

HEALTHY LONGEVITY GLOBAL COMPETITION

2023 Catalyst Awardees

Sponsor: Research Grants Council of the Hong Kong Special Administrative Region, China

A Cave Automatic Virtual Therapeutic Garden for Residential Care Homes for the Elderly

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Co-Investigator(s)	Siqiang Wang, PhD Angela YM Leung, PhD Yi, Sun, PhD Wayne LS, Chan, PhD

PROJECT DESCRIPTION

Older people living in Residential Care Homes for the Elderly (RCHes) have limited opportunity to access to public open space due to the mobility impairments or chronic illness, which may be harmful to their social and psychological well-being. Therapeutic garden can provide variety of health benefits to older people, but it is difficult to build it in RCHes due to limited land resources in Hong Kong. This study innovatively applies the concept of therapeutic garden by using Cave Automatic Virtual Environment to build virtual therapeutic garden in RCHes. It can provide older residents simulated experience of natural healing elements to reduce stress and improve psychological and emotional well-being. To facilitate the idea, older residents' needs of therapeutic garden will be collected by conducting focus group and interview. The experimental design workshops will be organized with the residents to decide the key design elements of the therapeutic garden. Around 20 older people will be invited to use the virtual therapeutic garden once per two-week over a period of three months. Their perceived stress and psychological well-being will be compared by using Paired Samples Test to test the effectiveness of the idea. The descriptive analysis will also be performed to analyse the changes of emotional status, by analyzing the electroencephalography (EEG) of older residents during the usage of therapeutic garden. The idea could be applied to different RCHes to promote older residents' psychological well-being and health in the future.

A multi-modal approach to decipher cellular resilience for improving healthspan

Principal Investigator	Prof Hiu Tung Tom CHEUNG, PhD
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Co-Investigator(s)	None

PROJECT DESCRIPTION

The rich phenotypic diversity of the human population demonstrates how genetic variation influences lifespan and healthspan. Aside from environmental factors, genetic factors play a role in disease development and aging. Indeed, aging research has largely focused on genetic variants affecting the cell state, leading to specific disease phenotype manifestations. Still, little is known about the variants contributing to healthy aging. We propose to explore genetic complexity and its role in healthy aging by identifying novel genetic variants conferring high resilience to various cellular stresses, using a genetically diverse mouse resource engineered to recapitulate the genetic richness of the human population. Muscle stem cells (MuSCs, also known as satellite cells, SCs), the adult stem cells responsible for muscle regeneration, will be studied as a proof of concept. SCs turn over slowly and remain in quiescence, a reversible G0 state, until receiving stimuli to activate and contribute to myogenic lineage progression. However, during aging, MuSCs lose their stem cell resilience (e.g., the capacity to respond to cellular stresses, maintain quiescence, and rapidly activate), leading to a loss of SC functions and numbers as muscle ages. Hence, SCs serve as an ideal stem cell model of aging. Here, we will first conduct transcriptomic and epigenetic analysis on SCs isolated from genetically distinct mouse strains subjected to various cellular stresses. Such approaches will identify unique genetic variants conferring a healthy aging phenotype, serving as a novel therapeutic target to improve the organismal healthspan.

AI-Powered Multimodal Patient Progressive Profiles for Personalized Depression Treatment by Repetitive Transcranial Magnetic Stimulation

Principal Investigator	Haoran Xie, PhD, EdD
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Co-Investigator(s)	Kee Lee Chou, PhD; Xiaohui Tao, PhD; Soman Elangovan, MBBS; Raj Gururajan, PhD

PROJECT DESCRIPTION

According to the World Health Organization, depression is a highly prevalent mental illness that causes serious harm on a global scale, affecting an estimated 3.8% of the population. The success rates of depression treatments are often unsatisfactory. Repetitive transcranial magnetic stimulation (rTMS) is known to be an effective clinical treatment for clinical depression. However, the operational parameters of rTMS treatment are chosen by clinical professionals largely on the basis of experience, leading to ineffective treatment outcomes and medical resource management. To overcome this limitation, it is vital to understand what types of patients are most likely to respond well to clinical rTMS treatment at the patient-specific level. In this proposed project, we will leverage the availability of Hong Kong and Australian rTMS intervention data, patient characteristic data, and the latest progress in artificial intelligence (AI) to develop an AI-empowered rTMS depression treatment recommendation model. The model will be based on data-driven progressive patient profiling, comprising three main steps: data collection and preprocessing, representation learning for patient profiles, and recommendation of personalized treatment. Specifically, self-supervised AI algorithms will transform the original patient data space into a latent representation space, in which similar patients can be accurately grouped, thereby facilitating personalized treatment planning. Through a randomized clinical trial, we expect to reliably deliver personalized treatment (e.g., number of pulses, amplitude, treatment frequency, and administration site) to improve the effectiveness of rTMS treatment.

An immune aging monitor based on the dynamics of TCR repertoire and machine learning

Principal Investigator	Shuai Cheng Li, PhD
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Co-Investigator(s)	None

PROJECT DESCRIPTION

Human aging is closely associated with changes in the immune system known as immunosenescence. Understanding the underlying mechanisms of immunosenescence is crucial for developing therapies for age-related diseases and for enhancing our understanding of human aging and longevity. However, this presents a significant challenge due to the complexity and heterogeneity of immune cell populations and the difficulty of integrating diverse datasets. Machine learning methods can address these challenges by capturing the key features of human immune aging from high-throughput sequencing data. Our project aims to leverage machine learning methods to identify key biomarkers of immune aging and develop an immune aging monitor. We propose a k-mer-based graph convolutional network framework to fit the relationship between TCR repertoire and age and explore age-associated TCR sequences. We also suggest a bioinformatics pipeline for monitoring immune aging using age-related TCRs and individual medical characteristics to evaluate an immunosenescence score for the TCR repertoire. This monitoring system will provide timely alerts for the excessive aging of the immune system beyond the individual's actual age and aid medical practitioners in selecting appropriate medical interventions. This project is expected to lead to new insights into immunosenescence and contribute to the development of healthy aging.

An Integrated Graph Convolutional Network Multimodal Platform (GCN-MP) for Early Detection and Prediction of Late Onset Alzheimer's Disease

Principal Investigator	Victor OK Li, ScD
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Co-Investigator(s)	Jacqueline CK Lam, PhD (Co-Lead); David C Rubinsztein, BSc (Med), PhD; James B Rowe, B.M. B.Ch., PhD; Lawrence Cheung, PhD; Yang Han, PhD; Jocelyn Downey, PhD

PROJECT DESCRIPTION

Alzheimer's disease (AD) is a leading cause of death worldwide. Early prediction of Late Onset Alzheimer's disease (LOAD) is critical to timely intervention before irreversible brain damage. Accurate early LOAD prediction is challenging due to the need for a wide range of multimodal assessments, which can be time-consuming, costly, and invasive, preventing those who might develop symptomatic LOAD from timely diagnosis and therapeutic interventions. An AI-driven-multimodal LOAD prediction based on readily available data as inputs to an AI model trained on heterogeneous data of high-dimensional modalities/features across different diseases/populations, can be desirable for early LOAD prediction/intervention. Our transformative multimodal platform aims, FIRST, to develop an integrated Graph Convolutional Network Multimodal Platform (GCN-MP) technology, to fuse small datasets of different modalities/features/diseases/populations via a multimodal GCN model for accurate prediction of LOAD onset age; SECOND, to uncover early biomarkers and principal pathways driving LOAD onset. Five novelties have been proposed, including, heterogeneous multimodal inputs, multimodal data fusion, potential causal pathways identification, and integrated multimodal risk scores (IMRS) based on high-saliency complementary modalities. Our work will greatly facilitate clinicians and at-risk AD populations to more conveniently and accurately predict LOAD onset via the IMRS and onset age prediction, based on their available data types, and advance our understanding of LOAD etiology. Our team's two consecutive grants awarded by NAM, and the numerous works done on AI-driven prediction and estimation and in neurological studies from our members in HKU-Cambridge-AI-for-Neuro-disease-Research-Platform have prepared us to achieve these meaningful goals of AI for Social Good.

Enabling the effective and safe epigenetic rejuvenation with re-engineered transcription factors

Principal Investigator	Ralf Jauch, PhD
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Co-Investigator(s)	Jason Wong, D.Phil; Michael Huen, PhD

PROJECT DESCRIPTION

The Yamanaka factors Oct4, Sox2, Klf4 and c-Myc can convert somatic tissues into induced pluripotent stem cells resembling the inner cell mass of pre-implantation embryos. Induction of pluripotency is accompanied by a remarkable rejuvenation of cells from aged donors so that they epigenetically, structurally and metabolically resemble newborn tissue. The time restricted expression of all or some of these factors can repair damaged tissues in mice. However, the prolonged expression of Yamanaka factor induces tumors preventing the application of this strategy for human gene therapy. We have identified several re-engineered transcription factors (eTFs) that enhance pluripotency and direct lineage reprogramming. We hypothesize that replacing the Yamanaka factors with eTFs can decouple epigenetic rejuvenation from pluripotency induction, speeds up age reversal, enhances safety and relieves cargo restrictions for gene delivery. We have previously identified re-engineered SOX17 (eSOX17), a miniaturized SOX (miniSOX) as well as enhanced POU and KLF factors (ePOU and eKLF) with established activity to convert mouse and human cells into pluripotent or multipotent stem cells. We will overexpress combinations of these eTFs in aged human fibroblasts and measure the epigenetic and cellular rejuvenation. We aim to identify factor combinations that lose the full potential to induce pluripotency but retain the ability to rejuvenate cells akin the full complement of Yamanaka factors. Our unique eTF centered approach could lead to the identification of a strategy that not only makes rejuvenation more efficacious and delivery easier but also eliminates the imminent risk of oncogenesis associated with classical Yamanaka factors.

Geometric Deep Learning on Radiomics for the Prediction of Brain Age, Cognitive Maintenance and Healthy Longevity

Principal Investigator	LU Hanna, PhD
PI Primary Affiliation	The Chinese University of Hong Kong
Co-Investigator(s)	LI Yu, PhD; ZHANG Li, PhD

PROJECT DESCRIPTION

Towards healthy longevity and successful ageing, brain age, rather than chronological age, has been increasingly used as a phenotype to evaluate the brain fitness and predict the cognitive maintenance at individual level. Brain age is closely related to a bunch of factors, including brain structure, functional connectivity, and cerebrovascular health. Recently, several models of brain age have been identified and strongly related to neurodegeneration and its progression. However, the utility of these models may be blunted by their reliance on the defined features drawn from single brain feature (e.g., gray matter). The current limitations lead to the motivation for developing an integrative model to evaluate brain age. In this project, we propose a novel deep learning framework capable of exploiting network-based radiomic features to learn the relationships between brain structure and function across the adult lifespan such that more accurate brain age could be predicted. This method will be trained on two large-scale cohort datasets and then tested on a longitudinal dataset of Hong Kong SuperAgers, utilizing novel brain age model to validate and improve the prediction accuracy. Multi-modal MRI data will be analyzed based on semi-automated platform, generated individualized radiomic models and then achieve the prediction of brain age. This project can interpret the individual differences between chronological age, brain age and cognitive maintenance for senior adults. Furthermore, it can be used to evaluate the cognitive maintenance, predict the conversion from healthy ageing to

dementia and disease progression, serve as a personalized biomarker for detecting, monitoring and preventing neurodegenerative diseases.

Leveraging brown adipose tissue to combat elderly stroke

Principal Investigator	Leiluo Geng, PhD
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Co-Investigator(s)	Aimin Xu, PhD; Boya Liao, PhD; Leigang Jin, PhD; Xinyao Yi, MS

PROJECT DESCRIPTION

Brown adipose tissue (BAT), consisted of brown adipocytes and stromal vascular fraction, plays a pivotal role in regulating thermogenesis and energy expenditure. BAT also modulates systemic metabolism and health via secreting endocrine factors, termed batokines. Ageing is associated with loss and dysfunction of BAT and poor prognosis of stroke, which has been a leading cause of death and disability in the aged population. Whether restoration of BAT function is able to alleviate stroke injury in the elderly remains unknown. Our preliminary studies demonstrated that both surgical and genetic depletion of BAT exacerbated ischemic stroke injury induced by middle cerebral artery occlusion in young mice. Aged mice transplanted with BAT from young mice showed alleviated cerebral injury after stroke, suggesting the protective role of functional BAT in elderly stroke. Additionally, we found BAT-derived exosomes, which contain multiple kinds of batokines, significantly alleviated the cerebral ischemia injury in aged mice. Based on these findings, this study aims to comprehensively reveal the beneficial role of BAT in modulating elderly stroke injury, clarify the fine-tuned crosstalk between BAT and central nervous system in stroke injury, and identify novel batokines of therapeutic potential for elderly stroke. Our study will provide phenotypic and mechanistic insights into both stroke biology and brown adipocyte biology as well as contribute to the development of BAT-based therapies for elderly stroke.

Reverse inflammaging by targeting nuclear PD-L1 in inflammatory macrophages

Principal Investigator	Rio Sugimura, MD, PhD
PI Primary Affiliation	School of Biomedical Sciences, The University of Hong Kong
Co-Investigator(s)	None

PROJECT DESCRIPTION

Inflammaging is one of the major drivers of aging and senescence. The identification of its mechanism will enable drug discovery to stop aging. Inflammatory macrophage is the main contributor to inflammaging. We recently identified that nuclear PD-L1 regulates inflammatory programs in macrophages. Loss of nuclear PD-L1 inhibits the production of inflammatory cytokines of macrophages, suggesting a promising target for anti-aging therapeutics. Here we propose to determine the molecular mechanisms of nuclear PD-L1 and discover a therapeutic approach to inhibit inflammaging. Our feasibility is demonstrated by preliminary data and accumulated literature. The success of the project will lead to drug discovery and R&D application in the industry of Hong Kong. The impact of targeting inflammaging for human health is immense.

Social prescribing of virtual reality urban greenness with peer support model to promote mental health among aging population: an effectiveness and feasibility study

Principal Investigator	Shiyu LU, PhD
PI Primary Affiliation	Department of Social and Behavioural Sciences, City University of Hong Kong
Co-Investigator(s)	Linyan LI, ScD; Cheryl Hiu-kwan CHUI, PhD

PROJECT DESCRIPTION

The COVID-19 has exacerbated mental health problems among the aging population. The Peer support model can help deliver mental health services without overreliance on professionals. Virtual reality (VR) natural environment therapy is an innovative approach to improve mental health, given its efficacy and low cost. However, knowledge remains unclear about how to design VR urban greenness to optimally improve older adults' mental health and enhance social connection. We aim to develop a protocol for social prescribing of VR urban green spaces using the peer support model and test its feasibility and effectiveness in improving older adults' mental health. We will adopt a three-phase study. First, we will use the photovoice method to invite older adults to collect photographs/videos of urban spaces in Hong Kong. Then we will understand key attributes of urban spaces that are preferable for the aging population based on the photographs/videos collected. Then, we will develop a 3-arm randomized controlled trial: VR urban green space with peer supporters, preferable VR urban green space without peer supporters, and non-biophilic VR intervention without peer supporters as control group. Lastly, we will conduct focus group interviews with participants to understand the challenges of implementing VR-based intervention among older adults. This model will provide a non-pharmacological approach to improve older adults' mental health, extending their life year with quality and health, and provide them with volunteering opportunities to help their peers, benefiting their longevity. The innovatively model will also help improve care workforce sustainability given the shrinking of care workforce nowadays.