Accelerating Medicines Partnership

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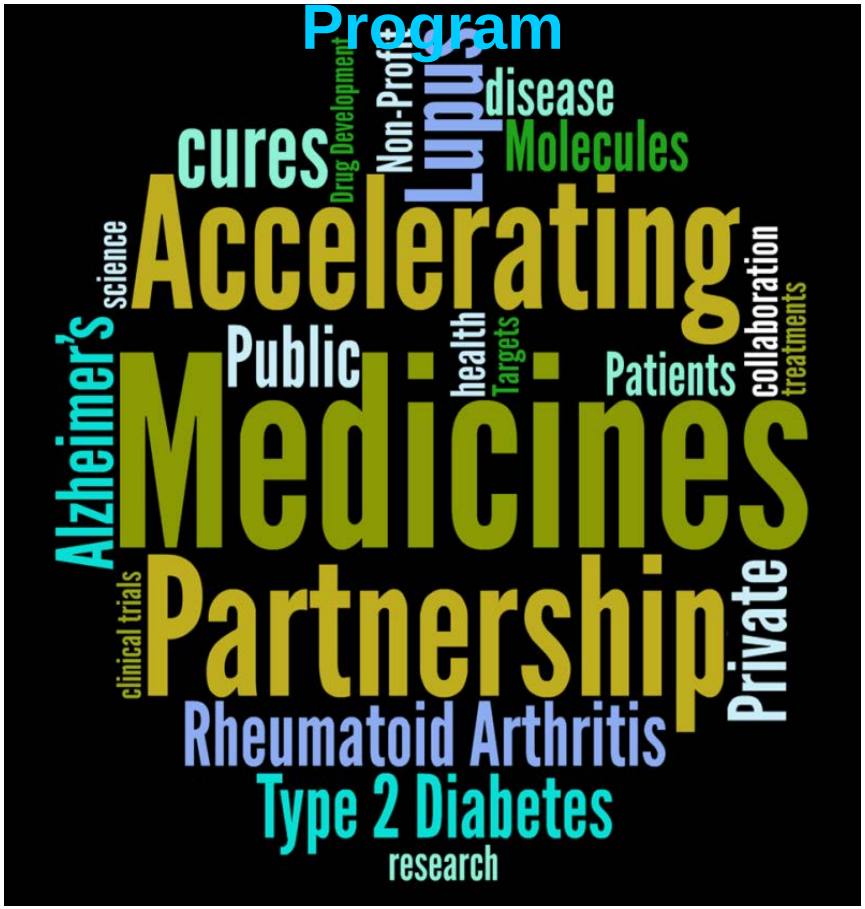
Alzheimer's Disease Program



Why AMP? Why now?

Developing effective new medicines

takes too long,

costs too much

and fails too often.

NIH National Institute on Aging

AMP Pilots:

Alzheimer's disease

Type 2 diabetes

Rheumatoid arthritis/systemic lupus erythematosus

NIH National Institute on Aging

National Alzheimer's Project Act
Public Law 111-375

Role of the Secretary of Health and Human Services (HHS):

- Oversee the creation and updating of the national plan and carry out an annual assessment of the Nation's progress in preparing for the escalating burden of Alzheimer's, including both implementation steps and recommendations for priority actions based on the annual assessment.

- Use discretionary authority to evaluate all Federal programs around Alzheimer's, including budget requests and approvals.

Advisory Council. An advisory council will be established to meet quarterly and advise the Secretary of HHS, or the Secretary's designee.

Annual Report. The Secretary of HHS, or the Secretary's designee, shall submit to Congress an annual report that includes an evaluation of all nationally and federally funded efforts in Alzheimer's research, clinical care, institutional, and home- and community-based programs and their outcomes.

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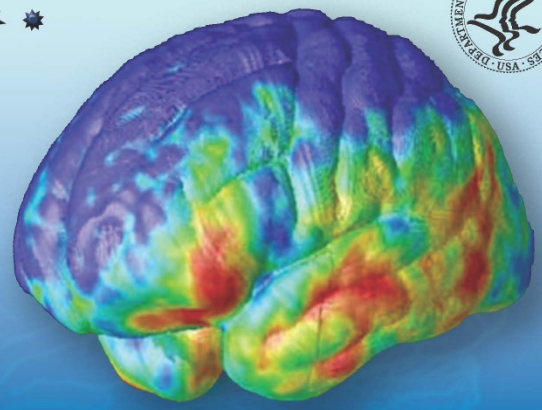

Alzheimer's Disease Research Summit 2012:

Path to Treatment and Prevention

May 14-15, 2012

A blueprint for an integrated translational research agenda.

Session 1: Interdisciplinary Approach to Discovering and Validating the Next Generation of Therapeutic Targets for AD

Session 2: Challenges in Preclinical Therapy Development

Session 3: Who to Treat, When to Treat and What Outcomes to Measure

Session 4: Drug Repurposing and Combination Therapy

Session 5: Non-pharmacological Interventions

Session 6: New Models of Public Private Partnerships

Alzheimer's Research Summit Recommendations May 2012

Recommendations related to Drug Trial Milestones

3.A. Initiate treatment trials in asymptomatic, at-risk individuals using uniform biomarkers and cognitive outcomes informed by data from Alzheimer's disease trials using patients with more advanced disease.

3.B. Collect DNA and other biosamples from these studies to enable subsequent interrogation based on treatment response and predictors of decline in the groups receiving placebo.

3.F. Develop treatments for patients with symptomatic Alzheimer's disease and support proof of concept studies to validate novel targets for cognitive and neuropsychiatric symptoms across all disease stages.

5.E. Develop standard outcome measures to enable data comparisons across studies. These include but are not limited to ecologically valid measures of real world function, quality of life, and physical and cognitive function.

National Plan to Address Alzheimer's Disease

http://aspe.hhs.gov/daltcp/napa/NatlPlan.pdf

U.S. Department of Health and Human Services
Office of Assistant Secretary for Planning and Evaluation

Goal 1: Prevent and Effectively Treat Alzheimer's Disease by 2025

Goal 2: Enhance Care Quality and Efficiency

Goal 3: Expand Supports for People with Alzheimer's Disease and Their Families

Goal 4: Enhance Public Awareness and Engagement

Goal 5: Improve Data to Track Progress

Research Goals

1.A.-- Identify Research Priorities and Milestones

1.B.-- Expand Research Aimed at Preventing and Treating Alzheimer's Disease

1.C.-- Accelerate Efforts to Identify Early and Presymptomatic Stages of Alzheimer's Disease

1.D.– Coordinate Research with International Public and Private Entities

1.E.– Facilitate Translation of Findings into Medical Practice and Public Health Programs

FY 2013 Alzheimer's Disease Funding Opportunity Announcements

RFAs
Interdisciplinary Approach to Identification and Validation of Novel Therapeutic Targets for Alzheimer's Disease (R01)
Alzheimer's Disease Therapeutics Program (U01)
Alzheimer's Disease Prevention Trials (R01)
Alzheimer's Disease Phase I Clinical Trials (R01)

2013 RFA: Interdisciplinary Approach to Identification and Validation of Novel Therapeutic Targets for AD

- **Supports interdisciplinary and integrative research focused on identification and preclinical validation of novel targets for AD treatment and prevention**

  - Encourages the pursuit of paradigm-shifting biological and therapeutic hypotheses and promotes the creation of new translational teams

  - Encourages the use of network-based approaches, such as systems biology and systems pharmacology to gain understanding of the molecular and physiological context within which potential therapeutic targets operate

Identification and Validation of Novel Therapeutic Targets for Alzheimer's Disease, RFA-AG-13-013: http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-13-013.html

2013 RFA: Alzheimer's Disease Prevention Trials

- Phase II or Phase III clinical trials testing pharmacological (small molecules and biologics) and non-pharmacological interventions, in cognitively normal individuals at-risk for AD (e.g., individuals at risk genetically, older adults positive for biomarker evidence of Alzheimer's disease pathology) or in individuals with MCI using a combination of biomarkers (fluid and imaging) and cognitive measures as outcomes.

AD Prevention Trials, RFA-AG-13-015:
http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-13-015.htm

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Alzheimer's Disease – AMP Proposal Development Group

	Name	Affiliation
Co-Chairs	Steve Paul	Weill Cornell Medical College
	Mike Hutton	Lilly
Industry	Charlie Albright	BMS
	Richard Hargreaves	Merck
	Holger Rosenbrock	Boeringer-Ingelheim
	Leslie Shinobu	Takeda
	Mike Decker	AbbVie
	Xiaoming Guan	GSK
	Tim Harris	Biogen Idec
Academia, Government, & Non-profit	Randy Bateman	Washington Univ St Louis
	Todd Golde	Univ of Florida
	Eric Karran	Alzheimer's Research UK
	Eric Reiman	Banner Alzheimer's Institute
	Neil Buckholtz	NIH/NIA
	Dave Holtzman	Washington Univ St. Louis

Original Research Proposal for Alzheimer's Disease

Key scientific elements of proposed research

A

Identify biomarkers correlated with therapeutic benefit

Embed exploratory biomarkers into upcoming Phase 3 clinical trails to identify those which predict clinical benefit

- Study includes supplemental biomarker assessments of 1000 patients in 5 different trials across 100 sites
- Specific assessments to include: Expanded MRI battery, FDG-PET, Abeta/Tau imaging, CSF markers and others
- Includes collaboration with the FDA to define what is needed to ultimately qualify biomarkers as surrogate endpoints in registration trials
- Timeline is 5 years

B

Identify & validate new targets in human brain tissue

Integrated systems analysis in human brain tissue to identify networks and validate targets relevant in AD

- Conduct RNA seq / GWAS studies in 3000 existing brain samples using validated methodologies (2000 AD, 1000 Control)
- Construction of ordered networks linked to disease is expected to identify novel targets and provide orthogonal target validation with human genetics (GWAS and deep sequencing)
- Timeline is 3 years

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Summary of recently announced NIH initiatives:

Identifying biomarkers correlated with therapeutic benefit

Proposal	Description	Principal investigator
Dominantly Inherited Alzheimer Network Trials Unit (DIAN-TU) Trial	• Phase II/III study to assess the safety, tolerability, and biomarker efficacy of gantenerumab, solanezumab, and another drug (TBD)	• Randall J. Bateman, WUSL • Collaborating companies: – Lilly – Roche – Alzheimer's Assoc. – Avid Radiopharm. – Cog State
The Alzheimer's Prevention Initiative APOE4 Trial	• Testing an anti-amyloid drug (TBD) in cognitively normal older volunteers who are at increased risk of developing late-onset Alzheimer's (APOE4)	• Eric Reiman, BANNER • Pierre Tariot, BANNER
Alzheimer's Disease Cooperative Study Anti-Amyloid Treatment in Asymptomatic AD Trial (A4)	• Secondary prevention trial of MAb in clinically normal older people with biomarker evidence of brain amyloid.	• Reisa Sperling, Harvard • Paul Aisen, UCSD

Click links to view full project descriptions

FNIH Foundation for the National Institutes of Health

NIH National Institute on Aging

NIH-funded Phase II/III studies in preclinical, at-risk patients

Source	Fluid	Imaging	Subjects
API APOE4	• CSF AB42 • p-tau • t-tau • Plasma AB1-40 • Plasma ABx-40 • Plasma AB1-42 • Plasma ABx-42	• MRI/fMRI • Axial T2 Star/ Gradient Echo • FDG PET/AB PET • Axial T2 FLAIR • MPRAGE/IRFSPGR • fcMRC EPI BOLD • Axial DTI • Axial T2 TSE • Flutemetamol PET	• 650
DIAN	• CSF tau • CSFAB42 • CSFAB40 • CSF p-tau • BACE	• Hippocampal volume • Ventricle volume • FDG PET • PET PIB • MRI • DTI	• 155
A4 prevention	• CSF AB1-42 • CSF tau • CSF p-tau	• PET PIB • MRI • fcMRI	• 1000

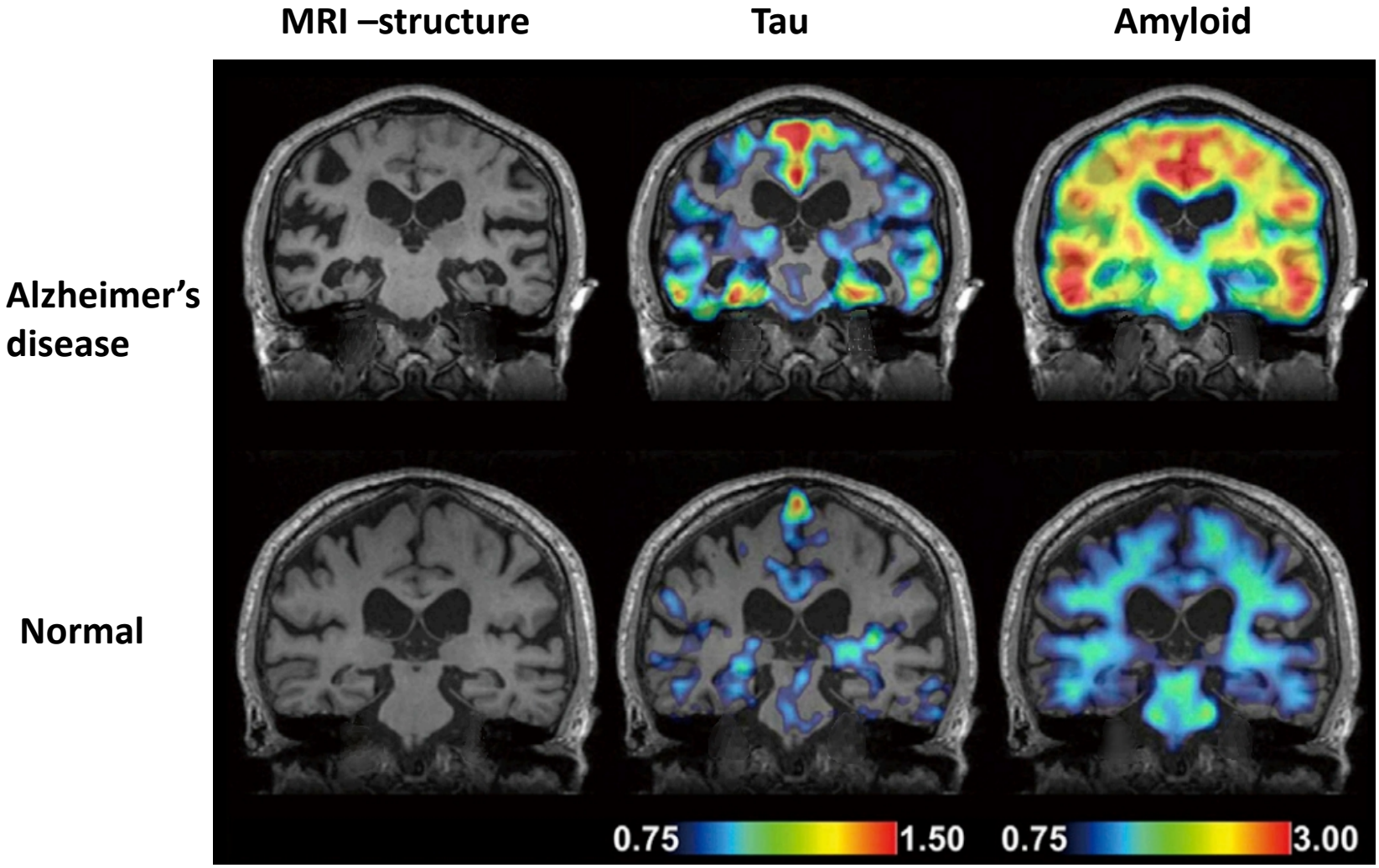
Each trial collects CSF & plasma; Access to samples would need to be defined

FNIH Foundation for the National Institutes of Health

AMP Project A

- Supplement the biomarker panels already included in these three NIH-funded Phase II/III registration trials in presymptomatic Alzheimer's through the addition of tau PET imaging, EEG measures and novel fluid biomarkers.
  - AMP will support appropriate CSF and plasma sampling and storage as necessary to ensure that the full range of future analytes can be measured including protein and miRNA biomarkers.
  - The identity of the specific analytes will therefore be based on progress in the field over the next 5 years; however, output from the ADNI proteomics project among other large scale fluid biomarker programs will be available in this timeframe.

Diagnosing AD: Present and Future



Summary of recently announced NIH initiatives:

Identifying & validating new targets in human brain tissue

Proposal	Description	Principal investigator
Pathway Discovery, Validation and Compound Identification for Alzheimer's Disease	• Characterize and validate complex molecular networks & candidate genes that influence susceptibility to AD • Analyze rich clinical, pathological, genomic and other large-scale molecular data collected from brain tissue from over 1,000 subjects	• Philip De Jager, BROAD • David Bennett, RUSH
Integrative Biology Approach to Complexity of Alzheimer's Disease	• Construct biological network models with large-scale molecular, cellular and clinical data (incl. human cells)	• Eric Schadt, MT SINAI
Systems Approach to Targeting Innate Immunity in Alzheimer's	• Identify and characterize novel therapeutic targets within the innate immune system using data from Alzheimer's patients and Alzheimer's mouse models	• Todd Golde, U Florida • Nathan Price, Seattle • Nulifer Ertiken-Taner, Mayo

Click links to view full project descriptions

AMP will support enabling effective data integration across these three NIH-funded studies

FNIH Foundation for the National Institutes of Health

AMP Project B

- Expand the application of integrated network analysis (both RNA and proteomic studies) in human AD brain samples to identify biologic nodes and networks that are linked to the development or progression of AD

- Plan to work with Sage Bionetworks to create standardized open-source data structures and formats to aid the accessibility and ease of analysis of biological data in a manner not currently practiced in the AD field.
  - SAGE will provide coordinated and centralized enablement of the data components for public use.

Projected AMP funding contributions

Disease area	Total project funding ($M)	Total NIH funding ($M)	Total industry funding ($M)
AD	135	67.6	67.4
T2D	58.4	30.4	28.0
RA/SLE	41.6	20.9	20.7
Total	235	118.9	116.1

Industry is also providing AMP with additional in-kind contributions, *e.g.*, clinical trials, drug, tracer, databases, etc.

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NIH National Institute on Aging

AMP Participation by Disease Area

	Alzheimer's disease	Type 2 Diabetes	RA, SLE & related
Industry members	abbvie biogen idec GlaxoSmithKline Lilly	Johnson & Johnson Lilly MERCK Pfizer SANOFI	abbvie Bristol-Myers Squibb MERCK Pfizer SANOFI Takeda
Government members	NIH National Institute on Aging NIH National Institute of Neurological Disorders and Stroke FDA	NIH National Institute of Diabetes and Digestive and Kidney Diseases	NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases NIH National Institute of Allergy and Infectious Diseases
Non-profit members	alzheimer's association GEOFFREY BEENE US Against Alzheimer's		