

HEALTHY LONGEVITY GLOBAL COMPETITION

2022 Catalyst Awardees

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A novel human cellular system for studying normal ageing and for anti-ageing drug screen

Principal Investigator	Pentao Liu
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Co-Investigator(s)	Shuofeng Yuan Degong Ruan; Zhuoxuan Li

PROJECT DESCRIPTION

Ageing is a natural process, but healthy ageing and longevity can help alleviate the heavy burdens that ageing brings to the society. Besides causing detrimental health deterioration in elderlies, the biological process of ageing is implicated in many human diseases such as cancer. Studying human ageing directly is time-consuming. Model organisms such as yeast, *C. elegans*, *D. melanogaster* and mouse are often used to investigate ageing mechanisms at the molecular, cellular and systematic levels. However, findings from these model organisms may not fully reflect the molecular and physiological events in human ageing. Human cellular models have also served to investigate ageing but may only represent partial insights into normal ageing processes.

During pregnancy, trophoblasts in the placenta nourish and protect the foetus. The generation of mature trophoblasts (syncytiotrophoblast or STB, and extravillous trophoblast or EVT) from progenitors is an accelerated ageing process accompanied by multiple ageing manifestations. We find that trophoblast stem cells (TSCs) derived from the embryo tissues and human pluripotent stem cells can differentiate in culture to mature trophoblasts in vitro mimicking the natural process in the placenta. We propose to use the generation of mature human trophoblasts from TSCs as a new cellular model for studying human normal ageing process and screening anti-ageing drug candidates. This new cellular system is expected to facilitate ageing-related fundamental and translational research.

AI-driven causal model to determine upstream definitive genetic biomarkers for early detection of Late Onset Alzheimer's Disease

Principal Investigator	Victor OK Li
PI Primary Affiliation	The University of Hong Kong
Co-Investigator(s)	Jacqueline CK Lam; Illana Gozes, Jocelyn Downey

PROJECT DESCRIPTION

Alzheimer's disease (AD) is a leading cause of death in China and the fifth leading cause of death worldwide. Early diagnosis is critical to provide timely intervention before irreversible brain damage occurs. 95% of the AD cases occur after age 65 and are considered late-onset AD (LOAD). Although plasma amyloid, phosphorylated Tau, and neurofilaments for individualized risk prediction in mild cognitive impairments (MCIs) are emerging, no

causal definitive genetic markers (DGMs) for early detection of LOAD have been established, making accurate early diagnosis and treatment difficult. With the availability of large AD datasets with genetic information and our own Israeli and Hong Kong datasets, it is now possible to analyse the relationship between genetic markers and LOAD. However, (1) traditional statistical or data-driven models only ascertain disease association rather than causation; (2) deciphering disease-driving somatic mutations from inconsequential mutations remains difficult. To overcome these challenges, we will develop an AI-driven causal model to investigate multiple AD pathological pathways and their convergence, utilizing existing AD datasets to efficiently and accurately identify upstream DGMs. To verify the DGMs identified from the AI model, two large ethnically-distinctive LOAD datasets with blood samples from the HK Chinese and Israeli populations developed/accessible by our team will be analysed. Our novelties include the development of an AI-driven causal model which incorporates key AD pathways, somatic mutations, and demographics, to identify what disease-driving biomarkers cause (rather than what associate with) LOAD, paving the way for the early detection and treatment of LOAD.

Bilobalide Derivatives as Therapeutics Against Ageing-Related Neurodegenerative Diseases

Principal Investigator	Billy Wai-Lung NG
PI Primary Affiliation	The Chinese University of Hong Kong
Co-Investigator(s)	Kim Hei Man CHOW, Owen Ho KO

PROJECT DESCRIPTION

Aging-related neurodegenerative diseases like Alzheimer's disease are substantial medical and socioeconomic burdens with no effective disease-modify treatments to date. The pathological hallmarks of neurodegenerative diseases involve the misfolding and toxic aggregation of neuronal proteins, leading to a progressive loss of neuronal function. Autophagy is the normal pathway by which healthy neurons digest and clear such proteins to maintain homeostasis. However, the autophagic ability of neurons decline with age and neurodegeneration accelerates at later stages of life. Therefore, the promotion of neuronal autophagy is an attractive strategy towards the prevention and reversal of ageing-related neurodegeneration.

Herbal extracts from the Ginkgo tree (*Ginkgo biloba*) is one of the most popular dietary supplements with various neuroprotective effects. One of the terpene trilactone natural products of *Ginkgo biloba* is thought to be responsible for neuroprotective effects against neurodegeneration. However, its chemical instability precludes its preclinical evaluation. We envision that the direct chemical modification of this natural product can rapidly produce diverse chemical libraries that are chemically stable and biologically active. Our preliminary data demonstrates that such derivatives can effectively promote the clearance of proteinopathy in an Alzheimer's disease model through upregulation of autophagy. Such an unprecedented chemical library would allow the exploration of previously unknown chemical and biological space for the pharmacological management of ageing-related neurodegenerative diseases.

Deciphering Disease Pathogenesis and Druggable Targets for Degenerative Tendinopathy using an Unbiased, Genome-wide, Single-Cell, Spatial Transcriptomic Approach

Principal Investigator	Patrick Shu Hang YUNG
PI Primary Affiliation	Department of Orthopaedics and Trumatology, The Chinese University of Hong Kong
Co-Investigator(s)	Pauline Po Yee LUI

PROJECT DESCRIPTION

Degenerative tendinopathy is a chronic musculoskeletal disorder presented with local tendon pain, physical disability and ultimately tendon rupture due to tendon overuse and aging. It is an unmet clinical challenge due to its unclear etio-pathogenesis. Single-cell RNA-sequencing (scRNA-seq) allows the discovery of previously unknown rare cell types/subtypes in normal and diseased tendons in tendinopathy. By adding spatial information to scRNA-seq data, spatial transcriptomics allows cell groups sharing similar and differential gene expression and in-situ cell-to-cell interactions to be identified in the tissue context, transforming our understanding of tissue functional organization. Formalin-fixed and paraffin-embedded (FFPE) tendinopathy and healthy tendon samples represent a rich resource for molecular profiling but is unfortunately incompatible with scRNA-seq due to RNA degradation in extraction. Recent advances in spatial transcriptomics supports the use of FFPE samples for transcriptome sequencing at the cellular level. However, there has been no similar study on FFPE samples of tendinopathy. This study aims to use a ground-breaking spatial transcriptomics approach of FFPE samples for the discovery of key players, biological processes, novel biomarkers, and cell-to-cell interactions, at the single cell and spatial levels, in degenerative tendinopathy. Single-cell spatial transcriptomic data of diseased and healthy FFPE tendon samples will be obtained and analyzed. The expression and co-localization of key genes or cell types in spatial transcriptomics will be verified by fluorescent in-situ hybridization and immunofluorescent staining of consecutive tissue sections and an independent cohort. The study will open new opportunities of using FFPE samples for spatial transcriptomic research in tendon to improve population health.

Development of Small-Molecule Modulators of the Secretin Receptor as Novel Anti-Hypertensive Agents

Principal Investigator	Billy K.C. Chow
PI Primary Affiliation	The University of Hong Kong
Co-Investigator(s)	None

PROJECT DESCRIPTION

Large segments of aging hypertensive patients are resistant to a wide range of conventional drugs and hence there is an urgent need for new initiatives to develop alternative treatments. Here, we develop the first small molecule-based Secretin receptor modulator (KSD179019), which not only has the similar blood pressure lowering effect as SCT peptide, but more importantly has a much longer half-life (~8 hours). Preclinical pharmacokinetics and toxicology studies revealed long bioavailability and low toxicity of this compound. Therefore, development of KSD179019 as a novel class of oral anti-hypertensive drug can be of critical importance, as it could tackle resistant hypertension. In addition, based on the recently CryoEM-resolved 3-D structure of human secretin receptor and the active pharmacophores of KSD179019, several analogues were designed and synthesized to further explore the structure-activity relationship. Our preliminary data suggest the presence of a functional structural core to be important for positive allosteric modulation of Secretin receptor. This observation is interesting and further studies could lead to improved and more potent small molecule drugs for Secretin receptor-involved health risks particularly for the aging population. Specifically, we believe that this project could potentially provide an important advancement in finding novel small molecule drugs for resistant hypertension by targeting Secretin receptor. The project describes the preclinical studies necessary to bring the project forward for GLP-labs and big pharma license agreements.

Empowering Acoustic Sensing and Learning on Accessible Speakers to Monitor and Detect Older Adult Falls

Principal Investigator	Chenshu Wu
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PI Primary Affiliation	The University of Hong Kong
Co-Investigator(s)	None

PROJECT DESCRIPTION

Falls are the leading cause of accidental injury death worldwide for older adults. Globally, about 70 thousand fatal falls and over 37 million severe falls requiring medical attention each year, resulting in substantial financial costs (totaling over US\$50 billion in the US alone). The problem is aggravated by the fact that millions of seniors live, who are most vulnerable to falls, which can be undetected and helpless for hours or days. Existing solutions to fall detection require seniors to wear a pendant or other sensors. Wearables, however, do not work well for the elderly, who typically find it cumbersome or forgettable to wear them. More attractive wearable-free solutions mostly require training and are either inaccurate or invasive today. This proposal seeks to transform device-free passive fall monitoring solutions with two goals: to detect falls accurately and responsively without prior training, and to monitor motions and vital signs before and after a fall, both in a non-contact and affordable manner. We propose a smart sensing system capable of continuously monitoring an older adult's motion, breathing rates, and walking speed, which allow reliable fall detection and offer unparalleled insight of fall-related activities. We achieve so by empowering the prevalent and accessible smart speakers with non-invasive acoustic sensing and learning. With improved user comfort and decreased costs, more people worldwide will benefit from contactless fall monitoring. Importantly, the accumulated fall-related data can provide physicians the medical insight to avoid falls. Ubiquitous fall monitoring today can prevent fall tragedies and improve healthy aging tomorrow.

Engineered osteochondral tissue (eOCT) as advanced therapeutic treatment for osteoarthritis (OA)

Principal Investigator	Barbara Chan
PI Primary Affiliation	The University of Hong Kong
Co-Investigator(s)	Patrick Shu-Hang YUNG; Chun Hoi Yan; Michael Tim-Yun Ong

PROJECT DESCRIPTION

Osteoarthritis (OA) is among the most prevalent degenerative disorders in aged populations worldwide. It affects the entire joint with eroded cartilage, compromised osteochondral interface and abnormally remodelled bone, leading to severe pain, reduced motility and poor quality of life. Most existing treatments are symptom-relieving rather than disease-modifying. Surgical treatment such as marrow stimulation and biological attempts such as mesenchymal stem cell (MSC) injection resulted in formation of fibrocartilage, which is poor in quality and easily degenerated. To date, no method can effectively regenerate hyaline cartilage, restore the lost osteochondral integrity and sustain the structure and function of the repaired tissues. We believe that osteochondral tissue engineering, which addresses both cartilage and bone, is able to effectively modify OA. We have developed engineered osteochondral tissue (eOCT) with proper zonal organization using bone marrow (BM) MSCs. Implanting autologous eOCT in traumatic osteochondral defects in rabbits resulted in rapid and sustained hyaline cartilage formation, tide mark regeneration, bony integration, recovery in matrix composition and mechanical properties, comparable to autografting. These promising results prompt us to hypothesize that eOCT is able to effectively modify OA by investigating its effectiveness in a post-traumatic OA model in rabbits and comparing with existing options. Another challenge in MSCs-based treatment is the poor proliferation and senescence of BM-derived MSCs from aged patients. We therefore aim to evaluate the effectiveness of the less age-dependent infrapatellar-fat-pad (IFP)-derived MSCs from aged OA patients, in producing eOCT. This work develops novel therapeutics for OA, contributing to the grand challenge in healthy longevity.

Intelligent ultrasonic assessment of muscle quality for a functionally healthy elderly life

Principal Investigator	Wei-Ning Lee
PI Primary Affiliation	The University of Hong Kong
Co-Investigator(s)	Jinping Dong; Haotian Guan

PROJECT DESCRIPTION

Maintaining functional ability is central to physical and mental well-being in older age. Motility, which is endowed by skeletal muscle, is an intrinsic capacity pertinent to functional ability. Despite a multitude of available measurement tools of muscular function in clinical settings, skeletal muscles exhibit intricate architecture, complex dynamics, individual compositional differences, and adaptive coordination, thus presenting diagnostic discrepancies and therapeutic challenges.

The goal of this project is therefore to develop a personalized data-driven model enabled by a physics-informed neural network (PINN) and noninvasive ultrasonic measures for assessment of muscle quality, which is herein defined by muscle stiffness and movement. More specifically, we will develop a scientific machine learning model, PINN, which is governed by muscle mechanics, instead of treating the model as a black box. This model, coined as mus-PINN, will learn from muscle stiffness and kinematics, which will be quantified by our recently developed ultrasound elastography method. We will evaluate the feasibility of mus-PINN on excised porcine muscle samples and in vivo human calf muscles, which are regarded as the second heart.

This project is foreseen to ultimately 1) provide a new mathematical formulation of the skeletal muscle mechanics in vivo, 2) establish an unprecedented quantitative tool for personalized examination of muscle conditions, and 3) promote a sustainable healthy lifestyle powered by high-quality skeletal muscle as we age.

Senolytic uPAR-CAR-T therapy for osteoarthritis

Principal Investigator	Chunyi Wen
PI Primary Affiliation	The Hong Kong Polytechnic University; Shenzhen University
Co-Investigator(s)	Li Yu, Chuan Yu

PROJECT DESCRIPTION

The prerequisite of healthy longevity is the prevention and treatment of age-related diseases. However, pro-inflammatory and fibrosis-inducing tissue microenvironment inevitably leads to tissue damage and chronic disease due to pathologically accumulated senescent cells (SCs) while aging. Fortunately, the urokinase-type plasminogen activator receptor (uPAR) as a promising immune therapy target has recently been identified to eliminate the SCs in mice. But its only been validated in animal models of lung cancer and liver disease. Here, we propose an innovative strategy that uses genetically engineered immune cells, (Chimeric antigen receptor T, CAR-T) to treat osteoarthritis, a common age-related disease, characterized by cartilage degradation, affecting more than 10% of the total population in Hong Kong, and hundreds of millions of people worldwide. We hypothesize that the targeted removal of senescent cells will lead to the significant improvement of osteoarthritis in animal disease models. If successful we will move on to explore the potential of this therapy in many other senescence-associated age-related diseases, including osteoporosis, diabetes, atherosclerosis, COPD, fatty liver diseases, and many more. As a collaborative effort between experts in both age-related diseases and cell therapy, this project could be quickly validated in proof of concept experiments and has the potential to significantly benefit the entire society.

Swallowable Encapsuled Multi-Stable Intra gastric Balloons for Obesity Treatment (SEMIBOT)

Principal Investigator	Hongliang REN
PI Primary Affiliation	The Chinese University of Hong Kong
Co-Investigator(s)	None

PROJECT DESCRIPTION

Global obesity has increased at an alarming rate and has become an increasingly serious threat to public health and longevity, as declared by the World Health Organization (WHO). Obesity, as an emerging medical condition, is caused by fat accumulations to the extent that it may negatively affect health. To treat obesity, medications and surgeries can reduce appetite (or decrease fat absorption) and reduce stomach volume leading to feeling full earlier. Placing the intragastric balloon (IGB) into the stomach is an alternative treatment approach when surgery and medication are unsuitable or recommended. This proposal hypothesizes that remotely controllable and Swallowable Encapsuled Multi-Stable Intra gastric Balloons for Obesity Treatment (SEMIBOT) in a tether-less manner can address this gap.