White Paper on a National Investment in Geroscience

Defining a National Research Vision Utilizing the Biology of Aging to Optimize Human Performance, Healthspan and Lifespan

Prepared for the Consensus Symposium

Organized by the

National Institute on Aging
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Abstract

Over the past decade, teams of researchers from institutions around the world have examined the relationship between aging, disease and function. They have worked to validate the hypothesis that the biological mechanisms of aging are central to the pathogenesis of most chronic diseases and that therapeutics targeting the biology of aging are feasible. The name of this relatively new field of scientific inquiry is geroscience and its goal is to identify therapies that will simultaneously halt, slow or treat the major, chronic diseases of aging.

Recent research has produced some remarkable demonstrations of modulated aging in model organisms and elucidated a number of pathways relevant to aging that are conserved across species, marking them as promising targets for intervention. First generation geroscience therapeutics, including metformin, rapamycin NAD agents and senolytics are currently undergoing clinical trials and novel, age-modulating compounds targeting the hallmarks of aging are in development.

The objective of this White Paper, and the consensus symposium that accompanies it, is to develop and solicit community feedback on a model, national science and technology initiative designed to rapidly advance the scientific understanding, regulatory framework and workforce engagement necessary to translate the promise of emerging geroscience research into the reality of clinical care in the United States. A comparable effort is already well defined in the United Kingdom and the success of such an initiative in this country holds profound implications for healthcare quality and cost and the well-being of our aging population.

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Section 1: Introduction and Background

Introduction

The signs of aging are easily recognizable. With sufficient time, the aging process will inevitably yield weakened muscles, greying hair, wrinkled skin, joint pain, blunted senses, failing organs and an exponentially increasing mortality rate. Aging has been a topic of fascination and investigation for centuries, but it has only been in the last three decades that science has begun to offer concrete answers to the question: "What is aging?" Scientific research is shedding light on the root causes of biological aging and its fundamental elements to determine whether the underlying processes can be slowed down or even reversed through behavioral and pharmacological intervention. The geroscience hypothesis, formally proposed in 2007 states that since "aging physiology plays a major role in many — if not all — chronic diseases, therapeutically addressing aging physiology could directly prevent or mitigate multiple chronic diseases."[*Kennedy]*

The ability to "therapeutically modify" aging has profound implications for the quality of life of the aging population of the United States. By the middle of the 20th century in the U.S., antibiotics, vaccines and public health initiatives had facilitated a shift in disease burden from acute to chronic conditions.[MMWR] Today Today, all five of the major causes of U.S. mortality- heart disease, cancer, stroke, pulmonary disease and dementia- are chronic conditions in which aging is the major risk factor. The COVID pandemic has also highlighted the vulnerability of aging individuals with dysfunctional immune systems to novel pathogens. [Rodrigues]

Analysis of the aging population in the U.S. necessarily involves large, intersecting, multivariate distributions.[Kirkwood] The causal relations and feedback loops among variables in the field of aging research are particularly complex, making analysis of past events, and prediction of future states, a daunting task. The challenges inherent in such complexities are well outlined in Judea Pearl's "The Book of Why", thus, the analysis and projections underlying the recommendations in this White Paper should be considered in light of such complexities.[Peal]

The Problem: Healthcare, Healthspan, Age-Related Decline and the Health Gap

The practice of healthcare in the United States is, conceptually and practically, organized around the treatment of individual diseases. Drugs, the principal therapeutic modality, are defined by the Food and Drug Administration as "A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease."[FDA Drugs] Medical diagnosis is accomplished through an analysis of the dysfunction produced by disease and other conditions and the interpretation of pathognomonic signs and symptoms in affected organ systems. Medical specialties are named by organ system (GI, Pulmonary, Neurology, etc.). The practice of geriatrics and pediatrics are bounded by chronologic age, but the approach taken by those practitioners is still based on this conceptual framework.

Current public health challenges in the United States, on the other hand, are defined by age-related decline, which encompasses a range of diseases, conditions and alterations in function. Those who experience age-related decline are often impacted, simultaneously, by multiple diseases, along with declining strength, failing senses and decreased resiliency. One of the concepts used with increasing frequency in both the geroscience and general literature relative to the impact of age-related decline is "healthspan". Healthspan is highly intuitive concept broadly perceived as a critical foundation for quality of life but, from a public health perspective, it is extremely difficult to define and measure.[Olshanksy] A common definition provided by Kaeberlein is that "*healthspan is the period of life spent in good health, free from the chronic diseases and disabilities of aging*."[Kaeberlein] This implies that healthspan may be measured as a linear period of time from birth to the onset of age-related decline. In this paper, we refer to the duration between healthspan and lifespan as the "healthgap", which we identify it as the primary challenge presented by the aging population. Some interventions have been proposed to increase healthspan without increasing lifespan, thereby narrowing the healthgap, while others may increase lifespan without increasing healthspan to a proportional or greater extent, effectively widening the gap. Measuring when healthspan effectively ends and age-related decline begins is extremely difficult, however, there is good evidence that the overall U.S. population is aging and there are some indications that, for certain groups in the U.S., the healthgap is actually increasing.

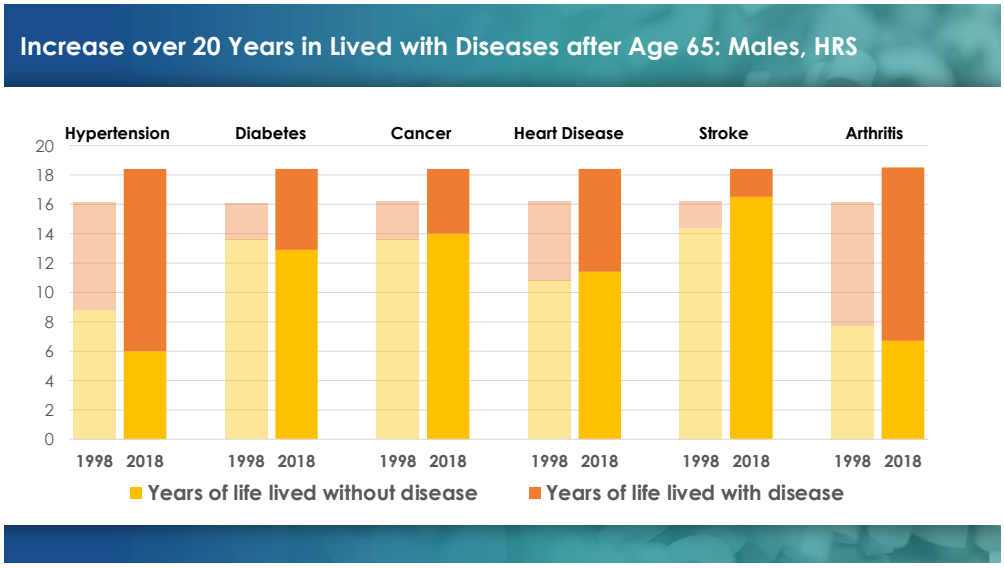

Figure 1. Illustrates the increase over a 20 year period in the overall period of time that men over 65 in the U.S. lived with disease. (E. Crimmons, PAA Presidential Address 2021)

Changing demographics alone make the healthgap in the U.S. a pressing challenge that profoundly impacts individuals, families, communities and the nation. The financial cost of providing health and personal care to those impacted by age-related decline is significant and, too often, the methods used to extend life, have an unacceptable impact on its quality. Treating age-related conditions and providing the support necessary for independent living to an aging population, already incurs high individual and social costs. By all accounts, these are expected to increase.

To present one example, as the aging population grows, age-related rates of Alzheimer's disease grow with it. Over the next 40 years, dementia-related costs to Medicare and Medicaid alone are projected to total $20 trillion in constant dollars, rising to over $1 trillion per year by 2050. [Report of the Alzheimer's Strategic Group]

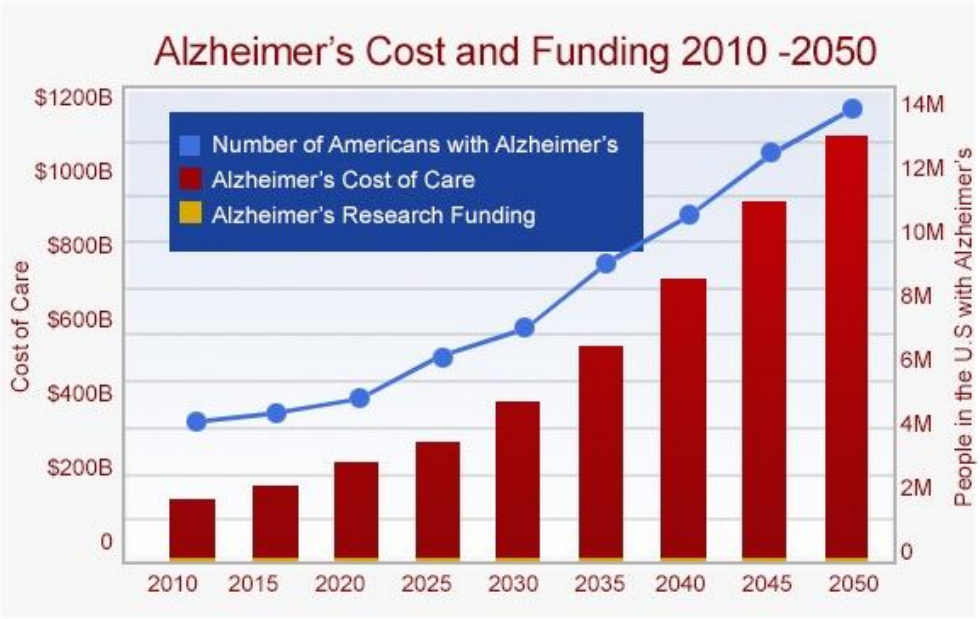

Figure 2. Cost of Alzheimer's dementia care, a single component of age-related decline

At the national level, there is significant ongoing investment in biomedical research aimed at finding cures for the major diseases of aging. In aggregate, such investments run into the tens of billions of dollars. Unfortunately, even if successful, these efforts will likely translate into relatively small gains in either healthspan or lifespan. A cure for cancer, for example, may be expected to increase average life expectancy in the U.S. by only about 3 years, since the rates of other diseases of aging, such as cardiovascular disease, respiratory disease and dementia, may be expected to increase as a result.

Poverty and racial inequality have also been linked to both decreased healthspan and lifespan. According to Crimmins et al, being poor lowers life expectancy by about 20 years and there is evidence that people who are poorer, and less educated experience earlier onset age-related decline, including loss of function, physical impairment and disease onset.[Crimmins] Hayward and his colleagues have found people with lower socioeconomic status experience disease onset 5–10 years earlier. Race and racial disparities are relevant demographic factors.[Hayward] There is substantial evidence of an accelerating wealth gap in the U.S. between African American and Latino families and their white counterparts. Moreover, much of the projected increase in the population age 65 and older in the next few decades will be composed of racial and ethnic minorities. In 2015, about 22% of those over 65 were members of minority groups, by 2050 the percentage is projected to increase to 39%. [2019 Profile of Older Americans]

The Solution: Geroscience, a Strategy for Increasing Healthspan, Improving Quality of Life and Reducing Healthcare Costs.

Different people experience aging differently, based on genetics, lifestyle and exposure. It is currently believed, however, that individual expressions of aging reflect a universal set of interlinked processes that lead to a diminished capacity for repair and renewal in the face of accumulated damage. Although it may be considered a part of "normal" growth and development, aging accelerates the rate at which multiple diseases progress. Therapeutically modulating the aging process, or set of processes, could simultaneously impact the onset of multiple diseases.[Siera] A single intervention, for example the effective removal of senescent cells, might concurrently slow the progression of arthritis, cardiovascular disease, and cancer. Alternatively, combinations of therapies might be used to address the specific expression and rate of aging in an individual patient. In this manner, therapeutically modifying the relationship between aging, disease and the individual patient, may prove to be the ultimate exemplar of personalized medicine.

From the perspective of public health, the changing demographics in the United States, together with the racial wealth gap, mean that in the near future seniors seeking health and long-term care will more likely be from racial or ethnic minorities and, consequently, have less ability to locate, or pay, for such care. A successful geroscience initiative to therapeutically modulate aging may be expected to achieve higher efficacy rates in poor and minority groups, based on the contribution to disparity made by accelerated aging in these communities. However, to truly facilitate health equity, such an investment would need to result in overall improvements in the Slope Index of Inequality and the Relative Index of Inequality (mean and ratio) between disadvantaged groups and the general population.[Wagstaff] Effective translation, communication and delivery strategies are critical to that outcome. Other vulnerable populations would also benefit from a national investment in geroscience. Aging with a disability has also been linked to earlier onset of disease (*e.g.,* metabolic syndrome, arthritis, cardiovascular disease, diabetes, *etc.*) and mortality and substantial resources are currently being dedicated to disease prevention and care delivery at veteran and military treatment facilities, particularly for veterans with war-related spinal cord injury or traumatic amputation. A strategy for addressing the biological and physiological underpinning of aging could be critical to establishing targeted and cost-effective interventions for these groups.

Geroscience: The State of the Science

A number of avenues are currently being pursued in the field of aging research to address the problem of age-related decline. The fundamental question "What is aging?" has produced a number of working hypotheses including: aging as damage accumulation, aging as epigenetic information loss, and aging as an integral component of growth and development, to name only a few.[Kennedy] This section provides a brief overview of the state of the science and details some of the specific therapeutic modalities that are emerging.

The Hallmarks of Aging

The conceptual framework for the field is provided by the so-called “hallmarks” or “pillars” of aging, defined as “*commonalities to all age-related variation”.* The original list of “hallmarks”, identified over a decade ago,[López-Otín] was not intended to be comprehensive but is comprised of a number of interdependent processes sharing the following characteristics:

i. *Should manifest during normal aging;*
ii. *Experimental aggravation should accelerate aging; and*
iii. *Experimental amelioration should retard the normal aging process and, hence, increase healthy lifespan*.

The Hallmarks of Aging

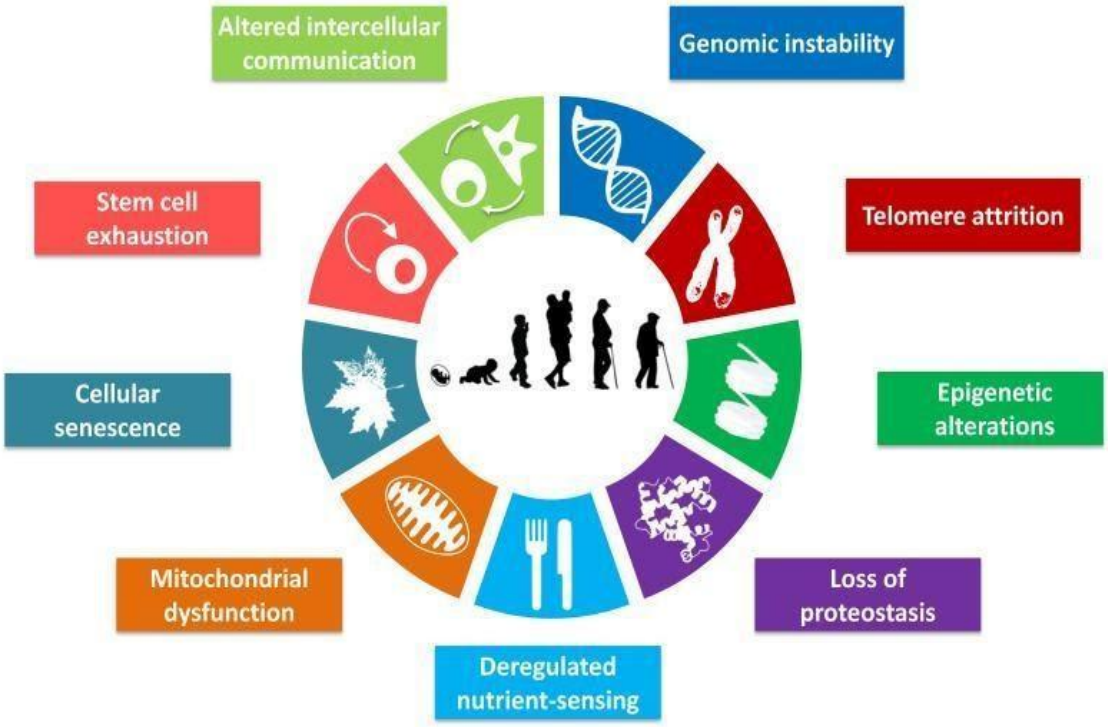

Figure 3. Illustrates the nine original hallmarks of aging: 1) genomic instability, 2) telomere attrition, 3) epigenetic alterations, 4) loss of proteostasis, 5) deregulated nutrient-sensing, 6) mitochondrial dysfunction, 7) cellular senescence, 8) stem cell exhaustion and, 9) altered intercellular communication.[López-Otín]

Biomarkers

The question of whether there is a central mechanism, system of dysregulation, or “clock” related to aging or some other objective biologic measure of it, has been central to aging research. In the past decade research detailing “epigenetic clock” biomarkers and, more

recently, “proteomic clock” and senescent cell burden biomarkers, represent key advances in the field.[Justice] When properly validated, such measures may serve as surrogate endpoints for clinical trials, effectively accelerating timelines to completion. Such biomarkers also may also reveal patterns, or “signatures”, consistent with successful aging, providing an aggregate read out indicating a biologic state conducive to increased health-span. Key issues remain, however, in the validation of biomarkers in the clinical setting. There remains a need to delineate ones that accurately reflect the impact of interventions on the “pillars of aging” and are useful clinically in predicting delayed onset or alleviation of more than one age-related disease.

Metabolic Pathways

In the early 2000s, researchers, following up on decades of experimental data from animals linking calorie restriction to extended lifespan, discovered genes that regulate a balance between energy consumption, on the one hand, and repair activities, such as autophagy, mitochondrial maintenance and genetic repair on the other.[Smith] They documented that restricting the number of calories, or timing of food intake, shifts metabolic activity in the direction of repair, yielding dividends in terms of both healthspan and lifespan. The result has been some remarkable demonstrations of modulated aging in model organisms and the elucidation of several pathways, conserved across species, that are promising targets for intervention.

Relevant therapeutics presented at the 2019 State of the Science Symposium entitled: *Metabolic Pathways and Therapeutics to Enhance Function, Promote Rehabilitation and Delay Aging* held at the Uniformed University of Health Sciences, for example, included: time restricted feeding, rapamycin, metformin, NAD agents, senolytics, resveratrol, ketone bodies, mitochondrial-derived peptides and PARP activators, among others.[Smith, Stubbs, Kim, Jhanji, Baur, Justice 2021, Smith DL,Duregon, Barandhorst, Selvarani]

Many metabolic interventions involve the mammalian target of rapamycin (mTOR) pathway and the closely connected AMPK pathway, which is stimulated by metformin and can upregulate NAD+. Partial inhibition of mTOR with rapamycin increases longevity in rodents and is one of the strategies currently being tested in humans.[Sevarani] Unfortunately, there are limits to the benefits that may be derived from the manipulation of mTOR in isolation since it plays a central role in the basic physiology of all growing and dividing cells. Strong inhibition of mTOR will likely have wide ranging impact and considerable adverse effects in humans. This has led to the search for more selective modulators, for example ones that affect only specific mTOR-downstream functions, such as autophagy, without affecting other mTOR functions.

New Frontiers and Expanded Efforts

Therapeutic Targets

In the past decade, the field has experienced impressive scientific progress and been the focus of significant commercial investment activity. In addition to utilizing novel metabolic targets, researchers are currently pursuing strategies that encompass all nine of the "Hallmarks of Aging" by developing therapies that seek to:

- Prevent the epigenetic damage (e.g., DNA methylation) associated with aging or restore a "youthful" epigenetic state
- Reduce senescent cell accumulation and modulate the senescent cell secretory phenotypes that are linked to increases in overall senescent cell burden
- Use bloodborne factors to reverse stem cell exhaustion
- Facilitate thymic regeneration, and other mechanisms, to reverse immune-senescence (age-related decline of the immune system) or decouple it from other aspects of aging
- Modulate brain-based neuroendocrine regulators of aging
- Utilize combination therapies, including gene therapies, to simultaneously address multiple elements of aging
- Enhance mitochondrial function
- Measure and enhance homeostatic capacity (bio-resilience)
- Reverse specific age-related damage, such as atherosclerotic plaques
- Reduce and eliminate chronic inflammation

These technical approaches and others, which are currently in varying phases of development, promise to generate powerful new generations of "anti-aging" therapies if scientific research, the regulatory framework and commercial efforts can be properly aligned.

Section 2: A National Science and Technology Initiative in Geroscience: Advancing Therapies that Target Age-Related Disease and Decline

Overall Objective

The overall objective of the initiative is to gain five additional years of healthy, independent life (as measured by Healthy Life Expectancy (HLE)) data for citizens of the United States by 2050 and significantly narrow healthspan disparities between disadvantaged and vulnerable groups and the general population.

Impact

If the geroscience hypothesis holds true and this initiative achieves this overall objective, the impact is considerable.

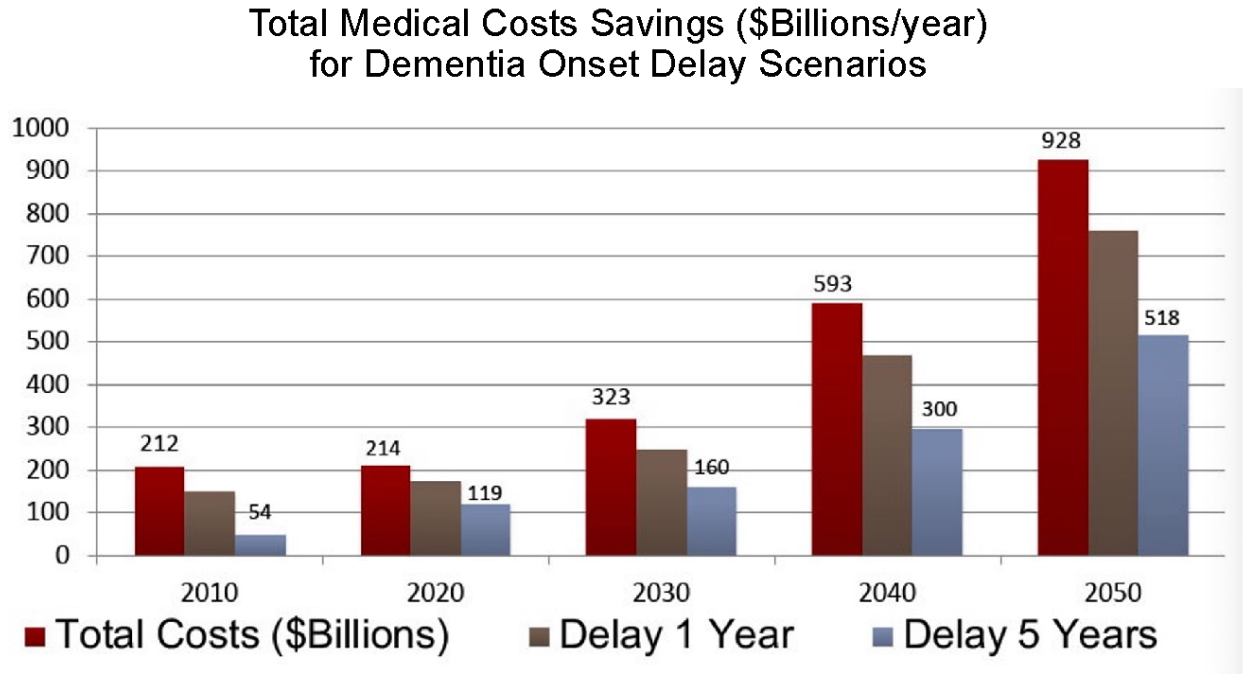

Figure 4. *Potential medical cost savings from delay of dementia onset (Zissimopoulos, et al.)*

The ability to push back, by five years, the onset of age-related dementia alone, has been projected to translate into medical cost savings of $410 billion per year by 2050. If this initiative were to achieve comparable delays in onset for all the major diseases of aging simultaneously, the return on investment, in terms of -the reduction of medical costs alone, would be many times higher.

Goals and Program Elements

Program Goals

- *Goal 1: Increase Support for Basic and Translational Geroscience Research*

- *Goal 2: Increase the number of early-stage clinical trials (Phase I and Phase IIA) focused on improving healthspan, with attention to relevant differences relating to race, ethnicity, sex, disability, occupation and access to care*

- *Goal 3: Utilize public-private partnerships and innovative program management to address the impact of socio-economic disparities on the R&D, distribution and delivery of geroscience solutions and speed translation to communities in need*

- *Goal 4: Increase the number of researchers with expertise in both geriatrics and geroscience, capable of conducting translational research and designing and implementing late pre-clinical studies and clinical trials*

Program Elements

Goal 1: Increase Support for Basic and Translational Geroscience Research

Justification: Despite recent progress, there are many fundamental, unanswered questions about the biology of aging and its correlation to disease. There remains a pressing need to better define the biological pathways related to aging so as to better identify and exploit potential targets for therapeutic modulation. Examples of important basic and translational research topics include:

- Developing novel preclinical therapeutic interventions that target the fundamental mechanisms of aging

- Accelerating biomarker discovery, classification and validation

- Increasing understanding, in preclinical models (cells, tissue explants, model organisms and others) of the intersections and relationships between the fundamental mechanisms of aging and the major chronic diseases

- Gain a broader understanding of how factors such as sex, ethnicity and race may impact the relative contribution of each hallmark to the generalized aging process

- Refining the core aging hallmarks, or mechanisms, and better understanding the interactions and feedback loops between them

- Systematically exploring the relationship in humans between naturally occurring, premature aging disorders, “normal” aging and centenarians

- Improving and increasing the use of aggregate data, artificial intelligence and *in silico* experimentation to supplement pre-clinical research and *in vivo* experimentation so as to accelerate timelines to discovery

- Developing better pre-clinical models for therapeutic interventions to increase healthspan and devising high throughput screening strategies to more rapidly advance candidate therapies to early phase clinical testing

- Designing and evaluating combinations of therapeutic interventions in preclinical models

The creation of novel organizational structures and shared infrastructure would accelerate translation from discovery to practice. Investment in such resources could prove extremely helpful in advancing therapeutics more rapidly through the successive phases of pre-clinical modeling, early phase trial design, regulatory review and clinical trial. A Focused Research Organization (FRO), for example, would facilitate extensive testing of combination therapies, and the assaying of large populations of genetically diverse animals thereby significantly extending the current capabilities of the NIA’s Interventions Testing Program. The creation of an expanded aging research biobank (https://agingresearchbiobank.nia.nih.gov/) would increase research efficiencies by expanding precompetitive access to biological samples and pre-clinical and clinical research data. Examples, of shared biobank services might include:

- Facilitation of “reverse translation” through the provision of information from interventional clinical trials to basic biological research laboratories

- Provision of “omics” using standardized protocols to allow accurate comparisons across clinical trials, institutions, and biospecimen types

- Development of standards and standard operating procedures for studies, outcome measures and clinical trials

- Formulation of a national data science strategy that includes integration of molecular markers, phenotypic traits, computable phenotypes, social determinants of health and patient reported outcomes

- Provision of accessible, mine-able, web-based inventory and data sets

- Facilitation of data mining and pre-clinical and pre-competitive research via a centralized data hub providing multi-parameter analysis of aging-related datasets

- Provision of stored dried, frozen and block, animal and human biologic samples (including treated vs. untreated specimens) such as: slides, cells, cDNA, epigenetic, tissue, blood, urine, fecal buccal, cerebrospinal, and microbiome

- Provision of pre-aged, genetically diverse, preclinical animal models (e.g., genetically diverse, pre-aged mouse strains)

- Provision of induced, stem cell and organoid models derived from the genomes of long-lived phenotypes or "super-centenarians"

It is worth noting that other nations are currently investing in powerful biobanks, notably the United Kingdom, but U.S. efforts lag behind. This is in part due to the decentralized structure of the health care system in the U.S. but, with investment, domestic efforts can be advanced to accomplish the same goals.

Goal 2: Increase the number of early-stage clinical trials (Phase I and Phase IIA) focused on increasing healthspan

Justification: A growing number of interventions, including lifestyle modifications and drugs already approved for clinical use, have been identified as having the potential to increase healthspan. There are substantial benefits to systematically evaluating such approaches in regards to their impact on healthspan, as opposed to disease specific effects. Commercial entities are unlikely to develop, evaluate or market many of these interventions, especially those involving off-patent drugs, natural products or behavior modification without incentive. Clinical trials evaluating them as geroscience therapeutics should be refined and advanced in close collaboration with the Food and Drug Administration.

Role of the Food and Drug Administration (FDA)

For many geroscience therapeutics to advance through translation and enter the market, they will need regulatory approval from FDA. National Science and Technology Initiatives such as the one envisaged in this white paper, necessarily place increased demands on certain federal agencies. Community stakeholders from across the board, including industry, academia and government, express the opinion that collaboration with FDA is necessary for basic research in geroscience to be effectively translated to clinical practice. FDA contributions to the field are both essential and urgently required. Necessary engagement can be time consuming and complex, particularly when contemplating areas of innovation, and may require appropriate investment in resources and personnel. An investment in regulatory science allows the FDA to optimize evaluation, communication and oversight of geroscience-generated nutritionals, pharmaceuticals, biologics and medical devices, while effectively meeting its other commitments.

Current Focus of Research and Development Efforts

Examples of relevant classes and compounds include:

Senolytics: Senescent cells accumulate in multiple organs with aging, as well as in many younger individuals with chronic diseases. They can release factors that contribute to inflammation, exacerbate tissue damage and spread senescence to previously normal cells. Senolytics are a recently discovered class of drugs that selectively destroy senescent cells, while sparing non-senescent ones. Senolytics have been shown to prevent, delay or alleviate over forty age or disease related conditions in animals and to ablate senescent cells in humans. Senolytic compounds are currently in early phase clinical trials for Alzheimer's, diabetes, obesity, COVID-19 (in the elderly, disabled, or chronically ill), elderly women with multi-morbidities and frailty, osteoporosis, childhood cancer, transplant, osteoarthritis, and other conditions. A small, proof of concept, clinical study of these compounds in humans shows promise in alleviating physical dysfunction associated with idiopathic pulmonary fibrosis, a currently untreatable and fatal disease. Inhibitors of JAK/STAT signaling (*e.g.*, ruxolitinib) decreases release of some inflammatory, fibrotic, and tissue-destructive factors released by senescent cells, as do rapalogs and metformin. Like senolytics, such agents may alleviate dysfunction. For example, ruxolitinib alleviates frailty in older mice, muscle weakness linked to mechanical ventilation, and other disorders. Clinical trials for conditions linked to age-related decline are in the planning stages.

Nicotinamide adenine dinucleotide (NAD+) precursors and PARPs: Nicotinamide adenine dinucleotide (NAD+) is a coenzyme that is found in all living cells. It is central to energy metabolism and serves as a co-substrate for enzymes, including sirtuins and PARPs, that prevent genomic instability through the activation of cellular DNA repair pathways that are significantly downregulated during aging. NAD^+ levels decline with aging and NAD+ precursors, such as nicotinamide mononucleotide (NMN) or nicotinamide riboside (NR), are small molecules that upregulate cellular NAD^+ levels. Long-lived mammals including centenarians, have higher ADP-ribosylation capacity. NAD^+ precursors may modify age-related diseases and dysfunction in animals and show promise in clinical trials.

Sirtuin Agonists: Sirtuins (SIRT1-7) are histone deacylases. In mice, drugs like resveratrol, which activates SIRT1 and may modulate other sirtuins, appear to have healthspan benefits. Clinical trials of resveratrol and other sirtuin agonists for the reduction of age-related decline are underway.

CD38 Inhibitors: CD38 is an enzyme on the surface of certain immune and endothelial cells. CD38 degrades NAD^+ and is upregulated by factors released from senescent cells. CD38 inhibitors alleviate the age-related decrease in NAD^+ and attenuate, or reverse, dysfunction associated with aging and age-related diseases.

Rapalogs: Rapamycin and rapamycin derivatives (rapalogs) inhibit mTOR (mechanistic target of rapamycin), the catalytic subunit of a protein kinase complex that signals nutritional sufficiency and increases anabolic processes, including production of proteins,

lipids, and nucleotides. mTOR is increased in senescent cells and rapamycin decreases release of some inflammatory, fibrotic, and tissue-destroying proteins by senescent cells. Rapamycin is currently used for immune suppression in transplant patients and patients with auto-immune diseases and certain cancers. Rapamycin increases healthspan and lifespan in mice. Rapalogs are undergoing clinical trials for use in elderly COVID-19 and influenza patients. Data from Mannick et al. indicates that concurrent use of rapalogs enhances influenza vaccine in the elderly by about 20% and may have beneficial effects on immune-senescence

Metformin and Derivatives: Metformin, which is used for treating diabetes, alleviates age-related mitochondrial dysfunction and acts on senescent cells to decrease the release of some inflammatory, fibrotic, and tissue-destroying proteins. Metformin modifies multiple age-related conditions in mice, including diabetes and cancers and, in some studies, increases healthspan and lifespan. Metformin use has been associated with reductions in mortality in geriatric populations. Clinical trials of metformin for various age-related diseases and disorders are underway. The Targeting Aging with MEtformin (TAME) trial will commence in the near future. TAME is a Phase III aging outcomes trial designed to create a regulatory pathway for the development of therapeutics targeting the biology of aging. TAME will study the effects of metformin on the incidence of multi-morbidity, functional decline and changes to biomarkers of aging.

Ketogens and Ketone Bodies: Ketone bodies including acetoacetate and beta hydroxybutyrate are induced naturally by fasting and ketogenic diets, and can also be provided as supplements. They appear to alleviate age-related conditions in mice and increase healthspan. A clinical trial of ketogens for the treatment of age-related physical dysfunction is in the planning stage and several commercial groups are developing drugs related to α-ketoglutarate.

Acarbose: Acarbose slows the action of certain enzymes responsible for breaking food down into sugars in the gut. Acarbose extends lifespan in mice. Acarbose has a good safety profile in humans and small proof of concept trials examining its effects on microbiome and transcriptomic biomarkers were recently completed. The impact of acarbose's effects on age-related functional decline and overall health in humans has not been established.

17α-Estradiol: 17α-estradiol is a naturally occurring isomer of 17β-estradiol, the primary female sex hormone in women, but is non-feminizing. In male mice 17α-estradiol substantially increases lifespan. Geroscience relevant, clinical trials in humans are currently being planned.

Pregnancy-associated Plasma Protein A (PAPP- α)) Antagonists: PAPP-A increases insulin-like growth factor-1 (IGF-1), which promotes cellular senescence. Mice lacking PAPP-A have increased lifespan and a related mutation in humans also appears linked to extended lifespan. Clinical trials of drugs that interfere with PAPP-A, termed "pappalysins" are in the planning stages.

Epigenetic Interventions: Over time, a number of factors cause methyl-groups to bind to DNA without affecting the DNA sequence itself. The pattern of methylation varies over time in a manner that appears to be a proxy for biologic age. This so-called "epigenetic clock" may be used to determine the risk of age-associated disease. Additional epigenetic modifications of DNA-associated histone proteins via chemical modification, including methylation and acetylation, causes age-related alterations in gene expression and increases the susceptibility of DNA to further damage. Stem cell factors, sirtuin agonists and NAD precursors may be used to reverse some epigenetic changes and restore function to older stem or progenitor cells.

Lifestyle Therapies: Aging is strongly affected by environmental and lifestyle factors such, as diet, exercise and overall social well-being. These environmental influences are among the most consistently validated modulators of aging. For example, fasting mimicking diets, calorie restricted diets that provide nourishment but mimic the effects of fasting on blood markers including IGF-1 and glucose, have been developed and tested both in animal models and humans. However, research to better identify the precise therapeutic elements of these interventions and adapt them to target populations is needed. There is also a need for larger trials focusing on both healthy patients and patients with age-related disease

Combination Therapies: Combining modulated aging therapies with modestly effective disease-specific interventions may produce significant clinical benefits. Pre-clinical and early clinical trials of such combinations, as well as combinations of different anti-aging therapies with each other and with lifestyle interventions, need systematic evaluation. For example, treating diastolic dysfunction, a common but essentially untreatable form of heart failure, by combining senolytics, which target the aging process with a disease-specific intervention, has shown powerfully synergistic effects in mouse models.

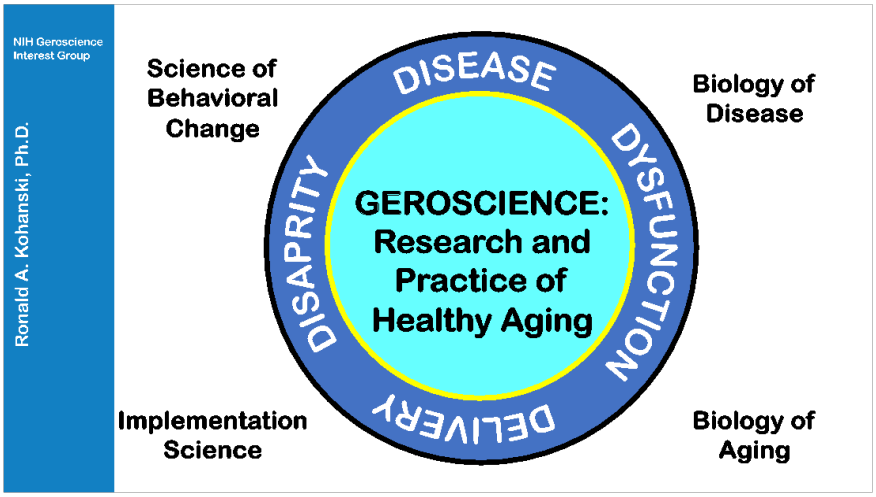

Figure 5. *Elements necessary for translation of scientific progress into clinical practice*

Goal 3: **Utilize public-private partnerships and innovative program management to address the impact of socio-economic disparities on the R&D, distribution and delivery of geroscience solutions and speed translation to communities in need**

Justification: A program manager model, such as the one employed by the Defense Advanced Research Projects Agency (DARPA) utilizing Other Transaction Authority (OTA) for contracting purposes, could facilitate the organization of a consortium geared toward public-private partnerships in geroscience that would be well suited to addressing health disparities and assisting with important pre-competitive, translational and educational activities. Rapid and profound advances in technological prowess often occur through effective collaboration among government, industry, academia. The combination has been termed the "triple helix" model of innovation, with each of the partners initially playing defined roles and government frequently serving as the catalyst. In the case of geroscience, the not-for-profit and philanthropic sectors also have an important role to play.

Description: Consortium activities include:

- identification and validation of biomarkers, and their dynamics, relative to the nine hallmarks of aging, to facilitate the drug discovery and approval process
- provision of matching funds for clinical trials of off-patent pharmaceuticals
- exploration of advanced imaging and other techniques to measure resilience and homeostasis as dynamic processes impacted by aging
- development and promotion of novel training and certification programs for professionals
- dissemination of new information and technologies to consumers via industry groups, professional societies and membership organizations
- research to better understand how social determinants and factors such as sex, ethnicity and race impact the generalized aging process

The consortium plays a critical role in the development of novel organizational structures and innovative translation strategies with a special focus on inclusion and identifying and addressing the importance of factors such as sex, race, ethnicity and disability to the generalized aging process. It allows non-traditional R&D partners, such as federally qualified health clinics, patient navigators, membership organizations for the elderly, medical specialty societies, veteran, minority and women owned small businesses and others to play a critical role in geroscience development, translation, education and distribution by identifying, developing and delivering cost-effective therapies to populations and communities in need.

Goal 4: Increase the number of researchers with expertise in both geriatrics and geroscience capable of conducting translational research and designing and implementing late pre-clinical studies and clinical trials

Justification: There is a need to educate a workforce capable of developing and delivering interventions that target fundamental aging processes. Relevant training is scarce. Existing and future professionals need programs that provide them with the skills and concepts necessary to move geroscience innovation from academic research centers into mainstream medicine and translate general insights on the biology of aging into treatment plans for individual patients.

Description: *Total: 135 trainees/year*

Geroscience Physician Investigators (15 /year)
Investigator Faculty from other Clinical and Research Disciplines (20/year):

Candidate Profile: Physicians, clinicians and allied health professionals with geroscience, clinical trial or geriatrics experience. Candidates include interested qualified professionals with graduate or post-graduate training in areas such as Internal Medicine, Family Practice, Geriatrics, Physiatry, Cardiology, Neurology, Endocrinology, Nursing, Pharmacy, Engineering, etc.

Structure: Three to five additional years of Master's to Ph.D. level training focused on design, development and conduct of late-stage pre-clinical and Phase 1 to 2A early phase clinical trials of geroscience interventions.

Goals and Outcomes: Graduates are Principal Investigators (PIs) or Co-PIs in biology of aging laboratories, lead early phase clinical trials, and/or serve as directors of Geroscience Clinics in academic medical centers. They introduce cutting edge therapeutics into clinical practice. They act as thought leaders, technical resources and mentors for colleagues wishing to engage in geroscience research and practice. They conduct educational activities relating to pre-clinical and clinical research, as well as communicating the principals of geroscience to medical and academic audiences, including undergraduate and graduate students, residents and the general population. As the number of trained geroscientists increases and understanding of the clinical potential of geroscience expands, career opportunities in established biotechnology and pharmaceutical firms become more prominent.

Geroscience Certificate Trainees (100 /year):

Candidate Profile: Faculty from allied clinical and research disciplines (e.g., nursing, physiotherapy, patient navigation, nutrition, physical therapy, social work, medicine, pharmacy, public health physiology, biochemistry, chemistry, computer science, dentistry, bioengineering).

Structure: One-year part-time courses covering the biology of aging in clinical settings, cell, animal, human studies, clinical trials and regulatory processes.

Goals and Outcomes: It is clear that the foundation for healthy aging is established in the first part of life. Healthy aging research and education, therefore, should be an integral part of healthcare service delivery throughout the lifespan. It is important to convey the principles of geroscience to the next generation of care-givers so they are able participate in advancing the field and informing patients of prevention and treatment strategies throughout care continuum. Program graduates have sufficient grounding in geroscience to be able to participate in geroscience research within their disciplines. They design and conduct of impact and outcome assessments related to healthspan, chronic disease progression and age-related decline, including loss of physical and sensory function and resilience. They serve as collaborators for inter-disciplinary, geroscience research groups, act as mentors, thought leaders and patient navigators and contribute to academic endeavors as members of inter-disciplinary, geroscience teams.

Conclusion

The promise of geroscience is that we may, in our lifetimes, be able to slow or reverse the major causes of disease and death in the United States. To reach that goal scientific investment must be melded with an innovation ecosystem that includes: government and regulatory agencies, academic institutions, the commercial market; biotech and healthcare companies; venture capital and philanthropy. All these stakeholders should contribute to program planning from the outset. The intention of this white paper, therefore, is to catalyze the necessary engagement.

If political and civil leadership recognize the promise of geroscience and can design and implement an effective program to rapidly advance the field, the relatively near-term impact on healthcare quality and cost, as well as the general wellbeing of our aging population, may be profound and lasting.

Part 3: Acknowledgement and Appendices

Acknowledgements

We wish to thank the distinguished members of the scientific review panel (listed in Appendix 2), whose contributions to this document and the field of Geroscience are foundational and invaluable. Thanks to the Translational Geroscience Network, which contributed much of the program outline and José Luis Ricón, Martin Borch Jensen and Adam Marblestone for their contribution to the background and state of the science and Thanks to Charles Bennett and Anne Ventrone for their assistance in preparing the manuscript and organize the symposium. Thanks to the Conference Organizing Committee (listed in Appendix 3), who were responsible for outlining the program and securing speakers for the virtual symposium, held on May 7th 2021, for the purpose of presenting this paper. Thank Senator Chris Van Hollen for serving as Honorary Chair of that symposium and to his staff for facilitating the Senator's participation. Finally, thanks to William K. Smith for serving as principal author of the white paper and organizer of the accompanying symposium.

Appendices

Appendix 1:

Glossary:

Health gap: divergence between mean lifespan and mean healthspan

Healthspan: the span of life during which an individual is unaffected by chronic or debilitating disease.

Lifespan: The duration of time between birth and death

Longevity Dividend: Lower health care costs, increased savings and worker productivity resulting from deceleration in the rate of aging.

Relative Index of Inequality: expresses the ratio between the health outcome levels at the (theoretical) bottom and top of the socioeconomic hierarchy

Slope Index of Inequality: measures the gradient of health across multiple socioeconomic groups that can be naturally ordered, after rescaling the socioeconomic groups in accordance to the relative position of each level,

Wealth gap: divergence in mean income between racial/ethnic minorities and white Americans.

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Goal 2: Increase the number of early-stage clinical trials (Phase I and Phase IIA) focused on increasing healthspan, with attention to relevant differences relating to race, sex, disability, occupation, or access to care

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Goal 3: Create a framework, utilizing public-private partnerships and implementation science, to speed translation of basic science to clinical practice and address the impact of socio-economic disparities on distribution

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Appendix 2: List of Scientific Review Panel Members (alphabetical order)

David B. Allison, Ph.D.
Dean, Indiana University School of Public Health

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Professor of Population Health
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Alan Cash
Founder & CEO, Terra Biological LLC

Pinchas Cohen, M.D.
Dean, University of Southern California
Leonard Davis School of Gerontology

Rory Cooper Ph.D. FISA/PVA Distinguished Professor, Past Chair, Department of Rehabilitation Science and Technology, Professor of Bioengineering, Physical Medicine and Rehabilitation, and Orthopedic Surgery, University of Pittsburgh

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Professor, AARP Chair in Gerontology
Director, Multidisciplinary Research Training in Gerontology PhD Program
Director, USC/UCLA Center on Biodemography and Population Health

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Robert and Renee Belfer Chair for the Study of Neurodegenerative Diseases
Albert Einstein College of Medicine

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Don Ingram, Ph.D.
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Jamie Nicole Justice, Ph.D.
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Tom Kalil
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President and Managing Partner
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Appendix 3 : Symposium Organizing Committee

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Members

Rory Cooper, PhD
FISA Foundation and Paralyzed Veterans of America Distinguished Professor and Assistant Vice Chancellor of Research for STEM - Health Sciences Collaboration, University of Pittsburgh and Director and Sr. Career Scientist, HERL, US Department of Veterans Affairs

G. Alexander Fleming, M.D.
Executive Chairman, Kinexum

Don Ingram, Ph.D.
Professor (ret.) Nutritional Neuroscience and Aging, Pennington Biomedical Research Center, Louisiana State University

Tom Koutsoumpas
Co-founder and Co-chair Coalition to Transform Advanced Care (C-TAC)

Major General (ret.) Lester Martinez-Lopez MD MPH Chairman, Medical Technology Enterprise Consortium (MTEC)

Bill Novelli
Co-founder and Co-chair Coalition to Transform Advanced Care (C-TAC)

Eric Perakslis PhD
Chief science and Digital Officer, Duke Clinical Research Institute

Mike Stebbins PhD
President, Science Advisors

Jeremy Walston MD
Raymond and Anna Lublin Professor of Geriatric Medicine & Gerontology, Johns Hopkins University

Yetsa A. Tuakli-Wosornu, M.D., M.P.H.
Associate Research Scientist in Epidemiology (Chronic Diseases), Yale University School of Public Health

Joon Yun M.D.
President and Managing Partner
Palo Alto Investors LP

Appendix 4: List of Collaborating Institutions (in the order received)

- National Institute on Aging, National Institutes for Health
- Uniformed Services University of the Health Sciences
- University of South Carolina, College of Pharmacy
- University of Pittsburgh, Human Engineering Research Lab
- Department of Veterans Affairs
- Paralyzed Veterans of America
- Oklahoma Nathan Shock Center on Aging
- Albert Einstein College of Medicine
- University of Southern California, Leonard Davis School of Gerontology
- University of California, San Francisco, Buck Institute for Research on Aging
- Medical Technology Enterprise Consortium
- Centre Hospitalier Universitaire de Toulouse, CHU
- Texas A&M Health Science Center
- Duke Clinical Research Institute

Appendix 6: Agenda for Consensus Symposium, May 7th 2021

Consensus Symposium

Defining a National Research Vision Targeting the Biology of Aging to Optimize Human Performance, Healthspan and Lifespan

Organized By:
Uniformed Services University of the Health Sciences
National Institute on Aging
University of South Carolina
Human Engineering Research Laboratories

Honorary Chair
Senator Chris Van Hollen

Friday, May 7th, 2021 12:30-16:00
Virtual Symposium via Zoom

Agenda

12:00-12:30
Session Registration and Admission

12:30-12:40
Welcome and Introductions of Conference Moderator and Hosts
Paul F. Pasquina, MD, Chair, PM&R, USUHS

12:40-12:50
Welcome and Introduction of Senator Van Hollen
Dr. Richard W. Thomas
President, Uniformed Services University

12:50-13:00
Remarks: The Importance of Health Science Research
Senator Chris Van Hollen

13:00-13:35
Background: Aging, the Geroscience Hypothosis and the Symposium

- *Background and Mission of the Symposium*
  William K. Smith MD
  Assistant Professor, USUHS, University of South Carolina
- *The Challenge of Aging*
  Charlotte Yeh, MD, Chief Medical Officer, AARP
- *The Geroscience Hypothesis*
  Ronald A. Kohanski, Ph.D.
  Director Designate, Division of Aging Biology, NIA
- *Research Spotlight*
  Ana Maria Cuervo, M.D., Ph.D.
  Robert and Renee Belfer Chair for the Study of Neurodegenerative Diseases, Albert Einstein College of Medicine

13:35-13:55
The Potential of a National Science and Technology Initiative in Geroscience
Tom Kalil, Chief Innovation Officer, Schmidt Futures

The Advanced Research Project Agency for Health: a Vehicle for High Risk, High Reward Investment in the Life Sciences
Mike Stebbins, President at Science Advisors, Former Assistant Director for Biotechnology, White House Office of Science and Technology Policy, Obama/Biden Administration

13:55-14:30
Keynote: *White Paper Presentation: A Model Science and Technology Program*
Luigi Ferrucci MD, PhD, *Scientific Director, National Institute on Aging, National Institute of Health*

14:30-14:45 Break

14:45-15:15
Keynote Panel*: Bringing The Community to the Table: Addressing Disparities, Inclusion and Special Needs Populations in the Design And Delivery Of Science and Technology Programs*

- *Patricia Jones DrPH, MPH, MS, Dir. Office of Special Populations NIA/NIH*
- *Rory A. Cooper, PhD, FISA/PVA Distinguished Professor, University of Pittsburgh(Pitt)*
- *Beth Calhoun, PhD, Professor Associate Dean for Population Health, Professor of Population Health, University of Kansas School of Medicine*

15:15-15:20
Introduction
G. Alexander Fleming, MD, Executive Chairman, Kinexium

15:20-15:45
Keynote: *Pharmaceutical Development Targeting the Biology of Aging: The FDA Perspective* Remarks
Ellis F. Unger, MD, Director, Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN) U.S. FDA

15:45-15:55
Q&A

15:55-16:00
Thank you and Next Steps

Overview and Objectives

The objective of this symposium is to present and solicit community feedback on a model research agenda and gap analysis designed to inform future research and clinical investment in the biology of aging and to help gage community interest in a National Science and Technology Initiative in this area. Registration link: https://bit.ly/2OALkKz

Who Should Attend

The workshop is designed to foster dialogue among stakeholders from academia, government, industry and the not-for-profit sector. The content of the sessions will benefit those interested in science and policy related to human aging, longevity, healthspan, performance and resilience including: not-for-profit organizations; government agency personnel; civilians; military service members, veterans and their families; care-givers, students, residents, researchers and healthcare providers.