Research Projects in the SMART BioSyM IRG

(April 27, 2010)

Major Research Areas

1. **3D in vivo Imaging to Understand How the Intestinal Epithelium Migrates**
   Regeneration of intestinal epithelial tissue is a complex dynamic process that involves division and differentiation of stem cells. To understand intestinal epithelium migration and the interactions between molecular motors and structural proteins, this project targets to develop new 3D imaging techniques with improved spatio-temporal resolution.

   MIT Investigator
   George Barbastathis (MIT, Mechanical Engineering)

   Singapore Collaborator
   Paul Matsudaira (NUS, Biological Sciences)

2. **High Throughput, High Content Multi-Focal Multi-Photon Microscopy**
   Commercial high numerical aperture microscope objectives are typically of low throughput, limited by the object-side field of view (FOV) which is typically less than 1 mm in diameter only. This project targets to develop a novel adaptive optics based high-resolution, wide FOV objective for multiphoton microscopy with a FOV of 7 mm. This system has the potential to greatly increase the throughput for many applications, including high-speed image cytometry for drug discovery.

   MIT Investigator
   Peter So (MIT, Mechanical and Biological Engineering)

   Singapore Collaborator
   Collin Sheppard (NUS, Bioengineering)

3. **Spatio-Temporal Image Analysis of Cell Sprouting with Bayesian Estimation**
   The aim of this work is to advance the understanding of cell behaviours and interactions with Bayesian estimation algorithms to provide more accurate interpretations of experimental data. The current focus is on analyzing the development of endothelial cell sprouts in “in vitro” experimentation. Results of this work would lead to closed-loop control of cell populations to a desired collective behaviour.

   MIT Investigator
   Harry Asada (MIT, Mechanical Engineering)

   Singapore Collaborator
   Marcelo Ang (NUS, Mechanical Engineering)

4. **Visualization of Angiogenic Pattern Formation Applying Hybrid Stochastic Dynamic Modeling to the Endothelial Cells Migration in the Microfluidic in vitro Environment**
   The dynamics of the tip cell and stalk cells migration in the gel matrix field are computationally modeled as a 3-dimensional stochastic agent. The objective of this project is to develop a computational tool that can visualize spation-temporal distribution of the multiple cells in the event of the angiogenic sprouting formation governed by novel hybrid stochastic dynamics based experimental observations.

MIT Investigator
Harry Asada (MIT, Mechanical Engineering)

Singapore Collaborator
Peter Chen (NUS, Mechanical Engineering)

5. Studies of Epithelial-Mesenchymal Transition (EMT) in Microfluidic Systems
These studies have the aim of understanding the nature of EMT from an epithelial cell line and identifying the nature of the phenotypical changes that lead to resistance of metastatic cells to normal cancer therapies.

MIT Investigator
Roger Kamm (MIT, Mechanical and Biological Engineering)

Singapore Collaborator
*Jean Paul Thiery (A*STAR, IMCB)*

6. Prolyl Hydroxylases-inhibitors Induced Angiogenesis in Microfluidic Device
The main goal of this project is to study the angiogenic effect of PHi on HUVEC cells in a defined way where the concentration gradient of growth factors can be established while the angiogenesis could be observed in a 3D scaffold which is a step closer to the in vivo condition.

MIT Investigator
Roger Kamm (MIT, Mechanical and Biological Engineering)

Singapore Collaborator
Michael Raghunath (NUS, Bioengineering & Biochemistry)

7. Micropatterned Hydrogels for Systems Biology of Mesenchyaml Stem Cell (MSC) Growth and Differentiation
Outstanding questions in the field of MSC biology revolve around the synergistic roles of autocrine and paracrine growth factors and extracellular matrix chemical composition and stiffness on growth, migration, and differentiation of stem cells. In this project, advanced 2D and 3D processing methods developed in the M.B.E.Chan/Hammond labs will be adapted to both existing hydrogel materials and new materials to create niches for MSC in the Griffith lab. An advantage of the approaches is the ability to pattern large areas with fidelity using robust processing methods.

MIT Investigators
Paula Hammond (MIT, Chemical Engineering)
Linda Griffith (MIT, Biological Engineering)

Singapore Collaborator
M.B.E.Chan (NTU, Chemical and Biomolecular Engineering)

8. Effects of Macromolecular Crowding on Mesenchymal stem cells (MSC) Structure & Function
MSCs are a type of pluripotent precursor cell found in bone marrow, which can be coaxed in vitro to express certain characteristics of differentiated mesenchymal tissue lineages. Many therapeutic applications of MSCs require isolation from a given patient, expansion to useful cell numbers in culture, and reimplantation. This project attempts to understand several fundamental questions of MSC through in-vitro studies and in vivo applications which remain unanswered.

MIT Investigator
Krystyn Van Vliet (MIT, Materials Science and Engineering and Biological Engineering)

Singapore Collaborator
Michael Raghnath (NUS, Bioengineering & Biochemistry)

9. Endometriosis

This project plans to integrate tissue engineering principles, novel biosensors, real time analysis and systems biology approaches in delineating the very early events leading to endometriosis. In addition, we will utilise advanced proteomic approaches to derive biomarkers of endometriosis activity which will be of relevance to the follow up of the disease course and its response to therapeutics.

MIT Investigators
Linda Griffith (MIT, Biological Engineering)
Steve Tannenbaum (MIT, Chemistry and Toxicology)

Singapore Collaborator
Jerry Chan (Duke-NUS Medical School)

10. Microfluidics Based Cell Sorting

The goal of this project it to develop and apply microfluidic tools for sorting cells based on their mechanical properties (size/deformability). Changes in the physical properties of cells are typically characteristic of many diseases as well as indicative of varying phenotypic functions within the same population.

MIT Investigator
Jongyoon Han (MIT, Electrical Engineering and Computer Science and Biological Engineering)

Singapore Collaborators
Lim Chwee Teck (NUS, Bioengineering and Mechanical Engineering)
Peter Chen (NUS, Mechanical Engineering)

11. Mesenchymal Stem Cell Interactions with Endothelial Cells

Endothelial cells require other cell types to develop into a mature and stable vascular network. In this study, microfluidic cell culture methods are used to examine these multi-cell type interactions.

MIT Investigators
Linda Griffith (MIT, Biological Engineering)
Roger Kamm (MIT, Mechanical and Biological Engineering)

Singapore Collaborator
Jerry Chan (NUS-Duke Medical School)

12. Single-Strand Binding Protein Binding to Single Stranded DNA

Such proteins are involved DNA replication and in DNA damage repairing process. This research aims to study the mechanical properties of DNA-SSB complexes. Two major experimental methods will be involved: (1).Magnetic tweezer manipulation of DNA-SSB co-polymer, (2) AFM imaging of DNA-SSB co-polymers.

MIT Investigators
Matthew Lang (MIT, Biological and Mechanical Engineering)
Patrick Doyle (MIT, Chemical Engineering)

Singapore Collaborator
Yan Jie (NUS, Physics)

13. Cross-Scale Image Quantification and Informatics Analysis of Liver Diseases

High throughput optical imaging capabilities will be developed to quantify molecular and cellular features in disease models in 3D tissue models, mice and rats; and correlate with data from clinical imaging modalities (MRI, ultrasound etc.) to establish the biological basis of the diagnostic imaging of liver diseases (cancer, cirrhosis and fatty liver).

MIT Investigator

Peter So (MIT, Mechanical and Biological Engineering)

Singapore Collaborators

Jagath Rajapakse (NTU, Computer Engineering, Bioinformatics)
Hanry Yu (NUS, Physiology)

14. Integrated Waveguide Based Particle Actuation and Imaging

A new concept for simultaneous manipulation and imaging of particles in an opto-fluidic platform. The main motivation is to enable cell and tissue manipulation and measurement functions while avoiding the mechanical complication of free-space optics surrounding the fluidic channel that plague traditional opto-fluidic systems. Our concept replaces the free space optics with a multimode waveguide where light localization for trapping and imaging is achieved through interference between field modes including reflections.

MIT Investigator

George Barbastathis (MIT, Mechanical Engineering)

Singapore Collaborator

Colin Sheppard (NUS, Bioengineering)

15. Manipulation of Stiffness Gradients in Extracellular Microenvironment through Stochastic Control of Magnetic-Particle Ensemble

The mechanical properties of microstructures that surround cells play an important role in determining the behavior of a cell population, including differentiation, proliferation, and apoptosis. The objective of this project is to develop engineering approaches to directly manipulate the extracellular microenvironment in order to produce desired changes in its stiffness.

MIT Investigator

Harry Asada (MIT, Mechanical Engineering)

Singapore Collaborator

Peter Chen (NUS, Mechanical Engineering)

16. Mesenchymal Stem Cell Differentiation as a Function of Forced Ligand-Receptor Interactions

This experiment-based project will focus on unique mechanical identification and sorting of stem cell state, particularly as a function of altered ligand-receptor binding kinetics.

MIT Investigators

Krystyn Van Vliet (MIT, Materials Science and Engineering and Biological Engineering)
Jongyoon Han (MIT, Electrical Engineering and Computer Science and Biological Engineering)
Linda Griffith (MIT, Biological Engineering)

Singapore Collaborators

Michael Raghunath (NUS, Bioengineering & Biochemistry)
Lim Chwee Teck (NUS, Bioengineering and Mechanical Engineering)

17. Mesenchymal Stem Cell Organization & Migration as a Function of Applied Stresses and Matrix Mechanics

This project will focus on mulitscale analysis of bone marrow-derived mesenchymal stem cells as a function of externally applied stresses and matrix/substrata properties such as mechanical stiffness.

MIT Investigators
Krystyn Van Vliet (MIT, Materials Science and Engineering and Biological Engineering)
Jongyoon Han (MIT, Electrical Engineering and Computer Science and Biological Engineering)
Linda Griffith (MIT, Biological Engineering)
Singapore Collaborator
Lim Chwee Teck (NUS, Bioengineering and Mechanical Engineering)

18. Kinetics of Adhesive Ligand-Receptor Interactions Under Force

This project will use molecular-scale experiments and simulations to predict the lifetime of key ligand-receptor complexes between cells and between cells and extracellular matrices.

MIT Investigators
Krystyn Van Vliet (MIT, Materials Science and Engineering and Biological Engineering)
Roger Kamm (MIT, Mechanical and Biological Engineering)

Singapore Collaborators
Michael Raghunath (NUS, Bioengineering & Biochemistry)
Lim Chwee Teck (NUS, Bioengineering and Mechanical Engineering)
*Jean Paul Thiery (A*STAR, IMCB)*

19. Primary Human Neural Stem Cells

To re-examine the role of FGF and EGF gradients in maintaining stemness and self-renewal, to examine the role of Notch in the same, and using lineage specific markers to track directed differentiation in real time.

MIT Investigators
Linda Griffith (MIT, Biological Engineering)
Roger Kamm (MIT, Mechanical and Biological Engineering)

Singapore Collaborator
Jerry Chan (NUS-Duke Medical School)

20. Viscoelastic Behavior of Cytoskeletal Network

To study experimentally and through theoretical modeling, the viscoelastic behavior of cytoskeletal networks.

MIT Investigator
Roger Kamm (MIT, Mechanical and Biological Engineering)

Singapore Collaborator
Kin Liao (NTU, Bioengineering)

21. Single-Molecule Studies of DNA Intercalators

Many ligands bind to DNA by intercalation. Famous examples are some commonly used DNA dyes and anti cancer compounds. This research investigates the interaction between DNA and DNA intercalators using a magnetic tweezer. Applying tensile force to the DNA enhances intercalation that results in DNA elongation. By monitoring the real time elongation of a single DNA, the kinetics and equilibrium properties of the interactions can be obtained with high accuracy.

MIT Investigator
Patrick Doyle (MIT, Chemical Engineering)

Singapore Collaborator
Jie Yan (NUS, Physics & Research Centre of Excellence in Mechanobiology)

22. Quantification of Crowding Induced DNA Folding

It was recently reported that crowding by PEG or dextran particles could induced DNA aggregation of single DNA folding. Details of the folding remain unclear. This research will investigate single DNA folding against a small force applied to the DNA by a magnetic tweezer. The critical force, at which folding and unfolding balance each other, is a direct measure of the energy involved in the process. In addition, the kinetics will reveal the energy barriers involved in the transition, from which one may figure out the most plausible geometry of the DNA condensate.

MIT Investigator
Patrick Doyle (MIT, Chemical Engineering)

Singapore Collaborator
Jie Yan (NUS, Physics & Research Centre of Excellence in Mechanobiology)

23. Single DNA Physics in Crowded Nanofluidic Devices

To perform single molecule experiments and modeling to understand DNA physics in highly confined nanofluidic devices and in the prescence of cell-mimicing crowding agents.

MIT Investigator
Patrick Doyle (MIT, Chemical Engineering)

Singapore Collaborators
Johan Van der Maarel (NUS, Physics)
Jeroen A. van Kan (NUS, Physics)
Jie Yan (NUS, Physics)

24. Nanofluidic Separation Chips for Large DNA Molecules

To design, construct and experimentally evaluate new nanofluidic ratchets and sieves for large DNA separations.

MIT Investigator
Patrick Doyle (MIT, Chemical Engineering)

Singapore Collaborators
Johan Van der Maarel (NUS, Physics)
Jeroen A. van Kan (NUS, Physics)

25. High-Speed Imaging of Cilia Motion from Nasal Biopsy Samples

Cilia motion of nasal epithelial cells will be imaged using a high speed camera and high resolution microscopy technique. The scientific goal is to develop and validate a multi-scale computational model for predicting cilia motion, as well as correlate the cilia motion parameters (beating frequencies etc.) to physiological/pathophysiological variables, in order to gain understanding and potentially identify physical 'biomarkers' from the measurement.

MIT Investigator
Jongyoon Han (MIT, Electrical Engineering and Computer Science and Biological Engineering)

Singapore Collaborators
Lee, Heow Pueh (NUS, Mechanical Engineering)
Khoo Boo Cheong (NUS, Mechanical Engineering)
De Yun Wang (NUH)

26. Biomechanical Study of Biofluids Using Micro/Nanofluidic Channels

To explore and study the rheological properties of various biofluids (e.g. mucus), especially within/around micro/nanofilter systems. The goal here is to identify useful physical biomarkers that can be correlated with the physiological/biochemical properties of these fluids.

MIT Investigator
Jongyoon Han (MIT, Electrical Engineering and Computer Science and Biological Engineering)

Singapore Collaborator
Yee-Choeng Lam (NTU, Mechanical & Aerospace Engineering)

27. On-Chip Magnetic Resonance Device for single cell and molecular-level detection

In this pilot project, we will design, fabricate and test such a microfluidic magnetic resonance spectroscopy system, with the intention of applying the tool to the magnetic, non-invasive cell monitoring and profiling. The two potential application modes are suggested, but more diverse applications are possible once the system feature is firmly identified.

MIT Investigator
Jongyoon Han (MIT, Electrical Engineering and Computer Science and Biological Engineering)

Singapore Collaborator
NGUYEN, Nam-Trung (NTU, Mechanical and Aerospace Engineering)