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Dynamic Resilience

Human life expectancy has doubled in the past 100 years. But for most people, our health span doesn't match our life span.

What if it could?

One of the greatest success stories of the last century is the doubling in human life expectancy, from a global average of 35 years in 1900 to 70 years today[1]. Advances in medicine, public health, and infrastructure have greatly reduced the number of children dying before adulthood and increased the chances of most adults reaching old age. The rising number of centenarians and supercentenarians (people over 110 years) shows that it is possible for humans to live well for a very long time. Such exceptional individuals have encountered many challenges to their health over the course of their long lives, but they show a remarkable resilience – an ability to 'bounce back' after a significant stress event, whether that is a fall, infection, surgery, or major psychosocial stress. Resilience is the result of complex physiological systems that maintain function and homeostasis through a series of feedback and feedforward mechanisms. Such biological resilience integrates several features including baseline reserve, capability to detect and adapt to stress, and the speed and appropriateness of responses including the ability to heal and repair. With a high baseline reserve along with correct and timely integration of other components of the stress response, the body can return to a state of homeostasis after disruption.

For most of us, however, our baseline reserves diminish as we get older and our biological maintenance systems start to fail, resulting in around half of adults over 65 suffering from at least two age-related long-term conditions (multimorbidity), increasing to ~80% of over 80s[2]. Our ability to cope with stress also decreases as we get older, and this loss of resilience makes us vulnerable to sudden and serious health deterioration when we encounter acute illness or injury. Such loss of resilience or vulnerability is encompassed by the clinical term frailty, with half of people 65 and older either frail or pre-frail (at risk of progressing to frailty)[3]. The consequence of reduced resilience is that the time we spend in good health (our health span) is much shorter than our overall lifespan[4].

With increasing ageing of populations around the world, frailty is an important and growing global health problem. Adults over 65 now account for >16% of the population in Singapore[5], 17% in the US, 19% in the UK and 30% in Japan[6]. By 2050, it is projected that 1.5 billion people will be over the age of 65, and the number of oldest old – over 85 – is set to triple[7]. A quarter of older people fall every year, with frailty a major contributing factor. In the US, 285,000 of those who fall are hospitalised with hip fracture and 32,000 die[8]. In the UK, frailty accounts for over 70% of unplanned hospital admissions and 20% of hospital bed occupancy[9], as well as an 8- to 10-fold increase in probability of dying after emergency admission to hospital[10]. Surgery in frail patients comes with higher risks of increased length of hospital stay and adverse outcomes including loss of

independence, discharge to long-term care or death[8,11]. The negative impact of frailty and age-related ill health on older people, their families, care-givers and societies is unsustainable[12].

Importantly, frailty does not just affect those old in years - many women experience rapid declines in their health including cardiovascular disease[13] and osteoporosis[14] following menopause, and life-saving cancer treatments can accelerate biological ageing[15]. Soldiers with traumatic injuries or PTSD[16] and young adults after serious road traffic accidents[17] show rapid onset of age-related diseases, equivalent to ageing by ~10 years. Sedentary lifestyles, accompanied by lack of adequate physical exercise, increase frailty prevalence ratio almost threefold[18]. It is now emerging that viruses such as SARS-CoV-2 can also drive premature ageing[19]. With even mild COVID cases showing accelerated neurodegeneration[20] and cardiovascular disease[21], as many as 76 million people worldwide may experience early onset of age-related conditions and frailty directly as a consequence of the recent pandemic.

Resilience as a new framework to promote healthy ageing.

We already have a strong understanding of biological ageing[22], with increasing recognition that age-related diseases, multimorbidity, and indeed frailty, result from fundamental cellular and molecular biological changes driven by ageing processes[23]. Looking through the lens of resilience gives us a new way to understand health as we age, highlighting the need to restore steady-state and dynamic resilience and to reverse loss of homeostasis in order to prevent frailty and age-related multimorbidity.

Development of ‘anti-ageing’ therapies is already garnering multi-billion-dollar investments[24], with teams across the world working on interventions to improve health as we age. What we need now to accelerate progress are quantitative, predictive and reliable measures of physiological steady-state maintenance mechanisms, and markers of dynamic resilience in response to stressor events. While frailty scores and indices can provide reasonable predictions of statistical outcomes after a stress event (recovery, infirmity or death), they are poor predictors of outcomes for an *individual*[25]. Even highly accurate methylation or immune-based ageing clocks[26] measure the steady state at a point in time, but they do not measure dynamic resilience – the ability to respond to and recover from stress.

We need to be able to identify and measure the parameters of resilience and the factors and processes in complex biological systems that maintain and restore homeostasis and health. Such processes may include enhanced immunity, better energy management or improved stress responses, as seen in centenarians[27]. Such parameters and factors, plus validated models associated with these measures at multiple scales – from molecules to tissues and ultimately the whole body – would help to uncover causal mechanisms, identify individuals at risk of stress-event-induced deterioration in health, and accelerate clinical studies of interventions that aim to maintain or restore resilience.

Why now?

We are now in a position to leverage the power of deeply phenotyped longitudinal human cohorts and biobanks, combined with modern -omics technologies and bioinformatics tools in order to identify dynamic prognostic markers of human resilience. We can exploit new *in vitro* and *in silico* platforms to establish physiologically relevant human-derived systems to assess responses to stress/challenge. To accomplish this, we will need to draw together academic, clinical and commercial expertise across multiple disciplines (biology, chemistry, engineering, data science, computation/AI, human clinical sciences and trials) to identify personalised biomarkers of physiological resilience and to develop and test new interventions to improve health outcomes in older people.

The Dynamic Resilience program seeks to identify and validate causal measures and models of dynamic resilience, at multiple scales, with predictive value sufficient to make clinical decisions and to test interventions. Importantly, reducing progression to frailty in those over the age of 65 by 25% would protect over 75,000 adults in the UK alone, and potentially as many as 87 million older adults worldwide. It is realistic to believe that this is possible – frailty can be halted and even reversed[28].

Program goals:

We have formulated the program goals below to address key fundamental questions to drive the measurement, modelling and testing capabilities needed to advance new methods of promoting healthy, whole lives: How do we measure and identify who is at greatest risk of health deterioration after a stress event? Why do some people stay in good health and others not? (In particular why is it that people who appear equally frail using steady state measures can show very different dynamic responses to stressor events?) What causes increased risk of health deterioration after a stress event (independent of individual disease states)? And how can we promote dynamic resilience and thus healthy aging for a greater number of people worldwide?

The three program goals are:

1. Discover and integrate markers of human dynamic resilience that identify individuals prior to a stress event (SE) with prediction accuracy of >85% sensitivity and >90% specificity for clinical outcomes post-SE (e.g., return to health, frailty progression, loss of independence, death).

2. Develop multi-scale models that link the biomarkers predictive of loss of steady state and dynamic resilience to mechanism. It will be necessary to show that identified mechanisms (some of which may overlap with known hallmarks of ageing) either promote and maintain homeostasis, or are causative of resilience loss. Such models and demonstration of mechanism can be at the cellular, tissue, system, or whole-body scale.

3. Validate the clinical and developmental utility of measures, models, and candidate preventative interventions to promote resilience in at-risk populations by undertaking specific, targeted trials. Of particular interest are trials involving preventative interventions in older adults prior to *predictable* stress events such as elective laparoscopic or orthopaedic surgery, or cancer therapy. Such trials should be able to demonstrate the predictive accuracy of resilience biomarkers (>85% sensitivity and >90% specificity) for the impact of interventions on clinical outcomes post-stress and seek at least a 25% reduction in the number of patients who experience frailty progression following the stress event in the intervention groups compared with controls.

Call for abstracts and proposals.

We are soliciting abstracts and proposals for work over three (3) years (with a potential additional one-year option) in one or more of the following thrust areas. Proposers should clearly relate work in these thrust areas to one or more of the program goals.

Thrust Area 1: Identify markers of physiological resilience in human populations that accurately predict health outcomes following a stress event (SE).

Since dynamic resilience is only unmasked after a stress[29], this thrust area seeks identification of resilience markers that change in response to a major stress event, and that vary between people who recover, reset to a lower baseline, or deteriorate further. A number of frailty indices and scores exist[30], but even high complexity electronic frailty indices show limited predictive power for individual patient outcomes (e.g., 76% sensitivity and 53% specificity for predicting death of frail patients 3 months after measurement[31]). This thrust area seeks to identify and quantify the accuracy of resilience biomarkers that predict health outcomes post-stress.

- Using existing longitudinal human cohorts of older adults (65+) of high sample density (i.e., regular sampling frequency for a variety of markers, deeply phenotyped, and preferably with bio-banked materials), identify those individuals who have experienced a stress event of sufficient magnitude to require medical intervention with follow-up data on outcomes (recovery, deterioration, death). Types of stress events may include falls or other accidents resulting in a need for hospital care, or other biological stressors such as surgery, serious infection (including COVID-19), genotoxic cancer therapy, onset of immune-mediated inflammatory disease, or abrupt loss of sex hormones (e.g. menopause, anti-androgen therapy). Cohorts of super-healthy and extremely long-lived adults such as centenarians are expected to be particularly useful in identifying resilience factors. Studies on younger populations with risk factors for frailty are not excluded. Cohorts with recallable subjects are of interest.

- From individuals pre- and post-stress, determine the biomarkers correlated with high steady state and dynamic resilience (or negative markers for loss of homeostatic

control) that provide predictive accuracy of individual health outcomes (return to baseline, progression to increased frailty or death) within 6 months of stress event with at least 85% sensitivity and 90% specificity. It is anticipated that such marker panels may be multiscale and multimodal and may integrate data from biological samples, with clinical, functional, imaging and/or digital measures sampled at time points pre- and post-stress event. Markers may include (but are not restricted to) molecular, chemical, biophysical, functional, or clinical factors, or associated with the microbiome, and can be derived for example from electronic health records, biobanked samples, high complexity -omics data sets, imaging, and/or functional data e.g. from wearables; markers may include factors currently used in calculation of frailty indices provided the final integrated marker panel meets the requirements for >85% sensitivity and >90% specificity for cohort subjects with post-stress outcome data. Existing ageing clocks and marker panels of known ageing drivers such as inflammation are not excluded but should be integrated with other marker types to achieve required sensitivity and specificity at multiple scales. Markers that are suitable for providing a resilience score in a continuum from robustness to severe frailty (rather than simply scoring deficit) are particularly sought.

- Markers from discovery cohorts should be assessed in validation cohorts (which may be subsets of the original cohorts or additional cohorts) to demonstrate that resilience markers significantly associate ($p<0.05$) with and predict recovery of health to baseline or deterioration for individuals within 6 months after stress. Identification of a 'universal signature of resilience' irrespective of the stress event would be particularly valuable. Other markers may be predictive of response to specific stress events such as infection; and some markers may be restricted to population subsets based on race, biological sex, etc. In this context, cohorts that represent a range of human demographic traits including biological sex, race, ethnicity, geography and socioeconomic status would be particularly useful (these may be single cohorts with wide demographic spread, or drawn from multiple focussed cohorts).

Thrust Area 2: Identify causal biological mechanisms underpinning loss of human physiological resilience at multiple scales.

This thrust area takes two complementary approaches to identify dynamic resilience mechanisms: mining of biomarker and other large datasets from human ageing cohorts, together with experimental analysis of causality in stress-testable human-derived model systems. A full mechanistic understanding of resilience has the potential to cross-inform on further biomarker discovery and to provide a powerful conceptual basis for development of mechanism-targeted preventative measures or interventions to protect from health deterioration.

- Emerging biomarkers and pathways identified in Thrust area 1 should be assessed in parallel for potential mechanistic roles, particularly if they map to known hallmarks of ageing such as inflammation/immune dysfunction, energy homeostasis and cell senescence/genome stability[32] (as indicated from studies in preclinical animal models subjected to stress[33]). Such putative mechanistic markers must be validated

through analysis of existing datasets of human intervention studies where improvement in frailty status has been demonstrated (e.g. on diet/exercise[34]) or in patient cohorts when potentially beneficial therapies such as anti-inflammatory drugs, statins or other putative 'geroprotectors' have been used[35]. In this thrust, the program seeks the ability to build associations between markers and health outcomes that are significant at $p<0.05$.

- Mechanistic studies to be conducted in human-relevant biological model systems are also of interest. Such systems may include validated human-derived *in vitro* platforms (for example cell and 3D tissue culture, organoids or organ-on-a-chip) suitable for discovery of biological mechanisms of resilience and restoration of homeostasis following perturbations such as inflammation or oxidative stress. Development of multiscale models are welcome providing they have been previously validated for causation in at least one scale (e.g. at the level of the cell). Models should inform on shared fundamental mechanisms underpinning maintenance or loss of physiological resilience rather than specific age-related diseases. Incorporation of senescent cells may be particularly informative in the context of age-related frailty. Models should be suitable to demonstrate statistically significant ($p<0.05$) changes in physiological and molecular readouts of resilience in response to stress or challenge, and possess homeostatic control, with restoration to baseline state after stress. Putative resilience mechanisms or pathways should be tested experimentally to determine whether they are necessary and sufficient to restore homeostasis following perturbation. Existing *in silico* models of human physiological systems may also be considered providing they can be interrogated to inform on mechanisms of homeostatic control. Evidence of resilience mechanisms may be provided in non-human preclinical models, but such mechanisms must be directly applicable to, and demonstratable in, human systems e.g. through direct correlation with biomarker studies in Thrust area 1.

- Mechanistic understanding of resilience mechanisms and biological pathways is expected to reveal targets for therapeutic intervention. These may include known biological ageing pathways[36] such as inflammation, senescence, energy dysregulation or genome instability, or new mechanisms identified in this program or elsewhere. Mechanism-targeting interventions should be tested in the validated human-relevant resilience models. In particular it will be helpful to assess whether combinations of interventions that target distinct resilience mechanisms lead to additive or synergistic improvements in restoring homeostasis, as determined by measures such as speed of return to baseline, or ability to return to baseline after extreme perturbations in the molecular environment equivalent to significant trauma (e.g. exposure to inflammatory cytokines at 100x physiological levels). The goal of these studies would be to provide quantifiable, proof of concept validation for 3 or more single or combination use interventions in humans for protection of resilience.

Thrust Area 3: Undertake human trials of interventions promoting physiological resilience in at-risk populations, targeting> 25% reduction in health deterioration

(frailty progression, need for long term care, or death) within 90 days following a predictable clinically scheduled major stress event.

This thrust area will validate the predictive value of the resilience biomarkers, provide proof of concept that such markers can guide clinical decision making and furthermore that mechanism-targeting interventions can be effective in preventing frailty progression in at-risk populations. In this thrust, we seek human trials of preventative measures or interventions to promote resilience in at-risk population to test and validate measures, models, and their predictive value in determining the outcomes of such interventions.

- As an example, in this thrust, trial populations of at-risk individuals such as older adults (65+) scheduled for elective orthopaedic or laparoscopic surgery could be established. Patient cohort sizes must be adequately powered to determine a 25% reduction in the number of individuals progressing to higher frailty scores or death following surgery (alpha 0.05) in the intervention group compared with standard-of-care controls (historic populations or, where possible, placebo control groups).

- In these trial populations, conduct human intervention studies; dynamically assessing changes in resilience biomarkers and targeting >25% reduction in frailty progression or death post-stress event as compared with controls. Trials may be experimental medicine studies or clinical trials, ideally administering interventions designed to support physiological resilience prior to the scheduled stress event (e.g. surgery). Anticipated types of interventions may include FDA-approved drugs with known clinical safety profiles that have putative geroprotective effects[37] (for example, but not limited to, statins, metformin, rapamycin, cardiac glycosides, etc.), drugs such as anti-inflammatories or senolytics that target known ageing drivers including inflammation and senescence, or other interventions to support resilience as identified through mechanistic studies in Thrust area 2 or through other research.

- Alternative patient groups may include women post-menopause at risk of cardiovascular disease and/or osteoporotic fragility fractures, older adults scheduled to undergo genotoxic cancer therapy, or older adults hospitalised with hip fractures; with the target of reducing to <15% the proportion of hip fracture patients age 65+ who enter long-term care or die in the first year after fracture. Other at-risk groups may also be suitable for testing interventions to promote physiological resilience and prevent deterioration including older adults admitted to hospital with sepsis.

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