MILLER INSTITUTE NEWSLETTER

Fall 2006

Miller Fellow Focus: Chris Fromme

Third-year Miller Fellow Chris Fromme is a biochemist working with Professor Randy Schekman in the department of Molecular and Cell Biology.

Cells are the basic building blocks of life, and all living things are composed of cells. The smallest living things are tiny bacteria, just a single cell about 1/10 of a cubic micron in size, whereas humans have approximately 10 trillion cells with a typical size of about 100 cubic microns each. Yet, as small as cells are, within each one there are thousands of different proteins performing various tasks essential for the survival, growth, and reproduction of the cell. Cells do not "think", but they are able to perform seemingly intelligent actions because the chemical properties of their constituent proteins (and of other important components such as DNA and RNA) have been fine-tuned by millions of years of evolution.

Chris' interests lie in understanding how proteins control sub-cellular events, and determining what aspects of a protein's chemical make-up are important for it to perform its function. During his thesis work with Professor Gregory Verdine at Harvard University, Chris studied a few proteins that repair DNA damaged by oxidation – those nasty free-radicals you may have heard of. These proteins, called DNA glycosylases, have a very important job. If damaged DNA is not repaired it can become mutated, thus permanently altering the genetic blueprint, usually for the worse. Many cancers, and the very act of aging itself, are thought to be caused in part by mutations arising from damaged DNA. Some of the potential sources of damage come from the environment, including cigarette smoke and sunlight, but the very act of "breathing" for a cell (called cellular respiration) generates free-radicals that can damage DNA. Therefore, even those organisms that do not smoke and live in the dark still possess DNA glycosylases to help maintain the integrity of their genomes.

In order to gain a further understanding of how these important proteins are able to detect and repair damage within DNA, Chris decided to find out what a few different DNA glycosylases actually look like during the repair process. Using a technique called X-ray crystallography, he was able to obtain atomic-level "pictures" of the proteins interacting with damaged DNA (Figure 1). He used chemical tricks to trap the proteins

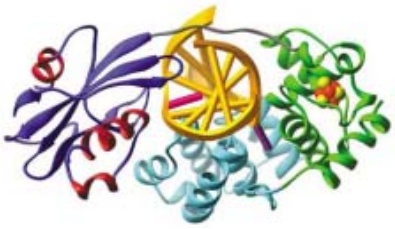

Figure 1: X-ray crystal structure of a DNA repair protein (in blue, red, and green) interacting with damaged DNA (in gold).

before, during, and after the repair process, and obtained atomic snapshots of each state, therefore allowing a very detailed look at which parts of the proteins are most important for repair.

Here at Berkeley, Chris has shifted focus and methodology. His host, Randy Schekman, is largely responsible for mapping out the genes involved in the sub-cellular secretory pathway. This pathway is responsible for the synthesis and movement of secreted proteins (such as insulin, which is secreted into the bloodstream

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Deadlines To Note:

Thursday, September 14
Miller Fellowship nominations due

Thursday, September 21
Miller Professor applications due

Monday, September 25
Visiting Miller Professor departmental nominations due

More competition information available on Page 3.

INSIDE THIS EDITION

by your pancreas after you eat). The secretory pathway's apparatus consists of numerous proteins and several distinct membrane-bound compartments. Cells themselves are bounded by a membrane at their periphery – the "plasma membrane" – which is critical for separating a cell from its environment (keeping the outside out and the inside in). But cells also have internal membranes used for compartmentalizing, and thus increasing the efficiency of, various sub-cellular functions. The secretion apparatus also controls the movement of proteins between many of these membrane-bound compartments, much like an intertwined subway system shuttling people between stations. It is for this reason that people who study the secretory pathway often refer to it as "protein trafficking".

Chris focuses on an early event in protein trafficking – the movement of secretory proteins out of the "endoplasmic reticulum" (the membrane-bound compartment into which secretory proteins are synthesized) and into a newly-forming membrane vesicle. A membrane vesicle is like a subway-car for proteins – it has a specific destination, and it moves proteins from one part of the cell to another. He studies vesicle formation by reconstituting the process in a test tube. This "*in vitro* (Latin for *in glass*) reconstitution" is a powerful technique for studying a complex biological event, because it enables one to determine the minimum requirements for that event to occur, and it allows for the event to be studied in isolation, therefore simplifying the analysis.

In order to reconstitute vesicle formation, he needs two things. First, it helps to have purified versions of the proteins responsible for forming the vesicle (these are the proteins that help to form the subway-car; they are not the protein passengers). He does this by genetically engineering viruses to encode the genes for the proteins of interest, using those viruses to infect a large culture of insect cells, allowing the infected insect cells to produce a large amount of the proteins over a few days, and finally isolating and purifying the desired proteins using some more chemical tricks. The second step towards reconstituting vesicle formation in a test tube is to isolate a crude preparation of the endoplasmic reticulum, which contains the passenger proteins that will be taken up into a newly-formed vesicle. The endoplasmic reticulum is isolated from living cells by using a special detergent to punch holes in cells grown on Petri dishes. Most of the soluble contents of the cell (the cytoplasm) are then washed away, and a functional endoplasmic reticulum remains.

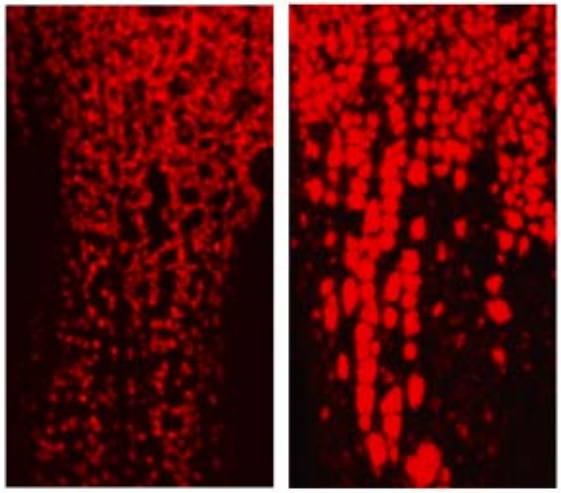

Figure 2: Comparison of the swollen endoplasmic reticulum (in red) of a cell from a CLSD patient (right) to that from a healthy individual (left).

Once the purified proteins and isolated endoplasmic reticulum are in hand, they are mixed together into a single reaction along with a chemical energy source. Then, if Chris is lucky, vesicles may form with protein passengers inside of them. These vesicles can be separated from the much larger endoplasmic reticulum by centrifugation and their contents can be analyzed by probing for the presence of certain protein passengers. The beauty of this system is that it can be perturbed in many different ways, such as by using different kinds of purified proteins to form the vesicles, and several different protein passengers can be studied simultaneously in a single reaction.

Recently, Chris has benefited from collaboration with Simeon Boyd, a clinical geneticist at UC Davis. Chris is using the *in vitro* reconstitution system to reveal the molecular basis for a rare genetic disease, cranio-lenticulo-sultural dysplasis (CLSD), that Simeon has shown to be caused by a mutation in one of the genes necessary for vesicle formation. Chris hopes his studies can help to explain how this specific defect in the secretory pathway (Figure 2) leads to the cranial and skeletal defects and cataracts seen in CLSD patients.

In the future, Chris hopes to combine his newfound love of cellular biochemistry with his old passion of structural biology in order to illuminate the deepest, darkest secrets of cells. When he is not in the lab, Chris might be found hiking, biking, skiing or backpacking with his wife Alison somewhere in California.

Miller Research Competitions

REMINDER

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

Miller Research Fellowships for 2007-2010: ***The deadline for receipt of nominations is 4:00 p.m. Thursday, September 14, 2006.***

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. 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 Name 2) Current, complete e-mail address, mailing address, phone & fax 3) Date *(Expected)* of Ph.D. & Ph.D. institution and 4) Recommendation and judgment of the candidate's promise.** To ensure that nominees receive our correspondence, the nomination letter *must* provide an active and accurate e-mail address for the nominee. 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.*

The Institute provides Miller Fellows with an annual stipend of $50,000 and a research fund of $12,000 per annum. Support funds of up to $1,000 per year are provided to departments to offset the costs associated with hosting a Miller Fellow. Each Miller Fellow is sponsored by a department of the Berkeley campus and performs his or her research in the facilities provided by the host 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. Non-US citizens are eligible for nomination, however such candidates must be eligible for J-1 scholar status for the duration of the Fellowship. The Miller Institute cannot support the 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: ***The deadline for receipt of applications is 4:00 p.m. Thursday, September 21, 2006.***

This program is open only to faculty of the University of California. Applications received will be considered for the full academic year, beginning July 1, 2007, or one semester of academic year 2007-2008, the semester to be determined by the applicant in consultation with the department. Salary and benefits for a standard 9/12 academic year or semester will be paid by the Miller Institute; other UC campus faculty should seek sponsorship of a Berkeley department before making an application. The Miller bequest requires that the research be performed on the Berkeley campus, so no extended absences from the campus should be planned for the term of the appointment. Please note that both full year or one-semester appointments will be considered, and applications for full year appointments should be adequately justified. Candidates will be notified of decisions in December.

Visiting Miller Professorship Program: ***The deadline for receipt of nominations is 4:00 p.m. Monday, September 25, 2006.***

Nominations by Berkeley faculty must be made by way of their Academic Department Chair. 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. The term for a Visiting Professorship ranges from two weeks to one full semester and must take place during Fall 2007 or Spring 2008. *Non-US citizens must be eligible for J-1 Scholar visa status for the duration of the appointment. The Miller Institute does not support H1B visa status.* 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 appointment terms with the Institute and the visit should run in consecutive weeks. Travel during appointment will result in adjusted stipend and living expense payments. Announcements of the awards will be made in December.

Questions concerning any of these programs may be directed to Kathryn Day at the Miller Institute office at 2-4088. Please send materials to the address below.

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(510) 642-4088 Office ~ (510) 643-7393 Fax ~ E-Mail Address: millerinstitute@berkeley.edu
http://millerinstitute.berkeley.edu

Next Steps

The Miller Institute congratulates outgoing Miller Fellows on their next endeavors.

ZACHARY BALL
Assistant Professor and
Norman Hackerman - Welch Young Investigator
Department of Chemistry
Rice University

IOANA DUMITRIU
Assistant Professor
Department of Mathematics
University of Washington

ERIC FORD
Assistant Professor
Department of Astronomy
University of Florida, Gainesville
(following one year of postdoctoral research at the Harvard-Smithsonian Center for Astrophysics in Cambridge, Massachusetts)

SUBHADEEP GUPTA
Assistant Professor
Department of Physics
University of Washington
(following one year of postdoctoral research at the UC Berkeley Department of Physics)

ANAT HERSKOVITS
Post-doctoral Fellow
Department of Molecular & Cell Biology
UC Berkeley

SÉBASTIEN MERKEL
Researcher
Centre National de la Recherche Scientifique
France

OVIDIU SAVIN
Assistant Professor
Department of Mathematics
Columbia University, New York

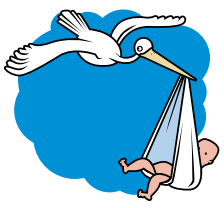
SERGIO SPEZIALE
Researcher
Geoforschungs Zentrum
Potsdam, Germany

TAIZAN WATARI
Moore Postdoctoral Scholar in Theoretical Astrophysics
Department of Physics
California Institute of Technology

RORY WATERMAN
Assistant Professor
Department of Chemistry
University of Vermont

Birth Announcements

Congratulations to Stéphane Bodin (Miller Fellow 2002-05) and his wife Lisa on the birth of their daughter, Alais. Alais was born on July 2, 2006.



Congratulations to Irit Dinur (Miller Fellow 2003-04) and Hadar Benyamini on the birth of their son Yonatan on April 15, 2006.

Congratulations to Adam Summers (Miller Fellow 1999-2001) and his wife Sharalyn on the birth of their daughter, Eleanor Elektra Lehman. Eleanor was born on August 5, 2006.

Awards & Honors

The National Academy of Sciences elected the following Miller Members: **Jillian Banfield** (Miller Professor 2006-07), **Michael Marletta** (Visiting Miller Professor 2000), and **Dan Voiculescu** (Miller Professor 1997-98)

George Oster (Miller Professor 1983-84, Fall 2003) and **Pravin Varaiya** (Miller Professor 1978-79) were named to the American Academy of Arts and Sciences.

Alison Galvani (Miller Fellow 2002-05) and **Bin Yu** (Miller Professor Spring 2004) were awarded 2006 Guggenheim Foundation Fellowships.

Gibor Basri (Miller Professor 1997-98) was awarded the Chancellor's Award for Advancing Institutional Excellence.

John Hardy (Miller Fellow 1967-69) was awarded the 2006 Tom Bonner Prize in Nuclear Physics from the American Physical Society. He also received the 2006 Distinguished Achievement Award for Research from the Association of Former Students of Texas A&M University.

Jiaxing Huang (Miller Fellow 2004-2007) will receive the 2006 National Starch & Chemical Award for Outstanding Graduate Research.

David Milstein (Visiting Miller Professor Spring 2006) was elected to the German Academy of Sciences Leopoldina.

Adam Riess (Miller Fellow 1996-98) was one of three recipients of the 2006 Shaw Prize, with an award of $1 million. He, Saul Perlmutter, and Brian Schmidt received this award for their leadership in the discovery of the current acceleration of the expansion of the Universe (and the early era of deceleration).

Mark R. Rosenzweig (Miller Professor 1958-59, 1965-66) was awarded the degree of doctor honoris causa by the University of Montreal.

Günter M. Ziegler (Visiting Miller Professor 2001) was elected the President of the German Mathematical Society (DMV) for 2006-07. In January 2006 he also received the Chauvenet Prize of the Mathematical Association of America.

The Miller Institute's Tenth Annual Interdisciplinary Symposium June 2006

Josh Eisner, Bjorn Poonen, Stacey Combes, Raghu Parthasarathy, Jarmila Pittermann, and Herbert Koch

Eric Ford, David Jenkins, Matt Reidenbach, and Greg Engel

L. Mahadevan and David Chandler

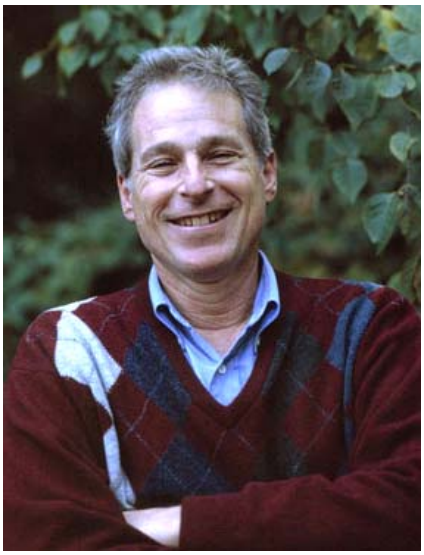
Raymond Jeanloz and Chris Dobson

Clockwise from back: Alex Thompson, Chris Fromme, Matt Reidenbach, Ed Feng, Greg Engel, Phil Chang, Matt Francis, Saurabh Jha, Josh Eisner, Erin Cunningham, Suling Tan, and Stacey Combes

Inez Fung and Akkihebbal Ravishankara

Miller Institute Leadership

The Miller Institute's leadership structure is comprised of an Executive Committee and an Advisory Board. The Executive Committee is made up of four Berkeley faculty members who meet on a regular basis to guide the activities of the Institute. The Advisory Board includes the Executive Committee as well as four members from outside of the University of California, 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 and Professor David Chandler serves as the Institute's Executive Director. Other members of the Institute's Executive Committee include Jonathan Arons, Alberto Grunbaum and George Oster.



Professor David Chandler, Department of Chemistry, appointed Executive Director of the Miller Institute July 1, 2006

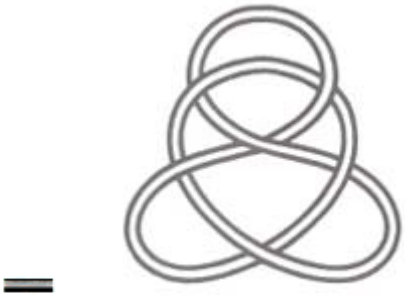
The Institute is pleased to welcome two new members to its Advisory Board. As of July 1, 2006 the Institute expanded the outside board from three to four members. Joining Nancy Kopell and Gerald Fink on the Board are Jennifer Chayes and Michael Klein.

Jennifer Tour Chayes is an expert in the emerging field at the interface of mathematics, physics and theoretical computer science. Her current research interests include phase transitions in combinatorics and computer science, structural and dynamical properties of self-engineered networks, and auction algorithms. Chayes is co-founder and co-manager of the Microsoft Theory Group, as well as Research Area Manager for Mathematics and Theoretical Computer Science at Microsoft Research. She is also an affiliate Professor of Mathematics and Physics at the University of Washington.

Michael L. Klein is the Hepburn Professor of Physical Science at the University of Pennsylvania. At present, his research is focused on quantum and classical computer simulation of condensed matter and biophysical systems at the atomic level with emphasis on the relationship between intra- and inter-molecular interactions and physical properties. The focus is on applications to realistic systems as well as developing new simulation methodologies.

Nancy Kopell is currently co-director of the Center for BioDynamics (CBD) at Boston University. This multidisciplinary, interdepartmental center aims to train undergraduates, graduates, and postdoctoral fellows in leading techniques from dynamical systems theory and its applications to biology and engineering. Her current research interests are mathematical modeling of networks of neurons in vertebrates and invertebrates; special interest in networks having oscillatory behavior, such as those governing rhythmic motor behavior, thalamocortical and hippocampal networks; and the use of mathematics to investigate how properties of cells and small networks affect the dynamics of the larger networks that contain them.

Gerald Fink is a Founding Member of the Whitehead Institute and American Cancer Society Professor of Genetics at MIT. Fink developed baker's yeast as a model for studying the fundamental biology of all organisms and his creative use of classical genetics, biochemistry, and molecular biology has yielded numerous discoveries in biology. His lab has pioneered a better understanding of gene regulation, mutation, and recombination. A key contribution to the field was his development of a technique for "transforming" yeast that allowed researchers to introduce a foreign piece of DNA into yeast cells and study the inheritance and expression of that DNA.



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Please send address corrections to:
miller_adm@berkeley.edu

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: http://millerinstitute.berkeley.edu/publications.htm

Zachary Ball
Miller Fellow 2004-06

Ioana Dumitriu
Miller Fellow 2003-06

Daniel Eisenstein
Visiting Miller Professor Fall 2005

Eric Ford
Miller Fellow 2003-06

Jiaxing Huang
Miller Fellow 2004-07

Sydney Kustu
Miller Professor 2005-06

Richard Losick
Visiting Miller Professor
Spring 2006

Sébastien Merkel
Miller Fellow 2004-06

Peter Molnar
Visiting Miller Professor
Fall 2005

Sergio Speziale
Miller Fellow 2003-06

Pierre Van Moerbeke
Visiting Miller Professor
Fall 2005

Taizan Watari
Miller Fellow 2003-06

Rory Waterman
Miller Fellow 2004-06

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."