

HEALTHY LONGEVITY GLOBAL COMPETITION

2024 Catalyst Awardees

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

A Large Language Model (LLM)-driven Approach for Advancing Low-cost Timely Speech-based Late Onset Alzheimer’s Disease (LOAD) Prediction

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

PROJECT DESCRIPTION

Timely LOAD prediction is critical to slowing disease progression. Existing works based on clinical biomarkers are generally invasive, time-consuming and expensive, focussing on diagnosis instead of prognosis. In our multi-modal study, linguistic markers are strong early-stage predictors of LOAD. However, speech datasets are typically small, lacking longitudinal representation and linguistic variation, making it difficult to train LOAD models to accurately predict LOAD. Our study revolutionises LOAD prediction via the development of an LLM-driven transformer model trained on sufficient amount of normal control (NC)/mild cognitive impairment (MCI)/LOAD speech samples. First, we develop a novel LLM-driven model to generate new speech and transcription samples based on limited NC/MCI/LOAD samples from DementiaBank and Framingham Heart Study. Particularly, more longitudinal Chinese and English speech samples of NC/MCI/LOAD will be generated from original samples to overcome data shortage. Second, our LOAD speech data are converted into speech and text embeddings capturing the linguistic information of pre-trained LLMs, subsequently fed into our Transformer for accurate prediction of timings for LOAD conversions (including pre-symptomatic LOAD), and identification of reliable linguistic markers discriminating these different conversion states. This has the advantage of increasing/enhancing (1) data volume, diversity, and temporal variability to improve accuracy, robustness and generalizability of LOAD prediction, (2) understanding of language-specific and cross-linguistic markers characterizing disease states (particularly Chinese and English contexts), (3) our detection of MCI/LOAD states, and prediction of the timings of pre-symptomatic onset. Our preliminary results show that LLM+Transformer (with-Generated-Transcription-Data) significantly outperforms Transformer Baseline (without-Generated-Transcription-Data) by 6% in NC/MCI/LOAD detection, achieving 91% accuracy.

Brain Connectome of exceptional longevity: magnetic resonance imaging of (near) centenarians in Hong Kong

Principal Investigator	Rongjun Yu, PhD
PI Primary Affiliation	Hong Kong Baptist University
Co-Investigator(s)	Yi Huang, PhD; Bobo Hi Po Lau, PhD, Vincent Chung Tong Mok, MD

PROJECT DESCRIPTION

Near centenarians and centenarians seem to be able to delay dementia pathologic changes. They are an informative and unique cohort to better understand the protective factors conferring resistance to age-related cognitive declines. However, the neural mechanisms of exceptional longevity in this valuable cohort are not well understood. We leverage the new 3T MRI facility and the existing centenarian cohort in Hong Kong to conduct multimodal brain imaging in a geographically representative sample of individuals who are above 95 years old. Thirty dementia free (near) centenarians, thirty (near)centenarians with dementia, and thirty dementia free younger participants (65-95 years old) will be recruited. Structural magnetic resonance imaging (MRI and resting state fMRI 15 mins in total) will be conducted. We will employ advanced brain network analysis to map the distinct neural connectivity patterns present in dementia free (near)centenarians. By conducting regression analysis, we will pinpoint the specific features of the brain connectome that correlate with cognitive abilities in adults of extreme old age. Our goal is to establish Asia's inaugural brain imaging centenarian dataset and utilize cutting edge methods in human connectome research. Our approach can reveal longevity related brain network signatures and identify the neural features that protect old adults from age related cognitive deterioration. Our findings may inform us of the theories of successful aging and models of neuroprotection from dementia.

Contrasting and Distinguishing Therapy-induced Senescence from Replicative Senescence and Oncogene-induced Senescence at the Molecular Level

Principal Investigator	Gao ZHANG, PhD
PI Primary Affiliation	The University of Hong Kong
Co-Investigator(s)	Martin Chi Hang CHEUNG, PhD; Yuanhua HUANG, PhD

PROJECT DESCRIPTION

Healthy longevity is largely impacted by ageing and cellular senescence. It is well known that there are three forms of cellular senescence, including replicative senescence, oncogene-induced senescence (OIS) and therapy-induced senescence (TIS). For normal cells, there is a definitive lifespan, which is termed Hayflick limit that determines replicative senescence. Oncogene-induced senescence (OIS) is a phenomenon that occurs both in vitro and in vivo as a tumor suppressive mechanism. Some small molecules, such as BRAF or MEK inhibitors, are more potent triggers of premature senescence in cancer cells than others, which is a phenomenon of TIS; however, cancer cells develop a sophisticated yet not well-understood mechanism to overcome and subsequently repress TIS in order to evade cancer therapy. Intriguingly, we uncovered two distinct forms of TIS, which were dependent on the specific type of therapies. By implementing a systems biology approach, we identified a core senescence component that was sufficient and necessary for the induction of TIS in cancer cells, which resembled OIS in normal cells. We were able to quantify heterogeneous responses of cells to various stimuli of cellular senescence by employing an integrated fluorescence-activated cell sorting (FACS) approach. In this project, we will aim to unravel molecular underpinnings of TIS in cancer cells which will be distinguished from replicative senescence and OIS in normal cells. Furthermore, we will aim to identify a rationale-based combination therapy that would have the potential of exploiting TIS and converting it towards apoptosis in order to maximize cell death of cancer cells.

Development of a Practical Elderly Fall Detection Solution via Non-Intrusive, Low-Cost Sensing

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

PROJECT DESCRIPTION

With the growing global aging population, the issue of elderly fall detection has become increasingly critical. Statistically, there are approximately 70,000 fatal falls among older adults worldwide every year, and over 37,000,000 falls that require medical attention. Moreover, many elderly individuals live alone, leaving them potentially unable to seek help for extended periods after a fall. This pressing issue acutely calls for innovative solutions for practical elderly fall detection, which, however, has been a long-standing challenge. This project seeks to develop a practical solution for accurate and robust fall detection that is privacy-preserving, non-intrusive, and low-cost, allowing large-scale deployment for ubiquitous settings. We propose to explore and exploit a unique opportunity underpinned by emerging modalities for non-contact human sensing, e.g., Thermal Arrays and ToF sensors. The combination of these modalities offers a compelling balance between sensing resolution and privacy, rendering a promising solution to ubiquitous fall detection that is unexplored. The project will shed light on practical solutions to fall detection, improving healthy longevity for our aging society to age well.

Optimizing and Validating the Integrated Digit-in-Noise Test (iDIN) for Global Screening of Hearing and Cognitive Function

Principal Investigator	Lena L N WONG, PhD
PI Primary Affiliation	The University of Hong Kong
Co-Investigator(s)	Shangqiguo WANG, PhD

PROJECT DESCRIPTION

Hearing loss and cognitive decline are common challenges faced by older adults worldwide. In fact, more than 42% of people over 60 experience some degree of hearing loss, and about 16% of those over 50 suffer from mild cognitive impairments. These conditions not only affect the quality of life but also bring significant economic burdens. For instance, the cost of dementia care reached \$1 trillion globally in 2018 and is expected to double by 2030.

Similarly, the economic impact of hearing loss was over \$981 billion in 2019. This burden is expected to continue to increase, as the global older adult population is anticipated to double between 2015 and 2050. Recognizing the urgent need for early detection of these conditions, our lab developed a promising tool in 2023: the Integrated Digit-in-Noise Test (iDIN). This innovative test quickly screens for hearing and cognitive function by measuring how well individuals recognize digit sequences in noisy environments. Our preliminary data indicates that iDIN has great potential to become a global screening tool, but it requires further refinement and more clinical evidence to achieve this goal.

In this study, we aim to optimize the iDIN testing process and explore its relationship with different cognitive domains to enhance test effectiveness. We will also gather more clinical evidence to support its global implementation. This research is a step towards providing an accessible and efficient tool for early intervention in hearing and cognitive decline, ultimately improving communication, wellbeing, and management for patients and caregivers worldwide.

Tales Weaver: An AI-Enhanced System to Foster Social Connectedness

Principal Investigator	Helene H. FUNG, PhD
PI Primary Affiliation	The Chinese University of Hong Kong
Co-Investigator(s)	Helen MENG, PhD Hongmei LIN, Mphil Yiwen WU, MA

PROJECT DESCRIPTION

Social connectedness is a significant factor in preventing cognitive decline and improving psychological well-being among older adults. However, older adults may suffer from social disengagement due to physical impairments and social loss. In an increasingly digital world, older adults also face challenges in building and maintaining social relationships due to low technological acceptance and a lack of appropriate tools.

Personal narratives, telling stories about one's past, contribute to cognitive and mental health among older adults. They boost self-confidence, enhance meaning of life, and have therapeutic value for those with mild cognitive impairment and dementia. Further, sharing biographical stories with others allows one to quickly build and deepen social connections, reducing stigma and fostering mutual understanding.

This project aims to develop an age-friendly digital storytelling social platform supported by AI-enhanced speech and image recognition technologies. This innovative system enables older adults to capture and record their personal stories and experiences, transforming them into digital narratives that can be shared through an online platform across generations. A multilingual AI speech recognition system is embedded to ensure accurate and reliable transcription of the spoken words. The system also installs an AI image recognition system to automatically identify the location and other key information from the user-uploaded photo to accompany and enrich the storytelling.

By building an age-friendly interactive social platform based on digital narratives, this project contributes to reducing communication barriers in old age and promoting meaningful social connections across generations.

Targeting Age-Related Memory Impairment: Novel Molecular Chaperones for Enhanced Cognitive Function

Principal Investigator	Rubén HERVAS MILLAN, PhD
PI Primary Affiliation	The University of Hong Kong
Co-Investigator(s)	None

PROJECT DESCRIPTION

Long-lasting memories involve converting temporary experiences into persistent changes in synaptic function. These changes depend on modifications in the synaptic proteome. Molecular chaperones serve as an interface between the environment and the proteome. Among the chaperone families, J-domain proteins (JDPs) have specific and diverse capabilities in regulating protein states. Recently, we manipulated the expression of 31 JDPs in a subset of neurons in the *Drosophila melanogaster* central brain. We identified a previously uncharacterized JDP, which we named Funes, that enhances long-term memory by acting on odor-responsive Kenyon cells and reward-responsive dopaminergic PAM neurons. Mechanistically, Funes improves memory by facilitating the amyloid aggregation of the cytoplasmic polyadenylation element binding (CPEB) protein, Orb2 in *Drosophila*, which serves as a physical substrate for memory by promoting the translation of memory-related genes (Patton et al, under review - Cell). Surprisingly, this suggests that promoting certain types of amyloids – protein structures often associated with diseases like Alzheimer's – may aid, rather than hinder, memory. However, it is unclear whether this finding applies to humans, where, similarly to *Drosophila*, CPEB forms

functional aggregates. In the "Healthy Longevity Catalyst Awards 2024," we aim to investigate the innovative idea that molecular chaperones regulate memory in humans. If this is true, identifying modulators could have commercial and therapeutic value. This discovery could lead to the development of strategies to enhance memory in Alzheimer's patients or the elderly population.

Targeting Nav1.8 via CRISPR-dCas9 for Treatment of Osteoarthritis

Principal Investigator	Michael Tim-Yun ONG, FRCS
PI Primary Affiliation	Department of Orthopaedics and Trumatology, The Chinese University of Hong Kong
Co-Investigator(s)	Mingde CAO, PhD; Yuchen LIU, MD, PhD

PROJECT DESCRIPTION

Osteoarthritis (OA), the most common form of arthritis, is characterized by the progressive degradation of joint cartilage, leading to pain, stiffness, and reduced mobility. Pain is the primary symptom of OA, prompting individuals to seek medical assistance as it affects their daily activities, emotional well-being, and overall functionality. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line treatment for OA symptom relief. However, long-term use of NSAIDs is often limited by gastrointestinal side effects and insufficient analgesic efficacy. Nav1.8, a sodium channel, has been implicated in the transmission of mechanical pain in a rodent model of OA, suggesting that targeting Nav1.8 on joint nociceptors may offer therapeutic potential for OA pain management. Small-molecule drugs targeting the NaV family have been unsuccessful due to side effects from a lack of targeting specificity and limited bioavailability through systemic administration. We hypothesize that an alternative approach involving the epigenetic modulation of NaV1.8 expression using CRISPR-dCas9 could engineer highly specific, long-lasting, and reversible treatments for OA pain. We anticipate that this study will facilitate the development of a novel therapeutic that can safely and effectively provide sustained relief of OA symptoms.

The Impact of ‘Digital Strolling’ on Depression and Quality of Life of People with Severe Mobility Impairment

Principal Investigator	Yan LI PhD
PI Primary Affiliation	The Hong Kong Polytechnic University
Co-Investigator(s)	Prof Janelle Yorke; Dr Richard Chen Li; Dr Mengqi Li

PROJECT DESCRIPTION

Severe mobility impairment (SMI) has a range of negative impacts on people's lifespan and overall quality of life. SMI is associated with increased rates of medical complications, hospital readmission, and mortality and substantial medical expenses with additional medical expenses increased by HKD 68,318 per case annually. Literature shows that over 50% of people with SMI have depression or anxiety symptoms. People with SMI often have poor mental health, which can lead to harmful behaviours and chronic health conditions and consequently shorten a person's lifespan. "Digital Strolling" refers to the use of virtual reality technology to simulate the experience of walking or moving around in a digital context. This can be particularly significant for people with SMIs, as it enables them to experience a sense of movement and exploration that they may not be able to achieve in the physical world. This can have positive effects on mental health, including reducing feelings of isolation and improving mood. It can also provide a form of gentle mental stimulation, which can be beneficial for overall cognitive function, and quality of life.

This study aims to develop and test the feasibility, acceptability, and preliminary effects of a “Digital Strolling” intervention among people with SMI. “Digital Strolling” is hypothesized to be able to improve depression, chronic

pain, and sleep quality of people with SMI. The research findings will lay the foundation for subsequent large-scale trials and provide recommendations for medical staff and rehabilitation experts to develop innovative and comprehensive community healthcare programs for people with SMI.