ADRC Directors’ Meeting
National Institute on Aging
Virtual
October 2, 2020

NIA Division of Neuroscience Update

Eliezer Masliah
Division of Neuroscience
NIA-NIH
NIA Division of Neuroscience

To support and advance research leading to better understanding of the mechanisms of brain aging and Alzheimer’s Disease and related dementias
DN collaborates with other NIA Divisions, NIH institutes and the community to advance NAPA.

Scientific community "gaps and opportunities"

Milestones

FOAs

Grants

NIH

NGOs

FNIH

NINDS

NHLBI

NIMH

others

NACA

DEA

DAB

GCG

BSR

DN

PUBLIC

AD Bypass Budget

2018

2019

2020

2021

2022

Scientific community
NIA AD Translational Research Program: Diversifying the Therapeutic Pipeline

A Pipeline of Translational Research Funding Opportunities (R21/R01, U01, SBIR/STTR)

ENABLING INFRASTRUCTURE FOR DATA DRIVEN AND PREDICTIVE DRUG DEVELOPMENT
NIA resources for data sharing in support of 2025

NIA Program Directors: Nina Silverberg, Cerise Elliott, Laurie Ryan, Suzana Petanceska, Lorenzo Refolo, Marilyn Miller, Dallas Anderson, Kristina McLinden

- **ACTC** - AD Clinical Trials Consortium
- **ADSP** - AD Sequencing Program
- **ADGC** - AD Genetics Consortium
- **ADNI** - AD Neuroimaging Initiative
- **ADRCs** - AD Research Centers
- **AMP-AD** - Accelerating Medicines Partnership for AD
- **MODEL-AD** - Model Organism Develop and Evaluation for Late-Onset AD
- **NACC** - National AD Coordinating Center
- **NCRAD** - National Centralized Repository for AD and ADRD
### NIA Division of Neuroscience New Organization

#### Directors Office
- Eliezer Masliah (Director) and Jennie Larkin (Deputy Director)
- Jean Tiong-Koehler, Toni Salazar, Donna Weaver, Sarita Chapman, LeKeisha Carroll, Alexander Bracy, Chelsea Dinneny

#### Leadership team
- Eliezer Masliah, Jennie Larkin, Bradley Wise, Molly Wagster, Suzana Petanceska, Laurie Ryan, Lorenzo Refolo

#### Strategic Development and Partnerships Office
- Suzana Petanceska (Director)
- Nadezda Radoja, Erika Tarver, Laurie Ryan, Jean Yuan, Alvin McKelvy

#### Population Studies and Genetics Branch
- TBN Chief
- Dallas Anderson, Marilyn Miller, Alison Yao, Jennie Larkin, Ananya Paria, Sharna Tingle

#### Neurobiology of Aging and Neurodegeneration Branch
- Brad Wise (Chief)
- Mack Mackiewicz, Paul Barrett, Amanda M. DiBattista, Austin Yang, Lisa Opanashuk, Elizabeth A. Newman

#### Behavioral and Systems Neuroscience Branch
- Molly Wagster (Chief)
- Luci Roberts, Coryse St. Hillaire-Clarke, Devon Oskvig, Matt J Sutterer, Dave Frankowski

#### Translational Research Branch
- Lorenzo Refolo (Chief)
- Suzana Petanceska, Zane Martin, Jean Yuan, Shreaya Chakroborty, Ali Sharma

#### Clinical Interventions and Diagnostics Branch
- Laurie Ryan (Chief)
- Nina Silverberg, John Hsiao, Cerise Elliot, Yuan Luo, Kristina McLinden, Akanni Clarke, Grayson Donley, Alvin McKelvy
Enable an integrated approach to program development on all aspects of brain aging, Alzheimer's disease, and related dementias to accelerate therapy development and to facilitate the Division of Neuroscience's collaborations.

- NAPA milestones, AD Summit, ADBB, Public-Private Partnerships, IADRP
Understanding the contributions of population and genetics studies in brain aging and neurodegeneration

- **Trajectory of cognitive decline** - MCI/AD, potential risk and protective factors
- **Morbidity/mortality** - in general populations and race/ethnic subpopulations
- **Novel genomic elements** - functional roles driving heterogeneity
- **Integrated genomics** - machine learning, functional genomics, harmonization
- ADSP, NIAGADS, CGAD, GCAD

Dallas Anderson, Damali Martin, Marilyn Miller, Alison Yao, Jennie Larkin, Ananya Paria, Sharna Tingle
Understanding how the nervous system is affected by normal as well as pathological aging

- **Fundamental Neuroscience** - functional changes, selective vulnerability, plasticity
- **Basic Science of AD/ADRD** - molecular and cellular mechanisms, repair, neurovirology
- **Integrative Neurobiology** - changes between organ systems and the CNS
- **Sleep and Biological Rhythms** - sleep-wake cycles/disordered biorhythmicity
- **BRAIN initiative, Stem cells, human connectome, Blueprint, single cell atlas**

Brad Wise (Chief)
Mack Mackiewicz
Amanda M. DiBattista
Lisa Opanashuk
Austin Yang
Paul Barrett
Elizabeth A. Newman
Rachel Sare
Neural and psychological mechanisms underlying age-related changes in cognition, emotion, sensory and motor function

- **Cognitive neuroscience** - learning, memory, attention, executive function, language
- **Sensory processes** - visual, auditory, somatosensory, pain, vestibular
- **Motor function** - neuromuscular, sensory-motor, balance, and movement disorders
- **Affective Neuroscience** - interface between emotion and cognition
- NIH Toolbox, HEAL Initiative, Delirium, Resilience, Super-Agers

Molly Wagster (Chief)
Luci Roberts
Coryse St. Hillaire-Clarke
Devon Oskvig
Matt J Sutterer
Dave Frankowski
Supports the spectrum of drug discovery and preclinical drug development from target discovery and validation through securing Investigational New Drug (IND)

- **Target discovery and validation** – systems and network biology approaches
- **Drug discovery and preclinical drug development** – development of small molecules and biologics for a diverse set of therapeutic targets
- **Drug repositioning and combination therapy development** – integrated computational and experimental approaches
- **Translational Infrastructure and Training** – open science consortia and centers, resources for increasing research rigor, reproducibility, and translatability
- ADDP, SBIR-STTR, Blueprint Neurotherapeutics, AMP-AD and Affiliated Consortia (M²OVE-AD, Resilience-AD, Psych-AD), MODEL-AD Consortium, TREAT-AD Centers, AD Knowledge Portal/Agora, ALzPED

Larry Refolo (Chief)
Suzana Petanceska
Zane Martin
Jean Yuan
Shreaya Chakroborty
Ali Sharma
Clinical Interventions and Diagnostics Branch

Supports research aimed at prevention, treatment, and management of individuals with or at-risk for cognitive decline, AD/ADRD

- **Biomarkers**- diagnostic procedures instruments, imaging, fluid and digital biomarkers, and clinical and neuropsychological instruments for diagnosis
- **Pharmacological and non-pharmacological clinical trials**- Phases I-III, small molecules, biologics, combination therapies, neurostimulation, behavioral, lifestyle

Clinical Trials Infrastructure and Training
- ADRCs, NACC, NCRAD, ADNI, ACTC, DIAN, DIAN-TU, ABC-DS

Laurie Ryan (Chief)
Nina Silverberg
John Hsiao
Cerise Elliot
Yuan Luo
Kristina McLinden
Akanni Clarke
Grayson Donley
Alvin McKelvy
NIA Division of Neuroscience Collaborations

Cross-cutting: DISPARITIES, DIVERSITY, TRAINING
Understanding AD in the context of Aging

Proteostasis
Mitochondria
Inflammation
Endosomes
Growth Factors
Epigenetics
DNA damage
Senescent cells
Immune surveillance

Aging

Proteinopathy

Abeta
Tau
Synuclein
TDP43
Others

Synapse damage

Neurodegeneration

HIV-1, HHV, other pathogens

NIH National Institute on Aging
New FOAs in Aging related cellular and molecular mechanisms in AD/ADRD FY2020

- Neurogenesis In aging and AD/ADRD (FOA pending)
- Oscillatory gene expression in aging and AD/ADRD (RFA-AG20-04)
- Cellular scale connectome in aging and AD/ADRD (FOA pending)
- Glial cell plasticity in Aging and AD/ADRD (RFA-AG-21-010)
- Cell senescence in Aging and AD/ADRD (RFA-AG-20-025)

https://www.nia.nih.gov/approved-concepts#Sept2020
Recent conflicting reports on adult human neurogenesis raise controversy.

Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults

Shawn F. Sorrells, Mercedes F. Paredes, Arantxa Cebrian-Silla, Dashi Qi, Kevin W. Kelley, David James, Simone Mayer, Julia C. Lee, Edward F. Chang, Antonio J. Gutierrez, Arnold R. Kriegstein, Michael C. Oldham, Eric J. Huang, Jose Manuel Garcia-Verdugo & Arturo Alvarez-Buylla

Nature 555, 377–381(2018) | Cite this article

Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer’s disease

Elena P. Moreno-Jiménez, Miguel Flor-García, Julia Terreros-Roncal, Alberto Rábano, Fabio Cafini, Noemi Pallas-Bazarra, Jesús Ávila and María Llorens-Martín

Is Alzheimer’s Disease a Neurogenesis Disorder?

Se Hoon Choi and Rudolph E. Tanzi

†Genetics and Aging Research Unit, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA
*Correspondence: tanzi@helix.mgh.harvard.edu

Dual Perspectives 50

Does Adult Neurogenesis Occur in the Human Brain?

Presenters: Arturo Alvarez-Buylla, PhD; Maria Llorens-Martin, PhD
NIA Workshop on Neurogenesis and Aging
March 16-17, 2020  Bethesda MD (VIRTUAL)
NIH leads- Molly Wagster, Brad Wise, Amanda Dibattista, Matt Sutterer
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Session I. Neurogenesis in the Adult Human Brain.
• Hippocampal neurogenesis linked cognitive deficits and AD
• Solving human neurogenesis in vivo toward therapy of brain disorders

Session II. Regulation of Neurogenesis in the Aging Brain.
• Regulation of neural stem cell aging with single cell
• Enhanced plasticity of new neurons in the hippocampus
• Blood-borne regulators of the hippocampal neurogenic niche

Session III. Functional Significance of Adult Neurogenesis.
• Blood: at the interface of aging and adult neurogenesis
• Re-engineering and Rejuvenating aging memory circuits
• Harnessing Neurogenesis to Improve Pattern Separation in Aging
Develop Tools and Resources.
Develop new genetic and molecular markers for human neurogenesis. Establish new models to study adult neurogenesis (e.g., non-mouse animal models, organoids, computational models), and identify species differences. Improve live imaging approaches for adult neurogenesis.

Establish New Collaborations.
Create multi-laboratory consortia to establish “virtual labs” across fields.

Evaluate the Costs and Benefits to Increased Neurogenesis.
Test the impact of new neurons on circuits and behavior. Collectively evaluate the neurogenic niche. Evaluate the ideal balance of neurogenesis and mature neuron maintenance in humans.
NIA FOAs investigating the cross talk between pathogens and aging and AD/ADRD research

Infectious etiology of AD/ADRD (NOT-AG-19-012)
HIV, brain aging and AD/ADRD (RFA AG18-023)
Microbiome in Aging (RFA-AG-20-030)
COVID-19 NIA NOSI (NOT-AG-20-022)

NIA FOAs investigating the cross talk between pathogens and aging and AD/ADRD research

Risk of Transmissibility From Neurodegenerative Disease-Associated Proteins: Experimental Knowns and Unknowns

David M. Asher, MD, Ermias Belay, MD, Eileen Bigio, MD, Sebastian Brandner, MD, Scott A. Brubaker, BA, Byron Caughey, PhD, Brychan Clark, MD, Inger Damon, MD, PhD, Marc Diamond, MD, Michelle Freund, PhD, Bradley T. Hyman, MD, PhD, Mathias Jucker, PhD, C. Dirk Keene, MD, PhD, Andrew P. Lieberman, MD, PhD, Mirosław Mackiewicz, PhD, Thomas J. Montine, MD, PhD, Susan Morgello, MD, Creighton Phelps, PhD, Jiri Safar, MD, PhD, Julie A. Schneider, MD, MS, Lawrence B. Schonberger, MD, MPH, Christina Sigurdson, DVM, PhD, Nina Silverberg, PhD, John Q. Trojanowski, MD, PhD, and Matthew P. Frosch, MD, PhD

(RFA-AG-20-030)
Notice of Special Interest (NOSI): NIA Availability of Administrative Supplements and Revision Supplements on COVID-19

Notice Number: NOT-AG-20-022

Key Dates
Release Date: April 2, 2020
First Available Due Date: April 06, 2020
Expiration Date: May 01, 2021

Related Announcements
PA-18-591 Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp Clinical Trial Optional)
PA-18-935 Urgent Competitive Revision to Existing NIH Grants and Cooperative Agreements (Urgent Supplement - Clinical Trial Optional)
NOT-AG-20-031

Wesley Ely, 3R01AG058639-02S1 - Evaluate if hospitalized adult COVID-19 survivors have a high burden of Post-Intensive Care Syndrome (PICS)-related AD, PTSD, and depression at 6-months. Secondarily, we will also determine if hydroxychloroquine versus placebo improves these outcomes

Eric Reiman- 3P30AG019610-20S1 - Neuropathological consequences of CNS SARS-CoV-2 in infected humans. investigations of 100 or more consecutive autopsies spanning the pandemic period.

Panagiotis Roussos– 3R01AG065582-01S1 - This supplement proposes to evaluate the molecular and neuropathological effects of SARS-CoV-2 in neurons and glial cells

Todd Golde – 3U01AG046139-08S1 - This supplement proposes to assess the potential mechanisms for the highly divergent immune responses to the SARS-CoV-2 infection

Suzanne Craft – 3P30AG049638-05S2 - Impact of COVID-19 related social distancing and stress on individuals with cognitive impairment as compared to older adults with normal cognition in the WF ADRC center cohort.
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