

# NASA Bioscience and Engineering Institute

## at The University of Michigan

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**The NASA Bioscience and Engineering Institute at the University of Michigan is a multi-component initiative of research, education and outreach which addresses important issues in microgravity environments which are at the interface of biology and engineering sciences. Currently there are 9 research projects involving 26 faculty members and 11 students/postdocs. A description of these projects is made with the goal of introducing the AIAA community to these efforts which can benefit from collaborative approaches between scientists skilled in aeronautical and astronautical areas with biologists and biomedical engineers. Also the goals of outreach and education are discussed. Details of the projects are also available at [www.umnbei.umich.edu](http://www.umnbei.umich.edu).**

### I. Introduction

The University of Michigan - NASA Bioscience and Engineering Institute (NBEI) represents a significant effort and commitment by an interdisciplinary cross-section of our the University academic community and industrial partners to forge a long-term investment in the future of space and earth exploration as it relates to the interface of biology and engineering. Evidence for the dynamic expansion of this interface appears on all fronts: (i) the surge of new departments and centers at our nation's colleges and universities in recent years that focus on bioscience and bioengineering; (ii) the rapid increase in novel and exciting technologies and companies that leverage from the interface; (iii) the creation of the National Institute for Biomedical Imaging and Bioengineering by NIH. The participating NBEI faculty members are from 6 units at the University of Michigan: the College of Engineering, the School of Medicine, the School of Dentistry, the School of Public Health, the Division of Kinesiology and the College of Literature, Science and the Arts. Within the College of Engineering, which is the lead unit, the Biomedical Engineering Department is extensively involved in several elements of the initiative. Initially the NBEI will consist of 26 current faculty and 11 graduate/postdoctoral students, a dozen companies and staff infrastructure. The initiative entails three interrelated programmatic areas: Education, Outreach, and Research. The reader may see more details at [www.umnbei.umich.edu](http://www.umnbei.umich.edu), including seminar and symposium information.

The Research is organized into 4 Research Themes, each with a distinguished faculty leader, totaling 9 projects. The Research projects are multidisciplinary investigations into basic biology and technology that underpin the bioscience and engineering interface. They vary from molecular to cellular to whole animal systems, each with its own relevance to NASA's goals, and common, crosscutting issues of analytical expertise and experimentation interconnect them. The BioMEMS and Biomaterials Theme brings together the interconnected activities of several faculty to address important topics in miniaturized instrumentation for bioscience applications in space and on earth. In concert with this activity will be the development and evaluation of biomaterials whose properties are explored at the micro and nano scale to guide the development of instrumentation and their effectors and sensors. The Molecular Biophysics and Engineering Theme investigates systems that integrate sensors and actuators onto a single carrier molecule to create a nanosystem for imaging targeted molecular species, delivering therapeutics, and validating the effectiveness of the therapy. It also explores techniques to monitor and manipulate single biological macromolecules, with the goal of developing sensors and actuators using single molecules. Life-detection systems are possible outcomes of this Theme. The Theme for Transport Phenomena in Biology and Devices deals with fluid dynamics and transport at multiple scale levels as it affects biological function in the brain and lung as well as

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microfluidic systems for compact devices that are used to evaluate cellular and molecular information. The Tissue Bioscience and Engineering Theme explores signal transduction, gene expression and cellular responses to various mechanical/chemical stimuli that affect hard and soft tissues. Understanding the influence of gravity on natural, as well as engineered tissues, will bring important new insights and opportunities in tissue engineering.

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## **II. Research Theme: BioMEMS and Biomaterials, Leader-Daryl Kipke, Ph.D.**

*BMI: Integrated Microsensors for Environmental and Physiologic Monitoring*

Participants: Participants: Daryl Kipke, David Martin, Kahlil Najafi, Zhan Chen

The BioMEMS and Biomaterials theme will focus on the design and evaluation of a novel type of minimally invasive medical device for integrated physiological and environmental sensing. The long-term goal is to develop a “skin-patch” type of polymer integrated microsystem that has an interface to the body for physiological sensing (e.g., biopotentials) and an interface to the external environment for environmental monitoring (e.g., air quality). This interdisciplinary and multi-faceted project will leverage extensive on-going research in wireless integrated microsystems, biological sensors, environmental sensors, materials science, and chemistry.

## **III. Research Theme: Transport Phenomena in Biology and Devices, Leader- Ronald Larson, Ph.D**

*TP1: Neural and neurovascular changes in simulated microgravity*

Participants: Rachael Seidler, Ph.D. (PI), Doug Noll, Ph.D., Shu Takayama, Ph.D., James Grotberg, Ph.D., M.D.

Microgravity environments are well known to produce deficits in motor coordination as well as sensory abilities. These are, at least, partially due to the altered sensory input present in microgravity environments. At the same time, microgravity (or simulated microgravity) can also induce a variety of global physiological changes, including a cephalad redistribution of fluids and impaired regulation of cerebral blood flow and on cortical function. This alteration in blood flow and potentially extravascular flows may directly or indirectly affect brain function by altering the release and transport of neurotransmitters and vasoactive factors. We will examine both systems level and cellular level changes in neural or neurovascular performance that result from simulated microgravity. The systems level studies will use magnetic resonance imaging (MRI) to examine two basic issues: how the brain responds to a head-down tilt (HDT) challenge, which simulates the cephalad fluid redistribution, in terms of degree of neural activity and vascular (flow/volume) responsiveness; and whether different neural systems (visual, audition, sensorimotor) respond differently. The vascular and neural cell culture studies will examine if changes in the shear stress environment mimic those seen in microgravity environments can induce a change in neural function described by changes in gene expression.

*TP2: An Earth-Based Model of Microgravity Pulmonary Physiology*

Participants: Ronald Hirschl, M.D. (PI), Joseph Bull, Ph.D., James Grotberg, Ph.D., M.D.

There are many important aspects of pulmonary physiology that have not been investigated in microgravity due to the constraints of space flight. Some examples include pulmonary blood flow distribution, ventilation distribution, and pleural pressures and flows. An earth-based model of microgravity effects on the lung will facilitate studying these and other features. The way to eliminate gravity effects in the pulmonary system on earth is to eliminate the density differences between the lung tissue and the fluid inside the lung (air in normal ventilation). Liquid ventilation involves filling the lungs with a liquid perfluorocarbon (PFC) that has high O<sub>2</sub> and CO<sub>2</sub> solubilities and achieving gas exchange by cycling the PFC in and out of the lung. Our group has considerable research experience with liquid ventilation, and when one also submerges the experimental animal in water, then there are no density differences affecting the lung. We will study alterations in cardiac output, arterial venous pressure, lung volumes and mechanics in the liquid-filled lung of submerged sheep. These results can be compared to similar measurements in space. The advantage of an earth-based model is that more complex measurements can also be made. These will be pulmonary blood flow distribution, distribution of ventilation, and ventilation-perfusion matching, and pleural pressure and flows. The work will also include fluid mechanical modeling of the pulmonary system to assist us in interpreting the data.

*TP3: Lab-on-chip devices for bio-medicine in space with focus on saliva analysis*

Participants: Ronald Larson, Ph.D. (PI), Mark Burns, Ph.D., William Schultz, Ph.D., Margaret Terpenning, M.D.

The focus of this project is on the development of miniaturized fluidic devices and tools for detecting biomarkers in saliva and manipulating DNA for health monitoring and detecting radiation damage to DNA. We will initially focus on characterization of saliva samples, and preparation of DNA for detection of radiation damage. For the latter, we will study the manipulation of DNA molecules in evaporating droplets and in microfluidic devices, where they can be anchored to substrates and DNA cleavage studied, due to radiation damage in space. In initial studies, to test our ability to detect DNA scission, restriction enzymes will be used to cut the DNA, and in later years begin working with radiation sources. The Burns lab has a separate project developing lab-on-chip technology, funded by the NIH, and a Sandia collaboration to develop a saliva-based Elisa-type assay. We will leverage this research, and in later years of the project (years 3-5), begin applying this to markers in saliva that could be used to detect astronaut health or bone loss. To work with saliva in such devices, we will study the rheological properties of saliva both to learn how to process saliva on a microfabricated device and to assess whether the rheological properties can themselves be indicators of health. We will obtain saliva from the dental school and the VA hospital at the University of Michigan.

#### **IV. Research Theme: Molecular Biophysics & Bioengineering, Leader - Matthew O'Donnell, Ph.D.**

*MB1: Molecular Nanosystems to Monitor Astronaut Radiation Sickness*

Participants: James Baker, M.D. (PI), Matthew O'Donnell, Raoul Kopelman, Ph.D., Ted Norris, Ph.D.

The molecular nanosystems theme will focus on the design and evaluation of a novel type of minimally invasive medical device for integrated physiological and environmental sensing with particular application to radiation monitoring. This is a slight re-focus from the original NBEI proposal. Bernell Williams is a graduate student who will work on this project, and his efforts will focus on the interface of the polymer system with biologic components of the skin. The first phase of the project (16 months encompassing project years 1 & 2) involves developing a prototype polymer with cell-binding ligands that when implanted in or on the skin will bind to cells to develop monitoring functionality. The primary milestones are (1) fabrication of polymer-based device with cellular attachment ligands, (2) ligand coating analysis and characterization and (3) testing of biologic adherence. The work will include bench, in vitro and in vivo testing. The primary deliverable of this project will be a prototype polymer that has functionality for binding to individual cells for environmental and physiological states, including radiation exposure.

*MB2: Single-Molecule Biosensor in the Search for Life*

Participants: Chris Meiners, Ph.D. (PI), Nils Walter, Ph.D.

The Single-Molecule Biosensor Project focuses on the development of an ultra-sensitive, specific, versatile and rugged biosensor based on catalytic RNA molecules to detect signature molecules for life on planetary systems. It will be integrated into a microfluidic platform and detect single analyte molecules through the cleavage of substrate RNA reporter molecules, which in turn are read out by fluorescence resonant energy transfer (FRET) techniques with a total-internal-reflection fluorescence (TIRF) microscope. Primary target molecules for the biosensor will be a suite of amino acid molecules of different chiralities that can be detected with high specificity and sensitivity. The first phase of the project is centered on the construction and validation of a prototype platform for the development of the single-molecule biosensor. This includes the development of suitable data acquisition and analysis procedures for the read-out of the catalytic RNA molecules on the detector chip, the adaptation of the TIRF microscope to accommodate the detector chips with their external infrastructure for reagent and analyte delivery and the observation of molecular conformational changes in such RNA molecules. The primary milestones for the first phase are (1) development and validation of an accurate sub-pixel image acquisition and analysis system for single molecules on the TIRF microscope (2) Adaptation of the TIRF microscope for use on microfluidic sensor chips, and (3) the observation of conformational changes of single RNA molecules with the TIRF microscope. Future benchmarks beyond the initial 16-months period include (4) The availability of catalytic RNA molecules to detect analytes of specific interest to NASA as described above, and (5) The demonstration of a fully functional biosensor chip based on this technology. This will also be the primary deliverable of the project.

## V. Research Theme: Tissue Bioscience and Engineering, Leader - Laurie McCauley, D.D.S., Ph.D.

### *TB1: Effects of Hind-Limb Unweighting on Muscle Function*

Participants: Susan Brooks, Ph.D. (PI), Robert Dennis, Ph.D.

As outlined in the original proposal, we will examine changes in skeletal muscle satellite cell function resulting from both short- and long-term exposure to simulated microgravity. Satellite cells are myogenic precursor cells that reside within skeletal muscles and are critical for muscle maintenance, growth, and repair. As depicted in our timeline, we will first implement a hind-limb unweighting model in rats to induce skeletal muscle atrophy similar to that associated with microgravity. We will expose animals to varying periods of hind-limb unweighting in order to establish the relationship between the duration of unweighting and satellite cell numbers. We will then conduct a series of experiments to assess the effects of short- and long-term unweighting on satellite cell function. We will limit these first assessments to an extensive quantitative description of satellite cell growth dynamics in 2-D cell culture. In future experiments will use satellite cells derived from muscles after exposure to simulated microgravity to engineer in vitro functional muscle (myoids). We will determine the effects of unweighting on the ability of satellite cells to self organize into myoids and investigate the potential role in these processes of deleterious effects of unweighting on the extracellular matrix.

### *TB2: Local delivery of PTH counter balances microgravity-associated bone loss*

Participants: Laurie McCauley, D.D.S., Ph.D. (PI), Peter Ma, Ph.D.

We will develop a polymeric system to locally deliver parathyroid hormone (PTH) in a pulsatile fashion as a method of counter-balancing bone loss resulting from microgravity. The system will be composed of a multilayered model with alternating layers of biodegradable polymer barrier and PTH to achieve the needed pulsatile delivery for the anabolic action of PTH. As depicted in the timeline, we will first synthesize three polymers of varied chemical compositions that are designed to surface erode for our application (polyanhydrides). The most challenging aspect of the synthesis of polyanhydrides is to achieve a high polymer molecular weight in a delivery system. Therefore, we will next optimize the synthesis process to improve the molecular weight of one of the three candidate polymers. With the polymer of high molecular weight, we will then study the degradation characteristics to verify the desired surface erosion feature, which is the basis of our delivery model design. We will then develop the multilayered delivery constructs with model proteins to test the pulsatile release in a biologically relevant system. The project will ultimately test this local delivery system in an animal model to verify the delivery and effectiveness of the goal of decreasing bone loss due to microgravity.

### *TB3: The influence of physical forces on bone adaptation*

Participants: Steve Goldstein, Ph.D. (PI), Barbara McCreddie, Ph.D.

We will utilize a novel hydraulically activated implantable bone chamber that promotes de novo bone formation in Sprague Dawley rats to identify the short and long term cellular and molecular events associated with mechanical stimulation in ground base experiments. Specifically, we will test the hypothesis that integrin-mediated signal transduction is dependent on both rate and magnitude of the physical forces. After completing the first experimental group, we will finalize the required protocols and assays. The experimental groups will then be expanded to complete the rate and magnitude evaluation with sufficient statistical power.

## VI. Education and Outreach

The Education component emerges at all academic levels. The Undergraduate Education Plan will rely substantially on the BS program in Biomedical Engineering (BME), which welcomed its first class in Fall Semester 2001. The BME Department oversees this degree and has received generous funding from the Whitaker Foundation, the Gerstacker Foundation and the University to establish a new building for its increasing student training responsibilities and faculty size. There will be 3 new undergraduate courses taught by NBEI faculty that focus on bioscience and engineering in space. Two of these courses will be university-wide, drawing from a large undergraduate student pool. The Institute will harness the Undergraduate Research Opportunity Program to match our motivated and inquisitive students with NBEI labs so that classroom work may extend to the hands-on environment. The Graduate Education Plan entails all departmental MS and PhD programs of the participating units as well as several interdisciplinary degree programs which cross departments and schools. We propose one new graduate course and 3 new Masters degrees. The latter are 5 year, BS-MS degrees that allow students to acquire unique skills and experience on their way to becoming future leaders in space-related bioscience and technology.

We plan further education for summer high school students, summer K-12 teachers, research internships for clinicians, and scientist exchanges among NASA, our industrial partners and Michigan, as the laboratories become educational tools for this important mix of scholars.

The Outreach plan will provide access to NBEI personnel and resources at many levels and to a wide community, both by direct interaction and by maintaining an information repository. This includes K-12 students, K-12 teachers, women, underrepresented minorities, professional societies and agencies, and our industrial colleagues. UM is already active in community outreach in these areas providing a foundation for the Institute's needs. The industrial outreach and educational arrangements incorporate the shared mentoring of research students and technology transfer of research developments to industry as well as government. Through their participation and input, member industries will be advantaged by early awareness of new developments in research and development and technology transfer. Projects will organize on the "Quad" research team concept where four entities collaborate on the research: faculty advisor, student, industry engineer or scientist, and government engineer or scientist. The Quad approach more effectively transfers technology since all parties are involved from the outset.