PI Name	Institution	Title	Grant	Years Awarded	Funding Institute
Bloom, David M	Alces Technology, Inc.	Microcontact Printer For Ophthalmic Tissue Engineering	R43 EY015029	1 year	NEI

This project will demonstrate a prototype microcontact printing aligner for use in ophthalmic tissue engineering. The performance of the microcontact printing aligner will be refined and validated by experiments conducted in collaboration with the Stanford Ophthalmic Tissue Engineering Laboratory. Functioning much like traditional rubber-stamping methods, microcontact printing is widely used to print molecules, such as growth factors or extracellular matrix proteins, in well-defined locations at the nanoscale. This project focuses on microcontact printing applied to a tissue engineering solution for age-related macular degeneration. Using microcontact printing on autologous lens capsule, the Stanford Ophthalmic Tissue Engineering Laboratory is developing a replacement retinal pigment epithelium for treating age-related macular degeneration. Current microcontact printing techniques depend strongly on the skill and ability of the researcher. A prototype tool will be built to improve the reproducibility of microcontact printing. This will require investigation into and enhancement of the stamping materials and techniques. Additionally, this tool will allow for printing of multiple layers, with alignment between the layers. A tool for aligned microcontact printing is a significant enhancement over the current techniques, and something that is neither commercially available, nor easily developed in most biological research facilities.

Chen, Wei	Nomadics, Inc.	Scintillation Luminescence System for In-Vivo Dosimetry	R43 CA110091	2 years	NCI

Nomadics proposes the development of scintillation nanocomposite materials that are capable of producing scintillation luminescence (SL) and the demonstration of their applicability for in vivo dosimetry and radiation dose imaging. Successful production of SL with such materials would suggest that this technology could be used to create a new type of radiation detection for use in dosimetry, radiation therapy dose-control, and X-ray and other energy source imaging techniques. Nanoparticle-based scintillation luminescence systems would provide enhanced sensitivity for in vivo dosimetry. In Phase I, we will focus on making scintillation nanoparticles that can be used for in vivo dosimetry in support of safer, more accurate radiation cancer therapy. Nomadics will do the chemistry and optical development tasks, while Dr. Angelo Russo of NIH will conduct tests to verify the biocompatibility of the approach. Additionally, Dr. Carey Pope of Oklahoma State University, a leading toxicologist, will conduct toxicology studies to verify the suitability of SL nanoparticles for in vivo dosimetry. Once the concept is successfully demonstrated, it will be a great improvement for dose control in radiotherapy and will greatly benefit cancer patients by offering protection to adjacent healthy tissues. Additionally, with regard to the extensive use of X-ray and similar technologies in the medical industry, manufacturing, security field, inspection and non-destructive testing processes, and other applications, the proposed use of quantum materials holds the potential for higher resolution imaging at lower energy levels, resulting in substantial reductions in cost, complexity, hazards, and other negative aspects of the use of these processes.

Daniels, Robert H	Nanosys, Inc.	Nanowire DNA hybridization sensor	R43 CA101567	1 year	NCI

The aim of this program is to develop a novel genetic analysis platform that will provide multiple cost, time and sensitivity advantages over conventional technologies. The ability to diagnose the susceptibility to diseases such as breast or colorectal cancer provides valuable information for affected individuals that can lead to early detection and treatment of the disease. Current technologies for identifying genetic mutations and polymorphisms are limited in their diagnostic utility because of the complex sample processing, amplification steps and expensive detection instrumentation. Most genetic analyses is thus relegated to sophisticated and costly testing laboratories. The nanotechnology enabled sensor described in this proposal will be capable of highly selective and sensitive detection of nucleic acid hybridization in an array based format without the need for sample labeling or amplification. Furthermore, instead of expensive optical detection this nanosensor will detect hybridization by changes in electrical conductivity that can be made with a simple, low cost, low power instrument compatible with a point of care or even portable sensor platform. This detection system is based on the discovery that nanoscale materials such as nanotubes and nanowires can act as field effect transistors (FET's) at room temperature. This effect is termed NanoChemFET and it works because the conductive properties of exquisitely sensitive nanowires are modulated by charges on the analyte molecule that act like a gate voltage in a conventional field effect transistor. Because captured DNA or RNA would deliver a defined number of negative charges, proportional to the number of nucleotides brought into the vicinity of the nanowire, nucleic acids are well-suited to sensitive, quantitative analysis by a NanoChemFET sensor. As described in this proposal we will develop processes to controllably manufacture nanowires and assemble them on functional devices. We will use these devices to test the sensor performance for sensing and discriminating specific DNA sequences. In phase I of the program we will detect hybridization of a specific DNA sequence and we will determine the basal sensitivity and discriminatory capabilities of the sensor. This will provide the baseline from which to develop multiple genomic analysis applications including expression arrays, SNP genotyping and the detection of infectious agents in an exquisitely sensitive, rapid and cost effective manner

Daniels, Robert H | Nanosys, Inc. | Nanowire Enhanced Substrates for Microarrays | R43 HG003480 | 2 years | NHGRI

Existing substrates for fluorescent microarray applications have many limitations including poor sensitivity, low dynamic range, variable spot uniformity and large feature sizes on mechanically spotted arrays. Despite these limitations the fluorescent microarray has become a major tool for large-scale genomic analyses and the emerging proteomic industry. Thus far, attempts to introduce new substrates have been unsuccessful, largely because of reduced kinetic performance and the requirements for major changes to the basic array fabrication and analysis infrastructure. In this program we will develop a novel, nano-enabled microarray substrate that will overcome all the major limitations of existing microarray substrates and yet will be entirely incompatible with existing hybridization protocols, array fabrication and analysis infrastructure. This technology is based upon our ability to control and pattern the growth of SiO_2 coated, nanometer diameter wires on the surface of a planar substrate. This novel material provides dramatic increases in effective surface area and yet retains the basic chemical characteristics required for surface functionalization and assay development. In Phase I we will optimize the material and develop methods for depositing and patterning it on planar surfaces compatible with conventional array fabrication and scanning instrumentation. We will link oligonucleotide probes to the enhanced surface using conventional chemistries and hybridize fluorescent targets to these probes using standard protocols. We will optimize the performance of the nanowire enhanced substrates to achieve a 100-fold increase in signal intensity per unit area with a concomitant increase in dynamic range. Furthermore, we will decrease feature sizes on spotted arrays to well below currently achievable levels and at the same time increase the uniformity of the spotted probe. Finally we will demonstrate the broad utility of this substrate by developing a protein binding assay on the nanowire enhanced surface. Preliminary experiments on non-optimized materials indicate that these milestones will be achievable. Our long term aims are to demonstrate the compatibility of this performance enhancing substrate with all array fabrication approaches, to increase the density of spotted arrays to those now achieved by lithographically synthesized formats and finally to manufacture well characterized high density DNA and protein arrays to carry out large scale genomic (proteomic) analyses on this substrate.

Deschatelets, Pascal | Potentia Pharmaceuticals | Bypassing Fluidics in Proteomic Screening | R43 GM070193 | 2 years | NIGMS

The goal of this proposal is to develop a new, groundbreaking technology for the rapid identification of ligands for proteins. Every year, the pharmaceuticals industry loses about $3 billion by targeting genes/proteins wrongfully identified as the cause of disease. In the past decade, thousands of new genes/proteins with a potential role in disease have been identified. Simultaneously, millions of small molecule ligands have been generated in pharmaceutical libraries with little knowledge on their binding potential to these novel gene/protein targets. Potentia has developed a technology that will pave the way towards the matching of these ligands with new potential drug targets. Intelligent access to these libraries of ligands will generate a wealth of knowledge on disease mechanisms that is deemed to revolutionize the process of gene/protein validation in the drug industry. Potentia's technology is unique in its capacity to circumvent the inherent 'slowness' of analyzing molecules in solution. Proteins are immobilized on the tip of an atomic force microscope and then exposed to arrays of biosensors. Each biosensor is individually functionalized with a different small molecule ligand, resulting in Potentia's groundbreaking screening platform. The first aim of this proposal will be to eliminate background noise when functionalizing specialized biosensors with ligands in order to generate sensors for protein binding. The second aim will be to show that an atomic force microscope tip can be used as a bias electrode to gate our specialized biosensors. The third aim will be to determine whether it is possible to retrieve quantitative information from a binding event when using an atomic force microscope tip as a 'robotic arm' to bring a protein in contact with a ligand-coated biosensor. The success of this proposal will generate intelligence on millions of small molecule-protein interactions, generating unprecedented insight in the various gene/protein pathways and their role in disease.

Freeman, Richard G Surromed, Inc. Highly Multiplexed, SERS-Based Quantitation Nanotags R43 CA111752 1 year NCI

Two of the priority research areas identified by the NIH Bioengineering Nanotechnology Initiative are Nanoimaging and Molecular and Cellular Sensing/Signaling. This proposal presents SERS nanotags (SERS = Surface Enhanced Raman Scattering), a new detection technology, which will enable the rapid and quantitative measurement of many chemical species both in solution and under a microscope. We propose to synthesize, fully characterize, and demonstrate initial bioassay results using these glass-coated nanoparticulate optical tags based on SERS. Our specific aims for this proposal are: 1. Prepare a set of five or more SERS tags with clearly different spectra. We will synthesize Au and Ag nanoparticles that provide SERS enhancement, show that molecules with five different spectra can be readily combined with the particles, and coat them with a controlled amount of glass. 2. Examine the ability of SERS nanotags to function as quantitation tags. This will include a determination of the signal generated per particle and a demonstration of the ability to extract accurate quantitative information from mixtures of particles. 3. Demonstrate ability to use SERS nanotags in a bioassay. To achieve this aim we will first show the attachment of biomolecules (specifically streptavidin and oligonucleotides) to the glass-coated SERS nanotags. Finally, we will carry out a competitive binding assay between biotin and desthiobiotin to show that the SERS nanotags can provide quantitative data in a bioassay format. The attainment of these aims will establish the foundation for unprecedented capabilities in optical tag-based localization and quantitation, with applications ranging from multiplexed gene expression analysis to multiplexed histopathogical analysis of cancerous tissue. SERS is the 10(6)- to 10(14)-fold enhancement in Raman scattering obtained from molecules in extremely close proximity to nanoscale-roughened noble metal surfaces. This enhancement is necessary in order to use Raman scattering as a sensitive tagging technique for bioassays.

Henderson, Eric R. Bioforce Nanosciences, Inc. Microfabricated Deposition Tools For Creating Nanoarrays R43 EB000613 1 year NIBIB

The goal of this proposal is to design and test novel microcantilever devices for the purpose of improving deposition of biomaterials in ultraminiaturized arrays. BioForce NanoSciences, Inc. (http://www.bioforcelab.com) is an industry leader in the development of next-generation biomolecular screening arrays, or NanoArrays, with patented technology permitting the construction of biochips with sub-micron spatial addresses. These nano-scale arrays allow a thousand or more molecular tests to be carried out in the same surface space occupied by a single state-of-the-art microarray spot. This format offers dramatic savings in reagent cost that accompanies ultra-miniaturization, and more importantly, it provides a realistic and sought-after platform for performance of array-based analyses in applications involving extremely small quantities of sample material where uses of current microarray formats are not feasible. These applications include single-cell protein profiling, prenatal diagnostics, forensic testing, high-throughput drug screening, and minimally invasive clinical diagnostic testing. Commercialization of this technology requires highly reproducible molecular deposition that is not feasible with current deposition tools. This research project will advance this technology through the following specific aims: 1. Design and construct front and back loading quill- and aperture-type single, and multiplexed deposition tools; and 2. compare iterative deposition-wash cycle with pre-load, continuous flow deposition methods using the devices designed in aim 1.

Israel, Barbara A Platypus Technologies, LLC Liquid Crystal Based Enzyme Activity Assay R43 CA108078 2 years NCI

The long-term goal of this Phase 1 SBIR is to develop optimized components (nanostructured substrates) and methods for use in the creation of a novel class of rapid, liquid crystal based assays capable of reporting enzyme activity. This proposal focuses on the activity of matrix metalloproteinases because of their central importance to cancer biology. There is a need for new technologies that are more cost effective, less labor intensive, consume less reagents, can be performed in less time, can distinguish between the total amount of MMP present and its activated fraction, and are amenable to high throughput formats. Platypus™ technology can be the foundation for such assays to accelerate basic research, drug discovery, evaluation of anti-cancer drugs and development of prognostic indicators. The combination of nanostructured substrates with liquid crystals requires no secondary labels or additional reagents to report enzyme activity. It will provide a unified platform for many diverse assays relevant to cancer biology. In this proposal, we will fabricate substrates with nanoscale topography by two methods: oblique deposition of thin films of gold and by rubbing of covalently immobilized enzyme substrates that introduce nanoscale order into the surface of the protein film. We will comparatively evaluate the ability of these substrates to: align liquid crystals; determine their tolerance to the presence of non-specific adsorption of proteins in cell media and to allow rapid quantification of matrix metalloproteinase activity. Additionally, we will explore strategies that allow specific identification of MMP-9 and its activated fraction. At the completion of these studies, we will have optimized the core component of a new technology for rapid, cost effective and accurate quantification of enzyme activity.

Kalkhoran, Nader M | Spire Corporation | Bio-Enhanced Neural Electrodes Based on Porous Silicon | R43 NS046957 | 2 years | NINDS

The overall objective of this program is to develop nanostructured porous silicon as neural electrode materials with enhanced biocompatibility, in particular for novel hybrid silicon/ceramic multi-site neural recording electrode arrays. We have previously shown that the pure ceramic-based multi-site neural electrode arrays can consistently record multiple single neuron activity chronically for up to six weeks. These results are similar to microwire electrodes and better than other thin film electrodes. However, in order for any electrode system to act as neural interface components of neural prosthetic devices, the electrode will be required to record consistently for many years. Preliminary studies have shown that by introducing widely varying porosity into silicon, its behavior can be tuned from that of a relatively bio-inert material to one that is bioactive, and even resorbable. In this proposal, we plan to investigate two types of semi-flexible nanostructured hybrid silicon/ceramic neural electrodes. In one type, the electrode material will be based solely on nanostructured porous silicon formed electrochemically on a thin Si substrate. In the second type of electrode, an additional ultra-thin layer of ceramic material will be formed conformally onto the nanostructured porous silicon using a special deposition process. The latter structure will allow us to directly compare the performance of electrodes with essentially nanostructured ceramic surface to conventional ceramic-based devices. In Phase I, the efficacy of nanostructured porous silicon neural electrodes will be evaluated in vivo using rat brain model. The neural tissue will be evaluated using histology methods to look for neural damage near the site of implantation and study the growth of neurons into the porous silicon electrodes. To promote neural growth at the electrode/tissue interface and for better contact of the recording sites on the array with neurons, we will test the ability of the porous silicon to deliver neurotrophic molecules. In Phase II, upon optimizing the parameters for nanostructured porous silicon electrodes, Spire and its collaborators will design, fabricate and test in vivo performance of a two dimensional array of porous silicon-based neural electrodes for chronic, long-term (greater than 6 months) multi-site recording.

Lichtenhan, Joseph D | Hybrid Plastics, LLC | Nanocomposite-Based Dental Materials | R44 DE014026 | 1 year | NIDCR

It is the specific aim of this proposal to develop an advanced adhesive and dental restorative system that is more quickly placed and reliable than current products. Thus improving patient satisfaction and general health care. The method for achieving this objective is to design a dental bonding agent and restorative system that are structurally controlled at the nanoscopic (1-10nm) level through the macroscopic level. Natural tooth contains both nanoscopic and macroscopic length scales. The development of such a restorative system will maintain the continuum of structure from the natural tooth through the adhesive and restorative system thereby improving compatibility and physical properties. Nanoscopic building blocks based on the nontoxic polyhedral oligomeric silsesquioxane (POSS) Nanostructured TM Chemical technology will be utilized in combination with conventional macroscopic and nanoscopic metal oxide fillers to design a dental restorative which benefits from multi-length scale structural control (nano to macro). POSS-Monomers will be utilized as isotropic 1.5nm structural segments in the base restorative resin. In this capacity the resulting nanostructured resin will provide an enhanced filler-resin interaction and lower shrink characterists as demonstrated in Phase I. Improvement of the filler-resin interface will also result in improved mechanical properties and reduced degradation of the restorative system. The performance of restoratives are also governed by the nature and integrity of the inherent bondline formed with natural tooth. Here again the design of bonding agents which utilize 1.5nm monomeric POSS building blocks provide a more natural interface with the 2nm sized apatite crystals present in natural tooth and with the l nm-10nm structural segments incorporated into the proposed restorative. Overall better bonding to the tooth and restorative per Phase I findings. By utilizing both nano (lnm-10nm) and macroscopic length scales in a dental restorative and bonding system, a continuation of length scale and properties with those in natural tooth can be acheived. It is the intent of the proposed Phase II work to develop a prototype system for transition to Phase III.

Montagna, Richard A Innovative Biotechnologies International Use Of Nanotechnology To Rapidly Detect Human Pathogens R43 AI060085 2 years NIAID

In order to reduce escalating health care costs, rapid "point-of-care" (POC) testing has dramatically grown over the last decade. Due to their relative ease, immunologic approaches are frequently used for such tests. Molecular analysis (i.e., based upon DNA and/or RNA), however, has largely been limited to the clinical laboratory setting, where the inherently more complicated sample preparation and analysis procedures can be performed. Nanotechnology provides a unique opportunity to bring molecular technology to the patient, thus improving diagnostic data and further reducing healthcare costs. We propose to develop a nanomedical device for the direct detection of specific nucleic acid sequences in human pathogens. By eliminating enzymatic gene amplification steps, POC testing can be more easily accomplished within the rapid time frame expected for such tests. The detection of pathogenic organisms will be accomplished by detecting abundant rRNA sequences. Two types of oligonucleotide probes will be designed and utilized. One ("capture" probe) will be bound to a magnetic bead that will serve to bind to and immobilize the target sequences within the proposed device. The second oligonucleotide probe ("reporter" probe) will be bound to liposome nanovesicles, which in turn, will encapsulate quantum dots (QDots). Because QDots can be "tuned" to fluoresce at specific wavelengths depending on their size, this feature will permit us to ultimately design a simple multianalyte test during Phase II. The target rRNA sequences of the pathogenic organism will be selected by first predicting their secondary structure (using free energy calculations) and then evaluating those sequences for specificity and availability for hybridization. The "capture" and "reporter" probes will be designed to hybridize to these available sequences. Integration of these technologies into a nanomedical diagnostic device will permit the rapid detection of specific nucleic acid sequences without the need for prior gene amplification, thus improving the speed and ease-of-use of molecular diagnostic assays in the POC and other human in vitro diagnostic marketplaces. Finally, the successful development of a "sample in - results out" device whereby no sample manipulation is required, will dramatically simplify the performance of such tests.

Mosher, Curtis L Bioforce Nanosciences, Inc. Biomolecular Profilometer R43 AI061881 2 years NIAID

The goal of this SBIR Phase I feasibility study is to create a novel instrument called a BioProfilometer (BioPro) for label free detection of biomolecular interactions. The instrument measures the surface profile of a planar chip designed to capture biological entities at specific domains. The BioPro does not incorporate force measurement or dynamic force feedback capability. Hence, it is not an atomic force microscope (AFM) and it will be faster, smaller, and less expensive than research-grade AFMs for the desired application. The BioPro does use a microfabricated device to rapidly read topographical events on a surface. The feasibility of this approach for molecular diagnostics will be tested using an affinity capture method called the ViriChip. The ViriChip captures viral particles to a surface, with each captured virus constituting an event that should be detectable by the BioPro. We anticipate that the novelty, simplicity and dedicated nature of this method and device will create value that can be translated into a commercially viable product.

Naqwi, Amir A Powerscope, Inc. Airborne Nanoparticles for Therapeutic Applications R43 EY016229 2 years NEI

A device for generating airborne particles in the size range 20-100 nm at the rate of micrograms per minute is proposed. This particle generator will utilize multiple heads of multi-jet electrosprays to obtain the desired throughput of the particulate matter. The proposed nanoparticle generator will be used to deliver certain potent drugs to animal models. The first set of animal experiments will involve delivery of drug nanoparticles to the lungs through inhalation. Particle deposition efficiencies in various parts of the animal lungs will be studied and efficacy of the candidate drugs in treating adenocarcinomas (cancer of the deep lung) will be examined. In a second set of animal experiments, the drug nanoparticles will be suspended in a perfluorocarbon gas bubble used to occlude and tamponade retinal breaks and tears. The drug composition in this application is intended to inhibit the proliferative vitreoretinopathy (re-detachment of the retina in the presence of a scar tissue). Tests will be designed to study the efficacy of the drugs in this respect. Effectiveness of the proposed technique in generating airborne suspensions of macromolecules will be examined. We will also study the feasibility of scaling up the throughput of the above device to milligrams per minute.

O'Neal, D Patrick | Nanospectra Biosciences, Inc. | Nanoshell-Based Detection of Beta-Amyloid for Alzheimer's | R41 AG025586 | 2 years | NIA

The goal of this Phase I STTR proposal is to develop a new detection platform and methodology for early detection and characterization of Beta-amyloid peptide (AB), the primary protein component of senile plaques in Alzheimer's disease (AD). An extremely sensitive surface enhanced Raman spectroscopy product has been developed by Nanospectra Biosciences and its collaborators at Rice University that provides enhancements equal to or exceeding 10^10 uniformly across the substrate, enabling rapid quantification of picomolar levels of targets in fluids. This substrate is based on a new class of nanomaterials, called nanoshells, with extremely high near-field electromagnetic effects at their plasmon resonance peaks. Beta-amyloid peptide plays an important role in neurotoxicity and is a marker for AD progression. Evidence, both in our collaborator's (Dr. Good, UMBC) lab and others, indicates that we can develop a clustered sialic acid containing dendritic polymer that is a biological mimic of the cell surface and will have high affinity for disease specific conformations of AB. More specifically, we believe that we can exploit the relatively high affinity binding of sialic acid clusters to aggregated/fibril AB for the detection of soluble amyloid oligomers present in biological tissues such as cerebral spinal fluid or post mortem tissue samples using our unique surface-enhanced Raman spectroscopy platform. The specific aims of this research include (1) development of the nanoshell surface sensor for detection; (2) synthesis of soluble clustered sialic acid dendrimers as mimics of ganglioside clusters on the membrane surface; and (3) development of detection methods that utilize the soluble clustered sialic acid dendrimers as a targeting agent for oligomeric/fibril AB.

Ofer, David | Foster-Miller, Inc. | High Surface Area Carbon Nanotube Nerve Electrodes | R43 NS047772 | 2 years | NINDS

Implantable micro-electrodes for electrical stimulation of neurons and recording neuronal responses are essential tools for neurophysiologists studying the behavior of neurons in the brain, spinal cord and peripheral nerve. Critical properties of an electrode interface include: low noise, low impedance, biocompatibility, and electrical stability during chronic use, and high charge capacity. Iridium oxide has all of these properties and thus has been utilized for significant developments in the neural prostheses arena. However, these electrodes have several shortcomings, including: high materials cost, labor-intensive processing, and deterioration of long-term stability. Foster-Miller proposes to demonstrate improved performance of neural electrodes imparted by high porosity, high surface area carbon nanotube electrodes. Nanotubes promise high electrochemically active surface area in a high porosity, high conductivity electrode, and leading to higher safe charge injection density at shorter pulse durations. They also will provide electrochemical charging in capacitively coupled monophasic pulse mode, lower cost, and improved electrochemical stability. Through this program, Foster-Miller will develop a suitable process for mass fabrication of nanotube electrode arrays, and characterize the performance of these arrays in in-vitro and in-vivo environments. Success in Phase I will lead to process design and long-term testing of prototype nanotube electrode arrays during Phase II.

Ong, Keat G | Sentech Corporation | Transcutaneous Nanotube Hydrogen Sensor | R43 HD049233 | 2 years | NICHD

We propose to develop a room temperature, transcutaneous hydrogen sensor based upon nanoporous-titania capable of 0.1ppm hydrogen detection in the presence of potentially interfering gas analytes. We anticipate that the resulting sensor will be applied as a bandage, and be inexpensive enough to be readily used on a disposable basis. The project will build upon work of the co-investigators in the fields of high performance gas sensors, sensor electronics, and sensor integration. The specific enabling objectives to be pursued under Phase I are: {1} Extend the TiO2-nanotube hydrogen sensor fabrication technique to enable precise control over pore dimensions which in turn determine its hydrogen sensitivity. {2} Extend the anodization technique established for fabricating nanoporous TiO2 and AI203 to additional compositions including SnO2 and WO3. {3} Correlate material structures and composition with gas sensing properties, establishing algorithms for the determination of hydrogen concentration within potentially interfering gas mixtures that include CO2, O2, nitric acid, ammonia and acetone. {4} As needed, cross correlate the response of different nanoporous metal oxide sensors in an e-nose format to eliminate the effect of interfering gases enabling precise transcutaneous measurement of hydrogen, in air and at room temperature, at sub 1 ppm levels. Reduce the needed data logic processing e-nose algorithms to a commercially available data acquisition system chip (about $25) having a 2 cm x 2 cm footprint. During Phase II in collaboration with D. James Kendig of the Neonatal Intensive Care Unit at the Penn State Children's Hospital (Hershey, PA) the transcutaneous hydrogen sensor will be applied to facilitate clinical determination of the onset of neonatal necrotizing enterocolitis, a devastating disease of uncertain etiology which causes ischemia and necrosis of the small and large intestinal walls of preterm infants.

Ozer, Ruya R | Lynntech, Inc. | Reactive Materials for Protective Clothing | R43 AI062032 | 2 years | NIAID

This project aims to develop a novel surface modification technique of textiles to impart properties to the fabric necessary for their use in protective clothing. The increase in disease transmission, the widespread use of pesticides in agriculture, and the increased proliferation of chemical and biological weapons worldwide have increased the need for the development of effective fabric treatments for protective clothing. During Phase I research nanoparticles will be covalently attached to the surface of the fabric in order to give them desired properties. The modified fabric will then be tested for antimicrobial activity against a broad spectrum of pathogenic microorganisms, for detoxification of chemical and biological warfare agent surrogates as well as skin cytotoxicity. Preliminary results demonstrated that it is feasible to permanently anchor these nanoparticles onto cotton fabric and they are effective against chemical warfare agents as well as pathogenic microorganisms. Potential applications for this technology include protective clothing and materials for medical and institutions, agricultural workers, fire fighters and military soldiers as well as for cloth products for household disinfection and various consumer products. Applications: Commercial applications for fabric that is active against pathogenic microorganisms as well as chemical agents are enormous. Protective coating for agricultural workers, fire fighters and military servicemen could be produced from this modified fabric. A multitude of applications could be found in medical area.

Paulose, Maggie | Sentech Corporation | Remote Query 'Smart-tube' NanoSensors | R43 HD044334 | 1 year | NICHD

We propose extending magnetoelastic sensor technology from the microscale to the nanoscale. This scaling of dimensions will enable the resultant sensor arrays to be placed within tube sidewalls, providing physical and chemical information of the tube interior (air or liquid) without interference of flow characteristics. Device sensitivity on the nanoscale should enable the instantaneous detection of single molecule binding events. The remote query nature of the sensor technology enables sensor information to be transmitted from the interior of the tube without the use of physical connections, avoiding possible contamination. Since the sensors transmit information via magnetic flux they are not susceptible to interference affects that might affect optical sensors, e.g. moisture condensation, smudges, misalignment, etc. Combining the best features of nanowire device fabrication and magnetoelastic sensor technology, the sensors should be able to distinguish mass changes of femto-grams but yet be inexpensive enough to be readily used on a disposable basis. It is anticipated that such sensors would find immediate application in clinical care, in effect creating a 'smart tube' technology. In Phase I, we will fabricate ordered magnetoelastic nanowire cantilever arrays, as described herein, of 1, 5, 10, and 50 cantilevers. Initially we will modify and extend the needed measurement electronics to monitor these uncoated nanocantilevers in air and liquid establishing baseline signal-to-noise values as a function of nanowire composition, properties and dimensions. The nanocantilevers will then be coated with a polymer of precisely controlled thickness, in incremental steps of less than 2 nm, to establish baseline sensitivity values and operating characteristics. In Phase II, the nanocantilevers will be coated with analyte specific layers and integrated with disposable tubes enabling their use as clinically relevant analyte and environmental sensors for, initially, neonatal monitoring.

Qhobosheane, Monde | Life Sciences, Inc. | Handheld Gene Analyzer Based On Dye-Doped Nanoparticles | R43 AI060321 | 2 years | NIAID

Life Sciences proposes the development of a novel pathogen detection system based on dye-doped nanoparticles (NPs) and supported by low cost, field portable instrumentation to facilitate the rapid detection of nucleic acid sequences present in low copy number; with or without amplification. Silica, dye-doped NPs to be used in this effort have been demonstrated to produce 10,000 to 100,000 fold increases in detectable signal from a single hybridization event with a DNA target when compared to commonly used fluorescent reporters. This high level of signal enhancement is expected to permit the use, with optimization, of an existing low cost, field portable fluorometer to support the application of the pathogen detection in products for rapid (10 minutes) low cost ($ 5-10 per test) for point-of collection diagnosis of infectious disease. The system may also be deployed for field detection and identification of environmental pathogens in food and water, to include agents that maybe employed as biological weapons. To achieve this goal there are two aims in this proposal. First, we will develop a novel DNA/RNA bioassay based on dye-doped NP. This assay will be performed on glass substrate and detected by a traditional spectrofluorometer. NP optimization will be completed and will emphasize smaller size, higher signal intensity, and ease of bioconjugation. Secondly, we intend to optimize an existing low-cost fluorometer such that it can be employed as a handheld gene detection analyzer. This part will be performed on magnetic beads and detected by the hand-held fluorometer. We will focus the immobilization of DNA on the surface of magnetic beads, optimization of the assay to detect DNA down to picomole range. More importantly, we will emphasize the combination of the hand-held fluorometer to the assay. Our project is an integrated one in which better NPs will be prepared, ultrasensitive optical detection systems will be optimized, NP bioconjugation and surface chemistry will be better understood and improved, new insights into NP's bioanalytical applications will be obtained, and portable protocols for ultrasensitive bioanalysis will be developed and utilized.

Reed, Michael W | Bioconjugate Consulting | DNA Purification and Analysis of Nanoengineered Surfaces | R43 GM072178 | 1 year | NIGMS

Analysis of genomic DNA is central to research in modem molecular biology, and is critical for medical diagnostics and therapeutics development. Isolation of genomic DNA from cells has been improved, but the methods are still labor intensive. Measurement and handling of DNA prior to genetic analysis often involves specialized liquid handling equipment, and evaporation of solutions makes miniaturization difficult. Technology to simplify the isolation, handling, and measurement of genomic DNA is required for portable medical diagnostics or biodefense applications. The long-term objective of the project is to develop disposable "lab-on-a-chip" microfluidics products that isolate genomic DNA from tissue, simultaneously capture and measure the DNA, and simplify genetic analysis. Novel solid supports will be developed which can capture DNA and measure the concentration in microfluidics chambers before and after release. The DNA binding properties of glass are well known, and form the basis of the DNA isolation process. Glass surfaces will be combined with other solid surfaces bearing nanoengineered "DNA reading stations". These will be prepared using "fluorogenic" DNA binding molecules, which are known to increase fluorescence upon binding to DNA. By linking these types of fluorogenic compounds to glass or plastic surfaces, capture and release of DNA will be monitored by fluorescence. These novel materials will allow in-process control of the DNA isolation process, and ultimately simplify downstream dilution and analysis. Incorporating these "fluorogenic" DNA binding materials into a microfluidics device will simplify and standardize isolation of DNA and provide more reliable genetic analysis.

Sauer, Jon R | Eagle Research And Development, LLC | Silicon-Based, Single Molecule, DNA Analysis Prototype | R43 HG002725 | 1 year | NHGRI

Abstract not available.

Singh, Waheguru P | Lynntech, Inc. | Acute Myocardial Infarction Sensor | R43 HL075955 | 2 years | NHLBI

Patients suffering Acute Myocardial Infarction (AMI) symptoms in Emergency Rooms are subjected to cardiac marker testing. These "cardiac markers" have great potential as early indicators of the presence of AMI when analyzed together for extended time periods. Traditional methods of detecting these protein concentrations such as Enzyme-Linked ImmunoSorbent Assay (ELISA) is expensive to perform, and only test one protein at a time. In a typical month, Hermann Hospital in Houston, TX submits over 9,500 samples for cardiac marker analysis. The average cost of performing these tests is $100 per sample, resulting in an expenditure of close to $1,000,000/month. With over 4,000 hospitals nationwide, this number extrapolates to an astonishing 48 billion dollars annually for cardiac marker testing. This data suggests the need for an inexpensive sensor, capable of in-house biological fluid analysis of all cardiac marker proteins: simultaneously. By combining the selective recognition element properties of Lynntech's patent-pending iprotein-imprinted conducting polymer, with a Field-Effect Transistor (FET) acting as the transducer, Lynntech, Inc. proposes to develop a hand-held, disposable cartridge sensor capable of determining the entire array of cardiac marker concentrations simultaneously. The proposed device would be a point-of-care AMI monitoring sensor, capable of relaying critical AMI cardiac markers (i.e. Myoglobin, Creatine Phosphokinase (CPK)-MB, Total CPK, CPK-MB isoforms, and Troponin I/T) statistics, thereby reducing the lag time between the onset of AMI symptoms and treatment. The proposed sensor platform circumvents the problems associated with other biological sensors such as signal drift, costs associated with expensive protein (antibody) ligands, lack of selectivity, sensitivity, biological molecule attachment to electrode surface and limited shelf-life. Lynntech has gathered a strong research team to help perform the tasks during the Phase I research effort by recruiting the help of Georgia Tech's Dr. Janata to assist in the area of FET technology and Dr. Roe, a research physician at The Duke Clinical Research Institute, to offer his expertise in cardiac marker testing. Within the $20 billion global market for in vitro diagnostics, the fastest-growing segments are "cutting-edge" diagnostic test systems & technologies such as molecular diagnostics, non-invasive technologies, point-of-care testing, flow cytology, and nucleic acid testing.

Wharton, Tim J Lynntech, Inc. Novel Nanomaterials for Use in Radioimmunotherapy R43 CA101275 2 years NCI

One of every four deaths in the US is from cancer, making it the second leading cause of death, behind heart disease. According to an NIH estimate, this year about 555,500 Americans will die of cancer. Radioimmunotherapy (RIT) is one of the emerging modalities for the treatment of cancers. In RIT, a therapeutic dose of ionizing radiation is delivered to the cancer sites by attaching a suitable radionuclide to an antibody that binds to a specific antigen expressed by the cancer cells. The suitable nuclear emission properties (Ebeta = 1.7 MeV), the physical half-life (t1/2 = 17 hr), the decay-characteristics, and its availability from a generator, makes rhenium-188 one of the most attractive radionuclides for potential use in RIT. However, the complex labeling chemistry required for Re-188 and non-availability of a good chelating agent that forms stable complexes with Re-188 at high specific activities, limits the use of Re-188 in RIT. To overcome these problems, Lynntech is currently developing nanoparticle technology for a convenient labeling of cancer-targeting antibodies with Re-188 obtained from a readily available 188W/188 Re generator. During Phase I, the proof of concept will be demonstrated by labeling anti-CEA antibody with Re-188 using the new nanoparticle technology.

Wharton, John T Lynntech, Inc. Photodynamic Blood Product Decontamination R41 HL075969 2 years NHLBI

The objective of this proposal is to covalently immobilize an all-carbon nanoparticle that is an excellent photosensitizer (PS) onto biologically inert polymeric backbones for the photodynamic inactivation of pathogens in blood products. The polymers will then be placed in a permeable cartridge and fixed into a flow-through reactor. After filling the reactor with the blood product, the fluid will be circulated and the photocatalyst illuminated with laser light. The illuminated PS catalyzes the formation of singlet oxygen, 1O2*, a reactive species of oxygen that will inactivate pathogens in the blood product. The decontaminated blood product is then simply removed from the reactor, leaving the C60-modified polymer behind. Three types of polymeric backbones will be investigated: 1) hydrophobic polymer, 2) polycationic polymer, 3) non-ionic hydrophilic polymer. The synthetic steps to modify the polymers with C60 start from commercially available polymers and are simple literature procedures. After photocatalyst synthesis and construction of the reactor, the pathogen inactivation system will be evaluated in a series of in vitro experiments to determine the optimal blood product decontamination applications of the new system. Several advantages are expected over conventional homogeneous PS such as methylene blue: 1) there is no post-treatment toxicity because the photocatalyst is heterogeneous and integrated into the reactor structure and upon completion of treatment, the blood product is simply removed from the reactor leaving the catalyst behind, 2) enhanced selectivity of pathogen inactivation is expected due to the polymeric backbone's tunable affinity relative to damage to blood components 3) the nanoparticle PS that will be used has a very high singlet oxygen quantum yield, higher than conventional PS. The vision of this project is to introduce a novel, economical system to the blood product market for the inactivation of pathogens in blood products.