

Spring ADRC Directors Meeting

National Institute on Aging

Los Angeles, CA

May 14, 2022

“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

Aging Genetics

- Proteostasis defects
- Mitochondria dysfunction
- Oxidative stress
- Epigenetic alterations
- DNA damage
- Senescent cells
- Immune surveillance



Aging



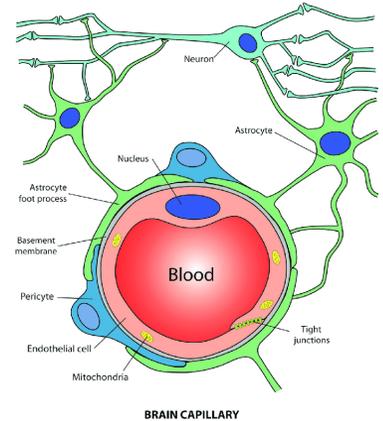
Genetics

- APP/Abeta
- APOE4
- Presenilin
- Inflammation genes
- Endosomal genes
- Synaptic genes
- Lipid metabolism genes

Accounts for 70% of the variance

Environment

Toxins, Pollution, Heavy metals, Trauma, Infectious agents

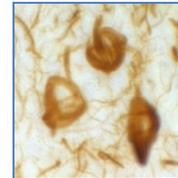
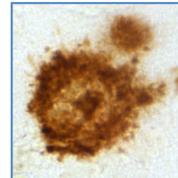


Neurodegeneration

- Synapse damage
- Neuronal loss
- Vascular damage
- Inflammation

Proteinopathy

- Abeta
- Tau
- Synuclein
- TDP43

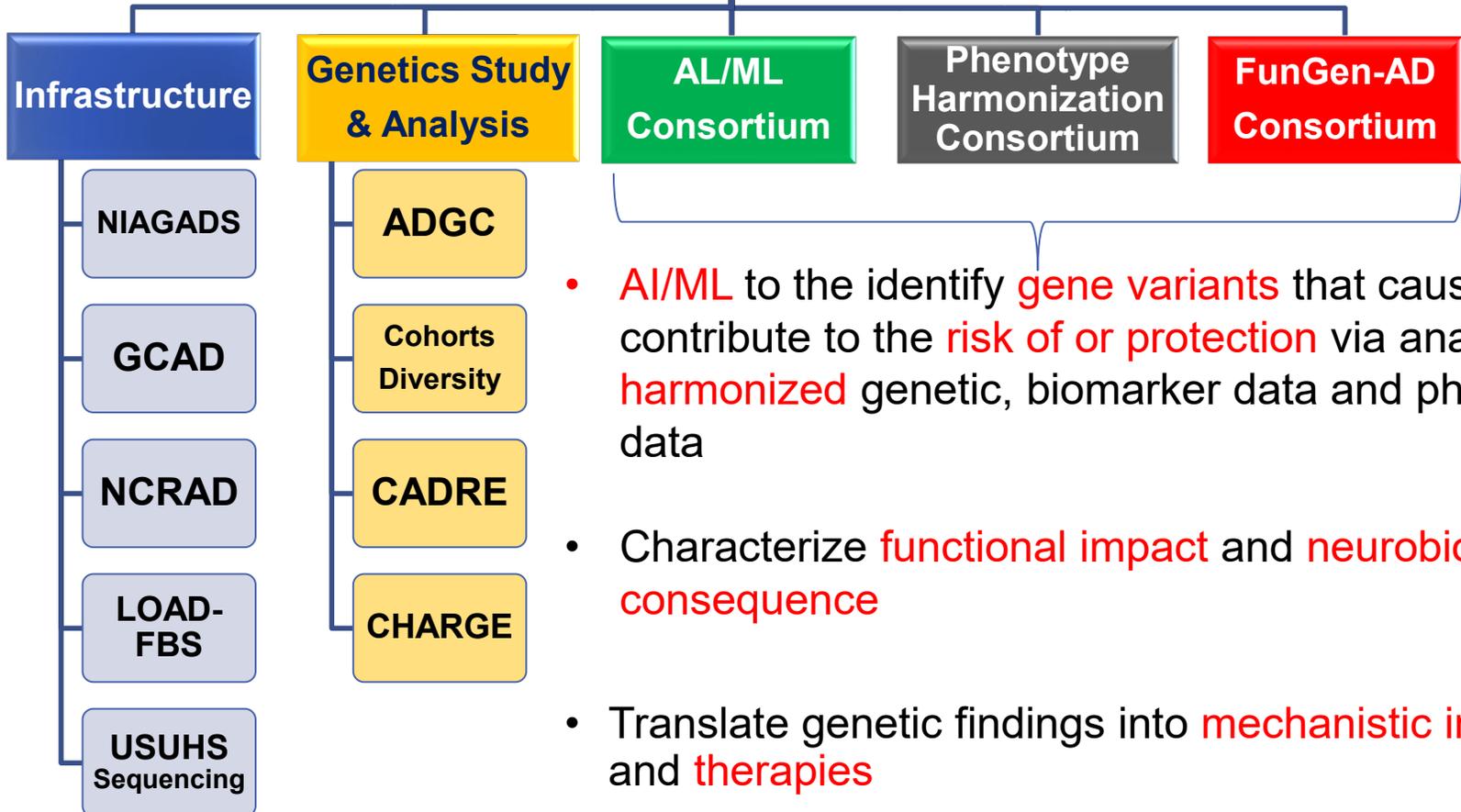


Diagnosis → **MCI/Dementia** ← **Therapeutics**

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)



Work Groups across consortia

Scientific collaboration and resource sharing

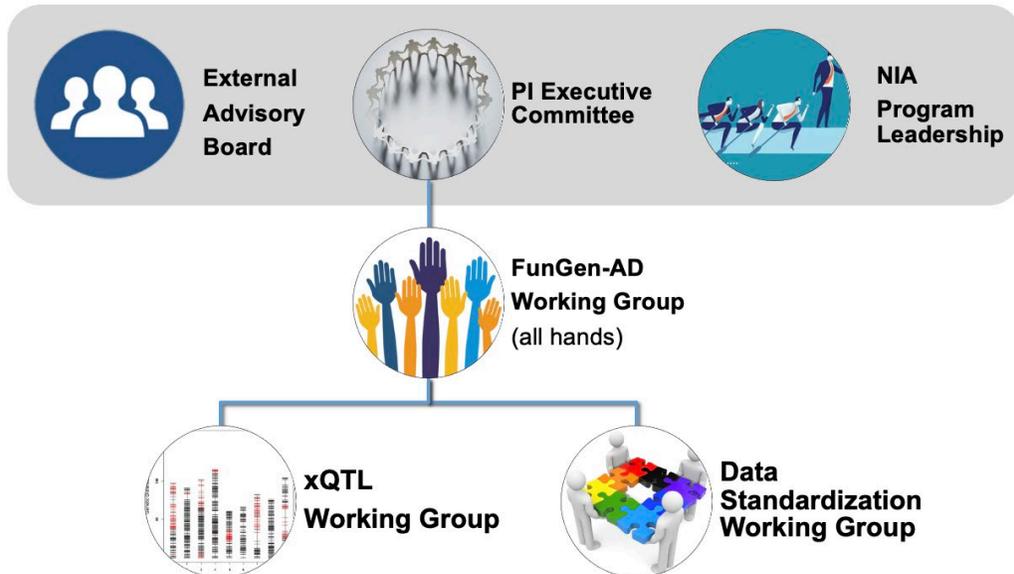


FunGen-AD

ADSP Functional Genomics Consortium

NIA Program Directors: Marilyn Miller, Alison Yao

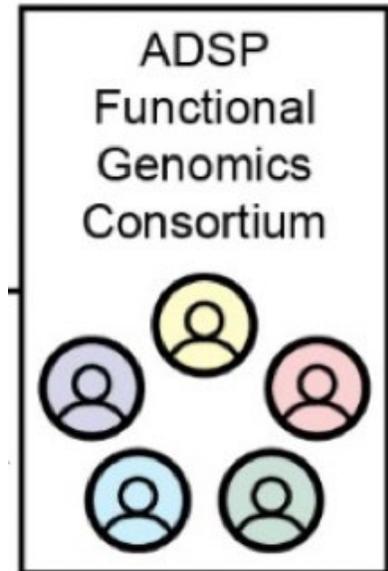
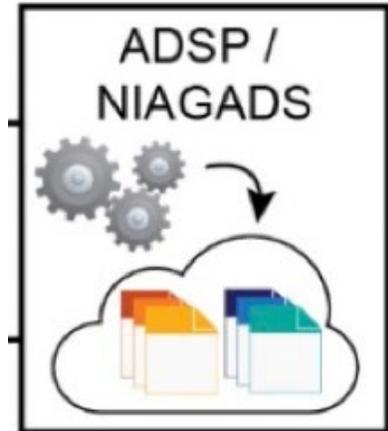
- To understand functional impact underlying the genetic basis of AD/ADRD
- Enable the discovery of genetics-guided targets for the prevention, diagnosis, and treatment of AD/ADRD.



Core Projects

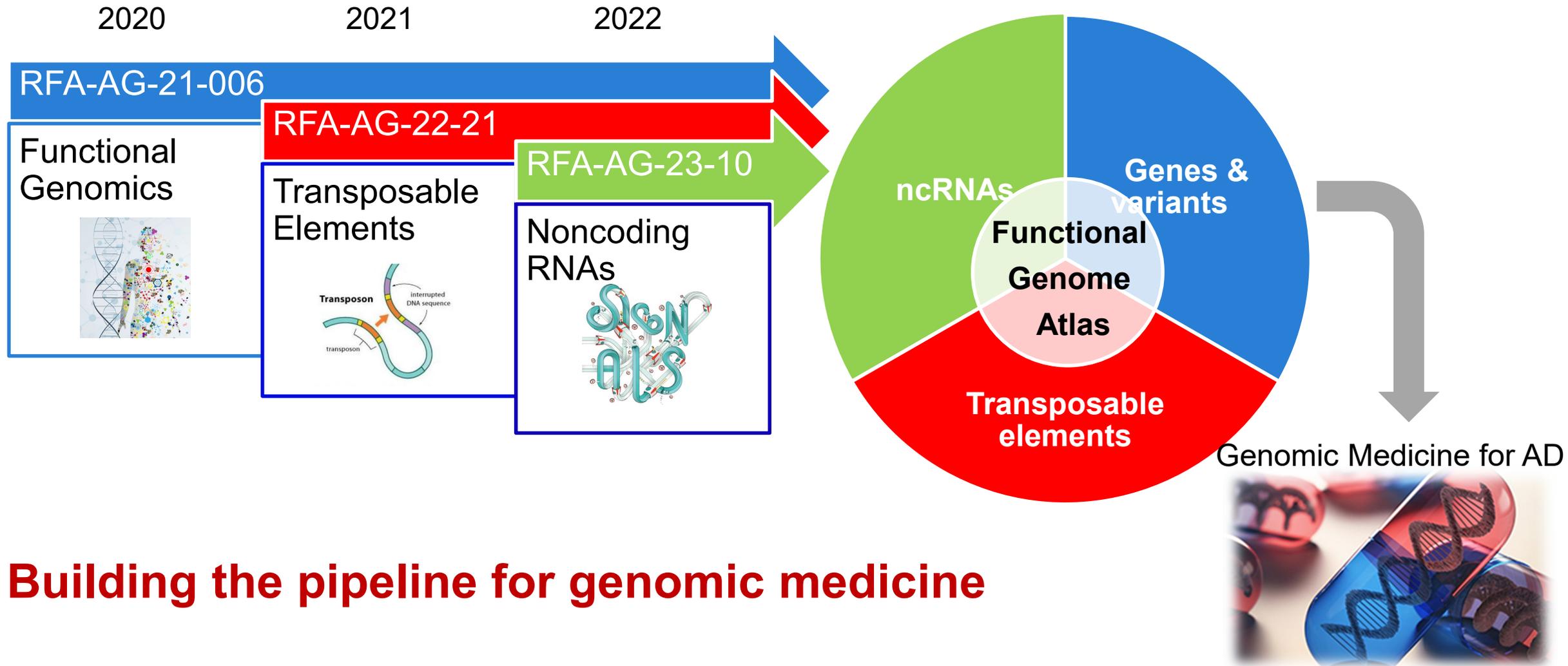
De Jager Columbia U	Shared functional changes across cellular networks
Montine Stanford U	Novel AD variants using high-throughput and single-cell technologies
Shulman Baylor	Functional Genomic AD in Humans and Drosophila Models
Temple Reg Res Fo	AD Risk Genes on Neuro-Vascular Interactions
Vance U Miami	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



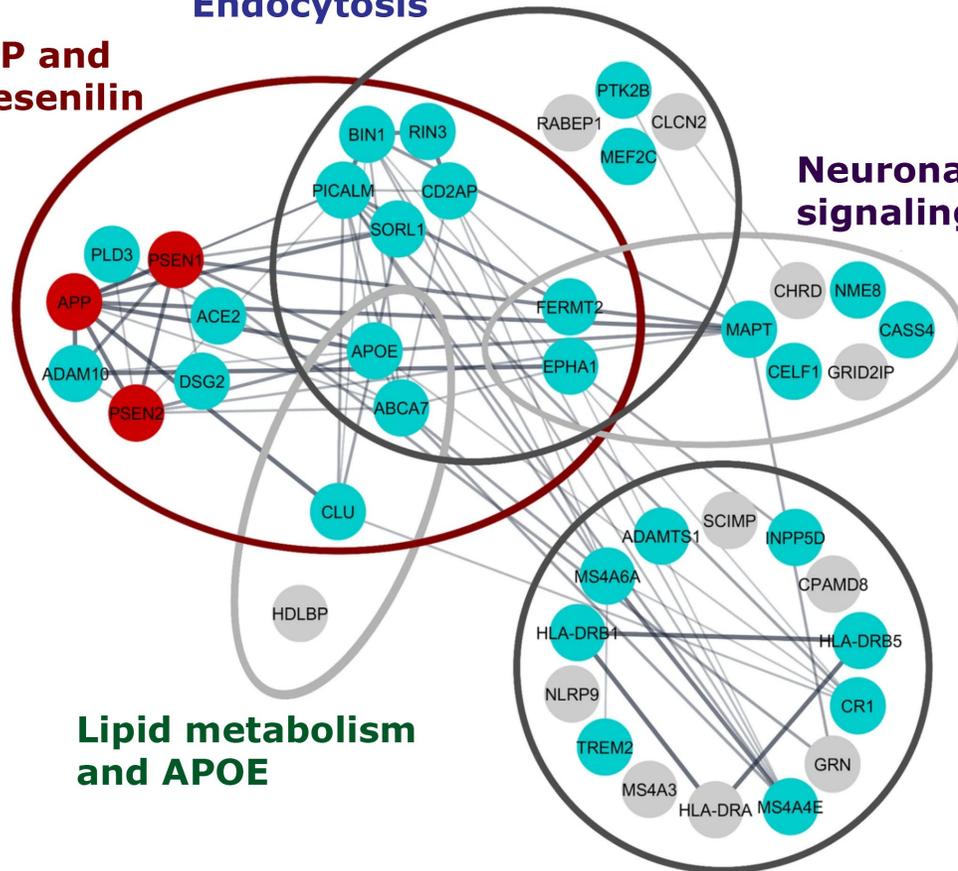
Building the pipeline for genomic medicine

Role of endosomal/lysosomal alterations in AD/ADRD

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

Endocytosis

APP and Presenilin



Neuronal/synaptic signaling and Tau

TMEM 106B (FTD)

TMEM 175 (DLB)

LETTERS

2010

nature genetics

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

Vivianna M Van Deerlin^{1,10*}, Patrick M A Sleiman^{2,10*}, Maria Martinez-Lage^{1,3,10*}, Alice Chen-Plotkin^{1,4,10*}, Li-San Wang¹, Nell R Graff-Radford², Dennis W Dickson⁶, Rosa Rademakers⁶, Bradley F Boeve⁷, ...

Cell

CellPress
OPEN ACCESS

Article

Homotypic fibrillization of TMEM106B across diverse neurodegenerative diseases

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

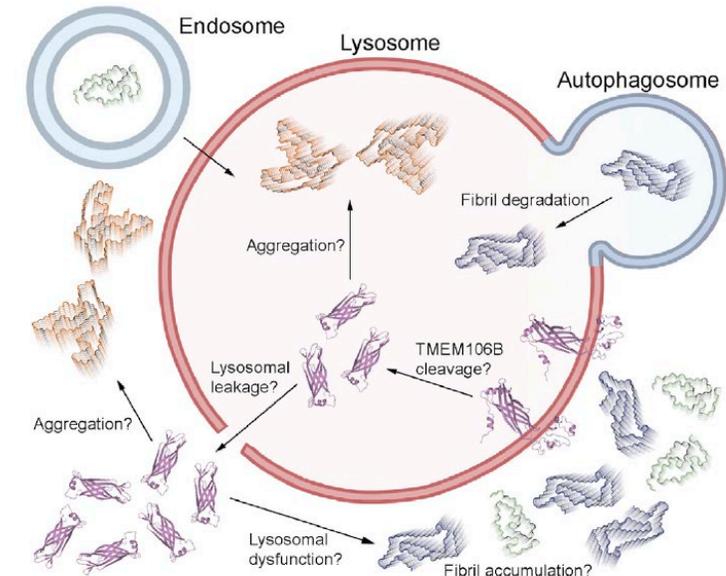
ARTICLES

<https://doi.org/10.1038/441588-021-00785-3>

nature genetics

Check for updates

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



Lipid metabolism and APOE

Neuroinflammation and Immune response

TMEM106B fibrillation in aging and AD/ADRD pathogenesis

Article

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

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

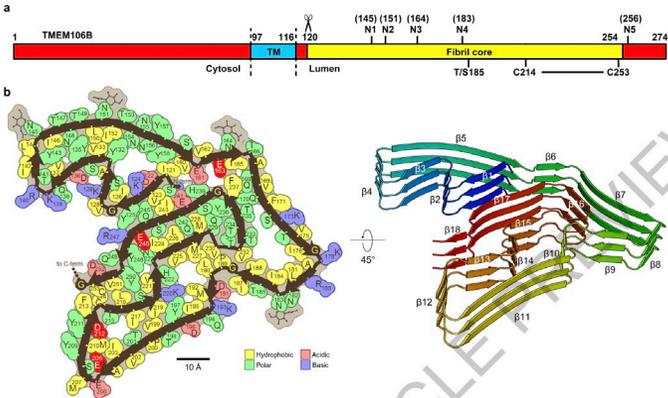
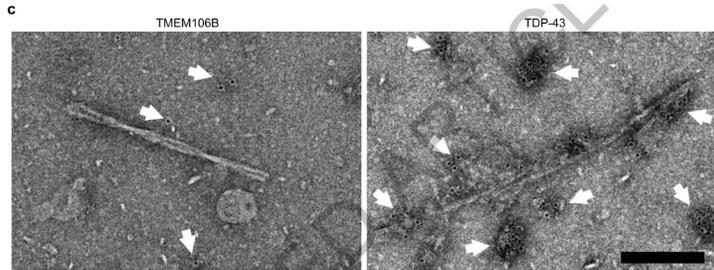
Received: 25 September 2021

Accepted: 22 March 2022

Published online: 28 March 2022

Yi Xiao Jiang^{1,2,3}, Qin Cao^{1,2,3}, Michael R. Sawaya^{1,2}, Romany Abkharon^{1,2}, Peng Ge^{1,2}, Michael DeTure¹, Dennis W. Dickson¹, Janine Y. Fu¹, Rachel R. Ogorzalek Loo¹, Joseph A. Loo¹ & David S. Eisenberg^{3,4,5}

Frontotemporal lobar degeneration (FTLD) is the third most common



Article

Age-dependent formation of TMEM106B amyloid filaments in human brains

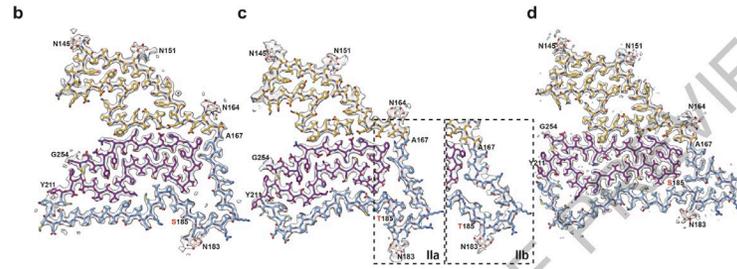
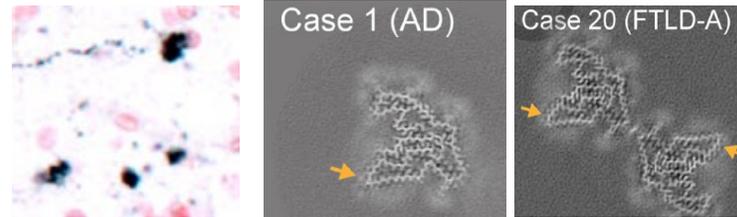
<https://doi.org/10.1038/s41586-022-04650-z>

Received: 9 November 2021

Accepted: 15 March 2022

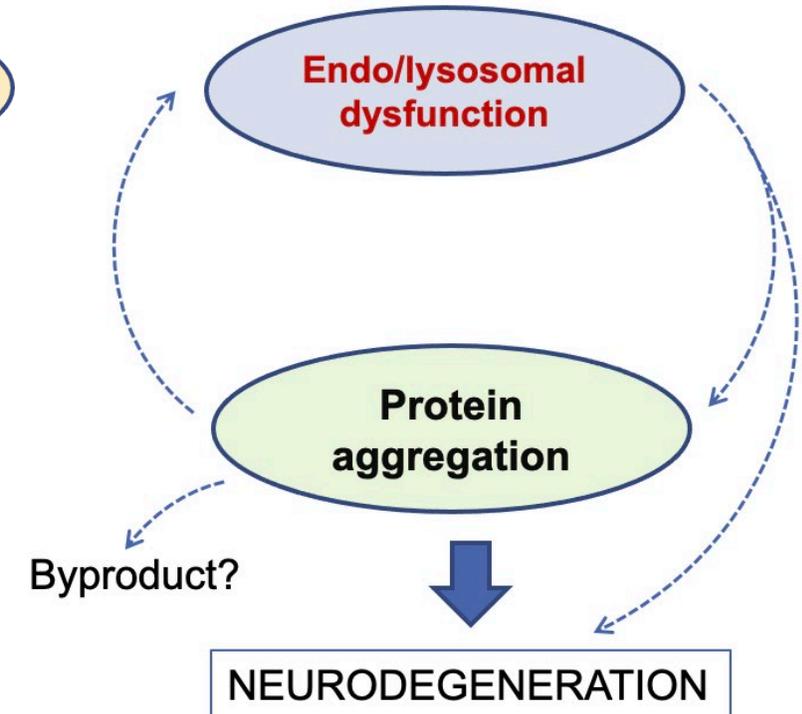
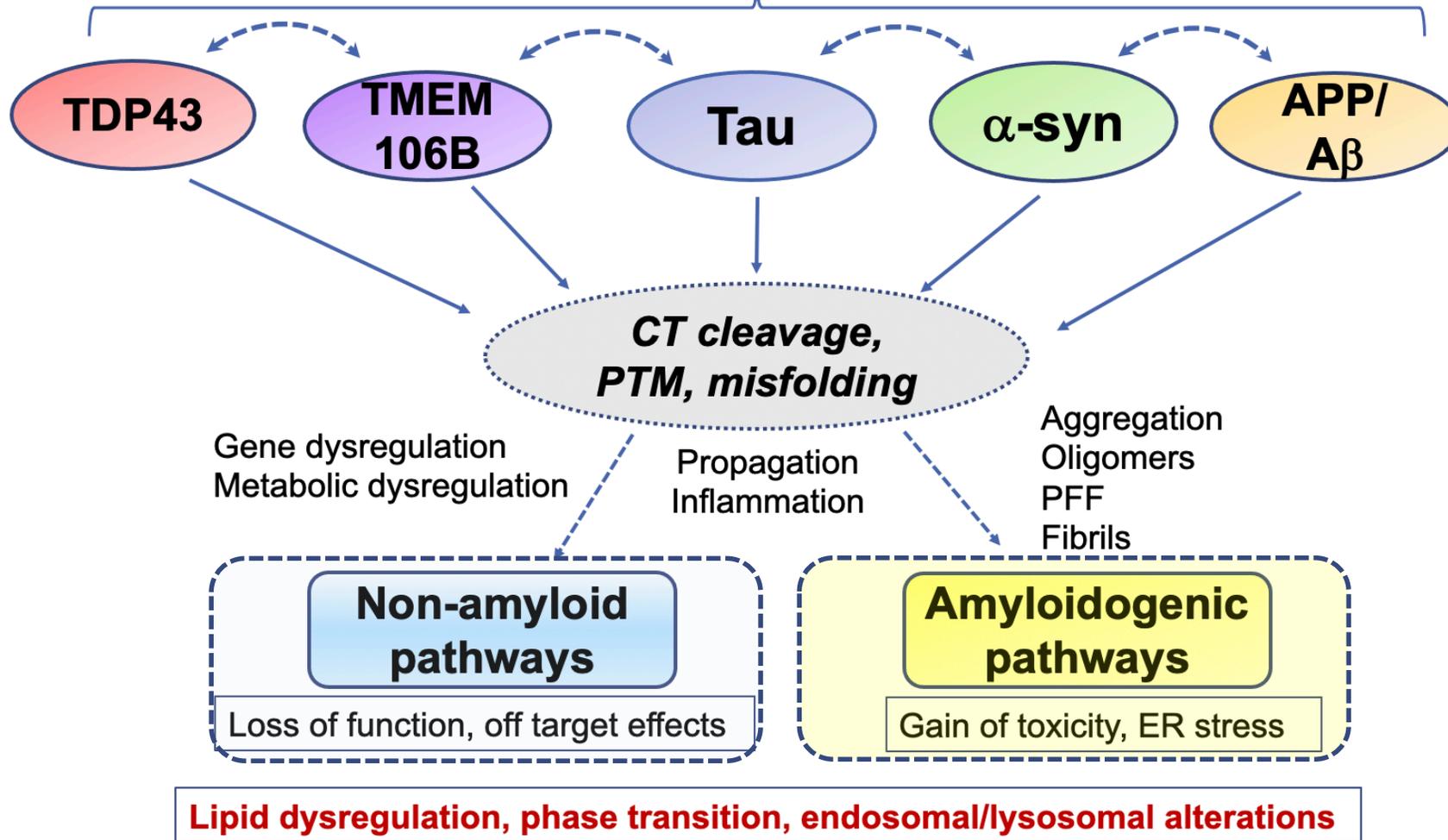
Published online: 28 March 2022

Manuel Schweighauser^{1,2}, Diana Arseni^{1,2}, Mehtap Baciglu^{1,2}, Melissa Huang^{1,2}, Sofia Lövestam^{1,2}, Yang Shi^{1,2}, Yang Yang^{1,2}, Wenjuan Zhang^{1,2}, Abhay Kotecha¹, Holly J. Garringer¹, Ruben Vidal¹, Grace I. Hallinan¹, Kathy L. Newell¹, Airi Tarutani¹, Shigeo Murayama¹, Masayuki Miyazaki¹, Yuko Saito¹, Mari Yoshida¹, Kazuko Hasegawa¹, Tammaryn Lashley¹, Tamas Revesz¹, Gabor G. Kovacs^{1,2,3}, John van Swieten¹, Masaki Takao^{1,2}, Masato Hasegawa¹, Bernardino Ghetti¹, Maria Grazia Spillantini¹, Benjamin Rysekeldi-Falcon¹, Alexey G. Murzin^{1,2}, Michel Goedert^{1,2,3} & Sjors H. W. Scheres^{1,2,3}



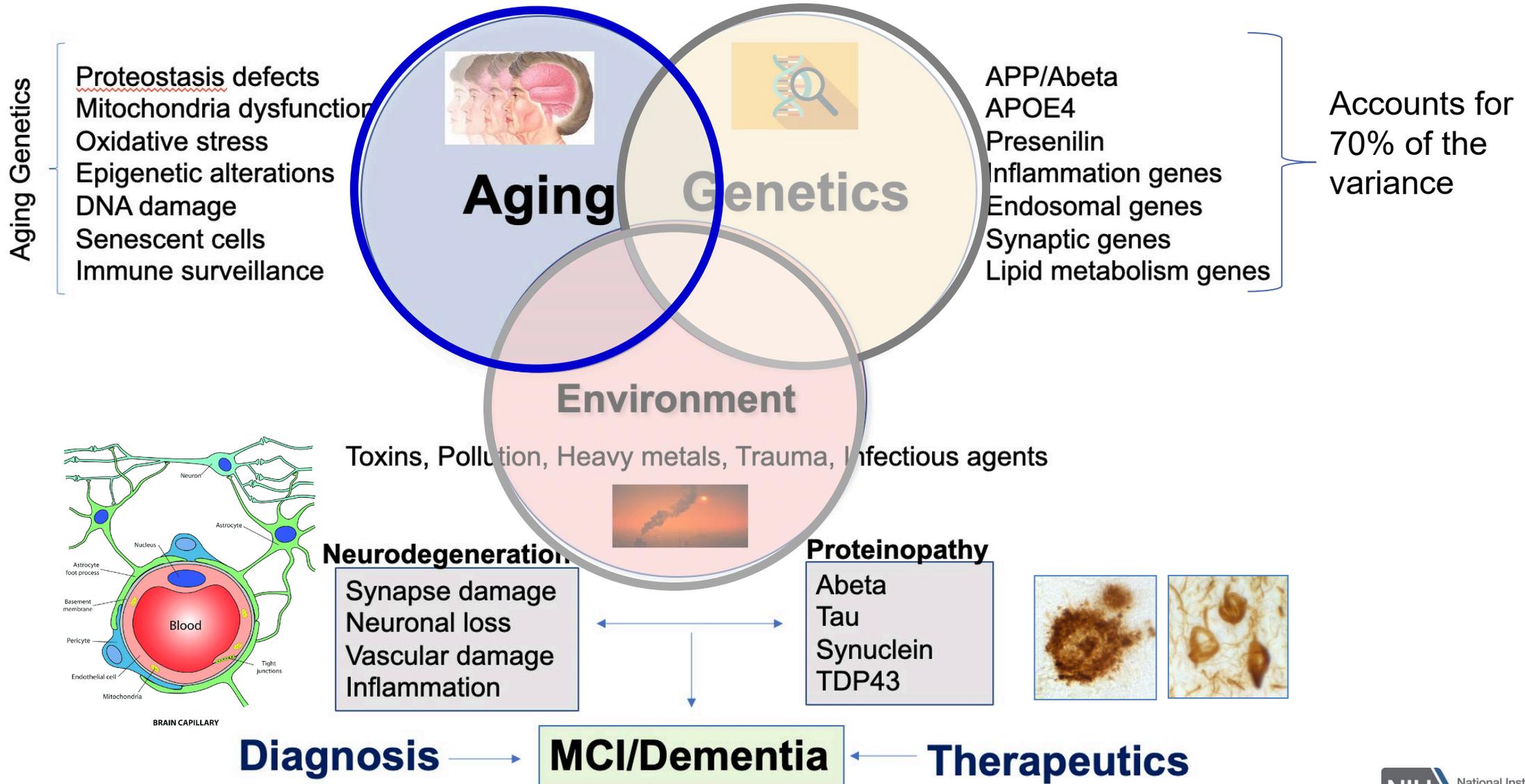
Re-considering the role of protein aggregation in AD/ADRD

Aging, environment, genetics



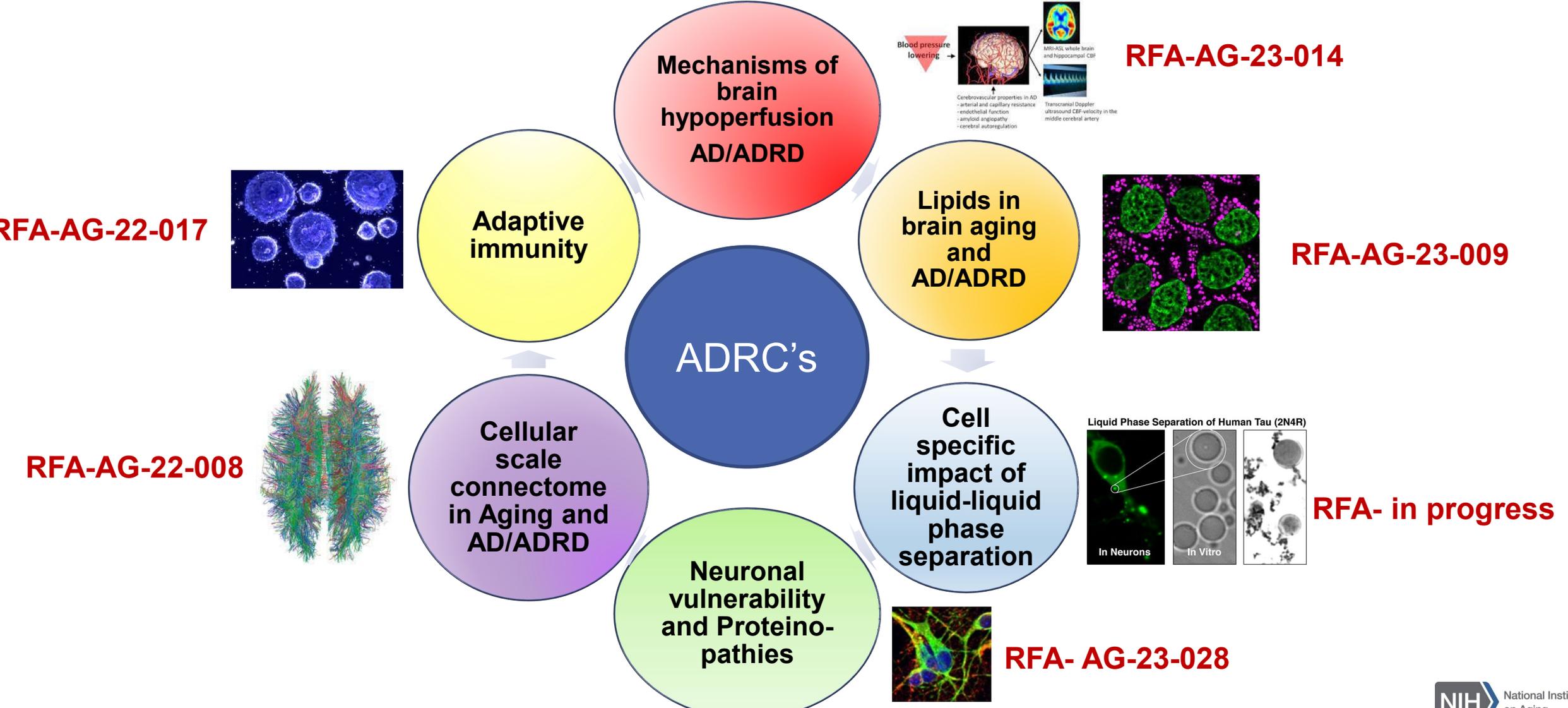
Neurodegeneration

Role of aging in the pathogenesis of AD/ADRD



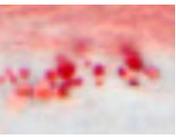
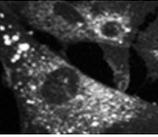
Contribution of aging mechanisms to AD/ADRD pathogenesis

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

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

Define "normal"

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

Pathological 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?

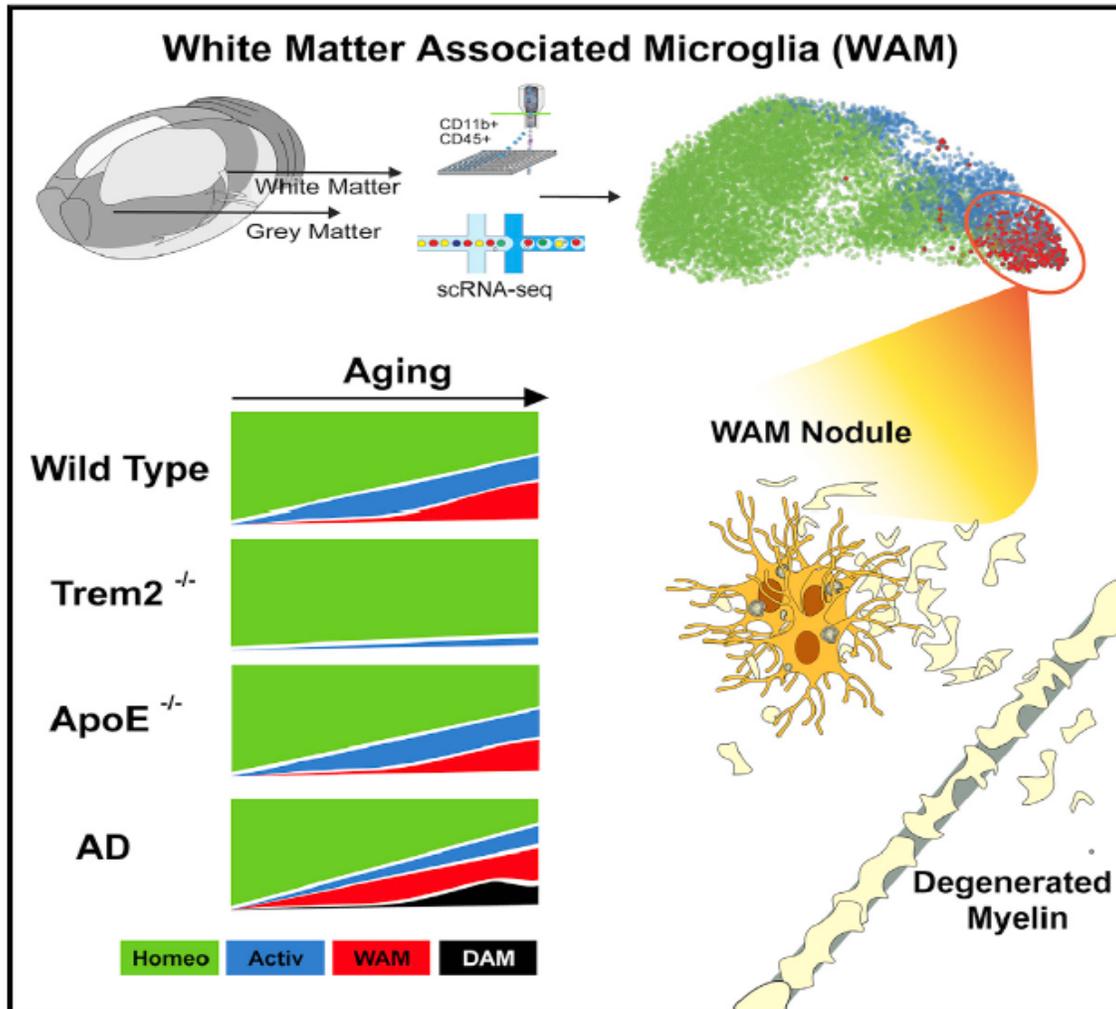
Biomarkers and the periphery

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?

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



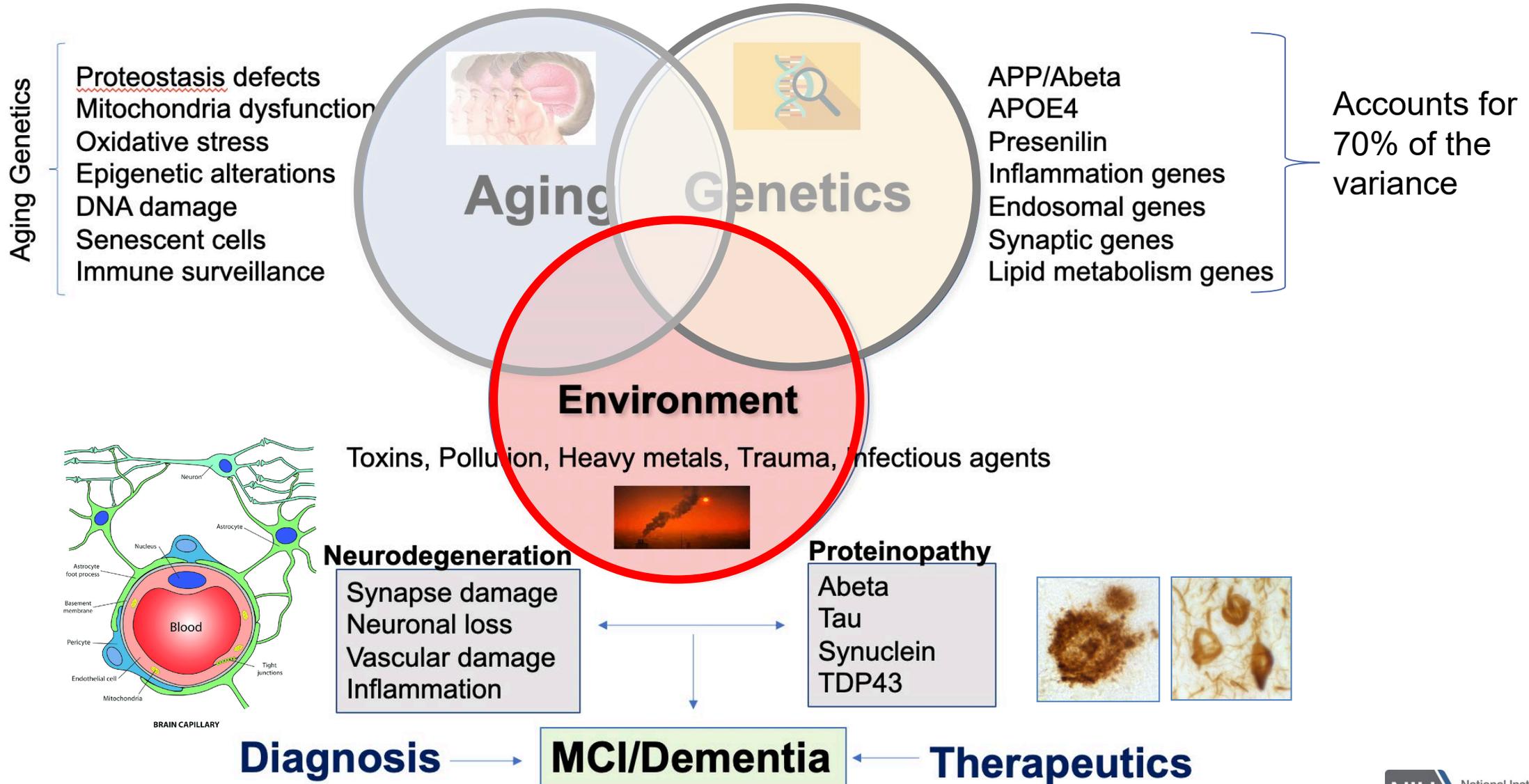
Aging induces release of lipid-rich myelin debris that accumulates.

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.

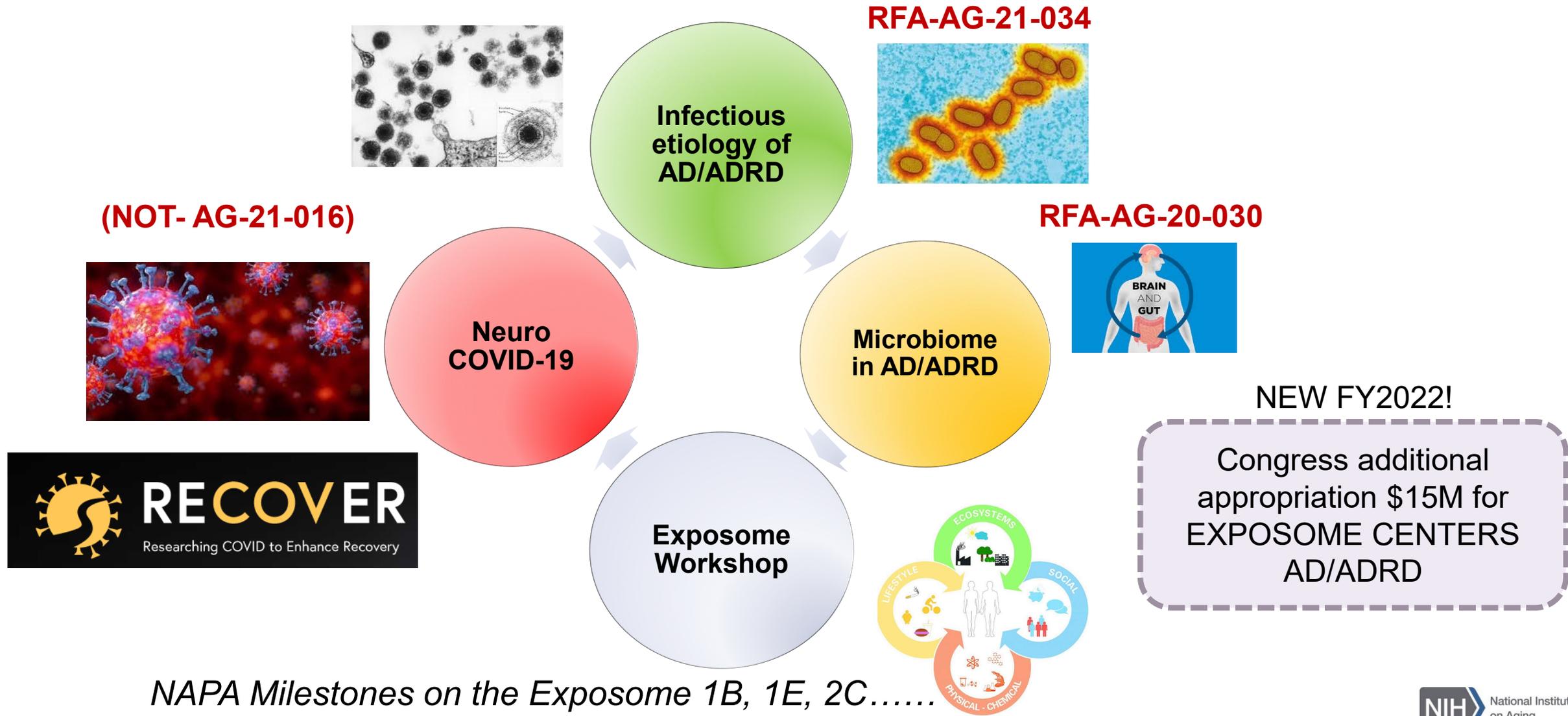
Safaiyan et al., Neuron, 2021

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



NAPA Milestones on the Exposome 1B, 1E, 2C.....

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

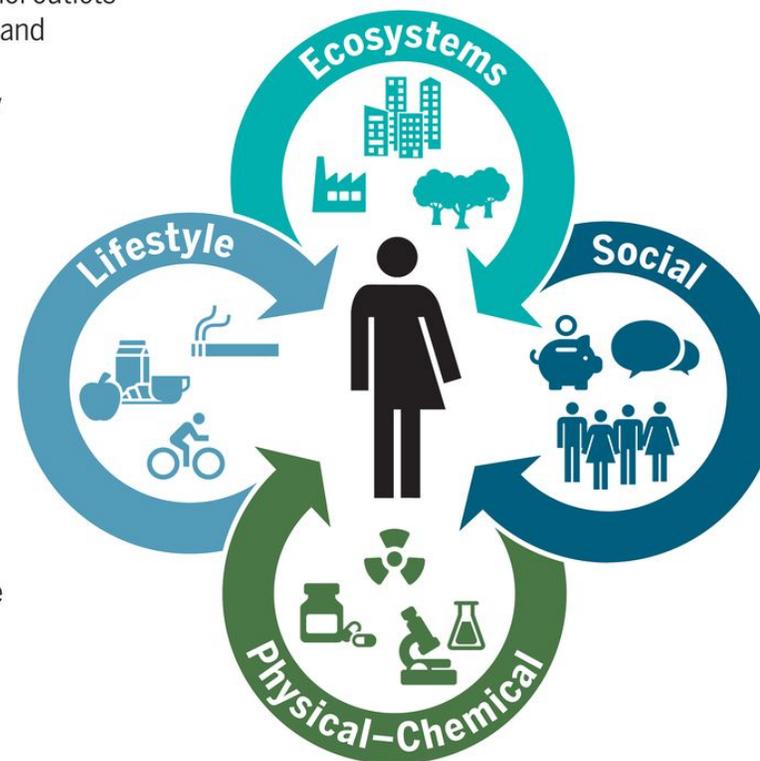
Food outlets, alcohol outlets
Built environment and urban land uses
Population density
Walkability
Green/blue space

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



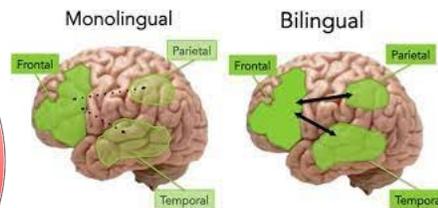
Collaborative Studies on AD/ADRD

RFA-AG-23-007



Screening for Cognitive impairment (U24)

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



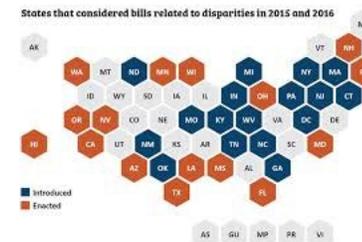
***RFA AG-23-01**

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.

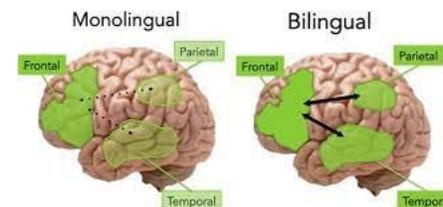
Identify factors of bilingual experience (e.g. age of acquisition, fluency, literacy, etc.)
Develop objective measures of bilingual proficiency and use

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

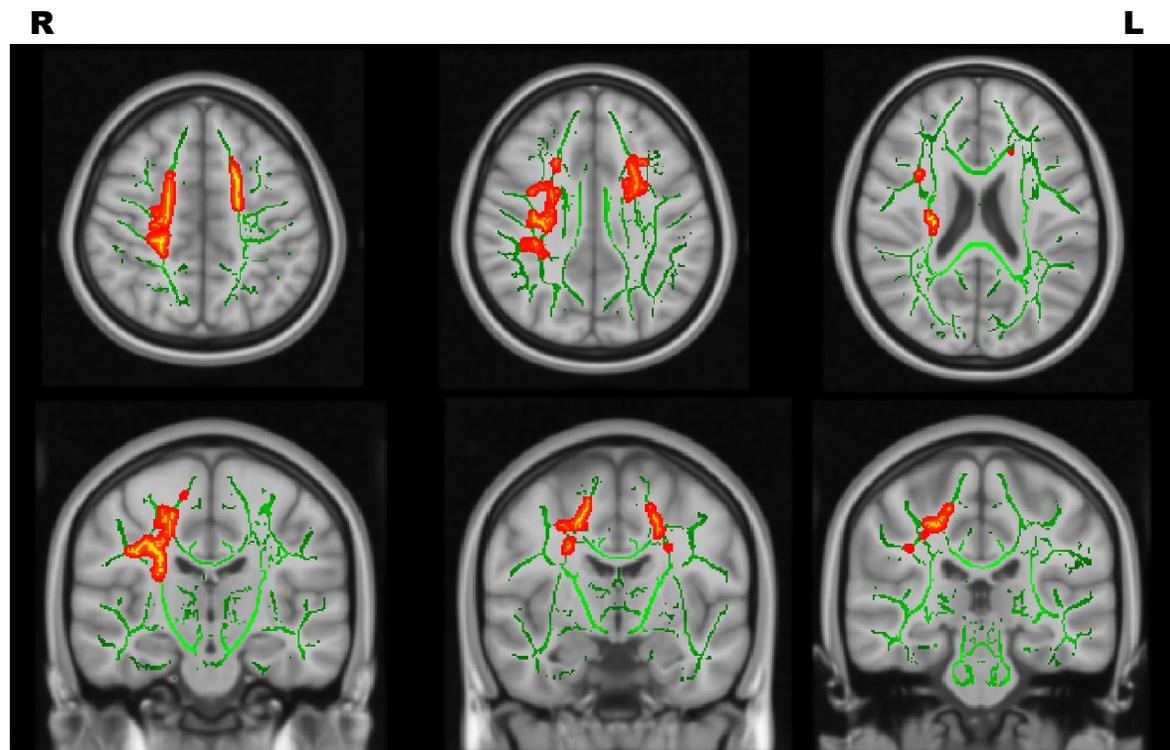
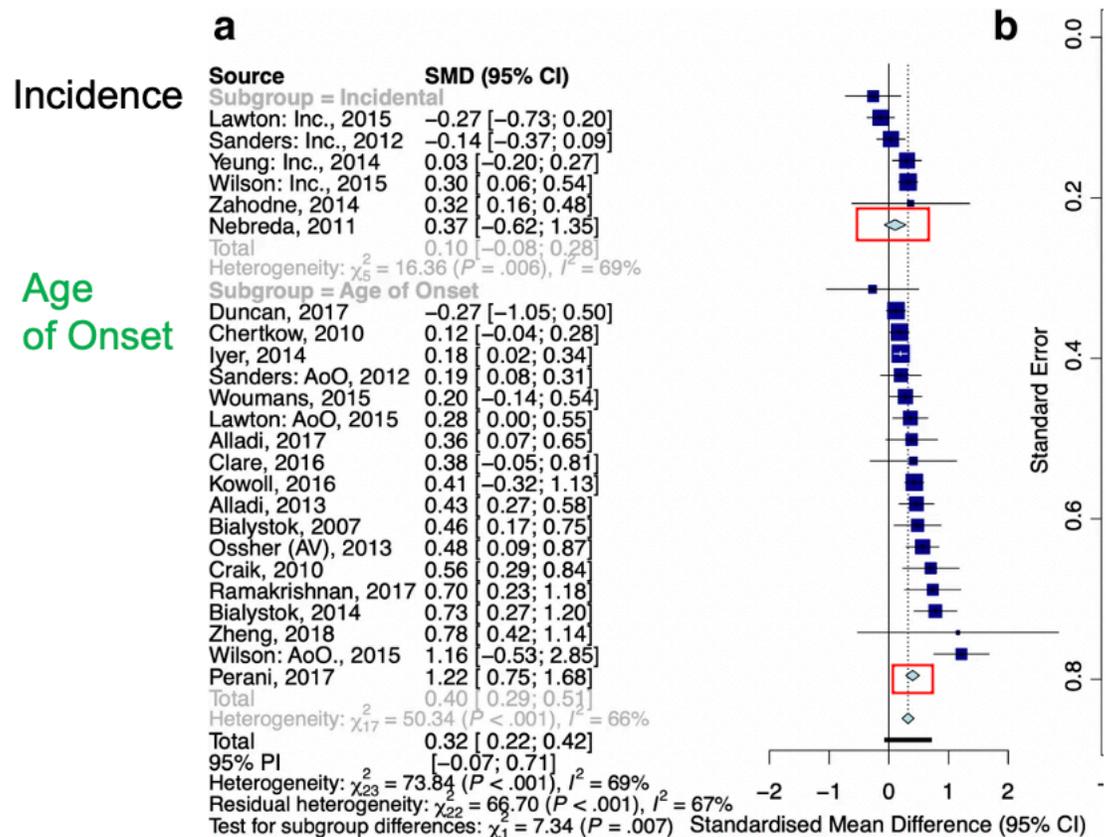


***RFA AG-23-01**

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.

Courtesy of Suvarna Alladi

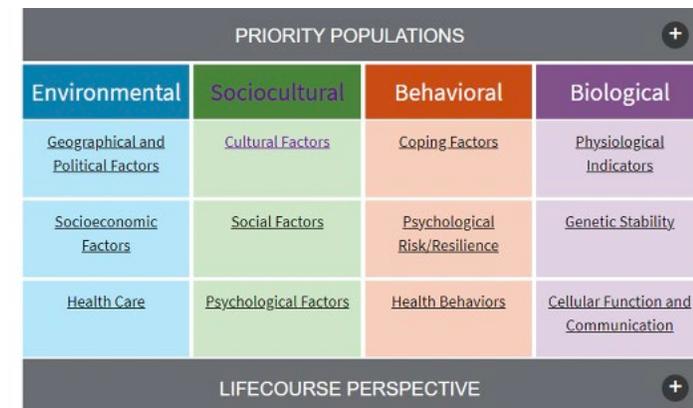
Anderson, Hawrylewicz, & Grundy (2020),
Psychonomic Bulletin & Review

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.

Diverse Vascular Contributions to Cognitive Impairment and Dementia (VCID)



<https://diversevcid.ucdavis.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.

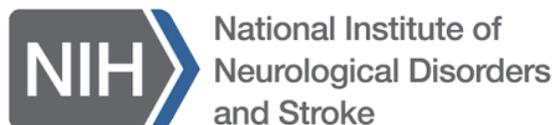
NOW ENROLLING



PI: Charles DeCarli,
UC DAVIS
UNIVERSITY OF CALIFORNIA



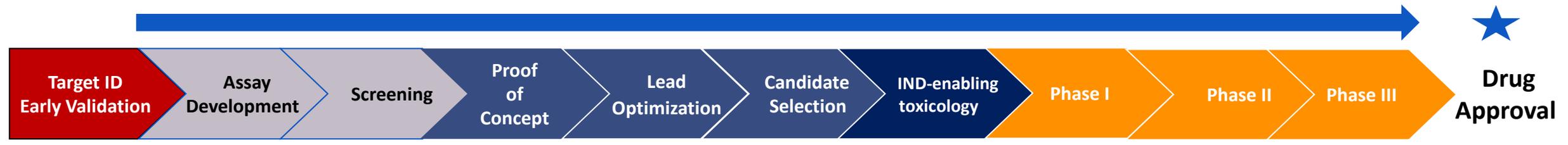
MPI: Myriam Fornage,
UT Health
The University of Texas
Health Science Center at Houston



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

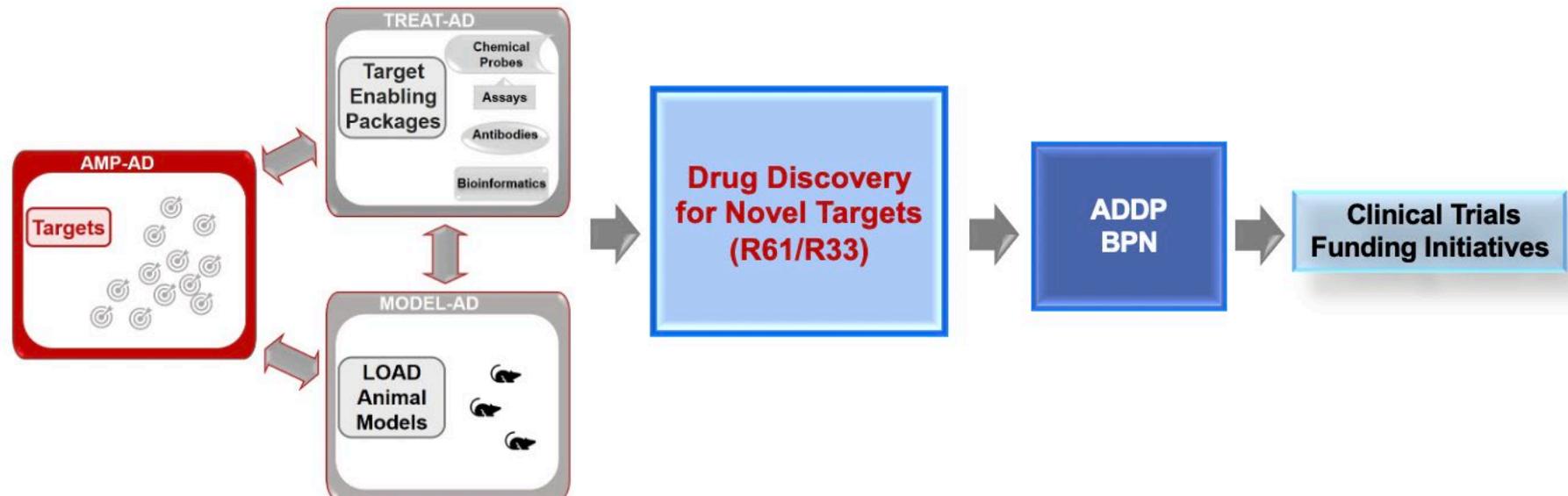
Early and Late-Stage Clinical Trials for the Spectrum of Alzheimer's Disease and Age-related Cognitive Decline (R01)

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



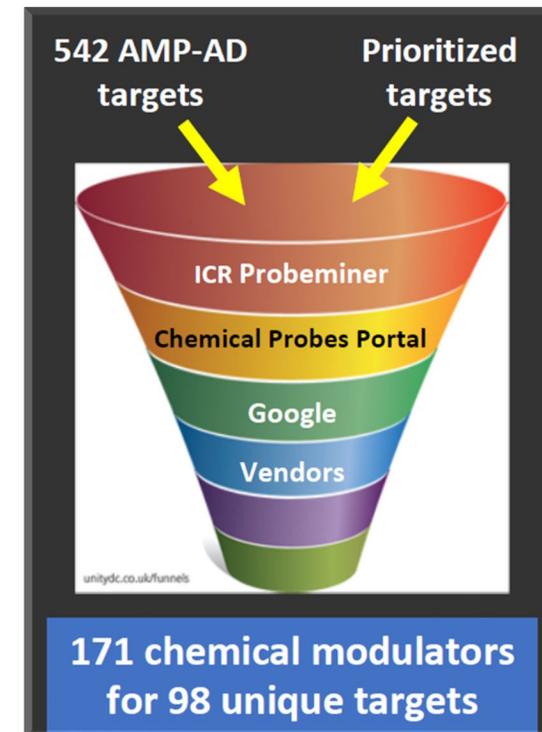
AD Informer Set: Chemical tools to facilitate drug discovery

Current AD Informer Set:

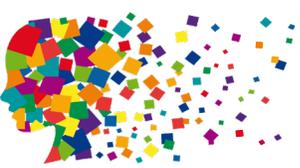
- 171 compounds sourced by UNC:
 - 36 are approved drugs
 - 40 are in clinical trials (Phases 1–4)
 - 68 have advanced into animal-based studies
 - 27 have not been explored beyond cellular studies
- 1–7 compounds per target (98 targets)
 - Ranging from inhibitors, substrates, activators, agonists, or antagonists
- QC'd and registered in laboratory information management system
- Data includes predicted BBB permeability, kinetic solubility measurements, and single concentration (10 μ 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 μ 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 Social Determinants of Health Ancillary Studies of Existing Longitudinal Cohorts
Concept Approved	Early-Stage Therapy Development for ADRD
Concept Approved	Pragmatic Clinical Trials in Community Settings to Decrease or Prevent VCID Outcomes, Including in Populations that Experience Health Disparities
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	Treatments for Lewy Body Dementias & Frontotemporal Degeneration - Exploratory Clinical Trial (Related to RFA-NS-21-008)
Concept Approved	Functional Validation of Novel Targets in ADRD (Re-issue RFA-NS-19-015)
Concept Approved	COVID-19 Related Revisions to NINDS ADRD Human Subjects Cooperative Agreement Programs
PAS-19-316 (NIA leads)	Advancing Research on AD/ADRD SBIR/STTR Programs (<i>Clinical Trial Optional</i>); Standard due dates
PAS-19-317 (NIA leads)	Advancing Research on AD/ADRD SBIR/STTR Programs (<i>Clinical Trial Optional</i>); Standard due dates

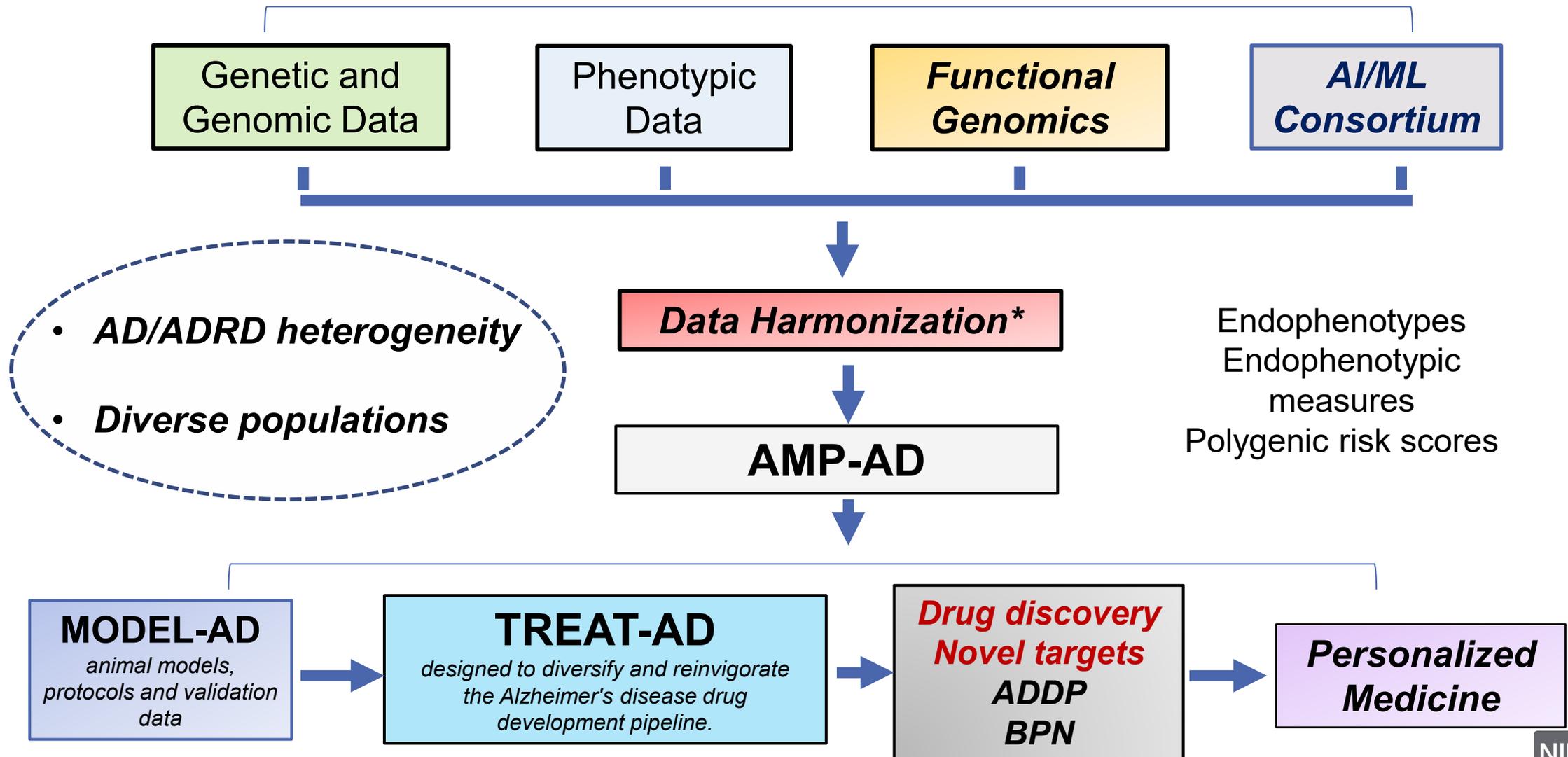
14 NINDS ADRD funding initiatives are planned for FY 2023, for more information see:
<https://www.ninds.nih.gov/Current-Research/Focus-Disorders/Alzheimers-Related-Dementias>

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

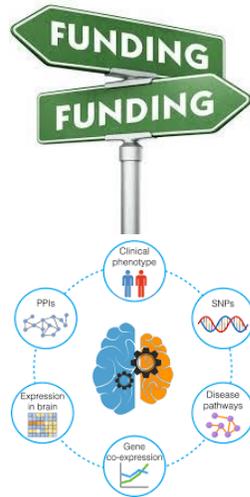


THANKS



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>