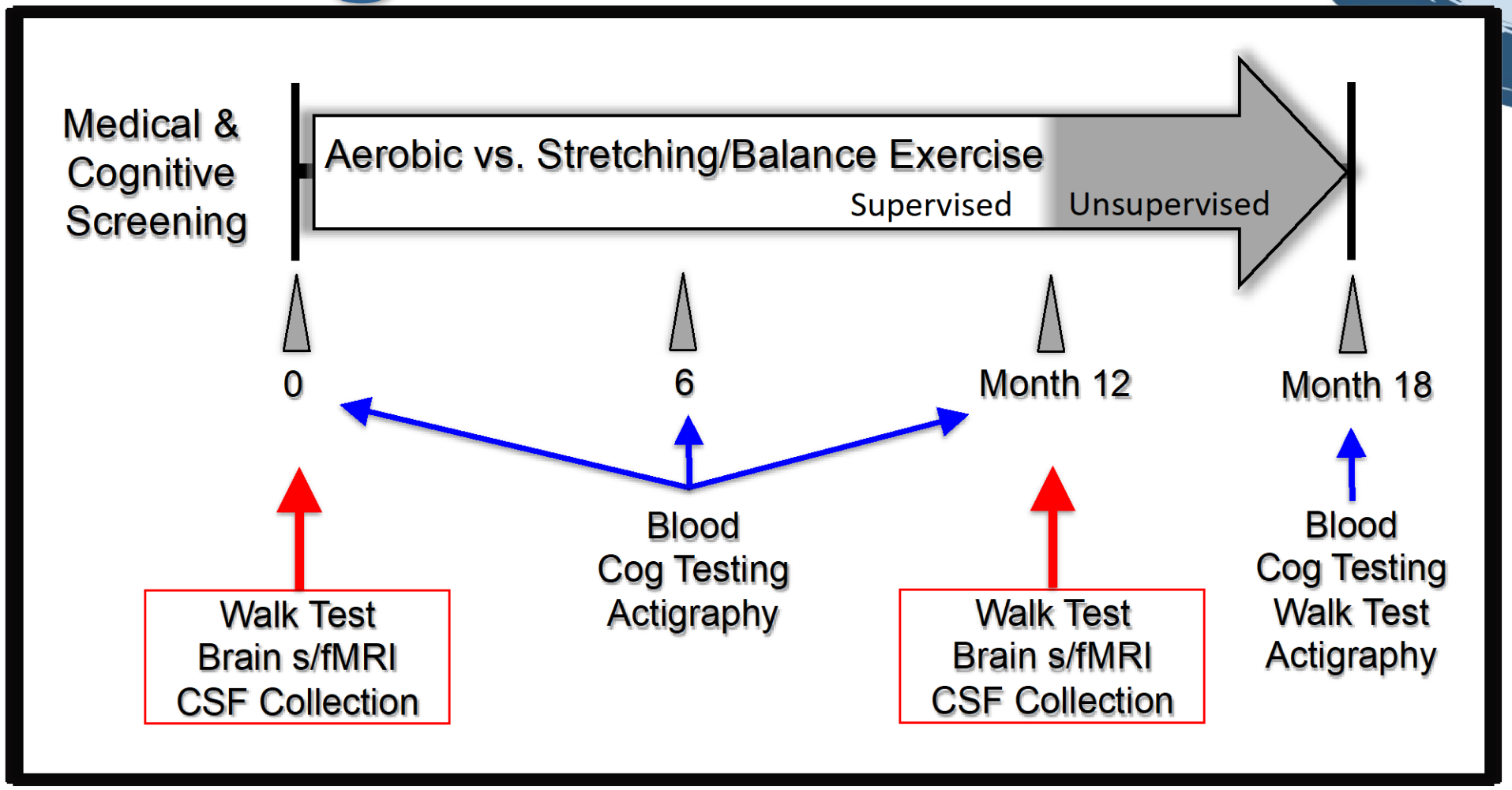
- Recruiting sedentary older volunteers (N = 300, ages 65 – 89) with MCI to participate in a year-long program in which one group will do high-intensity aerobic exercise and the other stretching

AG010483

Study Design

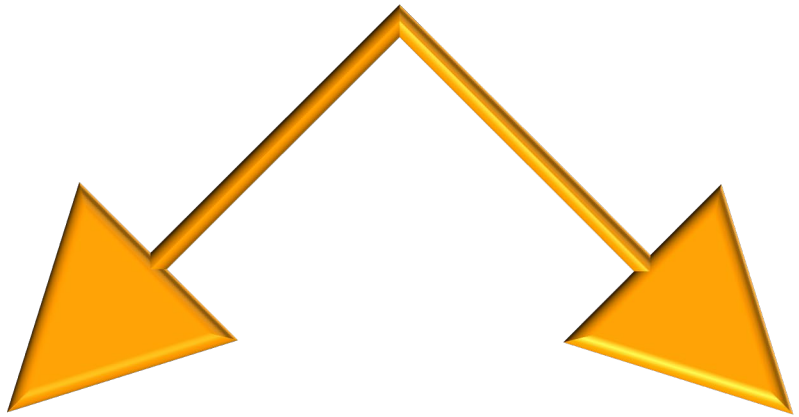
ALZHEIMER'S DISEASE COOPERATIVE STUDY

Wake Forest® School of Medicine



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

CLINICS

YMCA

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%

Slide Courtesy of Laura Baker

The MIND Diet Intervention to Prevent Alzheimer's Disease

MIND Study

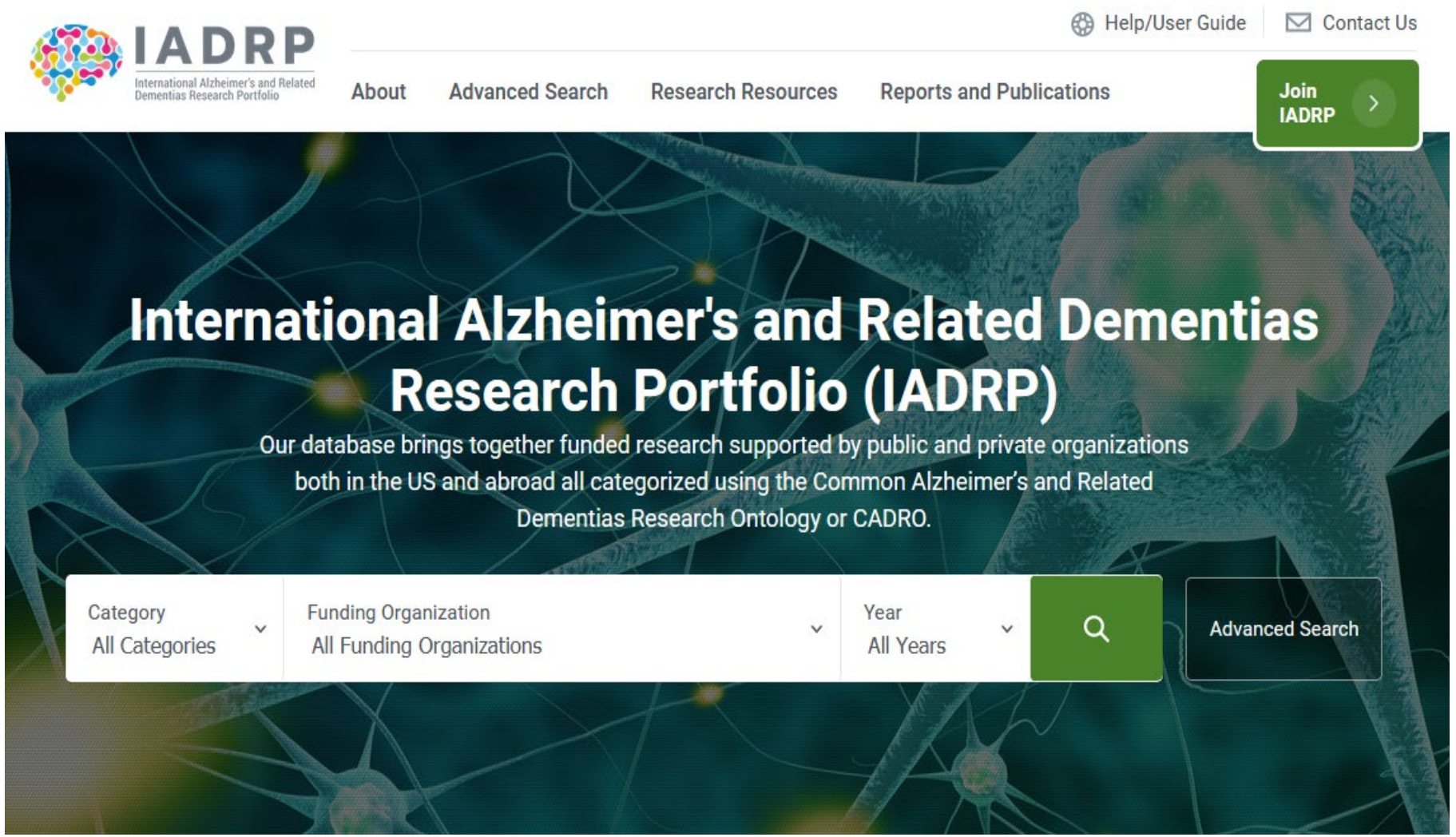
- Testing the effects of 3-year intervention of MIND diet (hybrid of the Mediterranean and DASH diets) on:
  - Cognitive decline, brain imaging, blood biomarkers for dementia, inflammation & oxidation, other conditions (diabetes, HTN, BMI, cholesterol, depression, chronic psychological distress)
- 2 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

AG052583, Slide courtesy of Martha Clare Morris with modifications, NIA Workshop: *Understanding The Role of the Microbiome in Aging and Age-related Disorders- Implications For Disease Treatment and Prevention,* Nov 2017

Interventions for Neuropsychiatric Symptoms

Grant Number	Trial Name	Principal Investigator/ Institution	Intervention	Population	Anticipated Completion Date
Pharmacological					
R01 AG047146	Treatment of psychosis and agitation in Alzheimer's disease	Davangere Devanand, Columbia University	Lithium	People with Alzheimer's disease and agitation/aggression	2020
R01 AG046543	Apathy in Alzheimer's Disease Methylphenidate Trial II (ADMET II)	Jacobo Mintzer, Krista Lanctot, Nathan Herrmann, Paul Rosenberg, Roberta Scherer, Medical University of South Carolina	Methylphenidate	People with Alzheimer's disease and apathy	2020
R01 AG052510	Escitalopram for Agitation in Alzheimer's Disease	Constantine Lyketsos, Johns Hopkins University Anton Porsteinsson, University of Rochester	Escitalopram	People with Alzheimer's disease and agitation	2022
R01 AG050515	Pilot Trial of Dronabinol Adjunctive Treatment of Agitation in Alzheimer's Disease	Paul Rosenberg, Johns Hopkins University Brent Forester, McLean Hospital	Dronabinol	People with Alzheimer's disease and agitation	2022
U19 AG010483	PEACE-AD (Prazosin for Agitation In Alzheimer's Disease)*	Elaine Peskind and Murray Raskind, University of Washington	Prazosin	People with Alzheimer's disease and severe agitation	2021
Non-Pharmacological					
R01 AG041781	Reducing Agitation in Dementia Patients at Home: The Customized Activity Trail	Laura Gitlin, Johns Hopkins University	Patient customized activity	People with dementia and a family caregiver	2019
R01 AG050514	Problem Adaption Therapy for Mild Cognitive Impairment with Depression	Dimitris Kiosses Cornell University Paul Rosenberg, Johns Hopkins University	Psychosocial therapy	People with Mild Cognitive Impairment and depression	2022

Thank You!



https://iadrp.nia.nih.gov/