



# NIH Funding for AD/ADRD Research (in Millions)

Fiscal Year:	2015	2016	2017	2018	2019	2020	2021	2022* estimated	<b>Difference</b> 2015 to 2021
AD/ADRD <sup>1</sup>	\$631	\$986	\$1,423	\$1,911	\$2,398	\$2,869	\$3,251	\$3,553	5.2-fold
Alzheimer's Disease (AD)	\$589	\$929	\$1,361	\$1,789	\$2,240	\$2,683	\$3,059	\$3,348	5.2-fold
ADRD <sup>1</sup>	\$120	\$175	\$249	\$387	\$515	\$600	\$725	\$788	6.0-fold
Frontotemporal Dementia (FTD)	\$36	\$65	\$91	\$94	\$158	\$166	\$164	\$169	4.6-fold
Lewy Body Dementia (LBD)	\$15	\$22	\$31	\$38	\$66	\$84	\$113	\$123	7.5-fold
Vascular Contributions to Cognitive Impairment and Dementia (VCID)	\$72	\$89	\$130	\$259	\$299	\$362	\$455	\$493	6.3-fold

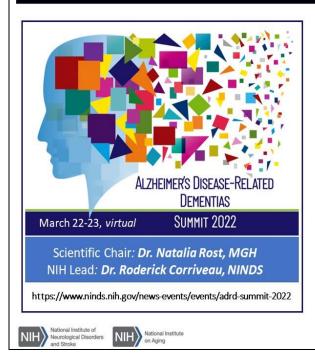
 $Spending\ Categories\ From\ NIH's\ Research, Condition, and\ Disease\ Categories\ (RCDC)\ System\ Source: \ https://report.nih.gov/categorical\ spending.aspx$ 

<sup>1 -</sup> The Alzheimer's Disease Related Dementias (ADRD) category reflects the sum of the three existing categories: Frontotemporal Dementia, Lewy Body Dementia and Vascular Cognitive Impairment/Dementia - where duplicates are removed. Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD) reflects the sum of the two existing RCDC categories: Alzheimer's Disease (AD) and the above Alzheimer's Disease Related Dementias (ADRD) - where duplicates are removed.



## **NIH ADRD Summits Shape ADRD Research Priorities** NAPA Goal 1: Prevent and Effectively Treat AD/ADRD by 2025 Triennial AD, ADRD Scientific Advances Research Milestones & Care Summits **Toward Goal 1** Recommendations **ADRD Summits:** 2013, 2016, 2019, 2022 ☐ NIA leads NIH response to the National Plan\* to Address AD/ADRD ☐ NINDS leads, across the NIH, LBD, FTD, VCID & ADRD Summits ☐ NINDS and NIA collaborate closely ☐ ADRD Summit 2022 occurred over 7 months with >125 stakeholders, including patients, researchers, and members of the public Planning effort that: (1) Delivers ADRD Milestones to National Plan to Address AD & (2) Informs AD Bypass Budgets National Institute of National Institute Neurological Disorders on Aging and Stroke \* https://aspe.hhs.gov/reports/national-plan-2022-update

# NIH ADRD Summits Shape ADRD Research Priorities



## **ADRD Summit 2022 Topics**

- Special Topics Related to MED
- MED
- Post-TBI AD/ADRD
- FTD
- LATE (TDP-43 Pathology in
- VCID
- Common, Late-Onset Dementias)
- LBD
- COVID-19 & AD/ADRD

## Stakeholder Engagement

- ☐ Registration = 1,527 attendees (400-700 during most sessions)
- ☐ Academic, Clinical, Government, Industry, Nonprofit, & Public
- 2 days, 8 scientific sessions, 128 panelists, 44 individual talks
- ☐ 210 minutes of open mic discussions
- ☐ Strong voice of patients and caregivers broad input
- ☐ Recordings are available:
  - Day 1: https://videocast.nih.gov/watch=45149
  - Day 2: https://videocast.nih.gov/watch=45150
- ☐ Result: 52 ADRD Research Milestones in the National Plan

# ADRD Summit 2022







## **HEALTH EQUITY**

Scientific Co-chairs: Hector González, PhD & Julie Zissimopoulos, PhD

Rec. 1 Advance equity in AD/ADRD research via inclusion science to improve representative sampling and retention of diverse communities.

Rec. 2 Increase training support and capacity of an AD/ADRD scientific workforce of persons historically under-represented in biomedical, behavioral, and social sciences.





# NINDS ADRD Programs That Address Health Equity



# Understanding How Stroke & Comorbidities Lead to Dementia



Determine specific subsets of incident stroke, and comorbidities, causing cognitive impairment and dementia in post-stroke populations, including in health disparities populations.

## Clinical Significance of Incidental White Matter Lesions for Dementia

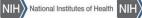


Large, prospective study <u>enrolling a diverse</u> <u>population</u> with cognitive complaints for indepth MRI characterization of white matter lesions and comorbidities to build a predictive risk model for cognitive decline.

### Development and Validation of Biomarkers for VCID



Multi-site national consortium to develop and validate VCID biomarkers for dementia clinical trials. Appropriately powered longitudinal validation studies, including in diverse populations.









# NINDS ADRD Programs the Address Health Equity



Leading the effort to improve the quality of patient evaluations for detecting cognitive impairment in everyday clinical settings

· Includes a strong focus on populations that experience health disparities

### VCID and Stroke in a Bi-racial National Cohort

 $REGARDS = \underline{RE}$  as ons for  $\underline{G}$  eographic  $\underline{a}$  nd  $\underline{R}$  acial  $\underline{D}$  ifferences in  $\underline{S}$  troke

- Epidemiologic/prospective study of stroke risk in diverse populations since ~1980
- · REGARDS has shifted its focus to "VCID and Stroke in a Bi-racial National Cohort"



AD/ADRD Research Supplements to Promote Diversity in Health-Related Research NOT-NS-21-047



Mind Your Risks\*

https://youtu.be/gte5j2S0RuY https://www.mindyourrisks.nih.gov/ Created By: NINDS ONCE Office



# ALZHEIMER'S DISEASE-RELATED DEMENTIAS SUMMIT 2022 Top Priority Recommendations from Disease Specific Sessions

### FRONTOTEMPORAL DEGENERATION (FTD)

Scientific Co-chairs: Adam Boxer, MD, PhD & Celeste Karch, PhD

Rec. 1 Understand FTD epidemiology and genetics in diverse populations, including how socioeconomic and ethnocultural status affects disease risk and manifestations.

Rec. 5 Advance understanding of FTD and identify therapeutic targets through the creation, validation, and use of preclinical and translational tools and resources.

### **LEWY BODY DEMENTIAS (LBD)**

Co-Chairs: James Leverenz, MD & Kejal Kantarci, MD

Rec. 1 Prepare for and initiate clinical trials that aim to alleviate or slow the course of LBD symptoms, and delay or prevent the onset of disease.

Rec. 5 Delineate genetic loci and their functions contributing to the onset and progression of LBDs using genetic, transcriptomic, epigenetic, and environmental characterization analyses.

## VASCULAR CONTRIBUTIONS TO COGNITIVE IMPAIRMENT & DEMENTIA (VCID)

Scientific Chair: Donna Wilcock, PhD & Ron Petersen, MD, PhD

Rec. 1 Establish and refine experimental models and technologies to identify disease-relevant mechanisms underlying VCID.

Rec. 4 Develop and validate markers of VCID in diverse populations using 1) cognitive, physical, or other functional assessments, and 2) biomarkers of key vascular processes, including in the most common scenario where VCID is accompanied by AD in human studies.



# National Consortium to Develop & Validate Clinical Trial Ready VCID Biomarkers







National consortium validating, for use in large clinical trials, predictive, diagnostic & progression biomarkers for VCID.

\*Independent of Dementia Diagnosis\*

# **IMAGING BIOMARKERS:**

Arteriolosclerosis Kit: MRI (MPRAGE, FLAIR, DTI) with post processing to generate maps of white matter hyperintensities (WMH), diffusion anisotropy, & WM

Cerebrovascular Reactivity Kit: MRI BOLD (bloodoxygenation level-dependent) during CO<sub>2</sub> challenge (CVR)

MRI Free Water Kit: MRI DTI (diffusion tensor imaging) derived mean WM free water fraction

Peak Skeletonized Mean Diffusivity Kit: MRI DTI-derived mean Diffusivity Dispersion in the WM Skeleton

### FLUID BIOMARKER:

Neurofilament Light (NfL) Kit: Plasma, Single Molecule Array (Simoa) immunoassay

Coordinating Center:

Mass. General Hospital

· Rush Medical Center & Illinois Inst. of Tech. · Washington U., U. of Texas Southwestern



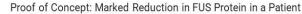
- UC San Francisco & Davis
- · U. of Southern California
- · Mayo Clinic Rochester · U. of Kentucky
- U. of New Mexico Health Sciences Johns Hopkins Medical Center CHARGE Boston U., U. of Vermont & UT Houston

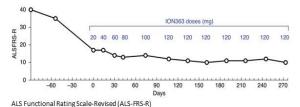
# Recent Investigator-Initiated Scientific Advance: Antisense Oligonucleotides as a Potential Therapeutic in ALS/FTD

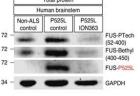


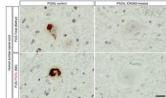
Targeting Mutant FUS (ION363, non-allele-specific FUS antisense oligonucleotide)

First in Human: Physical Function With Treatment









Korobeynikov et al., Nature Medicine (2022)

- Fused in sarcoma (FUS) gene encodes an RNA-binding protein
- Certain FUS mutations cause ALS and/or FTD (FUS P525L: toxic gain of function, with insolubility of FUS and related RNA-binding protein)
- In an ALS patient with FUS P525L, ION363 lowered wild-type and mutant FUS protein levels in central nervous system

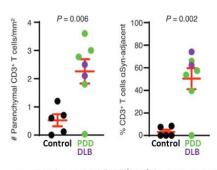
Korobeynikov et al., Nature Medicine 28,104-116 (2022) (Supported by NIH grant RO1NS106236; Tow Foundation, Project ALS and the ALS Association, Nancy Pzerlman and Tom Klingenstein, the Judith and Jean Page Adams Charitable Foundation).

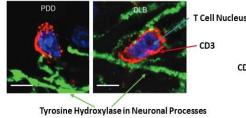
Also see Tran et al., Nature Medicine 28,117-124 (2022) for suppression of mutant C9orf72 using ASO. (Supported by NiH grant R01NS111990, the Angel Fund for ALS Research, the Ono Pharmaceutical Foundation, ALSOne, ALS Finding a Cure, the Cellucci Fund for ALS Research, and the Max Rosenfeld Fund)

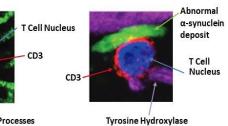


# T Cells In LBD: Adaptive Immunity as a Potential Therapeutic Target in Humans

T Cells are Adjacent to Dopaminergic Neurons and to α-Synuclein Deposits







- Cerebrospinal fluid (CSF) from LBD patients contained inflammatory and autoimmune T helper 17 (T<sub>H</sub>17) cells that highly expressed CXCR4 (chemokine receptor gene).
- In postmortem LBD brains, CXCR4-expressing T cells were found in the perivascular space near chemokine ligand (CXCL12)-expressing cerebrovascular endothelial cells.
- CXCL12 concentrations in CSF from LBD patients were increased and positively correlated with neurodegeneration (NfL).

If CXCR4-CXCL12 signaling drives migration of T cells into the brain to destroy neurons, then therapies that turn off this mechanism may help treat or prevent neurodegenerative disease.

Tyrosine Hydroxylase: Dopamine enzyme CD3: T cell marker

DLB: Dementia with Lewy bodies PDD: Parkinson's disease dementia

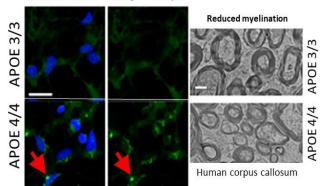
Gate et al., Science 374, 868-874 (2021) Iba et al. Journal of Neuroinflammation 17:214 (2020)

### **Recent Science Advance:**

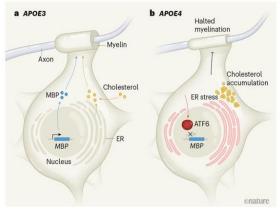
## APOE4 Impairs Myelination Via Cholesterol Dysregulation in Oligodendrocytes



Cholesterol inclusions in oligodendrocytes\*



Hypothesis: Cholesterol accumulation increases ER stress, resulting in the transcription factor ATF6 inhibiting MBP gene transcription.



Hoechst \*Derived from human iPs BODIPY-cholesterol

### Blanchard, J.W et al. Nature (2022)

Blanchard, J.W. et al. Nature 611, 769-779 (2022) for the impact of APOE4 on myelination via cholesterol dysregulation in oligodendrocytes (supported by NIH grants R01NS114239-01A1, UG3NS115064, RF1AG052377, RF1AG054012-01, US4NE008097, R01AG058002, R24AG062786, R01AG015819, RF1-AG0540124, RF1AG062377, the Robert A. and Renee E. Belfer Family, the JPB Foundation, the Carol and Gene Ludwig Family Foundation, the Cure Alzheimer's Fund, MIT BCS Brossly Graduate Student Fellowship

Karl, C. & Gonçalo Castelo-Branco Nature 611, 670-671 (2022) Alzheimer's risk variant APOE4 linked to myelin-assembly malfunction







# ALZHEIMER'S DISEASE-RELATED DEMENTIAS SUMMIT 2022

Top Priority Recommendations from Cross-cutting Sessions

# **MULTIPLE ETIOLOGY DEMENTIAS (MED)**

### Scientific Chair: Katherine Possin, PhD

Rec. 1 Evaluate pragmatic approaches to objectively detect cognitive impairment and link to quality care when a patient, care partner, or clinician reports cognitive, behavioral or functional changes.

Rec. 1 Conduct clinical studies on approved or promising interventions and treatments to mitigate risk for cognitive decline.

Special Topic: Post-Traumatic Brain Injury (TBI) AD/ADRD Scientific Chair: Kristen Dams-O'Connor, PhD

Rec. 1 Promote collaboration among TBI and dementia researchers through working groups, retrospective and prospective data and measurement harmonization, and interdisciplinary research.

Special Topic: LATE (TDP-43 In Common Late-Onset Dementias)
Scientific Chair: Julie Schneider, MD, MS

Rec. 1 Define LATE (pathologic, clinical, genetic, molecular) classification and diagnostic boundaries across FTLD-TDP, AD and other dementia related pathologies and their syndromes to enhance diagnosis, research, and awareness assuring diversity, inclusion and equity.

Special Topic: Impact of COVID-19 on AD/ADRD Risk and Outcomes

Scientific Chair: Sudha Seshadri, MD

Rec. 1 Establish research infrastructure enabling clinical, epidemiological and basic research studies of COVID-19 impact on AD/ADRD risk and outcomes, prioritizing disproportionally affected populations and clinical trials readiness.

# Priority: Detecting Cognitive Impairment, Including Dementia, in Everyday Care Settings in 10 Minutes or Less, With EHR Follow-up Recommendations



## <u>DetectCID Assessments in</u> <u>Pragmatic Clinical Trials</u>

UCSF Paradigm (TabCAT-BHA): Two required tests: Favorites and Match

Einstein Paradigm (5-Cog): Three components:

Picture-based Memory Impairment Screen, Timed
walk and Paper-Match

Northwestern Paradigm (MyCog): Based on two modified NIH Toolbox Cognition Batteries: Picture Sequence Memory and Dimensional Change Card Sort

"Recent finding highlight promising approaches to improving the detection of cognitive impairment, as well as approaches to partnering with primary care that could be useful across specialties"

Sideman, A.B. et al., J. Alzheimers Dis. (2022)

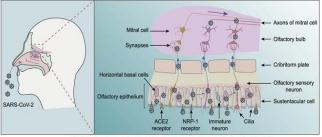
Detecting Cognitive Impairment, Including Dementia, in Primary Care and Other Everyday Clinical Settings for the General Public and Health Equity, Pragmatic Clinical Trials (RFA-NS-22-009)



# Priority: Impact of COVID-19 on Risk and Outcomes of ADRD

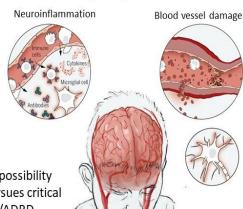


### Possible route of the virus from nose to the CNS via olfactory nerve



Chen, F. et al., Translational Neurodegeneration, 2022

### Putative neuropathogenic effects of COVID-19



Spudich & Nath, Science, 2022

- Clinical & pathological observations of COVID-19 have raised the possibility that it is a risk factor for dementia. NIH support research that pursues critical knowledge needed to understand the impact of COVID-19 on AD/ADRD.
- Impact of COVID-19 on Dementia Risk, Progression and Outcomes in ADRD Populations (NOT-NS-21-037)
- Neuropathological Interactions Between COVID-19 and ADRD (Planned Initiative)



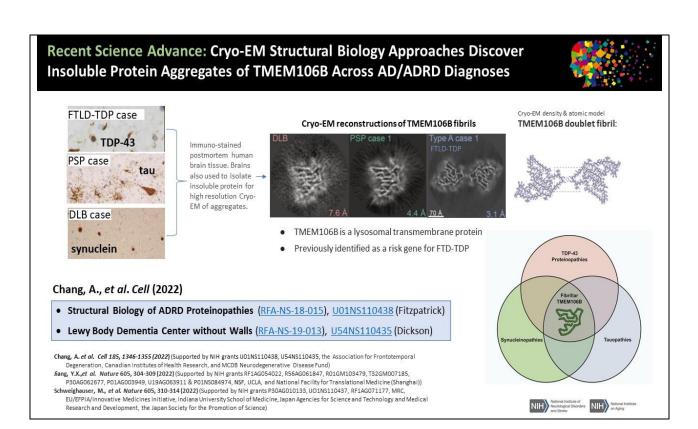


# NIH ADRD Summits Shape ADRD Research Priorities



### **Common Themes**

- Achieving health equity in AD/ADRD is a major unmet need.
- Need for research & implementation of pragmatic approaches and solutions in ADRD (includes pragmatic clinical trials).
- Precise biomarkers are needed to identify underlying disease processes in individuals.
- Personalized approaches to prevention and treatment are needed that by design address health equity and diverse populations.
- In clinical research: prevention, pre-symptomatic vigilance, and concerted attention should be paid to the immediate needs of individuals living with dementia.
- In basic research, needs include novel strategies and tools (models, biology paradigms) and/or seeking synergies, maximizing divergence in pathways.



## Recent Science Advance: Aggregated ApoE Protein Associated With Dementia Snap-frozen Detergent-insoluble, urea-soluble fraction Dementia with APOE3/APOE3 genotype: Amyloid amygdala plaque-like structures in amygdala with ApoE protein. High MW Mass spectrometry Dementia Controls cases **Biochemistry** Compare Analyses of dementia-enriched Conclusion: The most common genetic risk factor for dementia is APOE4. peptides from APOE3/APOE3 Unexpectedly, ApoE protein, including in people who are not APOE4 carriers, is homozygous and other cases: tau. present in large protein aggregates/amyloid-like plaque structures in the amygdala alpha-synuclein, APP/Aβ, and APOE. of people with dementia, consistent with a direct pathogenic role for ApoE protein. Jozsef G et al. The American Journal of Pathology (2022)

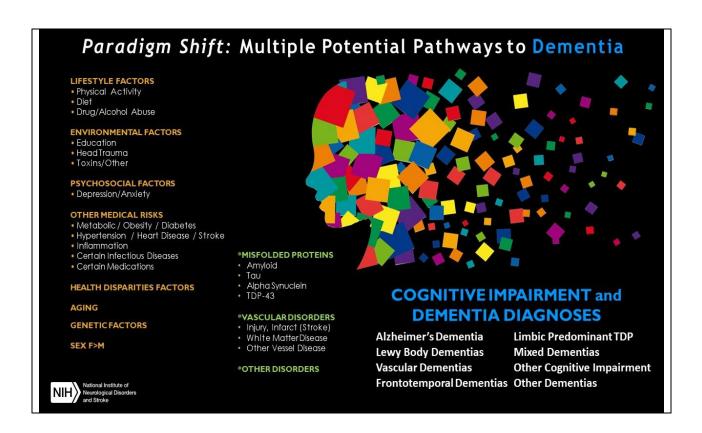
National Institute

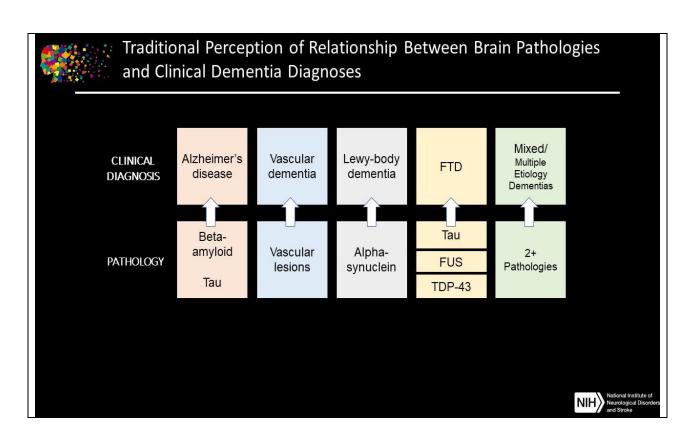
Neurological Disorders and Stroke

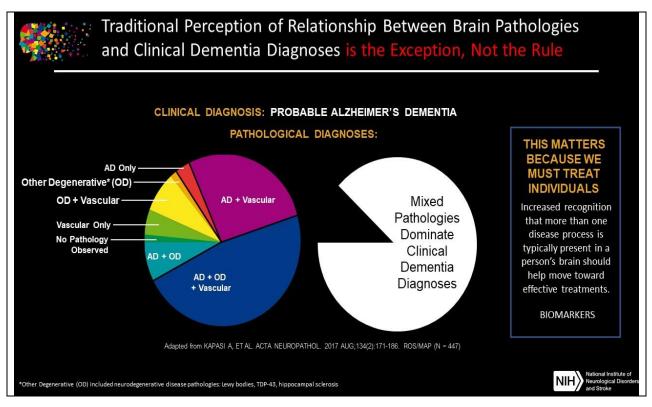
Jozsef, G. et al. The American Journal of Pathology 192, 564-578 (2022) (Supported by NIH grants R21NS095299, RF1NS118584, P30AG072946, R01AG042419,

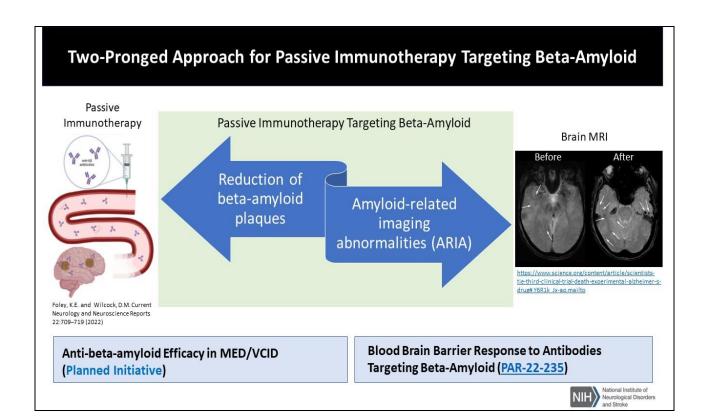
R01AG042475, R01AG061111, R01 AG057187, R21AG061551, R01AG060056, R01AG062550 and S10

RR029127, the VA MERIT award I01BX002149)









# Added Funds Since FY 2016 Allowed NINDS to Establish and Lead Major ADRD Research Programs and Consortia



ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degene

- DiverseVCID, impact of white matter vascular changes and comorbidities on dementia risk in diverse populations
- MarkVCID, consortium for vascular contributions to cognitive impairment and dementia (VCID) biomarkers
- **DISCOVERY**, impact of stroke types and comorbidities on dementia risk in people from diverse backgrounds
- DetectCID, increase detection of cognitive impairment/dementia in primary care settings in diverse populations
- FTD Center Without Walls, study molecular mechanisms that lead to FTD
- FTD Sequencing Consortium, to discover FTD-causing gene mutations
- · ALLFTD Natural History Study in FTLD, with the NIA
- PET Ligand Development and Structural Biology for AD/ADRD Proteinopathies
- Lewy Body Dementia Center Without Walls to characterize  $\alpha$ -synuclein and  $\beta$ -amyloid subtypes in LBD
- LBD biomarker discovery research
- CONNECT-TBI, consortia to study traumatic brain injury (TBI) links to AD/ADRD
- Center for Alzheimer's Disease Research (CARD), intramural center with NIA Tauopathy and TDP-43 Proteinopathy Structural Biology





















# **NINDS AD/ADRD Research Program – Summary**



■ NINDS ADRD Su	ımmits set Nationa	I Research Priorities
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- ☐ 75 NINDS ADRD funding initiatives inviting applications to fill critical needs, and investigator-initiated research
- ☐ Established new major ADRD programs and consortia
- ☐ NINDS ADRD program has guided transformative research and contributed to new advanced understanding toward interventions





# ADRD Funding Initiatives and Plans for FY2024



## NINDS led 15 funding announcements in FY2023

There are 5 AD/ADRD funding announcements currently open that NINDS participates in:

https://www.ninds.nih.gov/funding/find-funding-opportunities (Search "ADRD")

### NINDS funding announcement concepts are being planned for FY2024

### WORKFORCE

### **Diversity Training** Career

- Social Determinants
- Modifiable Risk(s)
- Mechanisms & Pathology
- Covid-19 & Dementia

### RESEARCH

- Translational
- Biomarkers & Diagnosis
- Clinical Trials

See the NINDS Focus on Alzheimer's Disease and Related Dementias page for details: https://www.ninds.nih.gov/current-research/focus-disorders/alzheimers-related-dementias





# NINDS AD/ADRD Program - Thank You to NINDS and NIA Leadership and Staff



### Walter Koroshetz (NINDS)

### Richard Hodes (NIA)

### Roderick Corriveau (NINDS)

Kiara Bates (NINDS)
Marci Bollt (NINDS)
Erin Bryant (ONCE)
Roger Campbell (NINDS)
Chi Chang (NINDS)
Sara Dodson (NINDS)
Amber McCartney (NINDS)
Arvind Shukla (NINDS)

Hibah Awwad (NINDS)
Debra Babcock (NINDS)
Patrick Bellgowan (NINDS)
Karrah Benson (NINDS)
Dawn Beraud (NIA)
Francesca Bosetti (NINDS)
Bo-Shiun Chen (NINDS)

Tom Cheever (NINDS) Jue Chen (NHLBI) Jessica Corley (NINDS) Will Daley (NINDS) Damali Martin (NIA) Cerise Elliott (NIA) Carlos Faraco (NINDS) Susan Fowler (NINDS) Jordan Gladman (NINDS) Amelie Gubitz (NINDS) Jane Hettinger (NINDS) Brandon Hartsell (NINDS) Rebecca Hommer (NINDS) Mir Ahamed Hossain (NINDS) John Hsiao (NIA) Sophia Jeon (NINDS) David Jett (NINDS)

Michelle Jones-London (NINDS) Melinda Kelly (NIA) Jim Koenig (NINDS) Stephen Korn (NINDS) Lyn Jakeman (NINDS) Tim Lavaute (NINDS) Pascal Laeng (NINDS) Quynh Ly (NINDS) Ernie Lyons (NINDS) Mack Mackiewicz (NIA) Gary Marlowe (NINDS) Eliezer Masliah (NIA) Marguerite Matthews (NINDS) Linda McGavern (NINDS) Barbara McMakin (NINDS) Daniel Miller (NINDS) Marilyn Moore-Hoon (NINDS) Ana Olariu (NINDS) Lisa Opanashuk (NIA)

Suzana Petanceska (NIA) Nia Pree (NINDS) Rebecca Price (NINDS) Shanta Rajaram (NINDS) Toya Rogers (NINDS) Paul Scott (NINDS) Beth-Anne Sieber (NINDS) Nina Silverberg (NIA) Natalia Strunnikova (NINDS) Christine Swanson-Fischer (NINDS) Amir Tamiz (NINDS) Anna Taylor (NINDS) Carol Taylor-Burds (NINDS) Natalie Trzcinski (NINDS) Nsini Umoh (NINDS) Andrea Varea (NINDS) Margo Warren (NINDS) Samantha White (NINDS) Kyle Whitehead (NINDS)

Shellie Wilburn (NINDS) Carl Wonders (NINDS) Clinton Wright (NINDS) Xiling Yin (NINDS)

### Review Branch

Karrah Benson Bo-Shiun Chen Gary Marlowe Marilyn Moore-Hoon

### **ADRD Summit Session Leads**

FTD: Tom Cheever

### Health Equity:

Richard Benson

LBD: Debra Babcock

 ${\sf MED\text{-}Overall, TBI, -LATE:}$ 

Linda McGavern

MED-COVID-19:



