OVERVIEW OF THE CLINICAL TRIAL PIPELINE FOR AD

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Advisory Meeting on Alzheimer's Research, Care, and Services, January 26, 2018

NIH National Institute on Aging

The Continuum of Alzheimer's Disease

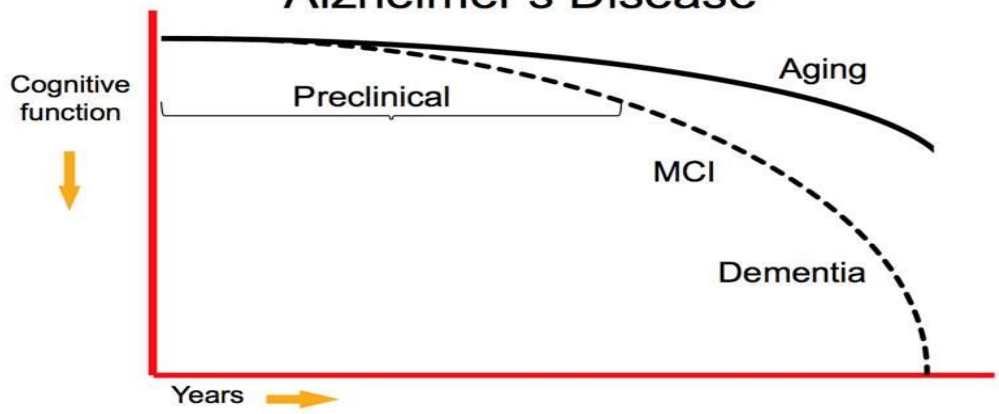
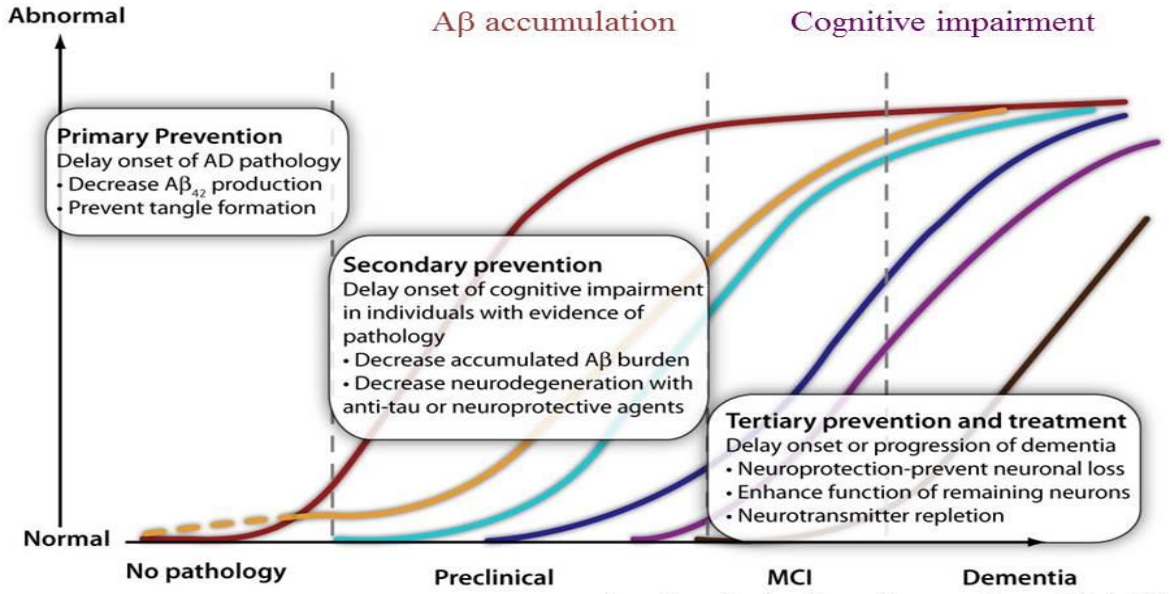


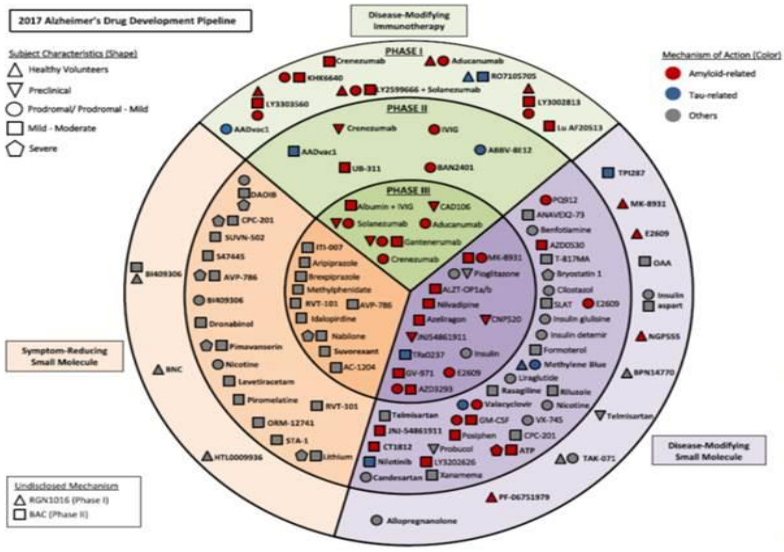
Fig. 1 The stage of preclinical AD precedes mild cognitive impairment (MCI) and encompasses the spectrum of presymptomatic autosomal dominant mutation carriers, asymptomatic biomarker-positive older individuals at risk for progression to MCI due to AD and AD dementia, as well as biomarker-positive ndividuals who have demonstrated subtle decline from their own baseline that exceeds that expected in typical aging, but would not yet meet criteria for MCI.
RA Sperling et al http://download.journals.elsevierhealth.com/pdfs/journals/1552-5260/PIIS1552526011000999.pdf

Testing the Right Target and Right Drug at the Right Stage of Alzheimer's Disease



Sperling, Jack, Aisen *Science Trans Med* 2011

Drugs in Clinical Development for AD 2017



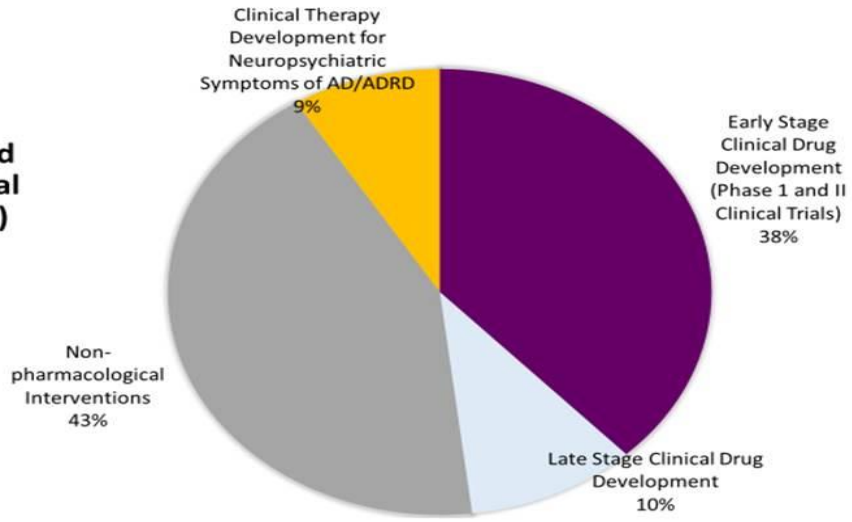
- 105 agents currently in development pipeline:
  - 25 agents are in 29 trials in phase I
  - 52 agents are in 68 trials in phase II
  - 28 agents are in 42 trials in phase III
- 70% are disease-modifying therapies
- 14 % are for cognitive symptoms
- 13% are for NPS

Cummings et al. *Alzheimer's & Dementia: TRCI* 2017

CURRENT NIA-SUPPORTED CLINICAL INTERVENTIONS FOR AD/ADRD

Current NIA AD/ADRD Clinical Trials

Pharmacological and Non-Pharmacological Clinical Trials (n=79)



Pharmacological and Non-Pharmacological AD Clinical Trials

Therapeutic Target	Number of Trials
Early Stage Clinical Drug Development (Phase 1 and II Clinical Trials)	30
Late Stage Clinical Drug Development (Phase II/III and III Clinical Trials	8
Non-pharmacological Interventions	34
Clinical Therapy Development for Neuropsychiatric Symptoms of AD/ADRD	7
Total	79

NIA AD Drug Trial Targets

Amyloid
ApoE, Lipids, and Lipoproteins
Neurotransmitter Receptors
Metabolism and Bioenergetics
Vasculature
Growth Factors and Hormones
Oxidatative Stress
Multi-target

Anti-Amyloid treatment in Asymptomatic AD (A4 Trial)

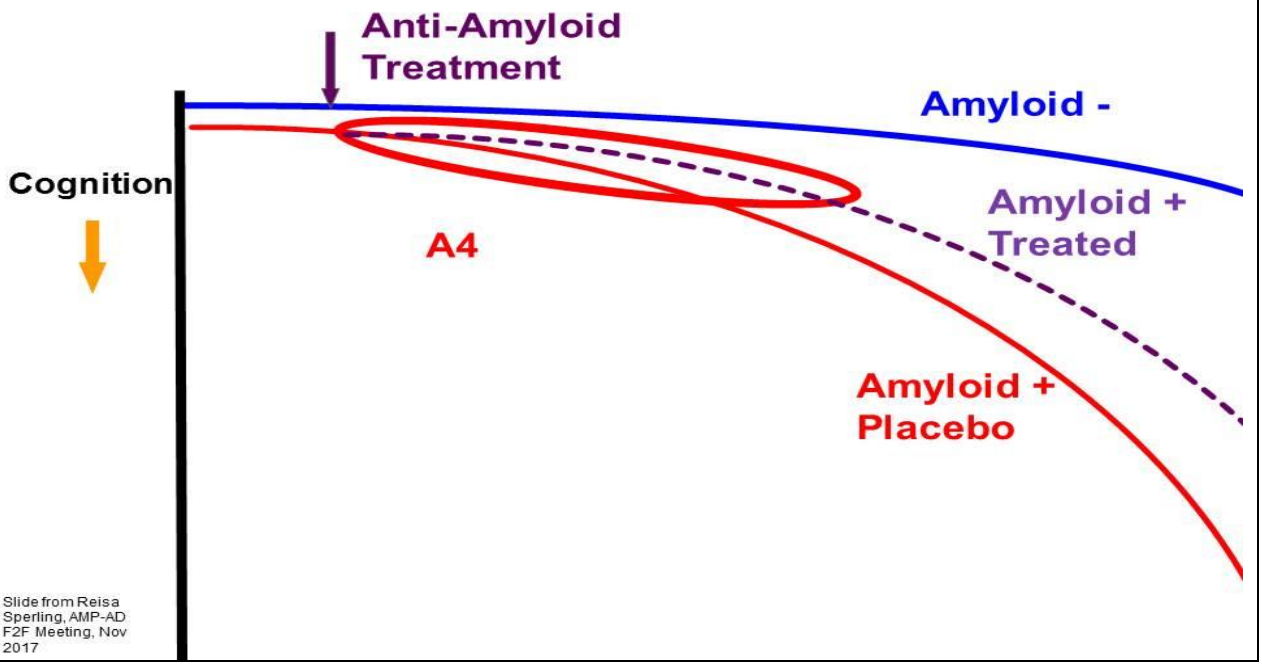
http://a4study.org/

A4 Trial Synopsis

- Secondary prevention trial in clinically normal older individuals (age 65-85) who have evidence of amyloid-β pathology on screening PET imaging
- Randomized, double-blind, placebo-controlled Phase 3 trial solanezumab (monoclonal Aβ antibody) vs. placebo for 240 weeks
- Trial N=1000+ (N=500+ per treatment arm)
- Observational cohort of Aβ negative "screen fails" – LEARN study (N=500; Alzheimer's Association)
- Ethics component – Disclosure of amyloid status
- Tau imaging added as part of AMP-AD
- Enrollment complete - December 15, 2017
- ~7,000 participants screened

The A4 Study
Now is the time...

The A4 Study



Slide from Reisa Sperling, AMP-AD F2F Meeting, Nov 2017

A4 Trial

- To determine whether decreasing Aβ burden will slow the rate of cognitive decline in clinically normal older Aβ+ individuals at risk for progression to MCI and AD dementia
- Test the hypothesis that altering "upstream" amyloid accumulation will impact "downstream" neurodegeneration and cognitive decline

*

The A4 Study
Now is the time...

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

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 AD Pilot Clinical Trials Program

Phase 2a of 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 40 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.
- Successful completion will provide a dose and end-point statistical and power basis for the design and execution of full phase 2b/3 testing

Non-Pharmacological Interventions

- Exercise
- Diet
- Cognitive Training
- Combination
- Technology
- Care Management

EXERT

EXERT Study

- 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.
- Cognitive testing, CSF biomarkers and MRI results will provide critical data on the efficacy of aerobic exercise on improving cognition and Alzheimer's-related pathology.

EXERT

mind

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 randomly older adults (ages 65 – 84) without cognitive impairment, overweight or obese (BMI≥25), suboptimal diet

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

Neuropsychiatric Symptoms of AD/ADRD Clinical Trials

	Number of Trials
Pharmacological	5
Non-Pharmacological	2
Total	7

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

PEACE-AD (Prazosin for Agitation In Alzheimer's Disease, U19AG010483)

- Phase IIb multicenter, 12 week, randomized, double-blind, placebo controlled trial evaluating the efficacy and safety of prazosin in 186 Alzheimer's disease (AD) participants with disruptive agitation in long-term care (LTC)
- Prazosin is an anti-hypertensive, generically available alpha-1 adrenoreceptor (AR) antagonist that crosses the blood brain barrier and blocks CNS alpha-1 AR activation when administered orally
- In a placebo-controlled pilot trial in predominantly LTC-residing AD patients, prazosin was superior to placebo for disruptive agitation
- Data from AD clinical and postmortem brain tissue studies suggest that noradrenergic stimulation via the CNS alpha-1 AR contributes to the pathophysiology of agitation in AD

CLINICAL TRIALS INFRASTRUCTURE

ALZHEIMER'S CLINICAL TRIALS CONSORTIUM (ACTC)

NEW AD CLINICAL TRIALS INFRASTRUCTURE: ALZHEIMER'S CLINICAL TRIALS CONSORTIUM (ACTC) (U24)*

RFA-AG-17-005:
http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-17-005.html

*Awarded December 2017: U24AG057437

PIs: **Paul S. Aisen, M.D.**, Alzheimer's Therapeutic Research Institute (ATRI), San Diego; **Reisa A. Sperling, M.D.**, Brigham and Women's Hospital and Massachusetts General Hospital, Boston; **Ronald C. Petersen, M.D.**, Ph.D., Mayo Clinic, Rochester, Minnesota

Alzheimer's Clinical Trials Consortium (ACTC) (U24)

- Establish an Alzheimer's disease Clinical Trials Consortium (ACTC) that will run trials focused on interventions that may prevent, delay, or treat the symptoms of Alzheimer's disease (AD) and other age-related dementias
- Will include multiple clinical trials sites with dedicated support and trial coordination and management infrastructure
- A separate Funding Opportunity Announcement (FOA) will solicit applications for clinical trials to be managed and supported by the ACTC*

*PAR-17-513

Alzheimer's Clinical Trials Consortium (ACTC) (U24) Continued

- Conduct clinical trials (Phase I to III) of promising **pharmacological and non-pharmacological interventions** for **cognitive and neuropsychiatric symptoms** in individuals with **AD and other age-related dementias** across the spectrum from pre-symptomatic to more severe stages of disease
- Provide a state-of-the-art clinical trial infrastructure to facilitate rapid development and implementation of protocols, including a centralized Institutional Review Board (IRB)
- Provide leadership in innovative trial design methods, outcomes and analyses as well as recruitment strategies, particularly in diverse populations; broad sharing of procedures and methods

Alzheimer's Clinical Trials Consortium (ACTC) Clinical Trials PAR-18-513, https://grants.nih.gov/grants/guide/pa-files/PAR-18-513.html

- Utilizing the ACTC, the goal of this FOA is to invite research grant applications that provide clinical testing (Phases I-III) of promising pharmacological and/or non-pharmacological interventions for cognitive and neuropsychiatric symptoms in individuals with AD or other aging-related dementias across the spectrum from pre-symptomatic to more severe stages of disease
- Clinical trials funded from this FOA will be implemented through ACTC; A cooperative venture between the applicant, the NIA, and the ACTC network; NIA and the ACTC leadership will provide guidance to potential applicants
- Collect blood and other biosamples for future genomic and other 'omic' analyses aimed at interrogating treatment responsiveness and examining predictors of decline and progression

ACTC Trials Data Sharing

- Data sharing will be achieved through the ACTC resources. Sharing of clinical trial data and biosamples is expected at the time of publication of the primary results or within 9 months of database lock, whichever comes first
- Additionally, late-stage prevention trials are expected to make screening/pre-randomization baseline data available to the scientific community within 12 months of enrollment completion as outlined in the Collaboration for Alzheimer's Prevention data and sample sharing principles. Moreover, emerging data from ongoing late-stage prevention trials should be made available as soon as possible without compromising trial integrity

OTHER NIA CLINICAL TRIAL FUNDING MECHANISMS

Alzheimer's Drug-Development Program (U01)
PAR-15-174, http://grants.nih.gov/grants/guide/pa-files/PAR-15-174.html

- The overarching goal of the ADDP is the development of a broad range of therapeutic agents for AD including small molecules, natural products, and biologics, which broadly include therapeutic modalities such as peptides, proteins, oligonucleotides, gene and cell therapies.
- The program is not designed to support research on basic mechanisms of disease, development of biomarkers, devices, non-pharmacological interventions, repurposed drugs and combination therapies or activities such as high throughput screening.
- Projects can enter the ADDP either at the:
  - **Early Stage** to optimize the agent's potency, drug-like properties, specificity, pharmacological properties, ADMET properties and undergo Investigational New Drug (IND)-enabling safety toxicology, or
  - **Late Stage**, to advance development candidates through (IND)-enabling toxicology studies and initial Phase I clinical testing.

Pilot Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01)

https://grants.nih.gov/grants/guide/pa-files/PAR-18-175.html

- To enable the clinical testing (Phase I and II) of promising pharmacological and non-pharmacological interventions for:
  - cognitive and neuropsychiatric symptoms
  - in individuals with AD/ADRD across the spectrum from pre-symptomatic to more severe stages of disease and
  - in individuals with age-related cognitive decline
- As well as to stimulate studies to enhance trial design and methods

Pilot Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01) Continued

Including but not limited to:

- Studies to refine the intervention strategy
- Studies to evaluate the safety and/or efficacy of the intervention(s)
- Studies that elucidate mechanism of action
- Studies to define and refine the target population and ensure adequate enrollment, protocol adherence and subject retention
- Studies that address heterogeneity of response
- Studies to establish/validate trial outcome measures

Phase III Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline

https://grants.nih.gov/grants/guide/pa-files/PAR-18-028.html

- To enable the testing of promising pharmacological and non-pharmacological interventions for:
  - cognitive and neuropsychiatric symptoms
  - in individuals with AD/ADRD across the spectrum from pre-symptomatic to more severe stages of disease and
  - in individuals with age-related cognitive decline
  - using a combination of biomarkers (fluid and imaging), cognitive, and functional measures as outcomes.
  - may include trials testing combinations of interventions

Advancing Research on Alzheimer's Disease (AD) and Alzheimer's-Disease-Related Dementias

https://grants.nih.gov/grants/guide/pa-files/PAS-17-064.html

- Applications to NIA's Small Business Innovation Research (SBIR) program to conduct research leading to the development of innovative products and/or services that may advance progress in **preventing and treating Alzheimer's disease (AD) and Alzheimer's-disease-related dementias (ADRD) and/or caring for and treating AD/ADRD patients.**

COLLABORATION FOR ALZHEIMER'S PREVENTION (CAP)

Collaboration for Alzheimer's Prevention

- A convening, harmonizing and consensus-building initiative to help stakeholders advance AD prevention research with rigor, care and maximal impact
- Founding Members: representatives from ADCS A4, API, DIAN-TU, Alzheimer's Association, FDA , National Institute on Aging (NIA), Fidelity Biosciences Research Initiative

Reiman, E. M. *et al.* (2015) CAP—advancing the evaluation of preclinical Alzheimer disease treatments *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2015.177

CAP Goals

- Where possible, works to standardize procedures and harmonize data collection to facilitate future comparisons.
- Seeks ways to share data and samples with the research community.
- Assists other investigators and organizations in the planning of their own prevention trials.
- Although primarily focused on drug trials, nonpharmacological preclinical AD trials would also benefit from CAP efforts.

Reiman, E. M. *et al.* (2015) CAP—advancing the evaluation of preclinical Alzheimer disease treatments *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2015.177

Table 1 | New trials in patients with preclinical AD

Trial	Participants	Trial duration	Compound and administration	Targeted Aβ species	Primary outcomes	Biomarker measures	Interim analysis
ADCS A4	1,000 amyloid-positive adults aged 65–85 years (500 per treatment arm)	168 weeks	Solanezumab IV every 4 weeks	Monomer	ADCS Preclinical Alzheimer Cognitive Composite	Florbetapir PET, MRI, CSF analyses, tau PET	Blinded sample size re-estimation
API ADAD	200 ADAD mutation carriers (100 per treatment arm) and 100 kindred non-carriers (placebo arm) aged 30–60 years without MCI or dementia	260 weeks	Crenezumab SQ every 2 weeks	Monomeric, oligomeric and fibrillar	API ADAD composite cognitive test score	Florbetapir PET, ^{18}F-FDG-PET, MRI, CSF analyses	After last participant enrolled completes 104 weeks of treatment
API APOE4*	Approximately 1,340 *APOE*ε4* homozygotes aged 60–75 years without MCI or dementia	260 weeks	CAD106 IM quarterly, CNP50 (oral pill) daily	Multiple species	API composite cognitive test score, time to diagnosis of MCI or dementia due to AD	Florbetapir PET, ^{18}F-FDG-PET, MRI, CSF analyses, tau PET	TBD
DIAN-TU Biomarker	138 ADAD mutation carriers (52 per active treatment arm, 34 pooled placebo) and 77 kindred non-carriers (placebo arm) –15 years to +10 years from parental age of symptom onset	Up to 104 weeks	Solanezumab IV every 4 weeks, gantenerumab SQ every 4 weeks	Monomer (solanezumab), aggregated (gantenerumab)	CSF Aβ (solanezumab), PiB-PET (gantenerumab)	CSF and plasma analyses, florbetapir PET, PiB-PET, ^{18}F-FDG-PET, MRI, tau PET	Biomarker interim analyses based on adaptive design
DIAN-TU Adaptive Prevention Trial	266 ADAD mutation carriers (133 per treatment arm) and 133 kindred non-carriers (placebo arm) –15 years to +10 years from parental age of symptom onset	208 weeks	TBD from DIAN-TU Biomarker	TBD from DIAN-TU Biomarker	Cognitive measure or composite TBD	CSF and plasma analyses, florbetapir PET, PiB-PET, ^{18}F-FDG-PET, MRI, tau PET	TBD
TOMMORROW	4,622 *APOE/TOMM40* high-risk (2311 per treatment arm) and 600 low-risk (placebo arm) individuals aged 65–83 years without MCI or dementia	260 weeks‡	Pioglitazone daily	Not applicable	Time to diagnosis of MCI due to AD	MRI volumetrics in subset	Futility analysis once 50% (205/410) of the anticipated events have occurred

*Subject to regulatory authority approval. ‡Estimate. Exact duration depends on the number of progression events. Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease; ADAD, autosomal dominant AD; ADCS, Alzheimer's Disease Cooperative Study; API, Alzheimer's Prevention Initiative; APOE, apolipoprotein E; CSF, cerebrospinal fluid; DIAN-TU, Dominantly Inherited Alzheimer Network Trials Unit; IM, intramuscularly; IV, intravenously; MCI, mild cognitive impairment; PiB, Pittsburgh compound B; SQ, subcutaneously; TBD, to be determined.

Reiman, E. M. *et al.* (2015) CAP—advancing the evaluation of preclinical Alzheimer disease treatments *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2015.177

National Strategy for Recruitment and Participation in Alzheimer's Disease Clinical Research

Goal: To engage broad segments of the public in the Alzheimer's and related dementias research enterprise, with a particular focus on underrepresented communities, to successfully and more quickly enroll and retain individuals in studies to better understand, treat and eventually prevent these disorders.

Areas of Focus

National Efforts that focus on broad policies and activities that can identify and support strategies for successful recruitment and retention.

Capacity Building aimed at changing the way study sites and multisite networks do business, so they can be most effectively structured and staffed for the number and types of clinical studies being undertaken.

Connecting at the Local Level to identify and implement best practices, to build trusting relationships with communities and individuals toward the shared goals of finding a way to effectively treat or prevent Alzheimer's disease and related dementias.

National Strategy Development

- Alzheimer's Association meeting at AAIC 2016 in Toronto
- NIA hosts a stakeholder meeting, including pharma in Bethesda, MD -- Dec 2016
- Steering committee and working groups established, with Alz Assn facilitation -- Jan/Feb 2017
- *Alzheimer's & Dementia* hosts webinar on strategy development -- Feb 2017
- NIA convenes workshop with working groups to discuss strategy -- April 2017
- Working groups refine draft strategies -- Second half 2017
- **Public comment -- Feb/March 2018**
- **Strategy finalized, implementation follow up begins -- June/July 2018**

Thank You!

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NIH National Institute on Aging
Turning Discovery Into Health

January 26, 2018 -- Advisory Council Meeting #27

The meeting was held on Friday, January 26, 2018, in Washington, DC. The Research Subcommittee took charge of this meeting's theme, focusing on the process from targets to treatments. The Council heard speakers on the preclinical pipeline, the clinical trial pipeline, and the industry perspective. The meeting also included discussion of a driver diagram to guide the Council's future work, updates and a report from the October Care Summit, and federal workgroup updates. Material available from this meeting is listed below and is also available at https://aspe.hhs.gov/advisory-council-alzheimers-research-care-and-services-meetings#Jan2018.

Comments and questions, or alerts to broken links, should be sent to napa@hhs.gov.

General Information

Agenda	[HTML Version] [PDF Version]
Meeting Announcement	[HTML Version] [PDF Version]
Meeting Summary	[HTML Version] [PDF Version]
Public Comments	[HTML Version]

Handouts

Care Summit Report Themes	[PDF Version]
NAPA Driver Diagram Draft Examples	[PDF Version]
Outline for Care Summit Final Report	[PDF Version]

Presentation Slides

AbbVie's R&D Vision for Alzheimer's Disease	[HTML Version] [PDF Version]
Care Summit Report	[HTML Version] [PDF Version]
Clinical Subcommittee Update	[HTML Version] [PDF Version]
Initiatives, Partnerships and Collaboration to Help Patients with the Highest Unmet Need: Dominantly Inherited Alzheimer's Disease Trials Unit (DIAN-TU) as a Case Example	[HTML Version] [PDF Version]
Long-Term Services and Supports Committee Update	[HTML Version] [PDF Version]

NAPA Driver Diagram	[HTML Version] [PDF Version]
Overview of the Clinical Trial Pipeline for AD	[HTML Version] [PDF Version]
Overview on NIA Preclinical Pipeline	[HTML Version] [PDF Version]
Participating in an Alzheimer's Clinical Study: Perspectives on Involvement of a Person Living with Dementia and Her Study Partner	[HTML Version] [PDF Version]
Progress Since October	[HTML Version] [PDF Version]
Research Progress on Alzheimer's Disease and Related Dementias	[HTML Version] [PDF Version]
Research Subcommittee Agenda: The Journey from Targets to Treatments	[HTML Version] [PDF Version]

Videos

Updates since October meeting	[Video]
NAPA Driver Diagram	[Video]
Federal Updates	[Video]
Public Comments	[Video]
Research Subcommittee Agenda	[Video]
Care Summit Update	[Video]

Last Updated: 06/09/2018