Advisory Council on Alzheimer’s Research, Care and Services  
Research Subcommittee: The Journey from Targets to Treatments  
DHHS, Washington, DC  
January 26, 2018

"Overview on NIA preclinical pipeline"

Eliezer Masliah, M.D.  
Director, Division of Neuroscience,  
National Institute on Aging, NIH

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NIA Translational research pipeline for AD and ADRD  
The Team

Genetics and Epigenetics  
ADSP, GCAD, NIGADS, ADGC  
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Target Discovery and Validation  
AMP-AD Targets, M²OVE-AD-AD, Resilience-AD  
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Drug Discovery and Preclinical Drug Development  
Drug development (U01), MODEL-AD, AlzPED, SBIR’s  
Lorenzo Refolo PhD  
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Clinical Drug Development  
AMP-AD Biomarkers, ABC-DS, ACTC, Clinical trials, DIAN-TU  
Laurie Ryan PhD  
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Dementias of the aging population

1. Alzheimer’s Disease
   - Aβ, Tau
   - TDP-43
   - α-syn
   - Amnesia
   - Fluency
   - Agnosia
   - Plaques
   - Tangles
   - Frontotemporal Dementia/ALS
     - >100K

2. Lewy body Disease
   - α-synuclein
   - Aβ, Tau
   - TDP-43
   - Motor
   - Amnesia
   - Visual Fluctuation
   - Lewy bodies

3. Vascular Dementia
   - 700K
   - Micro-vessel disease

Mechanisms of toxicity in neurodegenerative disorders

- α-syn, Abeta, Tau, TDP43 accumulation
- Mutations, toxins
- Multiplications, polymorphisms
- Aggregation, clearance
- Synthesis

Axonal/synaptic damage

Oligomers
Propagation
Mechanisms of neurodegeneration in Alzheimer’s Disease

- Trafficking
- Transport
- Autophagy
- Proteolysis

NEUROPROTECTION, ANTI-INFLAMMATION, VASCULAR

TAU
- Alterations in Cytoskeletal proteins
- Tau, tubulin, neurofilaments
- Alterations in Synaptic proteins
- Arc, Drebrin, synapsin

BDNF
NGF
CNTF

NIH National Institute on Aging

Alzheimer’s Disease drug development pipeline-2017

Cummings et al Alz Dem 2017
**AD pipeline - how does it compare to others?**

<table>
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<th>Alzheimer disease</th>
<th>MRSA</th>
<th>Industry average*</th>
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<td>Overall success rate</td>
<td>2.0%</td>
<td>0.5%</td>
<td>4.6%</td>
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_Nature Reviews | Drug Discovery_

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**Failure in the Clinic - where does the fault lie?**

- **Too late?**
  - Drug interventions are started at the wrong stage of disease
- **Too little?**
  - May need greater drug effects
  - Insufficient dose
  - Lack of BBB penetration
- **Lack of target engagement**
  - Drugs do not engage with intended targets in patients
  - Lack of translatable pharmaco-dynamic biomarkers
- **Wrong target?**
  - We are targeting the wrong pathophysiological mechanisms
  - We need to target networks rather than single molecules
  - Unclear which toxic species to target

_Sperling, Jack and Arisen, Science Translational Medicine, 2011_
Key AD Summits Recommendations

- Recognize the heterogeneity and the multifactorial nature of the disease.
- Support extensive 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.
- Employ new research paradigms such as systems biology and systems pharmacology.
- Enable rapid and extensive sharing of data, disease models, and biological specimens.
- Develop computational tools and infrastructure for storage, integration, and analysis of large-scale biological and other patient-relevant data.
- Build new multidisciplinary translational teams and create virtual and real spaces where these teams can operate.
- Support and enable open science.
- Develop new precompetitive public-private partnerships.
- Change academic, publishing, and funding incentives to promote collaborative, transparent, and reproducible research.
- Engage patients, caregivers and citizens as direct partners in research.

NAPA Research Goal #1: Treat and Prevent AD by 2025

New Funding Opportunities and Public Private Partnerships

Implementation Research Milestones

NIH AD Research Summits Recommendations

NIH National Institute on Aging

Integrated NIA AD-Drug Development Program

- ADGC/NIAGADS
- ADSEP

- SECONDARY PREVENTION TRIALS
- AD BIOMARKERS IN DOWN SYNDROME
- AD CLINICAL TRIALS CONSORTIUM

- TRANSLATIONAL CENTERS FOR ANIMAL MODEL RESOURCES
- PRECLINICAL EFFICACY TESTING DATABASE
- TRANSLATIONAL BIOINFORMATICS AND SYSTEMS PHARMACOLOGY
- NEW CROSS-DISCIPLINARY TRAINING PROGRAMS
  AD/Data Science/Drug Discovery

- ENABLING CLINICAL DRUG DEVELOPMENT
- PUBLIC PRIVATE PARTNERSHIPS
- NEW TRANSLATIONAL CAPABILITIES
- COMPLEX BIOLOGY OF DISEASE AND RESILIENCE
- RESEARCH TOOLS AND DISEASE MODELS

- SYSTEMS AND NETWORK BIOLOGY
- OPTOGENETICS
- Human iPSC
- Next generation animal models

- GENETICS
- DISCOVERY AND VALIDATION OF MARKS AND BIOMARKERS
- INFLAMMATION
- PROTEOSTASIS
- METABOLIC AND VASCULAR ETIOLOGY

NIH National Institute on Aging
NIA and Trans-NIH translational pipeline for AD and ADRD

Blueprint Neurotherapeutics (UH2/3)
SBIR (R43/44) Preclinical therapy development

NIA Drug discovery program R21/R01
NIA AD-Drug Development program (U01)
NIA Clinical Trials program (R01)

Target ID
Early Validation
Tool/assay Development
Screening
Hit to Lead
Lead Development
Candidate Selection
AD-enabling technology
Phase I
Phase II
Phase III
Drug Approval

ADSP
AMP-AD
M²OVE-AD
Resilience-AD

MODEL-AD
AlzPED

ACTC
AD Centers
ADNI

ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT

adsp
Alzheimer’s Disease Sequencing Project

PI: G. Schellenberg; L. San U Penn; NIA Contact: Marilyn Miller

1. New genomic variants contributing to Late-Onset AD (LOAD)
2. Identify genomic variants contributing to protection against AD
3. Provide insight as to why individuals with known risk factor variants escape developing AD
4. Examine these factors in multi-ethnic populations to identify new pathways

- Associated Programs
  - ADGC- Alzheimer’s Disease Genetic Consortium
  - GCAD- Genome Center for AD
  - NIAGDS- NIA Genetics of AD storage site

Now WGS in 10,000 controls and 10,000 AD, 10,000 diverse populations
From single target to networks approach for AD-drug development

Complexity of Drug Action

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

**Real life scenario**
- Drug affects many targets
- Targets interact

**Polypharmacy**
- Targets lead to multiple physiological responses

**Chronopharmacy**
- Drug is delivered at specific times
- Network changes with time

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ACCELERATING MEDICINES PARTNERSHIP (AMP)

**Alzheimer’s Disease Program**

**Target Discovery and Preclinical Validation Project**
- NIA Contact: Suzana Petanceska
- ~2,500 brains
- Predictive Modeling
- Data Integration
- Experimental Validation
- Rapid and Broad Sharing of Data
- 6 Academic Teams — NIA grants —

**Biomarkers Project**
- NIA contact: Laurie Ryan
- tau PET imaging
- novel fluid biomarkers
- A4, DIAN, API-ApoE4
- Secondary Prevention Trials
- anti-amyloid treatment
- GAAIN
ACCELERATING MEDICINES PARTNERSHIP (AMP)

Progress over 4 years:
- Centralized data resource established
- All data deliverables/milestones met
- Over 100 novel targets discovered; currently undergoing data-driven prioritization for further preclinical validation
- A variety of experimental validation models developed
- Novel biomarker discovery initiated

AMP-AD Partners

Secreted peptide VGF (non-acronymic)

Specifically expressed in a subpopulation of neuroendocrine cells, and is upregulated by nerve growth factor. The encoded secretory protein also shares similarities with the secretogranin/chromogranin family; however, its exact function is not known. Multiple VGF peptides reported to be significantly decreased between converting and non-converting MCI patients (ADNI). Spielman et al.

Differential Expression of VGF in Different Regions

Correlation of VGF with Traits

Gene Causal Network

Protein Causal Network

NIH National Institute on Aging
Protein Networks as Novel Biomarkers

AMP-AD Emory Team
Pl: Allan Levey

Hub proteins from brain networks are found in human CSF and discriminate AD from control and PD patients. Hub proteins are defined as proteins with the highest intra-modular connectivity (i.e., proteins that are most central within the module) in the M1, M4 and M7 modules. Red symbols are proteins that were also identified in the CSF.

Building on and expanding the AMP-AD Target Discovery Project

M²OVE-AD
Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease

NIA contact - Suzana Petanceska

- ~$30 million over 5 years to support cross disciplinary research teams:
- 5 research teams will generate various “omics” data from brain and peripheral fluids from individuals participating in several natural history and population studies
- Predictions about molecular mechanisms will be explored in animal models (AD models and models of vascular/metabolic risk factors).
- Goals and deliverables:
  - rapid and broad sharing of data
  - deeper understanding of the phenotypes of risk and the mechanisms linking vascular risk factors, cerebrovascular disease and AD
  - new disease-relevant therapeutic targets for prevention
  - molecular signatures that can be non-invasively measured and used for patient stratification

A collaboration between NIA and NINDS
NINDS ADRD Translation Research Initiatives

In collaboration with NIA

NINDS contact: Roderick Corriveau (roderick.corriveau@nih.gov)

- TAU CWOW
- MPOVE
- VCID
- MarkVCID
- M2OVE
- FTD
- LBD Biomarkers
- Mechanisms
- DetectingCID
- Planning Grant
- Trials for LBD
- Phase III Clinical
- Investigator Initiated
- Blueprint Neurotherapeutics
- CREATE Bio
- IGNITE
- Exploratory Trial
- NeuroNEXT
- Phase 3 Clinical Trial

Some examples of NIA pipeline for AD and ADRD

ADSP
AMP-AD
M2OVE-AD
Resilience-AD
NIA-Drug discovery program R21/R01 (8/84)
NIA AD-Drug development program (U01) 14/136, 4 IND's
NIA Clinical Trials program (R01)

AD Drug Development Program

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<td>Tuszynski M.</td>
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<td>Catalano C.</td>
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Blueprint, Drug Discovery for CNS, and Preclinical Drug Development

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<td>All oligomerization inhibitors, HE3, ICT and 3-amino-2, 3- dimethylbutane (3AB)</td>
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NIA Translational Center for Animal Model Resources
MODEL-AD
NIA contact, Larry Refolo

- RFA AG16-014 (U54): Indiana University/Jax Labs/Sage Bionetworks (Bruce Lamb, PI) and UCI (Frank LaFerla)
  - Maximize human datasets to identify putative variants, genes and biomarkers for AD
  - Generate, phenotype and validate the next generation of Tg mouse models of AD
    (50 new models over 5 years; deep, longitudinal phenotyping)
  - Develop a preclinical testing pipeline that implements rigorous study design and data analysis
  - Make data and animal models available to the research community for use in therapy development without IP barrier.
Alzheimer's Disease Preclinical Efficacy Database
NIA contact, Larry Refolo

AlzPED is a publicly available, searchable, data resource that aims to increase the transparency, reproducibility and translatable of efficacy testing studies for Alzheimer's disease candidate therapeutics performed in animal models.

GETTING STARTED
- How to Enter Data
- Frequently Asked Questions
- Search Guides
- AlzPED Team
- Glossary of Terms

REPRODUCIBILITY GUIDELINES
- NIH Principles and Guidelines for Reporting Preclinical Research
- ARRIVE Guidelines (National Centre for the Replacement, Retirement & Replacement of Animals in Research)
- Additional Reproducibility Guidelines

Current AlzPED Members:
- NIA
- NIH Library
- ADDF
- Alzheimer Association
- Center for Open Science

https://alzped.nia.nih.gov/

New* NIA funding opportunities for translation research

Network biology of resilience to AD risk
RFA AG18-029

Closing the expertise/skills gap in data science and drug discovery
PAR18-524 (T32)
PAR17-052 (K18)

Sex-differences in AD risk and responsiveness to treatment
PAR 17-033

Translational biinformatics for drug repositioning and combination therapy development for AD
PAR 17-032

SBIR/STTR opportunities
- Advancing Research on Alzheimer's Disease (AD) and Alzheimer's Disease-Related Dementias (ADRD) (R41/R42/R43/R44)
- Tools for Clinical Care and Management of Alzheimer's Disease (AD) and its Comorbidities (R41/R42/R43/R44)
- Development of Socially-Assistive Robots (SARs) to Engage Persons with Alzheimer's Disease (AD) and AD-Related Dementias (ADRD), and their Caregivers (R41/R42/R43/R44)

https://www.nia.nih.gov/research/grants-funding/small-business-innovation-research-and-technology-transfer-programs
Next steps toward developing an AD Translational pipeline

Attaining the Goal of Precision Medicine for AD

Figure 6. Areas in which QSP models will impact drug discovery. An alternative view of the impact of combined modeling and measurement approaches on key steps in drug discovery which range from identifying the right target to treating the right patients. (Courtesy of Piet Van Der Graaf, Pfizer Inc.)


COMMENTARY

ALZHEIMER'S DISEASE

Testing the Right Target and Right Drug at the Right Stage

Reisa A. Sperling," Clifford R. Jack Jr.,* Paul S. Aisen

NIH National Institute on Aging

Alzheimer's Disease Summit Program- 2018

- Novel Mechanistic Insights into the Complex Biology and Heterogeneity of AD
- Enabling Precision Medicine for AD
- Translational Tools and Infrastructure to Enable Predictive Drug Development
- Emerging Therapeutics
- Understanding the Impact of the Environment to Advance Disease Prevention
- Advances in Disease Monitoring, Assessment and Care
- Building an Open Science Research Ecosystem to Accelerate AD Therapy Development

NIH National Institute on Aging

The 2018 Summit will build on the foundation laid by the NIH AD Research Summits held in 2012 and 2015. It will feature progress towards achieving the AD research implementation milestones and continue the development of an integrated multidisciplinary research agenda necessary to enable precision medicine for AD treatment and prevention.
THANKS