

HEALTHY LONGEVITY GLOBAL COMPETITION

2020 Catalyst Awardees

Sponsor: Ministry of Health of Singapore

Characterizing the Role of Microglia-Mediated Cognitive Function in the Aging Brain

Principal Investigator	Thameem Dheen
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Jai S. Polepalli

PROJECT DESCRIPTION

With a rapidly aging population, an increase in frequency of individuals with cognitive dysfunction and progressive deterioration of memory, represent an enormous socio-economic burden. Recent studies show that microglia, the resident immune cell of the brain, express memory molecules which are involved in synaptic plasticity in the healthy brain. During aging, microglia become dystrophic and may show a reduction in their ability to maintain synaptic functions, thereby resulting in cognitive decline. Given the plasticity of microglial cells in the CNS, we hypothesize that microglia, which have been shown to be involved in learning and memory, can be targeted to complement and enhance neuronal functions by providing memory molecules in the aging brain.

To address this hypothesis, we will employ a combination of cutting-edge techniques for morphological (in vivo imaging using 2 photon microscopy and histology), molecular, epigenetic and functional (electrophysiology) analyses to investigate 2 overarching objectives. Firstly, we will characterize microglia in healthy aging brain using single cell RNA sequencing, histone profiling, and morphological analysis using multiphoton microscopy techniques to understand the molecular and epigenetic profile of dystrophic microglia. Further, we aim to develop in vitro models of aging microglia to perform functional analysis of the dystrophy associated genes. Secondly, we propose to explore how dystrophic microglia influence cognitive functions using electrophysiology studies in the aging rat brain, and to evaluate if these cognitive functions can be improved by administration of epidrugs such as HDAC inhibitors. A key outcome of this proposal is a comprehensive understanding of dystrophic microglia in the aging brain which will form the basis for microglia-centric therapies (epidrugs) to improve microglial functions and subsequently delay cognitive decline in the aging brain.

Deciphering Aging-Dependent Human Neuronal Activity Changes, Tissue Microenvironment and Gene Expression Patterns

Principal Investigator	Jai S. Polepalli
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Thameem Dheen; Vincent Nga Diong Weng; and Yeo Tseng Tsai,

PROJECT DESCRIPTION

The aging-related decline in brain function is attributed to changes in gene expression patterns, molecular, cellular and synaptic function of the various types of cells – encompassing changes in biophysical properties of neurons and neuronal communication through synapses. This proposal aims to address the question of how changes in neuronal activity, gene expression patterns and cellular function in the human brain correlate with mental aging, and how these changes are exaggerated in pathological conditions. The idea central to this

proposal is that examining and correlating changes in the structural, functional and genetic profiles of the human brain will enable us to identify human brain-specific molecular markers of mental aging. This identification (of molecular markers of aging) will advance drug discovery targeted towards delaying and slowing the mental aging process. To achieve the objectives of this proposal, we will perform experiments on fresh cortical tissue extracted from neurosurgery patients of different age groups, at the National University Hospital- Singapore during routine surgical procedures. We will employ a combination of tools in single-cell RNA sequencing, in-vitro electrophysiology, and neurochemistry. This combination of approaches is being employed for the first time to study human mental aging.

Detecting Parkinson's Disease-Associated Metabolites with Colorimetric Sensor Array and Machine Learning

Principal Investigator	Koh Tong Wey
PI Primary Affiliation	Temasek Life Sciences Laboratory
Co-Investigator(s)	Ian Cheong; Tan Eng Kind

PROJECT DESCRIPTION

Parkinson's disease (PD) is a common aging-related debilitating neurological disorder. No drug can reverse disease progression and clinical diagnosis can be challenging during early stages of the disease. There is an acute need for affordable, objective, biomarker-based methods both for diagnosis of patients and for accurate identification of subjects for new drug trials. We propose the use of colorimetric sensor array and machine learning algorithms to discern changes in urine metabolites as a PD diagnostic. Similar arrays have been designed to mimic sophisticated olfactory sensory systems of animals for discerning complex chemical mixtures. We have validated our array on hepatitis B and various cancers, and the current proposal to test it on PD is novel. Our array consists of 70 hydrogel spots; each spot contains a unique combination of derivatized acrylamides and acrylates that undergo distinct color reactions with urine metabolites. The resulting color pattern of the 70 spots is an emergent property of the urine metabolites, which in turn reflects health status. The color pattern of each array is analyzed by machine learning algorithms for diagnosis. In this pilot project, we will test the array with normal urine and urine spiked with 50 PD-enriched metabolites chosen from literature. Normal and simulated PD urine will be profiled and classified using a pre-trained machine algorithm. The performance will be evaluated in terms of sensitivity, specificity, PPV and NPV. Limit of detection of each metabolite will be assessed. In addition, we have identified colorimetric reactions designed to detect specific metabolites known to be enriched in PD urine and will incorporate these reactions into the array to improve performance. Success of this pilot will lead to a clinical trial for PD diagnostic. We envision that our technology will be generalizable to many aging-related conditions and will enable personalized preventive approaches for healthy longevity.

Enhanced Single Cell Transcriptomics for New Biomarkers and Targets in Cardiovascular Ageing

Principal Investigator	Roger Foo
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Matthew Ackers-Johnson

PROJECT DESCRIPTION

Cardiovascular disease (CVD) is the primary cause of morbidity and mortality globally. Related annual US healthcare expenditure exceeds \$200bn, of which heart disease alone costs \$100bn, surpassing all other diagnoses. Age is a fundamental predictor of CVD risk, and as populations age, associated social and economic burden is projected to become increasingly severe. Survivors of acute myocardial infarction (MI) may develop

progressive deterioration of cardiac function and heart failure (HF), prognosis for which remains worse than most cancers. New platforms for biomarker and drug discovery are urgently needed.

We propose to leverage an advanced sequencing protocol, developed in our lab, to identify novel age-associated and disease-relevant cardiac cell types, states, interactions, biomarkers and drug targets. This will begin with a comparison of MI disease response in young and aged mice, at single cell resolution, with key findings later validated in banked human patient tissue samples.

Our protocol is optimised for unbiased, high quality capture and sequencing of dissociated, whole, live cardiac cells, and offers significantly higher sequencing detail than commercial platforms, including a five-fold increase in gene detection. Sequencing of over 2000 cells from young mouse hearts has already demonstrated powerful utility. This innovative approach can thus lead to transformative breakthroughs in understanding, monitoring, management and treatment of age-related CVD. Furthermore, we envisage future applications in a multitude of complex heterogeneous disease settings (vascular, cancer, neurological), unlocking advances in health and longevity research across disciplines.

Ergothioneine, the Lesser Known Longevity Nutrient

Principal Investigator	Irwin Kee Mun Cheah
PI Primary Affiliation	National University of Singapore (NUS)
Co-Investigator(s)	Feng Lei; D.Phil.; and Barry Halliwell

PROJECT DESCRIPTION

The naturally occurring thione, ergothioneine, accumulates in the human body at high concentrations primarily from diet. Studies suggest this compound may play an important physiological role, however this has yet to be fully elucidated. We have recently observed that blood levels of ergothioneine significantly decline with age and onset of certain neurodegenerative disorders. We propose that the decline in blood ergothioneine levels may be a factor predisposing elderly to age-related conditions, and as such supplementing this compound may prevent or delay the onset of those conditions and prolong healthy longevity. This proposal will uncover the associations between ergothioneine levels, the onset of age-related disorders, and biomarkers of oxidative damage and inflammation in elderly subjects and help establish a baseline for healthy levels of ergothioneine in the blood. Furthermore, the study aims to investigate the possible mechanisms of protection by ergothioneine using a range of cell and animal models. This proposal lays the foundations for future clinical studies into prophylactic and therapeutic supplementation of ergothioneine for a range of age-related chronic disorders.

Examining Evidence for Transmissible Alzheimer's Disease

Principal Investigator	Ajay Sriram Mathuru
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Jan Gruber

PROJECT DESCRIPTION

Alzheimer's Disease (AD) is known to develop among many individuals in an age dependent manner. A few genetic variants in enzymes or proteins associated with production of amyloid beta (A β) peptide from A β protein have been identified as potential candidates associated with AD. However, for most part, it is unclear if some individuals are more susceptible than others. In the last 5 years, 2 studies have been published that suggest the possibility for A β plaque formation to be associated with seeding of contaminated A β plaques to healthy people. This is surprising and it is still debated if AD can be transmitted, just like a prion disease to provide nucleation sites that facilitates further misfolding and aggregation of A β peptides and tau proteins in the brain. Only a couple of studies have shown some evidence. Here we take the step to test if transmission can occur via ingestion of A β

aggregates. We plan to test this transmissibility hypothesis by feeding genetically engineered laboratory model nematode that express the human A β aggregates to another laboratory model, the zebrafish. We will then examine the brains by histopathological techniques and the behavior of the fish to evaluate if A β associated toxicity and neurodegeneration is detectable due to transmission in a prion-like manner. We also plan to observe inter-generational transmission, if any, and the effectiveness of drug-combinations in attenuating any effects found.

Organismal Aging and Oxidants Beyond Macromolecules Damage

Principal Investigator	Marie-Veronique Clement
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Shazib Pervaiz

PROJECT DESCRIPTION

One prediction of the free radical theory of aging is that oxidative stress shortens organisms' lifespan because of the damaging effect of oxidants on macromolecules, thereby resulting in loss of tissue/organ functionality as seen in age-related diseases. Based on this prediction, observational studies and small interventional studies accumulated to justify large-scale double-blind interventional trials of antioxidants for many age-related diseases. Unfortunately, by early 2000, sufficient clinical evidence had accumulated to indicate little to no significant health benefits of supplementation with antioxidants. Notably, age-related decline in health and organ functions is also linked to the accumulation of IL-6 secreting senescent cells. While, most interventions using anti-oxidant to benefit human health appear to target oxidants that are implicated in macromolecule oxidation, primarily hydrogen peroxide (H₂O₂), our recent in vitro work provides evidence for a distinctly different redox milieu involved in the phenotype of senescent cells. We have identified a superoxide/nitric oxide (O₂⁻/NO)-driven redox state which has an effect different from H₂O₂ on the secretion of the senescence-associated interleukin, IL-6. While inhibiting O₂⁻/NO signaling mitigated IL-6 secretion, scavenging H₂O₂ increased it. Based on these data, we hypothesize that two distinctly different redox states are at play as the stimulus for human aging. Hence, we propose that for an anti-oxidant approach to have significant benefits on human life-span the antioxidants and/or redox modulators used should mitigate not only the damage to macromolecules but also the accumulation of senescent cells with an age-associated phenotype. As such, this project intends to generate data to get a deeper understanding of the newly discovered redox state in age-related cellular senescence. Moreover, going forward, these results will enable us to establish a cell-based model system that could be used to screen novel redox modulators, able to mitigate both macromolecules oxidation and the accumulation of age-associated senescent cells.

p75 Neurotrophin Receptors in Forebrain Medial Septum Mediate the Enhanced Experimental Chronic Pain in Aged Rodent?

Principal Investigator	Sanjay Khanna
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Low Chian ming

PROJECT DESCRIPTION

This proposal tests the hypothesis that the p75 neurotrophin receptors (NTR) in the forebrain medial septum (MS) is a basis of increased chronic pain in aged rodent. Chronic pain affects about 20% of the world population and is debilitating, especially in aged. Indeed, chronic pain is co-morbid with depression, anxiety and cognitive decline and thus affects the lifestyle of patients. Aged rodents, as with humans show enhanced pain on injury in comparison to young. Preliminary experiments from the laboratory suggests that blocking the function of p75

NTR in MS reverses experimental pain due to neuropathy in young rat. However, the role of septal p75 NTR in mediation and enhancement of chronic pain in aged remains unclear. Interestingly, the expression of p75 NTR increases in brain of the aged. Using rodent models, behaviour and cell biology techniques, the proposal will examine (a) the changes in expression of p75 NTR, specifically in MS with age, and (b) the effect of functional antagonism of septal p75 NTR on chronic experimental pain. The function of p75 NTR will be antagonized either with knockdown of the receptor or by microinjection of drugs that antagonize the function of the NTR by binding to it. A demonstration that antagonism of septal p75 NTR effectively blocks pain in aged will be very novel and will be a precursor to a wider investigation into the role of the septal receptor as a common target mediating changes in emotion-motivation in aged of which enhanced chronic pain is one manifestation.

Personalizing Exercise for Enhancing Healthspan: Using Artificial Intelligence for N-of-1 Exercise Prescription

Principal Investigator	Goh Jor Ming
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Brian Kennedy; Ph.D.; and Dean Ho

PROJECT DESCRIPTION

Exercise exerts physiological effects on multiple organs and tissues and is a powerful “drug” that improves healthspan, depending on the “dose” (frequency, intensity and duration) administered. A significant heterogeneity of inter-individual physiological responses to any standardized exercise regimen exists, however. Some individuals demonstrate adverse or no response to exercise training. Furthermore, adverse reactions may occur independent of improvements in cardiorespiratory fitness. Hence, to maximize public health efforts for primary prevention and healthspan, exercise prescription needs to be personalized.

CURATE.AI is a neural network-based optimisation platform that correlates inputs- in this case, exercise, and its respective doses or intensities, to outputs, which can include treatment efficacy or training-induced adaptations. This correlation is based on a quadratic algebraic series previously validated in over 40 disease indications that span the in vitro through clinical/human stages of development. These have included solid cancers to infectious diseases as well as cognitive training, among others.

We will compare 2 “doses” of exercise intensities and measuring physiological parameters e.g. heart rate (HR) and molecular biomarkers (e.g. IL-6, FGF-21, lactate) that are responsive to dynamic changes in metabolic demands. Our feasibility study cohort will comprise young (21-30 years) and older (50-64 years) family members (mothers and daughters) undergoing 3-weeks of high, or low-intensity exercise training. After a 2-week washout, subjects will repeat another 3-weeks of exercise of either low, or high-intensity training, whichever was not performed previously. Importantly, at the end of each week, CURATE.AI will optimize the subsequent week’s training session to either increase, maintain or decrease exercise intensity, based on the subject’s i) VO₂, ii) HR, and iii) lactate concentrations during exercise. The exercise-induced changes in biomarkers and physiological responses will be assessed by CURATE.AI to generate unique parabolic curves for each subject. These individualized parabolic responses will yield further insight into personalized responses to exercise.

Small RNAs: Big Answers to Healthy Longevity?

Principal Investigator	Hataitip Tasena
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Brian Kennedy; Ph.D.; Yvonne Tay; Ph.D.; and Maximilian Unfried

PROJECT DESCRIPTION

Humans have long been searching for the path to longevity. Among the latest but less known possibilities being proposed is PIWI-interacting RNAs (piRNAs). These small non-coding RNAs could prevent DNA damage and genomic instability, ones of the key hallmarks of aging and significant players in various age-related diseases.

The main function of piRNAs is transposon silencing. A piRNA guides a PIWI protein to its DNA target, including a transposon, resulting in transcriptional repression through epigenetic modifications or by inducing post-transcriptional mRNA degradation. Active transposons, known to increase with age, can lead to aberrant gene expression and cause damage to genomic integrity. Meanwhile, several mRNAs associated with age have been identified. We hypothesize that piRNAs could contribute to healthy aging, possibly by suppressing transposons or other aging-related mRNAs.

Although some piRNAs associated with heart failure, cancer or Alzheimer's disease have been identified, no study to date has reported piRNAs associated with aging. In this proposed study, we will take the first step to identify aging-associated piRNAs using the relatively inexpensive approach.

Firstly, genome-wide piRNA expression will be profiled in young (n=6) and old (n=6) mice to identify piRNAs differentially expressed with age. Next, the significant piRNAs that are also expressed in human (using online piRNA database "piRBASE" as a reference) will be shortlisted. Among these, the most differentially expressed piRNA will be overexpressed in human cells, of which genome-wide mRNA expression will be profiled to identify mRNAs potentially targeted by the piRNA. Finally, the pathway analysis will be performed on the list of mRNAs differentially expressed with the overexpressing piRNA.

This study will shed light on the potential mechanisms through which piRNAs may regulate aging. The findings will enable researchers to utilize more targeted approaches to confirm the aging-related functions of piRNAs in humans in the future.

Studying Epigenetic Ageing and Telomere Length as Possible Biological Predictors for Healthy Ageing – The Singapore Chinese Health Study

Principal Investigator	Rajkumar Dorajoo
PI Primary Affiliation	Genome Institute of Singapore
Co-Investigator(s)	Brian Kennedy; Heng Chew Kiat; Liu Jianjun; Woon-Puay Koh

PROJECT DESCRIPTION

We recently showed that telomere length is associated with age, chronic diseases and various mortalities and have highlighted on important ethnic specific genetic loci that control telomere attrition in the Singapore Chinese population. How much telomere length correlates with other ageing biomarkers and whether these interact to affect predictions of future health outcomes is unknown in the Chinese population. We hypothesize that ageing molecular biomarkers are not completely independent but may interactively coalesce to affect ageing outcomes. In this initial proof-of-concept study, we aim at studying two well-characterized ageing molecular biomarkers, telomere length and epigenetic ageing, to determine their associations and correlations with each other (Aim 1) and evaluate if jointly modelling these two biomarkers could improve associations and predictions of prospective health outcomes in the Singapore Chinese population (Aim 2). The Singapore Chinese Health Study (SCHS) has recently characterised the prospective collection as healthy ageing (N=2,834, 20.02% of the sample collection, mean age = 73) defined as the absence of specific chronic diseases, no impairment of cognitive function, no limitations in instrumental activities of daily living, good mental health and overall self-perceived health, good physical functioning and no function-limiting pain after a median 20-year follow-up. For this initial proof-of-concept study we would leverage on the SCHS data to select 100 cases and 100 controls based on pre-defined healthy ageing status and determine epigenetic ageing at baseline (mean age = 53). Readily available telomere length information at baseline from the same study samples will enable understandings on correlation and association patterns of these ageing molecular markers and allow for an initial evaluation on the joint utility of

these molecular markers, determined during midlife, to predict prospective healthy ageing status in the Chinese population.

Towards Personalization: Identifying Life-History Patterns of Loneliness as the Basis for Effective Early Interventions

Principal Investigator	Wei Ming Angelique Chan
PI Primary Affiliation	Duke-NUS Medical School
Co-Investigator(s)	Abhijit Visaria, MA, and Nur Adlina Maulod, DPhil, MS ; Ursula M. Staudinger,

PROJECT DESCRIPTION

Loneliness is a public epidemic, particularly among older adults (aged 60 years and older). Our proposal is to identify different types of loneliness as a basis for effective interventions. Previous research has shown that loneliness increases the probability of death over and above physical illness and disability. In recent work, our team has shown that being lonely reduces life expectancy by 4 years in the older Singapore population. At present, 53% of older Singaporeans (aged 60+) report being sometimes or mostly lonely using the UCLA 3-item loneliness scale, particularly those living with children only. By alleviating loneliness we can improve healthy longevity. We hypothesise that in order to develop successful interventions for loneliness we must first understand clusters of lonely individuals with particular characteristics. We use a mixed-method design to identify patterns of loneliness and qualitative narratives using a life course approach. We challenge the traditional assumption that older persons living with children in Asian countries are well taken care of and have a higher quality of life compared to older adults in other types of living arrangements. I. We will conduct cluster analyses for the subgroup sometimes/mostly lonely, by gender, ethnicity, education, income, housing type, marital status, personal mastery, social network size, and quality of social network. II. Conduct semi-structured interviews asking participants to define what loneliness means to them using a life-history calendar method. III. Photovoice methods include using images to capture what triggers loneliness in individuals everyday situations Findings from the study will inform the conceptualization of a complex phenomenon: loneliness into key typologies of experience. Next steps are to: (i) cluster older persons at risk of loneliness, (ii) design and develop programmes and intervention with stakeholders and community partners and (iii) match at-risk persons to these programmes and community intervention.

Uncovering Rejuvenation Factors in Muscle Stem Cells for the Reversal of Age-Related Sarcopenia

Principal Investigator	The Bin tean
PI Primary Affiliation	National Cancer Centre Singapore
Co-Investigator(s)	Koh Hong Xiang Frederick

PROJECT DESCRIPTION

Sarcopenia is defined as the progressive loss of muscle mass with age. One major pathophysiology of sarcopenia is the inherent loss of regenerative capacity of skeletal muscle progenitors (SMPs) which is essential for muscle fiber repair and homeostasis. However, less is known on the regulation of the regenerative capacity of aged SMPs. We hypothesized that by identifying longevity factors and subsequently using it to immortalize aged SMPs, we can restore the regenerative capacity of aged SMPs. We aim to identify targets for rejuvenation of sarcopenic skeletal muscle. In order to achieve this, we intend to first replicate our successes with immortalization in aged and sarcopenic muscle.

Following isolation, a number of validation studies will be performed to confirm that these isolated cells are indeed SMPs. After validation, sarcopenic and control healthy SMPs will be subjected to transduction of unique cocktail of transgenes using our previously published methods. A successful transgenic combination is one that rejuvenates aged SMPs and maintains the ability to differentiate into myotubes. Once achieved, the rejuvenated aged SMPs and primary sarcopenic aged myoblasts and myotubes will be subjected to RNA-sequencing and metabolomics in order to identify the underlying mechanisms that drive rejuvenation. Upon identification of the pathways involved, we will perform a targeted screen from small molecules that can modulate these pathways. From these investigations, we hope to derive a working model as well as viable targets for the rejuvenation of sarcopenic myoblasts.

Digital Technology Solutions to Improve the Vision-Specific Quality of Life

Principal Investigator	Tan Cheng Sim Anna
PI Primary Affiliation	Singapore Eye Research Institute
Co-Investigator(s)	Angelique Chan; and Ecosse Lamoureux

PROJECT DESCRIPTION

Aim: To assess the level of digital readiness and the effectiveness of digital technology solutions (STAAR-Q) on vision-specific quality of life (VS-QOL) and social engagement in visually impaired (VI) older patients. **Hypotheses/Background:** A robust assessment tool (STAAR-Q) can assess the digital readiness and the impact of various digital technologies on the VS-QOL and social engagement. The VI older population compared to a healthy older population, is likely to have lower levels of digital readiness and hence have more barriers to use digital technology. Customized accessibility feature training can improve the digital readiness of the VI older population and help increase usability of digital technology solutions likely to improve visual functioning, VS-QOL and social engagement. **Methodology:** We plan to develop, validate and implement an assessment tool (STAAR-Q), which will consist of an electronic questionnaire and pre-specified digital tasks to assess various aspects of digital readiness. Through the implementation of the STAAR-Q in a prospective case control study, digital readiness will be compared between the normal sighted and visually impaired older individuals. The STAAR-Q will also assess the efficacy of various methods of accessibility training for mobile SMART devices, software applications and other assistive technology devices and will evaluate the impact of digital readiness on using digital technology solutions to improve visual function, VS-QOL and promote social engagement. The results of this study can help with planning effective future accessibility feature training programs, provide an objective, standardized manner to assess the impact of digital technology solutions and provide ideas for future development of new devices.

Three-Tier Biomarker Discovery Platform for Ageing Frailty

Principal Investigator	Alfredo Franco-Obregon
PI Primary Affiliation	National University of Singapore
Co-Investigator(s)	Santhosh Kumar Seetharaman; Ivan Goh Jiewen

PROJECT DESCRIPTION

Two principal factors predominantly determine the onset of age-related frailty and morbidity, mitochondrial and muscular function. Muscle is our largest tissue mass and greatest single source of mitochondria. Stimulating muscle energy production, as during exercise, improves overall health and promotes longevity. The homeostatic role of muscle over systemic metabolism and health extends from its evolutionarily-designed capacity to synthesize and release a collection of trophic and metabolic factors, known as myokines, into the systemic circulation. Accordingly, mitochondrial activation induces myokine function. We have developed a non-invasive and efficient method to activate muscle mitochondrial respiration that is capable of promoting in vitro and in vivo

myogenesis as well as improve mitochondrial function, downstream survival adaptations and secretome activation with as little as 10 minutes of treatment applied once or weekly, respectively. Our intervention consists of a very low energy magnetic signature that acts on the quantum biological level to stimulate mitochondrial energy metabolism. Our magnetic fields are non-disruptive, being only ~15-times greater than the Earth's standing field. Indeed, we have shown that normal development depends upon environmental magnetism, as shielding cells from all ambient magnetic fields arrests their growth and differentiation. Magnetism is thus an authentic developmental force of underexploited clinical potential. We have demonstrated our magnetic intervention to produce: 1) mitochondriogenesis (Sirt1, PGC-1, Nrf2 transcriptional upregulation); 2) mitochondrial survival adaptations (telomere lengthening and reduced apoptosis); 3) improved metabolism (increased mitochondrial fatty acid oxidation, adipose browning, microbiome shifts towards metabolic enhancement, reduced serum ceramide levels, reduced serum insulin and inflammatory markers levels); 4) improved muscle functioning in animals (increased physical performance and reduced fatigue); and 5) enhanced myokine release. In essence, our magnetic fields emulate the mitochondrial effects of exercise, yet without the damaging mechanical stress associated with exercise, having profound clinical implications for the elderly frail.