Fall ADRC Directors Meeting

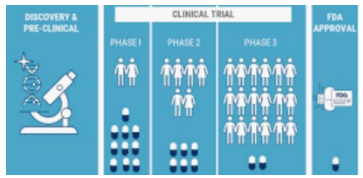
National Institute on Aging

San Diego, CA
October 20, 2023

"Division of Neuroscience Update"

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

Progress in AD/ADRD research at a time of increased funding



NIA funded over 400 clinical trials

Lecanemab and other Mabs

2025

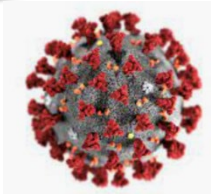
Precision Medicine

AD Knowledge Portal

NIA supported data sharing and harmonization

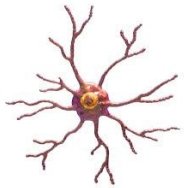
Inclusion of DIVERSITY in research

COVID19



Plasma biomarkers

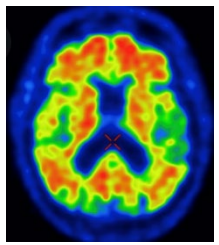
Immune, endosome Synaptic, Lipid metabolism, APP, Signaling pathways

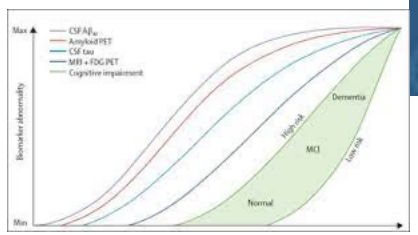


NAPA and increased NIH funding for AD/ADRD

PET imaging,

CSF biomarkers





Partners- **NINDS, NIMH, NHLBI, NCI, NICDC, NIDA, NIAAA, NICHD, VA, CDC, FDA, CMS**

NIH National Institute on Aging

NIA is funding trials to evaluate Lecanemab treating different stages of AD

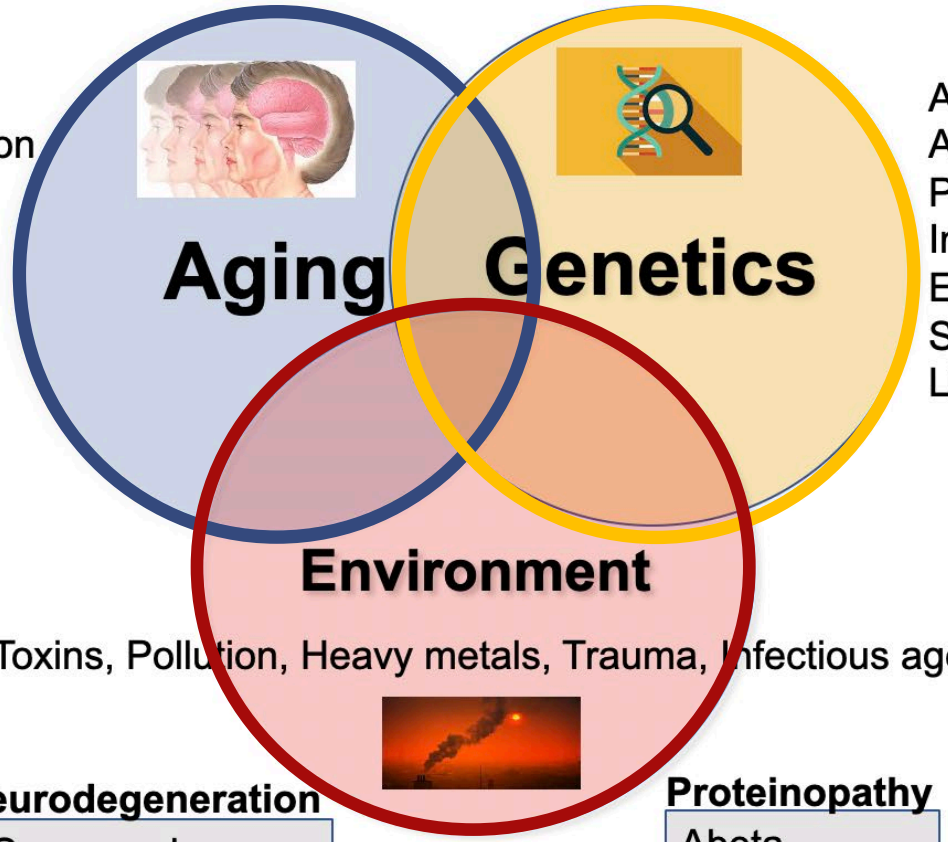
Trial Name	Drug Description	Phase	Population	Funding End Date
The A3 Study: Anti-Amyloid Prevention of Alzheimer's Disease (AHEAD STUDY)	**Lecanemab**, anti-amyloidβ antibody	III	Cognitively healthy older adults with "intermediate" amyloid levels on screening PET. Ages 55-80; Adults 55-64 must also carry at least one APOE ε4 allele.	2024
The A-45 Study: Anti-Amyloid Therapy for Preclinical Alzheimer's Disease (AHEAD STUDY)	**Lecanemab**, anti-amyloidβ antibody	III	Cognitively healthy older adults with "elevated" amyloid levels on screening PET. Ages 55-80; Adults 55-64 must have an additional risk factor.	2025
DIAN-TU: Tau Next Generation Prevention Trial	Combination of an anti-tau immunotherapy with **Lecanemab**, anti-amyloidβ antibody	III	Cognitively healthy or mildly impaired adults who are Alzheimer's disease genetic mutation carriers.	2025

NIH National Institute on Aging

NIA Approach to AD/ADRD reserach

Aging Genetics

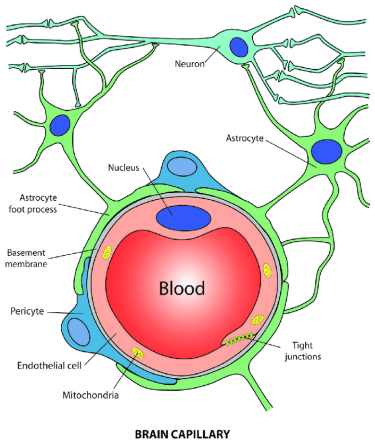
- Proteostasis defects
- Mitochondria dysfunction
- Oxidative stress
- Epigenetic alterations
- DNA damage
- Senescent cells
- Immune surveillance



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

Accounts for 70% of the variance

Toxins, Pollution, Heavy metals, Trauma, Infectious agents



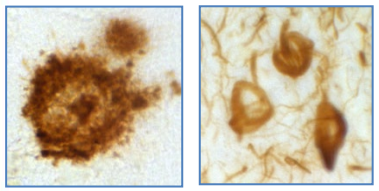
BRAIN CAPILLARY

Neurodegeneration

- Synapse damage
- Neuronal loss
- Vascular damage
- Inflammation

Proteinopathy

- Abeta
- Tau
- Synuclein
- TDP43



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

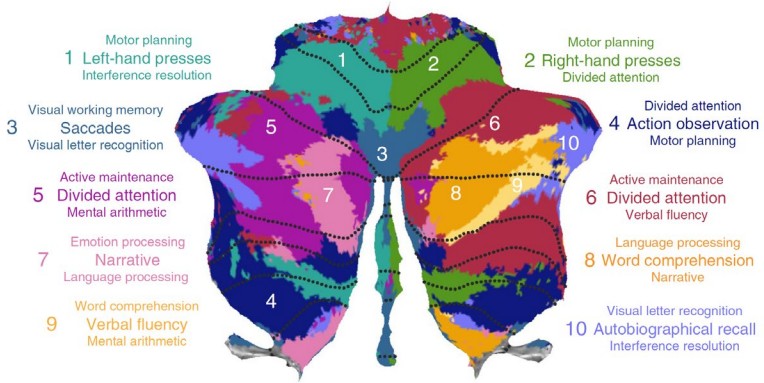
NIA Workshop on Understanding Cerebellar Contributions to Cognitive and Affective Functions in Aging and AD/ADRD

Matt Sutterer, Coryse St Hillaire, NIA

September 12-13, 2023

Overview: The Cortico-Cerebellar System: Organization and Function

Narender Ramnani

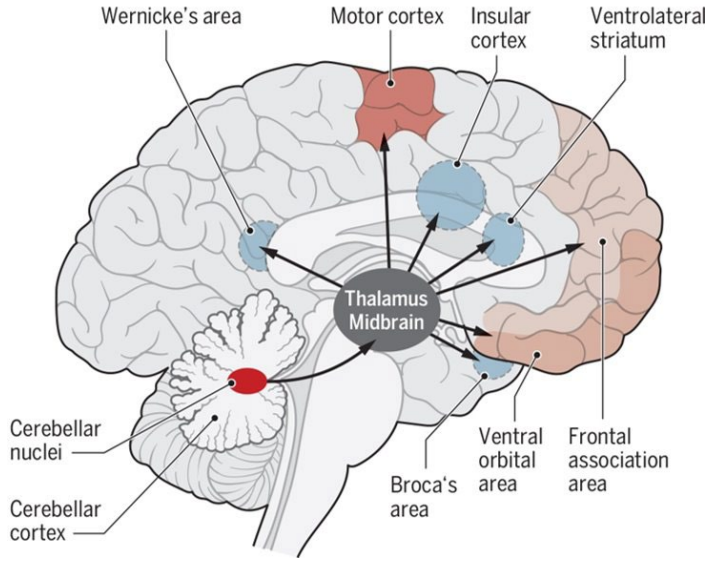


King M, et al Nat Neurosci. 2019; 22: 1371-1378.

Session I.

Cerebellar Contributions to Cognitive Aging

Jessica Bernard, Jeremy Schmahmann, Erik Carlson, Vonetta Dotson



Session II.

Preclinical Evidence of Non-motor Cerebellum Functions

Sam Wang, Yi-Mei Amy Yang, Michael Hausser, Kamran Khodakhah

Session III.

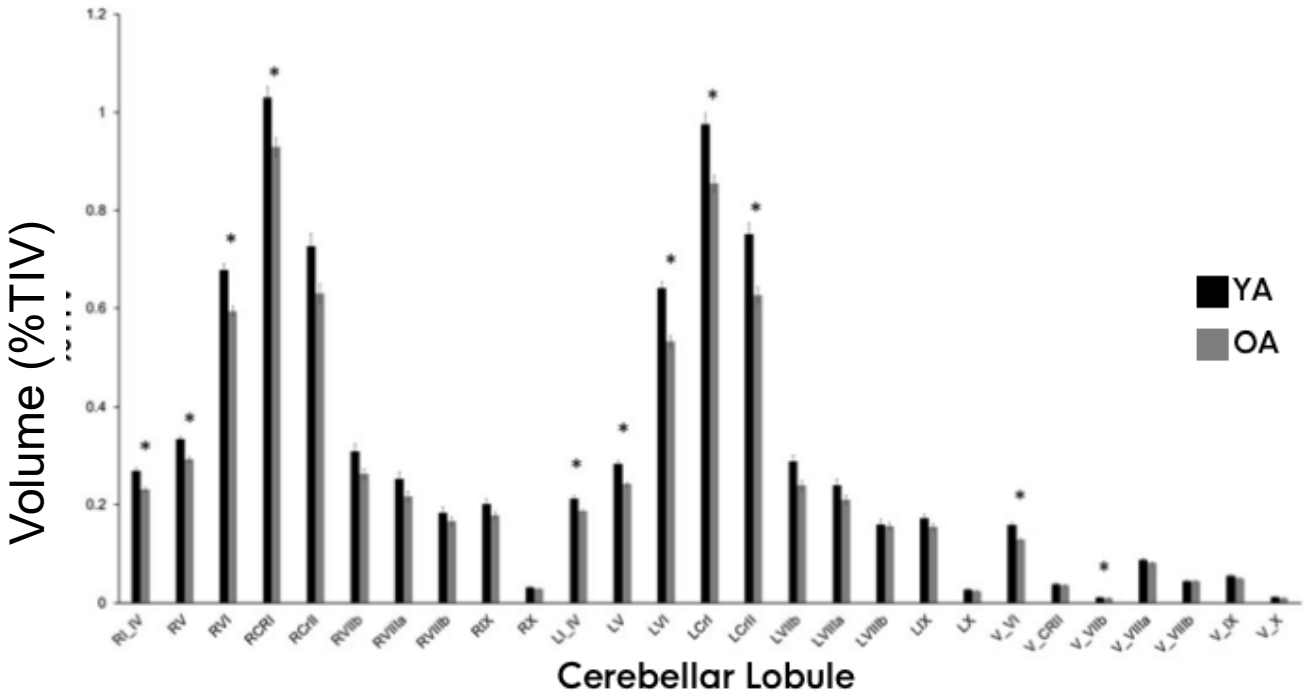
Cerebellar Roles in Affective Processing, Social Function, and Cognition

Krystal Parker, Zeynab Rezaee, Richard Ivry, Ingrid Olson

NIH National Institute on Aging

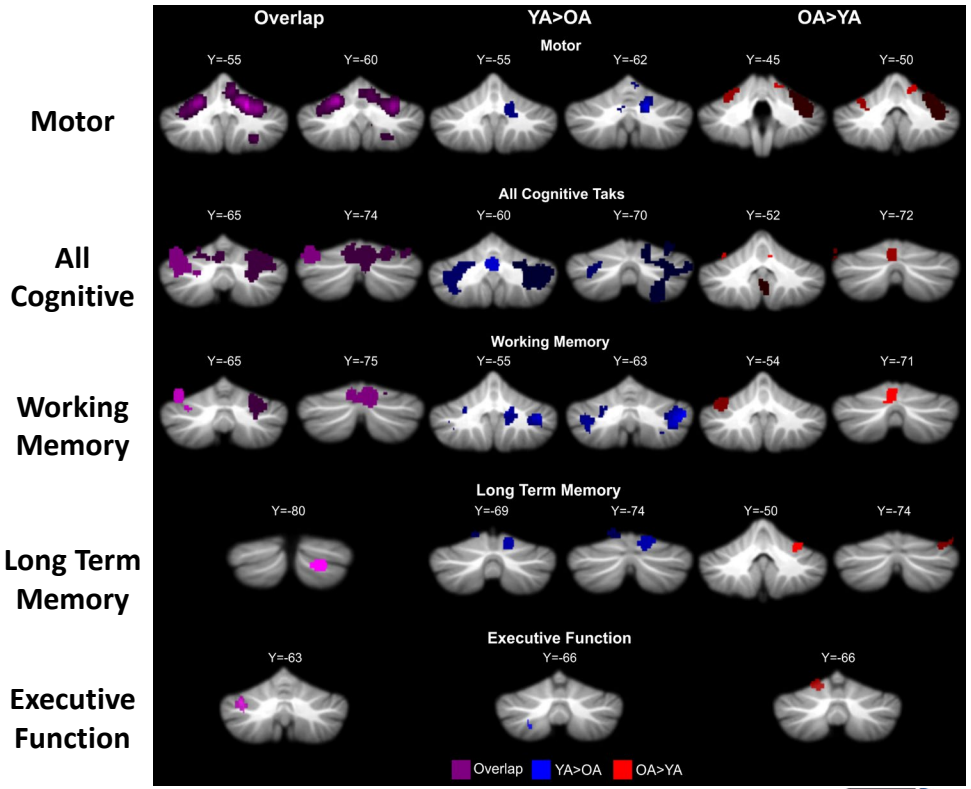
Aging dependent differences in the cerebellum structure and resting state connectivity that are also associated with behavior

Bernard & Seidler, 2013; Bernard et al., 2013; Bernard et al., 2022; Hausman et al., 2020



Both meta-analysis and task-based fMRI suggests activation differences in the cerebellum in older adults.

Bernard et al., 2020, *Hum Brain Mapp;* Jackson et al., 2020, *Neuropsychologia*



Gaps and Opportunities

NIA Workshop on Understanding Cerebellar Contributions to Cognitive and Affective Functions in Aging and AD/ADRD

Better translation of animal to human work on the cerebellum in aging and AD/ADRD

Studies of cerebellar function/pathology in aging and AD/ADRD animal models

Robust histological and anatomical studies of human cerebellum

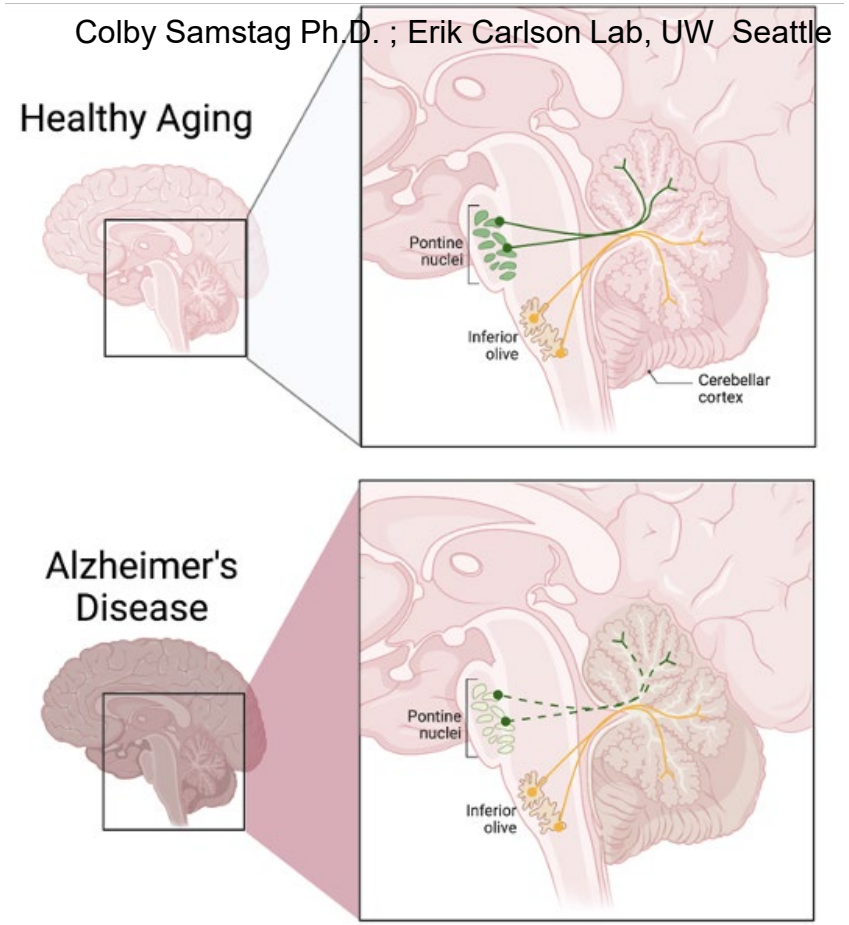
Need to improve existing/develop new tools and technologies for studying cerebellar function

(Computational, neuroimaging, neurostimulation parameters)

Cerebellum as a target for neurostimulation

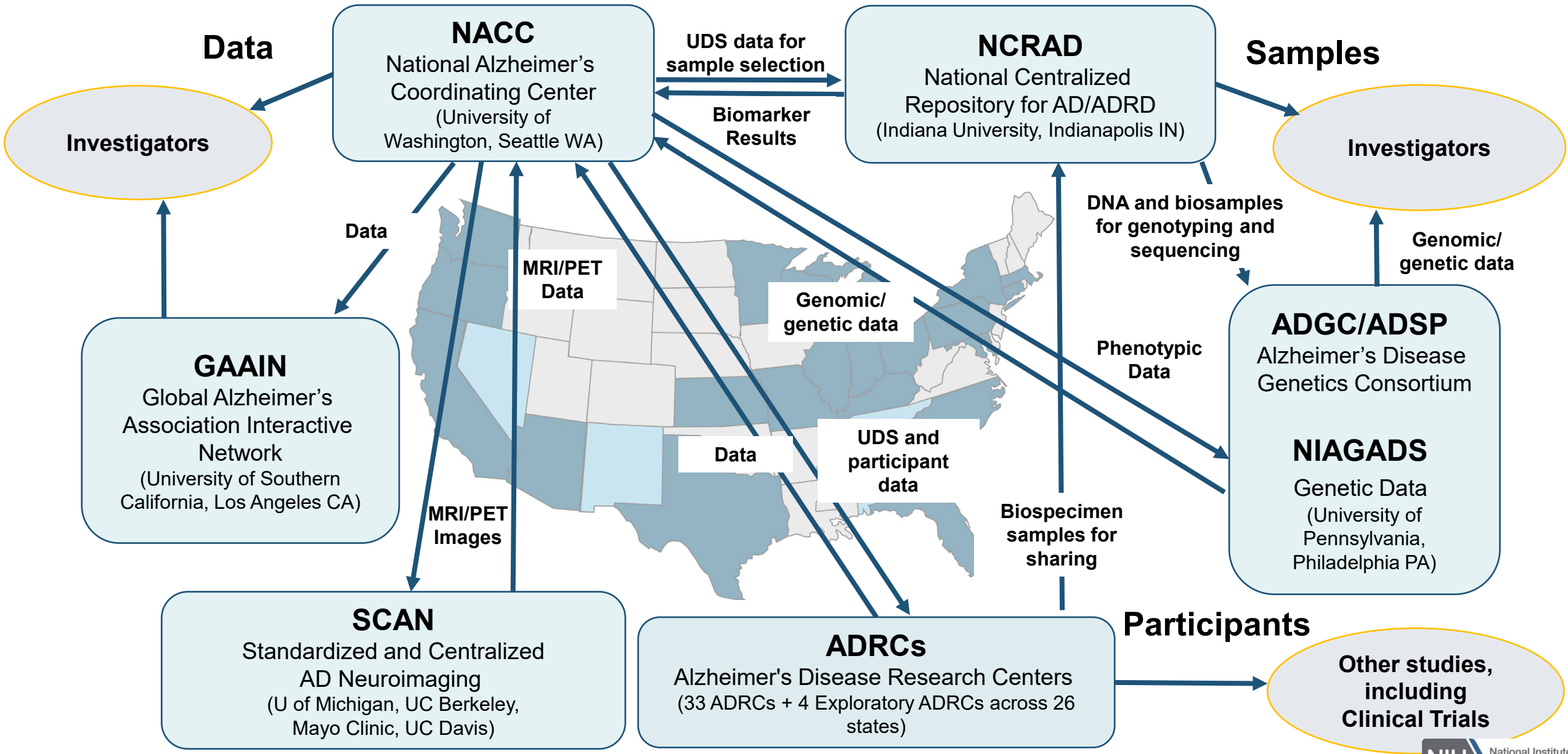
Given extensive cerebellar connectivity-could cerebellum be more accessible target for treatment of neuropsychiatric conditions by noninvasively stimulating deep cortical and thalamic regions?

Colby Samstag Ph.D. ; Erik Carlson Lab, UW Seattle



- Dementia associated with **reduction of glomeruli** (synaptic structure in the granular layer); **reduction of Vglut1 expression in the molecular layer**

ADRC Data and Sample Sharing Infrastructure



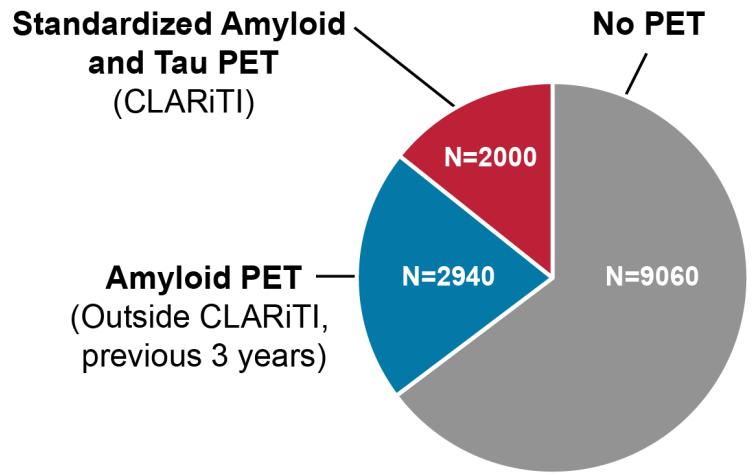
NIH National Institute on Aging

ADRC Consortium for Clarity in ADRD Research Through Imaging (CLARiTI)

- U01 mPIs: Johnson, Mormino, Foroud, Rabinovici, Okonkwo, Rivera-Mindt, Dickerson, Wolk, Kukull

Individualized temporo-etiologic profiles from biomarkers			
Need	Scientific Objectives	Infrastructure	Expected Outcomes
• **Multi-etiology is common but undetected** • **This obfuscates true effect sizes in cohort** • **Person level prognosis and treatment outcomes are difficult due to undetected copathology**	• Identify constituent diseases in an individual • Leverage fluid, PET and MRI biomarkers to derive individualized etiologic profiles • Derive individualized biomarker timelines • Bridge the field to blood-based biomarkers	• Leverage ADRC local and national infrastructure: expert workforce, NACC, NCRAD, SCAN, neuropath • Lower site barriers to PET • Centralized PET reads, biomarker quantification • A large plasma repository anchored to ground truth measures	• Populate publicly accessible SCAN/NACC database with critical data • Tools to identify MED • Neuropath-informed imaging templates • Uniform digital pathology • Plasma assay to ground truth validation

Total Active ADRC Participants: N = 14,000



Create individual etiologic profiles from imaging and biofluid biomarkers

- *ATN imaging and plasma study superimposed on longitudinal UDS*
- *Paid to sites from NACC*
- *2,000 clinical core participants; 60% impaired, 40% CU; brain donors*
- *> 25% enrollment from under-represented groups*
- *Upload to SCAN*
- *Two time points [2-3 years apart]*
- *detect heterogeneity: syndromes/pathologies — multi-etiology*
- *Optional advanced MRI, optional FDG*
- *Centralized resources for study operation, core workgroups*
- *Results flow back to centers via NACC portal*

NIH National Institute on Aging

The contribution of CLARiTi in the context of NIA funded consortia

Table 1. Prominent active cohort studies related to ADRD and their primary enrolling diagnosis

Cohort*	Size (Goal)	AD	VCID	LBD	FTLD	Atypical	LATE	Imaging A/T PET	Purpose
CLARiTI - ADRCs	(2,000)	Y	Y	Y	Y	Y	nk	Y	Etiologic characterization of ADRD mixture
DVCID**	(2,250)	n	Y	n	n	n	nk	N	Vascular risk for cognitive decline* will partner
ADNI4	(1,100)	Y	n	n	n	n	nk	Y	Clinical trial planning for AD with biomarkers
LEADS	(700)	Y	n	n	n	n	nk	Y	Clinical trial planning in early onset AD
ALLFTD	1,479	n	n	n	Y	n	nk	N	Clinical and biomarker progression
PPMI	(4500)	n	n	Y	n	n	nk	N	Biomarker progression in PD
DLBC	200	n	n	Y	n	n	nk	N	Dementia with Lewy bodies
DIAN	(600)	Y	n	n	n	n	nk	Y	Cohort of autosomal mutation carriers

Notes: *Single-site aging and AD-risk cohorts are not listed.

nk= not known

LATE is a neuropath entity—clinical criteria are not defined and it is assumed all older cohorts contain some as yet unknown burden of LATE-NC; LBD includes Dementia with Lewy Bodies and Parkinson's disease dementia and their prodromes. Other abbreviations: VCID vascular cognitive impairment. LEADS Longitudinal early onset AD study; PPMI Parkinsons Progression marker initiative; DLBC Lewy Body consortium.

**DVCID Diverse VCID study: Participants may co-enroll because DVCID does not do PET and the core MRI is the same and will be at SCAN

NIA Recently approved concepts FY23

Alzheimer's Disease Research Centers (ADRCs) Program Renewal

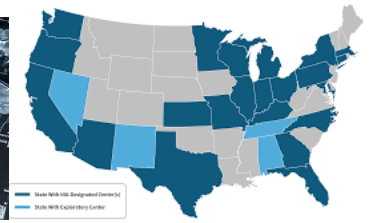
Microphysiological Systems to Advance Precision Medicine for Alzheimer's Disease and Related Dementias Treatment and Prevention

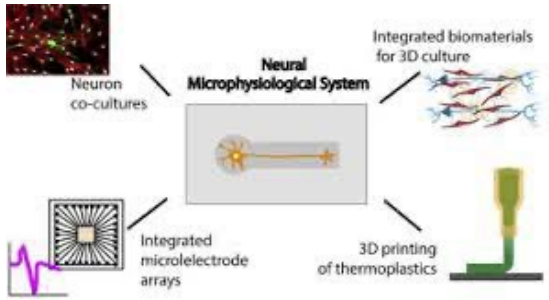
Team Science Approaches Integrating Experimental and Computational Brain Aging Models

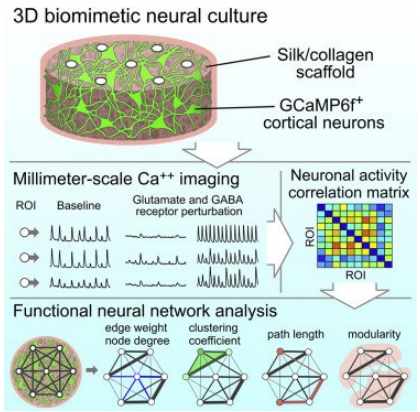
Quantifying the Impact of Environmental Toxicants on Alzheimer's Disease and Related Dementias Risk in Cohort Studies

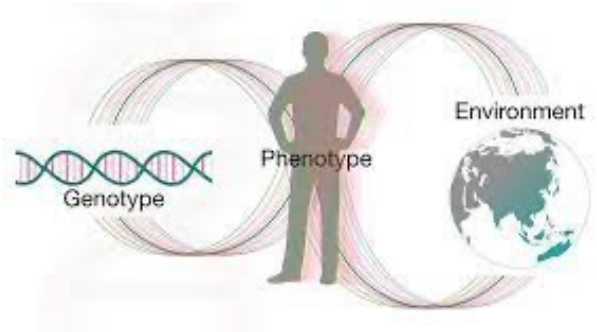
Understanding Gene Environment Interactions in Brain Aging and Alzheimer's Disease and Related Dementias

Preclinical Studies to Characterize the Impact of Toxicants on Brain Aging and AD/ADRD





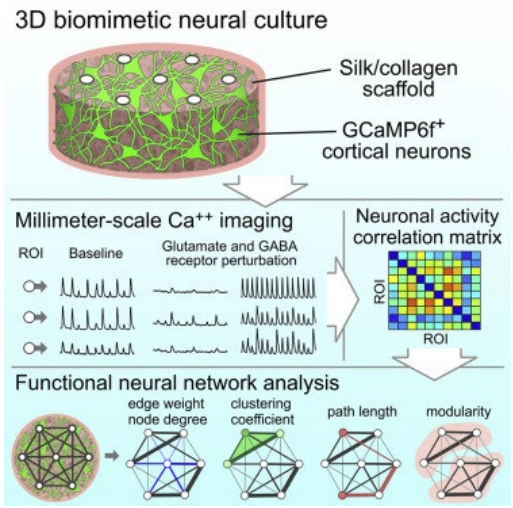


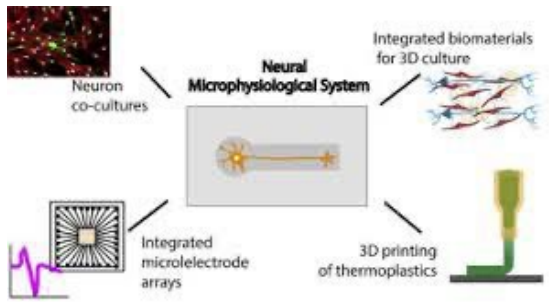


Microphysiological Systems to Advance Precision Medicine for AD/ADRD Treatment and Prevention

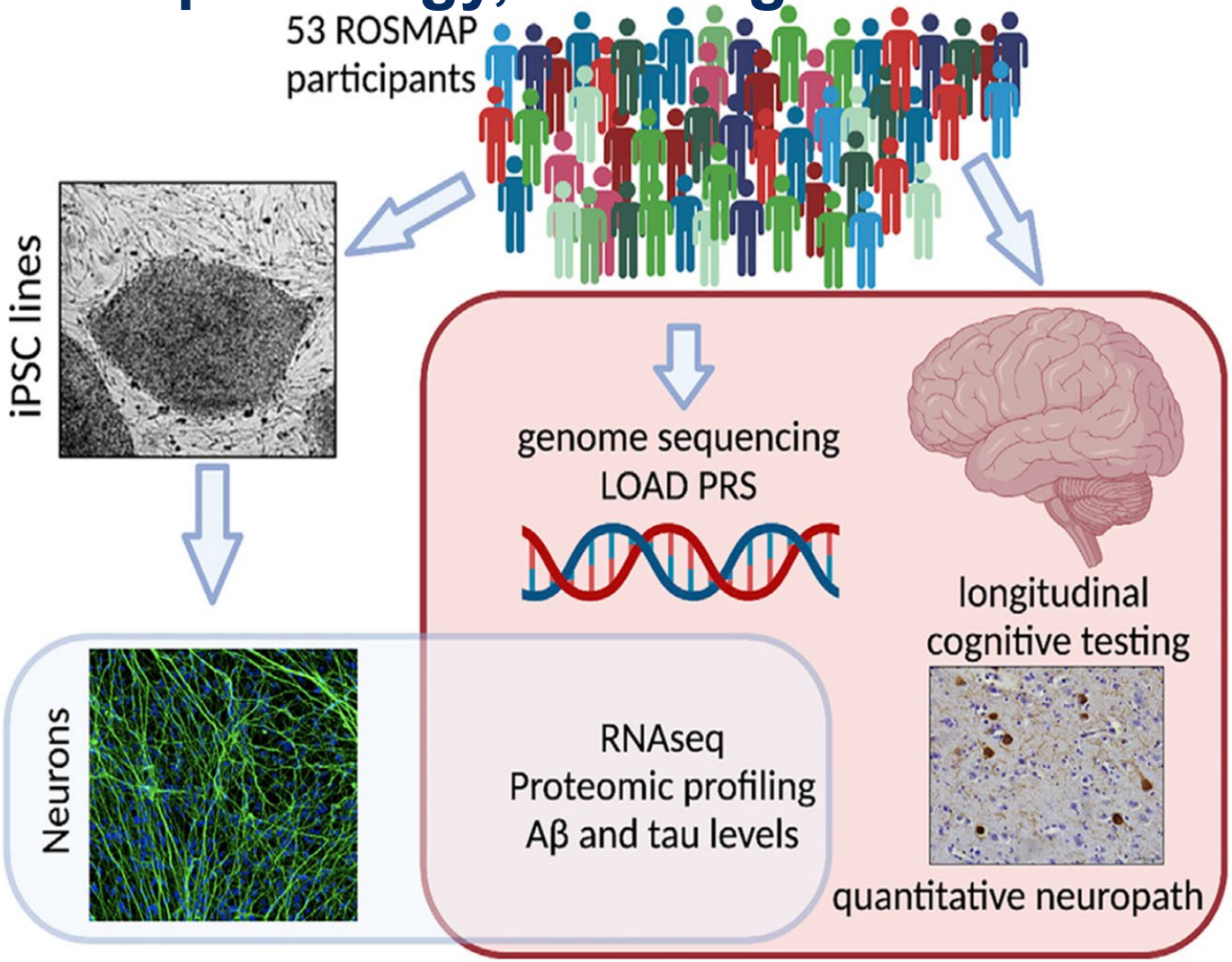
Zane Martin, Lorenzo Refolo and Suzana Petanceska, NIA

- Stimulate more predictive AD/ADRD models that encompass features of human pathophysiology and operate as **precision medicine research tools**
- Spur development of **standardized and phenotyped AD/ADRD MPS** models, establishing the **translational validity of these MPS** models to recapitulate AD/ADRD
- Develop MPS technologies that **allow for the testing of potential AD/ADRD therapies** in a manner that incorporates **disparities** and differences in the specific pathogeneses across populations
- **Provide MPS models to all qualified researchers** for their use in preclinical therapy and transparent reporting of research methodology and preclinical efficacy testing findings





Stem cell-derived neurons reflect features of protein networks, neuropathology, and cognitive outcome of their aged human donors



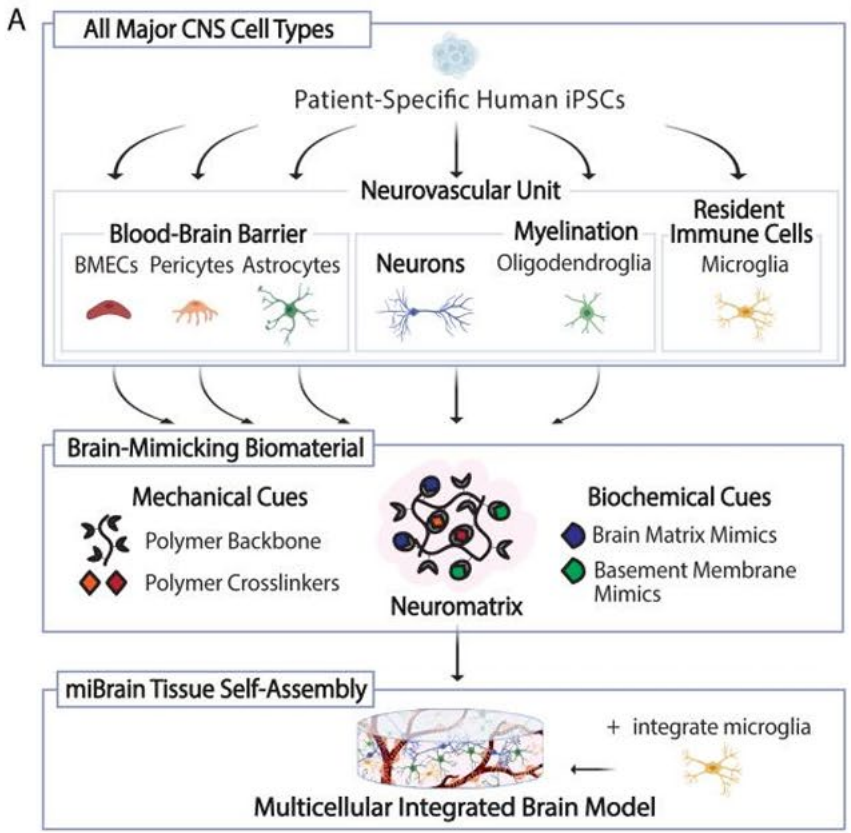
Lagomarsino et al., 2021, *Neuron*

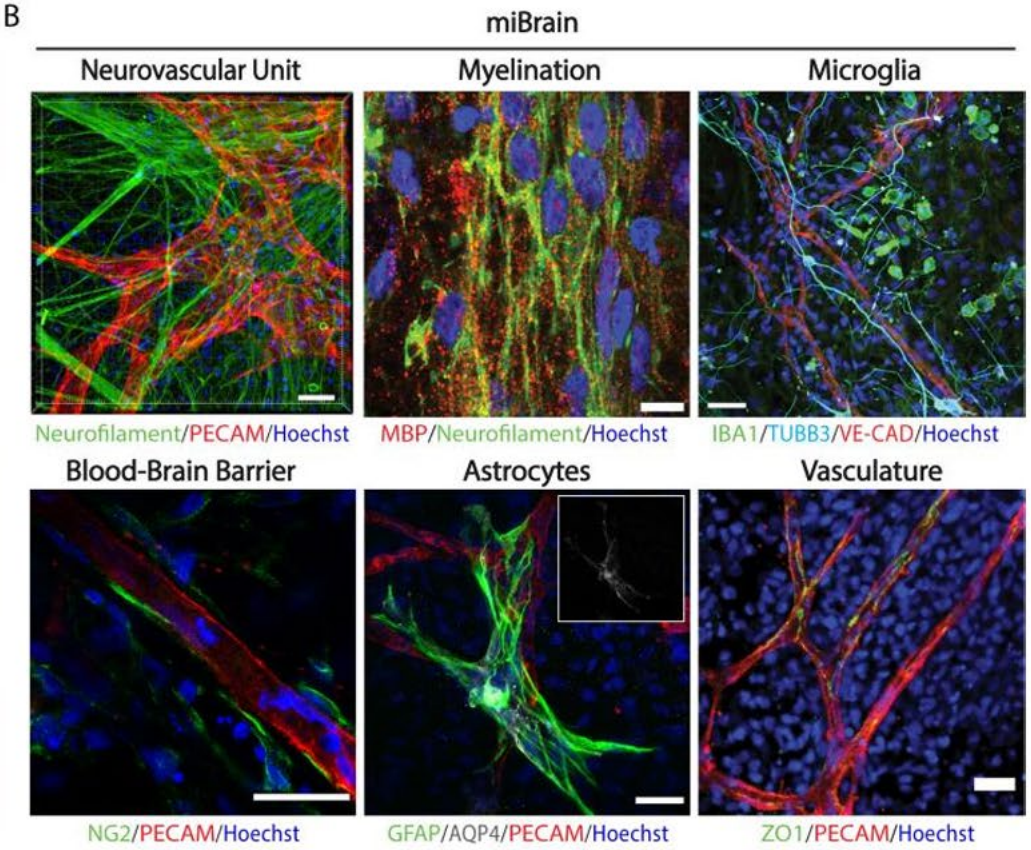
- Generation and characterization of iPSC lines from 53 deeply phenotyped aged humans
- High Aβ42 production in induced neurons reflected plaque load in the donor brain.
- Likewise, aggregated phospho-tau correlated with tangles.
- Association of cognitive decline and measures of Aβ and tau in iPSC-derived neurons

NIH National Institute on Aging

Human Integrated 3D-Immuno-Glial-Neurovascular miBrain Model

- miBrain formation harnessing patient-specific iPSCs differentiated into each of the resident brain cell types
- encapsulated in Neuromatrix hydrogel
- co-cultured for integral cell network self-assembly and microglia-like cell integration





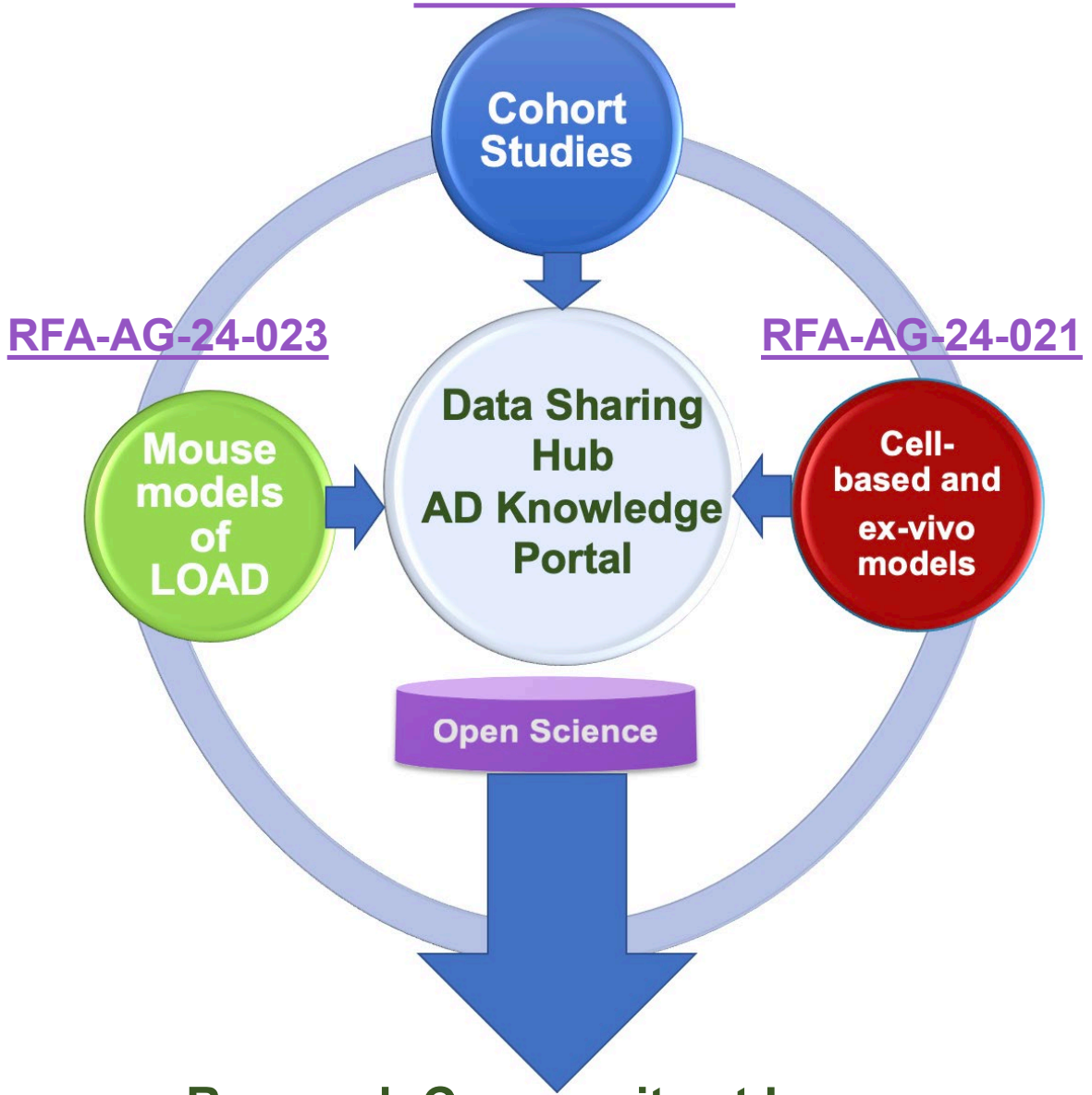
- *robust neuronal electrical activity and electrophysiological properties*
- *transcriptional signatures closer to human brain tissue than their individual cell counterparts*
- *mature neuronal and BBB markers*
- *functional interactions between cell types*

Stanton, Tsai et al. 2023

Exposome in AD/ADRD new Funding opportunities

RFA-AG-24-022

NIA: S.Petansezka, L. Refolo, D. Martin, R. Kwok, L. Opanashuck, A. Yao



AD/ADRD Implementation Milestones

1B. Quantify the exposome in existing and new AD cohorts

1F. Support the inclusion of measures of AD-related phenotypes and environmental exposures in non-AD cohorts

2Y. Support research that utilizes animal models of LOAD and iPSC-derived cerebral organoids from human donors,

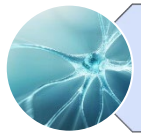
Ensure that all data and analytical outputs are made widely available according to open-science and FAIR data practices and encourage the adoption of exposomics-related ontologies for data interoperability.

NIH National Institute on Aging

Understanding Gene Environment Interactions in Brain Aging and AD/ADRD

GOAL: Stimulate research to gain mechanistic insights into gene-environment (GxE) interactions using human cell-based *in vitro* and *ex-vivo* models

SCOPE of FOA

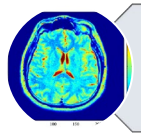


Systematically interrogate genetically diverse and disease relevant human *in vitro* and *ex-vivo* models with well characterized environmental toxicants (chemicals, metals, pollutants).

Identify novel genetic risk/protective factors and regulatory elements responding to environmental toxicants.

Profile multi-omic signatures. Identify cell type specificity. Elucidate the role of sex difference and ethnic diversity in phenotypic outcomes influenced by toxicants.

Characterize downstream effects of GxE interactions on gene regulation, cellular function, and molecular pathways.



Elucidate molecular and cellular mechanisms underlying GxE interactions in brain aging and AD/ADRD.

Research resource and sharing

- Omics data – AD Knowledge Portal, the data sharing hub for the exposome tri-consortia
- iPSC lines – NCRAD

NIH National Institute on Aging

NIA Workshop *"Traffic!! Health Impacts in Aging"*

Luci Roberts, NIA

February 2-3, 2023

Session I.
Air Pollution Health Impacts on Aging: Part 1 *Kaufman, Casey, Ailshire,*

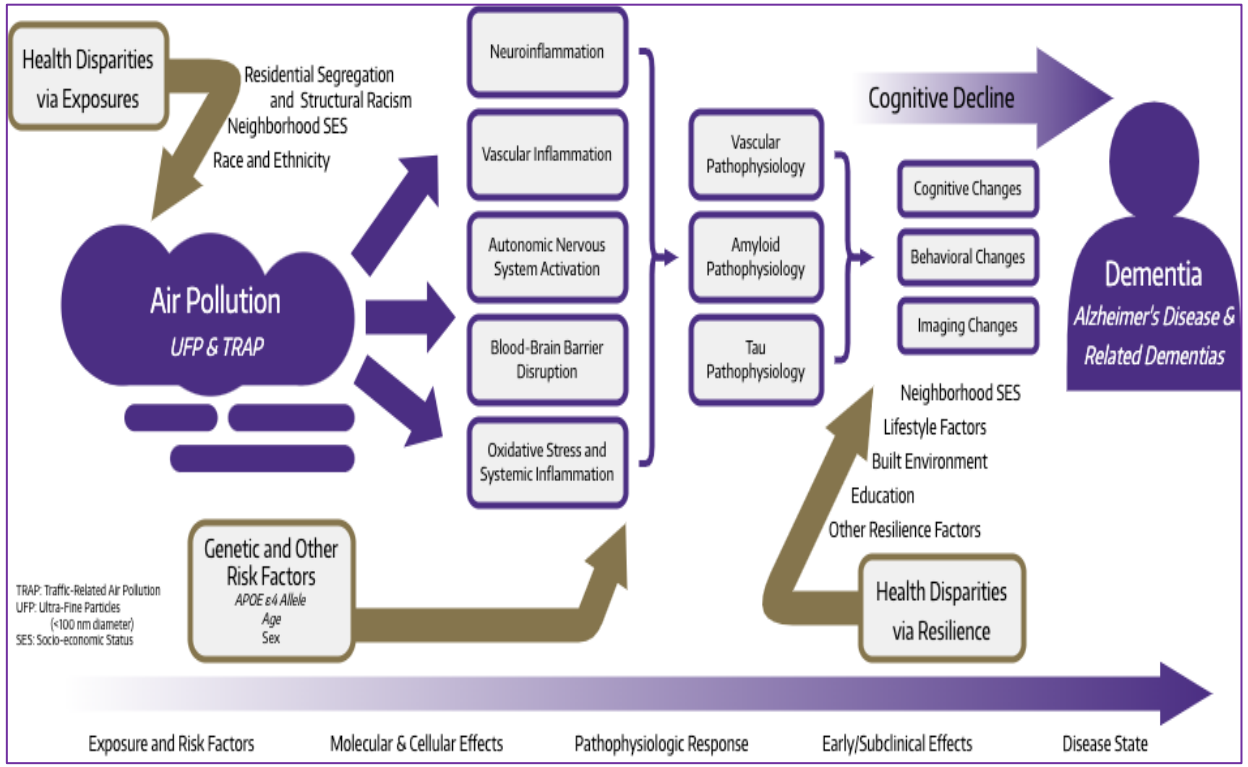
Session II.
Air Pollution Health Impacts on Aging: Part 2 *Finch, Brugge, Pinto, Weuve*

Session III.
Traffic Noise Exposure Health Impacts, and Driving in Aging *Stewart, Peters, Betz, Rizzo*

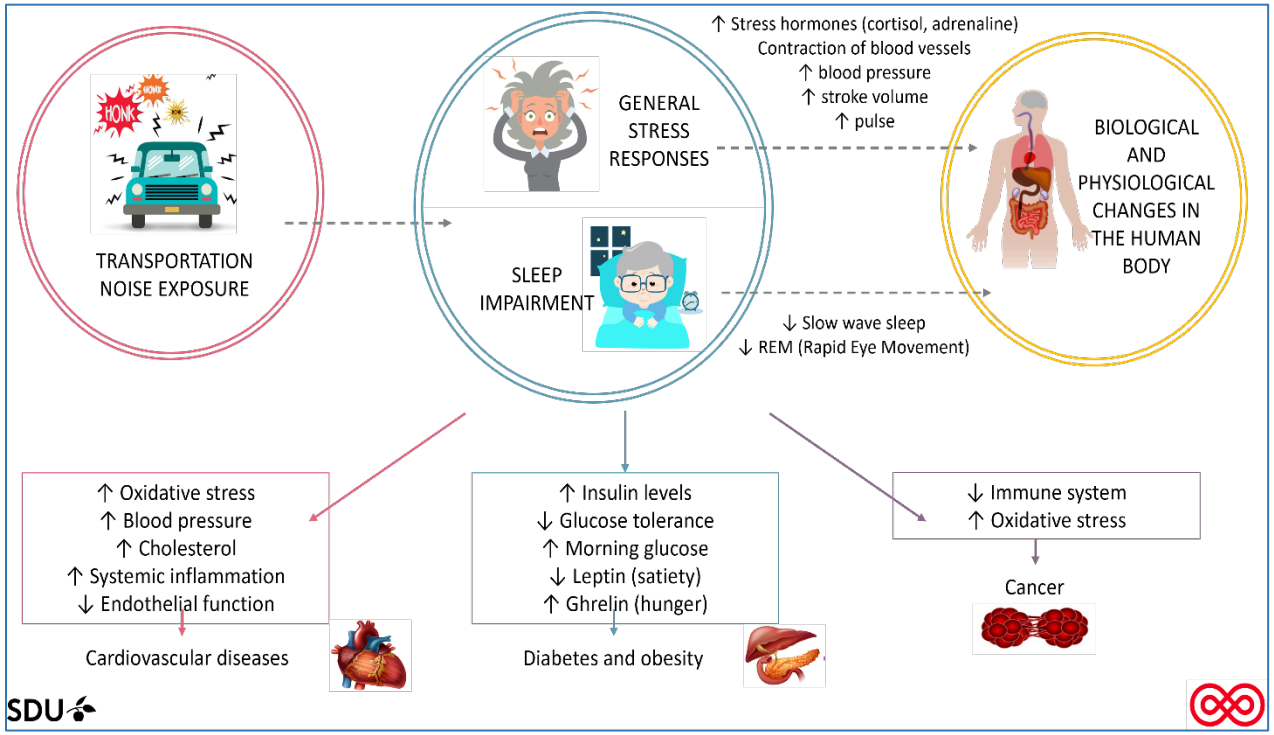
Session IV
Health Impacts of the Built Environment, *Hui Rising, Laden, Besser, Brown*

Traffic!! Health Impacts in Aging

Air Pollution



Noise Pollution



Unknowns and unmet needs emerged from the talks:

- *Knowledge of impacts of ultrafine particulate matter on health and cognition; identification of critical periods across the lifespan*
- *Better monitoring data: In US, more noise monitoring, finer geographic monitoring of air quality, more detailed particulate monitoring*
- *Knowledge of impacts of indoor air quality and indoor noise pollution on health and cognition*

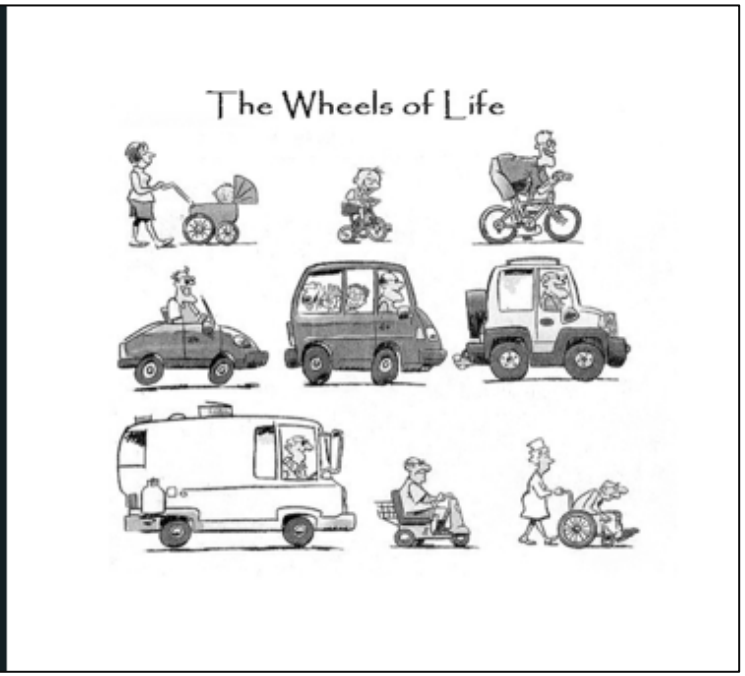
NIH National Institute on Aging

Traffic!! Health Impacts in Aging

Driving

Most older adults outlive their safe driving ability by 6-10 years *(Foley 2002)*

How do we help older drivers make decisions about driving?

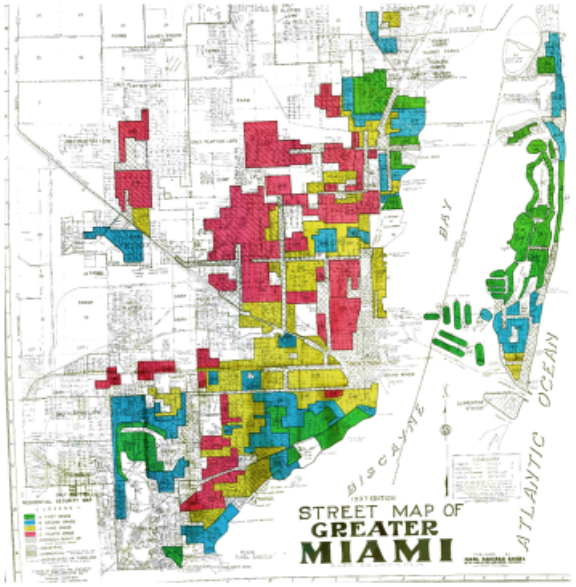


Built Environment

Redlining and neighborhood walking in older adults: The 2017 National Household Travel Survey. Besser et al. Am J Prev Med. 2022 Dec;63(6):926-934.

Redlining: 1930s, US government policy (FHA) resulted in:

- Black, working class, and immigrant neighborhoods color-coded on maps
- Indicating investment risk
- Negatively impacted mortgage attainment/homeownership
- Led to long-standing segregation by race/ethnicity and socioeconomic status



Map source: Robert K. Nelson, LaDale Winling, Richard Marciano, Nathan Connolly, et al., "Mapping Inequality," *American Panorama*, ed. Robert K. Nelson and Edward L. Ayers, accessed April 29, 2022, https://dsl.richmond.edu/panorama/redlining

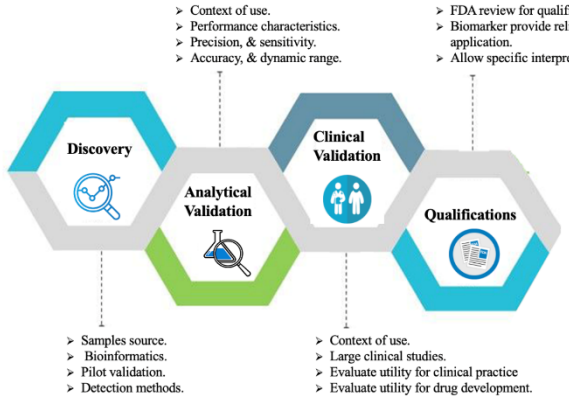
Unknowns and unmet needs emerged from the talks:

- *Knowledge of factors influencing older adults' choice to continue driving; evidence-based approaches to support decision to stop driving*
- *Knowledge of factors that promote or impede neighborhood walking; evidence-based approaches to promote safe neighborhood walking*

NIH National Institute on Aging

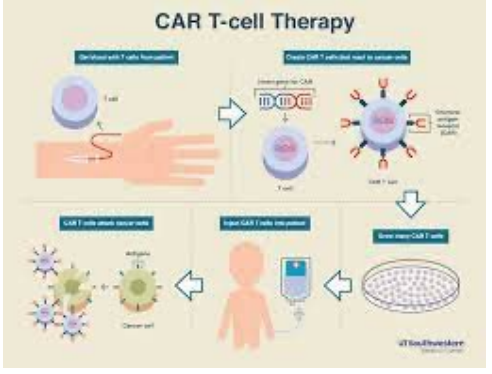
NIA Recently approved concepts (Translation) FY23

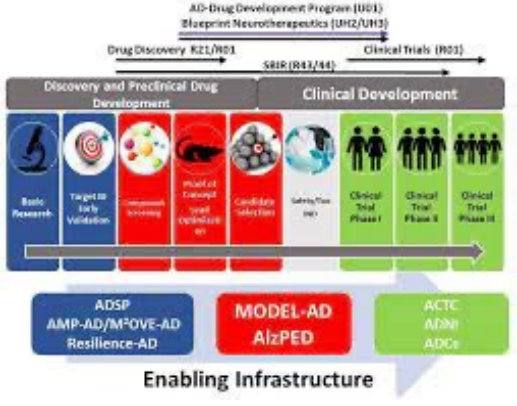
Analytical and Clinical Validation of Biomarkers for AD/ADRD
PAR-23-258, Alessandra Roscovelli



Artificial Intelligence in Pre-Clinical Drug Development for AD/ADRD
RFA pending, Nadini Arunkumar, Suzana Petaseska

Chimeric Antigen Receptor (CAR) Approaches to AD/ADRD
RFA pending, Maja Maric and Mack M



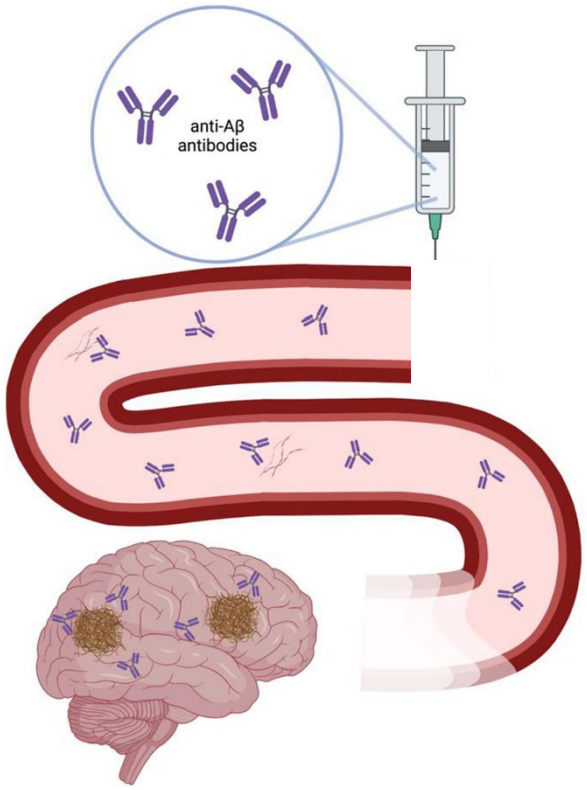


Seamless Early-Stage Clinical Drug Development (Phase 1 to 2a) for Novel Therapeutic Agents for AD/ADRD
PAR-23-274, Laurie Ryan, Akanni Clark, Kristina McLinden

Small Research Grant Program for the Next Generation of Researchers in AD/ADRD Research
PAR-23-179 Luci Roberts

NIH National Institute on Aging

NINDS opportunities in immunotherapy



Adapted from Foley, K.E. and Wilcock, D.M. Curr Neurol Neurosci Rep 22:709–19 (2022)

NIH National Institute of Neurological Disorders and Stroke

NIH National Institute on Aging

NINDS Funding Opportunities:

Phase III Clinical Trial (U01):

Efficacy and Safety of Beta-Amyloid Directed Antibody Therapy in Mild Cognitive Impairment and Dementia with Evidence of Both Beta-Amyloid and Vascular Pathology (Funding Announcement Planned for FY 2024)

Understanding Mechanisms With Goal of Protecting the BBB (R01):

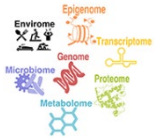
Blood Brain Barrier Response to Antibodies Targeting Beta-Amyloid (PAR-23-140)

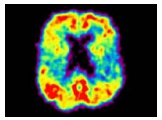
Drug name	Clinical Trial	Company	FDA Status
ADUHELM (Aducanumab)	EMERGE (NCT02484547) ENGAGE (NCT02477800) PRIME (NCT01677572)	Biogen	Accelerated Approval
LEQEMBI (Lecanemab-IRMB)	Clarity-AD (NCT03887455)	Esai	Accelerated Approval
Donanemab	TRAILBLAZER-ALZ (NCT03367403) TRAILBLAZER-ALZ 2 (NCT04437511)	Eli Lilly	Under Consideration

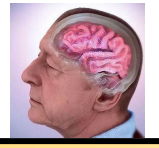
NIH National Institute on Aging

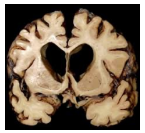
Translating AD/ADRD studies in diverse populations to personalized medicine

NIA Program Directors: N. Silverberg, C. Elliot, M. Miller, A. Yao, J. Larkin, D. Martin, D. Anderson, S. Petanceska, L. Ryan, N. Arunkumar









Genetic and Genomic Data

Multi-OMICS Data

Clinical Data

Biomarkers Data

Neuropath Data

Data Harmonization*

ADSP/NEW COHORTS

NIAGADS

ADRC's, DIVERSE DPPOS, COHORTS

NACC

AMP-AD DIVERSITY

AD Knowledge Portal

ADNI4, HABS-HD, ACTC

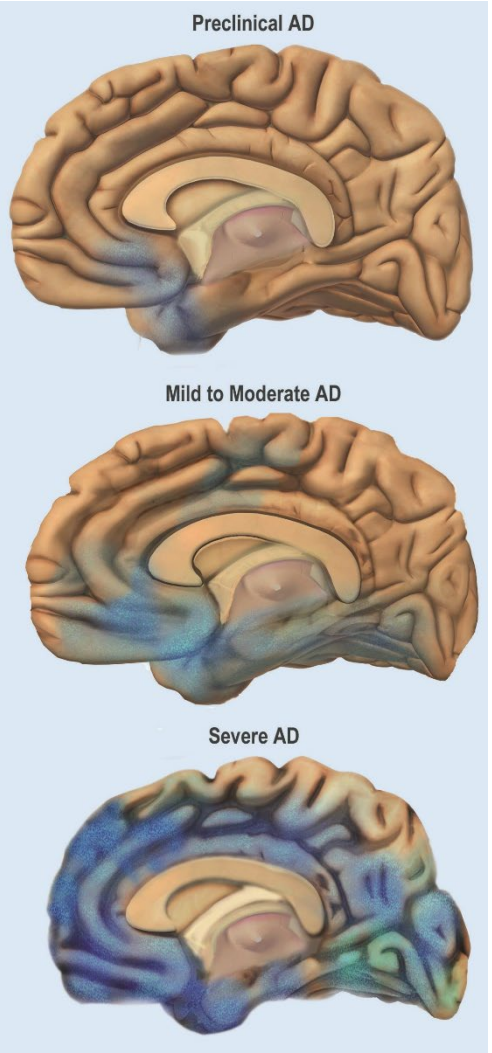
LONI Laboratory of Neuro Imaging

Personalized Medicine

NIH National Institute on Aging

NIA-AA Revised Clinical Criteria for the Diagnosis of Alzheimer's Disease

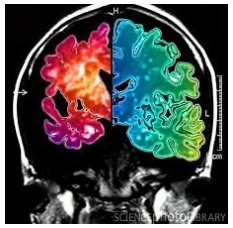
- **AD should be defined biologically**, rather than based on a clinical syndrome(s).
- The disease **is a continuum first evident with pathologic changes** in asymptomatic individuals and progresses through stages of increasing pathologic burden eventually leading to the appearance and progression of clinical symptoms.
- Pathophysiologic mechanisms **involve aggregation and clearance** of protein fragments relevant to early in the disease, but not yet fully understood.
- Since the last update in 2018, **new blood-based biomarkers have become available** and Lecanemab has received traditional FDA approval
- The Alzheimer's Association has convened a committee that has drafted revisions to the existing clinical criteria **to define Alzheimer's disease biologically** instead of symptomatically.
- NIA is serving in an **advisory capacity** for this effort.



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

NIH National Institute on Aging