

**NATIONAL INSTITUTES OF HEALTH
NATIONAL INSTITUTE ON AGING**

Summary Minutes

**The 147th Meeting
NATIONAL ADVISORY COUNCIL ON AGING
September 7-8, 2022**

**National Institutes of Health
Virtual Meeting
Bethesda, MD 20892**

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Department of Health and Human Services
Public Health Service
National Institutes of Health
National Institute on Aging
NATIONAL ADVISORY COUNCIL ON AGING
SUMMARY MINUTES
September 8, 2022

The 147th meeting of the National Advisory Council on Aging (NACA) was convened on Thursday, September 8, 2022, at 10 a.m. by videoconference. Dr. Richard Hodes, Director, National Institute on Aging (NIA), presided.

In accordance with the provisions of Public Law 92–463, the meeting was closed to the public on Wednesday, September 7, from 3 p.m. to 5 p.m. for the review, discussion, and evaluation of grant applications in accordance with the provisions set forth in Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of Public Law 92–463.¹ The meeting was open to the public on Thursday, September 8, from 10:00 a.m. to 1:30 p.m.

Council Participants:

Dr. Darren Baker
Dr. Shalender Bhasin
Dr. Anne Case
Dr. Yanira Cruz
Dr. Monica A. Driscoll
Dr. Terry T. Fulmer (not in attendance)
Dr. Susan Greenspan
Dr. Yadong Huang
Dr. Rev. Cynthia Huling Hummel
Dr. Frank Longo
Dr. Jennifer Jaie Manly
Dr. Charlotte Peterson
Dr. David B. Reuben
Dr. Julie Schneider
Dr. Linda Van Eldik
Dr. David R. Weir
Dr. Keith E. Whitfield (not in attendance)

Ex Officio Participants

Dr. Radha Holavanahalli, Administration for Community Living (ACL)
Dr. Anne Ordway, National Institute on Disability, Independent Living, and Rehabilitation, ACL

¹ For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure only applied to applications that were discussed individually, not to “en bloc” actions.

Members of the Public Present:

Dr. Rose Maria Li, Rose Li and Associates, Inc.
Mr. Alexander Sagona, Rose Li and Associates, Inc.
Dr. Alcino Silva, University of California, Los Angeles
248 live views via NIH videocast

I. REVIEW OF APPLICATIONS

This portion of the meeting was closed to the public, in accordance with the determination that it concerned matters exempt from mandatory disclosure under Sections 552(b)(c)(4) and 552(b)(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix).²

A total of 1,843 applications requesting \$4,585,513,271 for all years underwent initial review. The Council recommended 1,025 awards for a total of \$2,803,360,604 for all years. The actual funding of the awards recommended is determined by the availability of funds, percentile ranks, priority scores, and program relevance.

II. CALL TO ORDER

Dr. Santora welcomed members to the open session of the 147th NACA meeting. Dr. Hodes called the meeting to order at 10:00 a.m. on Thursday, September 8, 2022.

A. Director's Status Report

NIH/NIA Budget Status

Dr. Hodes reported that the House Labor-HHS spending bill, which had advanced out of committee, would appropriate \$47.5 billion for NIH, with \$4.443 billion reserved for NIA. This amount includes an additional \$200 million for Alzheimer's disease and Alzheimer's-disease related dementias (AD/ADRD) research compared to the previous year, as well as \$2.75 billion for ARPA-H, \$541 million for *All of Us*, and \$620 million for the *Brain Research through Application of Innovative Neurotechnologies (BRAIN) Initiative*. The Senate's FY23 Labor-HHS Appropriations Bill, released by the Appropriations Committee on July 28, 2022, would provide nearly \$48 billion for NIH, with \$4.34 billion reserved for NIA. The federal government is currently funded through September 30, 2022.

For general applications reviewed by the Center for Scientific Review (CSR) and requesting less than \$500,000 (direct costs) in any one year, pay lines are 15% for most regular research applications, 18% for new investigator applications, 20% for early-stage investigator applications. For CSR-reviewed applications seeking \$500,000 or more, pay lines are 12% for most, 15% for new investigator, and 17% for early-stage investigator applications. Pay lines are higher for applications focused on AD/ADRD: 28% for most, 31% for new investigator applications, and 33% for early-stage investigator applications.

² For the record, it is noted that members absented themselves from the meeting when the Council discussed applications (a) from their respective institutions or (b) in which a conflict of interest may have occurred. This procedure applied only to applications that were discussed individually, not to "en bloc" actions.

For NIA-reviewed applications, the priority scores for general pay lines are 20 for program projects, 20 for other NIA-reviewed research, 21 for career development awards, and 30 for fellowship awards. The corresponding AD/ADRD pay lines are 40, 40, 35, and 40, respectively.

FY2024 Alzheimer's Disease Bypass Budget

Dr. Hodes presented on the FY2024 Alzheimer's Disease Bypass Budget (ADBB) that is required by law to be submitted for each fiscal year through FY 2025 by the NIH Director directly to the President for review and transmittal to Congress for NIH initiatives pursuant to the National Alzheimer's Plan (including an estimate of the number and type of personnel needs for the institutes). To develop the FY24 ADBB, NIH drew from combined external and internal input gathered through multi-stakeholder meetings from 2012-2022 and trans-NIH development of comprehensive milestones. The overarching framework for the FY24 ADBB and narrative highlights six research areas derived from the Common Alzheimer's and Related Dementias Research Ontology (CADRO): (1) epidemiology/population studies; (2) disease mechanisms; (3) diagnosis, assessment, and disease monitoring; (4) translational research and clinical interventions; (5) dementia care and impact of disease; (6) research resources; as well as one cross-cutting area, health equity and inclusion. The FY24 ADBB narrative includes a new, prospective overview of research opportunities in these areas that could be pursued with additional investment. Previous versions of the ADBB featured a retrospective progress report, which will now be released separately in Fall 2022; it will feature examples of recent science advances from basic to clinical research, care/caregiving interventions, and more.

The ADBB for FY2024 projects total costs of \$498 million for AD/ADRD research, including \$321 million for additional resources needed for new research. Using the FY2022 enacted level for AD/ADRD research as the baseline estimate (\$3.55 billion), the total FY2024 budget needed is thus estimated at \$3.87 billion.

NIH has created a web-based tool for tracking funding initiatives and activities: <https://www.nia.nih.gov/research/milestones>. CADRO also provides the framework for the International Alzheimer's Disease Research Portfolio (IADRP) and allows tracking of implementation of funding across research areas. The IADRP will continue to offer detailed tracking of awards under the CADRO categories at <http://iadrp.nia.nih.gov>.

Dr. David Reuben asked for additional clarity on the relationship (if any) between budget amount and research priority. Dr. Hodes responded that budget and priority do not correlate directly; the budget reflects only the amount of funding needed to complete each project, not its level of priority.

Upcoming Events and Updates

The NIA Small Business Program has announced the first class of finalists for the NIA Healthy Aging Start-Up Challenge and Bootcamp to Foster Diversity and Accelerate Innovation. The 20 finalists represent a diverse group of researchers and entrepreneurs with innovative ideas for science-driven technologies and products with the potential to advance the fields of aging and age-related diseases. The finalists will build their business skills by participating in a four-month entrepreneurial bootcamp and ultimately compete for five \$60,000 cash awards.

Research Diversity Day 2022 will take place on October 20, 2022, from 1-2 p.m. (ET). The 2023 Dementia Care & Caregiving Research Summit will take place virtually March 20-22, 2023. The Fourth Geroscience Summit: *Geroscience for the Next Generation* will take place April 24-26, 2023, in Bethesda, MD.

Since May 2022, NIA has released 13 research highlights featuring one or more NIA-supported publications, 11 blog posts, and six news announcements. Dr. Hodes, Dr. Melinda Kelley, and other senior NIA staff have participated in seven stakeholder and advocacy group meetings and five Congressional briefings or hearings.

Dr. Hodes honored the life and work of Dr. James P. Smith, who died on August 4, 2022, at the age of 79. Dr. Smith was an expert on the health and economics of aging who conducted significant research on education, immigration, wealth inequalities and health, and cross-national health disparities. He was a key contributor to the development of the Health and Retirement Studies (HRS) around the world, a long-time NIA grantee, including recipient of two NIA MERIT awards, and a former member of the National Advisory Council on Aging. Drs. David Weir and Lis Nielsen reflected also on Dr. Smith's appreciation for the Council's work, and his commitment to interdisciplinary initiatives.

NIA division directors introduced new NIA staff members from the Divisions of Neuroscience (DN), Behavioral and Social Research (BSR), Aging Biology (DAB), and Extramural Activities (DEA); the Office of Administrative Management (OAM)'s Financial Management Branch (FMB), Workforce and Administrative Management Branch (WAMB), and Information Technology Branch (ITB); the Office of Communications and Public Liaison (OCPL); and the Intramural Research Program (IRP).

Discussion

Dr. Weir raised concerns about transitioning from COVID-19's work-from-home accommodations to in-person, in-office operations. Dr. Hodes explained that NIH seeks to leverage and optimize both in-person and virtual workflows to achieve a balance that is efficient and effective. He also highlighted the ongoing discussions that NIH leadership has initiated to make onboarding new employees as seamless as possible.

Dr. Bhasin observed increasing regulatory burden on investigators that hinders clinical research; he advocated streamlining the grant application process to help expedite the clinical trials research made possible by tremendous NIA growth. Dr. Santora reported that DEA is creating a new Office of Clinical Research to help support NIA investigators, especially in the regulatory arena. He added that the NIH is also continually examining ways to address investigator administrative burden during the review and grants management process, especially for early-stage and new investigators who are navigating the complexities of NIH funding for the first time.

B. Future Meeting Dates

January 18-19, 2023 (Wednesday and Thursday), Virtual
May 16-17, 2023 (Tuesday and Wednesday), Building 45
September 19-20, 2023 (Tuesday and Wednesday), Building 45

C. Consideration of Minutes of the Last Meeting

The minutes of the May 2022 Council meeting were considered. A motion was made, seconded, and passed unanimously to approve the minutes.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Dr. Jennifer Manly provided an overview of Dr. Patricia Jones' announcements and updates shared with the Task Force. The NIH Common Fund released a request for information to solicit suggestions for new programs to support in FY2025 and beyond. The NIH Tribal Health Research Office released a new publication about tribal health research partnerships with tribal nations. Dr. Jamelle Banks (NIA Office of Planning, Analysis, and Evaluation) updated the Task Force on diversity administrative supplements. The Task Force also heard from the AD/ADRD Real-World Data Platform Concept Planning Committee and from Dr. Tyson Brown (Duke University) about structural racism and minority aging.

In summarizing Dr. Brown's efforts to measure, map, and quantify the impact of structural racism, Dr. Manly observed that although researchers have long documented racial inequalities in health, this documentation was often followed by the now discredited and racially biased attribution of inequalities to biological essentialism or cultural deficit. Dr. Brown highlighted that researchers today are conceptualizing racism itself as a fundamental driver of racial inequalities in health and seek to measure both racism and its health impacts. He considered structural racism, which he defined as systemic racial exclusion from power, resources, opportunities, and well-being, as a multi-faceted, institutionalized social system of subordination that manifests in racial inequalities. Dr. Brown's research has used the HRS data and has linked state-level systemic racism within educational, judicial, economic, political, and residential systems to poor health outcomes. He outlined several innovative ways to address area-level racism, including harnessing the data revolution and digital tracing, encouraging the evolution of future research to emphasize longitudinal research, and further understanding the social pathways and biological mechanisms that relate structural racism to poor health outcomes for minority populations. Dr. Manly highlighted the need to bridge the gap between science and policy.

IV. REPORT: WORKING GROUP ON PROGRAM

Dr. Monica Driscoll, Chair of the Working Group on Program (WGOP), led the updates.

A. Clinical Trials Advisory Panel (CTAP) Report

Dr. Driscoll reported that NIA's Division of Geriatrics and Clinical Gerontology (DGCG)'s Clinical Trials Advisory Panel (CTAP) met on March 23, 2022, via videoconference to review a concept proposal for an investigator-initiated, pragmatic clinical trial concerning anemia in older adults. Based on concerns raised by CTAP, the application was not accepted for peer review.

B. Funding Opportunity Announcement (FOA) Concept Clearances

Dr. Driscoll invited the primary reviewers to summarize the 18 proposed concepts, organized below by division. The Council members unanimously and enthusiastically concurred with approval of all 18 concepts.

Trans-NIA

NIA AD/ADRD Real-World Data Platform

This concept aims to transform the AD/ADRD research enterprise by establishing an NIA platform to provide access to Real World Data (RWD) – data collected in the context of routine delivery of care – and the innovative methods and practices needed for using RWD ethically and effectively. This platform, which will work through public-private data partnerships, will enable researchers to gain insight on AD/ADRD disease trajectory, identify a more diverse pool of individuals for trial recruitment, enable rapid drug trials (RDT) and other trials for improving care for older adults with multimorbidity, including dementia, and analyze sensitive RWD through secure cloud workspaces while protecting privacy of the study participants. The platform could potentially be used by other NIA-funded researchers for recruitment, which could lower costs for other NIA-funded research and support increased diversity in recruitment for NIA-funded studies (i.e., beyond academic centers).

Division of Behavioral and Social Research (BSR)

Research Coordinating Center on the Exposome and AD/ADRD: Elucidating the Role of Social and Behavioral Determinants of Health in AD/ADRD Etiology and Disparities

This concept seeks to establish a national coordination network to act as a centralized hub for accessing, harmonizing, linking, and sharing environmental contextual data and individual exposure data with NIA/NIH-funded projects that hold potential for advancing understanding of the links between life course exposures and Alzheimer's disease and related dementias risk and resilience, and disparities across populations. This work will build on NIA's population-based longitudinal studies, educational cohort studies, and Behavioral and Social Research Networks, and has the potential to capture the unequal distribution of factors that shape AD/ADRD risk and resilience.

The Health and Retirement Study (HRS) and the Harmonized Cognitive Assessment Protocol (HCAP)– Joint Renewal

The HRS is a longitudinal panel study that surveys a representative sample of approximately 20,000 people aged 50 and older in the United States every two years via mixed-mode data collection to support multidisciplinary research on life course health and aging. It supplements core and supplemental survey collection with linkages to administrative records from Medicare and Social Security, contextual data on participant living environments, and biomarker data from saliva, dried blood spots, and more recently venous blood. The HRS HCAP seeks to measure and understand dementia risk by using a select set of established cognitive and neuropsychological assessments as well as informant reports to better characterize cognitive function among older people and establish similar protocols in the HRS comparator studies in countries around the world in order to facilitate AD/ADRD research in different social, cultural, environmental, and economic contexts. Joint renewal of HRS and HCAP streamlines the grants management process and enables expanded analyses, including of minoritized populations and health disparities, new elements of the exposome, and the medium- and long-term impacts of the COVID-19 pandemic, among many other of the challenges and opportunities of aging.

Roybal Centers for Translational Research in Aging

Since 1998, the Roybal Centers program has played a critical role in supporting translational clinical trials that harness the breadth and depth of basic behavioral and social research to inform practical solutions that promote the health and well-being of individuals as they age. In 2019, the program expanded to include dedicated centers focused on dementia care to create potent and easily implementable dementia care and caregiver support interventions. Also in 2019, a Coordinating Center was established to serve as a hub for the Roybal Centers' cross-cutting activities. The proposed renewal of the Roybal Centers program intends to support the development, adaptation, and testing of behavioral and social (i.e., nonpharmacological) interventions to promote the health and well-being of people as they age, to prevent cognitive decline and AD/ADRD, and to help care providers and institutions to administer dementia care. The current proposal expands the Roybal program to explicitly invite centers focused on behavioral interventions to prevent AD/ADRD, including support for Stage V research to study the mechanisms underlying successful strategies to implement and disseminate evidence-based interventions. Each of the new or renewing Roybal Centers also will be required to have a behavioral intervention development core.

Division of Geriatrics and Clinical Gerontology (DGCG)

Nursing Home Explanatory Clinical Trials Network (NEXT)

This concept will support the formation of a network of transdisciplinary aging researchers to develop the infrastructure to conduct explanatory randomized clinical trials of prevention and treatment of selected chronic diseases and AD/ADRD within nursing homes. The investigators will create a centralized research infrastructure that will address essential core functions, including (1) overall coordination, (2) recruitment, (3) training, (4) data management and resources, (5) methods and measures, and (6) communication and dissemination, potentially leveraging emerging infrastructure known as the Long-Term Care Data Cooperative, which is part of the NIA IMPACT Collaboratory. Support of pilot studies within the network would provide a means to jumpstart new areas in preventive and therapeutic research in this setting.

Research Projects on Determinants of Differences Among Human and Nonhuman Primate Species in Lifespans, Life Histories, and Aging-Related Outcomes, and Prospects for Translation

This concept proposed two distinct, but interdependent initiatives, for: (1) research projects focused on primate species comparisons to identify factors and targetable mechanisms that may influence human longevity and health span (including neurodegenerative disease risk); and (2) a single networking and infrastructure project, to enhance interactions among researchers funded under this initiative as well as other researchers, support pilot projects, and develop research infrastructure for the field for future collaborations across multiple disciplines. This two-pronged approach will help combine and integrate the multiple disciplines (e.g., human longevity studies, comparative biology of aging, evolutionary genetics and biology, biological anthropology, primatology) that are critical to developing a full understanding of the determinants of differing primate life spans and their translational implications. It also offers an opportunity to engage integrative studies from fields that participate in NIA research less often, such as evolutionary biology and biological anthropology.

Renewal of the Longevity Consortium (LC)

This proposed renewal of the LC is intended to preserve the study infrastructure and operations to continue and complete integrative data analyses of multi-omic datasets from human and nonhuman species and replicate and validate findings on protective gene(s)/protein(s)/metabolite(s). In addition, the renewal will expand strategies to clarify potential therapeutic targets and assess candidate interventions.

Division of Aging Biology (DAB)

Interventions Testing Program (ITP)

The ITP was established in 2003 to test, under standardized conditions, potential intervention strategies which may delay aging in mice. The ITP's main goals are to provide robust evidence on compounds with translational potential for human use to improve human health span with age, and to propose pathways that influence aging and are therefore targets for interventions. The proposed concept is to renew the ITP, and to expand and focus its efforts on geropathology with the goal of further investigating the effects of aging and interventions on organs and tissues.

Interventions Testing Program Data Coordinating Center (ITP DCC)

The ITP DCC supports the three laboratories of the ITP and houses and maintains a public access website and data repository. These resources will provide archival and current information concerning experimental design, protocols, analytical methods, and raw and annotated data from ITP studies. With the renewal, the ITP DCC will place additional emphasis on real-time data collection; the expansion of data sharing to pilot studies of compound stability and bioavailability and to geropathology data generated by the ITP; the interactivity of the public-facing website; and the role of the DCC statistical core in complementing the statistical resources housed at the three ITP testing sites. The proposed FOA will invite applications to achieve the following four objectives: (1) maintain current information on experimental design, protocols, and SOPs; (2) house and maintain a public-access interactive website and data repository to provide access to experimental design, protocols, analytical methods, and annotated data from ITP studies; (3) coordinate real-time data collection and sharing among the three laboratories and

the public-facing portal; and (4) establish a common statistical core for the additional analysis of primary and secondary data obtained by the ITP.

Interorgan Communication (IOC) in Aging

This concept proposes to support a consortium of 10 U01 awards to study basic molecular mechanisms of interorgan communication explicitly in the context of aging. Research is especially encouraged to include human participants or to be informed by data on human conditions but is open to any species in the animal kingdom, whether laboratory, domestic, or wild populations. General areas of research may include changes with age or health status in communication between two or among three organ systems; changes in IOC with age and environmental exposures; and changes in IOC by interventions that extend lifespan or health span, which may include pharmaceuticals, diets, or exercise.

Division of Neuroscience (DN)

Team Science Approaches Integrating Experimental and Computational Brain Aging Models

This concept encourages experimental biologists to work in tandem with computational researchers in order to gain new insights into brain aging and AD/ADRD. Collaborative teams of experimental and computational researchers working together from the onset of a project would have the opportunity to develop multi-scale models bridging the gap between studies at the cellular level with those of the whole brain in the context of aging and AD. This concept builds on recent successes with this approach, such as a collaboration of the Alzheimer's Disease Neuroimaging Initiative (ADNI), Dominantly Inherited Alzheimer Network (DIAN), and PRE-symptomatic EValuation of Experimental or Novel Treatments for Alzheimer's Disease (PREVENT-AD) program on a model that predicts chronological age across the lifespan, revealing that the pre-symptomatic phase of AD includes acceleration of functional brain aging (Gonneaud et al., 2021). Reviewers were enthusiastic about this concept and received reassurance from program staff that the funding limits on an R21 mechanism should not be a cause for concern for nucleating activity in this arena.

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

MPS platforms representative of human AD/ADRD can lead to more predictive drug development and eventually to greater success of candidate drugs in the clinic. This concept proposes to establish multi-component AD/ADRD MPS Translational U54 Centers focused on development and characterization of AD/ADRD MPS, discovery and validation of translatable biomarkers, and development of standardized methods for preclinical efficacy testing. The initiative will rapidly disseminate MPS models to all qualified researchers for their use in preclinical therapy and transparent reporting of research methodology and preclinical efficacy testing findings. Grantees are expected to participate in the NCATS Tissue Chip Consortium and leverage the FDA hub.

Alzheimer's Disease Research Centers (ADRC) Program Renewal

The ADRCs are a congressionally mandated Centers of Excellence program that has played a central role in leading the progress of AD/ADRD research in the United States and internationally for almost four decades. ADRC investigators collaborate on well-phenotyped

longitudinal research spanning the causes of and risk factors for AD/ADRD, train the next generation of scientists, and develop innovative clinical research recruitment initiatives. The new competition will leverage the increase in geographic representation (new sites were added in Ohio, Texas, and North Carolina within the past three years) and enhance the recruitment infrastructure to increase Clinical Core participant diversity. Four P20 Exploratory Centers will have an opportunity to transition to P30 Centers. Additional resources are intended to support the increasing needs for studies that leverage the ADRC network and infrastructure at each center, including deep phenotyping, support for clinical trials, and autopsy confirmation of diagnosis.

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

This concept's goal is to establish a research consortium (designed similarly to the National Institute of Environmental Health Sciences Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription [TaRGET] II consortium) that utilizes mouse models of late-onset AD (LOAD), including polygenic mouse models, for comprehensive assessment of the impact of AD/ADRD-relevant environmental exposures on multiple aspects of brain aging and AD/ADRD-related outcomes. Projects funded through this initiative will focus on major toxicants known to be associated with elevated AD risk and will explore the impact of early and midlife exposure on late-life brain health and the impact of genetic diversity and sex differences on exposure-related AD outcomes. The data resources and mechanistic insights delivered by this initiative will inform new strategies for AD/ADRD risk reduction and disease prevention.

Understanding Gene Environment Interactions in Brain Aging and AD/ADRD

This concept aims to stimulate research to gain mechanistic insights into gene-environment (GxE) interactions in response to major toxicants using human cell-based in vitro and ex vivo models. The proposed FOA will support interdisciplinary U01 research projects using disease-relevant human in vitro and ex vivo models (e.g., minimally transformed human cells from patients, directly reprogrammed cells and induced cell organoids, tissue/organ-on-a-chip platforms) to characterize the effects of GxE interactions on gene regulation and cellular functions, and to elucidate toxicant-mediated molecular and cellular mechanisms in brain aging and AD/ADRD. Collaborations between neuroscience researchers and environmental health scientists will be strongly encouraged.

Quantifying the Impact of Environmental Toxicants on AD/ADRD Risk in Cohort Studies

This concept aims to generate high-quality, high-dimensional environmental exposure data that can be used by the greater research community for downstream multi-scale modeling/systems biology analyses aimed at understanding the molecular mechanisms of the effect of toxicant exposure on AD/ADRD risk. The FOA will solicit U01 projects to examine the impact of environmental exposures on AD/ADRD across diverse populations, including under-represented populations (e.g., racial/ethnic minorities, veterans, rural populations, first responders), focusing on those most at risk both for AD/ADRD and environmental exposures (e.g., farm or factory workers). The initiative will achieve these goals by enriching existing longitudinal cohorts with measures of toxicant exposures and multi-omics molecular profiling of the body's responses; supporting the development of multidisciplinary teams needed for assessment of these exposures at the population level; and creating an environmental epidemiology consortium to facilitate data sharing and harmonization.

The above three concepts combine environmental toxin data to AD/ADRD cohorts or conversely examine cognitive data in non-AD/ADRD cohorts. These proposed programs will operate under open-science principles: all data and analytical outputs will be shared rapidly and broadly via the NIA-supported AD Knowledge Portal and/or databases that are interoperable with the AD Knowledge Portal.

Division of Extramural Activities (DEA)

NIA Postbaccalaureate Research Education Program

This concept seeks to develop a one- to two-year intensive research education experience with a focus on mentorship for pursuing future research careers. These paid research opportunities will provide immersive, full-time laboratory experience aimed at building technical and operational skills. The programs will be expected to have a research training component paired with career development activities which might include, but are not limited to: coursework, entrance exam preparation, and conference and workshop participation. The expectation is that such programs will help to transition the next generation of investigators, particularly from underrepresented groups and diverse backgrounds, to pursue a career in Alzheimer's disease and related dementias research.

NIA Summer Research Educational Experience Program (R25 Clinical Trial Not Allowed)

This concept proposes an intensive summer research education program for high school students, college students, or K-12 teachers, to provide exposure to and enhance interest in research careers. This opportunity aligns with recent NIH efforts to expand the Science Education Partnership Award and the recognition in the field of the importance of innovative K-12 STEM programming to build a diverse and competitive scientific workforce. The program goal is to develop the next generation of investigators to pursue a career in aging research (and specifically Alzheimer's disease and related dementias).

V. A WORD FROM RETIRING MEMBERS

Dr. Santora announced the retirement of four Council members and invited them to make remarks.

Having been an NIA grantee throughout his career, Dr. Bhasin considered it a great honor to serve on Council and gain a greater understanding of how the NIA and NIH works. He is deeply impressed with the quality and diligence of the NIA program staff. His experience reinforced his belief that NIH is a crown jewel in the government and scientific enterprise.

Dr. Driscoll shared similar sentiments, impressed with the dedication and responsiveness of NIA staff. She described her interactions with program staff as super inspiring and enlightening. She echoed Dr. Bhasin's expression that it has been a humbling privilege to work with such a talented group of colleagues.

Drs. Fulmer and Whitfield were not present this day due to scheduling conflicts, but each sent written notes of appreciation. Dr. Fulmer considered it an enormous privilege to serve and learned much from the deliberations. Dr. Whitfield shared his great pride to serve on Council,

and his confidence in the capabilities of Drs. Manly and Jones to continue to carry out the important work of the Task Force on Minority Aging Research.

Drs. Hodes and Santora acknowledged that NIA asks a lot of its Council members, so the least the NIA staff can do is be responsive to Council members' questions.

Dr. Santora concluded by noting that, if approval of the next slate of NACA members is delayed, then some retiring members may be asked to serve additional time in their position. He will contact members individually to determine their interest in extending their service on Council.

VI. PROGRAM HIGHLIGHTS (DN)

Molecular, Cellular, and Systems Mechanisms of Memory Linking: Impact of Aging

Dr. Alcino Silva, Ph.D., Professor, University of California, Los Angeles

Dr. Silva's research explores the molecular, cellular, and systems mechanisms of memory linking—the ability to associate one memory with another—and their vulnerability to aging. Studies suggest that memory linking is affected by age-related cognitive decline in middle-aged mice, even when the mice can still retain single, discrete memories. One specific mechanism of this decline may be increased levels of CCL5/CCR5, which inhibits neuronal overlap in memory encoding and thus decreases cross-activation of memories themselves. Identification of this pathway points to new potential approaches to address age-related declines in human memory.

Previous work in the lab demonstrated that mice transferred a fear response between memories of cages were linked over short periods of time. Mice who occupied two cages within a five-hour timespan and then were shocked in just one of the cages demonstrated a similarly fearful freezing response to both cages; however, mice who underwent the same procedure for cages separated by seven days tended to associate their fearful response with only the cage in which the shock took place. Dr. Silva's lab found that an overlap between neuronal memory ensembles drove this memory linking. Using miniscopes to monitor activity of neurons over time, they demonstrated a significant overlap in neuronal activity for the cages that were memory linked across a five-hour timespan. Overlap occurred in the CA1 region of the hippocampus, which is critical for contextual memory creation. Using TetTags, a method that tags active neurons via immediate early gene promoters, they demonstrated an overlap of more than 20 percent active neurons for linked memories compared to non-linked memories. Dr. Silva's research suggests that CCL5/CCR5 plays a critical role in closing the temporal windows for memory ensemble overlap and memory linking. They adapted the iTango sensor system to fluorescently report which cells express activated CCL5/CCR5. Dr. Silva's lab produced evidence that contextual conditioning triggers a delayed increase in CCL5/CCR5 in CA1 cells engaged in memory and that activation of CCR5 by CCL5 triggers a decrease in neuronal excitability, which ultimately undermines memory linking. The team corroborated these findings through further experimental manipulation: CCL5 infusion in dorsal CA1 impairs the five-hour memory linking observed in mice whereas CCR5 knockout extends the window for such memory linking from five hours to seven days. Similar results were obtained using a new "Opto-CCR5" tool that enables activation of CCR5 through exposure to light.

These experimental findings on CCL5/CCR5 intersect with studies of aging to suggest that this molecular pathway may account for midlife decline in memory linking capacity. CCL5 and CCR5 expression in CA1 is elevated in older mice, and this elevation is accompanied by a decline in performance on the five-hour cage linking test: older mice can still learn to fear a specific cage in which they were shocked, but they do not tend to transfer that fear to the other cage linked with it in a five-hour timespan; knockout of CCR5 reverses this effect. This set of results suggests that an existing FDA-approved drug for HIV, Maraviroc, that acts as a CCR5 antagonist may be useful for treating age-related cognitive decline. Dr. Silva shared results suggesting that the restoration of memory linking can occur with the administration of Maraviroc in older mice.

Discussion

Dr. Hodes asked Dr. Silva to clarify the impact of Maraviroc on memory in older mice. Dr. Silva noted that Maraviroc not only renders mouse response to a “shocked” cage and a temporally associated cage nearly the same, but also specifically rescues the underlying mechanism of memory ensemble overlap. In addition, data show a clear difference between responses to cages in which a shock was experienced and novel cage exposures. Dr. Silva has also tested whether selective deletion of CCR5 in microglia recapitulates the effects of CCR5 knockout; preliminary data suggest it may have a similar impact.

One member asked how sleep impacts CCR5’s effects. Dr. Silva mentioned Dr. Cai’s ongoing studies that explore how sleep may moderate CCR5’s ability to trigger a fairly rapid impairment in memory linking.

Another member asked about the mechanisms of age-related effects on episodic (not linked) memory. Dr. Silva acknowledged such changes, including locus coeruleus dopamine activation in CA1 and changes in excitability, but emphasized that loss of memory linking *precedes* loss of episodic memories and may foreshadow such age-related changes in molecular chemistry and cell biology and thus offer a new pathway to addressing them.

Members asked whether real-world evidence from HIV-positive patients on Maraviroc displays any preventive effect against dementia. Dr. Silva noted that sufficiently large studies have not been conducted to explore this question. However, studies have shown that Maraviroc can improve post-stroke plasticity in both mice and humans, suggesting that memory effects in mice may also ultimately be observed in human clinical trials. One member asked what CCR5-related biomarkers can be used in clinical studies translating some of Dr. Silva’s findings. Dr. Silva noted that the answer to this question is not yet clear. However, current findings regarding changes in brain biochemistry enable the development of testable hypotheses.

VII. COUNCIL SPEAKER

NIH-wide Opportunities for Behavioral and Social Science Research (BSSR) Advancement and Integration

Christine Hunter, Ph.D., Acting Associate Director for Behavioral and Social Sciences Research, and Acting Director, Office of Behavioral and Social Sciences Research (OBSSR), NIH

Dr. Hunter defined BSSR at NIH as the systematic study of *behavioral* and *social phenomena* relevant to *health*. “Behavioral phenomena” refer to observable actions of individuals or groups and to mental phenomena such as knowledge, attitudes, beliefs, motivations, perceptions, cognitions, and emotions. “Social phenomena” refer to interactions between and among individuals and to the characteristics, structures, and functions of social groups and institutions (such as families, communities, schools, and workplaces), as well as the physical, economic, cultural, and policy environments in which social and behavioral phenomena occur. “Health” refers to a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity (as per World Health Organization).

Dr. Hunter reviewed OBSSR’s mission, and the seven key areas highlighted in the OBSSR Strategic Plan for 2017-2021, noting that a new strategic plan is expected to be released in 2023: (1) basic and applied research synergy; (2) methods, measures, and data infrastructures; (3) application and adoption of BSSR research; (4) communication; (5) program coordination and integration; (6) training; and (7) policy and evaluation. OBSSR’s goals include improving the synergy between basic and applied BSSR, facilitating the adoption of BSSR findings in health research and practice, and enhancing the methods, measures, and data infrastructures to encourage a more cumulative BSSR. To advance these goals, the NIH Council of Councils launched two BSSR Working Groups (WG): (1) Trans-NIH Research Opportunities in the Basic Behavioral and Social Sciences (bBSSR) and (2) Integration of the Behavioral and Social Sciences Research at the NIH. Both issued reports over the last year.

The bBSSR WG, co-chaired by Drs. Graham A. Colditz and William Riley, identified eight promising and emerging areas of bBSSR: (1) behavioral, cognitive, and social neuroscience; (2) epigenetics; (3) basic functions of sleep and sex; (4) infectious disease-related basic behavioral and social processes; (5) social interactions and influences on health; (6) maintaining behavior change; (7) positive rather than only disease-focused health processes; and (8) science of science, which examines social and behavioral challenges to conducting human subjects research. The WGs also identified several crosscutting considerations, including workforce diversity, workforce capacity and training, team science and transdisciplinary integration, and research infrastructure and processes.

An NIH-wide Implementation Working Group was then convened to recommend immediate priorities. Its recommendations included involving bBSSR expertise in the early stages of developing activities; supporting transdisciplinary teams to build capacity; creating shared vocabularies and ontologies; incorporating rigorous causal models and measurement at all levels from cellular to social; investing in cross-disciplinary training and multicomponent/cross-disciplinary research; identifying promising research opportunities that build on prior investments; and investing in harmonized approaches to contextual data linkage.

The formation of the Integration of Behavioral and Social Sciences Research at the NIH WG responded to a Congressional call to the Director to convene a special advisory panel of behavioral scientists and other community experts. This WG, co-chaired by Drs. Paul Kenny and Hunter, was charged with assessing and identifying ways to better integrate behavioral research

into the NIH research portfolio and to realize the benefits to overall health from behavioral research at NIH.

The WG developed recommendations on eight processes that would support integration: (1) inclusion of BSSR in strategic plans; (2) expanded numbers and diversity of BSSR staffing; (3) adequate representation of BSSR on IC advisory councils; (4) adequate involvement of BSSR expertise during peer review; (5) increased BSSR research funding; (6) increased funding for center and resource grants; (7) increased OBSSR resources; and (8) engagement of BSSR expertise in development of research policies and practices. It also identified several cross-cutting considerations, including enhanced approaches to measurement of NIH funding, enhanced diversity of the NIH and extramural research workforce, improved team science and multidisciplinary integration, and enhanced conduct of science. NIA leads the NIH in integration of BSSR in its activities.

Dr. Hunter expressed excitement at the momentum driving BSSR-related activities in NIH plans. Several ongoing initiatives will advance collaborations between NIA and OBSSR.

Discussion

Dr. Weir served as a member of the NIH BSSR Integration WG and asked Dr. Hunter to clarify the OBSSR's initiatives to improve diversity. Dr. Hunter explained that drawing on BSSR will help shape NIH's research goals, including at the larger workforce enterprise level. Dr. Santora asked how BSSR can help contribute to research on climate change. Dr. Hunter noted that it is unlikely for OBSSR to call out specific topics like climate change, aging, or specific disease areas; it mainly investigates cross-cutting issues, is also deeply engaged in many of the groups within NIH, and looks forward to contributing to substantive topics, including especially those impacted by social determinants of health.

VIII. ADJOURNMENT

The open session of the 147th meeting of the National Advisory Council on Aging adjourned at 1:22 p.m. on September 8. The next meeting is scheduled for January 18-19, 2023.

IX. CERTIFICATION

I hereby certify that, to the best of my knowledge, the foregoing minutes and attachments are accurate and complete.³

Richard J. Hodes -S
Digitally signed by
Richard J. Hodes -S
Date: 2023.01.24
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Richard J. Hodes, M.D.
Chairman, National Advisory Council on Aging
Director, National Institute on Aging

Prepared by Kenneth Santora, Ph.D.
With assistance by Rose Li and Associates, Inc.

³ These minutes will be approved formally by Council at the next meeting on January 18-19, 2023, and corrections or notations will be stated in the minutes of that meeting.