Bioengineering and Engineering Health Care

at the

National Science Foundation

Advances in Breast Cancer Research

University of Arkansas | 27 October 2010

Theresa Good, Program Director - tgood @ nsf.gov

Biotechnology, Biochemical and Biomass Engineering | Division of Chemical, Bioengineering, Environmental, & Transport Systems (CBET)

Directorate for Engineering

National Science Foundation

NSF Mission

To promote the progress of science; to advance the national health, prosperity, and welfare; and to secure the national defense

Where does cancer research fit into the NSF mission?

NSF Organizations

- Biological Sciences (BIO)
- Computer and Information Sciences and Engineering (CISE)
- Education and Human Resources (HER)
- Engineering (ENG)
- Geosciences (GEO)
- Mathematical and Physical Sciences (MPS)
- Social, Behavioral and Economic Sciences (SBE)
- Polar Programs
- Office of Cyber Infrastructure
- Office of International Science and Engineering
- Office of Integrative Affairs

NSF Research and Related Activities

Active Awards Related To Cancer

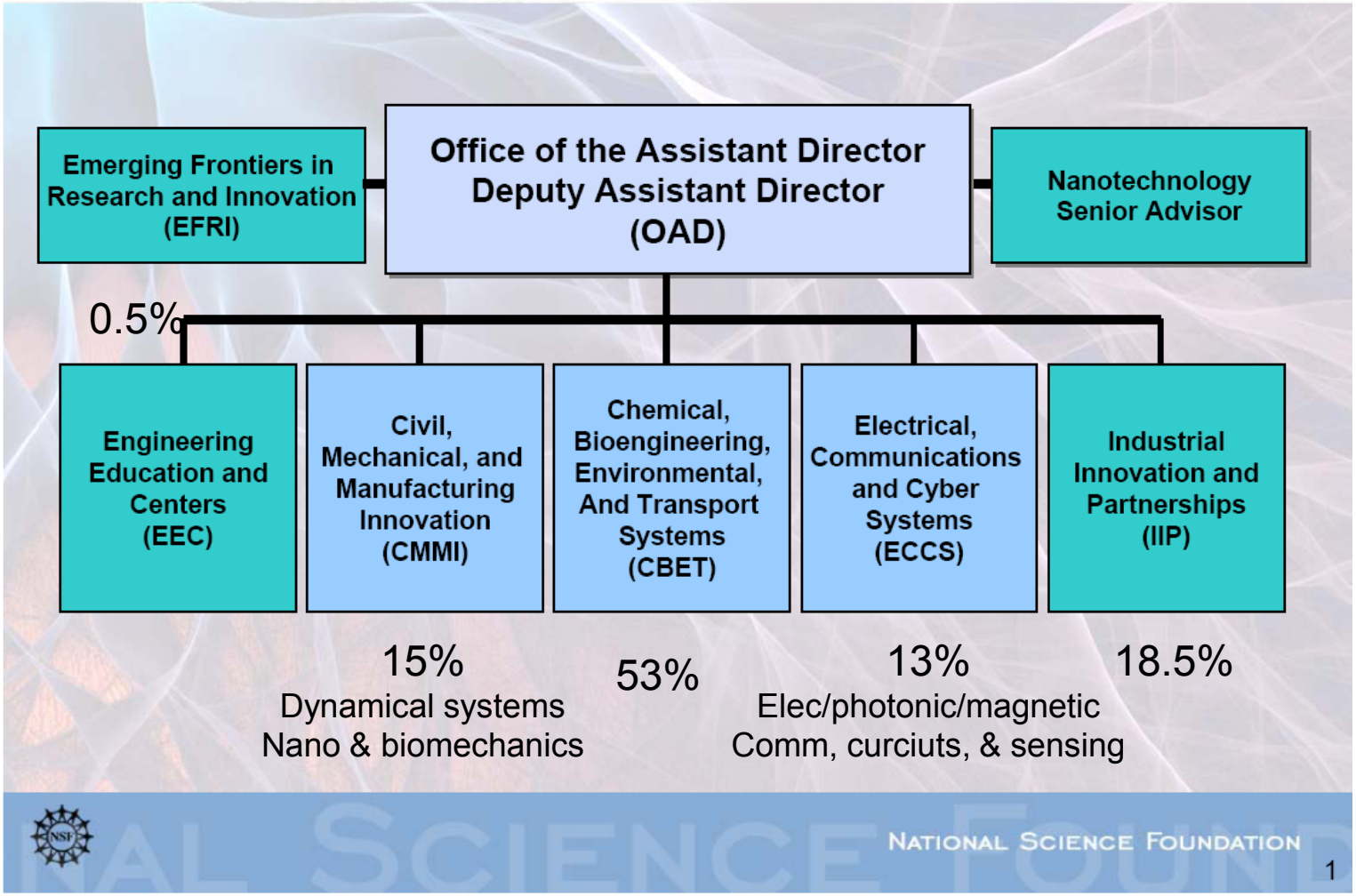
	FY 2009	Cancer Proposals	Percent of Total
Biological Sciences	$655.81	66	13.1%
Computer and Information Science and Engineering	573.74	68	13.5%
Engineering (includes SBIR/STTR)	**693.34**	**188**	37.3%
Geosciences	807.13	0	0.0%
Mathematical and Physical Sciences	1,255.96	167	33.1%
Social, Behavioral, and Economic Sciences	240.3	0	0.0%
Office of Cyberinfrastructure	199.28	10	2.0%
Office of International Science and Engineering	44.03	5	1.0%
U.S. Polar Research Programs	470.67	0	0.0%
Integrative Activities	241.34	0	0.0%
Arctic Research Commission	1.5	0	0.0%
Total, R&RA	**$5,183.10**	**504**	100.0%

~$50M/year or 1% of total

Dollars in millions. Totals may not add due to rounding.

Directorate for Engineering

FY 2007

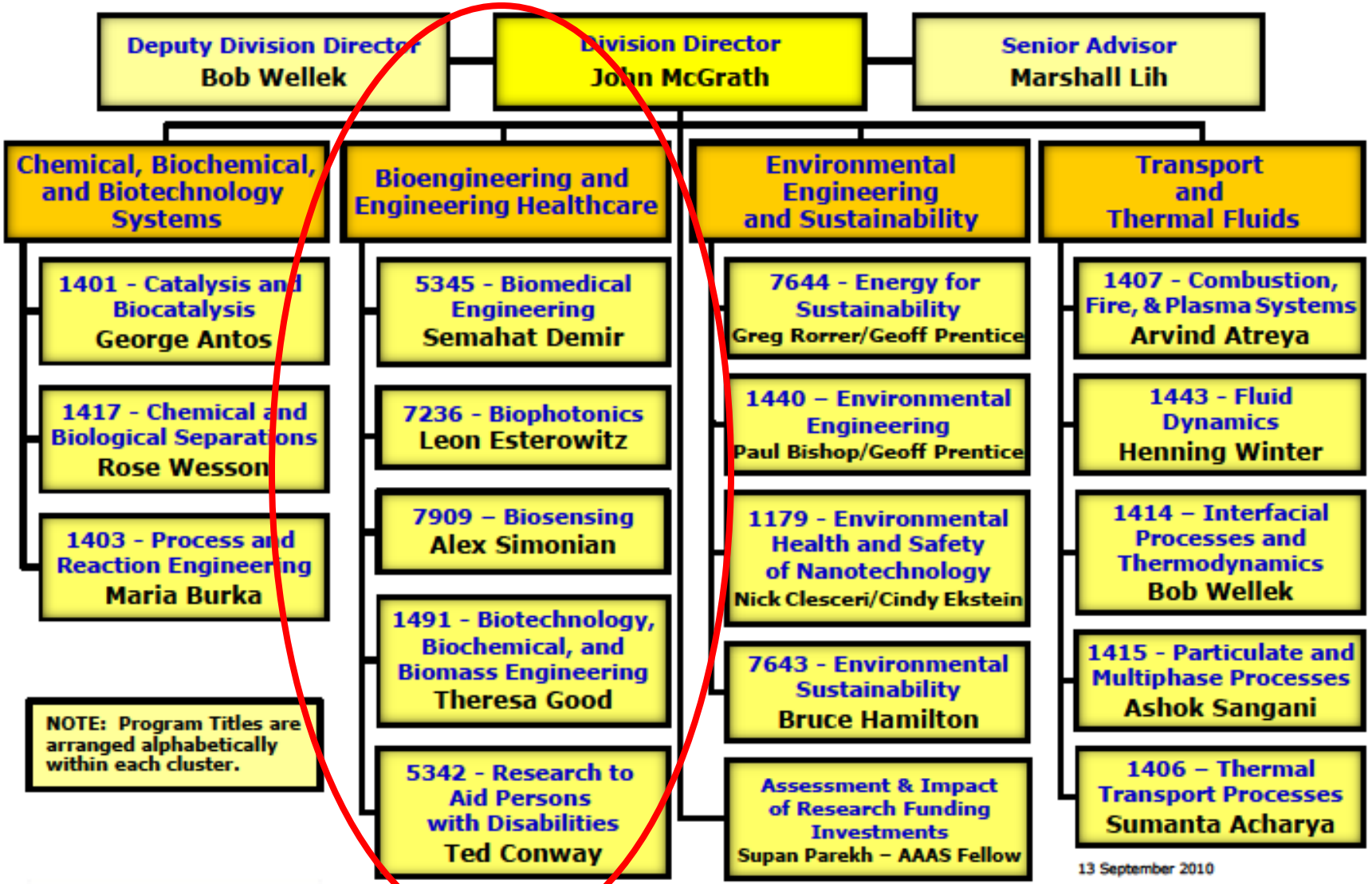


~ 3% of ENG, 8%+ of CBET budget spent on cancer research

Funding Rates in Engineering FY2009

National Science Foundation | Directorate for Engineering

Chemical, Bioengineering, Environmental, and Transport Systems Division (CBET)



Funding Statistics FY 2010

	BME	Bio-photonics	Bio-sensing	BBBE	RAPD
Proposals Received	**410**	**170**	**285**	**250**	**158**
Annual Budget (M)	**$10.8**	**$6.6**	**$5.6**	**$8.3**	**$4.6**
Unsolicited	**12**	**12**	**12**	**11**	**16**
CAREER	**10/70**	**6/40**	**2/30**	**6/42**	**3/17**
EAGER	**0**	**4**	**1**	**1**	**2**
Workshops/Conf	**18**	**0**	**4**	**2**	**2**
Supplements	**23**	**4**	**1**	**17**	**10**

NSF Directorate for Engineering | Division of
Chemical, Bioengineering, Environmental, and Transport Systems (CBET)
Bioengineering and Engineering Healthcare Cluster

Biomedical Engineering

Program Director - Semahat Demir, Ph.D. - sdemir@nsf.gov

Mission:

- to provide opportunities to develop novel ideas into discovery-level and transformative projects that integrate engineering and life science principles in solving biomedical problems that serve humanity in the long-term

- to advance both engineering and life sciences with biomedical engineering projects that are at the interface of engineering and biomedical sciences.

Currently, BME Supports Projects in the Following Theme Areas:

- **Neural engineering**
  - Brain science
  - Computational neuroscience
  - Brain-computer interface
  - Neurotech
  - Cognitive engineering
- **Cellular biomechanics**
  - Motion, deformation, and forces in biological systems
  - How mechanical forces alter cell growth, differentiation, movement, signal transduction, transport, cell adhesion, cell cytoskeleton dynamics, cell-cell and cell-ECM interactions
  - Genetically engineered stem cell differentiation with long-term impact in tissue repair and regenerative medicine

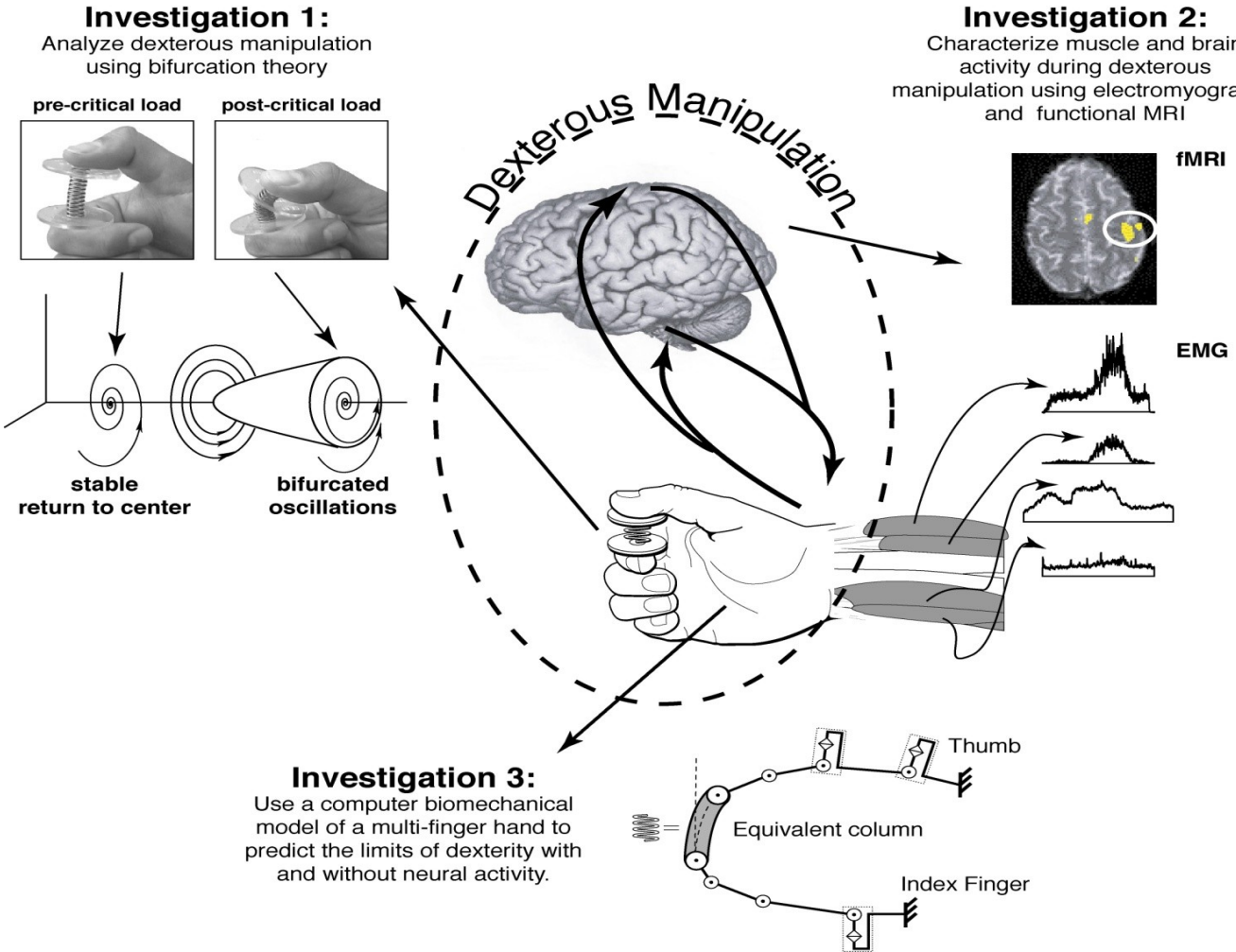
Interagency Programs in which BME Currently Participates

- **Collaborative Research in Computational Neuroscience (NSF/NIH)**
- **Transforming Biomedicine at the Interface of the Life and Physical Sciences (R01) Program Announcement (PA) Number: PAR-10-141 (NIH/NSF)**
- **New Biomedical Frontiers at the Interface of the Life and Physical Sciences (R01) Program Announcement (PA) Number: PAR-10-142 (NIH/NSF)**

Neuromuscular Biomechanics

CAREER PI: Francisco Valero-Cuevas Cornell University

Analysis of dexterous manipulation; characterization of muscle and brain activity; and computational modeling of dexterity



ITR: High-Resolution Cortical Imaging of Brain Electrical Activity

Bin He University of Minnesota

Aim: Develop and evaluate functional neuroimaging techniques integrating functional MRI and EEG source imaging.

Results: fMRI and EEG during visual stimulation were acquired simultaneously and integrated together.

(a) outside of MRI scanner;

(b) inside MRI scanner without fMRI;

(c) simultaneous fMRI-EEG recordings.

Multimodal neuroimaging shows enhanced spatial resolution compared to source imaging using EEG alone.

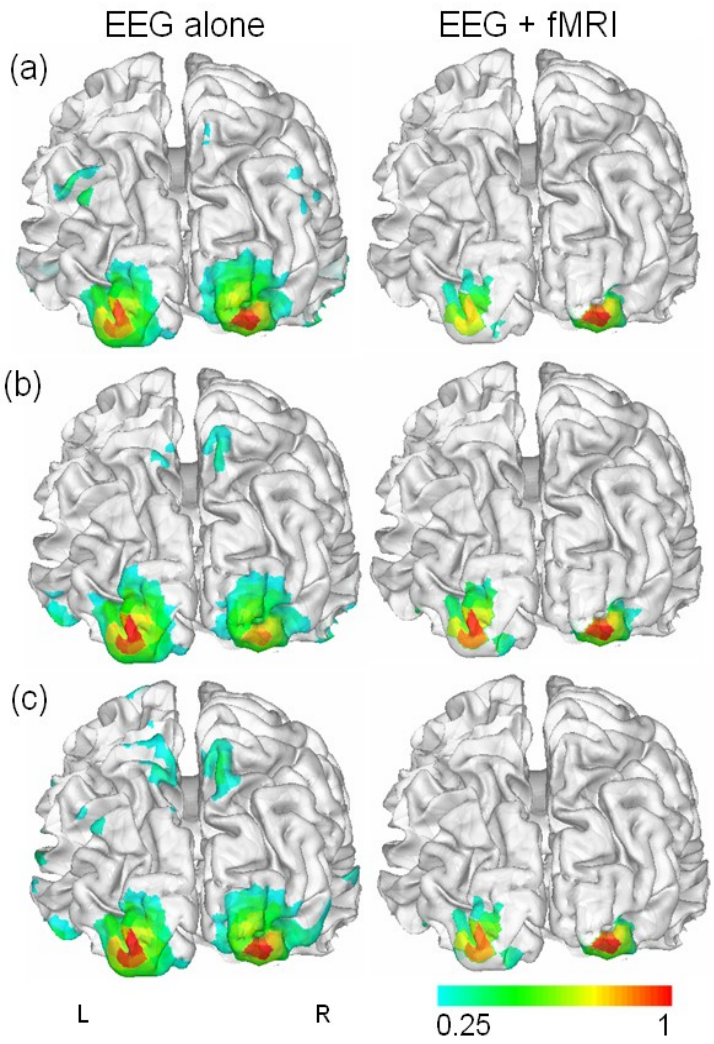
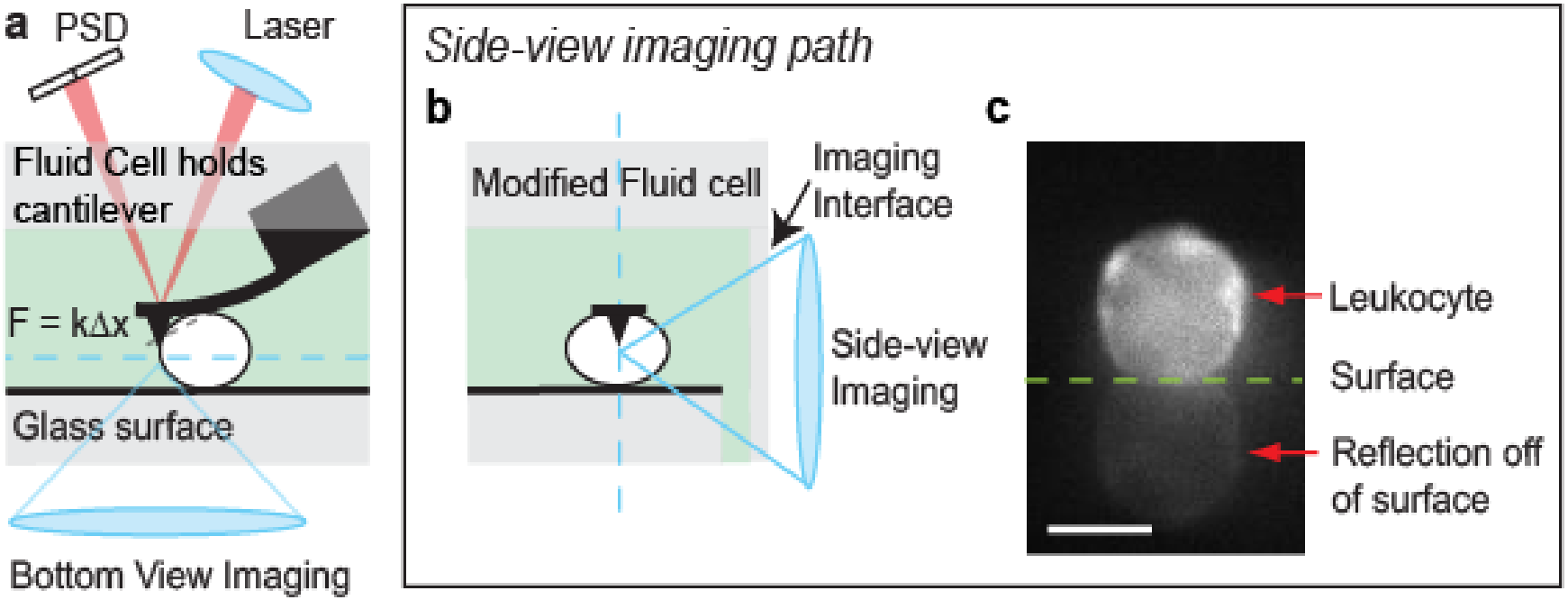


Image from Im et al., J. Neurosci. Meth, 157(1): 118-123, 2006.

NSF BES-0411898

CAREER: Biomechanics of Polymerization Motors and Cell Motility

Daniel A Fletcher University of California-Berkeley

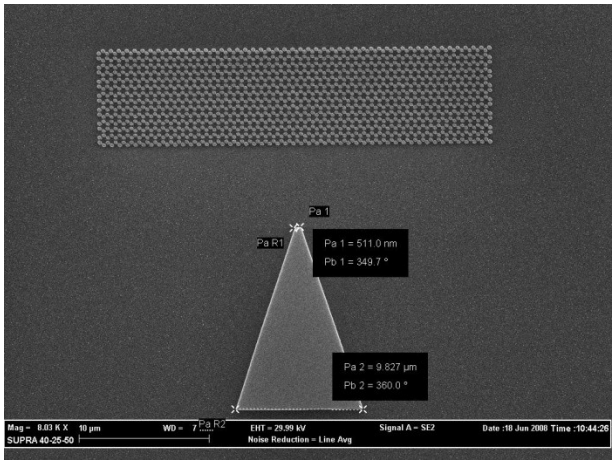


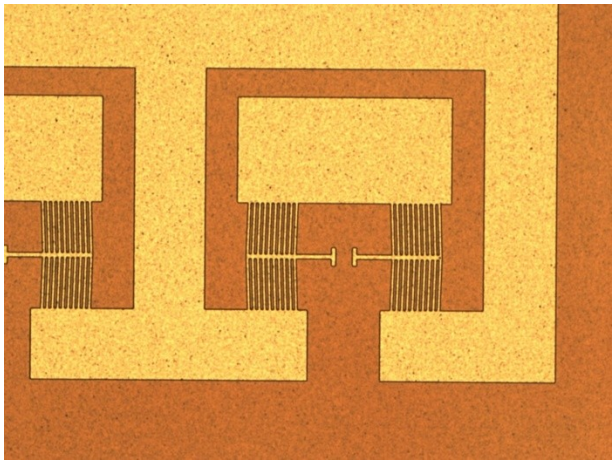
The cytoskeleton of cells changes dynamically in response to mechanical forces. In order to study reorganization of the actin cytoskeleton in the direction of an applied force, the Research Team developed a "side view" Atomic Force Microscope.

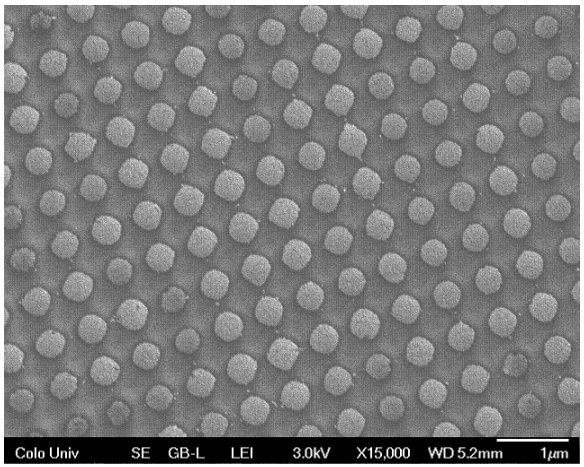
CBET-0348758

NIRT: Active Nanostructure Enabled On-Chip Spectroscopy System for Cancer Detection

Won Park University of Colorado







Ultimate goal: On-chip spectroscopy system for cancer detection

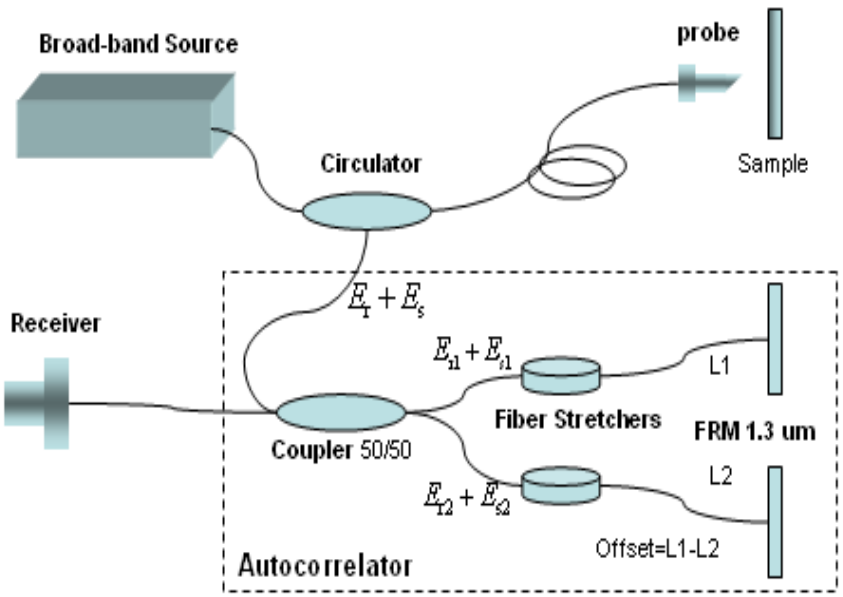
(1) ***Tunable nanostructure for focusing and frequency selection:*** **Fabricated tunable photonic crystal structure for focusing and spectroscopy (Fig. 1). Also fabricated mechanical actuators (Fig. 2) for mechanical tuning. Currently working on optimizing mechanical flexibility for stable operation.**

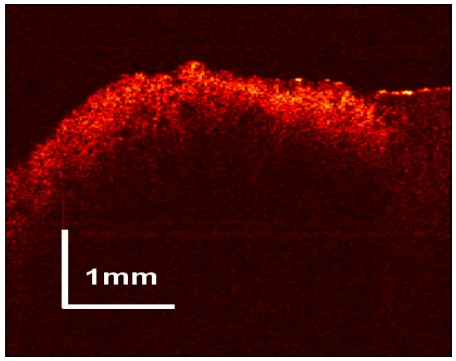
(2) ***New nanostructure design based on nanoclusters*****: Demonstrated high-quality periodic array of nanoclusters by template-directed self-assembly (Fig. 3). The new design provides strong magnetic response at optical frequencies.**

(3) ***Nanoprobes for biomarker detection*****: Demonstrated synthesis of nanoprobes and DNA conjugation, Demonstrated detection of point mutation both in solution and in cells, Achieved enhanced sensitivity by scattering measurements.**

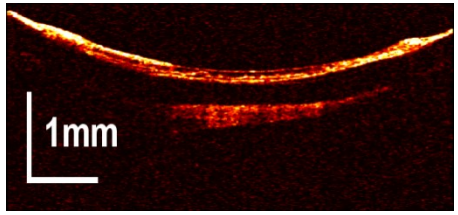
NSF/FDA SIR: Fiber-Optic Common-Path Endoscopic Optical Coherence Tomography for Non-Invasive Optical Biopsy

Jin U. Kang Johns Hopkins University





Rat Brain Tumor



Frog Retina

Aim: The aim of this work is to investigate a novel method of achieving ultrahigh-resolution, high speed, *in-vivo* cancer imaging based on common-path endoscopic optical coherence tomography (CP-OCT)

Result: The Kang Research Team has fully investigated, experimentally and theoretically, the signal-to-noise issues with both time domain CP-OCT and Fourier-domain CP-OCT. Based on that the Team has optimized the CP-OCT and obtained in-vivo images of rat brain tumors, retina and other tissues.

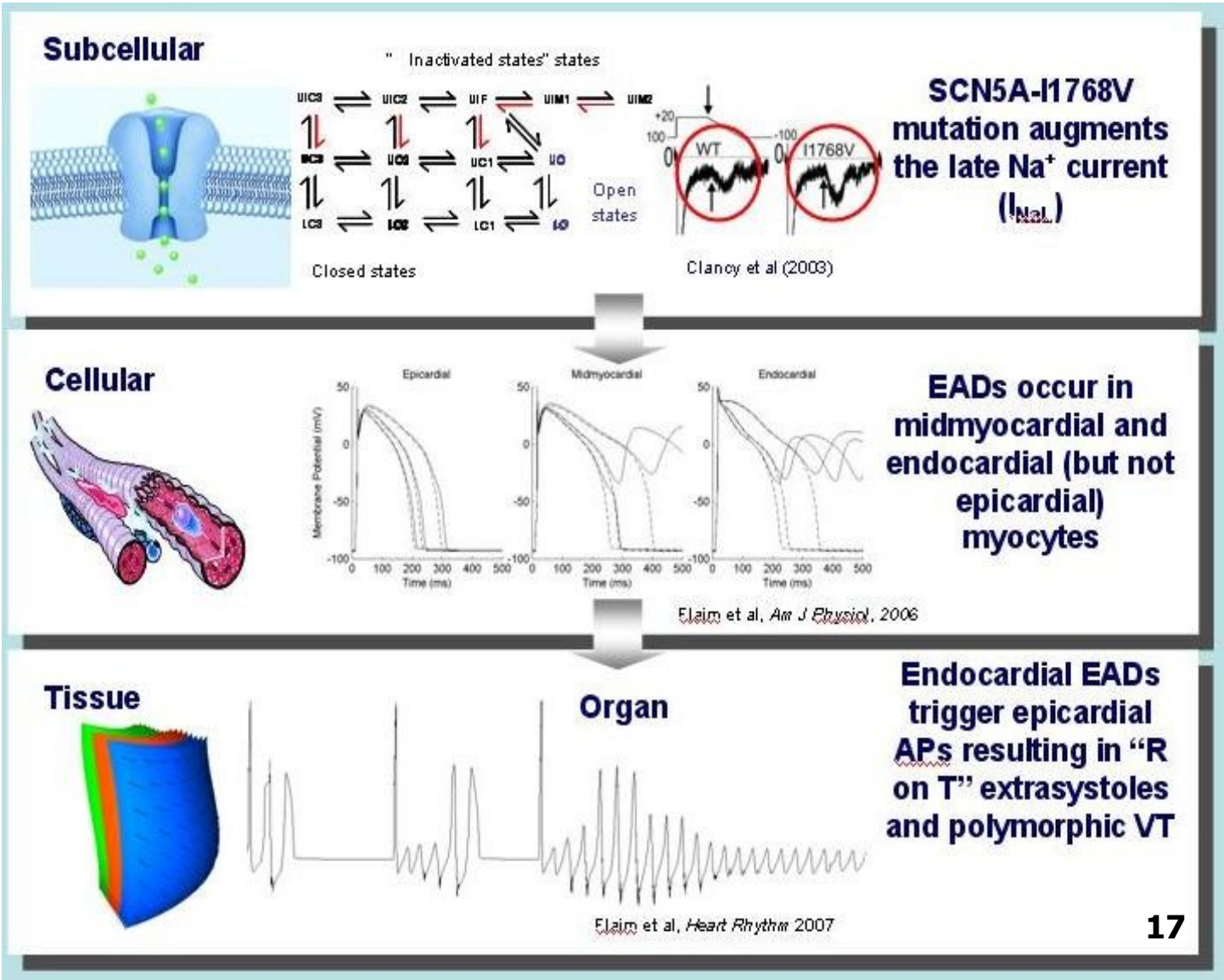
CBET-0716515

Multi-Scale Modeling of the Heart: From Genotype to Phenotype

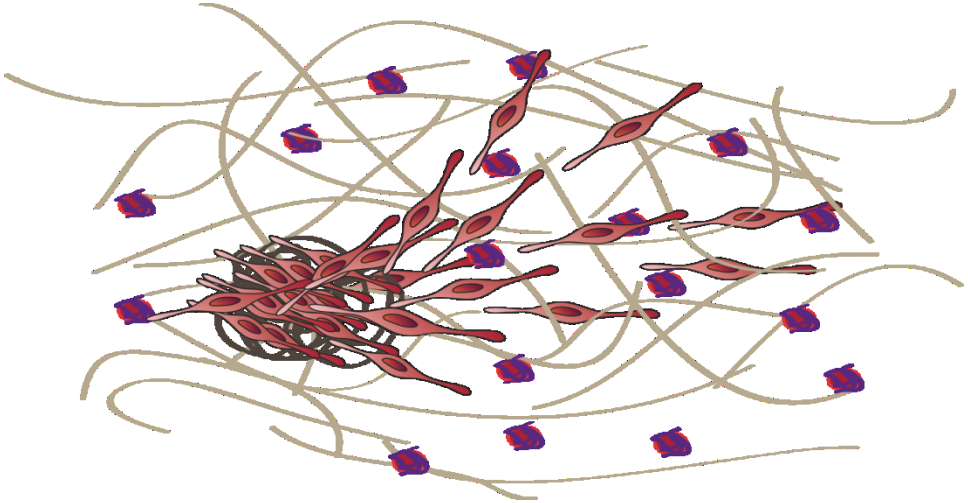
Andrew D. McCulloch University of California San Diego

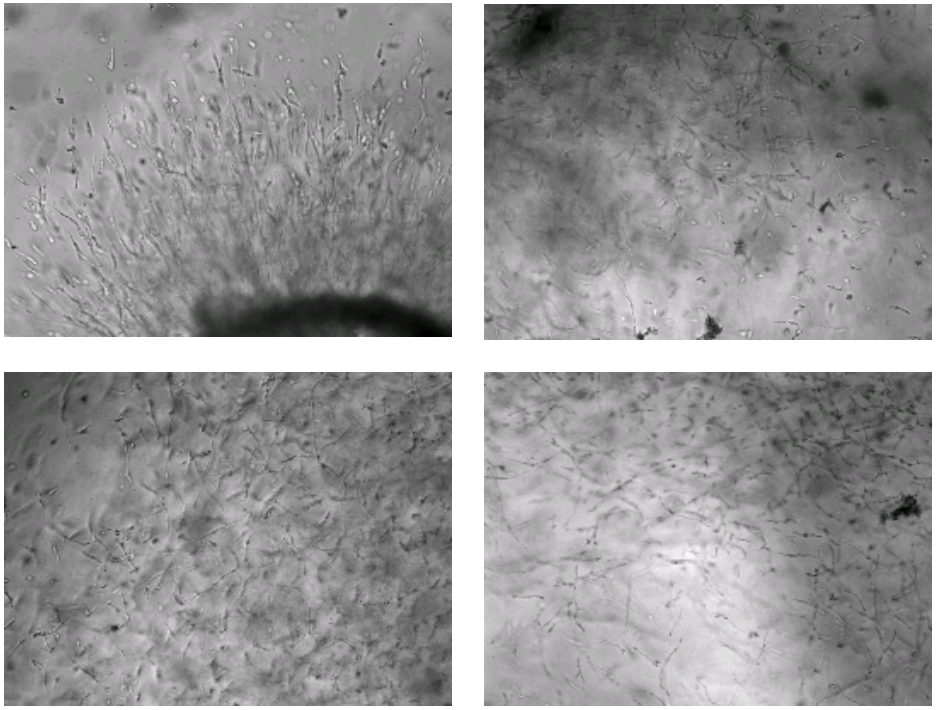
New multi-scale models of cardiac electromechanical interactions, that integrate from molecular to organ system scales, have provided new mechanistic insights into the molecular mechanisms of inherited arrhythmias (in this case LQT3).

BES-0506252



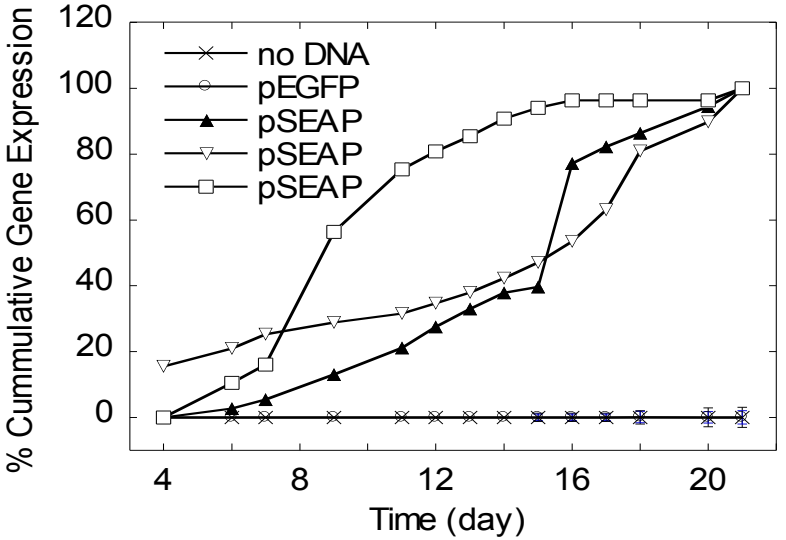
CAREER: Hydrogels for Matrix-Tethered Gene Delivery





Tatiana Segura
University of California Los Angeles

The Segura Research Team is interested in the design and synthesis of hydrogel materials that can deliver DNA to infiltrating cells. The aim of these results was to synthesize an enzymatically degradable hydrogel scaffold that contained DNA nanoparticles that could transfect cells. The Research Team found that cells seeded in this scaffold were able to infiltrate the scaffold, internalize DNA nanoparticles and express the transgene for the 21-days of incubation.



NSF Directorate for Engineering | Division of
Chemical, Bioengineering, Environmental, and Transport Systems (CBET)
Biomedical Engineering and Engineering Healthcare Cluster

Biophotonics

Program Director - Leon Esterowitz - lesterow@nsf.gov

- Photonics is the technology of generating and harnessing light and other forms of radiant energy whose quantum unit is the photon
- Biophotonics applies photonics to the fields of medicine, biology and biotechnology

Examples of Biophotonic Topical Areas

- **CONTRAST AGENTS** - New classes of photonic probes and contrast agents to label structures and push the envelope of optical sensing to the limits of detection, resolution, and identification

- **MOLECULAR IMAGING** - Image and data fusion between optical imaging, spectroscopic techniques, and conventional imaging modalities for imaging diseases at the molecular and cellular level

Examples of Biophotonic Topical Areas

- **NEUROPHOTONICS** - Development and application of photonic tools such as large scale parallel interfaces and interconnects for study and control of neural systems

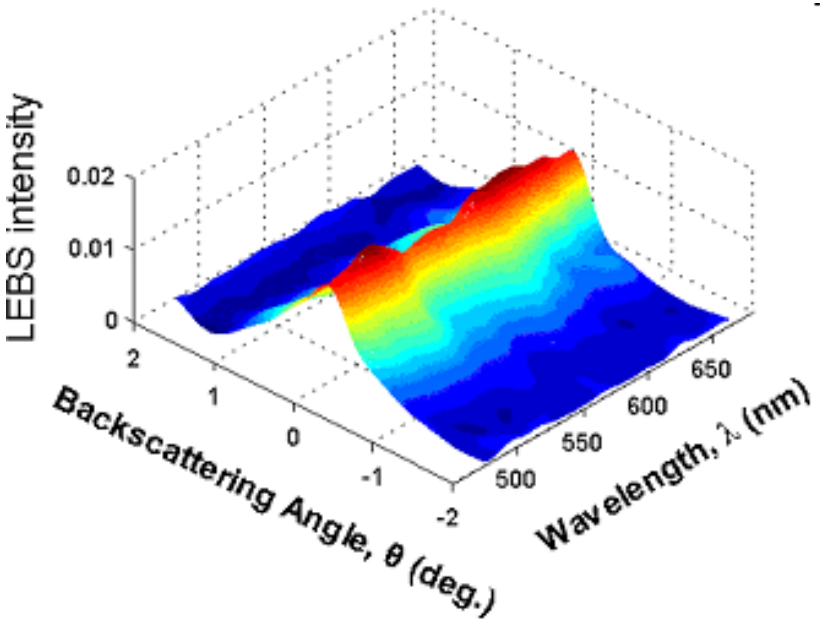
- **MICRO- and NANO-PHOTONICS** - Development and application of nanoparticle fluorescent quantum-dots; sensitive, multiplexed, high-throughput characterization of macromolecular properties of cells; nanomaterials and nanodevices for biomedicine

SGER: Advances in Biophotonics to Enable Pancreatic Cancer Screening

Vadim Backman - Northwestern University

Of all major types of cancer, pancreatic cancer is the most lethal. The disease carries a dismal five-year survival rate below 5%. The major reason is that no currently available techniques allow diagnosis of pancreatic cancer at a stage when a tumor is amenable to surgical resection.

Sponsored by NSF, this group invented and developed a novel optical technology, low-coherence enhanced backscattering (LEBS), which senses subtle changes in tissue nanoarchitecture otherwise undetectable by histopathology. LEBS can detect alterations in histologically normal-appearing cells due to the presence of precancer in a different part of an organ.



Low-coherence Enhanced Backscattering (LEBS) signal from duodenal mucosa. It is signals like this one that contain information about tissue nano/microarchitecture and whose alterations in otherwise histologically normal-appearing tissue are diagnostic for the presence of pancreatic cancer.

Credit: Vadim Backman & Young Kim, Northwestern University

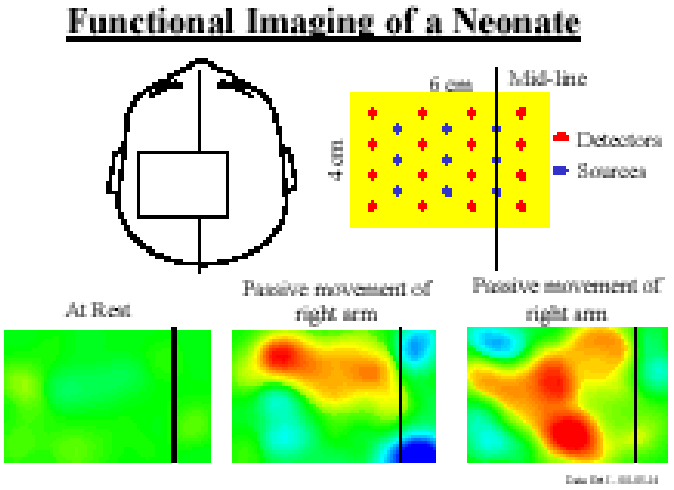
This group showed that LEBS-derived optical markers from normal-appearing periampullary duodenal mucosa can discriminate between pancreatic cancer patients and normal controls with 95% sensitivity and 91% specificity. Moreover, the diagnostic performance of these optical markers was not compromised by confounding factors such as tumor location and stage. Thus, these data provide the first evidence that optical analysis of histologically normal duodenal mucosa can predict the presence of pancreatic cancer without direct visualization of the pancreas.

Functional Imaging with Diffuse Optical Wavefields

Eric L. Miller - Northeastern University

Aims of Project:

- Develop reduced order non-linear inversion schemes that exploit MRI-based structural information
- Develop new methods for processing DOT data over time
- Develop fast forward model for DOT brain imaging



Diffuse optical tomography of brain function

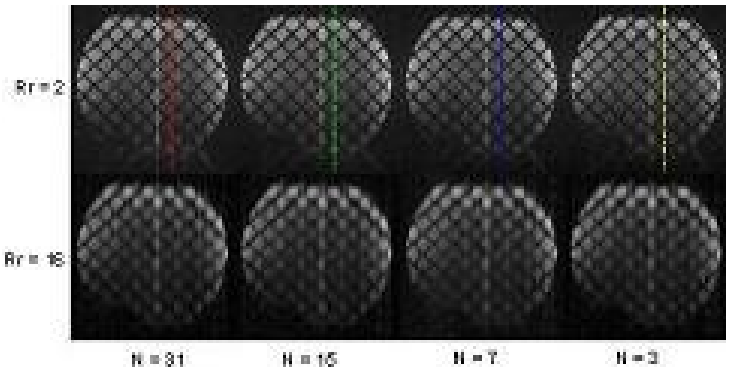
Passive movement of the right arm of a premature baby stimulated brain activation as indicated by increased blood flow causing an increase in blood volume and hemoglobin oxygen saturation.

MRI with massive arrays

Jim Ji - Texas A&M University

Magnetic Resonance Imaging (MRI) is a premier noninvasive imaging modality. One recent paradigm shift in MRI technology is to use large arrays of transmision/ receiving elements to acquire images. With arrays, magnetic resonance (MR) systems can transmit and/or receive radio-frequency (RF) signals simultaneously through multiple channels and improve performance over single-channel systems.

Dr. Jim Ji at Texas A&M University is actively developing next generation signal processing algorithms to realize the full potential of massive arrays for high-speed and high-field MRI. He is developing novel RF pulse design methods and image reconstruction algorithms to enable ultrafast imaging at a high-field strength (4.7 Tesla).



Credit: Jim Ji, Shuo Feng and Steven Wright; Texas A&M University

Phantom MRI images reconstructed from a 64-channel linear array system data with different acquisition acceleration factor (2 and 16) using the proposed method with increasing efficiency (from 31- to 15-, 7-, and 3-neighborhood). No obvious quality loss is observed. This can improve the large array image reconstruction speed by an order of magnitude.

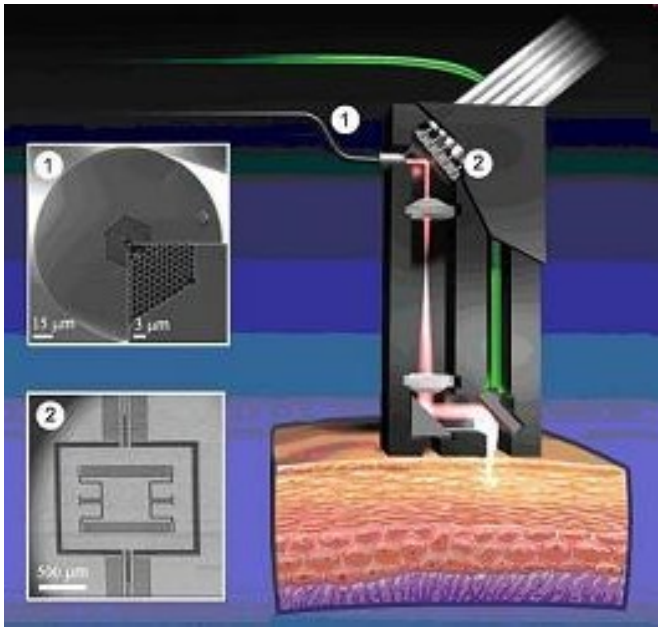
CBET - 0748180

An Ultrafast Micro-Scalpel with Vision

Adela Ben-Yakar - University of Texas at Austin

The Ben-Yakar group has developed a unique miniaturized probe that combines femtosecond-laser microsurgery (FLMS) with two-photon microscopy (TPM). The successful development of the probe has been achieved due to a novel optical design and photonics devices such as photonic crystal fibers and MEMS scanning mirrors.

Using this probe, the Ben-Yakar group has demonstrated three-dimensional (3D) imaging of live cancer cells in tissue phantoms, which are 3D cell cultures engineered to mimic the optical properties of natural biological tissue. In addition, selective ablation of individual cells was demonstrated with high precision.



An Ultrafast Micro-Scalpel with Vision. A three-dimensional rendering of the combined femtosecond laser microsurgery and two-photon imaging probe designed by the Ben-Yakar Group.

SEM micrographs (inset) of:
(1) the air-core photonic crystal fiber and
(2) the MEMS scanning mirror design are shown.

Credit: Adela Ben-Yakar, University of Texas at Austin

Such a device constitutes a novel all-optical seek-and-treat tool, capable of diagnostics as well as microsurgery with unrivaled precision. This combined FLMS/TPM device would be valuable in a variety of medical applications, from early cancer detection and removal, to dermatology.

CBET - 0846868

Large-Vertical-Displacement (LVD) Microactuator: MEMS-based Micromirrors and Microlenses for Biomedical Imaging

Huikai Xie - University of Florida

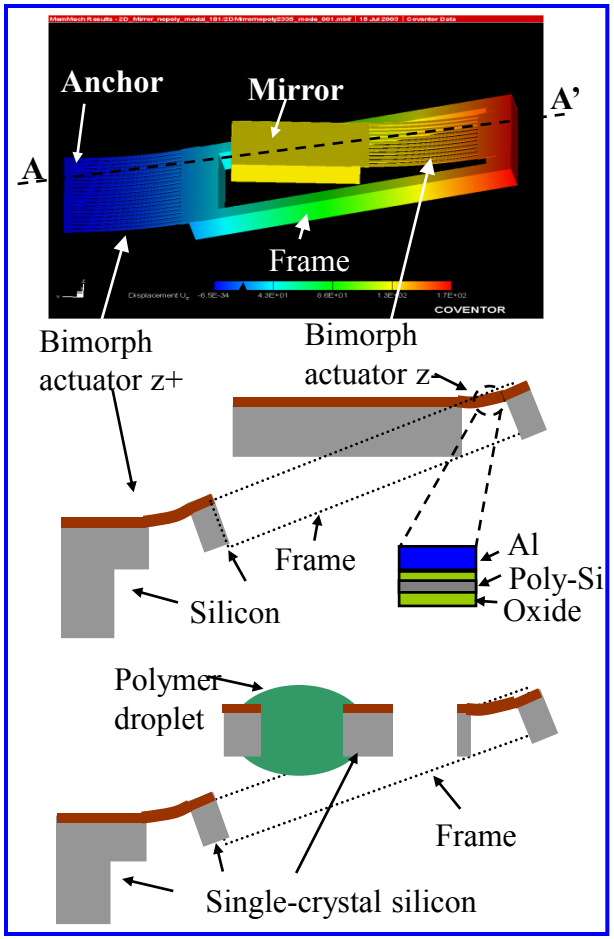
1. Motivation

- High mortality of cancers is due to lack of early detection modalities.
- Commonly used biopsy is risky and has low early detection rate.
- Optical coherence tomography (OCT) is a non-invasive high-resolution imaging technique, but conventional OCT is bulky and not suitable for *in vivo* internal organ imaging; and OCT has poor lateral resolution.

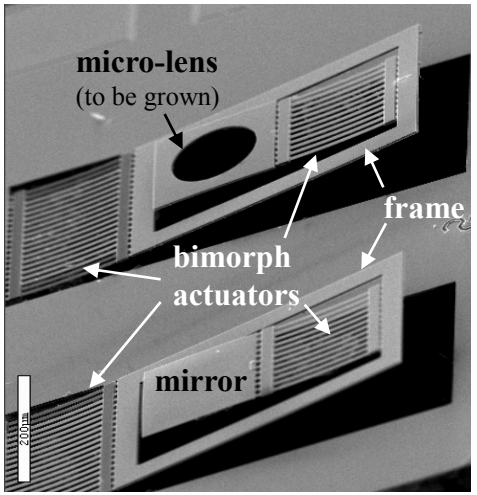
2. Objective

- Design MEMS actuators for large vertical displacement of micromirrors and microlenses, for phase-only scanning, and focusing, respectively
- The micromirror can be used for axial scanning in interferometry, while the tunable microlens can be used in confocal microscopy
- Develop MEMS-based confocal microscopes

3. Design Concept



4. Fabricated Devices



0.2mm vertical displacement at 6V DC, scan rate of ~ 2kHz

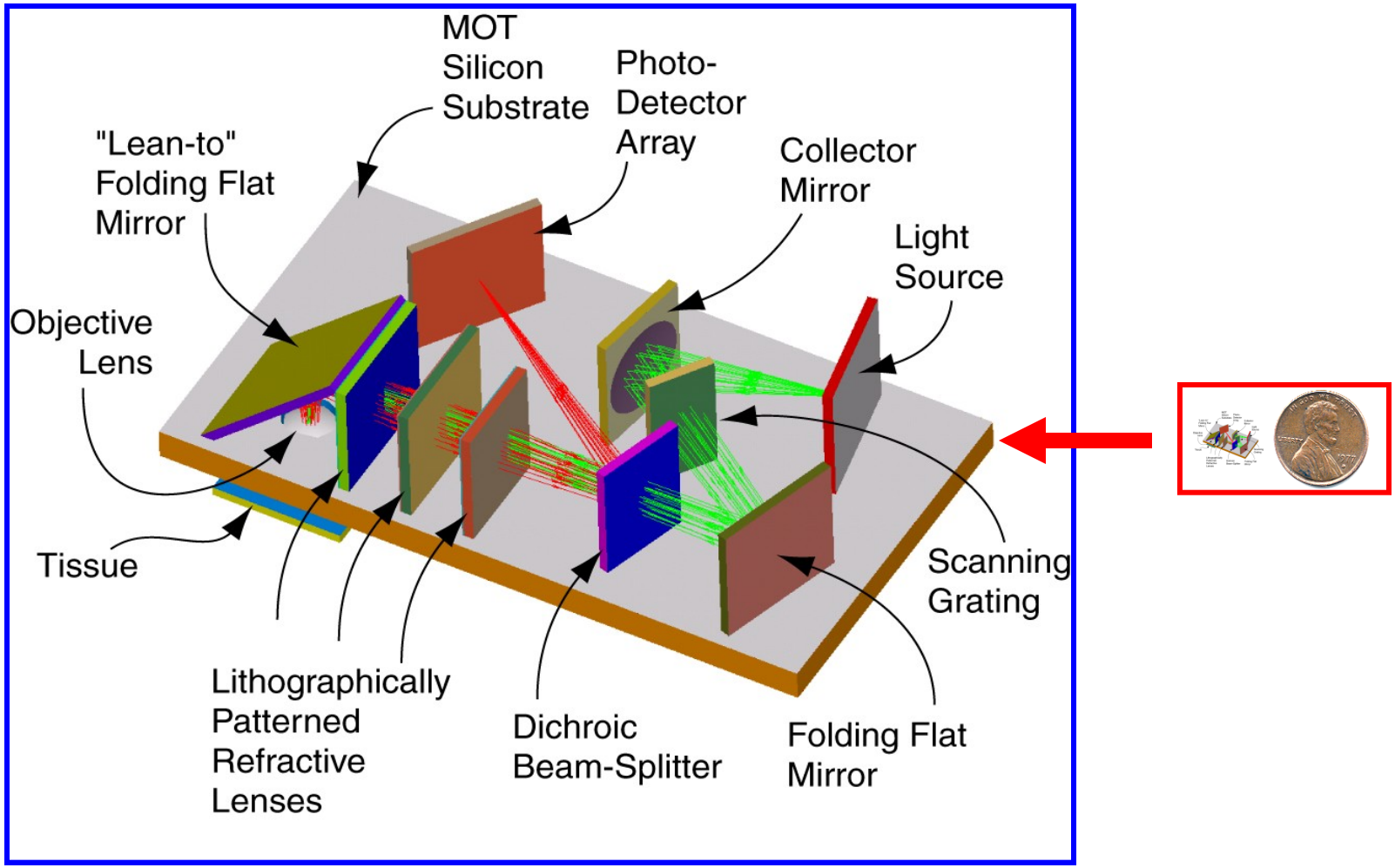
5. Research Plan

- Integrate microlens on a LVD device using polymer droplets
- Integrate capacitive vibration sensors for position control
- Develop MEMS-based confocal imaging probes for *in vivo* imaging of internal organs

The basic idea is to use an oppositely tilted bimorph beam to compensate the tilted mirror, and thus the mirror surface will move vertically when a current is applied to both bimorph actuators.

Multimodal Miniature Microscope for Early Cancer Detection

M. Descour - University of Arizona



NSF Directorate for Engineering | Division of
Chemical, Bioengineering, Environmental, and Transport Systems (CBET)

Bioengineering and Engineering Healthcare Cluster

Biosensing

Program Director - Alex Simonian - asimonia@nsf.gov

- **The term "biosensing" is used here to mean not devices but *systems* that produce verifiable signals for detecting biological occurrences through a variety of means, for a variety of purposes.**
- **Biosensing systems** can include electrical, electronic, photonic, or mechanical devices; biological materials such as tissue, enzymes, or nucleic acids; means to provide chemical analysis; and advanced imaging and information processing technologies.
- **Biosensors**, which are systems that employ biological mechanisms or materials to provide selectivity and amplification for sensing biochemical materials, often are components of biosensing systems.

Program Mission

- The Biosensing program primarily supports innovative fundamental and applied research that serves humanity in the long-term
- The program is targeting activities in the area of *monitoring or identification of biological phenomena* and will support potential technological breakthroughs that exist at the intersection of life science, engineering, nanotechnology and information technology

Biosensing Unsolicited Projects

- Should be fundamental, transformative, and discovery research
- Develop novel ideas integrating engineering and life science principles in solving biosensing problems
- Emphasize the advancement of fundamental engineering knowledge, possibly leading to the development of new methods and technologies
- Highlight multi-disciplinary nature, integrating engineering and the life sciences

Topical Examples

- Highly sensitive and discriminative biosensing
- Novel robust and easy to operate sensor systems with a highly selective response to multiple analytes under variable conditions, with significantly reduced false positives and false negative responses and increased sensitivity
- Innovative ideas in the development of novel biorecognition strategies
- Multifunctional nanomaterials with predefined physical, chemical or biological characteristics for biosensing applications

Topical Examples

- Fundamental understanding and study of bio-macromolecules confinement and orientation at the micro- and nano-interfaces for high-throughput biosensing applications
- New biorecognition strategies based on (but not limited to) artificial recognition elements and synthetic peptides
- Molecular sensors capable of monitoring biological structures interaction (protein-protein interactions, cell-to-cell talk, interkingdom signaling, etc.)
- New approaches that allow for highly selective and reversible recognition events (i.e. methods for triggering dissociation of analytes from antibodies) for extending continuous monitoring technologies

Topical Examples

- **Highly sensitive & discriminative biosensors** based on functionalized micro- and nano-structures (CNT, metal-oxide nanostructures, dendrimers and switchable polymers, etc.) and advanced material concepts (e.g., single molecule techniques)

- **Stimuli-responsive materials** in bioengineering and biosensing

Topical Examples

- **Development of novel bio-recognition elements**
  - **Engineered proteins and signaling aptamers**
  - **Ionophores**
  - **Natural and artificial ion-channels**
  - **Bio-designed and molecular-imprinted polymers**

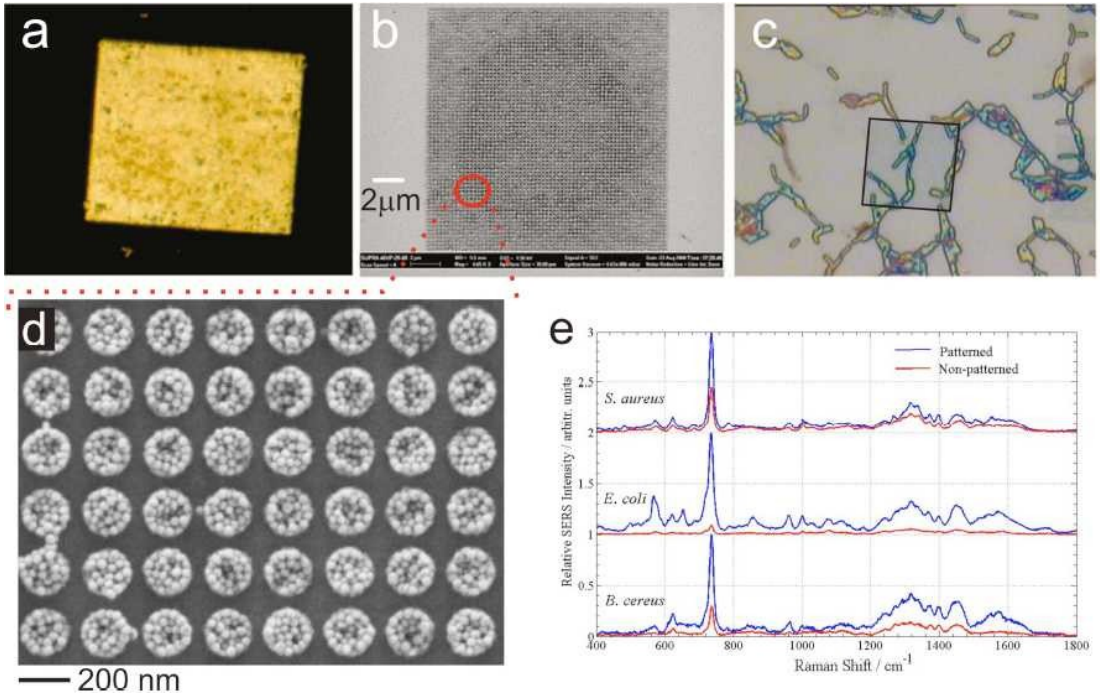
Rationally Designed Plasmonic Nanostructures for Rapid Bacteria Detection and Identification

Bjoern Reinhard - Boston University

CBET-Biosensing-0853798

The specific aims are:

1. **Rapid and reliable identification of potentially life threatening bacterial pathogens using the strong sensitivity of SERS vibrational spectra to molecular composition and structure;**
2. **To obtain spectral 'fingerprints' of the bacteria surface non-invasively and without the need of complex sample preparation**



- **The SERS spectra of individual bacteria will be recorded using the nanofabricated SERS substrate**
- **Spatially controlled clustering of the nanoparticles and rational design of the SERS active area will increase the reproducibility of the resulting SERS enhancement.**

NSF Directorate for Engineering | Division of
Chemical, Bioengineering, Environmental, and Transport Systems (CBET)
Bioengineering and Engineering Healthcare Cluster

Research to Aid Persons with Disabilities

Program Director - Ted A. Conway - tconway@nsf.gov

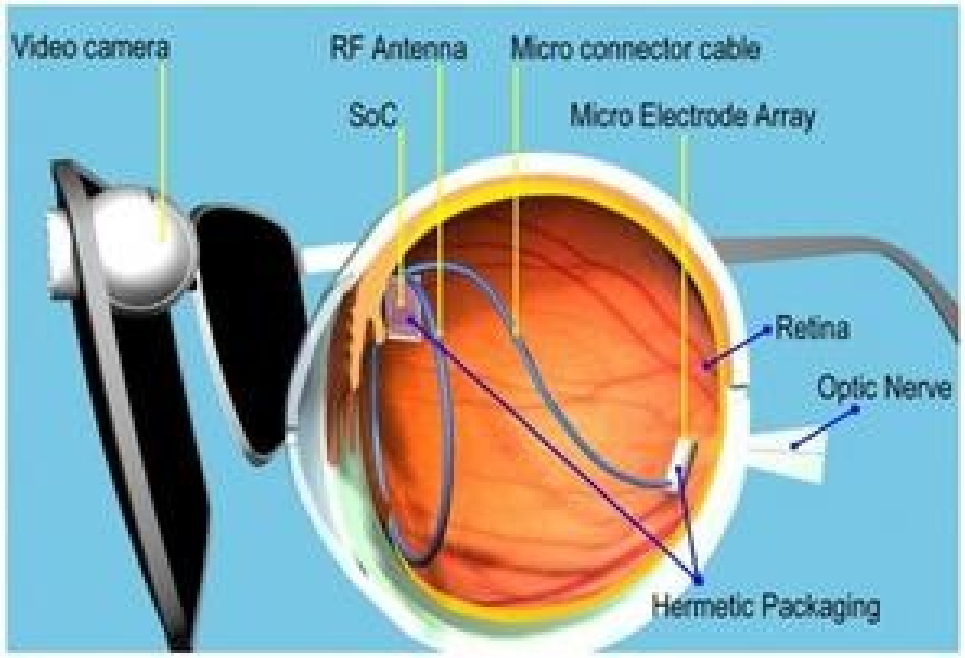
- RAPD supports research that will lead to the development of new technologies, devices, or software for persons with disabilities. This includes:
  - The characterization, restoration, and/or substitution of human functional ability or cognition
  - The interaction of persons with disabilities and their environment
- Areas of particular recent interest are:
  - Disability-related research in neuroscience and/or neuroengineering, rehabilitation robotics

Recreational Technology for Persons with Disabilities

Karen May-Newman - San Diego State University

Undergraduate students in mechanical engineering designed and built equipment to make a racing yacht usable by a crew of five individuals with disabilities and a non-disabled captain. The yacht placed 4th in class in the 2005 Transpac Race from Los Angeles to Hawaii.

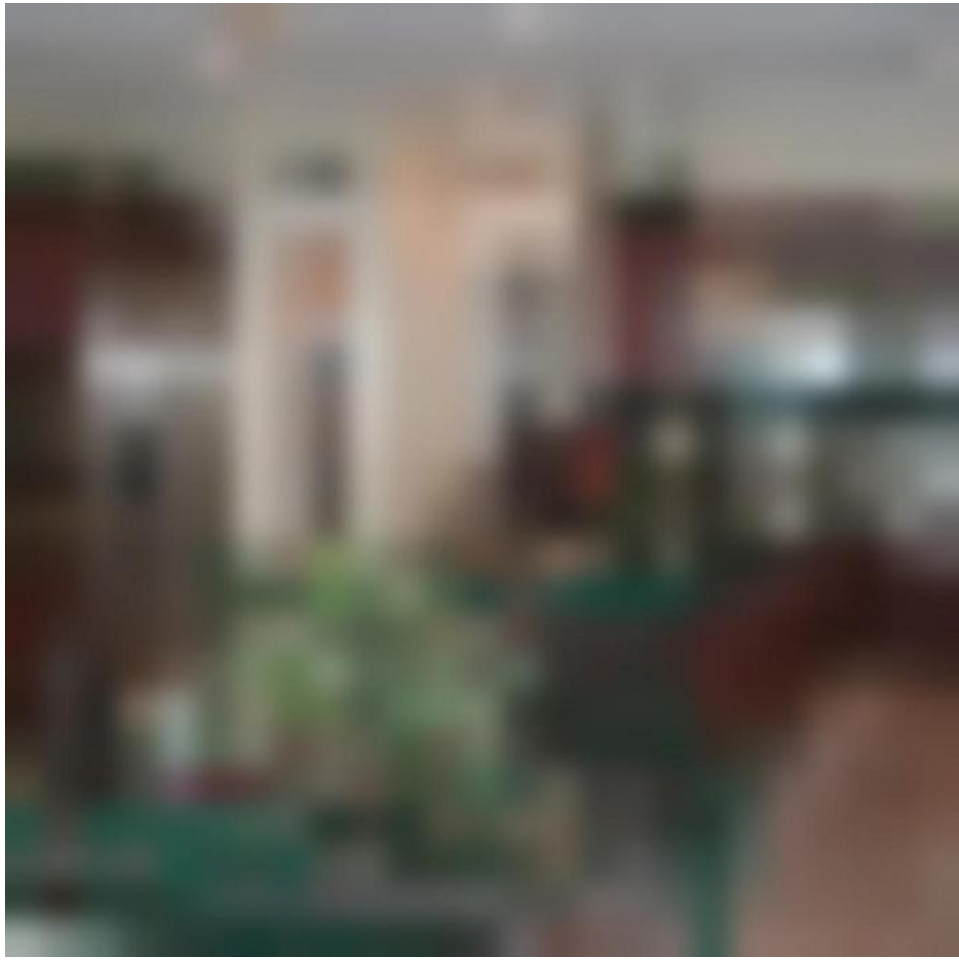
Artificial Retina



Dr. Mark Humayun, Director of the Engineering Research Center for Biomimetic MicroElectronic Systems, and his research group have developed a prosthetic device that enables previously blind people to perceive light and patterns.

Artificial Retina Results

Image of a kitchen scene, 1024 x 1024 pixels.



Square pixellated image of a kitchen scene, 25 x 25 pixels with 34% Gaussian blur, showing object recognition.

Credit: Armand R. Tanguay, Jr. and Noelle R. B. Stiles; University of Southern California

Post-Stroke Mobility Rehabilitation

Greg Burdea - Rutgers University

This project includes work on Virtual Reality-based Dual Haptic Platforms.

These platforms are being developed to deliver rehabilitation in the home.

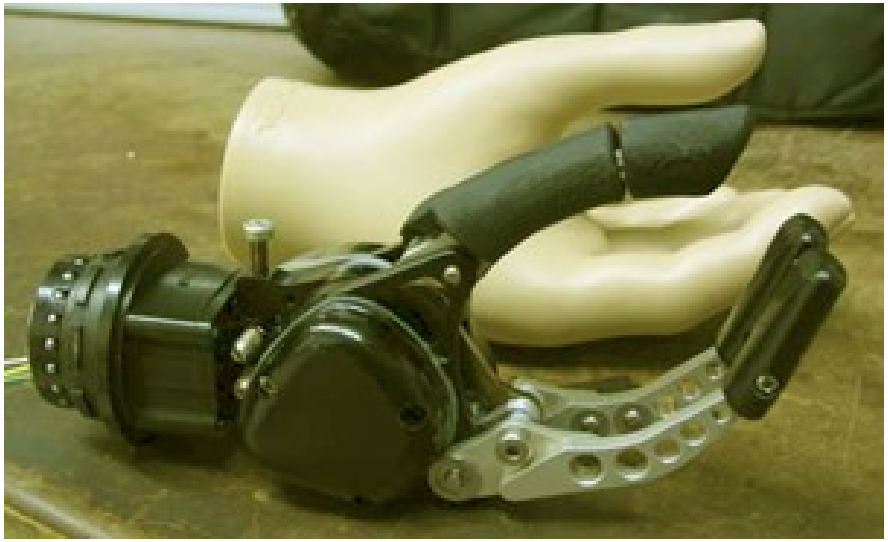
While still in the early stages of research, a new technique to lower the cost of rehabilitation and allow it to be delivered in a home setting could have a profound impact on people recovering from stroke.

Towards a Neuroprosthetic Hand

Kenneth Horch - University of Utah

Background: **Body powered and myoelectric systems (systems controlled by electrical signals from the body) are the most widely employed techniques for controlling upper limb prostheses. One of the shortcomings with these systems is the lack of feedback on reach and grasp movements.**

Recently, Horch's group at Utah has shown that localized electrical stimulation of nerve stumps in amputees can produce sensations of touch and joint movement referred to the missing hand, thus providing pseudo-natural sensory feedback. Coupled with a prosthetic hand equipped with appropriate sensors and a control algorithm that makes the hand respond more like a natural hand, this could provide the basis for an artificial arm and hand that is better incorporated into the amputee's body image and provides better function.



Motion Control hand with cosmetic glove removed, as used in the development project for a Neuroprosthetic Hand.
(Motion Control, Inc. Salt Lake City, Utah)

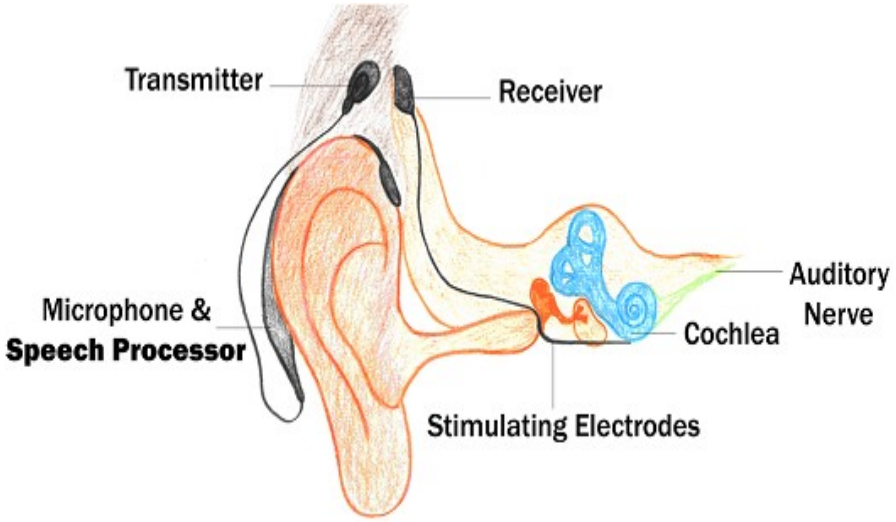
Credit: Erik Engeberg, University of Utah

CAREER: Signal Processing Technology for Cochlear Implants

CBET-BES-0447705

Alireza Ziarini - Clarkson University

Background: A cochlear implant is an electronic device that helps to provide a sense of sound to a person of profound deafness or sever hearing impairment. It consists of an external module that sits behind the ear and an internal module that is surgically implanted beneath the skin on the skull. While cochlear implants do not restore normal hearing, they are widely used as the most viable prosthetic substitute for hearing. A key component of a cochlear implant is its speech processor that
determines how the electrodes should be stimulated for best possible performance.



Scientific Uniqueness: This research addresses the technical challenges of cochlear implant technology at its core. Unlike the currently used speech processing technology that fails to accurately model the complexity of speech, in the developed technology speech is modeled in it full complexity providing high-resolution estimates of instantaneous frequency and amplitude of components that are used to stimulate the electrodes. This precision results in an improved recognition of the sounds and offers significant advantages to the user in terms of sound quality.

NSF Directorate for Engineering | Division of Chemical, Bioengineering, Environmental, and Transport Systems (CBET)
Bioengineering and Engineering Healthcare Cluster

Biotechnology, Biochemical, and Biomass Engineering (BBBE)

Program Director – Theresa Good- tgood@nsf.gov

The BBBE Program Supports: Fundamental engineering research that advances the *understanding of cellular and biomolecular processes* and eventually leads to the *development of enabling technology* and/or applications in support of the biopharmaceutical, biotechnology, and bioenergy industries, or with applications in health or the environment.

Biotechnology, Biochemical, and Biomass Engineering (BBBE) Program Supports:

Fundamental engineering research that advances the *understanding of cellular and biomolecular processes* and eventually leads to the *development of enabling technology* and/or applications in support of the biopharmaceutical, biotechnology, and bioenergy industries, or with applications in health or the environment.

Biotechnology, Biochemical, and Biomass Engineering (BBBE) Program Emphasizes:

- Metabolic engineering and synthetic biology
- Tissue engineering and stem cell technologies
- Protein engineering and design
- Systems biology
- Development of novel molecular level and "omics" tools in support of biotechnology

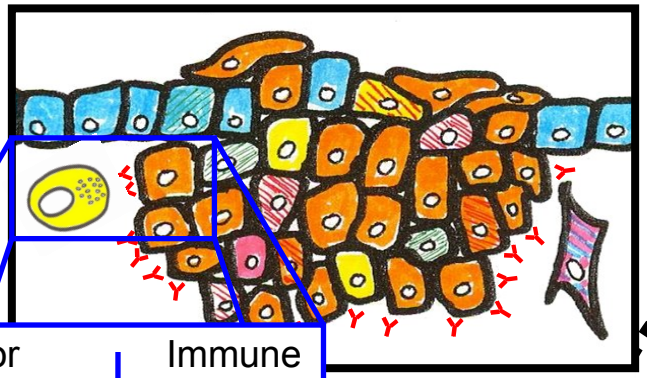
Recent CAREER Award Examples

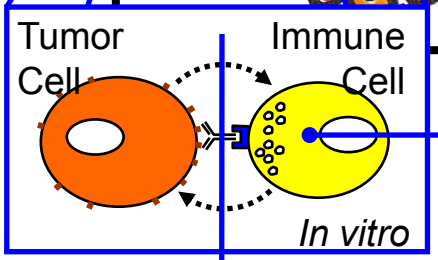
- Interrogating antagonistic mechanisms of signaling cross talk in natural killer cells
- Functional heterogeneity in cell chemotaxis
- A novel approach for deciphering cellular metabolic phenotypes using tandem mass spectrometry
- Engineering Functional Tissue Assembly and Remodeling Through Developmental Biology
- Design, Construction and Characterization of Metabolite Valves

Using systems biology & experiment in cancer signaling

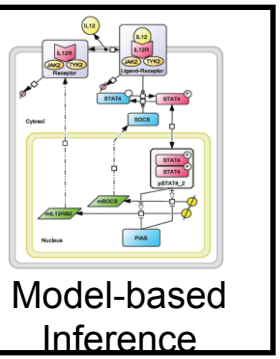
David Klinke West Virginia University CBET 1053490

Klinke *Mol Cancer* 2010

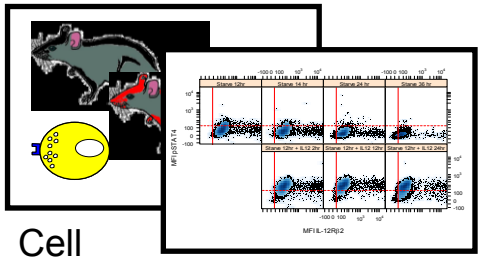




Prior information



Model-based Inference



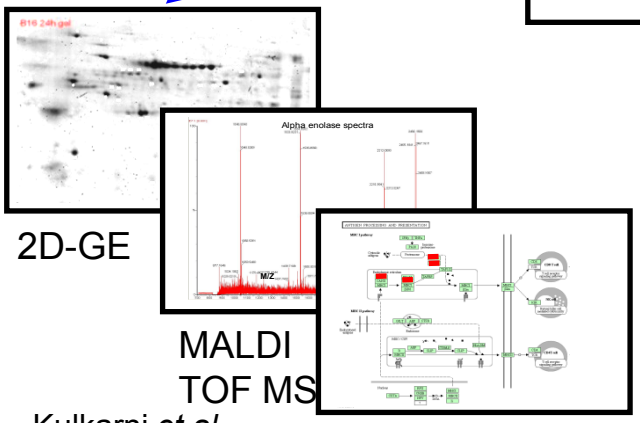
Cell Models

Flow Cytometry

Klinke *et al. Biophys J* 2008
Klinke *et al. Cytometry A* 2009

siRNA nAb

Experimental Validation

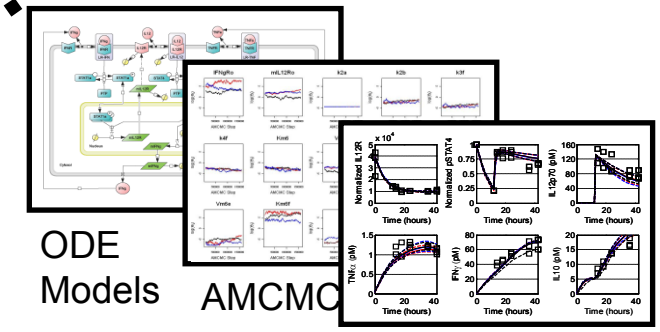


2D-GE

MALDI TOF MS

Pathway Enrichment

Kulkarni *et al.* *BMC Cancer* 2010



ODE Models

AMCMC

Klinke *BMC Bioinform* 2009
Finley *et al. Immunol Cell Bio* 2010

Pr(Predictions | Model, Data)

Novel device development to probe chemotaxis

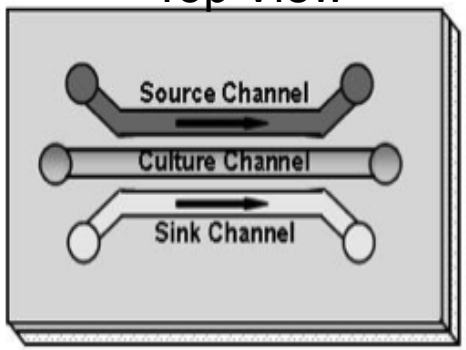
Cynthia Reinhart-King Cornell CBET 1055502

APPROACH

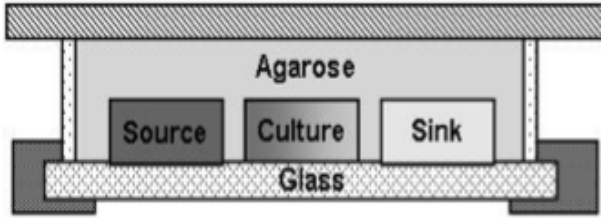
Expose endothelial cells to a chemotactic gradient → Select for cells based on chemotactic ability → Analyze molecular-level differences of cell sub-populations

DEVICE

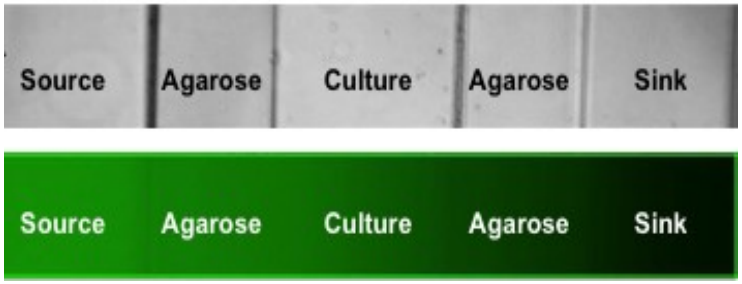
Top View



Side View



Microfluidic chemotaxis device. Gradients are created based on the diffusion of a chemoattractant from the source to the sink channels through a porous agarose scaffold.

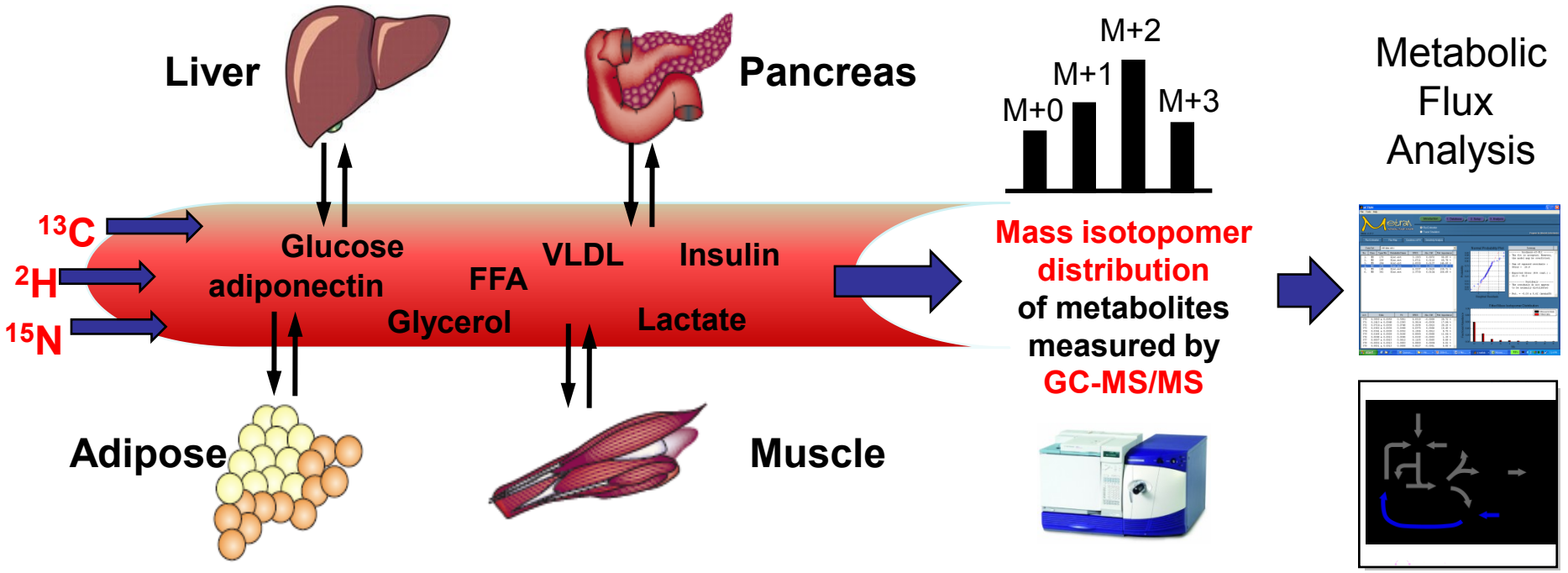


Fluorescent images of a FITC-dextran gradient in the microfluidic device.

Mass spectrometry to decipher metabolic phenotype

Maciek Antoniewicz University of Delaware CBET 1054120

Isotopic tracers → Biological Reactions → Tandem MS Analysis → Calculation of metabolic flux



Antoniewicz MR, Metab Eng 9: 68-86, 2007
Antoniewicz MR, Anal Chem 79:7554-9, 2007

Recent Unsolicited Award Examples

- Probing delays and memory in gene activation using a gene oscilloscope
- Biosynthetic approaches towards generating new tetracycline antibiotics
- Transcriptional Control of Alkaloid Biosynthesis in C. roseus cultures
- Unravelling the molecular regulation of mesendodermal differentiation in human embryonic stem cells
- An epigenetic understanding of transcriptional regulation in CHO cells

Exploring tetracycline biosynthesis

Yi Tang, UCLA, CBET

1.) Biosynthetic pathway elucidation:

•Identified two different biosynthetic routes to similar tetracycline intermediate

Fungal iterative type I PKS

Single multifunctional polypeptide chain

+ additional tailoring enzymes

Bacterial type II PKS

Set of discrete enzymes

+ additional tailoring enzymes

•Identify/characterize unique tailoring enzymes which differentiate final structures

Oxidoreductases
Prenyltransferase
Cyclase

Oxidoreductases
Aminotransferase
Methyltransferase

Acyltransferases
Glycosyltransferase
Oxidoreductases
Methyltransferases

Viridicatumtoxin
Penicillium aethopicum
Broad-spectrum antibiotic

Oxytetracycline
Streptomyces rimosus
Broad-spectrum antibiotic

SF2575
Streptomyces sp. SF2575
Anticancer

2.) Engineered biosynthesis of novel tetracyclines

- Combinatorial Biosynthesis
- Mutasynthesis
- Protein Engineering

⇒ Isolate and evaluate novel compounds

Example of possible hybrid compound

Highlights

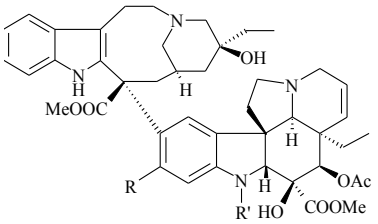
- 3 producing organisms
- 2 vastly different biosynthetic strategies
- 2 therapeutic areas
- Novel tailoring enzymes discovered
- Novel analogs produced

Transcriptional Control of Alkaloid Biosynthesis in *C. roseus* cultures

Carolyn Lee-Parsons & Erin Cram, Northeastern Univ. CBET 1033889

Research Vision:

The *C. roseus* plant produces highly-valued pharmaceuticals, including the anti-cancer drugs vincristine & vinblastine. The high cost & need for these drugs motivate our research to better understand their biosynthesis & ultimately over-produce these compounds using *C. roseus* cultures.



vincristine: R = H, R' = CHO
vinblastine: R = OMe, R' = Me

Research Goals:

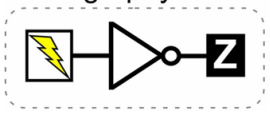
- To investigate & refine a proposed model for the transcriptional regulation of alkaloid biosynthesis using 1) transgenic cultures & 2) molecular biology tools.
- To design effective engineering strategies for overcoming innate blocks to alkaloid biosynthesis based on the model.

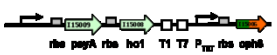
CAREER:Multi-input Multi-output Cellular Control

Christopher Voigt UCSF CBET 0547637

Individual Circuit Design

Photography





Mask *in vivo* *in silico*

genomatica DSM

Applications

Thermodynamics

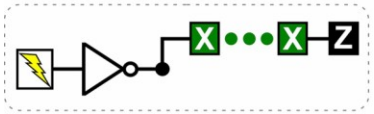
RBS CALCULATOR BETA

Kinetics, Transport

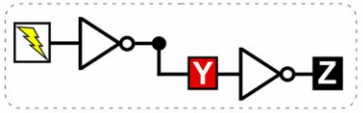
Computer Aided Design

Multi-Circuit Genetic Programs

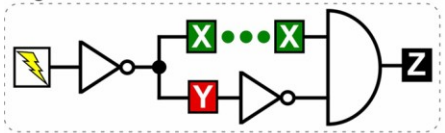
Communication

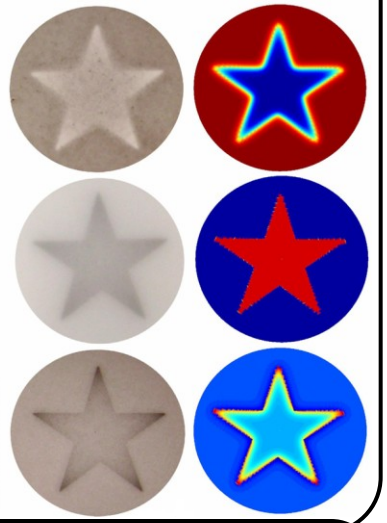


Inverter

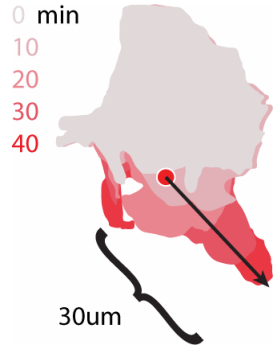


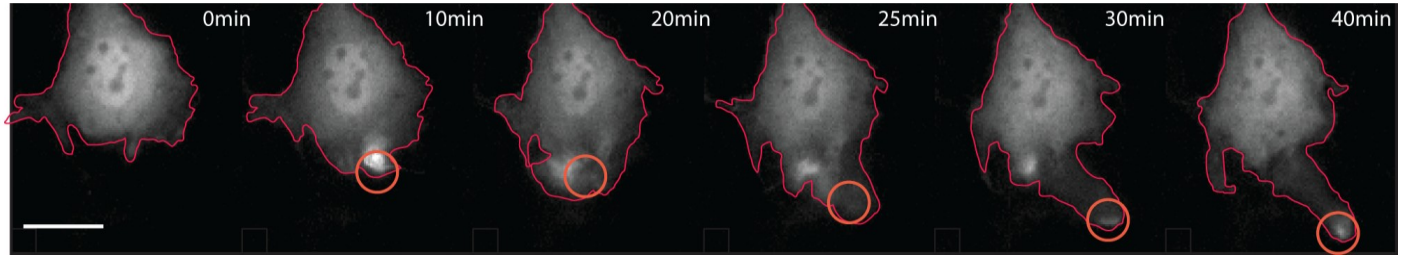
Edge Detector





More Complex Hosts





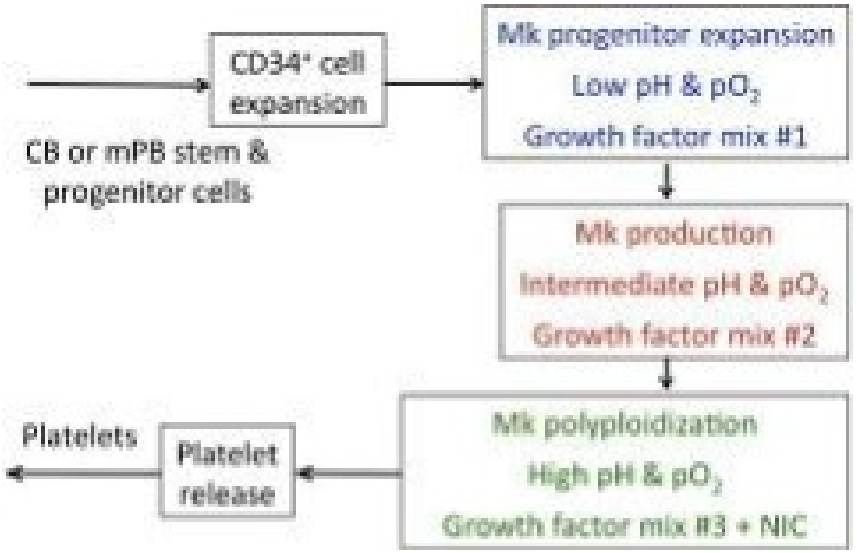
Edge detection is just one example of the type of logic circuits that can be designed and then implemented in bacteria using *synthetic biology* tools developed in the Voigt lab.

Towards Large-Scale Platelet Production from Adult Hematopoietic Stem and Progenitor Cells

William Miller, Northwestern University CBET 0853603
Eleftherios Papoutsakis, University of Delaware

During chemotherapy, a number of cells in the blood get depleted. Investigators Miller and Papoutsakis have been working on ways of getting specific *hematopoietic stem cells* to multiply outside of the body, so that the depleted cells can get replaced after chemotherapy. The researchers have *optimized reaction and growth conditions based on the bone marrow niche environment* to get maximum megakaryocytic cell production by changing pH and oxygen concentrations in the cell reactor. Having ways of growing specific blood cells outside of the body will increase the safety and decrease the need for transfusion for individuals with blood diseases.

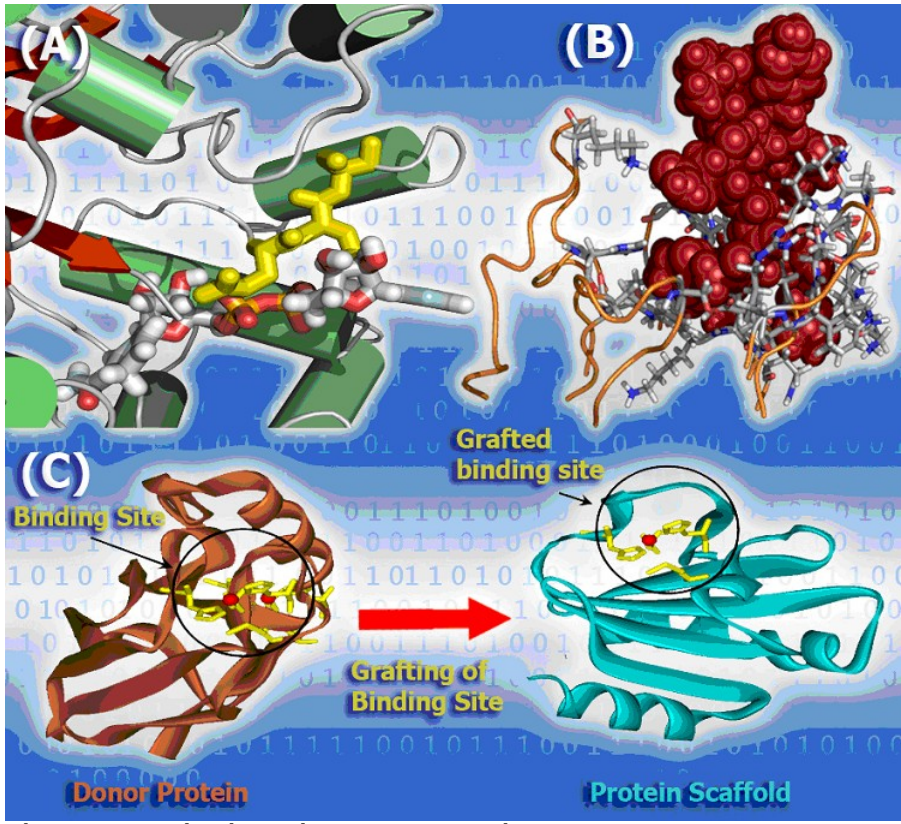
Schematic diagram of niche-inspired multi-phase process for platelet production in cultures of CD34-selected stem and multi-potent progenitor cells from umbilical cord blood (CB) or mobilized peripheral blood (mPB) carried out with different pH, oxygen partial pressure (pO_2), growth factors, and nicotinamide (NIC).



Development of Computational Tools and Experimental Verifications for Protein Design

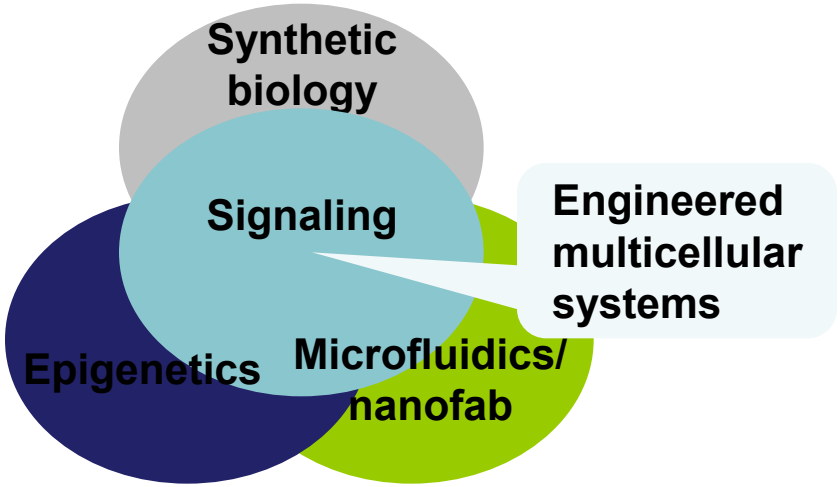
Costas Maranas & Pat Cirino Penn State CBET 0639962

Proteins are versatile molecules tuned to perform a diverse set of functions, including catalysis, signaling and regulation, however, their commercial utility can be limited by substrate cost and stability. Investigators Maranas and Cirino have developed *computational tools to design or redesign proteins* to bind more cost-effective substrates as well as antibodies to tightly bind antigens, and then have conducting experiments to test the effectiveness of the developed computational frameworks and reveal opportunities for improvement.



(A) The nicotinamide binding site of a redesigned CbXR is shown, with the alternative substrate, NADH bound. Residues in yellow are designs selected by algorithm to increase binding affinity for NADH, and were shown to experimentally have new activity.
(B) OptCDR-designed complementarity determining regions in complex with their target antigen, a peptide from the capsid of hepatitis C.
(C) Pictorial description of OptGraft transferring the naturally occurring binding pocket of a donor protein into a new scaffold without disrupting its function.

ERFI: Engineering new technologies based on Multicellular and Inter-Kingdom Signaling



Goal: Use molecular tools to understand multicellular and inter-kingdom signaling and engineer new multicellular systems to solve problems in energy, health, food safety and environment.

Expected Transformative Impacts:

- Fundamental knowledge in multi-cellular systems and bacteria–eukaryote interactions
- Basic sciences, including developmental biology, stem cells, bacteria–eukaryote interactions
- Enabling technologies including synthetic biology, high-throughput tools
- Novel engineered multicellular systems
- New collaborations between different research communities