Previously Funded Proposals
ATRS Pilot Award

Institute for Clinical and Translational Research
UNIVERSITY OF WISCONSIN–MADISON

Advancing Translational Research & Science Pilot Awardees
2024

Of Note: In 2024, the ATRS Pilot Award consisted of 2 Tracks:

1. Project Planning Grant: Designed to assist groups of investigators from a diverse range of disciplines refine cutting-edge research ideas, build collaborations, create shared research agendas, and develop strategic action plans for externally funded grant proposals.
2. Translational Science Project: Support for impactful translational science pilot projects or for development of novel translational methods addressing either mentorship science, team science, recruitment science, diversity science, or implementation science including projects applicable to Learning Health Systems (LHS).

Track	Principal Investigator/s	Affiliation	Title
1	Corinne Henak, PhD Keith Knurr, DPT, PhD	College of Engineering, Mechanical Engineering SMPH, Department of Orthopedics and Rehabilitation	*A Step Towards Precision Medicine: Collaborative Team Building to Leverage Quantitative MRI for the Clinical Management of Knee Osteoarthritis*
2	Filiz Yesilkoy, PhD	College of Engineering, Biomedical Engineering	*A Rapid and Multiplexed Protein Biomarker Screening Test for Early Diagnosis of Alzheimer's Disease and Dementia*
2	Pallavi Tiwari, PhD Anand Narayan, MD, PhD	SMPH, Department of Radiology SMPH, Department of Radiology	*Artificial Intelligence-based Diagnostic Risk (AIDeR) Score to Predict 5-year Risk of Advanced Breast Cancer*
2	Jomol Mathew, PhD	SMPH, Department of Population Health Sciences	*Development of a Data Science Framework for Enhancing Cross-Disciplinary Translational Science using Long COVID as a Model System*
2	Mohun Ramratnam, MD	SMPH, Department of Medicine	*Assay development for mitochondrial K+ channel activity to test novel cardioprotective therapies*

A Step Towards Precision Medicine: Collaborative Team Building to Leverage Quantitative MRI for the Clinical Management of Knee Osteoarthritis

Corinne Henak, PhD – Assistant Professor, College of Engineering, Mechanical Engineering
Keith Knurr, DPT, PhD – Assistant Professor, SMPH, Department of Orthopedics and Rehabilitation

Osteoarthritis (OA) affects 14% of the US population and accounts for 4.3% ($18.4 billion) of all hospitalization costs. The knee is the most frequently affected joint, and knee OA commonly progresses to require total knee arthroplasty (TKA). The TKA volume in the US is projected to increase as much as 8-fold by 2050, which will place an unprecedented burden on the healthcare system. There is a pressing need to better understand the onset and progression of OA and to develop strategies to halt the disease.

Although knee OA can stem from multiple factors (e.g., age, obesity, joint injury/surgery, genetics), the mechanical environment of the joint, specifically the articular cartilage, can play a critical role in the disease onset and progression. However, accurately measuring mechanical fields (e.g., stresses and strains) experienced by the cartilage during daily activities is challenging. Computational models (primarily finite element (FE) models) are commonly used to predict mechanics of interest in the cartilage, but these often have multiple assumptions or simplifications that preclude the models from being fully subject-specific. The current state-of-the-art models include patient-specific boundary and loading conditions captured from movement analysis and patient-specific geometry from MRI, but use generic sub-failure and failure material behavior. As such, the purpose of this proposal is to develop a FE modeling pipeline that incorporates these critical patient-specific factors to more accurately estimate the cartilage stresses and strains experienced across common tasks.

Patient-specific factors will come from quantitative magnetic resonance imaging (qMRI) and three-dimensional motion capture data during walking, running, and jumping. qMRI data will be used define the cartilage material properties and joint morphology, while motion capture data will define model boundary and loading conditions. The resultant models can be used to assess associations with clinically relevant metrics and aid in elucidating novel interventional targets to alter the loading environment in those susceptible to OA progression. As a first step in this translational project, we will achieve the following specific aims:

1) Develop a pipeline for generating qMRI-informed, patient-specific FE models to estimate knee cartilage mechanics in individuals at risk for OA development.
2) Form an interdisciplinary, translational team that is ready to submit competitive extramural funding applications.

A Rapid and Multiplexed Protein Biomarker Screening Test for Early Diagnosis of Alzheimer's Disease and Dementia

Filiz Yesilkoy, PhD – Assistant Professor, College of Engineering, Biomedical Engineering

Significance of the proposed project: It is estimated that 6.7 million Americans and 55 million people worldwide are living with Alzheimer's disease (AD), and its prevalence is expected to increase due to the aging population. The growing burden of AD on healthcare systems, social services, and families calls for new, effective diagnostics and treatment strategies. Recent studies report that the time between the onset of AD and its diagnosis, based on current clinical practices, can be decades long. Early detection of AD before the symptom onset is important because it enables proactive management of the disease, which leads to a better quality of life, and gives patients the chance to participate in clinical trials, which can enable the development of effective new treatments. Notably, new diagnostic biomarkers are emerging with implications for early AD diagnosis before symptoms appear. For example, in a very recent study published in 2024, a group of UK-based researchers associated increased blood levels of four specific proteins – GFAP, NEFL, GDF15, and LTBP2 – with dementia by screening a large cohort of adults. The discovery of such novel biomarkers can facilitate the early diagnosis of AD and enable population screening efforts.

However, a combination of factors, including shortages of specialists (geriatricians and neurologists) who can order such tests, limited access to healthcare, stigma, and fear associated with AD diagnosis, limit equitable access to AD diagnostic tests and hinder the benefits of early diagnosis. This project aims to tackle these challenges by developing a rapid, low-cost, and accessible AD screening test. Once successful, our approach can help primary care providers proactively screen large populations and make AD management more equitable for diverse populations.

Proposed translational technology: In the Yesilkoy group, we develop label-free nanophotonic biosensors that can directly detect target proteins from small quantities of blood plasma samples at ultralow concentrations (~ 20 pg/mL). Our approach does not require laborious multi-step bioassays, expensive equipment, and expert technicians, yet it can rapidly detect multiple protein biomarkers in a simple single-step assay. Notably, we have been working to employ high-throughput manufacturing techniques to develop a low-cost, accessible biosensor technology. In this project, to address the unmet diagnostics needs of AD, we propose to employ our powerful biosensor technologies to detect glial fibrillary acidic protein (GFAP), an AD biomarker, at ultralow detection limits via the following aims:

Aim 1: Develop a bioassay using our already developed nanophotonic biosensor technologies to detect the recently proposed protein biomarker, GFAP, for early AD diagnostics.

Aim 2: Demonstrate that the proposed biosensor platform can detect GFAP from real human samples with high sensitivity and specificity and benchmark our technology to commercial bioassays.

Artificial Intelligence-based Diagnostic Risk (AIDeR) Score to Predict 5-year Risk of Advanced Breast Cancer

Pallavi Tiwari, PhD – Associate Professor, SMPH, Department of Radiology
Anand Narayan, MD, PhD – Associate Professor, SMPH, Department of Radiology

Need for integrated risk-assessment tools for predicting 5-year risk of advanced breast cancers: 40,000+ women die of breast cancer/year, a burden weighing particularly heavily on marginalized communities. In Wisconsin alone, an average of 4,600 women received a new diagnosis of breast cancer and 740 women died of this disease/year from 2011-2017, according to the Wisconsin Cancer Collaborative. Current risk-assessment models include known risk-factors such as classic hormonal and reproductive risk factors with family history, genetic testing that includes polygenic risk scores, and mammographic density on digital breast tomosynthesis (DBT). Breast density is recognized as an independent risk factor and reflects the amount of glandular and fibrous connective tissue versus fatty tissue as seen on DBT. However, breast density is considered a coarse measure due to its limited ability to comprehensively capture the complexity of breast parenchymal pattern. Multiple studies have demonstrated that current screening approaches are neither sufficiently predictive nor targeted at the most harmful cancers (i.e., advanced cancers). Consequently, there is a call to action to develop risk models that keep the focus on improving ways of identifying over 20% of breast cancer patients who will develop advanced breast cancer that currently go undiagnosed despite regular 1 to 2-year screenings.

Advanced breast cancers (defined as pathologic stage II or higher) require surgery and systemic treatment. Early identification of women at high risk for advanced cancers could enable tailored options of supplemental screening and ultimately provide clinically-actionable information to decrease advanced cancers and associated mortality. Further, worse outcomes - often associated with advanced cancers, are disproportionately influenced by community-level social determinants of health (SDOH) (e.g., social conditions and policies, social context) and their influence on individual-level factors (e.g. screening behavior, race, ethnicity). These considerations point to the pressing need for developing reliable predictive tools that incorporate multilevel, non-invasive determinants of breast cancer in conjunction with SDOH factors as potential risk-factors of advanced disease.

Scientific Premise: The central hypothesis of our project is that, while not visually distinguishable on DBT, artificial intelligence (AI)-driven quantitative image-based (i.e. radiomics) features that capture the spatial arrangement of fibroglandular tissue will be able to comprehensively characterize the sub-visual mechanistic changes in patients with high likelihood of advancing to aggressive breast cancer from those who are not at risk for advanced disease. We further hypothesize that incorporation of individual- (e.g., race, weight, insurance status) and area-level SDOH (Area and Community Deprivation Index) will complement the radiomics-based risk-stratification to create a personalized and reliable risk-assessment score for advanced breast cancer.

Proposed Solution: In this pilot project, we propose to develop a clinically translatable AI-based Integrated Diagnostic Risk (AIDeR) score that will combine artificial intelligence (AI)-derived image features, along with known risk-factors and demographic SDOH factors, to predict 5-year risk of developing an advanced breast cancer. We will leverage new classes of radiomic attributes developed by our team that capture quantitative image patterns corresponding to (1) micro-architectural tissue changes captured via the disorder (i.e. entropy) in local intensity gradients and (2) lesion heterogeneity under the influence of the unique individual hormonal milieu inherent in “seemingly normal” breast

parenchyma on DBT. These features, when monitored over serial DBT images, can glean subtle patterns associated with the disease and its progression, that may not be visually appreciable even to trained experts. AIDeR will be optimized and validated using a case-control dataset derived from the over 48 thousand screening DBT examinations/year collected via the electronic health record (HER) from University of Wisconsin Health patients catalogued in the Women's Health Cancer Registry (WHCR).

Development of a Data Science Framework for Enhancing Cross-Disciplinary Translational Science using Long COVID as a Model System

Jomol Mathew, PhD – Associate Professor, SMPH, Department of Population Health Sciences

Traditional scientific inquiry relies on a structured top-down approach, starting from the generation of a research hypothesis, obtaining necessary data, and testing this hypothesis on the study population. This approach, however, requires extensive background knowledge on the research topic and is often limited to siloed disciplines. Visual analytics, on the other hand, allows researchers to first explore already collected data, identify systematic patterns, and generate data-driven research hypotheses. This bottom-up approach is especially useful when dealing with large volumes of data and in situations requiring fast decision-making. For example, advanced analytics played a crucial role during recent coronavirus disease (COVID-19) pandemic, when rapid decisions were made in healthcare planning and treatment based on the evolving data on disease symptoms, treatment outcomes, vaccination coverage and available resources.

The overarching aim of this proposal is to develop a data science framework, encompassing advanced algorithmic approaches and visual analytics, to facilitate generation of research hypotheses for Long COVID. We hypothesize that implementation of a translational science framework using computational phenotyping and visual analytics will create a thought-provoking environment that will catalyze team science and advance evidence-based research and teaching at the University of Wisconsin-Madison (UW). Promoting translational science to enhance clinical research and improve human health is one the priority areas of the National Center for Advancing Translational Sciences (NCATS).1 In accordance with this, the UW Institute for Clinical and Translational Research (ICTR) over the past six months has assembled a cross-disciplinary translational research team (ICTR COVID Research Team), comprising of professionals with diverse backgrounds and expertise, to enhance the understanding of Long COVID and to maximize the efficiency of treatment efforts. This team includes practicing physicians, epidemiologists, informaticians, and data scientists with experience in Artificial Intelligence (AI) and Machine Learning (ML). With the team of experts in place, we are poised to apply data integration and visual analytics approaches for hypotheses generation, and advanced AI/ML approaches for computational phenotyping of Long COVID, to ensure accurate diagnosis and appropriate treatment of patients with this complex phenotype that would improve the health-related quality of their lives and lead to savings in healthcare costs.

Aim 1: Establish the COVID-19 Data Commons utilizing UW Health Electronic Health Records (EHR) and other related data.

Aim 2: Implement advanced computational phenotyping algorithms to identify Long COVID patients within the established COVID-19 Data Commons.

Aim 3: Organize data science dry lab studios to evaluate how advanced data visualizations can foster hypotheses generation across the translational science spectrum.

Assay development for mitochondrial K+ channel activity to test novel cardioprotective therapies

Mohun Ramratnam, MD – Associate Professor, SMPH, Department of Medicine

The burden of ischemic heart disease is inescapable for society as myocardial infarction and heart failure are common, costly and deadly. While mitochondrial K+ channels are potential therapeutic targets for patients afflicted with ischemic heart disease, no pharmacologic agents are available for clinical use. The modulation of ion channels that increase mitochondrial matrix K+ lead to mild mitochondrial swelling which promotes bioenergetic efficiency, mitochondrial signaling ROS and protection from myocardial ischemia-reperfusion (IR) injury. Currently, CCDC51 and ROMK2 are the leading mitochondrial K+ channel pore forming subunits in cardiomyocytes. While CCDC51 activation leads to cardio-protection, we have found that inhibition of ROMK2 leads to cardio-protection. This was unexpected and we hypothesize that conditions during myocardial ischemia promote K+ efflux through ROMK2. We have preliminary and published data showing that ROMK2 inhibition leads to mitochondrial uncoupling and swelling – features associated with increased $[K+]_{mito}$. However, current methodologic challenges impair the study of mitochondrial K+ handling and the development of specific therapies targeting CCDC51 or ROMK2. This is explained by a lack of a robust and reproducible cellular based assay to test therapies that modulate mitochondrial K+ channels. Currently, the field uses isolated mitochondria or lipid bilayer preparations to assess mitochondrial K+ channel activity. In addition, mitochondrial specific K+ sensitive reporter dyes are unavailable and nonspecific outputs such as mitochondrial swelling, uncoupling and ROS production are used. The lack of a robust cellular in vitro assay to study mitochondrial K+ channels will significantly delay the development of therapies targeting mitochondrial K+ channels for the treatment of ischemic heart disease.

Recent scientific discoveries make it possible to fill this methodological gap in knowledge. In 2016, investigators discovered a K+ binding protein in E.coli which was later fused with florescent probes to make a genetically encoded K+ sensor called GEPII. (Genetically Encoded Potassium Ion Indicators). We have acquired this genetically encoded FRET based K+ sensor with a mitochondrial targeting sequence. Our preliminary data in HEK293 cells show that GEPII targets mitochondria and displays an increased FRET signal. In collaboration with Timothy Kamp and Francisco Alvarado we plan to use the GEPII probe to image $[K+]_{mito}$ in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs).

Our long-term goal is to accelerate the development of therapies targeting mitochondrial K+ channels to treat ischemic heart disease. Our overall objective in this proposal is to identify the factors that regulate $[K+]_{mito}$ in cells using a novel genetically encoded FRET based K+ sensor. Our central hypothesis is that conditions that alter the function of CCDC51 and ROMK2 will lead to measurable changes in cardiomyocytes expressing the GEPII K+ sensor. This hypothesis was formulated largely from the recent development of the GEPII probe and our data showing targeting of GEPII to mitochondria as well as our preliminary data supporting ROMK2 as a mitochondrial K+ channel. The rational for this project is that the cultivation of a cell based in vitro reproducible assay to assess changes in $[K+]_{mito}$ will offer a strong foundation to test compounds targeting mitochondrial K+ channels prior to costly in vivo experiments. The following two specific aims are proposed.

1. Determine the effect of ROMK2 and CCDC51 overexpression on $[K+]_{mito}$.
2. Determine the conditions that lead to real time dynamic changes in $[K+]_{mito}$.