Biomedical Innovation Program Awardees

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

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.

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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.