Select a Project from one of the Four Categories Below and Apply

I. Optical Coherence Tomography

Goal: Develop new techniques for interferometric sensing, imaging, and the integration of diagnostics with therapy via narrow diameter fibers, catheters, and endoscopes for biomedical applications.

Project 1: Novel optical coherence tomography devices and techniques.

(*Faculty Mentor: Prof. Brett Bouma, WCP)*

OCT provides high-resolution cross-sectional images of biological tissue. Commercial instruments are now widely available for research as well as clinical applications. There remains, however, a pressing need for advanced instrumentation including new laser sources, novel techniques for beam scanning in miniature probes, and methods that provide functional information in addition to structural imaging. In addition, machine learning is increasingly important tool for signal and image processing. Advances will draw from expertise in physics, mechanical engineering, electrical engineering, and computer science.

For further information regarding Dr. Bouma and his research interests please refer to: http://wellman.massgeneral.org/faculty-bouma-pi.htm and http://wellman.massgeneral.org/faculty-bouma-projects.htm

Project 2: Micromechanical mapping of cancer invasiveness

(*Faculty Mentor: Prof. Seemantini Nadkarni, WCP)*

The goal of this proposal is to develop a new tool that measures micromechanical properties and residual stresses in tumors. This innovation will enable comprehensive mechanical profiling of tumor biopsies for improved treatment planning, and for advancing research on tumor mechanobiology. The viscoelastic behavior of the extracellular matrix (ECM) is a powerful regulator of many oncogenic processes including proliferation, invasion, differentiation, and metastasis. Increased ECM stiffening or elasticity, primarily due to collagen deposition by fibroblasts, drives the malignant transformation of cells. Macrophage infiltration on the other hand degrades and liquidizes the ECM, resulting in viscous or 'liquid-like' stromal properties that aid cancer cells in metastasizing by squeezing through stromal boundaries. Thus, elastic, and viscous behaviors of the ECM co-exist and act

concurrently to drive malignant transformation and metastasis. As the tumor grows, residual stresses develop that compress lymphatic vessels, suppress favorable T-cell infiltration, aiding lymph node metastasis. Thus, the crosstalk between various mechanical factors and oncogenic signaling, drives malignant transformation, invasion and metastasis. Comprehensive profiling of the mechanical landscape of cancers is therefore a crucial need, directly addressed in this project. Our objective is to develop a new tool for micromechanical mapping of the tumor landscape to comprehensively interrogate critical mechanical markers that promote oncogenic signaling. This project is well suited for a postdoctoral fellow with expertise in optical instrumentation and machine learning approaches.

For further information regarding this research project please refer to: https://nadkarnilab.mgh.harvard.edu/laser-speckle-rheological-microscopy-shear/

Project 3: Development of integrated photonic optical coherence tomography light sources and systems.

(Faculty Mentor: Prof. Ben Vakoc, WCP)

We are working collaboratively with investigators at Harvard to pursue new implementations of OCT based on emerging integrated photonic platforms. This project is ideal for a post-doctoral fellow with a background in physics, applied physics, or electrical engineering and an interest in photonics and the development of next-generation coherent imaging systems.

For further information regarding Dr. Vakoc and his research interests please refer to: http://wellman.massgeneral.org/faculty-vakoc-pi.htm

Project 4: Early detection of cancer-related lymphedema.

(Faculty Mentor: Prof. Ben Vakoc, WCP)

Cancer-related lymphedema (CRL) is a chronic, progressive condition that affects millions of cancer survivors, particularly those who have undergone lymph node removal. Characterized by fluid buildup, tissue inflammation, fibrosis, and abnormal fat deposition, CRL leads to swelling, discomfort, impaired mobility, and increased risk of infection. This project will develop and evaluate a non-invasive OCT imaging tool to detect early signs of cancer-related lymphedema, helping cancer survivors receive preventative treatment sooner and improving their chances of avoiding the disease's long-term complications. This project is well-suited for a fellow interested in the early clinical translation of novel technology with expertise in optical imaging, bioengineering, and machine learning.

For further information regarding Dr. Vakoc and his research interests please refer to: http://wellman.massgeneral.org/faculty-vakoc-pi.htm

Project 5: Handheld ultrawide-field retinal OCT for pediatrics.

(Faculty Mentor: Prof. Ben Vakoc, WCP)

Retinal imaging in infants requires ultrahigh-speed systems and handheld microscopes. In this project, we will develop 10 MHz retinal OCT technology based on circular ranging and stretched-pulse mode-locked laser technology to bring rapid, ultrawide-field retinal imaging to pediatric screening of diseases such as retinopathy of prematurity and retinoblastoma. Fellows interested in contributing to the next generation of eye diagnostics with expertise in imaging instrumentation, laser technology, and/or clinical translation are encouraged to apply.

For further information regarding Dr. Vakoc and his research interests please refer to: http://wellman.massgeneral.org/faculty-vakoc-pi.htm

Project 6: Elastography to measure mechanical properties.

(*Faculty Mentor: Prof. S. H. Andy Yun, WCP)*

Changes in mechanical properties of tissues are linked to underlying structural and molecular changes. Optical coherence elastography (OCE) based on acoustic wave analysis has high potential for mapping the mechanical properties of tissues and bioengineering materials. The project will develop this technique for assessing various tissues and analyzing elastic properties at high resolution using finite element analysis and machine learning and apply the technique to analyze ocular tissues in vivo for ophthalmic applications.

For further information regarding Dr. Yun and his research interests please refer to: http://www.intelon.org

II. In Vivo Microscopy

Goal: Cellular and molecular imaging for more accurate and less invasive diagnosis of disease in living human patients and in animal models of human disease.

Project 1: Targeted intracoronary imaging for inflammatory activity.

(Faculty Mentor: Prof. Guillermo Tearney, WCP)

Our laboratory has pioneered multimodal intracoronary imaging technology, combining intravascular optical coherence tomography (OCT) with near-infrared autofluorescence (NIRAF) and near-infrared fluorescence (NIRF) detection. Recently, a multi-cathepsin protease molecular beacon called LUM015 has been developed and clinically approved for NIRF imaging of inflammation in human cancer in vivo. In this project, we aim to advance intracoronary NIRF-OCT imaging so that it can be optimally used with LUM015 to enable the assessment of coronary microstructure and inflammatory activity in living patients. This project will involve development of a clinical NIRF-OCT imaging system, novel multimodal imaging catheters and rotary junction interfaces, and advanced multichannel spectral detection and unmixing methods. This system will be validated in preclinical studies of atherosclerotic animal models and subsequently translated to clinical use. The capacity to evaluate active coronary inflammation at the individual patient level could enable more effective, personalized CAD management, potentially preventing many heart attacks from occurring.

For further information regarding Dr. Tearney and his research interests please refer to: http://www.tearneylab.org

Project 2: Transepithelial Voltage/Current Measurement

(Faculty Mentor: Prof. Guillermo Tearney, WCP)

Our lab has developed an OCT image-guided intraluminal transepithelial voltage/current measurement technology for real-time investigation of epithelial transport function in living patients. Studies have shown that conditions such as celiac disease, irritable bowel syndrome, type II diabetes, and epithelial malignancies lead to changes in the permeability of the accompanying epithelium that can be probed by the proposed voltage/current measurement techniques. In addition, genetic defects that impact ion transport across these epithelia such as cystic fibrosis, which affects the airway epithelium, can be diagnosed using this method. We have projects open to develop and clinically validate this image-guided physio-electrical measurement platform, with clinical applications in the gut and the airway.

For further information regarding Dr. Tearney and his research interests please refer to: http://www.tearneylab.org

Project 3: Dynamic micro-optical coherence tomography (μOCT) of tissues

(Faculty Mentor: Prof. Guillermo Tearney, WCP)

A high-resolution form of OCT, termed μOCT, is capable of visualizing sub-cellular microanatomy of a wide range of organs, tissues, and cells. Recently, we have introduced dynamic μOCT (dμOCT) that images metabolism-driven intracellular

motion within living tissues. By detecting differences in intracellular motion of different cells, dμOCT can be used to distinguish cell types, monitor metabolic status, and enhance image contrast. A variety of projects are open in the lab to advance dμOCT's capabilities with applications in label-free optical biopsy and longitudinal evaluation of chemotherapeutics for personalized cancer therapy.

For further information regarding Dr. Tearney and his research interests please refer to: http://www.tearneylab.org

Project 4: Counting blood cells without drawing blood.

(Faculty Mentor: Prof. Charles Lin, WCP)

The white blood cells (WBC) count is one of the most frequently ordered clinical laboratory tests and a key parameter for assessing the immune system. Standard WMC count requires taking blood samples that can be difficult in certain patient populations such as preterm infants. We are developing a method called i*n vivo* flow cytometry that enables noninvasive detection and quantification of WBCs as they circulate in the blood vessels. In a related project, we are imaging WBC function directly in humans by tracking their movement in response to injury and inflammation.

Project 5: Blood stem cells, blood cancer, and the bone marrow microenvironment.

(Faculty Mentor: Prof. Charles Lin, WCP)

All blood cells are made from hematopoietic stem cells in the bone marrow. Blood cancers such as leukemia and multiple myeloma also originate in the bone marrow. We are developing an optical platform that integrates multiphoton intravital microscopy with image-guided single cell sequencing (Image-seq) to enable spatial, temporal, and molecular analysis of the bone marrow.

Project 6: Direct channels connecting the skull bone marrow to the brain border

(Faculty Mentor: Prof. Charles Lin, WCP)

Except for the resident microglia, immune cells such as T cells, B cell and neutrophils are normally excluded from the healthy brain by the blood brain barrier. Instead, they are sequestered in the meninges, poised to mount an immune response when the brain is injured or infected. The newly-discovered skull channels

provide a direct route for the immune cells to traffic from the skull bone marrow to the meninges. We are developing methods to image these channels deep in the skull in order to study the communication between the hematopoietic system and the central nervous system.

For further information regarding Dr. Lin and his research interests please refer to: http://wellman.massgeneral.org/faculty-lin-pi.htm and http://wellman.massgeneral.org/faculty-lin-projects.htm

Project 7: Visualizing and Quantifying Dermal Pharmacokinetics and Pharmacodynamics

(Faculty Mentor: Prof. Conor Evans, WCP)

There are numerous challenges in the development of topical drugs, from identification of potential molecules, formulation of the active pharmaceutical ingredients, tracking drug transport, and determining therapeutic effect. While the pharmacokinetics (PK) of systemically- delivered agents can be traced via chromatographic assessment of blood samples, the targets for topical drugs are in the skin itself, requiring direct measurement of drug flux and flow. We have developed chemical imaging tools that make use of coherent Raman imaging to directly visualize and quantify the uptake of pharmaceuticals in skin. Combined with machine learning approaches, these imaging tools are now being applied to measure and map, on the cellular level in humans, PK and PD.

For further information regarding Dr. Evans and his research interests please refer to: http://scholar.harvard.edu/conorlevans

Project 8: Brillouin microscopy.

(*Faculty Mentor: Prof. S. H. Andy Yun, WCP)*

Brillouin microscopy uses Brillouin light scattering to probe the hydromechanical properties of tissues and cells. This project aims to improve the speed and sensitivity of this technique and explore various applications in basic sciences, bioengineering, and clinical medicine.

For further information regarding Dr. Yun and his research interests please refer to: http://www.intelon.org

Project 9: Cardiac intravital microscopy.

(*Faculty Mentor: Prof. Aaron Aguirre, WCP)*

Intravital microscopy can offer an unprecedented window into cellular pathophysiology of disease and has found widespread application in the neurosciences and in cancer biology. These techniques have been very difficult to apply in the cardiovascular field due to cardiac motion. Our laboratory has developed novel approaches for high-speed gated imaging of the heart and major blood vessels in small animal models. This project will develop new methods for two-photon microscopy and optical coherence tomography to study remodeling of the heart after myocardial infarction. Specifically, the research fellow will work with cardiologists and cardiovascular scientists to use advanced imaging to study alterations in the microvasculature of the heart after injury and to explore new therapies to promote recovery.

For further information about Dr. Aguirre and his research interests, please refer to: https://csb.mgh.harvard.edu/aaron_aguirre

III. Micro-Optical and Point-of-Care Devices

Goal: To develop micro-optical devices for point-of-care diagnosis and light-based therapy.

Project 1: Nano-lasers.

(Faculty Mentor: Prof. S. H. Andy Yun, WCP)

This project aims to develop ultra-small lasers with the size of bacteria and viruses. Progress has been made using inorganic and organic semiconductor materials as the gain media and plasmonic cavities.

For further information regarding Dr. Yun and his research interests please refer to: http://www.intelon.org

Project 2: Blood Coagulation sensing at the point-of-care.

(Faculty Mentor: Prof. Seemantini Nadkarni, WCP)

The goal of this project is to design, fabricate and translate a low-cost, multi-functional and portable blood coagulation sensor that can measure a patient's coagulation status within a few minutes using a drop of blood. This device addresses the critical unmet need to identify and manage patients with an elevated risk of life-threatening bleeding or thrombosis, the major cause of preventable death in hospitals. The coagulation sensing technology is based on a novel optical rheology

approach developed in our laboratory to quantify the mechanical properties of tissues with microscale resolution. This project is well suited for a post-doctoral fellow with entrepreneurial interests with expertise in optical instrumentation and/or microfluidic devices who is interested in working with a collaborative team of physicists, engineers and clinicians focused on the development and rapid translation of low-cost diagnostic technologies towards point of care use in patients.

For further information regarding this research project please refer to: https://nadkarnilab.mgh.harvard.edu/coagulation-and-platelet-sensing/

Project 3: Biodegradable photonics.

(Faculty Mentor: Prof. S. H. Andy Yun, WCP)

This project aims to develop novel optical devices made entirely of biocompatible and biodegradable polymers. Such implantable devices may be used in the body for diagnostic and therapeutic purposes and absorbed *in situ* over time without the need for invasive removal.

For further information regarding Dr. Yun and his research interests please refer to: http://www.intelon.org

Project 4: Application of laser particles to multi-dimensional single-cell analysis.

(Faculty Mentor: Prof. S. H. Andy Yun, WCP)

Biomolecular analyses to probe the genome, epigenome, transcriptome, and proteome of single-cells have led to identification of new cell types and discovery of novel targets for diagnosis and therapy. While these analyses are performed predominantly on dissociated single cells, emerging techniques seek understanding of cellular state, function and cell-cell interactions within the native tissue environment, by combining optical microscopy and single-cell molecular analyses. This project aims to develop novel multiplexed imaging probes, called laser particles, which allow individual cells to be tagged in tissue and analyzed subsequently using high-throughput, comprehensive single-cell techniques such as flow cytometry and single-cell sequencing

For further information regarding Dr. Yun and his research interests please refer to: http://www.intelon.org

Project 5: A portable optical device for diagnosis, monitoring, and treatment of bacterial infections

(Faculty Mentor: Prof. Mei X. Wu, WCP)

An all-in-one device will be fabricated to combat bacterial infections with high effectiveness when combined with a newly developed pro-photosensitizer. This innovative device will deliver both blue and red lights and incorporate sophisticated monitoring capabilities to track treatment efficiency and infection severity and facilitate seamless follow-up care—all from the comfort of one's home. By integrating a fluorescent amplifying and imaging system, the portable device allows for real-time visualization of bacterial activity, ensuring precise treatment delivery and ongoing assessment of therapeutic progress.

For further information regarding Dr. Wu and her research interests please refer to: http://wellman.massgeneral.org/faculty-wu-pi.htm and http://wellman.massgeneral.org/faculty-wu-projects.htm.

IV. Photodynamic Therapy (PDT)

Goal: To develop molecular mechanism and optical imaging-based combination treatment regimens in which the first treatment primes/sensitizes cancer cells for the second treatment.

Project 1: Development of bioengineered/patient derived 3D tumor models to design and evaluate PDT-based combinations.

(Faculty Mentor: Prof. Tayyaba Hasan, WCP)

In this project, postdoctoral fellows will gain foundational knowledge and hands-on experience relevant to culturing cancer cells in heterocellular 3D *in vitro* models that incorporate stromal cells and physical forces like flow. Patient-derived tumor organoids will also be evaluated as they mimic the tumor microenvironment more closely and may be beneficial in developing personalized treatment plans. Models established for assessing pancreatic cancer, oral cancer, brain tumors or ovarian cancer will be used to evaluate drug delivery strategies, employing rationally designed combination therapies and targeted multi-agent nanocarrier-based treatments. Following treatment, imaging techniques will be used to assess and characterize delivery, uptake, and tumor cell death. The results of these studies will contribute to biologically relevant cancer models and a platform for rapid image-based screening of therapeutic agents.

Project 2: Image-based quantification of molecular responses to cancer therapy.

(Faculty Mentor: Prof. Tayyaba Hasan, WCP)

This project involves online multi-molecular imaging to quantify cellular phenotypes in the pancreratic tumor microenvironment and analyze their spatio-temporal location during various modes of treatment in mouse cancer models. This will be enabled by a hyperspectral fluorescence microendoscope developed at the Hasan lab. Our goal is to determine the key time points of maximum effector immune cell infiltration in the tumor microenvironment and their spatial localizations in context of immunosuppressive cells and tumor cells. This information is expected to be key in determining post-treatment survival, tumor recurrence, and rationally design and optimize new combination treatments. Postdoctoral fellows will participate in molecular imaging using the hyperspectral fluorescence microendoscope, including GPU programming and video-rate image analysis in small animal models in addition to *ex vivo* histopathological validation. Substantial image analysis will be involved in the project. The anticipated outcome of these studies is a clear understanding of mechanisms that ensue after therapy administration and image guided treatments.

Project 3: Multi-inhibitor nanoconstructs for Cancer Therapeutics: addressing tumor heterogeneity, tumor microenvironment and drug resistance.

(Faculty Mentor: Prof. Tayyaba Hasan, WCP)

One of the major challenges to developing successful cancer therapies is drug resistance due to tumor heterogeneity. This project addresses the problem of resistance by the combined use of hyperspectral imaging and nanoconstructs. The poor diagnosis, early metastasis, limited drug accumulation in the tumor microenvironment, and acquired resistance to salvage chemotherapeutic cocktails lead to poor clinical outcomes. Therefore, the combination of various diagnostic and/or therapeutic approaches, targeting multiple mechanisms, has consequently become an attractive strategy for managing diseases. This scenario highlights the importance of understanding pharmacokinetics and determining optimal dosing sequence. In the context of combination therapy, the use of novel drug delivery systems combined with light as an external targeting tool offers distinct advantages including enhanced localized cytotoxicity, controlled drug release and modulation of the tumor microenvironment, and the use of one photon to image the cancer tissue by fluorescence approaches. The nanoconstructs are designed to interrupt several tumor cell growth pathways. These pathways may be intrinsic or may have evolved due to

extrinsic forces. The multi-inhibitor nanoconstructs will be developed to uniquely deliver multiple treatments including photosensitizers, chemotherapy agents, receptor tyrosine kinase inhibitor or imaging agents, with consideration of their mechanistic interactions. Hyperspectral imaging will allow for monitoring of the therapeutics delivery, reduction of normal tissue toxicity, and the specific cell population that is destroyed. Postdoctoral fellows will work collaboratively on the many aspects of this problem, contributing to the synthesis, physical characterization, and optimization of tumor-targeting, photo-activatable nanoconstructs that can co-deliver multiple inhibitors without pre-mixing the agents. The anticipated outcome of this study is technology development, fabricating multi-inhibitor agents and establishing their efficacy *in-vitro* and *in-vivo*.

Project 4: Dual function theranostic constructs for photoacoustic guided surgery and photodynamic therapy. (a Global Health-Related Project)

(Faculty Mentor: Prof. Tayyaba Hasan, WCP)

Survival rates in patients with oral cavity tumors (e.g., tongue cancers) have remained nearly stagnant in the past decade with exceptional morbidity. The goal of this project is to develop, for the first time, a single theranostic agent namely targeted Dual Function Antibody Conjugate (DFAC) enabling deep tissue photoacoustic imaging (PAI) with targeted photodynamic therapy (PDT), and an integrated PAI-ultrasound imaging (US) module for surgery guidance such that the two main barriers to oral cancer treatment outcomes are overcome.

We postulate that DFAC-enabled fluorescence and deep-tissue PAI-guided surgery and intraoperative PDT of residual disease will achieve local tumor control. This is a project requiring multiple skills and the postdoctoral fellow will work on aspects that are most aligned with training and interests. For example, chemistry/biology training will involve synthesizing DFACs, in vitro testing and *in vivo* evaluation on pre-clinical oral cancer models. If imaging and image analysis are strengths, the work will be more focused on analyzing fluorescence and PA images to determine tumor specificity that could assist in delineating tumor margins for resection surgeries. The modular design of DFAC and integrated PAI-US enables adaptation of the platform to other cancers. Fellows will be provided exposure to chemistry/biology training during synthesis of DFACs, *in vitro* testing (imaging and therapy on tumor phantoms), and *in vivo* testing (on small animal models of oral cancer).

Project 5: Early prediction of sepsis based on biomarkers of bacterial metabolism using optical methods.

(Faculty Mentor: Prof. Tayyaba Hasan, WCP)

Sepsis, a life-threatening condition primarily induced by pathogenic bacteria, poses a severe threat to individuals. In sepsis, bacteria originating from a localized infection traverse the bloodstream, resulting in a cascade effect that progresses to severe sepsis or septic shock, often culminating in multiple organ dysfunctions and, ultimately, patient mortality. Timely detection of sepsis plays a pivotal role in controlling and managing cases within hospital settings. Delays in initiating antibiotic treatment have been unequivocally linked to increased mortality rates, with a 7.6% rise in death observed for patients with severe sepsis and septic shock for every hour of delayed antibiotic administration. Despite this urgency, a rapid and robust sepsis diagnostic methodology remains elusive.

Building upon our preliminary observation that fluorescent markers can detect bacterial metabolism in human whole blood during the initial stages ($\leq$2 hours) of infections, this project proposes the development of a swift, early sepsis prediction platform using optical methods based on bacterial metabolism. The project encompasses the following key objectives: i) Establishing an optical platform for in vitro early sepsis prediction utilizing fluorescent biomarkers of bacterial metabolism; ii) Validating the performance of the early sepsis prediction platform in a murine model; iii) Demonstrating the *in vivo* efficacy of sepsis treatment guided by the early sepsis prediction platform. This initiative holds the promise of revolutionizing sepsis diagnosis and treatment, offering a timely and precise approach to mitigate the devastating impact of this critical medical condition. Fellows will be provided with an opportunity to learn and perform sepsis modeling, bacterial infection diagnosis, and fluorescent biomarker imaging.

Project 6: Combating Antibiotic Resistance with Photoactivatable Multi-inhibitory Liposomes.

(Faculty Mentor: Prof. Tayyaba Hasan, WCP)

Bacterial infections, often originating in localized areas such as wounds, traditionally find their primary recourse in antibiotics. Yet, the pervasive overuse and misuse of these antibiotics have spawned a disconcerting predicament known as antimicrobial resistance (AR), rendering these drugs increasingly impotent against bacterial

infections. The ramifications of AR are alarming, resulting in a minimum of 35,000 deaths annually and imposing a financial burden ranging from $55 to $70 billion in the United States alone. Left unaddressed, this menace could escalate to a staggering 10 million deaths per year by 2050, a statistic on par with global cancer fatalities. Hence, it becomes imperative to pioneer a novel therapeutic approach capable of effectively neutralizing or weakening the predominant bacterial AR mechanisms.

Excitingly, research conducted by our team and other pioneers has revealed the potential of photodynamic therapy (PDT) as an effective, non-traditional modality for treating local infections. PDT involves the activation of photosensitizers by specific light wavelengths, generating reactive molecular species that effectively disrupt a broad spectrum of major bacterial AR mechanisms. Building upon this promising foundation, our project sets out to create a revolutionary treatment platform known as the photoactivatable multi-inhibitor liposome (PMIL). This innovative approach aims to address the global crisis of AR, offering a transformative tool that, upon successful completion, could revolutionize clinical practices. Fellows will be provided with an opportunity to learn and perform AR evaluation, PDT, and liposome synthesis and characterization.

Project 7: Flexible, wearable QLED system to enhance antibiotic treatment efficacy in wound infections with aPDT

(Faculty Mentor: Prof. Tayyaba Hasan, WCP)

The escalating prevalence and misuse of antibiotics have propelled the rise of Multidrug-Resistant (MDR) bacteria to a critical juncture, posing a severe threat to our well-being and imposing substantial economic burdens on society. Urgently addressing this crisis, there is a compelling need for an alternative or adjunctive therapy capable of directly targeting MDR bacteria and overcoming their resistance mechanisms, thereby enhancing treatment efficacy.

In response to this imperative, Photodynamic Therapy (PDT) has emerged as a promising strategy for both preventing colonization of wounds by MDR bacteria and treating established MDR bacterial infections.. PDT involves the activation of drug molecules known as photosensitizers (PS) by light at a specific wavelength in the presence of oxygen. This activation leads to the generation of reactive molecular species (RMS). The unique multitargeted nature of RMS enables PDT to deactivate bacterial strains irrespective of their MDR levels and mechanisms. Importantly, PDT carries a lower risk of inducing MDR compared to conventional antibiotics.

Despite its potential, the clinical translation of antimicrobial PDT (aPDT) for wound infection management faces challenges, primarily due to limitations in existing medical light source systems, typically based on lasers or Light Emitting Diodes (LEDs). Both lasers and LEDs, being inherently hot and featuring rigid, point-specific light sources, present obstacles to widespread application.

This project aims to address these challenges through the implementation of our innovative Quantum Dot Light Emitting Diode (QLED) technology-based system. QLED technology represents a distinctive evolution, akin to a "special OLED," where organic emitters are replaced by colloidal quantum dots (QDs). This approach combines the flexible form factor of OLEDs with the unique optical properties of QDs, providing an ideal platform for a less painful, low-irradiance (LI) aPDT. Postdoctoral fellows will work on prototyping and packaging a wearable QLED system, developing optimized QLED protocols to combat MDR wound infections, and validating its efficacy using an in vivo animal model.

Project 8: Modulation and real time monitoring of immune responses induced by photodynamic therapy.

(Faculty Mentor: Prof. Tayyaba Hasan, WCP)

Immunotherapy using immune checkpoint blocking antibodies such as PD-1/PD-L1 has produced impressive results in a wide range of cancers. However, the response remains heterogeneous among patients. This is also attributed to lack of robust methods to stratify patients into responders/non-responders and identify treatment outcomes in real-time that help to distinguish success or failure of a therapeutic approach during the course of treatment. The primary focus of this project is to evaluate immune responses (both systemic and local) in pre-clinical pancreatic cancer models, post-photodynamic therapy, and develop strategies to enhance response of immune checkpoint inhibitors in pancreatic cancers. Photodynamic therapy (PDT) is a photochemistry-based treatment modality involving the administration of a photosensitizer (PS) followed by light activation and is being clinically evaluated in pancreatic cancers. Fellows will be provided with an opportunity to learn and perform experiments using orthotopic/sub-cutaneous syngeneic mouse models and evaluate immune responses through flow cytometry and immunofluorescence.

The project also involves *ex vivo* culturing tumor tissues, as organoids or in heterocellular 3D *in vitro* models, to integrate stromal cells, extracellular matrix and the complex immune microenvironment. These models will be established for studying complex biological responses, as observed in pancreatic cancers, and

evaluate drug delivery strategies employing rationally designed combination treatments, including photodynamic therapy, immunotherapy, chemotherapy, etc using multi-agent nanocarrier-based treatments. The outcome of these studies will assist in developing biologically relevant models and a platform for rapid screening of therapeutic agents. Fellows will be provided with an opportunity to learn and perform immune organoid cultures along with developing nanoplatforms for co-delivery of multiple therapeutic agents.

Project 9: Development and evaluation of an integrated imaging and treatment device for image-guided photodynamic therapy of oral cancer. (a Global Health-Related Project)

(Faculty Mentor: Prof. Tayyaba Hasan, WCP)

Of the 300,000 to 700,000 new cases of oral cancer that occur globally each year, about two thirds are in low to middle-income countries (LMICs). The detrimental effects of this public health crisis are exacerbated by lack of medical infrastructure, especially in rural areas. Even when early cancer or high-grade dysplasia (HGD) and oral potentially malignant lesions (OPML) are detected, insufficient access to clinical centers providing surgical oncology or radiation therapy will ultimately often lead to disease progression and death. Photodynamic therapy (PDT), a photochemistry-based treatment modality involves the administration of a photosensitizer (PS) and light activation, has previously demonstrated promise for oral malignancy, though a lack of robust affordable technology has limited broader adoption.

To address this, we developed a low-cost, portable platform for ergonomic intraoral PDT for use with 5-aminolevulinic acid (ALA)-photosensitization. The current NCI funded project is aimed at developing low-cost technology (developed at University of Arizona), for imaging and treatment of oral cancers in low resource settings. The integrated "Screen, Image and Treat Optical System" (SITOS) will utilize an FDA approved pro-drug (5-ALA) that is preferentially converted into a fluorophore/photosensitizer, Protoporphyrin-IX (PpIX) in malignant cells. The integrated platform enables the use of the same hardware for initial imaging, and a single theranostic molecule for image-guided PDT and online monitoring during therapy. Fellows will be provided with an opportunity to learn and perform experiments involving preliminarily validation of the device on optical phantoms, *in vitro* 3D tumor models and orthotopic/sub-cutaneous mouse syngeneic models

Project 10: Superhydrophobic Dressing for Singlet Oxygen Delivery in Antimicrobial Photodynamic Therapy against Multidrug-resistant Bacteria.

(Faculty Mentor: Prof. Tayyaba Hasan, WCP)

The rise of antimicrobial resistance poses a critical public health threat worldwide, creating the urgent need for the development of innovative therapeutic strategies. Antimicrobial photodynamic therapy (aPDT) has proven effective against multidrug-resistant bacteria pathogens due to its ability to generate cytotoxic reactive oxygen species (ROS), particularly singlet oxygen (^1O_2). However, challenges in delivering the photosensitizer (PS) to the targeted site can limit its efficacy. Superhydrophobic (SH) antimicrobial photodynamic therapy (SH-aPDT) is an attractive new technology that isolates the PS into a superhydrophobic membrane, thus producing airborne singlet oxygen for aPDT. In SH-aPDT, singlet oxygen is delivered as the reactive species via the gas-phase to the wound surface. Airborne $^1O_2$ diffuses as a gaseous species ~1 mm without the PS contacting the tissue. This unique ‘‘contact-free’’ technique improves aPDT efficiency, hence addressing the current limitations. This makes SH ideal candidates for aPDT, hence providing a tremendous opportunity for a wide range of applications, including the treatment of infected wounds.

Postdoctoral fellows working in this area will have the opportunity to contribute to the advancement of SH-aPDT by designing and conducting original research projects. Possible areas of investigation may include:

- **Mechanistic studies** to characterize ^1O_2 diffusion, ROS, and bactericidal mechanisms in various biological environments.
- **Preclinical evaluation** of SH-aPDT efficacy using in vitro and in vivo models of infected wounds, including multidrug-resistant bacterial strains.
- **Development of integrated delivery devices or wound dressings** incorporating SH-aPDT technology for clinical translation.
- **Exploration of combinatory therapies**, such as SH-aPDT with antibiotics or immune modulators, to overcome severe or chronic infections.

Project 11: Versatile Platform for Diverse Antibody–BPD Photoimmunoconjugates in Cancer Phototherapy

(Faculty Mentor: Prof. Tayyaba Hasan, WCP)

A major barrier to the clinical translation of photoimmunoconjugates (PICs) is the poor aqueous solubility and stability of many photosensitizers (PSs), which limits conjugation efficiency, reproducibility, and biocompatibility. Previous studies have explored the synthesis of PICs by conjugating benzoporphyrin derivative (BPD), a hydrophobic PS, to cetuximab, an anti-EGFR antibody, for targeted photodynamic therapy. However, these approaches have required up to 40–50% DMSO during the conjugation reaction, raising compatibility concerns with sensitive biomolecules and antibodies are PEGylated before PS conjugation to avoid

aggregation. Even after synthesis, formulations often retained ~5% DMSO for stability, and multi-step protocols involving centrifugation, spin columns, and Amicon filters made the process labor-intensive, difficult to scale, and prone to product loss. Furthermore, antibody selection has been limited mainly to cetuximab, without exploring broader receptor targets, and no quantitative assessment of PEGylation has been routinely performed to ensure optimal pharmacokinetics.

In this project, we address these limitations by designing and synthesizing a **modified benzoporphyrin derivative (mBPD)** with improved water solubility, chemical stability, and conjugation efficiency. The enhanced physicochemical profile of mBPD allows direct PIC synthesis under fully aqueous conditions, eliminating the need for high organic cosolvent concentrations, thus improving biomolecule compatibility and reducing purification complexity. Our optimized protocol achieves high conjugation yields in a single streamlined step, while enabling precise PEG quantification to fine-tune in vivo pharmacokinetics.

This platform provides flexibility in antibody choice, allowing the development of mBPD–antibody conjugates against a range of clinically relevant tumor markers, thereby expanding therapeutic reach beyond anti-EGFR targeting. The resulting PICs are designed for superior tumor selectivity, minimal normal tissue toxicity, and enhanced therapeutic efficacy through the combination of light-activated cytotoxicity and antibody-mediated targeting.

The anticipated outcome of this study is the establishment of a scalable, biocompatible, and versatile PIC synthesis platform that overcomes key chemical and formulation barriers. This will pave the way for preclinical evaluation of mBPD-based PICs across multiple tumor models, supporting their future translation into multimodal cancer treatment regimens.

For further information regarding Dr. Hasan and her research interests please refer to: http://wellman.massgeneral.org/faculty-hasan-pi.htm and http://wellman.massgeneral.org/faculty-hasan-projects.htm