Miller Fellow Focus: Tom Hunt

Biologists have amazing tools to perform chemical manipulation and analysis. In contrast, the techniques for mechanical analysis of cells are relatively primitive. As a Miller Fellow, Tom explores the junction of biology and mechanics, building systems to help us understand this fascinating field.

**How do mechanical cues from the environment influence cellular changes?**

An exciting paper recently demonstrated that the stiffness of the substrate on which stem cells grow will tell the cells to differentiate into neuron, muscle, or bone cells. Tom would like to apply dynamic mechanical stress to developing tissue to further elucidate how the mechanical environment influences cellular changes.

Tom is collaborating with Mina Bissel’s lab at LBNL to determine how mechanical stress plays a role in the organization of tissue. The Bissel lab studies breast cancer and breast development. They have fashioned a model system to mimic the morphogenesis of breast tissue in 3D cell culture. They are currently working to set up mechanical stress fields to act on the 3D cell culture with the goal of understanding how physical stress influences tissue development, specifically mammary duct formation.

**How do the mechanical properties of cells cause disease?**

Tom is working with other researchers in the Fletcher lab to build artificial capillaries lined with cells. These artificial capillaries serve as a controlled system for studying diseases where blood cells jam in the microvasculature, such as sickle cell anemia and varieties of leukemia.

Biologists are constantly confronted with finding an experimental model that is simple enough to be manipulated and understood, while still relevant to the complex system under study. Typically, that means choosing between an *in vivo* system, such as a mouse model that can be hard to control and observe, or an *in vitro* system such as cultured cells, which are easy to work with, but are one step farther away from function in an organism.

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**Announcement: Call for Nominations**

Miller Fellow nominations are due on
**Thursday, September 11, 2008**

Miller Professor applications are due on
**Thursday, September 18, 2008**

Visiting Miller Professor Departmental nominations are due on **Monday, September 22, 2008**

More competition information on Page 3.
Figure 1: Stem cell differentiation as a function of substrate stiffness. Adapted from Ref. 1.

Our artificial capillaries have benefits of both *in vivo* and *in vitro* experimental systems. The capillaries can be precisely tailored for each experiment with identical, controlled geometries. Unlike *in vivo* capillary beds, input fluid can easily be controlled and microscopic imaging is straightforward. At the same time, because the capillaries are lined with endothelial cells just like capillaries in an organism, we will be assured that blood flowing through the channels interacts with the walls in a similar manner to the blood in your capillaries.

Along with Dr. Wilbur Lam, a hematologist and post-doc in the Fletcher lab, Tom’s research group will send cells from patients with blood diseases such as sickle cell anemia and leukemia through the artificial capillaries and observe the statistics of the jamming process and the effect of various drugs. Their first experiments will focus on blood diseases. Extensions of this work might investigate the details of clots and plaque that jam in the vasculature, causing stroke or heart attack.

**How can we develop mechanical assays for single cells?**

A high throughput cell mechanics analysis system would be useful both for fundamental studies in biology and to diagnose disease in the clinic. The ideal cell mechanics analysis system would interrogate a suspension of cells and output the mechanical properties of each one. Obtaining the properties of many individual cells is critical. A population average is insufficient because the information contained in the variation among cells is lost. On the other hand, analyzing just a few cells falls short of providing meaningful statistics for a highly variable population.

High frequency ultrasound is an excellent candidate for a cell mechanics analysis system. By measuring the amplitude and phase of ultrasound scattered by single cells, the stiffness of an individual cell can be determined in just a few microseconds.

If you know about light microscopy, it is interesting to note its parallels with ultrasound. For both techniques, resolution is limited by diffraction to approximately the wavelength that is being used for imaging. Wavelength is inversely proportional to frequency. A typical medical ultrasound uses frequencies (limited by absorption in tissue) of a few MHz, resulting in mm resolution. To resolve a single cell, radiation with wavelength on the order of a single cell, approximately 50 MHz, needs to be used. With borrowed transducers and a suite of cobbled together electronics, (including HAM radio / vacuum tube amplifiers purchased off of E-bay!), the scattering off of single cells could be seen. Unfortunately, there was an insufficient signal-to-noise ratio for measuring cell stiffness. Further optimization of the ultrasound transducers may enable us to turn ultrasonic cell analysis into a reality.

The ultrasound system was soon employed in another research direction. Vesicles, bags made from lipid bilayers, are ubiquitous in biology. Lipid bilayers form the cell membrane and other compartments for chemicals. Vesicles have applications as chemical containers for biological studies, and for targeted drug delivery: many molecules that will not otherwise enter cells can be delivered by vesicles that fuse with the cell membrane.

By aiming a tightly focused pulse of ultrasound at a lipid bilayer, a jet of liquid distends the bilayer, eventually pinching off a vesicle.

Figure 2: Edge of an artificial capillary lined with fluorescently labeled endothelial cells.
The Miller Institute seeks to discover and encourage individuals of outstanding talent and to provide them with the opportunity to pursue their research in the sciences. The Fellowships are intended for brilliant young women and men of great promise who have recently been awarded or who are about to be awarded the doctoral degree. Early nominations are encouraged to allow the candidate more time to prepare and submit their application materials and request references by deadline. Nominations can be submitted by e-mail, fax or mail to arrive on or before deadline. Nominations may be submitted by UC faculty, faculty from other universities, current and former Miller Institute members and other distinguished scientists worldwide. A Nomination Form is available on our website. Nominations can also be a letter that must include the nominee’s: 1) Full Legal Name 2) Current, complete E-mail address, Mailing address, Phone & Fax numbers 3) Date (Expected) of Ph.D. & Ph.D. Institution and 4) Recommendation and judgment of the candidate’s promise by the nominator. To ensure that nominees receive our correspondence, the nomination letter must provide an active and accurate e-mail address for the nominee. Incomplete nominations cannot be processed. Suitable nominees will be invited to submit documentation supporting their nomination. Such material will be accepted only following invitation from the Institute. Direct applications are not accepted. Please note that persons in positions on the Berkeley campus are not eligible for nomination or receipt of an award. This means that an individual cannot be on campus at the time of nomination or throughout the competition cycle.

The Institute provides Miller Fellows with an annual stipend of $60,000 and a research fund of $12,000 per annum. Each Miller Fellow is sponsored by an academic department of the Berkeley campus and performs his or her research in the facilities provided by the host UC Berkeley academic department. The Miller Institute also provides benefits including medical, dental, vision and life insurance. Fellowships will be awarded for three years, generally beginning August 1. Miller Fellows are selected on the basis of their academic achievement and the promise of their scientific research. Approximately eight to ten Fellowships are awarded each year. Eligibility for non-US citizens is contingent upon their ability to obtain J-1 Scholar visa status for the duration of the Miller Fellowship. The Miller Institute cannot support H1B status. Candidates will be notified of the results of the competition in January and a general announcement of the awards will be made in the spring.

The Miller Research Fellowship Program is open only to faculty of the University of California. Applications received will be considered for either the full academic year, beginning July 1, 2009, or one semester of Academic Year 2009-2010, the semester to be determined by the applicant in consultation with the department. Professorial salary and benefits for a regular 9/12 academic year or semester will be paid by the Miller Institute; other UC campus faculty must seek sponsorship of a Berkeley campus academic department before making an application and need to submit endorsement letters from the Berkeley campus Department Chair as well as their home campus Department Chair. The Miller bequest requires that the research be conducted on the Berkeley campus, so no extended absences from the campus should be planned for the term of the Miller appointment. Candidates will be notified of decisions in December.

*Visiting Miller Professorship Program*

Deadline for RECEIPT of nominations is 4 p.m. Monday, September 22, 2008

This program is open only to faculty of the University of California. Applications received will be considered for either the full academic year, beginning July 1, 2009, or one semester of Academic Year 2009-2010, the semester to be determined by the applicant in consultation with the department. Professorial salary and benefits for a regular 9/12 academic year or semester will be paid by the Miller Institute; other UC campus faculty must seek sponsorship of a Berkeley campus academic department before making an application and need to submit endorsement letters from the Berkeley campus Department Chair as well as their home campus Department Chair. The Miller bequest requires that the research be conducted on the Berkeley campus, so no extended absences from the campus should be planned for the term of the Miller appointment. Candidates will be notified of decisions in December.
The Miller Institute congratulates the following Miller Fellows on their next endeavors.

**Sophie Chen**  
Member  
School of Mathematics  
Institute for Advanced Study  
Princeton, NJ

**Josef Dufek**  
Assistant Professor  
School of Earth and Atmospheric Sciences  
Georgia Institute of Technology

**Josh Eisner**  
Assistant Professor  
Astronomy  
University of Arizona

**Ed Feng**  
Postdoctoral Fellow  
Sandia Laboratories  
Lawrence Livermore National Labs

**David Jenkins**  
Assistant Professor  
Chemistry  
University of Tennessee

**Corrie Moreau**  
Assistant Curator  
Zoology  
Field Museum of Natural History  
Chicago, IL

**Feng Wang**  
Assistant Professor  
Department of Physics  
UC Berkeley

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### Birth Announcement


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### Obituary

**Murray Protter** (Miller Professor 1959 - 1960, 1967 - 1968; Miller Executive Director 1981 -1983) passed away on May 1st due to congestive heart failure. He was a former chair of the Mathematics Department at UC Berkeley and the co-author of a very popular calculus textbook. He was 90 years old.
The technique is analogous to a child blowing bubbles, with water on the inside and outside of the bubble instead of air.

When Tom is not studying the intersection of mechanics and biology, you can find him enjoying the outdoors somewhere in California.

Endnotes

1AJ Engler et. al. Cell 126, 677, 2006

Figure 3: A focused pulse of 17MHz ultrasound, incident from the left, distends the lipid bilayer, and membrane tension pinches off a vesicle.
Interdisciplinary Symposium
June 2008

Nima Arkani-Hamed, Avi Loeb, Salil Vadhan, and Phil Chang

David Chandler, Horst Rademacher, Haynes Miller, Madeleine Nash, and Susan Lindquist attempt to unravel a knot.

Michael Manga, Joe Dufek, and Sasha Turchyn

David Shelly, Maryam Modjaz, Jacqueline van Gorkom, and Alice Shapley

Above: Attentive audience; Right: Speaker Susan Lindquist

For more pictures from the Symposium, visit:
http://millerinstitute.berkeley.edu/page.php?nav=125
Mimi Koehl Begins Term as Executive Director

On July 1, 2008, The Miller Institute named Professor Mimi Koehl as Executive Director. For the next two years, she will lead the Executive Committee which is made up of four Berkeley faculty members who meet on a regular basis to guide the activities of the Institute. Members of the Institute’s Executive Committee include Jonathan Arons, Alberto Grünbaum and Richard Saykally.

The Institute’s Advisory Board includes the Executive Committee, as well as four members from outside of the University of California Berkeley, who join together once a year to select Miller Professors and Visiting Miller Professors and to review the Institute and to advise on its policies and programs. Berkeley Chancellor, Robert Birgeneau serves as the Chair of the Advisory Board. Other members of the Advisory Board include Roger Blandford (Stanford University), Elizabeth Blackburn (UCSF), Jennifer Chayes (Microsoft Research) and Michael Klein (U Penn).

Randy Schekman Named First Miller Senior Fellow

The Miller Institute for Basic Research in Science has named Randy Schekman, professor of molecular and cell biology, as its first Miller Senior Fellow. The new program provides selected faculty with significant discretionary research funds as recognition of their distinction in scientific research.

Senior Fellow appointments of tenured Berkeley faculty will be made (at a rate of roughly one per year) for five years, possibly renewable for a subsequent five years. Each Senior Fellow will receive an annual research stipend of $50,000 for use at his or her discretion. Formal obligations to the Institute will be limited.

Nominations, solicited by invitation only, will be due no later than Sept. 30 for appointments to take effect in 2009-10. For more information, contact Kathryn Day at 642-4088, millerinstitute@berkeley.edu, or visit millerinstitute.berkeley.edu/page.php?nav=126.

Welcome 2008-2011 Miller Fellows

Pascal Audet  Philip Hopkins  Prashant Jain  Isamu Matsuyama  Dan Nicolau

Marcus Roper  Raman Sanyal  Eva Schmid  Rebecca Schulman  Jonathon Shlens
The following Miller Institute members have recently published works resulting from research during their Miller Institute terms. For more information about these publications, please visit the Miller Institute’s website at: millerinstitute.berkeley.edu/publications.htm.

**Bernhard Blümich**  
Visiting Miller Professor Fall 2006

**Corrie Moreau**  
Miller Fellow 2007-2008

**Steven Brenner**  
Miller Professor 2007 - 2008

**David Shelly**  
Miller Fellow 2007-2008

**Josef Dufek**  
Miller Fellow 2006-2008

**Annie Tsong**  
Miller Fellow 2005-2008

**Feng Wang**  
Miller Fellow 2005-2008

*The Miller Institute is “dedicated to the encouragement of creative thought and the conduct of research and investigation in the field of pure science and investigation in the field of applied science in so far as such research and investigation are deemed by the Advisory Board to offer a promising approach to fundamental problems.”*