

HEALTHY LONGEVITY GLOBAL COMPETITION

2020 Catalyst Awardees

Sponsor: National Academy of Medicine

Anti-Aging Effects Discovered in a New Form of Plasma

Principal Investigator	Benjamin Scherlag
PI Primary Affiliation	University of Oklahoma Health Science Center
Co-Investigator(s)	Ronald Scherlag

PROJECT DESCRIPTION

Anti-Aging Effects Discovered in a New Form of Plasma Our recent experiments discovered that free water molecules¹ (size, 2.75Å) passed through glass pores (8 -12 Å). When confined, the inherent kinetic energy of free water molecules reacted to produce plasma. Experiments with this plasma demonstrated anti-aging effects on produce, live plants and living organisms. Two 500ml storage jars were filled with distilled water and stacked on top of each other in a four-liter sealed acrylic cylinder outfitted with hygrometers. Free water molecules filtered through the glass pores of the jars by osmosis and diffusion until concentration gradient in the cylinder reached 99% on the hygrometer. Experiments exposed living things to plasma. Mobile unicellular organisms exhibited a hibernating state, when removed from the plasma normal function returned. Tomatoes exhibited a fresh, unblemished appearance after 30 days in plasma, non-plasma tomatoes were severely wrinkled. Mung bean plants placed in plasma, without water for 7 days, showed under- developed leaves, compared to non-plasma plants. Normal growth resumed when plants were returned to the hydroponic condition. Plants placed in a waterless, non-plasma environment wilted in 24 hours. Lowering metabolic rate can result in reduced obesity and increased vitality as people age. As average life expectancy increases, more focus is placed on the economics of healthcare, diet and exercise are effective but difficult, plasma can be a supplement to daily a regimen. ¹Penkov NV et al. Calculation of the portion of free water molecules in water solutions by means of spectral analysis, Bf 2013;58: 942-6.

App for smartwatches that uses AI to detect early signs of Parkinson's Disease

Principal Investigator	Igor Dzhekiev
PI Primary Affiliation	Co-founder of Insubiq Inc
Co-Investigator(s)	Eugene Nikolaev

PROJECT DESCRIPTION

App for smartwatches that uses AI to detect early signs of PD such as initial tremor, dyskinesia, or other anomalies in the movements typical to PD.

Expanding the eldercare workforce to meet the needs of our aging populations

Principal Investigator	Claude Goodman
PI Primary Affiliation	CareWheels Corporation

Co-Investigator(s)	Narjala Bhasker
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PROJECT DESCRIPTION

Loneliness and medication nonadherence are epidemic public health problems unsolved by conventional interventions. Recognizing these problems as Interrelated offers new opportunities to develop synergistic solutions that engage elders to participate in the eldercare workforce by empowering them with holistic innovations designed to enhance their longevity. Peer to peer care services, or PeerCare, transforms elders from societal burdens into shared resources capable of expanding the eldercare workforce to meet the needs of our aging populations. Elders are one resource capable of scaling-up to meet the growing magnitude of unmet eldercare needs. PeerCare engages elders to positively impact their longevity and social determinants of health by expanding their social support networks to tackle loneliness and foster helpful relationships based on mutual support, trust and camaraderie. It provides social incentives that improve healthy behaviors like diet and medication adherence to reduce preventable disease, emergency room and hospital admissions. We propose to maximize the positive impact of PeerCare by innovating the CareBank: a PeerCare Platform that rewards mutual support by fostering service exchanges between elders to help them help each other age-in-place safely. The CareBank will integrate smartphones with activity sensors and social incentives to connect, detect, alert and reward PeerCare participants. The CareBank App will connect elders to exchange PeerCare by providing real-time alerts and automatic credits for mutual monitoring and response services. It will empower elders to help save lives by detecting problems before they become emergencies, and money, by rewarding elders for providing equitable PeerCare services from the comfort of home.

Retinal Imaging for Diagnosis of Aging-Related Brain Disorders

Principal Investigator	Alessandro Biffi
PI Primary Affiliation	Mass General Hospital, Harvard University Medical School
Co-Investigator(s)	Elena Biffi

PROJECT DESCRIPTION

Vascular and degenerative brain disorders, such as Alzheimer's disease, Parkinson's disease, stroke, vascular dementia and many others, are primary contributors to aging-related medical conditions and decreased longevity. In order to study, prevent and treat these conditions we rely on accurate diagnosis, ideally as early as possible in disease course (up to an including asymptomatic stages). Unfortunately, our current diagnostic tools (chiefly brain scans and blood tests) are either unsuitable for early diagnosis or too expensive for large-scale deployment in an ever-growing population of elderly persons. Recent technological advancements allow for rapid, non-invasive, user friendly imaging of neurons and blood vessels in the retina (the posterior portion of the eye, where images are captured). The retinal neurons and blood vessels are very similar in function and structure to those of the brain. Imaging of the retina may therefore allow for screening and early diagnosis of brain degenerative and vascular conditions, potentially transforming our research and clinical approaches to brain aging. We propose to leverage existing data on brain and retinal imaging at two large academic hospitals, to test the hypothesis that ocular scans allow for accurate, cheap, large-scale diagnosis of brain aging-related disorders. If successful, our project would arm researchers with a new, highly efficient way to study brain aging disorders - and provide doctors with new tools in the fight against brain health deterioration associated with aging.

Testing whether 'activated' Natural Killer cells improve various markers of health-span

Principal Investigator	Amit Sharma
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PI Primary Affiliation	SENS Research Foundation
Co-Investigator(s)	Alexandra Stolzing

PROJECT DESCRIPTION

Senescent cells are characterized by an irreversible arrest of the cell cycle and secrete a milieu of pro-inflammatory cytokines, chemokines, and growth factors collectively referred to as the Senescence-Associated Secretory Phenotype (SASP) due to which these cells have been implicated in a large number of age-related diseases, and recent efforts to develop therapeutic interventions are centered around either selectively eliminating senescent cells (senolytics) or by reducing secretion of inflammatory factors from these cells (senomorphic). While these approaches present possible avenues for reducing the impact of senescent cells, they still lack specificity. Innate immune cells like Natural Killer cells can selectively eliminate senescent cells, thus providing another avenue for removal of senescent cells. However, a lack of understanding as to how aging influences the specificity and sensitivity of NK cell to target senescent cells is a major hurdle in realizing potential therapy. Based on our preliminary data from FACS analysis of blood samples of healthy human subjects, we hypothesize that NK cell functions decline with age, and as a consequence senescent cells accumulate faster in aged organisms. Our animal experiments demonstrate that blood (including young NK cells) transferred from young mice to old mice drastically reduces senescent cell burden in older mice. The central aim of the proposed project is to determine if the NK cells lose their ability to selectively target senescent cells and if this can be restored. We would use ex vivo and mouse model to test if these 'activated' NK cells improve various markers of health-span.

Resilient Brains: New Insights for Healthy Brain Aging

Principal Investigator	Michael McConnell
PI Primary Affiliation	Lieber Institute for Brain Development
Co-Investigator(s)	Daniel Weinberger

PROJECT DESCRIPTION

Healthy lifestyle choices and modern medical advances are extending human lifespan. But longer life is not yet broadly associated with continued mental agility and cognitive awareness. Brain aging and neurodegenerative disease are still barriers to quality of life even though physical longevity continues. Advances in neuroimaging have identified rare individuals that maintain normal brain function despite ongoing Alzheimer's Disease pathology. We propose that these individuals have won a genetic lottery, and that understanding their unique genetic make-up will identify novel ways to promote healthy brain aging for everyone. Our study of rare resilient brains aims to reveal new brain resilience pathways that can be engaged to extend brain health and quality of life that is concordant with physical longevity.

Care Corps National Service Model - Addressing an Aging Sector Workforce

Principal Investigator	Nihal Satyadev
PI Primary Affiliation	University of Medicine and Health Sciences
Co-Investigator(s)	Norma Bostarr

PROJECT DESCRIPTION

In the United States, more than 10,000 people turn 65 every day. Put this statistic alongside the fact that our birth rate is at an all time low, and you are looking at a dependent society of older adults with not enough of a workforce to support aging-related needs. Our growing aging population is currently supported by millions of

family caregivers, many of whom are overburdened and depressed. The Care Corps is a new service model that addresses the lack of an aging sector workforce, family caregiver stress and depression, social isolation of persons with dementia (PWDs), and helps to prevent spend-down by families to qualify for Medicaid-funded in-home care. This model would allow for family caregivers to re-enter the workforce, build a graduate-to-labor pipeline for caregiving, and save billions in taxpayer dollars through aging-in-place. The Care Corps will incentivize young American high school and college graduates to provide 1-2 years of near-full-time respite care for older adults with dementia in exchange for a stipend and educational grants upon completion of the service. National service models like AmeriCorps, PeaceCorps, and TeachForAmerica have been successful in leveraging youth interest to address key societal issues. At a time when our elders need us the most, what could be more patriotic?

Centenarian Species Genomes Project

Principal Investigator	Glenn Gerhard
PI Primary Affiliation	Lewis Katz School of Medicine at Temple University
Co-Investigator(s)	None

PROJECT DESCRIPTION

The central tenet to our idea is that in order to extend the human healthspan, the biological mechanisms that specify maximum lifespan must be understood upon which interventions may then be developed. However, almost all available data is derived from short-lived model organisms. We therefore hypothesize that the genome sequences of species whose maximum life spans are 100 years or more will share longevity-related molecular mechanisms that will serve as targets for the development of interventions into healthspan. We propose the “Centenarian Species Genomes Project” to identify molecular mechanisms of extreme longevity because no systematic and comprehensive evolutionarily based genomic analysis of species with extreme longevity has yet been conducted. The convergence of improvements in sequencing technology, and computational approaches make the proposed project feasible with existing technology. The project design will be to 1) conduct association analyses of relative evolutionary rates and longevity of available centenarian and non-centenarian species genome sequences and 2) assemble draft genome assemblies of two unsequenced centenarian species, the American lobster (100 year maximum longevity) and Ocean quahog clam (>500 year maximum longevity). The Catalyst Award phase represents the modest pilot phase of a much larger project that will serve to establish protocols and procedures so that they can be easily scaled to generate and analyze data from the remaining centenarian species in the Accelerator phase. We believe this will be a prerequisite for developing interventions that extend healthspan through understanding lifespan.

Development of a fully implantable, continuous hemodialysis device as a bridge to kidney transplant

Principal Investigator	Nikhil Shah
PI Primary Affiliation	Nephrodite, Inc.
Co-Investigator(s)	Hiep Nguyen

PROJECT DESCRIPTION

We are developing a fully implantable, fully mechanical, continuous hemodialysis device that is designed to be a bridge to transplant for eligible patients and/or a destination therapy for transplant ineligible patients. Our device, inspired by a patient named Ms. Holly, serves as a more effective renal replacement therapeutic as it minimizes the impact/burden of treatment, facilitate mobility, and reduce disease maintenance and complications. The key functionality is provided by the novel coupling of an arterial-based mechanical pump, long-lasting semi-

permeable filtration membrane, and an implanted reservoir that allows for solutes < 30kDa to be removed from the blood via exchange with dialysate. The dialysate, including the waste product, is contained in the implanted reservoir, and exchanged daily during sleeping hours via an implanted catheter that is connected to an external fluid exchange device. Key proof-of-concept testing has been completed in construction of the mechanical pump termed the Filtration Unit (FU). These include: feasibility of implantation of the FU, pressure and flow testing of the device, and demonstration of sufficient urea removal over an extended period of time. We currently seek funding to validate prior experiments using blood and to build an operational benchtop prototype.

Improving Health for the Aging through Daily Vital Signs Monitoring

Principal Investigator	David Borkholder
PI Primary Affiliation	Rochester Institute of Technology
Co-Investigator(s)	Adam Smith

PROJECT DESCRIPTION

Vital signs are objective measures of physiological function that are used to monitor acute and chronic diseases, providing critical data on an individual's health status. Monitoring daily vital signs in the home with a smart toilet seat would transform how we manage a broad range of disease states for the aging population. This is especially critical for cardiovascular disease (CVD), which impacts over 80% of those over the age of 65, and 90% of those over the age of 80 in the US. CVD is the leading cause of death in the US, and has become our nation's costliest chronic disease, costing the nation \$555 billion in 2016. By 2035 this number is expected to rise to over \$1.1 trillion. Hypertension, a subset of CVD, impacts 78% of those over 65 and is known to be the most important risk factor for premature cardiovascular disease and death in older adults. Effective, in-home vital signs monitoring could dramatically reduce these trends. However patient adherence to in-home self-monitoring of vital signs is poor. This challenge is exacerbated in the context of subjective cognitive decline which impacts 1 in 9 people aged 45 and older. Importantly, 40% of these individuals also suffer from at least one chronic condition. Toilet seat vital signs collection each day, automatically without patient engagement, would transform our ability to detect subtle changes in health for the aging population. Early detection enables intervention to reduce healthcare burden and improve outcomes and quality of life for the individual.

Nanocatalysis for the improvement of human healthspan and lifespan

Principal Investigator	Karen Ho
PI Primary Affiliation	Clene Nanomedicine, Inc.
Co-Investigator(s)	None

PROJECT DESCRIPTION

The remarkable property of metal-based nanoparticles to efficiently catalyze chemical reactions has been recognized by the manufacturing industry, where there is growing interest in nanocatalysts as highly active, 'green alternatives' that enhance various chemical reactions. However, nanocatalysts have not been widely applied to human health and disease due to the significant challenges associated with producing nontoxic nanoparticles while maintaining their catalytic potential. Using electrocrystal chemistry, we have innovated a method of synthesizing clean-surfaced, highly faceted nanocrystals of metal transition elements (US Patent, Anonymous) resulting in concentrated, stable, aqueous nanocrystal suspensions. Our gold nanocrystal suspensions (AuNCs) displayed superior catalytic activities compared to other commercially available gold nanoparticles, while exhibiting no toxic effects in chronically dosed animals in standard toxicology studies. Oral administration of AuNCs to healthy human volunteers in a Phase 1 First-in-Humans study demonstrated oral dosing was safe and well-tolerated. Notably, oral administration of AuNCs improved clinical scores, behaviors, motor functions, and lifespan of several genetically modified or toxically-injured animal models of

neurodegenerative diseases: multiple sclerosis, Parkinson's disease, and amyotrophic lateral sclerosis. AuNCs favorably altered the bioenergetic profiles of central nervous system cells, resulting in increased neuronal survival against stressors such as excitotoxic glutamate, amyloid-beta 1-42 peptide, mitochondrial inhibitors, and/or oxidative stress. Our studies revealed that the mechanism of action of AuNCs involves the stimulation of core pathways that are known to enhance longevity. Here we propose further studies to demonstrate that our AuNCs represent a transformative innovation with potentially wide-ranging beneficial impacts on human healthspan and lifespan.

Genetic Regulation of Exceptional Longevity in Rockfishes

Principal Investigator	Stephen Treaster
PI Primary Affiliation	Boston Children's Hospital
Co-Investigator(s)	None

PROJECT DESCRIPTION

Rockfishes (Sebastes genus), with nearly twenty-fold variation in longevity, are an untapped source of natural experiments in modulating, and resisting, the deleterious effects of age. The longest-lived can maintain health and function for over two hundred years, while within the group, other species survive for only eleven. Knowledge of the genetics underlying this trait would have untold therapeutic value. After a phylogenomic mapping endeavor, I have revealed genetic variation that is associated with the evolution of longevity in Rockfish. I intersected these results with human population variants, revealing significant SNPs associated with human longevity. These genes and their architecture are a powerful insight into the evolutionary toolkit for longevity, and once validated in conventional models, could be used to delay or ameliorate aging and age-related diseases.

Automated Cell Profiling Platform for Anti-Aging Drug Discovery

Principal Investigator	Bianca Migliori
PI Primary Affiliation	New York Stem Cell Foundation Research Institute
Co-Investigator(s)	None

PROJECT DESCRIPTION

Age-dependent diseases are the leading cause of death and morbidity in industrialized countries. It is increasingly recognized that a more efficient strategy than targeting individual diseases will be to counteract aging itself, which would prevent or delay the onset of age-dependent conditions like cardiovascular pathologies, neurodegeneration and overall physiological decay. Fortunately, recent findings in model organisms reveal that aging is not an unstoppable phenomenon as once believed, but can be decelerated or even reversed by specific interventions. However, identifying molecular mechanisms of human aging that can be targeted with drugs remains a major challenge, as conventional drug discovery methods are incompatible with the complex biology of aging. We have developed an innovative system that takes advantage of robotics, advanced cellular imaging, and artificial intelligence to define new cellular features of aging and discover drugs that can modify them. Our project will apply this technology to human skin cells from a large, age-diverse cohort, developing an algorithm that can reliably predict donor age based on cell images. Leveraging recent evidence of the critical role that epigenetics plays in regulating aging, we will initially screen a collection of epigenetic drugs on these cells to identify new anti-aging molecules. We will later apply this technology to the screening of larger collections of drugs as well as genetic factors. This pioneering project will establish an unbiased, unconventional approach for unraveling the biology of aging and fueling new strategies for promoting healthy longevity.

Deep learning to predict biological age and longevity from chest radiographs

Principal Investigator	Vineet Raghu
PI Primary Affiliation	Massachusetts General Hospital
Co-Investigator(s)	Michael Lu

PROJECT DESCRIPTION

Age-related chronic disease causes 60% of deaths in the US. Primary prevention (e.g. statin to prevent cardiovascular disease) and screening (e.g. screening for lung cancer with chest CT) interventions are based on chronological age, but we know that chronological age is an imperfect measure of the aging process. A more accurate measure of biological age would enable healthcare providers to better personalize care and help researchers address factors underlying the aging process. The goal of our project is to develop a pragmatic measure of biological age using a convolutional neural network (CNN) and a chest x-ray image. We will evaluate whether this chest x-ray age predicts longevity and age-related disease better than chronological age. Chest x-rays are among the most common tests in medicine and leveraging these existing x-rays to more accurately assess biological age has the potential to transform care of the aging population. The CNN will be developed and tested using over 30,000 publicly available chest x-rays as well as up to 18-year follow-up for mortality in 60,000 individuals from two large multi-center clinical trials, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial and the National Lung Screening Trial (NLST).

Investigating the Role of Intestinal Alkaline Phosphatase in the Aging-Associated Changes in Gut Barrier and Microbiome Using a Novel Microfluidic Intestine-on-Chip Model

Principal Investigator	Vidisha Mohad
PI Primary Affiliation	MGH & Harvard Medical School
Co-Investigator(s)	Richard Hodin

PROJECT DESCRIPTION

Aging increases the vulnerability to many gastrointestinal diseases and is associated with the chronic inflammation, referred to as inflammaging. Aging-associated alteration in the microbiota has been associated with increased gut permeability and increased barrier dysfunction. Although the microbiome has been established as an important regulator of homeostasis, the role of the intestinal alkaline phosphatase (IAP, brush border enzyme secreted into the intestinal lumen by enterocytes) in regulation of the commensal bacteria in aging gut is largely unknown. Our goal is to advance the knowledge of IAP-microbiota relationship and identifying mechanism of microbial modulation to improve epithelial barrier function. The overall aim of this proposal is to investigate the role of IAP in barrier function by enhancing the healthy gut microbiome in a microfluidic intestine-on-a-chip model. The novel intestine-on-a-chip model will allow a stable coculture of the anaerobic and aerobic microbial communities along with the mucus producing intestinal epithelium derived from primary mouse epithelial cells. We will first elucidate how the aging-induced microbial dysbiosis results in an increased gut permeability and epithelial barrier dysfunction. As a second aim, we will determine how IAP contributes to the crosstalk between the aged microbiome and aging-induced gut barrier dysfunction. Determination relationship between IAP, age-related intestinal barrier dysfunction, and microbiota dysbiosis will help in novel breakthrough approach to prevent a variety of aging-related diseases in humans.

Paradigm Shift in the Molecular Transport to Brain through the Direct Central Nerve-Innervation Based Retrograde Axonal Transport of Craniofacial Tissue Exosomes (RATCE)

Principal Investigator	Shigemi Nagai
PI Primary Affiliation	Oral Medicine, Infection and Immunity, Harvard School of Dental Medicine
Co-Investigator(s)	None

PROJECT DESCRIPTION

“Paradigm Shift in the Molecular Transport to Brain through the Direct Central Nerve-Innervation Based Retrograde Axonal Transport of Craniofacial Tissue Exosomes (RATCE)” Along with life expectancy, age-associated Alzheimer’s disease (AD) has been increasing. While dysfunction of the blood-brain barrier (BBB) may contribute to AD, the BBB also limits the passage of beneficial molecules. Alternative routes into the brain remain to be explored. We previously reported that masseter muscle packaged neprilysin (NEP), which breaks down amyloid β , in exosomes and sent them to hippocampus by retrograde axonal transport along trigeminal nerve, bypassing the BBB. The direct central nerve-innervation exceptionally occurs in craniofacial tissues (CFT) such as masseter/ facial expression/ tongue-muscle, periodontal fibroblasts, submandibular gland cells, and dental pulp stromal cells. Every CFT can also transport neuroprotective agents to the brain through RATCE. The first aim of this proposal will identify neuroprotective RATCE cargo through comparative mRNA transcriptome profiling between hippocampal neuron cells and CFT cells with glial astrocytes as positive competitor owing to their neuroprotective functions. Proteins corresponding to neuron-negligible and CFT/glial-dominant mRNA transcripts will be validated in corresponding exosomes and hippocampal neuron as the RATCE cargo. The cargo comparison between CFT and glial astrocytes will shed light on the significance of RATCE. The second aim will compare the therapeutic efficacies of RATCE with conventional intravenous and body muscle injections on AD onset in the amyloid-based disease model mice. This proposal offers a paradigm shifting innovation in the physiological maintenance of brain homeostasis and therapeutic drug delivery through the BBB-independent RATCE pathways.

Virtually Young: Can Embodying an Avatar of Your Younger Self Extend Your Healthy Lifespan?

Principal Investigator	Dr. Alexandra Ivanovitch
PI Primary Affiliation	Equity Lab Global
Co-Investigator(s)	None

PROJECT DESCRIPTION

One in four older adults experiences some mental disorder such as depression, anxiety, and dementia. This number is expected to double to 15 million by 2030 (National Council on Aging). We will design, develop and test virtual reality (VR) experiences which will enable older adults to virtually embody computer-generated avatars of their young and healthy selves and engage in a series of stimulating interactive immersive activities in an effort to improve their mental and behavioral health over extended periods of longevity. Peer-reviewed scientific studies have already repeatedly demonstrated that virtual embodiment can help transform human perception and behavior in the real world in a variety of domains. A landmark Stanford study has shown that embodying older avatars of oneself allows subjects to identify with older adults, reduces ageism and elicits behavioral change: it encourages participants to start saving for retirement. The hypothesis underlying this project is that the opposite is true too. We will build and test a VR working prototype which will enable older adults to be virtually young again and perform a series of engaging activities such as visiting bucket-list destinations, seeing the great wonders of the world up close, swimming with dolphins, going on a safari together with their friends or family

members, planting a flag on the Moon, etc. We will crowdsource desirable content from older adults, build senior-friendly immersive experiences and test their efficacy on a variety of desired outcomes: subjective well-being (Geriatric Depression Scale and Geriatric Anxiety Inventory), social connectedness (Social Connectedness Scale), etc.

Can Hormetic Stress Increase Vagal Tone and Slow Cell Aging?

Principal Investigator	Elissa Epel
PI Primary Affiliation	UCSF
Co-Investigator(s)	Wendy Mendes

PROJECT DESCRIPTION

There have been remarkable discoveries about life extension in lower organisms such as worms using hormetic stress. Hormetic stress includes short term moderate stressors (such as temperature stress, or hypoxia) that trigger natural endogenous mechanisms of healing and repair. Hormetic stress has positive effects in cells and in organisms as well. Hormesis provides an incredible opportunity to promote lifespan in humans. However, besides exercise, there are no studies we are aware of examining hormesis effects on aging biology in humans. This is in part because there have not been well developed programs for inducing hormetic stress. We propose to compare a program of daily hormetic stress (hyperventilation, hypoxia, and cold exposure). Initial published evidence suggests this method may improve immune function but vagal tone and key biomarkers of aging have not been examined. Vagal tone, an index of parasympathetic activity, is an integrative regulator of salutary processes and is linked to healthy longevity globally. We propose to examine if daily exposure of hormetic stress for one month leads to an increase in resting vagal tone, as well as secondary changes such as greater baroreceptor sensitivity, and slower aging in immune cells (less inflammation, slowed epigenetic clocks, higher telomerase) and more resilient responses to acute psychological stress. We will compare this to high intensity exercise and a sham control group. If one month of hormetic stress shows improvement of vagal tone and indices of homeostatic capacity, this highly disseminable intervention has tremendous implications for slowing human aging.

Elucidating mechanisms through which the gut microbiome can be optimized across the human lifespan

Principal Investigator	Nathan Price
PI Primary Affiliation	Institute for Systems Biology
Co-Investigator(s)	Leroy Hood

PROJECT DESCRIPTION

The gut microbiome has important effects on human health, yet its roles in human aging remain largely unclear. We have recently demonstrated (paper submitted) that, starting in mid-to-late adulthood, gut microbiomes become increasingly unique to each individual with age. At the latest stages of lifespan, two distinct patterns emerge wherein individuals in good health demonstrate continued microbial drift toward a unique compositional state, while the same drift is absent in individuals who perform worse on a number of validated health measures. Consistently, having low gut microbial uniqueness, including retaining a high *Bacteroides* dominance into old age, predicts decreased survival. We hypothesize that gut microbiome uniqueness is an intriguing new dimension to healthy aging, and a critical new component for personalized medicine and precision health to enhance healthspan. We propose a strategy to elucidate the functional differences that are brought about by these individual paths towards uniqueness, and also whether gut microbial aging trajectories can likely be optimized through interventions. We will also explore how these microbiome functional trajectories relate to

known mechanisms affecting aging and longevity. Elucidating mechanisms through which the gut microbiome can be optimized across the human lifespan will have important clinical implications for healthy aging, longevity and personalized medicine. Our phase 1 studies would provide the data needed for the larger follow-up studies that would focus on additional experimental validation (phase 2) and then deployment of microbiome-focused strategies for modifying health via in a clinical trial (phase 3).

Halting inflammaging through skin barrier restoration

Principal Investigator	Katrina Abuabara
PI Primary Affiliation	University of California San Francisco
Co-Investigator(s)	None

PROJECT DESCRIPTION

Like all organs, skin function declines with age. This is particularly important because the skin is the body's primary barrier and is essential for protection from toxins and microbes. Clinically, age-related barrier decline may only manifest as dry, itchy skin. However, sub-clinically, it results in chronic stimulation of inflammatory processes designed to protect against external exposures. Although intermittent increases in inflammation are critical for survival during physical injury and infection, a growing body of research shows that chronic inflammation is one of the key biological processes underlying aging. Termed 'inflammaging,' chronic elevations in blood inflammatory markers have been linked to disability, frailty, and premature death. The skin is the body's largest surface for direct contact with external factors and first layer of immune defense, and preliminary data suggests that age-associated skin barrier decline is an important source of chronic inflammation. Our overarching hypothesis is that skin barrier dysfunction is an important source of chronic inflammation, and that skin barrier restoration with emollients can reduce inflammatory levels and equitably improve the healthspan of older adults. This idea is particularly compelling because emollients are safe, low-cost, widely available, and can be used in community settings across racial/ethnic, urban/rural, and socioeconomic contexts. We seek to provide confirmatory experimental evidence that skin barrier restoration in humans lowers blood inflammatory markers, and to leverage a large ongoing study of aging to define how skin barrier function is correlated with longer-term health outcomes.

Affordable, Accessible Hearing Care for Aging Well

Principal Investigator	Carrie Nieman
PI Primary Affiliation	Johns Hopkins University School of Medicine
Co-Investigator(s)	None

PROJECT DESCRIPTION

Age-related hearing loss is nearly universal and is strongly and independently associated with negative outcomes in almost every domain of the aging process. The broader individual and public health implications of hearing loss in older adults are now being recognized at the national and international level. Strategies to ensure affordability and access to hearing care for adults are urgently needed. The 2017 U.S. legislation that created the designation of over-the-counter (OTC) hearing aids, which are expected to debut in the U.S. market by the end of 2020, creates a unique and timely opportunity to expand hearing care delivery models. The overarching objective of this proposal is to implement a community health worker (CHW) approach to providing a basic level of hearing care to vulnerable older adults. Within public health, CHW models of care have long been considered an efficacious and cost-effective approach to increasing access to care and addressing disparities but has traditionally not been incorporated into hearing care practice. This proposal will extend an unconventional approach to hearing care that advances a new model of hearing care while simultaneously building capacity and

addressing the growing hearing care needs of aging societies, regardless of resource setting, in order to ensure all older adults have the tools needed to age well.