Welcome to the webinar!
The program will begin momentarily.
Advisory Council:
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Alzheimer’s Foundation of America
National Alliance for Caregiving
National Association of Area Agencies on Aging
National Consumers League
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Dean College of Sciences
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The University of Texas at San Antonio
Suzana Petanceska, Ph.D.
Program Director
Division of Neuroscience
National Institute on Aging
National Institutes of Health
Thank you for your attention!

To ask a question now, use the chat function.
TARGETS FOR THE NEXT GENERATION OF ALZHEIMER’S DISEASE TREATMENT

George Perry
Semmes Foundation Distinguished Chair in Neurobiology
University of Texas at San Antonio
99.6% of Clinical Trials in AD Have Failed

- Billions of dollars and the efforts of over 30,000 talented researchers have been directed toward studying AD since the mid 1980s, yet the only approved drugs are based on concepts from the 1970s.
- With failure, key opinion leaders have chosen to modify rather than abandon a cascade model of AD that puts Aβ or tau as the initiator.
- Here we explore an alternative holistic approach, one that has benefited patients of other age-related chronic disease.
AD is Dementia with Senile Plaques and Neurofibrillary Tangles

• Did Alois Alzheimer lead us astray? He did not confuse causality with association.

• The link developed with the modern era in AD research focused on the structure and composition of the lesions and later the genetics and cell biology, all of which showed the proteins of the lesions are important

• But is linkage causality? Or is it a role that must be revealed?
Is Removing Plaques and Tangles Beneficial?

- Amyloid cascade hypothesizes that all aspects stem from Aβ.
- Tau cascade hypothesizes that while AD might stem from Aβ, tau is the major driver of cell death.
- Major problem is that Aβ and tau are common features of the brain in normal aging and can exist in and outside of neurons without killing them.
- Clinical trials have effectively removed Aβ, yet there was NO clinical benefit.
- AD patients show variable neuronal loss and atrophy, yet NONE benefitted, indicating that removing Aβ earlier is unlikely to be better.
Alternative View of AD Pathology

• The field has now focused on refining cascade hypotheses with greater complexity, or instead rejecting Aβ and tau as irrelevant tombstones.

• A third ground is that lesions reflect the brain’s response to the most common chronic injury: aging.

• Aβ and tau are not passive, but rather key elements necessary for continued function of the brain throughout life.

• Deposition of both in AD indicates chronic induction rather than causality, a pattern seen in other amyloidoses.

• Mutations in Aβ or tau metabolism leave the brain more vulnerable due to improper deployment of the response, rather than causality.
How Can Aβ Be Protective?

• Aβ as plaques and intraneuronal oligomers is associated with reduced oxidative damage in AD (sporadic and genetic) and Down syndrome.

• Oxidative damage is the earliest change of AD, and is highest in MCI, decreasing with Aβ.

• Aβ in plaques contains and redox silences copper, preventing it from causing oxidative stress in aging and AD.

• Aβ is a regulated response that alternatively can cause oxidative stress when outside physiological bounds, e.g. mutations and rodent models.
Could Removing Aβ be Harmful?

• Removing Aβ, especially prior to dementia, could alter the brain’s redox balance.

• Aβ and tau are critical responses to aging that must be understood prior to drastic intervention that so far has not benefited patients, and in some cases has become harmful.

• Risk benefit ratio must be considered when applying Aβ therapeutics to asymptomatic individuals.
What Does This Change?

• Aβ accumulation marks a response to the underlying changes of aging rather than pre-AD; Aβ may be a key element of successful aging.

• Gross removal of Aβ is unlikely to show benefit, although modulation of the pathway is a viable therapeutic pathway and biomarker.

• Understanding what drives Aβ in aging will provide new therapeutic targets.
Therapeutic Targets

• In aging, levels of Aβ correlate with mitophagy suggesting Aβ is linked to mitochondria dysfunction and sequestering redox active copper that is released through mitochondria turnover.

• Functional mitochondria are required for Aβ toxicity.

• AD may fundamentally be a metabolic syndrome with a brain specific protective response.

• Therapeutic benefit of insulin, leptin, or other metabolic hormones is showing promise.
AD Prevention

• Numerous epidemiological studies support AD linkage to diet and exercise, the primary controllers of metabolism.

• Intervention studies show lifestyle modification significantly reduces AD.

• AD is joining the list of age-related diseases that can be managed through lifestyle and, in the future, therapeutics that modulate key factors: metabolism, Aβ and tau levels.

• Working with rather against the biological response of the aging brain could offer new windows to delay AD much as it has to reduce heart disease: not by curing but rather by reducing the impact.
Summary

• Failure of the amyloid cascade needs to open AD to new ideas and hope, rather than adding complexity to failed ideas that could stall progress for further decades.

• AD is emerging as a chronic illness in which age-related metabolic abnormalities are met by protective responses.

• Holistic interventions are the only demonstrated paths to offer benefit to patients NOW.
ACT- AD Webinar

New Approaches to Target Discovery for Alzheimer’s Disease

Suzana Petanceska PhD
National Institute on Aging
National Plan Goals:

1. Prevent and effectively treat Alzheimer’s Disease by 2025.

2. Optimize care quality and efficiency.


4. Enhance public awareness and engagement.

5. Track progress and drive improvement.
Phase III Randomized, Double-blind, Placebo Controlled, Clinical Trials for AD:

<table>
<thead>
<tr>
<th><strong>Agent</strong></th>
<th><strong>Target/Mechanism</strong></th>
<th><strong>Outcome</strong></th>
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<tbody>
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<td>HMG CoA reductase</td>
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Failure due to lack of efficacy or unforeseen toxicity.
A publicly available database developed by the National Institute on Aging/NIH and the Alzheimer’s Association.

Housing the AD portfolios of ~30 funding agencies (over 4,000 projects) classified using a common AD research ontology.

Providing funders, researchers and the public with a detailed picture of the scale of ongoing research on AD in the US and internationally.

Enabling funding agencies to coordinate planning, leverage resources, avoid duplication, and identify opportunities for collaboration.

A tool for developing research milestones and tracking progress.

http://iadrp.nia.nih.gov
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
Recognize the heterogeneity and the multifactorial nature of the disease.

Employ new research paradigms such as systems biology and systems pharmacology.

Enable rapid and extensive sharing of data, disease models, and biological specimens.

Build new multidisciplinary translational teams and create virtual and real spaces where these teams can operate.

Develop strategies to overcome intellectual property barriers to Alzheimer’s disease drug development.

Develop new public-private partnerships.

Establish a National IRB.
NIA/NIH Funding Initiatives and Programs
-developed in response to recommendations from the 2012 AD Summit-

- ADGC/NIAGADS
- ADSP

- SYSTEMS AND NETWORK BIOLOGY

- GENETICS

- PUBLIC PRIVATE PARTNERSHIPS

- RESEARCH TOOLS AND DISEASE MODELS

- DISCOVERY AND VALIDATION OF NOVEL TARGETS

- NEW TRANSLATIONAL CAPABILITIES

- ENABLING CLINICAL DRUG DEVELOPMENT

- BIOLOGY OF DISEASE

- INFLAMMATION
- VASCULAR ETIOLOGY

- QUANTITATIVE SYSTEMS PHARMACOLOGY
- in development-

- OPTOGENETICS
- Human iPSC

- SECONDARY PREVENTION TRIALS
- AD BIOMARKERS in DOWN SYNDROME
### Phase III Randomized, Double-blind, Placebo Controlled, Clinical Trials for AD:

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*Failure due to lack of efficacy or unforeseen toxicity.*
- We are targeting the wrong pathophysiological mechanisms
- Drugs do not engage with the intended target
- Interventions are started at the wrong stage of the disease
- Lack of translatable pharmacodynamic biomarkers
- Poor predictive power of animal model preclinical efficacy testing

- Complexity of disease
- Complexity of drug action
Complexity of Disease

Multiple Etiologies
Multiple Prodromal Phenotypes
Multiple Progression Trajectories

Genetics

Environment

Healthy State

Disease progression

Disease modifying therapy

Disease State
Complexity of Drug Action

Idealistic view
- Drugs
- Targets (genes, proteins)
- Physiological Responses

Real life scenario
- Drug affects many targets
- Targets interact
- Targets lead to multiple physiological responses

Polypharmacy
- Drug is delivered in specific times

Chronopharmacy
- Network changes with time
RFA AG13-013: Interdisciplinary Approach to Identification and Validation of Novel Therapeutic Targets for AD

A funding opportunity (multi PD/PI R01 mechanism) inviting interdisciplinary research that integrates identification of novel targets for AD with initial target validation required to make a decision to pursue drug discovery for a specific molecule/pathway. The FOA encourages the use of network-based approaches such as systems biology to enable target prioritization and to gain understanding of the molecular and physiological context within which potential therapeutic targets operate. grants.nih.gov/grants/guide/rfa-files/RFA-AG-13-013.html
NIA Funding Opportunities
-developed in response to recommendations from the 2012 AD Summit-

**RFA AG13-013**: Interdisciplinary Approach to the Identification and Validation of Novel Therapeutic Targets for AD

**RFA AG15-013**: Alzheimer’s Disease Prevention Trials

Accelerating Medicines Partnership – AD (AMP-AD)

[Link to AMP-AD website](http://www.nia.nih.gov/alzheimers/amp-ad)
GOVERNMENT-INDUSTRY-NON PROFIT

A PRECOMPETITIVE PARTNERSHIP FOR KNOWLEDGE CREATION
Alzheimer’s Disease Program

Target Discovery and Preclinical Validation

~2,500 brains
Clinical
Pathologic
Genomic
Epigenomic
RNAseq
Proteomic

Biomarkers

tau PET imaging
novel fluid biomarkers

A4 DIAN API-ApoE4

Secondary Prevention Trials
anti-amyloid treatment

Rapdi and Broad Sharing of Data

Data Integration
Predictive Modeling
Experimental Validation

AMP-AD Knowledge Portal

ICahn School of Medicine
NY Stem Cell Foundation
Broad Institute
Rush University
Emory University
UCLA
U Florida
ISB
Mayo Clinic

GAAIN
alzheimer's association
Data to be Generated by the AMP-AD Target Discovery Consortium

systems
- human
- mouse
- drosophila
- iPSC

perturbations
- shRNA
- compounds
- RNAi

data types
- RNA-seq
- Whole exome
- WGS
- methylation
- miRNA
- proteomics
- phenotypic measurements
This Knowledge Portal is supported by contributions from all members of the Accelerating Medicines Partnership for Alzheimer’s disease.

- Open and Controlled Access data
- Data released as soon as QC is completed
- No publication embargo imposed on the use of data after they have been made available through the public portal

First public data release: March 4, 2015

www.nia.nih.gov/alzheimers/amp-ad
Building a pipeline to discover and validate novel therapeutic targets and lead compounds for Alzheimer’s disease

Understanding the Heterogeneity and Multifactorial Etiology of AD

Transforming AD Therapy Development: From Targets to Trials

New Strategies for AD Prevention

Innovating Disease Monitoring, Assessment and Care

Empowering Patients, Engaging Citizens

Enabling Partnerships for Open Innovation
data → information → knowledge → understanding
Laying the Foundation for Precision Medicine for AD
Some key messages:

- Integrate AD research with research on the fundamental biology of aging.
- Support intense molecular profiling of existing and establish new cohorts to fill the gaps in large-scale human data needed to build predictive models of disease and wellness.
- Expand systems biology and systems pharmacology programs.
- Maximize the availability and usability of data, network models and analytical tools.
- Expand the precompetitive space for target validation through clinical proof of mechanism.
- Build a new translational and data science workforce.
- Change the reward systems in academia, publishing and funding agencies to enable large-scale team science and transparent, reproducible and translatable research.
- Engage patients, caregivers and citizens as direct partners in research.
Update and expand the implementation research milestones for the NAPA Goal: Treat and Prevent AD by 2025

2015 AD Summit Recommendations

New Funding Opportunities and Public Private Partnerships