Biochemistry NEWSLETTER 2008

UNIVERSITY OF WISCONSIN-MADISON

For friends of the Department of Biochemistry at the University of Wisconsin–Madison

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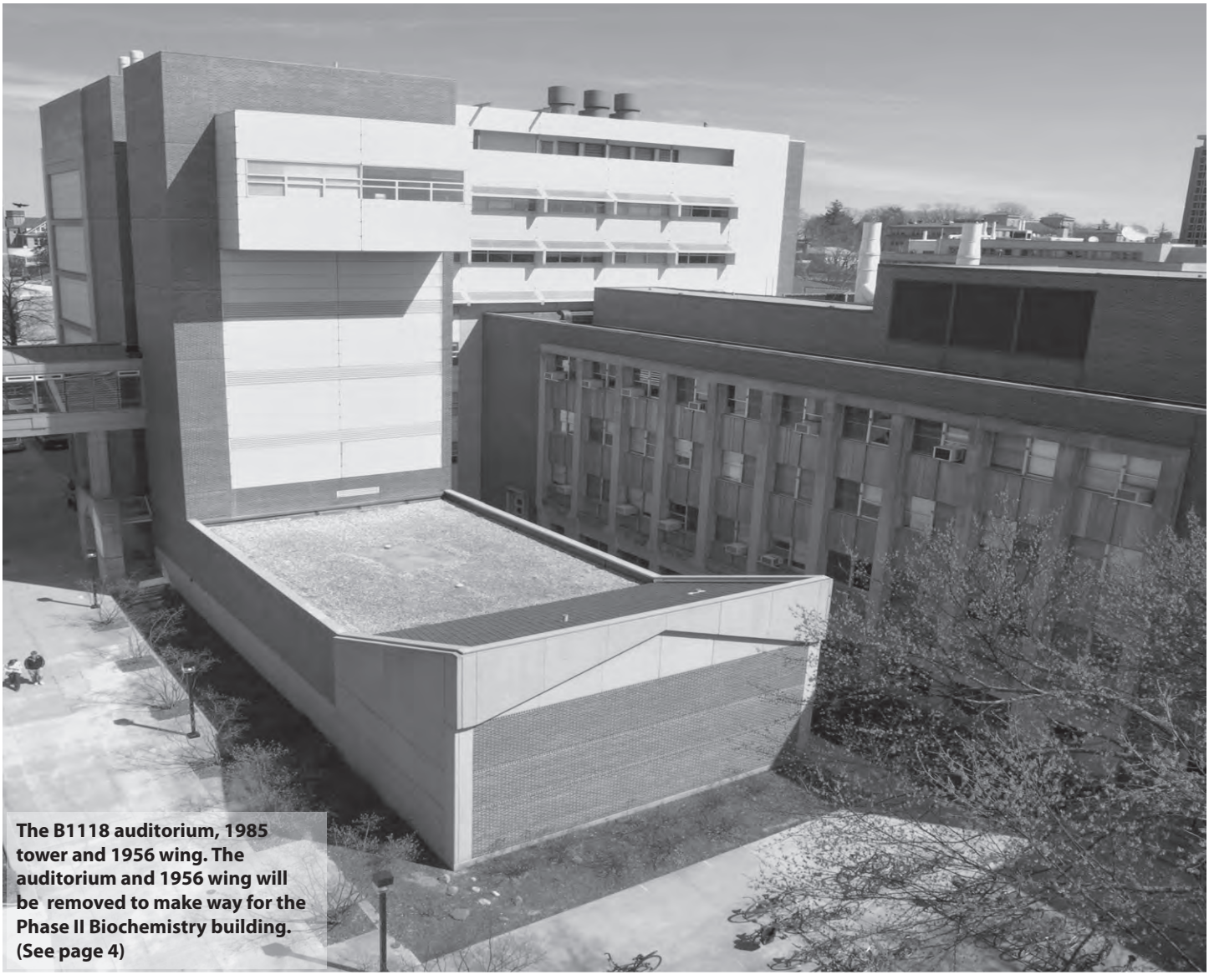

The B1118 auditorium, 1985 tower and 1956 wing. The auditorium and 1956 wing will be removed to make way for the Phase II Biochemistry building. (See page 4)

If you would like to learn more about the exciting new building project, please feel free to contact:

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From the Chair

by Professor Betty Craig

It is my pleasure to bring you greetings from the Biochemistry Department for the year 2008. As I write this dispatch, the last piece of the newsletter, which Marv Wickens and his collaborators have put together for you, there are true hints of spring – very welcome after a winter, the likes of which Madison has not seen in years. The pages that follow bring you not only the year's "news" from the department, but also slices of the exciting science going on in our labs. Here is a preview of a bit of what you will find inside.

For decades the department has had an international presence, training many students and hosting many scholars from abroad in individual laboratories. In the past few years the character of our international endeavors have begun to change, taking on a broader perspective, thanks to the efforts of two faculty in particular. An update of the program "Uganda Study Abroad: International Health and Nutrition", initiated and run by James Ntambi can be found on page 5. He is "on sabbatical" this spring semester and we look forward to hearing the latest on his work in Uganda when he returns. In the fledgling stage a year ago, but moving rapidly forward, is an exchange program with India, the brainchild of Aseem Ansari (see page 26). Dr. Har Gobind Khorana, who won the Nobel Prize in 1968 for his work at the interface of chemistry and biology while a faculty member in the Biochemistry Department and Enzyme Institute, has lent his name to the program, now officially the "Khorana Program for Scientific Exchange". Last summer three students spent 10 weeks in labs on campus; hopefully they are the first of many exchanges, which will also include Wisconsin students and faculty visiting and working in labs in India.

Closer to home: In my past two dispatches I have mentioned the Biochemistry Phase II Building Project, last year saying "I hope when I write you a year from now I can report that we have broken ground…". The news this year is – almost. By the end of the summer demolition of the 1956 wing (and the animal quarters and auditorium built in 1985) should commence, with ground-breaking in early fall. We are keeping our fingers crossed and scurrying around to temporarily relocate those to be displaced by the construction - animals to the Biotron, the BMRB computer group to the library in the Biochemistry Addition and seminars and teaching labs to the new Microbiology building. On page 4 Mike Cox provides a more expansive description of our exciting project.

Faculty comings and goings: As noted in last year's newsletter, Bill Reznikoff packed up his lab and moved to Wood's Hole Biological Labs last July. Perry Frey, who retired at the end of the year (see page 10), is staying closer to home. You can still find him in his office in the Enzyme Institute Building. Within the next year, two faculty will join our ranks: John Ralph, a long-time Madison resident will make the switch from the US Dairy Forage Research Center to Biochemistry, making his home in the Enzyme Institute. John will be heavily involved in research in bioenergy, interfacing with the Great Lakes Bioenergy Research Center (see page 6). I am also pleased to tell you that in the fall Alessandro Senes will join us as an Assistant Professor. Coming from his postdoc position at the University of Pennsylvania, Alessandro will set up a research program concentrating on the structure of membrane proteins, using computational and biophysical tools.

I hope you have had an enjoyable and productive year. We would be pleased to hear from you anytime. Visit us when you can, to meet with old friends and to see what's new in Biochemistry for yourself.

New building set to break ground

by Professor Mike Cox

Phase II Biochemistry. This view is from the "Elmer" (the elm tree) courtyard.

The department is building again. With the state and the Wisconsin Alumni Research Foundation contributing most of the funding, the older part of the Biochemistry complex is about to be transformed.

Readers may remember that the department largely abandoned the old 1912, 1937, and 1956 wings when it occupied the new Biochemistry addition in 1998. The older wings have been occupied by several temporary tenants, including the Bacteriology department. With the recent completion of the new Microbiology building, the older Biochemistry wings are being vacated again and we are ready for Biochemistry phase II.

Planning has been complex. The program includes research facilities, teaching facilities, service facilities, and an animal care suite, with the entire project encompassing 265,000 gross square feet. The research labs are designed to house the faculty from the Enzyme Institute, as well as several other Biochemistry faculty and the entire Biomolecular Chemistry Department. The teaching facility will include two large modern lecture halls, many smaller teaching rooms, new teaching laboratories, administrative space for student services, and a student lounge.

The site includes the footprints of all the older wings, as well as the Agricultural Journalism building. Pressure from many quarters in the state and university administrations (and including many faculty in the Biochemistry Department) quickly led to the shelving of any plan that envisioned the razing of any of the older buildings on the west side of Henry Mall. This called for some creativity, and the Flad architects have not disappointed.

Thus, the 1956 wing is now scheduled for demolition, along with the portion of the 1912 wing that connects the Henry Mall rectangle to the 1937 wing. The auditorium and animal rooms in the 1985 wing will also be demolished. A new research tower will rise on a footprint south of and adjacent to the 1985 tower, with a footprint that includes the northern part of the 1956 wing, as well as the current 1985 auditorium and animal rooms. With six floors above ground, this tower will rise higher than the current 1985 tower. The research space will be connected on its east side with a gutted and refurbished Ag Journalism building, which will now house a variety of Biochemistry support facilities and a café. A new pedestrian corridor will separate this facility from the 1912/37 wings, and will provide easy access to the Elm tree courtyard from Henry Mall. The 1912/37 wings will be transformed into modern teaching and administrative facilities.

It is an ambitious project, with many features that will enhance both teaching and research for many decades to come. Demolition is to begin in late summer of 2008, with ground-breaking to occur in early fall. Completion and occupancy slated for early 2011. Henry Mall will again be a staging area for the construction teams. Hopefully, this landmark will be left undisturbed for awhile after we are finished. Expect regular updates as the construction moves into high gear next year.

Phase II Biochemistry. This view is from Henry Mall.

Since Fall of 2002, Professor James Ntambi has led an extraordinary and invaluable program for undergraduates, taking them to Uganda to both learn about nutrition and put what they learn into practice – an experience that brings new meaning to their education.

The program combines a semester course with a 3-week field experience in Uganda. During the fall course, Professor Ntambi provides students with background information on the economics and health issues particular to Uganda, so that when students arrive they have a good grasp of the realities faced by Ugandans as they make their health and nutrition decisions. Students come to realize that necessities that many of us take for granted, such as clean drinking water, food, education, and financial resources, present daily struggles for the majority of Ugandan citizens.

A common water source

The success of the program is reflected in what the students do when they return. A key example is the creation of the student organization called the Village Health Project (VHP). The goals of this project are to support health and nutrition projects in developing countries and to increase awareness about international health issues on the UW-Madison campus and beyond. So far, Village Health Project has supported the building of 28 rainwater tanks in Uganda. These tanks are a simple, effective way of obtaining clean drinking water. Current groups are now involved in helping to solve the water problem by building BioSand Water filters, which are cheaper than tanks and are used at the household level. Water collected from their current sources is poured through the filter and comes out pathogen-free. The students in the program do all this because they believe that in order to improve human health, good nutrition practices and clean water go hand in hand.

Workshop participants learn how to test their water

Not surprisingly, the program has a powerful ripple effect, with valuable consequences long after the students' Ugandan experience. For most students, the program is their first exposure to the importance of public health. Many then go on to attend elite Public Health programs across the US that include University of Michigan, Johns Hopkins, Tufts, George Washington University, the University of Minnesota and our own UW-Madison program. There are also currently 12 students in different medical schools across the US and most of the others continuing their studies in graduate programs. By exposing students to critical health issues, Professor Ntambi provides students with opportunities to learn more about themselves as future health care professionals.

Please take a moment and visit the program's website: **http://www.villagehealthproject.org** to learn more about what Dr. Ntambi and his students are doing and have done in the past. If you would like to make a donation to this program, please send it to: Village Health Project, 239 Red Gym, 716 Langdon Street, Madison, WI 53706.

James Ntambi (right) with Paul Kimera, a civil engineer at Makerer University, who helps produce the BioSand water filters thay are standing next to.

GLBRC

Great Lakes Bioenergy Research Center

This past fall, the Department of Energy (DOE) awarded one of three nationwide Bioenergy Research Centers to the University of Wisconsin-Madison. Our center is known as The Great Lakes Bioenergy Research Center (GLBRC; **www.greatlakesbioenergy.org**); the GLBRC is a close partnership with Michigan State University, and other partners in the center so far include Pacific Northwest National Laboratory, Oak Ridge National Laboratory, Illinois State University, Iowa State University, and Lucigen Corporation. The centers will receive $125 million in total costs over 5 years, and the goal of all of the centers is to perform research that may facilitate the production of transportation fuels from biomass. Several faculty from Biochemistry participate in the GLBRC including **Bob Landick, Brian Fox, George Phillips, Mike Sussman, John Markley, Laura Kiessling, Ron Raines, Sebastian Bednarek, Rick Amasino, Betty Craig, Aseem Ansari and Julie Mitchell.**

Before discussing the activities of our center, I will provide some background. At present, most of the so-called biofuel used in the U.S. is ethanol derived from corn grain. The reason for this is simple: corn grain provides a readily fermentable feedstock, and the industrial processes to produce ethanol from it are well established. An issue with using corn grain for biofuel production is that most estimates indicate the amount of fossil fuel used to produce corn ethanol equals or exceeds the energy of the ethanol that is produced. Of course corn grain contains only a fraction of the energy that is captured by the plant; most of the energy is sequestered in the cell walls of the "body" of the plant. For bioenergy to have the greatest impact on reducing CO2 emissions and dependence on fossil fuels, it will be critical to 1) grow biofuel crops that are less energy intensive to produce than current corn varieties and 2) convert most of the fixed carbon in the plant into biofuels, rather than just the carbon in the seeds.

Perennial grasses are an example of a type of biofuel crop that would be less energy intensive to produce than corn. (Switchgrass is one example of a perennial grass often mentioned in the press or political speeches). Once established, a field of perennial grass can be harvested year after year at the end of each growing season; it does not need to be replanted for the next season. Also at the end of each growing season, perennial grasses recycle most of their nutrients into below ground parts of the plant to be used to support next season's growth; thus, such plants require fewer inputs such as fertilizer (fertilizer production and distribution is quite energy intensive) and do not require cultivation in the spring.

A major issue is how to efficiently convert the energy stored in plant cell walls into transportation fuel. Plant cell walls are comprised of cellulose, lignin, and a range of other compounds which vary somewhat among species. Cellulose is a polymer of glucose residues, and all of that glucose would


Amasino


Ansari


Bednarek


Craig


Fox


Kiessling

be a great source of energy for any organism that could access it. Cell walls form the body and the skeleton of the plant, and thus, over evolutionary time, the acquisition of cell walls that are resistant to breakdown has conferred an obvious advantage. One challenge is to discover ways to "deconstruct" these highly stable cell walls so that their components can be converted into biofuels.

The GLBRC efforts are organized into the following four scientific areas. More details are provided at **http://www.greatlakesbioenergy.org/research.**

1) Improving Plant Biomass. There are two sub-areas in improving biomass. One is to increase the yield of biomass per acre in ways that minimize agricultural inputs and environmental degradation. The other is to modify the chemistry of the biomass. For example, genetic manipulations might render plant cell walls easier to convert to biofuels. Furthermore, some of our efforts (at Michigan State University) are to evaluate the possibility of creating plants that accumulate potential biofuel chemicals in addition to cell walls, such as sugar, starch or oil – compounds that could readily be used for biofuel production with existing technologies. (In Brazil, ethanol is made from the sugar in sugarcane rather than from sugarcane cell walls, but sugarcane cannot be grown in most of the U.S.)

2) Improving Biomass Processing. How plant biomass is processed is likely to play a key role in rendering the biomass more accessible to the conversion process. Physical, chemical and enzymatic pre-treatments are being explored. For example, a process involving pressure changes in the presence of ammonia is one component of this area (see **http://pubs.acs.org/cgi-bin/abstract.cgi/bipret/2007/23/i04/abs/bp070098m.html**).

3) Improving Biomass Conversion to Energy Compounds. This key area is focused on developing efficient technologies for converting biomass into biofuel. Research includes prospecting for organisms that might contain novel and useful enzymatic activities, and designing microbes that are well-suited to fermentation approaches to biomass conversion. In addition, the GLBRC is pursuing chemical engineering approaches – the identification of catalysts for the direct conversion of biomass-derived products into fuels.

4) Fostering Sustainable Bioenergy Practices. The GLBRC also has a group exploring the environmental and socioeconomic dimensions of converting biomass to biofuel. Members of this group study how to minimize energy and chemical inputs for bioenergy crop production, how to reduce greenhouse gas emissions from the biofuel production cycle, and how to predict environmental impacts of harvesting biomass repeatedly in an area. This group also studies the social financial components that will be needed to make the biofuel industry most environmentally sustainable.

It is important to keep in mind that although biofuels may be part of the solution to our energy needs, biofuels cannot provide all that is needed. A DOE report indicates that U.S.-produced cellulosic biomass could provide a carbon-neutral source for ~30% of current U.S. transportation fuel needs by the year 2030 (**http://genomics-gtl.energy.gov/biofuels/b2bworkshop.shtml**). It is important to note that the transportation sector accounts for ~30% of U.S. fossil fuel consumption. Thus, overall biomass and biofuels will not provide an alternative for all U.S. fossil fuel use. Nevertheless, biofuels are likely to be part of a portfolio of approaches that help the U.S. to become more energy independent and more carbon neutral, and the GLBRC hopes to contribute to making biofuels a larger part of our energy portfolio.


Landick


Markley


Mitchell


Phillips


Raines


Sussman

Honors & Awards

Faculty

Richard Amasino – WARF Kellet Mid-Career Faculty Research Award 2007-2012

Samuel Butcher – 2007 CALS Pound Award for Excellence in Research

Elizabeth Craig – American Association for the Advancement of Science

Hector DeLuca – CALS Distinguished Service Award

Perry Frey – Hilldale Award; Career Leadership from American Chemical Society

Laura Kiessling – Harrison Howe Award; Fellow, National Academy of Science

Laura Kiessling and Ronald Raines – MIT Technology Award

Thomas Martin – Earl W. Sutherland Professor of Biochemistry

Julie Mitchell – Vilas Award

James Ntambi – Fulbright Scholar, African Regional Research Program

Ronald Raines – American Peptide Society's Makineni Lectureship

Thomas Record – Fellow, American Academy of Arts and Sciences

Marvin Wickens – RNA Society Service Award

Christiane Wiese – NSF Career Grant

Classified Staff

Cheryl Adams Kadera – CALS Classified Staff Recognition Award

Theresa Pillar – CALS Classified Staff Recognition Award

Graduate Students

Graduate Teaching Excellence Award

Ed Huttlin

This award is intended to recognize a Biochemistry graduate student who has consistently shown evidence of quality, commitment, and innovation in teaching.

Graduate Mentoring Award

Ian Lewis

This award is designated to honor Biochemistry graduate students who consistently provide quality guidance and scientific training in mentoring undergraduate students in their research efforts.

Sigrid Leirmo Memorial Award in Biochemistry

Christopher Warren

This award is to be given to a postdoctoral or graduate student who displays clear promise as a research scientist. The award is to be designated in appreciation of the student's consistent willingness to contribute to the intellectual and technical potential of his or her fellow students and colleagues through the selfless help of others.

Undergraduate Majors

Mary Shine Peterson Scholarship Recipients

Siang Yun Ang
Kevin Campbell
Hao Li
Mariko Hasebe
Matthew Vogt

Biochem 501 Peer Mentoring Scholars

Robert Erdmann
Katherine Gielissen
Molly Lowndes
Brad Nelms

Kimberly Clark Scholarship Recipient

Brad Nelms

Marion A. Hicks Scholarship Recipient

Jia Luo

Genentech Scholarship Recipients

Molly Isola
David Ziehr

Postdoctoral Fellowships

Name	Lab	Fellowship
Matthew Flowers	Ntambi	American Heart Assn Postdoctoral Fellow
Declan James	Martin	American Heart Assn Postdoctoral Fellow
Peizhen Yang	Craig	American Heart Assn Postdoctoral Fellow
Enpeng Zhao	Attie	American Heart Assn Postdoctoral Fellow
Ngan Lam	Kimble	Damon Runyon Fellow
Takashi Higurashi	Craig	Human Frontier Science PD Fellow
Matthew J. Allen	Raines/Kiessling	NIH Postdoctoral Fellowship
Dana Byrd	Kimble	NIH Postdoctoral Fellowship
Bryan Phillips	Kimble	NIH Postdoctoral Fellow
Thomas Lee	Craig	NIH NRSA Postdoctoral Fellow
Amy Prunuske	Craig	NIH NRSA Postdoctoral Fellow

Graduate Student Fellowships

University

Name	Lab	Fellowship
Thomas Gisel	Rayment	Advanced Opportunity Fellow
Khanh Ngo	Cox	Advanced Opportunity Fellow
Juan Rodriguez-Molina	Ansari	Advanced Opportunity Fellow
Bryan Becklund	DeLuca	R.H. Burris Fellow
Rebecca Turcotte	Raines	RATH Fellow
Edward Huttlin	Sussman	Thomsen Wisconsin Distinguished Fellow

Departmental

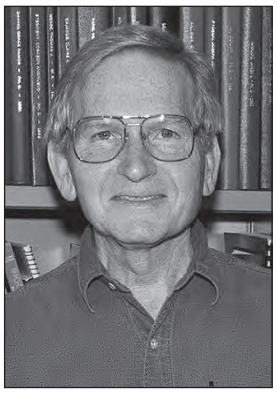
Name	Lab	Fellowship
Alison Meyer	Craig	Biochemistry Scholar
Frederick Porter	Palmenberg	Biochemistry Scholar
Tzu-Yuan (Cindy) Chao	Raines	MAO Wisconsin Distinguished Fellow
Lori O'Brien	Wiese	Steenbock Fellow
Graeme Garvey	Rayment	WARF Research Scholar

National/International

Name	Lab	Fellowship
Clayton Carlson	Ansari	AHA Predoctoral Fellow
Justin Brumbaugh	Coon	NSF Fellow
Amanda Johnson	Amasino	NSF Fellow
Rex Watkins	Raines	NSF Fellow

Perry Frey Retires

by Professor Brian Fox



Gaining a view of the world through the lens of chemistry and the molecules of life.

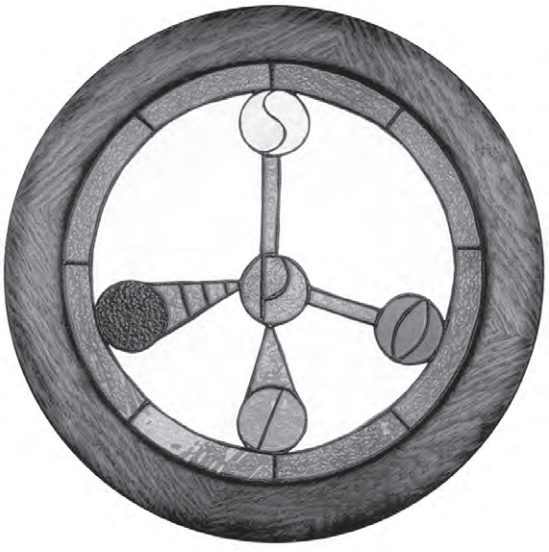
For a considerable time, the involvement of free radicals in enzyme catalysis was curiously confined to the realm of only a few flavoproteins, the cytochrome P450s, and cobalamin-dependent enzymes. Likewise, the cofactor S-adenosylmethionine was usually considered to be a methyl group donor. However, the role of radicals in enzyme catalysis has exploded in recent years, and we can attribute much of this to Perry Frey's leading insight and experiments.

It is a great honor to prepare this short commentary, which reprises a remarkably productive, long, and eventful career that has generated deeper understanding of many essential biochemical processes. It celebrates research thoroughly grounded in basic chemical principles, and honors the deeply appreciated efforts of more than ninety former graduate and postdoctoral students who chose to train in research with Perry and share in his thrill of scientific discovery. It is also noteworthy that thirty senior collaborators have contributed to this sustained scholarly experience.

Perry started out in Plain City, Ohio, a small town about 18 miles northwest from Columbus. As a boy, he delivered newspapers during World War II and earned enough to buy his first bicycle. He made a point of reading the newspapers and learning about warfare. Later, as a youth, he did every kind of farm labor during vacations from school, including working the land, planting, harvesting, and tending animals. Later, he worked for his father, a painting contractor, to support his higher education. Few know that Perry served in the US Army for two years. After this informal education in the military, his formal scientific education began at the Ohio State University, where he obtained a B.S. in Chemistry. After graduation, Perry worked for the US Public Health Service as an analytical chemist in Cincinnati, where he published on the properties of paralytic shellfish poison, saxitoxin, his first of now more than two hundred eighty professional papers. During this time, Perry and Carolyn Scott met and were married in 1961. Perry's and Carolyn's first daughter, Suzanne, was born in 1962 in Cincinnati, Ohio. Perry also attended Evening School at the U of Cincinnati during this time, where he studied Chemistry.

Based on the recommendation of a mentor at the Public Health Service, Perry applied for graduate studies with Prof. R.H. Abeles in January 1964 at the University of Michigan and received an NIH pre-doctoral fellowship to support this effort. After only a short time in Michigan, he moved with Abeles to Brandeis University. It was an outstanding opportunity at an exciting time that led to the discovery of many basic principles of catalysis by cobalamin-dependent enzymes. In 1965, Perry's and Carolyn's second daughter, Cynthia, was born in Waltham, Massachusetts. After three years, his Ph.D. studies were complete, and Perry began an NIH postdoctoral fellowship with Prof. F.H. Westheimer, one of the preeminent enzymologists of all time, at Harvard University. This fellowship lasted for a year, and led to an unsolicited offer to join the faculty of Chemistry at the Ohio State University. There, Perry rose through the ranks to Professor and Academic Vice Chair.

During his time at the Ohio State University, Perry began many new projects, including studies of UDP galactose-4-epimerase, pyruvate dehydrogenase, galactose-1-phosphate uridylyltransferase, UDP-glucose pyrophosphorylase, adenylate kinase, and many other phosphotransferases. This work brought the role of cofactors NAD, thiamine pyrophosphate, and pyridoxal phosphate to the light. Moreover, it was during this time that Perry began his decades long, definitive work on the mechanism and stereochemistry of enzymatic phosphoryl transfer by the synthesis of isotopically labeled nucleoside phosphothioates and experimental test of these molecules.

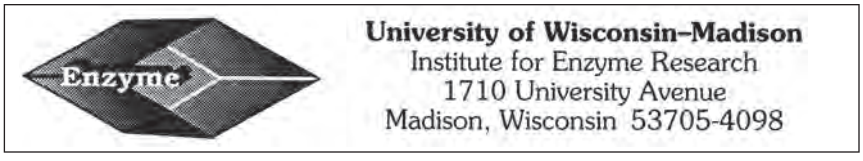


The picture **above** shows a leaded glass window commemorating Perry's work on using the isotopically labeled nucleoside phosphothioates to

elucidate the mechanism of phosphoryl transfer. His students created this art piece for his 50th birthday in 1985. Each student cut a section of glass, and the sections were fitted and leaded by Rahda Iyengar, an Assistant Scientist in the lab at the time. The work shows chiral [^{16}O, ^{17}O, ^{18}O]thiophosphate, with each isotope of oxygen in a different style.

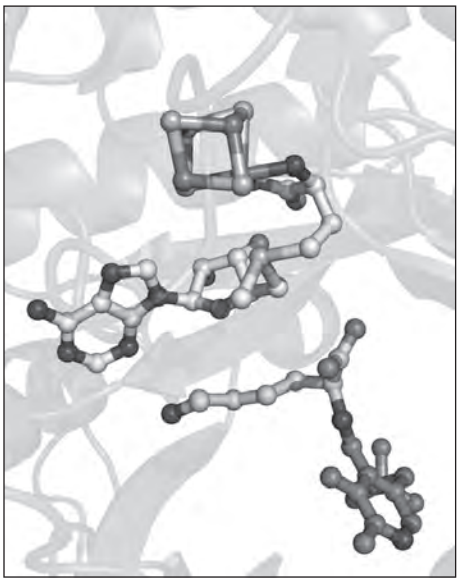
Perry and Carolyn moved to Madison and the University of Wisconsin in 1981. He was recruited to join the world-renowned Institute for Enzyme Research, which had begun to struggle with the retirement of leading researchers. Over about a 15-year period, Perry led the UW effort to establish and expand campus-wide strength in study of the structure and function of biological molecules, most notably enzymes. With Henry Lardy and Helmut Beinert already housed in the Institute, Perry was able to recruit Mo Cleland from across the street in Biochemistry and George Reed from University of Pennsylvania to join the Institute. This core strength was extended to structural studies when John Markley was recruited to the UW Biochemistry Department from Purdue University, Ivan Rayment was recruited to the Institute from the University of Arizona, Hazel Holden was recruited to the Institute and the UW Chemistry Department, and later transferred to the Biochemistry Department, and Brian Fox was recruited as a new Assistant Professor. Thus assembled, the Institute for Enzyme Research was reinvigorated as a premier site in the world for collaborative studies in enzymology. One defining characteristic of this time in the early and mid-1990s was the sharing, cooperative, environment of the Institute, where students, post-doctorals, academic staff, and faculty members roamed freely, with respectful access to all of the substantial resources assembled to bear on problems of collective interest. There was no corner where a receptive ear to a new idea in research or a helpful comment could not be found.

Enzyme Institute Letterhead



At UW, Perry and his research group continued the studies of phosphoryl transfer enzymes and exploited the power of chiral phosphothioate analogs to expand the understanding to more enzymes and to chemical systems. In the strong Institute research environment, previous studies of pyruvate dehydrogenase expanded, and studies of another complex thiamine pyrophosphate-dependent enzyme, alpha keto glutarate dehydrogenase were begun. Undecagold clusters were produced and used as biochemical labeling agents, and the participation of strong hydrogen bonds in enzymatic reactions came into vogue.

Likewise, the work on the clostridial enzyme lysine 2,3-aminomutase began. In a prescient 1993 manuscript in FASEB Journal, Perry first queried with the title, "Lysine 2,3-aminomutase: Is adenosylmethionine a poor man's adenosylcobalamin?" Now we know the extent of the poor man's strategy for generation of a reactive radical species in an enzyme active site: a gene family found in all kingdoms of life, with more than 2400 different family members at this writing.



The figure **above** shows the active site of lysine 2,3-aminomutase from the crystal structure solved by Bryan Lepore, Frank Ruzicka, and Perry in Dagmar Ringe's lab at Brandeis University. The protein has a triose phosphate isomerase fold, and also revealed the locations of a site-differentiated [4Fe-4S], pyridoxal phosphate, S-adenosylmethionine, and bound lysine. S-adenosylmethionine is bound to the unique iron atom in the [4Fe-4S] and has the critical 5' carbon within - 4 Å of the 2,3-carbons of lysine, which is held into enzyme active site as a Schiff base with pyridoxal phosphate. This beautiful structural study reveals the ternary complex so elegantly documented in the other biochemical work on the enzyme from Perry's lab.

Alongside the growing appreciation and understanding of radicals in S-adenosylmethionine dependent enzyme reactions, Perry and co-workers performed one of the decisive early experiments on the reaction mechanism of the diiron enzyme methane monooxygenase. Along with the cytochrome P450s, these powerful oxidants were thought to react by hydrogen abstraction, a radical process, but evidence was scant. By using methylcyclopropanes as radical rearrangement probes, they showed that 1e– and 2e– oxidations of unactivated hydrocarbons were both possible from this enzyme reaction. This laid the groundwork for much future experimental and computational analysis of the reactivity of diiron enzymes. This is an enduring characteristic of Perry's research: early insights supported by crucial experiments and extensive subsequent research undertaken by Perry's group and many others.

Upon contemplation, Perry has regarded his position as a professor of Chemistry and Biochemistry as the best job in the world for him. From his view, nothing could have been more rewarding than a career working with bright young people, who were in his group by their own choice, and whose aspirations were to improve themselves and have some fun along the way. Research and teaching became an essentially linked continuum, the one always informing, shaping, and improving the other.

Once I asked Perry which course he most liked teaching. His initial answer was all of them, including the undergraduate introductory courses, which included Biochemistry 201 Survey of Biochemistry, Biochemistry 511 Undergraduate Seminar, Biochemistry 601 Proteins and Enzyme Structure and Function, Biochemistry 624 Mechanisms of Enzyme Action, Biochemistry 625 Coenzymes and Cofactors in Enzymology, and Biochemistry 660 Biochemical Techniques. However, upon reflection, Perry stated, "my favorite course is Biochemistry 990 Enzymology Research. I derived the most pleasure teaching research to graduate students and watching them become mature scientists. I would like this to come through." But, anybody who ever attended Biochemistry 990 would already know this to be true.

Departures

Two long time employees, **Kay Fitzgerald** and **Janice Carberry,** retired this past February.

Kay joined the department in 1988, and Carol Marth – a legend in her own time – was her supervisor. Kay really enjoyed both Carol and her co-workers. She took a state test to upgrade her work title and so for a brief time worked at Physical Plant, but soon found she missed the professors and students. When the opportunity presented itself to return to Biochemistry she jumped at it. She says: "I'd learned my lesson: Stay in Biochemistry. The people here are the best!" Over the years, Kay's jobs varied enormously, and became concentrated on payroll duties of all kinds.

Kay now looks forward to a wide range of things, including travels to visit her children. Her son, his wife, and Kay's grandson, are all off in Montana. Her daughter, a free-lance singer, lived in Germany for 11 years, was married in Italy last year, and now is going back to Germany, so Kay will be logging the frequent flyer miles. Here's a brief description in Kay's own words of what's coming:

"In retirement, I hope to pick up my needlework again, refresh my knitting skills, and make a dent in all the fabric in my basement waiting to be sewn. I'll still be playing for the St. Joseph choir, masses there and at Our Lady Queen of Peace. And hopefully, weddings will still be going on needing an organist. Did I mention de-cluttering the basement? So, don't worry that I'll be twiddling my thumbs in retirement. But I will be missing my wonderful Biochemistry friends."

Janice joined the department in 1996, after working at other UW-Madison positions and at UW-Whitewater. Janice work tirelessly at handling travel payments, reimbursing our grad student hosts, and the various seminars, including the department's granddaddy, the Steenbock Symposium.

Janice's husband Dennis, also a UW employee, retired around the same time that she retired. Here is Janice's report on her retirement plans:

"Brett Favre and I have the same retirement mantra. We could have continued physically, but we are mentally spent. We both look forward to

decompressing and being a sofa-slug for a short recovery period. During the winter cold I have been enjoying reading in the sun room, snow-shoeing, chipping ice, tutoring 3 kids and attacking those piles of "life stuff" that accumulate so quickly. We will remain in our Verona home and complete some renovation projects. Volunteer opportunities abound and I will continue to do part-time work close to home. Warmer weather will find us biking, exploring the mid-west and heading north in our camper to spend more time with the three grandchildren."

Also leaving the department are **Danielle Tolzmann and Michael Eckblad.**

Danielle has been our purchasing supervisor since 2004. Danielle took a new position across campus to Visitor & Information Programs, housed in the Red Gym. Her last day was in early March.

If you had a computer problem during the last five years or so, you likely talked with **Michael Eckblad,** or possibly, his spot-on impersonation of George W. Bush. Starting in 2002 as a student hourly with IT, Michael happily answered your technical questions, and maybe even told you about new bands on the horizon. He also had a knack for systems administration, and in 2004 was instrumental in the rollout of the "new" file and email servers.

Later on, as a full-time IT staffer, Michael's influence continued to expand. He took charge of the new Biochem website and helped with the development of our first content management system, MyBiochem. He spearheaded the department's transition to the WiscMail email system, successfully managing one of the largest email migrations on campus. Michael was also the driving force behind the recent expansion of our file server infrastructure, helping define policy committed to protecting our critical research data.

Alas, as a conceptual artist, Michael's tenure in IT could not last long. Whether it was video shot in multiple camera angles, helium balloons filled with light, or large, industrial wooden peg smashers, his art was first. He left Biochem in September and began his newest project, "Drop Everything and Run."

We all wonder precisely what it means to be alive. We now can answer this question empirically: What minimal set of genes are needed to make a reproducing, living creature? But Michael, not surprisingly, has taken a different tack. On leaving the department in September, Michael gave up all of his possessions to see where that would lead, and as an offshoot, what might actually be required for his existence. To learn about this newest project - "Drop Everything and Run" - and others that inhabit his fertile and congenial mind, visit his website - MichaelEckblad.com We look forward to delineation of the minimal Eckosome.

We will miss all four of them and wish Kay and Janice the best in their retirements, Danielle at her new position and Michael in his journey.

Janice Carberry (left), Kay Fizgerald (center) and Micheal Eckblad (right)



A simple approach to understanding stem cells

by Professor Judith Kimble

Stem cells have the magical ability to produce more of themselves and to also make specialized cells, such as muscle or nerve (**Figure 1)**. The capacity of stem cells to replenish tissues as they get damaged, diseased or worn out holds tremendous promise for human health. But to fulfill that promise, we must learn how to control stem cells within an organism. Many cancers are thought to result from unleashed stem cells gone awry, and stem cells — with their virtually unlimited capacity for growth — will certainly wreak havoc if they are not carefully controlled.

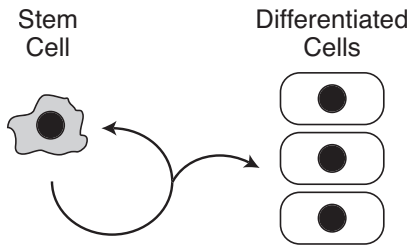


Figure 1: Stem cells can both self renew and generate differentated progeny

My lab focuses on unraveling molecular mechanisms of stem cell regulation, and in particular, analyzing those mechanisms in an organismal context. Our approach has been to use a genetic scalpel for the identification of stem cell regulators in a relatively simple animal, the nematode *Caenorhabditis elegans.* Once a regulator is in hand, we then use a variety of approaches to figure out how it works. Over the years, we have learned that many stem cell regulators found in this small roundworm turn out to be broadly conserved for the control of stem cells throughout the animal kingdom, including humans.

C. elegans as an organism to study stem cells

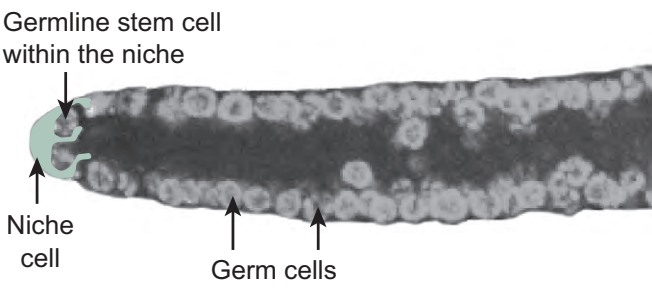
C. elegans turns out to be an extraordinary model for basic biomedical research. This little roundworm is only one millimeter long and can be grown like *E. coli* on Petri dishes or in liquid media, so that millions of animals can be readily obtained to purify regulatory molecules for biochemical analysis. The complete genome sequence is known, and individual genes can be manipulated by classical mutagenesis or by the newer technique of RNA-mediated interference. Moreover, gene products can be visualized in individual cells of living animals with fluorescent proteins introduced via transgenes.

In human tissues, many stem cells exist throughout adulthood and replenish tissues that continuously make specialized cells (e.g. germline stem cells in the testis, hematopoietic stem cells in the blood, neural stem cells in the brain). In *C. elegans*, only one type of stem cell persists throughout adulthood, and that is the germline stem cell, which replenishes sperm and oocytes as they are used for reproduction. Germline stem cells are unusual in that they retain the capacity to create all cells of an entire organism when triggered by fertilization and therefore are the ultimate stem cells for all tissues in the body. Our work therefore focuses on germline stem cells, in part because they are the only game in this roundworm town and in part because their totipotency makes them particularly interesting.

Conserved molecular regulators control stem cell maintenance

We have found *C. elegans* stem cell regulators that are conserved in all animals and that appear to control stem cells in many different biological settings. One example is Notch signaling. In *C. elegans*, a special regulatory cell provides a stem cell 'niche' that is essential for maintenance of germline stem cells **(Figure 2)**. That regulatory cell makes a ligand for the Notch receptor, and the activated Notch receptor responds in germ cells by turning on genes critical for stem cell maintenance. Most importantly, germline stem cells are lost when Notch signaling is turned off, and germline tumors arise when Notch signaling is left on aberrantly. In vertebrates, Notch signaling has been implicated in stem cell control, and in particular for hematopoietic and neural stem cells. In humans, defects in Notch signaling cause leukemia and have been implicated in Alzheimer's. Therefore, our work on Notch signaling in the *C. elegans* germline has important implications for human health.

Figure 2: Germ cells begin to differentiate when they leave the niche



Another example is FBF, which belongs to the PUF family of conserved RNA-binding proteins. We first honed in on FBF in collaboration with my long-term colleague, Dr. Marvin Wickens. Using the Wickens yeast three-hybrid system and Kimble regulatory mutations, our labs together identified FBF as a key regulator of the sperm/oocyte decision. When FBF was deleted fully from the genome, we found that FBF is also essential for stem cell maintenance. Remarkably, PUF RNA-binding proteins control germline stem cells in both *C. elegans* and the fruitfly Drosophila, and they have been implicated in control of germline and embryonic stem cells in vertebrates, including humans. In addition, PUF proteins are critical for regeneration in planaria flatworms, and perhaps function in other regenerating tissues, where latent stem cells are activated to proliferate and replenish tissue. Therefore, PUF proteins stand out as critical regulators of stem cells in virtually all animals.

One major goal of the lab has been to figure out how Notch signaling and PUF RNA-binding proteins control stem cells, and we have made some progress. For Notch signaling, one of our first finds was that Notch directly upregulates FBF, a step that links the Notch and PUF stem cell controls. FBF, on the other hand, binds to specific messenger RNAs and downregulates production of proteins that promote differentiation. In particular, FBF downregulates expression of MAP kinase and a battery of other differentiation regulators. Indeed, in collaboration with Dr. James Thomson, also here in UW-Madison, we have found that two human MAP kinase mRNAs are regulated by a human PUF protein, Pum2, in human embryonic stem cells. Therefore, the PUF repression of MAP kinase is broadly conserved.

A regulatory network controls the decision between self-renewal and differentiation

Our work on Notch and FBF targets has revealed the framework of a regulatory network that controls germ cells to remain as stem cells or embark on a path to differentiation. In broad strokes, Notch signaling induces expression of regulators that inhibit differentiation, including FBF, and therefore maintains an undifferentiated stem cell state. FBF in turn represses expression of proteins that induce differentiation. The regulatory network is not simple but it is remarkably robust – any one component can be removed without abolishing stem cell maintenance or the switch into differentiation. Moreover, the network provides multiple points of regulation that can be modulated in response to a variety of cues (e.g. nutrition, pathogenesis, aging).

A novel β-catenin controls generation of the niche

The stem cell niche is a key factor in stem cell control. Thus, a larger or smaller niche maintains more or fewer stem cells, respectively. To understand how a niche is formed, we analyzed specification of the niche for germline stem cells, which consists of a single regulatory cell (Figure 2). We recently found that this regulatory cell is specified by the Wnt signaling pathway, which activates target genes by a conserved DNA-binding protein (TCF) and its transcriptional co-activator called β-catenin. What is perhaps most exciting in our work is that Wnt signaling uses a novel protein that belongs to the β-catenin family based on both functional and structural criteria. Our structural studies have been done in collaboration with the laboratory of a crystallographer from the University of Washington-Seattle, Dr. Wenqing Xu. Our work also shows that Wnt signaling uses a branched pathway to control the ratio of its DNA-binding protein and transcriptional coactivator, an insight that may prove applicable to Wnt signaling more broadly. Pathway activation drives β-catenin abundance up and TCF abundance down to generate an activated complex that drives transcription. The target of that complex for niche specification is a homeodomain transcription factor, the *C. elegans* homolog of human Nkx2.5.

Lessons of stem cell control from a model organism

So why use *C. elegans* to study stem cell control? If all the molecular regulators are conserved, why not work on them in vertebrates instead? The basic answer boils down to the simplicity and experimental power of this small nematode. Stem cell regulation is presented in a particularly simple form in *C. elegans* with its single-celled niche and use of Notch signaling for stem cell maintenance. By contrast, mammalian stem cell niches have not been easy to find at a cellular level and even less easy to analyze genetically and biochemically. Moreover, *C. elegans* genetics, when combined with biochemistry, provides a way to delineate a stem cell regulatory network within a single tissue and within the context of the organism. This simply is not yet possible in a vertebrate.

IPiB: its first two years

by Professor Ivan Rayment, Chair of the steering committee

IPiB Research Topics:

Cell and Developmental Biology

Chemical Biology

Computational Biology

Enzymology

Molecular Genetics

Molecular Medicine

Structural Biology

Virology

In 2006, the Departments of Biochemistry and Biomolecular Chemistry formally merged their graduate programs to form the Integrated Program in Biochemistry (IPiB, **www.ipib.wisc.edu)**. The reasons for this change were many, but foremost it permits a streamlined recruiting and admission process for prospective students. Combining the programs also seemed the logical thing to do since the two departments are going to be close neighbors when the new Biochemistry Phase II building is completed.

In the first year (2006), 16 students were admitted. This was a smaller class than perhaps the faculty would have liked, but considering the changes in the curriculum and organization, it was a good size to initiate the program. This year, we nearly doubled our class size (31 students were admitted!), which is better than anyone could have anticipated. It is a clear indication that IPiB is off to a good start. Comments from our students indicate they like the new program's simplified admission process, and the greater number of laboratories in which to study. IPiB students currently have around 50 laboratories to rotate in during their first semester!

The new program demanded a complete examination and overhaul of the curriculum. As it turned out, the programs in Biochemistry and Biomolecular Chemistry were already similar so that the major changes have been organizational rather than thematic. The Charter for the new program has been approved and is officially in place.

So what are the major changes in the program? From the perspective of the students, there is a new professional development and bioethics course offered in the first semester (Mike Cox and others). In addition the "Advances in Biochemistry" course (Biochem 875) that had been offered in the Fall for the past four years has been merged with Biomolecular Chemistry (710) and is now offered in the Spring to create a new course entitled "Exploring Biochemical Functions of Macromolecules (Ivan Rayment/Dave Brow and others)." There is also a new seminar requirement for the third and fourth years of the program in which the students will present their research to the program. Lastly, a few changes to the prelim process have been made in the hopes of allowing more feedback to the students during the oral examination. As is evident, the changes have been very modest. I would say that the greatest changes are in the organization of the program, because all of the graduate committees are now represented by members of both Departments. All of these committees are now under the guidance of the Steering Committee.

The Steering Committee, made up of 7 faculty members from both departments, oversees the graduate program. Graduate student issues, such as recruiting, laboratory assignments, and teaching assignments are now handled within this committee rather than each of the respective departments. As chair of this committee, I have to admit that the organization works well because the individual committees have done a fantastic job of recruiting students, guiding them through laboratory assignments and providing direction for the forthcoming prelim examinations. The net result of their hard work is that there are fewer faculty meetings which is a benefit to the entire faculty, except of course for those on the Steering Committee!

The final significant change in the program is that the students can combine the social activities of both departments into a greater graduate student experience. The net result is that there are more opportunities for the students to get together and mingle. The academic year begins with the Welcome Picnic (welcoming the new class), followed by a Halloween Party (check out the SFLC website for the costume contest), Friday Social Hour at BMC almost every Friday, Holiday Party (which includes an ornament contest, and new this year, a toy drive), Joint Poster Session that draws a huge crowd each year (is it the research or the food that draws the crowd??!!), Student Seminar Series, and the year concludes with the SFLC (Student-Faculty Liaison Committee) election picnic.

Finally, those who might worry that Madison's reputation for a top-ranked program in biochemistry would be overshadowed by the attention of a merger and new program name, the formal degree title for those who graduate from the IPiB will be "a doctorate in Biochemistry." I think there is a good chance that the first crop of Ph.Ds from the IPiB will occur around the 100th anniversary of the first graduate student from Biochemistry. I am told by Dave Nelson that the first Ph.D. in Biochemistry (from the department of Agricultural Chemistry) was awarded in 1910 to J.N. Currie who was a graduate student with E.B. Hart. Based on the current program I think we can plan on another 100 years of great graduate education in Biochemistry.

Student Faculty Liaison Committee (SFLC)

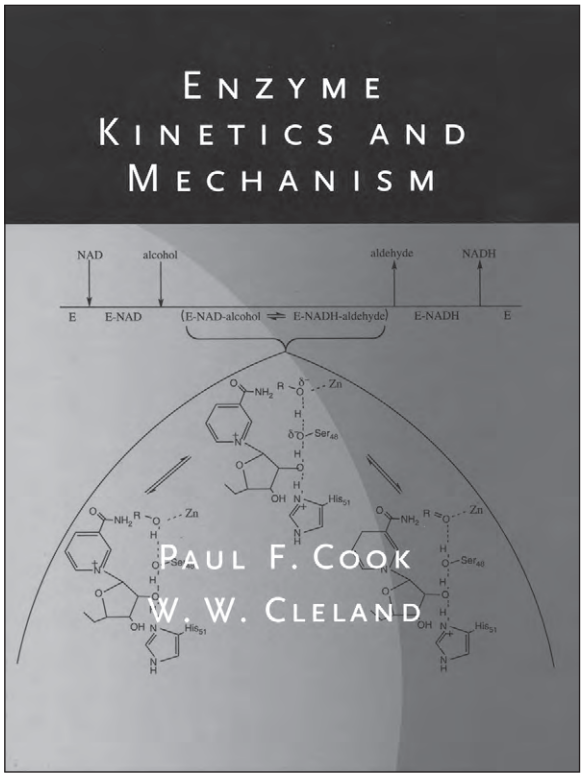
by Alison Albee, Chair IPiB SFLC

The Student Faculty Liaison Committee (SFLC) provides a mechanism for graduate student service to the department. The SFLC is involved in many activities. There are so many graduate students that work hard to make SFLC successful that I can't name them all here, but I would like to mention our social chairs, **Sarah Slauson** and **Marielle Gruenig**, who have done a wonderful job to organize some spectacular events. At our annual fall picnic, they put together the first ever kickball face-off between the new and old students. It was a great idea and a lot of fun! We look forward to them continuing their social magic with the Halloween party and annual holiday party at the end of the year. **Samantha Herbst** has been instrumental in organizing our departmental art show and we eagerly anticipate seeing more wonderful art, hearing beautiful music, and watching lovely dancing again this year thanks to her hard work. The student seminar series provides a forum for graduate students and post-docs to present their research to their peers. Due to lack of enthusiasm, we did not have the seminar series last year, but this year **Greg Ellis** has done an outstanding job rejuvenating the student seminar series for this year. The seminar meets every other Tuesday at noon in the Bock Labs Penthouse and we encourage you to come hear about the exciting research your colleagues are doing. **Greg Kabachinski** has done a remarkable job with the student invited seminar speaker and has lined up speakers for the next two years! Dr. Tom Rappaport will speak in 2008 and Dr. David Allis will speak in 2009. The graduate students play a critical role in recruiting and this year we have **Mark Marzinke** and **Allyson Anding** heading up the recruiting efforts. I know they will do a fantastic job and recruit another great class! This year we are also excited to try something new for the SFLC. We are organizing volunteer opportunities as a way to give back to the community. Our first activity will be a toy drive this December. We are delighted to add this new dimension to the SFLC and we look forward to another great year!

IPiB welcoming picnic 2007
New class

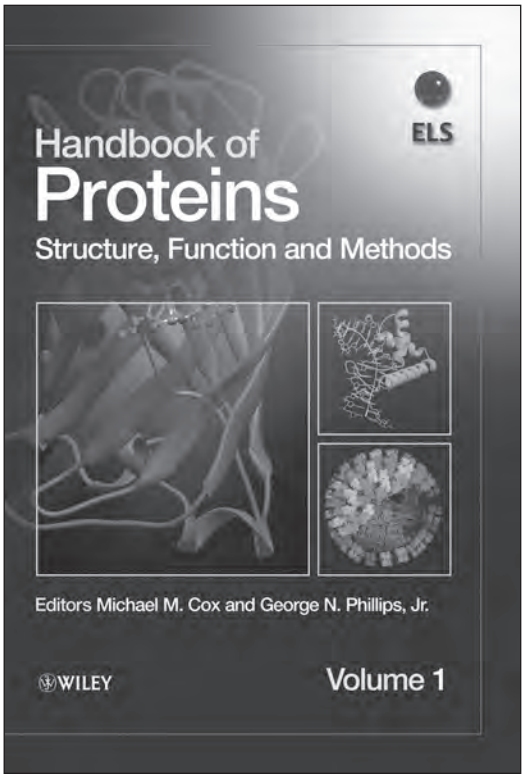
IPiB welcoming picnic 2007
Upperclass kickball champs

Mo Cleland



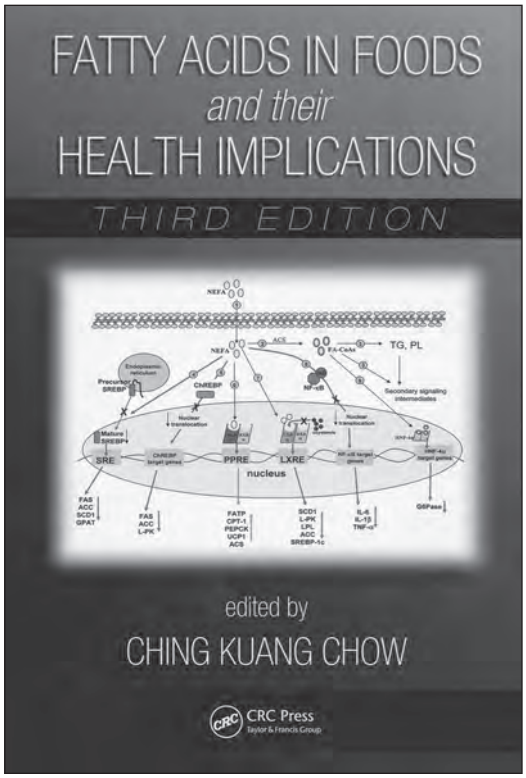
This book, which should serve as a text for graduate students and a reference for the senior investigator, provides an in-depth coverage of steady-state kinetics as it is used for determination of the kinetic and chemical mechanisms of an enzymatic reaction. The cover art is a collaboration of Paul Cook (for the structures) and the publisher.

Micke Cox and George Phillips



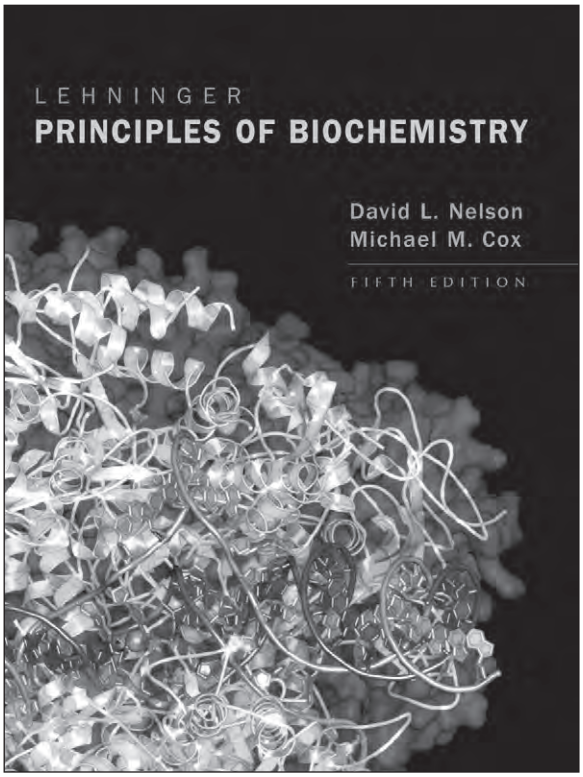
The study of proteins is central to life sciences. The cover of the book highlights the glowing structure of green fluorescent protein, a protein-DNA complex and an assembled virus capsid. Artwork by Tod Romo and John Wiley press.

James Ntambi



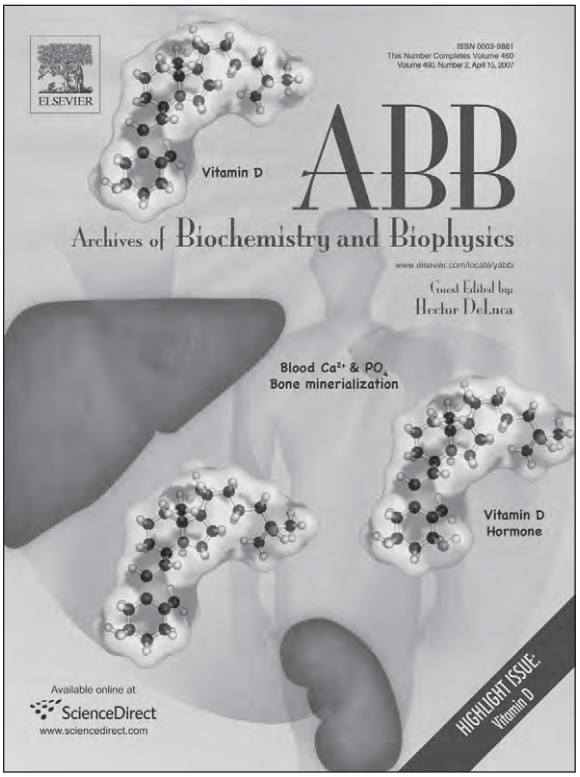
Fatty acids, especially polyunsaturated fatty acids, regulate gene expression via interactions with multiple transcription factors and nuclear receptors, resulting in downstream changes in flux through metabolic pathways. Chapter by Harini Sampath and James Ntambi. Cover art by Harini Sampath.

Dave Nelson and Mike Cox



RNA polymerase II from yeast, bound to DNA and in the act of transcribing it into RNA. Image created by H. Adam Steinberg using PDB ID 1I6H as modified by Seth Darst.

Hector DeLuca

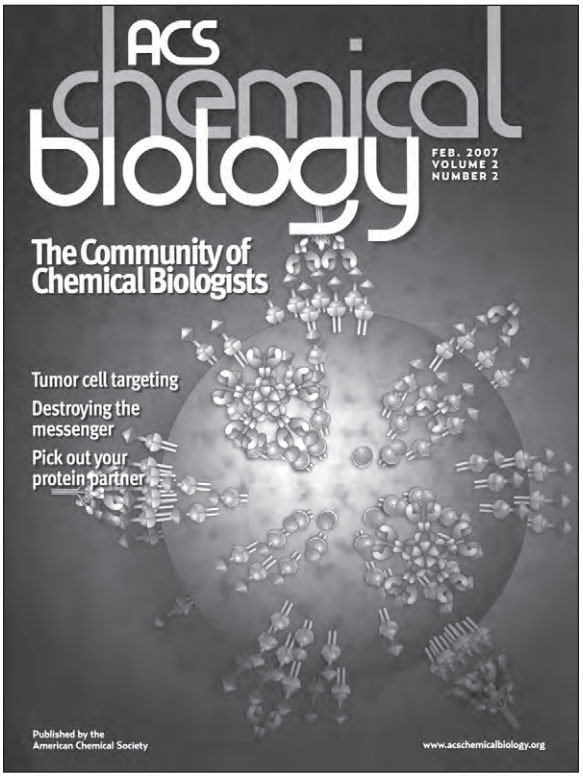


The vitamin D endocrine system is pictorially shown including regulators and structures. The illustration, by H. Adam Steinberg, introduced an issue of ABB devoted to current vitamin D research.

Hazel Holden

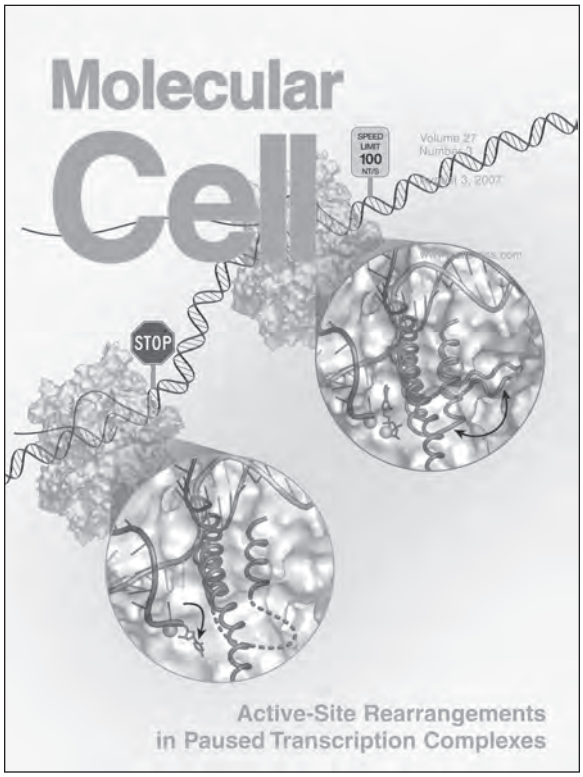
Glucose-1-phosphate uridylyltransferase catalyzes the formation of UDP-glucose from glucose-1-phosphate and UTP. Artwork by Hazel Holden and H. Adam Steinberg.

Laura Kiessling



Traditional anticancer targeting strategies rely on high-affinity interaction to recognize tumor over normal cells. In contrast, Carlson et al. describe a new strategy that takes advantage of low-affinity, multivalent interactions to target a cell for destruction by the immune system. Cover image courtesy of H. Adam Steinberg. Cover designed by Theresa M. Dubé.

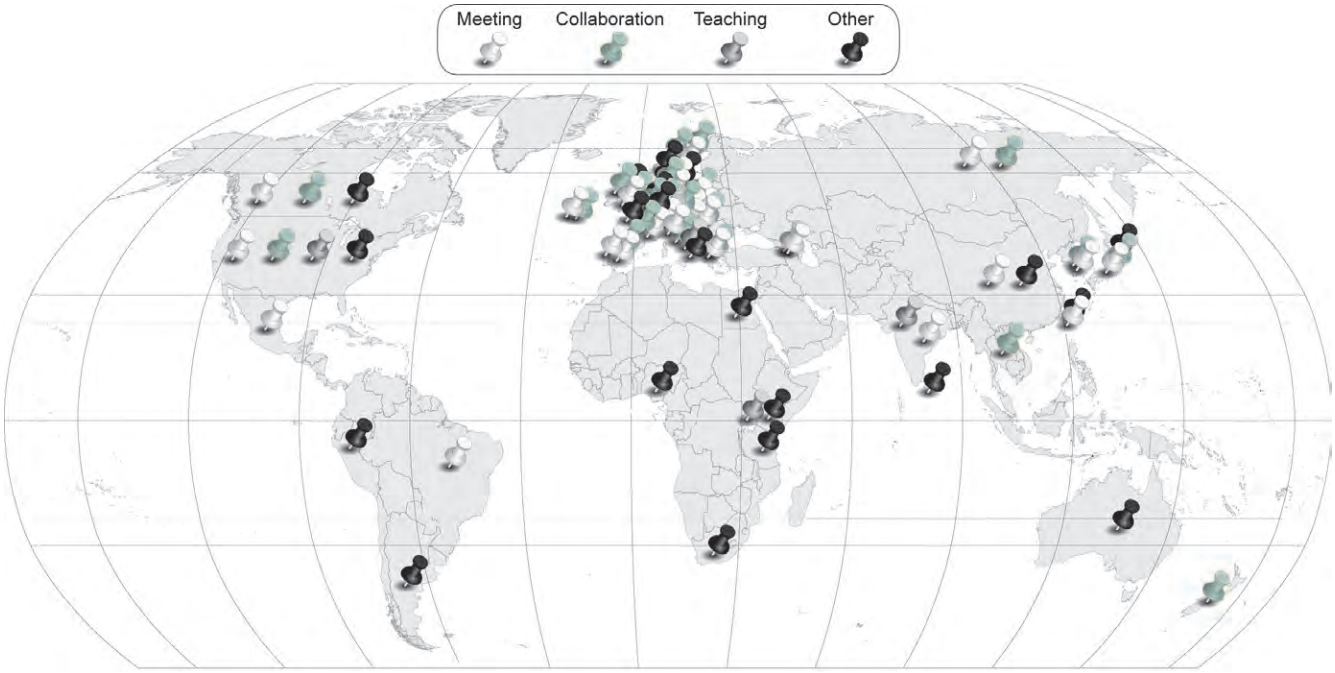
Bob Landick



Transcriptional pausing by RNA polymerase (RNAP) regulates transcript elongation. Toulokhonov /et al.,/ report rearrangements of the RNAP active site upon formation of an initially paused transcription complex, featuring a trigger-loop conformation positioned near the RNA 3' nucleotide, which frays away from the DNA template. Artwork by H. Adam Steinberg, Jinwei Zhang, and Robert Landick.

The Department Around the World

Each pin represents one faculty member's involvement in that country, either through a collaboration, a meeting, teaching (or, in a few cases, something else entirely). We only allowed one type of pin per country, no matter how many PIs had contacts there. You can see instantly that Europe is a densely perforated pin cushion; but the map also makes clear that the department reaches out to every other continent as well. Which lab will be the first in Solomon Islands?



From the Covers cont.

Ron Raines

"Arginine grafting"– installing a patch of arginine residues – enhances the toxicity of a ribonuclease for human erythroleukemia cells. The image depicts electrostatic potential maps of bovine pancreatic ribonuclease (RNase A) and a model of its E49R/D53R variant (dark gray = cationic; medium gray = anionic). Artwork by Stephen M. Fuchs.

Doug Weibel

'Nanoart', by Tom Wilson, based on an image from the Weibel Lab of microstructured polymers. The image consists of rectangular arrays of tens of thousands of micron-scale structures for manipulating bacterial cells that are embossed in the surface of a polymer and make it possible to confine and study bacterial physiology. The dimensions of the structures are on the wavelength of visible light, which gives each rectangle a unique color.

Dave as the Warthog's goalie

In the Wickens Lab

After rotating through (and helping move) half the 3d floor labs in Biochemistry during fall of 1998, David Bernstein settled in with the Wickens lab. He had come with a BA in Biochemistry from Clark University, and was ready to surprise and impress his new advisor. Unfortunately, that first surprise came in Group Meeting, with an impressively overpriced set of oligonucleotides that led to apoplexy in his mentor.

This early oligonucleotidyl indulgence foreshadowed Dave's later career. Early on, Dave began studying the interaction of a translational regulator, FBF, with its mRNA targets. Hundreds of oligos and mutations later, he deciphered a consensus binding sequence that predicted new targets of regulation. Bernstein collaborated with many in the Wickens and Kimble labs, ending up with five research papers and four reviews in journals running the gamut from Nature to Promega Notes. These attest not only to Dave's skills and smarts, but also to his willingness to work freely and generously with others.

Outside the lab

Bernstein spent what was likely too much time away from the bench while at UW. He was the second head of the Student Faculty Liaison Committee, and a superb goalie of the hockey Warthogs' two intramural championship seasons (the Warthogs are the Chemistry and Biochemistry departments' unofficial ice hockey ambassadors). Dave also spent a good deal of time debating the finer points of democracy with the lab's resident communist, Labib Rouhana. These and other discussions helped redirect Bernstein's career.

Dr. Bernstein goes to Washington, D.C.

Dr. Bernstein Goes to Washington

Inspired not only by Labib, but also by work he had done in Senator Kohl's office, Dave became intrigued with science policy. From the biennial Biosciences Career Day, he learned of AAAS Congressional Fellowships, which enable Ph.D. level scientists, doctors and engineers to hold staff positions in the US Congress. Bernstein applied and was awarded one for 2005-2006, and spent that year working for Senator Kennedy's Health Office. He dealt with many technical issues, but focused on the Pandemic and All Hazards Preparedness Act of 2006. His UW training prepared him for the cornucopia of activities, everything from lab safety to pathogen detection methods. Topics closer to home were surprisingly common, like the intricacies of a new PCR technique or trying to describe RNAi the morning of the Nobel Prize announcement. Dave was impressed by the influence a small group of staffers could have on policy, and found the entire experience exhilarating and exhausting.

Life Outside the Bubble

In late 2006, Bernstein left frenetic Capitol Hill, and now is a Senior Science Policy Analyst for the American Association for Cancer Research. Bernstein was the first hire for the new AACR office in Washington, DC and is helping expand their government relations activities. Much of his time is spent trying to convince Congress to spend more on NIH research, and convince researchers that it's hard for Congress to spend more, even though there seems to be a lot of money for other things. But it's working on the bills that supports research, fosters innovation, and speeds drug discovery – the bills that draw on the scientific and political worlds – that are the most fun, and the most rewarding.

Computational approaches to studying molecular interactions

by Professor Julie Mitchell

Molecular interactions provide the essential language of biochemistry, and networks of such interactions control physiological communication processes. It is natural to examine interactions in terms of the individual behaviors, which are largely dictated by structural features and random fluctuation. Because kinetic rates can be altered by environmental conditions such as temperature, and the basis for this is largely structural, the system-wide behavior is intimately tied to structural detail. Our goal is to use mathematical models to explore both structural and systems characterizations of protein association, and we hope to develop models that address biological phenomena across scales.

Predicting Molecular Interactions

A fundamental question in biochemistry is how the structure of molecules determines their function. Predicting or determining a protein's three-dimensional fold is one piece of the puzzle. Given structures for a pair of interacting proteins, the next question is how they bind one another. This is just as complex as predicting a protein fold, though many fewer structures have been determined experimentally, and we have yet to find an equivalent to the fold classifications and homology-based approaches that have proven successful in folding.

Our approach to predicting the structure of molecular complexes is based in mathematics and physics. We have developed an energy function that can distinguish native binding configurations from non-native ones. This is coupled to numerical methods for finding the global minimum of this energy function.

Future work will explore what is a continued stumbling block in protein docking -- protein flexibility. We are presently exploring new ways to represent proteins mathematically and to characterize their flexibility using only a few parameters that are naturally suited to optimization.

Hot Spots and Binding Energetics

Some sidechains make a large energetic contribution to binding, and these residues can be more sensitive to substitution by another amino acid. We combined biochemical and geometric considerations, such as hydrophobicity or precise shape match, to predict these ``hot spots.'' Various features were analyzed to determine which of them have the ability to distinguish hot spots from other interface residues.

To maximize the predictive capabilities of the model, statistical methods were applied to a data set consisting of binding energetics data for alanine substitutions within protein interfaces of known structure. The result is a model able to predict when substitution to alanine is likely to cause a binding free energy increase of at least 2 kcal/mol. We have also used the model to predict when other types of sidechain substitutions will enhance or inhibit binding. Figure 1 shows the Smad4-Ski interface along with white and black spheres that indicate favorable and unfavorable regions of the binding interface. Such information is useful toward selecting mutations that can enhance or inhibit binding affinity in this system.

Our hot spot model is computationally very efficient and scalable. Most systems can be analyzed within a minute or two, and the entire *E. coli* 50S ribosome can be analyzed in under 15 minutes. To make our computational tools most useful to bench scientists, we have created a server to help researchers analyze hot spots within protein systems of interest. Using Jmol, we created an interactive display with which hot spot residues can be explored. Our server (**http://www.mitchell-lab.org/kfc**) is now available, and a more fully featured interface is in its final testing stages.

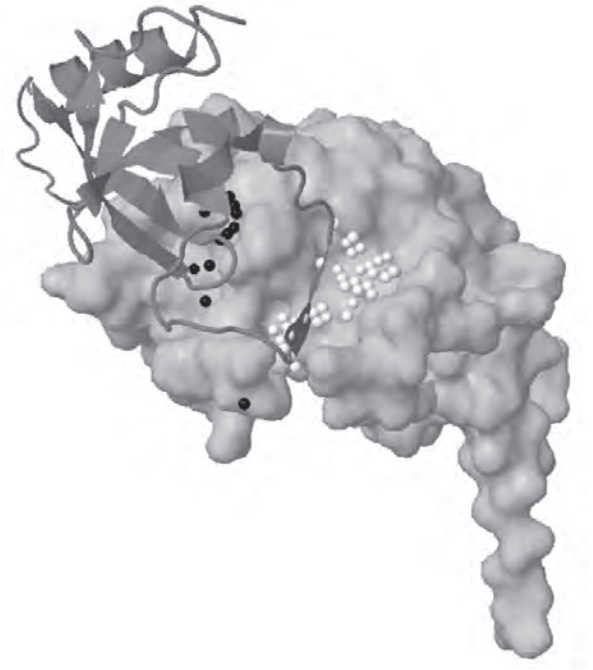


Figure 1: The Smad4-Ski interface is shown with favorable and unfavorable regions of the interface marked using white and black spheres, respectively.

Optimizing Biological Systems

Changes in rate constants can have system-wide effects. Though much of our group's research involves structural biology, we are interested to apply optimization tools more generally toward problems in systems biology. We have recently completed two projects in this area, which are related to bioenergy and remediation.

Using metabolomics data derived from NMR or other sources, it is possible to fit time-dependent models to observed metabolite concentrations. Because kinetic models may include nonlinear relationships between metabolite concentrations, this can be nontrivial. We have used models with different functional forms, such as Michaelis-Menten and Generalized Mass Action, as there is no established gold standard for the form of models fit to *in vivo* concentrations.

Once these empirical models have been obtained, they can be used to make conjectures about the possible effects of increasing the concentration of a given metabolite or the rate of a particular reaction. One of our projects examined the rates of converting uranium from soluble to insoluble forms by species of *Shewanella*. In particular, examined the reaction rates for this conversion in the presence of iron species and other metals. This is due to the fact that *in situ* rates for contaminated soil can differ considerably from those observed in the laboratory. The ability to predict reaction rates in the presence of varied types of metals can help environmental biologists better plan cleanup efforts at remediation sites.

A second project examined the selectivity of glucose to ethanol conversion, with the goal of minimizing CO_2 generation. In some organisms, there is a 1:1 ratio between the number of ethanol molecules and CO_2 molecules created, whereas in other organisms there are alternate branches within the glycolysis pathway that do not lead to CO_2 release. In addition, some organisms have the ability to convert CO_2 into commodities, such as biodegradable plastic. This leads to interesting questions in design and optimization for biology-based industrial engineering.

Our initial examination of glycolysis studied data from *L. lactis* to predict conditions under which the bacteria would selectively produce ethanol over acetate, and for which the ratio of ethanol to CO_2 production was maximized. The trends were comparable between the two empirical models (Michaelis-Menten and Generalized Mass Action), and the conclusions suggest specific bioreactor designs that we hope to test in collaboration with chemical engineers.

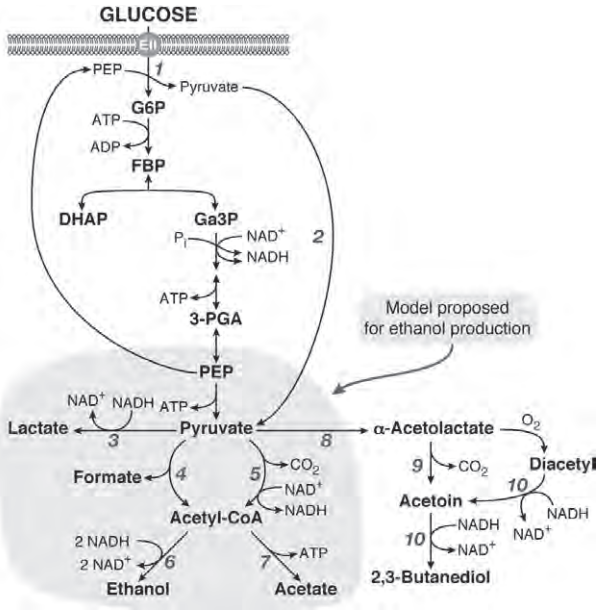


Figure 2: The glycolysis pathway in *L. lactis* has a branched path between pyruvate and ethanol. Only one branch produces CO_2.

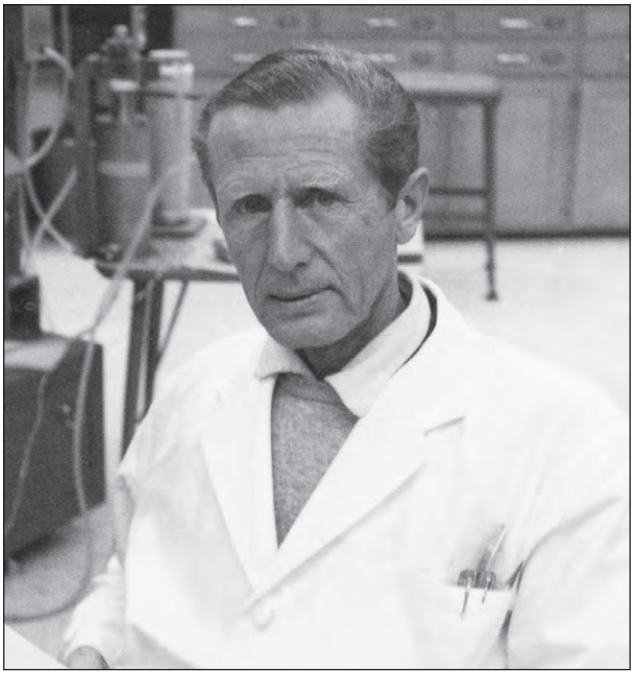
High Performance Computing

The computing costs encountered in biology can be considerable. In the past, we have addressed these needs using large supercomputers and clusters of machines. However, we are presently working on some exciting new innovations. Modern graphics cards can perform many of the types of calculations required by our software, and these graphics processing units (GPU's) can perform up to 128 calculations at once. By combining a number of cards within a single machine, a low-cost and space efficient supercomputer can be created.

Our first endeavor has been to adapt our desolvation model for this hardware. Based on use of clear design principles, we are able to achieve a speedup of more than 100 when using two graphics cards. Thus, we are already seeing the benefits of developing for this emerging computing framework. In the future, we will adapt our computationally expensive docking prediction codes to utilize this new technology.

Remembering Helmut Beinert

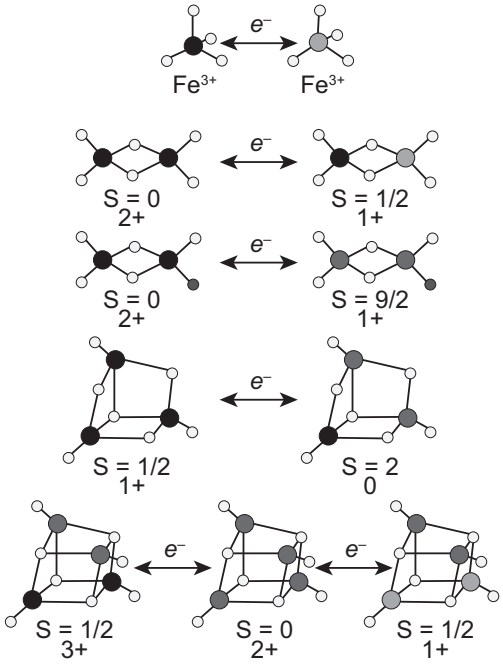
by Professors George Reed, Brian Fox, Henry Lardy and Tricia Kiley



Professor Emeritus Helmut Beinert died on December 21, 2007, at the age of 94. He was born Nov. 17, 1913, in Lahr, Germany. He received a bachelor's education in the classical traditions of Latin, Mathematics, Greek and French, along with some Chemistry and Physics. He then studied acting at the State Theater and became a professional actor prior to being drafted into the army. Helmut asked for and was granted a leave to pursue graduate studies in Chemistry at the Universities of Leipzig and Heidelberg. His thesis work, completed in 1943, was carried out at Kaiser-Wilhelm Institute for Medical Research in Heidelberg. Dr. Beinert was careful to avoid research that would stimulate any interest from the military, and surviving the turmoil of the war years was something that he attributed to the good fortune of simply being born in 1913 instead of 1914.

After the war, the Control Commission of the Allied Forces moved a group of medical doctors and chemists to Randolf Field in Texas, where Dr. Beinert carried out studies of the fate of exogenously administered cytochrome c in tissues. In 1950, Dr. Beinert came to the Institute for Enzyme Research to carry out postdoctoral work. One of his early projects was to develop a new method for the isolation of coenzyme A. Dr. Beinert was promoted to professorial rank in 1952 and became a full professor in 1962. He retired from the University of Wisconsin in 1984 and took a professorship at the Medical College of Wisconsin in Milwaukee where he remained until returning to Madison in 1994. He remained actively engaged in research and scholarly activities, and his passion for science continued until his death.

Dr. Beinert leaves a remarkable record of contributions and accomplishments in biochemistry and biophysics. His name is always associated with the field of iron-sulfur proteins, although he was adamant in pointing out that he was not the original discoverer of this class of proteins. Rather, he was the leading figure in characterizing the electronic structures and functions of many members of this large family of metalloproteins. Dr. Beinert was an early proponent of the use of electron paramagnetic resonance (EPR) spectroscopy to study paramagnetic intermediates in flavoproteins as well as metalloproteins such as the iron-sulfur proteins. His collaborative EPR experiments in the 1960's wherein ^{57}Fe and ^{33}S and subsequently ^{77}Se were incorporated into iron-sulfur proteins revealed the covalent nature of the iron-chalcogen core were classic achievements. Dr. Beinert's work on fatty acid oxidation and tissue respiration led to many important discoveries including an abundance of iron-sulfur centers in proteins of the respiratory chain of mitochondria. The discovery of an iron sulfur cluster in the tricarboxylic acid cycle enzyme, aconitase, expanded the repertoire of iron-sulfur clusters beyond electron carriers to catalysts.

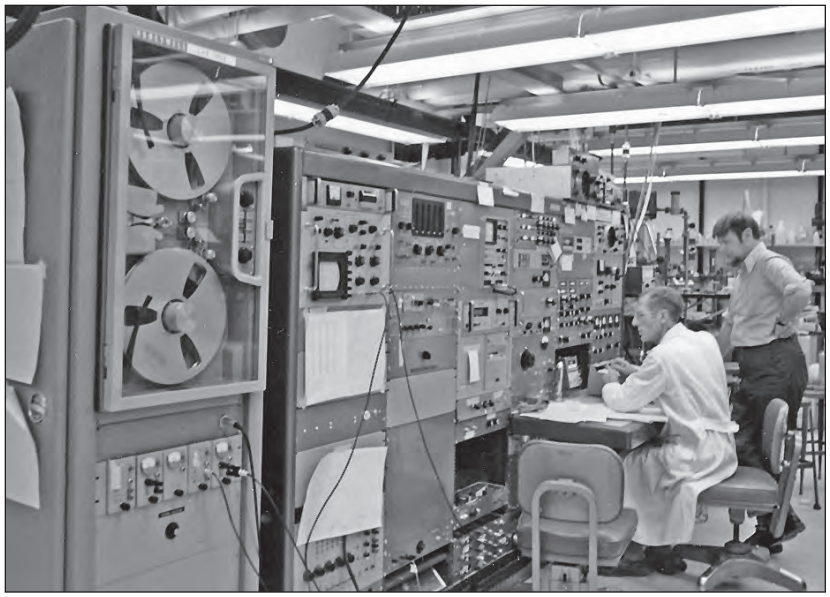


Localization and delocalization patterns in Fe-S clusters

Subsequently, Dr. Beinert participated in revealing the roles of iron-sulfur clusters in transcriptional and translational regulation. Dr. Beinert's scientific contributions span a period of more than 60 years.

Dr. Beinert's accomplishments were recognized internationally. He was respected as a pioneer in the areas of bioinorganic chemistry and biophysical spectroscopy. He was a recipient of a lifetime NIH Career Development Award. He was elected a member of the US National Academy of Sciences in 1980. Dr. Beinert's numerous awards included the Keilin Medal of the British Biochemical Society, the Sir Hans Krebs Medal of the European Biochemical Societies, the Fritz Lipmann Award from the American Society of Biochemistry and Molecular Biology, the Otto Warburg Medal of the German Society for Biochemistry, and Honorary Doctorates of Science from the University of Wisconsin-Milwaukee and the University of Konstanz.

Ray Hansen and Helmut Beinert conducting an EPR experiment



For the last several years Dr. Beinert maintained a quiet presence at seminars and symposia around the campus. His early morning trips to the Steenbock Library equipped with his briefcase, dark glasses, and flat cap were a familiar and comforting sight. Dr. Beinert was popular with students and postdoctoral fellows who benefited from his encyclopedic knowledge of biochemistry and his willingness to share his perspective on science. Dr. Beinert had many collaborators here at UW and around the world. Many of these projects established new areas of investigation that provide a continuing legacy for Dr. Beinert. His sharp wit, remarkable intellect, exceptional standards, and indomitable spirit will be sorely missed.

In Memoriam

Beinert, Helmut
(Professor 1967-1984 and Emeritus Professor 1994-2007)
December 21, 2007

Colovos, George Charles
(MS 1943, Johnson)
2006

Frea, James Irving
(PhD 1963, Strong)
November 28, 2005

Marsh, Eloise Margueritte
(Dept. Secretary 1955-1982)
April 22, 2007

Morris, Mark Jr.
(worked in PH Phillips lab, PhD Vet Science 1962-63
January 14, 2007

Ogilvie, Marvin Lee
(MS 1959 Hoekstra, PhD 1962 Hoekstra)
February 1, 2008

Quackenbush, Forrest Ward
(MS 1935, Peterson PhD 1937, Steenbock)
May 21, 2007

Savage, Jane Ramsdell
(MS 1963, Harper)
June 5, 2002

Thorne, Curtis
(MS 1944 Peterson, PhD 1948 Peterson)
January 10, 2008

Weaver, Robert
(Post Doc 1958-60 Lardy)
February 13, 2008

The Department, the University and India: *Khorana Exchange Program*

by Professor Aseem Ansari

Aseem's web photograph

Dear Sir/Madam,
I have read about your very exciting research on the website and am seeking the privilege of working in your esteemed laboratory, under your excellent guidance….

or so went the request from a faceless, eager, and potentially capable young applicant from India. "Dear Sir/**Madam!**" had this person really visited my website and failed to unambiguously tell my gender from my mugshot? Even if this were true, coming from India, they should have guessed my gender from my first name. My annoyance faded as I recalled a request that I had sent 20 years earlier to a preeminent scientist, Professor **Obaid Siddiqi**, at one of the best research institutes in India. I had laid bare my soul and waxed on about how this experience would truly permit me to decide whether I should pursue a career in science or, like my mother, become a member of the Indian Navy. I expected an immediate and equally long response by return mail. And so when just a 10-word reply arrived, I was crushed– even though the message was "I welcome you to join my laboratory for the summer."

The experience changed the trajectory of my life. I realized that there was pressing need for a high quality "match making" program that identified qualified students and placed them in labs where they would be nurtured and given the opportunity to engage in solving exciting problems at the frontiers of science, medicine and technology.

Genesis and Ken Shapiro

These thoughts crystallized one evening at the Fall 2005 annual gathering for the A*star students from Singapore. The government of Singapore identifies a handful of outstanding students – "A*star" students – who they then fund from college all the way through their final degree (for example, a PhD). The students have the freedom to choose any institution and roughly any area of study. The students are exceptional and an absolute joy to mentor.

Ken Shapiro and Kim Santiago

At the end of the reception, I was standing around awkwardly chatting with Chancellor **John Wiley** when I pointed out that we were missing the boat by not establishing a similar program with India. He smiled and walked me over to **Ken Shapiro** (Associate Dean of CALS) and **Kim Santiago** (Asia outreach coordinator, who had organized the A*star evening). "Ken," he said, "Aseem here is volunteering to build an Indian A*star program." I had done no such thing, but Ken, a charming, mild-mannered, but very action-oriented Dean for International Programs was not about to let that get in his way. He chatted with me quietly about Indian institutions, post 9/11 visa complications, UW policy on foreign students, and his interest in connecting UW to as many countries as was possible. Kim would interject whenever we digressed, expressing enormous enthusiasm for engaging India and linking the many UW alumni who hailed from that subcontinent.

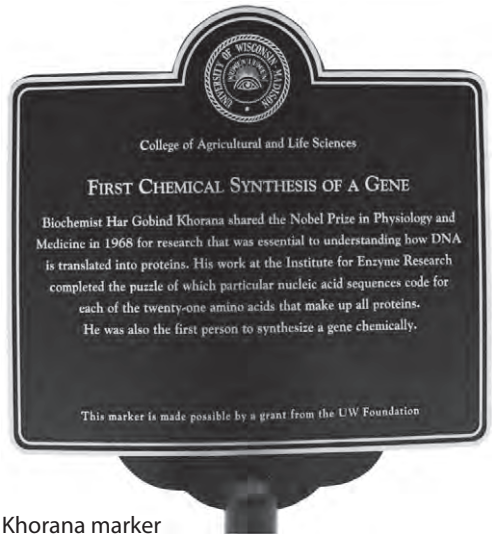
Har Gobind Khorana

In January of 2006, at a conference in India I heard **Arabinda Mitra** of the Indo-US science and technology forum, or the IUSSTF, extolling the virtues of joint research and exchange of scientists. "Tired maxims," I thought, but Mitra jolted me out of my cynical state with the magic phrase: "Money is not a problem. We have money and are looking for interesting ideas to fund." The IUSSTF was brimming with funds and had contributed to the joint Indo-US meeting that had brought 40 high profile US scientists to India. Mitra offered to seriously consider anything consistent with the IUSSTF mission to foster

productive and long-term interactions between India and the US. Could we get support from the IUSSTF to develop a UW program with India? The answer may take the form of travel awards for students and scholars from both nations.

Nucleation: Khorana and Adler

Ken Shapiro was unrelenting in his mission to ensure that the program took form. We had several meetings over 2006. Ken would pull out his little leather bound black book and take copious notes and then, abruptly, nearly a year after the A*star gathering, he put down his pencil and in a soft but firm way he said, "enough talk, let's just do it."



Khorana marker

But do what exactly, and how? Shaped by incessant grant writing, my instinct was that approaching IUSSTF without "preliminary data" was premature. Moreover, the college (CALS) had just told us that they had no money for a non-essential program. "So start a pilot project that I will fund from the tin can under my pillow," Ken countered. Walking back from that meeting I nearly ran head-on into a no-nonsense metal marker that honored the work of **Har Gobind Khorana** at UW. The marker declared that Khorana won the Nobel prize at UW in 1968 for his work in deciphering the genetic code. He went on to make synthetic genes. No scientist from India is complete if they don't know these factoids from the moment when they are anointed as "science majors" in their late teens. They may not know what the genetic code is or what a synthetic gene may be or how this led to the birth of modern molecular and chemical biology, but by God, we know of Khorana's greatness and that he did transcendental things at MIT.

Gobind with Julius and David Adler

So why was this unyielding marker claiming that he had cracked the code at UW? I re-read it a couple of times to make sure I hadn't misunderstood. **Julius Adler** caught me in the act and explained that, in fact, Gobind had been a faculty member in our department (and the Enzyme Institute) for nearly a decade. "He did it all here, in that building." Why then is there no endowed chair in his name in the department? Julius shrugged and then in his wonderful way went on to recount some of the memorable times he had with Gobind. "But you know, he is unwell these days." It took less than a second to suggest that we name the coalescing student program the "Khorana Scholars." Julius followed through with an email to Gobind to let him know about this nascent plan. A few days later he informed me that Gobind seemed pleased by the suggestion. The "Khorana Scholars Program" was born.

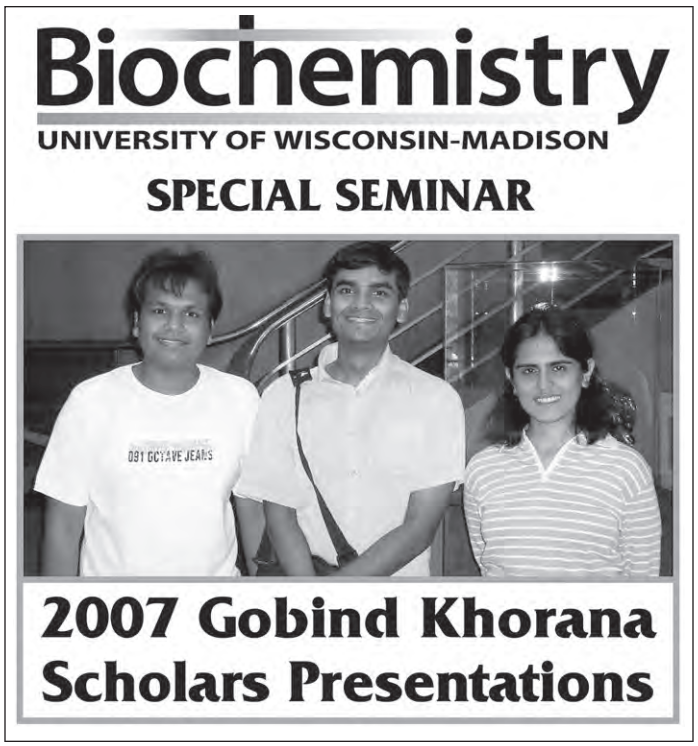
The pilot project

I asked my colleagues to send me the "Dear Sir/Madam" letters that they found interesting but inscrutable in terms of scholastic aptitude, quality of institutions, and such. I pruned a very long list to 50 very talented candidates, got transcripts and letters, and narrowed it to about 10 candidates; phone interviews cut it to 5 finalists. In the end we matched five students with five colleagues. To my horror, one colleague erupted, "But this student was ranked a thousandth in the entrance exam!" I rushed to explain that nearly 400,000 students prepare for nearly two years to take the grueling IIT-JEE (Indian Institutes of Technology - Joint Entrance Exam) and only the top 1-2% get into these elite institutions. The Infosys chairman famously quipped "IIT rejects" win top honors at Caltech and Harvard, so a rank of 1000+ from the best IIT was actually quite respectable. In the end, Ken could fund only three students. To help the program take its first tentative steps, the department chairperson **Elizabeth Craig** generously offered a supplement of $1000 per student– an amount that made an enormous difference in the students' ability to buy food.

The pilot project was on!

Transformation

Graduate students from the host labs at UW made the visitors feel welcome. *Jackie Reading* warmly introduced them at the departmental retreat and *Jeet Kalia*, a former IIT graduate, took them under his wing. We took pains to place them in nurturing and exciting labs at



Mukul, Ishan and Arpita, the first group of Korana Scholars

UW. **Arpita Mandan** worked on RNA-protein molecular recognition (in Marv Wickens' lab), **Ishan Chaturvedi** spanned a couple of labs working on nanofabrication with Franco Cerrina in engineering and Robert Blick in physics, and **Mukul Garg** worked on bioinformatics and microbial genomics (in Bob Landick's lab). At the end of their 10 weeks they were fighting tooth and nail with the IIT administrators to stay on another week and another day and another hour… Finally, they could stay no more and they gave their presentations to the department. The subsequent windup meeting with Dean Shapiro was especially touching.

Exchange

An amazing and quite different program soon came to my attention. **James Ntambi**, has created a remarkable program takes a group of students to Uganda and intimately introduces them to various health and nutritional issues facing the populace (see page 5 in this newsletter, for his update). Students take a class in the fall semester and then over the winter break, under James' tutelage, attend workshops and work in camps in Uganda. Many students find it a transformative experience: some have gone on to start their own non-governmental organizations to continue work on the projects that they encountered during their trip. Ken Shapiro too had gone to Uganda with James and was tremendously moved by the work. Greatly impressed, I wondered if the Khorana program should also seek to incorporate a similar "exchange" component to take UW students to India? The program thereafter was rebaptized the "Khorana Exchange Program."

A whirlwind through India

At the end of summer 2007, with the pioneering Khorana fellows back in India and my tenure process in full swing, Ken gracefully stopped asking me to more meetings. As soon as a positive departmental vote on my tenure came through, Ken suddenly reemerged from the shadows with the request that we visit India. Our goals were ambitious– we wanted to identify partner institutions in India, gauge the interest of these institutions in a scientific exchange program, learn about areas of relevance to Indian scientists, engage the Indian government and lay the ground work to formally launch the program in the fall of 2008– all this in time for the 40th anniversary of Khorana's Nobel Prize award.

At this stage we reconnected with Kim Santiago, who arrived with a list of alumni going back to when India was still part of the British Raj, and Mahatma Gandhi had not yet returned from South Africa to spur on the Indian freedom movement. In looking at the alumni list, **Sankar Adhya's** name jumped out at me. A prominent molecular geneticist at the National Cancer Institute in Bethesda and member of the prestigious National Academy of Sciences, I had known him from the start of my graduate career. I asked him for advice and he suggested we contact **Dr. Mashelkar,** (a visionary former head of the Council for Scientific and Industrial Research (CSIR) and **Dr. Balaram,** another leading scientist and the director of the Indian Institute of Science (IISc) in Bangalore. The latter institution seemed like a natural home for UW students, because of its scientific excellence, academic breadth, setting in the former royal botanical gardens in the lovely city of Bangalore, and the sheer volume of the UW alumni on its faculty.

Working non-stop for two and half months, Ken, Kim and I lined up 50 meetings that we would have in 7 cities across India over a span of 14 days! We met with Directors/Chancellors, Deans, Department chairs, and students from

over 12 academic institutions - and even explored experimental farms. We met with the former Prime Minister (**Mr. I. K. Gujral**), the current cabinet Minister of Science and Technology (**Mr. Kapil Sibal**), and heads of the major scientific organizations (CSIR and the Dept. of Biotechnology). As we crisscrossed India, ministers, governors, academicians, industrial giants, alumni - nearly everyone - added new dimensions to our objectives. The breadth of excellence across UW allowed us to flesh them all out. In Bangalore, we met with Obaid Siddiqi, who nearly 20 years earlier had started me on my academic path.

None of this would have been possible without the help of alumni and friends such as **Krishna Ella** of Bharat Biotech, who went out of his way (literally, he came to Delhi and Bangalore from his company head quarters in Hyderabad) to arrange and shepherd the meetings with the government. **Dipankar Chatterji,** at IISc, allowed us to introduce the Khorana program to biomedical scientists from all over India and the Pacific Rim at the Asian Conference of Transcription (ACT-X at Bangalore). And through the courtesy of **Raj Rajaram,** a member of the UW alumni board, and **Sam Pitroda,** the chairman of the Indian National Knowledge Commission, the program was given a prime time showing by **Srinivasa Rao** at the annual meeting of the Indian National Science Academy (INSA) with its 5000 attendees. **S. Viswanathan,** who visited UW and was the first to suggest that we work with his foundation on agricultural productivity, invited us to present the program to the Governor and the former Governor of Tamil Nadu and a slew of influential agricultural technocrats. **Masood Akhtar,** a Madison-based entrepreneur who was once with Forest Products lab, set up meetings with the Vice Chancellor of his alma mater and in an inspired moment he even offered to fund a Khorana fellow from Aligarh to Madison. Finally, in Delhi, we benefited from the charm and hospitality of **Ravi Khanna** who helped fire up an informal alumni meeting. Trained as an electrical engineer at UW, this real estate magnate also expanded our horizons with discussions of metaphysics and nature of consciousness – between libations that foster fluidity of mind.

Finally, as tangible evidence of the widespread enthusiasm for the program, the Indian government's Minister Sibal and UW's Chancellor Wiley, both known for fiscal prudence, offered to bankroll the program - *completely unsolicited*.

A new and ambitious identity

From our discussions with friends and potential partners, three major objectives emerged:

1. Provide Indian and American students with a transformative experience

2. Engage in Indian rural development

3. Increase interaction between academia and the private sector between the two nations

The third objective illustrates how the objectives of the program were shaped by suggestions of the people we met. In a meeting arranged by Raj Rajaram we presented our objectives to Sam Pitroda, who then strongly encouraged us to aggressively engage in rural development. The Indian consul-general in Chicago (**Mr. Ashok Attri**) seconded that notion and another dimension to our program was added – rural development in all its avatars is now a major objective of the Khorana Program. Soon after our first visit we were immediately invited back to India by **Mr. Rahul Gandhi** and the Rajiv Gandhi foundation to flesh out this objective.

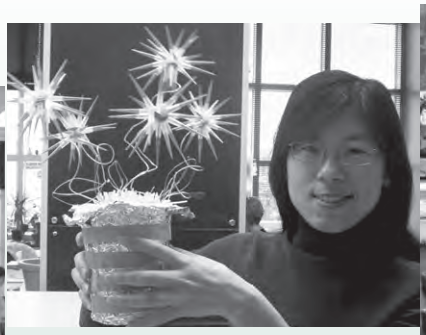
The Khorana program, we anticipate, will provide a life-enriching experience for students from both nations, build bridges between scientists/institutions and lead to virtual and seamless scientific communities across the world. If it continues along its current trajectory, and if it garners further support from friends and alumni, the program will grow beyond undergraduates, beyond summer exchanges, beyond chemical biology, beyond the current boundaries and would make UW the focus of a much broader program between US and India. The scope may match that of the Fulbright program but with an emphasis on Science, Medicine and Technology. The challenge now will be to make the Khorana program self-sustaining and retain its nimbleness to adapt to new and unanticipated areas of interest and most importantly, to maintain its excellence.

More information on the program can be found at the following website:
https://www.biochem.wisc.edu/faculty/ansari/khorana_program/

Biochemistry Degree Listing May 2007-December 2007

Degree	Name (Major Professor)	Thesis Title
PhD	**Kanin, Elenita** (Ansari)	Chemical Genomics Analysis of TFIIH Kinase Function in *Saccharomyces cerevisiae*
PhD	**Raess, Phillip** (Attie)	A novel role for cholecystokinin in beta-cell growth and survival
PhD	**Davis, Jared H.** (Butcher)	Structure, thermodynamics and metal ion association of the GAAA tetraloop-receptor interaction in solution
PhD	**Cox, Julia M.** (Cox)	The Coordinated ATP Hydrolysis Activity of the *Escherichia coli* RecA Protein
PhD	**Harris, Dennis R.** (Cox)	Investigating the Phenomenon of Radioresistance in Bacteria using *Deinococcus radiodurans* and Hyper-evolved *Escherichia coli*
PhD	**Rudolph, Ehren N.** (DeLuca)	Characterization of the protective effect of 1α, 25-dihydroxymitamin D_3 in the nonobese diabetic mouse
PhD	**Borrock III, Martin J.** (Kiessling)	Ligand Recognition and Signal Transduction in Bacterial Chemotaxis
PhD	**Puffer, Erik B.** (Kiessling)	Exploring B Cell Receptor Function Using Defined Multivalent Ligands
PhD	**Chesney, Michael** (Kimble)	Molecular and genetic analyses of GON-14 and other transcriptional regulators of early gonadogenesis in *C. elegans*
PhD	**Suh, Nayoung** (Kimble)	Molecular controls of mitosis/meiosis decision in *C. elegans* by conserved RNA regulators, FBF and GLD-2
PhD	**Lynch, Kara L.** (Martin)	Determination of the functional relevance of synoptotagmin and its Ca^{2+} dependent interactions in exocytosis
PhD	**Lim, Pei-Yin** (Montgomery)	The glycosaminoglycan-independent entry pathway utilized by herpes simplex virus
PhD	**Groppo, Rachel P.** (Palmenberg)	Characterization of cellular translation components during cardiovirus infection

Degree	Name (Major Professor)	Thesis Title
PhD	**Fretz, Jackie A.** (Pike)	Exploring the Transcriptional Activities of NFATc1: The Master Regulators of RANKL-Induced Osteoclast Formation
PhD	**Meyer, Mark B.** (Pike)	Molecular Mechanism Controlling TRPV6 Gene Expression and Calcium Homeostasis by Vitamin D Ligand
PhD	**Johnson, Randal Jeremy** (Raines)	Ribonucleases: Structural and biochemical insights into cytotoxic activity
PhD	**Davis, Caroline A.** (Record)	The Role of Upstream DNA Wrapping in Transcription Initiation by *Escherichia coli* RNA Polymerase
PhD	**Vander Meulen, Kirk A.** (Record)	Characterization and Analysis of the DNA Binding Thermodynamics of Integration Host Factor
PhD	**Gradman, Richard J.** (Reznikoff)	Analysis of control mechanisms in Tn*5* transposase
PhD	**Krusemark, Casey J.** (Sussman)	Synthetic Chemical Approaches to Proteomics: Affinity Labeling and Protein Functional Group Modification
PhD	**Kwak, Jae Eun** (Wickens)	GLD2 proteins: polyadenylation, polyuridylation and memory formation
PhD	**Liu, Lingling** (Wiese)	Centrosomal proteins required for microtubule organization
MS	**Thomson, Brian J.** (Clagett-Dame)	2-Methylene-19-nor-1α-hydroxyvitamin D_3 analogs inhibit adipocyte differentiation and PPARγ2 gene transcription
MS	**Davis, Melissa L.** (Holden)	Structural and functional analysis of selected enzymes involved in the biosynthesis of the S-layer glycan of *Aneurinibacillus thermoaerophilus* L420-91T
MS	**Weir, April M.** (Kiessling)	A Chemical Biology Approach Towards the Elucidation of Human Embryonic Stem Cell Signaling

Department of Biochemistry Alumnus – Jason Gestwicki

by Professor Doug Weibel

Jason 2001, Madison

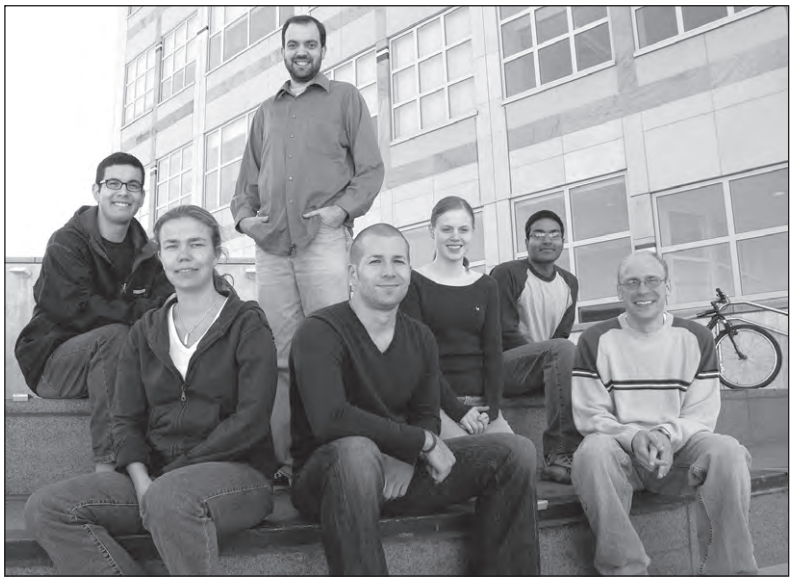
The Wisconsin Years

Jason Gestwicki grew up in New York State and studied chemistry at SUNY Fredonia. Several faculty members at Fredonia remember Jason fondly and recount his flair for fashion with a sense of nostalgia. Fredonia alumni remember Jason for his unusual humor and his unique comic strips. In 1997 he moved to the University of Wisconsin-Madison as a graduate student in the Department of Biochemistry and fell in love with chemical biology.

Jason's first encounter with the emerging field arose during his first conversation with Professor Laura Kiessling. Laura gave Jason a reprint of a paper from Professors Gerald Crabtree and Stuart Schreiber that described the application of small molecules to regulate protein dimerization. That paper introduced Jason to the concept of using synthetic ligands to dissect biological systems and inspired him to pursue a path in chemical biology that he continues to tread along.

Following his rotation, Jason joined the Kiessling laboratory and used synthetic, multivalent ligands to study the regulation of receptor signaling in bacterial chemotaxis. Jason's graduate dissertation advanced our understanding of how bacterial cells rectify incoming signals and produce a coherent behavioral response. Using chemical probes to study chemoreceptor clustering in bacteria, Jason identified how inter-receptor interactions play a role in amplifying and integrating chemotactic signals in *Escherichia coli.* This work built upon the pioneering work of Professor Julius Adler on chemotaxis in *E. coli* and the distinguished history in this department of decoding signal transduction in bacteria. Jason was remarkably productive at UW-Madison and published 17 papers and review articles. His love of science was obvious to those around him and he was a central character in a variety of events focused around discussing science and philosophy late at night in the lab, at the Terrace, and at the Regent Street Retreat.

Jason with his lab group, 2006 Ann Arbor



Chemical Biology Gold Rush – Go West!

After graduating in 2002, Jason joined Gerald Crabtree's group (remember that influential paper mentioned earlier?) at Stanford as a postdoctoral fellow. At Stanford Jason explored a new strategy for inhibiting protein/protein interactions. In 2004 they published an important paper that outlined a strategy for using small molecules to inhibit the aggregation of amyloid β *in vitro* (Science, 2004, 306, 865).

From Badger to Wolverine

In 2005, Jason moved back into the Big Ten and became an Assistant Professor in the Life Sciences Institute at the University of Michigan. The Gestwicki group uses small molecules to study the roles of molecular chaperones in disease. Using an approach based largely on chemical biology, they are exploring how chaperones recognize and process misfolded polypeptides, and how these interactions determine the outcome of neurological disorders, including Alzheimer's and Huntington's disease. He's back in the Big Ten where he started. This time, however, he is the one handing out classic papers in chemical biology to eager first year students and extolling the virtues of using small molecules to understand biological systems. The educational circle of life, which began at UW-Madison, continues today.

From the Labs

Alan Attie Lab

The Attie lab is delving ever more deeply into genetics of diabetes. Our lab has completed a large study where we are identifying gene loci that control gene expression of many thousands of genes in various tissues in relation to obesity and diabetes. The volume of data before us has made us develop a web site that allows us to probe our large data sets. We have made part of our data publicly available: **http://diabetes.wisc.edu.**

Below are some news items from various past and present members of the Attie lab.

Angie Oler is a biochemist turned geneticist. She is currently chasing diabetic genes on mouse chromosomes 16 and 2. Most of her days, she is up to her ears in pancreatic islets. She spends her free time playing volleyball on her home court and traveling the ever expansive globe.

Summer Raines is continuing her graduate work in the Attie Lab, with a focus on vascularization of the pancreatic islet. Outside of lab, she recently became engaged to Greg Jakubczak (former Raines lab manager), and is planning a wedding for September 2009, (hopefully) following her graduation.

Phil Raess is enjoying his third year of medical school, doing clinical rotations at the UW hospital and in outlying communities. He and his wife Nicole have been enjoying cross-country skiing this winter in their rare free time. Phil will graduate from the MSTP in 2009, and has yet to decide on his medical specialty.

Susie Clee left her position in the Department of Biochemistry at the end of June last year. She is currently establishing her own lab as an Assistant Professor in the Department of Cellular and Physiological Sciences at the University of British Columbia in Vancouver. Her work will continue to focus on using genetics as a tool to identify novel pathways increasing susceptibility to developing obesity and type 2 diabetes.

Jaap Twisk has been working at Amsterdam Molecular Therapeutics (Amsterdam, The Netherlands) since 2002, where he is involved in a number of gene therapy projects. The most promising project involves adenovirus-associated virus (AAV)-mediated expression of Lipoprotein Lipase (LPL) in muscle, as a treatment for Type I LPL deficiency in man. The project has evolved from designing the vector, testing it in LPL-deficient mice and cats, to clinical testing in patients. Jaap is mostly involved in research management but spends part of his time at the bench as well. Jaap and Arlene live in Hillegom in the Netherlands, between the tulips, where they spend most of their free time rebuilding and refurbishing their (old) house. They have 2 cats for company. Free time is otherwise spent on softball, dancing, playing the trumpet (very early stages), and of course enjoying those beautiful flowers!

Dan Gretch is now an Associate Professor at Carroll College in Helena, MT. He is teaching Biochemistry and Genetics, as well as conducting research on prion protein misfolding in Chronic Wasting Disease. Living in Helena places him within 20 miles of 4 lakes, dozens of hiking trails, 20+ campgrounds, and the continental divide. If you are visiting MT, stop by and say hello!

Scott and Amy Cooper are enjoying a very white Wisconsin winter. Scott's new challenge in his 13th year of teaching at UW-LaCrosse is a course in radiation biology. He's already hit **Scott Lowe** up for some suggestions on using p53 in the lab section.

Paul Bates is teaching Freshman and Advanced Placement Biology at Edgewood High School. He is also an Adjunct Professor at Edgewood College, teaching Biotechnology as well as supervising some undergraduate students in their research projects. They are studying hybridization between native and invasive species of the aquatic plant milfoil at the anatomic and DNA levels. In his free time, he's building furniture for his home and training for his second marathon.

After completing her doctorate degree in 2006, **Jessica Flowers** went on to become a registered dietitian after completing an internship in dietetics at the University of Wisconsin Hospital and Clinics. She is currently participating in the Waisman Center Leadership Experience in Neurological Development interdisciplinary training program and she recently started working as a nutritionist for the research diet design company Harlan-Teklad.

Don Gillian-Daniel is now an Associate Director of the Delta Program in Research, Teaching and Learning at UW (www.delta.wisc.edu). He recently co-authored a book chapter about the program, "Preparing Future STEM Faculty," to appear in the Monograph Series: "New Directions in Teaching and Learning." Don also teaches metabolism in the Vet School each spring (Alan's old course), where he gets to try out all kinds of new pedagogy on the unsuspecting students! Anne Lynn is the Program Administrator for the

NMRFAM with John Markley.

Dawn Brasaemle, Associate Professor in Nutritional Sciences, Rutgers University, organized the first ever conference dedicated to the biology of lipid droplets as a 2007 FASEB Summer Research Conference. The conference was a huge success, and was attended by Attie lab alum **Steve Sturley,** who gave a brilliant talk (as usual). The conference will continue as a regular meeting with the next one scheduled for Summer 2010.

Thomas Baranski was promoted to Associate Professor at Washington University where he continues his research on signal transduction by G proteins. He has also initiated a new project in the lab that focuses on glucose toxicity and insulin resistance in a Drosophila model system. As an added benefit, this project has precipitated discussions and video chats with his former mentor, Alan. Capitalizing on this technology, Tom co-founded a company, Medros (Medicines from Drosophila) that uses whole animal screening to identify novel drugs for cancer and diabetes. Tom remains happily married to Karen and his family continues to grow. He has three children--Katie (9), Elizabeth (6), and Jack (4).

I have been on the "dark side", pharmaceutical industry as my academic friends call it, for three years. I chase new drug targets in obesity and diabetes. An industry job relies heavily on team work and collaborations. I don't need to run all the experiments, but I need to work with my colleagues or with outside service companies to get results as fast as possible. I spend a large amount of time writing e-mails and attending various meetings, coordinating group efforts. I enjoy working with my colleagues.

Kurt Grunwald is taking his last class towards his degree(s) in Physics with Astronomy Emphasis and Math. He has accepted a new position at UW-La Crosse as the equipment maintenance manager. He will be responsible for maintenance and repair of the Biotech equipment in Biology. He is also the Radiation Safety Officer at UW-L. His oldest son is in middle school, his daughter is in elementary school and his younger son will start kindergarten this fall. Kurt and his son Alex are active Boy Scouts. Kurt is slated to become the Scoutmaster for their troop next year. With any free time Kurt is a part time business partner in a woodworking business making yoga props at "Yoga Place Props."

Sam Butcher Lab

Another year has flown by, and it has been an exciting and productive one in the Butcher lab. Below are a few highlights.

Science:

We determined our first protein structure! We (meaning mostly **Nick Reiter**) solved the NMR structure of Prp24, an essential splicing factor and U6 RNA binding protein. Collaboratively with George Phillips and Dave Brow, we also solved its crystal structure. Thankfully the two structures agreed nicely. Over the past year, we've also solved a few (actually around 5) new NMR structures, all very interesting RNAs that include: a U2 spliceosomal RNA domain (**Dipa Sashital**), a retroviral frameshift site RNA from SIV (**Ryan Marcheschi**), an HIV-1 frameshift site RNA bound by a drug-like small molecule (**David Staple**), an anti-NF-kappaB aptamer (Nick Reiter), and a tetraloop receptor domain from a self-splicing intron complete with bound metal ions (**Jared Davis** and **Trent Foster**). Additionally, we developed a new method for probing the surface accessibility of nucleic acids, using NMR and a highly soluble paramagnetic probe (**Vincenzo Venditti**). Second year graduate students **Steve Martin-Tumasz** and **Ashley Richie** are continuing our work on pre-mRNA splicing, focusing on the structure and function of the U6 small nuclear ribonucleoprotein particle. **Rita Warden** helps to keep things running on the first floor and divides her time administratively helping out all 3 first floor labs (Markley, Butcher and Fox).

New Arrivals:

We are really happy that two wonderful new graduate students joined the lab: **Jordan Halsig** and **Katie Mouzakis**. Jordan will be investigating the structure of the spliceosomal U2-U6 RNA complex, and Katie is working on the HIV-1 frameshift site RNA and trying to target it with small molecule antagonists. Additionally, two new postdocs have recently joined the lab: **Kirk Vander Meulen,** (from the Record lab), and **Larry Clos**. Kirk is studying the thermodynamic forces that drive RNA folding, and Larry is working on the structure of U6 RNA. Two new undergraduates also joined the lab (**Hyunjae Lee and Chen Yuan Kam**).

Departures:

Nick Reiter left after 6 productive years and 5 first author publications, setting a great example for future graduate students. Nick is now a postdoc with Prof. Alfonso Mondragon, an outstanding crystallographer at Northwestern. **Dipa Sashital** left for her postdoctoral position (with a Damon-Runyon Postdoctoral Fellowship Award in hand!) in Jennifer Doudna's laboratory at Berkeley. Finally, our fabulous undergraduate and RNA biochemist extraordinaire **Trent Foster** left for medical school here at UW-Madison.

Mo Cleland Lab

Our group has increased in size by 2 this year. **Tonya Zeczycki** is a new postdoc in our lab. She received her Ph. D. in organometallic chemistry from Marquette University. She moved here in August with her husband Jay. Besides spending a zillion hours in lab, she likes to paint with watercolors. She is working on determining isotope effects on pyruvate carboxylase and its mutants. **Nate Bruender** is new graduate student. He is originally from near Mankato, Minn and received his degree in biochemistry from the University of Minnesota-Duluth. He is a big hockey fan and plays intramural hockey in Madison. He is doing a joint project including both kinetics and x-ray crystallography with the Holden lab.

Professor **John Marlier** finished his project on determining the isotope effects of slow substrates with urease, and Professor **Jill Rawling's** work on the reduction of hydroxyamine was utilized by both John and **Jeremy Van Vleet,** in his last year of graduate school. Jeremy and **Laurie Reinhardt,** associate scientist, published a paper in Biochemistry supporting the formation of a discrete carbanion intermediate in the decarboxylation reaction of orotidine-monophosphate decarboxylase, perhaps putting an end to that controversial story. Martin St. Maurice, a postdoc in the Rayment Lab, and Laurie published a report in Science on the X-ray structure of pyruvate carboxylase, a multifunctional enzyme. The structure reveals a previously unrecognized mechanism for intermediate transfer between active sites and a structural basis for allosteric activation.

Mark Anderson completed an isotope study showing the symbiotic relationship between leaf-cutter ants and nitrogen fixing bacteria. The work was done in collaboration with Adrian Pinto from the Currie lab in the Department of Bacteriology. The manuscript will be submitted to Nature in February. He is also collaborating on the kinetic isotope effect (KIE) studies of the reactions catalyzed by nicotinamidase and Sir2 with Brian Smith from the Denu lab at the Department of Biomolecular Chemistry. Other projects include collaboration with Russ Poyner of the Reed lab to determine kinetic isotope effects for ethanolamine ammonia lyase using various ^{15}N, ^{13}C, and ^{2}H labeled substrates.

Mo and Laurie went to the Enzyme Mechanism Conference in St. Petersberg, Florida, in January. It was gorgeous there. Mo went to the Enzymes Gordon Conference in Maine, and is looking forward to the Isotopes Gordon Conference in Ventura, CA, this February.

We have five undergraduates working with us. **Fiona Chu** runs the high vac lines and mass spectrometer like a pro. **Greg Peters**, our kinetics and columns undergrad, is graduating this year. **Dan Pensinger** and **Min-Hee Han** are working with Jeremy. **Ryan Gries** is starting to work with Tonya. **Elisa Parks** graduated in December.

Mike Cox Lab

Current Lab News:

Vessela Petrova passed her prelim exam in April 2007. Congratulations Vessela!

Mike Cox and Dave Nelson completed the *Principles of Biochemistry, Fifth Edition*, as well as Mike and George Phillips completing the *Handbook of Proteins: Structure, Function and Methods*. Two books in one year, along with chairing the New Building committee, teaching, speaking, and all the other things a PI does. How does he find the time to do it all?

Awards:

Audrey Klingele received a 2007-2008 Vilas Travel Award to use to attend the Keystone Symposium on DNA Replication and Recombination in Santa Fe, New Mexico, in February 2008. She'll attend the meeting with Mike Cox, Jong-Il Kim and Marielle Gruenig.

Comings:

Graduate students **Asher Page** and **Khanh Ngo** joined the lab after fall rotations.

Cédric Norais joined the lab as a postdoc in November 2007. He was previously a graduate student in the lab of Dr. Hannu Myllykallio at the University Paris-Sud. He received his PhD in July 2007. He is joined in Madison by his wife, Virginie and his son, Alban.

Welcome to the Cox Lab Cédric, Khanh and Asher.

Goings:

Dmitry Baytin left the Cox Lab to return to St. Petersburg, Russia and the lab of Vladislav Lanzov in July 2007.

Julia Cox defended her thesis February 2007 and is working as a patent scientist at Michael Best & Friedrich, LLC. Congratulations Julia – we miss you.

Dennis Harris defended his thesis in May 2007 and is currently a postdoc in the Miro Radman Lab, Institut National de la Santé et de la Recherche Médicale (INSERM). On the evening of the day that Dennis defended his thesis, he and Yeajin Song were married - a day full of excitement and instant memories. Congratulations to both Dennis and Yeajin! Dennis sent us an email in September 2007 soon after they arrived in Paris, saying that they have a full view of the Eiffel Tower right outside their apartment window and that they get a light show every night before they go to sleep. Nice!

Past Lab News:

Kevin Rice is now an Assistant Professor at Colby College in Waterville, Maine. His website is: www.colby.edu/chemistry/Rice/Welcome.html.

Sarita Jain is now at PDL BioPharma, Inc in Fremont, California. She said she's on the Corporate and Business Development team.

Brian Webb now works for Thermo in Roscoe, Illinois. He leads a group of scientists developing antibody arrays and siRNA products.

Former Cox Lab undergrad news:

Mike Modica wrote a note in early 2007 saying he finished up medical school and was in the process of interviewing for medical residency. He said he's interested in molecular imaging as a research focus during residency. **Reece Goiffon** joined the MD/PhD program at Washington University in St. Louis.

Babies and Weddings:

As mentioned above **Dennis Harris** and Yeajin Song were married in May 2007. They had another ceremony in Maryland on a beautiful day in August to include all family and friends. Immediately following the ceremony they were off to Paris.

Kevin Rice, Anna, and TJ gave us news that they are now a family of four. Jenna was born on March 21, 2007 and weighed 7 pounds 15 ounces. Welcome to the Cox Lab family Jenna. Kevin sent us a note in July saying that along with all his other news, he and Anna just purchased their first house too. What a year for the Rice family!

Julie Schultz (Bork) wrote that she and Todd are now the proud parents of Jessica Lena Schultz, born October 11, 2007 and weighed 6 pounds 7 ounces. Julie says Jessica has lovely red hair and that their lives will never be the same. Congratulations to Julie, Todd, and Jessica - all the best to you.

Brian Fox Lab

Hello from 141B Biochemistry Addition and 4th floor of Old Genetics.

It has been a couple of years since I wrote, so there is some catching up to do. Our projects are still the desaturases and toluene monooxygenase along with cloning, expression, growth, and purification subgroups in the UW Center for Eukaryotic Structural Genomics (CESG). Most recently, our group has also begun work in the biofuels area, using our expression approaches to prepare enzymes useful for cellulose degradation.

Over the past couple of years, the lab personnel has included **Abolfazl Arabshahi, Lucas Bailey, Lai Bergeman, Paul Blommel, Brendan Burns, Yong Chang, Nate Elsen, Ronnie Frederick, Mike Goren, Carrie Loushin-Newman, Thomas Malone, Lea McMartin, Luke Moe, Karl Nichols, Brad Pierce, John Primm, Megan Riters, Kory Seder, Pablo Sobrado, Dmitriy Vinarov, Frank Vojtik** and **Russell Wrobel. Rita Warden** helps to keep me organized, which is no small feat. Undergraduates working in the lab have included **Petar Duvnak, Andy Hauser, Steve Kaul, Jacob Ludington, Yi Han Ng, Kaitlin Statz, Justin Tannem, Nicholas Turco** and **Abby Wochinski.** We have also had **Carissa Amundson** and **Cody Sizemore** from the Dane County Youth Apprenticeship program. Of note, Petar is now in medical school at Medical College of Wisconsin, Steve works at Sigma/Aldrich, Andy is our lab manager, and Yi Han has a Hilldale Fellowship to complete her dissertation research.

Brian Hoffman and **Jeremie Pikus,** please contact me sometime.

Joe Studts and **John Broadwater** both work at Boehringer Ingelheim. I have had the good fortune of working with them and their coworkers over the past few years and hope that this activity will continue. **Kevin** and **Tracey** are now living and working in the Boston area at biotech companies. **Enrique** returned to Mexico to continue his research career after a strong contribution and an important learning experience in the UW Medical School. **Jeff** and family are in Davis, CA, still the most ideal place in the Universe. Jeff made a summer visit to Madison a year back, and it was nice to hear how well things are going for him and his family. **Karen** and **Brandon** have returned from Europe and now live in the San Francisco area, finding the climate and temperament to their liking. No desiccation there. **Cory Rogge** is still in the Houston area, and publishing frequently with distinguished colleagues. Latest score from PubMed: Post-Fox, Rogge:6; Fox-Rogge:3; Pre-Fox, Rogge:0. Way to go Cory!

Luke Moe and **Michelle Sizemore** got married last summer just before July 4th at the Olbrich Gardens. Even yours truly was photographed on the dance floor. It was a good time, and I had a nice, by-chance visit with Luke's parents at the Ground Zero coffee shop the next morning. Luke is now a postdoctoral fellow in Jo Handlesman's lab. Luke has the unique career path of moving to a new lab in every position he has accepted so far. He has our best wishes that he might continue on this lucky course.

Tom Malone finished his PhD dissertation in December 2006, and **Paul Blommel** finished his PhD dissertation in May 2007. Tom identified a new XenB enzyme by Cartesian analysis of product specificity, and recently my friends at Shaw Environmental (formerly Envirogen) have gotten interested in this enzyme. Paul is working at a startup company on converting sugar to gasoline, so there is at least some glimmer of hope that Hummer drivers (and Professors with mini-vans) will be able to continue their profligate way.

After a minor scare on renewing her visa last summer (biophysics and Mycobacteria, possibly scary), **Yong Chang** made it back to Madison and has completed work for at least two papers on *Mycobacterium tuberculosis* desaturase proteins. Recent news is that Yong Chang will be married this year. She is currently in China planning the wedding. Our congratulations.

Pablo Sobrado is now an Assistant Professor in the Department of Chemistry and Biochemistry at Virginia Tech University. He is setting up his program and has identified some interesting topics on enzymology of pathogen enzymes and multiprotein complexes. This is an exciting time as he begins to build his new research lab. Last year, I gave a presentation at the Chicago ACS meeting at the Bader Symposium in honor of Prof. Eckard Münck. I talked on the protein-protein interaction model for desaturase, ferredoxin, and acyl-ACP that emerged from the work of Pablo and Karen.

Brad Pierce has accepted a position as Assistant Professor of Chemistry at University of Texas Arlington. Brad has worked on many different metalloproteins in the past years including desaturase, toluene monooxygenase, cysteine dioxygenase, and FNR with Trica Kiley's lab. He is one of the EPR experts on campus. Brad has

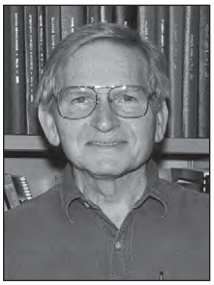
also been a leader in the Metals in Biology supergroup, which meets once a month.

Lucas Bailey and **Nate Elsen** are working on toluene monooxygenase. Some exciting results have emerged recently, including a 2008 New Year's morning transmission of pdb coordinates. After many years of effort by many different workers, Lucas Bailey succeeded in preparing the enzyme in a form that readily crystallizes. With these crystals, Lucas has solved many different structures of the hydroxylase at resolution lower than 2 Å. We owe a great deal of thanks to Jason McCoy, Craig Bingman, and George Phillips for help along the road to solving the T4moH structures. These structures complement the X-ray structures of T4moC solved by Craig Bingman, Luke Moe and Gary Wesenberg, and T4moD solved by George Lountos and Allen Orville. We see new information on several early steps in the reaction cycle, and the crystal forms we have obtained show great promise to yield further information. In parallel, Nate has made major advances in our understanding of protein-protein interactions by use of stopped-flow and rapid freeze quench approaches. The linkage of the kinetics work and the crystal structures to our large body of prior results will be an exciting future effort. The first presentation of this work will be at the New Orleans ACS meeting at the Bader Symposium in honor of Prof. Larry Que.

Mike Goren is the newest member of our group, coming from Glaxo Smith Kline by recommendation of Jeff Gross, a former postdoctoral of Perry Frey's when we were located in the Enzyme Institute. Mike is working on development of cell-free translation methods for membrane proteins. He recently won an NSF fellowship to visit Japan and work with Prof. Yaeta Endo on this topic. I had the pleasure of traveling twice to Matsuyama, Japan to meet with Prof. Endo in the past year.

My part of the CESG project has now moved to the fourth floor of the Old Genetics building. This is a great space where everybody involved in the Protein Production team is together. The current team is John Primm, Frank Vojtik and Donna Troestler (project management), Russell Wrobel and Kory Seder (cloning), Ronnie Frederick, Lai Bergeman and Kasha Gromek (expression and large-scale production), Karl Nichols and Mike Poplears (purification), Shin-Ichi Makino (cell-free translation) and Dave Aceti (quality control). Brendan, Megan, Dmitriy and Carrie left the project to move on to bigger and better things in the past year or so. Since the start of Protein Structure Initiative Phase II in 2005, over 50 undergraduates and 7 high school students have worked with this group. I thank all of them for their hard efforts as they learn new skills that so strongly contribute to the project progress while also helping them advance their own careers. CESG increasingly focuses on human proteins, and the thought that we can consider the function of some of these is a satisfying new direction. We wish them the best in their future efforts. The expression vector tools and methods we have developed are very useful for production of proteins, and if this is still in your work program, I encourage you to talk to us about these methods.

In closing, I hope you and yours have been safe and happy over these past few years. It is my wish that this will continue well into the future. Please stop by Madison if you have a chance.



Perry Frey Lab

The Frey Group made the transition to retirement for Perry during 2007. The symposium at the 234th National Meeting of the American Chemical Society in August went off very well, and more than a third of the former associates of the Frey Group were able to make their way to Boston for the symposium and evening dinner. Thanks to **John Richard, Joe Wedekind, Squire Booker, Ken Gruys** and **Doug Sammons** for their excellent presentations. Special thanks to **Claire CaJacob** for organizing the symposium and hosting the dinner. Thanks also to the Division of Biological Chemistry of the ACS for proposing and scheduling the symposium with the co-sponsorships of the Divisions of Organic Chemistry, Medicinal Chemistry, and Biochemical Technology and the Biotechnology Secretariat and Biotechnology of Health and Wellness. Perry is very grateful to these organizations for sponsoring the symposium marking his retirement and for their past support of the activities in the Frey Group.

Several members of the group have secured new positions this year. **Glen Hinckley** is Assistant Professor of Chemistry at Elmhurst College, **Sue Wang** is Assistant Professor of Molecular Biosciences at Washington State University, **Dawei Chen** is a research chemist at the Nanomaterials & Nanofabrications Laboratories, **Adrian Hege-**

man is Assistant Professor of Horticulture and Plant Biology at the University of Minnesota, and **Ab Arabshahi** has transferred to the Great Lakes Biofuels Center in the laboratory of Brian Fox. **Phil Schwartz** is a postdoctoral associate at the Albert Einstein College of Medicine, and **Alejandro Yevenes** is a postdoctoral associate at Utah State University. Congratulations to all.

Perry and members of the group are indebted to Ab Arabshahi and the Media Center for creating the group website **http://perryfreygroup.biochem.wisc.edu/.** The site includes information about the members of the group, with links to their websites, as well as information about the research activities of the group. We thank Ab for his good work in setting up the website.

In retirement, Perry will continue working with national organizations, editing and writing; he will pursue new personal challenges, and he will spend more time with his family.

Judith Kimble Lab

The Kimble lab has continued to thrive in 2007 and early 2008. Indeed, for the first time in living memory, every one has a bench of their own — a situation we will try to maintain if at all possible. A real milestone for the lab has been solving the SYS-1 crystal structure, a project accomplished by posdoc **Bryan Phillips** in our lab in collaboration with Wenqing Xu and Jing Liu at the University of Washington in Seattle. It is tremendously exciting to move all the way from mutant to crystal structure, and finally demonstrate unambiguously that SYS-1 is indeed a bona fide β-catenin. Another milestone has been the discovery of a conserved link found in the regulatory circuits controlling both nematode and human stem cells. Postdoc **Myon-Hee Lee** found that PUF proteins downregulate MAPK-encoding mRNAs in both *C. elegans* and human embryonic stem cells, a project done in collaboration with Jamie Thomson and Marv Wickens here in Madison.

On the personal side, the lab has expanded considerably over the past year, especially on the baby front – our baby explosion makes our lab parties more fun than ever, albeit chaotic. One grownup who has joined lab is **Dr. Karla Knobel,** a scientist from Maureen Barr's lab who joined us when Maureen moved to the east coast. Karla has a passion for cell biology and is focusing her work on the distal tip cell and its role in forming a stem cell niche. And another grownup is **Clint Morgan,** an M.D./Ph.D. student, who has joined the lab to do the research part of his dual degree. These additions were made possible by the departures of others. **Nayoung Suh** defended her Ph. D. and departed for San Francisco, where she will do her postdoc with **Dr. Robert Blelloch** on the topic of microRNAs in stem cells. Some of you may remember that Robert did his Ph. D. thesis with me – so needless to say, I am excited about the idea that Nayoung will be with Robert for her postdoc. **Mike Chesney** defended his Ph. D. and departed for Cambridge, England, where he will do his postdoc with Dr. Jim Smith on the topic of molecular mechanisms of vertebrate development. And **Kate Schmitt,** an undergraduate, who worked with us for several years, has also left us, moving on to find her way in life. Well, this is obviously the short version of news from the Kimble lab, so please stop by to say hello and get caught up if you are in the neighborhood!! – Judith

Henry Lardy Lab

The greetings from the Lardy Lab are brief in keeping with our small research group. The year has been scientifically productive but the discoveries have not yet been polished sufficiently for release.

We have lost some of our cherished colleagues. You will read elsewhere that Prof. Helmut Beinert died a few months ago. Among our former students, **Dave Garbers** died suddenly this autumn, and **Bob Weaver**, Chair of Chemistry at U.W. Stevens Point, died after a prolonged illness.

We finally have secured a research grant but it is so small that **Dr. Padma Marwah** is on a 75% appointment and **Dr. Ashok Marwah** is receiving only 60% of his former salary. Both are so enthusiastic about their research that they have turned down lucrative, full-time appointments elsewhere to pursue our steroid work. **Nancy Kneer** continues her work on an hourly basis.

We have leads that are highly interesting but they cannot be discussed until we decide on patentability. More next year! – Henry

John Markley Lab

Comings and goings:

M. Francisca Jofre recently joined NMRFAM as a research specialist on the metabolomics project and has added a significant number of compounds to our ever growing standards database. Two graduate students joined the Markley group this year: **Ziqi Dai** is a biophysics student working with **Hamid Eghbalnia** and **Arash Bahrami** on developing the automated assignment software, and **James Ellinger** is a biochemistry graduate student, who will be working on a joint metabolomics project with **Ian Lewis** and **Mike Sussman**.

Klaas Hallenga will be retiring at the end of March after five years at NMRFAM. Klaas plans to move back to The Netherlands to be closer to his children and grandchildren. We will miss Klaas and his vast library of Varian knowledge. **Zsolt Zolnai,** who continues to develop the 'Sesame' laboratory information management system (LIMS) used by CESG, NMRFAM and other groups, now works out of his apartment in Brooklyn that overlooks the East River. The reason for the move is that Zsolt's wife, Nevena, is doing her residency at several different hospitals in the New York area. We miss having Zsolt on site, but he is in regular contact via phone, e-mail, and video conferencing. Zsolt became the PI of an NIH 'R01' grant last fall that is funding open source distribution of Sesame. **Jurgen Doreleijers** recently left BMRB to move closer to his family in Netherlands. He is currently working at the Centre for Molecular and Biomolecular Informatices at the Radboud University Nijmegen Medical Center.

News from former lab members:

Ken Prehoda was recently granted tenure at the University of Oregon. His lab is up to 10 people now, which he says caused him to stop micro-managing, because he is squirreled away in his office submitting papers and grant proposals most of the time. We are seeing more of **Mike Reily,** now that he has joined the NMRFAM External Advisory Board. Mike was recruited recently by Bristol-Myers Squibb in Princeton.

Meetings:

John wisely started 2007 with a trip to Maui for the Pacific Symposium on Biocomputing, where he presented a talk on "New Bioinformatics Resources for Metabolomics." From there, John traveled to Utah for a Keystone Symposium and then to Italy for an "Advances and Management of NMR in Life Sciences" meeting. After spending an entire month in Wisconsin, John went to Osaka, Japan for a meeting on the role of isotope aided NMR methods for protein structural analysis. In April and May, John traveled to Colorado and California to present a talk entitled "Lessons from the Worldwide Structural Proteomics Programs." After a trip to the UK in June for presentations on Structural Proteomics programs and Quantitative Metabolomics, John traveled to Paris in July to give a presentation on automated protein structure determination at the Institut Pasteur. In October, John traveled to Taiwan for the 2nd Asia-Pacific NMR Symposium in Taipei and the ISMAR Meeting in Kenting, which **Milo Westler** also attended. **Honggao Yan,** from Michigan State also attended the meeting. They were hosted in Taiwan by former lab member **Winston Wu. Ian Lewis** gave a talk at the Red Blood Cell meeting in Boston. **Arash Bahrami** presented a poster at the Keystone Conference in Steamboat Springs last January.

New Grants and Equipment:

Fariba Assadi-Porter hit the jackpot this year by becoming the PI of a Wisconsin Institutes for Discovery grant on the metabolomics of polycystic ovarian syndrome (PCOS). Other lab members involved in the project are John, **Hamid Eghbalnia,** and **Marco Tonelli**. Fariba also became a co-investigator on an NIH grant. We have been awarded funds from the new DOE grant that funds the Great Lakes Bioenergy Research Center (GLBRC) to develop NMR-based metabolomics support for the project and to carry out related research. We were awarded an equipment grant for a new NMR spectrometer console with a cryogenic probe for direct detection of ^{13}C and ^{15}N. This system will recycle the magnet from NMRFAM's 500 MHz spectrometer without a cryogenic probe. A new high sensitivity cold probe was installed on the 900 MHz spectrometer this past August.

Other News:

In June, NMRFAM presented a "Protein Structure Determination" workshop. This introductory workshop exposed participants to the steps involved in solving a protein structure from data processing through structure calculation and refinement in a series short lectures and hands-on exercises. The workshop was run primarily by NMRFAM staff (**Gabriel Cornilescu, Marco Tonelli, Anne Lynn Gillian-Daniel, Milo Westler, Klaas Hallenga, Hamid Eghbalnia, Arash**

Bahrami, Eldon Ulrich (BMRB), **Nick Reiter** (Sam Butcher's group)) and brought in 27 participants from throughout the United States. Due to the high level of interest, we are holding the workshop again in June of 2008. **Anna Füzery** received a Vilas Travel Fellowship this year which she will use to visit collaborator Larry Vickery's lab at the University of California-Irvine. As the temperatures are now in the negative numbers here, we recommend she go soon. **Ian Lewis** won the Biochemistry Graduate Mentoring Award for his great work with undergraduates. Ian has several students working with him collectively referred to as Team Metabolon.

Milestones:

Congratulations to **Sannali Matheson** and Joseph Dittli, who were married in July. Joseph works as a computer programmer at Epic Systems Corporation in Verona, WI.

Julie Mitchell Lab

2007 was a year of many changes. **Roummel Marcia** moved on to Duke University as a research scientist, where he is working on medical imaging applications with Rebecca Willett. **Steve Darnell** is working hard to graduate by year's end. After presenting his work on predicting protein binding hot spots at the ISMB/ECCB conference in Vienna, he refocused his efforts to validate predicted mutations that improve the binding affinity between two proteins. The preliminary results are very encouraging, and Steve hopes to finish these experiments very soon. **Sarah Cunningham** has been studying how proteins recognize DNA from a structural and statistical perspective. By clustering spatial patterns of hydrogen bond networks, she developed a set of structural motifs that represent strategies proteins employ to recognize DNA base pair steps. Stitching the motifs together may provide a new way to understand and predict protein-DNA interactions. **Omar Demerdash** has been working a data mining/machine learning-based model to accurately predict residues that will perturb allostery when mutated. **Jennifer Losaw** and **David Dynerman** are two new members of the group. Jennifer is a mathematician who will work on multibody protein studies. David has been working on graphics accelerated versions of some of our protein energetic algorithms. We've implemented a fast desolvation model and are seeing nice speedups compared with previous implementations.

James Ntambi Lab

This past year has been a year of changes for the Ntambi Lab. **Dr. James Ntambi** is currently on a 6-month sabbatical in Uganda, where he is interested in working with AIDS patients on anti-retroviral therapies. Dr. Ntambi is interested in obtaining plasma samples for clinical analyses from these patients, many of whom suffer from lipodystrophy due to their anti-retroviral treatments.

Makoto Miyazaki, a prominent fixture of the Ntambi Lab over the past seven years, recently left us to take on an Assistant Professor position in the Division of Endocrinology, Metabolism and Diabetes at the University of Colorado and Health Sciences Center at Denver. While we were sad to see him go, we wish Makoto continued success at his new post.

Before Makoto and Dr. Ntambi left Madison, the Ntambi Lab took a "field trip" to the Gordon Conference on Molecular and Cellular Biology of Lipids at Waterville Valley, NH, in July. Makoto, **Matt Flowers, Harini Sampath, Kiki Chu** and **Xueqing Liu** all presented posters at the conference that were very well received. Apart from the scintillating scientific program, we participated in a variety of activities, including mountain biking, canoeing, hiking and catching up with peers over a pint (or more) of NH beer.

As for those of us currently in Madison, **Matt** continues to feed his fascination with fat. Matt and others are using the Cre-loxP system to generate a panel of tissue-specific SCD1 knockout mice to help us answer "Where in the body does SCD1 deficiency elicit its metabolic effects?" He is also planning to begin his home-based *S. cerevisiae* fermentation research program.

Harini presented her thesis seminar in the Department of Nutritional Sciences in December and has been wrapping up her studies on regulation of SCD1 by dietary fats. She has also developed an interest in understanding the role of SCD1 in the skin in regulating energy expenditure and whole body metabolism. She recently

returned from a two-week vacation in Vishakapatnam, a coastal town on the southeastern coast of India, where her family currently resides.

Similarly, **Kiki** is also trying to finish up her studies on deciphering the molecular mechanism by which SCD1 deficiency protects against elevated plasma triglyceride upon LXR activation. With the plan to defend her thesis by the end of summer, she is pushing herself to work hard but, at the same time, remembers to stay healthy by getting enough rest and participating in extracurricular activities.

Xueqing has been continuing his studies on the regulation of SCD1 in inflammatory responses during the past year. The research is now moving on to elucidate the role of liver SCD1 in diet-induced inflammation by using liver-specific SCD1 knock-out model. Xueqing's research will provide new insights into the interplay between diet and SCD1 deficiency in the inflammatory responses in liver.

The Ntambi Lab has also welcomed several new members to our group this year. **Michael Griffin** joined the lab as a postdoctoral fellow in May 2007. Michael received his Ph.D. at the University of California, Berkeley, where he studied transcriptional regulation of the fatty acid synthase gene. His research interests include adipocyte differentiation, metabolism, and obesity, and he is currently using rodent knockout models to examine the roles of SCD proteins in the growth and development of fat cells. Michael's career goal is to eventually run and manage his own independent fat cell biology lab.

Chad Paton joined the Lab as a postdoctoral fellow in July 2007 after a two-year post doc at the Blood Research Institute in Milwaukee where he studied coagulation biology. He is currently investigating the role of SCD in breast cancer and splits his free time between triathlon training, skeet shooting, and bird hunting.

Another recent addition to the lab is **Minghui Zhao,** who has joined us as a lab technician. Since starting in January, Minghui has been working on general lab maintenance and lab inventory database construction. She has also set up a paperless, database-driven web interface ordering system for the Ntambi Lab.

We hope that you have enjoyed catching up on recent happenings in the Ntambi Lab. Good luck to you in the upcoming year! Please do stop in if you are in the neighborhood.

Wes Pike Lab

The Pike laboratory is entering its 7th year of operation in Madison, and I have to say that I have enjoyed every minute of it (well, almost every minute). Our group is comprised of eight individuals, four postdocs, three graduate students, and one undergraduate lab helper and researcher. This group is as highly dedicated a collection of talented individuals as I have ever had the pleasure of working with, and they make coming to the laboratory and exploring new things both fun and exciting.

Dr. Lee Ann Short is now in her second year as a postdoc, having remained in my laboratory following successful completion of her Ph.D. degree in 2006. Lee continues to work on my favorite transcription factor, the vitamin D receptor, and has made enormous progress recently in furthering our understanding of how the gene for this receptor is regulated and how the protein functions as well. Lee has been instrumental in developing emerging technologies that will enable us to examine the transcriptional activities of very large DNA constructs, as exemplified by the vitamin D receptor gene. Both Lee and her husband Zack live in Sun Prairie, and while the commute in the winter is sometimes difficult, both enjoy living on the "outskirts" of the big city of Madison.

Dr. Jackie A. Fretz completed her Ph.D. degree this past August and moved to Connecticut, where she is currently a postdoc with Dr. Mark Horowitz at Yale University. Jackie was interested in osteoclastogenesis, identified novel components of the RANKL activation pathway, among other discoveries, and has chosen to continue many aspects of this work with Dr. Horowitz.

Dr. Mark B. Meyer also successfully completed his Ph.D. degree during the past summer, finishing a project aimed at understanding how vitamin D regulates genes involved in calcium homeostasis. This work defined how the vitamin D hormone through its receptor modulates calcium ion channel genes TRPV5 and TRPV6, both of which are involved in intestinal and renal calcium uptake. Mark and his wife Carol have also chosen to remain in Madison. Thus, Mark will continue in this laboratory as a postdoc, and is now focused on the development and implementation of methods that will allow us to study gene regulation in greater depth. His talents, not only at the bench, but at the computer as well,

have facilitated this laboratory's whole-scale entre into novel genomic studies. Mark has a "thing" for hockey, so we pray for continued frozen ice.

Dr. Melissa Martowicz joined our laboratory in 2006, having completed a Ph.D. in the laboratory of Dr. Emery Bresnick in the Department of Molecular Pharmacology. Melissa is focused upon understanding how the RANKL gene is regulated, and has employed a variety of topical techniques towards that understanding. Interestingly, we are discovering that many of the principles that we thought were originally unique to this gene may be more the norm rather than the exception.

Dr. Seong Min Lee joined the laboratory as a postdoc in September of last year, having arrived from South Korea with his wife and young daughter. He is a great asset to the laboratory, although he is, perhaps too quiet (if that is possible). Seong Min is currently advancing several of the projects that were initiated by Jackie, and has also taken on new ones, all focused upon a better understanding of RANKL induced osteoclast formation. He is currently attempting to identify regulatory targets of the osteoclast differentiation factor NFATc1. Unfortunately, it has been Seong Min's misfortune to have had to experience one of the most difficult winters in Madison in many years. Indeed, records for snow fall have been set this winter.

Rob D. Nerenz passed his Preliminary Exam in Biochemistry almost a year ago, and is now a third year graduate student focused on defining differential mechanisms whereby hormones regulate human RANKL gene expression. The results of his initial work were recently published, providing Rob with his first first-author paper. While still working on the "geometry" of RANKL activation, Rob has more recently become involved in our return to defining the molecular actions of estrogens and androgens in the skeleton. Recent advances in this area have suggested some novel opportunities. Rob keeps his energy level high for work in this laboratory by lifting weights-lots of them.

Katie Bishop also passed her Preliminary Exam, and now focuses full time on understanding how cytokines and other regulatory components operate to regulate the RANKL gene. Like so many projects, one observation led to another and then another, such that her project is now comprised of multiple components. And like so many projects, observations we thought would be quite simple to solve have turned out to be much more complex that originally anticipated. Katie's successful completion of Madison's Triathlon Event this past summer suggests that she will likely have the stamina for this work. We expect Katie to make important discoveries and add new insight into her chosen projects.

Paul Goetsch becomes the newest graduate student member of the laboratory, having just joined in the past month of February. Under the tutelage of Dr. Meyer, however, Paul is rapidly coming up to speed with respect to the techniques we employ in the laboratory, and I anticipate great things from him as well. Paul brings several protein chemistry skills to the laboratory, and his interest in mass spectrometry raises the possibility that we may be able to advance experimentally our understanding of the role of phosphorylation in vitamin D receptor function.

Finally, last but not least, is **Heidi Coy,** who is an undergraduate helper and researcher in the laboratory. Heidi is a trustworthy and hard-working addition to the laboratory and plays an important facilitating role in everyone's work. She is currently learning several of the techniques used routinely in the laboratory, and is experiencing the thrill of exploring the effects of vitamin D on gene regulation in culture cells. She is a great addition to the group.

In closing, I must say that I have been blessed with a great group of highly interactive, hard working scientists who are making exciting new discoveries in the area of steroid hormone action. Thanks to the efforts of each of these individuals, our funding remains excellent even in these tough times, and I am confident that that will continue. Given the interesting observations that we continue to make, I believe that the next few years will be not only productive but exciting.

Tom Record Lab

Greetings from our '85 wing laboratory, where a lot has been going on in the calm-before the storm of demolishing the 1950s wing and building the new tower for people in this wing and our medical school biochemistry colleagues. Steered by senior members **Mike Capp, Ruth Saecker, Irina Shkel** and me, a near-tidal wave of six graduate students, one postdoc, and three undergraduates have finished in the last year and a half. In the process, they have greatly advanced our understanding of how *E. coli* RNA polymerase opens promoter DNA to initiate transcription, how solutes and salts affect biopolymer processes including DNA wrapping on protein surfaces and coupled folding of protein surface loops on DNA, and how *E. coli* functions as an chemical and osmotic system.

Carrie Davis (Biochemistry Ph. D. 2007) started this recent wave of Biochemistry graduates; her research used DNA footprinting and kinetic studies to characterize the structure and function of the extensive wrapping (100 bp) of promoter DNA on RNA polymerase in an early intermediate in the mechanism of forming the transcriptionally-competent open complex. Carrie is now studying HIV reverse transcriptase as a postdoc with Stephen Hughes at the National Cancer Institute in Fredrick, Maryland. **Kirk Vander Meulen** characterized DNA wrapping for his Biochemistry Ph. D.'07), using Integration Host Factor (IHF) as the protein and fluorescence (FRET) and titration microcalorimetry as techniques. Kirk moved just far enough to be out of the direct path of construction, to a postdoc with Sam Butcher in the newer building. Recent Physical Chemistry Ph. D. graduates are **Wayne Kontur** ('06) and **Laurel Pegram** ('07). Wayne characterized DNA opening and other large-scale conformational changes in the steps of open complex formation by RNA polymerase, and is now a Biofuels postdoc across Linden Drive in Bacteriology with Tim Donohue. Laurel discovered a straightforward but powerful quantitative method of predicting or interpreting Hofmeister effects of salts on protein processes, using model compound data and structural information about the protein surface buried or exposed to solvent in the process. Laurel is staying on as a postdoc to continue this very productive research. **Michael Konopka,** a Ph. D. ('06) with Jim Weissshaar in Chemistry, stayed for a short postdoc in our lab to use recovery of GFP fluorescence after photobleaching (FRAP) to study diffusion of GFP and characterize crowding and confinement effects in osmotically stressed *E. coli.* Michael is now a postdoc at the University of Washington, Seattle. **Jonathan Cannon** obtained his Ph. D. in Biophysics ('06) for his research into the interactions of denaturants and osmolytes (stabilizers) with protein surfaces, and the interpretation or prediction of these effects in terms of structure. Jonathan is now a postdoc at Case-Western Reserve University. Left behind, in addition to many lab books and good memories, are many papers to write.

In addition to these Ph. D. graduates, three very talented Biochemistry undergraduates (**Kevin Beier, Kate Engel,** and **Sara Heitkamp**) finished their undergraduate research projects (on IHF, RNA polymerase, and lac repressor, respectively) and headed for graduate school (to Harvard, Berkeley and Yale, respectively). Left behind are more good memories and more papers to write.

New Biochemistry graduate students in our group include **Amanda Drennan** from Beloit College and **Ben Knowles** from Washington State University. Amanda is investigating effects of DNA and polymerase variants on the late steps of open complex formation, and Ben is quantifying the effects of polyethylene glycol (PEG) on protein processes. Continuing graduate students are **Junseock Koh** (Biophysics, HU-DNA interactions by FRET and calorimetry) and **Ted Gries** (Biochemistry, RNA polymerase-promoter mechanism), as well as undergraduates **Brad Nelms, Rob Erdmann** and **Tim Wendorff,** all studying solutes or salts, **Ben Strick** and **Kara Kaplan** (both studying RNA polymerase), and **Kevin Metcalf** (studying HU). Our creative, dedicated and hard-working senior members are **Ruth Saecker** (RNA polymerase-promoter mechanism and other protein interactions), **Irina Shkel** (analysis of GFP diffusion in vivo and salt effects on biopolymer processes in vitro), and **Mike Capp** (solute-biopolymer interactions, solute effects on biopolymer processes, and jack of all trades as well as lab manager). Senior scientist **Charles Anderson** (theory of solute and salt effects) transitioned to emeritus status. My election to the American Academy of Arts and Sciences and selection as a fellow of the Biophysical Society honor our collective accomplishments as a lab.

Thanks and best wishes to all,

Tom

Ron Raines Lab

The Raines lab remains in a steady-state. While some students prepare for "retirement," others are just starting to explore the interface between chemistry and biology.

Departures

In the last year, four graduate students were able to defend Ph.D. theses. **Jeremy Johnson** is now a postdoctorate at Harvard University. **Annie Tam,** our former artist-in-residence, is a postdoctorate at The Scripps Research Institute. **Luke Lavis** will continue to use chemistry to "shed light" on biology as a Fellow at the Janelia Farm Research Campus of the Howard Hughes Medical Institute. **Tom Rutkoski** is a postdoctorate with George Phillips in the campus Great Lakes Bioenergy Research Center. (Tom had the distinction of receiving the 30th Ph.D. degree awarded to the group!) Also, former postdoctorate **Matt Allen** is now on the faculty at Wayne State University.

Arrivals

We are excited that two graduate and three undergraduate students joined the Raines Lab in 2007: **Mike Palte,** who is an M.D./Ph.D. student, and **Ben Caes,** who is a chemistry student. **Jackie Blank** and **Anthony Cefali** have teamed up with Joe Binder to help develop new cellulosic biofuels. **Jonathan Pua** works with **Kelly Gorres** to study the active-site residues of proyl-4-hydroxylase.

Couplings

Kelly and **John May** (Kiessling lab) along with **Margie Borra** and **Adam Garske** (Denu lab) plan to get married this summer.

Progeny

Jeremy Johnson and his wife Carol brought Soren Randal Johnson into the world, and **Nicky McElfresh** and her husband Patrick created Colin. **Rex Watkins** and his wife Natalie are expecting their second child.

Armchair Quarterback

Daniel Gottlieb has maintained his Fantasy Football supremacy by capturing the championship yet again, despite claiming to know little about American football.

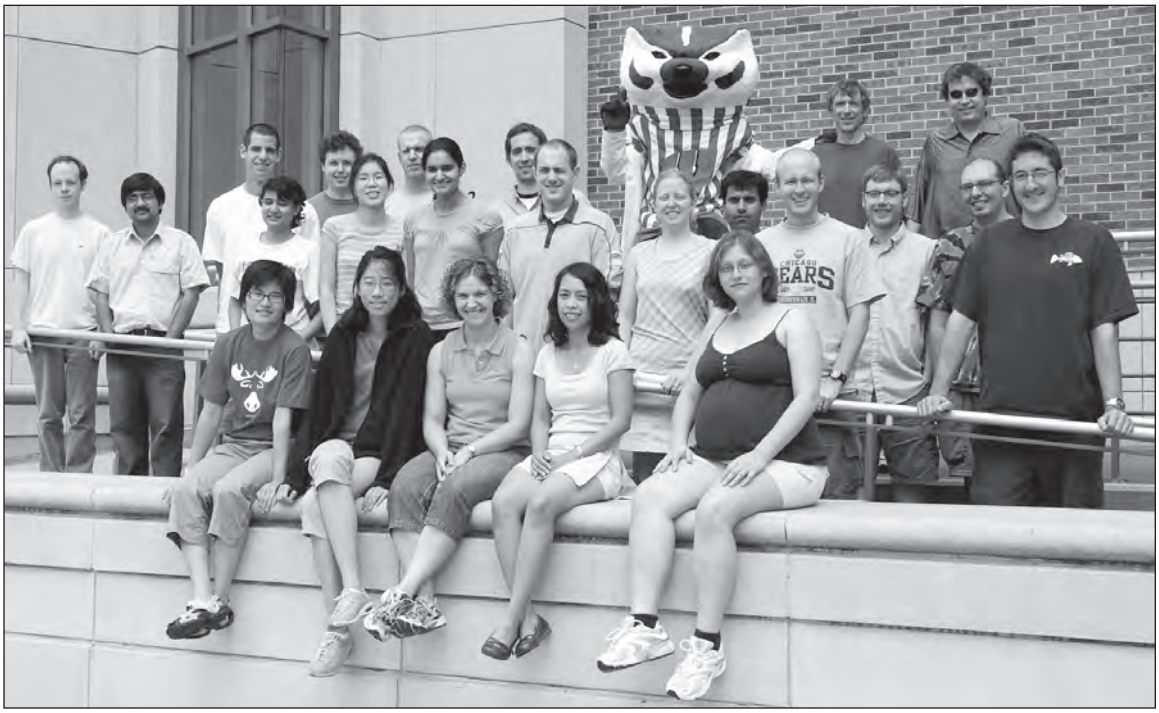
Armchair Chucker

Ron had his "one shining moment," winning the UW Biosciences NCAA basketball pool in a hard-fought contest. Although picking Kansas over Memphis in the final game, he still needed the total-points tie-break to win. Parties ensued, and he now has vindication for watching all those college basketball games.

Current Events

Of special note is **Greg Ellis** being the Halloween-costume consultant for the group, with specialties like "Mr. Potato Head."

Although there has been much turnover in the lab, we still maintain a collegial atmosphere that fosters creativity in a broad range of research projects. Please stop by if you are in town – we always enjoy seeing you!



George Reed Lab

Greetings from the 4th floor of the Enzyme Institute (EI). We have experienced some turnover since our last report. **Steven Mansoorabadi** completed his Ph. D. back in the spring of '06. He is currently a postdoctoral fellow in the lab of our good friend, Ben Liu at UT-Austin. Steve's artwork made the cover of J. Org. Chem. back in August of '07 to highlight his review article with Chris Thibodeaux and Ben. **Paul Sims,** who finished his Ph. D. in August of '05, immediately took a position as assistant professor in the Chemistry Department at Minot State in North Dakota. Last summer Paul moved to the Department of Chemistry & Biochemistry at the University of Oklahoma in Norman. **Todd Larsen** joined Bruker as an applications engineer back in August of '06. **Güneş Bender** completed his Ph. D. in December of '07 and recently joined the laboratory of another good friend, Steve Ragsdale at the University of Michigan in Ann Arbor, as a postdoctoral associate. George, **Russ Poyner,** and **Ann Menefee** are presently "holding down the fort." In July of '07, Ann, Güneş, Russ, and George attended the Gordon Research Conference on B12 that was held in Biddeford, ME. We met up with former lab member **Vahe Bandarian** (Univ. of Arizona) who made certain that no one was "thirsty" following the evening scientific sessions. In January '08, George traveled with Brian Fox to Ventura, CA for the Gordon Research Conference on Protein Cofactors, Radicals, and Quinones. They met up with former EI researchers and collaborators **Squire Booker** (Penn State) and **Oli Magnusson** (Reykjavik, Iceland). It rained for almost the entire week, but the outstanding meeting was ample compensation for the soggy weather. Brian and George acquired "the latest" information for several of their upcoming lectures in the Cofactors course.

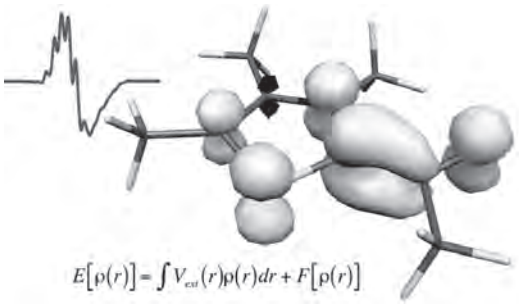


Image right shows the electronic structure of a radical intermediate in pyruvate, ferredoxin oxidoreductase

Doug Weibel Lab

Comings, comings, and more comings.

One and a half years have flown by since we moved into Anant's former space. In that time our lab has taken shape and many projects are emerging. Below is a summary of all of the students in the lab (in alphabetic order) and a brief description of their research projects.

Graduate students:

Abishek Morali Mohan is a first year student in IPiB from Anna University, India. Abi brings a background in engineering and biology to the group and is exploring: 1) the mechanics of the bacterial cell wall in *Escherichia coli;* and 2) the mechanism of polar localization in cells. **Basu Bhattacharyya** is not a graduate student per se, but will be soon. Basu graduated from Biochemistry at UW-Madison ('05) and has managed the lab for two years while working on research projects – he is an integral member of the team and we will be sad to see him leave for graduate school. Basu is studying the transport of nanoparticles across the bacterial cell wall to lay the foundation for a new ultra-resolution imaging technique we are developing for studying sub-cellular organization in bacteria with our collaborator, Dmitri Vezenov (Lehigh University, Department of Chemistry). **Matt Copeland** is a second year graduate student in IPiB who is studying the role of iron in swarming motility in *E. coli* in collaboration with Tricia Kiley (Biomolecular Chemistry, UW-Madison) and the basis for collective motility in populations of cells on surfaces. Matt has emerged as a budding geneticist and is hoping to attend the Cold Springs Harbor Short Course in Bacterial Genetics this summer. Matt received a training grant from the NIH Biotechnology Training Grant Program at UW-Madison in January. **Jenna Eun** is a first-year student in the IPiB program who graduated in '07 with a B.S. in Biochemistry from UW-Madison. Jenna brings a background in biophysics and chemistry to the group and is developing a technique for creating biofilms that makes it possible to understand the role of surface gradients in their formation. She is also working on the discovery and characterization of small molecules that bind to cytoskeletal proteins in bacteria. **Hannah Tuson** is a second year student in IPiB who is studying how cells sense surfaces and the physical, chemical, and genetic mechanisms that regulate differentiation of *E. coli* into the swarming phenotype. Hannah is a

trainee of the NIH Molecular Bioscience Training Grant; she will attend the Physiology Course at the Marine Biological Labs at Woods Hole this summer. **Abbey Vangeloff** is a first year IPiB student who received a B.S. in chemistry from Duke University and spent a subsequent year studying protein/protein interactions. Abbey's research focuses on the bacterial cytoskeleton. In one of her projects—a collaboration with Zemer Gitai (Molecular Biology, Princeton)—Abbey is using a genome-wide screen in *Caulobacter* to discover and study small molecules-cytoskeletal protein interactions. Abbey received a training grant from the NIH Biotechnology Training Grant Program at UW-Madison in January. These students are outstanding, motivated, creative, and fun to work with.

Undergraduate students:

Charles Burns is a junior majoring in Biochemistry and Spanish who has been in the lab for over one year. Charlie is studying the connection between cis-platin and the prokaryotic analog of eukaryotic tubulin, FtsZ, in the process of cell filamentation. He recently received a Hilldale Research Fellowship. **Mariko Hasebe** is a senior majoring in Biochem who has been in the lab since Fall 2007 and is developing a technique for measuring the Young's modulus of the bacterial cell wall. Mariko recently received the Mary Shine Peterson Award. **Sean McMaster** is a sophomore majoring in Biochemistry and Mathematics who has been in the group for over one year now. Sean's project is to develop a chemically defined minimal medium that supports cell swarming. Sean is the 2007 'Steenbock Stairmaster' and holds the group stair-climbing record. He recently received a Hilldale Research Fellowship. **Joseph Molenda** is a junior who has been in the group for over one year. Joe is studying 'synthetic' shape transitions in *Neisseria* in collaboration with Joe Dillard's group (Med. Micro., UW-Madison). He received a Hilldale Research Fellowship in 2007. **Tanner Peelen** is a sophomore majoring in Biochem who joined the lab last semester. Tanner's project involves optimizing semiconductor quantum dots to transform bacterial cells. **Peter ValdenVelder** is not yet an undergraduate at UW-Madison but he acts the part. Peter has been working in the lab for the past year – he recently graduated from West High School and will be an undergrad at UW-Madison this coming year. Peter's project is exploring swarming in *Vibrio.* We are hoping Peter will stay with us in the coming years.

PI:

In addition to teaching, research, and advising, I am involved in several outreach projects both on and off campus. In 2007, Aseem Ansari, Mike Sussman, Franco Cerrina (Electrical Engineering), and I co-founded the UW-Madison International Genetically Engineered Machines (iGEM) Competition Team). The team introduces undergraduate students in the life sciences and engineering to interdisciplinary research in synthetic biology and culminates in a competition held at MIT in November. Our first year was a success and we are actively organizing the 2008 team.

In November, Basu and I co-founded an outreach program to introduce local K-12 students to optical microscopy to help them explore 'the microworld.' MicroExplorers is a collaborative effort that combines the expertise of a half-dozen young microscopy-oriented scientists across campus who share an interest in educational outreach (**www.MicroExplorers.org**). The program is made possible by the commercial availability of relatively inexpensive digital optics. We have already carried out pilot projects with local K-5 students and are currently in the process of raising money to purchase more microscopes.

2007 saw the departure of two students:

Corinne Lipscomb is a Chemistry graduate student who worked in the group for a year and left in December. **Tae Won "Bryce" Kim** is a junior who spent the Fall semester with us while working on a research project for Bio 152.

We wish you a wonderful 2008 and look forward to keeping you informed of our future progress.

Marv Wickens Lab

As I write this newsletter this year, we sit in 9,000 feet of snow and ice, and await the next ice age, despite Greenland's thaw. In our igloos, we continue to focus on how mRNAs are controlled, how proteins and RNAs find one another, and the many ways in which biology uses RNA.

Continuing…

JJ Chritton has passed her prelim with flying colors and convinced her committee that she could "do three complete experiments a day without breaking a sweat" which of course led them to suggest that "she should do six experiments a day so that she sweats." We hope she will soon gain the acclaim of reviewers with equal aridity. She is working on how one class of repressor proteins work, using cell-free systems that parallel in vivo studies in yeast, and has made great headway. **Aaron Goldstrohm,** a post-doc, after a flurry of papers and job interviews, is returning to the bench to figure out which proteins talk to a central group of regulators (the PUF proteins, for the avocados among you), as a means to understand how they repress translation and cause mRNAs to be destroyed. Along the way, Aaron has written a review of deadenylases and another of how to study poly(A) removal, both published in prominent journals. These grew out of his studies with **Brad Hook** and **Daniel Seay.** Brad has moved on to Promega (a local Biotech company) where he thrives developing and analyzing new products and applications. Rumor has it that he is soon to make an appearance at a lab bench here again – most welcome.

Laura Opperman, soon to defend her thesis, has been working on how PUF proteins find their RNA targets. This work has gotten an elating boost through our collaboration with Dr. Traci Hall (North Carolina) who has determined the structure that goes along with Laura's earlier molecular genetics. Once she finishes collecting the data and writing ten additional papers, she will be moving on to Scott Kennedy's lab on campus to study RNAi. **Craig Stumpf,** another student, is soon to defend his PhD as well; and will be staying for a while after to explore PUFinalia in new ways. Craig and Laura have been joined in this endeavor by **Yvonne Koh,** a graduate student, whose work in short order revealed some new surprises in recognition, and now is moving off in new directions. **Andrew Prigge** and **Leah Gross,** two undergrads, have joined in developing new ways to fly through PUF–RNA space.

Amy Cooke, a CMB student, has been using frog oocytes to understand how mRNAs in eggs and embryos are controlled; a long-term issue here is to try to understand to what extent the mechanisms seen in yeast and embryos are really the same, and what features of each are idiosyncratic. A paper is becoming visible on the horizon.

Labib Rouhana and **Jae Eun Kwak** both defended their theses at the end of 2007. Labib, who continues to work on new regulators and new ways to detect RNA-protein interactions *in vivo,* is planning a radical change of setting, and has arranged a post-doc with Dr. Agata in Kyoto, Japan. He anticipates working on how mRNA control contributes to regeneration. Jae Eun has fingers in many pies. Right now, she is juggling work on the role of mRNA control in memory – some major breakthroughs there in which she identified an enzyme critical for long-term memory in particular – with studies of a new group of enzymes that add poly(U) rather than poly(A) to RNAs. The memory studies have benefited immeasurably from a collaboration with Jerry Yin in Genetics, who in a triumph of inbreeding, was in fact Bill Reznikoff's grad student when Marv first arrived in Madison. **Jacque Baca,** is figuring out how protein and microRNA mechanisms of repression may interface in the *C. elegans* germline.

Moving on…

Daniel Seay, graduate student here and a man of exothermic life style, exuding energetic radiation in many forms, has moved on to Rockefeller as a post-doc with Mike Young, studying rhythms in flies. My impression is that he really likes New York, but is looking forward to being done with his work from here. He continues to wrap up a very interesting group of studies on a new form of regulation, for which he was incessantly teased here at first – kudos to him.

Coming back….

Natascha Buter, who had received a Master's in the lab a few years ago, has returned and now takes care of us all in maintenance, ordering, etc. It's a great pleasure to have her back to lend her energy, insight and great

spirit. **Laurel Bessey,** an undergrad, continues to pour plates and help with lab maintenance.

A few alumni….

Omissions are inevitable, but let me mention a few small developments that relate to alumni with whom I have had some sort of special contact in the last year. It was delightful to have a visit from **Niki Gray** and **Kris Dickson,** in a birthday celebration in Madison, and to meet their Significant Others and hear what they are up to – namely, science in Edinburgh (Niki) and Big Shot editing in Boston (Kris). Judith and I have had the good fortune to see a bit more of **Dave Zarkower** and **Vivian Bardwell,** both on the faculty at University of Minnesota, now that Zach goes to college nearby. It's always a treat to see them both. **Scott Ballantyne,** at UW River Falls, continues to have creative ideas about how regulation works, and is always great to hear from. Had a chance to visit **Sunnie Thompson** in Birmingham last year, and it was a special pleasure to see how happy she was in her new professorial state. **Cameron Luitjens,** now a lawyer raking in the billable hours, was recently accosted with an email from me about work he did 10 or more years ago, which we are thinking about trying to write up at last, since it keeps getting asked for. This will really challenge the long-term memory bank. **Mike Sheets** and **Catherine Fox,** both on the faculty here, are buoyed by their delightful son, Max, who has the great wisdom to be oblivious to deadlines. **Dave Bernstein,** in Washington and still involved in science policy, married this last year and appears from a distance to be thriving. From the words we exchange, **Pete Wigley,** down under, seems to be entirely unchanged, though I suspect he now weighs 340 pounds, carries a machete and smokes cognac-laced cigars (but still has those shorts). My apologies to the many of you that I have been unable to mention.

Marv is graduating, defending, writing grants and letters, and greatly enjoying science and the people in the lab, however bizarre their behavior becomes (you have no idea). **Carol** continues to keep him on track. Marv enjoys a temporary trip to the third person, as it makes him feel so athletic, as in "He really loves to step back behind the three point line and write the Abstract as he drives to the hoop and slams the Discussion through the net." But shocking himself back to first-person reality…. I am doing fine, or so I think, with no increased athleticism. Our son, **Zach,** is off at Macalester, where as the British say, the world is his oyster, and he is devouring them on the half-shell by the dozen. Chemistry, mathematics, computer science and writing are offered up with horseradish, lemon and dipping sauce. Children, whether biological or scientific, whether newborn or middle aged, are one of the great graces of my life, and I thank you all. Come by sometime. You will always be welcome.

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