

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 cells¹. 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 orga-

nization 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 culture². 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 ex-



perimental 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.

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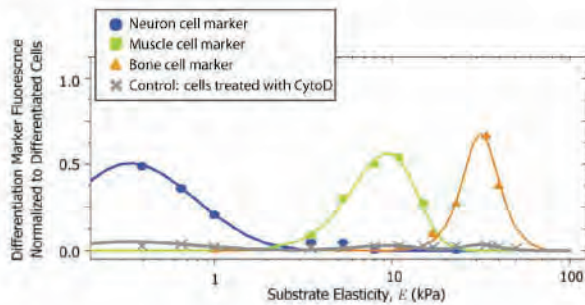


Figure 1: Stem cell differentiation as a function of substrate stiffness Adapted from Ref.1

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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.

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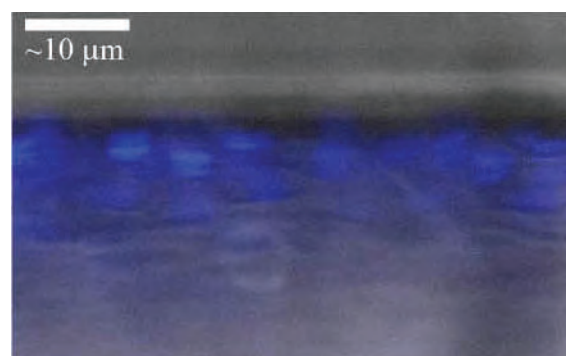


Figure 2: Edge of an artificial capillary lined with fluorescently labeled endothelial cells.

Miller Research Competitions

REMINDER

Forms and information are available on our website at <http://millerinstitute.berkeley.edu>

Direct questions to Kathryn Day at the Miller Institute office at 642-4088 or at millerinstitute@berkeley.edu

Miller Research Fellowships for 2009-2012 Deadline for RECEIPT of nominations is 4 p.m.

Thursday, September 11, 2008.

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.

Miller Research Professorship Program Deadline for RECEIPT of applications is 4 p.m.

Thursday, September 18, 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.

*Visiting Miller Professorship Program Deadline for RECEIPT of nominations is 4 p.m.

Monday, September 22, 2008

*See new submission procedures details on the website.

*Departments submit nominations by way of their Department Chairs by email attachment. The Institute will make copies. Each complete nomination packet should be submitted separately by email or personally delivered to the Institute. The Chair and Faculty Sponsor will receive an email reply of receipt of nomination. Incomplete nominations cannot be processed and the Chair will be notified. If a receipt email is not received, please contact us to ensure the nomination was received for processing. Please note that nominations are to be submitted by Berkeley faculty by way of their Department Chair. Direct applications are not appropriate. Terms for Visiting Professorships range from two weeks to one full semester and must take place during Fall 2009 or Spring 2010. Please note that nominees who are non-US citizens are contingent upon eligibility for obtaining J-1 Scholar visa status for the duration of the Visiting Miller Professor appointment. The Miller Institute does not support H1B visa status. The purpose of the Visiting Miller Professorship is to bring promising or eminent scientists to the Berkeley campus on a short-term basis for collaborative research interactions. It is required that awardees be hosted by UC Berkeley academic departments and that their research be conducted on the Berkeley campus. Awardees are expected to be in residence at Berkeley during their entire Miller Institute appointment terms and the visit should run in consecutive weeks. Travel during appointment is not allowed and will result in adjusted stipend and living expense payments. Announcements of the awards will be made in December.

Next Steps

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

Birth Announcement

Congratulations to **Noelle** and **Alex Filippenko** (Miller Fellow 1984 - 1986, Miller Professor Spring 1996, Spring 2005) on the birth of their son, Orion Nikolai Alekei Filippenko — born July 1, 2008.

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.

Awards & Honors

July 29, 2008: **Marius Crainic** (Miller Fellow 2001 - 2002) was awarded the André Lichnerowicz Prize in Poisson geometry.

July 7, 2008: **Tamas Hausel** (Miller Fellow 1999 - 2002) was awarded a Whitehead Prize from the London Mathematical Society for his work on hyperkähler geometry.

June 20, 2008: **Richard Karp** (Miller Professor 1980 - 1981 and Miller Institute Executive Director 1994 - 1995) has been named a 2008 Kyoto Prize laureate.

June 10, 2008: **Reinhard Genzel** (Miller Fellow 1980 - 1982) was awarded the Shaw Prize in Astronomy.

May 9, 2008: The University of California, Santa Cruz, has appointed **Ingrid Parker** (Miller Fellow 1996 - 1998), Associate Professor of Ecology and Evolutionary Biology, to the newly established Jean H. Langenheim Endowed Chair in Plant Ecology and Evolution.

May 1, 2008: **Rory Waterman** (Miller Fellow 2004 - 2007) was awarded an NSF Career Award for "Investigations of Zirconium-Catalyzed Phosphorus-Element Bond-Forming Reactions".

April 29, 2008: **Jasper Rine** (Miller Professor Fall 1993) and **Jack Wisdom** (Visiting Miller Professor Fall 2007) have been elected to the National Academy of Science.

April 29, 2008: Six Miller affiliates have been elected to the American Academy of Arts and Sciences:

Eddie Dekel-Tabak (Miller Fellow 1986 - 1988)

Mark Kirkpatrick (Miller Fellow 1983 - 1985)

Marsha Lester (Visiting Miller Professor Spring 2003)

Adam Riess (Miller Fellow 1996 - 1998)

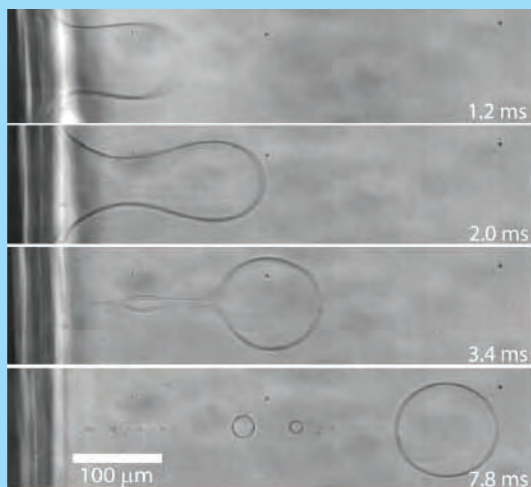
Jasper Rine (Miller Professor Fall 1993)

Ewine Van Dishoeck (Visiting Miller Professor Fall 2000)

April 22, 2008: **Alexandre Chorin** (Visiting Miller Professor Fall 1971, Spring 1972, Miller Professor 1982 - 1983) was awarded the Sarlo Distinguished Graduate Student Mentoring Award.

Miller Fellow Focus

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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

²JE Fata et. al. *Developmental Biology* 306, 193, 2007

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



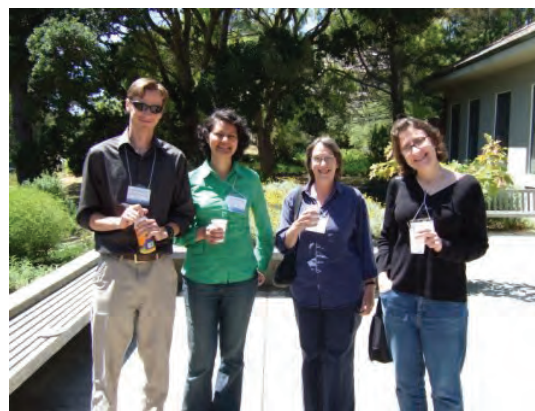
Nima Arkani-Hamed, Avi Loeb, Salil Vadhan, and Phil Chang



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>

New Miller Institute Appointments

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



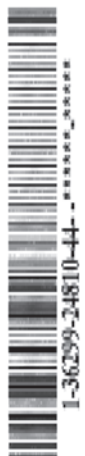
Rebecca Schulman



Jonathon Shlens



Non-Profit
Organization
U.S. Postage
PAID
University of
California



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Publications

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."