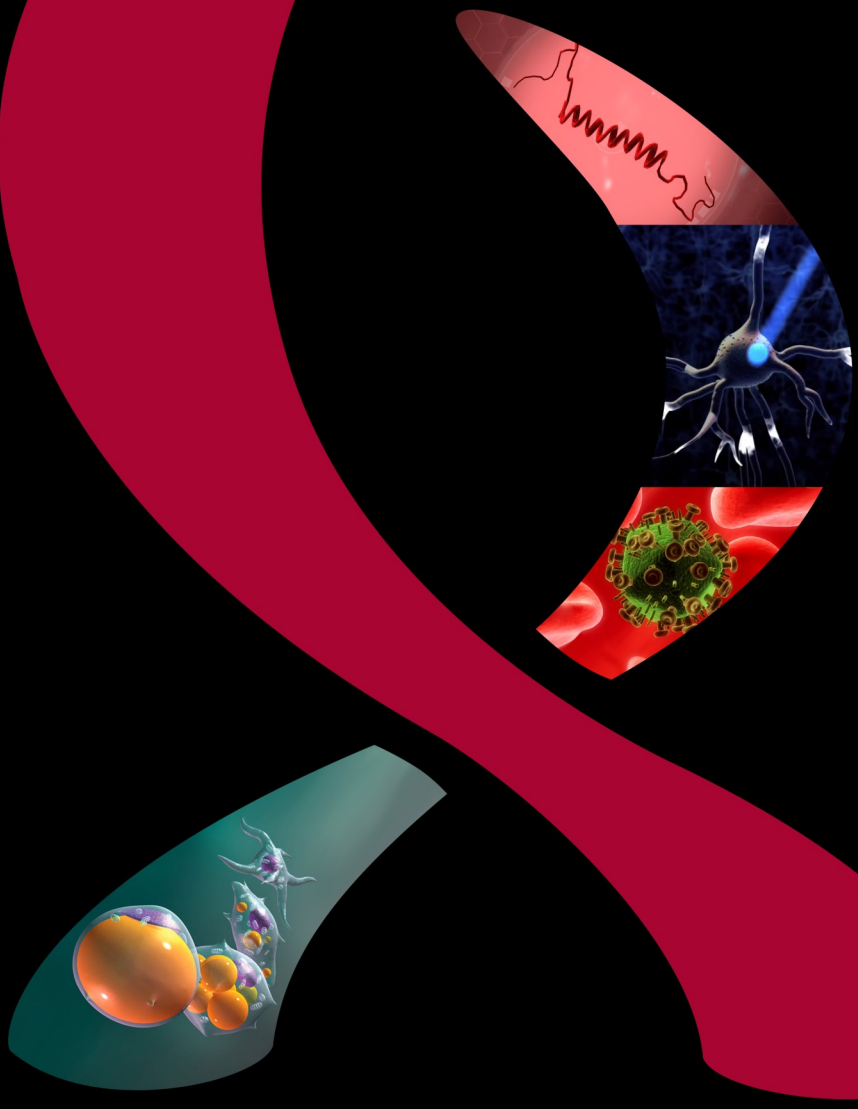
Stanford Bio-X Interdisciplinary Initiatives Seed Grants Program Symposium

February 17, 2016



STANFORD BIO-X

Seed Grants for Success: The Stanford Bio-X Interdisciplinary Initiatives Program (IIP)

The Stanford Bio-X Interdisciplinary Initiatives Seed Grant Program (IIP) brings together researchers in computer science and technology, engineering, the basic sciences in H&S, the earth sciences and the pre-clinical and clinical sciences in the School of Medicine in areas related to biosciences, biomedicine, and bioengineering. The IIP awards provide seed funding for high-risk, high-reward collaborative proposals including basic research leading to fundamental discoveries, as well as innovative technology.

Stanford Bio-X is a fertile environment for visionaries, and the IIP awards give them the seed funding they need to allow high-risk ideas to germinate and grow. Our investment in the seed grants has resulted in over $220 million in external funding awarded to the university. Funding has supported hundreds of graduate students and post-doctoral fellows, resulted in hundreds of publications and dozens of patents filed, and accelerated the pace of scientific discovery and innovation. The Bio-X Seed Grants catalyze intellectual property and the formation of start-up companies, in addition to making the faculty much more competitive for federal grants, which contribute valuable resources to the university.

Our Investment: Bio-X awards two-year grants at $200,000 per project, for a total of $2 million every year. The program has provided critical early-stage funding to 165 interdisciplinary projects out of 700+ applications, involving over 750 faculty representing five Stanford Schools and dozens of departments.

The IIP awards have stimulated a striking increase in the number and diversity of collaborations between faculty across Stanford University.

Clark Center Auditorium

***1:00PM* — Introduction**

Carla Shatz, David Starr Jordan Director of Stanford Bio-X

***1:10PM* — Fully-Internalized Wirelessly-Powered Optogenetic Devices to Study Pain in Unconstrained and Complex Environments**

Ada Poon (Electrical Engineering), Scott Delp (Bioengineering, Mechanical Engineering), David Clark (Anesthesia)

Ada Poon

Original Proposal Abstract:

This project will produce a fully-internalized, wirelessly-powered optogenetic device to chronically and controllably perturb neuronal circuits involved in the perception of pain. Pain is an enormous healthcare problem. Unfortunately, intense basic research efforts have not yet translated into clinical breakthroughs. Our limited knowledge of how specific pain signaling pathways affect behavior is the major obstacle to the design of better treatments. The rise of optogenetics within neuroscience has enabled unprecedented levels of direct control over the activity of specific neuronal populations. This allows, in principle, the deciphering of how specific pain circuits influence complex behaviors without using highly artificial non-specific stimuli. In current systems, however, the need for tethered fiber cables or bulky external light sources constrain opportunities for studies of pain in freely moving and socially interacting animals; understanding pain, a multidimensional subjective sensation, requires an understanding of its impact on activity patterns and social interactions. Therefore, there is much interest in developing models of pain that feature animals freely interacting with their environment. The goal of this project is to design and build a wireless optogenetics system for the discovery of the relationships between the activation of specific pain fibers and animal behaviors in naturalistic environments, without constraints on animal location/interaction or requiring high levels of researcher intervention.

***1:30PM* — Innovating High-Resolution Novel Imaging Approaches to Elucidate Mechanisms of Prion-Like Spreading of Neurodegenerative Disease**

Jin Hyung Lee (Bioengineering, Neurology), Aaron Gitler (Genetics)

Jin Hyung Lee

Original Proposal Abstract:

Neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) are increasing in prevalence with our aging population. There are virtually no treatments for any of these devastating and ineluctably fatal disorders. Although disparate in their clinical presentation, a unifying theme is the accumulation of misfolded proteins in the brains of patients afflicted with these diseases. An exciting new area in neurodegenerative disease research (perhaps the most exciting) is the emerging phenomenon of prion-like spreading of neurodegenerative disease proteins. Prions are well established as the protein-based infectious agent underlying transmissible spongiform encephalopathies, such as mad cow disease. In these rare but devastating diseases, the prion protein converts from the normal soluble form to an aggregating self-templating infectious form. This process initiates an inexorable spread of neurodegeneration and functional failure throughout the brain. But could this phenomenon extend to the more common neurodegenerative diseases like PD and AD? If so, it represents a game changer in terms of understanding disease mechanisms and opens up many new and completely unexplored avenues for therapeutic development. However, any therapeutic or mechanistic investigation into prion-like spreading will require the development of powerful new imaging approaches to track the path of prion-like spread and understand how these protein aggregates alter the brain function as they spread. We aim to understand why they take some routes but not others and how this impacts brain function.

***1:50PM* — A Circadian Code for Fat Cell Differentiation**

Mary Teruel (Chemical & Systems Biology), Sanjay Lall (Electrical Engineering, Aeronautics & Astronautics), Allison Okamura (Mechanical Engineering)

Mary Teruel

Original Proposal Abstract:

The overall goal of this proposal is to understand how glucocorticoid oscillations link to fat cell production. Glucocorticoids are a powerful tool to treat many human illnesses, including asthma, rheumatoid arthritis, autoimmune diseases and cancer, and to prevent rejection following organ transplantation. While use of glucocorticoids has many beneficial effects, their use also leads to obesity, insulin resistance, diabetes, and osteoporosis. These harmful side effects are closely linked to production of too many or dysfunctional fat cells, resulting from the fact that glucocorticoids potently stimulate stem cells to differentiate into fat instead of bone.

We have recently shown that the conversion of precursor cells into fat cells is controlled by a bistable molecular switch that is driven by multiple feedback loops between critical regulator proteins and PPARG, the master transcriptional regulator of fat cell differentiation. Intriguingly we have shown that only certain frequencies of stimuli can be transmitted through the bistable switch to result in fat cell production. In using the Bio-X Seed Grant funding to understand this powerful filtering mechanism in fat cells, we hope to develop ways to deliver glucocorticoids to human patients for therapeutic purposes while preventing the harmful side effects resulting from glucocorticoid-driven fat cell production. In addition, given that many physiological signals are circadian, ultradian, or otherwise oscillatory in nature, the instrumentation and computational modeling tools that we are developing in this Bio-X seed grant work will likely open up many areas of new research.

***2:10PM* — Developing Mechanically Malleable Biomimetic Hydrogels for 3D Cell Culture and Tissue Regeneration**

Ovijit Chaudhuri (Mechanical Engineering), Yan Xia (Chemistry), Manish Butte (Pediatrics)

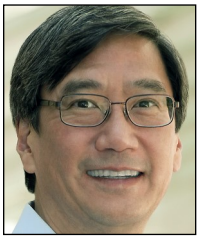
Ovijit Chaudhuri

Original Proposal Abstract:

Hydrogels are soft water-containing polymer networks, and have been used extensively to mimic the tissue microenvironment of cells *in vivo* for biological studies of cells in the lab, and to locally deliver drugs or cells to promote tissue regeneration. Despite this great interest, hydrogels exhibit significant limitations, as key cell behaviors such as cell migration or cell proliferation are inhibited when cells are placed within hydrogels. We have recently found that modulating the viscoelasticity of alginate hydrogels has a potent effect on key cell behaviors including cell proliferation and stem cell differentiation. Here we describe our work towards developing a new class of hyaluronic acid (HA) based hydrogels with unique and tunable viscoelastic properties for use in 3D cell culture and tissue engineering. New biocompatible chemistries were used for dynamic crosslinking of HA into hydrogels. These led to hydrogels that had tunable stress relaxation and creep responses. The hydrogels were found to be biocompatible and used in 3D cell culture studies. The long-term goal of this project is the development of a new class of materials that can be used to mimic the natural extracellular matrix for models of tissue and for use in promoting tissue regeneration.

2:30PM — Initial Feasibility Determination for a Novel AIDS Vaccine

Peter Kim (Biochemistry), James Swartz (Chemical Engineering, Bioengineering)



Peter Kim

Original Proposal Abstract:

Creating an AIDS vaccine remains a major unmet need—worldwide, 37 million people (1 in 200) are infected with HIV. In spite of over 30 years of intense efforts, an HIV vaccine is still not in sight. The proposed project aims to create an HIV vaccine in a novel manner, by targeting the process by which the virus infects cells.

In order to infect a cell, the viral membrane must fuse with the cell membrane. This membrane-fusion event is mediated by a specific protein on the surface of the virus (called gp41). Earlier work has identified an intermediate state of gp41 during membrane fusion, called the pre-hairpin intermediate. An FDA-approved drug, Fuzeon, works by binding to the gp41 pre-hairpin intermediate. In addition, we have shown that a monoclonal antibody against the pre-hairpin intermediate can prevent infection of cells by diverse clinical isolates of HIV. Taken together, these results validate our approach to target the pre-hairpin intermediate as a vaccine target.

In the current project, we aim to attach multiple copies of peptides that mimic the pre-hairpin intermediates (the antigens) to the surface of engineered nanoparticles developed in the laboratory of Prof. James Swartz (Departments of Chemical Engineering and Bioengineering, Stanford). These nanoparticle conjugates will be presented to the immune system together with immune stimulators (adjuvants) to elicit a more effective response. Our goal is to address this compelling global need to create an HIV vaccine by combining the expertise of the Kim and Swartz labs.

2:50PM — *In Vivo* Metabolic Imaging of Senescent Cells Using Hyperpolarized 13C MRS

Daniel Spielman (Radiology), Jianghong Rao (Radiology), Dean Felsher (Medicine)

Daniel Spielman

Original Proposal Abstract:

Senescence cells, cells that have lost the ability to divide, are now understood to have both positive effects in stopping the growth of cancer and negative effects driving the degenerative changes underlying aging and age-related disease. A growing appreciation of the significance of cellular senescence in health and disease has spurred considerable research into their role in tumor suppression while, at the same time, a landmark study demonstrating removal of senescent cells delaying ageing-associated disorders in mice, has driven an ongoing search for methods to remove or reduce the accumulation of senescent cells as a potential therapeutic intervention. Despite their importance, imaging of senescent cells remains limited to cell cultures and small animal models. Although multiple agents have been suggested for the detection of senescent cells, none of the existing methods have sufficiently low toxicity and high sensitivity and specificity to be currently applicable to human imaging studies. Furthermore, none of these agents target the more challenging problem of detecting and quantifying the removal or death of senescent cells. Exploiting the recent development of hyperpolarized substrates, i.e., MRI-visible compounds whose signal is orders of magnitude larger than that achieved under standard *in vivo* conditions, presents an unprecedented opportunity for *in vivo* metabolic imaging. The overall goal of this project will be to evaluate two novel magnetic resonance spectroscopy 13C-labeled hyperpolarized probes for the noninvasive in vivo metabolic imaging of the presence and removal of senescent cells respectively. These new metabolic imaging agents could provide important new abilities to assess the efficacy of senescent cell targeting agents for the treatment of cancer and age-related pathologies in both preclinical and clinical trials.

3:10PM — Benchtop Gene Synthesizer: Oligo-Templated Polymerization (OTP)

Mark Kay (Pediatrics), Ron Davis (Biochemistry)

Mark Kay

Original Proposal Abstract:

The ability to manipulate cellular function for biological discovery and medical therapeutics was greatly enhanced by molecular cloning and DNA sequencing technologies. However, the capacity to synthesize desired DNA gene sequences lags far behind, slowing the rapidity in which important experiments can be performed. De-novo DNA synthesis of large DNA molecules (3000 bp or longer) is generally avoided because even though the first non-templated DNA synthesis occurred 40 years ago, the technology remains old, inefficient, labor intensive and expensive. The current technology sets the practical limit of short DNA synthesis at no more than 200 bases with a minimal cost of ~$0.2 per base. Longer stretches of DNA substantially increase the cost because these short stretches have to be assembled which increases the production time to about 1 week per 1000 bases. Currently DNA-synthesis and assembly requires specialized equipment and training ultimately making out-sourcing a requirement. Our goal is to build a benchtop DNA synthesizer that can synthesize large stretches of DNA in a reliable, fast, simple, and cost effective manner. To do this, we have proposed Oligo-Templated Polymerization (OTP) as a process to synthesize DNA. OTP utilizes an array technology that will allow any desired single DNA base to be sequentially added to a chain in a manner dictated by simply typing in the desired DNA sequence. Based on our preliminary results, we plan to develop an instrument that can synthesize up to 10,000 DNA bases of choice at a rate of ~100 DNA bases per hour and a cost of $0.01 per base. The creation of such a device would allow every scientist in every lab to build a DNA sequence of choice in a simple, cost-effective, fast and reliable way. Vector cloning, one of today's most time and money consuming procedures, may become obsolete, along with the associated use of costly specialized kits and reagents. Scientific questions that were difficult to answer would become much simpler to accomplish.

3:30PM — Nanostraw Sampling to Monitor Cellular Reprogramming

Joseph Wu (Cardiovascular Medicine, Radiology), Nicholas Melosh (Materials Science & Engineering)

Nicholas Melosh

Original Proposal Abstract:

Human induced pluripotent stem cells (iPSC) have generated significant interest among biologists and clinicians for their potential to take a person's own cells and turn them into heart or other specialized cell types. However, how these cells become reprogrammed and the factors that lead to cell heterogeneity is not entirely known. One of the key impediments is being able to monitor what the cell is doing over time. This is normally done by rupturing the cells and looking at the internal contents, but this destructive process makes it impossible to use the cells afterwards. Ideally we would be able to follow what is inside the cell over time, without killing it. This has not been possible before for cells, however with the advent of nanotechnology we are building structures that are small enough to non-perturbatively penetrate the cell and 'sip' small quantities of material from the cell periodically. We show that we can sequentially sample the same cell or set of cells for a week or more, and further show the extracts are quantitatively related to the amount inside the cell. This technique can lead to safer and more reliable cell transformation techniques.

4:00PM

Poster Session

Nexus Café

Over 100 posters will be presented!

Odd-numbered posters will be presented from 4:00—4:45pm.
Even-numbered posters will be presented from 4:45—5:30pm.

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To learn more about Stanford Bio-X, please visit our website:

https://biox.stanford.edu/

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