

HEALTHY LONGEVITY GLOBAL COMPETITION

2021 Catalyst Awardees

Sponsor: National Academy of Medicine

A multi-sensor wearable system with a personalized AI and multimodal biofeedback to improve balance of older adults at home

Principal Investigator	Alparslan Emrah Bayrak
PI Primary Affiliation	Stevens Institute of Technology
Co-Investigator(s)	Zaferiou, Antonia

PROJECT DESCRIPTION

Falls remain a leading cause of morbidity and decreased quality of life in our older adult community. About half of older adult falls occur in the home. In order to extend functional aging and healthy longevity, the multifaceted nature of fall risk requires holistic solutions that leverage emerging technology that can enter older adults' homes. In our proposed research, we will leverage and develop technology that uniquely integrates wearables, personalized Artificial Intelligence (AI), and multimodal real-time biofeedback- including music-based biofeedback. We propose that, in order to provide older adults with the agency to understand and improve their balance day by day, we will need to deeply engage older adults in the design phases through a collaborative process. Within this user-centered design framework, we will innovate a multi-sensor wearable system to monitor older adults' balance patterns and provide multimodal biofeedback that includes precise musical cues based on a personalized AI model running on a transparent user interface.

A new state-wide tele-health model to deliver ADRD tele-assessment and tailored care planning to older adults in low-access, high-risk rural communities

Principal Investigator	Jenay Beer
PI Primary Affiliation	University of Georgia
Co-Investigator(s)	Renzi-Hammond, Lisa

PROJECT DESCRIPTION

People are living longer than ever with Alzheimer's disease and related dementias (ADRD), but the key to increased longevity and quality of life with ADRD is early and accurate diagnosis. ADRD are underdiagnosed, in part because rural older adults lack access to specialty care needed for diagnosis. The U.S. healthcare system is unprepared for the increase in dementia incidence anticipated within the next 30 years. Tele-health is one feasible, acceptable solution to help fill the gap in providing ADRD staging and individualized post-diagnosis support. We propose a bold idea that utilizes telehealth to increase access to care and improve rates of ADRD diagnosis. We aim to create an innovative center (referred to as Center X) that mitigates telehealth pitfalls in rural communities: unreliable broadband, privacy issues, information accuracy, and usability. Center X is a new concept under development at a research institution with a large physical campus and a physical presence in all of the counties in our state, through a Cooperative Extension program. Using the University-supported networking, information storage, and staffing resources at these rurally located extension offices, we plan to adapt and validate clinical interviews and neuropsychological assessments delivered via telehealth. We will also

test our center model at an Extension office pilot site, to evaluate the implementation requirements to scale this model throughout – and beyond – our state.

A novel treatment for age-induced loss of muscle strength (frailty)

Principal Investigator	Stephen Meriney
PI Primary Affiliation	Department of Neuroscience
Co-Investigator(s)	None

PROJECT DESCRIPTION

More than one third of adults aged 65 and older will fall each year. The Centers for Disease Control report that falls are the leading cause of death relating to injury, and that aged adults are at the greatest risk. Falls in the elderly most often result from frailty, which is caused by muscle weakness, balance deficits, and gait instability. Dynapenia (defined as the age-induced loss of muscle strength) has been used to define weakness in the elderly and incorporates both neurological and muscle factors. Therefore, strategies to prevent dynapenia and to improve quality of life for the elderly are desperately needed. In this proposal, we will utilize a novel compound (GV-58) to enhance weakened communication at aged contacts between nerve and muscle. We hypothesize that daily treatment with GV-58 will not only directly strengthen these nerve-muscle contacts, but also trigger trophic effects that will further support muscle strength. We expect that these effects will reverse or prevent age-induced loss of muscle strength. Our goal is to transform the management of frailty in older adults.

A platform for identifying synergistic longevity interventions

Principal Investigator	George Sutphin
PI Primary Affiliation	University of Arizona
Co-Investigator(s)	None

PROJECT DESCRIPTION

We are on the precipice of real anti-aging medicine. Over the past several decades, research into the biology of aging has identified nearly a thousand genetic changes and hundreds of drugs capable of extending lifespan in eukaryotic organisms. The discovery of new pro-longevity drugs is growing at an unprecedented rate. The first clinical trial designed to evaluate the anti-aging potential of a drug—Targeting Aging with Metformin (TAME)—was approved in 2019. The biology of aging is complex, encompassing the progressive deterioration of various molecular systems across cell and tissue types. No single intervention is likely to simultaneously correct the full range of these changes, which is reflected by the fact that only a few interventions extend average lifespan beyond 20-30%. The most impressive longevity enhancement achieved results from targeted combination of two genetic interventions, resulting in lifespan extension in excess of 400% in the roundworm *Caenorhabditis elegans*. This and other studies suggest that substantial synergy may be achieved through combined therapy. To date, no systematic effort has been made to assess interactions between pro-longevity compounds, largely because standard methods for measuring lifespan are costly in terms of labor, resources, and time. Recent advances in automated data collection and analysis using robotic tools and machine learning have substantially reduced these barriers in invertebrate models of aging. Here we propose a proof-of-concept study using one of these systems to systematically screen drug combinations to identify beneficial additive and synergistic interactions in the context of healthy *C. elegans* longevity.

Advancing Cardiovascular Monitoring: Long-term, Accessible, Multi-Modal Soft Bioelectronics

Principal Investigator	Tan Philip
PI Primary Affiliation	University of Texas at Austin
Co-Investigator(s)	None

PROJECT DESCRIPTION

Cardiovascular disease (CVD) remains the largest cause of death in the world, leading to significant financial and emotional drain. However, current methods of assessing CVD are inadequate: it is impossible to assess the highly variable nature of the cardiovascular system in occasional clinical examinations. While office blood pressure can be useful for predicting CVD, critical metrics such the nocturnal blood pressure (BP) dip, beat-to-beat blood pressure variability, and arterial stiffness change are oft neglected due to the difficulty of acquiring these metrics. This proposal seeks to transform the world of preventative health care with two specific goals: first, to increase accessibility and uptake of cardiovascular monitoring in the general population; and secondly, to develop new methods to extract difficult-to-measure cardiovascular metrics. Here, I propose a nearly-imperceptible, continuously monitoring electronic tattoo (e-tattoo) capable of cuffless beat-to-beat BP, pulse wave velocity, SaO₂, SvO₂, heart rate analysis, respiratory rate, and cardiac output. The advent of wearable devices has demonstrated the power that health monitoring can have on medicine; however, the innate rigidity of these sensors limits them to the wrist. The proposed e-tattoo is an affordable, reusable, epidermal, sticker-like sensor. It will measure long-term cardiovascular metrics from the carotid artery, providing unparalleled insight to the central vasculature and the brain. By improving user comfort and decreasing costs, more people will benefit from wearable technologies. With enhanced cardiovascular data, physicians will have the insight to provide necessary preventative measures earlier and more effectively. Widespread, equitable, powerful health monitoring today will prevent health catastrophes tomorrow.

Automatically Refocusing Reading Glasses

Principal Investigator	Robert Konrad
PI Primary Affiliation	Zinn Labs
Co-Investigator(s)	None

PROJECT DESCRIPTION

With age, humans gradually lose the ability to focus to near distances. By their late 40s, most people struggle to view objects within arm's reach clearly, making it difficult to read text on a smartphone or newspaper, for example. This normal reduction in the refocusing range is known as presbyopia and eventually affects everyone. Presbyopia affects close to 2 billion people today and is set to become more prevalent as the population ages. Though presbyopia can be managed using reading glasses, bifocal lenses, or progressives, none of these solutions restore natural vision. Zinn Labs creates a new presbyopia correction called autofocals, a pair of automatically refocusing eyeglasses that mimic the focusing ability that was lost. With seamlessly integrated eye-facing cameras and focus-tunable optics, autofocals detect where a user is looking and then automatically refocuses to that distance. Simply looking at an object pops it into focus.

Combating Arterial Aging by Engineering the Gut Virome to Transmit Equol Producing Genes

Principal Investigator	Justyn Jaworski
PI Primary Affiliation	University of Texas at Arlington
Co-Investigator(s)	Trott, Dan

PROJECT DESCRIPTION

Advanced age is the major risk factor for cardiovascular disease (CVD), which is one of the leading causes of death in the industrialized world. Vascular aging manifests itself primarily through increases in large artery stiffness and impairments in endothelial function which are present in patients with clinical CVD and predictive of future cardiovascular events. A natural product known as equol has proven to be a key dietary factor in reducing large artery stiffness and the risk of age related CVD through estrogen receptor beta signaling. Unfortunately, only a minor fraction of Western population's possess the proper intestinal bacteria capable of converting daidzein, an abundant isoflavone in soy based products, into the natural product equol. Our goal is to produce and test an engineered virus (specifically a non-lytic bacteriophage) that infects the gut bacteria to provide new genes without harming the bacteria. This virus will thus allow re-engineering of the existing gut bacteria such that they can produce the enzymes required for conversion of daidzein present in dietary soy into equol. By providing a consumable bacteriophage drink, we provide a more widely acceptable alternative to engineering the intestinal microbiota to produce equol which will be protective against arterial aging. Through this we create the opportunity for every individual to have an equol-producing gut phenotype, such that they may benefit in living longer, healthier lives.

Community Brain Health in African American Faith-Based Organizations

Principal Investigator	Dean Sherzai
PI Primary Affiliation	Healthy Minds Initiative
Co-Investigator(s)	None

PROJECT DESCRIPTION

Alzheimer's disease is the fastest growing epidemic in the United States. Though the disease has affected every family, certain communities are disproportionately affected. The black community and women are at twice the risk of developing the disease. To date we have no treatment for Alzheimer's disease, but there is now consensus that Lifestyle intervention is very effective in preventing the disease. In the black population, given that poor environmental and lifestyle factors are main contributors to the greater risk, promulgation of appropriate information and implementation of lifestyle changes will have profound effect, but as extant literature has revealed, only when using the traditional venues of care such as the faith community and circumventing the usual limitations of access through use of novel technology and tele-communication can we make meaningful lifestyle changes that can reduce the burden of this terrible disease, and create sustainable structures. Our approach is based on a three-pronged process based on use of traditional community structures (faith communities), community women trainers, and technology and telecommunication to circumvent the usual impediments to change and adherence and create opportunities for sustained change with women at the lead.

Deciphering mechanisms of disease resistance and longevity in centenarians

Principal Investigator	George Murphy
PI Primary Affiliation	Boston Medical Center
Co-Investigator(s)	Perls, Thomas

PROJECT DESCRIPTION

Rare individuals with exceptional longevity suggest we have within us the potential for longer, more healthful lives. In the last decade, several studies have provided evidence that many centenarians and their offspring delay or escape aging-related diseases, such as cardiovascular disease and Alzheimer's disease, while markedly delaying disability. Tragically, the COVID-19 pandemic has disproportionately impacted older people with the majority of deaths due to the disease occurring in those over the age of 65. Yet, there appears to be a subgroup of select survivors, centenarians, that despite this age-related trend, survive COVID-19. These findings provide an unexpected and promising entry point for understanding healthful aging and the mechanisms that limit or embolden disease. In this study, we will combine innovative, longevity-specific induced pluripotent stem cell (iPSC)-based models capable of recapitulating human development with next generation sequencing approaches to identify the transcription factors, signaling pathways, and protein interaction networks that are linked to longevity and act to sustain cellular integrity and functionality during acute disease and in old age. This work has the potential to revolutionize our thinking concerning regenerative medicine and the aging process while unlocking a detailed roadmap to healthful living, disease resistance and longevity.

Defining drivers of ovarian aging to balance the scales toward healthy longevity

Principal Investigator	Jennifer Garrison
PI Primary Affiliation	Buck Institute for Research on Aging
Co-Investigator(s)	None

PROJECT DESCRIPTION

The female reproductive system ages precociously – females rapidly lose their reproductive capacity by midlife while somatic tissues continue to function normally. Beyond reproduction, the end of fertility sets off a cascade of negative health effects in women's bodies that impact bone, cognitive, cardiovascular and immune function. During the earliest stages of reproductive decline, prior to any changes in ovarian cyclicity and circulating estrogen, changes in the brain play an important role in the initiation of reproductive senescence. We think that menopause originates from signals in the brain. Our goal is to elucidate the complex interactions between the ovary and brain during middle-age and identify the neuronal factors that lead to the onset of reproductive decline in females in order to develop strategies to prevent or delay ovarian aging. Understanding mammalian limits to female reproductive capacity may provide important clues about aging in other tissues.

Delaying menopause and increasing reproductive longevity with Mullerian Inhibiting Substance

Principal Investigator	David Pepin
PI Primary Affiliation	Massachusetts General Hospital
Co-Investigator(s)	Donahoe, Patricia

PROJECT DESCRIPTION

Fertility clinics around the world measure the levels of a hormone called Mullerian Inhibiting Substance (MIS) as a marker of ovarian "age". Women are born with a set number of dormant follicles, the "ovarian reserve", which gradually get used over time until they are depleted at menopause. MIS is produced by growing follicles in the ovary where it inhibits the activation of dormant follicles by negative feedback, thus regulating the rate of depletion of ovarian reserve during aging. We have recently demonstrated that treatment with high levels of MIS in mice can inhibit dormant follicle activation and prevent the growth of new follicles. Because MIS acts on the first step of follicle activation, unlike oral contraceptives inhibit the final step of ovulation, MIS has the potential of preserving follicles in their dormant state, and thus extend the ovarian lifespan. Furthermore, the persistence of estrogen production even during complete suppression by MIS suggest there may be a therapeutic window at

which MIS can both extend ovarian lifespan and maintain hormonal health. We hypothesize that low-dose chronic administration of MIS by gene therapy could delay ovarian aging by reducing the rate of follicle activation while still maintaining sex steroid production. We propose to evaluate long-term treatment with MIS in female mice and assess their reproductive longevity and hormonal health. Thus, MIS may provide a novel paradigm of a natural hormone that combats ovarian aging and prevents or delays the negative consequences of menopause on bone, cardiovascular, neurological, and overall health.

Designing music-based interventions for aging-related pain: Sonifying body movement using interactive mobile technology to improve physical and psychological outcomes

Principal Investigator	Elizabeth Murnane
PI Primary Affiliation	Dartmouth College, School of Engineering
Co-Investigator(s)	None

PROJECT DESCRIPTION

Music is potent medicine, positively contributing to human development, disease treatment, and overall well-being throughout the lifespan. Exploring how music-based interventions can transform how we promote healthy aging, this proposal focuses on managing pain, which increases with age and is linked with numerous aspects of functioning, mental health, and quality of life. Given the experience of pain is both physical and psycho-emotional, we propose an integrative new paradigm: leveraging music's physiological, psychological, and neurological effects by developing interventions that combine self-expressive, music-making activities with movement-based therapies that aid pain recovery and management. We see interactive, sensor-embedded personal phones and wearables as a major opportunity to deliver and monitor the impacts of these interventions in an adaptive, personalized, and broadly scalable manner. We are particularly keen to explore musical interfaces that sonify body movement; for example, hand and finger exercises for osteoarthritis could be delivered through a virtual piano displayed on a smartphone screen, while a low-back pain patient's reaching exercises could be sonified by mapping Fitbit gyroscope data to musical frequencies, notes, and chords. Our research will pursue the participatory design and proof-of-concept evaluation of such interactive musical interventions. Focusing on establishing feasibility, generating design guidelines, and informing technical implementation, we will examine people's engagement with and the early efficacy of this style of intervention, in terms of short-term physical improvements (e.g., in pain intensity, impairment, proprioception) and psychological benefits (e.g., in anxiety, fear, mood, self-efficacy) as well as user experience metrics that foreshadow longer-term adoption and adherence.

Dynamic Signature of Cuffless Blood Pressure and Risk of Subclinical Brain Disease and Dementia

Principal Investigator	Yuan Ma
PI Primary Affiliation	Harvard T. H. Chan School of Public Health
Co-Investigator(s)	Hofman, Albert

PROJECT DESCRIPTION

Dementia is the most common neurodegenerative disease in older people, associated with high disability and dependency. Hypertension is a key player in the vascular etiology, but the relationship between blood pressure (BP) and dementia is not fully understood. Emerging evidence suggests that long-term BP variability contributes to dementia risk independent of BP level, possibly through autonomic disturbance or hemodynamic mechanisms. However, little is known regarding dementia risk in relation to short-term BP variability and other hemodynamic

features of BP waveforms, which can be obtained more conveniently via wearable devices. Therefore, we hypothesized that beat-to-beat BP variability predicts dementia risk independent of BP levels and that a “dynamic BP signature” derived from BP waveforms through novel prediction algorithms predicts dementia risk better than BP variability alone. We will test our hypothesis in a population-based cohort study among ~2,000 dementia-free older adults who underwent beat-to-beat BP measurements and subsequent long follow-up of dementia cases for up to 20 years. We will select the most informative set of dynamic features of BP waveforms and develop a novel dynamic BP signature using Cox models and random survival forest models. Model performance will be compared using model fit parameters. Our proposal is highly transformative with the rapid advances of wearable devices and cuffless BP monitoring techniques that enable us to quantify dynamic BP waveforms conveniently with low cost. Our proposal will inform the potential of dynamic BP measures as novel targets for dementia prediction and prevention.

Enabling Healthy Longevity by Investigating the Aging Extracellular Environment

Principal Investigator	Xi Ren
PI Primary Affiliation	Carnegie Mellon University, Department of Biomedical Engineering
Co-Investigator(s)	None

PROJECT DESCRIPTION

When a car is zigzagging, it may be due to the car being compromised, or the road being slippery, or both. Aging is a result of chronic, system-level changes of almost all organs within the body, and affects not only the cells (“car”) but also their microenvironment, the extracellular matrix (ECM, “road”). Prevailing anti-aging therapeutic development focuses on targeting cellular signaling but remains ineffective. Despite being one of the most significant pathological hallmarks of aging and end-stage organ failure, the ECM itself has rarely been explored for direct drug targeting. This research will lay the foundational work to promote a transformation in aging research and therapeutic development by cataloging for the first time how aging modulates the ECM synthetic programs and identify common aging ECM signatures that are shared across different organs (the lung, heart and liver) in the mouse model. In particular, this research will develop a newly synthesized ECM (newsECM) profiling strategy for selective labeling, enrichment and ultrasensitive detection of nascent ECM proteins synthesized over defined short time spans with unprecedented daily temporal resolution, irrespective of the complex pre-existing ECM background. In the short term, this research will inspire interventions targeting key aging ECM molecular signatures to slow down aging progression on cell and tissue levels, and thereby promote longevity of organs and individuals. In the long term, this research will enable investigation of the extracellular mechanism underlying the interplay of aging and chronic diseases, such as organ fibrosis, and thereby promote healthier longevity.

Human Activity Recognition to Avoid Fall Related Injuries in the Older Adult Population

Principal Investigator	Rebecca Tarbert
PI Primary Affiliation	ActiveProtective Technologies, Inc
Co-Investigator(s)	Arun Jayaraman

PROJECT DESCRIPTION

One out of four older adults experience a fall each year and falls are the leading cause of death from injury for older adults in the United States. The cost of falls average greater than \$50 billion and continues to create ongoing cost for individuals and families due to subsequent disability. Fall management and mitigation strategies have focused on identification of fall risk factors and assessment provided by health care providers when accessible. The mystery of why falls occur is many times due to the unwitnessed events of falls and near-

falls that occur leading up to a serious fall injury. The ability of a body worn sensor which accurately detects fall motions to provide fall analysis by which to offer specific interventions can provide answers to avoiding falls and fall injuries for the most vulnerable. Clinic visits allow only a sample of physical performance assessment during examination and cannot provide the medical professional with specific information regarding how the person reacts to perturbations in natural contexts. This research will be using a wearable smart belt containing a 3D sensor on the lower back area which continuously monitors human motion to provide activity recognition and insight for recognition and categorization of types of falls. What motions the individual encounters and how they physically respond within near-fall and fall-type scenarios can provide insight on where areas of intervention including strength, flexibility and balance training can be provided. This information regarding activities precipitating falls can offer medical insight to avoid serious fall injuries.

Identifying Predictive Biomarkers of Effective Immunity in Aging Populations

Principal Investigator	Wayne Koff
PI Primary Affiliation	Human Vaccines Project
Co-Investigator(s)	None

PROJECT DESCRIPTION

The world is aging at an unprecedented rate, and we are not prepared. By 2050 nearly 1.6 billion people will be over age 65, creating widespread public health challenges. This aging population will dramatically increase the burden of non-communicable diseases and enhance our vulnerability to infectious diseases. The human immune system holds the key to improving human health, and within this system lies an immense capacity for disease prevention. Technological innovations are now allowing us to reimagine and reshape the future of human health by understanding and harnessing the immune system in new ways. We have embarked on an ambitious effort to decode the human immune system, identify the biomarkers of effective immunity, and utilize this information to accelerate the development of novel therapeutics, vaccines, and diagnostics for diseases of aging populations. We use licensed vaccines to probe immunity across the age spectrum and differentiate responders from non-responders, and then utilize artificial intelligence and machine learning to develop predictive models for effective human immunity. We have recently conducted pilot trials with licensed hepatitis B and shingles vaccines in adults and elderly subjects, and performed the most comprehensive immunologic and systems biological assessment of host responses ever undertaken. Catalytic support will enable data integration and frontier supercomputing analyses to identify biomarkers of effective immunity, which we will then validate in larger-scale trials in well-studied cohorts of aging individuals. These studies may open the door for transformative new approaches to enhancing human immunity, preventing disease, and prolonging healthy lives among aging populations.

Joy for People Living with Dementia using a Virtual Assistant

Principal Investigator	Lisa Fournier
PI Primary Affiliation	University of Southern Indiana
Co-Investigator(s)	None

PROJECT DESCRIPTION

“Joi” is an Artificial Intelligence (AI) Virtual Assistant to improve emotional well-being and independence for people living with dementia (PLWD), especially those aging-in-place. A positive emotional atmosphere is important for PLWD to thrive and age well. This can be facilitated by creating a joyful environment. This project seeks to investigate whether a virtual assistant can help create such an environment for the PLWD. Joy is a moment in time, not a mood. Joy is linked to dopamine systems that reward the brain when having a positive experience, as well as reinforce behavior, motivating a person to repeat an activity. According to Dr. Allen Power,

being joyous is a durable strength that can help PLWD grow and rise above the challenges of cognitive disabilities by providing meaning, positivity, happiness, contentment, pleasure, and resilience. The Virtual Assistant (VA) creates personalized “joy pops” for the PLWD within a smart-home living environment. The “joy pops” by the VA are triggered based on input from sensors in the smart home, including motion, sound, temperature, and light. The smart home environment is designed and personalized for the PLWD to provide a comfortable and moderately stimulating environment to reduce agitation, apathy, and anxiety. Most virtual assistants or technology solutions for PLWD, which are limited, focus on social connection or safety. However, this can clash with the PLWD quality of life, feelings of independence, and ultimately their well-being. Rapid prototyping methods will be used throughout the 12-month project, in collaboration with people living with dementia.

Repurposing the lightbulb to support healthy ageing

Principal Investigator	Daniel Joyce
PI Primary Affiliation	University of Nevada, Reno
Co-Investigator(s)	Webster, Michael

PROJECT DESCRIPTION

Light is a powerful modifier of human behavior and drives the way that we feel, think, and act. However, in today’s society we don’t get enough light during the day while getting too much light at night, and this is compounded by degradation of the sensory pathways during aging. This results in dysregulated sleep and wake rhythms, exacerbating mental and physical illnesses. One solution is to harness the lightbulb to not only help us see better, but to help us feel better too. Scientific advances mean that we are now discovering and mapping the dedicated visual physiological pathways that drive wellbeing, coupling this with new LED lighting technology could allow us to craft lightscapes that support health too. This program of research will determine the potential for such technology to support aging, by developing lights specially tuned to drive these pathways and counteract the extensive sensory deficits that occur with aging, and measuring how reactions by the brain, body and mind are improved by these lights. In doing so, we will understand the best ways to target such pathways using nothing but light. Ultimately, we will repurpose the lightbulb as an extremely cheap tool that can support healthy ageing throughout the lifespan.

The Aging Exposome: Characterizing Bidirectional Effects of Exposures and Aging

Principal Investigator	Ram Gouripeddi
PI Primary Affiliation	Department of Biomedical Informatics, University of Utah
Co-Investigator(s)	Facelli, Julio

PROJECT DESCRIPTION

Effects of a lifetime of environmental and lifestyle exposures on aging or age-associated diseases are not well understood. Exposures not only directly affect biological pathways but also have genetic mechanistic influences on disease and well-being. Aging leads to reduced reserve capacity to compensate for the effects of exposures due to changes at molecular and cellular levels. The challenge in generating aging exposome is the absence of readily available records for individuals over the course of their life. Instead, these would need to be assimilated from historic person reported data along with publically available data. In this proposal we explore the use of machine learning and artificial intelligence to generate exposome records and demonstrate their value in aging health studies.

The Role of Mitochondrial in Stem Cell Transplantation and Repair

Principal Investigator	Atena Zahedi
PI Primary Affiliation	Stem Cell Research Center
Co-Investigator(s)	None

PROJECT DESCRIPTION

Transplantation of human neural stem cells (hNSC) to repair damaged tissues in traumatic injuries has shown promise in pre-clinical studies and early clinical trials. Spinal cord injury (SCI) is marked by a secondary injury phase characterized by an ischemic oxidative microenvironment, secreted pro-inflammatory factors, and mitochondria dysfunction in the surviving damaged cells/tissues. We hypothesize that survival and engraftment of transplanted hNSCs is hindered in a manner reliant on their intrinsic mitochondrial properties. Mitochondria are vital for the bioenergetics of cells during times of high demand such as proliferation, stem cell differentiation, and migration. To test this hypothesis, we utilize tissue-derived hNSC lines derived in our lab, previously tested for their repair potential (efficacy) in restoring functional recovery after SCI. Transcriptomic analysis comparing an efficacious line (UCI161) versus a non-efficacious line (UCI152) revealed differences in “mitochondria fitness traits” (MFTs): mitochondrial bioenergetics, mitochondrial biogenesis, permeability transition and redox potential, and autophagy and mitophagy. We identified drug candidates to target mitochondrial function by screening FDA-approved mitochondrial drugs. Treatment of hNSC with a bioenergetics-enhancing drug led to increased mitochondrial hyperfusion and tunneling nanotube (TNT) formation, whereas treatment of hNSC with a biogenesis drug led to enhanced mitochondria mass and proliferation in UCI161. MTT, autophagy analysis, mitochondria membrane potential (MMP) and ATP analysis revealed UCI161 were better responders to bioenergetic drugs, where UCI152 responded optimally to biogenesis enhancement. hNSC with improved mitochondrial response capabilities show promise for translation to neuro-transplantation in chronic traumatic injuries and neurodegenerative diseases characterized by mitochondria dysfunction and loss of bioenergetics.

The Role of Sirolimus in Delaying Aging and Age-Related Diseases

Principal Investigator	Irina Timofte
PI Primary Affiliation	University of Maryland
Co-Investigator(s)	None

PROJECT DESCRIPTION

Recently there is a growing interest in developing effective interventions to slow the aging process and reduce the risk of chronic disease. Drugs that inhibit the mammalian target of rapamycin (mTOR inhibitors) such as sirolimus are promising modulators of the aging process by delaying the mechanisms of ageing at the cellular level. Changes in mTOR signaling are closely associated with inflammation, and cell growth and survival. Therefore, there is a growing appreciation of the potential impact of Sirolimus in slowing aging process and prolonging healthy lifespan. The proposed work has the potential to identify a new and critical therapeutic intervention in geriatric medicine to decrease progression of aging-related disorders and improve long term outcomes. Our hypothesis is that sirolimus is one of the first pharmacological agents that impact the aging process and chronic disease development of aging associated chronic disease. We propose the following specific aims: SA1: To determine whether sirolimus will improve phenotypic/functional markers of aging as measured by walking speed, chair stand, standing balance, grip strength, body mass index, waist circumference muscle mass at 1 year follow-up when compared to elderly patients not receiving sirolimus. SA2: To determine if sirolimus will impact circulating biomarkers (ESR,CRP, Hb) of aging.

Toward Safe and Independent Senior Mobility: Development of a supportive tool to self-assess driving performance

Principal Investigator	Kate Hyun
PI Primary Affiliation	University of Texas at Arlington
Co-Investigator(s)	Park, Seri

PROJECT DESCRIPTION

The National Highway Safety Administration showed that the population of people 65+ increased by 32 percent from 2009 to 2018 while traffic crash fatalities of this age group increased by 30 percent. Recognizing the importance of safety of older drivers, researchers have explored older driver's self-reported driving behavior patterns. However, little is known about the gaps existing between older adults' perception on driving efficacy and their actual driving performances, and the corresponding impacts on road safety. Considering the significant deterioration of cognitive ability and responsiveness to dangers with aging, it is imperative to understand older driver's driving performance and develop a decision-support tool that enhances self-awareness and self-control of driving. The goal of this study is (i) to understand the in-depth correlations between older adults' perceived driving patterns and observed driving performance and (ii) develop a supportive tool for older adults to self-evaluate their driving performances and for agencies to support mobility decision making. This study develops an innovative standardized tool that could be adopted by government agencies such as DMV or DPS as well as health institutions to support older adults' self-assessment of driving efficacy. The tool uses state-of-the-art sensors and driving simulators to accurately capture the driving performances of older adults. If this study successfully establishes a proof-of-concept and a prototype tool that supports older drivers' safe mobility by enhancing their self-awareness on driving, this research will significantly advance the current state-of-practice and contribute to a new framework to improve the healthy longevity of older adults.

Transcranial focused ultrasound for enhanced glymphatic-based delivery of antibodies for brain imaging and therapy

Principal Investigator	Aryal Muna
PI Primary Affiliation	Biomedical Engineering Department, University of Texas at Austin
Co-Investigator(s)	Porter Tyrone

PROJECT DESCRIPTION

We purpose to develop a new strategy for efficient delivery of large-sized agents to a big portion of the brain which is not possible from the existing brain drug delivery technologies. Given that antibodies have the unique capability to be used for both diagnostic and therapeutic applications in the brain, we propose a simple, transcranial ultrasound procedure that we can noninvasively apply throughout the brain to effectively transport antibodies that are injected intrathecally. Completion of the proposed study may have an important positive and immediate impact by offering a novel drug delivery method that can give brain-wide access to many biological agents for managing brain disorders. It is expected that this work will lead to the development of novel imaging and therapy strategies to combat aging-related brain disorders such as Alzheimer's disease and cancer in a minimally invasive and potent manner, which will increase the quality of life and will extend the lifespan of those patient populations. Given the low intensity of ultrasound with FDA-approved clinical ultrasound systems, there will be a clear path for clinical translation of the method. Further, this method will provide a means for on-demand and spatiotemporal control of enhanced glymphatic transport, which could be used for causative evaluation of the role of the glymphatic system in a variety of physiological states, like sleep, and diseases like Alzheimer's disease or traumatic brain injury, or chronic neuroinflammation. Thus, the method will prove useful for discovery and translational research in neuroscience and age-related neurological disorders.

Transformative oral drugs that reverse muscle weakness and aging in older adults

Principal Investigator	Stan Watowich
PI Primary Affiliation	Ridgeline Therapeutics
Co-Investigator(s)	None

PROJECT DESCRIPTION

Every adult over 40 years old faces the relentless loss of skeletal muscle strength, caused primarily by the inability of aging muscles to regenerate fully. In the elderly, decreased muscle strength leads to reduced mobility and physical activity, which places older adults at high risk for falls, fractures, chronic diseases, assisted living, and cognitive disorders. Muscle stem cells (muSC) are responsible for the muscle regeneration and repair that maintains muscle strength and function. Unfortunately, muSC become increasingly senescent during aging and cannot sufficiently regenerate and repair skeletal muscle to maintain strength. Current recommendations to reduce age-linked muscle weakness include resistance exercise and protein-rich diets; at best, these approaches provide modest benefits. Given the critical unmet need to prevent muscle weakness during aging, we are developing transformative drugs that reactivate aged muSC and reverse muscle degeneration and aging in older adults. Our drugs utilize a novel mechanism-of-action to reactivate aged muSC. We discovered that the enzyme nicotinamide N-methyltransferase (NNMT) is upregulated in skeletal muscle during aging and disrupts muSC energetics and function. In paradigm-shifting preliminary studies with aged animals, we demonstrated that NNMT inhibitors could double muscle strength, size, and muSC regenerative capacity. Support from the Healthy Longevity Global Competition will help accelerate preclinical development of a safe, once-daily pill that restores full muscle strength and function in aging adults. Our innovative therapy will provide numerous health, wellness, and economic benefits to the world's ever-increasing elderly population, including increased healthy, productive, independent living. No comparable drugs exist in this space.

Unraveling the Mycobiome: Fungi as a novel class of probiotics to target inflammaging

Principal Investigator	Schott Eric
PI Primary Affiliation	Solarea Bio, Inc
Co-Investigator(s)	Kiel, Douglas

PROJECT DESCRIPTION

An aging population has led to a significant global increase in age-related diseases including cardiovascular disease, Alzheimer's, and others. At the core of this is chronic low-grade inflammation known as inflammaging, and recent evidence describes the gut microbiome as a key regulator of the inflammaging process through direct impact on immune system development and function. Studies have demonstrated the efficacy of probiotic bacteria in treating inflammatory disorders through several biological processes (epigenetic alteration, mitochondrial dysfunction, others) known as hallmarks of aging. While the impact bacteria have on the immune system and human health is well described, fungi, a major component of the gut microbiome (mycobiome) have been largely overlooked due to multiple factors including fungi's large, complex genomes that require deep sequencing and a hybrid assembly, lack of fungal genome databases for functional gene prediction, and underdeveloped bioinformatic tools to identify fungal metabolites important to human health. We hypothesize the mycobiome could offer a large, untapped reservoir of probiotic fungi with the ability to combat inflammaging. Given this, we propose to sequence a subset of our fungal collection with Nanopore technology and develop bioinformatic tools to complete hybrid assembly, annotation, and gene prediction to identify fungi with probiotic potential. Further, we will assess candidate strains with in vitro cell culture systems to identify fungi with anti-inflammatory properties to be tested in vivo. Here, we have the opportunity to discover safe and novel fungal

agents and open an entirely new class of probiotics to specifically reduce inflammaging and related chronic illness.