OREGON CLINICAL & TRANSLATIONAL RESEARCH INSTITUTE

Biomedical Innovation Program Awardees

The Biomedical Innovation Program (BIP) accelerates the delivery of healthcare technologies from academia to the marketplace, thereby, improving human health. Three tracks of funding are available: Device, Diagnostic, & Software development; Drug Discovery; and Digital Health. This funding mechanism is offered in close collaboration with OHSU Technology Transfer and the Office of Collaborations & Entrepreneurship, and is open to all OHSU faculty and eligible employees.

2024 – DRUG DISCOVERY

Daniel Streblow, Ph.D., Professor of Vaccine & Gene Therapy Institute; Division of Pathology & Immunology, Oregon National Primate Research Center (ONPRC)

Novel Therapeutics Targeting Human Cytomegalovirus

The goal of this project is the identification of novel small molecules capable of inhibiting replication of Human cytomegalovirus (HCMV), a β-herpesvirus that infects a large portion of the population. HCMV is the most common congenital viral infection and the virus remains a significant cause of morbidity and mortality in transplant recipients. To date no FDA approved vaccine exists against HCMV and treatment for reactivation and disease is limited to antivirals such as Valganciclovir that have potent toxic side effects including myelosuppression. Resistance to these antivirals occurs specifically in transplant patients with high viral burden. Therefore, we propose to use our new reporter HCMV replication cell-based assay to perform an high through put screen to identify novel small molecules to prevent HCMV infection and disease.

CONTACT BIP

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Dr. Sanjay V. Malhotra, Ph.D., FRSC, Professor & Endowed Chair In Cancer Research, Department of Cell Development & Cancer Biology, Director, Center for Experimental Therapeutics, Knight Cancer Institute

Non-allosteric inhibition of PIM1 to reduce treatment resistance in triple negative breast cancer

Triple-negative breast cancer (TNBC) is the deadliest form of breast cancer. TNBC growth is particularly aggressive and invasive, which often leads to treatment resistance (TXRES), and, as a result, the cancer becomes terminal. Therefore, interventions to increase sensitivity to chemotherapies and prevent TXRES are desperately needed in the clinic. Such an intervention would restore treatment sensitivity, increase remission rates, and revolutionize patient care. To combat TXRES, one target is PIM1, a pro-oncogenic serine/threonine-protein kinase involved in tumor growth and the development of TXRES. PIM1 has a well-established role in several cancers, including TNBC, where PIM1 upregulation is associated with TXRES. Prior attempts to inhibit PIM1 have targeted the active center (ATPase binding cleft) to render it catalytically inactive. These inhibitors have faced two significant challenges-low efficacy and high toxicity. Thus, to overcome these challenges, we synthesized a non-allosteric PIM1 inhibitor, which does not affect kinase function but does induce PIM1 degradation. In vivo, our PIM1 inhibitor reduces TNBC tumor growth kinetics, and, by one measure, is not toxic. To move our inhibitor to the next phase of development, we must determine its specificity, toxicity, and pharmacokinetics. With this information, we will move forward with a highly promising clinical compound and potential solution to the lack of interventions that can limit TXRES in TNBC.

Rebecca Spain, M.D., MSPH, Associate Professor of Neurology, School of Medicine

Optimizing lipoic acid drug delivery using novel molecular derivatives for maximal neuroprotective treatment of progressive multiple sclerosis

Half the million people in the United States with multiple sclerosis (MS), a debilitating, life-long, neuroinflammatory disease affecting the brain, spinal cord, and optic nerves have a progressive form. Progressive MS causes gradual and inexorable neurological decline in strength, sensation, balance, mobility, cognition, bladder and bowel control, energy, and mood. Current FDA-approved MS therapies that cost upwards of $90,000/year do little to halt MS progression once begun. Drs. Chaudhary and Spain are the leading published experts in, respectively, pre-clinical and clinical trial data supporting the safe and well-tolerated supplement lipoic acid (LA) as treatment for progressive MS. LA is thought to counteract neurodegenerative pathologies predominating in progressive MS through anti-inflammatory and antioxidant mechanisms. Dr. Spain's phase 2 clinical trials demonstrate brain atrophy reductions, supporting LA as neuroprotective. For the BIP award, we have selected 4 derivatives of LA, which we will redesign to maximize the drug-like properties of each. Our approach to treating progressive MS is unique among pharmaceutical and investigator-initiated competition, and the market opportunity for a progressive MS therapy is currently without viable competition.

2024 – DEVICE, DIAGNOSTIC, & SOFTWARE

Stephen Kurtz, PhD., Research Associate Professor, Knight Cancer Institute

A Rapid Test to Identify Responsiveness to Acute Myeloid Leukemia (AML) Therapy

The combination of azacitidine and venetoclax (Aza + Ven) is standard-of-care therapy for newly diagnosed patients with AML who are elderly or too frail for intensive chemotherapy. Approximately 70% of these patients respond to Aza+Ven and they have a distinct ('primitive') tumor phenotype whereas those who are resistant or relapse following Aza+Ven often have 'differentiated' tumors. For patients who are non-responsive to Aza+Ven, there are alternative treatments. AML tumor differentiation status can be determined by RNA sequencing technology, and this provides impetus for obtaining these data to guide treatment selection. However, the laborious nature of RNA-sequencing and the analytical time required impedes its capacity to support treatment decisions, prompting our development of Myelo-ID, rapid gene expression assay to classify tumors and provide timely results to inform treatment.

Yifan Jian, PhD., Associate Professor

A Ultrawide field of view low-cost retina imaging for screening retinopathy of prematurity

Retinopathy of prematurity (ROP) is a pervasive issue, leading to significant cases of childhood blindness globally due to delayed or inadequate diagnoses. Conventional retinal imaging devices, though effective, are marred by their exorbitant costs and limited field of view, especially in resource-constrained settings. Our research group introduces an innovative, cost-effective scanning laser ophthalmoscope (SLO) system, engineered to overcome these limitations and facilitate widespread, efficient ROP screening. The prototype, priced under $10,000, offers an ultra-wide field of view, enhanced contrast imaging, and employs near-infrared light for non-stressful, non-mydriatic exams, ensuring patient comfort and safety. Our device targets neonatal intensive care units globally, addressing a market need estimated at $500 million worldwide. It stands distinct in its affordability, efficiency, and patient safety, compared to current ophthalmoscopes and retinal cameras used in ROP screening. Preliminary data underscores our expertise in ROP research, with a near 100% success rate in eye examinations using handheld optical coherence tomography (OCT). Our SLO system prototype has demonstrated efficacy in retinal imaging and is poised for tests in the OHSU NICU for ROP screening. This innovative device promises not just substantial healthcare savings but, most critically, a significant reduction in the incidence of irreversible vision loss among newborns globally, marking a milestone in preventative healthcare and childhood blindness mitigation.

2023 – DRUG DISCOVERY

Robert Eil, M.D., Assistant Professor, Division of Surgical Oncology, Cell, Developmental & Cancer Biology

Alexandra Bartlett, Ph.D., Postdoctoral Scholar, Eil Lab

Safe application of CAR-T cells for the treatment of solid cancer

Traditional cancer treatments such as chemotherapy or radiation clear disease in less than 1% of patients; instead, the most promising new treatments for advanced cancer leverage the immune system to recognize and destroy the cancer. One kind of immune-based therapy, CAR T cell therapy, uses genetic engineering to instruct a patient's own immune cells to attack their cancer. CAR T cell therapy has been wildly successful in blood cancers with complete destruction of advanced cancer in 40-78% of patients. However, this success has not translated to cancers growing in solid organs (e.g. liver) due to safety. Patients with cancer in their liver have very poor survival rates; thus, it is imperative that new, bold strategies are developed for advanced cancer in the liver. Previous efforts to use CAR T cells to treat solid cancers have failed to balance effectiveness with safety for surrounding healthy tissues. In this project, we modify existing CAR T cell technology to build a safer, more effective CAR T cell to treat cancers that have spread to the liver. Our approach would be readily translated to the clinic for treatment of patients with cancer in their liver. Furthermore, this approach would create a template that could be applied other solid cancers.

2023 – DEVICE, DIAGNOSTIC, & SOFTWARE

Albert Chi, M.D., Associate Professor of Surgery, Division of Trauma, Critical Care and Acute Care Surgery, School of Medicine

Xiao-Yue Han, MD, General Surgery Resident

Advanced Imaging for Diagnostics: Deep Learning in Surgery

Accurate early diagnosis of surgical disease improves outcomes and improves healthcare efficiency. Unfortunately, many patients present to the hospital or clinic with symptoms concerning for multiple diseases where the diagnostic uncertainty is only resolvable in the operating room due to inadequate non-operative diagnostic tools. Necrotizing fasciitis is one such life-threatening disease difficult to distinguish from severe soft tissue infections without operative evaluation. We are developing an advanced imaging system to serve as a non-operative tool for making this distinction, saving patients from the OR that don't need it while preserving critically deficient OR capacity for those that do. In addition, we also believe that the system can offer diagnostic utility in other surgical (and medical) conditions where diagnostic uncertainty or inaccurate screening persist. We have designed a relatively inexpensive bedside imaging platform for advanced diagnostics in surgical patients with hardware that enables reproducible measurements. BIP funds will be a catalyst in building a proof-of-concept platform and producing preliminary data. This will be fundamental for secure follow-on funding, nurture emerging commercial partnerships, and bring the imaging system to the point-of-care.

David Huang, M.D., Ph.D., Peterson Professor of Ophthalmology, Professor of Biomedical Engineering

Novel Riboflavin and Oxygen Delivery Methods for Transepithelial Corneal Collagen Crosslinking

Corneal collagen crosslinking (CXL) halts the progression of keratoconus by creating covalent bonds between collagen fibers strengthen the stroma. The photochemical reaction occurs by activating riboflavin under UV light in the presence of oxygen. The standard CXL procedure requires epithelium removal (epi-off) so that riboflavin, oxygen, and UV can easily enter the corneal stroma. The epi-off CXL procedure is highly effective, but delayed epithelial healing is common, raising the risk of corneal haze and infections. Alternative transepithelial CXL procedures that preserve epithelial integrity have been tried, but have been shown to be less effective in corneal strengthening. We have developed an advanced transepithelial CXL technology (Casey CXL) that has the potential to yield better cross-linking results and reduce negative outcomes. A computational finite element model of the reaction kinetics showed it produces stronger CXL compared to standard epi-off CXL. We propose to validate the advantages of Casey CXL. The aims include 1. optimizing the Casey CXL system. 2. Using optical coherence tomographic elastography to measure cornea stiffness before and after experimental CXL in ex vivo rabbit corneas. The experiments will test the hypothesis that Casey transepithelial CXL can stiffen the cornea more than standard epi-off CXL. These experiments would validate the Casey CXL protocol to help prepare for clinical trials in human patients.

2022 – DRUG DISCOVERY

Dr. Sanjay V. Malhotra, Ph.D., FRSC, Professor & Endowed Chair in Cancer Research, Department of Cell Development & Cancer Biology, Director, Center for Experimental Therapeutics, Knight Cancer Institute

Developing a novel drug to combat triple negative breast cancer progression through metabolic modulationYBX1 inhibitors

Triple-negative breast cancer (TNBC) is one of the aggressive forms of breast cancer and frequently relapses and metastases. Currently, very few options are available for TNBC treatment. Cancer cells exploit glycolytic machinery for the Warburg effect and aerobic glycolysis. Enolase 1 (ENO1) is the glycolytic enzyme expressed in the majority of tissues and many cancer cells have higher expression of this enzyme. Apart from the glycolytic role in the cytosol, ENO1 also plays different roles in cancer cells including function as a surface receptor. Our systematic studies in various TNBC models have led to discovery of a small molecule (CET12) that strongly binds to ENO1, restrain its activity and subcellular localization. CET12 treatment arrests the TNBC cells in the mitotic phase and leads the apoptotic cell death via AMPK activation. Global proteome profiling suggested that CET12 pushes the cells toward oxidative phosphorylation. It also inhibits cell migration and invasion in vitro. In vivo studies in 4T1 and EMT6 syngeneic mouse models, and a Patient-Derived xenograft model showed that CET212 treatment inhibits tumor progression and metastasis. This was further supported by studies in lung metastasis and intra cardiac injection mouse model. These extensive studies provide strong merit for further development of CET12 for the treatment of TNBC. Support by the BIP program will be crucial in successful completion of the proposed work to attract additional funding for IND enabling studies and move CET12 toward clinical trials.

Dr. Jonathan Pruneda, Dr. Ruth Napier, Dr. Sanjay Malhotra

Small molecule restoration of UBA5 to treat early-onset neurodegenerative disease

Compound heterozygous loss-of-function mutations in the gene UBA5 lead to a rare and debilitating neurodegenerative disease called "UBA5." Within 0-2 years of life, children with UBA5 disease suffer from early-onset epileptic encephalopathy that leads to hypotonia, spasticity, epilepsy, microcephaly, and often death. UBA5 translational research is urgently needed, as there are currently no treatment options for children with UBA5 disease. We have assembled a multidisciplinary team of OHSU researchers that bring the expertise, innovation, and commitment necessary to address this dilemma. We have developed a novel high throughput assay capable of measuring UBA5 enzymatic activity. With this assay, we will screen 43,000 bioactive compounds to identify small molecules that correct the activity (i.e., restore enzymatic function) of mutated UBA5 variants. Compounds identified from this screen that are capable of rescuing UBA5 variants will be validated in orthogonal assays, including cell-based assays using patient-derived fibroblasts. UBA5-activating compounds will be further optimized and characterized for therapeutic potential. As heterozygous carriers of single UBA5 mutations exhibit no disease symptoms, we are hopeful that even modest activity correction of one UBA5 variant will dramatically improve the quality of life for children with UBA5 disease, as well as their families. With funding from the Biomedical Innovation Program, we are poised to make a significant impact in understanding and treating UBA5 disease.

Yali Jia, Ph.D., FAIMBE, Associate Professor of Ophthalmology & Biomedical Engineering, Jennie P. Weeks Professor of Ophthalmology, Associate Director of Center for Ophthalmic Optics & Lasers, Casey Eye Institute

COOL-ART-DR, a Comprehensive Diabetic Retinopathy Reading Platform Based on Optical Coherence Tomography

Angiography Diabetic retinopathy (DR) is already the leading cause of blindness in working age adults in the US, and the prevalence of diabetes is rising. Innovative DR screening models are urgently needed to efficiently and accurately identify patients with clinically significant disease without overstressing the eye healthcare system. With the invention of clinical OCT angiography (OCTA) by our group, it is now possible to provide precise, noninvasive, and three-dimensional vascular pathologies in DR. One OCTA based biomarker, non-perfusion area (NPA), has been shown to correlate with DR staging based on the standard but tedious ETDRS protocol. This raises the possibility that OCTA could be applied for primary DR screening in clinical or research settings. However, a reliable software platform for reading NPA (grading DR) on OCTA scans is unavailable in both the clinic and in the clinical research setting. Therefore, using our extensive knowledge of OCTA signal and image generation, we propose to evaluate, validate, and optimize a deep-learning-based NPA detection algorithm and integrate this algorithm into a novel reading platform, COOL-ART-DR. With these aims achieved, we can license COOL-ART-DR to OCT companies as a software tool equipped in OCTA devices used in clinics, and expand its use at OHSU to read OCTA data for the benefit of clinical trials and sponsors.

Gregory Landry, M.D., Professor and Chief of Vascular Surgery, Department of Surgery, OHSU School of Medicine

Smart Socket: A Novel and Dynamic Microprocessor-controlled Pneumatic Socket that Optimizes Prosthetic Fit via a Smartphone Application

Over 185,000 Americans suffer limb loss each year, with numbers felt to be increasing due to the proliferation of diabetes and peripheral arterial disease. Current prostheses are significantly limited by poor socket fit, as current sockets are not equipped to accommodate changes in residual limb size and shape that occur daily and over the course of the patients' lifetime. At the 2020 OHSU Invent-a-thon, we developed the concept of Smart Socket. The Smart Socket system consists of a matrix of bladders, at the interface between the hard socket and residual limb, that automatically inflate and deflate in response to changes in heat and pressure. Manual control is available via a simple smartphone application. In future iterations, machine learning will be leveraged to optimize fit throughout the day on the fluctuating limb. Thus far, we have developed an initial prototype. With BIP funding we plan to refine our initial prototype to incorporate a more refined and adaptable series of air bladders, the smart phone app, and we will begin to introduce artificial intelligence to learn and adapt to individual gait patterns. We have also developed a comprehensive survey that will be distributed to patients and prosthetists. With our refined prototype, we plan to apply for additional funding as well as to work with prosthetics manufacturers to initiate clinical trials of this technology. Our team is uniquely qualified to develop this technology, consisting of a physician, engineer, and prosthetist whose combined knowledge can take this concept from bench to bedside.

Martin Pike, Ph.D., Associate Professor, Advanced Imaging Research Center

Development of Activity MRI (aMRI): Direct Comparison to PET

Options for metabolic activity [MA] imaging are limited. PET imaging is expensive, has relatively poor resolution, is sparsely available compared to MRI, and requires radioactive tracers. We propose a novel MRI-based MA imaging approach, Activity MRI (aMRI), which has advantages over PET: improved resolution, lower cost, wider availability, non-invasiveness, and potentially higher sensitivity that could provide early and accurate inferences on the effectiveness of the patient's cancer treatment regimen. A large component of trans-membrane water transport is MA driven. This active water cycling is coupled to Na+/K+ ATPase [NKA] activity, the vital enzyme which maintains the trans-membrane Na+ and K+ concentration gradients, which drive most active cellular trans-membrane ion and metabolite transport. The NKA thus utilizes a large proportion of cellular energy consumption. Many of these coupled transport processes actively transport large stoichiometries of water. We have shown that diffusion MRI (DWI) is sensitive to trans-membrane water transport and have developed a novel DWI approach which quantifies this, providing estimates of kio, the cellular H2O efflux rate constant. Because kio is coupled to NKA activity, it constitutes a key metabolic indicator. Furthermore, our approach quantifies cell volume (V), and cell density (ρ), important diagnostic cytometric parameters. This also enables quantification of the kio*V product, which normalizes V dependence, providing the cellular NKA metabolic rate [cMRNKA]. We propose to map kio and kio*V in rat and human brain (healthy and diseased), and compare these to PET images from the same subjects, hence validating our approach via comparison with an accepted MA imaging modality. We hypothesize aMRI will be a valuable tool for the detecting and monitoring of numerous disease processes, including cancer.

Dr. Nabil Alkayed, M.D., Ph.D., Professor of Anesthesiology and Perioperative Medicine; Director of Research, Knight Cardiovascular Institute

A Novel Therapeutic Target in Subarachnoid Hemorrhage (SAH)

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating form of stroke with high morbidity and mortality and few therapeutic options. Past research has focused on alleviating large-vessel vasospasm, thought to be responsible for delayed cerebral ischemia (DCI), which can lead to new strokes, worse functional outcome and death. However, drugs that effectively reduced angiographic vasospasm failed to improve clinical outcome. This led to a shift in focus from DCI to early brain injury (EBI; edema and inflammation) and from large-vessel vasospasm to microvascular vasospasm. We have identified a novel receptor that mediates the biological actions of an endogenous lipid signaling molecule with protective properties that include dilation of cerebral microvessels and suppression of edema and inflammation. Proposed studies will validate the receptor as a therapeutic target in SAH by determining the effects of gene modification and pharmacological modulation on SAH outcome using experimental models.

Dr. Sanjay V. Malhotra, Ph.D., FRSC, Professor & Endowed Chair in Cancer Research, Department of Cell Development & Cancer Biology, Director, Center for Experimental Therapeutics, Knight Cancer Institute

Addressing paclitaxel resistance and disease progression in ovarian cancer with small molecule YBX1 inhibitors

Ovarian cancer represents the fifth leading cause of cancer death in women, even though it does not make the top ten list for total cancer cases. Chemotherapy for ovarian cancer suffers from a significant failure rate as well as frequent relapse with treatment-resistant disease. Our focus is the development of a new class of chemotherapeutics that address the mechanisms of drug resistance in ovarian cancer, especially for paclitaxel. Through inhibition of the protein YBX1, our lead compound has the potential to enhance cancer cell killing by paclitaxel while also addressing paclitaxel resistance development. YBX1 is a multifunctional protein involved in the damage response as well as cell cycle control, functions that cancer cells utilize to establish tolerance and survival even with chemotherapeutic treatment. We propose to characterize the differential gene expression of cancer cell states induced by our lead compound and paclitaxel to validate the mechanism of synergy for these drugs for translational efforts. Furthermore, we will identify cytokine markers of our lead compound and paclitaxel drug interactions to guide analysis of tumors from future animal model studies. The outcomes of these efforts will support the development of future grant proposals to fund the key toxicological and pharmacological translational studies and establish the foundation for an OHSU-associated start-up to commercialize the product.

Dr. Mallesh Pandrala, PhD, Assistant Staff Scientist at the OHSU Knight Cancer Institute's Center for Experimental Therapeutics

Development of a Pan-BCR-ABL inhibitor for chronic myeloid leukemia with improved safety

Development of Tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL oncogene constitute an effective approach to treat Chronic myeloid leukemia (CML) and/or acute lymphoblastic leukemia (ALL) patients. However, drug resistance or intolerance limits current inhibitors. For example, despite durable initial response of imatinib against CML, it fails in up to 40% of patients due to drug resistance or intolerance. Mutations within the kinase domain of BCR-ABL constitute the most frequent mechanism of drug resistance. This includes the T315I "gatekeeper" mutation reported in ~20% of CML patients. The second-generation inhibitors are ineffective against the T315I mutation. Ponatinib, a third-generation inhibitor, has demonstrated excellent efficacy against T315I mutation; yet it is the most cardiotoxic TKI among FDA approved TKIs. We approached elimination of TKI liabilities by combining our drug design paradigm with cardiomyocytes derived from induced pluripotent stem cells (iPSC-CMs) models to identify cardiac-safe analogues at an early stage. Extensive SAR studies resulted in lead compound 1, which has inhibited the kinase activity of BCR-ABLT315I, has potently inhibited proliferation of K-562 cells harboring both WT and T315I BCR-ABL, and has improved cardiac-safety compared with ponatinib. Notably, compound 1 has achieved durable tumor regression in the K-562T315I xenograft model in mice with oral administration. Moreover, these inhibitors are the most cardiac-safe TKIs reported to date. Therefore, our proposed investigation will act to further optimize the lead inhibitor to improve its properties, such as pharmacokinetics, solubility, etc. As potent activity and drug-like properties are complementary, and both are necessary for an optimal drug product.

DEVICE, DIAGNOSTIC, & SOFTWARE

Elise Erickson, Ph.D., CNM, Assistant Professor, Midwifery Division, School of Nursing

Deciphering the Due Date-using AI to Predict and Improve Childbirth

Not knowing when labor will begin during human pregnancy stresses people, health care providers and hospital systems. Our best estimates are imprecise and impersonal; built off of large population averages. We have no personalized knowledge of when labor will begin for an individual person, despite other advances in medical and obstetric technology. When babies arrive unexpectedly (very quickly or preterm) or extend well past the "due date," the family is at risk for adverse perinatal outcomes and higher costs. Knowing labor is coming, before labor symptoms start, would allow pregnant people to make plans, health care providers to make more precise recommendations and ultimately help us decrease morbidity and health care costs. Interestingly, body temperature changes in pregnancy have been used to indicate the future onset of labor in mammals. Our own data supports this finding in humans as well. In this proposal, we will leverage BIP funding to validate an algorithm from continuous temperature monitors worn during pregnancy to build a predictive model that can be built into a smartphone application and lead to a useable tool for patients and providers. Using machine learning, we will train and validate the algorithm to predict the onset of labor within at least 24 hours. Our application seeks funds to finish data gathering, validate the algorithm, begin application development (informed by market research) and develop a business plan.

Xin Li, Ph.D., CNM, Associate Professor, Advanced Imaging Research Center

Improving Practical Activity MRI Quantification

Metabolic activities can change quickly and generally occurs before anatomic/morphologic alteration. Therefore, functional activity maps could provide physicians with crucial early insights on metabolic details that can alter their practice for better patient outcomes. A functional mapping with MRI has emerged after the recent OHSU discovery of Active Trans-membrane Water Cycling, which links the cross-membrane water transfer rate constant to cellular metabolic activity. In particular, MRI's diffusion-weighted imaging (DWI) is sensitive to cross-membrane water movement. We use the "forward" approach in creating an in silico DWI data library based on realistic and biological-relevant simulation parameters. By comparing in vivo DWI data to library DWI curves, we can extract the relevant parameters. The success of this activity MRI (aMRI) approach offers the possibility to visualize cellular activity at an MRI spatial resolution about 10x better than any other current metabolic imaging modalities. We first seek to apply aMRI to prostate cancer. The goal of this project is to validate that aMRI produces in vivo cell density parametric maps analogous to such maps derived from ex vivo prostatectomy samples. The finished work will further provide a priori detail in refining other aMRI parameter's extraction.

The success of the project will pave the way for its licensing and move forward to the PMA trial followed by the application of FDA 510k clearance. For prostate MRI, adding aMRI can reduce the total number of biopsy procedures performed, preserve patients' quality of life, and generate meaningful savings for the health care system.

Austin Peters, M.D., Associate Professor, Department of Anesthesiology & Perioperative Medicine, School of Medicine

Self-administered Palate Stimulation Device for Non-invasive Headache Relief

Chronic headache pain is a burdensome, widespread condition, and current therapies are costly, limited in their effectiveness, and present risks for side-effects and complications. There is a need for non-invasive, non-pharmacologic, self- administered therapies for headache pain. To meet this need, I have developed a prototype device providing safe and effective relief to headache pain. Unlike competing products, my device is specifically designed for non-invasive, self-administration to the palate to relieve headache pain. My current prototype is fully functioning, reusable, and uses methods of nerve stimulation, but designed in a way to maximize comfort and minimize safety risk. It is also cost-effective: a chronic migraine patient using this device would see a cost-savings of more than $600/year compared to pharmaceutical costs alone, and far greater savings when compared to higher-risk surgical options. If awarded the BIP Device Award, over the next 12 months I will refine the prototype into a self-contained personal-use medical device, and perform a clinical study to validate this technology.

David Warner, M.D., Research Resident, and Albert Lwin, M.D., M.P.H., Research Resident, Department of Surgery, School of Medicine

Novel Vascular Doppler Device for Blood Flow Detection

The routine care of a postoperative vascular patient hinges upon assessment of peripheral blood flow which is essential for timely responses to potentially dangerous complications. The current go-to tool for quick assessment of peripheral blood flow is the bedside Doppler device which utilizes ultrasound technology to measure

velocity of blood flow and convert it into an audible sound. However, existing doppler technology is limited by inter-user error, device shelf-life resulting in diminishing hospital supply over time, and provider time constraints, which can expose the patient to undue risk and increase health care costs. We propose a new device - SureFlo – a wearable device leverages and advances existing doppler technology by allowing for continuous, reliable, and non-invasive monitoring of peripheral blood flow. Our team includes physicians, engineers, and commercialization advisors with dedicated time to develop this device.

DRUG DISCOVERY

Raymond Bergan, M.D., Professor of Medicine; Associate Director, Medical Oncology, OHSU Knight Cancer Institute

Development of Dual Acting Bone Defending Agents, Expanded Toxicology Assessment

Prostate cancer (PCa) is the second most common cause of cancer death in US men. Mortality results from the development of metastasis. Metastasis to the bone dominates the clinical management of people with advanced PCa and is a major driver of morbidity. If PCa-mediated bone destruction could be delayed or inhibited, it would improve both the duration and quality of life. Our current ability to therapeutically target this process is limited. The current proposal describes our synthesis of a first-in-class set of dual acting bone defending agents (DABDs). We have shown that DADBs are so effective at inhibiting human PCa mediated bone destruction that they prolong survival even in short term murine models. We have filed a patent application to protect DABDs and their use, started working with the OHSU Entrepreneur-in-Residence Program, plan to move DABDs into the clinic, and to license and work with investors to develop this into novel therapy directed at a large unfilled market need. While current findings support the hypothesis that DABDs have low systemic toxicity, we need to perform dedicated toxicity studies in order to move forward. Proposed investigations focus on quantifying DABD toxicity in clinically relevant models designed to inform the design of IND enabling GLP-toxicology studies, to provide critical information for ultimate use in humans, and to foster development. Dedicated toxicity studies will serve to de-risk DABDs, which is important for attracting investors.

John Brigande, Ph.D., Associate Professor of Otolaryngology; Associate Professor of Cell, Developmental, & Cancer Biology

Generation of a Mouse Model Susceptible to SARS-CoV-2 Infection by i-GONAD

Mouse models susceptible to SARS-CoV-2 infection are essential to study COVID-19 pathogenesis and to screen pharmacotherapeutics designed to perturb infection and prevent disease. Cell lines derived from susceptible mice are also required to study viral effects on cellular structure and physiology. Common laboratory mouse strains, however, are resistant to SARS-CoV-2 infection. The virus gains entry into human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. Mice harboring the human ACE2 gene are susceptible to infection but in critically short supply worldwide as research interest in SARS and MERS waned. The Jackson Laboratories has over 1,000 requests for their human ACE2 knockin mouse: breeding pairs will only be available sometime this summer. We propose to address this roadblock to COVID-19 research progress at OHSU by creating a transgenic mouse harboring a modified ACE2 allele capable of interacting with the SARS-CoV-2 spike-binding motif (SBM). Our research strategy is to deploy improved-Genome editing via Oviductal Nucleic Acids Delivery (i-GONAD), an in vivo CRISPR/Cas9 approach that enables precise genomic edits.

Recent ACE2-viral SBM structural studies implicate three hotspots of viral binding in human ACE2 that we will edit into mouse ACE2. We will validate our mouse model in collaboration with OHSU colleagues using SARS-CoV-2 pseudotyped viral vectors that do not require biosafety level 3 protocols. Our long-term goal is to define what amino acids are minimally necessary to confer mouse SARS-CoV-2 susceptibility and validate this mouse model for drug discovery efforts aimed at preventing infection and disease.

Dexing Zeng, Ph.D., Associate Professor of Diagnostic Radiology; Director of Organic Chemistry, Center for Radiochemistry Research, School of Medicine

Erik Mittra, M.D., Ph.D., Associate professor of Diagnostic Radiology; Division Chief, Nuclear Medicine & Molecular Imaging

Novel albumin binder incorporated peptide for αvβ6-targeted pancreatic cancer radiotheranostics

Small molecule albumin binder, such as 4-(p-iodophenyl) butyric acid (ABI) and Evans Blue (EB), have been incorporated into different radiopeptides to improve radiopeptide tumor uptake by increasing circulation times in the blood. However, the enthusiasm for clinical utilization of those ABI/EB-incorporated radiopeptides was tempered because of reduced tumor/non-tumor ratios, compared to the corresponding radiopeptide without ABI/EB. Therefore, we designed a series of novel albumin binders that possess comparable albumin binding to ABI/EB, but moderate lipophilicity, and incorporated them into various radiopeptides. The radiopeptide-albumin binder (AB) conjugates were then evaluated in different preclinical models, and the results indicated that our AB is superior to ABI/EB. One such radiopeptide, FRGD, is an integrin αvβ6-targeted cyclic peptide. Because of excellent clinical specificity and sensitivity, αvβ6 has been recognized as an attractive target for tumor-specific delivery of imaging and/or therapeutic payload(s). Several αvβ6-targeted radiotracers have been tested in early-phase clinical trials in pancreatic cancer, however key improvements (tumor uptake and/or retention, and tumor/non-tumor ratios) are needed to be introduced before it can be used in a clinical radiopeptide therapy application. Given that the FRGD-AB conjugate demonstrated significantly improved tumor uptake and tumor/non-tumor ratios, over FRGD alone, we propose to develop an optimal AB for use with FRGD in pancreatic cancer radiotheranostics. Because there is no effective imaging or therapy available for pancreatic cancer, a great clinical need exists for new radiotheranostics for this lethal disease.

In this project, to further improve in vivo performance of our FRGD-AB conjugate, we will optimize the AB by screening an additional 20 meticulously designed AB analogs. The optimal AB (ABX) will be incorporated into FRGD peptide for in vitro and in vivo tests to select an optimal FRGD-ABX for clinical translation and commercialization activities.

2020 – COVID- 19 RAPID RESPONSE

Albert Chi, M.D., Associate Professor of Surgery, Division of Trauma, Critical Care and Acute Care Surgery, School of Medicine

OHSU 3D Printed CRISIS Ventilator

The worldwide pandemic of COVID-19 is a monumental public health threat that has led to significant impacts on the US healthcare systems. Based on current data, somewhere between 10% to 25% of patients sick with COVID-19 eventually require assistance breathing. Roughly 5% of patients will develop acute respiratory distress syndrome (ARDS), at which point only mechanical ventilation can give them a chance of defeating COVID-19. The United States has approximately 173,000 ventilators scattered across the country, according to the Center for Health Security at Johns Hopkins University but experts from Harvard University predict that there could be 1.4 to 31 times as many patients who need one. The US Food and Drug Administration (FDA) has issued Emergency Use of Authorizations (EUAs) to help alleviate the ventilator shortage. Here we propose the CRISIS VENT system as a solution, a single use device that can be created with a standard 3D printer in a sterile environment and rapidly produced and deployed at minimal cost. This new device design has the capacity to treat patients requiring standard mechanical ventilatory support but can also effectively treat the sickest patients with progressive ARDS. The CRISIS Vent diminishes supply chain issues, is rapidly scalable, is low cost, and usable in austere environments. It does not require specialty manufacturing of parts. Here we propose a five-animal study to further study the device and gather preliminary data for larger preclinical and human studies that will lead to premarket approval for patient use under normal situations.

Bory Kea, M.D., M.C.R., F.A.C.E.P., Associate Professor, Department of Emergency Medicine, Director of Clinical Trials, Department of Emergency Medicine

Evaluating the use of brown paper bags for storage of limited re-usable PPE exposed to SARS-CoV-2

The rapid spread of the novel coronavirus (SARS-CoV2) has led to a global disruption of supply chains with subsequent shortages of the Personal Protective Equipment (PPE) needed to protect healthcare workers from an outbreak. This has prompted the Centers for Disease Control and Prevention (CDC) to recommend conservation strategies including limited re-use of disposable PPE items such as disposable surgical and N-95 masks and face shields. These guidelines recommend storage of PPE in brown paper bags while awaiting re-use. There is currently no published evidence that addresses the safety of placing PPE contaminated with SARS-CoV2 in paper bags for re-use. This study examines the effectiveness of brown paper bags as a barrier for re-used PPE. The aim is to inform health care workers and policy-makers for risk analysis purposes. This study investigates the risk of fomite transmission by PPE with direct aerosolized exposure from confirmed COVID-19 patients to the inside and outside surfaces of brown paper bags. PPE will be obtained from hospitalized patients and exposed health care workers during an aerosolized procedure in a COVID-19 cohort ICU. Samples will be collected from the surfaces of the PPE, the interior and exterior surfaces of the paper bag storing the item at 30 minutes and 12 hours from exposure. Samples will be tested via CDC guidelines (RT-PCR). The primary outcome measure is the presence of detectable virus RNA on the exterior of bags containing confirmed contaminated PPE. Secondary outcomes include fomite transmission to the interior of bags and storage time effects.

Fikadu Tafesse, Ph.D., Assistant Professor of Molecular Microbiology and Immunology, School of Medicine

SARS-CoV-2 Nanobodies as Therapeutics Against COVID-19

The emergence of SARS-CoV-2 has caused a devastating pandemic that is crippling healthcare systems, destroying economies and is predicted to kill over 100,000 people in the United States and has already killed more than 175,000 people worldwide. There is no vaccine or antiviral therapy, and novel therapeutics are desperately needed. We are proposing to harness the potentials of nanobodies for therapeutics against COVID-19. Nanobodies are functional antigen-binding domain fragments derived from the single variable domain (VHH) of heavy-chain only antibodies derived from camelids and sharks, with several unique properties: they are one-tenth the size of conventional antibodies, they do not require glycosylation for expression or stability, they are amenable to bacterial expression and refolding strategies, they have exceptionally long complementarity-determining loops, and they are ideal as probes for conformational epitopes and for broadly neutralizing viral infections. This proposal has two specific aims:

1) Characterization of Nanobodies Directed Against SARS-CoV-2 Surface Proteins. We plan to immunize alpacas with a combination of inactivated whole SARS-CoV-2 virus, non-infections virus-like particles and purified Spike proteins. Using a phage display technology platform that is established in our lab, we will identify candidate hits, which will then be characterized further using various biochemical assays. We anticipate discovering 5-10 unique nanobodies that target SARS- CoV-2.

2) Analysis of Antiviral Activities. We will test the ability of our nanobody hits to block SARS-CoV-2 infection and assess their therapeutic potential to treat COVID-19.

Timur Mitin, M.D., Ph.D., Associate Professor of Radiation Medicine, School of Medicine Wencesley Paez, M.D., Department of Radiation Medicine, School of Medicine

A Smartphone Mobile Application Using Artificial Intelligence for Pain Control and Management for Bone Metastases

Bone is a frequent site of metastases in cancer patients and major cause for morbidity including excruciating pain, and devastating skeletal-related events (SRE) such as cord compression and pathologic fractures. Bone support is often sub-optimal and opioids provide temporary relief. Short course palliative radiation therapy (SCPRT) is an effective option with minimal side effects for bone pain management. Barriers exist, however, for access to the radiation oncologist, delaying SCPRT, and often leading to sentinel events. We are developing a smartphone mobile application that tracks pain levels and use of pain medication that could bridge direct communication to the radiation oncologist, expedite timelier evaluation and treatment with SCPRT, providing better pain control, avoiding opioid dose escalation and SREs, and improving quality of life. For the BIP, we will evaluate the effects of a mobile app on: (1) pain control, opioid maintenance in palliative care cancer patients with metastatic bone disease; (2) patient QOL; (3) impact on access to outpatient radiation oncology evaluation/treatment; (4) emergency department (ED) visits for pain or SRE's.

Peter Schulman, M.D., Professor of Anesthesiology and Perioperative Medicine, School of Medicine

Novel Artificial Intelligence Algorithm to Automatically Detect, Diagnose, and Determine the Severity of Cardiac and Pulmonary Disease

Although it is now sometimes argued that ultrasound and other imaging modalities have made the stethoscope ostensibly obsolete, there are reasons why this 200-year-old instrument remains ubiquitous in health care today. When properly used, the stethoscope is a readily available, patient-friendly, inexpensive, and highly effective screening tool. Auscultation, consequently, continues to be a key component of virtually every physical examination, and also plays an incredibly valuable role in educating health-care providers. However, the prognostic value of the stethoscope is entirely user dependent, and numerous studies have demonstrated that the proficiency of even very experienced clinicians can be extremely poor. Thus, it has been suggested that it is either time to dramatically improve auscultatory skills, or no longer consider the stethoscope among the devices with a meaningful role in modern medicine. However, we believe there is a better, more elegant technological solution to this problem, and that the stethoscope is ripe for disruptive innovation. Our aim is to develop a novel artificial intelligence algorithm that would be used in conjunction with a currently available digital stethoscope to automatically detect, diagnose, and determine the severity of a broad range of cardiopulmonary disorders. Our algorithm would be marketed as a smart phone application to a wide variety of clinicians. By significantly improving the speed and accuracy of cardiopulmonary screening our application would benefit millions of patients and dramatically reduce healthcare costs.

Ellen Tilden, Ph.D., C.N.M., Assistant Professor, School of Nursing; Assistant Professor of Obstetrics and Gynecology, School of Medicine

Preventing Postpartum Depression: Combining Content Delivery and Data Capture

An effective postpartum depression prevention model exists but it is not currently widely available and, consequently, it is not reaching most women. Our team will implement a new care model that enhances access to a proven effective intervention for prevention of PPD. We will use business market analysis to begin garnering foundational information for shaping the final commercial product/s. The model of delivery we propose is informed by childbearing women's growing interest in digital health solutions and the current viral pandemic crisis. The commercial product is a CBT model tailored for digital health delivery for pregnant women in a variety of settings and circumstances. Our initial work will focus on telehealth delivery but this does not preclude resuming aspects of face-to-face care when this is safe.

2020 – DEVICE, DIAGNOSTIC, & SOFTWARE

Cristiane Miranda Franca, DDS, MS, PhD, Post-Doctoral Associate, Department of Restorative Dentistry, School of Dentistry

The Tooth on a Chip: A Microdevice For Development and Screening of Dental and Oral Therapies

Dental caries is a concerning public health issue in the U.S. It is the most common non-communicative infectious disease in humans, with a striking incidence of over 90% of adults in western countries. The primary treatment for caries is based on the removal of the diseased dental tissues and replacement with a restorative material. Only in the U.S. $113 billion are expended in dental procedures yearly, and most of these are restorative treatments. Typically, dental materials are placed directly onto the inner calcified structure of the tooth, dentin, which is a highly porous matrix lined by micrometer-scale through holes (dentin tubules) that establish a direct communication path to the 'living part' of the tooth, the dental pulp, where dental cells reside. Currently, there are no methods that allow for dental materials to be tested in-vitro in a manner that efficiently replicates this biomaterial-dentin-cell interface. To address this gap, we have developed the 'Tooth-on-a-chip', a microfluidic model of the biomaterial-tooth-cell interface that can be used to test dental materials and drugs at near- physiological conditions. The tooth-on-a-chip is intended to be used by oral pharmaceutical and dental materials companies, as well as academic researchers, in the development and testing of both new and existing dental therapies. To accomplish the commercial translation of the tooth-on-a-chip to the market, we have planned four quarterly milestones aiming to address the device reproducibility, scalability, validation with in-vivo models and market assessment by conducting market evaluation and sales strategy interviews with key opinion leaders.

Matthew Hansen, MD, MCR, Associate Professor of Emergency Medicine and Pediatrics

Ultrasound Guided Vascular Access Assistance Device

There are over 40 million difficult IV placements in the US alone each year. In the Emergency Department, delays in IV access can increase length of stay by over an hour as well as delay diagnosis and treatment. In addition, patients also experience significant discomfort when poked for repeated IV attempts. Ultrasound guided IV-placement is an excellent solution, but it is a challenging procedure requiring both hands to move simultaneously in 3 dimensions. As a result, it is difficult to learn and few providers are proficient. We are developing a medical device that guides the ultrasound probe using a simple mechanism to facilitate more accurate and less difficult IV placements. This device will allow more providers to become proficient with typically difficult IV placements with less training. As a result, there will be fewer delays in care due to difficult vascular access, and improved patient experience. Ultrasound guided IV access is a billable procedure with an existing CPT code. We anticipate this procedure will be performed more frequently in sites that use our device and will have increased billing. In addition, reducing ED length of stay allows for more patients to be seen and increases revenue for the hospital. In this proposal, we will perform design engineering work that will improve our intellectual property position. We will also perform a study of our device among nursing students placing ultrasound guided IVs on highly realistic models.

David Sheridan, M.D., MCR, Assistant Professor of Emergency Medicine
Jessica Grant, MS, CCC-SLP, CNT, Neo-natal Speech Pathologist, Rehabilitation Services

Koala - Optimizing Baby Feeding Position

The 2 million infants yearly experiencing reflux currently have no treatments on the market as medications are unhelpful, and the infants are often labeled as colicky. Current feeding positioners are not aimed at improving medical outcomes or maintaining the recommended semi-upright prone position to alleviate reflux. The Koala Kushion fulfills this unmet need by providing a secure and supportive tool to feed these infants in a position that relieves the discomfort of reflux and allows for successful feeding. There is no other positioner on the market that is suited to provide these results. By providing this device, parents will finally have an option to mitigate the stress that comes from attempting to feed a baby with reflux. Having this on the market will reduce unnecessary medical visits and improve medical outcomes, which will lead to decreased healthcare spending, increased parent satisfaction, and improved life-long feeding outcomes for these infants.

2019 – DRUG DISCOVERY

Luiz Bertassoni, D.D.S., Ph.D., Assistant Professor of Restorative Dentistry

BoneMimetics: A Drug Discovery Platform for Bone-related Therapies

BoneMimetics is a bone replacement product intended for pharmaceutical companies and laboratory researchers developing bone targeted therapies, and is the first and only to replicate real human bone-like structure and function on a dish. Current products and models of preclinical bone function fail to replicate the far majority of characteristics that are the hallmarks of human bone, including composition, structure, and biological response. As a consequence of that, over 70% of developed drugs fail in clinical trials because pre-clinical model systems (both in-vitro and in-vivo) provide inaccurate tissue response in the laboratory phase. BoneMimetics addresses this unmet need by offering a revolutionary bone-replacement product that mimics the properties of real human bone to levels that were never possible before. The product consists of an extracellular matrix hydrogel-based biomaterial that is embedded with human cells, that is calcified in the laboratory using a proprietary cocktail of ions and proteins that naturally make up the human bone matrix. Combination of these ingredients using a method developed in our laboratory results in the formation of a bone- like tissue that shares the physical and biological characteristics of real human bone in as little as 72 hrs. Here we propose to develop this technology into a drug discovery/screening platform (kit) that can be used for R&D in industry and academia.

Michael Cohen, Ph.D. – Associate Professor, Department of Physiology & Pharmacology

Allosteric Modulation of PARP1-DNA Binding with Small Molecule Inhibitors: A Potential Therapeutic Strategy for Treating Ewing Sarcoma

Ewing sarcoma is the second most common type of bone cancer in children. Treatment options are limited to surgery and general chemotherapy; however, relapse often occurs in children with metastatic disease. In these cases, prognosis is especially dismal-less than 30% survival. It occurs because of the aberrant expression of a chimeric protein known as EWS/FLI-1, which is a potent driver of transformation. EWS/FLI-1 itself has eluded drug discovery efforts, and unlike other cancers, Ewing sarcoma has no obvious candidate drug targets. Previous studies have shown that Ewing sarcoma cells are sensitive to drugs (e.g. irinotecan, an FDA-approved DNA topoisomerase I inhibitor) that induce replication stress.

Combining irinotecan with an inhibitor of an enzyme known as PARP1 causes cell death in Ewing sarcoma cells. However, the general cytotoxicity and poor pharmacokinetic properties of irinotecan limit the effectiveness of this combination therapy. We have identified novel PARP1 inhibitors that exhibit a unique mechanism of action-allosteric modulation of DNA binding, which induces replication stress in a similar way to irinotecan. Because these novel PARP1 inhibitors also inhibit the catalytic activity of PARP1, they induce rapid cell death in Ewing sarcoma cells. Therefore, the dual mode of action of our inhibitor allows them to be used as a potential monotherapy for Ewing sarcoma. The short-term focus of the proposed work is to perform in vitro and in vivo pharmacokinetic studies of our lead compounds. Additionally, we will test the efficacy of our compounds in a mouse model of Ewing sarcoma.

Summer L. Gibbs, Ph.D., Associate Professor, Biomedical Engineering

Near Infrared (NIR) Nerve-Specific Probes Enable Improved Surgical Outcomes

Iatrogenic nerve injury is one of the most feared complications of surgery. Nerves are critically important to function and injury can lead to permanent disability. Surgery is performed commonly in the U.S. with ~40 million operations annually, incurring up to 600,000 nerve injuries. Currently there is no technology to improve visual recognition of nerves during surgery, and surgeons largely rely on anatomical knowledge to locate small or buried nerves invisible to the naked eye. Fluorescence-guided surgery (FGS) is a nascent field with demonstrated efficacy in improving surgical outcomes for cancer using tumor-specific, molecular-targeted fluorophores and commercially available FGS systems. We have developed a library of first-in-kind targeted near-infrared (NIR) fluorophores that label nerve tissue with high affinity for direct nerve visualization during FGS. To date, our library of probes has been screened at a single time point and dose, where we have discovered four lead compounds for future clinical translation. However, surgical procedures vary dramatically in length and thus both short- and long-acting nerve-specific contrast would find clinical utility. Herein, we propose to complete pharmacokinetic screening of the compounds known to be both NIR and nerve-specific by direct administration (n=21). Additionally, we will screen for compounds with the largest window between dose limiting toxicity and the required imaging dose to ensure safety. The deliverable from this project will be characterization of one short- and one long-acting NIR nerve- specific fluorophore that generates nerve signal to background ratio >2 using an imaging dose at least 10x less than the dose limiting toxicity.

2019 – DEVICE, DIAGNOSTIC, & SOFTWARE

Young Hwan Chang, PhD, Assistant Professor, Biomedical Engineering and Computational Biology

paradigmSHIFT: Speedy Histopathological-to-Immunofluorescent Translation of Clinical Images Through Deep Learning

Pathologists histopathological evaluation is the gold standard for cancer diagnostics, but there are situations in which histology does not allow for a definitive and accurate diagnosis. Due to the limitation of the Hematoxylin and Eosin stain, additional staining by immunofluorescence or immunohistochemistry has often been explored and allowed advances in cancer classification, treatment, and associated companion diagnostics. While recent advances in multiplexed imaging technologies would significantly improve understanding of cancer, they have distinct disadvantages that prevent their integration into routine clinical histopathology workflows, mainly due to costly, labor-intensive and time-consuming tasks for image data acquisition as well as lack of quantitative image analytics.

To facilitate compatibility with clinical histopathology, we have developed a novel deep learning method to efficiently infer the distribution of specific protein abundance from tissue and cell morphologies in histopathological images.

First, the proposed models could potentially provide appropriate augmented digital interpretation based on H&E by efficiently substituting for multiplexed methods so pathologists can easily detect the cancerous cells in a less time-consuming manner and improve their efficiency and accuracy. Second, we could use this framework as development of improved and standardized method for validating antibody specificity and selectivity.

Michael Chiang, MD

Optimization of the i-ROP DL System for Commercial Development

This proposal is intended to commercialize a machine learning system developed for performing automated diagnosis of an ophthalmic disease, retinopathy of prematurity (ROP), using retinal images. This technology will improve the quality and accessibility of ROP care for premature infants in the United States and throughout the world. This has resulted from research projects that have been continuously funded at OHSU by NIH and NSF since 2010. ROP is a leading cause of childhood blindness worldwide, and has enormous clinical and public health impact in the United States as well as the developing world. Although blindness from ROP is largely preventable with accurate diagnosis and timely treatment, clinical diagnosis is heavily subjective and variable.

Development of an objective and quantitative method for disease detection could change the paradigm for the diagnosis and management of ROP. The PI is an international expert in ROP, telemedicine, and ophthalmic informatics, and is overall PI of a research consortium with collaborators from computer science and ophthalmology who have developed the "i-ROP DL" system which has been rigorously validated in peer-reviewed literature.

Mark Engelstad, DDS, MD, MHI, Associate Professor, Oral & Maxillofacial Surgery

Software Applications with Medical Knowledge Can Improve Health Care Education

As a surgical educator, I have to answer the same difficult question several times a day: "How much of this procedure should I let this resident do?" While I know it's important to give the resident independence (autonomy), I also want to ensure the patient is safe and has the best outcome. We have developed a software platform (Entrustable) to help reconcile these competing interests and provide a more informed answer to this age-old question - so we can have the best outcomes today while still developing skilled providers for tomorrow. The answers lie in surgical logbooks, which are highly detailed representations of past experience. Theoretically, logs contain enough information to answer questions about someone's capabilities or how much supervision they might require.

Recent technological advances have allowed us to model human knowledge about surgery and medicine into structures that computers can use to interpret medical experiences, and grant the right amount of autonomy. Entrustable takes input about experiences and creates output about entrustability, educational progress, learning gaps, and surgical experience. It is currently a well-established and working prototype that is ready for testing in real-world situations where autonomy decisions are being made. There is no competing platform, so there is great opportunity in being first to market. The number of potential users in educational programs, as well as independent practice is enormous and largely untapped. Educators, institutions, accrediting bodies, insurance providers, risk managers, hospital administrators and the public would have much to gain from more accurate analyses of experience.

Leo Han, MD MPH, Assistant Professor, Department of Obstetrics and Gynecology

Development of a Rapid Bedside Test to Detect the Presence of a Copper-IUD

Over 100 million women worldwide rely on the copper intrauterine device (CuIUD) for contraception making it the most common form of long-acting reversible contraception used. CuIUDs are desirable for their "forgettable" nature and can be placed at any time, including immediately after the birth of a child. CuIUDs do not alter menstrual cycles and have no overt signs of use except for two monofilament threads that can only be seen or felt during a pelvic exam. If the strings are missing, the IUD can still be in perfect position, or it may have 'fallen out' (expulsion).

The prevalence of missing strings is common in IUDs placed immediately postpartum (20-60%) as is expulsion (as high as 20%). Outside of this period, missing strings are less frequent (4-18%). In both cases, users and clinicians may be unsure if the IUD is present, presenting a common clinical dilemma.

In high-income countries, such as the US, we utilize non- invasive imaging such as an ultrasound to confirm IUD position, but this is costly and may not be immediately available especially in primary care settings. In low- and middle-income countries, this option is not readily available and women must undergo a painful 'blind' exploration of the uterus where IUD position is checked by removing it. Thus, a rapid, low cost, bedside test for determining CuIUD placement would be a clinically important tool for clinicians and women. We estimate that over 4 million women could benefit this test. In this application, we propose the development of a low-cost, point of care test for determining if a CuIUD is in situ by sampling cervical mucus. Our team is uniquely positioned to produce this commercial product and bring it to market as we have laboratory expertise in cervical mucus (Han), copper chemistry and biology (Ralle) as well as clinical research experience in contraception and reproductive health care in LMIC (Edelman).

2018 – DRUG DISCOVERY

Martin J. Kelly, Ph.D., Professor of Physiology and Pharmacology

Novel Alzheimer's Disease Drugs and their Target

Alzheimer's disease (AD) affects over 5 million Americans, and the number continues to grow as the population ages such that by 2050 the number of Alzheimer's patients may triple to 15 million. Unfortunately, there are no treatments available to arrest or slow the progression of disease. Through the work outlined in this proposal, we will generate the basis for the development of a new lead compound that will be neuroprotective with respect to AD. The invention is based on the demonstrated ability of the non-steroidal small molecule STX to mimic the effects of estrogen without the carcinogenic side effects of estrogen, as STX does not bind to nuclear receptors. However, the nature of the STX target has been elusive. We therefore propose to synthesize a photo-crosslinkable and clickable derivative of STX to identify the putative receptor. Once the receptor has been identified, it will be fully characterized and expressed in model cells to serve as a high-throughput screening system for identifying additional molecules that interact with the receptor. Further, structure-activity relationship (SAR) data will be utilized to generate new derivatives in an effort to optimize the pharmacological characteristics of STX.

R. Stephen Lloyd, Ph.D., Professor, Oregon Institute of Occupational Health Sciences, Department of Molecular and Medical Genetics

Development of Agonists for the Prevention of Obesity and Obesity-related Diseases

The prevalence of human obesity continues to rise, with one-third of all U.S. adults classified as obese, and another one-third overweight. Ramifications of this growing trend are not limited to reduced quality of life and/or self-image, since obesity is highly correlated with comorbidities in a variety of other major secondary medical conditions including elevated heart disease, stroke, type 2 diabetes, fatty liver disease, chronic inflammation, and certain types of cancer. These medical conditions have enormous financial impacts on healthcare and insurance costs that are associated with the treatment and ongoing care for these individuals. Although this epidemic must be first addressed through education concerning the benefits of exercise, balanced diet, and adequate sleep, there are numerous circumstances in which weight gain is highly anticipated as a result of disease progression or pharmacologic treatment. Treatment of such patient populations represents large financial markets in which prevention of weight gain is a win-win-win situation for the patient, healthcare provider and insurance providers. To meet these challenges, our research has identified a mechanism through which diet- or genetic- induced weight gain can be largely prevented by enhancing a normal cellular activity. We propose to translate our findings into pharmacologically tractable approaches, expanding the core structure of our current lead drugs and testing their biochemical/cellular efficacies to enhance this activity. Thus, our goals are to optimize the structure of drug-like molecules that have been selected for enhanced catalytic activity.

Arthur Vandenbark, Ph.D., Professor of Neurology and Molecular Microbiology & Immunology, Senior Research Career Scientist, VA.

Novel CD74 Decoy Peptides for Treatment of Progressive Multiple Sclerosis

Macrophage migration inhibitory factor (MIF) and D-dopachrome tautomerase (D-DT) are two chemokines that have been implicated in the pathogenesis of progressive multiple sclerosis (MS). Upon binding to a common receptor, CD74/CD44, these factors enhance T cell activation and survival, promote secretion of other proinflammatory factors and recruit additional leukocytes into the central nervous system. Given that there is only one approved drug on the market for primary progressive MS and none for secondary MS, additional new therapies are urgently needed. To this end, we propose to develop a decoy CD74 peptide with high affinity for MIF and DDT to prevent their binding and signaling through cell-bound CD74. Our recent molecular modeling studies have identified two regions within the highly stable trimerization domain from each of three CD74 monomers that form the binding interface (hotspot) with MIF and D-DT trimers. Validity of these binding motifs has been confirmed using substitutions in full-length CD74 constructs that reduced MIF binding by >50% and ~30% respectively. We here propose to synthesize two CD74 decoy peptides containing the MIF/D-DT binding motifs, as well as a 30-mer peptide containing both motifs. These peptides would be predicted to cross the blood brain barrier and could be highly efficacious for inhibiting or reversing MS clinical progression in both male and female MS subjects. Support from the BIP program will be instrumental for demonstrating proof-of-concept of CD74 decoy peptides as the first step towards commercialization through additional grants and licensing agreements.

2018 – DEVICE, DIAGNOSTIC, & SOFTWARE

Luiz Bertassoni, D.D.S., Ph.D., Assistant Professor of Restorative Dentistry

EndoGel: A Smart-Material System for Regenerative Dental Applications

Dental caries has estimated prevalence of over 90% of adults in western countries. If not treated early, caries can progress from enamel into dentin, leading to necrosis of the dental pulp (the living part of the tooth) which require root canal treatment. Several millions of teeth are treated for 'root canals' each year, and the approach is to completely remove the infected or necrotic pulp tissue and replace it with an artificial cement. This results in complete elimination of the biological response of the tooth, generally leaving it in a weakened state, more prone to fracture and tooth loss. We have developed innovative strategies that have high translational potential for the treatment of caries-affected root canals at different stages of the disease. The proposed technology, EndoGel, consists of an intra-oral application kit for delivery of a patent- pending photo-curable hydrogel material for regenerative applications. The EndoGel is synthesized with a gelatin backbone, and retains a set of biologically active moieties that we have optimized for enhanced cell proliferation, attachment, spreading, viability, vasculature formation, odontogenic differentiation, and many other biological processes. We have also obtained NIH (R01) funding to support many of the basic science developments surrounding this material. Thus, we envision that the requested funds will enable us to address specific questions that pertain to product development and commercialization. In summary, we are convinced that the current opportunity will enable us to launch the commercial development of an exciting and feasible solution for an unmet need in dental and craniofacial therapies.

Kimberly Hutchison, M.D., Associate Professor of Neurology

Novel Mouth Sealer to Decrease Oral Leaking and Improve Compliance with Nasal CPAP for the Treatment of Obstructive Sleep Apnea (OSA)

OSA is an epidemic affecting more than 25 million Americans. Untreated OSA leads to short and long-term health consequences, tragic accidents, and billions of dollars annually in increased healthcare spending. OSA can be effectively treated with CPAP (continuous positive airway pressure), however long-term compliance with treatment is suboptimal at
55-60%. Mask discomfort, including oral leaking, is a common cause of CPAP non-compliance. The innovative mouth sealer is a conceptually simple device to seal the lips closed comfortably and safely to eliminate mouth leaking with nasal CPAP. Decreasing mouth leaking will improve compliance with CPAP and decrease the economic burden of untreated OSA. This BIP grant will bring together the ideas and experience of a sleep medicine physician with the technical expertise of bioengineers to develop a prototype that is ready to be tested in clinical trials.

David Sheridan, M.D., Assistant Professor of Emergency Medicine

HydraSense Non-Invasive Dehydration Monitoring

Dehydration is a commonly encountered problem worldwide. The most common cause of dehydration in young children is secondary to an acute illness. We plan to focus on two pediatric markets: (1) Developed countries and (2) under-developed countries. Why? Because the access to medical resources are vastly different and, in the case of under-developed countries, early identification has a major impact on mortality/morbidity. Goal: A simple, fast and effective way to determine whether a child is dehydrated and requires medical attention. The potential impact a device such as ours can provide is different based on the setting of use. In the United States, significant dehydration is relatively uncommon yet parents are often worried about it. When used at home, this simple device has the potential to decrease unnecessary medical visits significantly by telling parents their child is safe to stay home and trial oral rehydration. In the under-developed world there is significant impact on true morbidity and mortality. In these settings, children are dying every day and dehydration remains one of the leading causes. There are often providers with limited medical training in these resource-limited settings who are faced with a difficult decision of who to treat with IV fluids or transfer to higher levels of care. This device allows the identification of children with moderate-to-severe dehydration who would benefit from escalated care allowing earlier treatment and intervention that can save a life. The beauty of this device is that it is beneficial to both markets which increases the revenue potential

2017 – DRUG DISCOVERY

Monika Davare, Ph.D., Assistant Professor of Pediatrics, Division of Hematology and Oncology, School of Medicine

Development of a 'Hit to Lead' Compound as a Therapeutic Agent to Treat Ewing's Sarcoma and Subsets of Hematological Malignancies

Cancer is the second leading cause of death in children ages 1 to 14. Ewing's Sarcoma (EwS) is the second most common type of primary bone cancer in children. With high-dose cytotoxic chemotherapy and surgical intervention, including limb amputations, about 70% of EwS patients go into cancer remission. However, survival rates for EwS patients with metastatic disease and adolescent patients (15-19 years) are around 30% and 50%, respectively. Importantly, current cytotoxic treatments have long term deleterious effects in children resulting in more than 95% of childhood cancer survivors having some chronic health problem, and 80% having life-threatening conditions, including death from a secondary malignancy resulting from EwS treatment itself. Therefore, EwS is a rare disease with unmet clinical need, offering the opportunity to develop more effective targeted therapeutic agents. Here we present a novel lead compound with high potency and selectivity for targeting EwS, offering a commercialization potential with total addressable market (TAM) of $56MM-$104MM. Notably, based on preliminary data, our lead compound will be an effective anti-cancer therapeutic agent in distinct molecular subsets of nonsmall cell lung cancer and myeloid leukemia patients, substantially boosting the TAM to $191MM - $783MM.

Beth Habecker, Ph.D., Professor of Physiology and Pharmacology, School of Medicine

Novel Compositions Targeting Protein Tyrosine Phosphatase Sigma for Nerve Regeneration

We have identified novel small molecules that target a receptor (Protein Tyrosine Phosphatase Sigma; PTPσ) responsible for preventing nerve regeneration through inhibitory scars. Lack of nerve regeneration through scars occurs in several contexts including myocardial infarction, spinal cord injury, and traumatic brain injury. There are no therapeutics in use that can block this receptor, but removing PTPσ in mice fully restores innervation after myocardial infarction and prevents arrhythmias.

Using rational drug design, our team has discovered novel small molecules that act on PTPσ and promote nerve regeneration over inhibitory scar components in vitro, representing the first in class potential therapeutic for this unmet medical need. OHSU proposes to use awarded funds for the crucial next step in the commercialization process: confirming the ability of these compounds to impact re-innervation in vivo. The test of efficacy will be restoring nerves to the cardiac scar after myocardial infarction, since removing PTPσ in mice is sufficient to fully restore innervation within 10 days of the injury. This support will position the team to secure a strategic industry partner. This project represents a significant opportunity to impact the quality of life and survival of millions of patients at risk for cardiac arrest following myocardial infarction. Since the compounds could also impact nerve regeneration after spinal cord injury and traumatic brain injury, support for this project could pave the way for regenerative therapeutics to help millions of insufficiently treated patients.

2017 – DEVICE, DIAGNOSTIC, & SOFTWARE

David Huang, M.D., Ph.D., Peterson Professor of Ophthalmology, Professor of Biomedical Engineering

Laser Thermal Conjunctivoplasty

Conjunctivochalasis (loose conjunctival folds) is a common cause of tear dysfunction and chronic eye irritation; however, it does not respond to the usual dry eye treatments. Effective treatment requires surgical reduction or excision of the redundant conjunctiva. We propose a novel device to provide a safe and fast procedure to treat conjunctivochalasis. Unlike conventional surgery, the new device does not cause bleeding. The gentler new treatment leads to faster and less painful healing compared to standard methods. The estimated annual accessible volume for the device is 1.52 million procedures per year. At a device price of $50,000 and a click fee of $60 for each treatment (one eye), the estimated annual revenue is more than $100 million. Medicare reimbursement for surgical treatment of conjunctivochalasis is $315 per eye (CPT 68115) which translates to $479 million per year. The surgical revenue generated per device would be $250,000 per year (791 procedures per device). So, eye physicians could generate significant additional revenue for their clinics while improving patient outcome. We will build the device prototype and perform ex-vivo experiment to establish the effectiveness of treatment. In the second year, in-vivo rat experiments will be performed to establish safety and healing characteristics. These will lay the groundwork for FDA trials and commercialization.

David Sheridan, M.D., Department of Emergency Medicine

Wearable Monitoring for Mental Health Patients

Mental health disease currently affects 1 in 5 individuals of the population (46 million people) in the United States. Over 10 million people each year experience a suicide attempt or significant thoughts of self-harm. According to the CDC, in 2010 there were over 500,000 self-harm injuries costing $44 billion in medical and work losses. Compounding the issue, the number of inpatient beds for mental illness has consistently decreased nationally from a peak in 1970 of 350,000 beds to less than 50,000 in 2010. With decreased availability of inpatient services with mental health, better options need to be available to direct care and identify high risk populations. Suicide is often an impulsive act happening in times of short-lived crises and patients often will describe not knowing that their condition had worsened before it was too late. Self-identification and support of worsening symptoms is vital in these circumstances rather than relying on scheduled outpatient visits to identify these behaviors, yet nothing is available beyond subjective assessments. This device aims to noninvasively, continuously monitor certain parameters in patients with depression and suicidality to allow early identification resulting in decreased suicide attempts and Emergency Department (ED) visits. The most likely route of revenue generation will be to license our IP rights to an industry development partner.

David Simons, M.D., Ph.D., Glaucoma Fellow, Casey Eye Institute

Glaucoma Tube Implant with Modulated Flow

Glaucoma results when elevated intraocular pressure (IOP) damages the optic nerve. This common eye disease affects up to 80 million people worldwide and can result in blindness. The goal of glaucoma tube implant surgery is to reduce IOP, but care must be taken to avoid hypotony (i.e. IOP that is too low). Hypotony is one of the most feared complications of glaucoma tube surgery, resulting in poor vision for patients and requiring unreimbursed resources from surgeons (i.e. additional procedures, appointments, and chair time). In this proposal, we describe a novel glaucoma tube implant device that is designed to reduce the rate of hypotony by incorporating a magnetic switching mechanism which provides surgeons with precise and modifiable control of flow through the tube. Our device was designed with both the patient and surgeon in mind. We expect surgeons to readily adopt this device due to its significant advantages over existing glaucoma tubes on the market. The surgical glaucoma device industry is booming, and the annual tube implant market has increased by over 400% since 1994 to over $21 million. We describe a 2-year strategy for taking our device from concept to validated prototype. Because this device will improve patient outcomes and provide value to surgeons and insurers, we believe there is a clear path to successful commercialization. Our glaucoma tube implant will decrease hypotony-related complications, reduce physician stress and costs, and save vision.

2016 – DRUG DISCOVERY

Penny Hogarth, M.D., Associate Professor, Molecular & Medical Genetics

Fast-track CoACT

Pantothenate kinase-associated neurodegeneration (PKAN) is a devastating inborn error of metabolism for which there are currently no disease-modifying treatments available. We have identified a rational therapeutic agent with highly promising efficacy data in animal models that could be on the market within a very short timeframe by exploiting an esoteric and inexpensive development path.

Xiangshu Xiao, Ph.D., Associate Professor, Physiology & Pharmacology, Knight Cancer Institute

Novel Lamin-binding Ligands for the Treatment of Triple Negative Breast Cancer

The goal of this project is to develop small molecule modulators of nuclear lamins as potential therapeutics for triple negative breast cancer. TNBC is subtype of breast cancer lacking expression of estrogen receptor (ER), progesterone receptor (PR) or human epidermal growth factor receptor 2 (HER2). Although targeted therapies exist for ER and HER2-positive breast cancer patients, the only available systemic therapies for TNBC are the conventional cytotoxic chemotherapies that lack sufficient efficacy and safety. Therefore, there is an urgent need to develop novel nontoxic TNBC therapies that are more efficacious and safer. We recently developed a novel class of compounds that have demonstrated selective toxicity in TNBC cells over normal human cells. The prototype of this class of compounds is called lamin-binding ligand 1 (LBL1). Further mechanistic investigations of LBL1 showed that it directly binds to nuclear lamins leading to inhibition of DNA doublestrand break (DSB) repair. While LBL1 shows in vitro promise as a novel therapy for TNBC, it does not possess appropriate drug-like properties to achieve pharmacologically relevant concentrations in vivo. In this application, we will take an integrated medicinal chemistry and pharmacology approach to identify an appropriate drug candidate for further preclinical and clinical evaluation.

2016 – DEVICE, DIAGNOSTIC, & SOFTWARE

Fergus Coakley, M.D., Professor and Chair, Department of Diagnostic Radiology

Novel Targeted MRI-guided Prostate Biopsy Device

Approximately one million prostate biopsies are performed every year in the U.S., typically after a screening prostatic specific antigen (PSA) level or digital rectal examination is considered abnormal, and about 20% are positive. The current standard-of-care, ultrasound-guided biopsy, often misses cancer or underestimates cancer aggressiveness. Substantial evidence from multiple centers indicates MRI-targeted biopsy can transform baseline cancer evaluation, but this requires two distinct procedures for the patient (MRI followed by biopsy). We propose to develop a device combining a novel, targeted endorectal biopsy template with a fully incorporated coil for MRI signal reception. The product allows an entirely new "single stop" pathway for combined diagnostic prostate MRI and MRI-targeted biopsy. No such device is currently available. During the initial phase, we will use the BIP funding to develop a proof-of-concept device and plan to contemporaneously file for patent protection. Given that prostate cancer is a well-funded disease topic (over $1B in NIH funding, in the last four years) and with an abundance of research to build on, moving this device from proof-of-concept to bedside is possible within a five-year timeframe

James Dolan, M.D., M.C.R., F.A.C.S., Associate Professor of Surgery

An Improved Enteral Access Device for Surgical Patients

Our project proposes to significantly improve the safety and cost of current jejunal feeding access devices used in gastrointestinal surgery. Such devices are used worldwide to allow patients who cannot take oral intake to receive hydration, nutrition and medicines. Commonly, this process involves placement of 4 independent T-fasteners to fix a segment of bowel (usually the jejunum) to the inside of the abdominal wall. A flexible feeding tube is then inserted through the abdominal wall and through this fixed area into the lumen of the bowel. However, various problems have been identified with this technique and devices, especially in obese patients. The fasteners have broken and necessitated surgical intervention to salvage the jejunostomy, the fixation devices cause pain and have also promoted skin infections at the jejunostomy site. These complications lead to poor patient outcomes and increased healthcare costs. Our current method of jejunostomy placement takes over 25 minutes of expensive operating room. Our novel product will improve upon the current system and enhance the stability and safety of the device.

Theodore Hobbs, D.V.M., M.C.R., Surgery Unit Head, Oregon National Primate Research Center

Blood Volume Determination Using an Intravenous Optical Fiber

Accurate blood volume determination is essential for case management in critical care as well as for patient evaluation throughout chronic disease states such as heart disease. However, the current methods of objective blood volume assessment are time-consuming, involve exposure of patients to radioactive substances, and require special licensing and handling of these radioactive substances. For these reasons, total blood volume determination occurs rarely and mostly in the domain of large medical research institutions. As a result, common clinical practice relies upon indirect clinical indicators of blood volume (e.g. heart rate, blood pressure, hematocrit, and hemoglobin) even though these may yield conflicting or misleading information. To improve the patient care, we are developing a prototype point-of-care analyzer to determine total blood volume within a few minutes without blood draws, radioactive substances, or outside laboratory processing. The rapid acquisition of patient blood volume will allow clinicians to utilize this information for immediate decision making as well as enable progressive monitoring of blood volume through therapeutic interventions. This technology promises to deliver a safe, reliable point-of-care device at a low cost that will take objective blood volume assessment from the domain of large medical research facilities to the front lines of clinical practice.

2015 – DEVICE, DIAGNOSTIC, & SOFTWARE

Erin W. Gilbert, MD, MCR, Assistant Professor, Department of Surgery, Division of Gastrointestinal and General Surgery

Eliminating Retained Surgical Items Using an Embedded Detector System

Introduction: Our product is intended to prevent the occurrence of retained surgical items (RSIs). The idea that an RSI should be a "never event" is in stark contrast with the reality that they occur consistently at an incidence of 1 in 5,500 to 7,000 operations at a cost of $500,000 per event regardless of the use of multiple types of safety checks. RSIs are always considered a preventable occurrence and, as such, are nearly indefensible. The liability cost of an RSI is approximately$200,000. If a hospital performs 36,000 operations a year they could expect 6 RSIs a year. Therefore, an RSI detection system that prevents RSIs would save the hospital over $1,000,000/year. Project Aim: Refinement of our RSI Detector System which uses magnetic fields to create a detection zone that encompasses the entire surgical field(s) coupled with a real-time visual display system in order to detect and locate RSIs. Methods: There is no commercially available device that utilizes magnetic field detection technology to identify RSIs. This technology is ideal for this application as it capitalizes on the inherent nature of surgical instruments (ferrous) and can easily detect altered surgical sponges previously developed by our project team. Our system will be easier, safer, more efficient and less costly than competing commercially available devices. Conclusion: Routine accurate RSI detection is possible. Following completion of the work outlined in the grant proposal OHSU will pursue licensing of the product, which may involve a start-up company to bring the product to market.

Gregory Landry, MD, Professor of Surgery, Division of Vascular Surgery, Department of Surgery, Knight Cardiovascular Institute

Remote Endarterectomy Device

Currently, peripheral arterial disease affects 8-12 million Americans with a growing incidence due to the rise in diabetes, continued smoking, and an aging population. Surgeons use remote endarterectomy as a method of removing plaque from occluded arteries through an incision in the groin. The current remote endarterectomy device on the market has limited application due to its design. Working with biomedical engineers I plan to develop a prototype of a new remote endarterectomy device and test it in cadaver models during the first six months of the grant period. After establishing proof- of-concept, I plan to apply for additional funding through the Knight Cardiovascular Institute to develop a large animal model of arterial occlusion to further test the device. This device will be marketed to surgeons who treat peripheral arterial disease and has the potential to replace the only current device available on the market. Additionally, its ease of use has the potential to greatly expand the currently existing market for this procedure.

John Muschler, Ph.D, Research Associate Professor, Biomedical Engineering

Developing Novel Bioconjugates for the Detection and Treatment of Bladder Disease

Diseases of the bladder are prevalent and formidable clinical problems. Bladder cancers are diagnosed in approximately 70,000 people each year in the U.S., and interstitial cystitis (painful bladder syndrome) effects between 4 and 12 million people in the U.S. Currently, the methods for detection, surveillance, and treatment of these common bladder diseases are costly and ineffective, and present a very large opportunity for improvements in patient diagnosis and treatment. We are creating novel affinity-based targeting agents (bioconjugates) that are designed to be selectively absorbed by diseased cells of the bladder where normal tissue structure is disrupted. These bioconjugates will have applications for imaging of diseased cells in the bladder, and also for targeted drug delivery. Multiple products can be developed through this platform technology, including imaging agents for early detection, diagnostic agents for disease stratification, fluorescent bioconjugates for guided surgery, and targeted therapeutics. Our initial focus is on the disease of bladder cancer, with applications for interstitial cystitis and other diseases to be pursued subsequently.

Our immediate goal is the validation of our bioconjugates for both imaging and treatment of bladder disease using a preclinical animal model of bladder cancer. The long-term goal of this work is to commercialize novel affinity-based targeting agents for the more effective detection and treatment of multiple human diseases. Data to be obtained through OCTRI funding will provide proof of principle for the utility of our bioconjugates, and set the stage for Fast-Track STTR funding and/or industry partnership, leading to clinical testing and commercialization.

2014 – DEVICE, DIAGNOSTIC, & SOFTWARE

Peter Kurre, MD, Pediatrics and Cell & Developmental Biology

Minimally-invasive Biomarkers to Monitor Treatment Response in AML

Acute myeloid leukemia (AML) is an aggressive and frequently fatal blood cancer, with frequent relapse and late detection leading to poor survival. There is currently no biomarker to prospectively track minimal residual disease (MRD), compromising timely detection and therapeutic intervention. Disease surveillance relies on decreased peripheral blood counts (late, poor sensitivity, non-specific) or interval bone marrow exams (invasive, infrequent). We propose an innovative way to track MRD in AML patients. Based on preliminary data, we hypothesize that a unique combination of specific polynucleotides can serve as an AML biomarker to noninvasively measure residual disease and identify at-risk patients in need of a bone marrow examination.

Christopher Madden, Ph.D., Department of Neurological Surgery

Deep Brain Stimulation for Obesity

Obesity is a major epidemic contributing significantly to morbidity and mortality. Obesity rates have been increasing at an alarming rate over the past couple of decades and now more than one-third of U.S. adults are obese. It is estimated that by 2030 there will be approximately 3 billion overweight or obese adults worldwide. Furthermore, the severity of obesity has been on the rise as well and now morbid obesity (body mass index >40kg/m2) affects more than 8 million American adults. Obesity contributes to the risk for coronary heart disease, type 2 diabetes, certain cancers, hypertension, stroke, respiratory problems, dyslipidemia, liver disease, and osteoarthritis. The medical costs of obesity in the United States are staggering. The work supported by this proposal will describe, design and test (in a rodent model) a novel deep brain stimulation (DBS) system for the treatment of obesity. Sensor outputs will aid in the precise functional placement of the DBS electrode and will provide feedback for optimizing the stimulation parameters. The proposed project will include design and testing of a prototype system in rats made obese by maintenance on a high fat diet to assess the fundamental 'proof-of-concept' that the system will decrease the body weight of obese rats.

Linda Musil, Ph.D., Department of Biochemistry & Molecular Biology

Device to Prevent Posterior Capsule Opacification after Cataract Surgery

Posterior capsule opacification (PCO) is the most common and costly vision-disrupting complication of cataract surgery. Using a primary lens cell model system we have developed to study PCO, we have discovered that, a set of small molecule drugs, block one or more of the four cellular processes that cause PCO. Remarkably, a single, one-hour treatment with the drug is sufficient. During cataract surgery, the cloudy natural lens is replaced by an artificial plastic lens referred to as an intraocular lens (IOL). We have shown that therapeutic doses of the drugs can be delivered from an IOL that had been incubated in a concentrated stock of drug. Funds are requested for studies that will: (1) define the optimal parameters to load drug into the most commonly used IOLs in the world, and (2) provide initial pharmacokinetic data of drug release from IOLs. With this essential information in hand, we will be well positioned to secure licensing and sponsored research agreements with pharma, and/or IOL manufacturers. Our longer-range goal is to conduct in vivo studies, first in rabbits subjected to cataract surgery and ultimately in humans.

Helané Wahbeh, ND, MCR, Assistant Professor, Department of Neurology

Internet Mindfulness Meditation Intervention

Group mindfulness meditation interventions improve a variety of health conditions and quality of life. However, the group format is a problem because it requires people to share in public (aversion to sharing), attend at a specific time and day (scheduling constraints), and travel to a specific location (travel and accessibility constraints). Internet Mindfulness Meditation Intervention (IMMI) solves these problems. IMMI is an interactive online platform with one 60-minute session per week for six weeks with daily home practice between sessions. Each online session includes 1) videos imparting content about stress, relaxation, meditation, and mind-body interaction, 2) guided audio meditations the user does during the session, 3) interactive enquiry where users type in answers to questions about their experiences, 4) home practice assignments including built-in guided meditations, and 5) text/email prompts encouraging behavior changes to practice the meditations. IMMI offers users the benefits of an evidence-informed mindfulness meditation intervention on the user's own terms, in private, and when they are available. The objective of this project is to take IMMI from its current research beta version to a market-ready commercial product.

2013 – DEVICE, DIAGNOSTIC, & SOFTWARE

Summer Gibbs, Ph.D., Associate Professor, Biomedical Engineering

Nerve-Specific Fluorophores to Guide Nerve-Sparing Prostatectomy

Prostate cancer cure is the primary goal of radical prostatectomy, however preserving the nerve structures responsible for continence and potency are vital for maintained quality of life. Nerve damage following radical prostatectomy continues to plague surgical treatment and is reported in some form in up to 60% of patients 1 to 2 years post-surgery. Surprisingly, no method exists to enhance direct nerve visualization in the surgical suite, and nerve detection is completed through a combination of palpation and visualization when possible. Thus, the success of nerve-sparing prostatectomy is dependent upon the surgeon's ability to master the technique, which is based on general knowledge of prostate nerve anatomy, rather than direct visualization. Few contrast agents exist for staining of nerve tissue in the operating room, and all current contrast agents are specific for myelinated nerve. Preservation of both myelinated and unmyelinated nerves in the neurovascular bundle (NVB) and cavernous nerve of the prostate are vital for preservation of function. I have previously synthesized and characterized nerve-specific fluorophores for systemic administration that bind to all nerve structures following a single intravenous administration, resulting in a library of 230 isomers of the distyrylbenzene (DSB) fluorophore structure. The prostate is a highly innervated organ, where direct labeling of the cavernous nerve and NVB will provide greater imaging contrast by comparison to labeling of all nerve structures in the gland. However, requirements for local administration differ significantly from the previously characterized systemic administration route. To demonstrate feasibility, this proposal aims to develop a local administration protocol for the top 3 candidate DSB fluorophores, for translation into first in human clinical trials. OCTRI funding of this proposal will enable validation of an optimized local administration formulation and protocol with a confirmed signal to background ratio in rodent nerves.

Michael Hutchens, MD, MA, Department of Anesthesiology and Perioperative Medicine

Electronic Device to Prevent Central Line Infections

Dr. Hutchens received funding to continue development of a device to reduce microbial contamination of central venous access ports. Reduction of central line associated bloodstream infections (CLABSI) is a priority of the World Health Organization, the Center for Disease Control and Prevention, and the Joint Commission. A "never event", CLABSI nonetheless occurs 41,000 times per year in the United States, and costs approximately $10,000 to $20,000 per event – a cost which is not reimbursed by the Centers for Medicare Services. The mortality from CLABSI is 12-25%. Existing strategies to reduce infection include hand hygiene, glove use, and conventional hub care, but despite wide adoption of these strategies, CLABSI is still common. Any new strategy must increase effectiveness without adding significant cost, nurse workload, or complexity in an already complex health care environment. In a pilot microbiology study, staphylococcus aureus counts following use of the Dr. Hutchens' device compared favorably with those after standard care, without need for human intervention.

Dennis Koop, Ph.D., Professor, Physiology and Pharmacology Co-Investigators: Andrew Chitty, M.B.A. and Amira Al Uzri, MD, Professor of Pediatrics, Division of Nephrology, School of Medicine

Designing a Convenient and Precise Device for Home Dried Blood Spot Collection

Successful organ transplantation requires life-long therapeutic drug monitoring. The current state-of-the-art methods require frequent laboratory visits for venous blood draws and subsequent analysis. There are no readily available methods for in-home collection of patient blood samples with the necessary accuracy to replace visits to the clinic. The realities of day-to-day living often result in an inconsistent testing regimen that prevents timely intervention and puts the patient at risk. There is a need for a simple, easy to use blood sample collection method with a demonstrated repeatability/accuracy that can substitute for a visit to the clinic. Our solution is to have a simple device that can be used alone in any environment to obtain a dried blood spot that is accurate, precise, and can be mailed without special packaging to a clinical laboratory for analysis. Our proposed device does exactly this. It will be user friendly for patients of all ages, especially children, and portable (can fit in a handbag or pocket). It will deliver accurate and precise blood spot samples to testing facilities and be mailable through standard mailing options. The OCTRI grant will allow us the opportunity to develop a prototype for collection and a method for analysis.

Theresa Koppie, Department of Urology

Development of a Urine Based Bladder Cancer Recurrence Diagnostic Using a Genomic Disease Signature

Bladder cancer is the fifth most common cancer in the U.S. According to the American Cancer Society (ACS), it is estimated that there were approximately 73,510 new cases of bladder cancer diagnosed in 2011 in the United States 1 . When bladder cancer is found at an early stage and properly treated, the five- year relative survival rate is 96 percent. As of 2012, the ACS reports an estimated 585,390 people live with bladder cancer in the U.S. and estimates are that there are well over one million patients living with the disease in the U.S. and Europe. Despite its prevalence and known risk factors, no screening test is currently available. It is also one of the most likely cancers to recur following treatment with a 70-80% recurrence rate. Surveillance for recurrence occurs on a quarterly to yearly basis for the rest of a patient's life, is costly, invasive (transurethral cytoscopy) with significant morbidity, and burdensome to patients. In addition, due to its high recurrence and lifelong surveillance it is the most expensive cancer to treat on a per patient basis (CITE BCAN). A significant need exists for diagnostic tests capable of detecting cancer recurrence in a minimally invasive and cost-effective manner. Funding from OCTRI would support initial proof of concept to validate reagents for detection of our genomic signature and the testing of validated reagents on 20 urine samples from our tumor bank.

Neil Roundy, MD, Department of Neurosurgery

Bio-Absorbable Clip for Watertight Closure of Human Tissues

During spine surgery, surgeons often encounter the dura, which is a tough rubbery sack that contains the brain, spinal cord and spinal fluid. On occasion, this membrane may be opened, either intentionally or otherwise. This is called a durotomy and it must be closed in a water-tight fashion in order to prevent leakage of the spinal fluid that if untreated can lead to problems of wound breakdown, infections, meningitis, severe headaches or other potentially fatal consequences. Closure of a durotomy involves suturing the opening with very fine suture and working down very narrow deep corridors using an operative microscope or surgical loupes. As the corridors we work in become narrower, it is more difficult to expeditiously close the dura in a watertight fashion. Often, subpar closures can result, leading to spinal fluid leaks and potentially a host of other complications. Therefore, we have proposed a tissue stapler that utilizes a bioabsorbable polymer to close the dura or other tissues in a watertight fashion. The benefit of this over other existing methods is that it is absorbable, leaving no trace after a period of time, does not obscure future imaging with metal artifact (as other tissue clips do), can be deployed in a minimally invasive setting in seconds, and everts tissue edges of the dura to prevent scarring to the spinal cord.