

HEALTHY LONGEVITY GLOBAL COMPETITION

2020 Catalyst Awardees

Sponsor: Agency for Medical Research and Development of Japan

A Fully-implantable Wireless Brain Machine Interface for Functional Restoration

Principal Investigator	HIRATA Masayuki
PI Primary Affiliation	Osaka University
Co-Investigator(s)	YOKOI Hiroshi; SUZUKI Katsuyoshi; SUZUKI Katsuyoshi; Jason Palmer

PROJECT DESCRIPTION

Physical disability due to various neurological diseases and spinal cord injuries enlarges dissociation between biological and healthy lifetime. We developed a fully implantable brain machine interface (BMI). This innovative BMI system records accurate brain activity (intracranial electroencephalogram), decodes the brain activity using artificial intelligence, and enables disabled people to manipulate communication assistive devices and robot arms. Now we are going to begin a pivotal clinical trial of the BMI for communication control. However, there are several issues regarding motor control. Rehabilitation and caregiving are standard methods to help physical disability. However, efficiency of rehabilitation is limited, and caregiving causes economic loss due to caregiving burden. This proposal helps to reduce caregiving burden, because the implantable BMI helps care recipients free from nursing care and to return to society, by manipulating communication assistive devices and robot arms by their selves. In addition, in globally progressing unprecedented ageing society, increased caregiving burden to elderly people seriously affects world economy. the implantable BMI may prolong healthy lifetime of elderly people by 5-10 years and promote reduction of caregiving burden to elderly people.

A Novel Strategy for Mucosal Immune Enhancement by an IgA Antibody Drug and an IgA-inducing Chemical

Principal Investigator	SHINKURA Reiko
PI Primary Affiliation	University of Tokyo
Co-Investigator(s)	None

PROJECT DESCRIPTION

In this project, we develop a novel strategy for enhancement of mucosal barrier function through high-affinity mucosal IgA, to solve the problems of non-curable infectious diseases and allergic diseases. Enhanced mucosal barrier function results in healthy longevity which does not rely on symptomatic treatments. Our findings demonstrated that monoclonal IgA can attack bacteria in a species-specific manner, which is totally different from antibiotic treatment. We would like to develop IgA antibody drugs as oral medicine against pathogenic infections as well as dysbiosis. Most of the current treatments for allergic diseases seek to inhibit IgE responses. However, these treatments are still not curative because they do not prevent the allergen invasion into our bodies. Our candidate chemical (Bryostatins) induces selective IgA, but not IgE class-switching of B cells so that the enhanced production of mucosal IgA can prevent allergen from invading mucosal surfaces. Our innovation will provide a means to not only treat but also prevent, various diseases.

Age-related Physiological Dysfunction Based on Clock Aging

Principal Investigator	YOSHITANE Hikari
PI Primary Affiliation	The University of Tokyo
Co-Investigator(s)	None

PROJECT DESCRIPTION

The circadian clock generates transcriptional rhythms with a cycle of about 24 hours, and makes genes function only at the required time. Therefore, deficiency of the clock gene causes not only sleep disorders but also many aging-like symptoms such as hypertension, cardiac diseases, immune depression, and cataract, and significantly reduces the lifespan. Here I define the age-related circadian clock abnormality as “clock aging”. The working hypothesis is that part of the aging-associated symptoms is caused by disruption of the functional rhythms from the circadian clock. Recently, we showed that the expression profiles of a series of rhythmic genes were dramatically changed in aged mice, and we created a mouse model in which the transcriptional rhythm of a single rhythmic gene was genetically stopped by small deletion in the promoter region of the gene, for imitation of the aging state: A mouse model for “clock aging”. In this study, I elucidate the mechanisms of aging-associated symptoms as phenotypes in the clock aging mice, and pursue the molecular mechanisms that cause abnormality in clock output with aging.

Artificial Intelligence-based Diagnosis and Treatment of Age-related Neuropsychiatric Disorders

Principal Investigator	KAWATO Mitsuo
PI Primary Affiliation	Advanced Telecommunications Research Institute International, Brain Information Communication Research Laboratory Group
Co-Investigator(s)	MOTEGI Tomokazu; Jessica E. Taylor

PROJECT DESCRIPTION

We have previously identified brain activity patterns specific to different neuropsychiatric disorders (called “biomarkers”). We showed the therapeutic effects of using fMRI neurofeedback to train patients to “rewire” these to better resemble the brain activity patterns of healthy people. Unlike drugs, such intervention has resulted in no known negative side-effects to date and directly targets impairment-specific brain activity. Here, we propose the development of a similar intervention for cognitive age-related disorders. Innovative AI techniques will be used in the analysis of brain data to develop a method that can predict the probability of having/developing different levels of dementia. These results could then be used for early detection, determination of disease-stage and appropriate treatment, and as a basis for neurofeedback. It should therefore provide a novel useful method for increasing the quality of life of elderly people and might also be used to improve the cognitive function of healthy people.

Basic Research for Creation of Exercise Pills that Improve QOL of the Elderly by Combatting Sarcopenia and Frailty

Principal Investigator	OGURA Toshihiko
PI Primary Affiliation	Tohoku University
Co-Investigator(s)	HAKOSHIMA Toshio

PROJECT DESCRIPTION

Medical intervention that keeps elderly people socially, economically and physically active would have great beneficial impacts on our society aging rapidly all over the world. To do an unprecedented trial, we propose here exploitation of exercise pills, one of the anti-aging geroprotectors, which combat sarcopenia and frailty, and eventually extend both healthspan and lifespan.

At the moment, only exercise and caloric restriction (CR) have been shown to definitely extend lifespan, and several chemical compounds that possess exercise-mimetic and CR-mimetic effects are under extensive analyses, although their molecular mechanisms of actions are largely unknown. This unsolved mystery is the biggest obstacle, preventing the development of effective geroprotectors and exercise pills. We are identifying molecular targets of exercise-mimetic and CR-mimetic chemical compounds. We have successfully identified several “druggable” targets and solved their X-ray crystal structures at an atomic resolution, which are essential to design safe and more efficient drugs. In our modern sedentary lifestyle, novel exercise mimetics, which will be developed based on our findings, could benefit the welfare of people and our society.

Cholinergic Input in Fast Versus Slow Cognitive Decline Upon Aging

Principal Investigator	TSUNO Yusuke
PI Primary Affiliation	Kanazawa University
Co-Investigator(s)	Ulkuhan Guler; Luisa V Lopes; SUSAKI Etsuo A.

PROJECT DESCRIPTION

As people age, some maintain the cognitive function, while others suffer from rapid cognitive decline. It is thought that the cholinergic circuit gradually degenerates with aging, resulting in impaired cholinergic function and memory impairment. However, the lack of a method to measure acetylcholine release in vivo with high resolution has hampered subsequent studies. Therefore, we bring together our specialized knowledge to propose the elucidation of the temporal and functional characteristics of cholinergic dysfunction, which may underlie the rapid and slow cognitive decline due to aging.

The establishment of a non-invasive synaptic surrogate of human cholinergic function has the potential to inform about a patient's condition and vulnerability to memory deficits in a personalized manner with prognostic value. The identification of the cholinergic input which is dysfunctional in age-impairment will add knowledge to the field and hopefully provide novel clues to interfere or delay memory decline upon aging.

Developing Next Generation Therapy for Age-related Fibrotic Disorders Targeting Secreted Type Pro-fibrotic Protein (A-FiD Research Consortium Study)

Principal Investigator	SHIMIZU Ippei
PI Primary Affiliation	Niigata University
Co-Investigator(s)	None

PROJECT DESCRIPTION

The Aim of this study is to 1) Establish the concept and biomarker of Age-related Fibrotic Disorder (A-FiD), 2) Generate therapies for A-FiD. Here I define A-FiD as disorders including heart failure with preserved ejection fraction(HFpEF), atrial fibrillation(Afib), chronic kidney disease (CKD), sarcopenia or non-alcoholic steatohepatitis(NASH) etc. Recently, I identified a circulating pro-Fibrotic Protein(cFP) in plasma of 1) aged individuals, 2) HFpEF, 3) Afib or 4) NASH patients. Dietary obesity increased cFP in plasma, and pilot studies analyzing loss or gain of function models showed cFP becomes pathogenic in HFpEF, atrial fibrillation,

sarcopenia or NASH models. To further examine the pathogenic role of cFP in A-FiD, and test its contribution for “synchronization of aging (sync-aging)”, I established international A-FiD research consortium. Members of this consortium have biobanks, skills in basic, translational, clinical and genomic research, enabling us to do comprehensive and conclusive studies (Figure).

Development of a New Device for Estimating Cognitive Function, with Application to a Remotely Supervised exercise training system

Principal Investigator	MASUKI Shizue
PI Primary Affiliation	Shinshu University
Co-Investigator(s)	NOSE Hiroshi

PROJECT DESCRIPTION

The goal of this project is to develop a device for estimating cognitive function (CF) from the heart rate (HR) response before everyday voluntary movements. Previously, we developed a remotely supervised exercise training system based on peak aerobic capacity (VO₂peak), comprising interval walking training (IWT) and an IoT system, and we reported that IWT increased VO₂peak and improved lifestyle-related diseases, cognitive function, and healthcare costs for 8,700 middle-aged and older people. We recently upgraded the system to a smartphone application to increase versatility. Separately, we found that HR response before starting voluntary movement increased as individual VO₂peak increased. Thus, we hypothesize that CF can be monitored via HR response before everyday voluntary movements. Accordingly, by adding a HR measurement function to our application, we seek to develop a self-management system to improve CF by increasing VO₂peak, using the plan-do-check-action (PDCA) cycle. This system will promote independence and enhance the quality of life in older people.

Development of a Non-invasive Pathological Diagnostic Tool Based on Integrated MRI-microscopic Imaging to Revolutionize Dementia Research

Principal Investigator	HANAKAWA Takashi
PI Primary Affiliation	Kyoto University
Co-Investigator(s)	SAWAMOTO Nobukatsu; HASHIMOTO Hitoshi

PROJECT DESCRIPTION

Cure for dementia is yet to be available despite of the past investment and effort, prompting us to think out of the box. To test a new hypothesis about a common pathological mechanism underlying cognitive decline in Alzheimer's disease (AD) and Parkinson's disease (PD), we launched a multi-center cohort study (PADNI) recruiting both healthy and cognitively impaired elderly people, and have been collecting neuroimaging, body fluids, and cognitive/clinical data. However, a critical limitation of the current dementia studies is the lack of definitive diagnosis until postmortem investigation. Therefore, we propose to develop technology bridging between neuroimaging and neuropathology. This technology is expected to allow us to investigate pathological mechanisms in both ex and in vivo and, moreover, to develop imaging methods, by which voxel values directly reflect neuropathology. The technology, when available, will enable non-invasive premortem pathological examination, allowing for early screening of dementia and precise evaluation of trial outcomes.

Development of a Novel Alzheimer's Disease Treatment Method by a Unique Brain Protein-derived Peptide with an Advanced Transdermal Absorption Device

Principal Investigator	OUCHI Yasuomi
PI Primary Affiliation	Hamamatsu University;
Co-Investigator(s)	SUZUKI Toshiharu

PROJECT DESCRIPTION

While many medical trials such as antibody therapies for amyloid to combat Alzheimer's disease (AD) are still in vain due to a difficulty in curing the disease, a new drug with a novel mechanism acting on unique targets has been expected to develop. This project entails a novel peptide drug for treating AD. The drug candidate is based on a newly discovered molecule Alcadin β which is intrinsic in the brain. Alcadin β is known to be cleaved to p3-A β , a brain-derived peptide that functions as a suppressor of AD progression. Experiments also show that a decrease in the p3-A β level in the brain relates to generation of dementia and that a peripheral administration of this peptide drug compensates its reduction, allowing to prevent from the development and progression of the disease. Removing a chance of AD onset has a great impact on the welfare in our recent longevity society. We will show substantial evidence on biochemical and pathophysiological changes in the brain before the onset of dementia and the effectiveness of our peptide drug acting on them in vitro and in vivo experimental settings using rodents and monkeys. Currently, we are performing animal experiments to verify the drug safety and a good transdermal delivery of the drug to the brain as a necessary step before first administration to the human (FIH) in a clinical trial. It is expected that the use of a newly-developed device enabling controlled transdermal absorption of the peptide drug allows the optimal drug-delivery to the brain. With a preclinical proof of concept in the efficacy of this drug in vitro and in vivo, we plan to start the clinical trial not only at an early stage of the disease but also during a preclinical period to prove its effectiveness in humans in our already-established cohorts.

Development of a Risk-estimation System for Alzheimer's Disease Using Blood-based Biomarkers

Principal Investigator	NAKAMURA Akinori
PI Primary Affiliation	National Center for Geriatrics and Gerontology;
Co-Investigator(s)	KANEKO Naoki; ISHII Kenji; ISHII Kazunari; ITO Kengo; KATO Takashi; ARAHATA Yutaka

PROJECT DESCRIPTION

It is known that brain amyloid- β (A β) deposition starts decades before the onset of dementia symptoms of Alzheimer's disease (AD), and about 20-30% of cognitively intact elders have A β pathology. Therefore, reliable stratification of such individuals "at risk for AD" is essentially important to develop effective drug/non-drug interventions for AD. However, as currently available methods, A β -PET and CSF testing, are costly and/or invasive, blood-based tests are strongly desired. Recently, we have developed a high-performance plasma A β biomarker that detect abnormal A β deposition, using the immunoprecipitation-mass spectrometry assay. Further investigations suggested that this biomarker can detect very earlier stages of A β pathology in cognitively intact elders, and it may reflect the speed of A β deposition. Thus, the aim of this study is to establish a risk-estimation system for AD using the plasma A β biomarker. Outcomes of this study are expected to contribute to researches and health care for dementia as follows: 1) It facilitates clinical trials for AD by screening target individuals efficiently. 2) It gives useful information to estimate risks for dementia at memory clinics. 3) It accelerates large-scale prospective researches to establish efficacious prevention strategies for dementia.

Development of Diagnosis and Therapeutics for Age-related Diseases Through the Research of D-amino Acids

Principal Investigator	KIMURA Tomonori
PI Primary Affiliation	National Institutes of Biomedical Innovation
Co-Investigator(s)	None

PROJECT DESCRIPTION

Most amino acids have D- and L-enantiomers (chiral bodies). Although D-amino acids are present only in trace amounts unlike abundant L-amino acids, we have demonstrated that trace amounts of D-amino acids are indeed present in human body, and that levels of D-amino acids, but not those of L-amino acids, are useful for early diagnosis and prediction of prognosis in chronic kidney disease, a representative of age-related diseases. Research of D-amino acids are now spreading to cover diagnosis of age-, life style-related, and rare diseases. D-Amino acids as biomarkers will greatly contribute to healthy longevity through the prevention of age-related diseases. Based on the direct reflection of disease activity, studies to elucidate the physiological function of D-amino acid are underway with an aim to establish a novel anti-aging strategy.

Development of High-precision Diagnostics and Treatment Evaluation Technique of Neurological Disorder using Quantitative fMRI Harmonization Technique

Principal Investigator	KOKURYO Daisuke
PI Primary Affiliation	Kobe University
Co-Investigator(s)	ITAHASHI Takashi; SATO Chika; SAITO Shigeyoshi

PROJECT DESCRIPTION

The proposed high-precision diagnostic and treatment evaluation technique aims to provide a quantitative evaluation that combines a harmonization technique across multiple imaging sites and scanners and a biological simulation technique based on the principle of Magnetic Resonance Imaging (MRI) for functional MRI (fMRI) data in order to compare past and present data, and use it as a reference point for future data. When the ideas presented in this proposal are implemented, the present fMRI data can be compared with past and future fMRI data quantitatively. As a contribution to the realization of a “society of health and longevity”, the proposed technique for the evaluation of the treatment effect and early prognostic prediction for mental and neurological disorders can be implemented rapidly and precisely. The extension of healthy life expectancy contributes to reducing the cost of treating and caring for patients in an aging society. Moreover, high-precision diagnosis and treatment prediction can be realized by only performing one test: an MRI.

Development of Personalized-prognosis Prediction for Pneumonia Including COVID-19 Using Artificial Intelligence

Principal Investigator	TAOKA Kazuki
PI Primary Affiliation	The University of Tokyo
Co-Investigator(s)	Idan Yelin

PROJECT DESCRIPTION

In the present project, the artificial intelligence-based system for assessing pneumonia in the elderly which was previously developed by the principal investigator would be adapted to create a triage system for determining the severity of COVID19 pneumonia cases. A major emphasis is upon the development of a system which can provide such assessments in real time. The predictive system would be immediately employable as long as COVID19 patient information is available. We believe this system provides a reliable method for quickly and accurately assessing the treatment priorities of COVID19 patients to determine which patients require hospitalization and intensive treatment the most. Thus, our system has the potential to assist healthcare professionals in the present challenge of priority-setting in hospitals, and provides a possible solution to the current overload of healthcare systems due to COVID19 infections.

Development of Rationally Designed Bacterial Therapeutics to Promote Healthy Longevity

Principal Investigator	HONDA Kenya
PI Primary Affiliation	Keio University School of Medicine
Co-Investigator(s)	Dan R. Littman; Jun R. Huh;

PROJECT DESCRIPTION

Centenarians, who are living more than a century and have survived the era of hunger and infectious diseases, are considered an ultimate model of successful longevity with well-being. Strikingly, most centenarians are less susceptible to age-related diseases, such as hypertension, diabetes, obesity, and cancer. It has been postulated that there are unique gut microbiota members in centenarians that act as direct factors in preventing these diseases. As we have extensive expertise relating to anaerobic bacterial culturing and gnotobiotic techniques, we anticipate that we will be able to isolate and select unique bacterial strains from centenarians' gut microbiota that are functionally beneficial for a healthy lifespan. Also possible is the understanding of potential mechanisms underlying the effects of bacterial isolates. Our long-term goal is to pave the way to delivering novel microbiota-based therapeutics to promote healthy longevity.

Dissecting the Role of Cellular Senescence in Hematopoietic Stem Cells During Aging

Principal Investigator	Sajid Nisar
PI Primary Affiliation	Kyoto University of Advanced Science;
Co-Investigator(s)	Raffaella Di Micco; Andrea Pavesi

PROJECT DESCRIPTION

The main objective of this research is to understand the molecular mechanisms associated with dysfunctions in human hematopoietic stem cells (HSCs) during aging. As by 2050, approximately 15% of the world population will be aged 65 and older, and increased life-expectancy poses unprecedented challenges of progressive degenerative changes in tissues and organs, including the hematopoietic system. Therefore, there is an urgent unmet need to face age-associated cellular dysfunctions and promote healthy aging. We aim to develop mechanism-based strategies to increase functionality of aged HSC, specifically for regenerative medicine applications, immune reconstitution, and cancer prevention. By employing advanced 3-D models and chemical screening of the differentially identified age-specific pathways, we attempt to boost aged HSCs' functionality. The novelty of our proposed study is that it would be among the first molecular study to generate a "blueprint" of human aged HSCs with the final goal to recover and enhance the health and longevity of the aged human hematopoietic system.

Elucidating the Mechanism of Action of Antidepressants by Generation and Sharing of Whole-brain Neurotransmitter Atlas

Principal Investigator	SUGIURA Yuki
PI Primary Affiliation	Keio University
Co-Investigator(s)	SUGIYAMA Eiji; JOHMURA Yoshikazu

PROJECT DESCRIPTION

The mechanism of antidepressants is still not clear despite the growing number of patients with psychiatry diseases. Such a knowledge gap made patients suffering from ineffective medicine as well as unnecessary antidepressant side effects. The monoamine brain atlas we generate (i.e., whole-brain monoamine concentration maps) and antidepressant accumulation maps will fill the gap for the following contributions;

- (i) Comparison of monoamine concentration maps of healthy control and depression model animal brains identifies brain circuits that cause depression.
- (ii) It is possible to clarify in which brain nuclei antidepressants are accumulated.
- (iii) Most importantly, the obtained chemical image dataset will be shared as a chemical brain atlas to academia and pharmaceutical companies researchers.

By opening the atlas to a wide range of researchers, I expect that the brain regions where antidepressants actually work will be revealed and functionally verified. As an ultimate goal, I'll provide valuable brain chemical atlases (including various types of psychotropic drugs) which accelerate the development of antidepressants, and further optimize the administration method (figure shows the research concept).

Elucidation of the Crosstalk Between Bone Homeostasis and Systemic Biological Systems

Principal Investigator	NAKASHIMA Tomoki
PI Primary Affiliation	Tokyo Medical and Dental University
Co-Investigator(s)	None

PROJECT DESCRIPTION

In an aging society, which is progressing on a global scale, fragility of bones and dysfunction of musculoskeletal locomotor system have become a serious social problem because it predicts prognosis and supports healthy aging. Bone-derived factors "Osteokines" have recently been found to be involved in the pathogenesis of metabolic diseases such as diabetes, and controlling brain functions such as appetite. The elucidation of systemic regulatory network implemented by bone is attracting to develop next-generation medical strategies. A database of bone cells established from this research project will lead to an understanding of bone cell biology and their functions. Elucidation of bone homeostasis and pathology will greatly contribute to the maintenance of musculoskeletal health, the establishment of innovative treatments for various musculoskeletal diseases such as osteoporosis and sarcopenia. In addition, many diseases (diabetes, obesity, dementia, etc.) caused, at least in part, by abnormalities in the bone linked with multiple organs can be redefined in novel framework.

Evolving the Existing CSF Biomarkers for Alzheimer's Disease into Blood Samples and Brain-derived Blood Exosomes, and Practical Application of the Newly Developed Multi-item Blood-Based Biomarkers for the Diagnostic System of Alzheimer's Disease

Principal Investigator	TOKUDA Takahiko
PI Primary Affiliation	National Institute of Radiological Sciences, National Institutes for Quantum and Radiological Science and Technology
Co-Investigator(s)	TATEBE Harutsugu

PROJECT DESCRIPTION

Many studies have established the usefulness of "ATN" BMs, which are imaging and cerebrospinal fluid (CSF) biomarkers (BM) reflecting A β aggregation (A), aggregated tau (T) and neurodegeneration (N), in the diagnosis of Alzheimer's disease (AD). However, these BMs are currently not widely used in medical sites providing treatment for dementia due to expensive, inefficient, and invasive nature of those BMs. In this study, we aim at the establishment of the blood-based diagnosis system for AD (Rapid, Easy, non-Invasive and Widely-Available Alzheimer's disease Diagnosis = REIWA-AD) by using multiple blood biomarkers that are rapid, easy, noninvasive, widely available, and accordingly able to overcome faults of conventional BMs. If such "blood BM panel for AD diagnosis" comes into practical use, it can provide an accurate diagnosis and staging of AD even at family doctors or in general hospitals. Moreover, blood BMs can be applied to large-scale screening and provide life guidance and appropriate preemptive therapies for asymptomatic subjects. In other words, blood BMs allowed us to shift the focus of dementia treatment to disease prevention, and it being the correct choice and stratification of the participants and objective evaluations of effectiveness of investigational drugs in the clinical trials for AD.

Exploring Ways to Maintain and Improve Elderly Muscle Function With Mitochondrial Mechano-medicine

Principal Investigator	HIGASHITANI Atsushi
PI Primary Affiliation	Tohoku
Co-Investigator(s)	NIKAWA Takeshi; KOBAYASHI Takeshi; TERANISHI Mika

PROJECT DESCRIPTION

Age-related frailty and decreased physical activity cause progressive loss of muscle mass and function, also known as sarcopenia or disuse atrophy. However, the molecular mechanisms underlying sarcopenia and disuse atrophy are poorly understood. Therefore, therapeutic approaches are limited. Recently, we found that intracellular organelle, mitochondria, can sense mechanical stress and generate a signaling factor maintaining muscular homeostasis. Actually, we have confirmed that genetic disruption of mitochondrial mechano-sensing or -signal transduction system contributes to abnormality in homeostasis of skeletal muscle. On the basis of our findings, we are now exploring pharmacological, nutritional or physical interventions to activate mitochondrial functions. At the same time, using animal models, we will verify the validity of those in stabilizing, alleviating and reversing sarcopenia or disuse atrophy. It not only improves the quality of life for individuals, but also significantly reduces the burden on caregivers and the social costs of public health.

Extending Healthy Lifespan by Manipulating Cell Competition

Principal Investigator	IGAKI Tatsushi
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PI Primary Affiliation	Kyoto University
Co-Investigator(s)	None

PROJECT DESCRIPTION

This study aims to establish the methodology for extending healthy lifespan and keeping youthfulness by manipulating the phenomenon called 'cell competition'. Cell competition is a form of cell-cell interaction whereby normal 'healthy' cells eliminate their neighboring low-fitness or harmful cells by actively killing them. In this study, we will first elucidate the molecular mechanism of cell competition during aging process of fruit fly *Drosophila* and then establish the methodology to artificially manipulate cell competition, thereby trying to establish the way to manipulate animal aging. This study is innovative because it focuses on the unique property of cell competition and tries to establish a novel way of extending healthy lifespan by enhancing cell competition-mediated elimination of harmful cells from the animal. Enhancement of cell competition would increase survival/adaptive activity of normal cells; thus it would be able to establish aging suppressor without having any side effect. Given that cell competition prolongs lifespan in *Drosophila* and its machinery is evolutionarily conserved in mammals, its application to humans would provide an innovative strategy to extend healthy lifespan.

Extending Healthy Longevity by Improving the Sleep Architecture

Principal Investigator	HAYASHI Yu
PI Primary Affiliation	Kyoto University
Co-Investigator(s)	None

PROJECT DESCRIPTION

Sleep architecture is a term that refers to the alternating cycles of REM sleep and non-REM sleep. Sleep architecture changes dramatically with age, especially evident in the reduction of REM sleep. However, little is known about the mechanisms of sleep architecture and its impact on health. Based on our discovery of neurons that control the sleep architecture, we aim to elucidate the mechanisms of sleep architecture disruption due to aging or diseases and how it affects the functional decline of individuals. Moreover, we aim to develop methods for improving the sleep architecture. These approaches are expected to lead to innovative cures for functional declines associated with aging as well as neurodegenerative diseases or lifestyle-related diseases with high unmet medical needs. Innovations that incorporate a new perspective of the sleep architecture may contribute to the well-being of elderlies in terms of physical, mental, and social health, which in turn may promote their active social participation and reduce the burden on families and caregivers.

Extracellular Vesicle (EV)-mediated Rescue of Immune Dysfunction and Cognitive Decline in Aging

Principal Investigator	YAMADA Hiroshi
PI Primary Affiliation	University of Tsukuba
Co-Investigator(s)	Noga Ron-Harel; Ayesha Saleem

PROJECT DESCRIPTION

The aging population around the world requires the development of therapeutic strategies aimed at improving health span to keep pace with the increase in lifespan. Previous research has shown that transfusing old animals with blood from young animals reverses some aspects of aging, leading to the hypothesis of "youthful" factors in young blood. Here, we propose that these factors are packaged in a type of secretory vehicle called extracellular

vesicles (EVs), and that treating old cells with EVs isolated from younger people would reverse physiological markers of aging such as impaired immune cell function, and subsequently alleviate age-induced deficits in cognitive memory. The unique scientific direction proposed here will serve as a potential launch point into new avenues of research that will address if we can reverse or rescue the rampant cognitive decline in older individuals by treating them with EVs isolated from young people. The therapeutic advantage comes at a pivotal point where the population of older adults has already outstripped that of children and improving health outcomes in the aging population worldwide to facilitate healthy longevity.

Group-based Dyadic Support Programs for Persons with Mild Cognitive Impairment or Dementia and Their Family Caregivers

Principal Investigator	SAITO Tami
PI Primary Affiliation	National Center for Geriatrics and Gerontology
Co-Investigator(s)	None

PROJECT DESCRIPTION

People with dementia (PWD) and their family caregivers (CG) are at risk of depression, caregiving burden, and deterioration in the quality of life. It is important to develop safe, effective support programs to alleviate such risks. However, at least in Japan, evidence-based nonpharmacological programs remain scarce. This study develops two distinct programs and examines their effect and feasibility with scientifically rigid study design.

We focus on dyadic group-based psychosocial programs, which have shown recent promise with regard to both health impacts and efficiency in healthcare provision. Furthermore, dyadic programs will be useful for developing effective partnerships among PWD, CG, and social and health care providers. Particularly in Japan, where caregiving is traditionally based on familism, it appears important to coordinate relationships between PWD and their CG.

Our findings will enable us to provide safe, effective, and satisfactory programs to improve the health and quality of life of PWD and their family members. In addition, expanding these programs in communities could facilitate social engagement among PWD and their family members, who tend to be socially isolated. Furthermore, such programs could provide additive value for healthcare and residential facilities for senior citizens.

Hand Rehabilitation Device and its Soft, Lightweight, Compact and Affordable Mechanism

Principal Investigator	ARATA Jumpei
PI Primary Affiliation	Kyushu University
Co-Investigator(s)	MUKAE Nobutaka; TANABE Tetsuro,

PROJECT DESCRIPTION

170 million people suffer from aftereffects of stroke worldwide, causing motor impairments in upper limbs for 65% of the patients. The hand is one essential tool in our life, providing various utilities, thus the motor impairment in hand causes serious degradation of quality of life (QOL). The proposed device provides neurorehabilitation and task-oriented training by a soft, compact, lightweight and affordable wearable robot. It supports the hand motion triggered by the patient's muscle signal, making the hand grasping/extending motion possible as if the healthy hand. During the rehabilitation with the device, the patient performs grasping tasks with objects by wearing it. This helps to rehabilitate the affected hand through re-learning the hand motion supported by the robotic device.

The device will provide an effective robotic rehabilitation that improves the patients' QOL, thus greatly contributing to Healthy longevity.

Histone Modifications as New Targets for Pathophysiology of Accelerated Brain Aging Associated with Mental Disorders: Application for Development of Treatment and Diagnostic Method

Principal Investigator	ARIOKA Yuko
PI Primary Affiliation	Nagoya University Hospital
Co-Investigator(s)	Amrita Basu; Simone Sidoli

PROJECT DESCRIPTION

Patients with mental disorders such as schizophrenia and bipolar disorder often die prematurely and are characterized by an overall poorer lifespan. Not to mention they cannot get healthy longevity. To improve this, early diagnosis and treatment are required. However, there is no biomarker that differentiates these diseases. To address this, the heterogeneity associated with mental disorders, age at onset, and other factors need to be taken into account to define biomarkers that help decipher a complex set of pathophysiological processes. Hence, we focus on epigenetic changes. We analyze various bioresources from patients with mental disorders, such as immortalized lymphocytes and iPS cells, using cutting-edge mass spectrometry that can quantify >200 histone modifications and variants at the same time. Our study will contribute not only to identify biomarkers but also to elucidate the accelerated brain aging in mental disorders. In the long term, our study can result in designing a clinical trial that will benefit patients by controlling and/or eliminating their disease, leading to better outcomes.

Identification of Biomarkers for Immune Ageing and Comprehensive Interventions for Age-related Disorders

Principal Investigator	HAMAZAKI Yoko
PI Primary Affiliation	Kyoto University
Co-Investigator(s)	None

PROJECT DESCRIPTION

Immunosenescence underlies increased lethal infection and inefficient vaccination efficiency in elderly people as well as various aging-associated chronic disorders after middle age. T cells play a central role in the immune system by promoting antibody production and directly killing target cells such as virus-infected cells and cancers. T cells also regulate immune reactions to prevent tissue damage and excess inflammation. Despite their importance for our lifelong health, T cells exhibit the most prominent phenotypic changes among immune cells with age due to the early involution of the thymus, which is the sole organ that can generate new T cells. From these perspectives, in this study, we will analyze the mechanisms of immunosenescence, especially focusing on T cells. We seek to identify biomarkers that will be useful for predicting the risk of age-related diseases and the severity or lethality of infections in elderly individuals. Furthermore, we will develop novel strategies to restore or rejuvenate age-related T cell dysfunction, which promises a wide range of age-related clinical applications.

Identification of Novel Lipid Species Generated by Autophagy that Promote Longevity

Principal Investigator	NAKAMURA Shuhei
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PI Primary Affiliation	Osaka University
Co-Investigator(s)	Mark A. McCormick; Gareth Lim

PROJECT DESCRIPTION

Evolutionally-conserved molecular mechanisms that extend lifespan have been identified in model organisms, including yeast, worms, flies and mice. These include reduced Insulin/IGF-1 and TOR signaling, dietary restriction, and reduced mitochondrial respiration. Recent studies suggest that an activation of a cytoplasmic degradation system, autophagy is a convergent downstream cellular process common to these pro-longevity paradigms, but how it promotes longevity is largely unclear. Based on several lines of evidence suggesting an intimate relationship between autophagy and lipid metabolism, we hypothesize that lipid species generated by autophagy could extend animal lifespan and health span. Our interdisciplinary collaborative team (Dr. Shuhei Nakamura, Japan, Dr. Gareth Lim, Canada, and Dr. Mark McCormick, U.S.A.) will identify specific fat species which extend animal lifespan. Furthermore, we will examine the underlying molecular mechanism(s) of how fat species can extend lifespan. The long-term goal is to apply these findings to a translational study to test in human subjects.

Integrated Approach of Medical and Long-term Care for Healthy Longevity

Principal Investigator	TAMIYA Nanako
PI Primary Affiliation	University of Tsukuba
Co-Investigator(s)	MORI Takahiro; SAKATA Nobuo; IWAGAMI Masao; HAMADA Shota

PROJECT DESCRIPTION

The concept of this proposal is “Proposals to global aging from Japan: based on medical and long-term care data”. In Japan, public universal coverage of medical and long-term care (LTC) have been established. Claims data and other related data are accumulated as one of the world’s largest databases. We will work on a variety of research questions based on medical and LTC claims databases linked to various types of databases, such as data on LTC needs certification, including health conditions (eg, physical and cognitive function), socioeconomic status (eg, income), and demographic statistics. Japan has played a pioneering role in the establishment and development of public universal medical and LTC insurance systems. Resolution of problems and issues raised in Japan would contribute to advancing the creation of a society for healthy longevity in Japan as well as other countries where will face similar problems and issues in the near future. Furthermore, we expect to reflect our findings to healthcare policy and related product development for healthy longevity at a high speed, by simple methods with a low cost.

Microbial Electricity Generation from Saliva Tells Your Oral Health Condition: Electrochemical Sensor Targeting Periodontal Pathogen in Saliva for the Longevity of Healthy Age

Principal Investigator	OKAMOTO Akihiro
PI Primary Affiliation	National Institute of Materials Science
Co-Investigator(s)	NISHIHARA Tatsuji; IMAMURA Gaku

PROJECT DESCRIPTION

Next-generation Medicine and Smart Health-care System for Prevention of Age-related Hearing Loss

Principal Investigator	HIBINO Hiroshi
PI Primary Affiliation	Niigata University
Co-Investigator(s)	KAWANO Satoyuki; KIKKAWA Yoshiaki

PROJECT DESCRIPTION

Numerous elder people are affected by “age-related hearing loss”. This irreversible disease not only serves as the greatest risk for developing dementia but also hinders conversation and the enjoyment of entertainment, the essential elements for a fulfilling life. The aim of this study is to overcome age-related hearing loss by integrating medical and engineering approaches. The goal will be establishment of the prevention method combining medicine and medical care with environmental improvement. Our achievements will contribute to a healthy and happy aging society.

Novel Implementation Science Toward Healthy Longevity Based on Community Multi-sectoral Partnerships Using Big Health Data

Principal Investigator	KONDO Naoki
PI Primary Affiliation	Kyoto University
Co-Investigator(s)	MIYAMOTO Yoshihiro; SAITO Junko; SAITO Masashige; HASEDA Maho; ANEZAKI Hisataka; ARAI Hidenori; KONDO Katsunori

PROJECT DESCRIPTION

Functional capacity declines with aging. However, its speed and pattern can vary across individuals. In this study we will conduct the following two analyses: 1) Explore the detailed trajectory patterns of physical and cognitive functioning before the end of life; 2) Identify the behavioral and social determinants of those patterns and their cost-altering effects. We use a large dataset from our longitudinal study: the Japan Gerontological Evaluation Study (JAGES) between 2006 and 2019, linked with payment receipt data from Japan’s public long-term care and medical insurance systems. The advantage of this project is its ability to utilize this unique data sources of over 200 thousand individuals residing in 56 municipalities nationwide. The results of our study should directly contribute to the formulation of governmental policies in the participating municipalities. Moreover, we have recently started our program in several countries in East Asia (Myanmar and Malaysia), and we believe that our study has the potential to make a meaningful contribution to many other countries in this era of global aging.

Prevention of Dementia in Elderly People by the Novel Antidepressant Arketamine

Principal Investigator	HASHIMOTO Kenji
PI Primary Affiliation	Chiba University
Co-Investigator(s)	None

PROJECT DESCRIPTION

The number of dementia such as Alzheimer’s disease (AD) is increasing worldwide. However, there are no prophylactic drugs for dementia. It is well known that elderly depression is a risk factor for dementia as well as a prodromal (MCI: mild cognitive impairment) of dementia. Given a risk factor of depression in dementia, we

propose the hypothesis that the novel antidepressant arketamine [(R)-ketamine] can block or delay the onset of dementia in elderly people with depression. This project has high originality and innovation since I am the inventor of the filed patent of arketamine in depression and dementia including AD. This project will have a high impact in elderly people and their family in the world if arketamine can block or delay the onset of dementia in elderly people with depression.

Priming Aged Hematopoietic Stem Cells by Imprinting Immune Competence

Principal Investigator	TAKIZAWA Hitoshi
PI Primary Affiliation	Kumamoto University
Co-Investigator(s)	Paola Betancur; Roland Huber

PROJECT DESCRIPTION

Hematopoietic stem cells (HSCs) are lifelong blood-forming stem cells that give rise to all blood and immune cells. Hematopoietic ageing results in decreased immune surveillance and in turn, increased incidence of infection and cancer in the elderly. Recent studies demonstrated that young HSCs can acquire epigenetic (inherited) and/or metabolic programs as “inheritable memory” and propagate it to their-derived myeloid cells, innate immune cells at the front line of host defense against diseases, to show better response to subsequent insults. Thus, we hypothesize that immuno-potent programs can be imprinted in aged HSCs by stimulation with microorganism-derived agents, and in turn, this imprinting will be inherited by their myeloid derivatives improving their immunocompetence against infections or cancer in the elderly. Knowledge generated in this study will help to develop a novel vaccination strategy that can curve the infection history in long-lived stem cells and ensure host immune protection.

Profiling the Metabolite-longevity Axis

Principal Investigator	ITO Minako
PI Primary Affiliation	Kyushu University
Co-Investigator(s)	Matthias Truttmann; James Chan

PROJECT DESCRIPTION

The gut microbiome represents a continuously changing community of microorganisms that interacts with the human immune system and pre-processes our food. Recent work has demonstrated direct links between the gut microbiota and host health and aging. As such, the development of probiotic interventions holds great promise as a novel approach to increase healthspan. However, our knowledge of how bacteria-derived metabolites alter host signaling and health is limited. Our overall objective is to define the core mechanisms by which bacterial metabolites contribute to the regulation of organismal health and longevity. Our central hypothesis is that gut bacteria-derived metabolites, such as colanic acid and hypotaurine, regulate lifespan through the hormetic activation of cellular stress responses. Understanding these processes will lay the foundation necessary to pharmacologically target the human gut microbiome and exploit engineered probiotics to prolong health- and lifespan in humans. These goals will be achieved by combining technically and conceptionally innovative approaches with rigorous validation across a series of model systems, that each provide unique advantages.

Randomized Control Trial for Dementia Prevention by Multimodal Interventions

Principal Investigator	ARAI Hidenori
PI Primary Affiliation	National Center for Geriatrics and Gerontology

Co-Investigator(s)	SAKURAI Takashi; FUJIWARA Yoshinori; KUZUYA Masafumi; TAKECHI Hajime; MICHIKAWA Makoto
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PROJECT DESCRIPTION

There is little evidence in Japan about what interventions may be effective for preventing dementia. Therefore, we plan to build solid evidence in Japan. In this study, the effectiveness of multimodal intervention programs (exercise, nutrition, cognitive training, lifestyle-related disease management) for high-risk older people for dementia will be addressed toward the social implementation of multimodal intervention programs by local governments and companies in the future. This is a multicenter randomized controlled clinical trial. The study results will be innovative in a sense of linking to social implementation, which can lead to a prolonged mental, physical, and social healthy life expectancy of older people. By making use of biomarkers and imaging, it is innovative to gain access to mechanisms related to cognitive improvement. It is expected that the effects of interventions on cognitive function as well as the effect on frailty will be shown, indicating the extension of the healthy life expectancy.

Regulation of Gut Dysbiosis-associated Mediators to Ameliorate Parkinson's Disease

Principal Investigator	OHNO Kinji
PI Primary Affiliation	Nagoya University
Co-Investigator(s)	None

PROJECT DESCRIPTION

Accumulating knowledge points to the notion that abnormally accumulated protein aggregates (α -synuclein fibrils) in the intestinal neural plexus behave like

Role of Cardiomyocyte Turnover on Age-related Cardiovascular Diseases

Principal Investigator	KIMURA Wataru
PI Primary Affiliation	RIKEN Center for Biosystems Dynamics Research
Co-Investigator(s)	YAMAGUCHI Osamu; OTSU Kinya; TANEIKE Manabu; MASUMOTO Hidetoshi

PROJECT DESCRIPTION

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, and aging is the highest risk factor for CVDs. Novel therapeutic strategies for treating or preventing aging-associated CVDs are needed given not only the developed but also developing countries are rapidly aging. We have previously shown that proliferative cardiomyocytes maintain oxidative metabolism and oxidative stress at a low level (Cell 2014). Furthermore, we identified cycling cardiomyocytes in the adult heart based on the lineage tracing of hypoxic cardiomyocytes (Nature 2015). In addition, we have shown that reduction in oxidative DNA damage is sufficient to induce cardiomyocyte cell cycle re-entry in the adult mammalian heart (JACC 2015; Nature 2017). In this project, we will examine whether cardiomyocyte turnover can be accelerated in the aged heart by modifying oxidative metabolism, and whether this is sufficient to recover and/or prevent aging-associated CV diseases.

Role of the Hypothalamus in Mammalian Aging/Longevity Through the Regulation of sleep Quality

Principal Investigator	SATOH Akiko
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PI Primary Affiliation	National Center for Geriatrics and Gerontology
Co-Investigator(s)	None

PROJECT DESCRIPTION**Search for Determinants of Cognitive Resilience in Old Age**

Principal Investigator	WATANABE Takamitsu
PI Primary Affiliation	University of Tokyo
Co-Investigator(s)	Akin Ojagbemi; Carolyn Parsey

PROJECT DESCRIPTION

Population aging has been increasing the global prevalence of dementia, whose impacts are overwhelming for the person, their families, caregivers and society at large. Although substantial efforts have been dedicated to understanding the risk factors for the disease, less research has focused on ‘Cognitively resilient’ individuals, who, despite having demonstrable risk for cognitive decline, defy the odds of dementia and lived to be cognitively healthy in late life. Also, such a limited number of prior studies were conducted in high-income countries, and no research has been found for the cases in developing countries. No information is available about factors that are facilitatory to cognitive resilience across different socio-economic, cultural and geographical contexts and those that are specific to certain populations. To address this overlooked but critical problem, we aim at identifying common modifiable factors for cognitive resilience in diverse populations, which can be the basis of future preventive interventions for cognitive decline and dementia that are applicable globally.

Study on Dietary Factors to Reduce Dementia Risk Related to Apolipoprotein E (ApoE) Genotype and Gender Difference (D-AGE)

Principal Investigator	YAMADA Masahito
PI Primary Affiliation	Kanazawa University
Co-Investigator(s)	HAMAGUCHI Tsuyoshi; NOGUCHI-SHINOHARA Moeko; ISHIGAMI Akihito

PROJECT DESCRIPTION

Major genetic risk factors for sporadic Alzheimer’s disease (AD) are “apolipoprotein E (ApoE) E4 (= 4 allele)” and “female”. To rescue women with ApoE E4 from dementia/AD, we have investigated dietary factors that reduce the genetic risk. In our population-based cohort study on dementia, we have found the association of higher blood “vitamin C” levels with reduced risk of future cognitive decline in women with ApoE. Elucidation of the dietary factors, such as “vitamin C”, that reduce the genetic risk of dementia/AD can contribute much to older people, providing safe and inexpensive tools for prevention of dementia/AD in a super-aged society in the middle of the 21st century. Furthermore, understanding of the interactions of “ApoE E4”, “female”, and “vitamin C” in AD pathogenesis would lead to the discovery of a novel target for treatment and prevention of AD.

The Regulation of Formation and Clearance of Amyloid by Photooxygenation

Principal Investigator	HORI Yukiko
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PI Primary Affiliation	University of Tokyo
Co-Investigator(s)	TOMITA Taisuke; KANAI Motomu; SOHMA Youhei

PROJECT DESCRIPTION

Amyloid-selective artificial photooxygenation is our original unique approach for amyloid proteins using small compounds (a.k.a. photocatalyst) and light irradiation. We have successfully showed that the photooxygenation induces the aggregation inhibition and the enhanced clearance of amyloids, such as A β and tau, which are causative proteins for Alzheimer disease (AD) or progressive supranuclear palsy (PSP) and so on, suggesting the possibility of photooxygenation approach as a therapeutic strategy for AD. The deposition of other amyloid proteins, such as α -synuclein or TAR DNA-binding protein (TDP-43), have also been implicated in the pathogenesis of other neurodegenerative diseases, Parkinson disease, and Amyotrophic lateral sclerosis, respectively. Therefore, through the proof of our concept in vitro and in vivo, we would like to propose the amyloid-selective photooxygenation as a common therapeutic optomedical strategy against various neurodegenerative disorders (Figure).

The development of therapeutic strategy for neurodegenerative disorders based on our proposal will contribute to overcome dementia in the aging societies among the world, leading us to live with health and happiness. Additionally, our method may also have big impact on amyloids associated with various systemic amyloidosis in heart, liver and pancreas that have no treatment so far, if it is developed as therapy.

Toward Genetic Diagnosis of Sleep Characteristics in Each Individual: Identification of Sleepiness at the Cellular and Molecular Level in Mice

Principal Investigator	NIWA Yasutaka
PI Primary Affiliation	University of Tsukuba
Co-Investigator(s)	None

PROJECT DESCRIPTION

Despite the fact that sleep insufficiency is the cause of sleepiness and, eventually, various illnesses, no one knows what sleepiness is at the cellular and molecular level. If sleepiness in mice can be evaluated based on gene expressions and electrophysiological properties in specific cells, technological development for objectively measuring sleepiness in human will be possible.

If genes that make up sleepiness are identified, the sleep characteristics of each person can be examined in advance by genetic diagnosis as alcohol tolerance can be examined by ALDH2 genotype. Knowing one's own sleep characteristics and keeping them in mind in our daily life, we will be able to prevent various illnesses and accidents caused by sleepiness. In the future society, I hope that sleepiness, which sometimes implies laziness, will be correctly recognized with scientific evidence. This research could help to realize such an environment that people do not have to work with sleepiness and that elderly people can live without concerns about sleep insufficiency.

Treatment of Musculoskeletal Diseases by Creation and Application of Bioligaments

Principal Investigator	ASAHARA Hiroshi
PI Primary Affiliation	Tokyo Medical and Dental University
Co-Investigator(s)	None

PROJECT DESCRIPTION

Disorders and diseases of the tendons/ligaments significantly impair motor function, forcing patients to significantly decrease their activity, which can severely impact their daily life. Additionally, these disorders increase the risk of developing osteoarthritis through joint instability. Thus, the treatment of tendon/ligament disorders is very important. However, tendons/ligaments have an extremely low self-healing ability and treatment remains very difficult. Currently, it has been difficult to engineer biomaterials by the conventional methods that can substitute for tendons/ligaments. We have established a method to create a tendon/ligament-like artificial tissue (bioligament) from the human induced pluripotent stem (iPS) cells using a three-dimensional tension loading hydrogel culture system. This bioligament will be applied as a new treatment to regenerate or reconstruct injured tendons/ligaments, contributing to the health and well-being of the elderly.