

NATIONAL INSTITUTES OF HEALTH  
NATIONAL INSTITUTE ON AGING

Summary Minutes

The 148th Meeting  
NATIONAL ADVISORY COUNCIL ON AGING  
January 18-19, 2023

National Institutes of Health  
Virtual Meeting  
Bethesda, MD 20892

|       |                                                     |    |
|-------|-----------------------------------------------------|----|
| I.    | REVIEW OF APPLICATIONS .....                        | 4  |
| II.   | CALL TO ORDER .....                                 | 4  |
| III.  | REPORT: TASK FORCE ON MINORITY AGING RESEARCH ..... | 7  |
| IV.   | REPORT: WORKING GROUP ON PROGRAM.....               | 9  |
| V.    | PROGRAM HIGHLIGHTS (DGCG).....                      | 15 |
| VI.   | COUNCIL GUEST SPEAKER .....                         | 18 |
| VII.  | INTRAMURAL PROGRAM REPORT.....                      | 20 |
| VIII. | ADJOURNMENT.....                                    | 22 |
| IX.   | CERTIFICATION .....                                 | 23 |

Attachment A: Roster of the National Advisory Council on Aging

Attachment B: Director’s Status Report to Council

Attachment C: January 2023 Minutes in PDF Format

Department of Health and Human Services  
Public Health Service  
National Institutes of Health  
National Institute on Aging  
NATIONAL ADVISORY COUNCIL ON AGING  
SUMMARY MINUTES  
January 19, 2023

The 148th meeting of the National Advisory Council on Aging (NACA) was convened on Thursday, January 19, 2023, 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, January 18, 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.<sup>1</sup> The meeting was open to the public on Thursday, January 19, from 10:00 a.m. to 2:00 p.m.

Council Participants:

Dr. Darren Baker  
Dr. Shalender Bhasin  
Dr. Anne Case  
Dr. Yanira Cruz  
Dr. Monica A. Driscoll  
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 A. Schneider  
Dr. Linda Van Eldik  
Dr. David R. Weir  
Dr. Keith E. Whitfield

Executive Secretary:

Dr. Kenneth Santora, NIA

Ex Officio Participants:

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

---

<sup>1</sup> 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.

Ad Hoc Members:

Dr. Sanjay Asthana, University of Wisconsin School of Medicine and Public Health

Ms. Maritza Ciliberto, Boston Green Academy

Dr. Sharon K. Inouye, Harvard Medical School

Dr. Sohail Khan, Cherokee Nation Health Services

Ms. Nancy E. Lundebjerg, American Geriatrics Society

Members of the Public Present:

356 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).<sup>2</sup>

A total of 1,941 applications requesting \$5,520,973,817 for all years underwent initial review. The Council recommended 1,087 awards for a total of \$3,261,759,295 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. Ken Santora welcomed members to the open session of the 148th NACA meeting. Dr. Hodes called the meeting to order at 10:00 a.m. on Thursday, January 19, 2023.

### **A. Director's Status Report**

#### ***New NIA Deputy Director***

Dr. Hodes introduced Dr. Amy Kelley, who joined NIA in September 2022 as Deputy Director. She previously served as Professor and Vice Chair for Health Policy and Faculty Development, Hermann Merkin Professor in Palliative Care, and Senior Associate Dean for Gender Equity in Research Affairs at the Icahn School of Medicine at Mount Sinai. At NIA, Dr. Kelley provides strategic leadership, supervises daily operations, serves as an ambassador and spokesperson, and oversees diversity, equity, inclusion, and accessibility (DEIA) initiatives.

#### ***Fiscal Year 2023 Budget***

Dr. Hodes reported that \$47.5 billion has been appropriated for NIH for fiscal year (FY) 2023, with \$4.41 billion reserved for NIA. NIA funding has steadily increased and nearly quadrupled since 2014 when NIA was appropriated \$1.17 billion. For FY 2023, NIH funding has increased in key areas, including for the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, big data and artificial intelligence research, and Down Syndrome research. The largest funding increase, \$226 million, was appropriated for Alzheimer's disease and

---

<sup>2</sup> 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.

Alzheimer's disease-related dementias (AD/ADRD) research. Of this amount, \$151 million was appropriated to NIA, and \$75 million was appropriated to the National Institute of Neurological Disorders and Stroke (NINDS).

Dr. Hodes also announced current FY 2023 grant pay lines. 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, and 20% for early-stage investigator applications. For CSR-reviewed applications seeking \$500,000 or more, pay lines are 12% for most regular research applications, 15% for new investigator applications, and 17% for early-stage investigator applications. Pay lines are higher for applications focused on AD/ADRD: 25% for most regular research applications, 28% for new investigator applications, and 30% for early-stage investigator applications.

For NIA-reviewed applications, the impact scores for general pay lines are 15 for program projects, 15 for other NIA-reviewed research, 21 for career development awards, and 30 for fellowship awards. The corresponding AD/ADRD pay lines are 30, 30, 35, and 40, respectively.

### ***AD/ADRD Clinical Trials***

Dr. Hodes reported that 459 NIA-funded clinical trials targeting AD/ADRD are currently active; 66 of these trials are evaluating pharmacological treatments for AD/ADRD, and 152 are evaluating non-pharmacological treatments. Further, 210 trials are focused on interventions for dementia care and caregiving; 22 on diagnostic tools, assessments, and imaging; and 9 on treatments for neuropsychiatric symptoms. Although 57.1 percent of phase II/III and phase III clinical trials for pharmacological treatments target amyloid accumulation, only 13.5 percent of current phase I and phase II clinical trials do, reflecting NIA researchers' evolving understanding of the heterogeneity of the AD/ADRD disease process. Clinical trials for non-pharmacological treatments are also testing a variety of interventions focused primarily on exercise, neurostimulation, cognitive training, and sleep.

### ***Center for Alzheimer's and Related Dementias***

Dr. Hodes announced that NIH held a dedication ceremony on September 19, 2022, for the new Center for Alzheimer's and Related Dementias (CARD) facility—the Roy Blunt Center for Alzheimer's Disease and Related Dementias Research. Senator Roy Blunt has been a longstanding champion for NIH research, especially NIA AD/ADRD research.

CARD is dedicated to resource sharing and career development. As part of its iPSC Neurodegenerative Disease Initiative, CARD has created a new online portal, through which researchers can access a catalogue of human stem cell lines engineered for the study of genes implicated in AD and other neurodegenerative disorders. In addition, CARD has developed the Alzheimer's and Related Dementias Independent Scholars (ARDIS) program that offers early-career researchers a time-limited independent Principal Investigator appointment, generous resources, and access to CARD and other NIH research cores and infrastructure.

### ***NIA Communications and Recognition***

Since September 2022, NIA has released 24 research highlights, each featuring at least one NIA-supported publication; 15 blog posts; and 5 news announcements. In addition, Dr. Hodes, Dr. Kelley, and other senior NIA staff have participated in 10 stakeholder and advocacy group meetings and six Congressional briefings and hearings. Active [funding opportunities](#), recently [approved concepts](#), and [blog posts](#) are publicly accessible on the NIA website.

NIH published an AD/ADRD progress [report](#), *Advancing Alzheimer's Disease and Related Dementias Research for All Populations*, in November 2022. The report features recent science advances across topics including basic, translational, and clinical research, and care and caregiving interventions.

NIA has released an Alzheimer's and Related Dementias Research video series, which features multiple investigators' work on exercise, cognitive health, and healthy aging; advances in biomarkers; the importance of increasing diversity in clinical trials; a rare genetic variant underlying early-onset AD; and dementia caregiving science.

*Forbes* recognized several NIA-supported researchers in "The World's Top Female Scientists in 2022," including three in the top 10: Drs. Virginia Man-Yee Lee, Tamara B. Harris, and Terrie E. Moffit.

### ***NIH Policy for Data Management and Sharing***

Dr. Hodes announced that the final [NIH Policy for Data Management and Sharing](#) will go into effect on January 25, 2023. The policy affirms NIH's continued commitment to sharing and making broadly available the results of publicly funded biomedical research. It applies to all research funded or conducted by NIH that leads to the generation of scientific data, and it requires submission of Data Management and Sharing (DMS) Plans and compliance with NIH Institute-, Center-, or Office-approved DMS Plans.

### ***NIH Strategic Plan for Diversity, Equity, Inclusion, and Accessibility***

A strategic plan has been developed with the mission to embrace, integrate, and strengthen DEIA across all NIH activities. Dr. Hodes reported that the plan is in its final phase of development and ready for release, pending final approval by NIH leadership.

### ***National Institute of Allergy and Infectious Diseases Director***

Dr. Hodes honored the work of Dr. Anthony Fauci, who recently stepped down as the National Institute of Allergy and Infectious Diseases (NIAID) Director. Dr. Fauci served as NIAID Director for 38 years and advised seven U.S. presidents.

On January 1, 2023, Dr. Hugh Auchincloss began service as Acting NIAID Director. Dr. Auchincloss previously served as NIAID Deputy Director since 2006.

### ***Advanced Research Projects Agency for Health Director***

Dr. Renee Wegrzyn was recently named inaugural Director of the Advanced Research Projects Agency for Health (ARPA-H). She previously led multiple biotechnology projects at the Defense Advanced Research Projects Agency (DARPA) and the Intelligence Advanced Research Projects Agency (IARPA), two institutions that helped inspire the creation of ARPA-H. Dr. Wegrzyn has

experience as both a researcher and administrator, with a robust background in synthetic biology and gene editing.

### ***Upcoming Events***

The National Research Summit on Care, Services, and Supports for Persons with Dementia and Their Caregivers will occur virtually on March 20-22, 2023. The fourth Geroscience Summit: Geroscience for the Next Generation will occur virtually and in person on April 24-26, 2023, in Bethesda, MD.

The [Butler-Williams Scholars Program](#), which hosts lectures and seminars focused on aging research, will be held on August 23-25, 2023, and is accepting applications from junior faculty and researchers new to the field of aging. Applicants must hold a doctoral degree (e.g., Ph.D., M.D., Dr.PH.) and apply by April 21, 2023.

## **B. Staff Introductions**

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

## **C. Future Meeting Dates**

May 16-17, 2023 (Tuesday and Wednesday), Building 45  
September 19-20, 2023 (Tuesday and Wednesday), Building 45  
January 23-24, 2024 (Tuesday and Wednesday), Virtual  
May 21-22, 2024 (Tuesday and Wednesday), Building 45  
September 18-19, 2024 (Wednesday and Thursday), Building 31

## **D. Consideration of Minutes of the Last Meeting**

The minutes of the September 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 presentations by Dr. Chantel L. Martin and Dr. Jamaine Davis to the Council, pertaining to their research on biological mechanisms of health and aging disparities. Dr. Manly noted that Drs. Martin and Davis are champions of community engagement in research and aim to center their work on the concerns of the populations they seek to serve.

Dr. Martin's presentation, titled "Embodiment of Place: Mechanisms of Aging Disparities," focused on how structural racism, or the ways in which society fosters racial discrimination through mutually reinforcing and inequitable systems, contributes to epigenetic changes and

acceleration of biological aging. Researchers have studied a variety of biomarkers to measure biological aging, such as allostatic load, telomere length, and immune function. Dr. Martin specifically examined DNA methylation, a biomarker of aging that is responsive to environmental stressors. Using data from the Detroit Neighborhood Health Study, Dr. Martin and colleagues found that neighborhood disorder, characterized by the presence of people on the street and abandoned cars, was associated with accelerated DNA methylation (DNAm) aging. Models stratified by social cohesion illustrated that associations between neighborhood disorder and accelerated DNAm aging remained elevated for people living in neighborhoods with low social cohesion but were null for those living amid high social cohesion. Thus, living in adverse environments may accelerate epigenetic aging, while positive neighborhood attributes may buffer those negative environmental effects.

Dr. Davis' presentation, titled "Towards Precision Medicine: Elucidating Mechanisms of Genetic Variants That Confer Alzheimer's Risk in African Americans," focused on the contribution of genetics to disparities in AD risk between African American individuals and non-Hispanic White individuals. AD disproportionately affects African American individuals, and certain gene variants associated with AD have been found to be more prevalent in individuals of African descent than in those of European descent. Dr. Davis examined the *ABCA7* T319A variant, which more strongly predicts AD risk in African American individuals than does the commonly studied *APOE* e4 variant. *ABCA7* codes for a transmembrane protein involved in lipid homeostasis and phagocytosis, and its dysfunction is associated with increased amyloid beta (A $\beta$ ) production, reduced A $\beta$  clearance, impaired microglial response to inflammation, and endoplasmic reticulum stress. Dr. Davis found that the *ABCA7* T319A variant may contribute to AD by reducing levels of a membrane phospholipid reportedly decreased in the AD brain, phosphatidylinositol bisphosphate (PIP2). Thus, targeting mechanisms that increase PIP2 levels may help treat AD and mitigate disparities.

### **Discussion**

Dr. Sanjay Asthana referenced research illustrating that people who reside in poor neighborhoods exhibit worse performance on cognitive tasks, increased cortical atrophy, and increased amyloid burden. He commented that the relationship between neighborhood disadvantage and AD biology should be confirmed with additional studies and asked whether transitioning from one neighborhood to another with a less adverse environment would affect the epigenetic mechanisms that Dr. Martin researched. Dr. Manly responded that researchers must consider what types of studies can be leveraged to answer Dr. Asthana's question. In diverse communities such as Washington Heights, where Dr. Manly works, some individuals have lived their whole lives there, whereas others have moved there from the South or from other countries. Thus, community members have rich life experiences that researchers should seek to understand by linking study participants' residential histories to administrative records. Dr. Manly remarked that valuable insight may arise from longitudinal studies, such as the National Longitudinal Study of Adolescent to Adult Health.

Dr. Sharon Inouye asked whether Council members will be briefed on NIA's progress regarding DEIA initiatives and efforts to recruit diverse investigators. Dr. Manly stated that such information would be provided and encouraged Council members to regularly ask for it.

Dr. Sohail Khan asked whether any comparative research on aging and AD/ABRD has been conducted in rural communities, where it might be more challenging to obtain services. Dr. Manly shared that multiple NIA-supported initiatives are studying rural populations, including the NINDS Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, which is evaluating the causes of racial and geographic differences in stroke mortality and cognitive decline in the United States. REGARDS oversamples from Stroke Belt regions, many of which are rural.

#### **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)**

Dr. Driscoll reported that WGOP heard a presentation from Dr. Steve Kritchevsky, who is overseeing efforts to review progress made by the Division of Geriatrics and Clinical Gerontology. WGOP members were impressed with CTAP's credentials, organization, and experience. A final CTAP progress report is anticipated to be released by May 2023.

##### **B. Funding Opportunity Announcement (FOA) Concept Clearances**

Dr. Driscoll invited the primary reviewers to summarize the 21 proposed concepts, organized below by division. The Council members unanimously and enthusiastically concurred with approval of 20 out of 21 concepts. The concept for a Dementia Care Coordination Research Center was deferred for final approval pending revision.

#### **Division of Behavioral and Social Research (BSR)**

##### ***Behavioral and Social Research on the Role of Immigration on Life Course Health and Aging, Including AD/ABRD***

This concept seeks to expand research on life course social and structural factors that shape health, aging, and AD/ABRD risk among Black, Latino, Asian, and other immigrant groups in the United States. Immigrants typically have lower morbidity and mortality than their U.S.-born counterparts, an effect referred to as the "immigrant health paradox," but their health may deteriorate the longer they reside in the United States. Longitudinal research examining measures of pre- and post-immigration health is extremely limited. Therefore, this concept calls for research using existing longitudinal data as well as mixed methods research involving primary data collection from the community. The goal is to expand the field of minority health in aging research by identifying factors affecting immigrant health over time and further elucidating racial and ethnic health disparities.

##### ***Enhancing Use of Harmonized Cognitive Assessment Protocol (HCAP) Data***

The Harmonized Cognitive Assessment Protocol (HCAP) is a sub-study within the U.S. Health and Retirement Study (HRS) and certain studies of the HRS International Family of Studies. The goal of HCAP is to evaluate dementia risk by collecting cognitive and neuropsychological assessment data and informant reports from older adults. Although HCAP offers a valuable resource for cross-national research on dementia, such analyses have been limited and require a

large investment of time and resources to leverage datasets from different countries. This concept seeks to incentivize researchers to address challenges to making international comparisons and to use HCAP data for large, cross-national studies of factors influencing the trajectory of AD/ADRD.

#### ***Consortium for Payment, Utilization, and Access for Dementia Care***

This concept emphasizes the need for research that addresses the extraordinary array of difficulties faced by people living with dementia and their caregivers. It proposes a consortium of researchers who will study how federal policies and payment models affect people living with dementia, how dementia care and access to care vary in different settings, and how payment mechanisms affect utilization of dementia care services. This concept proposes one U54 and six R01 mechanisms to support a coordinating center and multiple research projects designed to inform policy. The coordinating center will plan meetings, engage with stakeholders, facilitate the use of common data elements, develop training programs to support a diverse research program, translate findings into practice, and solicit funding via national competitions that directly address NIH AD/ADRD Research Implementation Milestones.

#### ***Dementia Care Coordination Research Center***

This concept was inspired by the 2020 NIA Dementia Care Summit and seeks to address the urgent need for dementia care coordination and community-level care integration. It proposes a U54 mechanism to support the development of a research center that organizes partnerships with regional researchers and hosts a datahub for sharing data and resources, including pilot data. This concept also proposes set-aside funds and a special application review panel.

Dr. David Reuben commented that this concept aptly acknowledges that multiple different stakeholders are involved in dementia care coordination, including health care and community-based organizations as well as insurers and state government. He reported that this concept was unanimously tentatively approved by Council members. A revised version will be circulated to Council for final approval.

#### ***Leveraging Social Networks to Promote Widespread Individual Behavior Change***

Initiating and maintaining behavior change, although difficult, may prevent or slow the progression of age-related diseases, including AD/ADRD. Research shows that the behaviors of people in an individual's social network strongly impact the individual's own health behaviors and outcomes. Therefore, this concept seeks to encourage the development of interventions that leverage social networks to promote healthy behaviors at both the individual and population levels, particularly in older adults. This concept proposes to solicit basic research (R01) studies of individual behavior change and social network processes as well as planning projects for social network-based interventions.

#### ***Networks to Develop Behavioral and Social Science Research in Aging and AD/ADRD***

This concept aims to support seven research networks or flexible programs intended to foster innovative, behavioral and social science research and research resources in the field of aging. Based on areas outlined in the [2019 NACA BSR Review Committee Report](#), these networks will target (1) stress measurement, (2) life course health and disparities at older ages, (3) aging research on criminal justice and health disparities, (4) rural aging, (5) genomics and omics of behavioral and social sciences, (6) behavioral and social research on aging in animals, and (7)

AD/ADRD data harmonization in the HCAP network. Networks may support meetings to develop research infrastructure, small-scale pilots to develop methods and data, and educational opportunities such as intensive summer institutes, advanced seminars, and workshops. The R24 mechanism proposed by this concept will foster interdisciplinary groups of scientists who are well equipped to advance BSR areas of priority and facilitate collaborations both within BSR and across NIA divisions.

### ***Measures of Financial Hardship Among People and Families Living with AD/ADRD***

Unlike other disease diagnoses, AD/ADRD diagnoses do not trigger special financial protections in the United States. Furthermore, all individuals with AD/ADRD will eventually become unable to report on the full range of financial stress, strain, and asset depletion that they or their support network encounter in the context of their disease. Since current financial wellness screeners are incapable of fully capturing the costs associated with AD/ADRD, this concept aims to support the development of improved methods for measuring financial burden and hardship for people living with AD/ADRD as well as their broader support network.

### ***National Health and Aging Trends (NHATS) and National Study of Caregiving (NSOC) (Joint Renewal)***

NHATS collects data on disability trends and individual disability trajectories from a nationally representative sample of approximately 8,000 Medicare beneficiaries. Complementing NHATS, NSOC collects data from caregivers of NHATS participants. Together, NHATS and NSOC data provide valuable insight into the impact of disability and disability care on well-being and function. Following the guidance of the NHATS Data Monitoring Committee, this concept seeks to renew and enhance NHATS and NSOC to support research focused on AD/ADRD and related care. Given the strengths of NHATS and NSOC in understanding disability and adaptation to disability, leveraging these studies to address the needs of AD/ADRD patients will be extremely beneficial.

### ***Grand Challenge: Predicting Early AD/ADRD (Contract)***

This concept seeks to support a contract that would provide the infrastructure for the development, coordination, and advertisement of competitions that address the challenge of predicting early AD/ADRD. Expert advisors would develop and evaluate competitions, provide scientific direction, and identify high-priority data sources. To build human capital, this concept aims to engage small businesses, engineers, and researchers, ranging from students to seasoned investigators, who have experience in a variety of different fields, including artificial intelligence, engineering, neuroscience, and ethics among others.

### ***Division of Geriatrics and Clinical Gerontology (DGCG)***

#### ***Development and Validation of Harmonized Methodologies to Measure NAD<sup>+</sup> and Related Metabolite Levels in Clinical Trials***

Nicotinamide adenine dinucleotide (NAD<sup>+</sup>) has long been known for its role in energy metabolism, but recent research has uncovered its much more expansive role in aging biology. Therefore, the development of interventions that target NAD<sup>+</sup> to treat age-related disease is of increasing interest. NAD<sup>+</sup> precursors have been investigated in preclinical and early-stage human studies, but data are difficult to interpret because of the methodological challenges associated with measuring NAD<sup>+</sup> and its metabolites in human serum and tissue. This concept

aims to fund, via U01, up to three studies to develop and validate standardized protocols for measuring NAD<sup>+</sup> and its metabolites. Awardees would be required to interact in a network consortium to discuss research progress and challenges as well as to contribute study specimens to NIA's Aging Research Biobank or another biorepository for use in designing future NAD<sup>+</sup> trials.

### ***Elucidating Variability of Physiologic and Functional Responses to Exercise Training in Older Adults***

Although substantial evidence exists to support the importance of exercise for the prevention of disease in older adults, significant variability occurs in individuals' responses to exercise. This variability occurs even under well-controlled experimental conditions, and its mechanisms are poorly understood. This concept aims to support human research studies that examine the factors underlying exercise response variability in older adults. Studies would assess multiple metabolic and physiological or functional outcomes, such as glucose metabolism, blood pressure, and gait speed. This concept encourages the use of multidisciplinary study teams to design trials that control for environmental factors and examine the interactions of drugs and exercise, mechanisms of sex- and age-based differences in exercise response, the impact of multiple chronic conditions on exercise response, and potential biological mediators of exercise response.

### ***Clonal Hematopoiesis in Aging Humans: Detection, Risk Factors, Relationships to Aging-Related Pathophysiology and Conditions, and Clinical Utility in Screening and Prognosis***

Clonal hematopoiesis (CH), the clonal expansion of mutated hematopoietic stem cells, increases with age and is associated with hematopoietic malignancies, cardiovascular disease, and other age-related diseases. With advances in genome sequencing technology, researchers can more easily detect CH and study its effects on healthy aging, disease, and longevity. The deleterious or protective effects of most CH mutations as a function of age remain largely unknown, and this concept seeks to elucidate how CH may impact aging phenotypes such as exceptional longevity, high risk of age-related disease, and all-cause mortality. This concept proposes an R01 mechanism to support research investigating CH in aging adults. It calls for research examining risk factors for CH and potential relationships between CH and age-related pathophysiology as well as research investigating the clinical utility of screening for CH in older patients.

## **Division of Neuroscience (DN)**

### ***Neuronal and Non-Neuronal Mechanisms Underlying Gait as a Preclinical Marker for AD/ADRD***

Research has shown that slowing gait is associated with cognitive decline, increased amyloid burden, and increased risk of developing AD. However, few studies have examined the cognitive systems required for motor planning and gait initiation in humans. Thus, this concept aims to promote research that investigates the relationship between cognition and mobility in aging and AD/ADRD. It encourages the construction of multidisciplinary research teams and seeks investigations that leverage a variety of experimental approaches, including omics, neuroimaging, and systems biology approaches.

### ***Analytical and Clinical Validation of Biomarkers for AD/ADRD***

NIA has supported a variety of projects aimed at discovering novel biomarkers for AD/ADRD. Although many biomarker candidates have been identified, few have progressed from discovery to analytical and clinical validation. Therefore, their potential clinical and scientific utility remains unclear. The goal of this concept is to advance robust AD/ADRD biomarkers for specific Contexts of Use by supporting the rigorous analytical and clinical validation of previously identified biomarkers. Applicants will be encouraged to leverage existing NIA research resources, adhere to U.S. Food and Drug Administration (FDA) standards, and apply for FDA approval through the Biomarker Qualification Program. This concept proposes a U01 funding mechanism, supporting a cooperative agreement that will include programmatic guidance for seeking FDA approval and developing and implementing project milestones.

### ***Chimeric Antigen Receptor (CAR) Approaches to AD/ADRD***

This concept aims to elucidate whether immunotherapies leveraging CAR proteins and immune cells (T cells or macrophages) can be used to treat AD/ADRD. CAR-T and CAR-M technologies have previously shown promise for treating cancer, and this concept will test whether CAR-T can successfully eliminate harmful senescent cells that contribute to AD/ADRD pathology and whether CAR-M can boost macrophages' ability to degrade toxic protein aggregates, including but not limited to amyloid beta and tau. This concept proposes an R61/R33 mechanism, with the R61 supporting an initial, two-year exploratory phase with clear research milestones.

### ***Building Neuroscience Research Infrastructure for AD/ADRD in Africa***

AD/ADRD represent a significant global health burden, particularly for low- and middle-income countries where the majority of cases occur. The sub-Saharan Africa region, for example, anticipates a large increase in AD/ADRD cases corresponding to the increase in the number of older adults in the region. Thus, this concept, proposed in collaboration with BSR, seeks to enhance the AD/ADRD research infrastructure in Africa and support collaborations between U.S. and African researchers through pilot and exploratory studies. The substantial genetic variation and range of environmental and lifestyle factors present in Africa may provide significant insight into mechanisms underlying AD/ADRD. Studies leveraging this insight can inform intervention and prevention strategies for AD/ADRD mitigation in both Africa and the United States. This concept proposes a staged mechanism, by which only studies that can successfully scale in Africa will proceed beyond the UG3 start-up phase to the UH3 phase of the award.

### ***Artificial Intelligence in Pre-Clinical Drug Development for AD/ADRD***

To accelerate the discovery of diverse AD/ADRD drug candidates, this concept seeks to promote research on artificial intelligence (AI) approaches for preclinical drug development. As biomedical data and computing power increase, AI and machine learning (ML) methods are continually refined and may help researchers overcome the most laborious and costly aspects of drug discovery and development. In fact, other NIA programs have been successful at leveraging AI and ML to identify non-amyloid and non-tau targets for AD/ADRD therapies. To enhance AD/ADRD therapeutic development, this concept proposes a UH2/UH3 mechanism to create a research program focused on developing AI and ML methods for AD/ADRD drug design and open-source analytical tools that will be made available to researchers in academia and industry.

### ***Small Research Grant Program for the Next Generation of Researchers in AD/ADRD Research***

This concept supports the reissuance of the “Small Research Grant Program for the Next Generation of Researchers in AD/ADRD Research,” which previously supported multiple funding mechanisms. The current concept calls for only one Request for Applications (RFA) and aims to encourage the next generation of researchers, including early career investigators with backgrounds outside of aging, to pursue AD/ADRD research. It also encourages investigators already in the field to explore new areas of aging and AD/ADRD research. This concept supports R03 pilot studies that will ideally lead to R01s focused on significant advancements within aging research.

### ***Seamless Early-Stage Clinical Drug Development (Phase 1 to 2a) for Novel Therapeutic Agents for AD/ADRD***

To prevent and treat AD/ADRD, efficient mechanisms are needed to fund clinical trials testing a variety of different therapies and interventions. Inefficient phase 1 safety and tolerability studies are a major limiting factor for the progression of therapeutic candidates from phase 1 to phase 1b/2a clinical trials. Therefore, this concept seeks to streamline early-stage evaluation of promising pharmacological therapies. Through UG3/UH3 mechanisms, this concept will invite applications that bundle independent proposals for phase 1 clinical trials with phase 1b/2a clinical trials in relevant populations, with the requirement that trials meet pre-specified, NIA-approved, peer-reviewed, go/no-go safety and tolerability milestones to advance from phase 1. Pharmacological therapies can be tested in individuals at any stage of disease progression, but trial cohorts must be diverse to ensure broad applicability of results. Furthermore, these therapies must target non-amyloid and non-tau mechanisms to address cognitive or neuropsychiatric symptoms.

### ***Division of Extramural Activities (DEA) and Office of Communications & Public Liaison (OCPL)***

#### ***NIA Institute on Aging Clinical Research Support Services (CRSS) (Contract)***

In light of growing public interest and urgency surrounding aging and AD/ADRD research, NIA’s budget for clinical research has increased substantially. As a result, NIA’s responsibilities for clinical research study management have also expanded. In 2021, a knowledge acquisition report found broad support for a centralized clinical research management system across NIA. Therefore, this concept proposes a contract to expand, centralize, and integrate administrative, regulatory, and statistical supports for NIA clinical research studies. These supports include guidance for tracking compliance and good clinical practices, maintaining databases, recruiting and retaining research participants from underrepresented populations, and assuring research operation quality.

#### ***NIA Information Resource Centers (Contract)***

This concept seeks to support NIA’s mission to disseminate information on scientific advances related to aging and AD/ADRD to researchers, health care providers, and members of the public. It proposes the renewal of a contract, ongoing since 1990, that will provide a variety of supports to facilitate broad communications, including public inquiry response; website design, development, and hosting; publication development, printing, and warehousing; editorial and science writing support; graphic design and video production; database development and

information management; communications research; and conference and event support. The contract also includes two information resource centers, the Congressionally mandated Alzheimer's and Related Dementias Education and Referral Center and the NIA Information Research Center.

### ***Discussion***

Dr. Santora thanked Dr. Driscoll for her work as Chair of WGOP and welcomed Dr. Greenspan as the new Chair.

Dr. Manly asked for clarification about post concept clearance activities and how researchers interested in certain concepts should prepare for follow-up funding opportunities. Dr. Santora responded that, once approved, concepts are posted on the NIA website along with program officer information. He encouraged researchers to discuss their ideas with program officers and to consider building potential project teams. Although NIA does not guarantee that funding opportunities will be generated for all approved concepts, all previously approved concepts have led to funding opportunities.

## **V. PROGRAM HIGHLIGHTS (DGCG)**

### **MrOS: A 20+ Year Study of Aging in Older Men**

Dr. Eric Orwoll, Professor of Medicine, Oregon Health & Science University

The Osteoporotic Fractures in Men Study (MrOS) is a multicenter, longitudinal, and observational study in men, designed primarily to understand musculoskeletal aging, osteoporosis, and fractures. From 2000 to 2002, 5,994 men aged 65 and older were recruited from six communities in the United States. Participants were extensively characterized at baseline through biospecimen analysis and X-ray, quantitative computed tomography (QCT), and dual-energy X-ray absorptiometry (DXA). They were then assessed regularly for more than 20 years via questionnaires administered every four months and five to seven clinic visits involving additional specimen collection and phenotyping. MrOS has maintained contact with greater than 95 percent of surviving participants, representing outstanding study retention. The study has also expanded to include international cohorts of approximately 3,000 men in Sweden and 2,000 men in Hong Kong.

More than 1,000 analysis plans leveraging MrOS data are currently active, and the study has generated approximately 500 peer-reviewed publications and 89 funded ancillary studies. Greater than 80 percent of participants have passed away, and the mean age of survivors has evolved from 74 years at baseline to 90 years currently. Thus, MrOS now has a cohort of fewer than 1,000 very elderly men and has offered valuable insight into the aging process.

Data from MrOS have been leveraged to study several important geriatric outcomes, including osteoporosis and sarcopenia, sleep, dental health, sex steroid levels, and cognition. The collaboration of MrOS with the Study of Osteoporotic Fractures (SOF) has enabled comparisons in musculoskeletal health between older women and men. For example, MrOS and SOF researchers found that both low- and high-trauma non-spine fractures are associated with low bone mineral density and subsequent fracture in older adults. Thus, high-trauma non-spine fractures should be added as outcomes in osteoporosis clinical trials and observational studies.

Another MrOS-SOF collaborative study found that the degree of trauma differs for major osteoporotic fracture events in older men versus older women. Fractures in older men, compared to fractures in older women, are much more likely to be related to high activity and trauma. This finding may be important for public health strategies targeting fracture prevention in older adults.

MrOS also serves as a platform for testing new methods for evaluating musculoskeletal health. For example, the use of D<sub>3</sub>-creatine dilution to measure muscle mass has been extensively leveraged in MrOS. Typically, muscle mass has been estimated using DXA-based calculations of lean mass that are fundamentally flawed because lean mass contains other tissue types in addition to muscle. In fact, D<sub>3</sub>-creatine muscle mass poorly correlates with lean mass, and studies have illustrated that walking speed is much more strongly related to D<sub>3</sub>-creatine muscle mass than to lean mass. The D<sub>3</sub>-creatine dilution method has also led researchers to reconsider the concept of muscle quality. Research has long shown that muscle performance declines with age, even in the absence of major changes in lean mass. Therefore, decline in muscle quality was thought to be independent of muscle mass. Research now shows that D<sub>3</sub>-creatine muscle mass declines quickly in proportion to decreases in gait strength and walking speed, reconfiguring sarcopenia research. In fact, both muscle density and D<sub>3</sub>-creatine muscle mass have independently been associated with physical performance.

In combination with longitudinal phenotypical data, data from the MrOS biobank facilitate unique opportunities to examine the biological underpinnings of age-related processes. In 2015, researchers leveraged broad spectrum, high-throughput mass spectrometry to measure levels of serum proteins in approximately 2,500 men at baseline. After 15 years of observation, the researchers identified differences in the abundance of several proteins, many of which were implicated in inflammation and complement activation, between long-lived men and those who passed away earlier. Lower levels of these proteins were more common in long-lived men and were significantly associated with better self-rated health status, higher scores on the 12-item Short Form Health Survey (SF-12), higher scores on the Healthy Aging Index, and lower scores on the Fried Frailty Index. In all men, the abundance of these proteins increased as death approached, suggesting that increases in these longevity-associated proteins may signal impending death.

In addition to investigating longevity, researchers examined the relationship between serum proteins and phenotypes such as bone loss and mortality. Interestingly, they observed considerable overlap in serum proteins associated with all three phenotypes.

To understand the biology of longevity and discover interventions that promote longer healthspans, NIA has supported the development of the Longevity Consortium. Consortium projects include mouse, cohort-based, and computational studies. Serum biorepositories from studies such as MrOS and SOF are leveraged for proteomics and metabolomics experiments and system analyses. Preliminary analyses comparing data from long-lived and control participants have confirmed two-thirds of the serum protein—longevity associations previously described in MrOS.

Lastly, Dr. Orwoll described the impact of MrOS on research related to aging and the microbiome. MrOS data from stool collections and 16S ribosomal RNA (16S) sequencing have contributed to publications on bone density and structure, activity, diet and dietary protein, body

weight, vitamin D metabolites, statins, and aging. In collaboration with researchers at the Institute for Systems Biology in Seattle, MrOS researchers found that individual gut microbiomes became increasingly unique with age, starting in middle adulthood. Relative abundance of *Bacteroides*, the most common and dominant genus of bacteria within the gut microbiome, decreased as a function of age in healthy individuals. By contrast, retention of *Bacteroides* and low gut microbiome uniqueness were associated with significantly decreased survival over the course of a four-year follow-up period. Thus, variable gut microbiome patterns may reflect health states and predict aging trajectories.

### ***Discussion***

Dr. Bhasin noted that creatine clearance is expected to decrease with age because of increased prevalence of kidney disease. He asked how changing renal function might affect D<sub>3</sub>-creatine-based estimates of muscle mass. Dr. Orwoll agreed that multiple elements of creatine biology must be considered but that changes in renal function appear to have limited effects on D<sub>3</sub>-creatine-based muscle mass estimates. This result is likely because muscle mass estimates are calculated as a ratio of labeled to unlabeled D<sub>3</sub>-creatine, and because the kidney processes both types of D<sub>3</sub>-creatine similarly.

Dr. Schneider asked whether MrOS researchers have evaluated muscle atrophy in hospital-bound patients or cognition-related outcomes. Dr. Orwoll responded that the MrOS cohort consists only of ambulatory, community-dwelling men. He stated that some studies have examined cognitive outcomes but encouraged more ancillary research on the topic.

Dr. Longo asked whether MrOS researchers have used proteomics data to characterize the biological clocks of participants. Dr. Orwoll responded that researchers have considered doing so but have not embarked on such studies yet. MrOS currently only has baseline proteomics data, so future work on biological clocks should longitudinally collect proteomics data.

Dr. Driscoll commented that many women take osteoporosis medications for extended periods of time. She asked whether such medications are given to men and whether research exists evaluating their impact on muscle health. Dr. Orwoll responded that although osteoporosis occurs frequently in men, men are less likely to receive interventions for the condition. A small proportion of MrOS men have received osteoporosis interventions, but researchers have not yet studied their influence on muscle mass.

Dr. Asthana asked whether MrOS researchers have collected AD biomarkers given the growing interest in elucidating the relationship between AD progression and gait or mobility changes. Dr. Orwoll responded that MrOS researchers tend to have a musculoskeletal research focus but agreed that they are well positioned to longitudinally assess the impact of AD on musculoskeletal health. He suggested that ancillary, R01-funded studies could pursue that line of research.

Dr. Khan asked what proportion of the MrOS cohort included minorities, particularly Native American individuals. Dr. Orwoll stated that the study's recruitment of minorities was worse than researchers had hoped. Minorities composed only 10 percent of the MrOS cohort: 5 to 6 percent were Black individuals, and a very small percentage were Native American individuals. Dr. Orwoll said he was receptive to learning about novel approaches to enhancing minority recruitment or conducting meaningful analyses on the small populations already recruited.

Dr. Greenspan referenced an ongoing debate on whether the fracture risk assessment tool, FRAX, should still be used in clinical practice. She asked whether risk of major osteoporotic fracture should consider falls or other musculoskeletal outcomes not included in FRAX. Dr. Orwoll responded that research on this topic is ongoing and suggests possible incorporation of fall and muscle density measures into FRAX risk assessment.

## **VI. COUNCIL GUEST SPEAKER**

### **ARPA-H: The Mission: The Advanced Research Projects Agency for Health**

Dr. Susan Monarez, Deputy Director, Advanced Research Projects Agency for Health

The Advanced Research Projects Agency for Health (ARPA-H) seeks to accelerate better health outcomes for all by funding transformational research activities. Although it is modeled after the Defense Advanced Research Projects Agency (DARPA), ARPA-H has a much broader focus. President Biden has long been a supporter of ARPA-H and has stated that it will “break the mold” on how research is typically supported in the United States. To create innovative health solutions, ARPA-H invests in high-risk/high-reward research that other agencies would normally not support. Congress provided ARPA-H \$1 billion and \$1.5 billion in funding in FY 2022 and FY 2023, respectively.

ARPA-H is an agency within NIH that reports directly to the Secretary of the Department of Health and Human Services. It consists of only program managers and business team members and houses no internal research laboratories. ARPA-H is disease agnostic and only funds programs proposed by program managers who have identified important health-related challenges that are not solvable through traditional means. These programs are contract-based and invite multiple performers to compete for a solution. Progress is assessed regularly, and performers may be dropped in favor of their more successful competitors. However, valuable lessons are shared from all competing projects. ARPA-H emphasizes that failure is an important aspect of innovation and an important source of learning. Once a challenge is solved, ARPA-H transfers winning solutions to community, government, or industry partners who can scale and implement them within diverse populations.

Program managers are brought onto ARPA-H for three to six years and thus face an urgency to join with well-defined challenges. Programs run from two to four years, so occasional handoffs between outgoing and incoming program managers are necessary. ARPA-H supports program managers with wraparound services and guidance for engaging with federal government agencies, moving their programs toward sustainable solutions, and working with solution transition partners. To increase the odds that programs generate sustainable solutions, ARPA-H has also developed the Project Accelerator Transition Innovation Office (PATIO), which supports program design, broad agency announcement (BAA) development, early and mature program processes, and solution scaling.

Initial ARPA-H focus areas include (1) health science futures and removing limitations that impede progress, (2) scalable solutions and generating solutions that can reach everyone quickly, (3) proactive health and preventing people from becoming patients, and (4) resilient systems and building integrated health care systems. Aging is one domain in which multiple health-related

problems are ripe for solving. Thus, ARPA-H is seeking program managers who are passionate about aging and are diverse in demographics, geography, and experience. Candidates should have recognized expertise in any area of research, serious drive, insatiable curiosity, no fear of failure, an interdisciplinary track record, and technical honesty. Interested researchers may apply through the [ARPA-H website](#).

ARPA-H has established a website and social media channels and has engaged 202 individuals in the program manager pipeline, with 121 in an initial triage stage, 57 under review, and three to give job talks in January 2023. In addition, ARPA-H has engaged with more than 30 members of Congress, 20 universities' administrators and faculty, and 10 patient advocacy and professional organizations. ARPA-H has hosted a number of summits and workshops in collaboration with other NIH groups and seeks to meet with directors of all NIH Institutes and Centers by spring 2023. ARPA-H is also coordinating small team brainstorming sessions to identify well-defined problems in health to pursue with the National Center for Advancing Translational Sciences, the *All of Us* Research Program, and the National Human Genome Research Institute.

### ***Discussion***

Multiple Council members asked whether research questions pursued by ARPA-H are solicited solely from program managers. Dr. Monarez responded that ARPA-H primarily solicits questions proposed by program managers. However, ARPA-H also conducts public outreach to identify research domains for which additional funding is greatly needed. Thus, ARPA-H may seek to recruit program managers interested in those research domains, such as researchers passionate about aging. Dr. Monarez added that ARPA-H plans to release a BAA within the next six months.

Dr. Hodes asked how ARPA-H will interact with other groups in NIH. Dr. Monarez emphasized that a productive collaboration between ARPA-H and NIH is her priority. She hopes that ARPA-H can address the riskier aspects of problems that NIH grants pursue, and that ARPA-H and NIH can discuss what types of solutions do and do not work.

Dr. Case asked about the cost-effectiveness of ARPA-H-driven health care solutions. Dr. Monarez responded that cost is a constraint for solution development and transition. Evaluators will consider what proposed products must look like to be affordable and broadly implementable.

Beyond commercialization capabilities, Dr. Inouye asked whether ARPA-H will explicitly consider how solutions contribute to the greater societal good. Although ARPA-H does not have the funding to sustain solutions, it is committed to advancing positive health innovations. For certain interventions that may not be financially self-sustaining, ARPA-H may facilitate their transition to philanthropic partners.

Dr. Greenspan asked how specific or broad ARPA-H projects can be. Dr. Monarez gave examples of proposals ranging from implanting cells that secrete therapeutic biomolecules to changing city design to promote health and wellness.

## **VII. INTRAMURAL PROGRAM REPORT**

### **Laboratory of Genetics and Genomics**

Dr. Myriam Gorospe, Senior Investigator, NIA Intramural Research Program

Dr. Gorospe provided an overview of the progress made by the Laboratory of Genetics and Genomics (LGG) since its Board of Scientific Counselors (BSC) review in October 2021. She reported that LGG has supported NIA's mission to reduce, delay, and prevent age-associated disease and disability by contributing tools and methods based in cell and molecular biology.

The LGG consists of seven components: sections for Genome Instability and Chromatin Remodeling, RNA Regulation, and Telomere Maintenance; units for Functional Epigenomics, Translational Senescence, and Computational Genomics; and a core for Computational Biology and Genomics.

The Section for Genome Instability and Chromatin Remodeling, led by Dr. Weidong Wang, has predominantly studied topoisomerase III beta (TOP3 $\beta$ ). Five articles on TOP3 $\beta$  have been published since the last BSC review. These articles include findings of TOP3 $\beta$  being dispensable for the replication of positive-sense RNA viruses, construction of an atlas of transcription factors important for human embryonic stem cell development, and a subset of messenger RNAs whose translation and stability is controlled by TOP3 $\beta$ .

The Section for RNA Regulation, led by Dr. Gorospe, focuses on regulation of RNA at each phase of processing, from transcription to protein synthesis. Since the last BSC review, this section has produced 30 publications focused on signaling pathways critical for senescence, the role of long noncoding RNAs in energy metabolism and stress response, and the role of circular RNAs in neurodegenerative diseases such as amyotrophic lateral sclerosis.

The Section for Telomere Maintenance, led by Dr. Yie Liu, focuses on molecular factors and mechanisms underlying telomere maintenance, pathways affecting short telomere syndromes and telomere loss in aging, and NAD-based intervention strategies to mitigate short telomere syndromes. This section was not specifically reviewed in 2021 but has produced four recent publications.

The Unit for Functional Epigenomics, led by Dr. Payel Sen, focuses on epigenetic mechanisms of tissue aging. This unit has published eight articles since the last BSC review, related to epigenetic modifications and functional outcomes, transcription, the 3D genome, and epigenetic drugs. One of the unit's major projects, which studies chromatin changes in the aging liver and reversal of these changes during liver regeneration, is currently under final stages of revision for publication.

The Unit for Computational Genomics, led by Dr. Manolis Maragkakis, studies gene regulation in healthy aging and disease through analysis of RNA dynamics. This unit has published two articles since the last BSC review and regularly leverages a wide range of experimental techniques, including cell culture techniques, mouse models, direct RNA-Seq, data science, and machine learning.

The Unit for Translational Senescence, led by Dr. Ali Herman, is the LGG's newest program. It focuses on developing cell culture and mouse models of vascular senescence and identifying drugs that target proteins involved in vascular senescence. Since the last BSC review, this unit published seven articles.

Lastly, the Core for Computational Biology and Genomics, led by Dr. Supriyo De, continues to support study design, data generation, and data analysis throughout the entire LGG. The core provides extensive and diverse omics data, coordinates data science expertise, acquires and maintains novel equipment, and works with individual groups to design projects. This work extends beyond the LGG to other groups at NIA and is very impactful.

Dr. Gorospe also highlighted how the LGG has directly addressed BSC recommendations, which included suggestions to verify findings in senescence models and patient samples and to conduct more drug testing and translational studies. LGG researchers have developed additional senescence models, including mouse models for senescence signaling and senescence-associated telomere shortening. They have also started to leverage patient muscle and skin samples. LGG research has shown, for example, that proteomes of primary skin fibroblasts show altered cell responses in healthy individuals across the lifespan. Other studies have utilized human liver and brain tissue samples. LGG studies have also tested a variety of senolytic drugs, including Gingerenone A, tropomyosin receptor kinase B (TrkB) inhibitors, Src kinase inhibitors, and yes-associated protein–transcriptional enhanced associate domain (YAP-TEAD) inhibitors.

The BSC also recommended that the Section for RNA Regulation receive additional funding, particularly to evaluate murine disease models and pursue translational research grounded in Geroscience. The NIA Office of the Scientific Director has committed permanent additional funds for senescence research, an additional postbaccalaureate position for murine work, and a bioinformatics staff scientist position. Dr. Krystyna Mazan-Mamczarz was recruited for the latter position and began serving in 2022.

### **Laboratory of Molecular Biology and Immunology**

Dr. Ranjan Sen, Senior Investigator, NIA Intramural Research Program

The overarching goal of the Laboratory of Molecular Biology and Immunology (LMBI) is to elucidate the molecular and cellular mechanisms that regulate immunity and thereby understand the basis for age-associated decline in immune response. LMBI investigators study multiple aspects of immunity, including immune cell development, immune response and regulation, effector functions, and memory. The LMBI also oversees the Flow Cytometry Unit, a core facility for the entire NIA Intramural Research Program that provides analytical flow cytometry and cell sorting services and training.

The LMBI consists of six components: a unit for Transcription Systems Dynamics and Biology and sections for Gene Regulation, Antibody Diversity, Replication Stress and Aging, Lymphocyte Differentiation, and Immunoregulation.

The Unit for Transcription Systems Dynamics and Biology, led by Dr. Myong-Hee Sung, recently published its novel method for real-time tracking of nuclear factor-kappa B (NF-kappa-

B), a stress-inducible transcription factor that regulates cellular inflammatory responses. This work has also been featured in Volume 31, Issue 1 of the [NIH Catalyst](#).

The Section for Gene Regulation, led by Dr. Sen, has recently been studying cell-specific gene expression, gene regulation by NF-kappa-B, and age-associated changes in the immune cells of healthy humans.

The Section for Antibody Diversity, led by Dr. Patricia Gearhart, has been investigating the trajectories of B cells during aging, mechanisms for high affinity antibody development over the lifespan, whether antibodies play a role in atherosclerosis, and how changes in hematopoietic stem cells may lead to antibody diversity as individuals age.

The Section for Replication Stress and Aging, led by Dr. Michael Seidman, has recently focused on the processes by which a very limited number of immune cells are selected and clonally expanded to mount an immune response against an antigen. This work examines the effects of aging on replication stress during immune cell clonal expansion.

The Section for Lymphocyte Differentiation, led by Dr. Nan-Ping Weng, has recently conducted studies demonstrating distinct, age-related reductions in the repertoire richness of human  $\alpha\beta$  T cell receptors. These findings lend support to the longstanding hypothesis that older adults' increased susceptibility to infection may be explained by age-related decline in immune cell diversity.

The Section for Immunoregulation, led by Dr. Arya Biragyn, has recently examined how B cell depletion reduces amyloid beta plaques and activated microglia in mouse models of AD, and how tumor associated macrophages are generated from *bona fide* B cells.

These insights from all LMBI sections converge on a common mission to understand the immune and inflammatory interactions involved in AD/ADRD.

## **VIII. ADJOURNMENT**

The open session of the 148th meeting of the National Advisory Council on Aging adjourned at 2:14 p.m. on January 19. The next meeting is scheduled for May 16-17, 2023.

## **IX. CERTIFICATION**

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

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.

---

<sup>3</sup> These minutes will be approved formally by Council at the next meeting on May 16-17, 2023, and corrections or notations will be stated in the minutes of that meeting.