

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of the Director

Geroscience

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INTRODUCTION

In its report on the fiscal year (FY) 2023 appropriations bill for the U.S. Department of Health and Human Services (HHS), the House Committee on Appropriations stated the following:

Geroscience. —The Committee applauds the National Institutes of Health (NIH) for recognizing the importance of geroscience to a wide range of chronic conditions and diseases by creating the Cellular Senescence Network (SenNet), an effort to identify and characterize the differences in senescent cells across the body, within the Common Fund. While the National Institute on Aging (NIA) serves as the lead Institute for geroscience, programs such as SenNet demonstrate how all Institutes and Centers (ICs) benefit from a greater understanding of this field, given the wide range of chronic conditions and diseases that are influenced by the biology of aging. To date, however, NIH has not analyzed which topics in geroscience are currently being addressed across the ICs or how much funding the ICs are using to support this research. The lack of this information limits NIH’s ability to address research gaps in a strategic way. Therefore, the Committee encourages NIH to submit a report within 180 days of enactment of this Act that describes current NIH research focused on geroscience and future plans in this area. The Committee would also welcome exploration of a trans-NIH initiative. Such an initiative might include increased funding for basic, translational, and clinical research, research infrastructure, workforce development, the development of platform technologies for geroscience, and collaboration with the FDA, industry, and academia on the discovery and validation of biomarkers. (FY 2023 House Report, pages 144-145)

The following report has been prepared by the National Institutes of Health (NIH), HHS in response to this request.

BACKGROUND

In 2021, more than 55 million Americans were age 65 and older.¹ This number could rise to an estimated 85.7 million in 2050,² representing a demographic shift that will have profound social, economic, and health impacts on our nation for many decades to come. Because the older adult population is growing—and aging is a major risk factor for many devastating disorders and conditions, including Alzheimer’s disease and Alzheimer’s disease-related dementias (AD/ADRD), most forms of cancer, many types of heart disease, osteoporosis and hip fracture, kidney failure, and diabetes—NIH is investing in geroscience research.

The field of geroscience seeks to translate knowledge gained from biology of aging research into methods and interventions to prevent, minimize, or reverse detrimental age-related changes and functional decline in older individuals. By studying what happens during the aging process at the cellular and molecular level, NIH investigators hope to identify interventions to improve the portion of life spent in good health, also known as healthspan, in older adults.

¹ data.census.gov/cedsci/table?q=s0103

² census.gov/content/dam/Census/library/publications/2020/demo/p25-1146.pdf#page=15

The following are examples of programs and activities that illustrate relevant NIH investments in geroscience research and highlights of forthcoming initiatives to expand opportunities for geroscience research.

OVERVIEW OF NIH'S ONGOING GEROSCIENCE RESEARCH ACTIVITIES

NIH-Wide Efforts

Geroscience research is a priority across NIH involving several institutes. While the National Institute on Aging (NIA) leads NIH's aging research portfolio, more than 20 Institutes, Centers, and Offices (ICOs) are actively involved in this field of research. To address the growing interest in geroscience across the ICOs and foster increased collaboration, NIA formed the NIH-wide "Geroscience Interest Group" (GSIG). The GSIG explores research opportunities at the intersection of aging biology and the biology of various diseases to look for ways to support basic, translational, and clinical geroscience research, as well as geroscience research infrastructure, and workforce development. A primary focus of the group is to develop ways to translate basic aging biology research knowledge into effective interventions that improve healthspan and reduce functional deficits in late life. By developing a collaborative framework that includes many ICOs, the GSIG expects to catalyze the development of new tools, models, and paradigms that address the translation of discoveries of the basic biological underpinnings of multiple diseases to clinical interventions. The group meets monthly to discuss updates from researchers in the field, potentially develop research initiatives, plan future geroscience events, and explore the challenges and gaps in the field. An interest identified by many GSIG members is the study of **cellular senescence, a process in which cells lose normal function, including the ability to divide and replicate, but continue to release molecules that may damage neighboring cells.** Cellular senescence is one of the twelve "hallmarks of aging" which have emerged as important molecular, cellular, and systemic contributors to aging and age-related diseases. Understanding the hallmarks of aging, and how they interact across the lifespan and in response to stresses and other perturbations, is anticipated to be important to the development of geroscience interventions.

To further understand senescence, the Cellular Senescence Network (SenNet) was launched as an NIH-wide priority area in 2021 as a program of the Common Fund, a unique resource at NIH through which high-risk, innovative endeavors with the potential for extraordinary impact can be supported. SenNet was developed to identify and characterize how different types of senescent cells affect multiple tissues to impact human health, disease, and lifespan. Though funded through the Common Fund, SenNet has relevance to many ICOs and is an NIH-wide effort managed collaboratively by the Common Fund, NIA, and the National Cancer Institute (NCI). SenNet is currently supporting the following initiatives:³

- **Human Tissue Mapping Centers** – Eight awards to map senescence across the lifespan in 18 solid human tissues and additional human fluids.

³ commonfund.nih.gov/senescence/fundedresearch

- **Murine (mouse and rat) Tissue Mapping Centers** – Five awards to map senescence in 19 solid tissues from multiple mouse strains.
- **Human Technology Development and Application** – Ten awards to develop, demonstrate, and validate new technologies to describe cellular senescence in human tissue.
- **Murine (mouse and rat) Technology Development and Application** – Two awards to develop, demonstrate, and validate new technologies to describe cellular senescence in murine tissue.
- **Consortium Organization and Data Coordination Center** – One award to serve as an organization hub for the SenNet consortium and to store, provide access to, and ensure interoperability and sustainability of the data.

NIH GEROSCIENCE RESEARCH EXAMPLES BY TOPIC AREA

Senolytics and Lifespan Extending Drugs

As a complement to the work of SenNet, NIH ICOs are investing in projects that explore cellular senescence and the mechanisms involved in aging outcomes that could be targets for novel treatments and/or other interventions. This includes the development and use of senolytics, a class of drugs that aim to target and clear senescent cells from the body. Senescent cells are unique in that they eventually stop multiplying, linger, and harm neighboring normal cells. As a result, these cells accumulate with age and can secrete factors that may result in inflammation or other negative impacts on surrounding cells and tissues. A few examples of NIH-funded projects to understand how senolytics may impact age-related conditions are discussed below.

- NIA-funded investigators previously found that treatment with senolytics extended lifespan and healthspan in naturally aging mice. Beyond animal studies, NIA is currently funding trials in humans to test senolytic compounds for the prevention or alleviation of several conditions, including frailty⁴ and sepsis⁵ and to improve skeletal health.⁶
- Identifying targets to prevent the development of epilepsy, also known as epileptogenesis, is another major focus of research in this field. The National Institute of Neurological Disorders and Stroke (NINDS) recently funded studies to understand the contribution of cellular senescence in the development of epilepsy⁷ and targeting cellular senescence to prevent epilepsy.⁸
- Investigators funded by the National Institute of Mental Health (NIMH) are studying the association between circulating molecular senescence markers and depression and cognitive impairment in late life.⁹ The ultimate goal is to identify novel targets for the development of new interventions for depression in older adults.

⁴ reporter.nih.gov/search/AvoKjWb_Zki26UtoOW9Ypw/project-details/10514069

⁵ reporter.nih.gov/search/R48kD19HjkWalri4kD6e5A/project-details/10434283

⁶ reporter.nih.gov/search/IA8AQ4_Fzk-cCTp25PkvLA/project-details/9873557

⁷ reporter.nih.gov/search/m4RzVhQep0WXgfoka9k2aw/project-details/10540532

⁸ reporter.nih.gov/search/m4RzVhQep0WXgfoka9k2aw/project-details/10362263

⁹ reporter.nih.gov/search/bAFTFddknUuBXzFFIpydjA/project-details/10534150

- In response to COVID-19 as an urgent threat to our older adult population, NIA-funded investigators found that the use of the senolytic drug fisetin, a flavonoid or compound found in many fruits and vegetables, suppressed mortality in aged mice infected with a mouse version of COVID-19.¹⁰ To build on these results and explore the translation of this finding to humans, NIA is currently funding a clinical trial to test whether fisetin can improve survival in older COVID-19 patients living in nursing homes.¹¹
- NIA-funded investigators are also studying the mechanisms underlying metformin, a drug commonly used to treat type 2 diabetes that has also been shown to extend lifespan and improve healthspan. For example, scientists are seeking to understand the mechanisms by which metformin produces benefits on longevity with a focus on the drug's effects on the mitochondria,¹² the part of the cell responsible for producing energy. Beyond basic research studies, NIA is also funding clinical trials examining the effects of metformin on delaying or preventing the onset of frailty in older adults that are pre-diabetic¹³ and improving immunological health and vaccine responses in adults 50 to 65 years of age.¹⁴

Proteostasis

Proteostasis, or protein homeostasis is comprised of a complex interconnected network regulating different steps of protein quality control, from production and folding, to degradation. The integrity of this network is essential for cell health and viability. Derailed proteostasis, a known hallmark of aging and a common feature of some diseases, is characterized by the appearance of foreign protein aggregates in various tissues. Examples of currently funded projects in this research area are provided below.

- NIA is funding several studies that explore the role of proteostasis in aging. NIA-funded investigators are examining drosophila (fruit flies) that are genetically altered to be long lived, and characterizing changes in proteins and metabolism to identify fundamental mechanisms in these organisms that may impact aging.¹⁵ Additionally, NIA-supported scientists are studying how metabolic interventions that restore proteostasis in older animals can accelerate recovery after pneumonia,¹⁶ a condition which disproportionately affects older adults.

Measures and Biomarkers of Aging

Identifying and validating novel biomarkers of aging is an ongoing and important challenge for the field of geroscience. Biomarkers of aging can serve as important research tools, but they also can be useful for the clinical development and testing of geroscience-based therapeutics aimed at slowing or reversing age-related hallmarks. Examples of research activities aimed at identifying and validating new measures of biological age are included below.

¹⁰ reporter.nih.gov/search/AIJdCE9wf0-25WvYdmuF2w/project-details/10145445

¹¹ reporter.nih.gov/search/MseI6up7KEuXLQcYIrxJSw/project-details/10208138

¹² reporter.nih.gov/search/n3YHB6EDEk674Dkxua8EZQ/project-details/10432084

¹³ reporter.nih.gov/search/GkT-u7FSFkKgwLzMfEuH2A/project-details/9239985

¹⁴ reporter.nih.gov/search/ExWKJPDnhkm4Pyf4zzwV8g/project-details/9953450

¹⁵ reporter.nih.gov/search/ggHtSJecDU22vlldW74oSA/project-details/10180830

¹⁶ reporter.nih.gov/search/hHjVvco4qkClifjngrgsKg/project-details/10417055

- Biomarkers which can both accurately reflect the activities of fundamental aging mechanisms and reliably predict the future health of individuals are critically needed. NIA is currently supporting several projects to address key stages of research for marker development, including: (1) the discovery of blood- and tissue-based candidate markers through biology of aging studies in animals and humans, (2) methods development (imaging, biological tools, etc.) for measuring the levels of candidate markers and in a high throughput manner, and (3) evaluation of the predictive accuracy/consistency of candidate markers in different human populations (across different age ranges and disease outcomes). One example of an NIA-funded biomarker study is the Comprehensive Evaluation of Aging-Related Clinical Outcomes and Geroproteins (CARGO). This study was designed to develop a test that could predict cardiovascular outcomes, and the research team has already demonstrated that using machine learning to analyze specific patterns of protein levels could be used to predict cardiovascular risk among clinical trial participants.¹⁷
- Identifying early biomarkers of biological aging that are related to cognitive and physical decline and dementia and disability onset in initially healthy older adults is a key step toward geroscience-guided prevention trials. To that end, NINDS is currently funding a study using statistical models to link biomarkers of aging to cognitive and physical decline and dementia.¹⁸
- Epigenetics, an area of research that involves studying how behaviors and the environment can cause changes to genes that affect the way they work, can be used to estimate biological age. This measure of aging is known as an epigenetic clock, and this line of research is beginning to help us understand how accelerated aging can lead to disease. For example, NIA-funded investigators are studying the metabolic regulation of epigenetic clocks.¹⁹ Additionally, NIA is funding a study to examine how accelerated aging as measured by epigenetic clocks may be connected to the accumulation of beta-amyloid (a hallmark of AD) and a greater risk of abnormal cognitive aging in midlife.²⁰
- Investigators funded by the National Institute of Environmental Health Sciences (NIEHS) are identifying early biological responses from environmental exposures that can accelerate brain aging. For example, NIEHS is currently funding a study to measure how air pollution impacts the function of extracellular vesicles, small structures released by cells into the bloodstream that facilitate cell communication and maintenance and may be predictive of future health-related conditions.²¹

Basic Research Studies and Interventions for AD/ADRD and the Aging Brain

The basic biology of aging affects all organ systems in the body, including the brain. Since aging is a major risk factor for many diseases including AD/ADRD, one of the aims of geroscience is to develop better targets for therapeutic interventions through a more complete understanding of the cellular and molecular mechanisms that underlie aging and the onset of

¹⁷ pubmed.ncbi.nlm.nih.gov/35385337/

¹⁸ reporter.nih.gov/project-details/10513438

¹⁹ reporter.nih.gov/search/xq63uEBTjkWpTmZfc4hmAQ/project-details/10543439

²⁰ reporter.nih.gov/search/LcGL-QqyjKSSnU7KwpSW8w/project-details/9800440

²¹ reporter.nih.gov/search/xNDPdXAQ5EOhFW1ygTo4lg/project-details/10445081

disease. The projects described below aim to identify the mechanisms underlying aging and whether interventions that modify the rate of aging can effectively modulate the incidence and progression of AD/ADRD.

- Geroscience examines the relationship between biological aging and age-related diseases through multiple processes. These processes are highly integrated with one another such that targeting them as a group may be an effective approach to developing therapies to prevent or delay age-related disease. Several NIA-funded investigators are using this approach of targeting multiple processes to modulate the progression of AD. For example, investigators are examining whether the use of rapamycin, acarbose, and phenylbutyrate, drugs that target multiple aging processes associated with Alzheimer's disease, can alleviate cognitive dysfunction in an aging AD mouse model.²² Another research group is studying the use of genetic and pharmacological interventions to potentially delay the onset and progression of neurodegeneration in fly and mouse models of AD.²³ Additionally, investigators are using calorie restriction and rapamycin treatment,²⁴ two methods known to extend lifespan and slow the rate of biological aging, in a mouse model of AD to determine whether these treatments may delay neurodegeneration and cognitive impairment. NIA is also funding investigators to develop pre-clinical therapeutics targeting fundamental mechanisms of aging, including inflammation, cell senescence, and proteostasis.
- NIA- and NINDS-funded investigators are studying age-related mechanisms contributing to vulnerability and resilience to AD/ADRD, including the role of senescence and the contributions of glia (a type of brain cell), lipids, and cells that make up the blood brain barrier in brain aging and AD/ADRD.
- Eye researchers have been collaborating with AD experts to identify ocular (eye) biomarkers for diagnosis and to monitor disease progression. Moreover, the National Eye Institute (NEI) funds a portfolio of grants examining links between eye disease and AD. An ongoing study of glaucoma examines whether there are mechanistic similarities in damage done by protein aggregation in glaucoma and AD, as well as other diseases.²⁵ Another investigator is studying the influence of the mitochondria on gene expression and is seeking to identify interventions that can reduce damage associated with aging in age-related macular degeneration and AD.²⁶

Longitudinal Studies

Tremendous gains in life expectancy and health at older ages have led to the overall aging of the population in the United States and elsewhere in the world. This shift has significant scientific and societal implications, with aging itself representing the most significant risk factor for many chronic diseases and conditions, including AD/ADRD. NIH is conducting and supporting large, long-term longitudinal studies to understand what biological mechanisms are related to different aspects of aging, including the decline of physical function and mobility in animal models and humans. A few examples of projects in this area of research are discussed below.

²² reporter.nih.gov/search/KraAmbAbEkqaOzSiV1dxYQ/project-details/10383741

²³ reporter.nih.gov/search/_MUjlp0C0EKfPbYyJuHH5A/project-details/10375432

²⁴ reporter.nih.gov/search/2E7Gxwwd8E-Yze9Z5tDAgw/project-details/10418637

²⁵ reporter.nih.gov/search/_6oGaA-eVEasQpDfDYuVXQ/project-details/10160908

²⁶ reporter.nih.gov/search/mgk9bER9aEKGclXbetkYzg/project-details/10433610

- One obstacle in translational research is identifying animal models that can be directly compared to human aging studies of health and disease. To address this challenge, NIA researchers are currently running the first mouse longitudinal cohort study to examine common metrics of aging across the entire lifespan in various mouse models, known as the Study of Longitudinal Aging in Mice (SLAM).²⁷ Researchers are seeking to identify and characterize predictors of mouse aging and age-associated conditions and assess whether these changes are consistent with alterations observed in human aging. For example, similar to observations found in humans, SLAM researchers demonstrated that a decline in walking speed was associated with functional decline in mice.²⁸
- Additionally, NIA is running a longitudinal study of rats that closely tracks the animals throughout their life called Successful Trajectories of Aging: Reserve and Resilience in Rats (STARRRS).²⁹ Launched in 2019, STARRRS will help researchers better understand why differences in cognitive decline or resilience occur among individuals by providing longitudinal, lifespan data from a well-defined model of neurocognitive aging in rats.
- In addition to longitudinal animal studies, NIA developed the trailblazing Baltimore Longitudinal Study of Aging (BLSA),³⁰ which explores the determinants and measures of healthy biological aging over time and is the nation's longest running scientific study of human aging. BLSA scientists recently published a new measurement of aging that is highly predictive of changes in health as well as in physical and cognitive functions. Researchers can use this new metric to identify novel biological mechanisms of aging that could be targeted for interventions to increase healthy aging.³¹ Another NIA-funded longitudinal cohort study is the Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing (GESTALT) study,³² which is aimed at discovering biomarkers and their connections to aging and the development of physical and cognitive disability. One outcome of the ongoing GESTALT study is helping to inform mechanisms of wound healing in older adults. Researchers examined the expression of various senescence-associated biomarkers during human wound healing. They found that p21 and p53 (senescence-associated biomarkers) increased during healing in younger, but not in older participants, providing a potential molecular clue for mechanisms involved in poor wound healing in the older adult population.³³
- The NIA-funded Health and Retirement Study (HRS) is NIA's largest longitudinal survey of a nationally representative sample of the U.S. population aged 50 and older. The HRS and its family of internationally comparable studies, provide publicly available, harmonized, multi-disciplinary longitudinal data on aging and the health and well-being of the older population, with dedicated sub-studies focused on cognitive aging and dementia. Using HRS data, researchers have established that a significant portion of the variance in late life morbidity and mortality is explained by behavioral and social exposures, after controlling for measures of biological age. Additionally, scientists have

²⁷ reporter.nih.gov/search/3pt7CI96QUSbTqrbyldUGA/project-details/10473349

²⁸ <https://pubmed.ncbi.nlm.nih.gov/33876723/>

²⁹ nia.nih.gov/research/labs/about-irp/successful-trajectories-of-aging-reserve-and-resilience-in-rats

³⁰ nia.nih.gov/research/labs/blsa

³¹ nature.com/articles/s43587-022-00243-7

³² alzheimers.gov/clinical-trials/genetic-and-epigenetic-signatures-translational-aging-laboratory-testing

³³ ncbi.nlm.nih.gov/pmc/articles/PMC8135007/

developed biomarkers related to chronic diseases and aging and physical performance measures. The HRS is currently in the field collecting a second round of biomarker data which should clarify the longitudinal relationships between changes in aging-related biomarkers and important outcomes including cognitive impairment, change in function, and mortality.

- Two NIH-funded research networks provide support for population-based studies seeking to integrate measures of biological aging and biological risk into ongoing longitudinal population-based studies. These include:
 - The Telomere Research Network,³⁴ an NIA- and NIEHS-sponsored network dedicated to facilitating the collaboration between biologists who study telomeres (repetitive DNA sequences at the end of a chromosome that are important for cell aging), population and exposure researchers, and other scientists across disciplines to advance interdisciplinary research on telomeres as sentinels of environment exposure, psychosocial stress, and disease susceptibility. Its goals include examining the value of telomeres as an integrative marker, either alone or in combination with other markers, and through a deeper understanding of telomere dynamics. This includes consideration of what is the most important set of tests for determining premature biological aging in healthy humans. Network members have published several methodological papers on the use of telomere length as a biomarker of human aging. These findings inform best practices in the field as work continues to better understand telomere changes across the lifespan.
 - The NIA Biomarker Network³⁵ supports an interdisciplinary group of scientists dedicated to improved measurement of biological risk for late life health outcomes in large representative samples of populations. Its aims include: (1) harmonizing molecular biomarkers of health and aging over the life course, (2) exploring emerging geroscience biomarkers for potential application in large representative studies of aging, including biomarkers of AD/ADRD, (3) examining biomarkers of environmental exposures (e.g., pollution, toxicants, severe weather), and (4) increasing representation of biosocial data and scholars from underrepresented populations. Findings from the Biomarker Network have added to our understanding of factors that contribute to both life expectancy and healthspan. For example, Network researchers studied how biological aging (the pace at which the body ages), relative to chronological age (the number of years a person is alive), changed in the United States between 1988 and 2010.³⁶ Their results suggested that biological age was lower compared to chronological age for more recent periods; however, decreases in biological age (relative to chronological age) varied across age and sex groups. These differences were partially explained by age- and sex-specific changes in behaviors, such as smoking, obesity, and medication use. Identifying modifiable risk factors that affect the rate of aging can inform intervention and prevention studies aimed at improving health outcomes.

³⁴ reporter.nih.gov/search/3eONYc2ZFEqL5U24MixAXg/project-details/10421390

³⁵ reporter.nih.gov/search/DLHpmiaMB0qVE4OgRZhGmg/project-details/10436475

³⁶ pubmed.ncbi.nlm.nih.gov/29511995/

- Long-term clinical studies also provide opportunities for investigators funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to study older adult populations with chronic disease and determine the long-term effects of interventions on aging and aging-related outcomes. For example, NIDDK’s ongoing Epidemiology of Diabetes Interventions and Complications (EDIC)³⁷ study has been following a cohort of people with type 1 diabetes for over 30 years, facilitating study of the impact of the disease in older adults on the development and progression of aging-related complications and morbidity. Notably, EDIC researchers have shown that, for people with type 1 diabetes, there are long-term benefits of a period of early and intensive diabetes therapy on future development of cardiovascular, eye, kidney, and nerve complications, and that this early and intensive treatment also lengthens life.³⁸ Additionally, NIDDK’s Diabetes Prevention Program Outcomes Study (DPPOS) demonstrated that for people with high risk of diabetes at an average age of 50, an intensive lifestyle intervention comprised of both weight loss and a physical activity goal may reduce frailty later in life (12-14 years later).³⁹ The DPPOS continues to follow study participants and beginning in 2022, in collaboration with NIA, is determining the long-term effects of a diabetes intervention on aging-related outcomes and evaluating predictors of long-term healthy aging.⁴⁰
- Longitudinal cohorts of cancer survivors funded by NCI allow investigators to examine alterations in the trajectory of normal aging after a diagnosis of and treatment for cancer. For example, the Women’s Health Initiative-Life and Longevity After Cancer (WHI-LILAC) cohort,⁴¹ which has been funded by NCI since 2013, is following women diagnosed with cancer to understand the effect of a diagnosis of cancer and its treatment on the trajectories of functional aging, the accelerated aging phenotype, and age-related comorbidities, compared to age-matched WHI participants with similar data who have remained cancer free. In a recently published manuscript from the WHI-LILAC cohort, researchers showed that cancer survivors experienced accelerated declines in physical function after diagnosis, and that physical function remained below that of age-matched women without a history of cancer even years later.⁴² Additionally, the NCI-funded St. Jude Lifetime study⁴³ has established a cohort of childhood cancer survivors to facilitate longitudinal clinical evaluation of both cancer- and aging-related health outcomes in aging adults who have survived pediatric cancer. Numerous geroscience-related St. Jude Lifetime study manuscripts have been published; for example, St. Jude investigators examined the incidence of chronic health conditions (i.e., cardiovascular, musculoskeletal, and pulmonary conditions) among childhood cancer survivors. By age 50, researchers reported that the St. Jude cancer survivor had experienced, on average, 17.1 chronic health conditions compared to 9.2 in the community controls. These findings demonstrate a high burden of long-term chronic health conditions in this cancer

³⁷ repository.niddk.nih.gov/studies/edic/

³⁸ niddk.nih.gov/about-niddk/research-areas/diabetes/blood-glucose-control-studies-type-1-diabetes-dcct-edic

³⁹ pubmed.ncbi.nlm.nih.gov/33428709/

⁴⁰ reporter.nih.gov/search/cwKO4ggKGkygTHq5aIBxcw/project-details/10507628#history

⁴¹ reporter.nih.gov/project-details/10479977

⁴² pubmed.ncbi.nlm.nih.gov/36656572/

⁴³ reporter.nih.gov/project-details/10428471

survivor population and inform future work to better understand the interplay between cancer and aging.⁴⁴

- Developing national surveys with measures to better assess healthy aging are important to understanding the needs of the older adult population and risks to this group. It is vital that relevant measures be added to national surveys so that more accurate estimates can be obtained on risks to the U.S. older adult population, including those concerning malnutrition and frailty. The NIH Office of Dietary Supplements (ODS) submitted a successful proposal to have content added to the Centers for Medicare and Medicaid Services' (CMS) Medicare Current Beneficiary Survey (MCBS),⁴⁵ a nationally representative survey that collects health and Medicare claims data from participants multiple times per year for up to four years. MCBS accepted a proposal from ODS to add measured height and weight, grip strength and questions on unintentional weight loss, appetite loss and dietary supplement use. Additionally measures of aging, including tests of timed walking, sit to stand, and balance have been added to MCBS.

Next Generation Models and Resources

The primary goal of the field of geroscience is to identify, test, and develop interventions that slow the rate of aging and prevent disease and disability in humans; however, it is important to have a variety of model systems on hand to carry out preclinical geroscience research. The projects below describe a few of NIH's efforts to develop both animal and non-animal model systems that will inform the field of geroscience.

Non-animal studies:

- The Tissue Chip for Drug Screening program,⁴⁶ supported by the National Center for Advancing Translational Sciences (NCATS), is developing human tissue chips that accurately model the structure and function of human organs to help predict drug safety more rapidly and effectively. Multiple tissue chips have been developed that model the effects of aging and allow researchers to better understand the genetic, molecular, and cellular mechanisms that underly the process of aging. For example, the Tissue Chips in Space program,⁴⁷ which is a partnership between NCATS, the National Aeronautics and Space Administration (NASA), and the Center for Advancement of Science in Space, was created to send tissue chips to the International Space Station to study the effects of the microgravity environment on the human body and gain insights into the mechanisms controlling age-related dysfunction. Findings from that program have expanded the current understanding of age-related conditions and may contribute to drug development that can slow the process of aging and lead to new interventions to improve human health.
- Neuroinflammation and neurotoxicity associated with human immunodeficiency virus (HIV)-1 is known to lead to cognitive impairments called HIV-1-associated neurocognitive disorders or HAND. As people living with HIV-1 age, a compounding effect occurs, with age-associated dementia added to HAND, leading to a complex web of neurocognitive deficit. To study this effect, investigators funded by the National

⁴⁴ pubmed.ncbi.nlm.nih.gov/28890157/

⁴⁵ cms.gov/research-statistics-data-and-systems/research/mcbs

⁴⁶ ncats.nih.gov/tissuechip/about

⁴⁷ ncats.nih.gov/tissuechip/projects/space

Institute on Drug Abuse (NIDA) are developing brain organoids that mimic the human brain to examine the impact of HIV-1, drugs of abuse, and aging on cognitive impairment.⁴⁸

Animal studies:

- As the human population shifts to a higher proportion of older individuals, it is critical to develop appropriate animal models to test interventional methods to maintain human health and to systemically treat age-related disease. NIH is supporting the development of several animal models of aging. This includes the NIA-funded San Antonio Marmoset Aging Program to study the effect of aging interventions on marmosets,⁴⁹ an animal model for geroscience. The National Institute of Dental and Craniofacial Research (NIDCR) is also funding a study to develop marmosets as a model of oral health aging.⁵⁰ Other investigators funded by NEI are developing animal models of aging in the eye that can be used to study the mechanisms of senescence. Additionally, the National Institute of Allergy and Infectious Diseases (NIAID) Radiation and Nuclear Countermeasures Program (RNCP) is investing in the development of geriatric animal models to better understand how older individuals might respond differently to radiation exposure, from both an immunity and frailty standpoint.

FUTURE OPPORTUNITIES FOR GEROSCIENCE RESEARCH

To continue robust support for geroscience research, NIH is launching new funding opportunities and expanding and renewing previously successful funding opportunities for researchers. To drive additional geroscience research in specific topic areas, funding opportunities that are active or upcoming include, but are not limited to:

Molecular Mechanisms of Aging

- Interorgan Communication in Aging⁵¹ supports the development of projects examining molecular mechanisms and consequences of age-related alterations in interorgan communication. This funding opportunity launched by NIA in May 2023 was open until June 2023.
- Complex Integrated Multi-Component Projects in Aging Research⁵² seeks large-scale research projects preferably with a multidisciplinary team of investigators to focus on a common research question relevant to aging. This funding opportunity launched by NIA in December 2022 will be open until September 2025.
- Identifying Innovative Mechanisms or Interventions that Target Multimorbidity and Its Consequences⁵³ invites projects designed to investigate shared mechanisms and the development of innovative interventions to address multimorbidity or multiple chronic conditions and its consequences. This funding opportunity launched by ODP, NCI, NIA,

⁴⁸ reporter.nih.gov/search/NRq9nnu6O0-TSobyI6xqSg/project-details/10398244

⁴⁹ reporter.nih.gov/search/6AqgVMp45Uy3I58nmfJFsA/project-details/10441593

⁵⁰ reporter.nih.gov/search/9dMCBcSkWE60FBJTJ0itmA/project-details/9783771

⁵¹ grants.nih.gov/grants/guide/rfa-files/RFA-AG-24-005.html

⁵² grants.nih.gov/grants/guide/pa-files/PAR-22-213.html

⁵³ grants.nih.gov/grants/guide/pa-files/PAR-20-180.html

NIDCD, NIDA, NIMH, NIMHD, NINR, NCCIH, ORWH, NICHD, OBSSR in September 2020 will be open until January 2024.

Immune System and Aging

- Immunity in Older Adults⁵⁴ supports the development of projects that provide mechanistic insights into innate and adaptive immune changes that occur during the aging process. This funding opportunity launched by NIAID, NIA, NIDCR, and ORWH in January 2023 was open until February 2023.

Exposures and Geroscience

- Using Telomere Status to Reveal Molecular Mechanisms Underlying Susceptibility and Resiliency in Response to Environmental Exposures⁵⁵ seeks projects investigating the effect of environmental exposures on telomeres and its potential impact on the early onset of age-related diseases. This funding opportunity launched by NIEHS in January 2023 was open until February 2023.
- Research Coordinating Center on the Exposome and AD/ABDRD⁵⁶ invites applications that propose establishing a national coordinating center to foster collaboration and accelerate life course research on the social, behavioral, psychological, and economic exposures that shape AD/ABDRD outcomes and inequities. This funding opportunity launched by NIA will be open from August 2023 to September 2023.
- Alcohol and Aging⁵⁷ supports the development of projects that improve our understanding of the effects of alcohol consumption on aging across different levels of biological organization including the molecular, cellular, tissue, organ, organism, and societal levels. This funding opportunity launched by NIAAA in October 2020 will be open until September 2023.

Animal Models

- Comparative Research on Determinants of Differences Among Human and Nonhuman Primate Species in Life Spans, Life Histories, and Other Aging-Related Outcomes, and Prospects for Translation⁵⁸ seeks projects proposing comparative studies of human and nonhuman primate species with differing life spans to identify factors that may contribute to differences in species life span and healthspan. This funding opportunity launched by NIA will be open from August 2023 to September 2023.

Geroscience Research in Specific Diseases

Alzheimer's Disease and the Aging Brain

- Understanding Alzheimer's Disease in the Context of the Aging Brain⁵⁹ invites projects that aim to establish the role and underlying mechanisms by which brain aging impacts

⁵⁴ grants.nih.gov/grants/guide/rfa-files/RFA-AI-22-060.html

⁵⁵ grants.nih.gov/grants/guide/rfa-files/RFA-ES-22-007.html

⁵⁶ grants.nih.gov/grants/guide/rfa-files/RFA-AG-24-011.html

⁵⁷ grants.nih.gov/grants/guide/notice-files/NOT-AA-20-019.html

⁵⁸ grants.nih.gov/grants/guide/rfa-files/RFA-AG-24-019.html

⁵⁹ grants.nih.gov/grants/guide/notice-files/NOT-AG-21-039.html

the development and progression of AD. This funding opportunity launched by NIA and NINDS in March 2022 will be open until November 2024.

Cancer

- Understanding the effects of cancer and cancer treatment on aging trajectories and aging outcomes⁶⁰ supports the development of projects that aim to better understand how cancer diagnosis and subsequent cancer treatment impact aging. This funding opportunity launched by NCI and NIA in March 2021 will be open until January 2024.

HIV

- The Catalyst Award for Early Stage Investigators (ESIs) Pursuing Research on HIV Comorbidities, Coinfections, and Complications⁶¹ seeks projects examining high-priority topics including immune activation and chronic inflammation, effects of the microbiome and virome on HIV-associated comorbidities, coinfections, and complications, as well as aging and immunosenescence. This funding opportunity launched by NIDDK, NHLBI, NICHD, and NCI in April 2023 will be open until May 2025.

PLANNED GEROSCIENCE ACTIVITIES AND TRAINING

NIH is sponsoring several upcoming activities that will inform ongoing and future geroscience research priorities. In April 2023, NIA held its fourth Geroscience Summit⁶² to discuss research gaps and opportunities related to disparities in aging, as well as multimorbidity (the co-occurrence of two or more chronic conditions in the same individual) and geriatric syndromes (common health issues observed in older individuals that do not fall into discrete disease categories), two pressing issues facing geriatricians and their patients. In May 2023, NIA, NIAID, and NIDCR hosted a workshop on Advances in Aging, Immunosenescence, and Chronic Inflammatory Disease.⁶³ It focused on recent advances in immunosenescence, aging, and their impact on chronic disease development. These workshops and other meetings to gather expert input will help set the stage for identifying vital future directions in geroscience research.

Along with workshops, NIH supports several training programs to bring in the next generation of geroscientists. To do so requires supporting career pathways for researchers that are knowledgeable in the aspects of the biology of aging, but also have expertise in the translational and clinical approaches needed to bring geroscience findings into the clinic. NIA is currently supporting Ruth L. Kirschstein National Research Service Awards (NRSA) for geroscience training at several institutions, including the University of Southern California,⁶⁴ the University of Oklahoma Health Sciences Center,⁶⁵ the University of Washington,⁶⁶ and the University of Texas Health Science Center.⁶⁷ Additionally, NIA is supporting an Academic Leadership Career

⁶⁰ grants.nih.gov/grants/guide/notice-files/NOT-CA-21-031.html

⁶¹ grants.nih.gov/grants/guide/pa-files/PAR-23-024.html

⁶² nia.nih.gov/2023-fourth-geroscience-summit#about

⁶³ nia.nih.gov/news/workshop-advances-aging-immunosenescence-and-chronic-inflammatory-disease

⁶⁴ reporter.nih.gov/search/d3-VKxAamESSf4757e1low/project-details/10393601

⁶⁵ reporter.nih.gov/search/emY5bzjcgEC9HgHoVoKHFA/project-details/10411717

⁶⁶ reporter.nih.gov/search/UpliAFhpJUia21q39g9nig/project-details/10407664

⁶⁷ reporter.nih.gov/search/BWA0doL_4UOosJXAp8yYjw/project-details/10427178

Award⁶⁸ to assist with geroscience investigator faculty development and research at the University at Buffalo. Moreover, NCI is advancing geroscience education through the Perspectives on Cancer and Aging webinar series⁶⁹ that aims to build a research community at the intersection of aging and cancer and to provide a platform to disseminate cancer and aging research. To help foster more training opportunities, NIA also released a funding opportunity to support educational activities with a primary focus on the development and integration of basic, applied, translational, and clinical topics in geroscience.⁷⁰

CONCLUSION

The ultimate goal of geroscience is to translate knowledge about the basic mechanisms driving aging into clinical interventions that improve the quality of life for older people. Toward that goal, some of NIH's efforts with geroscience—from studying aging at the genetic, molecular, and cellular levels, to identifying and testing geroscience interventions, to launching SenNet, an NIH-wide initiative to identify and characterize senescent cells across the body, to training the next generation of aging researchers—demonstrates NIH's commitment to furthering the field of geroscience. NIH will continue to support research on geroscience to advance discovery with the goal of slowing the rate of aging to improve healthspan.

⁶⁸ reporter.nih.gov/search/nokffltM9kCEtqMsRdMbSQ/project-details/10349503

⁶⁹ cancercontrol.cancer.gov/brp/bbpsb/aging-and-cancer/perspectives-cancer-aging-webinar-series

⁷⁰ grants.nih.gov/grants/guide/pa-files/PAR-22-214.html

APPENDIX A: GLOSSARY OF ACRONYMS

AD/ADRD	Alzheimer’s disease and Alzheimer’s disease-related dementias
BLSA	Baltimore Longitudinal Study of Aging
CARGO	Comprehensive Evaluation of Aging-Related Clinical Outcomes and Geroproteins
CMS	Centers for Medicare and Medicaid Services
DPPOS	Diabetes Prevention Program Observational Study
EDIC	Epidemiology of Diabetes Interventions and Complications
ESI	Early Stage Investigators
FY	Fiscal Year
GESTALT	Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing
GSIG	Geroscience Interest Group
HHS	Health and Human Services
HIV	Human immunodeficiency virus
HRS	Health and Retirement Study
ICOs	Institutes, Centers, and Offices
MCBS	Medicare Current Beneficiary Survey
NASA	National Aeronautics and Space Administration
NCATS	National Center for Advancing Translational Sciences
NCCIH	National Center for Complementary and Integrative Health
NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIA	National Institute on Aging
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIDA	National Institute on Drug Abuse
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
NIMHD	National Institute on Minority Health and Health Disparities
NINDS	National Institute on Neurological Disorders and Stroke
NINR	National Institute of Nursing Research
NRSA	National Research Service Award
OBSSR	Office of Behavioral and Social Sciences Research
ODP	Office of Disease Prevention
ODS	Office of Dietary Supplements
ORWH	Office of Research on Women’s Health
RNCP	Radiation and Nuclear Countermeasures Program
SenNet	Cellular Senescence Network
SLAM	Study of Longitudinal Aging in Mice
STARRRS	Successful Trajectories of Aging: Reserve and Resilience in Rats
WHI-LILAC	Women’s Health Initiative–Life and Longevity After Cancer