

Wallace H. Coulter Translational Partners Grant Program
School of Biomedical Engineering, Science and Health Systems
Drexel University

2009 PROJECT ABSTRACTS

PREVIOUSLY FUNDED PROJECTS

Development of the Drug Delivery Surgical Staple (M. Wheatley, A. Brooks, and B. Layton)

Abstract: The objective of this project is to develop a prototype new staple for small lumen structures fabricated from an FDA-approved biocompatible, biodegradable polymer that delivers bioactive agents at a pre-programmed rate to improve healing for in vivo proof of principle. As approximated tissue heals, the staple device will degrade, simultaneously releasing wound-healing agents, chemotherapeutic agents and / or radioactive therapy thereby assuring delivery of treatment to the site where it is needed most, the surgical margin. The proposed effort includes final staple design (rivet), materials optimization and animal experiments to measure efficacy of drug release and bursting pressure in vivo for wound healing, antimicrobial and chemotherapeutic applications. Prototype staples will be made of poly(lactic-co-glycolic acid) (PLGA). PLGA is a non-toxic, biodegradable, and biocompatible polymer approved for use in humans by the Food and Drug Administration. Material optimization will involve stress testing. Dr. Layton, a crucial addition to the team, will design the stapler machine using CAD. Animal experiments will be conducted in male Sprague Dawley rats. The drug delivery profile will be developed using radio-labeled drugs (¹⁴C) and efficacy tested in standard in vivo wound healing assay. Development of this drug delivery surgical staple will improve the speed, accuracy, and effectiveness of surgical procedures, while lowering the morbidity and mortality rates of surgical interventions. Because of the disease rate of the intended population, immuno-suppression and cancer, rapid translation of this technology will result in a real clinical benefit within the first year of clinical use.

VEUSim: A Virtual Endovaginal Ultrasound Simulator for Physician Training: Year II (T. Doehring and N. Handy)

Abstract: Endoscopic ultrasound is a valuable tool for early detection of life-threatening diseases such as ovarian cysts and ectopic pregnancy. Unfortunately, training is difficult and expensive, particularly for endovaginal ultrasound, which has severely limited widespread use. To address this clinical need, we propose a 3-D, portable virtual reality (VR) training system designed to train users in endovaginal ultrasound examination. A true 3-D visual display and touch sensitive haptic interface will provide an immersive VR experience with realistic endoscope "feel". Because the system is primarily software-based (using newly available off-the-shelf components) the simulator will be portable (new innovation), and much less expensive than existing systems that currently cost over \$100,000 per unit. Compared to most other bioengineering related technologies, VEUSim has very low development costs, a streamlined path to market (no FDA required), protected IP (training modules), and high volume of potential customers, beginning with integration into current medical student and physician training programs. In our first year of work on this project, we have met all of our stated milestones, and have developed a working prototype. In this second year, we propose four new major milestones, 1. Improve the ultrasound visualization using actual data, 2. Perform preclinical testing of training modules to validate the simulator performance, 3. Use the data gathered in part 2 to further improve the GUI interface and training algorithms, and 4. Initiate consumer and health care industry interest through a combination of internet exposure, conference presentations, and publications. We again wish to emphasize that our Coulter research project is aimed at creating an educational tool for physicians and technicians who perform endo-vaginal ultrasound procedures. It is not a medical device and will therefore not require formal clinical performance testing, FDA classification, or FDA approval prior to

product launch. Our contacts at the FDA have "informally" agreed with all of our assessments in this area. This means that the product development timelines are relatively short and the attendant costs relatively low compared to other biomedical technology based medical devices.

Optical Diagnosis and Treatment Optimization in Chronic Diabetic Wounds: A Pilot Clinical Study – Phase II (E. Papazoglou, K. Pourrezaei, L. Zubkov, and M. Weingarten)

Abstract: After the successful completion of all milestones set forth during the first year of Coulter funding for this project, we have demonstrated that the robust and portable near infrared-based device we designed and assembled can be used in assessing the early healing progression in healthy and diabetic animals. The prototype device incorporates the ability to assess the extent of hydration at the wound site in addition to the detection of oxygenated and deoxygenated hemoglobin. Chronic wound healing assessment is further enhanced with the added capability to vary sensor penetration depth by adjusting probe design. During the second year of funding we propose to complete a human pilot study and we **already have IRB approved protocol for such measurements on healthy controls and diabetic patients**. During the second year of funding, we will also develop the clinical interface (the display) for the device, by integration of the optical parameters measured by the near infrared device into an algorithm yielding results helpful to the physician.

Living Tissue Sterilization by the Dielectric Barrier Discharge Plasma (K. Barbee, G. Friedman, A. Fridman, A. Brooks, V. Vasilets, and A. Gutsol)

Abstract: Despite tremendous advances in surgical technique and technology, a fundamental requirement for a successful outcome is proper sterilization of the surgical field. For routine and non-emergent procedures, this is accomplished by pre-operative topical application of disinfectant solutions such as Betadine. However, there are many situations for which the use of chemical disinfectants is contraindicated. Open wounds are not amenable to chemical sterilization because of the potential for irritation, chemical burns, and tissue damage. Thus, there is a need for a nonchemical method of sterilization for a wide range of clinical applications that includes open wounds due to trauma, intraoperative sterilization of the peritoneum in the case of bowel perforation, post-operative wound care, surgery in the oral cavity, and diabetic ulcer care. Furthermore, a device capable of providing pre-operative sterilization of the surgical field without the use of chemical disinfectants would be useful in military applications or other situations in which supply line limitations make use of chemical disinfectants more difficult to support. Finally, non-chemical sterilization methods capable of eradicating parasites, fungi, bacteria and viruses on or just beneath the surface of living tissue would also be useful for the treatment of a wide variety of conditions mediated by infectious agents such as acne, cutaneous Leishmaniasis, onychomycosis (toenail fungus), and athlete's foot. We have developed a laboratory prototype Floating Electrode Dielectric Barrier Discharge (FE-DBD) system, which functions by applying an alternating or pulsed high voltage to one electrode covered by a dielectric and positioned in proximity (few millimeters) to tissue on human body. We have shown that the plasma generated is capable of rapidly killing bacteria and other microorganisms without damaging the underlying tissue. We will test efficacy and safety of this approach in realistic animal models simulating human skin and open wounds. The device itself will be optimized for portability and customized for specific applications.

LCL Grafts: Innovative Small Caliber Vascular Grafts for Coronary Bypass Operations (P. Lelkes, R. Levy, and R. Composto)

Abstract: Peripheral vascular disease is a widespread clinical problem, accounting for more than one million vascular graft surgeries each year in the United States. To date, attempts to develop a small-bore synthetic coronary artery graft (≤ 5 mm inner diameter) have been unsuccessful largely due to thromboembolic complications (clotting), incompatible, synthetic blood-contacting graft surfaces, and/or neointimal hyperplasia originating at the sites of anastomosis. Novel synthetic small vessel substitutes are needed because existing technologies for large vessel conduits cannot be reproduced for small diameter grafts, and small diameter grafts using the old paradigm and materials fail at clinically unacceptable rates. We propose to generate a novel medical device, operationally termed the "LCL

Graft™, which is an oxidation resistant, highly compliant small caliber vascular graft made of improved, oxidation-resistant polyurethane with physical and chemical modifications to its surface designed to concomitantly limit thrombogenicity and enhance endothelial cell attachment. The LCL Graft™ will be easily packaged and marketed due to its extended shelf life and readily available for use by surgeons, either as is, or following endothelialization. One possible application of the LCL Graft™ will be as a coronary bypass graft with or without endothelial seeding either prior to the procedure or directly in the operating room setting. We anticipate that our product will significantly improve the clinical outcomes of small-bore grafts for use as coronary bypass grafts and, eventually, also in the peripheral circulation.

Real-time Seizure Detection and Control System using Our Patented Ceramic-base Multisite Electrode (K. Moxon and S. Jenssen)

Abstract: Epilepsy affects between 0.5 to 1.0 % of the general U. S. population, or well over 2 million people. Approximately 20% of these patients do not respond to the best available treatments and continue to have intractable seizures. Epilepsy management translates to annual financial costs of approximately \$12.5 billion. This emphasizes the importance of seizure detection and control and its relationship to the total medical costs. Our approach for a seizure detection and control device is to detect changes in single neuron activity prior to the onset of a seizure. Our device consists of three parts: 1) a patented Ceramic-based Multisite Electrode (CBMSE) (Patent No. 6,838,200: Moxon and Chapin) that is chronically implanted into the affected neural tissue, 2) a commercially available 'neurochip' we helped to develop, that conditions the signal, 3) an IP protected (provisional patent) spike detection system that evaluates, in real-time, whether a seizure is imminent. Pre-clinical animal studies in the rat have shown that this system can predict seizures at least 4.6 seconds before onset. At this point, microstimulation would be triggered to prevent the full seizure. However, this system includes an invasive component that will be chronically implanted into the brain tissue of patients. Therefore, in order for this system to be used clinically, FDA approval of the implantable component is required. There are two goals for this proposal, 1) design and build a device for testing on humans and 2) develop a plan for a pilot study to form the basis of clinical trials for ultimate FDA approval. The deliverables for this proposal will, therefore, be 1) a prototype ready for clinical trials, 2) results of mock trials with neurosurgeons on cadavers, 3) local Institutional Review Board (IRB) approval for the clinical trial and, finally, 4) Investigational Device Exemption (IDE) from the FDA, a requirement for clinical testing of a class III medical device. Our business model is to sell or license the technology after we acquire FDA approval. Full cost for FDA approval is estimated at one million dollars. We expect to raise one-third of this from foundations, including epilepsy foundations and the remaining funds by partnering with a medium sized medical device company that manufactures other devices for epilepsy treatment.

SECOND YEAR ACTIVE PROJECTS

QLISA for Point of Care Detection of Inflammation (E. Papazoglou, S. Murthy, and J. Reynolds)

Abstract: Inflammatory diseases comprise of multiple diseases such as rheumatoid arthritis, inflammatory bowel disease (IBD), multiple sclerosis, neurologic disorders and myocarditis, a deadly disease. There is an unmet need to detect inflammation early, accurately and in a cost effective manner. Considering the population affected by these diseases, we believe this diagnostic market is of the order of over a billion dollars. Although IBD affects a smaller population (1 million in the US) our initial lowest estimation is that the use of diagnostic kits can generate revenues of approximately 30 million per year. We have advanced the application of next generation clinical diagnostic tools using nano crystals called quantum dots (QDs) interfaced with specific antibodies to specifically and quantitatively assess presence of Myeloperoxidase (MPO), Interleukin 1-alpha (IL-1_α) and Tumor Necrosis Factor-alpha (TNF-_α) either alone or in combination in tissue. We have demonstrated their expression to clinical disease activity observed in the dextran sulfate animal model of colitis which produces colitis reminiscent of human IBD. We now propose to develop a QLISA immunoassay based on QDs, and capable of quantifying biomarkers in feces, blood or urine samples. This technology is capable of producing cost-effective diagnostic kits for accurate diagnosis and for monitoring patients to evaluate treatment responses without the need of invasive procedures. We have already disclosed our invention for commercialization of this kit highlighting its novelty and have described the way the

information obtained from these tests can be used to quantitatively monitor a patient's disease condition and response to treatment. In the initial phase of this application we focus on developing sensitive and specific quantum dot conjugates and testing them in the QLISA assay (sandwich or competitive). Once this milestone is accomplished, we plan to partner with established medical diagnostic laboratories for commercialization.

Portable Breast Elasticity and Mobility Measurement for Tumor Location and Malignancy Screening (W.Y. Shih, A. Brooks, and W.H. Shih)

Abstract: In 2005 alone, more than 200,000 American women were diagnosed with breast cancer and more than 40,000 deaths occurred from breast cancer. The best prevention for cancer related deaths is early detection. In breast cancer, patients become aware of the first warning signs when they or their doctors discover lumps (tumors) that are stiffer than the surrounding tissues. The only way to find tumors that cannot be felt is through routine screening. To date, yearly mammography beginning at age 40 is the only FDA approved breast cancer screening technique. It provides no information about the tumor stiffness or mobility and has a typical sensitivity of 85%, which decreases to 65% in radio dense breasts. Even with routine mammography, there are many women, especially young women who are diagnosed at a late stage. It would be of significant advantage to have a device that can provide direct, in-vivo tissue elasticity and mobility measurement to allow accurate breast cancer detection and screening in these women who are too young or whose breasts are too dense to benefit from mammography. In addition, a device with a better size sensitivity than the current technologies will also allow earlier breast cancer detection and save lives. The goal of the proposed study is to develop a portable, all-electrical, breast elasticity and mobility measuring tool that not only is capable of locating small tumors but also able to predict tumor malignancy. With different levels of sophistication, this can be developed into a tool that physicians can use for diagnosis in a clinical setting as well as one that a woman can use at home for regular monitoring. The proposed portable breast elasticity and mobility imaging tool is a piezoelectric finger (PEF) complete with a hand-held, all-electrical measuring unit and a less than 5" x 5" x 5" 3-D automation unit (see Fig. 1). A PEF is a piezoelectric cantilever tissue *elastic and shear* modulus sensor developed in our laboratory, which has both the actuator and the sensor in one device using simple electrical means. Measurement of tissue elastic and shear properties is achieved by simply placing a PEF on a patient much like palpation. The innovations of the PEF sensor include (1) palpation-like tissue stiffness imaging both under shear and under compression with less than one-millimeter spatial resolution up to a depth of several centimeters, and (2) use of the shear modulus/elastic modulus ratio to measure tumor mobility to screen for malignancy. The capability of the proposed PEF has been well demonstrated in samples removed by surgery. The proposed study aims at developing the necessary instrumentation for and carrying out pre-surgery breast elasticity and mobility imaging on patients to generate *in-vivo* testing results. The key advantages PEF are as follows. (1) *The proposed PEF has better detection size sensitivity than all existing technologies* — has positively identified a 3 mm tumor missed by mammography, ultrasound, and the physician's palpation. All these techniques have a size limitation of at least 1 cm. (2) *It has also demonstrated that better than 90% correlation between the shear/elastic modulus ratio and tumor malignancy* — a capability all existing technologies lack. (3) With a 1.5 cm wide PEF of depth sensitivity of more than 3 cm, it can probe for breast cancer for almost all body-types. (4) In addition, the PEF is gentle. It only works with less than 1% strain, which would cause minimal discomfort to the patient. (5) It is also portable and can be low cost. The team combines the diverse and complementary expertise of the investigators. W.H. Shih will handle piezoelectric materials development and fabrication. W.Y. Shih will be in charge of PEF development, instrumentation, design and detection. Dr. A. Brooks is the physician who will work with patients to allow the PEF to be tested on real patients. It is expected that a low-cost and yet highly accurate breast elasticity and mobility-imaging tool complete with a portable measuring unit will be developed. Previously a portable unit of a size of a pocket calculator running on a 9-volt battery has been built for measuring the resonance frequency of piezoelectric microcantilever sensors. We envision a similar calculator-size electrical measuring unit and a less than 5" x 5" x 5" 3-D automation unit will be developed to operate the PEF. This imaging tool will help a physician and potentially a woman locate *smaller breast tumors than the current technologies and screen for tumor malignancy* at the same time to save lives. The results of this seed grant will enable the team to seek further funding from NIH or other funding sources.

FIRST YEAR ACTIVE PROJECTS

Functional Near-infrared Spectroscopy as a Monitor for Depth of Anesthesia (K. Pourrezaei, J. Horrow, and S. Bunce)

Abstract: Fear, dread, panic, and, less commonly, excruciating pain accompany unintended awareness during general anesthesia. No clinical device is currently available to measure reliably the depth of anesthesia, awareness during surgery. A reliable anesthesia depth monitor would find application in the vast majority of the 20 million general anesthetics administered (in 2004) in the United States. The objective of this proposal is to translate the existing laboratory functional near-infrared spectroscopy (fNIRS) system, into a first generation clinical prototype for a reliable depth of anesthesia monitor to prevent awareness during surgery. The fNIRS is a non-invasive, minimally intrusive and safe medical device which detects the hemodynamic response of brain cortex to cognitive activation. The proposed technology is intended to be utilized in the operating room (OR), intensive care unit (ICU) and a range of other settings where sedation is given. The preliminary testing of the device has been completed through collaboration with the clinical partners at the DUCOM, Department of Anesthesiology.

Treatment of Lower Back Pain Utilizing a Biomimetic Aggrecan Injection (K. Barbee, M. Marcolongo, E. Vresilovic, and B. Schauer)

Abstract: Degenerative disc disease of the spine causing lower back pain is one of the leading musculoskeletal disorders confronting our health system. Annually, 15%-20% of the population experiences lower back pain; 60% or more will experience back pain over a lifetime(2). The utilization of epidural injections for managing chronic back pain was shown to increase from 802,735 in 1998 to 1,776,153 (121% over 7 years) as reported by medicare. At the time of the steroid injection procedure, however, it would be possible to also inject the nucleus with a material that would augment the disc and restore normal mechanics, thus alleviating pain long term. We propose such a material that would serve as an injectable medical augmentation device. We believe that the treatment will be considered a device rather than drug by the FDA. The material system is philosophically based on the 3D brush-like structure of aggrecan, the primary proteoglycan of the nucleus. Aggrecan has two main mechanical functions in the disc: 1) it allows water uptake by the nucleus due to sulfated groups in the chondroitin and keratin sulfate rich regions which, in part, provide intradiscal pressure and 2) it provides electrostatic repulsion due to the 3D macromolecular structure, which contributes to intradiscal pressure and disc height. The applied engineering of the polymer structure using a biomimetic philosophy will enable the development of an effective early stage treatment to the spine.

Bioactive Alimentary Protein-Based Scaffolds (APS) for Wound Healing and Regenerative Medicine

(P. Lelkes, E. Papazoglou, and M. Weingarten)

Abstract: The focus of this proposal is to develop and commercialize APS into a readily available-off-the shelf skin substitute, which will promote accelerated wound healing. The unique aspect of this proposal is to utilize soy protein isolate, a common alimentary "green-protein" for generating a high-tech biomedical platform technological tool that a) will circumvent current and emerging problems with animal-protein bases skin substitutes and b) meet an unmet clinical need, i.e. to provide an affordable, bioactive scaffold for wound healing. As a first potential application, we propose to test the feasibility of a soy-bean based APS for the treatment of a "regular" full-thickness wound in a rat model, thus testing the hypothesis that APS will accelerate wound healing over that provided by the current standard of care. In addition to continuing our ongoing basic *in vitro* characterization of the physicochemical properties of APS, and its interactions with cultured dermal cells (*Aim1*), we propose to conduct initial feasibility tests of our scaffolds using an established rat model of acute wound healing, which has previously been used by our collaborators (*Aim2*). We propose to assess wound healing by using functional near infrared (fNIR) spectroscopy, in combination with conventional planimetry, wound biopsies and biochemical assays. Subsequently, if successful, in a second year of funding we will propose to explore the usefulness of APS as a treatment modality in a porcine model of chronic

wounds. Development of the porcine model will be essential for the proof-of-concept; however, if approved by the IRB, we might also be able to directly proceed to treating a small number of human patients, as happened in the prior study of our collaborators on fNIR. We expect that APS could be in initial clinical trials within 2-3 years at an expense of ~ \$ 500,000. Funding from the Coulter Foundation will help us to quickly propel our research towards a solid proof- of-concept validation, using established animal models, and translate APS into a clinically viable product.

SEED PROJECTS

A Wireless Embedded Intracranial Pressure Monitoring Device – Implantable at Bedside (A. Rosen, and F. Kralick)

Abstract: Elevation of the Intracranial Pressure (ICP) is one of the most important issues in neurosurgery and neurology in clinical practice. ICP monitoring is utilized in many pathological conditions of the brain including trauma, neoplasm, and infection, and is the most sensitive indication of shunt failure for the treatment of hydrocephalus. On average, each year, hydrocephalus accounts for over 50,000 hospital admissions, 10,000 people are diagnosed with brain tumors, and 100,000 have hemorrhagic stroke. The measurement of ICP is critical in the management of such neurosurgical patients. Hydrocephalic patients are treated with shunts, which divert the excessive cerebrospinal fluid (CSF) to a target distal from the ventricles for absorption and removal from CSF circulation. Shunt failure is a huge problem in the treatment of hydrocephalus with failure rates of 40 and 50% at one and two years respectively. Shunt malfunction rate is about 17% in the first year of placement in the pediatric population. The current method of ICP measurement requires cables that emanate from the scalp that tether the patient to monitors in an ICU setting. This is associated with patient morbidity, most commonly infection and mortality. These methods are not suitable for long-term ICP monitoring for patients suffering from chronic diseases like hydrocephalus. A novel method for measuring ICP especially in the long term is proposed. A wireless, completely implantable device, operating at Industrial-Scientific-Medical (ISM) band of 2.4 GHz was developed and tested. *In-vitro* and *in-vivo* evaluations were performed to demonstrate the feasibility of microwave pressure monitoring through scalp, device integrity over a long period of time, and repeatability of pressure measurements. The present prototype is implanted in a burr hole (12 mm) drilled in the skull during a neurosurgical procedure. A patient in need of such a monitor undergoes a surgery for the underlying cause of elevated ICP. Thus, no additional procedure is required for the device implantation. This device will be miniaturized further for a possibility of implantation at the bedside. In-vitro studies were conducted for a month to gauge the device reliability in terms of its performance and integrity in a medium emulating the biological environment. Long term *in-vitro* and *in-vivo* (canine) studies for up to a year will be conducted to evaluate the device performance. The goal of this research activity will be to collect data on the reliability of this device which will be a part of the statistical results needed to apply for FDA approval for performing clinical trials. The implantation of our proposed device in cases of chronic conditions (like hydrocephalus) will have a significant impact on the currently required post-operative medical cost.

Development of Electronic Blood Pressure Wristwatch (R. Lec, M. Swoboda, and H. Eisen)

Abstract: There are many cardiac-related health conditions, which are still difficult to diagnose and treat in spite of recent significant advancements in cardiac medical diagnostic and treatment technologies. Examples include aortic aneurysm, renal artery stenosis, aortic coarctation; in many cases some of these conditions can develop without any symptoms (like aortic aneurysm) or some can be confused with other conditions (for example, diagnostic problems with Raynaud's disease). In addition, continuous monitoring of cardiac patients faces several challenges as well. That is especially true with young children and in neonatal care. In the latter, continuous use of ECG is unworkable and invasive use of pressure catheters is limited. With the recent trends to lower the cost as well to involve more actively patients in their health care, home-care and point-of-care technologies are of growing interest. Here, novel medical devices, capable of dual applications as diagnostic and treatment monitoring, are providing a very desirable solution. Modern solid state, nanotechnology based biosensor technologies, are delivering appropriate technological manufacturing platform. Small, inexpensive, disposable, wireless, computer-and Internet-compatible, easy to use and wireless

biosensors are enabling many novel medical applications, and changing the way how medicine is being practiced. In our project we propose to address those unmet cardiovascular disease (CVD) needs by developing a novel sensor for continuous blood pressure measurements. Blood pressure, a basic cardiac diagnostic modality, though has been in use since the end of the XIX century, has been mainly focused on the measurement of its systolic and diastolic values, and their derivatives using bulky and inconvenient cuff-based technologies. Our initial focus will be to develop a Blood Pressure ring sensor for continuous monitoring absolute blood pressure.

Development of a Urine Screening Test for Liver Cancer (Y. Su and W. Shih)

Abstract: There is an unmet and urgent need for a noninvasive, sensitive, specific, and cost-effective screening test for the early detection of liver cancer. We have previously shown that urine contains circulation derived DNA that can be used for the early detection of diseases and cancers that occur at non-urinary tract sites. Given the numerous advantages of using urinary biomarkers, the goal of this project is to develop a noninvasive urine screening test for liver cancer that can ultimately improve the diagnosis and prognosis of the disease. Two approaches are being undertaken to develop a clinically-feasible urine screening test for liver cancer. One is to construct a panel of urinary DNA biomarkers for disease detection and monitoring. Due to the heterogeneity of cancer, a multiple markers panel will be needed to ensure sufficient sensitivity and specificity for such a urine test. The second approach is to develop a rapid, sensitive, high-throughput, cost-effective platform to profile DNA markers suitable for circulation derived urine DNA substrates. A unique piezoelectric microcantilever sensor (PEMS) developed in Shih and Shih's laboratories holds great potential for developing a multiplexed, sensitive, specific, rapid, and cost-effective test for the profiling of DNA markers for cancer screening. Drs Shihs' labs are currently working to optimize the PEMS for urine genetic testing. This project is currently supported by NCI and the Coulter Foundation. The success of this study will deliver a urine screening test for liver cancer and ultimately other cancers as well such as colon cancer which potentially can revolutionize cancer screening, early detection, the monitoring of recurrence, and disease management.