PI Name	Institution	Title	Project	Years Awarded	Funding Institute
Asher, Sanford A	University Of Pittsburgh At Pittsburgh	Development Of (Non) Invasive Real-Time Glucose Sensors	DK055348	4 years	NIDDK

Abstract: We propose to combine the expertise of chemists at the University of Pittsburgh and physicians at the University of Pittsburgh Medical School to further develop our unique glucose sensing materials based on Intelligent Polymerized Crystalline Colloidal Array (IPCCA) chemical sensor materials. The Diabetes Control and Complications Trial clearly demonstrated that glycemic control in patients with diabetes mellitus is crucial. This requires accurate and frequent blood glucose monitoring. However, current home glucose meters are only accurate to 15 percent, require a fingerstick for blood sampling, and must be carried as a separate kit everywhere with the patient. The present invasive methodologies often show poor patient compliance, which translates to negative health consequences for a significant proportion of patients with diabetes mellitus. Our IPCCA materials utilize a polymerized colloidal array (PCCA), which contains a recognition agent for glucose. The PCCA contains a cubic array of colloidal particles polymerized in a hydrogel. This PCCA diffracts light of a wavelength determined by the array spacing. Exposure to glucose changes the hydrogel volume, which changes the array spacing, which alters the diffracted wavelength. We developed important basic understandings of IPCCA glucose sensing in the work performed during our exploratory grant. We will develop IPCCA contact lens inserts to sense the glucose level in the tear fluid, which has been shown to track the glucose level in blood. The patient would wear a contact lens containing a small, unobtrusive section of IPCCA material, and would use a mirror to detect the lens insert color which would be compared to a color chart in order to define the blood glucose concentration. In addition, our research program will develop these IPCCA sensors for use as subcutaneous implants. The IPCCA would be implanted under the skin and the patient could continuously monitor the blood glucose concentration by observing the diffracted color. The work will involve: 1) fundamental studies of the sensing mechanisms of the IPCCA; 2) development of new sensing motifs based on the IPCCA materials; 3) optimization of the sensing response for in vivo use; 4) demonstrations of the utility of these devices for both subcutaneous and extraocular glucose sensing in normal and alloxan diabetic rabbits.

Bansal, Navin	University Of Pennsylvania	MR Spectroscopy And Imaging Of Sodium In Tumors	CA084434	1 year	NCI

Abstract: The main objective of this project is to develop and evaluate the use of multiple-quantum-filtered (MQF) 23Na magnetic resonance (MR) spectroscopy (MRS) and imaging (MRI) for measuring compartmental Na+ in experimental tumors so that the techniques may eventually be applied clinically. The central hypothesis in this project is that MQF 23Na MR techniques can provide completely noninvasive methods for monitoring and imaging abnormalities in transmembrane sodium gradients in tumors. The experiments outlined in the proposal will also provide information about the physiological role of the transmembrane sodium gradient and its relationship with cellular energy metabolism and pHi during untreated growth, sensitization of tumors to therapy and therapy. At least two NMR methods have been proposed to distinguish between intra- and extracellular sodium (Nai+ and Nae+), the use of paramagnetic shift reagents (SR) and MQF techniques. We introduced the in vivo SR, TmDOTP5-, which produces resolved Nai+ and Nae+ resonance in tumors and other tissues with minimal toxicity to the animal. However, an SR safe for use in humans is not yet available. Our preliminary data shows that although, some Nae+ contributes to the MQF 23Na signal in the subcutaneously implanted 9L glioma, this signal does not change during ischemia. If this is true under more general conditions, then MQF 23Na MR techniques can provide completely noninvasive methods for monitoring and imaging changes in Nai+ in tumors. The first goal of this study is to determine whether MQF 23Na MRS can be used to measure changes in Nai+ during more subtle acute manipulations. The effects of manipulating the tumor energy metabolism and ion exchange mechanisms will be studied. The chosen manipulations are used for sensitizing tumor to therapy. Our second goal is to evaluate the use of MQF 23Na MRS for monitoring changes in Nai+ during chronic physiological changes. For this purpose, effects of untreated tumor growth, radiotherapy and chemotherapy will be studied and the efficacy of MQF 23Na MRS/MRI for detecting tumor response to chemotherapy by a broad range of antineoplastic agents employed in clinical cancer chemotherapy will be investigated in RIF-1 and MCF-7 tumor models. The development of proposed 23Na MR techniques will provide methods for monitoring and imaging Nai+ that may prove useful in experimental studies of tumors and clinical management of cancer. In addition, the proposed research will enhance the understanding of sodium physiology in tumors, which may prove useful for designing more effective cancer treatment, and for predicting and monitoring response to therapy.

Barton, Jennifer K | University Of Arizona | Parallel OCT System For Endoscopic Imaging | EB001032 | 3 years | NIBIB

Abstract: One of the greatest challenges to successful treatment of cancers lies in early detection and staging. A novel imaging device is proposed to allow rapid, high quality imaging of the bladder and other endoscopically accessible organs. This instrument will be based on the principles of optical coherence tomography (OCT) to achieve micron-scale resolution over an imaging depth of up to several millimeters. Preliminary studies have shown that OCT can distinguish normal and cancerous bladder tissue. The proposed parallel optical coherence tomography (IIOCT) device represents a fundamental advance over existing OCT systems because it implements a parallel imaging approach with integrated arrays of optoelectronic sources, detectors, and specialized micro electronic processing and control systems. This allows rapid image acquisition (30 frames per second or greater) with inexpensive, low power light sources. The emitted and detected light is carried through a small (2mm) fiber bundle, eliminating the need for mechanical scanning at the distal end of the probe. A reduction in imaging system size and cost will be realized. The proposed design utilizes semiconductor manufacturing techniques to condense electro-optical and signal processing stages on a specialized microchip, which could be mass produced. Thus, the entire OCT system could potentially be housed in a small, lightweight box with a detachable probe. An inexpensive, portable system would allow greater patient access to this diagnostic modality. The specific aims of this proposal are: 1. Design and fabricate special optoelectronic and optical components for a OCT system. The considerable optoelectronic expertise and fabrication facilities at the University of Arizona will be recruited to create the sources, detectors, and signal processing electronics needed for this effort. 2. Fabricate electronics and integrate components into a miniaturized package. Optoelectronic and optical components will be integrated with the multi-fiber bundles used in the interferometer and endoscopic probe. 3. Assemble and test two II OCT Systems. A 10 parallel channel system will be created and interface software written. Feedback on probe design and user interface will be sought during animal and human studies and incorporated into the final, 100 parallel channel system. 4. Determine the ability of the I I OCT system to accurately determine the stage of transitional cell carcinoma of the bladder. A series of studies will be performed to determine the value of OCT in distinguishing between normal bladder tissue, carcinoma in situ (Tis), and cancer confined to mucosa (Ta) lamina propria (Ti) and muscle (T2).

Bates, Jason H | University Of Vermont & St Agric College | Assessment Of Lung Function In Mice | HL067273 | 3 years | NHLBI

Abstract: The assessment of respiratory mechanics in animal models of respiratory disease is bound by a phenotyping uncertainty principle which balances measurement precision against noninvasiveness. The method that currently represents the ultimate in precision is the measurement of input impedance using the forced oscillation technique in anesthetized, paralyzed, tracheostomized animals. At the other extreme, the least invasive (but also least specific method) is unrestrained plethysmography in conscious animals. Intermediate between these two methods is the measurement of transfer impedance in conscious but restrained animals. Although the application of these methods presents special problems in mice on account of their small size, all methods have been applied previously in this species. Nevertheless, each method has yet to be developed to its full potential in mice. Furthermore, it is not fully understood how the various mechanics estimates provided by these three methods relate to each other. The goal of this proposal is to extend the capabilities of these three methods in mice and to compare their respective measures of respiratory mechanics. We will pursue three specific aims: 1) to obtain respiratory mechanics and thoracic gas volume in mice by the simultaneous measurement of input and transfer impedances using forced oscillations in tracheal flow, 2) to compare and contrast the measures or respiratory mechanics provided by conscious transfer impedance to those of anesthetized, paralyzed, tracheostomized input/transfer impedance, and 3) to condition the inspired gas during unrestrained plethysmography in mice so that gas heating and humidification effects are eliminated from the box pressure variations measured during spontaneous breathing in order to develop a noninvasive approach to assessing respiratory mechanics. The proposed work is expected to result in a set of optimized measurement tools for assessing lung function in mice. These tools will span the phenotyping uncertainty spectrum, giving researchers maximum flexibility in choosing a tool appropriate for a given application. This should have significant impact on research into mouse models of respiratory disease.

Boppart, Stephen A | University Of Illinois Urbana-Champaign | Optical Imaging Of Dynamic 3-D Engineered Tissues | EB000108 | 3 years | NIBIB

Abstract: The goal of tissue engineering is to augment, replace, or restore complex human tissue function by combining synthetic and living components in appropriate configurations and environmental conditions. There are three key aspects to consider in any tissue-engineered construct - the cells, the matrix or biomaterial construct, and cell-material interactions. Although increasing numbers of research groups are developing techniques to control cell growth in artificial matrices, few have investigated cell-matrix interactions and the evolving mechanical properties of three-dimensional (3-D) mechanically-stimulated engineered tissues. The primary limitation has been inadequate imaging technology for high-resolution, real-time, non-invasive imaging deep within scattering tissue. The 3-0 arrangement of cell populations strongly influences the way in which cells dynamically respond within the engineered tissue. Optical imaging techniques that permit deep-tissue 3-D imaging offer the opportunity to non-invasively track the formation of engineered tissues. This project will integrate and apply two complementary state-of-the-art optical imaging techniques, optical coherence tomography and multi-photon microscopy, which are capable of performing these imaging tasks. Both optical techniques utilize the same laser source and will be integrated in a single microscope to investigate dynamic cell-matrix interactions and the evolving mechanical properties of two model engineered tissues. These optical imaging techniques will permit high-resolution, real-time, deep-tissue imaging in 3-D to non-invasively and non-destructively track changes in the tissue formation of 3-D blocks of cardiac myocytes and vascular structures composed of fibroblasts and endothelial cells. We will use these imaging capabilities and biomolecular focal adhesion assays to determine the influence that the 3-D microenvironment and dynamic mechanical forces have on the growth, organization, and mechanical properties of these model engineered tissues. The development and application of this unique investigative microscope will improve our understanding of cell function and tissue dynamics in 3-D mechanically-stimulated culture environments, enabling generation of engineered tissues with increasingly complex functionality.

Cheung, Anthony T | University Of California Davis | Bioengineering Methods To Study Blood Substitutes | HL067432 | 3 years | NHLBI

Abstract: Our emphasis is to develop and test bioengineering technologies and methods useful for characterizing vascular complications in an animal model, and to study the efficacy of a biomaterial (artificial blood/blood substitute) in a bioengineering research project. Our intention is not to test a specific mechanistic hypothesis (as in a standard R01 application), but rather to develop, enhance, build (assemble) and test bioengineering technologies and methods as expected in a BRG study. Based on pilot data from our laboratories, we have developed the following Specific Aims: (1) Use the UC Davis canine hypovolemic model as the center piece, and taking advantage of the state-of-the-art veterinary school animal facilities and animal surgery expertise, design and build a bioengineering research station (complete with monitoring instrumentation, measuring devices, systemic study accessories and an in vivo microcirculation-dedicated intravital microscope system) around it for hypovolemic shock and blood substitute resuscitation research. (2) Test the functionality of the research station built in Specific Aim (1) by using it to study mongrel dogs pre- and post- hemorrhagic shock --- serves to generate baseline references. (3) Apply the tested technologies and methods from Specific Aim (2) to study and quantify the effects of artificial blood resuscitation in hypovolemic dogs (using a commercially available blood substitute approved for canine use) --- serves to confirm the functionality of this bioengineering research station as a research base to evaluate blood substitute safety and efficacy. The emphasis of this BRG is to build a bioengineering research station around a canine hypovolemic model. However, in Specific Aims (2) and (3), we will also be conducting an evaluation of a commercially available blood substitute with emphasis on its physical and rheological effects on the microcirculation and its hemodilution characteristics, in addition to simultaneously studying its systemic effects and oxygen-delivery capability under monitored conditions.

Chilkoti, Ashutosh | Duke University | Thermally Targeted Drug Delivery By Elastin Biopolymers | EB000188 | 4 years | NIBIB

Abstract: The objective of the proposed research is to selectively deliver systemically injected radionuclides to solid tumors by a thermal targeting strategy. This objective will be achieved by conjugating radionuclides (131I and 211 At) to thermally sensitive polypeptide carriers, which will be targeted to solid tumors by focused hyperthermia of the tumor. The thermally responsive macromolecular carriers used for thermal targeting are polypeptides derived from mammalian elastin, composed of Val-Pro- Gly-Xaa-Gly (VPGXG) repeats, which undergo an inverse phase transition; below their inverse transition temperature (Tt), ELPs are highly soluble, but when the temperature is raised above their Tt, they undergo a phase transition within a 2-3 degrees Celsius range, leading to desolvation and aggregation of the polypeptide. The underlying hypothesis of the proposed research is that intravenously injected radionuclides, conjugated to a temperature-responsive ELP, can be designed such that they will selectively accumulate in the tumor, maintained at 42 degrees Celsius by local hyperthermia due to aggregation of the ELP in response to its phase transition. In preliminary research, we have demonstrated that thermal targeting provides a 2-3 fold increase in tumor localization versus non-heated controls and a approximately 2 fold enhancement with respect to a thermally insensitive control ELP in heated human tumor xenografts implanted in athymic mice. We propose the following specific aims to achieve the objectives of this proposal: (1) to synthesize ELPs with a Tt of 40 degrees Celsius by recombinant DNA methods; (2) to conjugate radionuclides to the ELPs; (3) to optimize the thermally targeted delivery of ELPs to human tumor xenografts implanted in athymic mice; (4) to carry out systemic radionuclide therapy with 211 At-labeled ELPs using the optimized protocols and external hyperthermia of solid tumors. The development of thermally responsive radionuclide-ELP conjugates that can be targeted to solid tumors by externally-induced local hyperthermia is a new paradigm for targeted delivery which directly targets the tumor microvasculature and circumvents the barriers associated with the interstitium and antibody-tumor cell surface antigen/receptor binding that are intrinsic to affinity targeting approaches for radionuclide therapy.

Constantinidis, Ioannis | University Of Florida | A Study Of Model Beta-Cells In Diabetes Treatment | DK047858 | 4 years | NIDDK

Abstract: The objective of the proposed research is to investigate the significance of cellular bioenergetics to insulin secretion in a bioartificial pancreatic construct composed of transformed beta-cells under environmental conditions that prevail in vivo at the site of implantation. Since transformed beta-cell lines are proposed as alternatives to islets in the development of a bioartificial pancreas, it is imperative that we understand how insulin secretion is affected at these sites. It is our hypothesis that transformed cell lines are more tolerant than mammalian islets to environmental conditions experienced in the peritoneal cavity, a site commonly used for the implantation of these constructs. Experiments proposed in this application will be performed both in vitro and in vivo. Specifically, in vitro experiments will focus on the quantification of glucose metabolism and resultant phosphorylation potential for bioartificial pancreatic constructs composed of betaTC-tet, and INS-1(832/13) cells, as well as porcine islets encapsulated in alginate/poly-L-lysine/alginate (APA) beads as a function of oxygen concentration and pH. Glucose metabolism will be assessed via 13C NMR spectroscopy by measuring the flux through glycolysis, citric acid cycle, and key anaplerotic pathways, while the phosphorylation potential will be quantified via 31P NMR spectroscopy. In vivo experiments will focus on a device that will contain the APA beads so that they are not dispersed throughout the peritoneal cavity and thus NMR experiments performed in vitro can also be performed in vivo. Preliminary data presented in this revised application support our hypothesis and provide the foundation to ensure that proposed experiments are feasible and can be completed successfully. Overall, we believe that the acquired data will contribute significantly to our understanding of the mechanism of insulin secretion, as well as extend our knowledge in the field of tissue engineering.

Cowan, Douglas B	Children's Hospital (Boston)	Engineering Of Pacemaker Tissue For Cardiac Implantation	HL068915	4 years	NHLBI

Abstract: Congenital and surgically-induced block of cardiac atrioventricular (AV) node conduction is a serious long-term clinical problem in pediatric patients. Currently, the permanent implantation of a cardiac pacemaker device is the only therapy available for the treatment of congenital complete heart block and AV block subsequent to surgical repair of inborn heart abnormalities such as ventricular septal defect, AV canal defect, and tetralogy of Fallot. Despite the technological advancements in cardiac pacemaker design and function, permanent pacemaker therapy in infants and children continues to be problematic. Since the survival rate for children that undergo complex surgical procedures to repair congential cardiovascular defects has greatly increased, the need for improved long-term pacing solutions in the pediatric patient population has provided the rationale for this project. The primary goal of the project is to engineer tissue that would act as an electrical conduit from the atrium to the ventricle of the heart for use in patience that lack normal AV node function. The engineered tissue will be comprised of skeletal muscle progenitor cells (myoblasts) or mesenchymal stem cells (bone marrow stromal cells) that can be autologously derived. The cells will be cast in a three dimensional tissue construct using natural polymers, such as collagen, in order to efficiently deliver cells to the AV groove of the heart. Accordingly, in the present proposal, we will address the following specific aims; (a) engineer electrically conductive tissue suitable for cardiac implementation (b) characterize the electromechanical properties of engineered tissue constructs in vitro, (c) determine the practicality of implanting tissue constructs in the cardiac AV groove, and (d) evaluate electrical conduction in hearts implanted with engineered tissue constructs. This is a conceptually simple research project that requires extensive expertise in a number of fields including cell biology, tissue engineering, and electrophysiology. The success of the research depends on a multidisciplinary group of individuals that will apply their knowledge to specific components of the project with the intention of developing a therapy to alleviate a substantial clinical problem. Ultimately, these experiments are intended to provide an alternative or adjunct treatment to conventional cardiac pacemaker therapy.

Crowe, James E	Vanderbilt University	Novel Methods For Generation Of Human B Cell Hybridomas	AI048677	4 years	NIAID

Abstract: Monoclonal antibodies (MAbs) have revolutionized the conduct of science since their first description in 1975. The use of these specific reagents also has made possible improved clinical diagnostics in the medical arena, and a few antibodies have found their way to clinical use as prophylactic or therapeutic agents. Nevertheless, the potential of MAbs for therapy remains largely unfulfilled. The principal reason for the lack of a large number of MAb therapeutics is simply the difficulty in generating human monoclonal antibodies of high affinity. The objective of this proposal is to develop novel methods for the rapid and efficient generation of human B cell hybridomas secreting antibodies of medical importance. The work will develop and employ new approaches to rare antigen-specific B cell sorting from memory cell populations, and will result in the design and manufacture of new cell-cell electrofusion hardware and protocols.Three specific aims are proposed: 1) To develop high-throughput methods for antigen-specific human B cell physical sorting and expansion; 2) To develop novel electrofusion devices and protocols that yield a high frequency of viable human hybridomas: 3) To develop high affinity neutralizing antibodies to respiratory syncytial virus, a medically important viral pathogen amenable to MAb prophylaxis, as a demonstration of the feasibility of making important antiviral antibodies using the novel techniques and equipment developed.

Daniell, Henry University Of Central Florida Expression Of Human Therapeutic Proteins In Chloroplasts GM063879 4 years NIGMS

Abstract: DESCRIPTION (provided by the applicant): Interferons (IFN) are cytokines with antiviral, antigrowth and immuno-modulatory properties. IFNalpha 2 is employed as a therapy for leukemia, metastasizing carcinoma, kaposi sarcoma and viral hepatitis. The annual cost of IFNalpha 2 therapy is $4000, making it unavailable for most patients worldwide. Among 120 million people infected with hepatitis C virus, 70 percent have abnormal liver function and 33 percent have severe cirrhosis. IFNalpha 5 expressed in liver has the most potent antiviral activity, making it an appealing therapeutic candidate. Insulin-like Growth Factor I (IGF-I) is a potent multifunctional anabolic hormone produced by the liver, and its deficiency results in several systematic complications occurring in liver cirrhosis. The annual requirement of IGF-l per cirrhotic patient is 600 mg, and the cost per mg is $30,000. Transgenic chloroplast technology provides a novel solution to recombinant protein production because of hyper-expression capabilities and ability to fold and process eukaryotic proteins with disulfide bridges (thereby eliminating the need for expensive post-purification processing). Tobacco is an ideal choice because of its large biomass, ease of scale-up (million seeds pen plant), genetic manipulation and an impending need to explore alternative uses for this hazardous crop. Oral delivery of functional biopharmaceuticals reduces 90 percent of the production cost, eliminating the need for expensive purification. Furthermore, bio-encapsulation within plant cells offers protection against proteolytic degradation during digestion. Interferon given orally has biological activity in human and animals. Therefore, IFNalpha2, IFNalpha5 and IGF-l will be expressed as follows: a) Develop recombinant DNA vectors for enhanced expression or oral delivery b) Generate transgenic tobacco and tomato plants c) Characterize transgenic expression of proteins or fusion proteins using molecular and biochemical methods d) Purify therapeutic proteins from transgenic chloroplasts e) Characterize and compare therapeutic proteins (yield, purity, functionality) produced in yeast, E.coli or transgenic plants f) Study in vitro and in vivo (pre-clinical trials) protein bio-functionality, parenteral and oral delivery. Large scale and low cost production via transgenic chloroplasts should provide treatment to patients at an affordable cost and tobacco farmers alternate uses for this hazardous crop.

Daugherty, Patrick S University Of California Santa Barbara Combinatorial Optimization Of Protein Biosensors EB000205 5 years NIBIB

Abstract: Biosensors derived from fluorescent proteins can now be manipulated to respond to specific molecular events within living cells. However, the application of resonance energy transfer (RET) based protein biosensors to a wide rage of medically important problems is currently limited by the lack of suitable donor and acceptor partners for efficient RET. New combinatorial approaches for generating molecular diversity wilt be coupled with quantitative cell sorting instrumentation in order to purposefully manipulate and design broadly applicable biosensors and component proteins. This approach will be used to create biosensors for use in the isolation and development of therapeutics, for improved medical diagnostic tools, and to enable real-time studies of protein-protein interactions and protease activities in living cells. Intracellular biosensors consisting of two fluorescent proteins capable of resonance energy transfer (RET) and joined by a peptide linker will be constructed and optimized. An expression system will be developed in bacteria which allows high-throughput screening of fluorescent protein variants directly for their ability to undergo RET using flow cytometry. Large designed protein libraries will be constructed in bacteria, containing more than ten million variants in which the chromophore and surrounding residues are randomized. Multi-parameter cell sorting will be Used to quantitatively screen for several criteria important for RET, allowing identification of rare; improved partners. The spectral properties of improved variants will be further characterized by fluorimetry, and a comprehensive database of sequence-function relationships will be developed using data from both previous and current studies. The sensitivity of detecting RET using flow cytometry wilt be improved using a flexible optical bench design that allows optimization of light sources and optics for biosensor excitation and detection. Methods will be developed for ultra high-throughput screening (>100,000/s) of large libraries. Biosensor expression levels, total signal-to-noise ratios, false positive events, and sort gating will be optimized for FCM screening on the basis of RET biosensor signals.

Federspiel, William J | University Of Pittsburgh At Pittsburgh | Percutaneous Respiratory Assist Catheter | HL070051 | 4 years | NHLBI

Abstract: The objective of this proposal is to develop a percutaneous respiratory assist catheter (PRAC) that can be inserted into the venous system to provide supplemental breathing support, independent of the lungs, for patients requiring short- term (less than 1-2 weeks) respiratory assistance. The PRAC will be designed for percutaneous insertion into a peripheral vein and placement in the central venous system, where it will be exposed to all the blood returning to the heart. The PRAC will incorporate a cylindrical bundle of microporous hollow fiber membranes woven as a fabric that is wrapped around a balloon. The balloon is pulsed with helium and enhances gas exchange by pumping blood past the hollow fibers at velocities much greater than would otherwise exist in the vena cava. The specific aims of the project are to: 1. Fabricate candidate PRAC devices with insertional diameters of 25-28 Fr (8-9 mm) and evaluate the functional mass transfer characteristics in an in-vitro test loop. We will establish how the gas exchange performance of the PRAC depends on key operating and design parameters. 2. Evaluate and optimize balloon pulsation in the PRAC to improve gas exchange. We will principally explore changes in balloon geometry and balloon pulsation mode, and we will use flow visualization, local gas tension measurements, and computational simulations to help guide our design development. 3. Perform acute calf implants of the PRAC to assess the gas exchange functionality in-situ and any adverse anatomical, physiological and biocompatibility effects associated with short- term implantation. We will also evaluate the hemolysis potential of candidate PRAC designs in-vitro using bovine blood in a bench flow loop. Our target is a percutaneous assist catheter that can provide 75- 85 ml/min of extrapulmonary CO2 removal at normocapnia and that could be used as an adjuvant or replacement to existing therapy for patients with acute lung failure (ARDS, pneumonia) or acute on chronic lung failure (COPD with exacerbation).

Gao, Jinming | Case Western Reserve University | Interstitial Drug Delivery To Thermoablated Liver Tumors | CA090696 | 4 years | NCI

Abstract: This research effort is a long-term commitment to develop intratumoral drug delivery as a local chemotherapy to supplement twnor thermoablation for the treatment of liver cancers. In this treatment, image-guided thermoablation first destroys the majority of the tumor tissue by heat. The drug delivery device, in the shape of a cylindrical millirod, is then implanted into the thermoablated tumors to kill any cancer cells remaining after thermoablation. The objective of the proposed application is to develop and evaluate drug delivery systems that can modulate the release of doxorubicin, an anticancer drug, for intratumoral drug delivery to thermoablated tumor tissues. The central hypothesis is that polymer millirods with dual release kinetics-an initial burst release followed by a sustained release of drugs-can provide the maximal therapeutic effect to supplement thermoablation in the treatment of liver tumors. To test this central hypothesis, we will carry out the following four specific aims: (1) rational design of polymer millirods with dual release kinetics by mathematical models; (2) development and characterization of polymer millirods with dual release kinetics; (3) pharmacokinetic analysis of implanted polymer millirods in rabbit VX-2 liver tumors; (4) validation of drug efficacy by monitoring of tumor size and histology analysis. Successful execution of the proposed application will establish a solid pharmacological basis and bioengineering foundation for the development of drug delivery systems for intratumoral drug delivery. In combination with image-guided thermoablation, this therapeutic procedure should provide an innovative, minimally invasive and less toxic therapy for the treatment of liver tumors.

Gard, Steven A | Northwestern University | Influence Of Ankle Motion On Bilateral Amputee Gait | HD042592 | 3 years | NICHD

Abstract: We propose to investigate the effect of prosthetic ankle motion on the mechanics of bilateral lower-limb amputee gait. Bilateral lower-limb amputees often walk with rigid or stiff legs, which may be due in part to insufficient compliance and ranges of motion in their prosthetic ankles. They may attempt to overcome prosthetic deficiencies with compensatory actions that increase their energy expenditure during gait. Most of the literature pertaining to amputee gait is concerned with persons having unilateral amputations, but it is difficult to identify areas where significant improvement is needed based upon data from unilateral amputee gait. Compared with unilateral amputees, persons with bilateral leg amputations have a greater need for improvement in prosthetic componentry because of their increased energy demand as they walk and their low speed of walking. Prosthetic performance during gait is easier to evaluate in bilateral amputees because they have fewer physiological control options available to them while they ambulate. Few outcome studies have been reported in the literature regarding their rehabilitation, and there have been no published quantitative gait studies on bilateral leg amputees to date. We will perform quantitative gait analyses in the VA Chicago Motion Analysis Research Laboratory on 30 bilateral transtibial (below-knee) and transfemoral (above-knee) amputees walking with and without prosthetic components that increase ankle motion. These components include the Endolite Multiflex Ankle to increase ankle dorsiflexion/plantarflexion and inversion/eversion, and the Otto Bock Ankle Torsion Adapter to increase transverse plane rotation. We hypothesize that increased ankle motion will significantly improve the gaits of bilateral lower-limb amputees. We will also study simulated bilateral amputee gait in 15 able- bodied persons by fitting them with orthoses that minimize knee and ankle motion. We hypothesize that able-bodied persons walking with constrained ankles and knees will have gait characteristics similar to bilateral amputees. The able-bodied walking pattern serves as a useful basis of comparison for different types of pathological gait, and we believe that altering the locomotor system of the able-bodied person can yield valuable information concerning the mechanisms of pathological gait. The results from this study will aid in identifying limitations in current prosthetic technology that inhibit normal patterns of walking in amputees.

Guo, X E | Columbia Univ New York Morningside | Bone Response To Combined Mechanical And PTH Stimulation | AR048287 | 4 years | NIAMS

Abstract: Trabecular bone adaptation plays a significant role in the etiology of many metabolic bone diseases such as osteoporosis and osteopetrosis, bone loss in microgravity, and the long term success or failure of porous implants in total joint arthroplasty. Parathyroid hormone (PTH) is an important anabolic agent when administered intermittently. We have developed a novel in vivo rat-tail vertebra model coupled with an uCT image based finite element technique. Specifically, a controlled mechanical load can be applied to a rat-tail vertebra and a detailed three-dimensional (3D) stress/strain environment in the trabecular bone tissue can be determined using an advanced finite element microstructural model. In this proposal, we designed a full-scale, long-term study to systematically quantify the molecular/cellular responses and changes in 3D morphology in trabecular bone to combinations of mechanical loading and PTH treatment. The molecular responses will be assayed using RT-PCR and in situ hybridization. The bone cellular response will be quantified using bone histomorphometric techniques. The specific aims of this project are: Specific Aim 1: To determine the changes in gene expression (c-fos, cbfa-1, IGF-1, collagen a1(I), osteopontin, osteocalcin, alkaline phosphatase, RANK-L, and osteoprotegerin) by RT-PCR and in situ hybridization, bone cell activities by bone histomorphometry, and 3D trabecular bone morphology by uCT of rat tail vertebrae at various levels of mechanical loading (ON, 50N and lOON) ranging from 1 day to twelve weeks. Specific Aim 2: To determine the changes (using the same measurements cited in Specific Aim 1) in rat-tail vertebrae in response to daily PTH administration (3O-ug/kg and 6Oug/kg) for various lengths of time. Specific Aim 3: To determine the changes (using the same measurements cited in Specific Aim 1) in rat tail vertebrae mechanically loaded at various magnitudes (ON, SON, and lOON) in the presence of PTH (30ug/kg and 6O ug/kg) for various lengths of time. Specific Aim 4: To perform uCT based PEA of the loaded vertebrae in Specific Aims 1 and 3, and to determine the changes in the distribution of trabecular bone tissue stress/strain parameters following the various treatments. Results from this study will help to clarify, in a quantitative manner, the cellular and molecular mechanisms of bone adaptation to mechanical loading, which are important in the understanding of the etiology and optimizing therapeutic interventions of menopausal, microgravity or age related osteoporosis, and improvement in total joint replacements.

Hallahan, Dennis E | Vanderbilt University | X-Ray Guided Drug Delivery Systems | CA088076 | 3 years | NCI

Abstract: The overall objective of the proposed research is to study the hypothesis that site-specific drug delivery can be accomplished by targeting delivery systems to radiation-induced proteins in tumor blood vessels. The limitation of other forms of site-specific drug delivery (immunoconjugates and gene therapy) includes specificity for particular tumors, nonspecific delivery to other organs (eg. liver) and inhomogeneity of drug within tumors. We propose that targeting drug delivery to antigens can circumvent each of these limitations and receptors expressed in irradiated tumor blood vessels. We have identified molecular responses that occur in all tumor blood vessels. Our preliminary data show that antibodies and proteins designed to bind to these targets can be linked to radionuclides, liposomes and gene therapy vectors. Our preliminary data show no binding to other organs and only tumor-specific binding. Moreover, the biodistribution of radiation-guided drug delivery is homogeneous throughout the vasculature of tumors. Radiation-induced antigens and receptors in tumor blood vessels include P-selectin, E-selectin and the b3 component of integrin a2bb3. The ligands that bind to the integrin a2bb3 include fibrinogen, fibronectin and vitronectin. To determine whether these ligands can be used to guide drug delivery, we labeled fibrinogen with 131j and studied 131I-fibrinogen biodistribution by gamma camera imaging. We found site-specific delivery to irradiated tumors. In the proposed studies, we will determine the sites of binding of fibrinogen within tumor blood vessels. We will determine whether small peptides and antibodies targeted against these fibrinogen receptors can be used for drug delivery. These peptides and antibodies will be conjugated or inserted within drug delivery systems to study biodistribution and pharmacokinetics of these systems. We will also test the hypothesis that x-ray-guided drug delivery systems are capable of delivering tumoricidal doses of drugs to irradiated tumors. Our future goal is to validate the pharmacokinetics and biodistribution of these x-ray-guided delivery systems in clinical trials.

Haselton, Frederick R | Vanderbilt University | Retinal Blood Barrier Permeability Using Optical Tracers | EY013451 | 3 years | NEI

Abstract: A key function of the microvascular endothelium is maintenance of barrier against fluid and solute transport. Breakdown of the retinal vasculature is a defining feature of some significant ocular diseases including diabetic retinopathy and age related macular degeneration. We propose to develop dual tracer fluorescence angiography as a novel quantitative tool for assessing retinal vascular permeability. The design of this Bioengineering Research Grant proposal identify specific features of this new technique for further development and testing. This dual tracer fluorescence angiography technique quantifies the permeability of the retinal vasculature by differential transport of small and large fluorescent tracers. We have implemented this retinal imaging technique in rats using the tracer pairs sodium fluorescein (376D) & Texas Red dextran (70kD) and, in fewer animals, using resorufin (235D) & FITC dextran (2,000kD). We have obtained preliminary induced by 5 minutes of mannitol infusion. Three aims for further studies are proposed. First, we plan to identify the best intravesicular and transvascular tracers for in vivo measurement of the permeability of the retinal microcirculation. Secondly, we propose to develop optical instrumentation and image analysis techniques for the simultaneous measurement of two fluorescent tracers in retinal vessels. And thirdly, we plan to develop mathematical models for the identification of retinal microcirculatory permeability characteristics from the dynamics of fluorescent tracers at the inlet and outlet of the retinal circulation. We will use simplified physical models, mathematical models, and principally, in vivo rat studies to carry out these aims. Our overall goal is to develop this methodology as a tool to measure retinal permeability which can be applied to diagnose and track the efficacy of treatments of this significant clinical retinal pathology which is a characteristic feature of many ocular diseases.

Hedrick, Marc H | University Of California Los Angeles | Engineering Bone From Human Adipose Derived Stem Cells | AR047637 | 4 years | NIAMS

Abstract: Bone engineering with osteoprogenitor cells has enormous clinical potential for the treatment of aging-related bone loss (osteoporosis) or traumatic bone defects. Osteoprogenitor cells such as mesenchymal stem cells (MSCs) from bone marrow are a source of such cells. When combined with polymeric scaffolds and/or osteogenic growth factors these cells may provide new therapies for bone replacement. Our long-range objective is the development of new treatments for human bone loss through tissue engineering. Our central hypothesis is that human adipose tissue contains stem cells or adipose-derived stem cells (ADSCs) which offer advantages over MSCs and other osteoprogenitor cell types. The specific aims of this application are: (1) to clone and characterize human ADSCs, (2) to investigate their ability to form bone both in vitro and in vivo and (3) to determine their ability to repair non-healing bone defects. An understanding of ADSC function and ultimately their regulation, has important implications. First, tissue engineering strategies will benefit by an autologous stem cell source (adipose tissue) that is easily obtainable in 'liter' quantities through a minor surgical procedure (liposuction) that is well tolerated by patients. Second, a detailed understanding of the regulation of stem cell differentiation in adipose tissue could significantly impact the treatment of diseases that are characterized by dysregulated mesodermal cell growth and differentiation such as osteoporosis, heterotopic calcification and obesity. Finally, fundamental issues of mesodermal cell differentiation, mesodermal phylogeny and ontogeny, may be better understood by study of these cells. At the completion of this grant, our expectation is that human adipose tissue will be shown to be a reservoir of stem cells. We will also begin to have a basic understanding of the phenotypic changes occurring in differentiating ADSCs after commitment to the osteogenic lineage. Finally, we will assess the clinical utility of ADSCs to repair critical-sized bone defects.

Jacobsen, Chris J | State University New York Stony Brook | Spectromicroscopy For Biochemical Analysis Of Sperm | EB000479 | 3 years | NIBIB

Abstract: We propose to develop the capabilities of x-ray spectromicroscopy to allow it to be applied to biochemical imaging of normal and abnormal sperm. This will be done by focusing "soft" X rays (in this case, x rays with a photon energy of 200-800 eV) to the smallest far-field focus of electromagnetic radiation of any wavelength, and scanning a dry or frozen hydrated specimen through that focal spot to form an image. Images at a series of photon energies will then be combined to deliver chemical-state-sensitive x-ray absorption spectra from an entire sperm at better than 50 nm spatial resolution. From this data, major biochemical constituents in individual sperm will be determined by fitting to reference spectra of isolated compounds; furthermore, expected and possibly unexpected spatial correlations between components will be studied using principal component analysis methods. This work will be carried out using x-ray microscopes developed by our group at Stony Brook which operate at a soft x-ray undulator beamline at the National Synchrotron Light Source at Brookhaven National Laboratory. The microscopes will be improved by the addition of better order sorting optics for quatitative spectroscopy, and by equipping a cryo microscope with a more accurate piezo stage and a higher efficiency detector for studies of frozen hydrated specimens without excessive radiation damage. These instrumentation developments will be guided by our goal of studying the correlation between morphological and biochemical variations in sperm, in order to better understand the causes of male infertility. By obtaining x-ray spectromicroscopic data on different sperm morphologies in infertile males, we hope to guide the in vitro fertilization (IVP) clinician in the choice of sperm use for intracytoplasmic sperm injection (ICSI) so as to improve the success rate of the procedure. Spectromicroscopic data anaysis software will be made available for free downloading by other researchers as it is developed.

Jung, Ranu	University Of Kentucky	A Rodent Model For Locomotor Training With FNS	HD040335	3 years	NICHD

Abstract: The long-term goal of this work is to develop strategies for using functional neuromuscular stimulation (FNS) of paralyzed muscles to enhance the recovery of individuals with incomplete spinal cord injury. The proposed work is motivated by three important developments. First, recent basic science and clinical studies have demonstrated that the degree of functional recovery of the injured spinal cord depends on the activity patterns of neural inputs to the spinal cord. Second, recent advances have produced adaptive controllers for FNS systems that provide a means of automatically adjusting stimulation parameters to reliably achieve specified rhythmic movements. Third, rodent models of spinal cord injury (complete and incomplete lesions) are extensively being used at the molecular, cellular, and systems level to investigate the effects of traumatic injury and to assess the results of therapeutic intervention. A combination therapy that utilizes locomotor training with FNS and pharmacological intervention is likely to be the most effective in enhancing the reorganization (plasticity) of the spinal circuitry that is spared after spinal trauma. A rodent model for FNS-assisted locomotion would facilitate quantitative evaluation of therapeutic regimens that include FNS and would provide the ability to characterize effects of FNS-assisted locomotion on the neuroanatomy and neurophysiology of the injured spinal cord. This biomedical engineering research grant proposal will develop a rodent model of locomotor training that utilizes treadmill walking and functional neuromuscular stimulation (FNS) with fixed-pattern and adaptive controllers. Kinematic and electromyogram (EMG) patterns of intact animals will be examined and then used to develop stimulation patterns for FNS-assisted movement. A series of tasks will be performed using FNS stimulation of hindlimb muscles in spinalized rats. These tasks will progress in difficulty from controlling suspended hindlimb movements to controlling hindlimb movements during treadmill locomotion in spinalized rats with partial weight support. Two different FNS control strategies will be used for each movement: a fixed-pattern, or open-loop, stimulation pattern and an adaptive stimulation control system. The adaptive stimulation control system will build upon our previous work and is expected to provide movement patterns that are more accurate and more repeatable. Successful completion of the proposed project will result in a novel animal model for FNS-assisted locomotor training and provide quantitative methods for evaluating locomotor behavior. In future studies, we plan to use a rodent model of incomplete spinal cord injury with FNS-assisted locomotion to test the hypothesis that FNS-assisted locomotor training enhances motor recovery after incomplete spinal cord injury. We anticipate that the improved performance provided by the adaptive control system may enhance the therapeutic effects of the technique. This locomotor training could also be combined with pharmacological intervention, tissue transplant, and neural repair therapies to determine if locomotor training can enhance the effectiveness of these therapies.

Karayiannis, Nicolaos B	University Of Houston-University Park	Video Technologies For Neonatal Seizures	EB000183	3 years	NIBIB

Abstract: Neonatal seizures are often the first, and, in some situations, the only clinical sign of central nervous system dysfunction in the newborn. Despite the importance of early detection and characterization of neonatal seizures with regard to diagnosis and management of underlying neurological problems, most neonatal intensive care units and nurseries have limited resources for seizure monitoring, detection and characterization. The research outlined in this proposal is the first attempt ever to utilize recent advances in video and computer technology toward the development of automated video processing and analysis procedures that can facilitate the characterization and recognition of neonatal seizures. These procedures will rely on quantitative information regarding the behavioral characteristics of neonatal seizures, which will be extracted from videotaped neonatal seizures in the form of temporal motion strength and motor activity signals. The proposed research is expected to produce novel computational tools for extracting quantitative information from image sequences, which may be utilized to support diagnosis and extend human analysis. The automated video processing and analysis procedures developed in this project will be evaluated and tested on an existing library of videotaped clinical events, which include neonatal seizures and normal or abnormal infant behaviors not due to seizures. The long-term goal of this research is the integration of the proposed video processing and analysis procedures into the development of a stand-alone automated seizure detection and characterization system that could be used as a supplement in the neonatal intensive care unit to: 1) provide 24-hour a day noninvasive monitoring of infants at risk for seizures, and 2) facilitate the analysis and characterization of videotaped neonatal seizures by physicians during retrospective review.

Khoury, Dirar S | Baylor College Of Medicine | Virtual Electrical-Anatomical Imaging Of The Heart | HL068768 | 4 years | NHLBI

Abstract: Atrial fibrillation (AF) is the most common heart rhythm disorder: it affects more than two million Americans, is responsible for one-third of all strokes over the age of 65 years, and annually costs 9 billion dollars to manage. Furthermore, about 300,000 Americans die of sudden cardiac death annually, primarily due to ventricular rhythm disorders (ventricular tachycardia (VT and fibrillation) which result in intractable, extremely rapid heartbeats. Unfortunately, current pharmacological therapy for managing these disorders is often ineffective, thereby shifting emphasis to nonpharmacological therapy (e.g. ablation and pacing). Catheter ablation has been successful in managing many atrial and a few ventricular rhythm disorders. However, due to limitations in present mapping techniques, brief, chaotic, or complex rhythms such as AF and VT cannot be mapped adequately, resulting in their unsuccessful elimination. Advancing the management of abnormal heartbeats is contingent on developing mapping techniques that identify their mechanisms, localize their sites of origin, and elucidate effects of therapy. Our objective is to develop a catheter-based, cardiac electrophysiological imaging technique that simultaneously maps multiple endocardial electrograms on a beat-by-beat basis and combines three-dimensional activation-recovery sequences with endocardial anatomy. The hypothesis is that virtual electrical-anatomical imaging of the heart based on (1) cavitary electrograms that are measured with a noncontact, multielectorde probe and (2) three-dimensional endocardial anatomy that is determined with integrated, intracardiac echocardiography (ICE), provides an effective and efficient means to diagnose abnormal heartbeats and deliver therapy. Therefore, we will: (1) build a noncontact, electrical-anatomical imaging catheter-system that carries both a multielectrode catheter-probe for acquiring cavitary electrograms from multiple directions, and a central ICE catheter for acquiring endocardial anatomical images; (2) advance novel mathematical methods to compute endocardial electrograms and reconstruct three-dimensional activation-recovery sequences based on noncontact cavitary probe electrograms and geometry determined by ICE; and, (3) prove the utility of virtual electrical-anatomical imaging in the canine beating heart by characterizing models of AF, myocardial infarction, and VT and identifying their components, and by quantifying ablation lesions as assessed by both electrical and echocardiographic criteria. The proposed catheter can be introduced into the blood-filled cavity without surgery and provides three-dimensional electrical-anatomical images on a beat-by-beat basis. With this approach, one can pinpoint the site of origin and type of abnormal heartbeats and advance their therapy. In line with a Bioengineering Research Grant, the research develops a system the outcome of which is to improve the benefit-risk and benefit-cost relationships of patient care and advance heart rhythm-related research.

LaPlaca, Michelle C | Georgia Institute Of Technology | Stem Cell-Seeded ECM Scaffolds For Neurotransplantation | EB001014 | 3 years | NIBIB

Abstract: Neural transplantation in the injured central nervous system (CNS) has had limited success. It is hypothesized that this hostile environment may require improved cell support through directed extracellular matrix (ECM) protein engineering to improve graft survival and cell function and hence, functional recovery. The overall objective of this research project is to develop minimally-invasive transplantation techniques for optimizing stem/progenitor cell attachment through ECM-based scaffolds and to utilize relevant experimental models (both in vitro and in vivo) for optimization and outcome assessment. This overall goal is divided into 3 interrelated specific aims: (1) To characterize neural stem (NS) cell-ECM-based 3-D constructs in vitro for minimally invasive grafting strategies and maximal cell survival and to elicit a desired degree of proliferation, migration, and differentiation; (2) To determine mechanisms of construct integration by testing NS-ECM constructs in a surrogate hostile in vitro environment; and (3) To analyze the in vivo function of tissue-engineered constructs by transplanting constructs into contused mouse brains and examining post-injury alterations in the host contusion, cell behavior, and cognitive and sensorimotor behavioral outcome. The research proposed is significant because it offers a novel approach to progenitor/stem cell transplant technology with detailed analyses of outcome. This research may have direct application to clinical practice in neurosurgery that would permit therapeutic, cellular replacement in the treatment of traumatic brain and spinal cord injuries and degenerative diseases of the CNS. In addition, this research will provide insight into the mechanisms of CNS regeneration and help to elucidate the necessary cellular environment for neurotransplantation success. By analyzing outcome in well-controlled multi-level systems, this research may also lead to acellular transplantation methodology and establish the requirements necessary for the transplantation of non-embryonic/fetal cell sources.

Matsumoto, Hiroyuki | University Of Oklahoma Hlth Sciences Ctr | Ocular Proteomics Of Retina | EY013877 | 4 years | NEI

Abstract: The long term goal of this project is to define all the proteins expressed in rodent retinas in order to provide vision researchers with information regarding the proteins actually expressed in retinal cells. Protein analysis by the combination of two-dimensional (2-D) gel electrophoresis, mass spectrometry, and genome database search has impacted on the progress of biomedical sciences. This new breed of technology is generally called "proteomics" and enables massive analysis of proteins extracted from cells or tissues. In the past two decades the understanding of visual transduction pathway and its underlying molecular mechanisms has substantially been improved by the use of rod outer segment preparations from various animal models including bovine, frog, and other animals. The recent transgenic mouse model also has substantiated and extended much of the previous knowledge on the molecular mechanisms underlying vision. In this proposal, a proteomic approach will be used to characterize the proteins expressed in the retinas of laboratory rodents, rats and mice. The reasons for the choice of rodents as a model to study retinal protein expression are three-fold. First is the similarity in gene sequence between human and rodents. Second is the availability of transgenic animal models and the accumulated literatures on the physiology and pathological changes of rodent retinas induced by environmental or genetic perturbation. Finally, the lower costs and ease of experimental manipulation makes a rodent model practical. There are three specific aims for this proposal. Aim 1 is to profile virtually all the retinal proteins that are extracted from rodent retinas and separated on 2-D gels. Protein profiling will be made along the developmental time axis by investigating retinas at different postnatal days. In this aim, efforts will also be made to develop a technique to remove abundant proteins from the protein extract in order to investigate proteins expressed in minor quantities, and also to develop a mass spectrometric technique to quantify proteins by stable isotope labeling. Aim 2 is to profile immunohistochemical localization of selected proteins identified in Aim 1. In this aim, a defined set of criteria will be used so that the proteins chosen will be classified into groups that are physiologically distinct. Aim 3 is to make the proteomic information accessible on a web-based database so that vision researchers can retrieve data when needed. Accomplishment of this project will help researchers investigating vision and its disorders at the protein level using rodent models.

Messersmith, Phillip B | Northwestern University | Bioadhesive Polymer Hydrogels: Basic And Applied Studies | DE014193 | 4 years | NIDCR

Abstract: Mussel adhesive proteins (MAPs) are remarkable underwater adhesive polymers that form tenacious bonds to anchor marine organisms onto the substrates upon which they reside. Even in the presence of water, the adhesive protein plaques form extremely tenacious bonds to solid objects, an accomplishment which is not often matched by synthetic adhesives. These protein 'glues' can be characterized as having a high concentration of L- 3,4-dihydroxyphenylalanine (DOPA), an amino acid that is believed to be responsible for both adhesive and crosslinking characteristics of MAPs. However, the chemical reactions in which DOPA residues can participate are complex and not fully understood, particularly as they relate to adhesion and crosslinking. Although simple bulk shear adhesion tests have yielded important practical evidence that DOPA-mimetic polymers may be useful as adhesives, the design of the polymers and the techniques that were previously used for measuring adhesion are not ideal for elucidating the underlying molecular aspects of bioadhesion. Thus, new strategies for adhesion testing and the development of the next generation of DOPA-containing polymers are needed, in particular those that enable detailed examination of DOPA chemical interactions and their contribution to adhesion. The goals of this research are to employ molecular-level adhesion experiments to gain a detailed understanding of the role of DOPA in biological adhesion, and to use this information to motivate the design of new DOPA-containing macromolecular biomaterials. New DOPA-mimetic polymers will be synthesized and adhesive properties assessed by a versatile fracture mechanics based adhesion test. In-situ control of DOPA chemical reactions will be used to reveal fundamental relationships between adhesive performance and DOPA content, DOPA oxidation, peptide composition, and substrate chemistry. Finally, an in vitro cytotoxicity assay will be used to assess the biological response to the DOPA-mimetic polymers. At the conclusion of this study we will have gained considerable insight into the fundamental role of DOPA and oxidized forms of DOPA on adhesion in biological systems, and utilized this knowledge for the rational design of new adhesive biomaterials.

Mushahwar, Vivian K University Of Alberta Intraspinal Microstimulation For Restoring Limb Movement NS044225 5 years NINDS

Abstract: The goal of this project is to evaluate the long-term efficacy of intraspinal microstimulation (ISMS) in restoring leg function after spinal cord injury (SCI). and to investigate certain aspects of neuronal and muscular plasticity induced by ISMS. The principal activity supported by this grant will be to provide spinal cord locations and stimulation parameters for long-term restoration of stable, weight-bearing standing and stepping after SCI. ISMS is expected to eliminate several of the difficulties associated with conventional peripheral nerve functional electrical stimulation (FES) systems used for augmenting limb movements in paralyzed individuals. The initial phase of the project entails mapping the lumbosacral region of the spinal cord during acute experiments in adult cats with complete spinal transections (T11) performed a week earlier. Once target locations within the spinal cord that yield reliable extensor and flexor limb movements after SCI are determined, 12 to 15 microwires will be chronically implanted in each side of the cord in intact cats. ISMS stimulus thresholds and elicited limb responses will be documented and the cats will be subsequently spinalized at T11. Patterned and tonic ISMS will be applied to generate weight-bearing standing and stepping of the hindlimbs. Stimulation sessions will take place 5 times per week (up to 6 months post-spinalization) and the quality of standing and stepping induced by ISMS will be assessed over time. Changes in the efficacy of reflex transmission will also be assessed throughout the experiments and will be used to estimate the level of ISMS-induce reorganization in spinal circuitry below the level of the lesion. The animals will then be euthanized and their spinal cords will be examined to determine the location of electrode tips and evaluate the effect of microwire implantation and long-term ISMS on neural damage. Immunohistochemical analysis of hindlimb muscles will be performed to determine the effect of ISMS on fiber type transformation. Finally, the efficacy of ISMS in generating functional limb movements under conditions of spastic hypertonus will be determined in adult rats with complete sacral cord transections rendering the tail paralyzed and spastic.

Nagarajan, Srikantan S University Of Utah Cortical Spatiotemporal Plasticity In Humans DC004855 1 years NIDCD

Abstract: Understanding the relationship between the complexity of human learning and associated brain function is one of the most fascinafing journeys of basic science. In addition to being an important academic question, studies of brain function assocIated with learning have very practical applications for improving diagnosis and therapy of learning disabilities. Learning disability affects between 10-20 percent of Americans with severe socioeconomic consequences on their quality of life and health. This proposal focuses on understanding the neural processes underlying normal human learning of auditory information that is transient and occurs in rapid succession. The most intuitive example of such processing is reflected in our ability to learn and understand speech. Deficits in learning such forms of information are associated with dyslexia and language-learning impairment. A few of the currently popular tools used to study the relationships between human learning and associated brain processes are Positron Emission Tomography (PET), Functional Magnetic Resonance Imaging (fMRI), Magnetoencephalography (MEG) and Electroencephalography (EEG). However, of all these methods only MEG and EEG offer adequate time resolution, essential for the proposed study because brain responses to auditory stimuli typically occur in the time-scale of milliseconds. Data obtained using MEG and EEG is often analyzed without consideration of the dynamics of cortical activity and often simplified source and head models are assumed, Information about brain plasticity obtained in this fashion is hard to understand and interpret. Recently several new methods have been developed to process MEG and EEG data. However, the usefulness of these methods has not been adequately demonstrated on real data. The first specific aim of this proposal is to research and to validate novel analyses methods that will enhance the interpretation of EEG and MEG data. We will use realistic head modeling for imaging distributed sources and account for the spatio-temporal dynamics of brain activity. We will empirically validate the usefulness of these methods to understand the dynamics of functional brain plasticity using computer simulations and experiments. The second specific aim of the proposal is to determine the relationship between the dynamics of functional brain plasticity in spatio-temporal responses to successive stimuli and changes in psychophysical thresholds that occur as a result of perceptual learning. We will focus on learning in rate discrimination of amplitude-modulated tone trains in normal adults as a first step towards understanding learning of simple time-varying auditory stimuli that occur in rapid succession. We will examine and correlate learning-induced behavioral changes with changes in the spatial and the temporal patterns of activity within and across cortical areas. Such a multidisciplinary approach which combines methods of scientific computing and functional brain imaging using MEG and EEG should enhance our understanding of general neural mechanisms underlying human perception learning. These results in normal individuals should provide crucial information for the development, refinement and evaluation of diagnosis and therapy for individuals with learning disability.

Ober, Raimund J	University Of Texas Dallas	Image Processing Of Immunological Microscopy Samples	AI050747	3 years	NIAID

Abstract: Microscopy and, in particular, fluorescence microscopy plays an ever increasing role as a tool to improve the understanding of cellular processes such as receptor clustering and trafficking. The present application originated from a number of immunological studies which are being carried out by the co-PI. These studies relate to questions of recognition by the T cell receptor in autoimmune disease models (experimental autoimmune encephalomyelitis (EAE); collagen induced arthritis (CIA) and trafficking of the MHC class I-related receptor, FcRn. The overall objective of this multidisciplinary bioengineering project is to provide important additional tools for the analysis of experimental results obtained using fluorescence microscopy, with the emphasis on tools for three dimensional image sets. The premise of the application is that in a number of respects the analysis capabilities lag behind the recent developments in hardware and sample preparation methodology. The proposed study will investigate new methods and approaches to various problems in immunology and cellular biology. All proposed approaches will be rigorously analyzed with simulated and experimental data. Our specific aims are: first, to investigate methods for quantitative analysis of clustering and co-localization. Second, deconvolution algorithms and several modifications will be analyzed. Third, a software suite will be written for acquisition and analysis of fluorescence microscopy images. The capabilities of this package will not only include the necessary functionality to carry out the earlier specific aims, but will provide a powerful development environment for advanced image analysis for microscopy.

Parel, Jean M	University Of Miami	Optomechanical Characteristics Of Lens Accommodation	EY014225	3 years	NEI

Abstract: The objective of the proposed collaborative program is to understand the relationship between the optical and mechanical properties of the crystalline lens and the amplitude of accommodation and its loss in presbyopia. The general application of these bioengineering studies is the development of suitable technology including devices and surgical procedures for the restoration of near vision to presbyopes, as well as the restoration of good visual performance to cataract patients. The specific aims of the proposed research are: 1. To measure the mechanical properties of the crystalline lens 2: To measure the mechanical properties of the lens capsule 3: To measure the mechanical properties of the zonules 4: To develop mechanical and optical instrumentation to simulate accommodation in explanted crystalline lenses of eye-bank eyes (lens stretcher) 5: To quantify changes in normal and refilled crystalline lens during simulated accommodation 6: To develop an opto-mechanical model of the lens during accommodation The static and dynamic lens mechanical properties will be measured as a function of age using a micro-Fourier rheometer. The mechanical properties of the capsule will be measured using a custom-made capsule stretching device. The mechanical properties of the zonules will be investigated using atomic force microscopy and tensiometry. An opto-mechanical lens stretching system will be constructed to simulate accommodation on human cadaver lens specimens that include the crystalline lens, lens capsule, zonules, ciliary body and sclera. The system will be used to measure and correlate stretching forces with changes in lens equatorial diameter, thickness, displacement, topography, power and aberrations during simulated accommodation as a function of age. The contribution of the lens capsule and zonules to the mechanics of accommodation will be quantified by conducting lens stretching experiments before and after lens refilling with injectable materials of controlled mechanical properties.

Pelc, Norbert J | Stanford University | Hybrid X-Ray/MR Systems For Image-Guided Procedures | EB000198 | 3 years | NIBIB

Abstract: Image-guided minimally invasive procedures have made a substantial impact in improving patient management, reducing the cost, morbidity and mortality of treatments, and malung therapies available to patients who would otherwise have no option. X-ray fluoroscopy and MRI are two powerful tools for guiding interventional procedures, but they have very different strengths and weaknesses. X-ray fluoroscopy offers very high spatial and temporal resolution and is excellent for guiding and deploying devices. However, it offers little in the way of soft tissue contrast. MR offers tomographic imaging with complete freedom of plane orientation, outstanding soft tissue discrimination, and the ability to portray physiology and directly observe the effect of therapies. However, it not ideal for imaging devices and is limited in spatial resolution. As a result of these disparate characteristics, the choice of guidance modality involves a compromise. Our preliminary work has shown that it is feasible to fully integrate an x-ray fluoroscopy system into the bore of an interventional MR scanner. The two systems can have congruent fields of view, enabling the physician to seamlessly and flexibly choose the modality that is best suited to each phase of the procedure. This type of hybrid system could have enormous impact in the diagnosis and treatment of oncologic, cardiovascular, and other disorders. The proposed work will take the system beyond proof of concept and into the clinic. We will develop and implement more powerful and reliable x-ray subsystems, perfect their MR compatibility, develop x-ray tube designs with increased immunity to magnetic field alignment, and more thoroughly integrate the two modalities by implementing graphic prescription of MR slices from x-ray projections. We believe this technology will have significant benefit to a number of important applications, ranging from endovascular procedures to biopsies and diagnostic studies. However, we are using two applications (TIPS placement and chemoembolization) as models with which to develop this technology, and as part of the proposed work we will conduct small clinical trials of these procedures. The hybrid system, once perfected, will remove the compromise involved in choosing a guidance modality, improving and enabling new minimally invasive procedures.

Phillips, Charlotte L | University Of Missouri Columbia | Biomolecular Mechanics Of Collagen Monomers And Fibrils | AR048195 | 3 years | NIAMS

Abstract: Biomechanical stability and strength of connective tissues have long been attributed to covalent intermolecular crosslinks between collagen monomers. Type I collagen, a major component of bone, tendon, skin, and the vasculature, is normally heterotrimeric, consisting of two al (I) chains and a single a2(I) chain, [al(I)2a2(I)]. However, type I collagen in oim mice is exclusively composed of al(I) homotrimers, [al(I)3] (result of a null mutation in the a2(I) gene). Oim mice are a superb model system for examining the functional necessity of the a2(I) chain. We hypothesize that the absence of a2(I) chains perturbs collagen fibril formation, collagen-collagen interactions, and intra- and inter-molecular crosslinking, compromising the structural and biomechanical integrity of connective tissues. In vivo studies using oim mice demonstrate that the presence of type I collagen homotrimers significantly decreases the biomechanical integrity of bone, tendon, skin and aorta. Further analyses using oim mice suggest non-covalent collagen intra- and intermolecular interactions and organization maybe the critical factors regulating mechanical integrity rather than collagen crosslinking. These results question the dogma that covalent intermolecular crosslinks between collagen monomers are the principal determinants of stability and biomechanical integrity of the fibrillar architecture, and compel us to consider other forces and interactions, such as the inherent mechanical properties of individual collagen monomers and non-covalent protein-protein interactions. Recent advances in the application of atomic force microscopy now make it possible to analyze inherent mechanical properties of single biomolecules and molecule-molecule interactions. We propose to use atomic force microscopy to define the role of a2(I) chains 1) in the inherent mechanical integrity of collagen monomers, 2) in non-covalent collagen-collagen interactions, and 3) in the inherent mechanical integrity of collagen fibrils, as well as provide a powerful new tool for defining and understanding the pathogenesis of fibrillar collagen mutations and other extracellular matrix components and their role in connective tissue disease.

Rinker, Kristina D | Colorado State University | Pressure And Angiotensin Effects On Vascular Endothelium | HL068916 | 4 years | NHLBI

Abstract: Endothelial cell properties are affected by hemodynamics, various systemic chemicals and signals, and their attachment matrix. In an effort to extend current understanding of both atherogenesis and factors complicating successful treatment of occluded coronary arteries, this project will investigate the effects of hemodynamic forces, angiotensin I/II, and the cellular inflammatory response on endothelial cell physiology. Local synthesis of angiotensin II by endothelial membrane bound angiotensin converting enzyme (ACE) and the angiotensin type I receptor (AT1) may have potent effects on local endothelial dysfunction and the development of coronary artery disease. The inflammatory cytokine interleukin-l (IL-1) likely plays an important role in the alteration of endothelial phenotype observed in the presence of cellular stressors such as extremes of hydrodynamic pressure and angiotensin I/II. Many effects of IL-1 upon vascular endothelial cells are identical to those associated with angiotensin exposure and vascular activation by fluid forces. As such, work will be performed to elucidate the contributions of IL-1 to the effects of culture stimulation with pressure and angiotensin. Syndecans-l (present in the glycocalyx) and 4 (co-localized to focal adhesions) are common endothelial cell surface molecules that can be readily shed in response to cellular injury or stress and thereby promote monocyte adhesion. We hypothesize that modulation of two in vitro endothelial cell culture properties 1) hemodynamic pressure and 2) angiotensin I/II concentrations affects endothelial cell phenotype as related to 1) glycocalyx properties, 2) receptor/protein expression, and 3) attachment characteristics. Encompassed by this hypothesis are the mechanisms by which pressure and angiotensin I/II exert their effects. It is proposed that pressure and angiotensin I/II activate cell stress signaling pathways (i.e. mitogen activated protein kinase cascades and protein kinase C) that result in the shedding of specific glycocalyx components (e.g. syndecan proteoglycans) and the induction of proinflammatory physiological responses (e.g. interleukin-1 production, monocyte adhesion receptor production, monocyte chemoattractant protein-1production). It is further proposed that while pressure and angiotensin directly induce these events, the production of intlerleukin-1 significantly amplifies each of the physiological responses and becomes a controlling factor upon endothelial dysfunction.

Roth, Charles M | Rutgers The St Univ Of NJ New Brunswick | Efficient And Selective Delivery Of Oligonucleotides | GM065913 | 5 years | NIGMS

Abstract: The ability to modulate cell behavior through genetic modification has great potential as a therapeutic strategy, as well as providing a powerful tool for elucidating gene function (so-called functional genomics). Antisense oligonucleotides, which are most commonly single-stranded DNA molecules 15-25 nucleotides in length, modulate gene expression by binding to a complementary segment on the mRNA from the target gene. While antisense technology is becoming a viable therapeutic entity and platform for functional genomics, a major barrier to its widespread practice still exists: the delivery of the genetic material (polynucleic acid) to cells in a quantity that is biologically effective and in a form that is functionally intact, yet non-toxic. Our overall goal is to deliver antisense molecules selectively to a target cell type (hepatocytes), resulting in low-dose inhibition of expression of genes of interest. To achieve this goal, we will develop a new family of multifunctional DNA delivery vectors (multiplexes) using a combinatorial synthesis approach. These vectors will possess biomimetic polymers that condense DNA, cationic peptides that destabilize cellular membranes, and galactose moieties that target them to hepatocytes (primary liver cells). Vectors will be characterized for size, stability, and cytotoxicity. We will study the adsorption of these materials to target vs. non-target cells, and interpret the results in the framework of a colloid-chemical mathematical model, which will be used to refine and optimize the composition of the vectors. The effectiveness of these vectors to deliver gene expression-modulating antisense oligonucleotides will be evaluated and assessed to further refine the approach. W expect the long-term outcome to be a selective and efficient method for oligonucleotide delivery for therapeutic and functional genomics applications.

Sacks, Michael S | University Of Pittsburgh At Pittsburgh | Biomechanical Optimization Of TE Heart Valves | HL068816 | 3 years | NHLBI

Abstract: Tissue engineering (TE) offers the potential to create replacement heart valves which have the potential for growth and remodeling, overcoming the limitations of current heart valve devices. Using autologous cells and biodegradable polymers, TE heart valves (TEHV) have been fabricated and have functioned in the pulmonary circulation of growing lambs for up to four months. Despite these promising results, significant questions remain. For example, the role of initial scaffold structure and mechanical properties to guide the development of optimal extra- cellular matrix (ECM) structure and strength are largely unexplored. While detailed biomechanical investigations of the in-vitro incubation process could shed much light on optimizing TEHV designs, little work has been conducted to date. Finally, our understanding of the structure-strength relations in native pulmonary valve (PV), which serves as the ultimate design paradigm, is profoundly incomplete. Our long-term goal is to develop a rigorous quantitative understanding of the biomechanical events that occur during in-vivo TEHV remodeling, and to use this knowledge to develop functionally equivalent TEHV designs. By functional equivalent we refer to the fact we aim to develop an engineered tissue that can perform an equivalent physiologic function (e.g. have requisite mechanical properties and durability) without having to precisely reproduce tri-layer cuspal structure. Prior to undertaking comprehensive in-vivo studies, we believe that detailed knowledge of the factors necessary for optimizing TEHV structure and biomechanics during in-vitro incubation must first be established. We hypothesize that precise control of 3D scaffold structure, initial scaffold mechanical properties and biodegradation rates, and well- controlled hemodynamic loading conditions can be used to optimize TEHV designs to duplicate native PV function. In addition, the structure-strength relations of the native pulmonic valve will be rigorously established in order to establish the TEHV design functional endpoint. We will explore our hypotheses with the following specific aims: 1) Quantify the shape of the ovine pulmonary outflow track and determine the mechanics of the native ovine PV cusp. 2) Quantify how initial scaffold structure, composition, degradation rates, and mechanical properties can be exploited to optimize the resultant engineered heart valve tissue. 3) Perform in-vitro evaluation of TEHV fabricated using optimal scaffold designs and 3D guided RV outflow track geometry using novel bioreactor loop imaging system.

Saidel, Gerald M | Case Western Reserve University | Thermal Model To Guide Tumor Ablation By RF Heating | EB001052 | 4 years | NIBIB

Abstract: Interventional Magnetic Resonance Imaging (I-MRI) provides an image-guided, minimally invasive method for ablating cancerous tumors. When a small diameter RF probe is inserted into a solid tumor, the energy delivered by the probe produces a current that heats the tissue to a sufficiently high temperature to kill tumor cells. This project is intended to quantify and predict the acute response of tumor cells and surrounding tissue to heat produced internally with a RF probe. A quantitative model analysis is essential in dealing with special challenges for clinical implementation such as ablating tumor cells near critical vessels or nerves. Furthermore, modeling can assist in predicting changes in the ablated region from the thermal response in tissue with a spatially varying perfusion. To accomplish these goals, we propose to analyze the dynamic changes of the three-dimensional (3-D) temperature field in tissue surrounding the RF heating probe during ablation. This process will be modeled using a 3-D bio-heat equation that incorporates a variable heat source and a distinct temperature-dependent perfusion to represent changes in tissue associated with ablation. The model will be solved numerically to simulate the temperature field dynamics in tissue. We will validate the model and estimate model parameters by comparison of model predictions of the temperature field during RF heating with corresponding data from MRI experiments using gel phantoms, excised tissues, and intact animals. We will develop faster numerical methods for solution of the model equations to allow more accurate, real-time simulations during the ablation procedure. The ablation analysis will include optimal estimates of model parameter estimation, multiple repositioning of the RF probe for sequential tumor ablation, and graphical displays. These methods will assist clinical evaluation and decision-making during the therapeutic procedure to kill tumor cells with minimal damage to normal cells.

Saltzman, W Mark | Yale University | Micro-And Nano-Engineering Of Biomineralized Materials | DE014097 | 5 years | NIDCR

Abstract: Biomaterials have a long and successful history in dental and bone restoration, but the current technology is imperfect. Three-dimensional, biomineralized templates are a necessary component of bone and dental tissue engineering strategies, but methods do not yet exist for controlling the formation of biomineralized substrates with chemical and physical features that promote cell integration and function. We will first fabricate two-dimensional substrates in which macromolecules with functional groups that appear during tooth and bone formation will be micropatterned to regulate calcium phosphate crystal nucleation and growth. A constant composition method will be used to mineralize the patterned surfaces with specific chemical composition and crystalline phase. In addition, three-dimensional matrices with micropatterns will be fabricated using natural ECM proteins or synthetic polymers in a silicon mold. The patterned hydrogel matrices will be mineralized in a controlled manner using a modified constant composition method and microfluidics. Mineralized structures will be extensively characterized for chemistry, crystal structure, and topography. The controlled microstructures will be used to study the interaction between cells and the extracellular environment. Experiments will focus on the effect of the mineralized material on cell behavior; the influence of chemistry and geometry on the attachment, migration, and specific functions of cells will be studied. Together, these studies will provide new insight on the interactions between cells and substrates that occur during biomineralization. Since precisely designed synthetic materials will be produced and characterized to meet the study objectives, this project will also lead to new approaches for engineering of dental and orthopedic tissue.

Shahidi, Mahnaz | University Of Illinois At Chicago | Retinal Image Quality In Retinal-Diseased Eyes | EY014275 | 3 years | NEI

Abstract: The optical properties of the eye and its imperfections limit visual performance, the ability for an individual to view the world, and retinal imaging, the ability for an ophthalmologist to view the retinal tissue. Recent advances in wavefront sensing and adaptive optics technologies have allowed measurement and correction of monochromatic wavefront aberrations in healthy human eyes. However, it is likewise important to investigate disease-related changes in the optics of the eye, since they can significantly contribute to degradation of both visual performance and resolution for retinal imaging. Particularly, there is a need to differentiate between vision loss that results from retinal disease and visual performance that is impaired due to imperfect optics, in order to anticipate optimal outcome for therapies applied to improve neural function of the retina in eyes with imperfect optics, or to foresee consequences of procedures that are targeted to improve the optical property of eyes with diseased retinas. Equally important is a need for high-resolution imaging of the retinal tissue that may be achieved by compensation for ocular aberrations with the use of adaptive optical components and image processing methodologies. Such imaging would allow visualization of fine retinal structures, thus providing for better understanding of retinal pathophysiology and enhanced diagnostic evaluation of retinal diseases. In the current research proposal, our novel technique for optical section retinal imaging will be coupled with wavefront sensing technology. Imaging will be performed in subjects diagnosed with diabetic retinopathy and age-related macular degeneration and the optical performance of retinal-diseased and healthy eyes will be compared. The relation between ocular aberrations and retinal imaging resolution will be determined. High-resolution retinal imaging will be achieved by compensation for ocular aberrations. Findings from the research study will provide knowledge on the nature and extent of disease-related changes in the optical properties of the eye, that is of value for evaluation of optical factors that contribute to degradation of visuai performance and for achievement of high-resolution retinal imaging in subjects with retinal diseases that are considered the most prevalent causes of blindness.

Sodickson, Daniel K | Beth Israel Deaconess Medical Center | Parallel MR Imaging: New Techniques And Technologies | EB000447 | 5 years | NIBIB

Abstract: Imaging speed is a crucial consideration for numerous clinical and research applications of MRE. In recent years, parallel magnetic resonance imaging (PMRI) has been shown to be an effective means of increasing MR imaging speed beyond previous limits. In contrast to traditional sequential MR acquisitions, which encode image data one point at a time, PMRI techniques use arrays of RF coils to encode and detect data in a parallel rather than a strictly sequential fashion. PMRI techniques have been advancing rapidly, and numerous potential applications have been identified. However, certain basic questions remain regarding the image quality which may routinely be achieved in PMRI scans. Two particular challenges relate to the areas of coil sensitivity calibration and signal-to-noise ratio optimization. We propose a program of research to address each of these basic challenges, by eliminating the need for separate sensitivity calibration scans, and by designing coil arrays specifically tailored for spatial encoding. The practical clinical value of these technical developments will be verified in a targeted clinical study of patients with known or suspected abdominal pathology. Specific Aims are as follows: 1. Optimization and comparative evaluation of a new generalized self-calibrating parallel MIRI technique Optimization of known free parameters in the self-calibrating approach Comparison with standard externally-calibrated PMRI approaches in phantoms, volunteers, and patients 2. Construction and comparative evaluation of novel RF coil arrays explicitly designed for parallel MIRI Design and construction of RF coil arrays tailored for spatial encoding, including arrays with independently positionable elements, 'multipole" arrays, and arrays of arrays ("superarrays') Comparative evaluation in phantoms, volunteers, and patients Exploration of the computational tractability of ultimate intrinsic SNR calculations for PMRI studies with arbitrary arrays 3. Implementation and evaluation of the developments of Specific Aims 1 and 2 in a clinical study of abdominal imaging using parallel MIRI Use of an externally-calibrated SMASH technique to reduce breath-hold durations and/or increase slice coverage in a clinical liver imaging protocol using an existing coil array. Comparison of clinical images obtained using the optimized self-calibrating technique from Specific Aim #1 with images obtained using externally-calibrated techniques in the same coil array Comparison of clinical images obtained using the coil arrays from Specific Aim #2 with images obtained using an existing standard array

Spear, Robert C | University Of California Berkeley | Local Strategies For Schistosomiasis Control | AI050612 | 5 years | NIAID

Abstract: The long-term objective of our research program is to design situation- and/or site-specific strategies for the suppression of environmentally mediated infectious diseases. The immediate issue addressed here is to determine if the intensity of transmission of Schistosoma japonicum can be predictably diminished by using a mathematical model, based on both local data and general knowledge of the transmission cycle, to design effective interventions. The specific alms of this project are: 1.Model Development: to further develop our model of schistosomiasis transmission, based on exposure-related risk groups, to more effectively utilize site-specific field data typically collected in China as well as data on spatial factors relevant to disease transmission now easily obtained using GPS technology. 2. Use the Model for Design: to design effective control programs in four to six villages selected from two sites. The first phase of this work will be to collect the standard field data set in three villages in the Changqiu Mountains west of Chengdu to supplement that available from the Qionghai Lake villages with the objective of full site-specific calibration of the refined model. 3. Implement the Designs: we propose to implement the designs resulting from Specific Aim 2 and evaluate the results in these villages, if sustainable environmental interventions using traditional methods do not emerge, we will determine whether the impediments to success are rooted in inadequate knowledge, technological limitations, or agricultural practices.

Stenger, Victor A | University Of Pittsburgh At Pittsburgh | fMRI Acquisitions In Regions With Field Inhomogeneity | MH066066 | 3 years | NIMH

Abstract: The purpose of this ROl proposal is to develop novel methods for the mitigation of magnetic susceptibility artifacts in T2* functional MR imaging (fMRI). The project has been motivated by the necessity for fMRl acquisition techniques in brain areas of vital importance for psychiatric and neuroscientific investigations but are, however, currently inaccessible to fMRI due to severe image degradation due to local field inhomogeneity. The primary goal of the proposal is to develop a rapid fMRI data acquisition strategy that is robust to local field inhomogeneity in both the in-plane and through-plane directions. The proposed acquisitions will allow for the collection of 14-18 slices in 1-2 seconds with significantly reduced signal loss and distortion compared to standard 2D methods with identical image resolution. As part of the research plan, variable density reversed spiral acquisitions, continuous gradient compensation methods, and 3D slice-select tailored RF pulses will be developed and systematically compared and combined. The comparison will be based on the criteria of acquisition speed, signal magnitude and resolution recovery, and T2* functional contrast. This project will lead to valuable new methods capable of imaging brain regions with large magnetic susceptibility variations in an accurate manner free of artifacts. Success in developing the methods described in this application will overcome a major limitation of fMRI, making feasible a broad range of clinical applications not previously possible. Many common disorders, such as schizophrenia, obsessive-compulsive disorder, depression, anorexia, and ADHD, which appear to involve disturbances in orbitalfrontal, striatal, and thalamic regions. will benefit from these techniques.

Sun, Mingui | University Of Pittsburgh At Pittsburgh | Data Communication With Implantable Micro Devices | NS043791 | 4 years | NINDS

Abstract: In recent years several exciting new engineering developments, such as sub-micron electronics, nanotechnology, and microelectromechanical (MEM) chips, have emerged which may have profound impairs on medicine. Following these developments, miniature, but highly intelligent, implantable sensors and devices could be built to perform in vivo diagnosis and therapeutic intervention. Currently, many technical barriers have been removed; however, there till exists a significant problem that an effective wireless data communication link which allows data exchange between external computer and implanted device through layers of tissue has not yet been developed. Traditional data communication modalities, such as those based on radio and optical mechanisms, cannot penetrate tissues well and do not support substantial miniaturization. As a result, valuable data obtained by implantable devices cannot be sent out, instructions/commands from computers cannot be sent in, and the development of the next-generation implantable devices has been hampered. We propose a biomedical engineering development project to attach the external/internal wireless data communication problem. We will build an innovative device consisting of two-way wireless data collection unit that both transmits subdural electroencephalographic signals and stimulates the cortex, fully controlled by an external computer. We will implant this device within the brain of laboratory dogs and evaluate its performance.

Tornai, Martin P | Duke University | Simultaneous Emission And Transmission Mammotomography | CA096821 | 5 years | NCI

Abstract: The overall goal of this proposal is to develop a hybrid, dual-modality x-ray computed tomography (XCT) and single photon emission computed tomography (SPECT) scanner for dedicated breast and axillary imaging, termed application specific emission and transmission tomography (ASETT). This noninvasive imaging tool is intended to provide volumetric, co-registered anatomical and functional imaging data for improved diagnosis of breast cancer. The XCT component of the system can provide structural three-dimensional images of the breast and axillary region with exposure near that of dual-view screening mammography, greatly improving the detectability of low contrast lesions in the breast, enhancing the spatially-dependent attenuation correction of the SPECT data, and facilitating better interpretation and quantification of the SPECT data by objectively guiding region of interest selection. This proposal represents the initial technology development for a dedicated breast ASETT system. A prototype, dedicated SPECT scanner has previously been investigated, and a gantry has been developed that facilitates a new class of hemispherical acquisition orbits about a pendant breast. This proposal will (1) extend the capabilities and performance characteristics of the SPECT camera and gantry, (2) develop and optimize the dedicated XCT scanner, and (3) integrate the two into a single system. The new SPECT system will have improved intrinsic spatial resolution (4.5mm) and intrinsic energy resolution (10% FWHM), and an expanded field-of-view, with fully computer controllable degrees of freedom. The XCT system will incorporate a novel x-ray source/filtration approach to mammographic imaging with a pseudo- monochromatic beam and a state-of-the-art, flat-panel, scintillator-based digital detector to reach <1mm isotropic reconstructed resolution. The ASETT detector system will be characterized and optimized for tomographic breast and axillary imaging. Novel orbits to sufficiently sample the pendant breast and axillary region will be developed, and trade-offs between sequential or simultaneous XCT/SPECT imaging, resolution, signal-to-noise, and radiation dose to the breast volume will be investigated. Appropriate phantoms will be used to quantitatively assess image quality and dose. Finally, the dual-modality ASETT system will be clinically evaluated with pilot patient studies.

Villanueva, Flordeliza S University Of Pittsburgh At Pittsburgh Echocardiographic Evaluation Of Endothelial Function HL058865 4 years NHLBI

Abstract: Coronary artery disease is the major cause of mortality in the United States. Although many patients come to medical attention because of hemodynamically significant coronary lesions, over one-half who die suddenly from coronary disease have had no pre-existing symptoms. It has been hypothesized that critical abnormalities in the coronary endothelial lining provide a milieu that ultimately promotes acute thrombotic occlusion in the absence of significant prior coronary stenoses. Moreover, in patients with angina due to severe stenoses, endothelial abnormalities likewise promote the development and progression of atherosclerotic plaques that culminate in acute ischemic syndromes. Aberrations in endothelial function in coronary disease involve the microcirculation and occur in other cardiovascular disease states such as heart transplant rejection and ischemia-reperfusion. Endothelial dysfunction is thus a critical mediator of the total burden of atherosclerotic heart disease and a major component of other cardiovascular pathologies, and the identification and treatment of this phenomenon would confer significant health benefits. Unfortunately, methods to identify patients with early endothelial dysfunction are limited. Studies have shown that endothelial overexpression of leukocyte adhesion molecules such as intercellular adhesion mnolecule-1 (ICAM1) promotes the development of the earliest lesions of atherosclerosis, suggesting that ICAM1 can serve as a marker of incipient endothelial disease. Using perfused cultured human coronary artery endothelial cells (ECs), we recently proved the principle that gas-filled microbubbles conjugated to a ligand that binds specifically to ICAM1 adhere to interleukin1á-activated ECs overexpressing ICAM1. Because these bubbles are acoustically active in the presence of ultrasound, we hypothesize that in vivo ultrasound imaging of bubbles targeted to specific cell surface markers of endothelial activation such as ICAM1 will permit non-invasive identification of pre-clinical endothelial dysfunction. To test this hypothesis, in vitro and in vivo models of endothelial activation will be used to address three Specific Aims with respect to bubbles engineered to bind to cell surface markers of endothelial disease: (1) Define shear conditions under which ICAM1-targeted bubbles attach to ECs and optimize bubble characteristics for binding; (2) Identify other EC surface proteins specific for endothelial dysfunction, including selectins, vascular adhesion molecule-1, or vascular endothelial growth factor receptors, evaluate their suitability as imaging targets, and design microbubbles for these targets; and (3) Image and quantify targeted bubble adhesion in vivo under clinically relevant conditions. The ultimate goal of this proposal is to develop targeted ultrasound imaging in order to enhance the early diagnosis of ischemic heart disease or other cardiovascular disease states associated with endothelial dysfunction. Principles gleaned from these studies can be extended to function-specific ultrasound imaging of other targets such as angiogenic markers, and may also provide a basis for targeted therapeutic approaches using microbubble carriers.

Yokota, Hiroki Indiana Univ-Purdue Univ At Indianapolis Mechanical Loading And Matrix Metalloproteinase HL058865 2 years NIBIB

Abstract: The long-term objectives of this proposal are to develop a high-resolution force loader for applying precise loads to connective tissues, and to elucidate the role of mechanical stress and strain to rheumatoid joints. A turnover of collagens, predominant components in soft connective tissues, is at least in part regulated by families of proteolytic enzymes, and the matrix metalloproteinases (MMPs) have been considered as the influential group of proteinases in bone and soft connective tissues. In analyzing the role of mechanical stress and strain in matrix degradation, precise control of mechanical loads is important since the expression and the activities of MMPs depends heavily upon intensities, gradients, and duration of shear and strain. In this revised 2-year bioengineering research project, a specific aim is to design and fabricate a state-of-the-art piezo-electric device that can be utilized with inverted fluorescence and optical microscopy. Life scientists will be able to characterize cellular morphology and molecular dynamics in real-time under mechanical stimuli. The proposed piezo-electric device will be able to apply precise deformation of 100-500 um to cultured cells at 0.1-100 Hz sinusoidal or impulsive waveforms in varying directions. The device will be validated by reproducing the previous results showing that gentle cyclic stain alters the expression and the activities of MMPs and tissue inhibitors of metalloproteinases (TIMPs) in human synovial cells. In determining the expression and activities of MMPs and TIMPs, we will use RT-PCR, Western blotting, zymography as well as in vitro and in situ fibril degradation assays. The proposed project will contribute to understanding effects of mechanical stimuli on cellular morphology as well as molecular activities. The device can be used to address fundamental questions about how mechanical forces affect cells in real time as well as to elucidate the mechanisms of inflammation and degradation of connective tissue under mechanical stimuli.

Yuille, Alan L	University Of California Los Angeles	Locating And Reading Informational Signs	HL058865	3 years	NEI

Abstract: Our goal is to construct computer vision systems to enable the blind and severely visually impaired to detect and read informational text in city scenes. The informational text can be street signs, bus numbers hospital signs, supermarket signs, and names of products (eg. Kellogg's cornflakes). We will construct portable prototype computer vision systems implemented by digital cameras attached to personal, or hand held, computers. The camera need only be pointed in the general direction of the text (so the text is only one percent of the image). A speech synthesizer will read the text to the user. Blind and visually impaired users will test the device in the field (under supervision) and give feedback to improve the algorithms. We argue that this work will make a significant contribution to improving human health (rehabilitation). Computer vision is a rapidly maturing technology with immense potential to help the blind and visually impaired. Reports suggest that detecting and reading informational text is one of the main unsatisfied desires of these groups. Written signs and information in the environment are used for navigation, shopping, operating equipment, identifying buses, and many other purposes (to which a blind person does not otherwise have independent access). The blind and severely visually impaired make up a large fraction of the US population (3 million). Moreover, this proportion is expected to increase by a factor of two in the next ten years due to increased life expectancy. Our proposal is design-driven. It uses a new class of computer vision algorithms known as Data Driven Monte Carlo (DDMCMC). The algorithms are used to: (i) search for text, and (ii) to read it. Recent developments in digital cameras and portable/handheld computers make it practical to implement these algorithms in portable prototype systems. The three scientists in this proposal have the necessary expertise to accomplish it. Dr.'s Yuille and Zhu have backgrounds in computer vision and Dr. Brabyn has experience in developing and testing engineering systems to help the blind and visually impaired. Our proposal falls within the scope of the Bioengineering initiative because we are applying techniques from the mathematical/engineering sciences to develop informatic approaches for patient rehabilitation. More specifically, our work will facilitate the development of portable devices to help the blind and visually impaired.