

HEALTHY LONGEVITY GLOBAL COMPETITION

2024 Catalyst Awardees

Sponsor: National Academy of Medicine

A humanized CHIP model for studying the origins of age-related chronic inflammatory diseases

Principal Investigator	Isak Tengesdal
PI Primary Affiliation	Stanford University
Co-Investigator(s)	None

PROJECT DESCRIPTION

Age-related chronic inflammatory diseases represent a major incoming burden as the proportion of the world's population over 60 years is expected to jump to 22% by 2050 according to World Health Organization. Inflammation is caused by production of small proteins, termed cytokines. As we age, our tissues and organs are constantly seeded by a pool of hematopoietic stem cells (HSCs) that become mature immune cells in the new tissue. This is thought to maintain tissue homeostasis, however, in age-related diseases it appears that increased tissue inflammation causes tissue damage resulting in disease. Therefore, understanding how increased cytokine production occurs remains a pivotal approach to preventing and treating age-related diseases. Recently, it has been revealed that certain mutations accumulate in our HSCs which give the HSCs harboring these mutations a seemingly preferential expansion compared to non-mutated HSCs as well as a hyperinflammatory phenotype. This process is termed clonal hematopoiesis of indeterminate potential (CHIP) and can be detected using next-generation sequencing in blood. CHIP is very common, affecting greater than 10-30% of those aged 70 years and older and is associated with increased mortality and with age-related, chronic inflammatory diseases such as atherosclerosis, liver disease, gout, osteoporosis and metabolic disorders 1. This is thought to occur due to excessive inflammation from cells carrying CHIP mutations. We present herein a humanized CHIP model to study the dynamics of this system and asses; (1) a screening method for drugs targeting this pathway; (2) a method for characterizing tissue cellularity in the setting of CHIP.

A Rugged, User-Friendly Desktop Detection System for Alzheimer's Disease Breath Biomarkers: to Broaden Access to Early and Accurate Non-Invasive Diagnostics of AD

Principal Investigator	Marshall Ligare
PI Primary Affiliation	Outlier Technology, LLC
Co-Investigator(s)	Cowart, John

PROJECT DESCRIPTION

Alzheimer's Disease (AD) is a neurodegenerative disease characterized by adverse neuropathological changes that compromise neural connectivity and the body's ability to repair brain tissue. The culmination of this damage is a fatal brain atrophy that robs its victims of their memories, independence and identity, and ultimately destroys the brain's ability to communicate with the body. Today, AD is best diagnosed via a combination of brain imaging and documented observations of cognitive decline. However, by the time these diagnostic tools are used it is often too late to mitigate the spread of the disease. Moreover, in the absence of biomarker confirmation, AD is frequently misdiagnosed. Correct diagnosis in the earliest stages of the disease would reduce health care costs,

as the disease is better managed once individuals are on the correct health care track. Here, we propose the development of a desktop tool for rapid diagnostics of AD via non-invasive analysis of the relevant breath-biomarkers. This technology aims to support the medical community in their efforts to broaden access to early and accurate detection of AD. The proposed technology implements 1) a breath-sampling device, 2) a low-cost, orthogonal (dual-column) gas chromatography (GC) system that uses ambient air as the carrier gas; 3) a low-cost Mass Spectrometer (MS) with detection targeted towards a panel of known AD diagnostic biomarkers in exhaled breath, and 4) proprietary chemometric machine learning algorithms. We anticipate the proposed development will demonstrate proof-of-concept with a robust, desktop breathalyzer for rapid screenings of AD to facilitate its early detection.

Antisense Oligonucleotide (ASO)-Based Approach for Enhancing Healthspan and Lifespan

Principal Investigator	Andrew Nguyen
PI Primary Affiliation	Saint Louis University
Co-Investigator(s)	Susan A. Farr

PROJECT DESCRIPTION

Aging is a major risk factor for many chronic diseases as well as geriatric syndromes, and therapeutics that delay or slow the progression of aging remain elusive. There is great potential to enhance healthspan and longevity with novel pharmacological interventions based on genetics. We propose to use an emerging therapeutic modality – antisense oligonucleotides (ASOs) – to selectively modulate levels of longevity-associated genes. This could fill a gap in the translation of decades of genetic studies on aging into targeted pharmacological interventions. Over the past three decades, genetic studies in model organisms and humans have identified and validated gene mutations and variants that prolong lifespan and enhance healthspan. Together, these findings show that modest changes in expression and/or activity of these genes can have a significant impact on aging and longevity. ASOs are emerging as a promising therapeutic modality, and they enable decreasing the expression of target genes in a specific manner in vivo. Importantly, we developed a novel ASO-based strategy for increasing levels of target proteins. With this, we are now well poised to pharmacologically target longevity-associated genes in vivo. In this project, we will: 1) design and test ASOs to modulate the levels of four longevity-associated genes, and 2) test if ASO treatment can extend lifespan and improve healthspan using a mouse model of accelerated aging. Completion of these studies will provide important preclinical insights into the promise of pharmacologically modulating longevity-associated genes to improve healthspan and increase longevity.

Building Social Capital and Wellbeing through the Older Adult Community Health Center Workforce

Principal Investigator	Thalia Porteny
PI Primary Affiliation	Mailman School of Public Health, Columbia University
Co-Investigator(s)	Brophy, SORCHA

PROJECT DESCRIPTION

Evidence suggests that older workers are reliable, capable of mastering new tasks and motivated to use their experienced skills to help others. These attributes serve to enhance supportive workplace environments and reduce turnover among workers of all ages, lowering costs for employers. Consequently, the Global Roadmap of Healthy Longevity recommends investing in age-friendly work environments to build social capital. The recommendation is relevant to the discussion of how best to respond to the recruitment and retention crisis

affecting Community Health Centers (CHC), which are key providers of primary care to underserved populations. With about 30% of its workforce being 55+ years of age, CHCs ought to consider recruitment and retention of older workers a high priority, especially since a recent (2022-2023) HRSA survey indicates that older adults within the CHC workforce self-reported significantly higher indicators of wellbeing (e.g. higher job satisfaction, higher intention to stay, and lower burn-out rate) relative to other age groups. But why is it that older CHC workers report higher wellbeing? And how can that well-being lead to the desired worker recruitment and retention? This study aims to answer these questions. Using a mixed-methods design that integrates community engagement, the proposed study will examine the predictive characteristics and on-the-ground strategies that contribute to wellbeing among older adults within the CHC workforce in comparison to younger adults. Evidence gathered will be used as the basis for a subsequent application for funding to pilot a program focused on improving older health worker recruitment and retention in CHCs.

Deep learning to estimate aging from magnetic resonance imaging (MRI)

Principal Investigator	Matthias Jung
PI Primary Affiliation	Massachusetts General Hospital and Harvard Medical School
Co-Investigator(s)	Raghu, Vineet, PhD

PROJECT DESCRIPTION

Background: Chronological age is an imperfect measure of aging. A new magnetic resonance imaging (MRI) based biological age measure has the potential to revolutionize 1) eligibility, 2) risk assessment, and 3) therapy monitoring for cardiovascular prevention, ultimately increasing longevity and reducing cardiovascular mortality, the leading cause of death in the United States. Aim: We aim to 1) use convolutional neural networks, a type of artificial intelligence, to measure biological aging from MRI and 2) demonstrate that this MRI age predicts non-fatal and fatal heart attack and stroke better than chronological age. Methods: First, we will build an MRI age model to predict chronological age in asymptomatic participants of the German National Cohort (NAKO) imaging sub study (n=30,770 MRIs). Next, we will evaluate this model in an independent testing dataset of 36,515 MRIs from the UK Biobank with detailed information on prevalent diseases, progression, outcomes, and genetic data: We will 1) compare the time to cardiovascular events using hazard ratios of MRI age versus chronological age and test whether this association remains robust after adjusting for traditional cardiometabolic risk factors (smoking, hypertension, and lipids), and 2) use the UKBB's whole genome sequencing data to place the MRI age in the context of genetic measures of aging. Relevance: We will develop a new tool to measure biological age from currently unused information on age-related changes in fat and muscle depots from existing MRIs. It will enable physicians to personalize prevention and researchers to better target aging and longevity mechanisms.

Empowering early Glaucoma detection in developing nations through a low-cost, small form-factor, portable, non-corneal IOP measurements device system for any setting.

Principal Investigator	Joshua de Souza
PI Primary Affiliation	Johns Hopkins University
Co-Investigator(s)	Digvijay Singh

PROJECT DESCRIPTION

In our endeavor to combat glaucoma—the leading cause of irreversible blindness—we propose a pioneering device. This compact, affordable, portable, and modular tool is crafted to effortlessly complement existing ocular instruments, aiming to significantly bolster early-stage glaucoma screening and treatment refinement. Given

glaucoma's insidious advancement, leading to considerable vision loss before detection, our device's capacity for precise, high-resolution intraocular pressure (IOP) readings marks a pivotal advancement in its early identification and management. Our motivation arises from the current technological and screening shortfalls that miss early glaucoma stages. Despite home monitoring technologies like iCare HOME, obstacles such as cost, adherence, and the necessity for training restrict their widespread use, particularly in developing regions. Conversations with medical professionals in high-volume eye care centers in the United States and India highlighted a critical need for an accessible, straightforward solution that delivers accurate IOP measurements across various corneal states without the need for extensive training or significant expense. We propose a dual-phase strategy: initially creating a benchtop mechano-optical system for accurate pressure detection on curved surfaces, then miniaturizing this system into a wearable prototype that aligns with daily optical accessories. This leap forward not only aims to make glaucoma screening universally accessible but also strives to preserve vision and enhance the quality of life for millions at risk. Our objective is to authenticate this technology through comprehensive testing and partnerships with leading eye care entities, paving the way for a future where glaucoma can be identified and addressed before causing irreversible damage.

Enhancing sleep in older adults using auditory stimulation: a machine learning approach

Principal Investigator	Stephanie Buss
PI Primary Affiliation	Beth Israel Deaconess Medical Center
Co-Investigator(s)	Westover, Brandon

PROJECT DESCRIPTION

Older adults face a risk of cognitive decline which increases with each decade of life, and are at risk of Alzheimer's disease and related dementias. New treatments are needed to maintain healthy cognition and delay onset of dementia during aging. Slow wave sleep declines with increasing age and is strongly linked with learning and memory. Prior studies using auditory stimulation during sleep to increase slow waves have shown promising yet inconsistent results. The optimal parameters for increasing slow wave sleep with auditory stimulation likely vary over the lifespan, between individuals, over time, and at different depths of sleep. This project will use machine learning to account for this variability and boost the effectiveness of auditory stimulation. Our study aims to enhance slow wave sleep in 15 older adults with normal cognition using auditory stimulation compared to Sham stimulation during separate daytime naps. We will use a novel closed-loop control algorithm, fine-tuned using machine learning, to personalize auditory stimulation parameters for each individual and adjust stimulation at different depths of sleep. We anticipate that this novel auditory stimulation technique will improve slow wave sleep in older adults, and that improvements in slow wave sleep will be linked to better performance on tests of memory and thinking. We expect the results of this study will set the stage for future clinical trials utilizing novel at-home auditory stimulation techniques to enhance slow wave sleep and promote healthy cognitive aging in older adults and patients at risk of Alzheimer's dementia.

Identifying language biomarkers to flag prodromal cognitive decline in at risk and underserved aging populations

Principal Investigator	Brielle Stark
PI Primary Affiliation	Indiana University Bloomington
Co-Investigator(s)	Newman, Sharlene

PROJECT DESCRIPTION

Identifying aging individuals in cognitive decline's prodromal stages is critical for implementing effective intervention to prevent or slow decline. However, prodromal changes currently cannot be reliably identified by standardized batteries of cognition. Presently, researchers and clinical practitioners must rely on self-report ratings of cognitive status, but these are not easily validated. This gap in diagnostic proficiency underscores the need to identify reliable objective behavioral markers that corroborate subjective ratings of cognitive decline. In this study, researchers in the Midwest and South will collaborate to collect objective data from a large and diverse aging population. This is imperative because research suggests that rural-living populations, and individuals from minoritized racial and ethnic groups, are underserved by the healthcare system and have an increased risk of developing cognitive impairment. Innovatively, the project will leverage speech and language data to extract objective metrics that can be acquired without intensive labor and significant expense in real settings, and are robust for differences in dialect and literacy. The aim is to validate whether the use of these behavioral markers drawn from speech and language testing can sensitively detect individuals who self-report as experiencing cognitive decline. The study will motivate longitudinal, prospective research evaluating the extent to which behavioral data serve as biomarkers of early cognitive change that then trigger early intervention.

MICROGRAVITY AS AN MODEL FOR STUDYING SARCOPENIA AND DRUG SCREENING

Principal Investigator	Ngan Huang
PI Primary Affiliation	Stanford University
Co-Investigator(s)	Rando, Thomas

PROJECT DESCRIPTION

With aging, skeletal muscle undergoes progressive muscle wasting known as sarcopenia. Sarcopenia is an aging-related syndrome associated with impaired muscle formation, as well as increased risk of frailty and poor health outcomes. Efforts to identify drug targets are hampered by the slow pace of its progression. Given the unique qualities of microgravity to accelerate the process of aging and muscle disuse, a tissue engineering approach to model sarcopenia in microgravity aboard the International Space Station National Laboratory (ISSNL) is a novel platform for testing potential drugs over a short period of time. We propose an engineered skeletal muscle-on-a-chip in microgravity platform for screening drugs that reverse sarcopenia using genetic and protein analysis. This project takes advantage of an upcoming flight in 2025 to perform drug screening aboard the ISSNL. The objective is to apply an established platform composed of engineered skeletal muscle-on-a-chip in microgravity for screening drugs that reverse sarcopenia by enhancing muscle formation. We hypothesize that a customized muscle-on-a-chip drug screening platform in the setting of persistent microgravity will accelerate drug discovery by identifying targets that promote muscle formation and a genomic signature approaching that of healthy muscle. Accordingly, Aim 1 will test the hypothesis that Earth-based studies in microgravity will refine the selection of potential drug compounds for testing aboard the ISSNL. In Aim 2, drug screening experiments will be performed concurrently by space astronauts in microgravity and by our personnel on Earth, followed by the collection of all samples for combined post-flight analysis on Earth.

Positive Childhood Experiences to Counteract Childhood Adversity for Healthy Longevity in Marginalized Communities

Principal Investigator	Angela Narayan
PI Primary Affiliation	University of Denver
Co-Investigator(s)	None

PROJECT DESCRIPTION

For the past 25 years, the fields of medicine, psychology, and public health have emphasized the effects of adverse childhood experiences (ACEs) on adulthood health problems, poorer longevity, and earlier mortality. The ACE literature has shaped a powerful narrative on preventing ACEs in children to reduce risk for lifespan health problems. Unfortunately, however, this narrative takes a “doom and gloom” approach and is often misrepresented as “those who experience ACEs will have poorer health outcomes and premature death.” This narrative is overly deterministic, pessimistic, and harmful, particularly to marginalized individuals who experience structural racism and systemic oppression, which render them particularly vulnerable to ACEs. This study will change this narrative to become “in spite of ACEs, positive childhood experiences promote long-term resilience and healthier longevity.” This project will recruit 500 adults with marginalized identities to test the hypotheses that higher levels of adults’ BCEs are associated with healthier longevity, operationalized as a) fewer lifespan physical health problems; and b) higher life satisfaction, over and above effects of adults’ ACEs. I will also test whether higher levels of adults’ parents’ BCEs are associated with parents’ a) fewer lifespan physical health problems, b) higher life satisfaction and quality of life, and c) their longer lifespan, over and above the effects of parents’ ACEs. This study would provide a novel proof of concept that higher BCEs relate to healthier longevity across two generations. This study would also help reframe the narrative that positive childhood experiences are healthy-promoting resources for marginalized communities.

Seek and destroy: Adoptive T cell transfer to clear senescence and extend health span

Principal Investigator	James White
PI Primary Affiliation	Duke University School of Medicine
Co-Investigator(s)	None

PROJECT DESCRIPTION

The decline in immune function is a common hallmark of aging. One critical role of our immune system is to identify and eliminate defective cells throughout the body including senescent and malignant cells. This too becomes dysfunctional with age and leads to an accumulation of senescence and increased susceptibility to cancers. T cells have become a popular target to improve immune function as they are capable to locating and clearing such cells. CART-cells, which have been engineered to identify cells with senescence markers are effective in cleaning senescence and improving health span. Unfortunately, CAR T-cell therapies have recently been shown to increase occurrence of T cell malignancy. This project will use young, unaltered T cells, which have far better function than aged cells, to enhance function of the aged immune system. We will use a heterochronic adoptive transfer approach to inject young T cells into old mice and measure senescence, malignancy and health span over time. Additional experiments will be performed using autologous transplantation, taking old T cells, eliminating “exhausted” T cells and expanding the healthy or naïve population and reinjecting into old mice. All donor cells will be GFP labelled for tracking. Health span measurements will include activity data, grip strength and exercise capacity.

Smart kneepads for aging monitoring and therapy

Principal Investigator	Shiqi Guo
PI Primary Affiliation	Mass General Hospital
Co-Investigator(s)	None

PROJECT DESCRIPTION

Our initiative aims to advance health equity for older adults through the introduction of innovative ‘smart’ kneepads integrating micro-scale sensors and stimulators. These cutting-edge platforms are meticulously designed to seamlessly integrate into daily life while addressing the specific challenges faced by the elderly

population in managing knee instability and pain. By continuously monitoring gait patterns, our kneepads provide real-time insights into the onset and progression of osteoarthritis and joint pain, facilitating early detection and intervention to alleviate discomfort and prevent further deterioration. Moreover, our system offers a comprehensive assessment of knee movement, serving as a valuable adjunct to traditional radiological evaluations. This wealth of supplementary data equips healthcare professionals with a more nuanced understanding of knee health, enabling them to make informed decisions regarding treatment strategies and rehabilitation plans. By harnessing the power of advanced sensor technology, our kneepads contribute to personalized care delivery, optimizing outcomes and enhancing the quality of life for individuals with knee-related conditions. Furthermore, our kneepads incorporate precision-targeted stimulation technology to facilitate accelerated recovery and improved functionality. By delivering tailored stimulation to the affected knee area, our system promotes muscle rehabilitation and joint mobility, complementing existing rehabilitation protocols and fostering better long-term outcomes for patients undergoing knee rehabilitation. Through the integration of advanced technology and data-driven insights, our initiative represents a significant advancement in promoting health equity and well-being among the aging population, empowering older adults to lead active and fulfilling lives.

System for Improving Quality of Life and Mobility in Kidney and Liver Failure

Principal Investigator	Dayong Gao
PI Primary Affiliation	University of Washington
Co-Investigator(s)	Novokhodko, Alexander

PROJECT DESCRIPTION

Advanced Multi-Organ Replacement (AMOR) is a life support system that removes protein bound toxins and excess fluid from patient blood. It has been validated in a pilot study in critically ill liver failure patients. It has the potential to improve the care of liver and renal failure because of the role of protein bound toxins in driving both diseases. It uses an innovative hemofiltration technology for fluid removal. In addition, it removes protein bound toxins using a mixture of albumin dialysis, charcoal-based albumin regeneration, and a regeneration wash for the charcoal filter. This enables it to have a smaller size than existing systems, creating the potential for home-based treatment in stable patients. To reach this potential, we are developing replacements for the highly expensive and scarce human serum albumin (HSA) typically used in such systems. We are also designing the system for automation, manufacturing, and ease of use. This funding will enable us to prepare the device for FDA approval, research alternatives to HSA, and test the usability of AMOR outside ICU settings.

The Neurobiological Mechanisms of Social Connection

Principal Investigator	Debra Karhson
PI Primary Affiliation	University of New Orleans
Co-Investigator(s)	None

PROJECT DESCRIPTION

Social relationships are a key modulator of healthy longevity. These relationships foster social connection between individuals and buffer the impact of longevity risk factors like cardiovascular disease, cognitive decline, and suicide. However, translating social interactions into social connections or even reinforcing social connectedness in pre-existing relationships can be a robust challenge for those with ill health (e.g., mental, physical, or emotional), marginalized identities (e.g., disabled people), and as we age. In the latest report the World Health Organization, 25% to 29% of older US adults report being lonely. While the ability to socially connect with others is a modifiable risk factor for loneliness and social isolation, few methods provide a biological approach. As such, clarifying the neurobiological mechanisms that facilitate the transition social interactions into

social connections would be transformative for improving the health and well-being of people as they age. Although previous research has focused on the “bonding” hormone (oxytocin) or the “feel good” hormone (dopamine), we suggest that anandamide (the “bliss” molecule), is best positioned to explain social connectedness. Our objective is to advance anandamide as a novel contributor to the neurobiology of social connectedness and its dysregulation contributes to loneliness and social isolation. Specifically, in aim one, we will combine the sensitivity and specificity of mass spectrometry with the versatility of capillary microsampling to define the relationship between circulating anandamide levels and individual differences in social pleasure. Then, in aim two, using two-person neuroimaging, we will assess how levels of anandamide impacts the synchronization of interacting brains.

Uncovering Health Risks: Machine Learning’s Role in Deciphering Body Composition Phenotypes for Disease Risk Prediction

Principal Investigator	Jonathan Bennett
PI Primary Affiliation	University of Hawaii
Co-Investigator(s)	None

PROJECT DESCRIPTION

Body composition represents the amounts of specific compartments that makeup a person's body weight, primarily driven by muscle, fat, and bone mass. Amounts of each compartment as well as the location of each are direct reflections of genetic and environmental factors, particularly driven by diet, physical activity, and age (or hormones). Countless studies have shown the role of the quantity and location of each compartment across the body being linked to health and/or disease risk. This has resulted in the development of body composition phenotypes that are used to predict disease risk. For example, an "apple" shape indicates greater fat storage in the abdomen as compared to in the legs in "pear" shaped individuals, placing these individuals at greater cardiometabolic, cancer, and mortality risk. With the advancements in noninvasive body composition assessment methods, capturing the composition of muscle, bone, and fat has become more routine in clinical practice. The proposed study will utilize body composition scans from multiple prospective studies with follow up sufficient to obtain health-related outcomes. Using advanced statistical models and machine learning, we will utilize these datasets to generate more comprehensive body composition phenotypes that incorporate whole-body and regional muscle, bone, and fat distribution. Connecting these phenotypes to outcome data, we will create improved risk prediction models to identify phenotypes (example: low muscle, high central obesity) that are at increased risk for negative health outcomes. These prediction models will be useful in clinical practice to improve health diagnostics and improve interventions to reduce risk across the lifespan.

Using naked mole-rat lymph nodes as bioreactor for ovarian rejuvenation

Principal Investigator	Miguel Brieno-Enriquez
PI Primary Affiliation	Magee-Womens Research Institute
Co-Investigator(s)	None

PROJECT DESCRIPTION

In humans, the ovary ceases its functions little more than the halfway through a woman's lifespan, leading to a very long post reproductive period. We recently found that the naked mole-rat (NMR, *Heterocephalus glaber*), amazingly maintains its fertility across its entire lifespan (~37 years). Moreover, we established that NMRs do not exhaust their oocyte stores and continue to produce primordial germ cells (PGCs) that could be a source for newly developed oocytes both in vivo and in vitro. The lymph node is a key organ of the mammalian immune system that has evolved to mount an immediate and orchestrated response against invading pathogens. Interestingly, the lymph node is also one of the first clinically observed sites of most cancer metastasis. In the

lymph node, tumor cells can survive, perhaps because the architecture of the lymph node provides direct access to essential nutrients and growth factors found in the blood. Since, lymph nodes support normal immune function as well as the survival of metastatic tumor cells, they might also promote the survival and expansion of healthy cells and tissues. Therefore, healthy cell and tissue growth in lymph nodes would provide a new approach for cell therapies in regenerative medicine. In this project we will test the hypothesis that when transplanted directly into the lymph nodes of NMR, PGCs, theca and granulosa cells engraft and show ectopic ovary functions in vivo, providing a strong evidence-based proof of principle for the develop of novel therapies for ovarian rejuvenation beyond just reproduction.