SUMMARY OF NEW AWARDS

BIOENGINEERING RESEARCH PARTNERSHIPS (BRP)

FY 2002

The following text provides a summary of new Bioengineering Research Partnerships (BRP) grants awarded during Fiscal Year 2002 by the BECON member institutes and centers in response to program announcements PA-01-024 and PA-02-010. 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:** **Bartlett, Robert** **Affiliation:** University of Michigan - Ann Arbor
   Project Title: Development of a Total Artificial Lung
   Grant Number: 1-R01-HL-69420-1- **Funding Organization:** NHLBI
   Abstract:

The use of mechanical devices (“artificial organs”) to replace vital organ function in acute or chronic organ failure has gone from theory to the intensive care bedside in the last 40 years. For 30 of those years our research on artificial organs has been supported by NIH, resulting in devices and techniques now used clinically to treat lung, heart, kidney, and liver failure. One of these techniques (Extracorporeal Life Support, ECMO) can replace lung function for weeks resulting in recovery of otherwise fatal acute lung disease. But ECMO is too complex and invasive to serve as a bridge to lung transplantation. A bridging system is needed because most of the patients listed for lung transplantation die on the waiting list, and because many potential lung donors are not accepted because borderline lung function might prove fatal in the postoperative period without mechanical support. An implantable prosthetic lung, which could function for 3-6 months, would solve both of these problems, just as the ventricular assist device has been applied to cardiac failure and transplantation. We have applied the expertise of our laboratory to the development of a paracorporeal/ implantable total artificial lung; perfused by the right ventricle and capable of total respiratory support. We have demonstrated safety and efficacy of a prototype design during seven days of implantation in sheep. Based on our preliminary studies demonstrating proof of principle, we propose to design and test a total artificial lung to the point of initial clinical trials. In this proposal, we further intend to establish a new collaboration and partnership between medical researchers and bioengineers who have specific expertise in fluid dynamics, gas transport, artificial organ development, extracorporeal support, and pulmonary physiology to develop and refine a TAL such that it can be implanted successfully as a total lung replacement

2. **Principal Investigator:** **Becker, Lance** **Affiliation:** UNIVERSITY OF CHICAGO
   Project Title: Optimizing Heart and Brain Cooling during Cardiac Arrest
   Grant Number: 1-R01-HL-67630-1-A1 **Funding Organization:** NHLBI
   Abstract:

This revised biomedical partnership proposal from the Univ. of Chicago and Argonne National Lab aims to develop an intra-arrest cooling system for field use by paramedics during cardiac arrest and is directly responsive to the NIH PULSE Workshop calling for new resuscitation methods. Two prototype microparticle slurries have been developed: one saline-based for intravascular use and another perfluorocarbon-based for pulmonary use. These slurries contain high percentages of small (100mum) highly fluid, smooth ice particles with 8 times the cooling capacity of the same liquid (0 degrees C) without ice. In initial swine studies saline slurry resulted in very rapid brain and heart cooling (>1 degree C every 2 minutes) during cardiac arrest with only chest compression to produce circulation, far superior to any external cooling techniques. Moreover, adverse effects of 30 minutes exposure to perfluorocarbon slurry instilled into the lungs of normal animals (not in cardiac arrest) were mild and improved with time. Animals survived unassisted for 48 hours with A-a gradients not significantly different from controls. Thus, creating an optimal cooling method with minimal adverse effects appears a realistic goal. Specific aims and milestones include: (i) bioengineering and developing two microparticulate slurries for pulmonary and intravenous use, (ii)

using these slurries to optimize "intra-arrest" cooling rates of the heart and brain of animals during cardiac arrest, (iii) describing and minimizing adverse effects of slurries, and finally (iv) testing whether slurry cooling to 2 different levels of intra-arrest low-flow cooling will improve survival in a swine model of cardiac arrest. Unlike any existing method, paramedics could use this cooling method after failed defibrillation in efforts to delay additional heart and brain damage until full reperfusion can occur. An international advisory committee of noted resuscitation experts will advise the project and many wish to test the slurries in their home laboratories after completion of these aims, increasing the potential impact of this work.

3. **Principal Investigator:** **Boone, John** **Affiliation:** UNIVERSITY OF CALIFORNIA DAVIS
Project Title: Breast CT scanner for earlier cancer detection
Grant Number: 1-R01-CA-94236-1- **Funding Organization:** NCI
Abstract:

Breast cancer is a disease with high incidence in the U.S. and elsewhere, and population-level methods of fighting this disease are aimed primarily on screening, using mammography for early detection. The median size of breast cancer found using mammography is approximately 11 mm. Based on extensive preliminary studies involving computer simulations, physical measurements, and cadaver breast imaging, we have found that breast CT may be able to routinely detect much smaller breast tumors, in the 3 to 5 mm range. Importantly, the radiation dose of breast CT performed at 80 kVp was found in detailed studies to be comparable to that of mammography. It is not possible to image the breast alone on a live woman using a clinical CT scanner. Therefore, in this Bioengineering Research Partnership proposal, we have teamed with scientists from around the country to design, build, and test a CT scanner designed to image the breast. A team comprised of medical physicists, physicians, mechanical and electrical engineers, and breast cancer advocates will collaborate on the design of the breast CT scanner. Cone beam flat panel technology will be used to produce a scanner capable of 10 second breast scanning, and the scanner development will also include a breast immobilization system (acrylic cylinders), a breast CT table, a fast reconstruction computer, and a computer workstation customized for efficient viewing breast CT images. The scanner will be built, tested, and optimized at UC Davis over a period of 3 years involving 9 specific aims. After the breast CT scanner is tested in a brief phase I trial (2 specific aims), it will be moved to the breast imaging clinic for a phase II trial where approximately 120 women will be imaged (4 specific aims). This phase II trial will evaluate the efficacy of breast CT for the early detection of breast cancer in a group of women likely to have breast cancer (BIRADS 4 & 5). Additionally, the breast image data will be studied for its utility in automating the analysis of the normal breast architecture, and for computerized cancer detection. In year 5 of the proposed research, two specific aims utilize the breast CT data and corresponding mammography images (on -240 breasts) to evaluate the ideal observer performance and human (mammographer) detection performance attributes of the breast CT scanner. At the end of the proposed research involving 17 specific aims, the potential of breast CT will have been evaluated both qualitatively and quantitatively. A tested, high quality prototype breast CT scanner would be ready to be enlisted in a phase III trial (beyond the scope of this proposed research), if further testing is warranted. Performance data acquired in the present study would allow the proper design (power, etc.) of a phase III trial. If breast CT lives up to its enormous potential based on initial imaging, breast cancer would be detectable far before metastases occurs - for example, a 3 mm tumor contains only 2 percent of the cell count of an 11 mm lesion, and a 5 mm lesion contains only 9 percent of the cell count. Based on a 100 day volume doubling time, detection of a 5 mm lesion would lead to 0.93 year earlier detection, and routine detection of 3 mm lesions would result in 1.5 year earlier detection over mammography. Surgical removal of early cancers will effectively result in cure for the majority of women screened using this technology. While breast CT would probably improve cancer detection in all women, some women may have risk factors (dense breasts, genetic markers, etc.) that particularly warrant screening using breast CT. The Phase II trial will shed more light on this issue.

4. **Principal Investigator:** **Bottlang, Michael** **Affiliation:** EMANUEL HOSPITAL AND HEALTH CENTER
Project Title: An organotypic model of traumatic brain injury
Grant Number: 1-R01-NS-42946-1- **Funding Organization:** NINDS
Abstract:

This abstract is not available.

5. **Principal Investigator:** **Brown, Emery** **Affiliation:** MASSACHUSETTS GENERAL HOSPITAL
Project Title: Dynamic Signal Processing Analyses of Neural Plasticity
Grant Number: 1-R01-DA-15644-1- **Funding Organization:** NIDA
Abstract:

In response to PAR-02-010 we propose to form a Bioengineering Research Partnership between a statistician (Dr. Emery N. Brown of Massachusetts General Hospital, Partnership Director), neuroscience experimentalists (Dr. Matthew A. Wilson of the Massachusetts Institute of Technology and Dr. Wendy Suzuki of New York University) and a control engineer (Dr. Victor Solo of the University of New South Wales) to develop a systems engineering approach to understanding neural plasticity. The area of bioengineering research will be the development of neural signal processing algorithms by combining the theory of point processes and adaptive estimation to study neural plasticity during learning and memory formation. The experimental investigations will study the dynamics of neural activity within the hippocampus and adjacent medial temporal lobe structures (entorhinal, perirhinal and parahippocampal cortices) in rats, genetically altered mice, and primates. These experimental studies will provide the basis for a focused investigation that designs new methods for neural signal processing appropriate for dynamic analysis of multiple simultaneously recorded neural spike trains. The algorithms we design will be used to analyze the data collected in the experimental studies proposed in this investigation. The close collaboration between the experimentalists and the quantitative scientists will ensure that the methods designed are appropriate for the data collected. The long-term objectives of this partnership are: to establish a combined experimental-signal processing approach to characterizing neural plasticity and how it relates to learning, memory formation and behavior; to develop broadly applicable signal processing tools for analyzing the dynamic behavior of neural ensembles; and to establish an interdisciplinary research environment so that undergraduates, graduate students and post-doctoral fellows can be well trained in both the cutting edge experimental methods and signal processing techniques that are jointly required to study a complex question such as the dynamics of neural information encoding in the brain. The health implications of this work are a more fundamental understanding of neural plasticity and, as a consequence, how it affects normal physiological processes such as growth, development and learning as well as pathologic conditions such as drug addiction, Alzheimer's disease and chronic pain. More accurate quantitative characterizations of neural information dynamics coupled with improved signal processing algorithms may also lead to innovative approaches to creating machine-brain interfaces and designing neural prosthetic devices.

6. **Principal Investigator:** **Buchanan, Thomas** **Affiliation:** UNIVERSITY OF DELAWARE
Project Title: FES and Biomechanics: Treating Movement Disorders
Grant Number: 1-R01-HD-38582-1-A2 **Funding Organization:** NHLBI
Abstract:

This Biomedical Research Partnership project proposes to combine resources from professors of Mechanical Engineering and Physical Therapy through our newly organized Center for Biomedical Engineering Research at the University of Delaware. The five-year goal of this project is to assist patients with CNS dysfunction to produce improved walking patterns through a combination of functional electrical stimulation (FES), robotic-assistive training and biomechanical modeling. In the first phase of this project, which is described in this proposal, the focus will be on individuals with stroke exhibiting hemiparetic leg impairment. The technique should be generalizable to a variety of neurological impairments. The movements for these individuals will be improved or "optimized" in four ways: Nonrisk Maximize postural stability, Injury Minimize musculoskeletal injury (e.g., arthritis) during movement, Cosmesis Develop a more natural looking gait, and Energy Minimize metabolic energy consumption during movement. The "NICE" optimization protocol will be realized through musculoskeletal modeling, robotic assistance, functional electrical stimulation, and neuromuscular training. The specific task we will study will be partial body weight suspension gait on a treadmill. The organization of this project has been divided into 3 distinct aims, which may be summarized as follows. Aim 1: Identify impairments in the locomotor patterns of the lower extremity in patients with hemiparetic stroke and create a paradigm to optimize the movement patterns ("NICE" optimization). This will be accomplished through biomechanical modeling using gait analysis and electromyographic data. Aim 2: Develop the methods and equipment ("NICE" rehabilitation system) necessary to implements the "NICE" optimization of locomotion in patients with stroke. We will achieve this through the use of a robotic device and an electrical stimulation system. Aim 3: Test the feasibility of the use of the "NICE" rehabilitation system in patients with hemiparetic stroke and make adjustments to the system based on the patient trials. Our ten-year goal is to produce a portable (wearable) FES system to assist patients with CNS dysfunction in the production of coordinated movements.

7. **Principal Investigator:** **Carson, Paul** **Affiliation:** UNIVERSITY OF MICHIGAN AT ANN ARBOR
Project Title: COMBINED DIGITAL X-RAY AND ULTRASOUND BREAST IMAGING
Grant Number: 1-R01-CA-91713-1-A1 **Funding Organization:** NCI
Abstract:

This abstract is not available.

8. **Principal Investigator:** **Chen, Zhongping** **Affiliation:** UNIVERSITY OF CALIFORNIA IRVINE
Project Title: Optical Biopsy Using MEMs Technology
Grant Number: 1-R01-CA-91717-1-A1 **Funding Organization:** NCI
Abstract:
This abstract is not available.

9. **Principal Investigator:** **Cheung, Alfred** **Affiliation:** UNIVERSITY OF UTAH
Project Title: PREVENTION OF HEMODIALYSIS VASCULAR ACCESS STENOSIS
Grant Number: 1-R01-HL-67646-1-A1 **Funding Organization:** NHLBI
Abstract:
Neointimal hyperplasia is a frequent cause of stenosis in blood vessels and is commonly observed in post-angioplasty coronary arteries and hemodialysis vascular accesses. In native arteriovenous (AV) fistulae and polytetrafluoroethylene (PTFE) grafts for hemodialysis, the stenosis is usually focal and occurs at the AV or graft-venous anastomosis. Effective strategies for the prevention of stenosis are lacking. We hypothesize that local delivery of anti-proliferative drugs and anti-growth factor antibodies using a novel drug delivery system, ReGel, will inhibit neointimal hyperplasia associated with native AV fistulae and PTFE grafts. ReGel is an injectable, thermosensitive copolymer designed for local, sustained-delivery of drugs. This is a multidisciplinary approach to address the following specific aims: (1) To examine the efficacy of two anti-proliferative drugs (dipyridamole or paclitaxel) and anti-platelet derived growth factor (PDGF) antibodies alone or in combinations in the inhibition of growth of human or canine vascular smooth muscle cells. These in vitro studies will set the stage for animal studies in this proposal and potential clinical trials in the future. (2) To study the release kinetics of the anti-proliferative drugs and anti-PDGF antibodies from ReGel in vitro and their transport kinetics across explanted native AV fistulae and PTFE grafts. The transport characteristics of the drugs and antibodies in ReGel applied to the perivascular area of the native AV fistula and PTFE graft around the venous anastomosis will then be evaluated in whole dog experiments. Comparisons of mathematical model predictions with results from these experiments will help optimize the therapeutic dose of drugs and antibodies and conditions for delivery by ReGel in vivo. (3) To examine the efficacy of the anti-proliferative drugs and anti-PDGF antibodies delivered by ReGel in inhibiting neointimal hyperplasia in dog models of native AV fistula and PTFE graft. Successful development of this technique will provide a novel approach of local drug delivery to prevent neointimal hyperplasia and stenosis in blood vessels. Furthermore, the results will provide the basis for local delivery of drugs and proteins of interest to a variety of tissues.

10. **Principal Investigator:** **Churchill, Bernard** **Affiliation:** UNIVERSITY OF CALIFORNIA LOS ANGELES
Project Title: Uropathogen Detection Using DNA Biosensors
Grant Number: 1-R01-EB-127-1- **Funding Organization:** NIBIB
Abstract:
Urinary tract infection is the most common urological disease in the United States and is a major cause of patient morbidity and health-care expenditure. This Bioengineering Research Partnership proposal involves development of a microelectromechanical system for the genotypic detection and species-specific identification of uropathogens within a time frame (5-10 minutes from sample collection to readout) that would enable point-of-care diagnosis and treatment. The focus of this proposal is to produce a self-contained microbial pathogen detection device and to examine its performance using clinical urine samples. Research at UCLA has provided two key technological advances that make development of a uropathogen sensor feasible. The first is microfluidics for sample processing. The second is an electrochemical microsensor which allows ultrasensitive detection of specific DNA-RNA or DNA-DNA hybridization events, without the need for target amplification. This project has been in development for over a year involving a multidisciplinary effort including leaders in the fields of microfluidics and microsensor technology, molecular microbiology, pediatrics and biomathematics. Specific Aim 1 describes how microfluidics studies will be applied to development of a crossflow filter for uropathogen concentration, micromixing for processing of uropathogen nucleic acids, and washing of the sensor surface. Specific Aim 2 involves fabrication of the microsensor array, development of a streptavidin self-assembled monolayer, and testing of oligonucleotide probes for electrochemical detection of uropathogen rRNA and mRNA on the microsensor surface. Specific Aim 3 will involve integration of the microfluidics and sensor components and testing of its analytic validity on simulated and actual urine specimens. Specific Aim 4 will involve batch fabrication of the device and clinical examination of the association between urosensor results and clinical correlates of urinary tract infection.

11. **Principal Investigator:** **Dale, Anders** **Affiliation:** MASSACHUSETTS GENERAL HOSPITAL

Project Title: Spatiotemporal Brain Imaging: Microscopic & System Level
Grant Number: 1-R01-EB-790-1-A2 **Funding Organization:** NIBIB
Abstract:
The last decade has brought revolutionary new techniques allowing visualization of the working brain in humans at the systems level. However, a large gap remains between the spatiotemporal resolution of tomographic techniques (fMRI, PET), and the circuit level where animal studies permit mechanistic neural models. It is the overall goal of this proposal to develop an integrated suite of technologies to bridge this critical gap. Two interrelated themes are found throughout this proposal: (1) to improve the spatial and temporal resolution of non-invasive technologies, which will enable direct imaging of discrete (e g column and laminar level) neural units which bridge the systems and cellular levels and (2) to clarify the mechanisms which relate the biophysics of neuronal activity "observables" in our imaging measurements. The two key technologies to be investigated are: (1) extremely high resolution MRI and fMRI, using very high strength gradients, phased-array coils, and other advances at 3T and 7T non-human primates, and 9.4T rats and (2) tomographic optical imaging, increasing the resolution and physiological range using three different optical technologies: direct reflectance imaging, optical scanning microscopy, and diffuse optical tomography. These technologies will be validated against invasive "gold standard" techniques in studies of rat whisker barrel cortex and macaque visual cortex, and further applied to animal models spreading depression in migraine and stroke. Each of these experiments is designed to allow us to serially step from more to less invasive, and move from systems where much is already known through to studies in humans that have not heretofore been explored within the spatiotemporal domains our newly developed tools will afford.

12. **Principal Investigator:** **Degrado, William** **Affiliation:** UNIVERSITY OF PENNSYLVANIA
Project Title: Proteomics to Biomimetic Polymers: Engineering Principle
Grant Number: 1-R01-GM-65803-1- **Funding Organization:** NIGMS
Abstract:
Our understanding of the structural basis for protein function is rapidly evolving as a result of modern approaches to structural proteinomics. Our intention is to use this understanding as a starting point for the design of biomimetic polymers that are much more stable and inexpensive to produce than natural proteins, but nevertheless mimic their key biological properties. A primary goal of this project will be to design polymers and defined-length oligomers capable of presenting functional groups in arrays similar to those found in natural, biologically active proteins. To illustrate this approach, we will design mimics of a class of membrane-active antimicrobial peptides and proteins. A large class of antimicrobial peptides adopt positively charged amphiphilic a-helices, in which charged, polar groups and apolar groups line up on opposite faces of the helical cylinder. We recently synthesized a series of mimics of these helices based on Beta-amino acids rather than a-amino acids. Here, we propose to use these highly simple beta-peptides as frameworks for further elucidating how chain length, helical potential, charge density, and hydrophobicity affect antimicrobial activity. Further, we propose to develop computational methods to aid in the design and analysis of a variety of other antimicrobial polymers that are simpler in structure and hence much less expensive to produce than either a- or Beta-peptides. The antimicrobial activities of these polymers will be tested in solution and when attached to solid surfaces. The structures and mechanisms of action of the polymers and oligomers will be evaluated using a battery of biophysical methods, as well as by using gene chips to examine which genes are turned on by sub-lethal concentrations of the compounds

13. **Principal Investigator:** **Deweerth, Stephen** **Affiliation:** GEORGIA INSTITUTE OF TECHNOLOGY
Project Title: A 3-D Microfluidic/Electronic Neural-Interfacing System
Grant Number: 1-R01-EB-786-1- **Funding Organization:** NIBIB
Abstract:
Investigators from multiple departments at the Georgia Institute of Technology / Emory University School of Medicine, from the University of Illinois at Urbana Champaign, and from the Southern Illinois University School of Medicine propose a multidisciplinary project to develop a microfabricated neuronal interfacing system (uNIS) for advanced interfacing to three-dimensional neural tissue in vitro, and to apply this technology to the study of plasticity and injury in neuronal networks. The specific aims of the project are formulated around the development and integration of a set of technological advances that facilitate the study of three-dimensional cell cultures and slices: (1) vertical towers with connecting crossbridges that provide infrastructure for the formation of structured networks as well as for the electrical connectivity; (2) the inclusion of microfluidic channels into these towers to selectively inject nutrients and trophic factors and to apply chemical stimulation to localized regions of the tissue; and (3) the design of integrated circuits that amplify, multiplex, and process the large number (>1000) of signals generated in the uNIS and that facilitate simultaneous recording and stimulation. This technology will be applied directly to the study of three-dimensional, in vitro neural tissue with a particular focus on hypotheses addressing the development of functional networks of neurons, the role of plasticity in these networks, and the study of injury and its effects on network behavior. During the first year of the grant, prototypes of the microtowers, microfluidic structures, and electronics

will be developed and integrated with neural tissue. The remainder of the five-year grant will focus on the refinement and testing of the technology and on a set of biological experiments that validate the approach and test the proposed hypotheses. The successful completion of this project will result in the creation of a technological framework for studying a wide variety of cells (neural and non-neural) as well as experimental data that would be inaccessible without this three-dimensional technology.

14. **Principal Investigator:** **Doyle, Mark** **Affiliation:** ALLEGHENY-SINGER RESEARCH INSTITUTE
Project Title: Rapid Flow Evaluaton by Magnetic Resonance Imaging
Grant Number: 1-R01-HL-72317-1- **Funding Organization:** NHLBI
Abstract:

Velocity encoded cine (VEC) imaging performed using magnetic resonance imaging (MRI) has great clinical potential for diagnosis of cardiovascular diseases. The non-invasive nature of MRI tomographic imaging, its uniform sensitivity to velocity in all directions and its intrinsic 3D nature make it a natural choice for clinical application. Of particular interest is the potential use that can be made of quantitative blood velocity imaging in the assessment of the complex flow fields associated with aortic valvular diseases. Currently, aortic valve diseases are primarily assessed using echocardiography which is widely available, but nevertheless has several important limitations in characterizing flow fields, including views are restricted by the availability of appropriate acoustic windows, results are operator dependant, velocity is detected in only one direction relative to the probe and that primarily 2D views are used to characterize a 3D flow field. While MR VEC imaging has the potential to provide more comprehensive flow field data than does echocardiography, clinical application of MR VEC imaging has been hampered by its relatively long acquisition times. The powerful gradient systems now available on MRI scanners allow high quality cardiac cine scans to be acquired in comfortable breath-hold times. However, the scan time required for VEC imaging with velocities resolved in 3D is still prohibitively long for most clinical applications. The goal of this proposal is to implement a rapid MRI approach that has potential to accomplish VEC imaging in a conventional breath-hold time. Development includes MR scanner sequences modification, determining its limits of applicability using computer modeling of flow fields and testing using flow models. In parallel with implementation and validation of the acquisition sequence, processing tools will be developed to analyze the time resolved 3D flow field data sets. Following the development stage, clinical application will be made to patients with aortic valvular diseases.

15. **Principal Investigator:** **Duncan, James** **Affiliation:** YALE UNIVERSITY
Project Title: Bioimaging and Intervention in Neocortical Epilepsy
Grant Number: 1-R01-EB-473-1-A1 **Funding Organization:** NIBIB
Abstract:

Magnetic resonance functional and spectroscopic imaging (fMRI, MRS) of the brain provides tremendous opportunities in the study and treatment of epilepsy. In neocortical epilepsy, where the epileptogenic region is highly variable in size, structure and location, deeper insight into the biochemical and functional characteristics of the region and surrounding tissue may provide critical data to assist the neurosurgeon and neurologist in localization and treatment. To fully utilize the multiple forms of information (MR and EEG), these data must be transformed into a common space and integrated into the intraoperative environment. We will develop high resolution MRS and fMRI at 4T and advanced analysis and integration methods to better define the epileptogenic tissue and surrounding regions, and enhance our understanding of the biochemical mechanisms underlying the dysfunction in neocortical epilepsy. We will validate these measurements against the gold standard of intracranial electrical recording. These goals will be achieved in this bioengineering research partnership (BRP) by bringing together six partners from 3 academic institutions (Yale (lead institution), Albert Einstein and the Univ. of Minnesota) and 1 industrial partner (Medtronics SNT) to carry out four integrated programs of scientific investigation and bioengineering development in the area of bioimaging and intervention: 1) development of high resolution fMRI and MRS at 4T for the study of epilepsy; 2) investigation with MRS of the relationship between neuronal damage or loss through the measurement of N-acetylaspartate (NAA), alterations in neurotransmitter metabolism through the measurement of gamma amino butyric acid (GABA) and glutamate, and abnormalities in electrical activity in the epileptogenic region and surrounding tissue; 3) investigation of the relationship between fMRI activation amplitude and the cognitive task, underlying cortical structure, cortical metabolic state, and physiology, and the impact of epilepsy on these factors; 4) development of integration methodologies for fusing multimodal structural and functional (image- and electrode-derived) information for the study and treatment of epilepsy. We anticipate that by developing and integrating these high resolution functional and metabolic images of neocortical epilepsy, we will improve our understanding and treatment of this difficult disorder. The first year's effort will include high resolution coil and integrated software platform design and development, as well as the acquisition of normal control studies. In years 2 through 5, the coils will be incorporated into the MR imaging platforms, the software platform will be fully developed and hypotheses related to the biochemical makeup of neocortical epileptogenic tissue and its relation to brain function will be evaluated.

16. **Principal Investigator:** Eaton, Gareth **Affiliation:** UNIVERSITY OF DENVER
Project Title: In Vivo EPR Bioengineering Research Partnership
Grant Number: 1-R01-EB-557-1-A1 **Funding Organization:** NIBIB
Abstract:

In vivo paramagnetic resonance (EPR) requires optimal signal-to-noise (S/N) enhancement in the shortest possible time. To study radicals in deep tissues it is necessary to perform the EPR measurements at low radiofrequency (e.g., 250 MHz), as in MRI. This decreases the S/N relative to the more common 9 GHz EPR. Physiological motions and metabolism occurring within the time of the usual EPR measurements necessitate the development of special techniques for in vivo studies. It is proposed to establish a partnership of engineers, research scientists, clinicians, and industry to fully engineer an EPR system dedicated to in vivo spectroscopy and imaging. As a first step, it is proposed to engineer a CW 250 MHz EPR spectrometer system optimized for the best in vivo free radical sensitivity per unit time. The specific tasks include the design, construction, and testing of an air-core magnet for in vivo EPR optimized for rapid magnetic field scans, and a control system for scanning the magnetic field rapidly. We introduce the innovation that the magnet will be resonated, and magnetic field scans will be sinusoidal. Measurement of the noise spectral densities of the spectrometer system, and of a spectrometer with a mouse in the resonator, will provide the basis for a mathematical model of the spectrometer noise characteristics from which one can predict the S/N per unit time expected for various magnetic field scan rates. The S/N for various scan rates will be compared with the predicted values. Software will be written to linearize and deconvolute the spectral information recorded under rapid-scan conditions. In subsequent effort it is proposed to extend the scope of the bioengineering research partnership to tackle the problems of optimal compensation for physiological motion, acquisition of the full RF spectrum and post-processing to replace analog pre-processing, and design of open magnet structures to achieve better patient acceptance and decrease costs.

17. **Principal Investigator:** Edgerton, V. R **Affiliation:** UNIVERSITY OF CALIFORNIA LOS ANGELES
Project Title: Robotically Generated Locomotion in Rodents
Grant Number: 1-R01-NS-42951-1- **Funding Organization:** NINDS
Abstract:

This abstract is not available.

18. **Principal Investigator:** Frangos, John **Affiliation:** LA JOLLA BIOENGINEERING INSTITUTE
Project Title: Anti-Inflamatory Coatings for Biomaterials
Grant Number: 1-R01-EB-823-1- **Funding Organization:** NIBIB
Abstract:

This abstract is not available.

19. **Principal Investigator:** Gilbert, Charles **Affiliation:** ROCKEFELLER UNIVERSITY
Project Title: Molecular Analysis of Visual Processing
Grant Number: 1-R01-EY-14103-1- **Funding Organization:** NEI
Abstract:

We propose to develop a set of molecular tools to link gene expression to, and to study the role of specific neural circuits in, visual perception and behavior. These tools will be adapted for work in non-human primates, which have distinct advantages in our knowledge of the functional anatomy of neural circuits, the functional architecture of cortex, the ability to study complex behaviors and to combine physiological and behavioral studies in awake, behaving animals, and because of their close relationship with humans. The components of the project include developing gene microarrays based on an expression library derived from the monkey cerebral cortex, high throughput techniques for studying patterns of gene expression involved in specific behaviors, anatomical studies of the patterning of gene expression relative to cortical functional architecture and cell type, developing viral vectors for delivering genes to neurons, reversible inactivation of specific cell classes using molecular tools, and a cortical plasticity model for monitoring changes in gene expression and altering function by changing levels of gene expression via viral transfection. Once developed, these techniques will make possible a top-down understanding of the

link between patterns of gene expression and behavior. They will also make it possible to alter gene expression in higher animals for the study of neural mechanisms of behavior.

20. **Principal Investigator:** Gore, John **Affiliation:** YALE UNIVERSITY
Project Title: Integrated functional imaging of the human brain
Grant Number: 1-R01-EB-461-1-A1 **Funding Organization:** NIBIB
Abstract:

This is an application to establish a Bioengineering Research Partnership (BRP) to develop and integrate new technologies for the comprehensive mapping of human brain function. These will be used to study functionally connected networks within the brain and will provide the information for systems analyses of the neural bases of normal and abnormal behaviors. They will be applied to study development in children and infants, as well as the neurobiological basis of various psychiatric, developmental and neurological disorders. The BRP would develop non-invasive instrumentation, techniques and algorithms to acquire and combine the information obtainable from advanced high field magnetic resonance imaging (MRI) at 4 Tesla, near infra-red optical imaging, electrophysiology (including evoked responses), trans-magnetic stimulation (TMS), and computer data analysis and image processing. It would develop and validate novel means of performing functional imaging studies and of recording cognitive and physiological responses within the environment of a 4T imaging magnet, as well as methods to combine the information from the various complementary techniques involved. The partnership would bring together 6 core laboratories within Yale University, the host institution, and would also closely involve 8 collaborating corporate partners as well as investigators from 8 other universities (Vanderbilt, Columbia and New York Universities, UNC, UConn, Oregon Health Sciences Center, Medical College of South Carolina, and the Bronx VA Hospital). The BRP will include physicists, engineers, computer scientists, neuroscientists, psychologists, psychiatrists, pediatricians and radiologists. During Year 1 advanced functional imaging methods will be implemented at 4T, and the equipment needed for ERP and NW will be modified for use in the magnet. Similar developments of these modalities, of TMS and psychophysical techniques, will continue through years 2 and 3. The first three years of the BRP would focus on the development and validation of novel techniques for inducing and assessing brain activation in response to stimuli, while years 4 and 5 would focus more on developing methods for the integration of data obtainable by different means and for their analysis and interpretation in specific applications. The establishment of a BRP would be an ideal mechanism for bringing together different approaches to the study of brain function, and the integration of the various methods will provide a valuable new resource for neuroscience research whose capabilities will far exceed the sum of the separate components.

21. **Principal Investigator:** Houck, Raymond **Affiliation:** AUTOMATED CELL, INC.
Project Title: Quantitation of Cellular Protein Production in Real Time
Grant Number: 1-R01-EB-1051-1-A2 **Funding Organization:** NIBIB
Abstract:

The study of individual cells and mixed populations of cells provides a powerful approach to unraveling the simultaneous effects of paracrine, juxtacrine, and matrix-associated factors in the poorly understood cellular processes that underlie normal and pathophysiological processes such as osteoblast differentiation and age related bone loss. In many cases, progress in the purification of progenitor cells and rare stem cells has outpaced development of technologies for gathering and interpreting information at the individual cell level. This proposal focuses on the development of tools for real time study of individual cells and mixed populations of cells in automated combinatorial cell culture systems. Goals include: 1) Development of software for real time analysis and dynamic manipulation of osteoblast progenitor/precursor cells; 2) Development of devices and procedures for coherent real time detection of phenotypic changes in rare human cells and the progeny of such cells deposited, tracked, imaged, and analyzed individually through time; 3) Innovation of technologies for real time quantitation of cellular protein production through miniaturized assay methods and off-line analytical systems; and 4) Application of these technologies to determine effects of aging on osteoblast differentiation potential of human bone marrow stromal cells, utilizing the subset, STRO-1+, in an in vitro model system. The tools developed in this project will provide valuable resources for a wide range of disciplines involving the study of cellular interactions and behaviors within various tissues.

22. **Principal Investigator:** Johnson, John **Affiliation:** SCRIPPS RESEARCH INSTITUTE
Project Title: Plant Viruses as Platforms for Biomaterials
Grant Number: 1-R01-EB-432-1- **Funding Organization:** NIBIB
Abstract:

Many icosahedral and helical plant viruses produce at high levels in susceptible hosts, with yields in excess of 1 gram/Kg of leaves being common. They have been the subject of assembly studies for decades and have more recently been

manipulated genetically through the use of infectious clones. High levels of heterologus expression in E. coli and yeast have also been achieved. Many are well characterized structurally with atomic coordinates available for the capsid protein subunits. These developments for cowpea mosaic virus made it a therapeutic agent for the development of inexpensive vaccines. Likewise, cowpea chlorotic mottle virus has been exploited as a molecular container with the internal properties modified by genetic alteration of the capsid protein. These qualities suggest that plant viruses can serve as a novel biomaterial. The goal of the proposed work is to now use these attributes of plant viruses and to exploit the particles as nanoblocks" and nano containers and to understand the principles of these alterations on their function. We will use plant virus particles as "symmetric dendrimers? that can be chemically modified for developing a variety of targeted bio sensors, centers of catalysis, delivery systems, and imaging agents. We will generate tailored 2 and 3 dimensional arrays of these particles and these will serve as templates for a variety of nano materials. All of the basic technology of virus genetic modification is fully developed for the systems employed, as is the linkage chemistry for generating specific constellations of covalently attached functional groups. Six research groups will collaborate to create a wide range of modified plant virus particles and to explore their properties in vitro and in vivo. The expertise of these groups include synthetic and catalytic chemistry, materials science, the biochemistry and biophysics of nucleoprotein assembly, molecular virology, crystallography, electron cryo microscopy, image reconstruction and solution scattering methods.

23. **Principal Investigator:** **Kahn, C R** **Affiliation:** JOSLIN DIABETES CENTER
Project Title: Diabetes Genome Anatomy Project (DGAP)
Grant Number: 1-R01-DK-60837-1-A1 **Funding Organization:** NIDDK
Abstract:

The Diabetes Genome Anatomy Project (DGAP) represents a new initiative in unraveling the interface between insulin action; insulin resistance and the genetics of type II diabetes. The project was developed in conjunction with NIDDK and in response to the report of the Diabetes Research Working Group, and is presented in the form of a Bioengineering, Bioimaging, and Bioinformatics Research Partnership (BRP), representing the efforts of investigators from five institutions. There are six projects and four cores that form a highly interactive matrix and also serve as a scaffold on which to build future projects or interactions with related projects and grants. The overall goal of the project is to identify the sets of the genes and gene products involved in insulin action and the predisposition to type 2 diabetes, as well as the secondary changes in gene expression that occur in response to the metabolic abnormalities present in diabetes. There are five major and one pilot project involving human and rodent tissues that will allow us to: (1) Create a database of the genes expressed in insulin-responsive tissues, as well as accessible tissues such as lymphocytes, that are regulated by insulin, insulin resistance and diabetes. (2) Assess levels and patterns of gene expression in each tissue before and after insulin stimulation in normal and genetically-modified rodents; normal, insulin resistant and diabetic humans, and in cultured and freshly isolated cell models. (3) Correlate the level and patterns of expression at the mRNA and/or protein level with the genetic and metabolic phenotype of the animal or cell. (4) Generate genomic sequence from a panel of humans with type 2 diabetes focusing on the genes most highly regulated by insulin and diabetes to determine the range of sequence and expression variation in these genes and the proteins they encode, which might affect the risk of diabetes or insulin resistance. The resultant information will be used to create a highly annotated and interactive public database, standardized protocols for gene expression and proteomic analysis, and ultimately diabetes-specific and insulin action-specific DNA chips for investigators in the field. In this manner, we propose to define the normal anatomy of gene expression (i.e. basal levels of expression and response to insulin), the morbid anatomy of gene expression (i.e., the impact of diabetes on expression patters and the insulin response) and the extent to which genetic variability might contribute to the alterations in expression or to diabetes itself. This will aid all investigators in the quest to unravel the complexity of insulin action and its alterations in diabetes, and ultimately help develop more effective and specific modes for classification, metabolic staging and therapy of the disease.

24. **Principal Investigator:** **Kirsch, Wolff** **Affiliation:** LOMA LINDA UNIVERSITY
Project Title: Iron Metabolism Alterations in Alzheimer's Disease
Grant Number: 1-R01-AG-20948-1- **Funding Organization:** NIA
Abstract:

The institution directing this Bioengineennng Research Partnership is the Loma Linda University (Neurosurgery Center for Research, Training and Education, Departments of Molecular Biology and Molecular Genetics, Biochemistry, Radiology, Radiobiology, Internal Medicine, Psychiatry and Pathology). Partners include BioErgonomics, Inc., St Paul, MN and the MRI Institute for Biomedical Research, St. Louis, MO. The goal of our multidisciplinary Bioengineering Research Partnership is to define the role of altered brain iron metabolism as a risk factor for Alzheimer's Disease in the in the context of elderly MCI patients. The engineering focus of the study is: (I) defining ex vivo markers in peripheral blood cells indicating iron or amyloid perturbations and (2) the development of a new magnetic resonance imaging (MRI) technology to quantitate and differentiate brain iron. Study subjects will be 75 patients (50 years of age or older) with minimal cognitive impairment who will be followed longitudinally for a three to four year period with sequential psychometric tests, special MRI sequences, and peripheral blood

cell studies. Control subjects will consist of 25 healthy age-matched individuals who will be subjected to the same tests as the MCI group. A genetically engineered mouse with an iron regulatory protein 2 "knockout" that accumulates abnormal quantities of brain iron and displays a neurodegenerative disorder will be used to validate our new technology. A search for polymorphisms in the IRP-2 gene will be part of each patient's evaluation. At four years of serial follow-up it is anticipated that about 15% of the 75 study subjects will have AD, and correlations of psychometric data, brain iron localization and quantitation, as well as immunocytochemical peripheral blood will be established using statistical consultation and autopsy information if available.

25. **Principal Investigator:** **Kuettner, Klaus** **Affiliation:** RUSH-PRESBYTERIAN-ST LUKES MEDICAL CTR
Project Title: NOVEL X-RAY TECHNOLOGY FOR DEGENERATIVE JOINT DISEASE
Grant Number: 1-R01-AR-48292-1- **Funding Organization:** NIAMS
Abstract:

We propose a program to integrate biomedical (Rush Medical College) with bioengineering (Illinois Institute of Technology and Massachusetts Institute of Technology) approaches to test and refine a novel X-ray technology for the diagnosis of joint pathology, particularly osteoarthritis. This technology may aid in the development of disease modifying agents and treatment strategies for the prevention and treatment of joint diseases. This project utilizes a novel synchrotron x-ray technique called diffraction enhanced imaging (DEI) which derives dramatic gains in contrast over conventional radiographs by exploiting x-ray refraction and scatter rejection (extinction) in addition to the usual absorption of conventional radiography. This technique, originally developed for mammary carcinoma imaging analyzes soft tissue as high contrast images with very high (greater than 0.05mm) spatial resolution. Although the synchrotron is currently used for DE imaging, the technique is not, in principle, tied to it. We have already shown that DEI is capable of imaging normal and degenerated articular cartilage of synovial joints showing features unique to this type of imaging using exposure times comparable to those of ordinary radiography. Beginning in the first year, we will interpret the cartilage and bone data obtained through our DEI methodologies by using the biological profiles of the matrix components as garnered through morphologic, biochemical and biophysical analysis. Some of the features observed in the DE images are not immediately explainable in molecular, chemical or structural terms. By using a unique integrated experimental approach, correlating biochemical and morphological tissue profiles with DE images, we hope to refine the overall DEI system for the detection of joint disease and, potentially, for other pathologies. We will image human and animal synovial joints and begin the refinement of the imaging technique for the optimal identification of early cartilage lesions. Animal models of cartilage degeneration will be used particularly for DE imaging of cartilage prior to visible signs of degeneration. Beginning in year two, we will image human cartilage that has been biomechanically damaged under controlled conditions for observation through DE imaging. We will also begin developing new DEI methodologies to produce images conveying more comprehensive information about the properties of the cartilage tissue, first for planar and then for 3D computed tomography. Throughout years one through five of the proposed project, there will be an iterative process of comparing biological analytical data with imaging data for the refinement of the DEI technique for joint tissues. Our long-term goal is to identify and localize initial phases of cartilage degeneration and follow their progression with the ultimate aim of monitoring disease progression and therapeutic interventions.

26. **Principal Investigator:** **Lin, Charles** **Affiliation:** MASSACHUSETTS GENERAL HOSPITAL
Project Title: Live microscopy and cytometry in vascular biology
Grant Number: 1-R01-EY-14106-1- **Funding Organization:** NEI
Abstract:

This is a multidisciplinary, collaborative research program bringing together investigators from several institutions to work across technology and disciplinary boundaries. The group shares a common interest in vascular biology, particularly in the eye, and specifically in the application of modern optical technology to answer critical questions related to vascular biology. The technology platform will be based on the scanning laser ophthalmoscope and the real-time in vivo confocal microscope previously developed at Schepens Eye Research Institute and at the Wellman Laboratories of Photomedicine. The existing technology will be enhanced with new development to improve image resolution, contrast, sensitivity, methods for quantification, and flexibility of imaging in living animals. Specific questions to be addressed include: 1. What are the cellular processes governing normal vascular development and stabilization? 2. What are the factors governing angiogenesis, lymphangiogenesis, and immune cell trafficking? 3. What are the cellular mechanisms for the development of sickle cell and diabetic retinopathy? 4. Can we visualize early changes in the retinal pigment epithelium noninvasively in vivo? 5. Can we detect circulating cells in vivo without drawing blood? Is the number of circulating tumor cells a good predictor for tumor burden and response to therapy? Imaging at the cellular level will enable biologists to study problems in living animals over time, gaining physiological insights beyond what can be obtained by classic static measurement (histology, immunocytochemistry, etc.), substantially reducing the number of animals required to answer these critical questions.

27. **Principal Investigator:** **Loeb, Gerald** **Affiliation:** UNIVERSITY OF SOUTHERN CALIFORNIA
Project Title: BION Treatment of Neuromuscular Dysfunction
Grant Number: 1-R01-NS-41807-1-A1 **Funding Organization:** NINDS
Abstract:

In theory, a wide range of sensory and motor dysfunctions can be treated by electrical stimulation to evoke patterns of neural activity similar to those that underlie normal function. In practice, however, such stimulation typically has required relatively expensive and large devices implanted by a surgeon or skin surface stimulation applied by a trained therapist. We have developed a new class of generic devices that can deliver precisely metered stimulation pulses to an arbitrary number of nerve and muscle sites. These leadless BIOnic Neurons (BIONsTM) can be injected through a 12 gauge hypodermic needle into the desired locations. They receive their power and digital command signals by RF telemetry from a single, externally worn transmission coil. They have been used extensively in preclinical animal studies of the effects of electrically induced muscle exercise. A clinical trial for shoulder subluxation began in November, 1999, and a second for osteoarthritis of the knee began in June 2000, both with excellent results to date. Under this BRP, we will design and build BION1 implants and accessory components for testing, programming and controlling them in patients. We will develop and test a range of clinical applications to determine safety and efficacy and to understand further the mechanisms underlying neuromuscular pathology and treatment. In the first five years, these applications include activating and strengthening muscles in the hand, shoulder, and ankle in patients suffering from stroke and cerebral palsy. Enhancements of the current BION1 technology are under development (with separate NIH funding) to improve power efficiency and portability and to incorporate sensing and back-telemetry for functional electrical stimulation (FES). In subsequent years, we will expand the clinical applications to provide more complete rehabilitation of multijoint dysfunctions that commonly occur in these disorders and we will incorporate advanced BION2 technology to provide functional reanimation of paralyzed limbs using neural prosthetic control.

28. **Principal Investigator:** **Maitland, Duncan** **Affiliation:** UNIVERSITY OF CALIF-LAWRNC LVRMR NAT LAB
Project Title: Shape Memory Polymer Devices for Treating Stroke
Grant Number: 1-R01-EB-462-1- **Funding Organization:** NIBIB
Abstract:

We propose to develop interventional devices for treating stroke victims that currently have no therapeutic alternatives (.400,000/yr in the USA). The development and testing of two complementary devices is proposed: a mechanical clot extraction system and a neurovascular stent. The clot extraction system will address the current clinical need for an acute ischemic stroke treatment and the stent will address the chronic problem of stenosis and/or restenosis of the neurovasculature. Both of these devices utilize photomechanica' micro-actuators based on laser-activated shape memory polymer (SMP). SMP is a material that will have a significant impact on clinical medicine. SMP is a relatively new material that is similar to shape memory metals in its ability to actuate from an initial deformed shape into a second, pre-determined shape. Shape memory metals are currently very popular in medicine as a material for making vascular stents. SMP has advantages over shape memory metals for certain applications, including cost, higher recoverable strain levels, ease of manufacturing, better flexibility in navigating tortuous paths, and great versatility in fabricating extremely small, highly complex actuators. Potential applications of SMP include stents, stent release mechanisms, embolic coil release mechanisms, thrombus extraction devices, and many others. The underlying hypothesis of this research is that mechanical devices can be used to treat stroke victims where there is currently no clinical alternative. There are five known private companies that are currently pursuing this hypothesis for the acute ischemic device and an unknown but presumed large number of companies pursuing neurovascular stents. Members of the current proposal team originally developed one of the technologies that are in FDA trials for treating ischemic stroke, photo-acoustic emulsification of the thrombus. However, in our opinion, none of the current devices under FDA trials is as promising or as straightforward as the devices proposed. Further, we believe that the technology developed and published from the proposed studies will lead to many other medical applications that are far beyond the scope of one proposal and one team of investigators. The proposed research is a unique combination of biomaterials, lasers and optics, immunology/biocompatibility and clinical interventional neuroradiology. The long-term goal of this research is to deliver clinical prototype devices that can begin FDA clinical trials.

29. **Principal Investigator:** **Matthews, Michael** **Affiliation:** UNIVERSITY OF SOUTH CAROLINA AT COLUMBIA
Project Title: Processing of Materials for Improved Biocompatibility
Grant Number: 1-R01-EB-552-1- **Funding Organization:** NIBIB

Abstract:
This Bioengineering Research Partnership (BRP) will conduct basic research to improve biocompatibility of materials used in biomedical devices such as prostheses and implants by providing a higher level of cleanliness and decontamination, while simultaneously providing sterilization. The BRP will determine the effectiveness of dense phase (liquid or compressed gas) carbon dioxide fluid technology for enhancing biocompatibility. The multidisciplinary partnership is led by the Department of Chemical Engineering at the University of South Carolina and includes two university partners; the Medical University of South Carolina and Clemson University, assisted by outside experts on surface preparation of implants and industrial applications of supercritical fluid based technology. A three-year BRP effort is proposed: Year 1 will confirm whether, and under what conditions, dense phase CO2 is an effective medium for sterilizing and cleaning common biomaterials and will focus on simple solid metallic, polymer, or ceramic coupons, using three typical microorganisms for tests of sterilization effectiveness and by processing samples that have been contaminated with known particulates (graphite, polyperfluoroethylene, and iron oxide) to determine the effectiveness of particulate removal and cleaning. Finally, tests to determine whether the materials treated with CO2, show improved resistance to bacterial adhesion and biofilm formation will be conducted. Year 2 research will focus on complex materials, namely flexible polymers (polyurethane and silicone rubber), as well as porous monoliths of titanium. Also in Year 2, the BRP will examine the material surface to search for adverse effects of CO2 processing, such as corrosion, pitting, and embrittlement. These experiments provide data needed for process optimization and permit comparison to known material/surface damage caused by existing cleaning and sterilization methods. Year 3 will focus on process design and optimization through the use of process design models and testing of representative devices (artificial joint, stent, and catheter) with CO2 under optimized conditions and determine the integrity and biocompatibility of the device. Also during Year 3, the ability of C02 processing to clean, decontaminate, and sterilize will be tested in vitro for material biocompatibility using cell culture methods and in vivo for histocompatibility using a subcutaneous implantation animal model.

30. **Principal Investigator:** **Maudsley, Andrew** **Affiliation:** UNIVERSITY OF MIAMI
Project Title: PARTNERSHIP FOR MR SPECTROSCOPIC IMAGING DATA PROCESSING
Grant Number: 1-R01-EB-822-1- **Funding Organization:** NIBIB
Abstract:
MR Spectroscopic Imaging (MRSI) enables non-invasive measurement of a number of tissue metabolite distributions and offers considerable potential as a diagnostic imaging technique. Widespread adoption of MRSI has been limited by complex requirements for data processing and analysis, which optimally require close integration of known spectral and spatial information, including MRI-derived tissue segmentation, morphological analysis, metabolite NMR characteristics, and detailed knowledge of normal tissue metabolite distributions. This Biomedical Research Partnership will address this limitation and increase the effectiveness of MRSI by developing an integrated set of data processing tools that emphasizes considerable automation and suitability for routine diagnostic imaging studies. This effort will combine multiple areas of expertise in MRSI and MRI data processing under 5 projects located at 4 institutions. Software tools will be developed for automated MRSI processing, tissue segmentation, brain region mapping, statistical analysis, and clinical presentation. The resultant technical developments will then be shared among several partners at collaborating medical research centers in the U.S.A., Europe, and Japan, where the package will be evaluated for diagnostic neuroimaging applications, with an emphasis on 1H MRSI of cancer, epilepsy and neurodegenerative disease. Results from metabolite imaging studies will be converted to standardized intensity units and transformed into normalized spatial coordinates, enabling the data to be pooled to form a database of MR-measured human metabolite values as a function of acquisition, spatial, and subject parameters. This information will then be used to enhance statistical analysis of individual MRSI studies. The developed methods will facilitate increased use of MRSI for diagnostic imaging, encourage the development of standardized MRSI acquisition, processing, and analysis methods, and map metabolite distributions in human brain.

31. **Principal Investigator:** **Mcknight, Timothy** **Affiliation:** UT-BATTELLE, LLC-OAK RIDGE NATIONAL LAB
Project Title: Nano Arrays for Real-Time Probing Within Living Cells
Grant Number: 1-R01-EB-433-1-A1 **Funding Organization:** NIBIB
Abstract:
This project will exploit the recent development of rigid, vertically aligned, carbon nanofiber arrays to provide nanoscale probes for mapping intra and extracellular molecular events in and around living cells in real time with extremely high spatial resolution (< 50 nm probing areas). Devices will be fabricated and characterized to determine the performance of nanoscale arrays as independently addressable electrochemical molecular probes. Characterizations will be performed using a set of standard analytes that have been routinely used for characterization of carbon-based electrode systems (year 1). Probe response to hydrogen peroxide and superoxide anion will then be characterized (year 1 into year 2). Strategies and methods will then be develop for coupling nanofiber arrays around individual and groups of living cells (year 2). Electrochemical analysis techniques will be applied at individual elements of carbon nanofiber arrays to spatially and temporally map the activity of peroxide around

and ultimately within individual cell locales (year 3). This research will be structured around development of these methodologies using microfluidic-based cell and analyte handling strategies, thereby promoting future high-throughput screening applications, such as clinical diagnostics of cell and tissue specimens and pharmaceutical exploration and discovery. This effort will be conducted by various organizational groups within the Oak Ridge National Laboratory. The Interdisciplinary team involved with this effort features mechanical and electrical engineers with experience in microfluide systems/semiconductor/and nanoscale fabrication, a biochemist and biologist with expertise in cell culture and single cell monitoring, analytical chemists, and a biophysicist, with expertise in cell signaling and environmental response. This effort will directly address BRP thrust areas including nanotechnology and microtechnology, functional genomics/microarray technology/gene expression analysis, cell and molecular imaging, and complex biological systems.

32. **Principal Investigator:** **Narayana, Ponnada** **Affiliation:** UNIVERSITY OF TEXAS HLTH SCI CTR HOUSTON
Project Title: MR Image Analysis in MS: Identification of a Surrogate
Grant Number: 1-R01-NS-41808-1-A1 **Funding Organization:** NINDS
Abstract:

Multiple sclerosis (MS) is the most common demyelinating disease in humans and has a complex clinical course that includes unpredictable relapses and variable remissions. This makes clinical evaluation of MS difficult. Therefore, current clinical trial designs must incorporate large numbers of patients followed over long periods. These designs are expensive and may deprive patients of timely access to effective treatment. The use of robust surrogate marker(s) that have predictive value could reduce problems in evaluating new drugs and improve the management of individual patients. MRI-based measures such as volumes of lesions, black holes, contrast enhancements, atrophy, and magnetization transfer ratios, are expected to serve as robust surrogates. However, a number of studies have shown that the correlation between these MR measures and clinical score is weak. We hypothesize that this weak correlation is in part due to the use of improper image analysis tools necessary for robust image quantitation and in part due to failure to define the correct MRI surrogate. In these studies we propose to develop an integrated image analysis package that is robust and automatic for accurate quantitation of tissue volumes. An important feature of this analysis package is its ability to analyze images acquired on a wide range of MR scanners using a plethora of MR sequences, greatly extending its utility. This package allows us to follow temporal changes in individual lesions, as well as currently used global changes. This analysis package will be rigorously evaluated using an extensive database that contains images on more than 2,000 MS patients, followed over several years. Using this database, we propose to identify surrogate(s) based on individual or some combination of MRI-measures. Finally, this software will be distributed to a few select centers for multicenter evaluation. While the main emphasis is on MS, this system should be readily adaptable to investigate and manage various neurological disorders that require accurate determination of tissue volumes and their temporal change.

33. **Principal Investigator:** **Pearson, John** **Affiliation:** UNIVERSITY OF CALIF-LOS ALAMOS NAT LAB
Project Title: Multi-scale observation and modeling of IP3/Ca signaling
Grant Number: 1-R01-GM-65830-1- **Funding Organization:** NIGMS
Abstract:

The liberation of calcium ions from intracellular stores into the cytosol is used as a signaling mechanism by virtually all cell types to regulate functions as diverse as secretion, contraction, proliferation, and cell death. Advances in observational techniques have revealed complex patterns of intracellular Ca2+ that serve to selectively regulate specific cellular responses, and are constructed hierarchically through the activity of individual ion channels, multiple channels within clusters, and interactions between clusters. It is impossible to resolve all these scales simultaneously in a single experiment and the shorter time and distance scales cannot be resolved by any available experimental approaches. We therefore propose to use a tightly integrated approach of modeling, electrophysiology, and high-resolution cellular calcium imaging to illuminate the mechanisms by which "elementary" Ca2+ events are triggered and coupled to produce global cellular calcium signals. Specific aims are to describe (i) the kinetic mechanisms underlying the flux of calcium through single channels, (ii) the functional coupling between individual channels within a cluster, and (iii) the coordination between clusters allowing the propagation of global signals and the effects of buffers on this process. Numerical models will be constructed based on hypotheses and parameter values derived from patch-clamp and confocal cellular imaging experiments, and will be iteratively tested by comparison with observations and by their predictive power. Our overall goal is to develop a comprehensive model of intracellular Ca2+ signaling that is consistent with a multitude of observations, has predictive value, and extends to crucial - but experimentally inaccessible -space and time scales (nanometers and microseconds). We will focus on inositol trisphosphate-mediated Ca2+ signaling, utilizing Xenopus oocytes as a well-characterized model system, but the emergent principles will be widely applicable across many cell types and species, as well as to calcium signalling mediated by ryanodine receptors.

34. **Principal Investigator:** **Sahn, David** **Affiliation:** OREGON HEALTH & SCIENCE UNIVERSITY
Project Title: High Frequency Ultrasound Arrays : Intracardiac Imaging
Grant Number: 1-R01-HL-67647-1-A1 **Funding Organization:** NHLBI
Abstract:
Invasive applications of echocardiography, including transesophageal echo, intravascular echo and intracardiac echo have been one of the most fertile areas driving new technology for ultraminiaturization and very high resolution. Among the most prolonged and detailed interventional catheterization procedures, electrophysiological mapping and ablation for recurrent atrial and ventricular arrhythmias have received recent attention because of the now-recognized need for spatial mapping in addition to fluoroscopic catheter localization, and because of the increased frequency of these debilitating rhythm problems in an aging population. We propose to design, develop and test a family of 2D and 3D ultrasound imaging devices which, at 10-15MHz operating frequency, will provide spatial localization, and both tissue velocity and strain rate estimates of mechanical activation in atrial and ventricular walls, to guide electrical mapping. This should greatly shorten time to localize critical areas. Our devices will be integrated with the EP electrode and RF ablation devices so that they can anatomically monitor the ablation procedure, visualize the lesion, and map the distribution of temperature during RF delivery focus. The devices we will build can also assess the heart before, during and after surgery as well as monitor anatomical catheter interventions for coronary artery, valvular or congenital heart disease. Our partnership is a multidisciplinary group of clinicians, surgeons, echocardiographers and electrophysiologists at OHSU, led by David J. Sahn, MD, Director of the Interdisciplinary Program For Cardiac Imaging, combined with bioengineers including: Matthew O'Donnell, PhD, Chair of the Department of Biomedical Engineering at the University of Michigan, Ann Arbor; Kirk Shung, PhD, director of an NIH Research Resource for Development of High Frequency Arrays at Pennsylvania State University, University Park; Kal Thomenius, PhD, Program Manager of Ultrasound Research at the General Electric Corporate Research and Development Center in Schenectady, New York; Douglas Stephens, Vice President of Strategic Technology at the Imaging Division of JOMED (formerly Endosonics Corporation) in Rancho Cordova, California, a pioneer in miniaturized array devices for intravascular and intracardiac imaging catheters; and Raymond Chia, PhD, of Irvine Biomedical, a small agile company with expertise in steerable multipolar electrode and ablation devices and their combination with other imaging modalities. The design and development of these devices combined with advanced functional imaging methods should open new vistas for applications in invasive echocardiography and ultrasound in general.

35. **Principal Investigator:** **Smith, Michael** **Affiliation:** PENNSYLVANIA STATE UNIV HERSHEY MED CTR
Project Title: High Field MRI: Limitations and Solutions
Grant Number: 1-R01-EB-454-1-A1 **Funding Organization:** NIBIB
Abstract:
The long-term objective of this research is to understand and develop engineering solutions to the difficulties presented to magnetic resonance imaging (MRI) at high magnetic field strength. Specific Aim 1: Develop and validate a methodology to analyze, quantify, and eliminate static field distortion artifacts produced in high field MR images by regional differences in magnetic susceptibility. This information will be used to develop artifact-correction techniques for high-speed functional MRI and distortion-free high field MRI of human, animal, and cellular anatomy. Specific Aim 1: Develop and validate models and methods to analyze and quantify radio frequency (RF) magnetic field distortions occurring in the human head and body of men, women, children, and fetuses in utero. These analyses will be used to evaluate regional RF power deposition from specific pulse sequences for patient safety and to develop methods to minimize RF inhomogeneity. In the spirit of the Bioengineering Research Partnership this proposal will draw expertise and partnership from the Center for Magnetic Resonance Research at the University of Minnesota (a premiere 7.0 Tesla whole body MRI research facility), REMCOM (a magnetic field modeling software company), and the National High Magnetic Field Laboratory (a National Research Laboratory incorporating 17.8 Tesla MRI microscopy and 11.7 Tesla small animal imaging). The results of these studies will aid a wide array of researchers in high speed distortion-free functional MRI, anatomical studies at both low and high field strengths, MR microscopy in animals and intact cells, evaluation of patient safety, and in many cases, reclaim techniques which have proven problematic at high field strengths.

36. **Principal Investigator:** **Sokurenko, Evgeni** **Affiliation:** UNIVERSITY OF WASHINGTON
Project Title: Dynamic Properties of Bacterial Adhesions
Grant Number: 1-R01-AI-50940-1-A1 **Funding Organization:** NIAID
Abstract:

The main goal of the proposal is to develop a comprehensive structural picture of how mechanical force affects the functional state of microbial adhesions. Specific adhesive proteins enable bacteria to recognize ligands leading to the adhesion and colonization of various living hosts or environmental niches, and finally infection. A growing number of experimental observations indicate that mechanical forces generated by shear-flow of body fluids are modulating the affinity and selectivity of adhesins to their ligands. In order to test the extent to which mechanical forces may alter the structure and thus the functional states of adhesins, we propose to characterize the dynamic properties of the most common type of bacterial adhesin - FimH -that is a lectin-like adhesive subunit of type 1 (mannose-sensitive) fimbria of Enterobacteria and Vibrio. In the course of our preliminary studies we have identified distinct structural variants of the Escherichia coli FimH adhesin where shear-flow can induce their preferential binding to target cells, obviously by switching their specificity between the mono-mannoside and tri-mannoside receptors. To develop structural hypotheses how mechanical forces acting on the binding site may affect the tertiary structure of FimH, we have been and will be conducting steered molecular dynamics simulations in which tension is applied between the receptor-binding residues and the C-terminal end of the FimH lectin domain. Deriving a comprehensive understanding of the structure-function relationship of adhesins under static and dynamic conditions requires that molecular biology tools are employed in concert with X-ray crystallography and novel powerful nano-analytical tools to probe, characterize and simulate non-equilibrium protein structures as they relate to function.

37. **Principal Investigator:** **Taylor, W R** **Affiliation:** EMORY UNIVERSITY
Project Title: Biology, Biomechanics and Atherosclerosis
Grant Number: 1-R01-HL-70531-1- **Funding Organization:** NHLBI
Abstract:

Cardiovascular disease remains the number one cause of death in the United States today. In addition to a plethora of genetic and environmental factors, the diet and lifestyle of Western populations continues to have a profound negative impact on the prevalence of atherosclerotic disease. Significant advances have been made in the management and treatment of the clinical sequalae of this disease process. However, many of these treatments are geared towards the management of catastrophic clinical events. Our understanding of the basic biology of the atherosclerotic lesion is still lacking in terms of a complete and fundamental understanding of the basic biology of the atherosclerotic lesion. The proposed Bioengineering Research Partnership (BRP) will be dedicated to establishing a consortium of investigators from Emory University School of Medicine and The Georgia Institute of Technology devoted to obtaining a greater understanding of the biology and engineering of this fundamental problem of great clinical importance. This BRP will expand upon established collaborations to incorporate expertise in basic vascular biology, imaging technologies, fluid mechanics, arterial wall mechanics, cardiac surgery, and interventional cardiology. We shall make use of explanted human hearts obtained from cardiac transplant recipients to provide a unique, model system to study living, human arteries with established atherosclerosis. The in vivo studies will be augmented by a series of cell culture studies designed to explicitly examine the effects of defined mechanical forces on inflammatory responses and apoptosis in a controlled setting. Finally, the impact of placement of clinically used coronary artery stents on the mechanical and subsequent biological responses of the arterial wall will be examined.

38. **Principal Investigator:** **Troyk, Philip** **Affiliation:** ILLINOIS INSTITUTE OF TECHNOLOGY
Project Title: Intracortical Visual Prothesis
Grant Number: 1-R01-NS-40690-1-A1 **Funding Organization:** NINDS
Abstract:

This abstract is not available.

39. **Principal Investigator:** **Vince, David** **Affiliation:** Cleveland Clinic Foundation
Project Title: High Frequency Nonlinear Acoustic Intravascular Imaging
Grant Number: 1-R01-HL-69094-1- **Funding Organization:** NHLBI
Abstract:

Intravascular ultrasound (IVUS) imaging is a technology that permits tomographic visualization of a cross section through the vessel wall. Its development has provided a powerful new method to assess plaque morphology in vivo. However, while new catheter designs are markedly improved on their predecessors, image quality has not seen significant gains due to the primitive nature of the ultrasound transducer designs. Increasing the frequency of the transducer above the current state of the art 40MHz holds the potential to improve image quality, although higher frequencies are attenuated rapidly in biological media and the depth of penetration is therefore reduced. One possible method of enhancing the quality of IVUS images may be to exploit the effect of nonlinear propagation (harmonic imaging) of the ultrasound signal as it passes through the tissue. Despite the fact that harmonic imaging is now becoming a standard modality in the latest commercial B mode ultrasound scanners with

a frequency range up to 4.0 MHz, there is no evidence of attempts to develop a harmonic imaging system for significantly higher frequencies, which would be suitable for intravascular applications. In this application we propose to investigate the generation of tissue harmonics at high fundamental frequencies (20 40MHz) suitable for intravascular application. This will be pioneering work in the field of medical acoustics. The major driving force for our project will be clinical necessity. We envisage that the implementation of high frequency harmonic imaging will dramatically improve image quality and allow better delineation of plaque geometry and composition. High frequency ultrasound transducers will be designed and built comprising traditional ceramic materials and novel polymeric devices fabricated using MEMS technology. Finally advanced signal processing methods will be designed and developed to accurately predict plaque composition from high frequency nonlinear acoustic data.

40. **Principal Investigator:** **Waggoner, Alan** **Affiliation:** CARNEGIE-MELLON UNIVERSITY
Project Title: Long Wavelength Quantum Dot-based probes - cell tracking
Grant Number: 1-R01-EB-364-1- **Funding Organization:** NIBIB
Abstract:

We will develop new technologies to employ quantum dots in biological imaging in vitro. In an evolving program, quantum dot technology will be developed specifically for (I) cell identification and tracking of cells in tissues, (2) tracking cell proliferation through multiple generations in tissues (3) vasculature location, and (4) deep 3-D imaging of Qdot-labeled polymer scaffold structures relative to the Qdot-labeled cells in engineered tissue models. Quantum Dots Corporation will prepare new types of Qdots that have properties suited to deep imaging of cells and structures in tissues. Particular emphasis will be placed on near infrared Qdots for imaging deeper in tissues. The Science and Technology Center at Carnegie Mellon University will then develop methods to derivatize Qdots for existing and new applications in cell biology. The STC will initially use available Qdots and conjugates, label cells by a variety of means, then test the cells for fluorescent brightness, stability of labeling, and cell survival and function. As newer quantum dots become available, they will be similarly tested and compared with existing Qdots and existing organic fluorescent probes, e.g., Alexa dyes and cyanine dyes. Fluorescence lifetime imaging capability will be added to the 3-D grating imager in the STC for enhancing signal-to-background in deep tissue imaging by taking advantage of the relatively long emission lifetime of Qdots. To obtain feedback for the development program we have included collaboration with the recently formed Bone Tissue Engineering Center at Carnegie Mellon University. In this collaboration we will examine the utility of the developing Qdot technology for studying cell location, movement and proliferation in the 3-D structures of engineered bone tissue. This is a particularly challenging and relevant system that requires Qdot technology to extend cell tracking to denser and more highly scattering tissue matrices, including hydroxyapatite-containing artificial bone matrices. By the conclusion of this project, we expect to have instrumentation and probes to perform time-resolved multicolor imaging at millimeter depth in many natural and artificial tissues. Thus the technology will be generic and have utility in many biological and medical applications.

41. **Principal Investigator:** **Wall, Jonathan** **Affiliation:** UNIVERSITY OF TENNESSEE KNOXVILLE
Project Title: SPECT/CT Imaging of Systemic AA-Amyloidosis in Mice
Grant Number: 1-R01-EB-789-1-A2 **Funding Organization:** NIBIB
Abstract:

High resolution imaging is becoming an invaluable tool in biomedical research much as it has to the clinician. In the clinic, imaging offers a precise, non-invasive means of diagnosis and directly influences both the therapeutic approach and prognosis. Unfortunately, the development of high-resolution imaging tools demanded by researchers has lagged behind that of the clinic; thus, characterization of the kinetics of in vivo pathology and the subsequent development of novel, effective therapeutics has been hampered. This is particularly true in the field of amyloid- related diseases which include Alzheimer's disease, type I1 diabetes and primary (AL) amyloidosis. It is impossible to fully appreciate and understand the complexity of these diseases, and the means by which they may be halted, without the ability to perform longitudinal studies in individual animals in vivo. To that end, the development high- resolution micro-imaging technologies capable of detecting and quantifying amyloid deposits in vivo is warranted and imperative. We intend to address these important issues through the design and application of a powerful new dual-modality imaging technology, microSPECT, combined with microCT, supported by state-of-the-art 3-D image reconstruction and analysis software. This new technology will be employed to identify radiolabeled amyloid ldeposits in live animals and present the amyloid distribution within the context of a high-resolution CT image of the 1 visceral terrain. With this technology, the goal of quantifying organ-specific amyloid burden in vivo is attainable. The goals are thus to: (i) Complete the design and implementation of a high-resolution, small-animal speciJic dual lSPECT/CT imaging system. (ii). Develop a system of amyloid quantijkation in which microSPECT image data can be directly correlated to amyloid burden. (iii) Use these technologies to study the progression of systemic AA- amyloidosis in two murine models and the regression thereof in response to novel immunotherapies. This study will not only result in technological advancements in the field of small-animal imaging and amyloid-specific radio- tracers but will also provide a wealth of information on the natural progression of

amyloidosis in vivo and establish a paradigm for the screening of therapeutic drugs in animal models of human disease. Furthermore, the translation of amyloid-specific imaging technologies will yield tangible clinical benefit.

42. **Principal Investigator:** **Wittrup, Karl** **Affiliation:** MASSACHUSETTS INSTITUTE OF TECHNOLOGY
Project Title: Engineered Antibody EGFR Antagonist Cancer Therapeutics
Grant Number: 1-R01-CA-96504-1- **Funding Organization:** NCI
Abstract:

This Bioengineering Research Partnership will develop biomolecular analysis and design tools for engineering next-generation therapeutic antibodies for cancer therapies. Generating antibodies to bind targets whose expression is increased in tumor cells has been a promising therapeutic approach for many years. However, antibody binding can produce a variety of different cellular responses and, ultimately, control over tumor cells will require careful study of the relationship between antibody binding and cellular response so that appropriate binding properties can be engineered to produce desired responses. In the research proposed here, antibodies against epidermal growth factor receptor (EGFR) will be isolated and engineered by directed evolution, guided by computational docking predictions and quantitative analysis of cellular responses to altered EGFR signaling, dimerization, and trafficking. EGFR is overexpressed in a broad spectrum of epithelial cancers, and blocking antibodies are currently progressing favorably through clinical immune response and limitations of screening assays rather than rational design for these initial antibody drugs, and consequently the molecular mechanism of efficacy in vivo is not fully understood. Targeting specific EGFR surfaces with antibodies designed to maximize receptor antagonism and downregulation should result in greater therapeutic efficacy. The proposed research will develop approaches applicable to antibody design against a broad range of targets, particularly cell surface receptors. The BRP team integrates expertise in protein engineering, cellular bioengineering, computational protein biophysics candidates; generic tools for engineering protein/protein recognition; and will develop analytical approaches to biological response modification via combined quantitative cell biology and protein engineering.

43. **Principal Investigator:** **Wolpaw, Jonathan** **Affiliation:** WADSWORTH CENTER
Project Title: GENERAL PURPOSE BRAIN-COMPUTER INTERFACE(BCI)SYSTEM
Grant Number: 1-R01-EB-856-1- **Funding Organization:** NIBIB
Abstract:

Signals from the brain can provide a new communication channel - a brain-computer interface (BCI) - for those with severe neuromuscular disorders such as amyotrophic lateral sclerosis, brainstem stroke, and spinal cord injury. BCI technology can allow people who are completely paralyzed, or "locked in," to express wishes to caregivers, use word processing programs, access the Internet, or even operate neuroprostheses. Up to now, BCI research has demonstrated that a variety of different methods using different brain signals, signal analyses, and operating formats can convey a persons commands to a computer. Future progress that moves from this demonstration stage to practical applications of long-term value to those with motor disabilities requires a flexible general purpose BCI system that can incorporate, compare, and (if indicated) combine these different methods, and can support generation of standard protocols for the clinical application of this new communication and control technology. The development and clinical validation of a general purpose BCI system is the goal of this Bioengineering Research Partnership (BRP) application. Each of the investigators in this partnership has been in the forefront of research into one of the current BCI methods, and together they have extensive experience in the development of BCI systems. The aims of this proposal are: (1) to develop a flexible general purpose BCI system that can incorporate any of the relevant signals, analyses, and operating formats and can be configured for laboratory or clinical needs; (2) to use the system to compare, contrast, and combine relevant brain signals and signal processing options during BCI operation and thereby develop a standard protocol for applying BCI technology to the needs of individual users; (3) to apply the system and protocol to address specific communication needs of people with severe motor disabilities and show that BCI technology is both useful to and actually used by these individuals;(4) to apply the system and protocol to develop the use of neuronal activity recorded within cortex for communication and control, and to define the relationships between this intracortical activity and scalp-recorded signals that might be used to guide or supplement invasive methods. Achievement of these aims and dissemination of the resulting technology to other research groups should advance BCI research from its current stage of laboratory demonstrations to development and validation of a general purpose BCI communication and control technology that can incorporate all relevant brain signals and has clear practical value for those with motor disabilities.

44. **Principal Investigator:** **Yarmush, Martin** **Affiliation:** MASSACHUSETTS GENERAL HOSPITAL
Project Title: Metabolic Engineering for Improved Liver Function

Grant Number: 1-R01-DK-59766-1-A1 **Funding Organization:** NIDDK

Abstract:

Steatosis or lipid accumulation in non-adipocytes occurs in about 25 percent of cadaveric livers used for transplantation. Although usually asymptomatic, hepatic steatosis is a significant risk factor for postoperative liver failure, as fatty livers are much more sensitive to ischemia-reperfusion injury than normal "lean" livers. Thus, fatty livers are often considered to be "marginally acceptable" for transplantation. Our long-term goal is to develop a metabolic pre-conditioning regimen, which reduces hepatic lipid storage and increases the liver's ability to withstand ischemia-reperfusion injury. We hypothesize that metabolic pre-conditioning will reduce the risk of postoperative liver dysfunction to a level similar to that observed in non-steatotic livers.Our specific aims are: (1) To characterize the metabolic and vascular homeostatic mechanisms in steatotic livers; (2) To intervene via metabolic conditioning techniques to reduce the sensitivity of hepatocytes and perfused livers to ischemia-reperfusion injury; (3) To optimize metabolic conditioning techniques for livers used in pre-clinical models of liver surgery. In the short-term, the proposed studies could (1) provide the rationale basis for increasing the liver donor pool size, as severely steatotic livers are usually discarded; (2) improve the outcome of patients which receive liver transplants with mild to moderate steatosis; and (3) provide new ways to prevent or limit hepatic fibrosis, as hepatic steatosis often precedes fibrosis in degenerative liver diseases. The long-term outcomes of this project are (1) scientific and technology bases to develop defatting methods for other organ systems affected by steatosis, such as pancreatic beta cells and cardiomyocytes in obese individuals; and (2) warm perfusion techniques with the potential to significantly increase organ storage time beyond the limits of current cold storage techniques

45. **Principal Investigator:** **Yoganathan, Ajit** **Affiliation:** GEORGIA INSTITUTE OF TECHNOLOGY

Project Title: Improving Flow Dynamics in Fontan Surgeries

Grant Number: 1-R01-HL-67622-1-A1 **Funding Organization:** NHLBI

Abstract:

The incidence of congenital heart defects is 1 percent with 20 percent of these incidences corresponding to complex congenital lesions with only one effective pumping chamber; the latter are termed single ventricle heart defects. These statistics show that 2 babies out of every 1,000 births will be born with a single ventricle. Surgical treatment for these defects consists of bypassing the right side of the heart and connecting the systemic and pulmonary circulations in series with the univentricular pump. Patients who survive surgery require lifelong, intensive medical attention. Cardiologists report that the 20 percent of their caseload consisting of such patients requires over 50 percent of their time; this underscores the gravity of problems in patients as well as the need for improvements in existing treatment methods. The current surgical procedure of choice for patients with a single ventricle is the total cavopulmonary connection (TCPC). The central hypothesis for this Multi-Institutional BRP Project is that development of pre-operative computer-based surgical design methods will advance the state-of-the-art in clinical treatment of single-ventricle patients and improve their quality of life. The development of these methods will be guided by six specific aims: (i) development of baseline TCPC surgical templates based on fluid dynamic assessments of various TCPC configurations; (ii) study the impact of graft materials on local fluid dynamics following TCPC; (iii) compile anatomic and materials databases for validating computer-based surgical planning and design protocols; (iv) improve surgical planning and design through development of computer-based simulation tools facilitating prediction of potential post-operative flow conditions in any given patient; (v) investigate improvements in post-TCPC hemodynamics achieved by treating congenital abnormalities associated with the ascending aorta; (vi) determine the feasibility of reducing post-TCPC central venous pressure using a pressure regulator/pump.