

# Spring ADRC Directors Meeting

National Institute on Aging

**Los Angeles, CA**

**May 14, 2022**

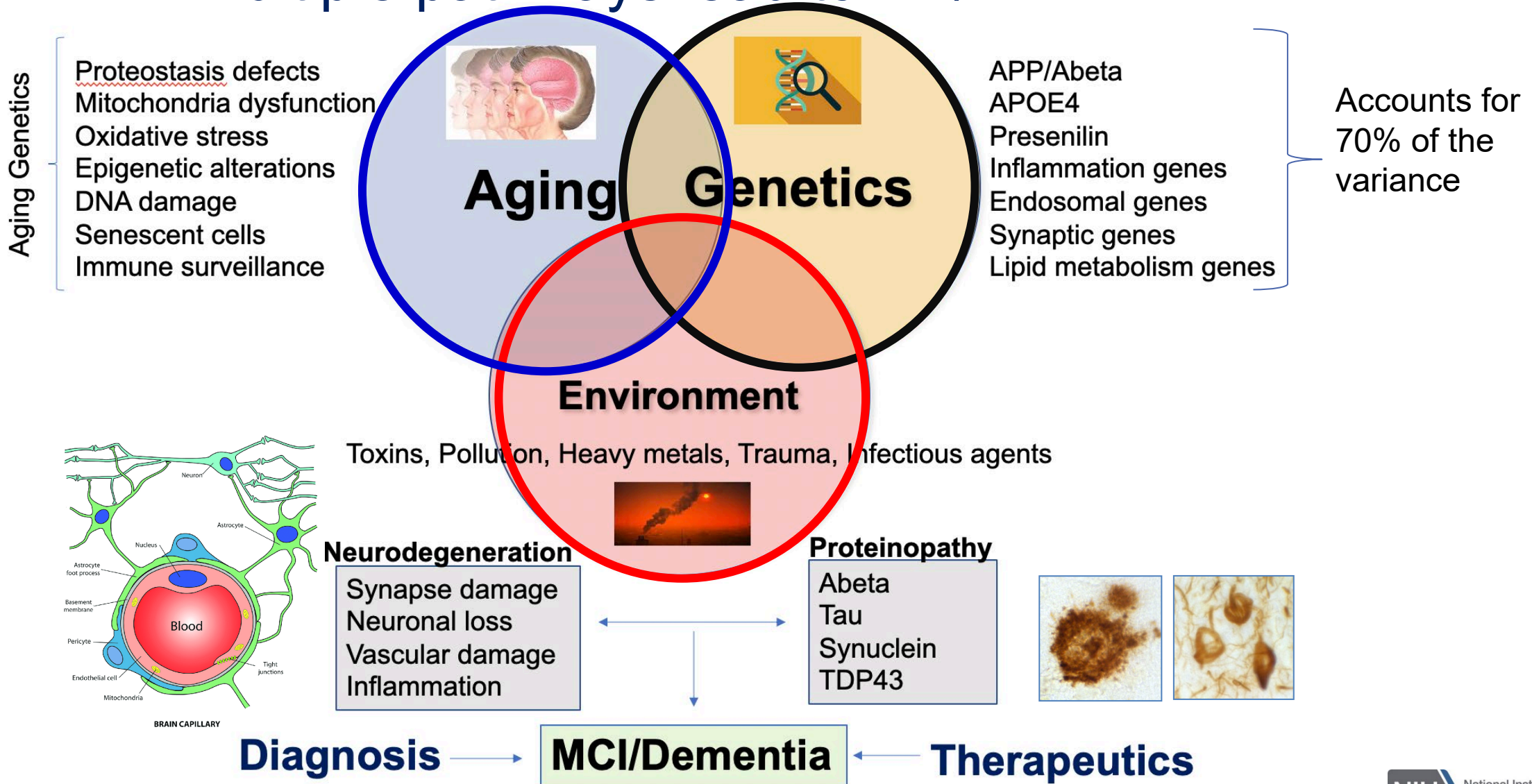
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## ***“NIA-DN Update”***

**Eliezer Masliah, M.D.**

Director, Division of Neuroscience,  
National Institute on Aging, NIH

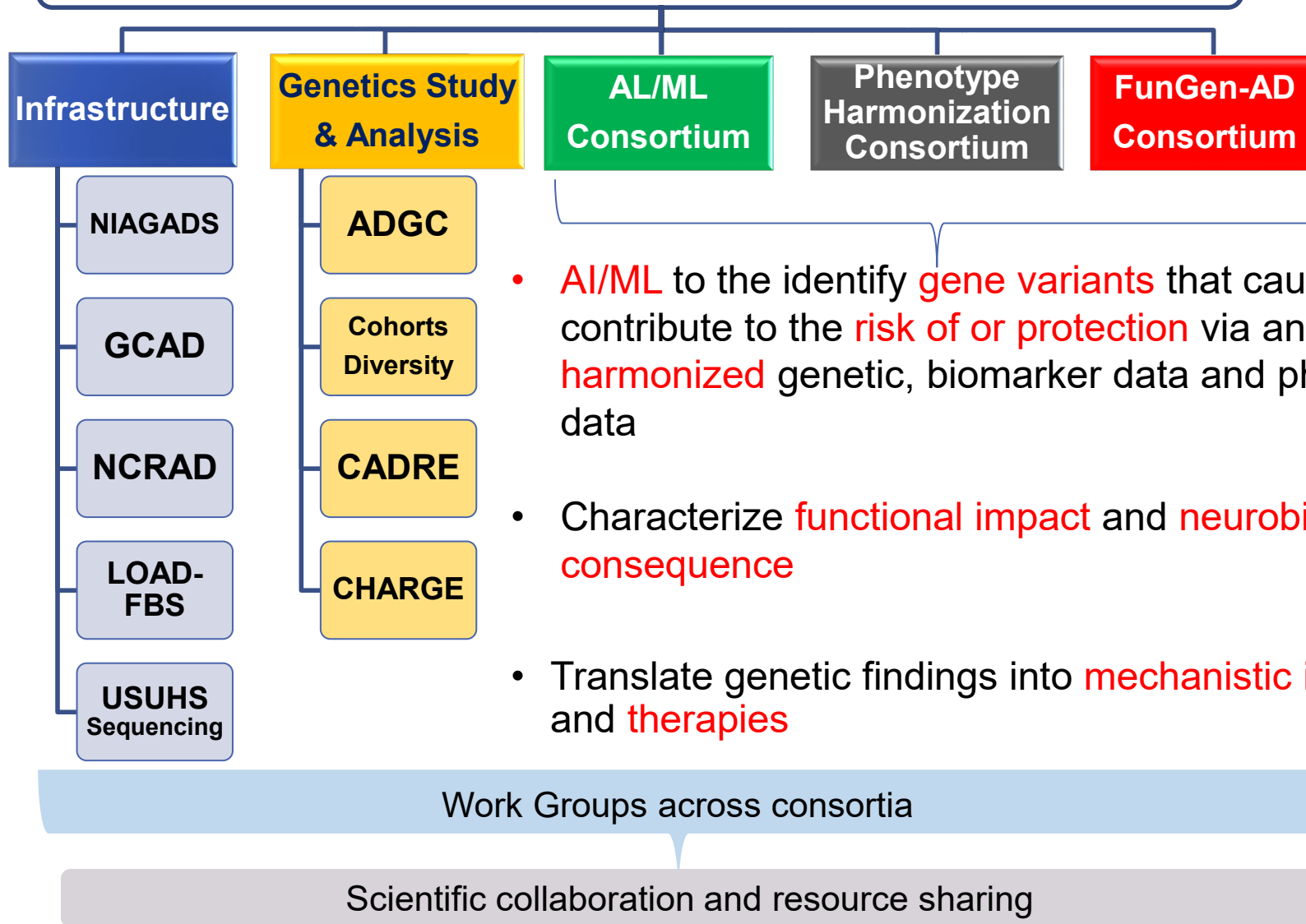
# Progress toward understanding the pathogenesis of AD- multiple pathways lead to AD/ADRD



# Alzheimer's Disease Sequencing Project

100,000 WG by 2025 **includes diverse population**

- Over 75 risk loci and 20 genes (from the 75 loci) for AD identified
- Examples: *BIN1*, *TREM2*, *CR1*, *PCALM*, *ADAM10*, *ABCD4*, *PLGC2*, *ANAX5*, *MEF2*
- Involved in *immune*, *neuronal/synaptic*, *endocytosis*, *lysosome* and *lipid metabolism*
- Common *polygenic variation* increases risk prediction (*APOE*+others)



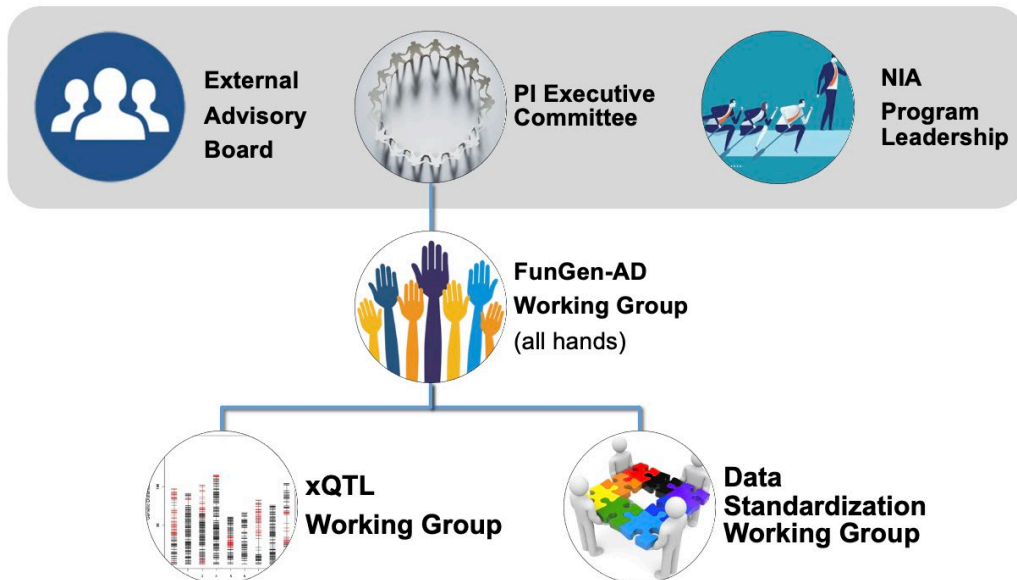


# FunGen-AD

ADSP Functional Genomics Consortium

NIA Program Directors: Marilyn Miller, Alison Yao

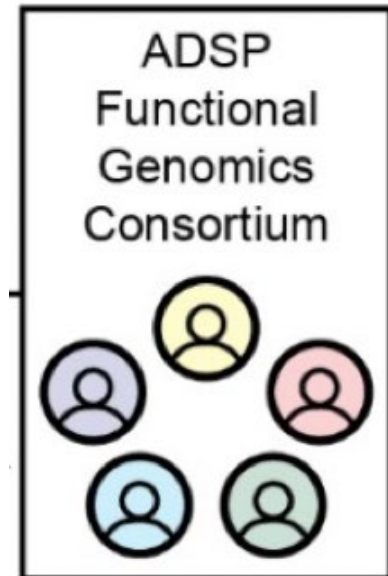
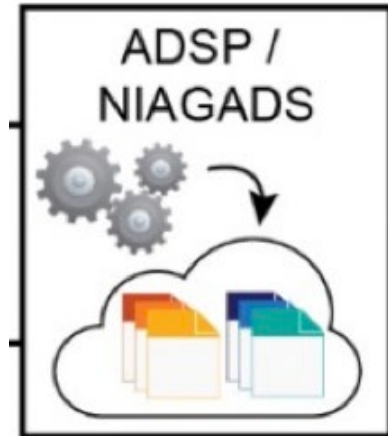
- To understand functional impact underlying the genetic basis of AD/ADRD
- Enable the discovery of genetics-guided targets for the prevention, diagnosis, and treatment of AD/ADRD.



## Core Projects

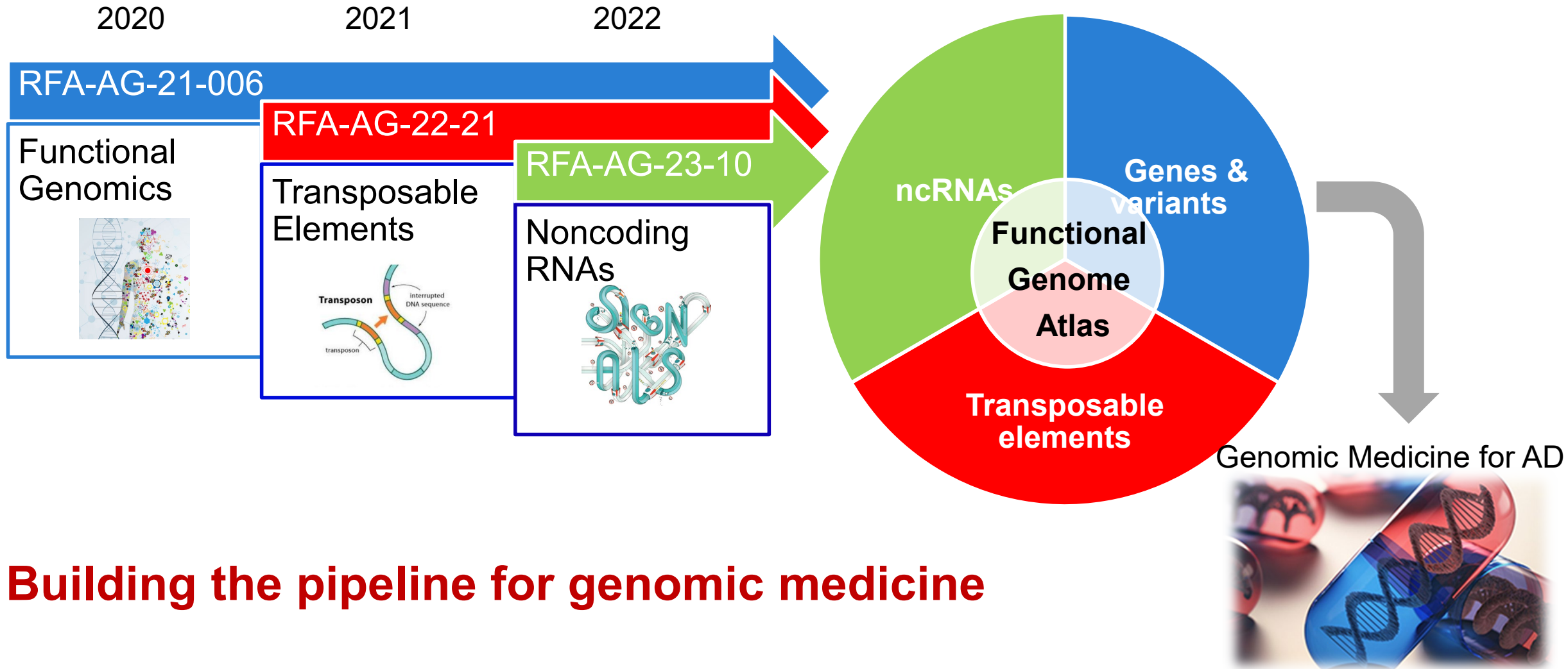
De Jager Columbia U	Shared functional changes across cellular networks
Montine Stanford U	Novel AD variants using high-throughput and single-cell technologies
Shulman Baylor	Functional Genomic AD in Humans and Drosophila Models
Temple Reg Res Fo	AD Risk Genes on Neuro-Vascular Interactions
Vance U Miami	Diverse populations to characterize risk loci for AD
Zhang Boston U	Circular RNA and interactions with RNP in AD

Multi-omics data  
Cell specific atlas  
Genetic targets for therapeutic intervention  
Epigenetic data  
Vascular genes  
Microglia genes  
Diverse populations  
Data sharing



# Towards a comprehensive characterization of AD genome

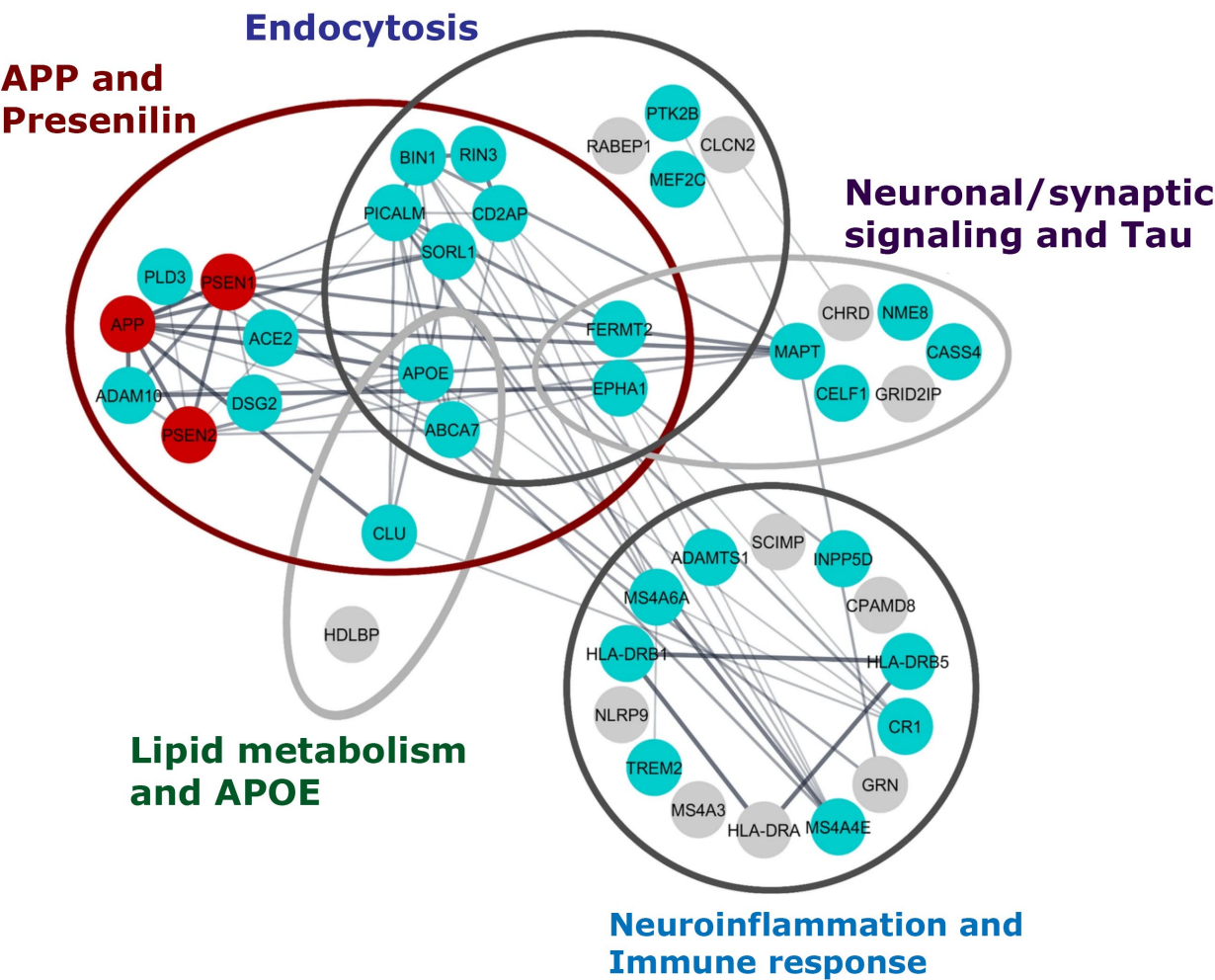
NIA Program Directors: Marilyn Miller, Alison Yao





# Role of endosomal/lysosomal alterations in AD/ADRD

## NOT-AG-21-034 Endosomal Trafficking as a Pathological Hub in AD/ADRD



### TMEM 106B (FTD)

LETTERS

2010

nature  
genetics

Common variants at 7p21 are associated with fronto-temporal lobar degeneration with TDP-43 inclusions

Vivianna M Van Deerlin<sup>1,106</sup>, Patrick M A Sleiman<sup>2,106</sup>, Maria Martinez-Lage<sup>1,3,106</sup>, Alice Chen-Plotkin<sup>1,4,106</sup>, Li-San Wang<sup>1</sup>, Neil R Graff-Radford<sup>2</sup>, Dennis W Dickson<sup>6</sup>, Rosa Rademakers<sup>6</sup>, Bradley F Boeve<sup>7</sup>, ...

Cell

CellPress  
OPEN ACCESS

Article

Homotypic fibrillization of TMEM106B across diverse neurodegenerative diseases

Andrew Chang,<sup>1,2,3,14</sup> Xinyu Xiang,<sup>1,2,3,4,14</sup> Jing Wang,<sup>1,2,3,14</sup> Carolyn Lee,<sup>1,2,3,5,14</sup> Tamta Arakhamia,<sup>1,2,3,14</sup> Marija Simjanoska,<sup>1,2,3,14</sup> Chi Wang,<sup>2</sup> Yari Carlomagno,<sup>6</sup> Guoan Zhang,<sup>7</sup> Shikhar Dhillon,<sup>1</sup> Manon Thierry,<sup>8</sup> Jolien Perneel,<sup>1,10</sup> Bavo Heeman,<sup>1,10</sup> Lauren M. Forgrave,<sup>1,10</sup> Michael DeTure,<sup>6</sup> Mari L. DeMarco,<sup>1,12</sup> Casey N. Cook,<sup>6</sup> Rosa Rademakers,<sup>1,11</sup> Dennis W. Dickson,<sup>6</sup> Leonard Petrucelli,<sup>5</sup> Michael H.B. Stowell,<sup>10</sup> Ian R.A. Mackenzie,<sup>1,1</sup> and Anthony W.P. Fitzpatrick<sup>1,2,3,15,\*</sup>

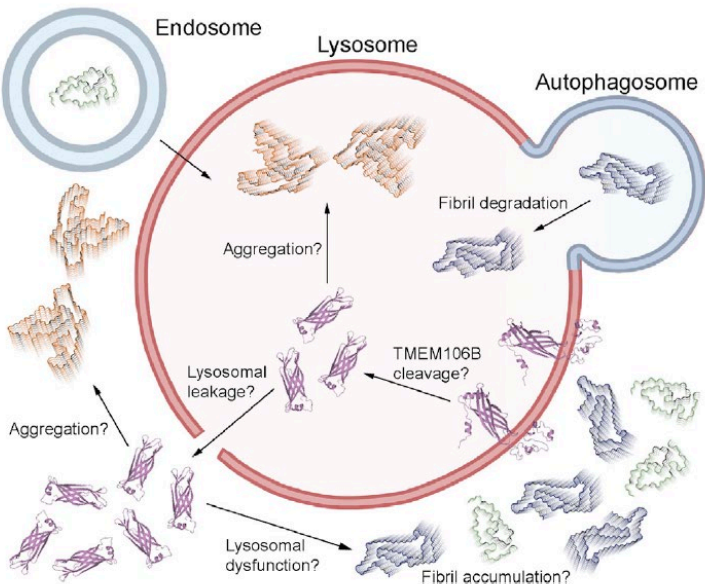
### TMEM 175 (DLB)

ARTICLES

<https://doi.org/10.1038/415188-021-00785-3>

nature  
genetics

Genome sequencing analysis identifies new loci associated with Lewy body dementia and provides insights into its genetic architecture



# TMEM106B fibrillation in aging and AD/ADRD pathogenesis

## Article

### Amyloid fibrils in disease FTLN-TDP are composed of TMEM106B not TDP-43

<https://doi.org/10.1038/s41586-022-04670-9>

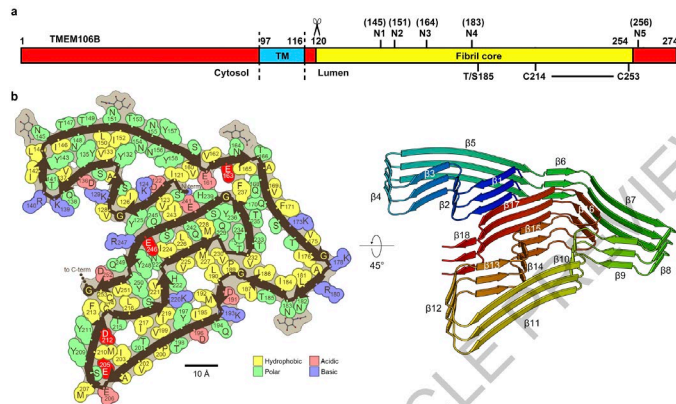
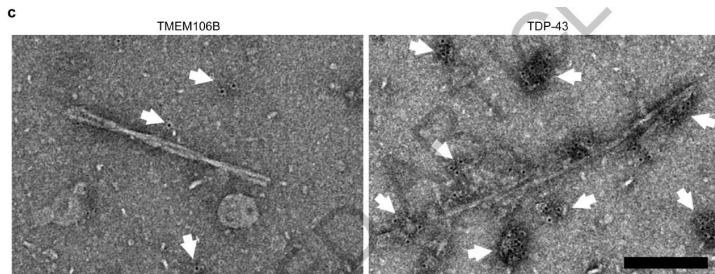
Received: 25 September 2021

Accepted: 22 March 2022

Published online: 28 March 2022

Yi Xiao Jiang<sup>1,2,3</sup>, Qin Cao<sup>1,2,3</sup>, Michael R. Sawaya<sup>1,2</sup>, Romany Abukharon<sup>1,2</sup>, Peng Ge<sup>1,2</sup>, Michael DeTure<sup>1</sup>, Dennis W. Dickson<sup>1</sup>, Janine Y. Fu<sup>1</sup>, Rachel R. Ogorzalek Loo<sup>1</sup>, Joseph A. Loo<sup>1</sup> & David S. Eisenberg<sup>1,2,3</sup>

Frontotemporal lobar degeneration (FTLD) is the third most common



## Article

### Age-dependent formation of TMEM106B amyloid filaments in human brains

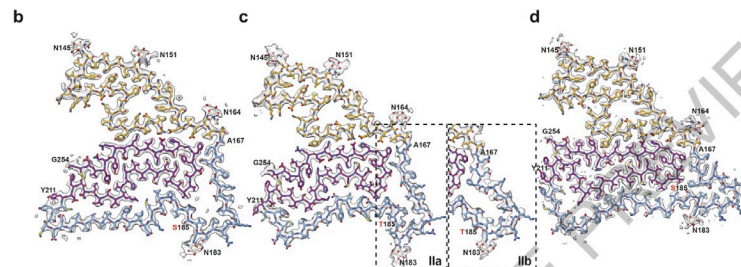
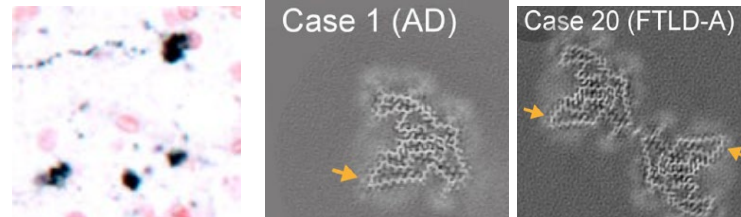
<https://doi.org/10.1038/s41586-022-04650-z>

Received: 9 November 2021

Accepted: 15 March 2022

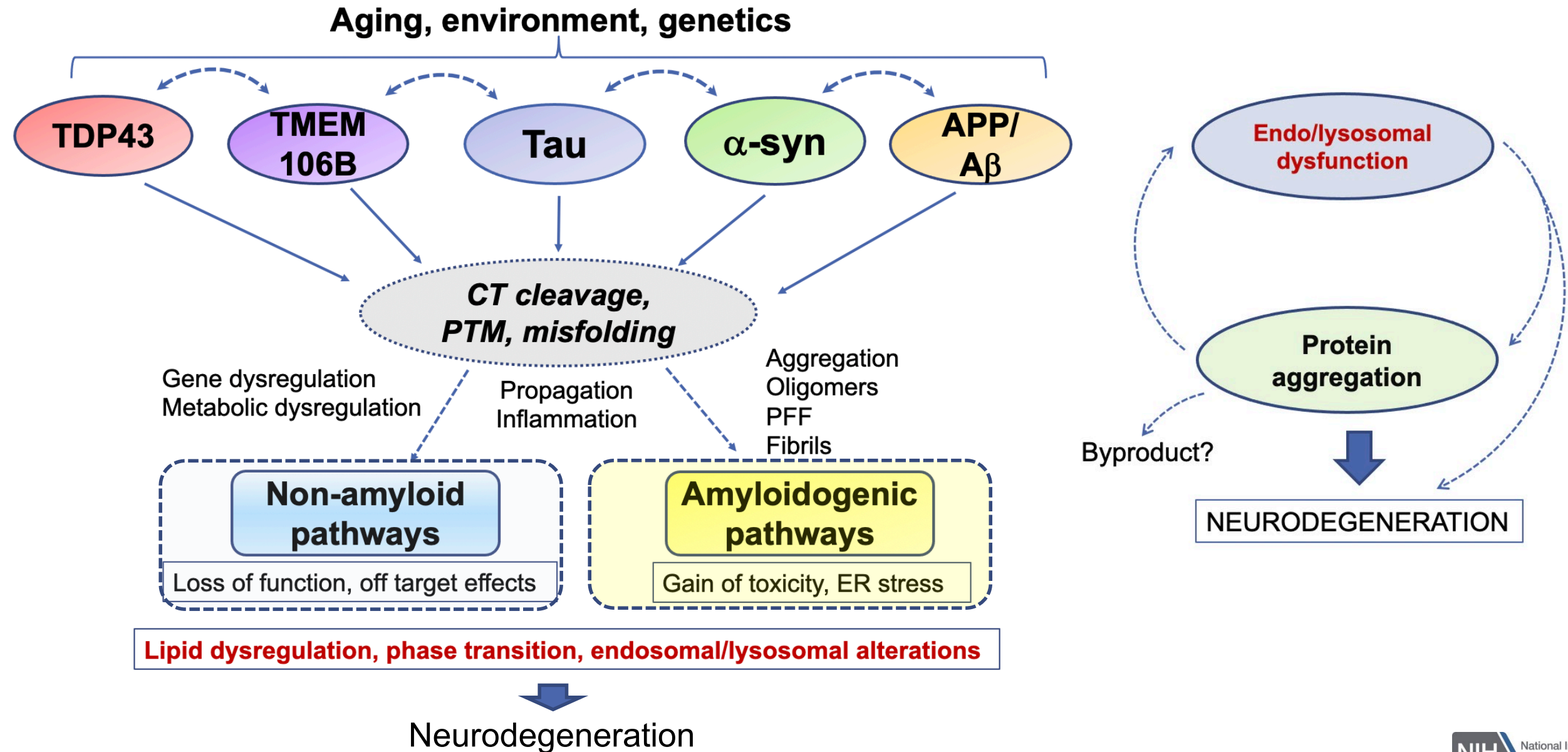
Published online: 28 March 2022

Manuel Schweighauser<sup>1,2</sup>, Diana Arseni<sup>1,2</sup>, Mehtap Bacioglu<sup>1,2</sup>, Melissa Huang<sup>1,2</sup>, Sofia Lövestam<sup>1,2</sup>, Yang Shi<sup>1,2</sup>, Yang Yang<sup>1,2</sup>, Wenjuan Zhang<sup>1,2</sup>, Abhay Kotecha<sup>1</sup>, Holly J. Garringer<sup>1</sup>, Ruben Vidal<sup>1</sup>, Grace I. Hallinan<sup>1</sup>, Kathy L. Newell<sup>1</sup>, Atri Tarutani<sup>1</sup>, Shigeo Murayama<sup>1</sup>, Masayuki Miyazaki<sup>1</sup>, Yuko Saito<sup>1</sup>, Mari Yoshida<sup>1</sup>, Kazuko Hasegawa<sup>1</sup>, Tammaryn Lashley<sup>1</sup>, Tamas Revesz<sup>1</sup>, Gabor G. Kovacs<sup>1,2</sup>, John van Swieten<sup>1</sup>, Masaki Takao<sup>1,2</sup>, Masato Hasegawa<sup>1</sup>, Bernardino Ghetti<sup>1</sup>, Maria Grazia Spillantini<sup>1</sup>, Benjamin Ryskeldi-Falcon<sup>1</sup>, Alexey G. Murzin<sup>1</sup>, Michel Goedert<sup>1,2,3</sup> & Sjors H. W. Scheres<sup>1,2,3</sup>



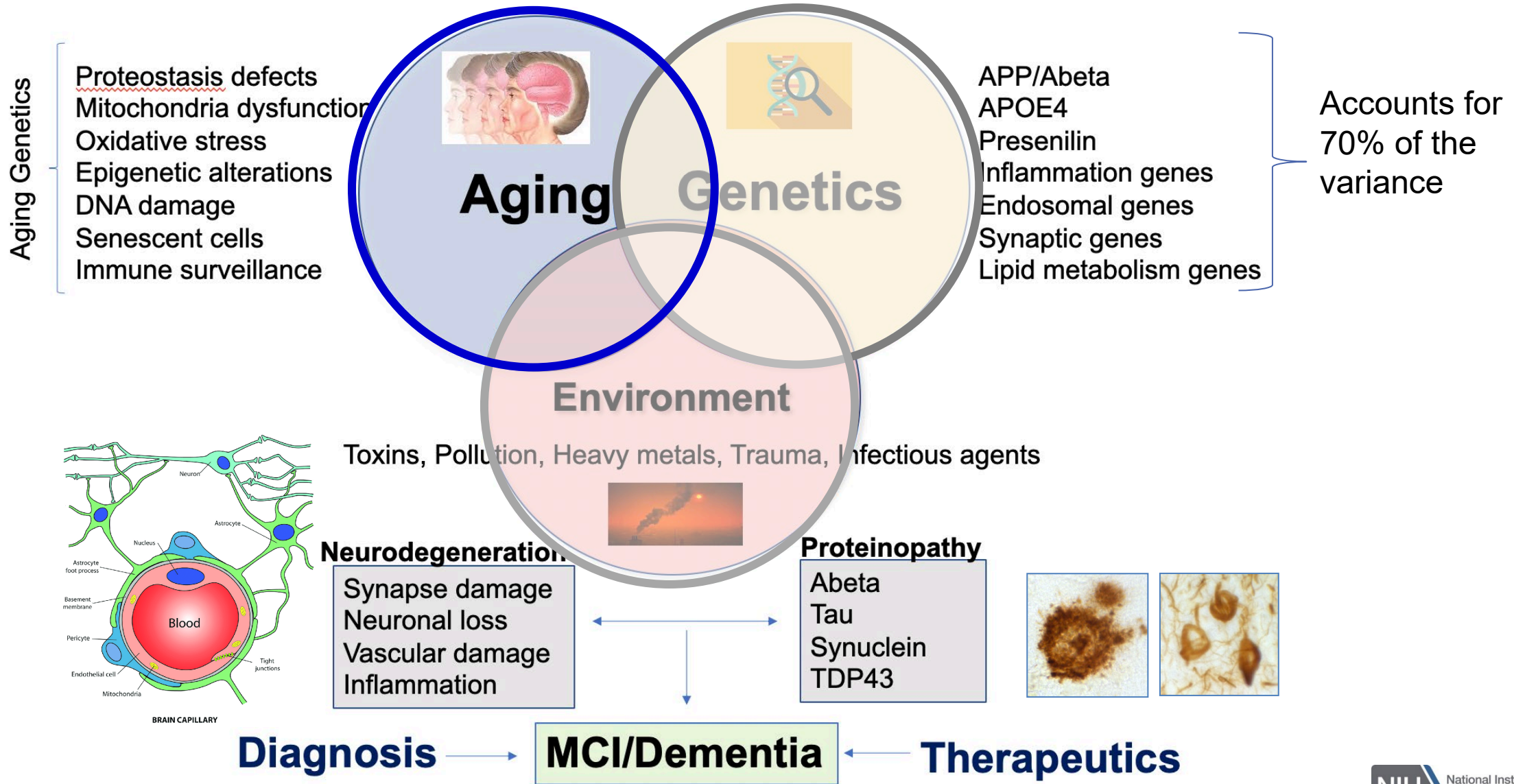


# Re-considering the role of protein aggregation in AD/ADRD



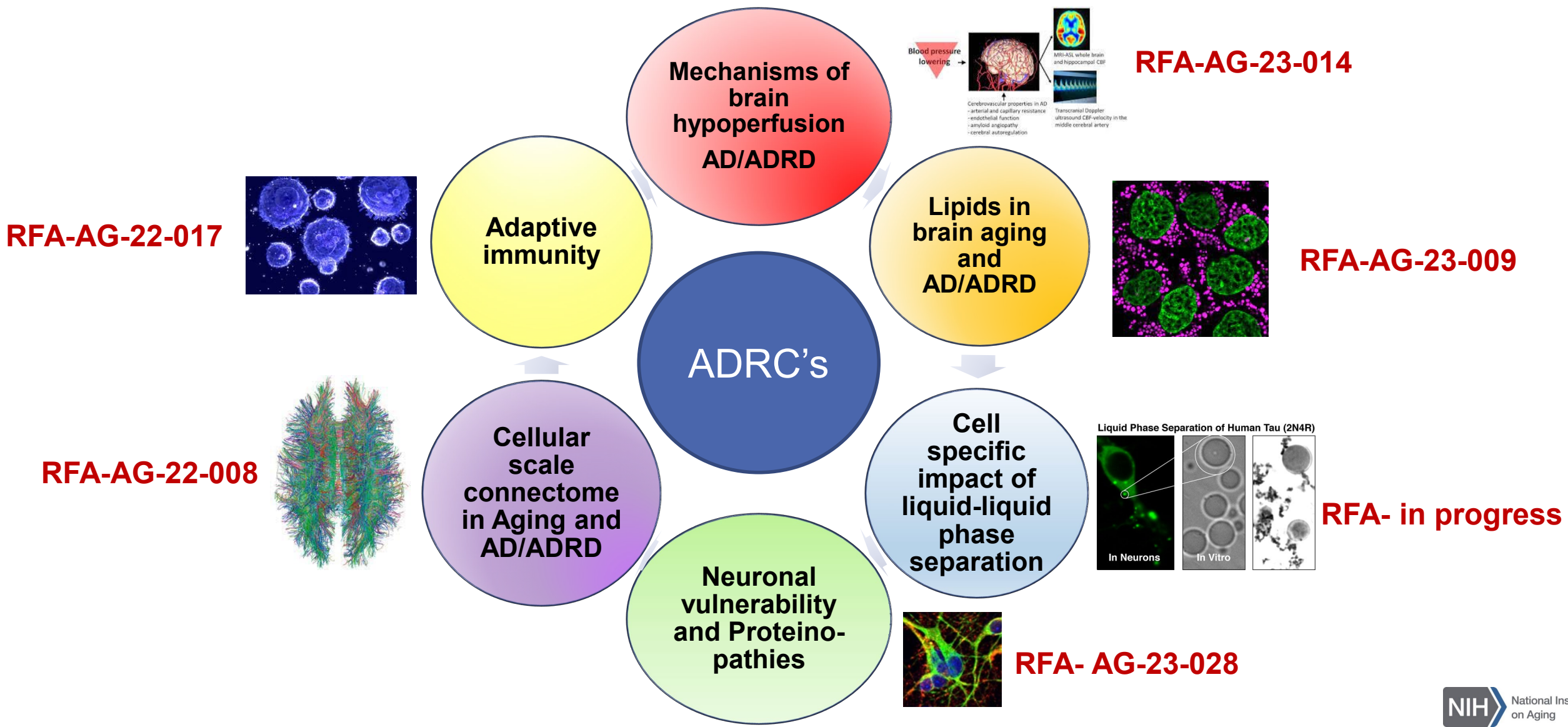


# Role of aging in the pathogenesis of AD/ADRD



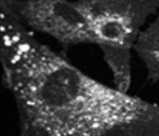
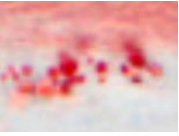
# Contribution of aging mechanisms to AD/ADRD pathogenesis

NIA Program Directors: Mack Mackiewicz, Amanda Dibattista, Austin Yang, Brad Wise, Paul Barrett, Lisa Opanasuck



# NIA workshop on Lipids in Brain Aging and AD/ADRD April 2021.

NIA organizers: Amanda DiBattista, Paul Barrett, Brad Wise



## Session I

### *Lipid Droplets in Aging and AD/ADRD.*

Lance Johnson\*, Maria Ioannou, Sarah Cohen, Ana Maria Cuervo, Tony Wyss-Coray

#### Define "normal"

What is the lipid composition of LDs, and more generally in the brain (particularly in myelin), with aging and disease?

#### Pathologic al and/or Protective?

What are the consequences of LD accumulation in the aging brain? How does lipid signaling, lipid metabolism, and apoE change during brain aging and AD?

#### Biomarker s and the periphery

Could lipids represent a target for new central or peripheral biomarkers of aging or disease? Could the periphery be leveraged to understand cognitive outcomes?

#### Selective Vulnerability

What are the consequences of *APOE* status and/or sex differences on vulnerability to LD accumulation or lipid-related dysfunction?

## Session II

### *Myelin in Aging and AD/ADRD.*

Robbie Brinton\*, Doug Rosene, Xianlin Han, Vivek Swarup, Kim Bruce

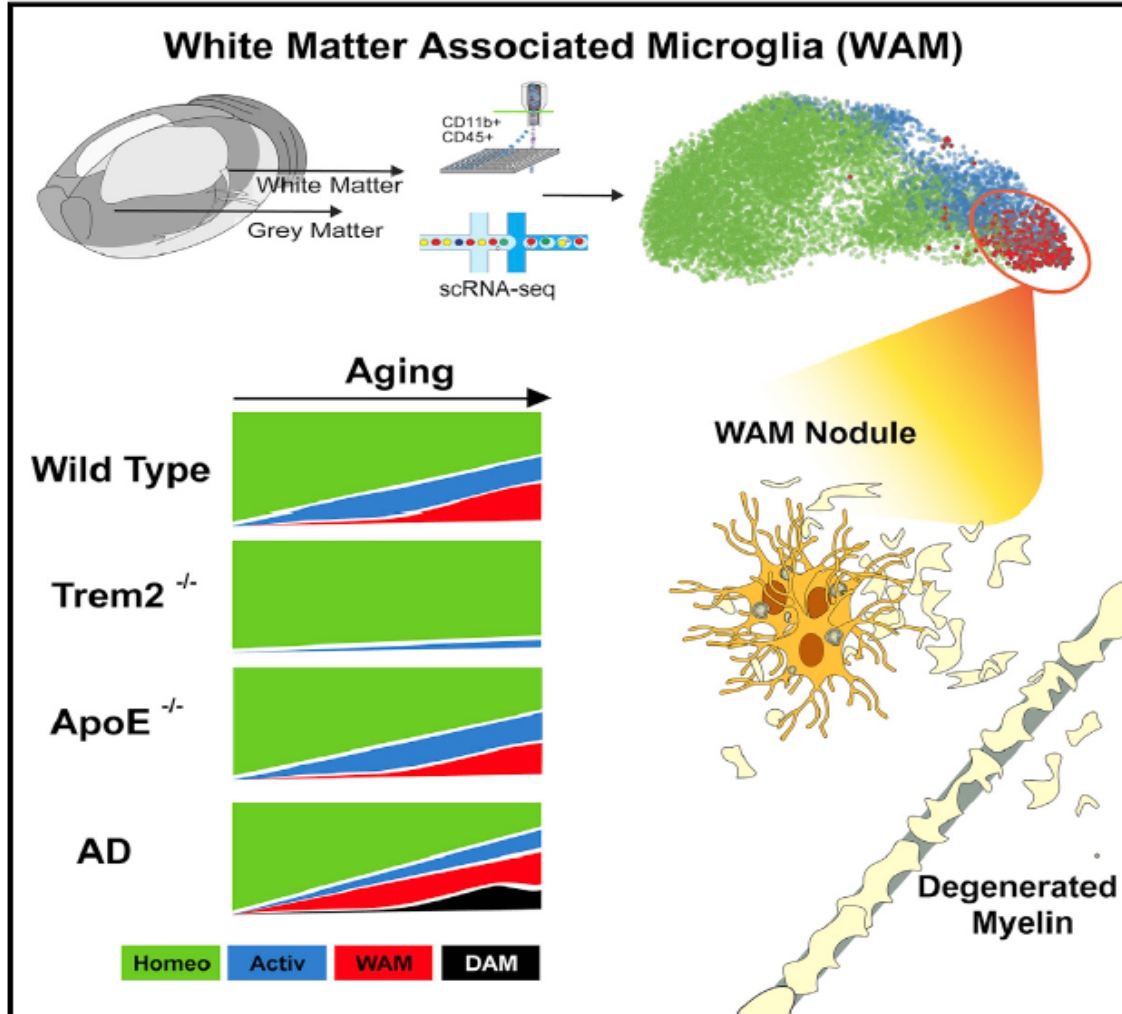
## Session III

### *APOE and Lipid Homeostasis in Aging and AD/ADRD.*

Guojun Bu\*, Ana Valencia-Olvera, Bill Rebeck, Chris Ramsden, Dongming Cai, Fei Yin, Laila Abdullah, Hussein Yassine



# White Matter Associated Microglia (WAMs) clear lipid-rich degenerated myelin accumulating during aging



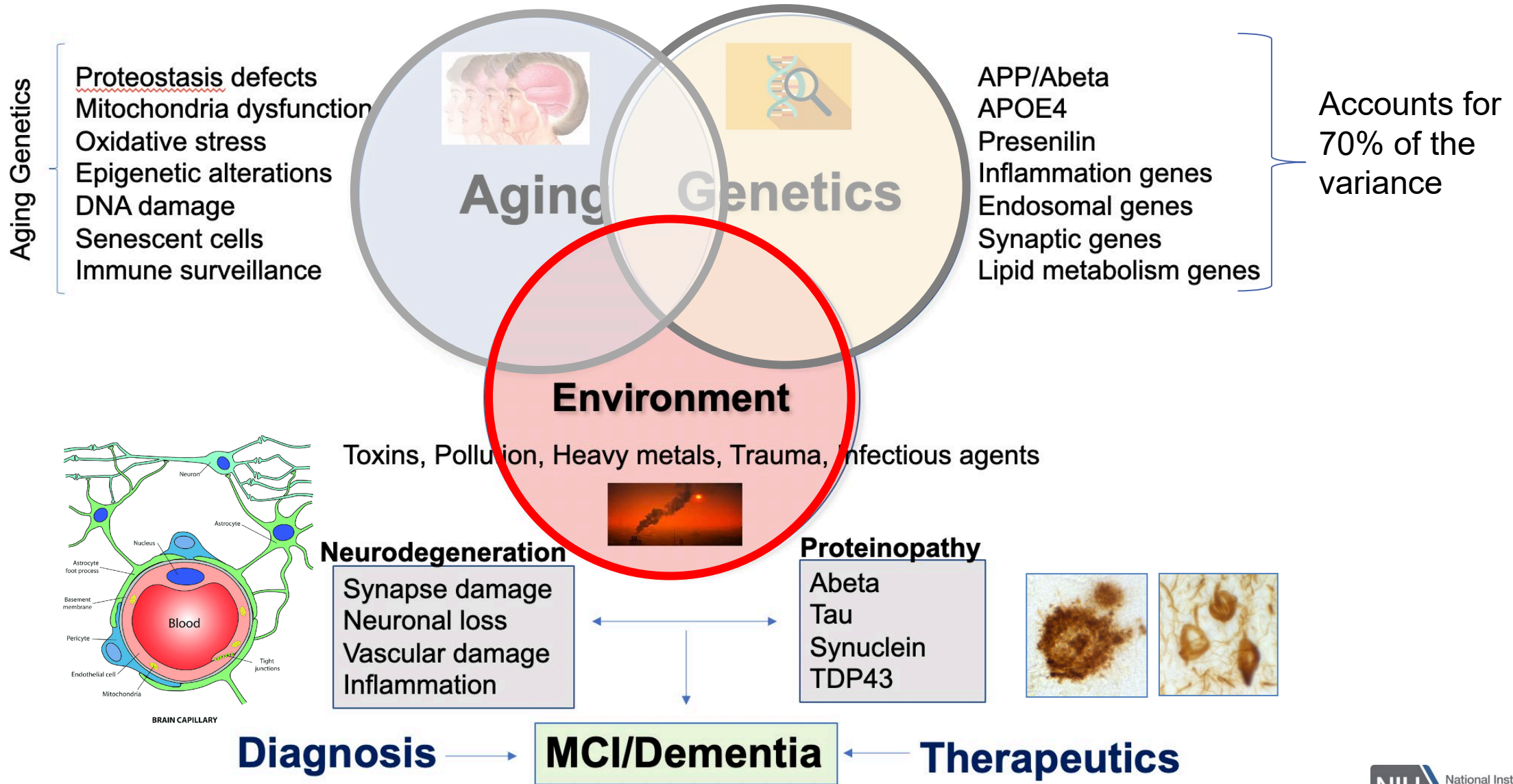
**Aging induces release of lipid-rich myelin debris that accumulates.**

**The protective WAM response depends on TREM2, but not APOE, to clear it.**

**WAM precedes DAM in AD mice, and both activate lipid metabolism genes.**

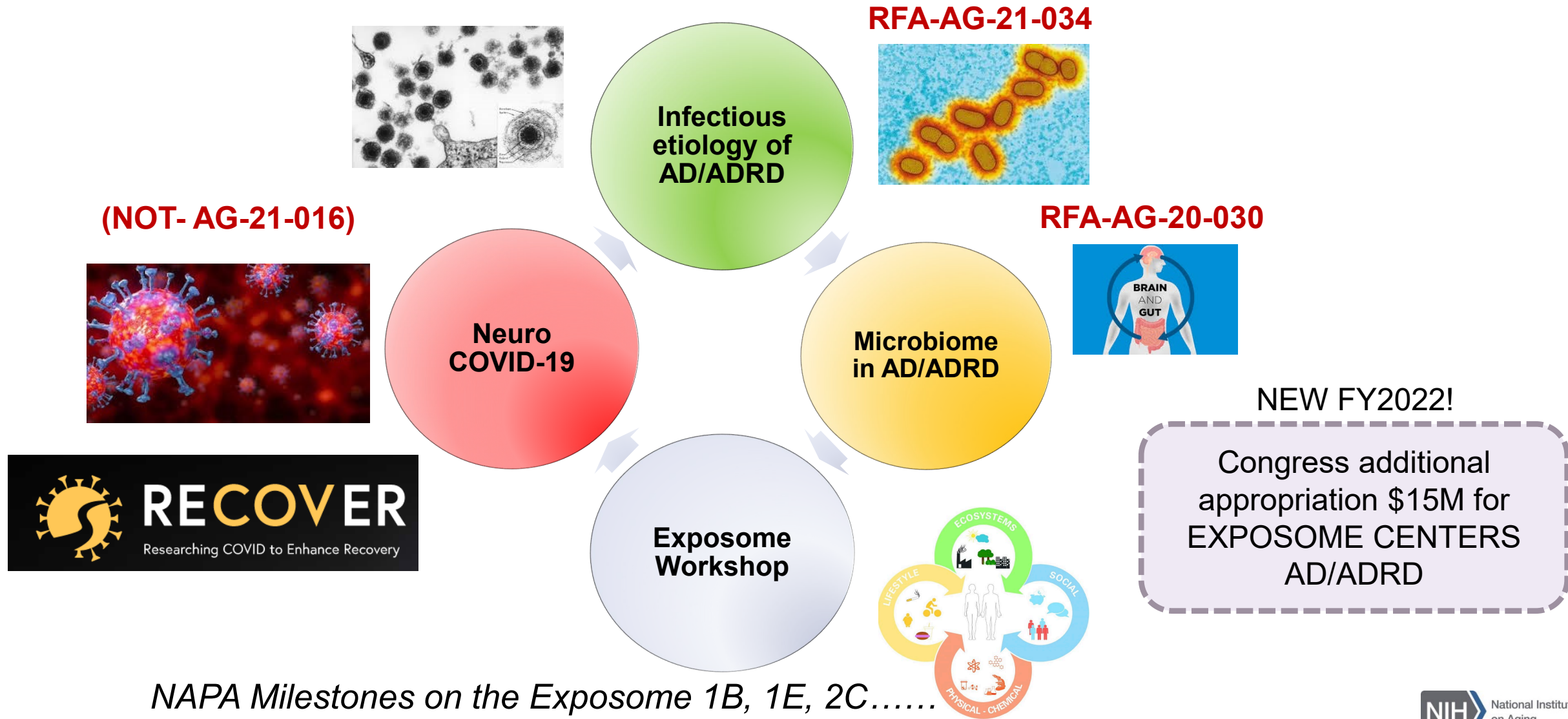
*Safaiyan et al., Neuron, 2021*

# Role of environmental factors in the pathogenesis of AD/ADRD



# Understanding the Role of the Exposome in Brain Aging, AD and ADRD

NIA Program Directors: Brad Wise, Mackiewicz, Amanda Dibattista, Austin Yang, Paul Barrett, Lisa Opanashuk





# What is the Exposome?

## Understanding the Role of the Exposome in Brain Aging, Alzheimer's Disease (AD) and AD-Related Dementias

December 2-3, 2020

NIA- Lisa Opanashuck, Suzana Petanceska, Dallas Anderson, Damali Martin

### Plenary Lectures

- Chirag Patel (Harvard Medical School): “Quantifying the Impact of Gene and Environment Interactions on Health and Disease”
- Peter James (Harvard Medical School/Harvard Pilgrim Health Care Institute ): “Embedding Mobile Health and Deep Learning into Prospective Cohort Studies to Study the Exposome”

- **Session 1:** Translational Epidemiology
- **Session 2:** Overview of NIH Initiatives: ABCD study, NIEHS Exposome/Exposure Programs and Resources, NASEM Environmental Neuroscience Workshop highlights
- **Session 3:** From Clinical Research to Molecular Mechanisms: “Environmental Epigenomics/Mechanisms of Transgenerational Inheritance of Risk and Resilience” (part 1) and “Microbiome and Lifestyle Factors” (part 2)
- **Session 4:** The Impact of Air Pollution on the Etiology of AD

### Ecosystems

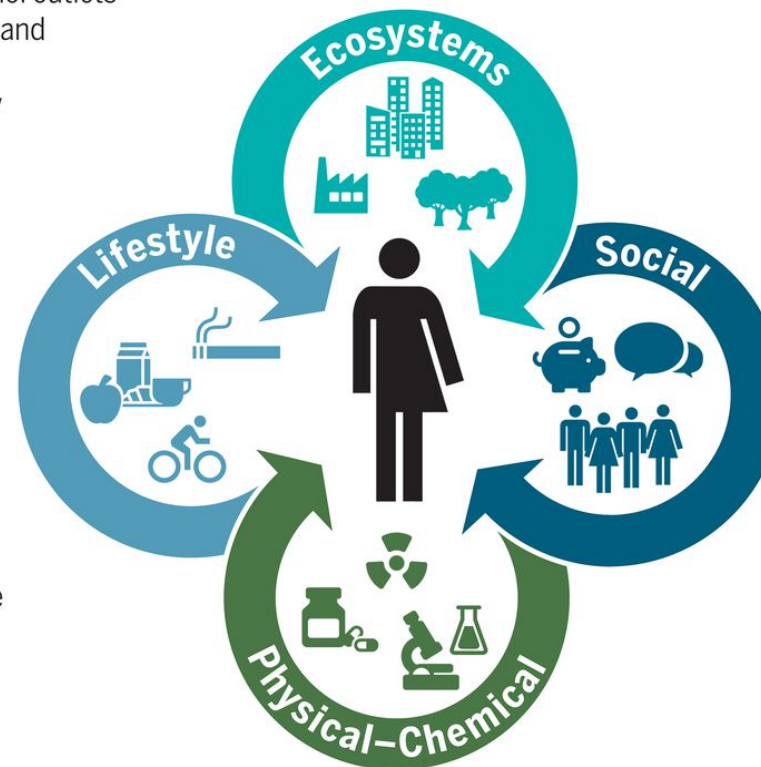
Food outlets, alcohol outlets  
Built environment and urban land uses  
Population density  
Walkability  
Green/blue space

### Lifestyle

Physical activity  
Sleep behavior  
Diet  
Drug use  
Smoking  
Alcohol use

### Social

Household income  
Inequality  
Social capital  
Social networks  
Cultural norms  
Cultural capital  
Psychological and mental stress



### Physical-Chemical

Temperature/humidity  
Electromagnetic fields  
Ambient light  
Odor and noise  
Point, line sources, e.g., factories, ports  
Outdoor and indoor air pollution  
Agricultural activities, livestock  
Pollen/mold/fungus  
Pesticides  
Fragrance products  
Flame retardants (PBDEs)  
Persistent organic pollutants  
Plastic and plasticizers  
Food contaminants  
Soil contaminants  
Drinking water contamination  
Groundwater contamination  
Surface water contamination  
Occupational exposures

# Exposome and diversity research in AD/ADRD

NIA Program Directors: Matt Sutterer, Molly Wagster, Damali Martin, Nina Silverberg, Cerise Elliott, Marilyn Miller, Alison Yao, Jennie Larkin, Laurie Ryan, Suzana Petanceska

Leveraging **ADRC's**, NCRAD, NACC, AMP-AD, MODEL, ADNI...

**NOT-AG-21-035**



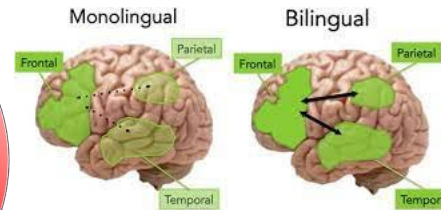
**Collaborative  
Studies on  
AD/ADRD**

**RFA-AG-23-007**



**Screening  
for  
Cognitive  
impairment  
(U24)**

**Bilingualism  
in cognitive  
reserve and  
resilience in  
Aging and  
AD/ADRD**



**\*RFA AG-23-01**

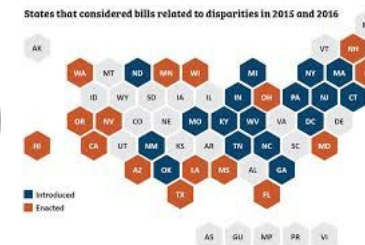
**Precision  
medicine  
approaches  
minority  
health and  
disparities**



**RFA- in progress**



**Health  
disparities**



**NOT-AG-21-033**

# NIA Workshop on bilingualism and cognitive reserve and resilience

March 2-3, 2021

NIA organizers: Molly Wagster and Matt Sutterer

## Program and Speakers

### Overview: Cognitive Reserve & Resilience in Aging

Dan Mungas

### Session I.

Bilingualism across the lifespan and its impact on reserve and resilience

Judith Kroll, Erika Hoff, Arturo Hernandez, Ellen Bialystok

### Session II.

Factors complicating the study of bilingualism and its impact on cognition and the brain

Thomas Bak, Miguel Arce Renteria, Boon Lead Tee, Karen Emmorey, Tamar Gollan

### Perspective: Is there a bilingual advantage?

Ken Paap

### Session III.

Mechanisms by which bilingualism may drive neuroplasticity in brain

Christos Pliatsikas, John Grundy, Jubin Abutalebi, Suvarna Alladi, Esti Blanco-Elorrieta

## Gaps and Opportunities

### Improved Measurement of Aging Bilingual populations.

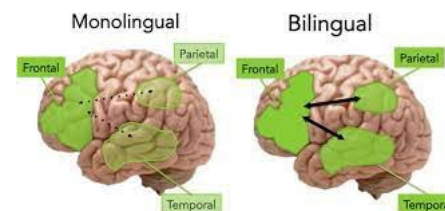
Identify factors of bilingual experience (e.g. age of acquisition, fluency, literacy, etc.)  
Develop objective measures of bilingual proficiency and use

### Establish new multidisciplinary collaborations.

Better contextualize environmental and sociocultural factors  
Integrate bilingualism into existing longitudinal studies of aging

### Develop and test new theoretical frameworks of bilingual effects on cognitive reserve/resilience.

Identify mechanisms for bilingual effects for focused data collection and testing  
Construct validation of bilingualism as an indicator of cognitive reserve  
Incorporate computational modeling approaches



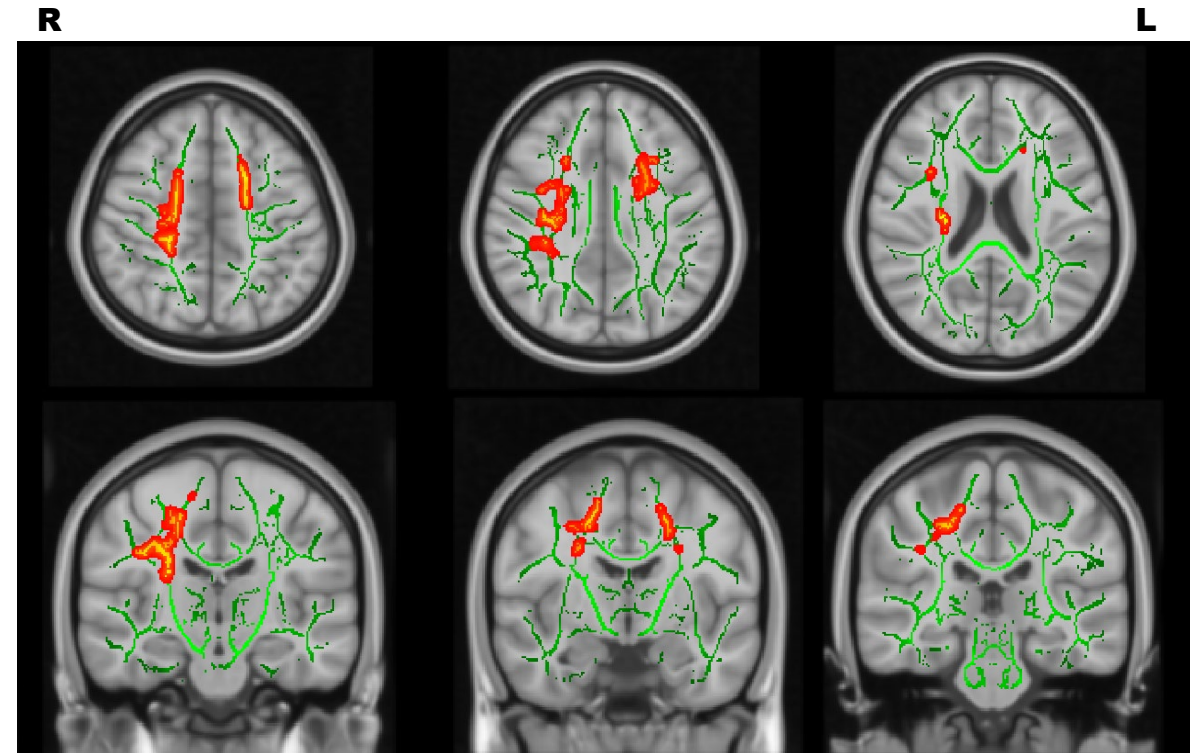
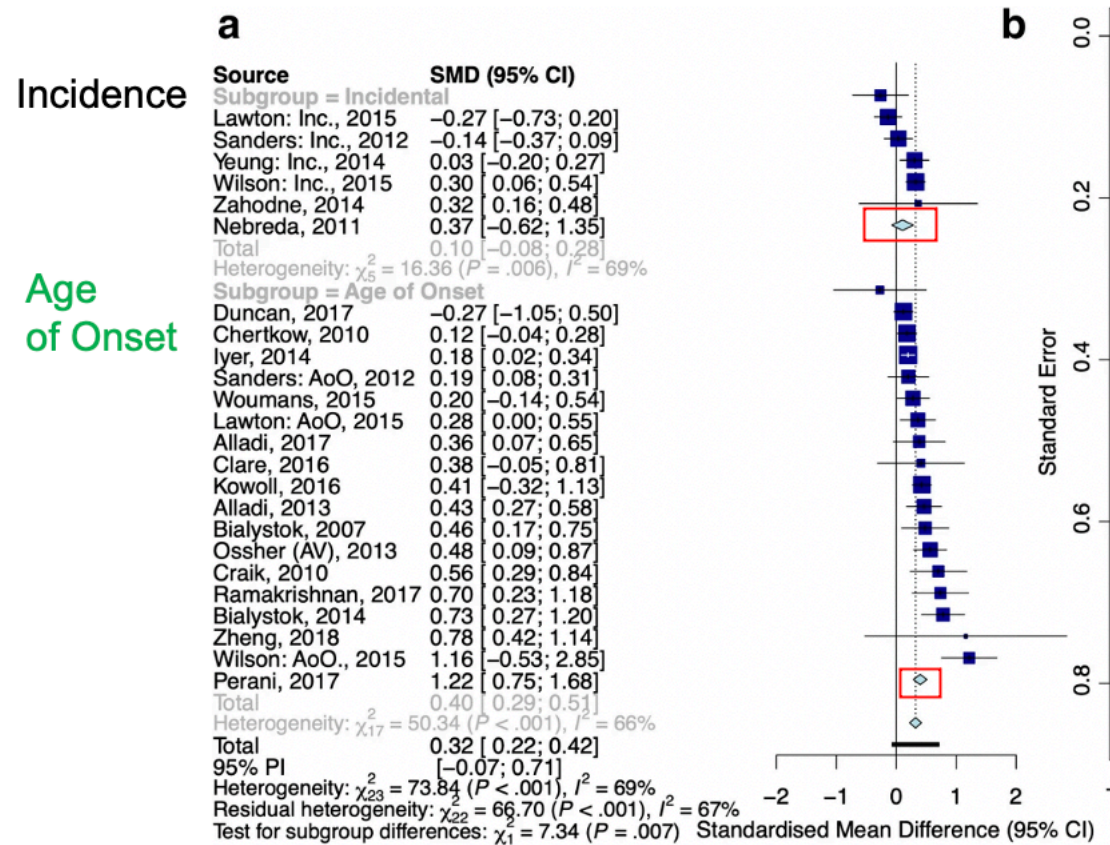
**\*RFA AG-23-01**



# NIA Workshop on bilingualism and cognitive reserve and resilience

Evidence points to Bilingualism influencing age of AD onset, rather than incidence

White matter changes in Bilinguals with FTD



Bilinguals demonstrated better FA in bilateral SLF, left ATR, forceps minor, IFOF and right corticospinal tract.

Anderson, Hawrylewicz, & Grundy (2020),  
*Psychonomic Bulletin & Review*

Courtesy of Suvarna Alladi

# Building Infrastructure for Precision Medicine approaches in AD/ADRD Minority Health and Health Disparities

NIA Program Directors: Damali Martin, Nina Silverberg, Cerise Elliott

## The NIA's Health Disparities Framework:

*A need for research that captures neuropathological process along with environmental, sociocultural, behavioral and other demographic factors that often intersect with race and ethnicity.*

## Objectives:

- Development of research infrastructure and resources for precision medicine studies of AD/ADRD in **minority** populations.
- Support pilot projects to demonstrate feasibility for future larger-scale projects.
- Support formation of transformative, multi-disciplinary teams to address disparities and/or burden, or resilience among minority populations.

## Milestones:

1A: Enable precision medicine; ensure efforts include special populations, ethnic minorities and other under-represented groups.

1I: Test early mechanistic pathways of multiple etiologies of AD/ADRD health disparities; move forward potential opportunities for precision medicine.

PRIORITY POPULATIONS			
Environmental	Sociocultural	Behavioral	Biological
Geographical and Political Factors	Cultural Factors	Coping Factors	Physiological Indicators
Socioeconomic Factors	Social Factors	Psychological Risk/Resilience	Genetic Stability
Health Care	Psychological Factors	Health Behaviors	Cellular Function and Communication
LIFECOURSE PERSPECTIVE			

# Diverse Vascular Contributions to Cognitive Impairment and Dementia (VCID)



<https://diversevciducdavis.edu/>

To use advanced brain imaging and blood-based techniques to understand how vascular changes in late life cause brain injury and cognitive decline among 750 Caucasians, 750 African Americans and 750 Hispanics.

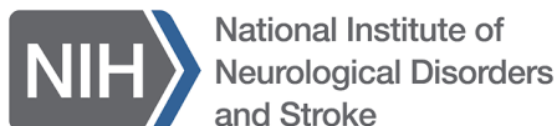
## NOW ENROLLING



PI: Charles DeCarli,  
**UC DAVIS**  
UNIVERSITY OF CALIFORNIA



MPI: Myriam Fornage,  
**UT Health**  
The University of Texas  
Health Science Center at Houston

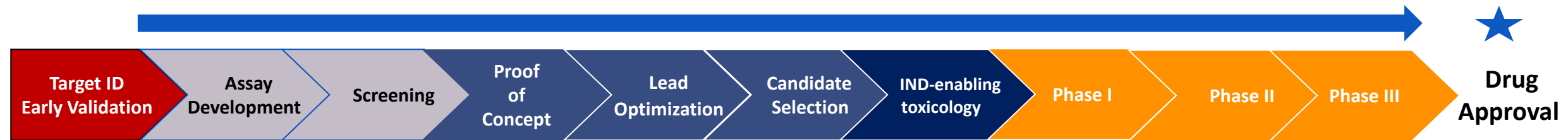


**U19 NS120384**



# Bridging the “Valley of Death” with A Pipeline of Translational Research Funding Opportunities

NIA Program Directors- Larry Refolo, Suzana Petanceska, Zane Martin Jean Yuan, Kristina McLinden



Discovery of Cell-Based or in vivo Chemical Probes for Novel Brain Targets (R21/R01)

Advancing Basic Neurobiology Toward Translation Through Assay Development (R01)

**NEW program!**

Drug Discovery for Novel AD/ADRD Target (R61/R33)

**Just re-issued!**

AD Drug Development ADDP (U01)

Blueprint Neurotherapeutics BPN

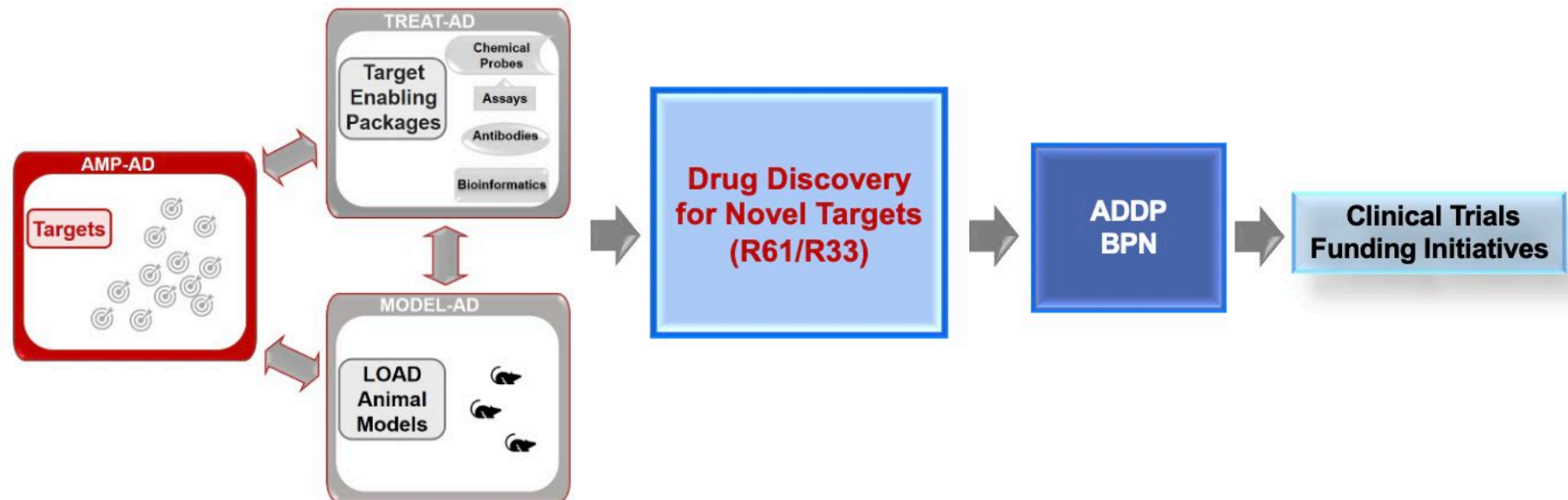
Early and Late-Stage Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01)

Advancing Research on Alzheimer's and Related Dementias SBIR (R43/44) / STTR (R41/42)

# New FOA! Drug Discovery for Novel Targets for AD/ADRD (R61/R33)

NIA Program Directors- Larry Refolo, Suzana Petanceska, Zane Martin

- **Leverage** the NIA investment **in open science discovery programs (AMP-AD, MODEL-AD, TREAT-AD)** to advance novel targets into drug discovery
- **Create a robust** feeder program **for the ADDP/BPN** preclinical development programs by increasing the number of high-quality, early-stage drug discovery projects for novel targets
- **Expand the portfolio of new therapeutic modalities** for novel disease-relevant targets
- Enable data-driven, **precision medicine approaches** to AD drug discovery to increase the likelihood of success in



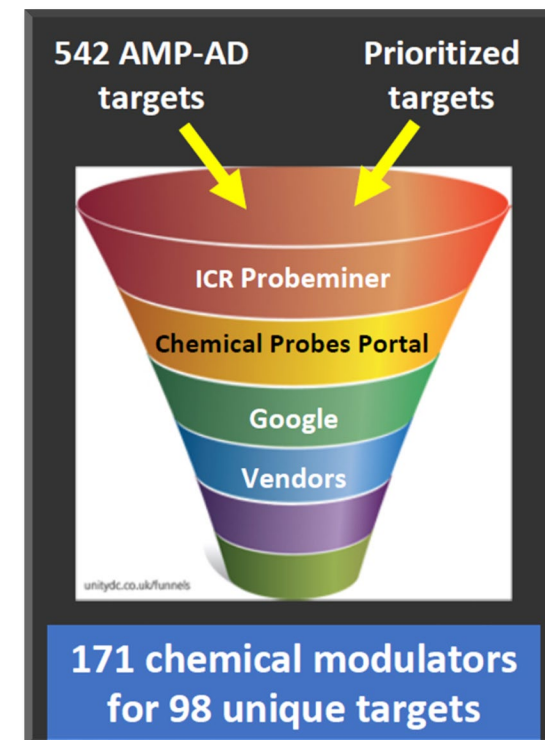
# AD Informer Set: Chemical tools to facilitate drug discovery

## Current AD Informer Set:

- 171 compounds sourced by UNC:
  - 36 are approved drugs
  - 40 are in clinical trials (Phases 1–4)
  - 68 have advanced into animal-based studies
  - 27 have not been explored beyond cellular studies
- 1–7 compounds per target (98 targets)
  - Ranging from inhibitors, substrates, activators, agonists, or antagonists
- QC'd and registered in laboratory information management system
- Data includes predicted BBB permeability, kinetic solubility measurements, and single concentration (10  $\mu$ M) results in cell-based assays related to microglial activity.

## Uses for the Scientific Community:

- To interrogate target validity in established and emerging AD models
- As positive controls/comparators
- To qualify assays



**The AD Informer Set is provided as a single 384-well plate containing 1 $\mu$ L of each compound as a 10mM stock in DMSO. All information about ordering can be found on the AD Knowledge Portal.**





# NINDS AD/ADRD Current and Planned Funding Announcements: Clinical Trials, Clinical Research and Translation

ANNOUNCEMENT	TITLE
Concept Approved	ADRD, Adverse Childhood Experiences, and <b>Social Determinants of Health</b> Ancillary Studies of Existing Longitudinal Cohorts
Concept Approved	<b>Early-Stage Therapy</b> Development for ADRD
Concept Approved	Pragmatic Clinical Trials in Community Settings to Decrease or Prevent VCID Outcomes, Including in <b>Populations that Experience Health Disparities</b>
Concept Approved	Postmortem Neuropathology, Cellular, and Molecular Analyses, Including Ex-Vivo Imaging, to Assess the Significance of Human TBI and VCID AD/ADRD-Relevant Imaging and Clinical Findings During Life
Concept Approved	<b>Treatments for Lewy Body Dementias &amp; Frontotemporal Degeneration</b> - Exploratory Clinical Trial (Related to RFA-NS-21-008)
Concept Approved	<b>Functional Validation of Novel Targets</b> in ADRD (Re-issue RFA-NS-19-015)
Concept Approved	<b>COVID-19 Related Revisions</b> to NINDS ADRD Human Subjects Cooperative Agreement Programs
<a href="#">PAS-19-316</a> (NIA leads)	Advancing Research on AD/ADRD SBIR/STTR Programs ( <b><i>Clinical Trial Optional</i></b> ); <b>Standard due dates</b>
<a href="#">PAS-19-317</a> (NIA leads)	Advancing Research on AD/ADRD SBIR/STTR Programs ( <b><i>Clinical Trial Optional</i></b> ); <b>Standard due dates</b>

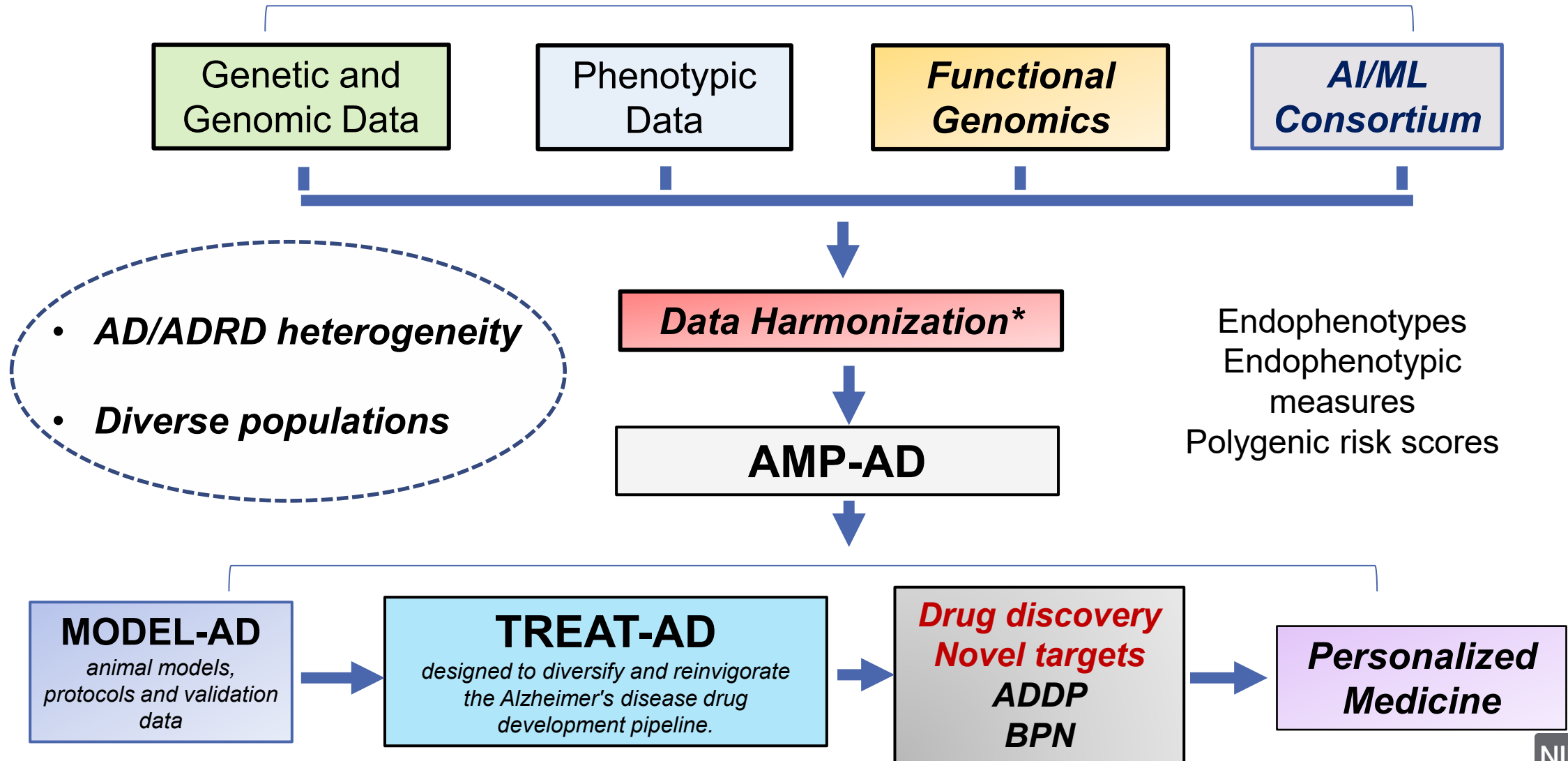
14 NINDS ADRD funding initiatives are planned for FY 2023, for more information see:  
<https://www.ninds.nih.gov/Current-Research/Focus-Disorders/Alzheimers-Related-Dementias>

**No RFA is needed to apply!! NINDS special AD/ADRD payline for investigator-initiated research applications to NIH Parent R01 and NINDS R21 ([PA-21-219](#))**

# Translating AD genomics data to personalized medicine

NIA Program Directors: Marilyn Miller, Alison Yao, Jennie Larkin, Damali Martin, Dallas Anderson

*ADSP, ADRC's, Biomarkers and Epidemiology programs*

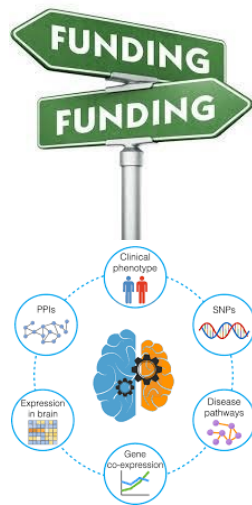


# THANKS



## Concept Approvals:

<https://www.nia.nih.gov/approved-concepts>

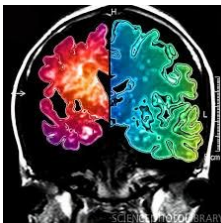


## General FOAs:

<https://www.nia.nih.gov/research/funding>

## Alzheimer's Disease and Related Dementias FOAs:

<http://www.nia.nih.gov/AD-FOAs>



## NIA- Division of Neuroscience

<https://www.nia.nih.gov/research/dn>