

HEALTHY LONGEVITY GLOBAL COMPETITION

2023 Catalyst Awardees

Sponsor: National Academy of Medicine

A new approach to treating cataracts, the world's leading cause of blindness, without energy or capital equipment

Principal Investigator	Kunal Parikh
PI Primary Affiliation	Johns Hopkins University School of Medicine
Co-Investigator(s)	Shameema Sikder

PROJECT DESCRIPTION

Globally, 17 M people are blind and 83.5 M have moderate-to-severe visual impairment due to cataracts, which are primarily a disease of aging. Cataracts are the world's leading cause of blindness and account for more than 90% of the total disability adjusted life years in low- and middle-income countries where reduced income, increased ultraviolet radiation, and lack of access to treatment has led to a disproportionate burden of cataracts. Cataract surgery is a simple, 15-minute procedure which almost immediately restores an individual's vision, and has been shown to significantly reduce the risk of dementia and improve physical and mental health, income, productivity, quality of life, and life expectancy. However, the current gold standard of phacoemulsification has high costs and training burden, requires potentially damaging ultrasonic energy, and has limited utility for patients with mature cataracts. Manual approaches to cataract surgery have lower costs and are suitable for mature cataracts, but require a larger incision and lead to significantly worse visual outcomes, causing inequity and reduced patient acceptability. We propose development of an inexpensive, manual, handheld cataract fragmentation device that eliminates the need for capital equipment and ultrasonic energy and is capable of safely fragmenting mature cataracts. By achieving manual cataract fragmentation and removal through a 3 mm incision, the system will provide outcomes comparable to the current gold standard, fit into the existing training and surgical workflow, and improve accessibility of cataract surgery.

A Wearable Ultrasound Sensor for Continuous Blood Pressure Tracking

Principal Investigator	Shu Xiang
PI Primary Affiliation	Softsonics LLC
Co-Investigator(s)	Sheng Xu

PROJECT DESCRIPTION

Hypertension, a major risk factor for heart disease and stroke, affects nearly 47% of adults in the United States. However, 1 in 5 patients are unaware of their condition. Correct diagnosis is often hindered by the fact that blood pressure can be greatly influenced by the stress associated with a clinical setting. Current cuff-based measurement protocols only capture a snapshot of ever-changing blood pressure levels, leading to life-threatening tragedies, under or over-medication, and millions of dollars wasted in the healthcare system. Here we propose a soft wearable ultrasound sensor patch that continuously measures the dimension of the brachial artery to provide beat-to-beat blood pressure tracking. The proposed approach aims to address these challenges by providing an easy-to-use continuous blood pressure sensor which packs medical ultrasound into a wearable band-aid format. Stretchy sensor packaging enables the device to conform to the skin surface, eliminating the

need for a trained professional operator or coupling gel typically used in traditional medical ultrasound. The device design employs an island-bridge structure that accommodates deformation with buckled metal wires. The device is designed to have a large acoustic window that ensures the artery remains within the sensing range of the transducers even during motion. An easy-to-use blood pressure data tracker with clinical accuracy will play an important role in reducing cardiovascular disease-related deaths and substantially expand the life expectancy of the U.S. population. By transforming medical ultrasound into a wearable format, the proposed approach also has implications beyond blood pressure.

Brain stimulation targeting shared networks to improve physical and cognitive functions in older adults

Principal Investigator	On-Yee Lo
PI Primary Affiliation	Marcus Institute for Aging Research, Hebrew SeniorLife
Co-Investigator(s)	Brad Manor

PROJECT DESCRIPTION

Promotion of physical and cognitive function is critical to maximizing healthspan. Mounting evidence indicates that physical and cognitive functions are closely dependent upon one another; and most of the time, these physical and cognitive functions are linked to the brain functions. Emerging work revealed that the ability to remain stable while walking and the ability to remain focused while engaging in a goal-oriented task, along with numerous age-related disorders, are linked to a unique antagonistic relationship between two brain networks, named the dorsal attention network (DAN) and the default network (DN). The purposes of this project are to 1) develop a personalized non-invasive brain stimulation aimed to optimize the inter-network connectivity and communication, and to 2) examine the effects of this novel, network-based brain stimulation on resting-state functional connectivity, walking and attention performances. This proof-of-concept project is expected to demonstrate direct, cause-effect evidence that the nature of between-network connectivity can be modulated. By linking the changes in the brain to changes in physical and cognitive behaviors, we are hopeful that this work will improve our understanding of the cortical regulations of gait and attention and provide initial, immediate evidence that this characteristic of functional connectivity may serve as a target for fall prevention, rehabilitation, and other behaviors and diseases (e.g., Alzheimer's disease) that are known to be dependent upon the modularity of the DAN and DN. If proven successful, this approach through modulating other brain network communication promises to have a tremendous application to numerous age-related syndromes and diseases.

Cataract screening for elderly nursing home residents using smartphones and artificial intelligence

Principal Investigator	Nakul Shekhawat
PI Primary Affiliation	Johns Hopkins University School of Medicine
Co-Investigator(s)	Kunal Parikh

PROJECT DESCRIPTION

Cataract is a common cause of visual impairment among elderly nursing home residents, who disproportionately suffer from visual impairment due to lack of access to eye care specialists such as ophthalmologists. Cataract surgery leads to dramatic improvements in vision, cognition, and quality of life but lack of access to cataract screening remains a key barrier to cataract surgery among nursing home. We propose to develop a decentralized, de-skilled, semi-automated, smartphone-based platform for screening and diagnosis of cataracts in the nursing home setting. In Aim 1, we will develop hardware to enable in-focus imaging of complex, multiplanar anterior eye segment anatomy and illumination of critical aspects of crystalline lens/cataract

anatomy. In Aim 2, will develop software to enable reliable image capture of cataract anatomy by combining images taken from multiple anatomic planes of the eye, adjusting camera exposure across different patient subgroups, automatically detecting pupil centration prior to image capture, and providing healthcare workers with instant feedback on image quality. In Aim 3, will use 1,200 images and linked clinical data collected via our smartphone platform to develop a machine learning algorithm designed to enable healthcare workers to perform real-time, point-of-care diagnosis of cataract in nursing homes. Our algorithm will incorporate several innovations including bias mitigation, domain adaptation, and incorporation of clinical metadata to improve diagnostic performance. The proposed approach to cataract diagnosis has potential to bypass several longstanding constraints and significantly expand access to cataract screening and vision care in the vulnerable elderly nursing home population.

COBRA: Cancer, Older adults, Balance, and Resistance Activities

Principal Investigator	Kristen Fessele
PI Primary Affiliation	Memorial Sloan Kettering Cancer Center
Co-Investigator(s)	Andrea Cuadra

PROJECT DESCRIPTION

The COBRA (Cancer, Older adults, Balance, and Resistance Activities) project will develop and test the use of a self-paced digital health promotion program, delivered by an interactive voice assistant through a smart speaker/display in the home setting. It will be created using participatory design methods in partnership with a diverse group of older adult cancer survivors to create culturally inclusive messaging and activity options that are engaging and promote genuine, positive changes towards long term healthy behaviors. Most cancers occur among older adults, and without intervention, cancer treatment can result in long-lasting fatigue, decreased physical endurance and ability to care for oneself independently. Fortunately, health promotion activities, like gradually increasing physical activity and eating a healthy post-cancer diet can help to improve energy and function, but there are few available resources to educate survivors right after treatment ends, when they may be most receptive to this information. The proportion of older adults is growing quickly around the world, making this an urgent issue. The digital COBRA intervention will be easily accessible at the end of cancer treatment and will assess a survivor's current physical function and tailor the education and activities to their individual needs and preferences. Use of an interactive voice assistant has been shown to be an effective method for older adults less familiar with computers to engage with digital interventions. We believe that COBRA's early assessment and individualized intervention will enhance recovery after cancer treatment and improve independence and healthy longevity for this population.

Dawn-to-Dusk Dry Fasting for Rapid Reversal of Aging

Principal Investigator	Ayse Leyla Mindikoglu
PI Primary Affiliation	Baylor College of Medicine
Co-Investigator(s)	Sung Yun Jung

PROJECT DESCRIPTION

DNA double-strand breaks and DNA methylation pattern changes (epigenetic change) are strongly associated with aging. Previous studies showed that fasting from dawn to dusk without eating or drinking (dawn-to-dusk dry fasting) showed upregulation of proteins associated with extreme longevity, increased autophagy, tumor suppression, DNA repair, and reduction in several oxidative stress and inflammatory biomarkers. Dawn-to-dusk dry fasting with meals just before and after fasting likely acts as a robust zeitgeber, aligns mealtimes with day-night cycles, and entrains metabolic regulators of the circadian clock to dawn and dusk, thereby increasing mRNA amplitude and improving downstream protein synthesis for multiple metabolic pathways. In this project,

we will evaluate the changes in key regulator proteins and DNA methylation patterns in the peripheral blood mononuclear cells (PBMC) collected from healthy subjects and subjects with metabolic syndrome who fasted from dawn to dusk for 4 weeks. To quantify proteins in PBMC before, during, and after dawn-to-dusk fasting, we will perform nano ultra-high performance liquid chromatography-tandem mass spectrometry. We will perform DNA methylation array analysis using genomic DNA to estimate epigenetic age before, during, and after dawn-to-dusk fasting. This proof-of-concept study will be conducted by a unique team of experts in state-of-the-art facilities and provide a mechanistic understanding of the effects of dawn-to-dusk dry fasting on human DNA repair proteins and DNA methylation patterns. The results of this study will provide a valuable guide to the design of future larger-scale clinical studies on the health and longevity effects of the dawn-to-dusk dry fasting regimen.

Developing therapeutic agents reverse ageing and metabolic decline

Principal Investigator	Cary Depel
PI Primary Affiliation	
Co-Investigator(s)	Guy Barry

PROJECT DESCRIPTION

Magnaetus Therapeutics believes that in order for longevity measures to be most effective, lifespan increases must be twinned with supportive metabolic interventions. This will ensure the ultimate aim of greater quality, as well as quantity of life, for the increasing majority of our population that is overweight/obese. To deliver on this aim, Magnaetus is working with Genflow Biosciences to develop peptide therapeutics based upon the multiple metabolic activities of a novel circulating protein. Serum levels of this hormone are increased by exercise and calorie restriction, and suppressed by ageing, obesity and inactivity. It exhibits endocrine effects across numerous aspects of the energy economy, acting to mimic the downstream benefits of exercise and calorie restriction.

Longevity is directly targeted through a feed-forward loop with mTOR suppression. This is coupled with additional capabilities, including appetite suppression, fat burning and insulin production/sensitivity. The discrimination of these activities is realised through selection of individual loops of the parent protein's repeated helical structure, enabling tailoring of therapeutic response to patient needs through production of specific peptide therapeutics.

Development of next-generation antibiotic adjuvants to enhance antibiotic efficacy and improve infection outcomes

Principal Investigator	David Kitzenberg
PI Primary Affiliation	Primer Pharmaceuticals Corp
Co-Investigator(s)	None

PROJECT DESCRIPTION

Infections are a major cause of morbidity and mortality in older populations. Human immunity senesces, causing increased susceptibility to a range of infections. Furthermore, increasing antibiotic resistance is alarming because when antibiotics fail to clear an infection, patients are subject to greater morbidity, adverse events, and health risk. Thus, improving treatment of bacterial infection has tremendous potential to positively impact health and longevity across all populations, and older populations in particular. Antibiotics can fail to kill bacteria without the bacteria possessing traditional antibiotic resistance due to a phenomenon called antibiotic tolerance or persistence. Recent scientific findings have demonstrated that these antibiotic tolerant or persistent bacteria function as a stepping-stone for resistance acquisition and serve as a bacterial reservoir to repopulate an infection, thereby driving treatment failure and antibiotic resistance. This proposal aims to reduce antibiotic

treatment failure and the emergence of antibiotic resistance by developing antibiotic adjuvant drugs that bolster the efficacy of commonly used antibiotics against tolerant and persistent bacteria. This project will, (1) utilize validated screening platforms to identify small molecule antibiotic adjuvants against common human pathogens; (2) use infection models to test antibiotic/adjuvant combination therapy for superiority over standard antibiotic therapy; (3) use bacterial evolution studies to determine an adjuvant's potential to reduce antibiotic resistance emergence. Improving infection outcomes with antibiotic adjuvants will promote health and longevity for a significant number of people, worldwide. To solve the antibiotic resistance problems of the future, we need to start now.

Digital Solutions to Reduce Maternal Morbidity and Mortality in Refugee Women

Principal Investigator	Gunisha Kaur
PI Primary Affiliation	Weill Cornell Medicine
Co-Investigator(s)	Richard Boyer

PROJECT DESCRIPTION

Pregnant refugee women have an elevated risk for uncontrolled hypertension, which increases gestational complications including preeclampsia, eclampsia, and maternal mortality. Gestational hypertension and preeclampsia also substantially increase the incidence of cardiovascular disease later in life, and pose significant risk to the fetus. Our research demonstrates several barriers that prevent refugees from accessing in-person healthcare. However, we have found that digital approaches are a pragmatic means to overcome these challenges, and that >90% of refugees have personal smartphones compatible with digital health applications. We have created a customized digital refugee health system, which includes a wearable device plus a customized app, for early risk stratification and identification of gestational hypertension, cardiovascular and preeclampsia risk, and related biomarkers using predictive machine learning, ecological momentary assessments, and remote digital data. In this research, we will clinically train and validate this digital system. Our hypothesis is that our digital system can detect gestational hypertension and preeclampsia in pregnant refugee women with >85% sensitivity as compared to the gold standard, a clinic diagnosis. We have over a decade of experience in refugee health research, including with digital tools, and are based at one of the only federally funded refugee research centers in the U.S. Increasing the diagnosis of hypertension and preeclampsia risk in pregnant refugees enables targeted interventions that can positively alter health outcomes. This project has the potential to improve the healthy longevity of this vulnerable and understudied population for generations, and can be scaled for use across global humanitarian emergency settings.

Enhancing Health Longevity of Individuals with Limited Mobility

Principal Investigator	Sungmee Park
PI Primary Affiliation	Georgia Institute of Technology
Co-Investigator(s)	Sundaresan Jayaraman

PROJECT DESCRIPTION

According to the CDC, one in four adults in the United States has a functional disability and the percentage of adults with mobility-related disabilities is 11.1%. Around 3.3 million individuals rely on wheelchairs for their daily living. One of the major challenges for those using wheelchairs continuously, especially those with spinal cord injuries (SCI), is the occurrence of a pressure injury (PI) which is localized damage to the skin and underlying soft tissue usually over a bony prominence. A PI is a serious, lifelong complication with the potential to “interfere with physical, psychological and social well-being and to impact overall quality of life.” Thus, there is a critical need for a technological solution to address this challenge and remove the barriers to health longevity for wheelchair users. Research in the Principal Investigator’s lab has led to a first-of-its-kind prototype in which a

fabric-based sensor network serves as an unobtrusive information infrastructure to continuously monitor both pressure and moisture at an individual's contact points with a surface (e.g., bed, wheelchair); the acquired data is then harnessed to trigger an evidence-based alert and provide a personalized intervention in real-time to relieve the pressure and moisture at the specific contact points, and potentially prevent a PI. The research team will work with veterans using wheelchairs at the VA to understand their needs and adopt a transdisciplinary approach to refining the building blocks in the current prototype that will reduce the potential for a PI, and lay the foundation for an innovative assistive technology.

HyperReact: Game-Changing Magnetic Resonance Imaging Technology

Principal Investigator	Clifford Bowers
PI Primary Affiliation	University of Florida
Co-Investigator(s)	Austin Evans

PROJECT DESCRIPTION

Magnetic Resonance Imaging (MRI) is a non-invasive, non-ionizing imaging technology that is a critical tool towards maintaining health longevity. However, the broad usefulness of this technique is constrained by its inherently low sensitivity and high operational complexity. Clinical MRI is restricted mainly to the observation of protons in water, the most concentrated chemical species in the body, while the much weaker carbon-13 signatures of metabolites present at much lower concentrations remain undetectable. We will exploit parahydrogen, a metastable form of dihydrogen that exists in an entangled quantum state, as an inexpensive generator of ¹³C MRI sensitivity enhancement. This will allow fluxes of key metabolites to be imaged, affording a superior approach to disease diagnosis and treatment monitoring. Our objective is to create a portable and inexpensive platform, termed HyperReact, to generate hyperpolarized ¹³C contrast agents for in-vivo MRI. HyperReact will combine flow-chemistry with state-of-the-art spin order transfer techniques developed in our lab to rapidly synthesize, purify, and deliver ¹³C-hyperpolarized pyruvate, a critical metabolic substrate whose metabolic fate is oftentimes altered in many diseases including cancer. HyperReact enabled MRI will be validated in a non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (NAFLD & NASH) mouse model using the small animal MRI facilities at the National High Magnetic Field Lab. HyperReact will also enable clinical MRI in low-field magnets instead of the complex and expensive superconducting magnets required for conventional MRI. By overcoming the sensitivity problem of conventional MRI, HyperReact will transform and democratize access to this powerful medical technology.

Leveraging Genetic Determinants of Age-Retained Brown Fat to Identify Novel Therapeutic Targets for Cardiometabolic Disease

Principal Investigator	Paul Cohen
PI Primary Affiliation	The Rockefeller University
Co-Investigator(s)	None

PROJECT DESCRIPTION

Weight gain is a common feature of human aging and contributes to decreased longevity by contributing to the risk of diabetes, heart disease, and many types of cancer. Humans possess white fat, which contributes to cardiometabolic disease and increases with aging, and brown fat, which protects against this pathology but declines with aging. Given the promise of brown fat to protect against obesity and associated diseases, the goal of this project is to understand the mechanism responsible for the age-related decline in brown adipose tissue function. We will use the power of human genetics to identify and characterize the genetic basis for age-retained brown fat function. To achieve this goal, we will utilize a unique human cohort with age-retained brown fat, that has undergone whole exome sequencing. Using a computational pipeline, we will prioritize rare coding variants

predicted to be functionally deleterious that are enriched in our cohort with age-retained brown fat relative to controls. Candidate variants will then be tested in a brown fat cell line to assay their effects on cellular function. Promising candidates will then be studied further in animal models. This approach would provide the first genetic underpinnings of brown fat regulation in humans and entirely new insights into understanding healthy aging. The genes identified may also represent novel therapeutic targets for age-related weight gain and associated cardiometabolic disease.

Mitochondria plaques as a novel therapeutic target for Alzheimer's Disease

Principal Investigator	Xiuli Dan
PI Primary Affiliation	University of Minnesota
Co-Investigator(s)	A Bohr

PROJECT DESCRIPTION

AD is one of the most prevalent neurodegenerative diseases associated with human aging. Although mechanisms based on the pathology of tau proteins and amyloid plaques are well recognized, therapeutic approaches based on these hypotheses have failed in clinical trials, leaving AD a still incurable disease. Thus, a clearer understanding of AD pathology is needed. Using our newly established APP/PSEN1/mtKeima mouse model, we discovered that damaged mitochondria which are transported to lysosome for degradation largely accumulate around the A β plaques in AD mouse brain. We term these plaques mitochondrial plaques (MPs). These MPs largely co-localize with lysosomal-associated membrane protein 1 (lamp1), which confirms their presence within acidic lysosomes. Importantly, these MPs are different from Beta-amyloid (A β) plaques that they localize closely, but with no overlap. We demonstrated that A β plaques are not the only type of plaques in AD. Other types of plaques, like the novel MPs identified in our preliminary studies, can also form. This novel finding provides a possible explanation for failure in current clinical trials that targeting A β plaques may not be a wrong approach, but insufficient. Based on our novel and exciting findings, we now propose to provide an in-depth understanding of the molecular mechanism of AD and propose new treatment strategies by targeting MPs or both MPs and A β plaques. If proven true, our hypothesis will provide new thoughts and directions for AD treatments.

Reducing “Inflammaging” for Healthy Aging

Principal Investigator	Prashant Nagpal
PI Primary Affiliation	Sachi Bioworks Inc.
Co-Investigator(s)	None

PROJECT DESCRIPTION

Older age is the leading risk factor for AD, cognitive decline, and a range of cardiometabolic diseases. While different mechanisms can drive these aging related diseases, a key upstream mechanism identified in all these diseases is low-grade chronic inflammation with age, termed “inflammaging”, that drives downstream pathology seen with age and perhaps the biggest obstacle in healthy aging. For example, brain aging involves decline in cognitive function that can develop into mild cognitive impairment (MCI, which further increases AD risk), and both brain aging and MCI are associated with adverse processes that are also central to AD, like the deposition of amyloid beta (A β) and hyperphosphorylated tau. Taken together, these observations suggest that upstream, age-related processes underlie the development of AD. The central tenet of this application is that inflammation is perhaps the most upstream/central hallmark of aging, and that targeting it specifically may be a promising therapeutic strategy. The key aspect is not non-specific immunosuppression, but a highly targeted suppression of “rouge” chronic inflammation, while still preserving the key functions of the immune system, like fighting infections or cancer. Our proposed work will enable us to understand how NF-kB/NLRP3-Nan oligomer treatment

improved: 1) specific domains of cognitive function with aging and identify underlying mechanisms; and 2) assess potential improvement in cardiometabolic health in aged mice with treatment. Comparing our findings with aging databases will provide insight on age- vs. pathology-specific mechanisms, and on timing (i.e., prevention vs. treatment).

Reimagining Product Regulation by Quantifying the Economic Externalities of Commercial Influences on Health Behaviors

Principal Investigator	Sara Singer
PI Primary Affiliation	Stanford University
Co-Investigator(s)	Stephen Downs

PROJECT DESCRIPTION

The “product environment,” the collection of products and services people use in everyday life, from industries such as entertainment, food, technology and transportation, is a major driver of the chronic disease epidemic in the United States. Its impact dwarfs efforts to reduce chronic disease through medical treatment or programs aimed at individual behavior change. This impact represents an economic externality – a social cost external to the market, that, if properly captured within our economic system, could ultimately transform the product environment to become more supportive of health. This project will demonstrate the feasibility of identifying population health impacts of individual consumer products and services, estimating societal costs of those impacts, and applying those estimates to financial reporting documents. It will build on two pioneering efforts: the Building H Index, which has assessed the impacts that popular products and services have on five key health behaviors, and the Impact-Weighted Accounts project at Harvard Business School, which has developed an approach for creating financial accounting reports that measure and value in monetary terms the impact a company has on its employees, customers, and the environment. The project will serve as a proof-of-concept for a new paradigm for product regulation – in which businesses are held accountable for the influences that products have on people’s health behaviors.

Restoring mitochondrial function using viral gene reconstitution therapy in aged muscle and heart

Principal Investigator	Olga Bielska
PI Primary Affiliation	Buck Institute for Research on Aging
Co-Investigator(s)	Eric Verdin

PROJECT DESCRIPTION

Mitochondrial dysfunction is a major contributing factor in age-related loss of skeletal muscle mass and cardiovascular disease. Mitochondrial division is a critical process for maintaining mitochondrial function. We and others have recently discovered that loss of mitochondrial division protein (MDP) is an age-related phenomenon. It affects multiple tissues and is regulated by a complex molecular mechanism. In humans and in mice, the loss of MDP due to genetic mutations results in cardiac and neuromuscular diseases, and severely shortened lifespan. We hypothesize that restoration of normal levels of MDP should help to revitalize mitochondrial function in aging and reverse negative age-related changes. As a proof of concept study, we aim to test whether our adeno-associated virus (AAV) gene therapy can restore mitochondrial function and improve overall health and lifespan, by first testing in mice with engineered MDP deficiency, and next in naturally aging mice. We will target heart and muscle tissues, which suffer the most from age-related mitochondrial division loss. If effective, this therapy could be applied to other affected organs. Our AAV-based therapy has unique advantages over traditional pharmaceutical interventions, including its ability to target specific tissues and cells, minimal side

effects, and long-term benefits. Our research could significantly impact the field of healthy longevity, and we are committed to developing this therapy further. The Healthy Longevity Catalyst Award would provide invaluable support for our ongoing research. Overall, AAV gene therapy holds great promise for the future of medicine by leading to development of cures for many age-related diseases.

Sound Asleep

Principal Investigator	Maggie Li
PI Primary Affiliation	Carle Illinois College of Medicine
Co-Investigator(s)	Nafisa Mostofa

PROJECT DESCRIPTION

Sleep is tied to every aspect of health. Insufficient sleep is associated with adverse cardiovascular outcomes such as obesity, elevated serum glucose, hypertension, and metabolic syndrome. Furthermore, tasks that rely on higher cognitive functions, such as logical reasoning, parsing complex sentences, complex subtraction tasks, and tasks involving a flexible thinking style and the ability to focus on many goals simultaneously, are significantly affected even after one single night of sleep deprivation. In population-based survey studies, approximately one-third of adults between the ages of 18 and 60 report sleeping less than seven hours per night on weekdays or workday nights, which is widely deemed insufficient by the current scientific consensus. Slow wave sleep (SWS) is a stage of sleep characterized by the presence of low-frequency brain waves. It is considered the most restorative stage of sleep and is crucial for many physiological processes and functions, including memory consolidation, immune function, and emotional regulation. While the science surrounding the relationship between sound and sleep has existed for some time, until now, no device has been developed to specifically increase slow-wave sleep via auditory stimulation. This device presents a novel approach to addressing the growing demand for noninvasive, effective sleep solutions. Our device will utilize a closed-loop system that measures EEG waves and adjusts stimulation parameters, such as amplitude and frequency, to enhance slow wave sleep. This device represents a significant milestone in the field of sleep medicine: an accessible easy-to-use wearable has the potential to change the way people approach sleep.

The Human Element: A Gesture-Powered Software Platform of Neurologic Music Therapy-Based Games and Puzzles: To Stimulate Neuroplasticity And Prolong Functional Independence in Individuals with Alzheimer's Disease

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

PROJECT DESCRIPTION

Alzheimer's Disease (AD) is a neurodegenerative disease that compromises neural connectivity and the body's ability to repair brain tissue. The culmination of this damage is a dehumanizing, fatal brain atrophy that robs its victims of their memories, independence and identity. Recent insights into the pathogenesis of AD however, suggest therapies which stimulate neuroplasticity will be central to future treatments which slow and/or reverse its progression. Furthermore, the emerging field of Neurologic Music Therapy (NMT), which uses the neuroscience of music to design tailored therapeutic interventions that stimulate neuroplasticity and improve cognition, shows promise of revolutionizing the treatment of AD. More specifically, for AD patients, nostalgic music from the patient's childhood, or other reverential period of their life, may be leveraged with NMT as a vehicle to access portions of their memory and/or identity that are being lost to the disease. The brain's complex use of disparate neural networks to process music is believed to be key in unlocking access to this information

via new alternative neural routes, if/when typical neural pathways have been compromised by AD. Therefore, we are developing NMT software featuring a curriculum of interactive, adaptive, and therapeutic, gesture-powered games/puzzles designed to enhance neuroplasticity and prolong functional independence in AD patients. Our technology is based on a motion-powered “smart instrument” that uses computer vision to map body-motion onto sensible musical outcomes, which can be customized to the user’s sensitive medical needs and musical tastes, allowing them to instantly harness the neurological benefits of creating music from body-motion.

The Liver Protects Against Aging Related Dementia

Principal Investigator	Sui Seng Tee
PI Primary Affiliation	University of Maryland School of Medicine
Co-Investigator(s)	Xiaobo Mao

PROJECT DESCRIPTION

Parkinson’s disease (PD) affects the elderly, with devastating symptoms affecting movement and mobility. This is due to the death of brain cells, resulting in PD traditionally being viewed as a brain disorder. However, increasing evidence points to the involvement of the intestines. PD patients have mutated proteins called alpha-synuclein that are improperly folded. These proteins have also been found in the intestines, leading to experts to believe PD may originate from food or the environment. The intestines are connected to the liver by a major blood vessel called the portal vein. The liver plays an important role in removing toxins from blood, in a process called autophagy. Autophagy can be seen as ‘housekeeping’, recycling toxins into useful molecules for liver cells. This proposal studies the role of the liver in PD. We believe that the liver plays a protective role, detoxifying mutant alpha-synuclein from the intestines to delay spread to the brain. We test this assumption in mice, where mutant alpha-synuclein is directly injected into the gut. Alpha-synuclein is expected to travel from the gut to the brain, passing through the liver. We will measure traces of the mutant protein in the liver, followed by blocking gut-to-liver spread by surgically ligating the portal vein. Finally, we use genetic methods and drugs to up-regulate autophagy in the liver, expecting a delay in gut-to-brain spread of mutant alpha-synuclein. If successful, these experiments lay the groundwork for future drugs that target the liver, to prevent or delay the debilitating symptoms of PD.

Using Methioninase as a methionine restriction mimetic to delay aging and age-dependent diseases

Principal Investigator	Andrey Parkhitko
PI Primary Affiliation	Aging Institute / University of Pittsburgh
Co-Investigator(s)	None

PROJECT DESCRIPTION

Aging is a major risk factor for various human pathologies. The incidence of many chronic diseases including cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases increases exponentially with age. Aging is characterized by the altered activity of different metabolic pathways. Targeting the metabolic pathways, whose activities are altered with age, has been shown to increase healthspan and delay the incidence of age-related diseases. The activity of methionine metabolism is dramatically altered during aging and under different age-dependent pathological conditions. Moreover, dietary methionine restriction (MetR) has been shown to extend health and lifespan in different species. However, it is very hard to implement MetR protocols in clinical practice due to the low palatability of MetR foods, which represents a major obstacle for bringing dietary MetR into clinical practice. This project aims to address this by using a bacterial enzyme, Methioninase, as a novel tool for the degradation of methionine and for delaying aging and age-dependent diseases. In this proposal, we will

use a novel mouse model that will allow us to express Methioninase either in the whole body or in a tissue-specific manner. We will test whether degrading methionine is sufficient to prevent obesity in mice fed a high-fat diet or delay age-dependent deterioration of healthspan. The goal of this project is to test whether the benefits associated with dietary MetR could be achieved without limitations of methionine amounts in food by using Methioninase, which would then allow the use of this enzyme to delay aging in healthy individuals.