SUMMARY OF
BIOENGINEERING RESEARCH PARTNERSHIPS (BRP)
FOR PROGRAM ANNOUNCEMENTS
PAS-99-010 AND PAS-00-006
FY 2001

The following text provides a summary of grants from BECON member institutes and centers for Bioengineering Research Partnerships (BRP's) in response to program announcements PAS-99-010 and PAS-00-006. The objective of the BRP program is to support basic bioengineering research addressing important biological or medical problems with the work being done by a multidisciplinary research team which applies an integrative, systems approach to develop knowledge or methods to focus on the project objectives.

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

1. **Principal Investigator:** **Berns, Michael**
   Affiliation: University of California - Irvine
   Title: Integrated Platform for Chemical Analysis of Live Cells
   Application Number: RR14892
   Funding Organization: NCRR
   Abstract:
   The general objective of this project is to design, build, and test an integrated optical and microfluidics system that will enable the performance of novel biochemical assays in living cells. Specific project objectives are to (1) develop a laser microscope platform for single cell manipulation and analysis; (2) develop a multipurpose, modular microfluidics chip for single cell assay; and (3) develop a broad range of analytes which can be assayed in single cells. The device will be tested in biomedical systems relating primarily to cancer, and cell growth and development. However, it will have wide application to areas of molecular medicine, drug development, and biomedical research.

2. **Principal Investigator:** **Brown, Thomas**
   Affiliation: University of Iowa
   Title: Nonlinear Computational Biomechanics of The Hip
   Application Number: AR46601
   Funding Organization: NIAMS
   Abstract:
   Disorders of the hip comprise a substantial fraction of current musculoskeletal disease burden. Complex nonlinear mechanical phenomena pervade many aspects of treatment of hip disease and injury including total hip arthroplasty, intra-articular fractures, osteonecrosis, and developmental dysplasia. The focus of this research partnership is in applying nonlinear finite element formulations to address unquantified mechanical phenomena that are clinically recognized as being crucial to patient outcome. Building on previous and ongoing finite element work, new computational formulations will be developed to tackle nonlinearities currently limiting the accuracy of numerical simulations in five clinically important areas. The first two areas involve leading complications of total hip arthroplasty with regard to abrasive wear of polyethylene and dislocation. The third area involves intra-articular fractures of the acetabulum and involve estimating residual cartilage contact stress elevations accompanying attempts at surgical restoration of articular surface congruity. The fourth area involves osteonecrosis and includes computationally characterizing a new animal model (the emu) and using the models for in-vivo testing of computationally optimized placement of a novel head-preserving implant device. The fifth application area is surgical management of developmental hip dysplasia. The partnership will bring together a critical mass of surgeons and engineers to achieve clinically-grounded advances.

3. **Principal Investigator: Chien, Shu**
Affiliation: University of California - San Diego
Title: Molecular Basis for of Endothelial Remodeling By Flow
Application Number: HL64382
Funding Organization: NHLBI
Abstract:

The endothelial cells of the vasculature are constantly subjected to flow forces which vary with space and time. In the straight portion of the aorta, blood flow is primarily laminar and the shear stress is high. In the bends and branch points of the arteries, blood flow is unsteady and exhibits a disturbed flow pattern and flow separation, recirculation, and reattachment. These differential flow patterns are correlated with the preferential localization of atherosclerotic lesions. The goal of this project is to determine whether laminar flow and disturbed flow activate different molecular signaling pathways in the blood vessel wall to result in the expression of unique sets of genes that lead to the functional consequences of anti-atherosclerosis and pro-artherosclerosis, respectively. The proposal is based on partnerships among scientists with expertise in vascular biology, physiology, biomechanics, bioengineering, bioinformatics, cell biology, and molecular biology. Results from this study will generate new insights into the fundamental problem of mechano-chemical transduction and elucidate the molecular basis for the topographical nature of atherosclerosis. Also, the signaling molecules identified in this study could be potential therapeutic targets for modulating the balance between cell cycle arrest and proliferation.

4. **Principal Investigator: Crandall, Edward**
Affiliation: University of Southern California
Title: Absorption Mechanisms of Peptide/Protein Drugs Via Lung
Application Number: HL64365
Funding Organization: NHLBI
Abstract:

New biotechnology advances are leading to the production of numerous protein and peptide drugs that cannot achieve their therapeutic potential because of inefficient delivery. Recently, systemic drug delivery of therapeutic peptide and protein drugs via pulmonary routes has proven to be more effective than delivery via oral routes. However, information is lacking on specific pathways and transport processes in the lung alveolar epithelium. This represents the major barrier to drug absorption. The goals of this proposal are to understand the transport mechanisms and trafficking of peptides and proteins across the lung alveolar epithelium and to elucidate the properties contributing to differences in bioavailability of various compounds. Using experimental approaches which span cell biology to bioengineering, the results of this project should provide critical information on how to increase bioavailability and improve the strategies related to the design of peptide and protein drugs while at the same time retaining the integrity of necessary alveolar epithelial barrier properties.

5. **Principal Investigator: Davies, Peter**
Affiliation: University of Pennsylvania
Title: Cell And Molecular Studies in Cardiovascular Engineering
Application Number: HL064388
Funding Organization: NHLBI
Abstract:

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

focus on tissue engineered arteries ex vive, heart valve pathology (both ex vive and in vive), and the delivery of therapeutic factors to correct intracranial aneurysms in vive. The preclinical short-term objectives are sustained retention of structure and function of arteries maintained ex vive and their reintroduction in vive, the elucidation of heart valve gene expression, and both in vitro and in vive evaluation of the release of potential therapeutic agents from coated platinum microcoils.

6. **Principal Investigator: Deluca, Carlo**
   Affiliation: Boston University
   Title: Harnessing Motoneuron Activity: From Lab To Clinic
   Application Number: HD38585
   Funding Organization: NICHD
   Abstract:

   This project is aimed at developing an automatic system for decomposing the electromyographic (EMG) signal into the constituent action potentials corresponding to the firing of individual motor units activated by motoneurons. This system will be an outgrowth of an existing rudimentary system which has enabled the performance of various novel investigations that have provided new insight into motor control. The proposal is composed of five projects. The first will be deign-driven and describes the design and development of the new system which has knowledge-based algorithms at its heart for decomposing the signals. The other four projects will be hypothesis-based and will address basic science questions and clinical applications that will reveal the utility of the system. Project 2 will address the modifications which occur in the firing of motor units as a function of aging and the benefits that can be restored by exercise. Project 3 will address the phenomenon of motor unit substitution which will be useful in ergonomic work environments and the rehabilitation of patients with peripheral nerve injury ahd spinal cord injury. Projects 4 and 5 are clinical studies which will explore the use of quantified neutromotor activity and will study patients with acute ataxia.

7. **Principal Investigator: Dichter, Marc**
   Affiliation: University of Pennsylvania
   Title: An Implantable Device To Predict And Prevent Seizures
   Application Number: NS041811
   Funding Organization: NINDS
   Abstract:

   We propose to assemble an ensemble of accomplished investigators from the University of Pennsylvania, Georgia Institute of Technology, Children's Hospital of Philadelphia and IntelliMedix, a small start-up company through the GIT and Penn, in an intensive five to ten year effort to create a novel therapy for refractory epilepsy: an implantable closed loop system capable of predicting epileptic seizures prior to electrical and behavioral onset and triggering intervention to abort them before clinical expression. The work will have three major thrusts: (1) Seizure Prediction: Developing and refining seizure prediction algorithms derived from data obtained from implanted biosensors in adults, children and in animal models of human epilepsy, capable of predicting seizures hours to minutes prior to electrical and clinical onset, (2) Mechanisms of ictogenesis: Unraveling the cellular, molecular, neurophysiologic and neuronal network mechanisms underlying the observed signal changes identified by these algorithms through in-vitro and in-vivo experiments in animals, recordings in human candidates for epilepsy surgery, and modeling these findings via computer simulations in order to refine predictive and intervention strategies, and (3) Therapeutics: Developing strategies aimed at specific points in the "ictogenic" process, as discovered above, consisting of electro, physiological and pharmacological interventions to disrupt the cascade of events which lead to seizures, in ways which do not interfere with normal brain function. This work will directly give rise to commercially viable intellectual property including: implantable biosensors, miniaturized biocompatible electrical stimulation and drug infusion hardware, stimulation paradigms, customized pharmacologic agents, customized software/hardware interfaces for signal acquisition, processing and synchronization with algorithms for driving therapeutic interventions. It is hoped that a closed loop seizure prediction and prevention device will be implementable in a 5-I0 year period and will significantly improve the quality of life of individuals with epilepsy.

8. **Principal Investigator: Frazier, Albert**
Affiliation: Univeristy of Utah
Title: Integrated Sample Preparation for Genomic Analysis in Micro Device Format
Application Number: ES10229
Funding Organization: NIGMS
Abstract:

A consortium of four research centers will conduct a joint investigation to study and create a functional integrated sample preparation device. The strategy of this front-end sample preparation micro device is to produce a research tool that has the flexibility to be integrated with a number of downstream analysis objectives; i.e., either sequencing or genotyping. The proposed micro-scale sample preparation system is composed of three main micro compartments which include: (1) sample introduction combined with cell sorting and collection, (2) cell lysis, recovery of the nucleic acid material of choice (DNA or mRNA), and sample cleanup via solid-phase extraction or affinity capture, and (3) elution of the material to an amplification micro chamber and subsequent amplification. The expected applications address national health care by providing effective miniaturized instruments for biochemical analysis. This research should provide critical insight into portable biochemical analysis systems.

9. **Principal Investigator: Fredberg, Jeffrey**
Affiliation: Harvard School of Public Health
Title: Micromechanics of Airway Smooth Muscle Cells in Culture
Application Number: HL65960
Funding Organization: NHLBI
Abstract:

Acute narrowing of the airway lumen in asthma is driven by myosin motors that exert their mechanical effects within a cytoskeletal scaffolding that is both deformable and in a continuous state of remodeling. The mechanical properties of that scaffolding are not well defined. This is a multi-disciplinary design-directed bioengineering project to fill that gap of knowledge. We will develop a micromechanical technology to measure the rheological properties of adherent living airway smooth muscle cells in culture, and the time-course of mechanical changes that occur in response to contractile stimuli or after genetic manipulation of cytoskeletal proteins. Ligand-coated ferromagnetic microbeads are bound to the cytoskeleton, and oscillatory mechanical torques are then applied to the bead by a sinusoidally-varying external magnetic field. Resulting oscillatory bead motions deform the cell, and can be determined by measuring changes of the remanent magnetic field due to bead rotations or, alternatively, by direct observation of oscillatory bead displacements using light microscopy; these are complementary detection methods each with special advantages. This technology becomes, in effect, a micro-rheometry system that can probe - in cell culture conditions - contractile responses and underlying cellular rate processes over time scales as short as tens of milliseconds to as long as hundreds of seconds. Thus, it measures mechanical properties of cells using deformation times (and stress magnitudes) that span the physiological range. We will develop this technology and then use it to test the hypothesis that the contractile response of human airway smooth muscle cells in culture is attenuated by overexpression of heat shock protein 27 (HSP27) dominant negative mutants. This hypothesis bears upon a question whose importance has been identified only recently, namely, the stability of the cytoskeleton of the airway smooth muscle cell and the role of CSK stability in airway narrowing in asthma.

10. **Principal Investigator: Gilbert, Charles**
Affiliation: The Rockefeller University
Title: Imaging Activity in Visual Cortex At The Cellular Level
Application Number: EY12896
Funding Organization: NEI
Abstract:

The project proposes to combine advances in optics, molecular probes, and gene therapy techniques to monitor neural activity in the visual cortex of awake, behaving animals with single cell resolution. Two-photon imaging makes it possible to visualize fluorescent cells lying several hundred microns under the cortical surface and to minimize the photodynamic damage to the cells. Fluorescent proteins will allow visualization of details of cell morphology, and the fluorescence can be linked to neural activity. Adenovial vectors will be developed to insert genetic constructs that code for these proteins into the genome of cortical cells allowing one to label large numbers of cells with a sparse distribution and with minimal damage to the cells. The imaging instrumentation will be

merged with the animal recording devices for monitoring activity tied to visual stimuli and animal behavior. Probes that reflect neural activity will be determined and the imaging technique will be adapted to studies in behaving animals. The applications of this work include the study of morphological changes in cells, the biophysics of neuronal integration, the neural basis of learning and higher order cognitive function, and patterns of gene expression in the intact brain.

11. Principal Investigator: Gower, Laurie

Affiliation: University of Florida

Title: Role of Biopolymers And Lipids in Kidney Stone Formation

Application Number: DK059765

Funding Organization: NIDDK

Abstract:

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

12. Principal Investigator: Greenberg, Robert

Affiliation: Second Site, LLC

Title: Development/Testing of Artificial Retinas for the Blind

Application Number: EY12893

Funding Organization: NEI

Abstract:

This proposal is to develop a long-term, implantable retinal stimulator for patients blinded by outer retinal degenerations. Using technologies developed by the Alfred E. Mann group of companies over the past 30 years for implantable stimulators, the investigators will develop a chronic retinal stimulator and associated external hardware for use both in research and as a clinical device. To achieve this goal, several areas of research are needed. In this work, academia will collaborate with industry to accomplish the basic research necessary to make a chronic retinal prosthesis a reality. Areas of basic research that the project will focus on include electrode geometry and electrode material selection, surgical attachment of the retinal implant, low-power electronic circuit designs, and hermetic packaging. Each of these areas needs additional research for the creation of an optimal chronic retinal prosthesis which will enable persons blinded by outer retinal degenerations to regain the most important loss they have suffered – the loss of mobility. The aim of this proposal is to complete the design and manufacture of a retinal prosthesis and associated external hardware and test it chronically in animals so that an investigational device application can be made to the FDA in preparation for a clinical trial.

13. **Principal Investigator: Halperin, Henry**
Affiliation: Johns Hopkins University
Title: Magnetic Resonance Guided Electrophysiology Intervention
Application Number: HL64795
Funding Organization: NHLBI
Abstract:

A major limitation in studying arrhythmias in patients is the inability to accurately correlate anatomical and electrical information. Another major limitation is the inability to viaualize ablated areas of myocardium during catheter ablation procedures which makes it difficult to confirm the presence of ablated lesions in the desired locations. This project is aimed at developing imaging technologies that combine anatomic information with electrophysiologic testing and catheter ablation. Although these imaging technologies primarily will address atrial fibrillation, they should be broadly applicable to using MRI to guide interventional procedures in the heart and other organ systems.

14. **Principal Investigator: Hasegawa, Bruce**
Affiliation: University of California - San Francisco
Title: Imaging Structure And Function in Small Animals
Application Number: CA091771
Funding Organization: NCI
Abstract:

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

15. **Principal Investigator: Hirschl, Ronald**
Affiliation: University of Michigan
Title: Total Liquid Ventilation: A Bioengineering Partnership
Application Number: HL64373
Funding Organization: NHLBI
Abstract:

This project proposes studies to understand and optimize the technique of Total Liquid Ventilation (TLV) for treatment of patients with the Adult Respiratory Distress Syndrome (ARDS). ARDS is a devastating lung disease that affects 150,000 patients per year in the United States and has a mortality of greater than 40%. In TLV, the lungs are filled with a perfluorocarbon liquid and ventilated with a device that oxygenates and removes carbon dioxide from the perfluorocarbon. This proposal addresses several fundamental physiological and bioengineering issues that

underlie progress toward establishing TLV as a clinical tool. Factors to be studied include control of filling and distribution of the fluorocarbon in the lung, parameters of gas transport by the liquid, and flow limitation during expiration. The proposal combines image studies, theoretical fluid dynamic analyses, and animal studies.

16. **Principal Investigator: Hoffman, Eric**
Affiliation: University of Iowa
Title: Image and Model Based Analysis of Lung Disease
Application Number: HL64368
Funding Organization: NHLBI
Abstract:
With the emergence of innovative interventions in lung disease treatment at both early and late stages, it has become clear that sensitive, objective, accurate, and repeatable measures must be developed to determine the presence and regional distribution of lung abnormalities. This proposal is aimed at bringing together a team of engineers, scientists, and physicians from six academic institutions to collaborate on developing the technologies which will allow the use of dynamic, volumetric X-ray CT to assess the lung. This effort will involve the development of a comprehensive model of the human lung based on measurements from non-invasive, dynamic, volumetric X-ray CT imaging that can be applied to the early and pre-clinical assessment of lung abnormalities.

17. **Principal Investigator: Hollister, Scott**
Affiliation: University of Michigan - Ann Arbor
Title: Engineering Joint Scaffolds for Function/Regeneration
Application Number: DE013608
Funding Organization: NIDCR
Abstract:
Tissue engineering offers considerable promise for temporomandibular (TM J) joint reconstruction, a pressing clinical problem. To create durable engineered joint implants, the effects of scaffold material and architecture on tissue regeneration and function must be understood. In this project, we will determine the effects of designed and fabricated internal architectures on bone regeneration by bone marrow stromal cells in an in vivo model of osteogenesis. We will mechanically test these architectures to determine load carrying capability. To test bone-cartilage interface regeneration in vivo, we will create a scaffold interface design seeded with bone marrow stromal cells on one half of the scaffold (bone side) and auricular chondrocytes on the other half (cartilage side), creating a bone-cartilage interface inside the scaffold. Finally, we will then engineer a prototype Conylar Ramus Unit (CRU) based on the most promising data from the bone-bone and bonecartilage scaffold studies.

18. **Principal Investigator: Hood, Leroy**
Affiliation: Institute for Systems Biology
Title: Gene Expression by Multifunctional Biology
Application Number: CA091719
Funding Organization: NCI
Abstract:
The Institute of Systems Biology (ISB) will team with tile Oak Ridge National Laboratory (ORNL) to conduct research on Multi-functional Molecular Biology of gene expression and to develop all Advanced Diagnostic Biochip (ADB) system, the next generation of biosensor system for simultaneous detection of a wide range of gene expression biotargets for biomedical (cancer) diagnosis. Specific innovations of the fully integrated biochip system include: (1) Integrated circuit biochip; (2) Multi-functional bioprobes (DNA, antibody, enzymes); and (3) integrated microfluidics system for in-situ sampling. We will use prostate cancer cell lines, prostate cancer xenografts (human cancers growing in immunologically compromised mice), prostate cancer tissues, and prostate cancer cells isolated from tumors by fluorescence-activated cell-sorting to investigate the mRNA and protein expression patterns of genes that may serve as diagnostic markers. We will use conventional genomics and proteomics techniques to identify a set of diagnostic markers for prostate cancer (years I and 2) which can then be tested against the ADB system in year 3. The benchmarking of the ADB system against conventional microarray technology will be an important aspect of this grant. We also plan to automate and miniaturize techniques for the preparation of mRNA

and protein probes. Accordingly, the prostate cancer system will have mRNA (eDNA), protein, enzymes, and cells that can be analyzed by the ABD system.

19. Principal Investigator: Huse, William
Affiliation: Novasite Pharmaceuticals, Inc.
Title: Drug Discovery of Large-Scale Variant Targets By Hts
Application Number: AI48517
Funding Organization: NIAID
Abstract:

This partnership will develop a novel HTS system for Drug Discovery capable of screening 10 3 variant targets simultaneously in real time, at little additional costs relative to one-target screening systems. We will use this instrumentation to develop a novel approach to Drug Discovery via large scale generation and screening of variant targets, centered on identifying ligand-receptor interactions at large scale. The advantage is a combinatorial explosion in the number of ligand- receptor interactions explored relative to one-receptor screening approaches (from 10 3 to 10 8, for 10 3 libraries). Our aim is the discovery of an anti-inflammatory and immunosuppressive agent, by discovering an agonist for the cannabinoid-2 G protein coupled receptor (GPCR). We have set up a general expression system that efficiently transfects one single variant target cDNA per cell in a massive transfection step. We use a cell-based GPCR functional assay based on Ca2+ sensitive fluorescence dyes. In the first Specific Aim, we will develop a novel fluorescence microscope imaging system capable of visualizing (screening) thousands of individual cells (variant targets) simultaneously in one well at High Throughput. This system brings HTS to a new level, where each cell is a functional assay by itself, the physical limit for a cell-based assay. For lead optimization, another component aims at developing a special HTS flow cytometry system to sort cells with significantly lower EC5Os than the wild type receptor. The variant GPCR present in these isolated cells, identified by PCR, represents a mutation that enhances the potency of a given lead. This data will be analyzed by computational molecular models, attempting to match the variation of chemical moieties within the lead compound with the variation of amino acid residues within the receptor to guide docking procedures. Bioinformatic analysis of these biochemically-derived computational models will be used to translate the identified amino acid changes that enhance the lead's potency into mirror-image modifications proposed on the chemical compound that will guide the lead optimization process.

20. Principal Investigator: Intaglietta, Marcos
Affiliation: University of California - San Diego
Title: Bioengineering Design of Artificial Blood
Application Number: HL64395
Funding Organization: NHLBI
Abstract:

This proposal is aimed at designing, developing, and producing an economic oxygen-carrying plasma expander based on modified molecular human hemoglobin engineered with properties that insure the maintenance of microvascular function leading to improved survival and tissue oxygenation relative to the blood for treatment of trauma victims within 48 hours of injury. The program includes production of purified hemoglobin from red blood cells by means of a modified, self-contained plasma fractionation centrifuge that directly produces the necessary molecular modifications and a unit of artificial blood ready for use. The molecular modification to be pursued is surface modification with polyethylene glycol and other modifications that will result in molecules with large radius. The program encompasses all aspects of artificial blood production from obtaining the raw materials to the final commercial product and is aimed at establishing a blood transfusion technology that delivers a blood replacement material that is cost effective and as efficacious as blood.

21. **Principal Investigator: Izatt, Joseph**
Affiliation: Case Western Reserve University
Title: Partnership for Research in Optical Coherence Tomography
Application Number: EY13015
Funding Organization: NEI/NCI
Abstract:

This proposal represents a multidisciplinary approach to advance the state of the art in diagnostic anatomical and functional imaging in situ at the micron scale. This will be achieved by developing fundamental advances in the technology of Optical Coherence Tomography (OCT), validating new techniques using animal models, and employing new technologies in pilot clinical studies. The specific objectives of the proposal are to (1) enhance and expand the clinical utility of OCT by developing core technologies such as high frame imaging, ultrahigh resolution imaging, minimally invasive endoscopic and opthalmic delivery systems, and physiological function imaging; (2) apply these technologies for pilot studies of early cancer detection in the GI tract; (3) apply these technologies for studies of chemoprevention and early cancer detection in the lung; (4) improve the accuracy and safety of keratorefractive surgery; (5) improve imaging of retinal, subretinal, and vitreous pathologies; and (6) apply functional imaing technologies for the quantitative detection of retinal/choroidal blood flow and vitreoretinal strand motion in animals and humans.

22. **Principal Investigator: Jacques, Steven**
Affiliation: Oregon Medical Laser Center
Title: Biomedical Optics for Medical Research And Clinical Care
Application Number: CA84587
Funding Organization: NCI
Abstract:

Biomedical optics is a field that uses light to interrogate tissues for diagnostic purposes and to treat disease and assist surgery and has applications in both biomedical research and clinical care. This proposal establishes a Biomedical Optics Laboratory on the campus of the Oregon Health Sciences University (OHSU) as a core research facility to support the interface of new optical technologies from the bioengineering network with projects in the medical research and clinical activities at OHSU. This proposal would provide funding for the bioengineering network to initiate new projects for translation to the medical center. The initial projects fall into the two general areas of tissue engineering (biomaterials development with emphasis on bone regeneration and biomaterial implants) and cancer detection and treatment (optical imaging of dysplasia and superficial cancer, optical fiber devices for dosimetry during photodynamic therapy), and photodynamic therapy as a tool in basic medical research. This research program complements a Biomedical Optics curriculum at the OHSU.

23. **Principal Investigator: Jain, Rakesh**
Affiliation: Massachusettes General Hospital
Title: Integrative Biology of Tumor Angiogenesis, Invasion And Metastasis
Application Number: CA85140
Funding Organization: NCI
Abstract:

Now that numerous important genes associated with tumor angiogenesis, invasion, and metastasis have been discovered, the grand challenge is to understand their function in intact animals. A second major challenge is to integrate and apply this knowledge to cancer prevention, detection, and treatment. The proposed work aims at meeting these challenges with a new, more precise quantitative, integrative, and multi-disciplinary bioengineering approach. The approach builds on (1) genetically engineered mice to visualize gene expression, (2) in vivo models to visualize molecular and cellular events, (3) computer-assisted in vivo spectroscopy to quantify gene expression and function, and (4) mathematical modeling to integrate the resulting information. Using this technology, four critical aspects of tumor metastasis will be investigated: angiogenesis, invasion, hematogenous metastasis, and lymphangiogenesis and lymphatic metastasis. This work offers a new paradigm for integrative studies of the dynamics of gene expression and function in cancer that will facilitate translation of knowledge about the molecular biology of cancer into effective cancer prevfention, detection, and treatment strategies.

24. Principal Investigator: Karellas, Andrew

Affiliation: University of Massachusetts Medical School

Title: Digital Mammography High Resolution Flat Panel Imager

Application Number: CA088792

Funding Organization: NCI

Abstract:

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

25. Principal Investigator: Koller, Manfred

Affiliation: Oncosis, Inc.

Title: Laser Cell Processing for Basic And Clinical Research

Application Number: RR15374

Funding Organization: NCRR

Abstract:

Photosis is a technology platform that incorporates high-speed optical scanning of biological samples, image analysis, and computer-controlled laser-irradiation of specific targets within the sample for the purpose of inducing a biological response. Specific cells to be treated within a mixed population are identified by parameters such as size, shape, fluorescence, or other distinguishing features. Once identified, individual cells are targeted with a laser to induce a desired response, such as cell death, optoporation (for gene transfer), or even inactivation of a specific mRNA transcript within the cell. The current beta1-prototyle system can process hundreds of millions of cells in an hour under sterile conditions, making it useful for several research and clinical applications. Photosis has many potential uses, and this project brings together a number of institutions and researchers to investigate and define the possible applications of this novel technology. In its current configuration, the instrument uses a single color for cell detection and a laser to induce necrosis in every targeted cell. Additional applications will be developed, some of which will require modifications to the system design and building of new prototypes. The prototypes will be placed at four partnership sites where the basic and clinical applications research will be carried out, including: 1) in vivo study of purified stem cell subpopulations in the xenogeneic fetal sheep transplant model; 2) human clinical trials to assess NHL purging in autologous stem cell transplantation; 3) purification of genetically- modified stem cells and T-cells expressing a selectable transgene, as well as selective transduction of specific cells in a mixture via optoporation; and 4) accurate mRNA expression profiling from purified primary human prostate cancer cell populations. The proposed work will result in several types of novel bioengineering instrumentation for advancing the state-of-the-art in cell processing. These instruments will be used in this program to advance basic and clinical research in stem cell biology, cancer, immunology, and genomics.

26. Principal Investigator: Langer, Robert

Affiliation: Massachusettes Institute of Technology
Title: Microchip Drug Delivery System
Application Number: AI47739
Funding Organization: NIAID
Abstract:

The method by which a drug is delivered can have a significant effect on the drug's therapeutic efficacy. Controlled drug delivery can alleviate problems associated with conventional therapy by providing stable drug bioavailability in a therapeutically meaningful range and can be used to localize the therapy to the tissue site of interest. Recent studies have shown that it is possible to fabricate a solid-state silicon microchip in which a number of chemicals or drugs can be stored and released on demand by an external trigger. Based on this technology, it should be possible to fabricate a device that can be pre-programmed to deliver combination drugs in a pre-determined fashion. This novel delivery technology has broad utility in the biomedical areas of local delivery of anesthetics for pain management, sub-dermal delivery of vaccines, periodontal delivery of antibiotic and anti-inflammatory agents, localized delivery of anti-tumor and neoplastic agents, gene delivery, and delivery of antiarrhythmic agents. The objectives of this proposal are to (1) develop an active, silicon-based microchip for controlled release of drugs that con operate autonomously; (2) develop a passive, polymeric chip for the controlled release of drugs; (3) evaluate the biocompatibility of active and passive microchip delivery devices; and (4) evaluate the resulting drug release both in vivo and in vitro.

27. Principal Investigator: Levine, Simon

Affiliation: University of Michigan - Ann Arbor
Title: Direct Brain Interface Based on Event Detection in ECOG
Application Number: NS040681
Funding Organization: NINDS
Abstract:

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

28. **Principal Investigator: Ley, Klaus**
Affiliation: University of Virginia
Title: Biomechanics of Leukocyte Adhesion Molecules
Application Number: HL64381
Funding Organization: NHLBI
Abstract:

This proposal involves assembling a group of biomedical engineers and molecular biologists to focus on the biomechanics of adhesion molecules. Leukocyte and endothelial adhesion molecules govern the trafficking of cells in ischemia reperfusion, atherosclerosis, inflammation, immunity, cancer metastasis, and other processes. Some adhesion molecules, such as selectins, are specialized to mediate adhesion in the presence of blood flow. Quantitative measurements of forces and displacements generated by adhesion molecules at the molecular level and quantitative measurements at the cellular level when the adhesion molecules are clearly identified have not previously been feasible. This group of investigators proposes to lead the way in the emerging field of adhesion molecular biomechanics by providing an understanding of detailed molecular biomechanics of selectins and their ligands. This objective is critical to understanding many areas of vascular biology and pathology such as atherosclerosis and thrombosis. Advances in this area will also provide the basis for the construction of new diagnostic and therapeutic vehicles to detect and treat disease processes associated with inflammation and will impact drug and gene delivery in the vascular system.

29. **Principal Investigator: Li, Shu-Tung**
Affiliation: Collagen Matrix, Inc.
Title: Type 1 Collagen-Based Nerve Guide for PNS Regeneration
Application Number: HD041747
Funding Organization: NICHD
Abstract:

This proposal is a collaboration of multidisciplinary fields of peripheral nerve repair and regeneration, involving Collagen Matrix, Inc., specializing in extracellular matrix design and engineering; Eastern Virginia Medical School, specializing in neuroscience and neurosurgery; Duke University specializing in neuroscience, entubulation repair of peripheral nerve, clinical neurology and urology; and University of South Florida, specializing in clinical urology. The overall goal of this research partnership proposal is to design, engineer and evaluate in vivo a type I collagen-based bioactive nerve guide for peripheral nerve regeneration applications. The research team, through joint effort of the partnership, applies the current state-of-the-art knowledge of matrix technology, protein chemistry, neuroscience, neurosurgery and clinical urology to systematically evaluate the key design parameters. This systematic approach will lead to the development of a nerve guide that has the high probability of clinical success in nerve regeneration. The specific objectives of the proposal involve the isolation of the key design parameters and testing them in a rat sciatic nerve model. The final prototype, engineered from optimal design parameters, will be evaluated in two primate nerve models (median and cavernosal) as a potential entubulation repair method for clinical application.

30. **Principal Investigator: Ling, C**
Affiliation: Sloan-Kettering Institute for Cancer Research
Title: Multimodality Biological Imaging of Cancer/Tumor Hypoxia
Application Number: CA084596
Funding Organization: NCI
Abstract:

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

correlate invasive biological endpoints with image features from non-invasive imaging using spatially registered data-sets. Thus, this project integrates physics, chemistry, biology, engineering and computer sciences to study tumor biology and hypoxia, with considerable significance for cancer diagnosis and treatment.

31. Principal Investigator: Lizzi, Frederic
Affiliation: Riverside Research Institute
Title: Integrated Ultrasonic Systems for Noninvasive Therapy
Application Number: CA084588
Funding Organization: NCI
Abstract:

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

32. Principal Investigator: Long, Richard
Affiliation: Western Michigan University
Title: Blind Pedestrians' Access To Complex Intersections
Application Number: EY12894
Funding Organization: NEI
Abstract:

The objectives of this proposal are (1) to use the strengths of a multi-disciplinary team to understand the perceptual and cognitive requirements of negotiating complex intersections without vision and with low vision, (2) to design and test engineering and training solutions to problems of information access that are currently known and that are identified in the course of this research, and (3) to produce materials about the problems and solutions that are useful to transportation engineers, individuals with visual impairments, and rehabilitation personnel. This study will focus on intersections that are complex by virtue of their size, shape, and/or signalization. Particular areas to be investigated by the research team members include transportation engineering, characteristics of pedestrian signals,, acoustics research concerning the perception of moving sound sources as related to street crossing, auditory motion display for research and training, eye gaze strategies, and mental effort during street crossings.

33. **Principal Investigator: Majumdar, Sharmila**
Affiliation: University of California - San Francisco
Title: Morphological And Functional Musculo-Skeletal Imaging
Application Number: AG17762
Funding Organization: NIA
Abstract:

This partnership will focus on the systematic study of the morphology and function of the musculoskeletal system in disease and health. The aim of this consortium is to improve medical care through bioengineering developments, and to facilitate close interactions between bioengineers, computer scientists, clinical investigators, basic scientists and corporate partners. This effort will expedite the development of clinically-relevant quantitative imaging tools and propel the technical advances from the laboratories into the operating rooms and clinics. We hypothesize that high resolution, fast magnetic resonance imaging techniques and positron emission tomography, combined with quantitative image analysis, processing and visualization, can provide new insights and clinically viable and relevant methods for objective evaluation of disorders of the musculo-skeletal system. The long-term objective of this partnership is to understand the link between morphology, function, biochemical changes and clinical symptoms in the musculo-skeletal system. An immediate objective is to develop, implement and optimize novel non-invasive imaging methods (magnetic resonance imaging: MRI and positron emission tomography: PET) that will allow us to depict the musculo-skeletal system, quantitate morphology, function, provide unique 3D visualization and graphical representations of function and morphology, as well as correlate these with biochemistry and clinical status. This research partnership is aimed at quantitating early degenerative changes in two clinical areas of emphasis: the knee and the spine. The specific goals are: (i) to develop quantitative morphological and functional markers for degenerative diseases of the spine, (ii) to develop quantitative morphological and functional markers for the degenerative changes in the knee and osteoarthritis.

34. **Principal Investigator: Meaney, David**
Affiliation: University of Pennsylvania
Title: Force Transmission in The Central Nervous System
Application Number: HD041699
Funding Organization: NICHD
Abstract:

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

35. **Principal Investigator: Mitzner, Wayne**
Affiliation: Johns Hopkins University
Title: New Approach for The Treatment of Asthma
Application Number: HL066020
Funding Organization: NHLBI
Abstract:

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

36. **Principal Investigator: Olsen, Don**
Affiliation: Utah Artificial Heart Institute
Title: Magnetically Suspended Rotor Blood Pump
Application Number: HL64378
Funding Organization: NHLBI
Abstract:

The objective of this proposal is to develop a novel ventricular assist device for patients suffering from congestive heart failure. Several new technologies will be developed to overcome shortcomings of existing blood pump technology. Most important will be the development of a totally magnetically suspended impeller to eliminate the need for contact bearings and seals. Additionally, a responsive physiologic controller will be developed to match system output to patient need without the use of sensors. These technological developments will benefit CHF patients by providing devices with significantly improved system reliability and durability, quality of life, and reduced anticoagulation needs. The proposed completely implantable, continuous flow, ventricular assist device will initially be intended as a bridge to transplantation, but the reliability characteristics should ultimately facilitate development of a longer term bridge to recovery or a permanent device.

37. **Principal Investigator: Peckham, Paul**
Affiliation: Case Western Reserve University
Title: Development of Networked Implantable Neuroprostheses
Application Number: NS041809
Funding Organization: NINDS
Abstract:

Neuroprosthetic devices that electrically stimulate paralyzed muscles provide functional enhancements for individuals with spinal cord injury and stroke such as standing and stepping, reaching and grasping, and bladder and bowel function. Current implanted neuroprosthetic systems utilize considerable external powering and signal processing, and each system is tailored to the specific application for which it was intended. The need to design a customized implant system for each application severely limits progress in the field and delays introduction of new technology to the end user. Therefore, we propose to design, fabricate and evaluate an implanted neuroprosthesis with an open architecture that can be easily configured for current and anticipated neuroprosthetic applications, allows accommodation of new innovations by various participants in the field, minimizes external components, and can be clinically implemented. The implant design we propose is based on a network of small implanted modules, distributed throughout the body. A given system will consist of one or more "hubs" with significant processing

capability for implementing advanced control-algorithms and an inductive link for external programming and powering, as well as separate input and output "nodes" for sensing and stimulating. The network will initially communicate and distribute power internally using wire-based leads, but the feasibility of a wireless network and local power storage will also be investigated. Power will be provided via an external inductive link, with a rechargeable implanted battery used to provide un-tethered operation. A variety of modules will be developed, each with a specific function including: muscle-based stimulation, nerve cuff stimulation, biopotential (electromyogram, electro-oculogram, electro-encephalogram, electroneurogram) signal recording, body segment orientation measurement and acceleration measurement. Other potential modules that could be incorporated into this system include mechanical actuators, joint angle transduction, and strain gage based sensors. \

38. Principal Investigator: Peli, Eliezer
Affiliation: Stephens Eye Research Institute
Title: Engineering Approaches To Low Vision Rehabilitation
Application Number: EY12890
Funding Organization: NEI
Abstract:

This proposal applies novel engineering approaches to the problems of low vision rehabilitation. This will be accomplished by building prototype devices based on solid theoretical foundations that, eventually, will become marketable rehabilitation products. The devices will be tested critically using diverse patient populations with the help of clinical partners to determine the effects on function and on the quality of life. The work will develop and test both optical and electronic devices that implement three specific engineering approaches aimed at restoring at least part of the important interplay of central (high-resolution) and peripheral (wide-field) vision. The three engineering approaches are multiplexing, dynamic control of display, and image enhancement. The effort will show that various combinations of these approaches are possible and likely to be beneficial. The proposed assessment and testing will emphasize two approaches: a virtual environment for controlled and quantitative testing in the laboratory, and on-the-street evaluation for real-life determination of the effect and utility of the devices and techniques.

39. Principal Investigator: Rabbitt, Richard
Affiliation: University of Utah
Title: Micro-Electric Impedance Spectroscopy of Hair Cells
Application Number: DC004928
Funding Organization: NIDCD
Abstract:

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

40. **Principal Investigator: Ratner, Buddy**
Affiliation: University of Washington
Title: Engineered Cardiac Morphogenesis - Stem Cells And Scaffolds
Application Number: HL64387
Funding Organization: NHLBI
Abstract:

The long-term aims of this project are to produce tissue-engineering ventricular wall patches for myocardial repair, ventricular assist devices, and replacement ventricles. The research team collaboration will encompass three foci: (1) instructive tissue scaffolds using advanced biomaterial fabrication to engineer biodegradable matrices and meshes with controllable pore dimensions modified with receptor=specific molecules; (2) cell and developmental biology in which primary and stem cell-derived muscle and vascular cells will be studied on modified scaffolds to determine the optimal conditions for producing functional muscle tissues and vascular networks; and (3) clinical science and animal models to test contractile ventricular patches in an injured heart model. Integration with host tissue and restoration of contractile function will also be developed. The "tube hearts" will be conditioned to pulsatile flow circuits, assessed for mechanical performance in vitro, and eventually grafted into aortas of synergistic rats for in vivo evaluation. Progress toward these goals should establish design principles necessary for constructing more complex ventricular devices.

41. **Principal Investigator: Renshaw, Perry**
Affiliation: McLean Hospital
Title: High Field Mr Research in Drug Abuse
Application Number: DA014178
Funding Organization: NIDA
Abstract:

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

42. **Principal Investigator: Rylander, H. Grady**
Affiliation: University of Texas - Austin
Title: Polarization Sensitive Retinal Tomography for Glaucoma
Application Number: EY12877
Funding Organization: NEI
Abstract:

This proposal is based on the hypothesis that the retinal nerve fiber layer displays a characteristic decrease with the development and progression of glaucoma. The project is aimed at developing a diagnostic modality based on the polarization and coherent properties of light for morphologic and functional imaging of the eye. Measuring depth-resolved polarization changes of light reflected from the retina will allow determination of both retinal nerve fiber layer thickness and axon density.

43. Principal Investigator: Sackellares, James

Affiliation: UNIVERSITY OF FLORIDA

Title: Bioengineering Research Partnership in Brain Dynamics

Application Number: NS039687

Funding Organization: NINDS

Abstract:

Epilepsy is a common neurological disorder that causes spontaneous recurrent seizures. In spite of major advances in pharmacology, neuroimaging, clinical neurophysiology, and neurosurgery, many patients remain disabled due to uncontrolled seizures. We propose to develop novel diagnostic and therapeutic tools, based on recent discoveries regarding dynamical mechanisms initiating epileptic seizures. We have found characteristic preictal dynamical changes, detectable in the electroencephalogram (EEG), preceding seizures by over 30 minutes (preictal transition, PT). More recently, other investigators have confu'med the presence of PT. Our research indicates that the PT is demonstrable in the EEG in approximately 90% of seizures and that automated paradigms can predict seizures. The potential to predict seizures in advance provides an opportunity to develop innovative diagnostic and therapeutic approaches. Our specific aims are: (1) to continue development of dynamic measures for quantification of spatiotemporal properties of the epileptic transition (years I-3); (2) to develop specific pattern recognition algorithms for a seizure warning system (SWS) based upon the on-line features of the dynamical properties of brain electrical activity (years 1-4); (3) to implement the dynamic measures and pattern recognition algorithms in a SWS for on-line, real-time detection of the preictal dynamical transition (years 2-4); and (4) to evaluate the effects of therapeutic interventions during the preictal transition (years i-5). The specific spatiotemporal patterns of the PT vary from seizure to seizure and patient to patient. Thus, sensitive and reliable SWS will require sophisticated adaptive signal processing techniques. Dynamical measures will be augmented by other powerful analytic approaches, including multivariate time-series analysis, pattern recognition algorithms, and optimization techniques. To this end, we have gathered experts in signal processing, optimization, neurophysiology, neuroanatomy, epilepsy, and neurosurgery. The work will involve the coordination of several research sites throughout the University of Florida Campus (Brain Dynamics Laboratory {Malcolm Randall V.A. Medical Center}, Computer NeuroEngineering Laboratory {College of Engineering}, Center for Applied Optimization {College of Engineering}, an in vitro Neurophysiology Research Laboratory {University of Florida Brain Institute}, an in vivo Neurophysiology Laboratory {College of Medicine}, the Epilepsy Monitoring Laboratory {Shands Hospital}and Arizona State University {ASU Brain Dynamics Laboratory}. We anticipate that the proposed efforts will result in prototype diagnostic software and devices by the end of year 5. We also will obtain preliminary data that will be used for the design and testing of implantable devices that will activate pulsed therapeutic interventions during the preictal transition.

44. Principal Investigator: Shain, William

Affiliation: Wadsworth Center

Title: Brain Prostheses: Tissue Compatibility & Integration

Application Number: NS40977

Funding Organization: NINDS

Abstract:

Nanofabricated neural prosthetic devices provide tremendous potential for furthering understanding of central nervous system (CNS) function and treating CNS disease and injury. Such devices will permit precise localization of targets and control of electrode function. However, the success of these devices is currently limited by reactive biological responses. This proposal is aimed at comparing and contrasting events underlying early and prolonged responses observed following prosthetic insertion to develop strategies for successful design and use of neural prosthetics. Signaling events that produce these responses will be identified along with the sources of these signals, and technology advances in prosthesis insertion, design, and pharmacological delivery will be used to control these events. Cell and organic cultures, developmental staging, and mouse genetic models will be used to test experimental hypotheses developed from observations in adult rats. Prostheses will be made using nanofabrication techniques, and surfaces will be modified using chemical, physical, and topographic methods. Results from these experiments will provide important new information for the intelligent design of improved biomaterials and micro-devices to control dynamic biological events in the CNS and to insure successful long-term performance of neural prosthetic devices.

45. **Principal Investigator: Skalak, Thomas**
Affiliation: University of Virginia
Title: Integrated Control of Vascular Pattern Formation
Application Number: HL065958
Funding Organization: NHLBI
Abstract:

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

46. **Principal Investigator: Sklar, Larry**
Affiliation: University of New Mexico
Title: 7 TMR Drug Discovery, Microfluidics & Ht Flow Cytometry
Application Number: GM60799
Funding Organization: NIGMS
Abstract:

High throughput (HT) screening is integral to drug discovery. While flow cytometry is known for its ability to measure cell responses, its power in the homogeneous analysis of ligand binding or molecular assembly and its potential for high throughput are not well recognized. This proposal consists of four projects targeted at displaying virtually any molecule in a format compatible with particle-based analysis and developing a novel approach for plug-flow cytometry with sampling times of about one second which would make flow cytometry a powerful alternative for the real-time analysis of molecular interactions. The four projects include (1) expressing the proteins relevant to to signal transduction and termination in forms appropriate for flow cytometry, (2) employing biomaterial display and detection strategies compatible with flow cytometric analysis, (3) developing applicable fluid handling approaches for cells and beads, and (4) developing and implementing micro-fluidic sample handling approaches using novel elastomer-based micromachine technology. The expected test platforms for high throughput analysis to be developed during this project will have commercial potential in drug development and will allow definition of mechanistic details of cell activation through 7TMR mediated pathways.

47. **Principal Investigator: Snyder, Alan**
Affiliation: Penn State University - Hershey Medical Center
Title: Biomedical Applications of Electroactive Polymers
Application Number: HL65959
Funding Organization: NHLBI
Abstract:

The objective of this partnership is to refine materials and establish methods for application of electroactive polymers in prosthetics and interventional medical devices. Electroactive materials are materials that change shape when exposed to an electric field. They are attractive as actuators because of their high energy density - the amount of energy that can be imparted to a load for a given volume or mass of active material. Electroactive materials,

chiefly the piezoceramics, have found important uses in a variety of industrial, consumer and military systems, as well as in ultrasonic transducers for medical imaging, flow measurement and therapy. The piezoceramics have not been successfully applied, however, as actuators in other medical devices. A new class of electroactive polymers has recently been discovered, which make possible the development of devices using forms that would not have been practical using available materials. These materials remain flexible, can readily be formed into a variety of shapes, and provide much larger shape changes than do previously available materials. This will make possible the development of devices using forms that would not previously have been practical. Two target application areas have been chosen: (1) next-generation prosthetic blood pumps for treatment of end-stage heart disease, and (2) advanced instrumentation for minimally invasive surgery, particularly for use in confined spaces such as the thorax. These disparate applications share the need for very compact, efficient and uncomplicated means of actuation. Both suffer today from the need for bulky actuation mechanisms that must remain physically distinct from the parts which pump blood or manipulate tissue. The technology to be developed under this program will blur the lines between structure and actuator, leading to modes of therapy that are not currently available. The Materials Research partner will work to optimize electroactive polymers, which have been developed thus far for military applications, for use in the target medical devices, and develop methods for fabrication of the required multilaminate actuator materials. As these materials are fundamentally different from active materials of actuating mechanisms used by engineers in the past, the Mechanical Engineering partner will work to develop new design methodologies for use with the new materials. The Bioengineering partner will develop prototype devices to demonstrate the potential of the technology and lay the ground work for full development of new devices.

48. Principal Investigator: Soper, Steven
Affiliation: Louisiana State University
Title: The Design And Fabrication of Novel Micro-Instrument Platforms for Performing Genetic-Based Analyses
Application Number: CA84625
Funding Organization: NCI
Abstract:

The focus of this project is to fabricate novel micro-instrument platforms targeted at detecting mutations in genes associated with certain cancers (colon and breast). The mutational analysis tool to be developed will detect point mutations at a level of l mutant DNA in approximately 100 normal DNA's. The devices will be fabricated using high aspect ratio micromachining in plastics (PMMA) and LIGA processing. The ability to effectively use these PMMA materials is based on the use of near-IR fluorescence readout which alleviates much of the background signal arising from autofluorescence of the substrate or matrix interferences.

49. Principal Investigator: Stephanopoulos, Gregory
Affiliation: Massachusettes Institute of Technology
Title: Linking Genomics To Function Via Metabolic Phenotyping
Application Number: DK058533
Funding Organization: NIDDK
Abstract:

Recombinant strains with well defined genetic backgrounds are often found to exhibit small functional differences despite specific changes at the genetic level while in other cases, single gene alterations result in profound phenotypic variations. Although a first step in explaining such macroscopic differences is to probe the full detail of the expression phenotype by genome-wide expression measurements, transcription data alone are insufficient to elucidate the actual metabolic state of a cell and its functions. The latter require information about intracellular metabolic fluxes, which constitute fundamental determinants of cell physiology and excellent metrics of cell function. "Metabolic phenotyping" is the process and methods of determining intracellular fluxes as determinants of the cellular metabolic state. Combined with transcription data, the investigators provide a complete framework for analyzing the effect of drugs and studying disease. This project integrates the expertise of three participating laboratories for the purpose of combining metabolic and expression phenotyping to elucidate central carbon and lipid metabolism in model mouse hepatoma and hepatocyte cultures. Determination of intracellular fluxes will follow a systems approach termed metabolic reconstruction whereby the entire metabolic network is configured such as to best represent macroscopic rate and isotopic label distribution measurements made by GC-MS. Of particular attention are issues of observability, redundancy, and solution stability to ensure method feasibility and

accuracy of the results. Differential transcription data will be obtained by DNA microarrays for mouse genes involved in central carbon metabolic, gluconeogenic and lipid biosynthetic pathways, as well as for other genes with particular expression variability that will be identified in the course of the research. Bioinformatics methods and programs, developed over the past 12 years will be deployed for this purpose. The general goal of the research is to identify relationships between the metabolic phenotype as defined above and the transcriptional state as defined by expression data of consequence in pathways important to diabetes. The broader contribution of this research is to extend the paradigm of holistic transcriptional investigation introduced by DNA microarray technologies to the study of metabolic level processes by metabolic phenotyping. As such, it holds the promise of identifying most, if not all points in metabolism affected by the action of drugs or genetic modifications thus guiding future programs of drug development and gene therapy.

50. Principal Investigator: Sweeney, HL
Affiliation: University of Pennsylvania
Title: Bioengineering Research Partnership - Muscular Dystrophy
Application Number: AR47292
Funding Organization: NIAMS
Abstract:

The goal of this partnership is to utilize a number of aspects of bioengineering in order to develop tools and therapeutics for the treatment and monitoring of muscular dystrophies. The project is collaboration between three investigators and includes the following areas of bioengineering: 1) cell and tissue engineering, 2) imaging and 3) therapeutics. Collectively we will delineate factors that when expressed in muscle may slow that rate of degeneration that is concomitant with either the complete (Duchenne muscular dystrophy) or partial (Becker muscular dystrophy) loss of dystrophin. These studies will utilize the mdx mouse as the animal model for dystrophin deficiency. The long-term goal is to gain the understanding and tools necessary to develop adeno-associated (AAV)-based gene therapy for Duchenne and Becker muscular dystrophies. Three parallel lines of investigation (each directed by one of the three investigators) are proposed: (1) a dissection the mechanical role of dystrophin and muscle adhesion proteins; (2) an assessment of the functional benefits of restoring adhesion molecules to dystrophic muscle using recombinant adeno-associated virus gene delivery; and (3) development of non-invasive methods for monitoring therapeutic benefits of dystrophin gene transfer.

51. Principal Investigator: Thiel, Patricia
Affiliation: Iowa State University of Science & Technology
Title: Design of Biocompatible Niti (Nitinol) Surfaces
Application Number: HL067632
Funding Organization: NHLBI
Abstract:

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

52. Principal Investigator: Vo-Dinh, Tuan

Affiliation: UT-Battelle, LLC-Oak Ridge National Laboratory
Title: Advanced Multispectral Imaging for Medical Diagnostics
Application Number: CA088787
Funding Organization: NCI
Abstract:

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

53. Principal Investigator: Weiss, Shimon

Affiliation: Lawrence Berkeley National Laboratory
Title: Development of Q-Dots As Biological Probes
Application Number: RR14891
Funding Organization: NCRR/NCI/NHLBI
Abstract:

The long-term goal of this project is to develop semiconductor nanocrystalline fluorescent probe (q-dots) technology that will provide biomedical research with better tools for diagnosis of diseases and biomedical techniques and instruments necessary for basic research of cellular and molecular structure and function. This effort includes q-dot synthesis, bio-conjugation techniques, dedicated optical instruments, and unique imaging technologies. Optimized protocols for q-dot synthesis will be developed to obtain desired optical, physical, and chemical properties; and various spectroscopic measurements will be used to characterize q-dots. The utility and new possibilities afforded by q-dot technology will be demonstrated by studying protein trafficking and assembly in living cells and by physically mapping genes. A large number of distinct markers will also be physically mapped on chromosomes and combined DNA molecules, and the kinetics of chromosome pairing during the meiotic prophase will be monitored.

54. Principal Investigator: Westenskow, Dwayne

Affiliation: University of Utah
Title: Integration And Visualization of Physiologic Data
Application Number: HL64590
Funding Organization: NHLBI
Abstract:

This project seeks to enhance a clinician's ability to discover and rapidly respond to critical events by developing displays that help to visualize the patient's physiologic state. The hypothesis is that object-oriented graphical displays that map closely the physician's mental models of the actual physiological processes will facilitate faster recognition of abnormal states, reduce errors, and shorten treatment time. The display is to provide a comprehensive view of the surgical patient's physiologic state. The proposed research will identify the type of display which optimally informs the anesthesiologist to rapidly detect physiologic changes, to make accurate diagnostic decisions,

and to efficiently treat critical events. The final display should enhance patient safety during anesthesia and reduce morbidity.

55. Principal Investigator: White, Stephen

Affiliation: University of California - Irvine
Title: Cold Neutrons for Biology And Technology
Application Number: RR014812
Funding Organization: NCRR
Abstract:

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