

NATIONAL INSTITUTES OF HEALTH

NATIONAL INSTITUTE ON AGING

Summary Minutes

The 131st Meeting

NATIONAL ADVISORY COUNCIL ON AGING

May 16–17, 2017

**National Institutes of Health
Building 31, C Wing, 6th Floor, Conference Room 10
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
May 16–17, 2017**

The 131st meeting of the National Advisory Council on Aging (NACA) was convened on Tuesday, May 16, 2017, at 3 p.m. in Building 31, Conference Room 10, National Institutes of Health (NIH), Bethesda, Maryland. 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 Tuesday, May 16, 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 Wednesday, May 17, from 8:00 a.m. to 12:15 p.m.

Council Participants:

Dr. David A. Bennett
Dr. Maria Carrillo
Dr. Eileen M. Crimmins
Dr. J. Taylor Harden
Dr. David M. Holtzman
Dr. Raynard S. Kington
Dr. James L. Kirkland
Dr. Stephen B. Kritchevsky
Dr. Richard Mayeux
Dr. Terrie E. Moffitt
Dr. Charles P. Mouton
Dr. Anne B. Newman
Ms. Susan K. Peschin
Dr. Norman E. Sharpless
Dr. Reisa A. Sperling
Dr. Debra Bailey Whitman

Ex Officio Participants:

Dr. Jane Tilly, Administration for Community Living

Absent Ex Officio Participants:

Dr. Kenneth G. Pugh, National Naval Medical Center

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.

The Council Roster, which gives titles, affiliations, and terms of appointment, is appended to these minutes as attachment A.

In Addition to NIA Staff, Other NIH Employees Present:

Dr. Cheryl Boyce, National Heart, Lung, and Blood Institute
Dr. Gina M. Brown, Office of AIDS Research (OAR), Office of the Director (OD)
Dr. Penny Burgoon, National Center for Advancing Translational Sciences
Ms. Devon Drew, National Institute of Diabetes and Digestive and Kidney Diseases
Dr. Michael Lauer, Deputy Director of Extramural Research
Dr. Paolo Miotti, OAR, OD
Dr. Bruce Reed, Center for Scientific Review (CSR)
Dr. Elyse Schauwecker, CSR
Dr. Afia Sultana, CSR

Members of the Public Present:

Mr. James Appleby, Gerontological Society of America
Ms. Patricia D'Antonio, Gerontological Society of America
Mr. Todd Kluss, Gerontological Society of America
Dr. Nathan K. LeBrasseur, Mayo Clinic
Dr. Rose Maria Li, Rose Li and Associates, Inc.
Dr. Mathew Maurer, Columbia University
Dr. Frances McFarland, Rose Li and Associates, Inc.
Dr. Jenny Tung, Duke Population Research Institute

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 1290 applications requesting \$ 2,225,659,067.86 for all years underwent initial review. The Council recommended 750 awards for a total of \$ 1,368,497,218.82 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. Hodes welcomed members to the open session of the 131st NACA meeting and called the meeting to order at 8:00 a.m. on Wednesday, May 17, 2017.

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.

A. Director's Status Report

Dr. Hodes reported that Congress had passed a spending bill for FY17, increasing the overall appropriation to \$34 billion for NIH. This appropriation includes specifically targeted funds of \$120 million for the Precision Medicine Initiative/All of Us, \$110 million for the Brain Research through Advancing Innovative Neurotechnologies initiative, \$50 million for research on antibiotic resistance, and \$400 million for Alzheimer's disease (AD) research. The total appropriation for NIA, including the funding for AD research, is \$2 billion. This figure represents an increase of \$48 million for non-targeted research in addition to the increase for research on AD. Thus, funding for AD research has not increased at the cost of other research. Dr. Hodes pointed out that the appropriations for NIH and NIA continue recent trends of annual increases and that the growth in the budget for NIA (excluding Alzheimer's) parallels that for other NIH Institutes and Centers (ICs) and targeted initiatives.

The current NIA paylines for general R01 applications that are reviewed by the Center for Scientific Review (CSR) and cost less than \$500,000 are 11 percent for established investigators, 14 percent for new investigators, and 16 percent for early-stage investigators. For those costing \$500,000 or more, the paylines are 8 percent for established investigators, 11 percent for new investigators, and 13 percent for early-stage investigators. The paylines for AD-specific applications and NIA-reviewed applications are more generous, ranging from 22 percent to 40 percent. Dr. Hodes provided links to concept approvals and general and AD-specific funding opportunity announcements (FOAs).

Dr. Hodes then spoke of his participation in the Davos World Economic Forum in January 2017, noting that it was gratifying to see the amount of interest in aging research. He mentioned the third Cognitive Aging Summit, which took place on April 6 and 7. That Summit focused on resilience and reserve in brain aging. Dr. Hodes announced a workshop on Inclusion Across the Lifespan, which will be held on June 1–2, 2017, at the Natcher Conference Center. He also reminded Council members and visitors about the Butler-Williams Scholars Program (July 31–August 4, 2017), a research summit on AD care and services (October 16–17, 2017), and the third AD research summit (March 1–2, 2018).

Dr. Hodes next reported on a study, commissioned by NIA and conducted by the National Academies and the Agency for Healthcare Research and Quality (AHRQ), to assess the science of prevention strategies for AD, other dementias, and age-related cognitive decline. The first part of this assessment is available online, and the second part is expected to be released in June. The assessments have found that:

- Most interventions show no evidence of benefit in delaying or preventing age-related cognitive decline, mild cognitive impairment, or AD-type dementia.
- Some forms of cognitive training improve performance on specific training targets in adults with normal cognition, but little evidence supports the transfer of benefits to other cognitive areas or reduced dementia incidence.
- Some types of physical activity and vitamin B12 plus folic acid might benefit cognitive performance in some areas for adults with normal cognition.

Dr. Hodes noted the timeliness of these assessments in light of recommendations from policy organizations. NIA will consider the AHRQ/National Academies recommendations as it identifies public health and research messages.

Dr. Hodes closed his presentation by noting presidential appointees Tom Price, M.D., as HHS Secretary, Seema Verma as Administrator for the Centers for Medicare and Medicaid Services, and Scott Gottlieb, M.D., as Commissioner for the U.S. Food and Drug Administration (FDA).

In response to questions from the Council, Dr. Hodes speculated that the AHRQ/National Academies reports and the third summit on cognitive aging would likely overlap in their recommendations for future work. He noted that feedback from the summits and other communities contributes to the development of priorities and milestones for the AD National Plan, which in turn guides NIA and other stakeholders as they issue FOAs and try to anticipate changes in funding. Dr. Hodes commended the scientific community on its ability to generate creative research despite funding uncertainties. He also recognized the NIA staff, who are called upon to work even harder in response to increased opportunities.

B. Future Meeting Dates

September 26–27, 2017 (Tuesday and Wednesday, Building 31)

January 23–24, 2018 (Tuesday and Wednesday, location TBD)

May 22–23, 2018 (Tuesday and Wednesday, location TBD)

September 19–20, 2018 (Tuesday and Wednesday, location TBD)

C. Consideration of Minutes of the Last Meeting

The minutes of the January 2017 meeting were considered. A motion was made, seconded, and passed unanimously to approve the minutes with one correction: Dr. Debra Bailey Whitman was not in attendance at the January meeting.

III. REPORT: TASK FORCE ON MINORITY AGING RESEARCH

Dr. Charles Mouton reported that the Task Force had heard two presentations. The first, given by Dr. Steven Austad, discussed health disparities in Alabama and Mississippi, the two unhealthiest states in the United States. Life expectancy in these two states is lower than it is in all of Western Europe and developed Asia and similar to that in Algeria, Panama, Uruguay, Cuba, Vietnam, and Puerto Rico. Among the 50 states, Alabama and Mississippi rank in the top ten with respect to smoking and obesity and the lowest with respect to median income and birth weight. Dr. Austad's presentation noted county-level data highlighting the influence of education and income level, in addition to race, on health outcomes. He also noted that health inequality among groups is increasing.

The second presentation was a Diverse Scholar Research Spotlight given by Ms. Daniella Chusyd. This presentation explored associations between fat deposition and fertility. Ms. Chusyd presented studies showing similarities in fat deposition between humans and rats, as well as the effects of caloric restriction on long-term weight cycling and body composition in male mice. The bulk of her presentation focused on the relationship between body composition and ovarian cycle status, and the effects of that relationship on reproduction, among elephant populations in

zoos. Elephants in captivity weigh more and reproduce less, compared with those in the wild. Ms. Chusyd has turned this project into a conservation program and an outreach program to encourage high school students to engage in science.

Dr. Mouton reminded Council about the 2017 Butler-Williams Scholars Program and an NIA request for applications (RFA) supporting research addressing health disparities. He also noted an annual meeting of the Resource Centers for Minority Aging Research, a meeting on diversity and disparities among AD family caregivers, and a National Institute of Minority Health and Health Disparities meeting on structural racism and discrimination. Dr. Mouton also noted the NIH Women of Color Research Network, which had been discussed previously by Dr. Marie Bernard, NIA Deputy Director. Dr. Mouton closed by thanking NIA leadership and NACA for its continued attention to minority issues.

Council discussion focused on Dr. Austad's presentation and particularly to the question of access to health care. Although Dr. Austad's presentation did not focus specifically on this issue, the lack of access, particularly in rural areas, is likely a contributor to poor health and health disparities seen in Alabama and Mississippi.

IV. REPORT: WORKING GROUP ON PROGRAM

A. RFA/RFP Concept Clearances

The Working Group reviewed seven concept proposals. A motion to approve these concepts *en bloc* was forwarded and seconded. The motion passed unanimously.

Central Neural Mechanisms of Age-Related Hearing Loss

Age-related hearing loss is a common condition with a severe impact on quality of life. Improved understanding of mechanisms is needed to develop better therapeutics. The proposed FOA is a set-aside, with a special review panel, to encourage applications for basic, clinical, and translational studies addressing these mechanisms in both humans and animal models. The Working Group suggested that the special review panel bring together experts in hearing loss across the lifespan and that the FOA encourage studies into environmental factors that promote and accelerate hearing loss.

Demonstration Projects for Pragmatic Clinical Trials

This concept proposes that NIA participate in an NIA-wide RFA supporting pragmatic clinical trial designs as part of the NIH Collaboratory initiative. Ten other ICs are participating in this RFA. NIA-funded applications in this initiative would address topics such as multiple chronic conditions, cognitive impairment, and palliative care. NIA participation would fulfill part of the strategic plan for the Division of Geriatrics and Clinical Gerontology (DGCG).

Tailoring Cardiac Rehabilitation to Enhance Participation of Older Adults

Two million Americans experience an acute coronary event each year. Despite the existence of clear interventions for such events, most patients older than 65 years do not use them. The concept proposes a clinical trial focused on novel strategies to enhance referral, participation, and adherence of older adults and more vulnerable populations to these existing interventions. The Working Group noted that this robust concept addresses topics within the NIA strategic plan, as well as some social determinants of health and that it would encourage some collaboration between NIA and the National Heart, Lung, and Blood Institute. The Group also suggested that the proposed FOA will influence cardiac rehabilitation strategies outside the medical center. The Working Group suggested that the FOA also support pragmatic trials to address health systems issues.

Pathogenesis of Age-Related HIV Neurodegeneration

This concept, revised since its initial presentation at the January Council meeting, focuses on potential relationships among HIV, cognitive decline, and neurodegeneration. These relationships are increasingly relevant as more patients with HIV live into their 60s and 70s. The revised concept has been broadened beyond AD pathology and now includes both basic and clinical research.

Harmonizing Outcomes in Existing Cohorts to Enhance the Study of Risk and Protective Factors in AD and AD-related Dementias

The elucidation of the role of various factors in AD and related dementias is hampered by the small size of study populations. The proposed concept is a cooperative agreement to develop techniques for merging datasets and harmonizing measurements across them. The Working Group strongly supported this concept.

Enhancing Central Neural Control of Mobility in Aging

Gait is clearly an important measure of function and a predictor of future disability, cognitive impairment, and mortality. However, it has been studied only cross-sectionally, and few studies have integrated all systems, including the central nervous system (CNS), that control mobility. This concept proposes to improve the science of mobility by supporting studies on how the brain controls mobility, gait, and function. It will bring together investigators from multiple disciplines to develop a common language and common protocols to understand the contribution of the CNS to gait. The Working Group suggested that the concept include a longitudinal component to understand how gait abnormalities emerge over time, and underscored the importance of considering the peripheral nervous system.

Development of Valid Reliable Markers of Aging-Related Biologic Mechanisms for Human Studies

The field of geroscience is advancing quickly, but it is limited by the lack of reliable measures to characterize aging biology. The proposed concept will support the development and refinement of measures to characterize the biological aspects of aging for use in clinical studies. The Working Group agreed that set-aside funds and special review are needed because these types of

projects, which would incorporate engineering, would likely fare poorly in standard NIH review. The Working Group suggested that the concept also include aspects of translatability, including measures that can be used in parallel in animal models, as well as some attention to scalability and accessibility.

B. Alzheimer's Disease Research Centers

Dr. Maria Carillo commended Dr. Barry Greenberg and others on their review of the AD Research Centers. This review pulled together multiple voices and yielded an excellent overview of the many accomplishments these centers have made to date and the possibilities for the future of the program. A motion to approve Council endorsement of the reviewers' recommendations was forwarded and seconded. The motion passed unanimously.

C. Statement of Understanding

Dr. Robin Barr reviewed the Statement of Understanding and highlighted its important elements:

- If an application involving a Council member is identified for individual special action, a group of former Council members will be convened to provide advice.
- The Council can provide early concurrence for applications costing less than \$500,000.
- NIA can approve an administrative supplement up to a threshold of \$100,000. Beyond that threshold, administrative supplement requests must go to Council for individual action.
- Funds that an initial peer review group eliminates from an application can be reinstated administratively provided it is no more than \$100,000. Above that threshold, a decision to reinstate funds must come to Council for individual action.
- NIA reports these internal actions to Council.

The Council suggested that, in light of the timeline for new AD dollars, NIA consider raising the threshold for AD-related administrative supplements. A motion to approve the Statement of Understanding was forwarded and seconded. The motion passed unanimously.

V. COUNCIL SPEAKER: IMPLEMENTING THE GRANT SUPPORT INDEX

Dr. Michael Lauer, Deputy Director for Extramural Research, NIH, spoke to the council. NIH is entrusted to be stewards of taxpayer money and to ensure maximum impact from the research it supports. The agency is also committed to developing and sustaining a robust and qualified workforce. However, the research enterprise is under a large amount of stress. A paper published by Alberts et al. in the *Proceedings of the National Academy of Sciences of the United States of America (PNAS)* argued that the research system has assumed that it will enjoy never-ending growth and, as a result, has created an environment of extreme hypercompetition that could lead to long-term decline. The number of researchers supported by NIH research project grants has remained steady since the annual doubling of the NIH budget ended in 2003, but the number of unique applicants has increased substantially, from 60,000 in 2003 to 90,000 at present. Among researchers supported by NIH, the proportion of individuals who are early- and mid-stage investigators has fallen, while the proportion of late-stage investigators has increased. Moreover,

funding distribution is heavily skewed: approximately 10 percent of scientists receive about 40 percent of the funds. Thus, the system is highly unstable.

There are no clear metrics to determine whether this skewed distribution of resources yields optimal productivity. Bibliometric measures include the number of publications, whether these publications appear in high-impact journals, citation rates, and the h-index, but these metrics do not account for the characteristics of individual fields. For example, cardiologists tend to publish several papers and cite each other multiple times. The Office of Portfolio Analysis has developed the relative citation ratio, which assesses how often a publication is cited compared with how often it is expected to be cited compared with similar papers. However, 20 percent of papers catalogued in PubMed are never cited, even by their own authors. In addition, several studies have found a diminishing marginal return per researcher at the highest levels of funding. These studies argue that it is the number of researchers at work, rather than the amount of money invested, that primarily determined productivity. They therefore argue that funding a larger number of researchers will increase productivity and the likelihood of major discoveries. Moreover, a recent analysis has found that the success of early-stage investigators in obtaining an NIH research project grant is not associated with how well their mentors are funded.

Language in the 21st Century Cures Act addresses the issue of the hypercompetitive environment and its effects on the next generation of researchers. This language directs the NIH Director to coordinate policies and programs to promote earlier independence and increased funding for new and early-stage investigators. There have been several suggestions on how to accomplish these goals. The University of Wisconsin-Madison has found that too many scientists compete for too few dollars and that too many postdoctoral fellows compete for too few faculty positions. The University therefore suggests that funds be redistributed to support junior investigators and pioneering projects. A monograph by the Federation of American Societies for Experimental Biology has identified similar problems and recommends that research sponsors monitor the amount of money individual laboratories receive and that NIH cap the amount of funding per individual lab to enable funding for more investigators. Similarly, a request for information by NIH yielded suggestions to cap the number of NIH grants or amount of funds individual principal investigators (PIs) can have.

Dr. Lauer noted that NIH will continue existing approaches to support investigators at all career stages. However, none of these approaches addresses the problem of diminishing returns, and most highly funded investigators are funded by two or more ICs or Offices. NIH therefore proposes a new trans-NIH policy to monitor the level of research support per PI, using the Grant Support Index (GSI). The GSI is a modified grant count that applies points based on the type of grants an investigator has. The number of points for each grant type is the same regardless of the dollar amount of the individual grant. Research project support would be limited to an equivalent of three R01s. IC Directors can make exceptions based on a rigorous process that accounts for the unique research requirements of that IC, the commitment to support researchers at all stages, and the need to maximize the productivity of grant resources. The new policy would take effect with applications submitted in the fall of 2017, and it would initially focus on research project grants supporting research efforts and not infrastructure or training. NIH estimates that the new policy would affect 3.1 percent of investigators and redirect resources to support 900 new awards. An analogous program will be put into place for the NIH Intramural Program.

Dr. Lauer noted that the NIH leadership is aware of the many opportunities for unintended consequences for the proposed policy. Thus, implementation will be monitored closely. Dr. Lauer also noted that implementation continues to be shaped by feedback from all stakeholders.

In response to questions from Dr. Hodes, Dr. Lauer noted that initial criticism focused on the assignment of points to service grants, including training and centers grants. NIH also has considered how to assign points for cooperative or collaborative grants. At present, if an R01 is worth seven points, NIH would assign six or fewer points to each PI on an R01 with multiple PIs.

Dr. Tilly commended NIH for focusing on career stage, rather than age. She then asked whether NIH has considered how to address duplication. While some replication is important, for example, NIH should not fund 100 studies to tweak the same thing. Dr. Lauer responded that efforts are under way to address rigor and reproducibility. When discussing the scientific premise of their proposals, applicants are required to critically describe and appraise the scientific literature and where their idea would fit. NIH also assesses the pool of investigators who do good work but do not score well enough to get funded, and it chooses the most interesting ideas to fill out its portfolio.

Dr. David Holtzman noted that many Council members had known about this proposal and surveyed researchers at their institutions. He offered to send a compiled list of suggestions to Dr. Lauer. He also noted the general consensus on the need for a mechanism to fund more PIs and a wider breadth of science. He expressed concern, however, that PIs serving on program and center grants would be penalized when these grants serve as resources for an entire community. Dr. Holtzman pointed out that the proposed points system also disincentivizes senior investigators who do more to support early-stage investigators and that academic centers will discourage multi-PI networks because of the GSI. He also expressed concern that the GSI policy would prevent investigators who lead large programs from conducting science in their own laboratories. Dr. Holtzman suggested that IC Directors consider exceptions for top-earning investigators who yield high value. Dr. Lauer reiterated that the points system will not apply initially to training, center, and conference grants and that NIH is addressing the likely need for exceptions.

Dr. Carillo agreed that constant monitoring will be critical for the proposed policy and emphasized the importance of collecting data from the beginning of implementation. She suggested that fields such as aging and AD, which have had less funding in the past and have already lost early-stage investigators, be considered separately in the proposed GSI policy. She expressed concern that in such fields, which are beginning to ramp up, the GSI policy could disincentivize mentoring. Dr. Reisa Sperling echoed these concerns with respect to junior clinical research investigators. She suggested that NIH look at the percentage of K23 grantees that come from clinical labs with high GSIs, as well as the amount of time spent mentoring among grantees who become independent investigators 10 years later.

Ms. Susan Peschin emphasized the importance of transparency. She suggested that NIH seek input not only from advisory councils, but from other stakeholders, including internal staff and extramural researchers, and make implementation of the new policy public to minimize unnecessary political backlash. Dr. Raynard Kington echoed these suggestions and added that

NIH should seek input from early-stage investigators. He also suggested that NIH consider developing a statement about the GSI in terms of compelling interest. Such a statement, which will be used to guide future discussions, should synthesize all the reasons and a rationale for the GSI and discuss why other approaches do not achieve the desired results. Dr. Mouton added that the statement should state clearly how the GSI policy is expected to lead to more new investigators and sustained research careers. The statement should outline what NIH will monitor.

VI. PROGRAM HIGHLIGHTS

A. Division of Aging Biology: Cellular Senescence and the Pursuit of Healthspan

Dr. Nathan LeBrasseur, of the Mayo Clinic, discussed his work on cellular senescence. Scientific innovation has doubled the human lifespan during the past century. However, aging is still the greatest risk factor for many chronic diseases. With recent advances in understanding of the fundamental biology of aging, there may be opportunities to intervene on the aging process itself to delay the onset of aging-related conditions.

With advancing age, cells accumulate damage from several sources of stress, including DNA damage, telomere erosion, mitochondrial dysfunction, oxidative stress, and loss of proteostasis. One response to such stress is senescence, in which cells express the machinery, including the tumor suppression genes p16, p21, and p53, to stop dividing. Cells that have undergone senescence assume a senescence-associated secretory phenotype (SASP) that is metabolically active, producing growth factors, cytokines, and matrix metalloproteinases, among other chemicals.

Senescence serves as a fundamental defense against cancer, as senescent cells are cleared by the immune system in younger individuals. However, senescent cells accumulate with advancing age. Senescence could be an example of antagonistic pleiotropy, proving beneficial in younger individuals and detrimental in older ones. Senescence therefore could actually promote cancer as individuals age. Studies suggest that senescent cells drive age-related diseases partly by secreting factors that damage the cells around them, resulting in fibrosis and degeneration. Senescent cells also might promote chronic inflammation. Thus, removing senescent cells could improve health and physiology. One strategy under investigation is the genetic engineering of p16 so that it induces caspase 8 and promotes the death of p16-positive senescent cells. Another involves the use of senolytics, or selective drugs that target and eliminate senescent cells based on their specific properties. Exercise is yet another approach.

Dr. LeBrasseur described work targeting cell senescence in idiopathic pulmonary fibrosis (IPF), a disease that primarily affects older adults. He and his colleagues have found that higher numbers of p16-positive senescence cells are associated with poorer lung function, whereas a low burden of such cells is associated with better performance, for example in the ability to walk or rise from a chair. In a mouse model of IPF, Dr. LeBrasseur and his colleagues have found a strong p16 signal from fibroblasts and epithelial cells. They have also shown that treatment of this mouse model with the senolytics reduces senescent cell burden and improves compliance and resistance in the lung. Moreover, treated mice exercise to a greater distance and longer time

before they become exhausted. Recent work also has shown that targeting senescent cells improves pulmonary and physical function in adults with IPF.

Dr. LeBrasseur and his colleagues also have used mouse models to investigate whether “lifestyle choices” influence senescent cell burden and the SASP. They have found that exercise prevents body weight gain, secretion of cytokines from fat, and cardiac hypertrophy and improves glucose tolerance in mice given a high-fat diet. They have also shown that exercise prevents accelerated aging by preventing the accumulation of senescent cells. Dr. LeBrasseur also presented preliminary data exploring the role of senescent cell accumulation in the alterations in skeletal muscle composition seen with aging and obesity.

Council questions focused on the potential effects of targeting senescence in the brain and whether the benefits associated with exercise reach a plateau.

B. Division of Geriatrics and Clinical Gerontology (DGCG): Transthyretin Cardiomyopathy in Older Adults: Under Appreciated, Often Overlooked, and Treatable?

Dr. Mathew Maurer, of Columbia University, discussed work on the role of transthyretin (TTR) in cardiac amyloidosis, which is characterized by extracellular deposition of fibrillar protein in the myocardium. TTR, also known as pre-albumin, is made by the liver and transports thyroid hormone and retinol. It is a small protein that forms a tetramer to bind retinol-binding proteins. More than 120 TTR mutations have been identified since its sequence was elucidated in 1974. The most common mutation in the United States, valine 122→isoleucine (V122I), is a founder mutation originating from southern West Africa, affects 14,000 people in the United States, and appears almost exclusively in individuals of African descent. TTR-associated cardiac amyloidosis can also arise from wild-type TTR; wild-type TTR-associated amyloidosis has been reported primarily in older Caucasian men. Wild-type TTR-associated disease can appear as early as the mid-40s, whereas V122I-associated disease has an average onset of 70 years.

TTR-associated cardiac amyloidosis is assumed to be rare. However, TTR-associated amyloid was the fourth most common cause of heart failure and associated with worse survival in a study of Afro-Caribbean patients in London, and a study of older patients experiencing heart failure with preserved ejection fraction (HFpEF) found that TTR-associated amyloid accounted for 13 percent of acute decompensation heart failure. TTR-associated cardiac amyloidosis also has been underappreciated because of misconceptions about diagnosis. Cardiologists are trained to look for low voltage on electrocardiograms, but low voltage appears only in a third or less of patients with cardiac amyloidosis. Wall thickness is a better indicator. TTR-associated cardiac amyloidosis also appears to mimic other disease. However, HFpEF patients with cardiac amyloidosis show more right-sided heart failure, an intolerance of standard therapies, lumbar spinal stenosis, and bilateral carpal tunnel syndrome. Finally, TTR-associated cardiac amyloidosis has traditionally been identified through endomyocardial biopsy, which is invasive and performed only at specialized centers. Dr. Maurer and his colleagues have worked with investigators at Mayo Clinic to show that a noninvasive technique using the bone isotope technetium-99 can diagnose TTR-associated cardiac amyloidosis with 97 percent sensitivity and 100 percent specificity.

Dr. Maurer noted that HFpEF affects approximately 7 million Americans and accounts for an epidemic of hospital admissions and readmissions. He also noted a large disparity in heart failure incidence, which is higher among black and Hispanic individuals compared with the incidence among Chinese and white individuals. Despite several randomized clinical trials, no effective therapies have been identified for HFpEF. Data presented at the International Society of Amyloid have shown increased mortality among HFpEF patients who receive beta blockers or angiotensin-converting enzyme inhibitors. Dr. Maurer suggested that TTR-associated cardiac amyloidosis could be a driver of disparity in heart failure. He presented data from a clinical study showing that diflunisal, a nonsteroidal anti-inflammatory drug that binds TTR, reduces mortality by 90 percent among patients with HFpEF. He also noted that a phase II study is assessing tafamidis, another TTR stabilizer that does not have nonsteroidal properties, in older adults.

Council members discussed studies using monoclonal antibodies to remove fibrils as another strategy for TTR-associated cardiac amyloidosis. In response to questions from Dr. Hodes, Dr. Maurer also noted that patients with TTR-associated cardiac amyloidosis are distinct from those with typical HFpEF. Dr. Maurer and Dr. Anne Newman also discussed potential sex differences in the age of onset for TTR-associated cardiac amyloidosis; data from an international register show that the disease penetrates 10 years later among women than among men. In response to questions from Dr. Carrillo about more accessible or easily deployed screening, Dr. Maurer discussed work with a co-PI on a potential blood test followed by ⁹⁹Tc-pyrophosphate scans.

C. Division of Behavioral and Social Research (DBSR): Social Adversity, Immune Regulation, and Aging in Nonhuman Primates

Dr. Jenny Tung, of the Duke Population Research Institute, described two collaborative studies in non-human primates to identify how social adversity gets under the skin. Several studies on millions of individuals have shown that higher levels of social adversity predict negative outcomes with respect to cardiovascular disease and lifespan. However, these findings have raised additional questions, including the relationship between causality and correlation, the origin of the effects of social adversity, and mechanisms relating the experience of social stressors to physiologic outcomes.

One study was conducted on a natural population of 1,800 yellow baboons on the border between Kenya and Tanzania. Collaborative work has studied this population for eight continuous generations. Dr. Tung and her colleagues have found that females born into a poor environment fared worse in fertility in a poor adult environment, compared with those born in a high-quality early environment. They also have found that females born to high-ranking mothers did not suffer these long-term effects. Further examination showed that female baboons exposed to three or more sources of adversity early in life had a shorter median lifespan by an equivalent of 30 human years.

Dr. Tung and her colleagues also have looked at experimental models of social adversity in a captive population of rhesus macaques. Because rhesus macaques inherit dominant strength from their mothers, Dr. Tung and her colleagues can manipulate ranks by altering the introduction of animals into the group. They have also added a secondary manipulation by observing the macaques for 1 year, then introducing different ranks into new social groups. Dr. Tung and her colleagues have found that cell type composition differs by dominance rank and that effects of

dominance rank on gene regulation are specific to cell type. Individuals who moved to a higher rank after a year showed gene expression profiles that followed a plastic pattern. Dr. Tung and her colleagues also observed pervasive interactions between social status and immune stimulation. Genes that are more highly upregulated in low-ranking macaques were heavily enriched for pro-inflammatory factors, whereas those upregulated among high-ranking macaques were enriched for genes that respond to type 1 interferon.

Dr. Tung closed her presentation by noting the work of Dr. Robert Sapolsky on the influence of social hierarchy on primate health. She pointed out that ongoing work in the natural baboon population has led to an appreciation of the importance of a full lifecourse perspective on social adversity. She also noted the potential for genomic techniques in identifying and targeting causality in the influence of social adversity on health, and she suggested that these methods are translatable for comparative research.

Council discussion focused on possible explanations for the social adversity-associated differences in fertility and immune regulation, the potential implications of Dr. Tung's work for human studies on socioenvironmental factors in health, and potential application of Dr. Tung's findings to understanding health disparities.

VII. ADJOURNMENT

The open session of the 131st meeting of the National Advisory Council on Aging adjourned at 12:15 p.m. on May 17, 2017. The next meeting is scheduled for September 26–27, 2017.

VIII. CERTIFICATION

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

Richard J. Hodes, M.D.
Chairman, National Advisory Council on Aging
Director, National Institute on Aging

Prepared by Robin Barr, D. Phil.
With assistance by Rose Li and Associates, Inc.

³ These minutes will be approved formally by Council at the next meeting on September 26-27, 2017, and corrections or notations will be stated in the minutes of that meeting.