



1st Annual GREAT* Training Retreat



Laguna Beach, California
October 17 & 18, 2004

**UC Systemwide Biotechnology
Research and Education Program**

*Graduate Research and Education in Adaptive bio-Technology Training Program

1st Annual GREAT Training Retreat
Aliso Creek Inn
Laguna Beach, California
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UC Systemwide Biotechnology Research and Education Program

Director

Martina Newell-McGloughlin

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Graduate Research and Education in Adaptive bio-Technology Training Program

The University of California Biotechnology Research and Education Program, Graduate Research in Adaptive bio-Technology Training (GREAT) Program

Our graduate fellowships supports the training of the brightest young graduate students within the University of California system for research at the interface between the life sciences and any of the disciplines within the physical, chemical, material, engineering, mathematical and computational sciences. The result—the Graduate Research and Education in Adaptive bio-Technology (GREAT) Training Program awards individual fellowships up to \$50,000 each per year.

By providing funding directly at the fellowship level, our Program has more direct control of where the funds are allocated, has the potential to greatly increase distribution across campuses, has a greater impact in evolving cutting edge cross-disciplinary fields, and provides a means of tracking results.

The response to the first call for GREAT fellows was overwhelming! We received 109 pre-proposals of outstanding quality and tremendous diversity following a very short lead-time. From these, we selected 34 applicants to go forward with full proposal submission. The final proposals were all of exceptional quality and the competition was extraordinarily rigorous since the excellence of the proposals and the caliber of students were uniformly outstanding. From the 34 finalists, eleven proposals that best reflected the mission of the UC Biotechnology Research and Education Program and the GREAT Program were selected.

All projects provided an environment for non-traditional cutting-edge cross-disciplinary training from investigators who displayed the greatest expertise and creativity working at the interface of complementary disciplines in:

nanotechnology as it applies to the life sciences

novel biosensors

medical microdevices/delivery systems, bio-materials

bio-devices/instrumentation/bio-MEMS

microarrays

bioinformatics and molecular modeling

chemical proteomics,

genomics

bio-imaging

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PROGRAM OVERVIEW

Sunday, Oct. 17, 2004

- 1:00 – 2:00 p.m. Registration – Retreat will be held in **TERRACE ROOM**
- 2:00 – 2:10 p.m. Welcome by **Fred Fox, Chair**
Overview of program **Martina Newell-McGloughlin**, Director
UC Systemwide Biotechnology Research and Education Program
- 2:10 – 2:15 p.m. UC Davis: Overview of lab collaborations- Primary Faculty Sponsor:
Xiangdong Zhu, CoSponsor/Mentor: **Monique Cosman**, LLNL
- 2:15 – 2:35 p.m. **James Landry**, Student
Study of protein interaction with DNA and membranes in microarray
format using a novel label-free, real-time optical imaging microscope
- 2:35 – 2:55 p.m. Agilent Technologies: opportunities for collaboration in
microfluidics, microarrays, bioreagents, chromatography, mass
spectrometry, and informatics. **Mel Kronick**, Agilent
- 2:55 – 3:00 UC Berkeley: Overview of lab collaborations - Primary Faculty
Sponsor: **Richard A. Mathies**
CoSponsor/Mentor: **George F. Sensabaugh**,
- 3:00 – 3:20 **Stephanie Yeung**, Student
A microfabricated integrated genetic analyzer for rapid forensic
studies and human identification
- 3:20 – 3:30 BREAK
- 3:30 – 3:50 Rabbit MAbs (RabMAbs): A new generation of monoclonal
antibodies for target discovery, diagnostics and therapeutics.
Guo-Liang Yu, Epitomics
- 3:50 – 3:55 UCLA: Overview of lab collaborations –
Primary Faculty Sponsor: **Ming C. Wu**
CoSponsor/Mentor: **Edward R.B. McCabe**

- 3:55 – 4:15 **Pei Yu Chiou, Student**
Parallel Manipulation of Single Cells Using Optoelectronic Tweezers
- 4:15 – 4:35 GeneChip® arrays: from identifying genetic variations associated with disease to discovering new drug targets. **Alan Williams, Affymetrix**
- 4:35– 5:15 **BREAK/POSTER VIEWING** (still in TERRACE ROOM)
- 5:15 – 6:30 **HOSTED DINNER** (in **GREEN ROOM**)
After dinner, return to TERRACE ROOM
- 6:30 – 6:35 UCSB: Overview of lab collaborations - Primary Faculty Sponsor: **Hyongsok (Tom) Soh**, CoSponsor/Mentor: **Daniel E. Morse**
- 6:35 – 6:55 **Karen Qian, Student**
Dielectric Labeling and Dielectrophoretic Manipulation of Cells
- 6:55 – 7:15 Berlex, a leader in innovative drug discovery and development with centers of excellence in cardiovascular, cancer and immuno-based diseases **Gordon Parry, Berlex**
- 7:15 – 7:20 UCSF: Overview of lab collaborations - Primary Faculty Sponsor: **Alan Frankel**, CoSponsor/Mentor: **Hao Li**
- 7:20 – 7:40 **Alexander Pastuszak, Student**
MicroRNA binding sites in the human genome: targets for gene regulation and therapeutics
- 7:40 – 7:45 UCSF: Overview of lab collaboration - Primary Faculty Sponsor: **Kevan M. Shokat**, CoSponsor/Mentor: **David O. Morgan**
- 7:45 – 8:05 **Justin Blethrow, Student**
Chemical Proteomics: Mapping protein kinase signaling pathways through chemospecific purification of direct protein kinase substrates.

Monday, Oct. 18

- 7:00 - 7:55 a.m. **HOSTED BREAKFAST** in **TERRACE ROOM**
- 8:00 - 8:10 **OVERVIEW OF DAY**
- 8:15 - 8:20 UCSC: Overview of labs collaboration- Primary Faculty Sponsor: **David Haussler**, CoSponsor/Mentor: **Manuel Ares**
- 8:25 - 8:45 **Adam Siepel**, Student
Detection of functional elements in the human genome using comparative genomics and evolutionary models
- 8:45 - 9:05 Nanometer-sized Qdot particles: unique detection platform for biology. **Charles Hotz, Quantum Dot**
- 9:05 - 9:10 UCI: Overview of labs collaboration- Primary Faculty Sponsor: **Michael Cahalan**, Co-Sponsor **Ian Parker**
- 9:10 - 9:30 **Debasish Sen**, Student
Quantum dots as nano-scale probes of dendritic cell trafficking and antigen presentation in vivo
- 9:30 - 9:50 Development of innovative therapeutic vaccines for the treatment of cancer and infectious diseases using Dexosomes and Exosome Display Technology. **Sanjay Patel, Anosys**
- 9:50 - 10:05 **BREAK**
- 10:05 - 10:10 UCSD: Overview of lab collaborations - Primary Faculty Sponsor: **Sangeeta N. Bhatia**, CoSponsor/Mentor: **Erkki Ruoslahti**
- 10:10 - 10:30 **Austin M. Derfus**, Student
Modular approach to nanoparticle-based cancer therapeutics
- 10:30 - 10:50 Full moon glass substrates solution for increasing signal intensity and eliminating variables. **Youxiang Wang, Full Moon Biosystems**
- 10:50 - 10:55 UCSB: Overview of lab collaborations - Primary Faculty Sponsor: **Norbert Reich**, CoSponsor/Mentor: **Andrew Cleland**

- 10:55 – 11:15 **August Estabrook**, Student
Nucleoprotein and nanoparticle-based molecular electronics
- 11:15 - 11:35 Developing therapeutics from the Alnis nanoparticle technology platform. **Steve Barry, Alnis**
- 11:35 - 12:15 **View posters**
- 12:15 - 1:30 **HOSTED LUNCH in ART ROOM**
- 1:30 – 1:35 UCSB: Overview of lab collaborations - Primary Faculty Sponsor: **Samir Mitragotri**, CoSponsor/Mentor: **Lois Jovanovic**
- 1:35 - 1:55 **Kathryn Whitehead**, Student
Oral delivery of macromolecules using intestinal patches
- 2:00 - 3:00 Q&A, Poster Review, End of Program

**Fellow
Presentation
Abstracts**

Study of protein interaction with DNA and membranes in micro-array format using a novel label-free, real-time optical imaging microscope

Primary Sponsor: **Xiangdong Zhu**
Co-sponsor: **Monique Cosman, LLNL**
Mentor: **Jeff Gregg**
Fellow: **James Landry**
UC Campus: **Davis**

We propose to study protein-DNA and protein-membrane interactions in microarray format using label-free optical scanning microscopy developed by Prof. Zhu and James Landry (the nominee). In this method, we detect changes in molecular density and conformation of macromolecules as a result of their binding to surface-immobilized target DNA or membranes by following corresponding observable changes in the microscope such as in thickness, refractive index, and optical extinction coefficient. The microscope is coupled with flow cells that (a) contain DNA microarrays or membrane immobilized on glass or mica, and (b) enable optical access and introduction of fluids for reaction. Through a set of experimental studies of (1) protein-DNA interactions in DNA repair and replication, and (2) protein-membrane interactions in protein binding on functionalized lipid bilayers, we expect to train an exceptional physics graduate student, Mr. James Landry, into a truly interdisciplinary scientist whose expertise will abridge those of two, by tradition, vastly separated disciplines with respective backgrounds and scientific approaches. Through this UC-GREAT program, Mr. Landry will combine the expertise in surface chemistry and optical physics from Prof. Zhu's group and the know-how in microarray fabrication from Prof. Gregg's group with molecular biochemistry techniques from Dr. Cosman's group. Specifically, he will (1) learn to synthesize unmodified and modified DNA oligomers, and to overexpress and purify proteins in Dr. Cosman's laboratory; (2) fabricate microarrays of immobilized DNA oligomers in Prof. Gregg's laboratory; and (3) obtain and analyze the label-free, in-situ optical measurements of protein binding reactions with DNA microarrays and lipid bilayers in Prof. Zhu's laboratory. He will also aid Prof. Zhu in building a new high scan speed optical microscope for versatile, real-time imaging. In addition he will attend biophysics and biochemistry conferences and seminars regularly to communicate his research and interact with others in the field. This process will empower him to pursue a productive career in the cross fields of life science and physical science.

A microfabricated genetic analyzer for rapid forensic studies and human identification

Co-sponsor: **George F Sensabaugh**
Primary Sponsor: **Richard A. Mathies**
Fellow: **Stephanie Yeung, Hang Ieng**
UC Campus: **Berkeley**

DNA fingerprint analysis represents one of the most common tests performed by crime laboratories. With the increasing backlog of casework DNA samples in virtually all states and internationally, the need for higher speed, higher throughput, more reliable, more sensitive and less laborious methods for genetic and forensic studies are immediate. Polymerase chain reaction (PCR)-based short tandem repeat (STR) assays using capillary electrophoresis (CE) is the method of choice for genetic fingerprinting owing to the highly discriminating DNA profiles generated among individuals. However, this method is slow, cumbersome and costly using the current technology. To address these problems, a microfabricated capillary array electrophoresis (μ CAE)-based device with integrated nanoliter-scale thermal cycling and sample processing is proposed for STR analysis. The integrated μ CAE device can be applied to rapid genetic and forensic analysis of multiple samples in a highly parallel fashion and also can be adapted for a small portable device for point-of-care medical diagnostics and mass disaster forensic investigation. There will be two stages in the project: 1) the establishment of the optimal PCR and separation conditions for multiplex STR amplification and electrophoretic analysis using energy-transfer (ET) cassettes to label STR primers for simple fluorescence-dye labeling process and 2) the design and integration of PCR amplification and sample processing into a μ CAE device. The expertise in microfabrication and microfluidics in Professor Mathies laboratory together with the in-depth knowledge of genetics and forensics in Professor Sensabaugh's research group provide a powerful platform for performing this project. This effort will also be aided by collaboration with the Virginia Division of Forensic Science (VDFS) and Palm Beach Sheriff Office (PBSO) for device and assay validation. These two goals will require the knowledge, expertise and collaboration in the fields of genetics, biochemistry, microfluidics, microfabrication and engineering. Independent research activities will be conducted with regular discussion of research progress with my faculty sponsor, Professor Mathies and presentation to his entire research group. Co-sponsor Professor Sensabaugh will provide guidance in genetics and forensics. Forensic scientists from VDFS and PBSO will critically evaluate the technologies. The results of this project will be actively disseminated through relevant publications and conferences concerning the development of analytical chemistry, genetic analysis devices and methods and microanalytical devices. In addition, work of this project regarding the evaluation of forensic typing will be published in forensic journals such as Journal of Forensic Science and through presentation at the Promega Conference. This unique project requires a truly cross-disciplinary experience in biotechnology and advances the current limits of forensic science and human identification to the next level.

Parallel Manipulation of Single Cells Using Optoelectronic Tweezers

Primary Sponsor: **Ming Wu**
Co-sponsor: **Edward McCabe**
Fellow: **Pei Chiou**
UC Campus: **Los Angeles**

Single cell analysis plays an important role in the study of cell metabolism and protein expression. The ability to manipulate single cells is highly sought after in the biomedical and biological communities. The nominated student, Pei Yu Eric Chiou, has recently invented a revolutionary tool for single cell manipulation. This new tool, called optoelectronic tweezers (OET), enables trapping, moving, and sorting of cells at single cell level using a very low power optical beam (~ 1000 times lower than that of conventional optical tweezers). In this project, we propose to develop a programmable OET for parallel manipulation of single cells. Cell sorting, screening, separation, and parallel addressing of single cells will be accomplished by programming a digital light projector similar to that used for PC presentation. This will greatly increase the throughput of single cell analysis. There are three specific Aims for the proposed research. In Aim 1, we will develop an automatic cell manipulator by integrating OET with computer vision and programmable OET with Digital Micromirror Device (DMD) spatial light modulator. After successful development of the OET tool, we will focus on two biomedical applications. Aim 2 will focus on the implementation of micro-Fluorescence Activated Cell Sorter (FACS) using parallel OET cell cage array. Aim 3 will explore the use of OET array for organizing cells in an array to study the radiation effect (gamma rays and UV light) on cells. This project will be jointly supervised by Dr. Ming Wu, Professor of Electrical Engineering at UCLA and a Fellow of IEEE, and Dr. Edward McCabe, Professor and Executive Chair of Pediatrics at UCLA and Physician-in-Chief in Mattel's Children's Hospital. Professor James Liao of Chemical Engineering and Professor Bruce Dunn of Materials Science and Engineering, UCLA, will also serve as mentors for Mr. Chiao. Their recommendation letters are attached in the Appendix. The proposed project will provide cross-disciplinary training in physics, chemistry, engineering, and biology for the nominated graduate student.

Dielectric Labeling and Dielectrophoretic Manipulation of Cells

Primary Sponsor: **Hyongsok (Tom) Soh**
Mentor: **Daniel Morse**
Fellow: **Karen Jiangrong Qian**
UC Campus: **Santa Barbara**

The capability to amplify through polymerase chain reaction (PCR) technology has caused a revolution in biotechnology. It has provided the means to detect genetic mutations and pathogenic organisms. In this work, we propose to address an equally fundamental need—the capability to sort, that is, to separate and isolate particular molecules, viruses, bacteria and other cells, from a large background of complex mixtures, at very high throughput, purity and efficiency. This technology is the prerequisite to many promising applications in biological, pharmaceutical and medical fields that span from stem cell research to cell based therapies. As a part of this training program, we propose to combine a novel technique of molecular and cellular labeling with Microelectromechanical Systems (MEMS) technology to create a disposable, massively parallel, rare-cell sorting system. The separation mechanism will be based on dielectrophoresis (DEP) using inhomogeneous AC electrical fields. The technical goals of the training program are two fold; Firstly, we will demonstrate the principle of specifically labeling cells with dielectric particles with a pre-engineered dielectrophoretic response. This way, we may have complete control over the separation forces acting on the specifically labeled cells so that we may obtain an effective means to separate the labeled and unlabeled cells in inhomogeneous AC electrical fields. We will first simulate the electro- hydrodynamic fields inside the separation chamber to understand design principles and optimize the hydrodynamic-dielectrophoretic forces. We will consider such factors as shear stress on the cells and other factors that may affect cell viability. Secondly, using the dielectric labeling paradigm above, we will combine massive parallelism and multistaged design to create an integrated microfluidic devices that is capable of sorting the labeled and unlabeled cells with a dramatic performance improvement over current sorting technologies in the most significant aspects - throughput, purity and cell recovery. The ultimate goal for this research is to develop advanced tools to sort very rare cells for the purposes of diagnosis, treatment and fundamental understanding of cancers. The nature of this work is truly multi-disciplinary, and provides an uncommon opportunity to bring together many facets of engineering with life sciences; we will be engaged in problems that involve live cells, their surface markers as well as their manipulation through electric field driven mechanical motions in fluids. Almost all underlying infrastructure is in place and we have brought together expertise and collaborations to make this project successful. We believe this is an ideal training ground for the fellowship candidate.

MicroRNA Binding Sites in the Human Genome: Targets for Gene Regulation and Therapeutics

Primary Sponsor: **Alan Frankel**
Co-sponsor: **Hao Li**
Fellow: **Alexander Pastuszak**
UC Campus: **San Francisco**

Micro RNAs (miRNAs) are 21-23nt single stranded RNAs that are processed from 60-80nt stem-loop precursors. These small regulatory sequences pepper the genome and have been shown, in some cases, to regulate gene expression by inhibiting translation of mRNAs to which they are partially complementary. More than 250 miRNAs have been identified in numerous species ranging from *C. elegans* to humans and recent computational approaches have predicted many putative miRNA targets, the vast majority of which require experimental validation. Despite the significant advances in target identification, further advances are still required. Since miRNAs can regulate genes that are in control of fundamental life processes such as development, fat metabolism, stress, apoptosis, and hematopoiesis, the genomic target sites of these small regulatory RNAs are of great interest. We propose to complement the current methods using a combination of experimental and computational methods to identify genomic miRNA target sites with high sensitivity and specificity. The experimental approach utilizes an immunoprecipitation strategy to selectively enrich for target mRNAs, followed by microarray identification. The computational approach will enable us to define groups of genes that are targets of specific miRNAs, define the requirements for target sites for each miRNA, and potentially find sequence motifs involved in miRNA-mediated gene regulation. Finally, we will also examine the relationship between a miRNA's complementarity to its target mRNAs and the number of target sites per miRNA per target gene to assess how miRNAs affect gene suppression, providing new insights into the organization of gene regulatory networks.

Chemical Proteomics: Mapping protein kinase signaling pathways through chemospecific purification of direct protein kinase substrates

Primary Sponsor: **Kevan Shokat**
Co-sponsor: **David Morgan**
Fellow: **Justin Blethrow**
UC Campus: **San Francisco**

Kinase-mediated protein phosphorylation is a key regulator of nearly every cellular signaling pathway. Thus, the ability to map phosphorylation pathways is critical to understanding cell biology. Historically this process has been slow, and has of necessity relied largely on the performance of pair-wise examinations of interactions between individual kinases and candidate substrates. Given the very large number of protein kinases, and the fact that many likely have numerous substrates, methods to accelerate this process are badly needed. We have previously reported the development of a method for kinase-specific labeling of substrates using ATP analogs that are poor substrates for wild-type kinases, but which are efficiently used by engineered kinases bearing an altered ATP binding site. This method has been used to identify novel substrates of several widely divergent kinases; however identification still relies on laborious conventional purification methods subsequent to labeling. Herein we describe the development of a method for the simultaneous purification of entire sets of kinase specific substrate proteins. An ATP analog specific for engineered kinases and bearing a terminal thiophosphate group is used to specifically thiophosphorylate the substrates of a kinase of interest in a cell extract. The extract proteins are selectively protected at cysteine residues and then passed over an iodoacetyl-functionalized resin, covalently trapping the thiophosphorylated substrates in the solid phase. After washing, the substrates are released by specific cleavage of the thiophosphate linkage yielding a pool of purified substrates, which may then be analyzed by mass spectrometry. The proposed course of research will provide a broadly interdisciplinary training environment for the nominated fellow. Completion of this project will involve the application of methods in synthetic chemistry, biochemistry and molecular biology, cell biology, bioinformatics, and mass spectrometry.

Detection of functional elements in the human genome using comparative genomics and evolutionary models

Primary Sponsor: **David Haussler**
Co-sponsor: **Manuel Ares**
Fellow: **Adam Siepel**
UC Campus: **Santa Cruz**

We propose a research and training project to develop new statistical and computational methods for the detection of functional elements in the human genome. These methods will be based on the analysis of multiple, aligned mammalian genomes using phylogenetic hidden Markov models (phylo-HMMs), which describe molecular evolution as a stochastic process in the dimensions of both space (changes from one position in a genome to the next) and time (changes to the nucleotide at each position over evolutionary time). Besides being useful in the detection of functional elements, these models will be helpful in furthering our understanding of mammalian evolution. Newly developed methods will be applied to the complete human genome and the aligned genomes of other mammals, and results will be made available to researchers in the public and private sectors via the UCSC Genome Browser, which has become an important resource for genomics researchers around the world. Wet-laboratory experiments will be undertaken to validate a subset of novel, predicted elements. The proposed project will form the bulk of the nominated fellow's Ph.D. dissertation, and is highly complementary to other projects of the faculty sponsors. In addition, the project has potential to reveal novel functional elements and produce new analytical methods that can directly benefit the biotechnology industry and, ultimately, the economy of the State of California.

Quantum Dots as Nano-Scale Probes of Dendritic Cell Trafficking and Antigen Presentation in Vivo

Primary Sponsor: **Michael Cahalan**
Co-sponsor: **Ian Parker**
Fellow: **Debashish Sen**
UC Campus: **Irvine**

This proposal seeks support for a talented graduate student, Debasish Sen, to pursue thesis research on quantum dots as a unique platform of flexible probe design to modulate the immune response. Quantum dots are crystalline spheres of 3 to 6 nanometer diameter that exhibit very bright, photostable fluorescence with tunable narrow bandwidth emission characteristics. Containing a CdSe core, Qdot" particles are coated with a mixed hydrophobic/hydrophilic polymer, making them suitable for work with living cells, and can be conjugated with streptavidin, forming the basis for specific biological labeling. Preliminary studies carried out by the fellowship candidate have demonstrated that quantum dots are taken up avidly by dendritic cells and can be imaged through the endocytic pathway. We will use two-photon microscopy to investigate the dynamics of quantum-dot labeled dendritic cells as they traffic through the body and present antigen to lymphocytes inside the lymph node. The collaborative nature of this project, involving an immunologist and a neurobiologist at UCI, both with strong biophysical training and inclination, will provide expertise to carry out an ambitious series of experiments. Collaboration with Mark Ellisman's group at UCSD will provide complementary expertise in electron microscopy. With both in vitro and in vivo experimentation, the project will provide excellent training in immunology, multi-photon imaging microscopy and quantitative analysis, and probe design with single-particle detection. Laboratory research will be supplemented by coursework in cell biology, immunology, and microscopy. The candidate will attend seminars in the home department and in the monthly Immunology seminar series. He will also participate in the active journal clubs in the home department and in the Center for Immunology. This graduate training experience will provide excellent preparation for continued research in immunology with emphasis on applying discoveries in biophysics and biotechnology to biomedical problems that hold therapeutic promise.

Amplification of Tumor Targeting by Remote Heating of Nanoparticles

Primary Sponsor: **Sangeeta Bhatia**
Co-sponsor: **Erkki Ruoslahti**
Mentor: **Michael Sailor**
Fellow: **Austin Derfus**
UC Campus: **San Diego**

Targeted drug delivery to treat diseases is advantageous to reduce both drug dosage and collateral damage to other tissues. When applied to cancer therapy, the targeted delivery of cytotoxic agents to tumor vasculature has shown a therapeutic benefit¹. To increase the quantity of therapeutic agent delivered to the disease site, we propose to amplify the targeting signal, with a scheme similar to the aggregation of platelets at a clot. Our goal is to deliver nanoparticle conjugates to the extracellular matrix of tumors, and then locally heat the targeted area by inductively coupling RF energy to the magnetic nanoparticle core. We propose that this local heating will denature collagen proteins, exposing cryptic binding sites and recruiting additional particles from the bloodstream. The technology we plan to develop constitutes the design of multifunctional nanoparticles that can diagnose and treat disease in a minimally invasive manner. Our ultimate goal is to design these particles to recognize the target, bind to that site, exponentially accumulate, and then release their therapeutic payload. The merging of sponsors' expertise in nanomaterials design, tumor biology and surface chemistry with the fellow's background in electrical engineering and nanoparticle bioconjugation will facilitate the development of this novel treatment modality. Drs. Bhatia, Ruoslahti, and Sailor have a record of collaboration, including co-mentoring of students, co-authoring high impact publications²⁻⁵, and receiving shared funding. Austin Derfus, the nominated fellow, will benefit from monthly meetings with the three scientists and will be trained in the skill sets held by each of their laboratories. In addition to training the fellow for a scientific career, technology developed from this research has the potential to improve clinical medicine and generate revenue for the California economy.

Nucleoprotein and nanoparticle-based molecular electronics

Primary Sponsor: **Norbert Reich**
Co-sponsor: **Andrew Cleland**
Fellow: **August Estabrook**
UC Campus: **Santa Barbara**

The designated recipient for this GREAT award is August Estabrook, a Ph.D. candidate in Chemistry and Biochemistry at UCSB. Mr. Estabrook is a second year student, has finished his coursework and exams and thus advanced to candidacy, and is engaged in carrying out independent research involving the research groups of Professors Norbert Reich (Chemistry/Biochemistry) and Andrew Cleland (Physics). The proposed project brings together molecular biology, biochemistry, nanoparticle synthesis, nanoscale electrode construction, and single molecule electronics. Mr. Estabrook's part in this effort is largely focused on the first Aim involving the design, construction, and incorporation of various nucleic acids and proteins into nano-scale constructs that will be the foundation of single molecule electrical devices. He is also developing new approaches to attach nanoparticles to nucleic acids and modify nanoparticles for improved electronic characteristics. The second Aim proposes to use the engineered nucleic acid and protein assemblies in conjunction with various nanoparticle attachment strategies to probe simple molecular electronic configurations. Mr. Estabrook works closely with students in Physics in both the fabrication and testing of these simple circuits. The extremely interdisciplinary nature of the overall project demands that Mr. Estabrook continue to foster intellectual connections with his coworkers engaged in the electronic device construction and conductance measurements. Mr. Estabrook will continue to present his results via several venues, including our weekly meetings involving all members in both groups engaged in the bioelectronic effort (undergraduates Eran Levy and Tara Holstein, graduate students Gary Braun, Stephanie Wilkinson, David Wood and Professor Andrew Cleland), monthly participation in our Biomolecular Materials Seminar series for post docs and graduate students in all departments at UCSB, our weekly Literature in Biomolecular Materials series, and relevant conferences (e.g., the Veeco/UCSB conference to which Mr. Estabrook was invited to speak at in 2003). Mr. Estabrook is obtaining training as a research mentor in his supervisory role involving undergraduates engaged on projects directly related to his own research. Thus, Tara Holstein has worked under Mr. Estabrook's direct supervision for the last 12 months in constructing various DNA cruciforms; she is graduating June 2004. Eran Levy (UCSB electrical engineering major, UC LEADS participant), will start working with Mr. Estabrook this Spring quarter.

Oral Delivery of Macromolecules Using Intestinal Patches: Applications for Insulin Delivery

Primary Sponsor: **Samir Mitragotri**
Co-sponsor: **Lois Jovanovic**
Fellow: **Kathryn Whitehead**
UC Campus: **Santa Barbara**

Oral drug delivery, although attractive compared to injections, has been difficult to utilize for the administration of peptides and proteins due to poor epithelial permeability and proteolytic degradation within the gastrointestinal tract. We plan to develop a novel method for the oral delivery of peptides and proteins. In this study, we will utilize mucoadhesive intestinal patches to deliver therapeutic doses of insulin into systemic circulation. Our preliminary results indicate that the patches adhere securely to the intestine and that insulin patches with doses in the range of 1-10 U/kg induce dose-dependent hypoglycemia. The objective of the proposed studies is to understand the mechanisms of oral insulin delivery using intestinal patches and develop the technology so that it can be tested in diabetic volunteers. With the proposed research, intestinal patches could not only offer a novel methodology for the oral delivery of insulin, but for various other macromolecules, including growth hormones, heparin, and vaccines, as well. A significant emphasis will also be placed on the training activities of the nominee in engineering and life science. The nominee will gain proficiency in her laboratory skills in the Mitragotri Laboratory and affiliated facilities at UCSB, including the Materials Research Laboratory, California Nanosystems Institute, and Institute of Collaborative Biotechnologies. Moreover, she will gain clinical experience through her work with Dr. Lois Jovanovic, director and chief scientific officer of the Sansum Medical Research Institute. The nominee will also enhance her skills through supplementary coursework. Already proficient in the areas of chemical engineering, she will obtain further education in human biology in the context of the field of drug delivery. This will be achieved by taking courses on human immunology and pharmacology in the Department of Molecular, Cellular, and Developmental Biology at UCSB. The nominee will enhance her professional skills in oral and written presentation as well as in the supervision of undergraduate students.

Company Affiliates

Agilent

Mel Kronick, Chief Scientific Officer

Agilent has over 30-years of experience in delivering enabling, time-saving analytical tools to Pharmaceutical and Biotech firms. We're bringing this experience to bear on the Gene Expression application area. Based on customers' growing needs in Gene Expression Analysis, we've developed a robust, modular set of solutions to improve overall lab and research productivity.

Printed Microarray Solutions

In the era of 'systems biology,' life science researchers need a variety of integrated tools and platforms to address major questions. Agilent Technologies is providing to customers in this market a spectrum of products based on its strengths in microfluidics, microarrays, bioreagents, chromatography, mass spectrometry, and informatics. These offerings leverage our key technological strengths to create solutions for basic research and drug discovery. Because our products must be intimately tied to cutting edge developments, strong and properly structured relationships with flagship institutions such as those in the University of California system are necessary to enable Agilent to incorporate effectively the latest scientific insights into our product planning.

Epitomics

Guo-Liang Yu, CEO

Monoclonal Antibodies (MAbs): The Most Important Class of Molecules in Biotherapeutics and Research Discovery

Antibodies belong to a group of defense proteins called immunoglobulins and are made up of distinct structural and functional domains. These are Y shaped molecules comprising two identical heavy chains and two identical light chains.

MAbs are antibodies derived from a single B cell. Such antibodies recognize one and only one molecule called an antigen. There are different methods to produce monoclonal antibodies as research reagents or as therapeutics. The traditional hybridoma technology described by Köhler and Milstein in the mid-1970s involved fusing an isolated B cell (extracted from the spleen of an immunized mouse) with a murine myeloma cell (bone marrow tumor cell), which led to the scientists' 1984 Nobel Prize in medicine. The fused cells, called hybridomas, are capable of producing indefinite quantities of MAbs. This discovery facilitated a major breakthrough in biology and medicine because it made it possible to specifically define, purify, and analyze proteins. Over the last ten years, it has become clear that MAbs are not only outstanding research and diagnostic tools, but also excellent drug candidates.

Rabbit MAbs (RabMAbs): A new generation of monoclonal antibodies for target discovery, diagnostics and therapeutics. In 1995, Dr. Katherine Knight at Loyola University of Chicago succeeded in producing a myeloma-like tumor (plasmacytoma) in transgenic rabbits. In the following years, Dr. Robert Pytela and Mr. Weimin Zhu at UCSF improved the technology such that they were able to produce RabMAbs in a high throughput manner. Epitomics, Inc. has since exclusively licensed the technology and developed enabling platforms to use RabMAbs in the areas of research target discovery, diagnostics and therapeutics.

The availability of RabMAbs provides many advantages. First, antisera from rabbits generally contain higher-affinity antibodies, and recognize a greater variety of epitopes than antisera generated from mice. Second, RabMAbs are expected to recognize many antigens that are not immunogenic in mice. Third, because of the size of the rabbit spleen, more fusion experiments can be performed, making it a feasible task to screen hybridoma at large scale.

RabMAbs as Therapeutics: The market for therapeutic MAbs is forecasted to reach \$6.4B by 2004. It is anticipated that hundreds of therapeutic antibodies will be developed for the treatment of many diseases in the next decade. Despite of decades of knowledge on the potential of rabbit antibodies as high quality reagents, it has been a challenge to develop rabbit antibody repertoire MAb therapeutics. The arrival of RabMAb hybridoma and Epitomics' other proprietary technologies offer a new

opportunity to unleash the power of this new class of MAbs, and to search for novel humanized MAbs for unmet medical needs.

RabMAbs as Diagnostic Products: It has been known for years that rabbit immune systems offer the best antibody reagents for diagnostic purposes. Many small compounds and peptides only elicit good immune response in rabbits. For this reason, rabbit polyclonal antibody (a crude antibody product consisting of mixture of antibodies in the serum) has been used in many diagnostic kits, ranging from drug screening to clinical diagnosis. Epitomics' rabbit MAb technology has the potential to improve a vast number of current diagnostic products, by replacing polyclonal antibody or low affinity mouse MAb products with high quality RabMAbs.

RabMAbs as powerful tools for drug discovery: Complete sequencing of the human genome has significantly impacted the drug discovery process. The paradigm for new medicine has shifted from traditional disease-target selection to a systematic search for disease targets using genomics information. Proteins, however, are much closer to the cause of diseases than their DNA or RNA counterparts. MAbs are the most powerful tools available for detecting proteins specifically and sensitively. In addition, MAbs can specifically antagonize or enhance a protein's function, which makes them powerful tools for functional proteomics.

Epitomics' technologies will generate MAbs for a large number of gene products directly from DNA, peptides and proteins, screen for functional blocking MAbs, and validate therapeutic antibody leads. Over the years, Epitomics, Inc. will create a MAb bank for large number of human proteins. Such a reagent bank will accelerate the development of novel products in therapeutics, diagnostics and medical devices such as antibody chips.

Affymetrix

Alan Williams

GeneChip® arrays enable scientists to attain ambitious goals from identifying genetic variations associated with disease to discovering new drug targets.

Leveraging technologies adapted from the semiconductor industry, the manufacture of GeneChip arrays uses photolithography and solid-phase chemistry to produce arrays containing hundreds of thousands of oligonucleotide probes packed at extremely high densities. The probes are designed to maximize sensitivity, specificity, and reproducibility, allowing consistent discrimination between specific and background signals, and between closely related target sequences.

Attesting to their powerful capabilities, GeneChip arrays are applied in a wide variety of DNA and mRNA analyses. Recent analytical accomplishments include the elucidation of interactions between signaling pathways involved in development, the discovery of a new class of leukemia, and the development of new assays to track drug metabolism.

Berlex

Gordon Parry, Chief Scientist, Cancer Research

In the U.S., Berlex's singular approach to developing and making specialized medicines already has yielded innovations in treating multiple sclerosis, dermatological disorders, female health concerns, cancer and in the creation of new diagnostic imaging techniques. For the future, the pipeline of new products and the potential for developing better treatments will help make medicine work for those who need it most in the years ahead.

Berlex's research mission is to be a world leader in innovative drug discovery and development with centers of excellence in cardiovascular, cancer and immuno-based diseases by combining the best of biotechnology and pharmaceutical technologies.

Berlex has in its research pipeline candidate products in areas such as bone marrow transplants, cancer, leukemia, cardiac arrhythmia, heparin-induced thrombocytopenia (HIT), hormone therapy, MRI contrast agents, multiple sclerosis (ms), osteoporosis, rosacea and x-ray contrast agents.

Current research is focused on developing new therapies for Alzheimer's disease, Parkinson's disease and cerebral vascular accidents. The acquisition of Collateral Therapeutics by Berlex in 2002 provides an opportunity to explore the frontiers of cardiovascular research and biotechnology with one of the most advanced gene therapy projects anywhere in the pharmaceutical industry. Out of that research has come human angiogenic growth factor, now in Phase IIb/III trials. This gene therapy product is being studied for delivery directly to the heart muscle to help stimulate new cell growth, offering a potentially breakthrough treatment option for ischemic heart disease and other cardiovascular disorders. Betaseron ®(interferon beta-1b) is currently being investigated in a number of clinical studies (BEYOND, INCOMIN, BENEFIT) trials for a variety of potential indications (including use in early MS) at higher doses.

In the area of oncology, Berlex's parent is seeking breakthroughs through its research of anti-angiogenesis, where scientists are seeking to influence the mechanism through which tumors activate the regeneration of blood vessels.

Fludara ®(fludarabine phosphate), currently approved for second line IV treatment of chronic lymphocytic leukemia (CLL), is being investigated for first line therapy, as well as for use in stem cell transplants. HPV Vaccine - In early discovery is a vaccine for HPV, human papilloma virus, which causes cervical cancer in women. Leukine ® (sargramostim), a white-blood cell boosting adjunct therapy for leukemia and lymphoma patients is currently being studied in Phase II trials for Crohn's disease.

Quantum Dot Corporation

Charles Hotz, Director, Research and Development

Founded in 1998, Quantum Dot Corporation (QDC) develops and markets novel solutions for biomolecular detection. QDC's products and services employ quantum dot (Qdot®) particles, tiny semiconductor crystals that emit light brightly in a range of sharp colors. These nanometer-sized Qdot particles have unique, highly desirable properties that make them a superior detection platform for biology. QDC has invested many years in perfecting the methods for synthesis of high quality, high brightness quantum dots for biology.

QDC has raised over \$37.5M in financing from preeminent venture groups including Versant Ventures, Abingworth Management, Technogen Associates, Schroder Ventures, Frazier & Co, MPM Asset Management, and CMEA Ventures. With additional funding from corporate partnerships and major government grants, and with product revenue ramping up, QDC is well financed to aggressively build revenues toward profitability.

QDC currently sells its research products directly, and through distributors, to customers in research laboratories throughout the world. QDC is also seeking applications development and marketing partners to accelerate the market acceptance of the Qdot technology and to leverage existing sales channels.

With enabling applications in life science research, in vitro diagnostic testing, and in vivo imaging, Qdot nanocrystals are set to revolutionize biomolecular detection.

Anosys

Sanjay Patel, Senior Development Scientist

Anosys develops innovative therapeutic vaccines for the treatment of cancer and infectious diseases.

Anosys healthcare products are based on the utilization of Exosomes, a cutting edge immune therapy approach. Exosomes are small vesicles derived from immune cells that contain all the necessary components to trigger the the two major immune responses required to fight diseases:

The adaptive response with T Cells activation

The innate response with NK Cells activation

Anosys has conducted Phase I clinical trials of Dexosomes in the United States and in Europe for two different forms of cancer (Melanoma and Non Small Cell Lung Cancer (NSCLC)). Based on the very promising results of these Phases I trials, Anosys is initiating a Phase II clinical trial for NSCLC for which it has received FDA approval.

While advancing this breakthrough treatment towards regulatory approval, the company is also engaged in the pre-clinical development of recombinant vaccines using its proprietary Exosome Display Technology that enables the targeting of antigens and adjuvants to Exosomes. This second generation vaccine would present the advantage of triggering immune responses via the exosome route of antigen delivery and presentation without requiring the preparation of patient-specific vaccine.

Anosys is also engaged in developing other applications of the Exosome Display Technology including a novel approach to generating monoclonal antibodies against difficult targets.

Full Moon Biosystems

Youxiang Wang, CEO

Full Moon Biosystems are committed to delivering the highest quality microarray slides to their customers. Their new glass substrates provide a superior solution for increasing signal intensity and eliminating variables caused by arrays produced on poor quality substrates.

Full Moon Biosystems' new microarray slide has been developed using proprietary technology in chemistry. A thin layer of chemically engineered material is uniformly and consistently coated on the glass surface, which ensures results with the highest reproducibility and quality. The coating materials consist of chemical polymers with multi-functional reactive groups as each functional group takes on a particular role in immobilising biomolecules. The slides are ideal for attaching a variety of biomolecules, including cDNA, modified or unmodified oligonucleotides and proteins.

Alnis BioSciences, Inc.

Steve Barry, CEO

Alnis BioSciences, Inc. is a biopharmaceutical company that is developing therapeutics from its nanoparticle technology platform. Based in Emeryville, CA, Alnis' current efforts are focused on oncology and infectious diseases.

Shortly after its founding in 1997, Alnis was awarded a three year DARPA grant to develop a pathogen countermeasure technology. This grant allowed the company to gain considerable skill in the formulation and fabrication of polymeric nanoparticles.

Alnis is now applying its nanoparticle expertise to creating a platform from which many therapeutics can be rapidly and reliably advanced to commercialization. Alnis is developing drugs which will exhibit several outstanding attributes, including optimized pharmacokinetics and strong, specific binding to intended targets.

In addition to drug discovery, Alnis is also investigating targeted delivery of bioactive entities using its nanoparticle materials. Alnis' nanoparticles are constructed through the engineering of proprietary polymeric materials that are biodegradable, nontoxic, and nonimmunogenic.

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Participants

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