SUMMARY OF NEW AWARDS

BIOENGINEERING RESEARCH PARTNERSHIPS (BRP)

FY 2001

The following text provides a summary of new Bioengineering Research Partnerships (BRP) grants awarded during Fiscal Year 2001 by the BECON member institutes and centers in response to program announcement PAS-00-006. The objective of the BRP program is to support basic bioengineering research addressing important biological or medical problems with the work being done by a multidisciplinary research team which applies an integrative, systems approach to develop knowledge or methods to focus on the project objectives.

Funded grants are listed below in alphabetical order by the principal investigator's (PI's) last name. Other information provided for each grant includes PI affiliation, project title, grant number, funding organization, and a brief summary of the project.

1. **Principal Investigator:** Beebe, Thomas **Affiliation:** University of Delaware
   Project Title: Probing Single-Molecule Neuron-Ligand Pathfinding
   Grant Number: 1-R01-NS-43928-1- **Funding Organization:** NIBIB
   Abstract:

Among the most debilitating and costly human ailments are injuries and diseases of the nervous system. Currently there are a limited number of available therapies, none of which restore function to injured neurons of the CNS. Numerous studies in animals and man strongly suggest that restorative therapies based on cell transplantation are feasible. However, a major challenge that remains is the reconstruction of damaged and diseased neural pathways. Toward this end, biomaterials have been examined as bridging devices to support directed nerve outgrowth from regenerating neurons. This project is driven by the central hypotheses that the local surface density, conformation and discrete spatial distribution of substrate molecules are sensed by a neuron's integrin receptors, translated in an intracellular molecular sequence that regulates integrin receptor expression and controls further axonal growth and also determines the overall readiness of the neuron to regenerate and establish connections.. The three specific aims are to: (1) create and fully characterize model substrates with a controlled pattern and surface density of laminin, fibronectin and related oligopeptides for neuron and astrocyte attachment and axonal growth studies in the two other Aims; (2) Study neurite outgrowth (dynamic bond strength, diffusivity, surface density and bond-rupture force) of dorsal root ganglion neurons on the model substrates, employing single- molecule techniques such as AFM bond-rupture measurements and fluorescence correlation spectroscopy; (3) Study the axonal growth of neurons (dynamic bond strength, diffusivity, surface density and bond-rupture force) on confluent astrocyte monolayers of different ages, using the same methodologies. Underpinning all studies are extensive quantitative surface characterization techniques.

2. **Principal Investigator:** Brittenham, Gary **Affiliation:** Columbia University
   Project Title: High Tc Susceptometer for Magnetic Measure of Body Iron
   Grant Number: 1-R01-DK-57209-1-A1 **Funding Organization:** NIDDK
   Abstract:

This partnership will design, develope and clinically validate a high-transition-temperature (high Tc; operating at 77oK) superconducting susceptometer for the direct, non-invasive measurement of hepatic iron stores in patients with iron overload from hereditary hemochromatosis, thalassemia major, sickle cell disease and other disorders. Our laboratories originally proposed that storage iron (ferritin and hemosiderin) could be non-invasively assessed in vivo because of its paramagnetic properties. We subsequently developed low-transition-temperature (low Tc; operating at 4.2oK) superconducting quantum interference device (SQUID) biosusceptometry as a clinical method for the measurement of hepatic iron stores. Our low-Tc susceptometer has three elements which utilize superconductivity: (i) the SQUID, (ii) the field coils that produce a localized steady magnetic field near the liver, and (iii) the detection coils and flux transformer. Recent technological advances make possible replacement of each of these low-Tc elements, cooled by liquid helium, with components able to function when cooled by liquid nitrogen. To provide "proof-of-principle," we have constructed and operated a prototype high-Tc susceptometer with (i) a high-Tc SQUID, (ii) a NdBFe permanent magnet providing a strong localized magnetic field, and (iii) detection coils and flux transformer fashioned from a high-Tc Y1Ba2Cu3O7-delta film deposited on a flexible substrate. Magnetic studies permit accurate, direct, and repeated measurements of hepatic iron stores not possible with any other

method. The development of an affordable, readily usable instrument for the non-invasive measurement of hepatic iron would be a major advance in the diagnosis and management of patients with iron overload that would find immediate and widespread clinical use both in the U.S. and worldwide.

3. **Principal Investigator:** Clemens, Mark **Affiliation:** University of North Carolina - Charlotte
Project Title: Engineering Aspects of Liver Support Systems
Grant Number: 1-R01-DK-58503-1-A1 **Funding Organization:** NIDDK
Abstract:

In spite of many advances in liver transplant surgery, an increasing number of patients with terminal liver disease are dying while awaiting transplants. Consequently, further advances in the storage of donor livers, as well as alternative replacement options and mechanisms for supporting liver function while awaiting a donor liver are needed. A very promising area of research and development is in the development of engineered solutions to the problems of liver support for either natural donor organs or bioartificial livers. However, efforts undertaken within a single discipline are hampered by the complexity of both the engineering and biological aspects of such projects. This proposal constitutes a partnership between bioengineers, biologists and a liver transplant surgeon with the goal of combining their expertise to devise improved methods of liver support via bioartificial livers and improved preservation of donor livers via machine perfusion preservation (MPP). The partnership encompasses three inter-related projects. The first project focuses on delivery of oxygen and other nutrients to the cells in in vitro systems such as the bioartificial liver. The approach involves the modification of the support matrix to facilitate enhanced mass transport. The second project addresses the hypothesis that improved bioartificial liver function can be attained by providing a more physiological combination of cell types in the support device. Specifically, we will investigate the relationship between Kupffer cells and hepatocytes in maintaining prolonged hepatic-specific function in culture. The final project focuses on development of methods for optimization of microvascular perfusion in machine-perfused livers. This project uses a combination of intravital microscopy and mathematical modeling. Moreover, the unique environment that supports the partnership will maximize the potential for success in this interdisciplinary approach and provide an avenue for potential clinical application of laboratory advances.

4. **Principal Investigator:** Davies, Peter **Affiliation:** University of Pennsylvania
Project Title: Cell And Molecular Studies in Cardiovascular Engineering
Grant Number: 1-R01-HL-64388-1-A1 **Funding Organization:** NHLBI
Abstract:

This proposal is a partnership of interdisciplinary scientists in bioengineering and medical research focused on the biomechanics of cardiovascular cells, membranes, and tissues in the context of site-specific therapy and tissue engineering. The partnership is composed of two interactive components: (i) fundamental cell and molecular investigations of cardiovascular mechanotransduction, and (ii) preclinical studies of engineered arteries, heart valve calcification, and microcoil treatment of intracranial aneurysms. The basic studies focus on the continuum of force-membrane-cytoskeleton-adhesion and extracellular matrix. The experimental approaches include geometric constraints, spatial analyses, protein conformational changes, deformation properties, and mass transport characteristics that regulate vascular cell structure, gene expression, function, and maladaptation to hemodynamic forces that may lead to pathological change. Also proposed is the development of new materials to regulate cell adhesion (and hence phenotype), and to delivery of therapeutics in situ. Parallel, complementary preclinical studies focus on tissue engineered arteries ex vive, heart valve pathology (both ex vive and in vive), and the delivery of therapeutic factors to correct intracranial aneurysms in vive. The preclinical short-term objectives are sustained retention of structure and function of arteries maintained ex vive and their reintroduction in vive, the elucidation of heart valve gene expression, and both in vitro and in vive evaluation of the release of potential therapeutic agents from coated platinum microcoils.

5. **Principal Investigator:** Dichter, Marc **Affiliation:** University of Pennsylvania
Project Title: An Implantable Device To Predict And Prevent Seizures
Grant Number: 1-R01-NS-41811-1- **Funding Organization:** NINDS
Abstract:

We propose to assemble an ensemble of accomplished investigators from the University of Pennsylvania, Georgia Institute of Technology, Children's Hospital of Philadelphia and IntelliMedix, a small start-up company through the GIT and Penn, in an intensive five to ten year effort to create a novel therapy for refractory epilepsy: an implantable closed loop system capable of predicting epileptic seizures prior to electrical and behavioral onset and triggering intervention to abort them before clinical expression. The work will have three major thrusts: (1) Seizure Prediction: Developing and refining seizure prediction

algorithms derived from data obtained from implanted biosensors in adults, children and in animal models of human epilepsy, capable of predicting seizures hours to minutes prior to electrical and clinical onset, (2) Mechanisms of ictogenesis: Unraveling the cellular, molecular, neurophysiologic and neuronal network mechanisms underlying the observed signal changes identified by these algorithms through in-vitro and in-vivo experiments in animals, recordings in human candidates for epilepsy surgery, and modeling these findings via computer simulations in order to refine predictive and intervention strategies, and (3) Therapeutics: Developing strategies aimed at specific points in the "ictogenic" process, as discovered above, consisting of electro, physiological and pharmacological interventions to disrupt the cascade of events which lead to seizures, in ways which do not interfere with normal brain function. This work will directly give rise to commercially viable intellectual property including: implantable biosensors, miniaturized biocompatible electrical stimulation and drug infusion hardware, stimulation paradigms, customized pharmacologic agents, customized software/hardware interfaces for signal acquisition, processing and synchronization with algorithms for driving therapeutic interventions. It is hoped that a closed loop seizure prediction and prevention device will be implementable in a 5-l0 year period and will significantly improve the quality of life of individuals with epilepsy.

6. **Principal Investigator:** Gower, Laurie **Affiliation:** University of Florida
Project Title: Role of Biopolymers And Lipids in Kidney Stone Formation
Grant Number: 1-R01-DK-59765-1- **Funding Organization:** NIDDK
Abstract:

The objective of this project is to examine two key issues relevant to urolithiasis; 1) the effects of acidic biopolymers and lipid membranes on nucleation, growth and aggregation of calcium oxalate (CaOx) crystals in an artificial urinary environment; and 2) the injurious effects of a liquid-phase mineral precursor on tubular epithelial cells grown in culture. With regard to 1), many investigators have examined the promotory and inhibitory effects of acidic glycoproteins on crystal growth and aggregation. Our work differs in that a primary focus will be to investigate the relevance of a recently discovered polymer-induced liquid-precursor (PILP) process to pathological biomineralization. The PILP process generates non-equilibrium crystal morphologies which exhibit features similar to crystals found in kidney stones, such as, stratified spherulites. Mineral films and coatings are also deposited by the process, and repetitive depositions might lead to concentrically laminated structures, such as those commonly observed in composite stones. We hypothesize that the presence of this cementatious mineral precursor in the urinary tract could influence the attachment and retention of crystals to renal epithelial cells; or the highly ionic precursor phase could cause cell injury or death, leading to the release of modulatory factors or membrane fragments, which could promote heterogeneous nucleation and/or aggregation of crystals. This 5-year project will enable us to assess the relevance of the PILP process to pathological calcification, as well as to perform a comparative analysis with the more traditional concepts pertaining to the role of lipids and acidic biopolymers in stone formation, and will contribute to the development of bioengineering techniques that are new to the field of stone research. The long-range clinical goal of this partnerhsip is to provide a more effective means of diagnosis, treatment, and long-term prevention of renal calculi.

7. **Principal Investigator:** Hasegawa, Bruce **Affiliation:** University of California - San Francisco
Project Title: Imaging Structure And Function in Small Animals
Grant Number: 1-R01-CA-91771-1- **Funding Organization:** NIBIB
Abstract:

This partnership will develop a dual-modality CT/SPECT system for high-resolution imaging of radionuclides in transgenic and knockout mice that now are in widespread use to model the mechanism, diagnosis, and treatment of human diseases. This research will be focused on the development of techniques that correlate structure and function, and that can perform noninvasive and quantitatively accurate measurement of tissue metabolism and organ physiology in small animals using radiolabeled tracers. Within this context, the research program includes 5 specific aims. (1) A pinhole SPECT system will be developed using a pixellated silicon pixel array and thallium-doped cesium iodide (CsI(Tl)) scintillator for radionuclide imaging of small animals. Two interchangeable detector arrays will be developed, one for imaging low-energy radionuclides such as '25I (27.5 keV), and the other for imaging 99mTc (140 keV) and other radionuclides having higher photon energies. (2) The pinhole SPECT system from Specific Aim 1 will be integrated with a cone-beam computed tomography system volume to allow sequential acquisitions of CT and SPECT images without moving the animal. (3) Cone-beam tomographic algorithms will be implemented for reconstruction of the radionuclide and x-ray tomographic data from the small animal imager. Techniques will be developed that use the reconstructed CT and SPECT data to quantify regional distribution of radionuclide concentration at spatial resolutions suitable for mice. (4) The dual-modality imaging system will be used for in vivo measurement of cardiovascular physiology in transgenic mice to investigate the role of the sympathetic innervation in heart disease. These measurements will test the hypothesis that increased heterogeneity of sympathetic innervation is related to the development of congestive heart failure. (5) The dual-modality imaging system will be used to measure the tumor and organ distribution of humanized anti-HER2 monoclonal antibody in a transgenic mouse model of metastatic breast cancer. The overall goal of this project will develop a high-resolution imaging system that combines CT and SPECT to correlating structure and function. The

system also will be designed to perform noninvasive serial studies in mice, and to replace invasive direct tissue sampling and autoradiography for biodistribution studies and functional assessments using radiolabeled tracers in transgenic mice.

8. **Principal Investigator:** Hollister, Scott **Affiliation:** University of Michigan - Ann Arbor
Project Title: Engineering Joint Scaffolds for Function/Regeneration
Grant Number: 1-R01-DE-13608-1-A1 **Funding Organization:** NIDCR
Abstract:

Tissue engineering offers considerable promise for temporomandibular (TM J) joint reconstruction, a pressing clinical problem. To create durable engineered joint implants, the effects of scaffold material and architecture on tissue regeneration and function must be understood. In this project, we will determine the effects of designed and fabricated internal architectures on bone regeneration by bone marrow stromal cells in an in vivo model of osteogenesis. We will mechanically test these architectures to determine load carrying capability. To test bone-cartilage interface regeneration in vivo, we will create a scaffold interface design seeded with bone marrow stromal cells on one half of the scaffold (bone side) and auricular chondrocytes on the other half (cartilage side), creating a bone-cartilage interface inside the scaffold. Finally, we will then engineer a prototype Conylar Ramus Unit (CRU) based on the most promising data from the bone-bone and bonecartilage scaffold studies.

9. **Principal Investigator:** Hood, Leroy **Affiliation:** Institute for Systems Biology
Project Title: Gene Expression by Multifunctional Biology
Grant Number: 1-R01-CA-91719-1- **Funding Organization:** NCI
Abstract:

The Institute of Systems Biology (ISB) will team with tile Oak Ridge National Laboratory (ORNL) to conduct research on Multi-functional Molecular Biology of gene expression and to develop all Advanced Diagnostic Biochip (ADB) system, the next generation of biosensor system for simultaneous detection of a wide range of gene expression biotargets for biomedical (cancer) diagnosis. Specific innovations of the fully integrated biochip system include: (1) Integrated circuit biochip; (2) Multi-functional bioprobes (DNA, antibody, enzymes); and (3) integrated microfluidics system for in-situ sampling. We will use prostate cancer cell lines, prostate cancer xenografts (human cancers growing in immunologically compromised mice), prostate cancer tissues, and prostate cancer cells isolated from tumors by fluorescence-activated cell-sorting to investigate the mRNA and protein expression patterns of genes that may serve as diagnostic markers. We will use conventional genomics and proteomics techniques to identify a set of diagnostic markers for prostate cancer (years I and 2) which can then be tested against the ADB system in year 3. The benchmarking of the ADB system against conventional microarray technology will be an important aspect of this grant. We also plan to automate and miniaturize techniques for the preparation of mRNA and protein probes. Accordingly, the prostate cancer system will have mRNA (eDNA), protein, enzymes, and cells that can be analyzed by the ABD system.

10. **Principal Investigator:** Humphrey, Jay **Affiliation:** Texas A&M University
Project Title: Histo-Mechanics & Biology of Remodeling in Hypertension
Grant Number: 1-R01-HL-64372-1-A1 **Funding Organization:** NHLBI
Abstract:

Hypertension remains as a major risk factor for a multitude of cardiovascular diseases, and as such it is responsible for significant morbidity and mortality. Recent advances in vascular biology and mechanics suggest a paradigm shift in hypertension research. It is now clear that focusing on local regulatory activities of the vascular wall that are controlled by mechanotransduction mechanisms promises significantly increased understanding. In this proposal, we will focus on the molecular mechanisms of vascular adaptation in coronary and cerebral arteries and arterioles, and the associated integrated manifestations in vessel morphology and function at the cellular and tissue levels. Toward this end, we have developed a new micro-pig model of renovascular hypertension that allows us to detail the time-course of hemodynamic changes during the development and reversal of the hypertension. Using an externally controllable suprarenal aortic coarctation model, we will delineate between purely mechanical effects and those due to engaging the renin-angiotensin system. This will allow us to explore the hypothesis that the efficacy of pharmacological therapy depends strongly on the target vascular bed and the time that the intervention is initiated during the development of the hypertension. The overall working hypothesis is that hypertension-induced alterations in cell function and matrix biology are largely due to changes in the pointwise multiaxial stress field. These hypotheses will be tested by combining clinical, molecular, cell biological, immunohistochemical, morphological, and biomechanical methods to study 5-8 vessels at multiple times during the development and reversal of hypertension in a single animal model, although there are many calls in the literature for multidisciplinary attacks on the

problem of hypertension, this study will be the first to collect and synthesize such broad data. Subsequent parallel studies will focus on additional pharmacological agents and gender-related differences.

11. **Principal Investigator:** Karellas, Andrew **Affiliation:** University of Massachusetts Medical School
Project Title: Digital Mammography High Resolution Flat Panel Imager
Grant Number: 1-R01-CA-88792-1- **Funding Organization:** NCI
Abstract:

This partnership is aimed at developing and evaluating a new high resolution flat panel mammographic imager with a variable pixel size (40 microns and 80 microns) using tiled charged-coupled devices (CCD). The detector will cover an area essentially the same as the sensitive area of a conventional mammographic cassette. The specific hypotheses are: (a) the new imager will exhibit better detective quantum efficiency (DQE) than current screen-film technology. (b) Unlike current screen-film, the system will exhibit higher dynamic range. (c) The spatial resolution will be higher than current flat-panel imaging systems due to the smaller pixel size and 100 percent fill factor. (d) The contrast will be significantly better than existing screen-film systems resulting in better visualization of breast anatomy at a reduced radiation dose to the patient due to the improved DQE. (e) A well-designed mammographic system driven in an optimized acquisition mode will replace screen-film systems for full-breast mammographic imaging. Preliminary computational and experimental studies suggest that a CCD flat panel detector of this type is feasible. The partnership will develop and evaluate the next generation of high resolution digital mammography with high spatial resolution and without the detrimental loss in the signal-to-noise ratio, which is common with the older generation, which uses demagnifying fiberoptics. The proposed prototype using an array of seamlessly tiled CCDs coupled to a structured CsI:TI scintillator by a non-tapering fiberoptic plate will deliver the highest resolution than any other flat panel mammographic detector.

12. **Principal Investigator:** Levine, Simon **Affiliation:** University of Michigan - Ann Arbor
Project Title: Direct Brain Interface Based on Event Detection in ECOG
Grant Number: 1-R01-NS-40681-1- **Funding Organization:** NINDS
Abstract:

A number of people with physical disabilities have difficulty performing any physical movement and would benefit from a direct brain interface, an interface that accepts commands directly from the brain. The University of Michigan Direct Brain Interface (UMDBI) research partnership is a collaboration which includes the Departments of Biomedical Engineering, Electrical Engineering and Computer Science, Physical Medicine and Rehabilitation, Neurology, Surgery and Radiology from the University of Michigan; the Departments of Neurology from the Henry Ford Hospital, and the Institute of Biomedical Engineering from the Technical University Graz. These partners propose to address the functional evaluation of a direct brain interface and the optimization of detection methods used in the direct brain interface. The (time-domain based) template matching detection method developed by the UM-DBI has demonstrated sufficient accuracy in off-line experiments to warrant real-time, on-line implementation and testing with subjects at the University of Michigan and Henry Ford Hospitals who have implanted electrodes for purposes related to epilepsy surgery. The proposed functional evaluation includes: 1) Development of an on-line, real-time testing system for direct brain interface methods; 2) Examination of the ability of subjects to learn to voluntarily improve event-related potential (ERP) quality and detection performance given appropriate feedback; 3) Determination of the accuracy and speed with which a direct brain interface can be used to perform functional tasks; and 4) Identification of the relationship between the location of electrocorticogram (ECoG) recorded brain events and the activated portion of the brain as observed through functional magnetic resonance imaging. Improvements in the accuracy by which brain events can be detected will be approached through development and optimization of time-domain based detection methods and evaluation of the performance of frequency-domain based detection methods on EcoG. The proposed research is intended to conclusively demonstrate that a direct brain interface based on the detection of human ERPs recorded intracranially can be used for control of functional tasks.

13. **Principal Investigator:** Li, Shu-Tung **Affiliation:** Collagen Matrix, Inc.
Project Title: Type 1 Collagen-Based Nerve Guide for PNS Regeneration
Grant Number: 1-R01-HD-41747-1- **Funding Organization:** NICHD
Abstract:

This proposal is a collaboration of multidisciplinary fields of peripheral nerve repair and regeneration, involving Collagen Matrix, Inc., specializing in extracellular matrix design and engineering; Eastern Virginia Medical School, specializing in neuroscience and neurosurgery; Duke University specializing in neuroscience, entubulation repair of peripheral nerve, clinical neurology and urology; and University of South Florida, specializing in clinical urology. The overall goal of this research

partnership proposal is to design, engineer and evaluate in vivo a type I collagen-based bioactive nerve guide for peripheral nerve regeneration applications. The research team, through joint effort of the partnership, applies the current state-of-the-art knowledge of matrix technology, protein chemistry, neuroscience, neurosurgery and clinical urology to systematically evaluate the key design parameters. This systematic approach will lead to the development of a nerve guide that has the high probability of clinical success in nerve regeneration. The specific objectives of the proposal involve the isolation of the key design parameters and testing them in a rat sciatic nerve model. The final prototype, engineered from optimal design parameters, will be evaluated in two primate nerve models (median and cavernosal) as a potential entubulation repair method for clinical application.

14. **Principal Investigator:** Ling, C **Affiliation:** Sloan-Kettering Institute for Cancer Research
Project Title: Multimodality Biological Imaging of Cancer/Tumor Hypoxia
Grant Number: 1-R01-CA-84596-1-A2 **Funding Organization:** NCI
Abstract:

The long-range goal is to develop non-invasive multi-modality imaging that yields biological information of human cancers in 3-dimensions (3D). The short-term objectives are to use NMR and PET for imaging tumor biology and hypoxia in rodent tumors and xenografts. In addition, pO2 levels will be directly measured in the same tumors, and tumor sections characterized to provide a biological basis for the NMR and PET images. All the 3D data sets of images and tumor sections will be spatially correlated with a stereotaxic reference system implanted around the rodent tumors and xenografts. The results will be spatially-correlated using an implantable stereotaxic marker system that identifies the image coordinates of the multiple data-sets and image registration software adapted from existing algorithms in our radiotherapy treatment planning system. Of significance is the spatial correlation of all the 3D data sets, thus relating biological attributes to image features. We believe that this is the first attempt to directly correlate invasive biological endpoints with image features from non-invasive imaging using spatially registered data-sets. Thus, this project integrates physics, chemistry, biology, engineering and computer sciences to study tumor biology and hypoxia, with considerable significance for cancer diagnosis and treatment.

15. **Principal Investigator:** Lizzi, Frederic **Affiliation:** Riverside Research Institute
Project Title: Integrated Ultrasonic Systems for Noninvasive Therapy
Grant Number: 1-R01-CA-84588-1-A1 **Funding Organization:** NCI
Abstract:

The ultimate objective of this partnership is to develop a unified body of scientific knowledge and validated technology concepts that are needed to establish ultrasound as a practical non-invasive treatment modality and to inaugurate ultrasonic therapeutics as a new biomedical discipline. The applicants will systematically elucidate the spectrum of ultrasonic therapeutic lesions that can modify various classes of diseased tissues and develop integrated ultrasonic systems to position, induce, and monitor these lesions. They will focus on establishing a comprehensive basis for future treatments of cancer (primarily of the breast and prostate) and cardiac disease (primarily ventricular arrhythmia and myocardial insufficiency). This partnership involves biomedical engineering research at Riverside Research Institute; animal research studies at Weill Medical College of Cornell University (WMC) and Columbia University College of Physicians and Surgeons (CUCPS); and advanced systems development at Spectrasonics, Inc. Our multi-disciplinary research is designed to achieve a series of fundamental advances in the divers areas involved in therapeutic ultrasound. We will employ extensive theoretical modeling to elucidate physical ultrasound-tissue interactions that can be used to produce therapeutic changes in diseased tissues. We will validate model results for thermal and mechanical effects in a series of animal experiments. Validated results will be used to design and implement advanced therapy systems incorporating two-dimensional arrays and real-time lesion monitoring. The system will be tested and refined using animal experiments that investigate cancer and heart-disease therapy. Results are expected to be incorporated in a systems model of ultrasonic therapy which would permit comprehensive treatment planning and design of future system features.

16. **Principal Investigator:** Meaney, David **Affiliation:** University of Pennsylvania
Project Title: Force Transmission in The Central Nervous System
Grant Number: 1-R01-HD-41699-1- **Funding Organization:** NICHD
Abstract:

This partnership brings together a broad team of bioengineers, neuroscientists, molecular biologists, bioinformaticists, and clinical scientists to examine the molecular etiology of traumatic brain injury (TBI). The focus of this project is to study the genomic and protein expression of force transmission in the central nervous system, with the long-term goal of treating and

preventing neuronal necrosis and apoptosis in gray matter contusions, the most common form of damage in brain injured patients. Our overall hypotheses are (a) the mechanical threshold for neuronal apoptosis is lower than the threshold for necrosis; (b) a unique and consistent gene expression profile, or 'fingerprint', occurs in apoptic or necrotic neuronal populations that experience similar stretch levels; (c) genomic and protein expression profiles, as well as the distribution of apoptotic and necrotic cells, are attenuated by targeted pharmacotherapies. These hypotheses are tested by partnering resources from three strategic areas: cell and tissue biomechanics, gene and protein expression profiling, and neuropathology/treatment of traumatic brain injury. This integrated format allows us the unique opportunity to 'preprint' cells from the in vivo cerebral cortex with a well controlled mechanical load, screen these cells for stretch-induced changes in both transcription and translation, and use this information to evaluate and guide therapeutic strategies for rescuing damaged neurons. The central outcome of this project will be the identification of the temporal, biochemical and genomic responses of neurons within the cortex that have been exposed to well-defined mechanical conditions. This information will guide the development and evaluation of therapies to augment the endogenous repair processes in the cortical neuron population. Our long-term vision over the projected life-span of this project is to apply the same infrastructure to design new injury-specific therapies for other important forms of brain injury, with the goal of reducing morbidity and mortality in head injured patients.

17. **Principal Investigator:** **Mitzner, Wayne** **Affiliation:** Johns Hopkins University
Project Title: New Approach for The Treatment of Asthma
Grant Number: 1-R01-HL-66020-1-A1 **Funding Organization:** NHLBI
Abstract:

This proposal will develop and evaluate an innovative and potential clinical treatment for asthma. Although there are a multitude of different possible triggers, an acute asthmatic attack is always characterized by contraction of the smooth muscle in the airway wall. Despite this common end point, most of the clinical asthma research and therapies in recent years have focused on understanding the immunologic factors that often lead to asthmatic attacks. The present proposal describes research and development that focuses on a treatment of smooth muscle that will thus be effective in asthmatic attacks regardless of the initial trigger. It involves the design, construction, and application of a biomedical device that can prevent or minimize the ability of the smooth muscle in the airways to constrict. The project involves a close working partnership between the physiologic laboratories and expertise at the Johns Hopkins University and a small California biomedical engineering company, that is providing the mechanical and bioengineering skills needed for product development. The overall hypothesis governing this proposal is that, the treatment of airway smooth muscle with this innovative system will minimize obstruction caused by smooth muscle contraction, regardless of its origin. The information obtained from these functional studies will be essential, not only in the ongoing engineering and development of the optimal device, but also to help set guidelines for the use of this device, in future clinical trials. The studies proposed in this project will thus allow optimization of a biomedical device that has the potential to effectively cure all forms of human asthma.

18. **Principal Investigator:** **Peckham, Paul** **Affiliation:** Case Western Reserve University
Project Title: Development of Networked Implantable Neuroprostheses
Grant Number: 1-R01-NS-41809-1- **Funding Organization:** NINDS
Abstract:

Neuroprosthetic devices that electrically stimulate paralyzed muscles provide functional enhancements for individuals with spinal cord injury and stroke such as standing and stepping, reaching and grasping, and bladder and bowel function. Current implanted neuroprosthetic systems utilize considerable external powering and signal processing, and each system is tailored to the specific application for which it was intended. The need to design a customized implant system for each application severely limits progress in the field and delays introduction of new technology to the end user. Therefore, we propose to design, fabricate and evaluate an implanted neuroprosthesis with an open architecture that can be easily configured for current and anticipated neuroprosthetic applications, allows accommodation of new innovations by various participants in the field, minimizes external components, and can be clinically implemented. The implant design we propose is based on a network of small implanted modules, distributed throughout the body. A given system will consist of one or more "hubs" with significant processing capability for implementing advanced control-algorithms and an inductive link for external programming and powering, as well as separate input and output "nodes" for sensing and stimulating. The network will initially communicate and distribute power internally using wire-based leads, but the feasibility of a wireless network and local power storage will also be investigated. Power will be provided via an external inductive link, with a rechargeable implanted battery used to provide un-tethered operation. A variety of modules will be developed, each with a specific function including: muscle-based stimulation, nerve cuff stimulation, biopotential (electromyogram, electro-oculogram, electro-encephalogram, electroneurogram) signal recording, body segment orientation measurement and acceleration measurement. Other potential modules that could be incorporated into this system include mechanical actuators, joint angle transduction, and strain gage based sensors. \

19. **Principal Investigator:** Rabbitt, Richard **Affiliation:** University of Utah
Project Title: Micro-Electric Impedance Spectroscopy of Hair Cells
Grant Number: 1-R01-DC-4928-1- **Funding Organization:** NIDCD
Abstract:

This research effort is aimed at the development and testing of micro-electric impedance spectroscopy (mEIS) and tomography (mEIT) hardware and reconstruction software to record and image the distribution of electrical properties within the cytoplasm, organelles and membranes of vestibular and auditory sensory hair cells. A combination of flex-circuit technology and standard lithographic microfabrication techniques will be used to construct micro-recording chambers instrumented with arrays of metal electrodes at subcellular dimensions. Cells will be positioned within the recording zone under mircroscopic observation and interrogated using radio frequency electrical signals. Voltage and current will be measured around the outside surface of the cell and used to reconstruct three-dimensional maps or images of the conductivity and permittivity throughout the cell. mEIT systems will be used to interrogate electrical properties of cochlear outer hair cells and type II vestibular hair cells in response to stereocilia displacements, electrical stimuli, and acetylcholine efferent neurotransmitter stimulation. Results will contribute to our fundamental understanding of the spatial distribution and temporal response of electrical properties in these important sensory neurons. Perhaps more importantly, mEIT devices to be developed as part of the research, will provide an entirely new window through which to view the living machinery of a wide variety of normal and pathological cells. The project integrates bioelectricity, imaging, bioinstrumentation, micro/nano-bioesensors, physiological modeling/computation, biomechanics and microfluidics. Devices involve on-chip transport of solutions/pharmaceutics and living cells.

20. **Principal Investigator:** Renshaw, Perry **Affiliation:** McLean Hospital
Project Title: High Field MR Research in Drug Abuse
Grant Number: 1-R01-DA-14178-1- **Funding Organization:** NIDA
Abstract:

Magnetic resonance spectroscopy (MRS) and functional magnetic resonance imaging (fMRI) are extraordinarily promising new imaging modalities that are increasing our understanding of the nature of drug abuse and addiction. This partnership will conduct a series of ten engineering projects which will enhance the capabilities of the new Varian NMR Systems 4.0 T MR scanner to conduct studies of individuals with substance abuse disorders. This research program will involve bioengineering and clinical investigators at McLean Hospital, the Beth Israel Hospital, Tufts University, Boston University, the University of Washington, the University of Oxford, the University of California, San Francisco, and Wayne State University. Specific projects are summarized below: 1. Objective motion detection and correction in time series fMRI experiments. 2. Optimized phased array coil design. 3. fMRI image registration and signal dropout reduction in brain regions with high susceptibility effects. 4. Functional T2 relaxometry of brainstem and midbrain monoaminergic nuclei. 5. Estimation of cerebral blood flow and volume using dynamic susceptibility contrast MRI. 6. Proton echo-planar spectroscopic imaging at 4 T. 7. Two-dimensional, proton magnetic resonance spectroscopy of amino acid neurotransmitters. 8. Statistical methods for assessing drug effects and confounds in MRS and fMRI studies. 9. Concurrent, high-resolution optical imaging and fMRI. 10. Concurrent EEG and fMRI assessment of drug-induced alpha wave activity. All of the projects listed above have been designed to address technical limitations encountered in the course of conducting NIDA-funded clinical imaging studies at 1.5 T field strength.

21. **Principal Investigator:** Sackellares, James **Affiliation:** University of Florida
Project Title: Bioengineering Research Partnership in Brain Dynamics
Grant Number: 1-R01-NS-39687-1-A1 **Funding Organization:** NINDS
Abstract:

Epilepsy is a common neurological disorder that causes spontaneous recurrent seizures. In spite of major advances in pharmacology, neuroimaging, clinical neurophysiology, and neurosurgery, many patients remain disabled due to uncontrolled seizures. We propose to develop novel diagnostic and therapeutic tools, based on recent discoveries regarding dynamical mechanisms initiating epileptic seizures. We have found characteristic preictal dynamical changes, detectable in the electroencephalogram (EEG), preceding seizures by over 30 minutes (preictal transition, PT). More recently, other investigators have confu'med the presence of PT. Our research indicates that the PT is demonstrable in the EEG in approximately 90% of seizures and that automated paradigms can predict seizures. The potential to predict seizures in advance provides an opportunity to develop innovative diagnostic and therapeutic approaches. Our specific aims are: (1) to continue development of dynamic measures for quantification of spatiotemporal properties of the epileptic transition (years I-3); (2) to develop specific pattern recognition algorithms for a seizure warning system (SWS) based upon the on-line features

of the dynamical properties of brain electrical activity (years 1-4); (3) to implement the dynamic measures and pattern recognition algorithms in a SWS for on-line, real-time detection of the preictal dynamical transition (years 2-4); and (4) to evaluate the effects of therapeutic interventions during the preictal transition (years i-5). The specific spatiotemporal patterns of the PT vary from seizure to seizure and patient to patient. Thus, sensitive and reliable SWS will require sophisticated adaptive signal processing techniques. Dynamical measures will be augmented by other powerful analytic approaches, including multivariate time-series analysis, pattern recognition algorithms, and optimization techniques. To this end, we have gathered experts in signal processing, optimization, neurophysiology, neuroanatomy, epilepsy, and neurosurgery. The work will involve the coordination of several research sites throughout the University of Florida Campus (Brain Dynamics Laboratory {Malcolm Randall V.A. Medical Center}, Computer NeuroEngineering Laboratory {College of Engineering}, Center for Applied Optimization {College of Engineering}, an in vitro Neurophysiology Research Laboratory {University of Florida Brain Institute}, an in vivo Neurophysiology Laboratory {College of Medicine}, the Epilepsy Monitoring Laboratory {Shands Hospital}and Arizona State University {ASU Brain Dynamics Laboratory}. We anticipate that the proposed efforts will result in prototype diagnostic software and devices by the end of year 5. We also will obtain preliminary data that will be used for the design and testing of implantable devices that will activate pulsed therapeutic interventions during the preictal transition.

22. **Principal Investigator:** Skalak, Thomas **Affiliation:** University of Virginia
Project Title: Integrated Control of Vascular Pattern Formation
Grant Number: 1-R01-HL-65958-1-A1 **Funding Organization:** NHLBI
Abstract:

This partnership will focus on the integrative control of vascular pattern formation. While vascular assembly and pattern formation will be needed as critical elements of successful therapeutic collateralization of progressively ischemic organs and in tissue engineering of various tissue substitutes in the future, remarkably little is known of the cells involved, the array of signal molecules and their genetic regulation, and the biophysical factors regulating the spatial and temporal dynamics of vascular pattern formation. Key questions now are: what is the origin of cells responsible for the investment of arterioles with contractile cells and what are the signals that control their proliferation, migration, and differentiation? An integrative systems approach is proposed to measure the dynamics of arteriolar pattern formation in vivo across time scales from the embryo to the adult, and spanning spatial scales from genes to cells to whole networks, and to create a new generation of computational approaches to understand the complex interplay of multiple interacting cells and signal molecules. The multidisciplinary team will utilize unique gene-targeted mice in conjunction with innovative in vivo measurements, and integration of the data into the new computational models will improve understanding of the gene circuitry regulating arteriolar pattern formation. Year 1 milestones are to obtain the first microvessel mappings of contractile cell recruitment in transgenic mouse embryonic tissues, to implement spatial guidance of arteriolar pattern formation through application of focal growth factors in adult window chambers, and to implement a novel computational model of arterialization that represents smooth muscle cells and fibroblasts discretely. The long term goal is to define the mechanisms that control arteriolar pattern formation, and to provide the basis for powerful therapeutic vascularization that function in the native environment in vivo.

23. **Principal Investigator:** Smith, William **Affiliation:** Cleveland Clinic Foundation
Project Title: Magscrew TAH Testing thru Pre-Clinical Readiness
Grant Number: 1-R01-HL-67628-1- **Funding Organization:** NHLBI
Abstract:

The fundamental goal of the proposed program is to bring to the point of clinical readiness a new, electrically powered, totally implantable total artificial heart, based on the MagScrew actuator and the biolized blood pump. The specific aims to meet this goal are: (1) To design and develop an advanced technology, fail safe, electronic control unit (ECU), which will maintain the patient's life after an electrical failure, until maintenance is performed. The ECU also contains hardware and patient monitoring capability, and a telemetry function. (2) To build and test refined versions of the remaining system components, based on current state of the art technology. (3) To integrate the components into a functional, complete system. (4) To perform in-vivo performance tests, exercising system capabilities. (5) To perform in-vivo durability tests. (6) To perform bench endurance tests. (7) To complete this work in compliance with FDA Design Controls Regulations. As a consequence of this design and testing effort, surgeons will have another, superior choice among relatively limited TAH alternatives. The "biolized" pump of the MagScrew TAH has pericardial valves combined with biological, protein blood contacting surfaces, and a long track record of extremely rare thrombo-embolic episodes in calves, despite the absence of anti-coagulation. In addition, the MagScrew actuator is the conceptually simplest and most rugged of those available for TAHs, with very few contacting or rubbing surfaces. Mechanical failures have very few possible sources, which clearly increases both reliability and long-term durability. The "fail safe" controller will address the residual pinched wire, corroded solder joint, software hang-up and similar problems that are unavoidable, even with the best fundamental design, and rigorous quality control, in sophisticated, densely packed electronics that are implanted in a hostile environment, and that have caused failures of other, older systems. While the clinical need for TAHs is consistently estimated to be much smaller than that for VADs, it is of a size both nationally and

internationally to be of commercial significance. In the United States, it may exceed $1B per year in potential sales. The TAH market will support several suppliers, if not as many as now pursuing the VAD market. To those patients who will need a TAH, the potentially very limited supply of alternatives is of literally life and death significance.

24. **Principal Investigator:** Thiel, Patricia **Affiliation:** Iowa State University of Science & Technology
Project Title: Design of Biocompatible Niti (Nitinol) Surfaces
Grant Number: 1-R01-HL-67632-1- **Funding Organization:** NHLBI
Abstract:

The future of Nitinol (a NiTi alloy) as a biomaterial depends crucially on its surface characteristics. If the problem with possible Ni release from Nitinol implants could be solved through the design of a stable and inert surface, Nitinol would be superior to every other metallic biomaterial available. Efforts to modify the Nitinol surfaces using artificial coatings, laser and plasma treatments or ion implantation have not succeeded. The resulting surfaces are either enriched in Ni and are not passive, or degrade during shape recovery. A more promising direction to pursue, in the search for biocompatible surfaces, is chemical and electrochemical modification of native NiTi, to produce surface layers that do not crack and spall off during shape recovery of a device/implant. Therefore, we plan to: 1) design biocompatible, highly corrosion-resistant NiTi surfaces employing simple, cost-effective chemical and electrochemical procedures. 2) use X-ray Photoelectron Spectroscopy combined with Scanning Ion Mass and point Auger Electron Spectroscopies, and Back Scattering Electron Microscopy to provide extensive scientific information and understanding of Nitinol surfaces resulting after chemical, heat treatment and sterilization. 3) use standard ASTM potentiodynamic and potentiostatic corrosion tests as well as the immersion test employing Inductively Coupled Plasma Analysis to evaluate the stability of designed surfaces and Ni release in biological media, and 4) preliminarily evaluate the biocompatibility of Nitinol surfaces by exploring blood compatibility [platelet spreading, protein adsorption, cell proliferation (peripheral blood leukocytes, THP-1 monocytes)], and inflammatory mediators (expression of interlukin-1b and tumor necrosis factors-a) that determine implantation outcome.

25. **Principal Investigator:** Vo-dinh, Tuan **Affiliation:** UT-Battelle, LLC-Oak Ridge National Laboratory
Project Title: Advanced Multispectral Imaging for Medical Diagnostics
Grant Number: 1-R01-CA-88787-1- **Funding Organization:** NCI
Abstract:

This project will develop a novel multi-spectral imaging (MSI) system using the synchronous luminescence (SL) concept to rapidly detect cancer in vivo. The proposal will address the problem of real-time in vivo identification and characterization of malignant and pre-malignant tissues in the upper gastrointestinal tract. While presence of Barrett's mucosa is simple to detect endoscopically, at the present time dysplasia and early cancer is found by extensive biopsies. The typical protocol is four quadrant biopsies at 2-cm intervals of the Barrett's mucosa. While this is the standard technique, it only provides 3-5 percent sampling of the mucosal surface where dysplasia and diffuse cancer may be found. The remaining 97-95 percent of the mucosa is not sampled. To address this important need in imaging, a real-time synchronous imaging system will be developed, based on state-of-the-art acousto-optic tunable filter technology coupled to an endoscope. Novel MSI imaging technology will be developed to obtain spatially resolved images of the slight differences in SL properties of malignant versus non-malignant tumors. Synchronous luminescence analysis will greatly simplify the resulting fluorescence from the tissue. This in turn will provide a faster and more accurate in vivo analysis without biopsy. The unique imaging aspect of this MSI system will provide real-time spatial information, allowing for comprehensive diagnosis of large areas of interest. Following development of this technology, initial studies will be performed on two model systems, biopsied tissues as well as laboratory animals at Oak Ridge National Laboratory (ORNL) and the University of Tennessee. Once the system has been optimized, clinical in vivo studies will be performed on human subjects at the Thompson Cancer Survival Center (TCSC) in Knoxville, Tennessee. An interdisciplinary approach will be used to perform the proposed research to provide results in an efficient and cost effective manner.

26. **Principal Investigator:** White, Stephen **Affiliation:** University of California - Irvine
Project Title: Cold Neutrons for Biology And Technology
Grant Number: 1-R01-RR-14812-1-A1 **Funding Organization:** NCRR
Abstract:

This partnership consists of investigators from six universities, the National Institute of Standards and Technology (NIST), Los Alamos National Laboratory (LANL), and the NIH whom are committed to the development of advanced neutron scattering

instruments for studies of membrane systems at the NIST Center for Neutron Research (NCNR). Specifically, these instruments will be devoted to basic and applied studies of membranes and macromolecules in membranes, and to membrane-based technologies that include studies of protein complexes with relevance to bioengineering. The instruments, consisting of a fully dedicated biological advanced neutron diffractometer/reflectometer (AND/R) and a 30-meter small-angle neutron spectrometer (SANS) dedicated 10% to biology, will provide combined advantages and capabilities not currently available in the United States. During the first two years of the project, the AND/R, which has already been designed with the aid of a planning grant from the NSF, will be constructed and commissioned and an existing world-class SANS instrument will be optimized for membrane research. At the same time, a high-performance computer system will be put in place to support the concerted use of neutron diffraction and molecular dynamics methods in order to deduce 3-D structural information from 1- or 2-D diffraction data. Finally, new laboratory space adjacent to the neutron instrument hall will be renovated and equipped to serve the special needs of the partnership and the other biological users. Some early progress on the tasks of the partnership will be achieved using the existing non-optimized SANS and the existing reflection/diffraction instruments at the NCNR during these two years. The development of the new membrane-optimized instruments will be driven by distract experiments inspired by the research programs of the CNBT team. The expertise of the team members, drawn from departments of chemistry, physiology, cell biology, and physics, includes membrane diffraction, small angle neutron scattering, membrane molecular dynamics (MD), biosensors, and biomaterials. Linking neutron diffraction measurements to MD simulations of biomolecular structure is an important objective of the team. We foresee a future when computer simulations will allow three-dimensional detail to be inferred routinely from 1- and 2-dimensional neutron and X-ray data.