UNIVERSITY OF TEXAS MEDICAL BRANCH (UTMB)
Claude D. Pepper Older Americans Independence Center

James S. Goodwin, M.D. **Co- PI**	409-747-1987	jsgoodwi@utmb.edu
Melissa (Missy) Morrow, PhD **Co-PI**	(409) 266-0344	memorrow@utmb.edu
Roxanne Grover **Program Administrator**	409-772-3075	rmgrover@utmb.edu

CENTER DESCRIPTION

The UTMB Claude D. Pepper Older Americans Independence Center (OAIC) has been continuously funded since 2000. From the very beginning, we have nurtured a multidisciplinary translational research culture to fulfill our mission, which is to improve physical function and independence in older adults. Central to this mission has been the career development and training of the next generation of leaders in geriatric research. Our scientific focus has evolved over the years from a narrow interest in the mechanisms of sarcopenia to the translation of our findings in much needed patient-centered interventions to improve physical function and independence. This evolution derives not only from the natural progression of our research from basic discoveries to healthy humans and from healthy humans to patients, but also from a deliberate effort of the OAIC leadership to promote and support collaborations between scientists in muscle aging and investigators in population health and outcomes research on aging and rehabilitation. This second line of research has always been present from the beginning of our OAIC, but was conducted in parallel with muscle research. The intersection of these two lines has accelerated the development of new research foci. An example is the rapid development of patient-centered outcomes research in the elderly, which culminated with the funding of a large infrastructure grant and, more recently, with our participation in the trans-Pepper patient-centered multicenter clinical trials on fall prevention, the STRIDE Study, and the D-CARE.

Our current theme is to “Identify pathways of physical function loss and gain and develop targeted interventions to improve functional recovery from illness in older adults”.

Our general hypothesis is that aging induces mild but significant biological and metabolic changes that - in combination with patient factors – progressively lead to functional loss and predispose to potentially catastrophic declines in physical function during bouts of acute illness and hospitalization. Once hospitalized, variations in hospital and post-hospital care will significantly determine whether geriatric patients will recover physical function after their illnesses. Thus, we hypothesize that interventions involving rehabilitation, nutritional supplementation, pharmacologic anabolic treatments, as well as changes in decision making and healthcare delivery can prevent the age- and disease-induced functional loss and improve functional recovery from illness in older adults.

The specific aims of the UTMB OAIC are as follows:

1. Stimulate the growth of multidisciplinary translational research to improve physical function and functional recovery from illness in older adults by:
    - Funding pilot project research to generate preliminary data in promising new areas of investigation

    - Funding developmental projects to develop innovative technologies
2. Train future leaders in geriatric research on the mechanisms, prevention and treatment of functional loss and recovery in older adults
3. Recruit established investigators with expertise relevant to muscle function and functional recovery in older adults into interdisciplinary translational research related to the OAIC focus.
4. Provide core support and add value to funded translational research on functional loss and recovery in older adults.
5. Foster collaborations between UTMB investigators and investigators at other OAICs and other institutions on studies of physical function and functional recovery in older adults.

These specific aims will be accomplished through the Leadership/Administrative Core (LAC), as well as the activities of our Research Education Component (REC), the Pilot/Exploratory Studies Core (PESC) and the three highly productive Resource Cores (RC) that encompass the major areas of our multidisciplinary translational research model: Clinical Research RC1, Metabolism and Biology RC2, and Biostatistics and Data Management RC3.

CORES

Leadership and Administrative Core (LAC)

Leader 1:	James S. Goodwin, MD	jsgoodwi@utmb.edu
Leader 2:	Rebeca Wong, PhD	rewong@utmb.edu
Leader 3:	Stephanie Burt, MS	stburt@utmb.edu

The overall goal of the Leadership/Administrative Core (LAC) is to provide the administrative infrastructure and leadership to support the activities and growth of the entire UTMB OAIC, and fulfill our mission, which is to stimulate translation of the research findings to improve physical function and independence in older adults. The LAC specific aims are: 1. Provide overall leadership and direction for all activities of the UTMB OAIC. We will: a. Evaluate new opportunities for research and collaborations at the local, national and international level with support from our Internal Advisory Committee (IAC) and External Advisory Committee (EAC); b. Attract new investigators by providing training opportunities, as well as pilot and developmental projects; c. Coordinate and integrate Core functions, promoting scientific coherence, access to Core resources and expertise, and new utilization of Core resources; d. Coordinate and leverage OAIC Cores with other institutional resources; e. Foster collaborations between UTMB OAIC investigators and Cores with other OAICs and institutions.

Research Education Component (REC)

Leader 1:	James S. Goodwin, MD	jsgoodwi@utmb.edu
Leader 2:	Rebeca Wong, PhD	rewong@utmb.edu

The goal of the REC is to increase the number of rigorously trained, extramurally competitive, and scientifically competent scholars who will conduct translational investigations in aging, lead multidisciplinary research teams, and eventually mentor the next generation of investigators in aging research. To achieve this goal, the REC will address the following objectives: Objective 1: Identify, recruit and select qualified scholars who are beginning their academic/scientific careers in aging and demonstrate the potential for multidisciplinary translational research. Objective 2: Create Individualized Career Development Plans for each scholar that identify a lead mentor and a mentoring team with defined roles, and document expected milestones of research progress including publications, presentations, and submission of grant proposals, and training in the scientific integrity and the responsible conduct of aging related research. Objective 3: Develop and implement a high-quality program of education and training activities integrated with mentoring experiences that provide REC scholars with the skills necessary to establish productive scientific careers.

Pilot and Exploratory Studies Core (PESC)

Leader 1:	Kyriakos Markides, PhD	kmarkide@utmb.edu
Leader 2:	Brian Downer, PhD	brdowner@utmb.edu
Leader 3:	Monique Pappadis, PhD, MEd	mrpappad@utmb.edu

The goal of the Pilot/Exploratory Studies Core is to stimulate new research addressing the issues of functional loss and gain and promoting functional recovery from serious illness in the elderly. We target early stage investigators, and also investigators well established in other areas who can turn their expertise to studies consistent with the OAIC theme. We employ our assets and partner with other institutional resources to accomplish the following specific aims: 1. Solicit and select the most meritorious research proposals for PESC funding. 2. Identify opportunities for co-sponsorship of PESC studies. 3. Provide PESC investigators with access to resources from other OAIC cores and institutional research facilities/centers. 4. Monitor the progress of PESC studies. 5. Ensure regulatory compliance, safety and protection of human subjects enrolled in PESC studies. 6. Provide assistance and mentorship to develop PESC studies into independently funded grant applications.

Clinical Research Resource Core (CRRC)

Leader 1:	Elizabeth Lyons, PhD	ellyons@utmb.edu
Leader 2:	Steven Fisher, PhD, PT	stfisher@utmb.edu
Leader 3:	Meredith Masel, PhD	mcmasel@utmb.edu
Leader 4:	Roxana Hirst, MS	rmhirst@utmb.edu

The **Clinical Research Resource Core** is the primary resource for subject recruitment, tracking and retention activities, and for training Scholars in clinical research. This core has been instrumental in developing the infrastructure to support translation of basic discoveries in geriatric populations, developing the ACE Unit Research Laboratory, and participating in large clinical trials, such asASPREE, STRIDE, D-CARE, MoTrPAC, and STEP-HI. The core supports research studies on the mechanisms underlying function loss and recovery; development and testing of novel treatments; trajectories of physical function and disability in community-dwelling and hospitalized older adults; and pragmatic, patient-centered studies on recovery from illness.

Metabolism & Biology Resource Core (MBRC)

Leader 1:	Vineet Menachery, PhD	vimenach@utmb.edu
Leader 2:	Stanley J. Watowich, PhD	sjwatowi@utmb.edu
Leader 3:	Andrew Murton, PhD	ajmurton@utmb.edu

The **Metabolism & Biology Resource Core** promotes and supports basic science and translational research. The MBRC1 significantly contributes to the Center theme and goals by providing fundamental and innovative analytical services, biorepository facilities, training and expertise to explore the biological (molecular and cellular) and metabolic (protein, fat, glucose, and energy) pathways involved in muscle loss and functional recovery in older adults. It also develops and tests novel therapeutics in preclinical models. MBRC1 support has led to several new NIH grants.

Biostatistics & Data Management Resource Core (BDMRC)

Leader 1:	Yong-Fang Kuo, PhD	yokuo@utmb.edu

Leader 2: Heidi Spratt, PhD hespratt@utmb.edu
Leader 3: Xiaoying Yu, PhD xiyu@utmb.edu

The goal of the **Biostatistics and Data Management Resource Core** is to provide biostatistical collaboration and training, and develop biostatistics methodology and data management tools for research relevant to the Center theme. Core personnel are highly qualified faculty and staff with expertise in study design, computer science, data management, and statistical analysis from a wide range of research applications.

CAREER DEVELOPMENT

REC Scholar, Research & Grants Funded During Pepper Supported Time	Years / Publications

Yunfeng Chen, PhD (Phase I) 2023-2025 /
Assistant Professor / Department of Biochemistry and Molecular Biology 32 (total)
Molecular biology and mechanobiology approaches to study how aging and diabetes affect the glycosylation of proteins in the vascular system 9 (1st/Sr)

Dr. Chen's current research uses molecular biology and mechanobiology approaches to study how aging and diabetes affect the glycosylation of proteins in the vascular system, and how that contributes to the increased risk of arterial thrombosis in the elderly population. He will also explore a new strategy for preventing arterial thrombosis abiding by the emerging concept of 'mechano-medicine'.

Huiwen Xu, PhD, MHA (Phase I) 2021-2024 /
Assistant Professor / Population Health & Health Dispariites 47 (total)
Aging; cancer rehabilitation; long-term care 12 (1st/Sr)

Dr. Xu is a health services researcher with strong interest in aging, cancer rehabilitation, and long-term care. His past research has examined the hospitalization and emergency department (ED) visits of nursing home residents using national Medicare claims and Minimum Data Set data. His long-term career goal is to become a policy-relevant cancer rehabilitation researcher using large observational data. Dr. Xu's Pepper Center appointment focuses on improving physical function among older patients with cancer admitting to nursing homes. Functional impairments affect over 40% of hospitalized patients with cancer. After hospital discharge, about 20% of patients received rehabilitation in nursing homes to maintain functional independence. But existing literature did not examine the patterns, predictors, and potential disparities in the rehabilitation therapy received by patients with cancer admitted to nursing homes. More importantly, the benefits of excess rehabilitation on patient-oriented outcomes including physical function remains unknown. As an RL5 scholar, Dr. Xu will evaluate the effects of rehabilitation therapy on physical function, symptoms, survival, community discharge, and healthcare utilization among older patients with cancer admitted to nursing homes. He will leverage multiple data sources including the Surveillance, Epidemiology, and End Results (SEER), Medicare claims (inpatient, outpatient, SNF, carrier), Minimum Data Set 3.0, etc. Prior to joining UTMB, Dr. Xu worked as a Research Assistant Professor for two years at the University of Rochester NCI Community Oncology Research Program (NCORP) Research Base to design and analyze nationwide Phase III clinical trials in cancer survivorship and geriatric oncology. Dr. Xu has published extensively in leading medical journals including Lancet, JAMA Oncology, JAMDA, and Medical Care. He currently serves on the Executive Committee of the AcademyHealth Methods and Data Council and Analytics Core of the Cancer and Aging Research Group.

Past Scholars

Andrew Murton, PhD (Phase I), Department of Surgery (2000-2023)
Monique Pappadis, PhD, MEd (Phase II), Division of Rehabilitation Sciences (2016-2020)
Rafael Samper-Ternent, MD, PhD (Phase II), Division of Geriatrics (2017-2020)
Rachel Deer, PhD (Phase II), Division of Rehabilitation Sciences (2017-2020)
Kimberly Hreha, EdD, OTR/L (Phase I), Division of Rehabilitation Sciences (2018-2020)
Erin Hommel, MD (Phase I), Division of Geriatrics (2020-2023)
Neil Mehta, PhD (Phase I), Epidemiology (2021-2023)
Sadaf Milani, PhD (Phase I), Division of Geriatrics (2021-2021)

PILOT/EXPLORATORY PROJECTS (6 Pilot Projects Listed)

1. Project Title: Strength Training Treadmill Exercise to Reduce Compensatory Walking Patterns in Post-Stroke Hemiparesis

Leader: Mansoo Ko, PhD

Significance: Stroke is the leading cause of chronic neurological disability in older adults. Our focus is to optimize the delivery of a combined strength and aerobic training regimen to older adults with post stroke hemiparesis and reduce inefficiencies associated with compensation by the nonparetic leg during walking. Approach: We will optimize our combined neuromechanical and biobehavioral approach to enhance bilateral symmetry of limb propulsion using a newly acquired split-belt, force-plate instrumented treadmill that generates backward directed resistance forces. We will also determine feasibility and collect preliminary data for a larger study. With neuromechanics we will measure EMG muscle activity patterns, joint torque output, and trailing limb angle at different levels of resistance, while subjects walk under normal treadmill belt conditions versus the split-belt conditions. In addition, we will assess the maintenance of improved paretic limb propulsion immediately after the split-belt environment is restored to a single belt condition (i.e. aftereffects), and the ability to consciously reduce compensatory walking patterns when they are not engaged with the specialized treadmill setup. Muscle biopsies will be taken to measure differences in fiber type, gene expression and cell signaling in paretic and nonparetic leg. Innovation: This information will provide important feasibility and preliminary data to support an R21 or R01 proposal seeking to validate of the efficacy of a strength and aerobic training regimen to reduce compensatory gait patterns and improve post-stroke mobility.

2. Project Title: Evaluating the Usability of a Novel Hip Fracture Web-app, My Hip-Fracture (My-HF)

Leader: Peter Cram, MD

Mortality and morbidity are high for older adults after hip fracture (HF), particularly those with multi-morbidity and frailty. While mortality and morbidity after hip fracture is generally well understood by healthcare professionals, recent data suggest that both patients and surrogate decision makers (SDMs) are unaware of the seriousness of hip fracture. In response to this gap, our multi-disciplinary team developed, iteratively refined, and pilot tested the usability of a paper-based educational tool (My-HF) providing personalized estimates of post-HF prognosis among patients and SDM. Based on this initial testing, we have revised My-HF and converted it to a web-enabled mobile application. The aims of this pilot project are two-fold: (1) Assess the usability of My-HF among a sample of healthcare 20 healthcare providers including physicians (orthopaedic surgeons, geriatricians, hospitalists, and palliative care physicians), nurses, and social workers. (2) Evaluate the efficacy of My-HF in a pilot randomized trial enrolling 50 patients hospitalized with low-impact HF and their SDMs (25 randomized to My-HF and 25 randomized to a control group). Aim 1: Usability of the My-HF web-app in healthcare professionals. We will use a mixed-methods approach to solicit feedback from healthcare professionals at UTMB (total sample size 20) on issues of usability, touch, and interactivity. Participants will be provided with an Android Tablet and asked to open and navigate the My-HF, this will be supplemented by a structured survey and structured interview with open ended questions. Aim 2: Pilot randomized trial of My-HF. We will conduct a pilot randomized trial to evaluate the efficacy of My-HF among patients hospitalized with

low-impact HF and their SDMs (total sample size 50, 25 My-HF, 25 control). For participants randomized to receive My-HF, clinical teams will complete the My-HF report and a study RA will review the report with the patient and/or SDM. We will use and "attention control" whereby control group will receive augmented usual care with a RA visit reviewing general topics of ageing and fall prevention strategies. We will evaluate 4 co-primary outcomes: 1) HF knowledge and understanding of prognosis; 2) satisfaction with HF care; 3) anxiety and regret; and 4) readiness to engage in advanced care planning (ACP) using pre-identified questions from validated instruments. Outcomes will be evaluated at 10-14 days after intervention and 26-28 days after intervention. We hypothesize that providing HF education using My-HF will improve knowledge and understanding of HF prognosis, thereby improving satisfaction with HF care, reducing anxiety and regret, and improving readiness to engage in advanced care planning. We anticipate that the pilot data collected will generate 1-2 peer-reviewed publications, and more importantly but used to support an application for a multi-centre randomized controlled trial to definitively evaluate the impact of My-HF on each of the 4 outcomes described above.

3. Project Title: Inflammaging: Role of HMGB1 mediated chronic inflammation in aging-associated cognitive dysfunctions and decreased lifespan

Leader: Sagar Gaikwad, PhD

Advanced age is the main risk factor for most chronic diseases, functional and cognitive deficits, and decreased health- and lifespan in humans. Recent studies suggest that senescent cells accumulate with aging in various tissues and play a key role in the pathophysiology of aging-related disorders. Senescent cells are defined by an apoptosis resistant, arrested cell cycle with a distinct "inflammatory" phenotype known as senescence-associated secretory phenotype (SASP). Importantly, human aging is characterized by a chronic, low-grade inflammation known as inflammaging, which can exacerbate naturally occurring age-related tissue deterioration through paracrine mechanisms, and contribute to several diseases associated with aging, including atherosclerosis, osteoarthritis, cardiovascular disease, and Alzheimer's disease (AD). Although, SASP is a common pathogenic inflammatory process in the aforementioned pathologies, the precise etiology of inflammaging and its potential causal role in contributing to cellular senescence and decreased healthy lifespan remain largely unknown, impeding the development of interventions that might delay or prevent age-related disorders and maximize healthy lifespan. Modulation of inflammaging/SASP thus offers opportunities to develop novel therapeutics. HMGB1- a key component of inflammaging: Evidence suggests that release of high mobility group box protein 1 (HMGB1) is an early and central mediator of senescent phenotypes both in humans and mice tissues. It coordinates SASP related chromatin folding and RNA homeostasis and contributes to senescence progression. We recently demonstrated that HMGB1-the major component of SASP is actively secreted by senescent cells in the brain in both humans and mice. HMGB1 is a highly conserved, nuclear protein present in all cell types, and it facilitates DNA replication and repair. The extracellular HMGB1 is a key initiator of inflammation, which slows or stops tissue regeneration and homeostasis, and ultimately causes tissue deterioration. Our studies have shown that inhibition of HMGB1 release effectively prevents paracrine senescence, neuroinflammation, inflammaging and improves cognitive functions in aged human tau expressing (hTau) transgenic tauopathy mice. A very recent study demonstrated that particularly oxidized HMGB1 cause chronic inflammation and subsequent tissue damage and functional decline. In contrast, non-oxidizable HMGB1 (3S-HMGB1) or fully reduced HMGB1 facilitates resolution of inflammation, promote regeneration in multiple tissues and enhances functional recovery. However, the impact of HMGB1 release and

oxidation on accumulation of senescent cells, chronic inflammation, and cognitive and physical dysfunction, healthy lifespan has not been investigated. The central hypothesis is that "HMGB1 release and oxidation promotes paracrine senescence, and inflammaging, which cause cognitive and physical dysfunction and decreases healthy lifespan in animals". Recent studies from our laboratory and others provided evidence that modulation of HMGB1 release reduces inflammation and promotes tissue regeneration, which subsequently improve survival, health span, functional performance. HMGB1 has been shown to trigger hyperinflammation, and HMGB1 levels in blood or tissue are substantially elevated in many chronic inflammatory diseases including AD. Therefore, we wish to investigate the role of HMGB1 release and oxidation in inflammaging using an experimental mouse model of tauopathy as well as tissues and cells, and cerebrospinal fluid (CSF) from AD patients and age-matched control subjects. Our broad research goal is to understand how HMGB1 release and oxidation mechanisms influence inflammaging, cellular senescence, and tissue pathologies, and how de-regulation of these mechanisms contributes to aging and disease. This pilot study will generate preliminary data and provide proof-of concept to support this novel hypothesis. Aging and high-fat diet (HFD) are known to exacerbate effects of senescent cells. So, for subsequent funding applications, we will use genetic and pharmacological approaches to evaluate whether targeting HMGB1 release and oxidation prevents/delay inflammaging and restore cognitive and physical functions and improve lifespan in tauopathy mice subjected to normal diet or HFD. We will examine aging hallmarks such as cellular senescence, and inflammaging in mice and human cells as described earlier. Cognitive function, tau pathology, inflammation, neuron loss in mice will be investigated by methods described earlier9. Physical function and lifespan in old age mice will be examined as previously reported.

4. Project Title: **Neighborhood Structural Inequalities and Opioid Use Disorder among Older Adults: Before and During the COVID19 Pandemic Comparisons**

Leader: **Tse-Chuan Yang, PhD**

Despite a new interest in investigating the impact of the novel coronavirus disease 2019 (COVID-19) pandemic on populations with opioid use disorder (OUD), little attention has focused on how existing neighborhood inequalities, such as neighborhood social isolation, have shaped risk of OUD before and during the pandemic, particularly among older adults. Since the opioid crisis emerged in the 1990s it has become clear that individuals with OUD are at a higher risk of death, morbidity, and other undesirable health outcomes than those without. The COVID-19 pandemic has further complicated the opioid crisis because the fear for infection, uncertain prognoses, and potential shortage of medical resources are associated with various mental health issues, which are likely to increase the demand for opioids. Importantly, older adults have been disproportionately affected by COVID-19, and the recommended precautions to contain the pandemic (e.g., physical distancing and shelter-in-place orders) have severely interrupted older adults' daily routines. In particular, the pandemic has prohibited older adults from receiving regular social support or quality health care, and the time spent in their own residential neighborhood has been prolonged during the pandemic. Under these conditions, older adults' need for opioids, both prescription and illicit, may have increased. Moreover, older adults with extended exposure to poor neighborhood conditions may be at a particularly increased risk of OUD. Using the 2017-2021 Medicare Fee-for-Service Part A and Part B claims data and the American Community Survey 5-year estimates, this project will construct a before and during the pandemic cohort, with both OUD and non-OUD observations;

beneficiaries will then be linked to their neighborhood conditions. Utilizing these hierarchical data, this project has three aims: (1) Investigate whether individual-level characteristics among older adults with OUD have changed during the COVID-19 pandemic. We hypothesize that compared with the observations in the before pandemic cohort, OUD has become more prevalent during the pandemic among older adults with low socioeconomic status, from racial/ethnic minority backgrounds, and having mental and/or physical chronic health issues. (2) Investigate whether the associations between neighborhood-level factors and the risk of OUD have been enhanced during the COVID-19 pandemic. We hypothesize that neighborhood social isolation, concentrated disadvantage, and rurality have stronger associations with the risk of OUD during the pandemic. (3) Investigate whether neighborhood-level factors moderate the association between OUD and individual characteristics before and during the pandemic. We hypothesize that living in neighborhoods with high concentrated disadvantage and isolation aggravates the associations between OUD and individual low socioeconomic status and mental or physical chronic conditions only during the pandemic. The findings of this project will offer evidence for that the pandemic exacerbates the risk of OUD at both the individual and neighborhood levels.

5. Project Title: **Functional Recovery of Asian Older Adults in Skilled Nursing Facilities**

Leader: **Hoang T. Nguyen, PhD**

The Asian and Pacific Islander population aged 65 years and older in the United States is expected to grow to over 7 million by 2060. This study provides a profile of Asian Americans older adults residing in skilled nursing facilities and their functional recovery status. The study four aims are (1) to compare racial/ethnic differences in hospital referral patterns to SNFs and home/self-care for older adults (> 65 years) from 2013- 2019, (2) to compare differences in admission source to skilled nursing facilities between racial/ethnic groups for older adult residents in 2018 or 2019, (3) to compare demographic and clinical characteristics between Asian and other racial/ethnic older adults associated with first SNF stay in 2018-2019, and (4) to examine factors contributing to differences in functional recovery between Asian and non-Hispanic White older adults in SNF after a hospital stay. No comparison in functional recovery will be made between Asian and other minority groups. The study uses Medicare data, specifically the Master Beneficiary Summary File, the Medicare Provider and Analysis Review (MedPAR) file and the Minimum Data Set for Nursing Homes and Swing Bed Provider to address the aims.

6. Project Title: **Rejuvenation of Senescent Cells In vitro and In vivo**

Leader: **Michael Sheetz, PhD**

The UTMB Pepper Center supported our work this past year with a small developmental project. Those studies have indicated that low level ultrasound can rejuvenate senescent cells in vitro and in vivo. Because the treatments have not been optimized and we don’t know the molecular mechanism, we would like to have further evidence for an NIH program project grant and this grant is to help us obtain that evidence. This grant is in collaboration with Drs. Rasmussen and Murton to optimize the ultrasound parameters for improving aged mouse performance and wound healing, respectively. The results of these experiments are important for designing clinical trials to improve aged human performance and healing with ultrasound. The background for this grant comes from our studies of senescent cell rejuvenation, which

include massive expansion of fibroblasts and mesenchymal stem cells, without apparent alteration of cell phenotype. Thus, we expect that rejuvenation of cells in tissues will not alter their phenotype either. Our preliminary mouse studies over the last year have shown that ultrasound treatment can significantly improve aged mouse performance on the treadmill and inverted cling assays. The parameters used were not optimized but were the same parameters that produced optimal rejuvenation of cells in vitro. We hope to be able to improve the rejuvenation of the old mice further with more frequent treatments, optimized power level, frequency and duty cycle plus an optimized ultrasound chamber. Because there is preliminary evidence that ultrasound treatment increased the lifespan of the mice, we will undertake an expanded longevity study to determine if ultrasound treatment can significantly increase lifespan. In parallel, we will treat the wounds of aged mice with ultrasound to improve healing. Optimization of the healing effect of ultrasound may require optimizing the timing of delivery of the ultrasound, since it is not expected that ultrasound will be beneficial at all stages of the healing process. Of particular interest, is the effect of ultrasound on the proliferative phase of healing. In the case of senescent cells, we will focus on the molecular basis of the rejuvenation by ultrasound, since it may provide clues to ways to improve the rejuvenation of senescent cells in vivo. From the literature, it is clear that senescence involves mitochondrial fusion and the inhibition of sirtuin 1 activity. Our results show that reversal of senescence with ultrasound causes mitochondrial fission in a Drp1 independent process and requires Sirtuin 1 activity. In addition, inhibition of the Rho kinase is synergistic with ultrasound. Finally, we will fractionate the supernatant from ultrasound-treated normal cells that activates senescent cell growth to identify the critical growth factors. These results are all consistent with hypotheses that senescence involves protein aggregation with decreased autophagy, and ultrasound causes increased protein degradation leading to reversal of senescence. Based upon the outcome of these mice studies, we hope to develop plans with our collaborators for the use of ultrasound in treating aspects of human aging. Since the ultrasound power levels are well within the limits set for humans, we are moving to preliminary trials of the ultrasound effects on diabetic foot ulcers in the next several months. Thus, there are no apparent barriers to developing ultrasound treatments for aging.

DEVELOPMENT PROJECTS (3 Development Projects Listed)

1. **Project Title:** **Reversal of Senescence Phenotypes by Low Level Ultrasound Treatment**

   Leader: **Michael Sheetz, PhD**

   Core(s):

In preliminary studies of senescent cells that have a low growth rate and senescence associated secretory phenotype (SASP), we found that mechanical stimulation by structured bursts of low frequency ultrasound will stimulate growth and block SASP without heating. Further, such ultrasound treatment (US) also caused normal cells to secrete growth-activating factors, which further increased growth of senescent cells. This appeared related to mechanical effects on intracellular organelles particularly mitochondria following US treatments. To determine if these findings might be relevant to human aging, we have started collaborations with Dr. Blake Rasmussen, an aging expert and Dr. Andrew Murton, whose lab is studying wound healing. These collaborative studies will test if ultrasound therapy improves the performance of aged mice (Graber et al., 2020) and their healing (Bhattarai et al., 2020). Performance in mice will be measured with the new comprehensive functional assessment battery (CFAB), which was recently developed with support from a UTMB Pepper Pilot Award. The CFAB is similar to the SPPB (Short Physical Performance Battery) assessment tool developed by the NIA to evaluate physical function in older adults. In collaboration with the Murton lab, we will test the effect of ultrasound treatment on healing of mature and aged mice with 5 mm diameter skin excision wounds (an assay that has been working in their lab). In parallel studies, we are treating tumors in mice with structured bursts of ultrasound to cause mechanically-induced tumor cell death (Tijore et al., 2020) under the same conditions used in our preliminary senescence studies. Only minor modifications of the mouse restraining device in the treatment chambers are envisioned for the studies of effects on aging and wound healing. Based upon the outcome of these mice studies, we hope to develop plans with our collaborators for the use of ultrasound in treating aspects of human aging. Since the ultrasound power levels are well within the limits set for humans and we are moving to clinical trials of the ultrasound effects on human tumors in the next several months, there are no apparent barriers to developing ultrasound treatments for aging.

2. **Project Title:** **A non-parametric approach to predict the recruitment for a randomized clinical trial in an elderly inpatient setting**

   Leader: **Alejandro Villasante-Tezanos, PhD & Xiaoying Yu, PhD**

   Core(s):

Successfully recruiting the prespecified number of trial participants is critical and remains challenging to the success of clinical trials. The COVID19 pandemic changed inpatient hospitalization and outpatient visit patterns, thus significantly impacted recruitment for a substantial number of clinical trials. An important question to the clinical trial stakeholders is: Given the recruitment data we have so far, how long will it take to recruit the target number of patients now, and do we have to adjust our initial estimates and plans?1 Although various types of prediction models for recruitment have been developed in the past, they either relied on assumptions of parametric distributions or prior information on the recruitment rate. Also, these models did not consider sequential steps, such as, % eligible, % approached and % consented that may provide valuable information to model final recruitment. Furthermore, many of these

models were not tested with real trial enrollment data.2 The objective for this project is to develop and test the recruitment model using simulation-based non-parametric approach for clinical trials based on inpatient settings such as those taking place in acute care for the elderly (ACE) units at UTMB by leveraging the resources of the recruitment data from completed and ongoing trials and real-world data (TriNetX data) at UTMB.

3. Project Title: **Is the 3D position of aging-related genes a biomarker for aging?**
Leader: **Guy Nir, PhD**
Core(s):

Cellular senescence is one of the hallmarks of aging. A major phenomenon in senescing is the rewiring of gene expression programs, likely since the regulation of many genes goes awry. One major regulator of gene expression is genome organization. Indeed, several papers have shown that genomes are reorganized during senescence. However, it remains unknown whether the position of aging-related genes changes as cells age and whether that impacts gene expression. There are two main reasons for this knowledge gap. The need to map the 3D position of several (aging-associated) genes and compare their folding signatures between proliferating and (early and deep) senescing cells. The high degree of cell-to-cell structural and transcriptional variability, especially in senescent cells. My lab has the tools and desire to overcome these two hurdles. We employ multiplexed imaging approaches to describe how the restructuring of genomes, including senescent genomes, impacts gene expression and cell fate decisions at the single-cell level. Here, we propose to compare the position and structure of Senescent-Associated Secretory Phenotype (SASP) genes in proliferating and early and late senescing cells. Our goal is to determine whether the position and structure of these genes change during senescence and whether these structural changes correlate with transcriptional changes. In the long-term, we plan to transition from cells to tissues, taking biopsies from mice and then humans at different ages to look for structural, positional, and transcriptional rewiring that may occur during aging. We also plan to expand our scope to other forms of senescence. And we intend to study whether fully reversible biomolecular condensates carrying transcriptional machinery and encompassing chromatin domains turn into irreversible aggregates that impair genome functions.

RESEARCH (0 Projects Listed)

PUBLICATIONS

2024

2023

1. **The \double jeopardy\" of midlife and old age mortality trends in the United States."**
   Abrams LR, Myrskyl? M, Mehta NK
   Proc Natl Acad Sci U S A, 2023 Oct 17, 120(42): e2308360120
   https://doi.org/10.1073/pnas.2308360120 | PMID: 37812715
   Citations: NA | AltScore: NA
2. **Optimizing the Design of Clinical Trials to Evaluate the Efficacy of Function-Promoting Therapies.**
   Bhasin S, Cawthon PM, Correa-de-Araujo R, Storer TW, Volpi E, Newman AB, Dioh W, Tourette C, Evans WJ, Fielding RA
   J Gerontol A Biol Sci Med Sci, 2023 Jun 16, 78(Supplement_1): 86-93
   https://doi.org/10.1093/gerona/glad024 | PMID: 37325959 | PMCID: PMC10272979
   Citations: 1 | AltScore: NA
3. **Understanding Nursing Home Spending And Staff Levels In The Context Of Recent Nursing Staff Recommendations.**
   Bowblis JR, Brunt CS, Xu H, Grabowski DC
   Health Aff (Millwood), 2023 Feb, 42(2): 197-206
   https://doi.org/10.1377/hlthaff.2022.00692 | PMID: 36745835
   Citations: 2 | AltScore: 30.45
4. **Differences in the Cognitive Function of Mexican Adults Aged 60 and Older with Self-Reported Diabetes in 2001 and 2018.**
   Camarillo J, Villarreal Rizzo A, Cabrero Castro JE, Downer B
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EXTERNAL ADVISORY BOARD MEMBERS

Stephen Kritchevsky, PhD
Wake Forest School of Medicine
Serving since 2011 (13 years)

Thomas M. Gill, MD
Yale School of Medicine
Serving since 2019 (5 years)

Karen Bandeen-Roche, PhD
Johns Hopkins Bloomberg School of Public Health
Serving since 2022 (2 years)

RECOGNITION AND AWARDS (2023-2024)

Blake Rasmussen, PhD (2023)

- Appointed to Editorial Board for Aging Cell Journal

Guy Nir, PhD (2023)

- Selected to participate in the 2023 Butler-Williams Scholars Program

Huiwen Xu, PhD (2023)

- Selected as RCCN Scholar in Multidisciplinary Research

Sadaf Milani, PhD (2023)

- Invited to join the 2023 Research Centers for Minority Aging Research Scientist Advisory Board.

MINORITY RESEARCH

General Brief Description of Minority Activities:

UTMB Pepper Center Hispanic Council on Aging

For Administrative Core/LAC

The Pepper OAIC recognizes the need to formalize and extend its many connections to the UTMB strength in the study of older Hispanics. To do this, we have formalized our relationship with the longstanding UTMB Hispanic Center of Excellence by forming the Hispanic Council on Aging. The Hispanic Council on Aging serves as a focus for outreach in research and minority junior faculty development that will extend our strengths to make us a national focus for best practices in such research and a magnet for future scholars. The Hispanic Council on Aging does the following:

1) Identify Pepper scholars that will benefit from RCMAR funding, and making sure they have appropriate mentoring to develop their projects (REC activities);

2) Innovate approaches to increase recruitment of Hispanic populations as research participants (CRC project);

3) Serve as a portal for attracting and promoting Hispanic faculty, particularly those studying the health of older Hispanics.

The Hispanic Council on Aging consists of the Hispanic Center of Excellence Board: Norma A. Pérez, Kyriakos Markides, Rebeca Wong, Alfredo Torres, Soham Al-Snih, Maria Belelcazar, Monique Pappadis, and Myrna Serna. These senior faculty researchers represent the scope of scholarly activities throughout the university as well as leaders in recruitment and mentorship of minority faculty and students.

The Hispanic Council on Aging meets monthly or as needed to plan activities and report progress. A representative of the Council will attend all monthly Pepper meetings. The Council prepares an annual report as a part of the Pepper report provided to its External Review Panel. Results from their analysis will inform future activities.

For Clinical Research Core CRC

Developmental project: Best Practices in Recruiting Hispanic Research Participants

Recruiting participants into research is always a challenge. Older adults and minority populations each represent an additional challenge; recruiting older Hispanics is therefore doubly difficult. Recruitment strategies which work in other populations do not necessarily translate to Hispanic participants; also, the Hispanic population is widely diverse and different groups also may call for varying strategies. We therefore propose to develop best practices in recruiting Hispanic research participants. The aims of this pilot project are:

1) Review the existing literature to identify strategies used in the past;

2) Conduct qualitative studies within our local community to identify what Hispanics want and do not want in terms of their willingness to serve as research participants.

3) Develop recruitment materials and strategies that are culturally and linguistically appropriate for the target Hispanic population, particularly the aging population under the guidance of the Hispanic Council on Aging members. Develop best practices to increase the number of older Hispanics participating in research.

From these studies, we will be able to develop tailored strategies we think will be successful. We can then pilot them in our ACE unit and other local studies. We will disseminate results nationally to develop an understanding of what represents "best practices" in recruiting Hispanics as research participants.

For Education Core REC

The Hispanic Council on Aging will assist the Pepper OAIC to connect with junior investigators, institutionally and nationwide. Members of the Council will be assigned as advisors to incoming junior Hispanic faculty and help them to find appropriate mentors, development opportunities and career growth. Hispanic junior faculty will be encouraged to mentor underrepresented minority medical students and residents to encourage them early into research and expose them to aging research and geriatric medicine by participating in programs such as MSTAR and Summer Research Programs.

Hispanic Council on Aging/Hispanic Center of Excellence faculty aim to:

1) Attract and train scholars, providing contacts both institutionally and outside UTMB;

2) Develop protocols to attract Hispanics into research;

3) Disseminate best practices.

Publications on Racial Disparities (2022-2023):

Downer, B., Li, C. Y., & Al Snih, S. (2023). Hospitalizations and Emergency Room Admissions by Mexican American Older Adults with and without Dementia and Caregiver Mental Health. *J Alzheimers Dis*, *91*(3), 1185-1195. PMC9946698

Gutierrez, S., Wong, R., & Milani, S. A. (2022). The pain and depressive symptoms cascade: A bidirectional analysis of the Mexican Health and Aging Study 2012-2015. *Int J Geriatr Psychiatry*, *37*(10). PMC9725745

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(2022). Metformin and testosterone replacement therapy inversely associated with hormone-associated cancers (prostate, colorectal and male breast cancers) among older White and Black men. *Clin Endocrinol (Oxf)*, *97*(6), 792-803. PMC9637746

Nicot-Cartsonis, M. S., Digbeu, B. D. E., Raji, M. A., & Kuo, Y. F. (2022). Disparities in Late-Stage Breast and Colorectal Cancer Diagnosis Among Hispanic, Non-Hispanic White, and Non-Hispanic Black Patients: a Retrospective Cohort Study of Texas Medicare Beneficiaries. *J Racial Ethn Health Disparities*, 1-10. PMC9794104

Pappadis, M. R., Chou, L. N., Howrey, B., & Al Snih, S. (2023). Life-space mobility and post-hospitalization outcomes among older Mexican American Medicare beneficiaries. *J Am Geriatr Soc*, *71*(5), 1617-1626. PMC10175172

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Ventura, J., Downer, B., Li, C. Y., & Snih, S. A. (2023). Nativity differences in the relationship between handgrip strength and cognitive impairment in older Mexican Americans over 20 years of follow-up. *Arch Gerontol Geriatr*, *107*, 104903. PMC9974812

Minority Trainee(s):

- Monique Pappadis, PhD, MEd, Assistant Professor
  Mexican Americans have an increased risk of stroke in comparison to non-Hispanic Whites and report worse cognitive, functional, and neurological outcomes following stroke. It is well established that older adults with greater levels of mobility are likely to have lower rates of re-admissions and decreased mortality. Spatial mobility was initially conceptualized as ‘life space’, the space in which a person travels/moves over a specific time point. However, the initial assessment excluded the need for assistance. The Life-Space Mobility Assessment (LSA), developed at University of Alabama Birmingham, is a validated measure of community mobility in older adults during the 4 weeks prior to assessment. In addition, LSA accounts for assistance needed from a device or person. Using data from the Hispanic EPESE wave 7 (2010-2011) on Mexican Americans, the majority had restricted life-space, with nearly 80% limited to their home or neighborhood. To date, no study has identified the role of life space mobility as a potential protective factor in determining discharge destination, 30-day re-admission, and mortality following a stroke.
- Rafael Samper-Ternent, MD, PhD, Assistant Professor
  Dr. Samper-Ternent is a Clinician Scientist with a unique background in both patient care and research. Both his clinical and research activities focus on improving care and quality of life of older adults. He uses a multidisciplinary approach to analyze health disparities in different countries in Latin American and Hispanic adults in the United States. As an OAIC REC Scholar, he will focus on functional and cognitive decline of community dwelling older adults from different ethnic groups. Dr. Samper-Ternent is also serving as project manager for the UTMB clinical site of the D-CARE Study.

- Sadaf Milani, PhD, Assistant Professor
  Dr. Sadaf Arefi Milani's research focuses on how sociodemographic, behavioral, and health characteristics influence cognitive decline in old age. She works on the prevalence of diabesity, the co-occurrence of obesity and diabetes, among older adults in Mexico and its relationship with cognitive impairment. Additionally, Dr. Milani conducts research on pain and cognitive decline among older adults in Mexico, with a focus on gender differences.

No minority grant information specified.