Arizona-4-Arizona Pillar: Proposed Theme 3
Strategies to Promote Late Life Resilience by Combatting Inflammation

A. Need statement:

i) Clinical condition and currently available therapeutic options

Frailty Syndrome (FS) is a major age-related syndrome of diminished physiological reserve and marked vulnerability to adverse health outcomes, including repeated hospitalizations, institutionalization and death. Frailty is not aging, and aging is not frailty. The overall prevalence of FS among community-dwelling age 65+ older adults worldwide is ~10-15%, increasing in 80-year -olds to ~20-25% and up to 50% in those age 90+[4] [Estimates for frail adults in Arizona ~130,000. In Pima County, the over 65+ group is the fastest growing, increasing 48% from 2010-2022; total = 225,000 age 65+. Estimates for frail adults in Pima County ~22,000]. Frailty is not normal aging, but rather a complex and dynamic syndrome with physical, cognitive, psychological, and social aspects, resulting in markedly reduced quality of life, and high healthcare costs. FS, grounded in a biologically-based definition, is characterized by decreased vigor and reserve, and diminished resistance to stress such as illness, trauma or surgery, resulting in progressive and often *unexpected* dramatic functional decline, falls, disability, and death. Frailty among the strongest risk stratifiers to predict adverse outcomes in many clinical specialties, including surgery, oncology, cardiology, trauma, and transplantation[4]. It is clinically recognizable syndrome, and although patients on the extreme ends of resilience (e.g., markedly frail, or markedly robust) are easily identified, the majority of frail patients require FS screening to identify and characterize them (e.g., as normal, pre-frail, frail). For example, many frail patients are obese, in contrast to the commonly held stereotype of the "frail little old lady walking slowly with a cane." Current challenges in frailty research include the lack of an international standard definition of frailty, but a myriad of validated screening and assessment tools can clinically identify vulnerable patients at the pre-frail and frail stages.

Resilience is key to robust and successful aging. The current thinking is that FS is due to age-related dysregulation of inflammation (ARDI) and/or maladaptive energy metabolism. ARDI is an important mechanism that negatively affects resilience in aging. This is because ARDI is (a) one of the pillar mechanisms of aging[1]; (b) a mechanism through which several other pillar mechanisms of aging (including DNA damage, oxidative stress and altered proteostasis) ultimately manifest themselves[2]; and (c) the driver and/or potentiator of nearly all age-related chronic diseases[1,2]. Our preclinical evidence strongly suggests that ARDI is primary, and that it causes muscle and energy anomalies as its downstream consequences and manifestations. However, it is important to note that there is no rigorous definition of ARDI, and it appears in the literature under other names, including inflammaging. It is generally accepted that measuring 5-7 soluble inflammation-related molecules will provide a reasonable assessment of increased inflammation that occurs with aging, and the molecules are IL-6, TNFα, soluble TNF receptors I and II (sTNFR I& II). IL-1β, IL-8 and maybe IFNγ. Additionally, quantitative cutoffs of these molecules to qualify as ARDI has not been established, but normal values of all of them would argue against ARDI, informed within the context of clinical frailty measurements/evaluation.

While modulation of frailty is thought possible with IL-6 blockade, mTORC1 inhibition, and through defined microbiome replenishment, there are currently no accepted therapies for FS, and the impact of overall resilience-promoting interventions, including exercise and nutritional interventions range between modest and futile, and there are currently no comprehensive geriatric models of care devoted to specific management of FS. There is also a belief that fully developed frailty may be difficult if not impossible to reverse, and that treatments must be initiated at earlier stages, when subjects are diagnosed as being 'pre-frail', with the goal to either delay or prevent progression to full frailty, but these notions require validation in larger studies[5].

ii) Unmet clinical need
Based on the information provided above, there is an important and urgent need for approaches to modulate ARDI in pre-frail and frail older adults. ARDI is the principal component for pre-frailty and pre-frailty.

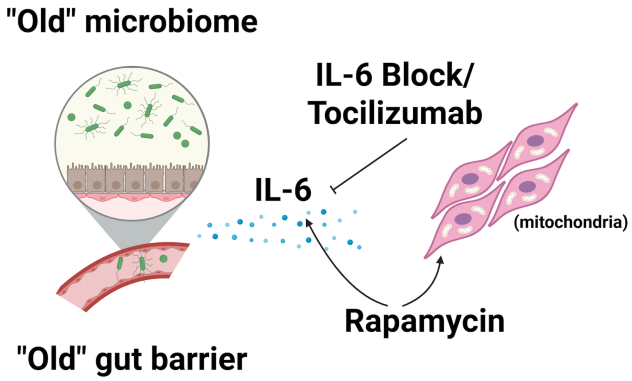
B. Existing investigational approaches – caveats

Need data on human trials on modulation of ARDI as a cause of FS in older adults (e.g., cytokine IL-6 blockade (1a), mTORC1 inhibition via low-dose Rapamycin (1b) and defined microbiome replenishment (1c)).

B. Existing investigational or clinical approaches

C. Transformative Innovation

Hypothesis: ARDI (age-related dysregulated inflammation) is the driver of frailty, by inducing metabolic / mitochondrial energy disbalance. Our mouse data with isolated conditional elevation of IL-6 directly support the inflammation underpinning of the hypothesis (Jergovic M et al, Geroscience 2019); the Parker A et al. Microbiome, 2022, paper supports that you may be able to change this via microbiome. Rapamycin treatments in animals and humans suggest that you can reduce both inflammatory and metabolic abnormalities via the mTORC1 complex attenuation (again, low dose, avoiding many side effects). The specific goal of all of our studies and of the SIP is to apply the above to the treatment of FRAILTY as a critical geriatric syndrome with no treatment at the present.



An integrated framework of our approaches would posit that age-related changes in the microbiome (perhaps together with the aging of the gut barrier, which becomes more permeable) trigger increased inflammation, dominantly via the LPS-IL-6 axis (b), which when chronically activated, leads to dysregulation of mitochondrial energy metabolism and consequent loss of energy, muscle mass and strength and other symptoms of frailty. Because the above construct needs fundamental validation at several steps, and because the steps need not be connected exactly as outlined above, we have broken down our experimental and possible clinical interventions into those targeting IL-6 (tocilizumab and other blockers), mTORC1 attenuators (Rapamycin), and microbiome (microbiome cocktails), for the purposes of testing the hypothesis.

The most reliable laboratory marker in frailty is an elevation of blood inflammatory markers, with interleukin 6 (IL-6) being the most robust and consistently elevated to the levels of between 20-80 pg/ml[3]. To interrogate whether this IL-6 elevation may be mechanistically driving FS, we developed a doxycycline (Dox)-inducible IL-6 mouse model whereby titrating Dox in chow was able to precisely elevate plasma IL-6 to the levels seen in FS patients[6]. We demonstrated that several cardinal features of FS were recapitulated by this isolated elevation of IL-6, including an increase in mouse clinical frailty score, loss of muscle mass, strength and adiposity[6]. The implication of this finding is that we should be able to treat or ameliorate FS by IL-6 neutralization, using tocilizumab [REF] or other IL-6 receptor antagonists (sarilumab and satralizumab), or monoclonal antibodies specific for IL-6 (eg, siltuximab and olokizumab)[7]. Feasibility of these studies is high and would require $100,000 to perform formal preclinical blocking studies in mice, after which it should be possible to rapidly proceed to clinical trials in pre-frail and/or frail human studies.

The second line of transformative innovation will come from an ongoing, philanthropy-funded clinical trial to use a low-dose of highly selective mTORC1 inhibitor rapamycin (Rapa) in treatment of frailty. It is predicated on the known ability of Rapa to reduce inflammation, improve energy metabolism and delay certain manifestations of aging[8-11]. This intervention trial has already been funded, IRB has been obtained and many initial steps have been undertaken towards development of a full clinical trial (please see below).

A third line of transformative innovation involves the intestinal microbiome, which has emerged as one of the most powerful contributors to health and disease. Aging is associated with pathogen colonization and decreased microbial diversity in the gut[12]. FS and pre-frailty are associated with increased risk for severe respiratory infections[13], which in turn are associated with decline in lung function[14] further aggravating frailty. Prebiotics significantly improve frailty and positively modify the intestinal microbiome[15], suggesting that exposure to protective microbial signals influences the course of FS. Oral bacterial lysates such as OM-85 have been shown to significantly decrease the incidence of respiratory infections[16], and by this mechanism, may change the course of FS. While we postulate that OM-85 will be as effective as prebiotics in delaying frailty, preclinical studies are needed before further translation.

D. Proposed Steps for Translation of Transformative Innovation

1) Clinical trials using IL-6-receptor alpha subunit blockade (tocilizumab] or similar approved drugs with proven preclinical effect[7] will be conducted in months 9-36 of this project. Double-blind, randomized trial to evaluate effectiveness of tocilizumab vs. placebo in the control, pre-frail (Fried Frailty Index[17-19]– FFI - 1-2) and frail (FFI 3-5) participant groups will be performed over 12-month treatments, with a flush-out of 12 months and a primary outcome of unchanged (stable, non-progressing) FFI in pre-frail after 12 and 24 months from treatment initiation. Secondary outcomes would include improvement of FFI in pre-frail and tertiary an improved FFI in frail patients. Discovery of additional molecular markers in response to treatment will be pursued under ancillary outcomes/studies.

2) Rapa trial for treatment of frailty has already completed the preparatory phases and is at the point of screening of potential participants towards enrollment into treatment groups. Thorough immune-inflammatory phenotyping will be performed, along with FFI assessment, for participant stratification. Enrollment is expected over the next 6 months, treatment will proceed for 24 months, followed by flush-out of 12 months. Participants will be followed for the same primary, secondary and tertiary outcomes as in 3a. above.

3) For microbiome intervention, preclinical studies need to be performed first, because while this is a powerful potential anti-inflammatory intervention, its proof-of-concept in treating frailty in rodents yet needs to be obtained. Intervention trial planning will therefore follow based on the results of preclinical studies. There is a cocktail, OM-85 from Europe. The IP belongs to OM-Pharma, a midsize biotech from Switzerland. They own the patents but anticipate that some form of license could be negotiated with them. Its use would require confirmation in preclinical studies that the product parallels in frailty the effects found in other immune conditions.

E. Proposed destination program to Promote Late Life Resilience:

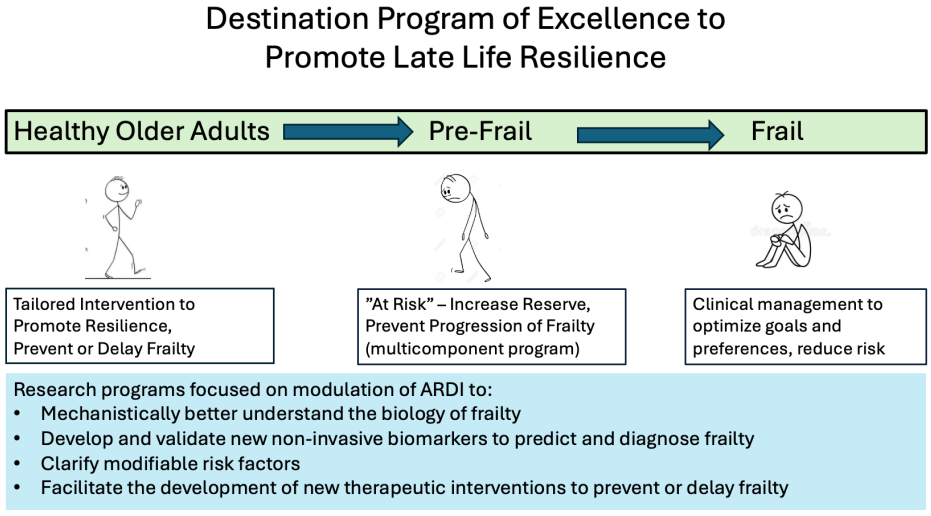
Although The number of older adults devastated by FS matches the prevalence of those living with Alzheimer's Disease and Related Dementias, the level of attention in current research efforts and clinical programs in FS is negligible. Clinical/research programs of excellence that can prevent, slow, or even reverse the development of frailty are of enormous importance for all older adults, especially as the population of older adults increases rapidly across Arizona, the U.S., and the world. Such clinical/research programs of excellence that can improve quality of life and reduce

healthcare costs will soon become a major priority of health systems. At the present, there are major gaps with respect to frailty prevention, screening, interventions and education.

We propose creating a comprehensive destination program of excellence anchored in the University of Arizona's Center for Aging to promote 'late life resilience', focused on modulation of ARDI to prevent progression of FS aiming to achieve optimal healthspan in older adults, defined as the length of time spent in good health, free from serious disease and disability. A key focus of this program would be to narrow the gaps in our knowledge of prevention and delay of progression of frailty. The program will evaluate, validate, and standardize outcome measures for the impact of frailty prevention interventions across degree of frailty (e.g., pre-frail, frail), the treatment effects, and cost effectiveness, through state-of-the art clinical trials designed to mechanistically better understand the biology of frailty, develop and validate new non-invasive biomarkers to predict and diagnose frailty, clarify modifiable risk factors, and facilitate the development of new therapeutic interventions to prevent or delay frailty.

The program would bring together a multispecialty practice to deliver currently recognized person-centered, frailty-guided clinical care strategies to promote resilience. For example, pre-frail and frail older adults facing high risk clinical care (e.g., intermediate or high-risk surgery, transplantation, or chemotherapy) are at significant risk of poor health outcomes. Although there are substantial gaps in our knowledge, current evidence suggests that a program that includes specialty assessment (e.g., cardiology, oncology, geriatrics, palliative care), pre-habilitation and tailored management can significantly improve health outcomes.

The program would serve four older adult populations: (1) Healthy older adults (Pima County total population ~1M, age 65+ = 22% = 225,000): Focus on prevention, including the development of a tailored intervention to promote resilience and prevent or delay the onset of FS. (2) "At risk" older adults (Pima County, 30% Pre-Frail = 67,000) Focus on four management strategies aimed at increasing physiological reserve to build resilience (e.g., exercise, nutritional supplementation, multicomponent intervention, and comprehensive geriatric assessment models) (3) Frail older adults (Pima County, 10% Frail = 22,000). Focus on tailored clinical management to optimize goals and preferences, reduce risk; and (4) Older adults facing high risk clinical care (e.g., surgery, oncology). Focus on pre-habilitation and tailored management to reduce stress, build resilience.



F. Impact

FS is a major epidemic dramatically impacting the healthspan and quality of life of 10-15% of all older adults and resulting in high healthcare costs. Ironically, it is "invisible" – and the devastating poor outcomes are commonly misattributed to "old age". In Pima County alone, 225,000 older adults are at risk for FS and would benefit from a tailored intervention to promote resilience and prevent or delay the onset of FS. An estimated 67,000 older adults are pre-frail and would benefit from innovative management strategies aimed at increasing physiological reserve to build resilience, in addition to current interventions (e.g., exercise, nutritional supplementation, multicomponent intervention, and comprehensive geriatric assessment models). Approximately 22,000 older adults in Pima County are frail, eligible for clinical management to optimize goals and preferences, and reduce risk. For the many older adults facing high risk clinical care (e.g., surgery, transplantation, chemotherapy), our clinical program of excellence will build an evidence base to promote effective pre-habilitation and tailored management to build resilience. Finally, given that frailty is a major negative mediator of outcomes across patient populations, including but not limited to surgical patients, healthcare systems would also benefit from advancing knowledge in this area due to the potential impact on healthcare outcomes.

In addition to helping build resilience in older adults, knowledge gained through activities in this clinical destination program of excellence might also benefit other ailments where inflammation known to be a causative agent. not only help but lessons learned from this experience.

G. Timeline/Milestones

Milestones	**Y1**	**Y2**	**Y3**	**Y4**	**Y5**
IL-6 therapy	Preclinical work	Trial preparation/trial begins	Trial	Trial	Clinical application/Destination program implements treatment
Rapamycin treatment	Trial initiated	Trial	Trial	Data analysis/planning for clinical application	Destination program implements treatment
Microbiome	Preclinical work	Preclinical work	Trial preparation & begin trial	Trial	Trial/clinical application
Destination program of	Education, marketing and referral	Expand referral network. Expand clinical	Expand referral network. Expand clinical	Expand referral network. Expand onsite clinical team	Expand referral network. Expand onsite clinical team to include medical and surgical

Excellence	process. Establish core clinical team for frailty assessment, support clinical trials	interdisciplinary team. Onsite pre-hab and nutritional support. Clinical trials	team to include medical specialties (e.g., cardiology, oncology)	to include medical and surgical specialties (e.g., cardiology, orthopedics, oncology, renal)	specialties (e.g., cardiology, pulmonary, orthopedics, oncology, renal)

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