

Biochemistry 2007 NEWSLETTER

UNIVERSITY OF WISCONSIN-MADISON

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



From the Chair
Betty Craig

I am pleased to send you greetings from the Biochemistry Department. In the second newsletter under my watch, we (being Marv Wickens et al.) have changed the format a bit, bringing you more of the exciting science going on in the department, as well as the “news” to keep you abreast of your friends and colleagues. I

hope you approve, and we welcome comments and suggestions to make the Biochemistry Newsletter both informative and fun.

Biochemistry Phase II Biostar Building Project

“Challenges and opportunities” is an expression commonly used these days. Although I am not particularly fond of this phrase, I do think it characterizes quite well the Biochemistry Phase II Biostar Building Project, now in an active design phase. The scope of the project, conceived over a decade ago, is broad, encompassing laboratory space to house both Biochemistry faculty (e.g., the FTEs in the Enzyme Institute) and the Biomolecular Chemistry Department; special facilities, such as chemical synthesis suites; a large vivarium; and a great deal of much-needed classroom and teaching laboratory space. An architectural study completed in 1997 envisioned a building that would take up the footprint defined by the 1937 and 1956 wings of old

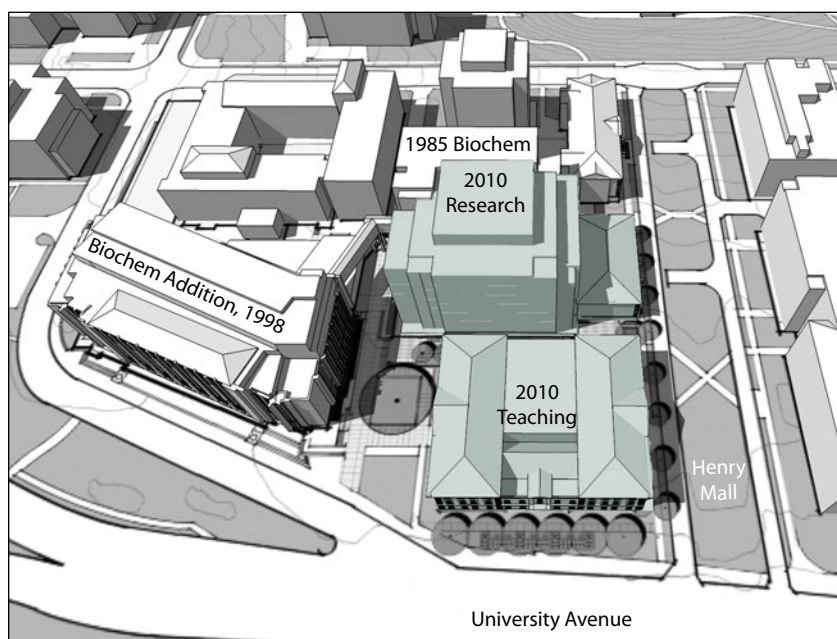
Biochemistry, plus the Ag Journalism building. At the time, historical preservation was limited to the 1912 building, which was slated to become office space. The Curry murals in the 1937 wing were to be moved to new quarters in the 1912 wing. The Ag Journalism building was viewed as suboptimal and structurally unsuitable for most uses.

The situation has changed dramatically in the interim. About 18 months ago, the entire west side of Henry Mall, as well as all of the 1912 and 1937 wings facing University Avenue, was listed as a National Historic District. The Ag Journalism building was determined to be in better shape structurally than we had thought, and the state and university have been reviewing the history of our little neighborhood. The west side of Henry Mall is actually one of the few districts on campus that remains true to the original campus plans. A consensus emerged that the preservation of the heritage of the district should be an important goal of the project, as it was in the best interests of the department, the university, and the state.

The architectural team from Flad and Associates have come up with a creative design that not only preserves the history of the older buildings (and **Elmer**, the elm tree), but puts even the older building space to exceedingly good use in ways that will invigorate Biochemistry’s teaching program. In effect, the 1912 and 1937 wings will become a dedicated teaching complex, with new auditoriums, classrooms, teaching labs, a student lounge,

New design for Biochemistry Phase II - "Inspired by the past, building for the future"

and some office space in support of the teaching effort. The new research tower will be built on a footprint that includes the 1956 wing, the alley between 1956 and Ag Journalism, and the animal rooms and auditorium south of the 1985 wing. The new structure will abut, and incorporate into the design, the old Ag Journalism building. This research tower will house the 20-24 research labs, animal facilities, conference rooms and state of the art chemical synthesis suites. A new corridor will be created between the 1912/1937 complex and the new research tower, facilitating pedestrian traffic in this part of campus.



The plan is ambitious, and will enable the department to enhance its research and teaching missions over the next decades. The added cost to renovate the older buildings and the high rate of inflation of construction costs over the past 2-3 years has left us with a gap in funding estimated to be about 12 million dollars out of the total budget of 117 million dollars for the project. We are embarking on a campaign

to raise the necessary funds and I hope when I write you a year from now I can report that we have broken ground for Biochemistry Phase II. We are all truly excited about the project, as it will provide state of the art research facilities for all Biochemistry faculty, while preserving our history.

Other updates

I am pleased to report that our new **IPiB (Integrated Program in Biochemistry)** graduate program has gone through all of the administrative hoops and is now official. In reality we have been acting like it was official for the past year, recruiting together this spring with the faculty of the Department of Biomolecular Chemistry, for what has become our first IPiB class. Ivan Rayment has taken on the job of being chair of the IPiB steering committee and is busy smoothing the road of integration of the two graduate programs into one.

This year we are pleased to welcome **Doug Weibel** into the department as a new Assistant Professor. Doug, who has his lab on the fourth floor of the Biochemistry Addition, comes to us from Harvard Medical School as a cluster hire in chemical biology. Learn more about Doug and his research on page 4. While welcoming new people into the department, we also need to say goodbye to **Bill Reznikoff** (see page 10) who, come July 1, will retire after 37 years as a Biochemistry faculty member. We are all sorry to see him go. We wish him all the best, and are glad to know that he will continue his science, but his lab will be on Cape Cod, rather than next to Lake Mendota.

Our good friend and jack-of-all-trades, **Al Jones** (see page 5) is also retiring after many great years with us and we wish him well.

I hope you all a happy and productive year. Remember, we are happy to hear from you anytime, and visit us when you can.

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

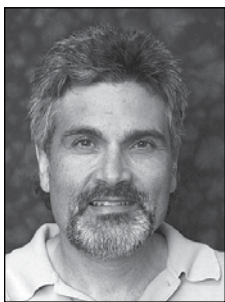
Elizabeth Craig, Chair
Department of Biochemistry
Phone: 608-262-3040
chair@biochem.wisc.edu

or

Marilyn Boland, Director of Development
University of Wisconsin Foundation
Phone: 608-890-1230
marilyn.boland@uwfoundation.wisc.edu

Links Between Obesity and Diabetes

by Professor Alan Attie



Although most people with type 2 diabetes are obese, most obese people do not develop diabetes. This dichotomy has inspired us to ask: what are the genetic differences between people who are susceptible to obesity-induced diabetes and those who are resistant? We also want to identify the pathways that trigger the transition to diabetes.

Obese people are insulin-resistant, meaning that their cells do not respond fully to normal insulin levels. They usually compensate for insulin-resistance by producing more insulin. This can occur by increasing the insulin secretion from each pancreatic beta cell and/or through the expansion of beta cell mass. However, in type 2 diabetes, this compensatory insulin response is inadequate and the gap between demand for insulin and the supply of insulin leads to diabetes.

Identifying a new gene

We have reproduced the obesity/diabetes dichotomy in mice. We study two mouse strains that have been made obese using a mutation that disrupts the normal suppression of appetite; the two strains differ in their susceptibility to diabetes. To identify the key genes responsible, we mapped several genes that control glucose and insulin levels. This past year, we positionally cloned one of these.

The gene is *SorCS1*, a member of the vacuolar protein sorting-10 (*vps10*) gene family. The protein binds to platelet-derived growth factor

(PDGF), a protein that plays an important role in the formation of the vasculature. Cells requiring new vasculature produce vascular endothelial growth factor (VEGF), which recruits endothelial cells to the tissue. Endothelial cells form tubes, the precursors of blood vessels. They also produce PDGF, which recruits pericytes (a cell resembling a smooth muscle cell) to coat the basolateral side of the vessel.

Mice with the diabetogenic allele of *SorCS1* have vascular abnormalities, while their congenic counterparts do not. To corroborate these findings, we have turned to zebrafish, another vertebrate with powerful genetics: zebrafish with reduced *SorCS1*-activity do indeed have dramatic vascular abnormalities.

If the gene really is critical in the onset of diabetes in people, we might be able to see that in natural human populations. In collaboration with groups in Los Angeles and San Antonio, we have found that variation in the *SorCS1* gene is associated with diabetes in Mexican-Americans. Other groups are determining whether or not this gene is involved in diabetes in other populations.

Dieting and diabetes

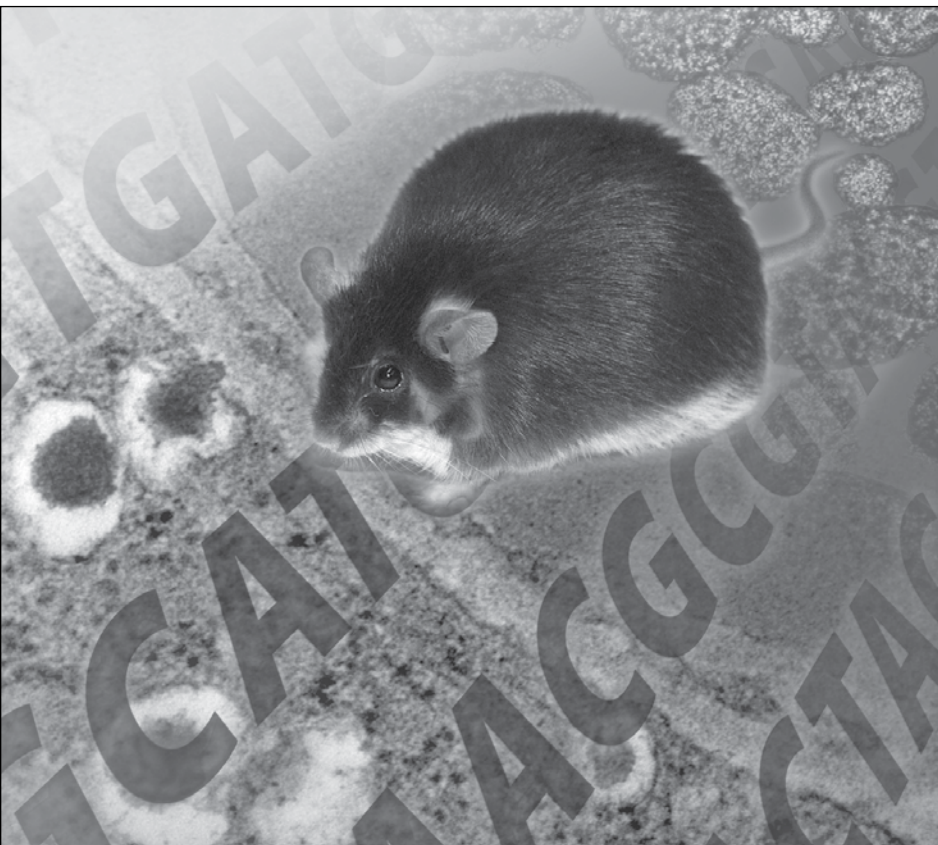
Another route to understanding the onset of diabetes has come from analyses of mRNAs present in obese vs normal mice. DNA microarray technology allows one to survey the entire populations of mRNAs in a cell or tissue. Using that approach, we discovered that the cholecystokinin (CCK) gene is massively upregulated in beta cells of the pancreas obtained from obese mice. What makes this interesting is that our studies also suggest that CCK is a mitogen for those same beta cells. Thus, CCK appears to be an autocrine regulator of the beta cell expansion that occurs when an animal is insulin-resistant and obese.

Relevant publications

Lan, H. Chen, M., Byers, J.E., Yandell, B.S., Stapleton, D.S., Mata, C.M., Mui, E.T., Flowers, M.T., Schueler, K.L., Manly, K.F., Williams, R.W., Kendziorski, C.M., Attie, A.D. (2006) Combined expression trait correlations and expression quantitative trait locus mapping. *PLoS Genetics* 2:52-61.

Clee, S.M., Yandell, B.S., Schueler, K.M., Rabaglia, M.E., Richards, O.C., Raines, S.M., Kabara, E.A., Klass, D.M., Stapleton, D.S., Gray-Keller, M.P., Boronenkov, I., Raess, P.W., Flowers, M.T., and Attie, A.D. (2006) Positional cloning of a type 2 diabetes quantitative trait locus. *Nature Genetics* 38, 688-693.

Clee, S.M. and Attie, A.D. (2007) The genetic landscape of type 2 diabetes in mice. *Endocrine Rev.* 28,48-83.



Notes From a New Faculty Member:

by Professor Doug Weibel



When asked what first drew them to science, chemists most often cite a youthful encounter with a chemistry set. My first experiences with chemistry and science, however, were quite a bit different. They grew out of my childhood interest in blowing things up. I like to think that my early fascination with explosives eventually paid off.

As a teenager my scientific interests abruptly shifted as I started working in my father's lab and was introduced to biochemistry. One of the first experiments I did in the lab involved a large-scale lipase-catalyzed hydrolysis of a butyric acid ester to butyrate, which I accidentally spilled on myself. Chemists affectionately refer to butyric acid as 'essence of barf' and it is—unfortunately—an odor that is notoriously difficult to remove once it comes in contact with the skin. This occasion left a strong impression on my memory, and undoubtedly, the memory of my family and friends as well.

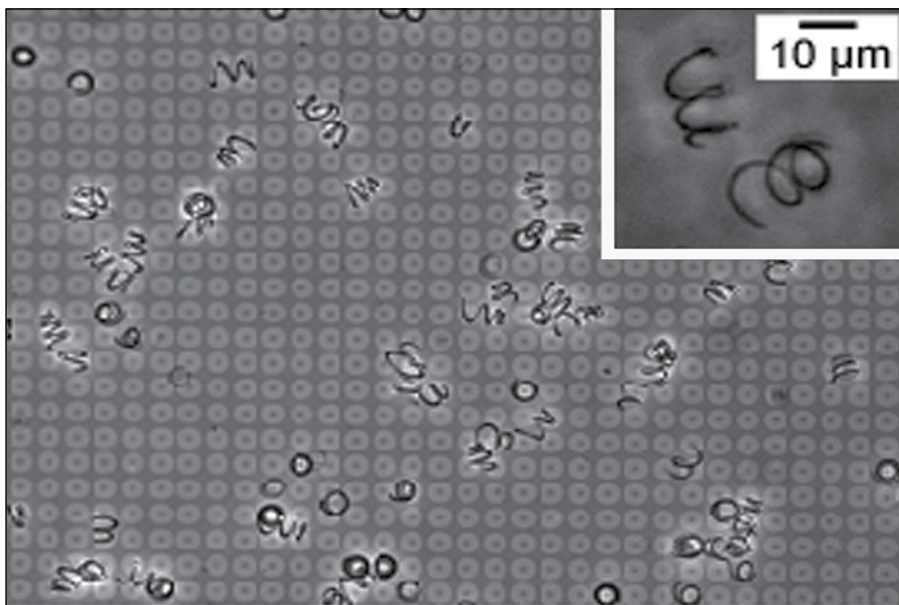
Chemistry runs in my family. My older brother is a physical chemist and my father a physical organic chemist turned biochemist. It was with great effort that I suppressed any serious interest in chemistry as a teenager to avoid following in their footsteps. However, chemistry captured and held my interest in science and I followed my brother's encouraging lead to join him at the University of Utah where he was a graduate student. While there I fell in love with Gina who was—you guessed it—a lovely young chemist.

As an undergrad I worked with C. Dale Poulter on research projects in isoprene biosynthesis. In my junior year I sweet-talked my way into taking several graduate courses and ended up in an 'industrial strength' class on enzyme mechanisms and kinetics in which we read a ream of papers by Mo Cleland and Perry Frey. It is an honor to now find myself a colleague of these two pioneers in enzymology. I graduated from the University of Utah with a degree in chemistry and spent a year in Japan on a Fulbright working on a project in organometallic chemistry with Yoshinori Yamamoto. Much of my free time in Japan was occupied trying to comprehend how little grammar I had actually learned in the Japanese classes I had taken (namake mono!).

After Japan, Gina and I married and moved to Ithaca where we both attended graduate school at Cornell. I worked with Jerry Meinwald on projects in organic chemistry and then shifted gears and accepted a postdoctoral position with George Whitesides at Harvard where I worked on projects in microbiology, mammalian biology, organic and surface chemistry, and materials science and engineering.

At UW-Madison I am in the process of building an interdisciplinary group of biochemists, biologists, chemists, and engineers interested in studying the molecular basis of physiology and behavior of bacteria. Bacteria were the model organisms for the development of molecular biology and genetics; they became our foundation for understanding fundamental biochemical processes that occur in prokaryotic and eukaryotic cells. Remarkably, we still understand little about the structure and general physiology of bacteria, yet the mechanisms by which they differentiate into a variety of different phenotypes and organize into multicellular structures are relevant to ecology and biomedicine. Our interest in the behavior of bacteria is largely based on the pioneering work of Julius Adler who changed the way we think about sensory transduction in microorganisms.

(Below) Rod-shaped bacteria can be manipulated into 'unnatural' shapes by controlling the geometry of their environment during growth. The image shows donut-shaped compartments (background) in which spiral shaped cells of *E. coli* were grown (foreground and image inset). This experiment leaves us questioning how cells control their shape at the molecular level.

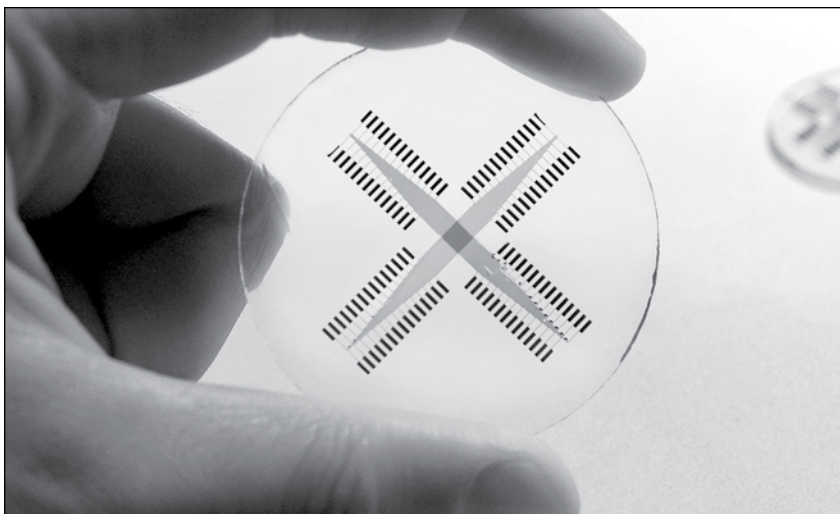


As part of the Chemical Biology Cluster at Madison, I am looking for opportunities to apply our interest in chemistry, biology, and engineering to develop a detailed understanding of the biochemistry in bacteria. Our initial projects are focused on understanding how cell shape in bacteria is controlled, the physical and molecular (and

mechanical) basis for differentiation of cells on surfaces, and the coordination of the motility of cells on surfaces. The results of these projects will find application in several areas of biomedicine.

In addition to research, I bring to Madison a deep interest in both teaching and educational outreach. I have been posing as an undergrad in several biochemistry courses at UW-Madison to get a feel for the teaching styles in the department and am impressed with the high standards of teaching.

All scientists have a scientific family tree through which they can trace their roots. I have had several outstanding mentors—Dale, Yoshi, Jerry, and George—through which I can trace my scientific genealogy. In addition to being a part of a scientific ‘family’, Gina and I have three wonderful and creative young children: Xander (age 6), Guy (age 3), and Zoe (age 1). My children constantly remind me—through their actions—that what is most fun in life is the discovery of something you love and a creative and focused way of approaching it. I strive to bring these principles to science. And wait to hear the explosions from our basement as our kids grow up and discover chemistry.



(Above) An array of gold microelectrodes fabricated on a glass wafer used to isolate and array bacteria for biophysical experiments using epifluorescence microscopy. The very thin lines are electrodes and the rectangles are contact pads that make it possible for us to apply a potential/current across a specific electrode.

Al Jones Retires!!!

For longer than many of us have even known the department (let alone been in it), Al Jones has been at its heart, making things work. And now – hard to believe – Al is retiring! Perhaps there really are no eternal truths – but Al is about as close as you can come.

After 28 years at the Department of Biochemistry and the University of Wisconsin, Al Jones has decided to spend more time at home. Al worked in many areas of the department, from animal care, the shops and maintenance, to the storeroom, and helping out wherever he was asked. He always was willing to lend a hand and so got to know, and help, almost everyone in the department. What is more, he did all these things with good spirit.

Al likes to say he has a roofers union card, “which pretty much covers everything”. You may not know it, but in addition to everything he did here, after Al got home from work, he would go over to his brother-in-law’s 200+ acre farm, just across the bridge in Prairie du Sac. He lent a hand with everything from planting, to mending fences, ear-tagging heifers and turning bulls into steers! Many a good story came of that!

Al has been a key person in Biochemistry for many years. His pleasant ways, sense of humor, and willingness to help out will be greatly missed by us all. Good luck Al, and congratulations on your retirement!





The Howard Hughes Medical Institute has a program for faculty who desire to promote science education (<http://www.hhmi.org/research/professors/>), and I was asked to discuss our plans for a recent award we received from this program.

For many years, I have been exploring models to teach classical, molecular, developmental and biochemical genetics in K-12 and undergraduate classrooms. In many respects, the ideal models already exist in the fruitfly *Drosophila* and the nematode *C. elegans*. But most teachers do not have sufficient technical skill or the equipment (microscopes, facilities for media preparation, etc.) for implementation of these models. Plants offer a simple alternative: growing plants requires little technical skill, equipment or effort, and stocks of mutants (i.e., seeds) are simple to store and organize. Thus I have focused on developing plant models for classroom use.

Ready for classroom genetics

A key feature of a plant model is that it have a rapid life cycle so that several generations can

be grown in a school year. Our first attempt was to use *Arabidopsis*, a common experimental model for plants. Although we had some success, *Arabidopsis* does have some drawbacks. For example, the seed is too small size to be planted individually by hand, and the small size of the flowers makes it difficult to cross-pollinate.

Fortunately, a classroom model, FastPlants (a variety of *Brassica rapa*), has been developed by Paul Williams at the University of Wisconsin (see <http://www.fastplants.org/>). FastPlants are in the same family as *Arabidopsis* (Brassicaceae) and, like *Arabidopsis*, have a rapid life cycle relative to other plants. Some of the desirable features of rapid-cycling *B. rapa* relative to *Arabidopsis* are shown in Figure 1. About 400 rapid-cycling *B. rapa* thrive in a 2 by 4 foot space under four 32 watt fluorescent bulbs. And a major advantage is that rapid-cycling *B. rapa* is already well established in classrooms: it has been estimated that FastPlants are used by as many as 10 million students each year, and 70,000 teachers have been trained in their use (<http://www.news.wisc.edu/7728.html>).

However, the existing FastPlants stocks have a significant drawback which limits their development as a genetic model – they are not self compatible. Without self compatibility, an enormous number of sibling “matings” would be required to find homozygous recessive mutants. Thus I began a breeding program to introduce self compatibility into rapid-cycling *B. rapa*. The challenge was to overcome the inbreeding depression which often results from the inbreeding of plants that normally are obligate outcrossers. After two years of breeding, I developed several robust, self-compatible lines, and **Scott Woody** (photo right) has joined me in the effort to use these lines for teaching genetics.

Comparison of flower and seed size between *Arabidopsis* and rapid-cycling *B. rapa*.



<p>Bok Choy Tatsoi Rosette Bok Choy <i>Brassica rapa</i> var. <i>rosinensis</i></p> <p>\$1.69 Net Weight 1.5 grams</p> <p>45 days Cool season crop - plant early spring or late summer for fall harvest</p> <p>The tender, sweet tasting stalks and leaves are commonly used in high quality stir-fry dishes and in salad mixes</p> <p>Botanical Interests</p>	<p>Turnip Seven Top <i>Brassica rapa</i></p> <p>\$1.59 Net Weight 7.5 grams</p> <p>45 days Cool season crop - plant early spring or late summer</p> <p>There simply are no other greens that have as much calcium as turnip greens. Tasty when steamed, stir-fried or in salads.</p> <p>Botanical Interests</p>
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Initial mutants

Our first goal is to work out the parameters for creating a mutant production stream. We then will assemble teams of undergraduates to keep this stream flowing at a rapid rate. The teams will be screening for mutants with educationally useful phenotypes, characterizing the mutants, and developing classroom exercises based on these mutants. For example, Scott recently found several mutations that result in albino plants. Such mutants provide a simple example of a deleterious recessive mutation that prevents survival to maturity (a nice segue to a discussion of topics from lethal mutations to photosynthesis). Students can be given seed from a heterozygous parent that germinates into seedlings that reveal a simple 3:1 segregation ratio of green to white plants. Interested students can consider how to determine the genotypes of the 3/4 of the plants that are green by saving their seed (most of the green plants will produce offspring that segregate albinos). This is a great K-12 lesson because students will need to work back from observation to a model.

Another example: dwarf mutants provide a great tool to teach biochemical genetics.

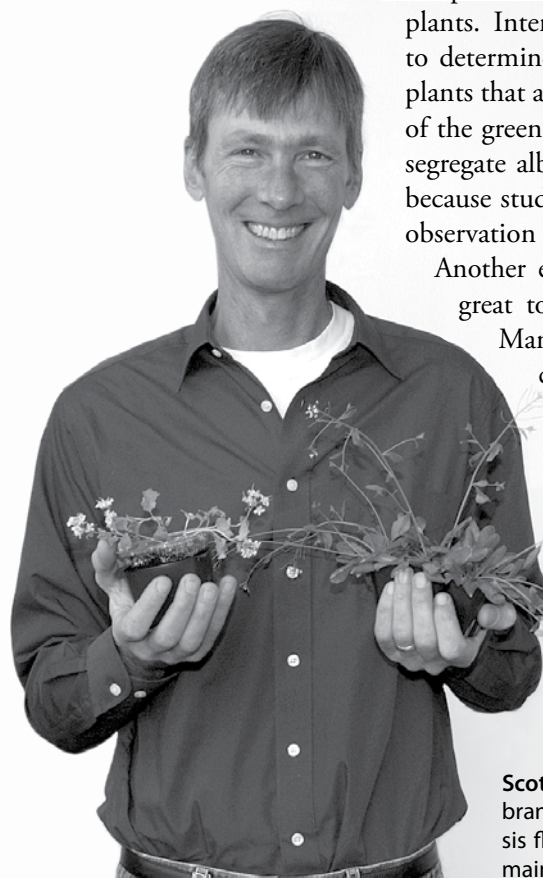
Many dwarf varieties of plants are deficient in the synthesis or sensing of the plant hormone gibberellin – a steroid-like hormone with several steps in its pathway of synthesis. We are likely to find mutations that abolish many of these steps, and complementation testing among such mutants illustrates the concept of using genetics to identify the steps of a biochemical pathway. Dwarf plants can

be treated with gibberellin to distinguish mutants defective in synthesis (restored to a normal phenotype) from those defective in sensing (no response to hormone treatment). Furthermore, treatment of a collection of mutants that have lesions at various stages of the synthetic pathway with gibberellin precursors will reveal that fewer mutants will be restored to a normal phenotype as one treats with precursors earlier in the pathway, illustrating the order in which the genes (and the enzymes they encode) act in the pathway.

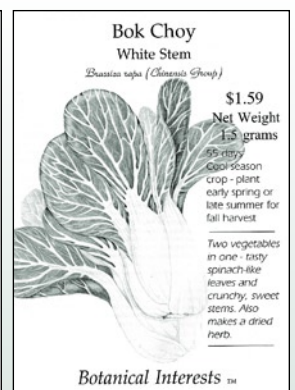
Another goal is to develop tools for learning molecular genetics. Gene mapping using DNA sequence polymorphisms (a.k.a. “markers”) is an important tool in wide use from plant breeding to tracking and cloning loci involved in human disease. To enable the use of such gene mapping tools in our system, I started the breeding program with several polymorphic parents, and selected several self-compatible lines that are polymorphic relative to each other. Thus, mutants in one line can be crossed to a polymorphic line and the mutant locus can be mapped relative to DNA markers in a resulting F2 population. Fortunately, we will not have to develop markers that detect DNA sequence polymorphisms single-handedly: there are projects around the globe to develop such markers because many varieties of *B. rapa* are used as crops. If any of this morphological variation has a simple genetic basis, there are obvious educational opportunities in this area.

The key educational advantage of using this plant model is that all stages of the exercises will be “hands on” and the system is amenable to students designing their own experiments. If any of you have educational interests, we intend to have a website established in a year or so at which you can track our progress and request materials.

Scott Woody (left) showing the extensive branching and intermingling of Arabidopsis flowering stalks compared to the single main stalk of a rapid-cycling *B. rapa* line.



The seven seed packages shown below are a sampling of the range of *B. rapa* crops, and the tremendous morphological variation within this single species.



Honors & Awards

Faculty



Laura Kiessling – Francis P. Garvan-John M. Olin Award, American Chemical Society, 2007

Ann Palmenberg – Elected President of the American Society for Virology, July 2007



Judith Kimble – Fellow, American Association for the Advancement of Sciences

Ronald Raines – Fellow, Royal Society of Chemistry



Academic Staff



Mary Rabaglia – Chancellor's Award for Excellence in Research (Research Support). 2006 Academic Staff Excellence Awards

Postdocs



Paul D. Boyer Excellence Awards

Aaron Goldstrohm

Genetic Switches of the Post-Transcriptional Kind



Matthew Allen

Increased-Utility Contrast Agents for Magnetic Resonance Imaging

Undergraduate Majors

Mary Shine Peterson Scholarship Recipients

Reece Goiffon
Molly Lowndes
Si Hui Tan
Meng Kwang Tan
Amanda Herzog

Kimberly Clark Scholarship Recipient

Kevin Beier

Biochem 501 Peer Mentoring Scholars

Sara Heitkamp
Paul Buske
Kathleen Fitzpatrick
Kevin Beier

This award acknowledges postdoctoral scholars who are acknowledged by her/his peers and advisors as one who displays clear promise as a research scientist. Most importantly, the award is to be designated in appreciation of the student's consistent willingness to contribute to the intellectual and technical potential of his/her fellow students and colleagues through the selfless help of others.

Postdoctoral Fellowships

Name	Lab	Fellowship
Declan James	Martin	American Heart Assn Postdoctoral Fellow
Pablo Sobrado	Fox	American Heart Assn Postdoctoral Fellow
Tao Wang	Craig	American Heart Assn Postdoctoral Fellow
Peizhen Yang	Craig	American Heart Assn Postdoctoral Fellow
Ngan Lam	Kimble	Damon Runyon Fellow
Leslie Donato	Ansari	Genomic Sciences Postdoctoral Trainee
Jason McCoy	Phillips	Genomic Sciences Postdoctoral Trainee
Joung-Min Jeong	Amasino	Global Research Laboratory PD Fellow
Takashi Higurashi	Craig	Human Frontier Science PD Fellow
Mitsutomo Abe	Amasino	Naito Foundation Postdoctoral Fellow
Matthew J. Allen	Raines/Kiessling	NIH Postdoctoral Fellowship
Dana Byrd	Kimble	NIH Postdoctoral Fellowship
Frank Kotch	Raines	NRSA Postdoctoral Fellow
Bryan Phillips	Kimble	NRSA Postdoctoral Fellow
Brad Pierce	Fox	NRSA Postdoctoral Fellow

Graduate Student Fellowships

University

Name	Lab	Fellowship
Alison Albee	Wiese	CALS Wisconsin Distinguished Fellow
Caroline Davis	Record	CALS Wisconsin Distinguished Fellow
Dennis Harris	Cox	CALS Wisconsin Distinguished Fellow
Thomas Rutkoski	Raines	CALS Wisconsin Distinguished Fellow
Harini Sampath	Ntambi	CALS Wisconsin Distinguished Fellow
Bryan Becklund	DeLuca	R.H. Burris Fellow
Jimmy Hernandez	Raines	Advanced Opportunity Fellow

Departmental

Name	Lab	Fellowship
Ed Huttlin	Sussman	Biochemistry Scholar
Mark Meyer	Pike	Biochemistry Scholar
Lucas Bailey	Fox	Mary Shine Peterson
Frederick Porter	Palmenberg	Mary Shine Peterson & E.W. Hopkins Fellowships
Graeme Garvey	Rayment	Peterson Fellow
Anna Fuezery	Markley	Wharton Fellow

National/International

Name	Lab	Fellowship
Clayton Carlson	Ansari	AHA Predoctoral Fellow
Kara Lynch	Martin	AHA Predoctoral Fellow
Melissa Davis	Holden	NSF Fellow
John May	Kiessling	NSF Fellow
Rex Watkins	Raines	NSF Fellow

Anticipating Rez's Retirement

by Professor Marv Wickens



A youthful seduction

Two blocks from the Atlantic, on Brooks Road in Woods Hole, two faculty and four children moved noisily each morning in a cape cedar shingle house. From the front door, it was just a quick walk to the Marine Biological Laboratory — a lab that had seen classic work in neurobiology, developmental biology and evolution. There, for several summers, Paul and Dorothy Reznikoff worked in their lab, and the children came along for a summer in Cape Cod, by the sea.

On a warm summer day in 1951, the four children of the house waded along the shoreline, meeting the water as it splashed over the rocks. **10-year old Bill, in a striped t-shirt and shorts,** (photo left), kneeled down on the rough wet stone to get a better look at the hermit crabs, starfish and sea urchins. Ten minutes later, the boy was on his bike and off to baseball; but the invertebrates and shoreline had set the boy's path just as surely as if they had written the CV for his job application.



That fall, the family went back together to New York for the academic year, as usual. On Sundays, Bill's Dad (a Professor of Medicine and head of Hematology at Cornell Medical School) would often take Bill into the lab. During one visit, Paul Reznikoff placed two slides on the lab bench next to his son.

"Have a look at this one first," he said. He slipped the stained blood sampled under the microscope lens, adjusted the focus, and then slid his son in on a rolling chair. Young Bill fiddled with the focus.

"Now have a look at this one." His Dad slipped in a second slide of stained blood.

"But this blood looks so different," Bill said. "There are so many of those things that are not just round. They are kind of differently shaped and don't look the same inside either."

The two samples, his father explained, were from a normal patient and from one with advanced leukemia. This patient had a Philadelphia chromosome — a DNA rearrangement that had caused all these cells to grow and take over. The sudden realization that biology, disease and genetics were connected hit home instantly.

And with that epiphany, Bill was hooked: the combined power of hermit crabs, genes, and his father were irresistible.

To college, to Africa, to Cathy

Bill Reznikoff (or Rez, as his friends call him)

attended Williams College, but was disappointed that its science offerings did not emphasize experiments. Feeling he had little to lose, he decided to apply to spend a year abroad in Ghana. In fact, he was the only student selected for the newly initiated education abroad program; only the science faculty agreed that a student would not miss too much material by spending a year away. There, in Africa, Bill saw entirely different perspectives on ways of living, and, on the side, collected reptiles as he had hermit crabs.

At graduation, Bill welcomed the inevitable, and entered graduate school at Johns Hopkins. He knew he loved biology and genetics, and so in classically Reznikovian orderliness, joined a lab that did little of either. Instead, Charlie Thomas, his thesis advisor, focused on the physical properties of DNA. Bill's thesis, entitled "Anatomy of the SP50 bacteriophage DNA molecule," looked at structure of DNA. Equally importantly, Phil Hartman, his co-advisor, became an inspiration: Hartman not only was a gifted geneticist, but treated people of all ranks with respect, a trait that resonated, and has stuck with Bill throughout his career.

In like fashion, the other graduate students and post-docs in the lab were as important in Bill's career as the science. Among them were several close friends who became terrific scientists and colleagues for years to come: John Abelson, Fred Blattner, and Tom Kelly, for example. This close-knit group reappeared in many guises and collaborations later in Rez' career. For those of you now in grad school, there is a lesson here: the person in the next bay may be with you much longer than you think.

One person Bill met in his first year at Hopkins was more important than all the others. Sitting in his first year classroom course in Biochemistry, Bill saw an attractive young woman a few desks away and thought he really should ask her out. Four years later, Cathy Armstrong married Bill Reznikoff. In the years to come, they were to both join the faculty in Madison, and have three children, Sarah, Joe and Charlie.

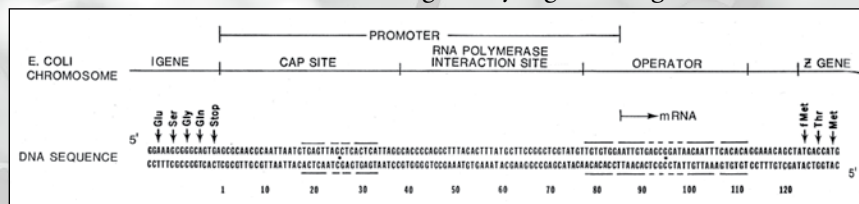
To Madison, lac and hopping genes

Once Bill and Cathy had finished their PhD work, they moved to Boston, where Bill joined Jonathan Beckwith at Harvard. Beckwith was up on all the new developments in molecular biology, excited, interested not just in science but in society, and a terrific mentor. And what was even

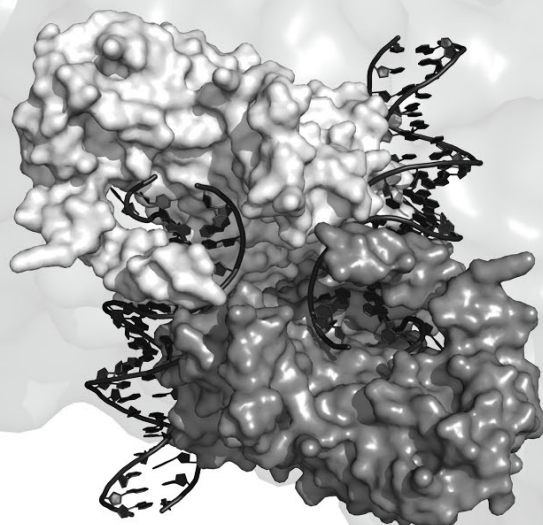
better – he was a dyed-in-the-wool geneticist. With Beckwith, Bill arrived at what was to be his intellectual home for years to come: molecular genetics. His first major focus was the lactose (lac) operon.

Understanding the basis of gene regulation, and of lac in particular, was at the heart of Bill's work when Bill joined the Biochemistry Department in 1970. Bill published a landmark paper five years after arriving: the sequence of the regulatory region of the lac operon¹. Here, the biochemistry of his PhD. thesis comingled with the genetics of his post-doc. As the work began, no regulatory region had ever been seen at high resolution. Using genetics, Bill isolated phage carrying portions of the lac operon. He then used these phage to prepare templates to make RNA, and in collaboration with John Abelson, determined the sequence of the RNA (and by inference, DNA) using now-arcane but then groundbreaking methods from the Sanger lab. Two people worked two years to determine this 120 base pair sequence: 30 base pairs per person per year, or 0.1 bp/person/day.

The immediate outcome of their experiments was stunningly simple, tangible and beautiful. The lac regulatory region (*image below*).



I was a graduate student at the time, and I can testify that it was a revelation. There, on blackboards around the country, was a real promoter in the flesh – two regulatory elements, one positive (CAP site) and one negative (the operator),



The Tn5 transposase DNA complex.

and the starts of transcription and translation. It was all there in black and white. Bill had provided physical reality to abstract genetic concepts.

In the years that followed, Bill continued to make important contributions to understanding how genes are regulated in bacteria. In the course of using bacterial transposons as tools, he was drawn into studying the regulation of a particular transposon, Tn5. How did this element move in the genome, and why did it do so as rarely as it did? The consummation of this work was the first structure of a transposase/DNA complex, caught virtually in the act.² This work, performed in collaboration with Ivan Rayment provided a model for the integrase of HIV and other viruses – a resurrection of the pivotal Philadelphia Chromosome blood sample 50 years earlier! And once again, the two sides of Bill's scientific personality gave reality to genetics: Charlie Thomas, meet Jon Beckwith.

In Madison and beyond

In addition to doing research, Bill has been an extraordinarily committed member of the university community, as mentor, teacher, and Chair of the Biochemistry Department from 1986 to 1991. Bill has trained many terrific students and post-docs, among them four who now are professors on campus (Gasch, Kiley, Lambert, and Yin). Rez's interest in education has drawn him into teaching several of key courses in the department; into being an outstanding and dedicated advisor to undergraduates; and being a key father figure for several of us faculty in our early years in Madison. Most recently, he has helped spawn programs that enable students in Madison to study abroad, much as he had done in Ghana.

Bill's commitment to the University has also drawn him into several trans-campus committees, including participation in the University Committee. When asked what was most critical in that undertaking, Bill describes helping to prevent passage of a State Assembly bill that would have banned *E. coli* from the State of Wisconsin!

When you ask Bill what he has valued most about Madison and the department, he points immediately to the supportive environment that the senior faculty (and Hector DeLuca, Julian Davies and Bob Wells, in particular) created, which he feels helped ensure his success; the great colleagues around campus, with whom Bill continues to collaborate; the lack of interdepartmental barriers, which made it easy to organize

and sustain active discussion groups, like the old Molecular Biology Club, or the more recent *E. coli* club. He cannot imagine having come up in a better environment.

And when you ask Madison what it values most about Bill, we point not only to his outstanding scientific contributions and intellect, but also to his exceptional humanity, his will to make things better for others, and to the many students, post-docs and junior faculty, of all ages and inclinations, whom he has helped.

This fall, Bill will ostensibly retire, and move back to Cape Cod, where he and Cathy have built a beautiful home not far from the Atlantic

and the hermit crabs, once again near the Woods Hole Marine Biological Lab. Bill will join the center in Comparative Molecular Biology and Evolution at the MBL, and has just submitted a grant to support that work: retirement, indeed! Now, his own three children fully grown and well on their way, along with his past 59 PhD students, post-docs, and undergrads, Rez will be back on the beach, in the lab, and at home.

1. Dickson, Abelson, Barnes and Reznikoff (1975) Genetic regulation: the lac control region. *Science* 187, 27.

2. Davies, Goryshin, Reznikoff and Rayment (2000) three-dimensional structure of the Tn5 synaptic complex transposition intermediate. *Science* 289, 77-85.

Rez's lab children as UW-Madison faculty:

Paul Lambert

Department of Oncology,

Audrey Gasch

Department of Genetics,

Bill Reznikoff

Department of Biochemistry,

Tricia Kiley

Department of Biomolecular Chemistry,

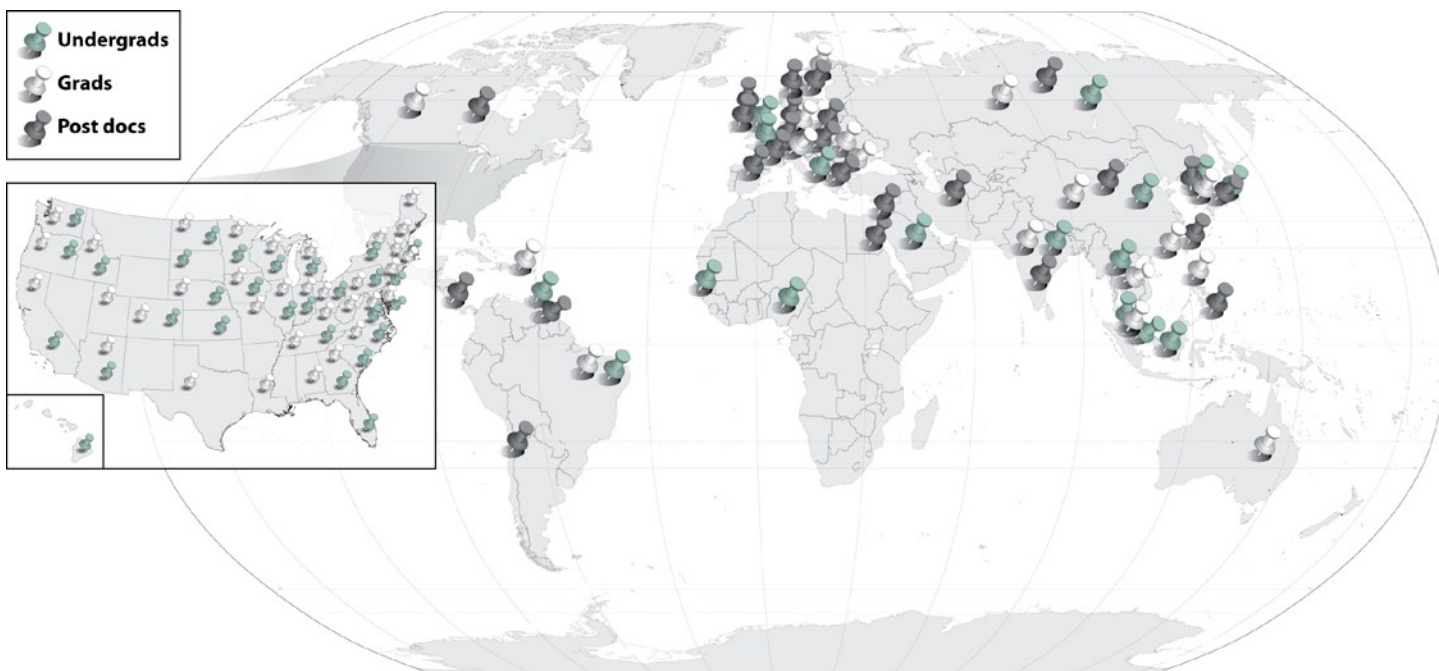
Jerry Yin

Departments of Genetics and Psychiatry.



The Department Around the World

The Biochemistry Department's undergraduate and graduate students, and post-docs, come from all over the country and globe—from 39 states and 44 nations. This diversity invigorates the atmosphere, heightens the energy level, and smells great at lab dinners. It is a testimonial to the internationalism of science, and is a vital part of the department's identity.



Note: only one pin per country or state, however more than one person may come from there.

Student Faculty Liaison Committee (SFLC)

by Jackie Fretz and Sheila Semaan, Co-Chairs IPiB SFLC



2006 has brought in a brand new class of graduate students to UW-Madison. In coordination with the Biomolecular Chemistry department we in biochemistry welcomed our first jointly recruited class of students into the newly formed Integrated Program in Biochemistry (IPiB). This united graduate program is interdepartmental and provides a wider range of potential faculty mentors to the new recruits who have chosen Madison for their graduate careers. The formation of IPiB has also served as a bridge between the student bodies of the two departments and with the help of several enthusiastic graduate students from both sides a real sense of community and fellowship has been fostered between the graduate populations of these departments.

In the spirit of this unity between the two similarly focused programs at UW the biochemistry Student Faculty Liaison Committee (SFLC)

has morphed into the new IPiB SFLC, which is jointly organized by representatives from both departments. As usual many of the social activities that you may remember from your own days in the department have been maintained including the annual welcome picnic, holiday parties, the egg drop competition, and the departmental art show. We are also glad to incorporate BMC traditions into the social scene of the Biochemistry department including Friday afternoon socials in the BMC library. Through the cooperation of the students in both departments the 2006-2007 academic year is shaping up to be memorable not only for the new era that IPiB ushers into the history of the biochemistry department at UW-Madison, but also for the welcoming spirit of community and unity that the respective student bodies have extended to each other during this time of transition.

The Department in Uganda

Professor James Ntambi continues to lead an extraordinary and invaluable program for undergraduates, taking them to Uganda to both learn about nutrition and put what they learn into practice. The experience is meaningful to each student involved. 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 and consider helping out.

The students come to realize that necessities we take for granted, such as clean drinking water, food availability, and receiving an education, are daily struggles for the majority of Ugandan citizens. Upon returning home, one of the student groups

formed a non-profit student organization called Village Health project. The goals of this project are to support health and nutrition projects in developing countries, and to increase awareness about international health issues.

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. In January of 2006, the group confirmed that all samples collected from water tanks were safe for drinking. They are also trying to help 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 are doing all this because they believe that in order to improve human health, good nutrition practices and clean water go hand in hand.

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.



BioSand Water Filter

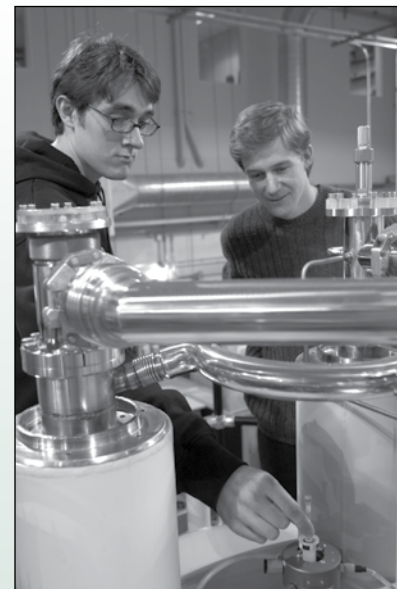
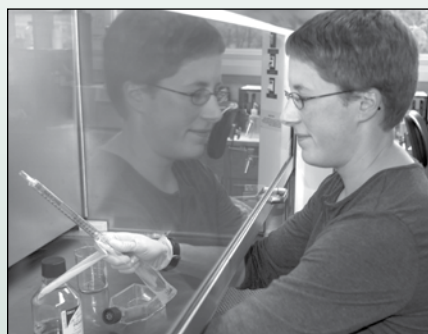
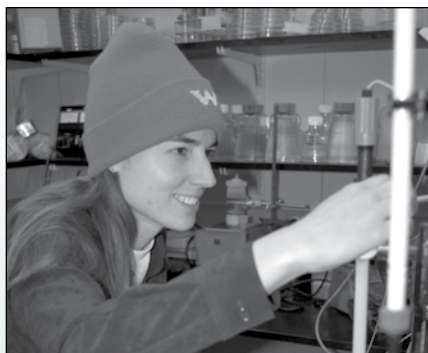
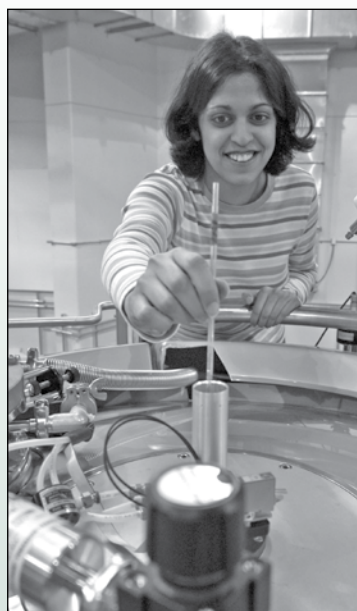


Water before and after it is processed with the BioSand filter.

Biochemistry Degree Listing May 2005-December 2006

Degree Name (Major Professor) Thesis Title

PhD	Miller, Russell (Attie)	Identification and characterization of ligand regulated peptides that inhibit the 5 amp-activated protein kinase
PhD	Reiter, Nick (Butcher)	Structure and conformational dynamics of U6 RNA and its chaperone Prp24
PhD	Sashital, Dipali (Butcher)	Structural investigation of U6 and U2 spliceosomal RNAs
PhD	Staple, David (Butcher)	Structural and thermodynamic investigation of the HIV-1 frameshift site RNA
PhD	Drees, Julia (Cox)	The Novel RecA Regulator Proteins RecX, DinI, RdgC and PsiB
PhD	Eggington, Julie (Cox)	<i>Deinococcus radiodurans</i> single-stranded DNA-binding protein
PhD	Hobbs, Michael (Cox)	On the Biochemistry of the Recombination Mediator Proteins RecO, RecR, RecF and RecX
PhD	Scancella, Jenifer (DeLuca)	Characterization of the biosynthetic pathway of the aryl hydrocarbon receptor ligand indole thiazole methyl ester (ITE)
PhD	Schwinn, Marie (DeLuca)	Influence of 1 α ,25-Dihydroxyvitamin D ₃ Analogs on Coactivator Recruitment to the Vitamin D Receptor Transcriptional Complex
PhD	Schwartz, Phillip (Frey)	On the mechanism by which monocations activate adenosylcobalamin-dependent dioldehydrase
PhD	Lamont, Liana (Kimble)	Molecular Regulation of Germ Cell Number and Fate in the Nematode <i>C. elegans</i>
PhD	Nojiri, Mari (Martin)	Analysis of CAPS Phosphorylation
PhD	Zornetzer, Gregory (Markley)	Modulation of the Structure and Dynamics of Acyl-Acyl Carrier Protein by Fatty Acids of Different Lengths
PhD	Man, Weng Chi (Ntambi)	Topology of SCD1 and its co-localization with DGAT2 in the endoplasmic reticulum
PhD	Han, Byung Woo (Phillips)	Structural Biology of Arabidopsis EMBRYONIC FACTOR 1 (FAC1) and Other Enzymes

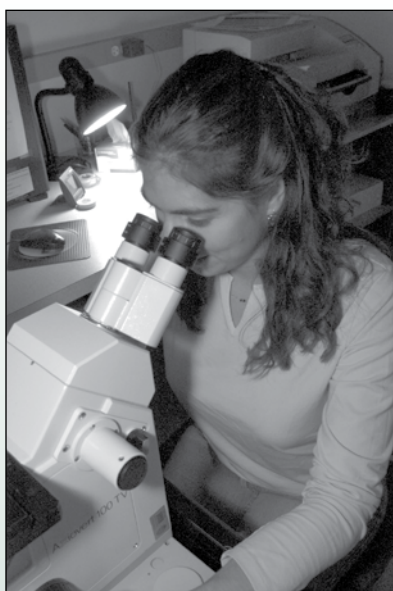


Degree Name (Major Professor) Thesis Title

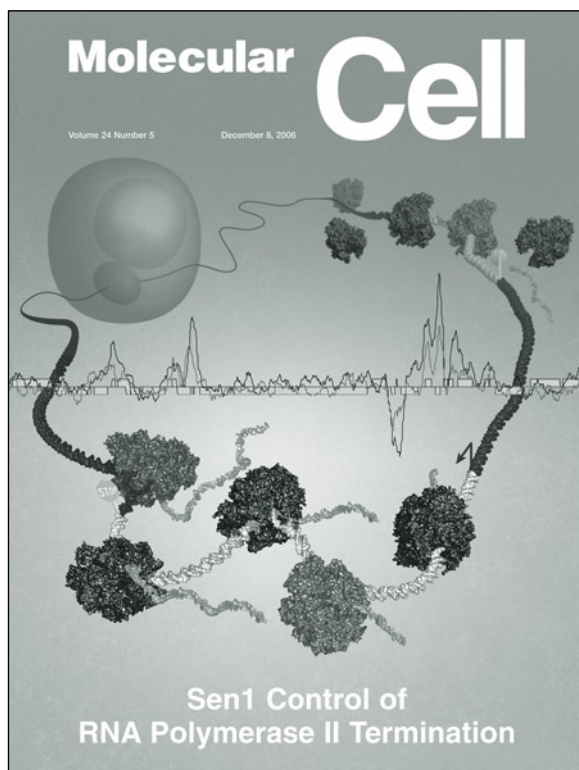
PhD	McCoy, Jason (Phillips)	Structure-Function Relationships in Structural Genomics Targets
PhD	Kim, Sungtae (Pike)	Gene Regulation by 1,25-dihydroxyvitamin D ₃ in Osteoblasts
PhD	Zella, Lee (Pike)	Mechanisms regulating ligand-mediated transcriptional activation by the vitamin D receptor
PhD	Dickson, Kimberly (Raines)	Effects of the ribonuclease inhibitor on the biological activity of pancreatic-type ribonucleases
PhD	Fuchs, Stephen (Raines)	Design and Application of a Cell-permeable Cationic Protein
PhD	Lee, Jinhwan (Eugene) (Raines)	Ribonuclease A Homologs: Catalysis and Cytotoxicity
PhD	Smith, Bryan (Raines)	Ribonuclease Activity: Basis and Control
PhD	Mansoorabadi, Steven (Reed)	Characterization of Paramagnetic Intermediates in Enzymatic Reactions
PhD	Adams, Christian (Reznikoff)	Single Molecule Studies of the Tn5 Transposon
PhD	Hook, Brad (Wickens)	PUF proteins: RNA binding, protein interactions and RNA regulation
PhD	Seay, Daniel (Wickens)	Marked for Death: mRNAs Targeted and Destroyed by MPT5, a <i>Saccharomyces cerevisiae</i> PUF Protein
MS	Bates, Barbara (Bednarek)	Initial Biochemical Characterization of Plant UBX-domain Containing Protein (PUX) 11
MS	Pillard, Sarah (Butcher)	Investigating the role of thermodynamic stability in frameshifting efficiency of the HIV-1 frameshift RNA

Correction to last year's newsletter

PhD	Hinckley, Glenn T (Frey)	Ligand Effect on the Reduction Potential of the $[4\text{Fe} - 4\text{S}]^{2+/1+}$ Couple in Lysine 2, 3-aminomutase
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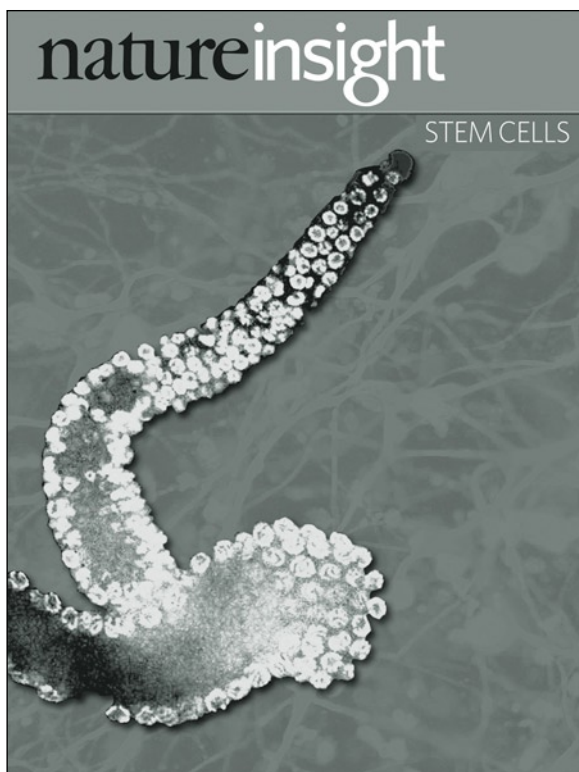


Aseem Ansari



Sen1 functions in termination of transcription by RNA Pol II. Steinmetz et al. map sites of Sen1-dependent termination by comparing Pol II occupancy across the entire yeast genome in wild-type and *sen1* mutant strains. The trace on the cover shows wild-type (dark gray) and *sen1* mutant (lighter gray) Pol II occupancy for a 50 kb segment of chromosome 12. The analysis reveals Sen1-dependent termination on many noncoding RNA genes and some short protein-coding genes (cover design by H. Adam Steinberg)

Judith Kimble



C. elegans germ cells (nuclei are orange) proliferate in response to signals from the somatic distal tip cell (grey cell at top of image). The distal tip cell is a component of the stem cell niche. From review by Morrison and Kimble pp 1068.

Judith Kimble

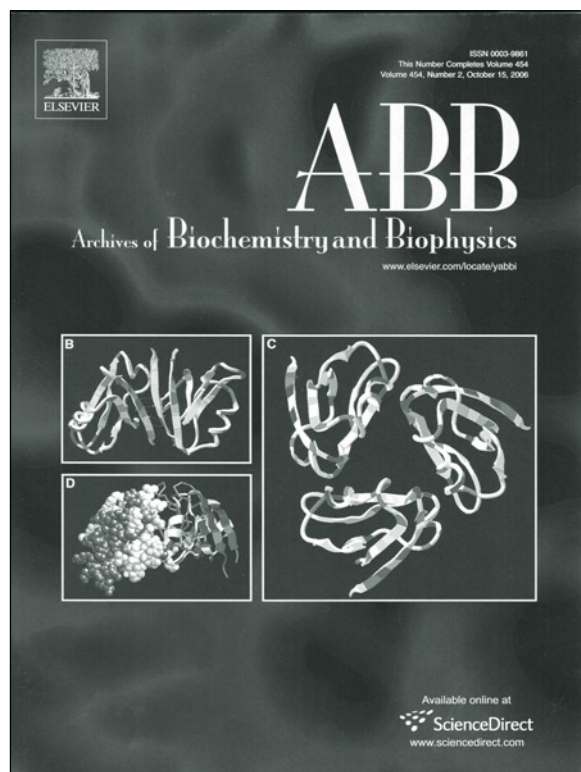


In the *C. elegans* germ line, germ cells proliferate (green nuclei) at one end and progress through meiosis and gametogenesis as they move away from the proliferative region. This image shows a germ line (nuclei are blue) obtained from a worm that was labeled with bromodeoxyuridine (BrdU, red) and then chased in the absence of BrdU. From Crittenden et al. pp 3051.

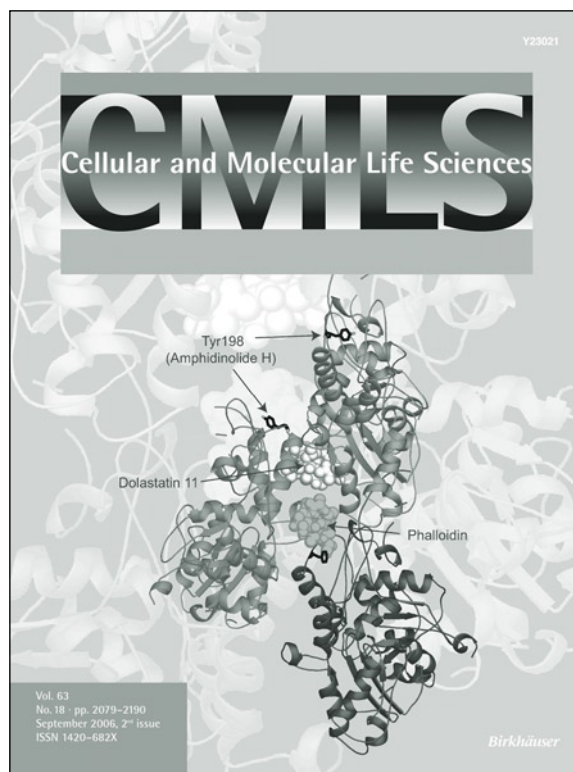
John Markley



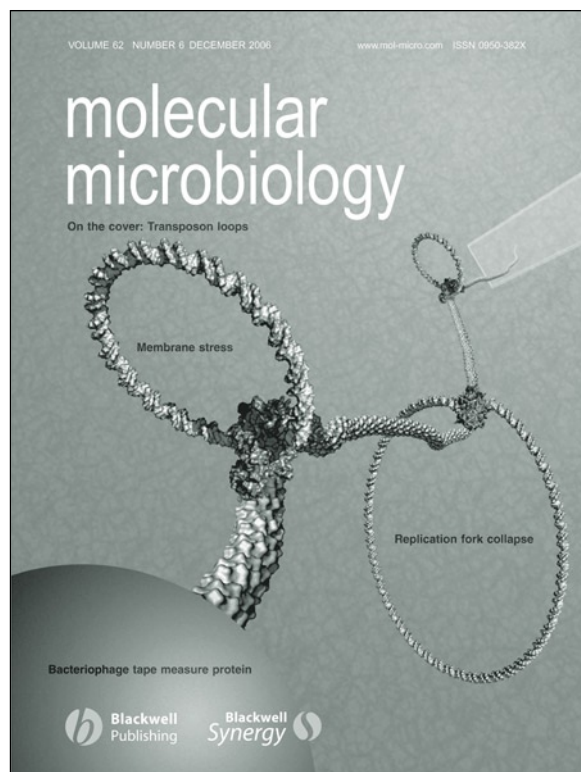
Cell-free protein synthesis and NMR spectroscopy of protein products (combined figure from the minireview series by N. E. Dixon et al., pp. 4131–4169).



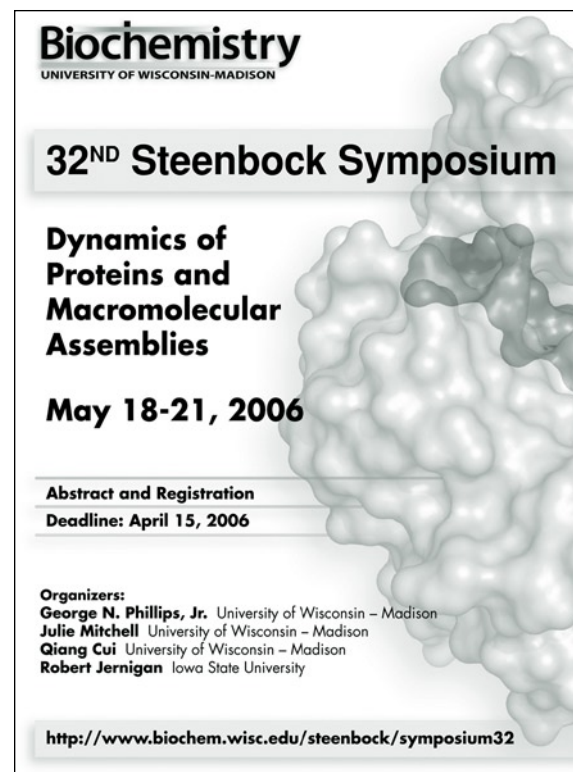
TRP1 interacting PDZ-domain protein GIPC forms oligomers and is localized to intracellular vesicles in human melanocytes.



Actin is the target of a wide range of natural products which stabilize the filamentous form of actin (F-actin) or bind to the monomeric state of actin (G-actin). Shown here are the approximate binding sites of the filament-stabilizing natural products amphidinolide H, dolastatin 11, and phalloidin on F-actin.



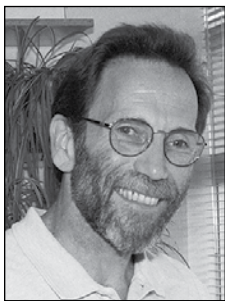
H. Adam Steinberg's rendering of Tn5 transposase-DNA complexes at non-specific DNA sites; a probable intermediate in transposase finding specific transposon sequences.



Proteins self-organize into structures that don't always coincide with observed crystallography or other methods because of their flexibility. Mounting evidence suggests that these induced motions play specific and essential roles in protein function. Adenylate kinase, shown above, offers opportunities for the study of dynamics (cover design by H. Adam Steinberg).

Membrane Choreography in the Martin Lab

by Professor Tom Martin



Life without membranes would be terribly difficult. The contents of our cells would diffuse away and enzymes would never meet their substrates. To avoid the disaster of dilution, barriers to diffusion were established early in the evolution of cellular life. Fortunately, this was relatively easy once molecules such as phospholipids appeared on the scene; these amphipathic molecules love and hate water at the same time, and spontaneously assemble into phospholipid bilayers.

The typical animal cell contains 10^{10} phospholipid molecules lined up in parallel register in a bilayer arrangement to cover the cell surface. The intrinsic physical properties of bilayers provide barriers to prevent the escape of required molecules inside the cell, and prevent invasion by undesired molecules from the outside. Yet contemporary cells are not simple closed systems; instead they import and export a wide variety of molecules. Transport mechanisms carry molecules across the relatively impermeable phospholipid bilayer membrane.

Little packets sent from inside the cell

Exocytosis exports large molecules out of a cell. In exocytosis, an intracellular membrane sac (vesicle) carrying cargo fuses with the surface membrane to form a pore that allows release of that cargo. In multicellular organisms, one important cargo comprises signaling molecules that mediate communication between cells. Neurotransmitters mediate signaling between nerve cells (and enable learning and memory) and peptide hormones communicate between groups of tissues to coordinate their physiology (such as insulin signaling of glucose utilization). The release of these signals into the extracellular space – secretion – occurs only when physiology demands. Demand is conveyed as an increase in intracellular calcium, which triggers vesicle fusion with the surface membrane. This controlled fusion of vesicles with the membrane is called “regulated exocytosis.” The time required for calcium triggering of vesicle fusion varies enormously: for example, it occurs within milliseconds in the nervous system, and more slowly in the pancreas, as it releases insulin in response to glucose.

In the Martin lab, we want to understand membrane fusion and its regulation. What is the cellular machinery that allows the mixing of vesicle bilayers with surface membrane bilayers to form a pore? How can a rise in intracellular calcium set this process in motion? How does

this complex process occur so quickly? Which constituents of the fusion machinery are dedicated to specific secretory processes and which are universal?

Understanding choreography through biochemistry

Membrane fusion is highly choreographed and controlled, and relies on at least three different mechanisms to promote membrane (phospholipid bilayer) fusion. Specific phospholipids are metabolized to make the bilayers more prone to fuse; soluble proteins are recruited to special membrane sites to prepare these sites for fusion; proteins within the membranes help draw them together. An important conclusion from our work, and that of many others, is that membrane phospholipids, membrane proteins and soluble proteins engage in sequential encounters that are choreographed on the spatially restricted stage of the membrane fusion site.

Our own work began by developing a new biochemical approach to the problem: we broke open and washed secretory cells, and asked whether filling them with calcium would trigger vesicle exocytosis. The answer was both yes and no. On the one hand, adding calcium to the membranous “ghosts” did trigger some vesicle fusion with the surface membrane and secretion. We now know this is because key proteins in the membranes comprise the basic machinery for vesicle fusion and its triggering by calcium. However, we also found that adding ATP and a number of soluble proteins back to the cellular ghosts markedly improved the calcium-triggered vesicle fusion. We now know that ATP and some of the soluble proteins catalyzed the modification of a phospholipid that is required for fusion. In addition, other key soluble proteins were discovered that bind to the vesicle and to membrane proteins to help vesicles line up at the membrane to establish a fusion-ready state.

Our current understanding of the choreography of membrane fusion reveals that it relies on many players, as seen in the figure. Firstly, the machinery is prepared for fusion when a phosphorylated lipid (called PIP_2) is synthesized by ATP-dependent phosphorylation. A protein (in black, called CAPS) that recognizes PIP_2 is then recruited. CAPS binds to both vesicle and surface membrane (in interactions with PIP_2 as well as the dark grey protein) and helps align the vesicle at fusion sites. When vesicles are prop-

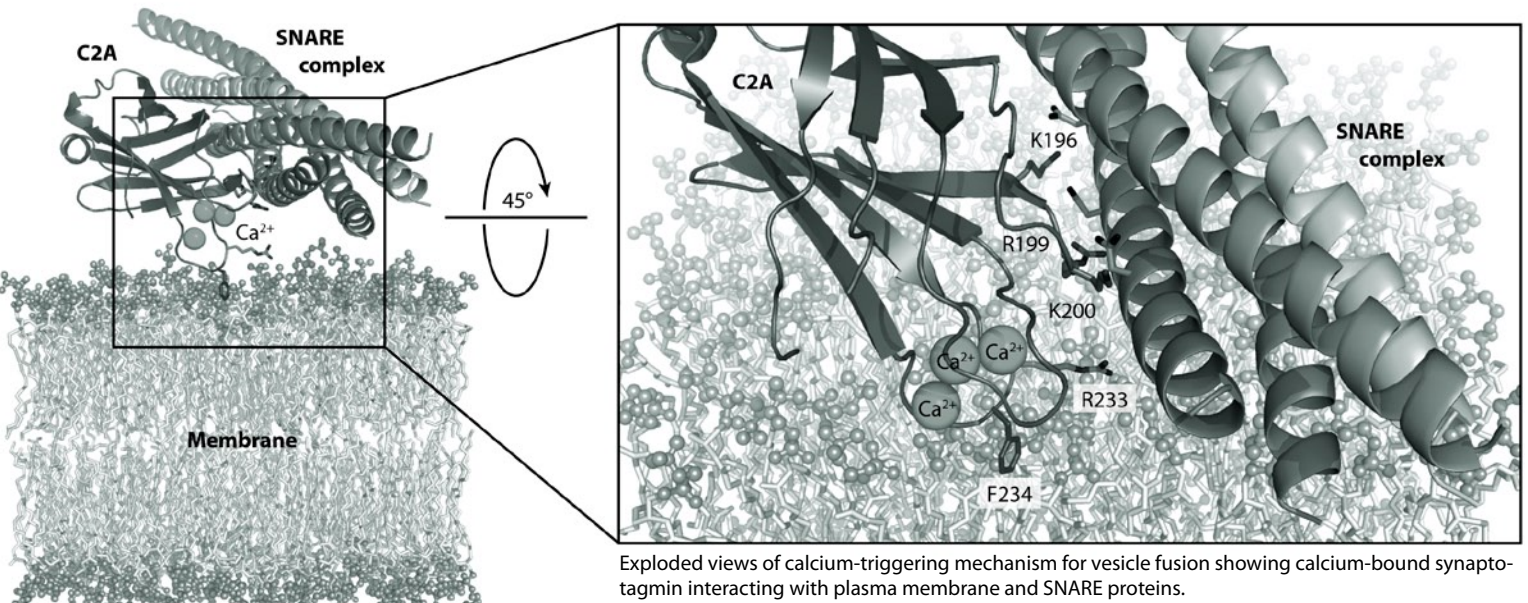
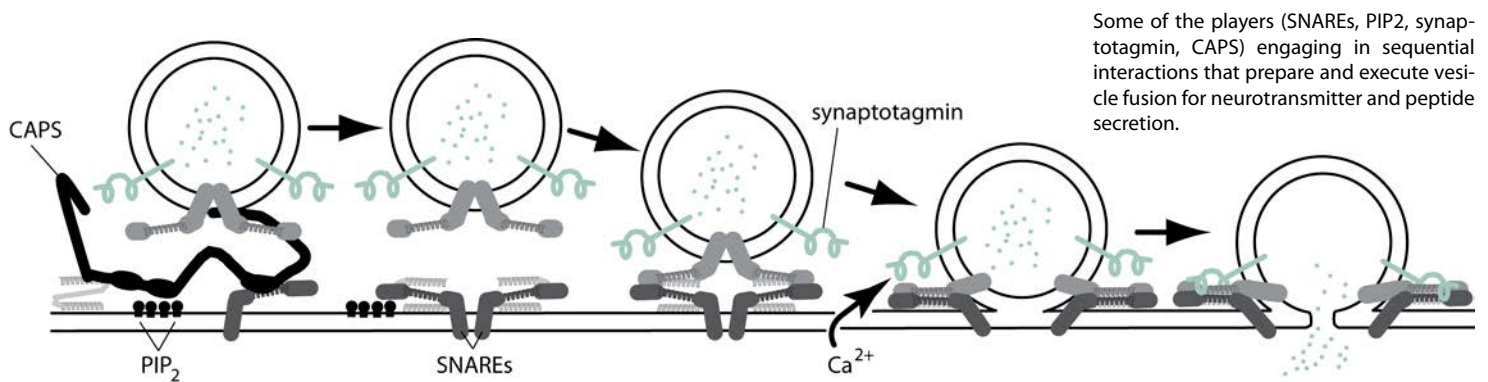
erly aligned, membrane proteins (in shades of grey) called SNAREs draw the membranes close together. SNAREs are pulled further into close apposition when a calcium-dependent switch (in grey-green, called synaptotagmin) binds to the SNARE proteins when calcium levels rise. This triggers membrane fusion at a focal site to form a pore that allows cargo (neurotransmitter or peptide hormone) to be released.

What lies ahead

The progress we and others have made is satisfying not only for its own sake, but also because it raises many new questions. How are fusion sites on the plasma membrane established? What driving forces overcome the repulsion of membranes to fuse? How do participating proteins tug on membranes to bend them through an orderly

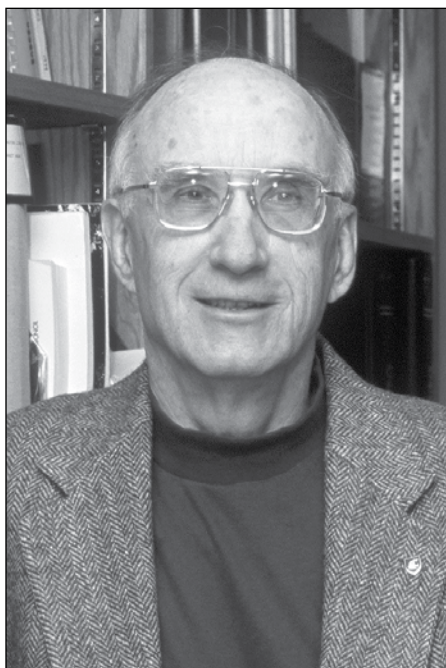
phospholipid mixing process? What is the exact alignment of the proteins that choreograph this process and in what temporal sequence do they interact? What is the role of numerous other proteins that are known to be required for the overall execution of regulated membrane fusion?

The last decade has revealed aspects of the choreography: who moves where and touches who to cause membranes to fuse only at the right place and time. A new era of synthetic biology now permits us to make artificial membranes of defined phospholipid composition and utilize purified proteins to reassemble the machinery of membrane fusion and reconstitute its function in the test tube (or rather microtitre plate or microscope slide). On this highly rarified stage, detailed mechanistic and biophysical studies of the individual players involved in the choreography await.



Rememering Jack Gorski

by Professor Henry A. Lardy



The death of Jack Gorski on August 30, 2006 took a brilliant but modest investigator, an effective teacher, and a practical dairyman from this community. Jack was born in Green Bay, Wisconsin on March 14, 1931. His family moved to Milwaukee and he attended school in Wauwatosa. He began college at California Polytech but chose the University of Wisconsin-Madison to complete a B.S. degree in 1953. His introduction to hormone research occurred at Washington State University, Pullman, where after seven research papers, he earned his M.S. (1956) and Ph.D. (1958) degrees. It was there that Jack and Harriet Fischer were married in 1955. Many knew them as tennis and biking friends. Their daughter, JoAnne Gorski Alkire, resides in Minneapolis and their son, Michael, lives in Stamford, Connecticut.

As a postdoctorate fellow he spent a year in the renowned steroid laboratory at the University of Utah and three years with another estrogen pioneer, Gerry Mueller, at the McArdle laboratory on this campus. With Gerry, Jack explored the earliest effects of estrogen on the induction of nucleotide and protein synthesis in uterine tissue.

"A gentle spirit, warm and unaffected, yet with great strength of character, a penetrating intellect and a fierce desire to learn and understand. Reading Jack's papers inspired me, as a beginning graduate student, to join the field; getting to know him helped keep me in it".

Keith Yamamoto at UCSF

Jack became an Assistant Professor of Physiology and Biophysics at the University of Illinois-Urbana in 1961. There, he and his students were the first to clarify the function of estrogens. The steroid bound to an 8S protein in the cytosol, was transported into the nucleus where it dissociated to a 5S complex. No receptor protein was found in the nucleus unless the tissue had been treated with estrogen. All of the steroid receptor proteins could be removed from the cytosol by administering relatively large doses of estradiol. The elucidation of the mechanism of estrogen function served as a pattern for the function of other hormones in many different laboratories.

These discoveries and Jack's continued work lead to his being recognized as a highly creative and competent investigator. He received the Oppenheimer Award (1971), the Robert Williams Distinguished Leadership Award (1987) and the Fred Koch Award (1995) from the Endocrine Society; the Mentor Award from Women in Endocrinology (2001); the NIH Merit Award (1986) and was elected President of the Endocrine Society in 1990. He was named Distinguished Graduate (1994) and Distinguished Alumnus (2001) by Washington State University. In 1973 Jack moved from his professorship at Illinois to become a Professor in three departments at this University—Biochemistry, Dairy Science, and Animal Sciences. UW-Madison presented Jack with the Paul

Phillips Professorship (1985) and the Hildale Award in Biological Science (1991). He was elected to the American Academy of Arts and Sciences (1986) and the National Academy of Science (1993). The University of Bordeaux added the title "Docteur Honoris Causa" to his list of honors and Current Contents recognized Jack as one of 500 "Most Cited" scientists in the world.

Jack's talents were expressed also in his hobby—dairy cattle. He worked on the show circuit while still in high school. When his profession provided the necessary capital, he bought purebred cows and placed them with farmers who received their milk in exchange for feed and care. Jack received their calves that had been sired by bulls with exceptional genetic potential for conformation and milk production. To increase the value and marketability of his cattle, Jack exhibited them at fairs and Dairy Breed Competitions. His wins included the Grand Champion Jersey Cow at the Wisconsin State Fair in 2002. Even this year when his health was a problem, Jack won the Reserve Grand Champion with one of his cows and placed a younger animal at the head of its class at the Wisconsin State Jersey Show.

Jack's greatest legacy came from his teaching and mentoring. Forty-five of his students earned Doctorate degrees and he trained fifty Postdoctorate fellows. We remember him as an outstanding scientist with a friendly, unassuming manner.

"We have all lost a great scientist and a great man, but he leaves a strong legacy in science, scholarship, and mentoring, and he still lives in our memories as a true human being".

John Katzenellenbogen, University of Illinois Urbana-Champaign

Bentley, Orville G
(PhD 1947 P. Phillips)
2006

Fager, Earl E C
(MS 1948 Burris)
2004

Feeney, Robert E.
(MS 1940, PhD 1942 Strong)
September 21, 2006

Garbers, David
(PhD 1972 Lardy)
October 2006

Gorski, Jack
(Professor 1973-1997 and
Emeritus Professor 1997-2006)
August 30, 2006

Johnson, Ralph M Jr.
(MS 1947, PhD 1948 Strong)
February 26, 2006

Lennon, James
(Animal Research Tech. 1990-2005)
August 11, 2006

MacLeod, Patricia Robinson
(PhD 1949 Lardy)
August 17, 2006

Olson, Lee Charles
(MS 1962 Burris)
2006

Pressman, Berton
(MS 1950, PhD 1953 Lardy)
June 2006

Rasmussen, Howard
(Assoc. Professor 1961-1965)
April 22, 2005

Roberts, Anita Bauer
(PhD 1968 DeLuca)
May 26, 2006

Stocking, C. Ralph
(Postdoc w/Burris 1956)
May 25, 2006

Wagner, Marion
Technician for Lardy
December 2006

When is motor not a motor?

by Ivan Rayment

A Kinesin Motor without a Nucleotide Binding Site

It is widely accepted that kinesin molecular motors contain a motor domain that hydrolyzes ATP and through a series of nucleotide-dependent conformational changes translate the free energy of hydrolysis into directed movement. Thus it comes as a complete surprise that the kinesin related protein Vik1 contains a motor domain, but does not include an active site. This non-motor polypeptide heterodimerizes with

the kinesin Kar3. Surprisingly,

Vik1 can bind tightly to microtubules independently of Kar3, but still permits movement of Kar3 along microtubules. These

traits demand that there

is communication between

Kar3 and Vik1, perhaps through

a novel strain-dependent mechanism,

that allows the binding affinity of Vik1

for microtubules to be modulated by the

nucleotide state of Kar3. From an evolutionary

viewpoint it appears that Vik1 evolved from a

primordial gene belonging to the same kinesin family as

Kar3. Remarkably, the ability to bind and hydrolyze nucleotide

was lost during evolution, but the ability to interact with

microtubules and communicate with its associated motor protein

Kar3 was retained. These studies suggest new variations of molecular

motor interactions await discovery. See the March 27th issue of *Cell* for

more details.

NMRFAM Continues to Break New Ground

by Professor John Markley

The National Magnetic Resonance Facility (NMRFAM), located in the Biochemistry Department, is one of the premier centers for biomolecular NMR spectroscopy in the world. Researchers from all over the world use NMRFAM as a site for data collection, advice, and training. In addition, NMRFAM carries out research in technology development and novel applications of biomolecular NMR.

Beginings

NMRFAM has a long history. John Markley established NMRFAM in 1985, modeling it after a facility he ran at Purdue. Initial funding came from the University of Wisconsin-Madison, National Institutes of Health, National Science Foundation, and U.S. Department of Agriculture. The facility opened in the 1985 Wing of Biochemistry with new spectrometers operating at 400 and 500 MHz. NMRFAM outgrew this site with the addition of its sixth spectrometer, a 750 MHz NMR instrument that had to be housed temporarily off site.

A new facility:

9 magnets, 1/3 of Lambeau field

The NMRFAM staff members got to design a world-class NMR laboratory as part of the Biochemistry Addition completed in 1998. Ed Mooberry, who retired from UW-Madison in March, 2006, was the major architect of the space and infrastructure. The new space has a hatch in the ceiling for delivery of large equipment. It has liquid nitrogen piped in through dewared lines for magnet fills. The temperature in the magnet rooms is controlled to within ± 0.5 °C. The facility has 18,000 ft² for NMR spectrometers and their support plus 2,400 ft² for computer serv-

ers, workstations, and facility staff offices (hence 35.4% the surface area on which the Packers play). The facility set a new standard and has been visited by groups from other institutions designing NMR laboratories, including Pacific Northwest Laboratories, the New York Structural Genomics Center, MIT, and the University of Utah. Sam Butcher joined the Biochemistry faculty in September, 2000, and became a co-PI on the grants that support NMRFAM. Local and External Advisory Committees review NMRFAM's progress and provide useful guidance.

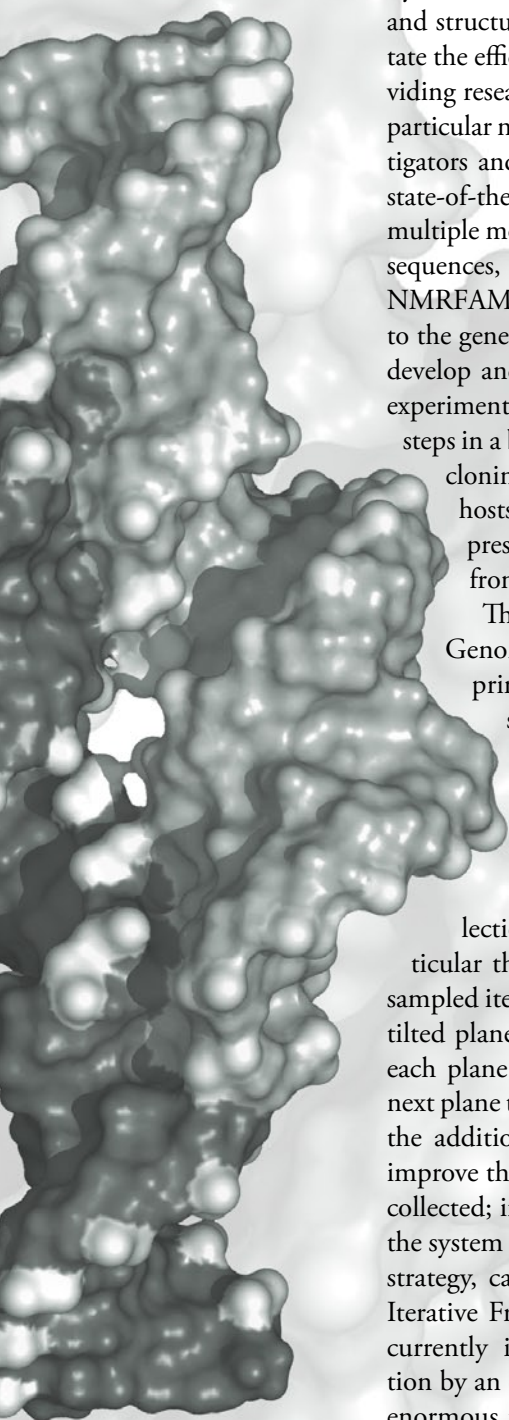
NMRFAM currently houses nine NMR spectrometers: one 900 MHz, one 800 MHz, one 750 MHz, three 600 MHz, two 500 MHz, and one 400 MHz. All but one 500 and the 400 MHz machine are equipped with state-of-the-art cryogenic probes, which enable nearly 10-fold faster data collection. Instrumentation funding has come from the NIH and NSF with generous matching from UW-Madison. All of the magnets in NMRFAM are of the superconducting variety and must be cooled by liquid helium. Very recently, NMRFAM installed a helium recycling system that captures boil-off helium (a non-renewable resource) in a huge bag. When the bag fills, the helium is compressed and sent through a pipe under University Avenue to Engineering Hall, where it is liquefied and sent back to NMRFAM in liquid form. The facility has excellent computational facilities for NMR data processing and quantum chemical calculations.

Cutting edge NMR

Under the able direction of William Milo Westler and other members of its scientific staff, NMRFAM continues to expand the frontiers of biomolecular NMR spectroscopy through resource technology development programs in the important areas of: (1) fast data collection and automated data analysis, (2) technology for larger proteins and complexes, (3) investigations of metal-containing (paramagnetic) proteins, (4) dynamics of macromolecules, (5) structure-function investigation of RNA molecules and their complexes with metal ions and proteins, and (6) the detection and quantification of small molecule metabolites in cell extracts.

A major goal at NMRFAM is to make these investigations faster and less costly. NMRFAM





offers start-to-finish support for biomedical NMR investigations and is prepared to lend support, as needed, in one or more of the following: (1) strategy evaluation, (2) sample preparation, (3) feasibility studies, (4) data collection, and (5) data analysis and structure determination. Our aim is to facilitate the efficient pursuit of new knowledge by providing researchers with resources matched to their particular needs. NMRFAM provides young investigators and experienced spectroscopists access to state-of-the-art instrumentation with support for multiple modes of data collection. Protocols, pulse sequences, and software tools developed through NMRFAM's research activities are made available to the general scientific community. The aim is to develop and disseminate advanced approaches to experiment design and data analysis that cover all steps in a biomolecular NMR investigation, from cloning through data deposition. NMRFAM hosts distinguished visiting scientists and presents workshops attended by scientists from all over the world.

The Center for Eukaryotic Structural Genomics (CESG) uses NMRFAM as its primary site for data collection and analysis for protein structure determinations and collaborates with NMRFAM staff members on the development of improved technology. This collaboration led to the first implementation of a new strategy for data collection in which the spectral space of a particular three-dimensional NMR experiment is sampled iteratively by collecting two-dimensional tilted planes with on-the-fly peak recognition of each plane and calculation of the most optimal next plane to collect. If the algorithm predicts that the additional information from the plane will improve the model of peak locations, the plane is collected; if not, the experiment is complete, and the system moves on to the next experiment. This strategy, called "HIFI-NMR" (High Resolution Iterative Frequency Identification for NMR), as currently implemented speeds up data collection by an order of magnitude. The approach has enormous potential in that it is easily interfaced with automated assignment of signals and other steps in solution structure determination.

Another collaboration with CESG has led to a complementary set of tools that take as input peak lists associated with particular NMR experiments (the output from HIFI-NMR or other data collection strategies) and the protein sequence and provides as output assigned chemical shifts

and the secondary structure. NMRFAM makes this capability, known as "PINE", available to the community from a webserver on its website. The output of PINE can be viewed for quality control by standard software packages used for manual assignments that display strips from experimental data. PINE takes minutes to perform operations that take days by hand.

In the last year

The 2005-2006 NMRFAM annual report lists >100 publications supported by NMRFAM. Some of these are by independent users of the facility, but many represent collaborations with researchers on or off campus. NMRFAM is always looking for challenging collaborative projects that can make use of its technology and serve to drive it in new directions. Examples of recently completed collaborative projects that involved NMRFAM include: the structure of essential pre-mRNA processing factor Prp24 (Sam Butcher, George Phillips, and David Brow); the solution structure of YggX, a prokaryotic protein involved in Fe(II) trafficking (with Diana Downs, UW Bacteriology); "solution structure of the N-domain of Wilson disease protein showing its unique nucleotide-binding environment and effects of disease mutations (with Oleg Dmitriev, Univ. of Saskatchewan, and Svetlana Lutsenko, Oregon Health & Science Univ.); NMR titration study of the Rieske protein from *Thermus thermophilus* demonstrating the role of iron-ligated histidines in the pH dependence of the reduction potential (with James Fee, Scripps); solution structures of spinach acyl carrier protein with decanoate and stearate (with Brian Fox); solution structure of CalC providing structural insight into the self-sacrifice mechanism of enediyne resistance (with Jon Thorson, UW Pharmacy School); micelle-induced folding of a spinach thylakoid soluble phosphoprotein and its functional implications (with Inger Carlberg, Stockholm Univ. Sweden, and Alexander Vener, Linköping Univ., Sweden); solution structure of a small protein containing a fluorinated side chain in its core (with Prof. Sam Gellman, UW Chemistry); NMR characterizations of an amyloidogenic conformational ensemble of the PI3K SH3 domain (with Eugene Deroose, Cindy Putnam-Evans, and Kwang Hun Lim, East Carolina Univ. and Robert London, NIEHS, Research Triangle NC).

For more information, please contact Anne Lynn Gillian-Daniel (608-262-3173) or consult the NMRFAM website: www.nmrfam.wisc.edu

by Mike Sussman

Senior Editor Nature Developmental Biology

From Wisconsin

Natalie DeWitt arrived in the Sussman lab fresh from a BS in Biochemistry at University of Maryland during a rotation in the fall of 1987, and graduated with a PhD from the CMB Program in 1994. She published three papers from her thesis, in the respected journals *Genetics*, *Plant Physiology* and *Plant Cell*. Her major accomplishment in that body of work was the demonstration that one of the 11 genes encoding the *Arabidopsis thaliana* plasma membrane proton pump (H^+ -ATPase) family is specifically and highly expressed in companion cells of the phloem. For those of you who work with animals, rather than our green friends, the plants, be aware that the proton pump performs the same essential function in plants as the sodium pump in animals. In addition, the phloem is sort of like the veins and blood since it is the tissue through which all of the sugar made in leaves moves to heterotrophic growing or storage tissues such as fruits and roots. Her work was one of the first in plants to use epitope tags to identify the location of any protein, at both the light and electron microscopy level. Furthermore, one of her modified genes turned out to be a dominant positive transgene that created 'acid resistant' plants. She was also involved in the early stages of the reverse genetic gene knockout technology that Sussman's lab developed (with large-scale gardening help from colleague Rick Amasino) and provided to the international research community, from 1996-2001. Natalie's research accomplishments helped Sussman get tenure (some people may say this is a blemish, rather than a plus).

Through a Transition

After escaping Wisconsin, she performed her postdoctoral work in the same lab where

Sussman received his polishing (?), in the yeast plasma membrane genetics laboratory of Carolyn Slayman at the Yale School of Medicine. Her decision to settle in at Yale as a postdoctoral associate with Carolyn, was preceded by interesting and brief detours caused by her first postdoctoral mentor at a Southern university not receiving tenure, and another brief sojourn to England to taste European culture. After finishing up at Yale in 1999, she proceeded on to her first real job, as a research editor at the then 'new' journal, *Nature Biotechnology*. In 2001 she was promoted to Senior Editor for the mother-ship journal *Nature*, and was also the founding editor for their San Francisco office.

To Editor at Nature

Over the past four years as *Nature's* editor in charge of developmental biology, Natalie has been responsible for scientific manuscripts on stem cells, embryology, cloning and angiogenesis, including some of the most highly cited papers in all of biology. She has authored many editorials, news stories, press releases and scientific highlights for *Nature* and other Nature Publishing group journals. She has organized Nature-sponsored scientific conferences and press conferences and serves on the editorial board of the International Society for Stem Cell Research and on the board of directors for the Northern California branch of the National Association of Scientific Writers Association. All of this arose after, and perhaps in spite of, her humble beginnings as an *Arabidopsis* researcher and graduate student in the Sussman lab working with the 'original' (green) stem cells! Whether in the lab, or at the keyboard, her work has always been typified as being innovative, careful, and timely.



Mike Sussman (lower left).

Jeff Harper (upper left) postdoc then, now professor at University of Nevada at Reno.

Eric Schaller (center) also CMB student then, now professor at Dartmouth University.

Lorelei Manney (center), technician then, now mom living somewhere in Texas.

Natalie DeWitt (right).

nature

From the Labs



Alan Attie
Lab

This has been a productive and exciting year in our laboratory. We are engaged in research aimed at identifying genes involved in diabetes susceptibility. This past year, we published our first positional cloning success, the identification of *SorCS1* as a diabetes susceptibility gene responsible for a quantitative trait locus we originally mapped when Jonathan Stoehr was in the lab several years ago. Much of the credit for this milestone goes to **Susie Clee**, who was quite resilient in pursuing a very tough project. Susie just was awarded a Scientist Development Grant from the American Heart Association. She has recently been on many job interviews and will likely be happily situated in an independent tenure-track position somewhere else later this year. Our collaborators in San Antonio and Los Angeles have discovered that single nucleotide polymorphisms in *SorCS1* are associated with diabetes in Mexican-Americans. Others are now investigating the involvement of this gene in diabetes in other human populations.

Summer Raines and **Oliver Richards** are studying *SorCS1* function. *SorCS1* binds to PDGF, a critical regulator of pericyte recruitment to blood vessels. So, they're exploring the hypothesis that *SorCS1* plays a role in angiogenesis in the islet vasculature.

This past year, **Mary Rabaglia** was awarded the Academic Staff Award at a ceremony in the Chancellor's Mansion. The award recognizes her many decades of dedicated work at the university and just how really fantastic she is.

We are also collecting highly informative data that links gene expression in various tissues, including pancreatic islets, with diabetes traits and with markers in the genome. With our wonderful statistician collaborators, Christina Kendzierski and Brian Yandell (and their wonderful graduate students), we're developing

network models that describe pathways that are dysregulated in diabetes.

We have been joined by several new people this year. **Jeremy Lavine**, an MD/PhD student is working with **Phil Raess** on β -cell proliferation mechanisms. **Bill Oliver**, a biochemistry PhD student, is working on our genetics projects. **Christine Ferara**, an MD/PhD student with Chris Newgard at Duke University, is spending a few years in our lab working on several joint projects between our lab and the Newgard lab. **Dawn Belt Davis** is an MD/PhD post-doc who just completed her Endocrinology fellowship at UW Hospital and is working with us on our gene discovery projects. **Enpeng Zhao** is also deeply involved in many of our projects. He is also eagerly awaiting the arrival of his first child, due this spring. **Angie Tebon Oler** and **Kathy Schueler** still travel all the corners of the world and have time to do wonderful work in the laboratory. **Dan Blasiolo** is bravely upholding a presence for the lab in the lipid field despite our much higher profile in recent years in the diabetes field. **Mark Keller** has a hand in virtually every project in the lab and has helped us move into several new and exciting areas. He is about to embark on a drug discovery project to follow up on some exciting leads we have with compounds that stimulate insulin secretion. **Jessica Byers Flowers** graduated last summer and is now doing a clinical nutrition internship at UW Hospital. She really enjoys the clinical work and envisions combining basic research and clinical nutrition in her future career.

Alan is thrilled by everything and everyone in the lab. We are involved in many areas we could not have predicted before. The lab has developed a lot of new infrastructure, which is extending our capabilities and our level of sophistication in genetics and genomics research.



Sam Butcher
Lab

This past year was an eventful one for the Butcher lab. It is a story of eight fantastic graduate students at different stages in their careers. Congratulations to **David Staple**, **Dipa Sashital** and **Nick Reiter** for successfully defending their Ph.D. theses. They were my first graduate students to join the lab (in 2001), and all three have done remarkably well. David is now a postdoc at the University of California at Santa Cruz in the laboratory of Harry Noller, where he is studying

the ribosome. Dipa and Nick's research projects are at such exciting stages right now that they have both decided to stay for a little while longer in the lab as postdocs while they wrap things up. This is great news for the lab, but it is just a matter of months before they go off to start their "real" postdocs. In light of the turnover this year, it was the perfect time to recruit some new graduate students. We were fortunate to have **Ashley Richie** and **Steve Martin-Tumas**, 2 very bright

first year graduate students, join the lab this year. Additionally, we had **Vincenzo Venditti** as a visiting graduate student on loan from the University of Siena, Italy. **Jared Davis** is finishing his

fourth year as a graduate student and will likely be defending his Ph.D. thesis in the upcoming year, and **Ryan Marcheschi** is finishing his third year and is busy solving his first RNA structure.



Mo Cleland
Lab

Jeremy van Vleet (5th year graduate student) has been spending an unprecedented number of hours in the lab since his wife Jennifer, of 8 months, left for Denmark on a Fulbright Fellowship. Jennifer is working for Lisbeth Olsson at the Center for Microbial Biotechnology at Technical University of Denmark.

Laurie Reinhardt (Assoc. scientist) has made gamma-amino ATP and ethyl-CoA for use in X-ray studies in Ivan Rayment's lab and is determining isotope effects on ornithine transcarbamoylase. Mark Anderson (Asst. scientist) has been determining N-15 isotope effects on ethanolamine ammonia lyase and tryptophan monooxygenase. He is also analyzing the N-15 content of leaf cutter ants and the food they eat in a collaborative study of nitrogen fixation in these insects.

We have three undergraduates (**Brian Wratney**, **Greg Peters**, and **Fiona Chu**) working in the lab this fall.

Yong Liu who graduated here in December with her master's degree now has a full time job with Genentech in San Francisco. **Kirk Wright** who finished his postdoc here in 2003 recently changed jobs to Novartis in Boston. He and his

wife had a baby girl, Sophia, in April. **Lac Lee** who graduated here in 1999 also works there.

Professor **Al Hengge** (Utah State University, Logan), past scientist in this lab, is here at UW-Madison for this fall on sabbatical. He has been working with John Denu in the Biomolecular Chemistry department.

John Marlier (Professor at Cal Poly in California) was here this summer working on the N-15 isotope effects on semicarbazide hydrolysis by urea. His work on urea catalyzed hydrolysis of formamide was published this year in Biochemistry.

Jill Rawlings (Professor at Auburn University-Montgomery in Alabama) was here this summer finishing up work on metal catalyzed hydrolysis of phosphodiesteres, with a paper in press in JACS from this work.

Mo went to the Isotopes Gordon Conference in California in February, but otherwise his out of town trips have been to visit his daughters or see operas (the Sarasota Opera in Florida in March and the Wagner ring cycle operas in Orange County in October). He and **Paul Cook** have written a book on Enzyme Kinetics which should be published in the spring and he is correcting page proof as this is written.



Mike Cox
Lab

Current Lab News:

Rachel Britt passed her prelim exam in April 2006. Congratulations Rachel!

Julia Cox plans to defend her thesis this coming February. She is the last of our Julie/Julias, with no more in sight for a while. She's got a job offer and will begin work as a patent engineer. She'll prosecute patents with a law firm as soon as she gets her Ph.D.

Vessela Petrova took some time off this past summer to travel from western Russia all the way across Asia to Beijing, stopping in Mongolia where she lived in a yurt (Mongolians call them ger) for several days. The pictures she showed us of her trip were amazing.

Reece Goiffon traveled to Ecuador this past summer and entertained us all with his blog that kept us up to date on all his adventures (includ-

ing his possible run in with a bot fly!).

There's no end to the excitement we get into in the Cox lab!

Awards:

Dennis Harris received a Sullivan Wisconsin Distinguished Graduate Fellowship.

Reece Goiffon received a 2006-2007 Wisconsin Hilldale Undergraduate Research Award.

Meng Kwang Marcus Tan received a 2006-2007 Wisconsin Hilldale Undergraduate Research Award.

Comings:

Postdoc **Akiko Sakasai** joined the lab this past summer after training with Akira Shinohara in Japan. Graduate students **Marielle Gruenic** and **Audrey Klingele** joined the lab after fall rotations. Welcome, Akiko, Marielle, and Audrey.



Goings:

Julia Drees, Julie Eggington and **Michael Hobbs** all defended their theses this past year. What a party!

Julia Drees is now a postdoc at The University of California, San Francisco in the Alan Wu lab. She did find time to travel to Yosemite and Alaska before really getting down to work as a postdoc.

Julie Eggington is now a postdoc at the University of Utah, Salt Lake City in the Brenda Bass lab. She wrote to say that she got a chance to visit Australia and her Grandma before beginning work in the lab.

Michael Hobbs is now a scientist at Invitrogen here in Madison.

Shelley Lusetti left us in August and is now an Assistant Professor at New Mexico State University, Las Cruces. She's contacted us to say that she and her family have settled into life in the

Southwest very nicely. We're giving her a few more months before we start dropping in for visits to escape this cold Wisconsin winter weather. We miss you all very much. Good luck in your new digs.

Past Lab News:

Li-Chun Huang wrote to say that she's joined Cell Genesys' Assay Development group for a nine-month assignment of a pre-validation project.

Weddings and Babies:

No weddings this past year, but we do have babies to report:

Alberto Roca and Nancy Aguilar sent us news that they became parents on September 21, 2006. Andrea Isabel weighed 6 lbs 12 oz and was 20 inches long. I looked at her website and can say that she is one very pretty baby girl. Congratulations to you both on your new baby.

Mike Cox attended a few meetings this past year that included a trip to the ASBMB Annual Meeting in San Francisco in April. He and Beth took a side trip in this little red car. Mike seems to have enjoyed himself.





**Betty Craig
Lab**

Greetings from the Craig Lab.

Since the last Craig Lab installment of the Newsletter, much has happened. The lab has successfully survived the past year with Betty as Chair of the Department, making steady progress uncovering the mysteries of molecular chaperone action. Here is the NEWS!

Peggy Huang has left her “ribosome-associated chaperone” life and moved on to her postdoctoral position in the lab of Arlen Johnson at the University of Texas – Austin, where she is studying ribosome biogenesis. As luck would have it, Peggy’s move dovetailed with the work of **Alison Meyer**, one of Peggy’s successors on the “ribosome/chaperone” project. Alison made the unexpected finding that the “other” ribosome-associated J-protein, Jjj1, works in ribosome subunit biogenesis. A productive collaboration between the Craig and Johnson labs is now underway.

During the past year **Peizhen Yang** joined Alison and **Samantha Herbst** on the ribosome-centric project. Peizhen moved across Henry Mall from Genetics, where she did her PhD in Rick Vierstra’s lab working on the proteasome. In addition, **Jeanette Waltner** a CMB grad student, has joined the lab and is following up the work of Helene Eisenman, trying to figure out how Zuo and Ssz, the “weird” Hsp70, are involved in turning on pleiotropic drug resistance.

Pascual Lopez has come and gone for his sabbatical year. This was Pascual’s third (fourth?) visit to the lab, first as a young bachelor postdoc, now on sabbatical from his position as Associate Professor at the University of Zaragoza and father of four. Antonio Pascual Lopez Peña, born on November 7th, is arguably the most visible product of his recent visit to Madison (although we are still working on that paper on stimulation of Hsp70 ATPase activity!).

Qinglian Liu, a Craig Lab grad from 2002, gave birth last summer to a daughter that she and her husband named Monona Jiayi. Pascual in jest protested – saying he owned that name, as he and Maria had named one of their daughter’s Monona several years ago. It is nice to see that lab

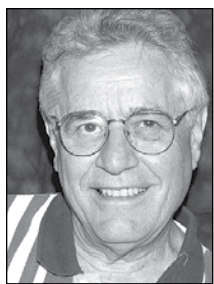
alumni have such fond memories of Madison!

Patrick D’Silva has returned home to take a position as Assistant Professor of Biochemistry at the Indian Institute of Science at Bangalore. He will continue his work on mitochondrial import, focusing on the mammalian import motor. Good luck Patrick (and Savita and Serena) in your new position! We are awaiting Patrick’s first report of life as a professor. During the past year **Thomas Lee** has joined **Brenda Schilke**, **Willy Walter**, **Dirk Schiller**, and **Masaya Hayashi** in the “mito import” group. Thomas came from the University of Colorado, where he studied the regulation of MAP kinase using Hydrogen and mass spectrometry in Natalie Ahn’s lab. He has taken on the challenge of understanding the dynamics of the Tim44:Ssc1 interaction and becoming immersed in yeast genetics.

Our focus on the complexity of the cytosol continues. But by the time you read this, **Rebecca Aron** will have defended her thesis and moved to San Francisco to join Paul Muchowski’s lab. After concentrating on how Sis1 works to maintain the yeast prion [RNQ⁺], she will delve into the world of protein aggregation and neurological disease model systems in mammalian cells. The chaperone:prion project will continue in the able hands of **Takashi Higurashi**, while **Chandan Sahi** has taken on the challenge of understanding the complexities of the multiple J-proteins that populate the cytosol.

As has become the norm **Jarek Marsalek** joined us as a visiting professor from the University of Gdansk for three months this fall, providing an infusion of energy into our Fe-S cluster and Yfh1 activities, working with Brenda, **Amy Andrew** and **Tao Wang**. Amy’s work has been going well and she will shortly receive the “Lame Duck” from Rebecca. For the alumni of the Lab, it will be reassuring for you to know that the “**Lame Duck**”, the oldest member of the lab (with the exception of Betty) who becomes the responsibility of the eldest grad student, is doing well, although that Ace bandage around his leg is becoming a little tattered.





**Hector DeLuca
Lab**

News from the Vitamin D DeLuca Lab:

Yesterday I was in the Information Technology Media Center getting their help on some of our needs and I was reminded by Laura Vanderploeg that it has been two years since I've written a laboratory communication to my former associates. Although I have always taken the position that probably former alumni don't really want to read newsletters, I decided that you don't have to read it but I would convey what the picture is currently in my laboratory.

Most important is that I am still active and I'm enjoying the things that we are currently doing. Fortunately, unlike many of you, I am not faced with deadlines and requirements of grant applications. It is precisely now that I am able to do only those things that I care to do. As a result, I am really enjoying myself in my current research setting without the responsibilities of being the Chair of Biochemistry and without the responsibilities of having to apply for research grants. Although my laboratory is somewhat smaller than it used to be, I still have approximately 25 people working in my group. This is exclusive of **Pat Mings** who continues to keep me "on track" with all of my University office work and **Wendy Hellwig** who does a great job of keeping the laboratory supplied and doing all of the paperwork needed to keep a lab operating. These two individuals make my life very easy. **Lori Plum** is Director of Research and Development for Deltanoid Pharmaceuticals and also is a senior investigator for the vitamin D laboratory. Other senior investigators include **Wendy Bedale** who has worked on inflammatory bowel disease and is currently working on the osteoporosis project, **Julia Zella** who works on a variety of projects including all aspects of renal failure patients and the use of vitamin D compounds as well as phosphate binders, and **Galina Gutuzova** who works on microarray analysis of the actions of vitamin D. **Jason Song** is just completing his work on the AhR ligand and will be leaving the laboratory to start his own company. As you may well know, **Janeen Vanhooke** has left Madison for an Assistant Professorship at Chapel Hill in North Carolina and thus our laboratory has lost its crystallography capability.

There are three graduate students remaining in my group. **Bryan Becklund** who is doing an excellent job in the study of experimental autoimmune encephalomyelitis, the mouse model of multiple sclerosis; **James Kim** who is working on the effect of vitamin D compounds in the disease Lupus Erythematosus; and **Gina Gial-**

amas who is studying the use of vitamin D analogs for the treatment of prostate cancer. During the past year, I have had two graduate students who have completed their work, namely **Marie Schwinn** and **Jeni Scancella**. Marie completed her work on the binding of coactivators as influenced by ligand modification and Jeni completed her studies on the biosynthesis of the precursor for the AhR ligand. In addition, I have had two graduating students who are enrolled in the medical program here on campus, namely **Katie Williams** and **Ehren Rudolph**. Katie has completed her Ph.D., whereas Ehren still has to write his Ph.D. thesis but will be completing it some time during the year. I will not be taking on any additional graduate students but will be accepting postdoctorates since the commitment to them is a much more shorter term than a graduate student.

I am both sorry and happy to report that **Claudia Zierold** has decided to develop her career further and has left my laboratory and has taken on an Associate Scientist position in the Dept. of Pathology & Lab Medicine in the Medical School. She appears extremely happy with her new position and is working very hard. Other postdocs who have left the laboratory are **Shirin Akhter** who carried out a very nice piece of work on demonstrating that calbindin D_{9k} is not required for vitamin D to increase intestinal calcium transport and **Moises Rivera** moved to Boston following his work here in the area of asthma. Two technicians left the laboratory, **Aaron Hirsch** and **Eric Danielson**. Eric has gone on to medical school and Aaron has taken a different position in the Madison area. We had added four technicians in the last year: **Jennifer Vaughan**, **Flora Sundersingh**, **Laura Jacobson** and **Shinobu Miyazaki**. They have all been excellent additions and I am very pleased with how hard they work. Of course, we have the reliable technical skills of **Jean Prahl** who is the jack-of-all-trades and on whom I depend heavily for many technical aspects of research that we do. **Xiaohong Ma** was a marvelous find because of her M.D. background that has made her a key person for the study of biological activity in animals. **Ellen Lake** is our expert on analytical aspects of vitamin D and is an important support for our drug development team. We also are fortunate to have **Jamie Nehring** (Mings) who received her MS degree from the biotechnology program on campus and is now working on colorectal cancer and on the mouse model of diabetes.

We have had a lot of activity in the chemistry portion of my research group. We have the

ongoing and continuing work of **Pawel Grywacz**. We are fortunate to have **Grazia Chiellini** who also holds a position at the University of Pisa, but spends a good share of the year doing chemical synthesis in my research group. We have a wonderful husband and wife team with **Rafal Barycki** and **Katarzyna Barycka**. Of course, **Rafal Sicinski** continues to work with us whenever he can since he has a very high administrative post at the University of Warsaw. He has sent us two great graduate students to work on their Ph.D. jointly between Rafal and our research group: **Agnieszka Glebocka** has received her Ph.D. and will now come here as a postdoctoral fellow. **Katarzyna Plonska** is still working on her Ph.D. but she spends her summers here in my lab and her winters in Poland working on vitamin D synthesis. **Padmaja Tadi**, a postdoctorate from Hyberadad; **Yun Luo**, a Ph.D. from our U.W. Chemistry Department; and **Agnieszka Szczepanska** from Warsaw are all carrying out excellent work in our chemistry group.

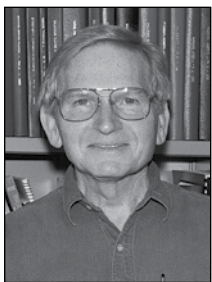
Besides my research group, I have an added advantage of being part of a company (Deltanoid Pharmaceuticals, Inc. located at the Research Park) that develops raw university inventions to a point where they can be sublicensed to large pharmaceutical companies. In this company, Margaret Clagett-Dame is Senior Vice President and Chief Scientific Officer while I serve as President and CEO. We have in the group at Research Park: Paul Radspinner, Vice President of Business

Development; Linda Leikness, Chief Operations Officer; and Karrie Dresen, an accounting/administrative assistant to Linda. We also have a large number of excellent undergraduates who work with scientists and graduate students in the laboratory.

Margaret and I were really so surprised and pleased when **Tatsuo** and **Umiko Suda** visited us at the end of May in 2005 to be sure that I was physically okay because of my bout with lymphoma. Tatsuo and Umiko had sent us origami chains to support the fight against lymphoma. Tatsuo has been very concerned about my health. He has also had some health issues himself but is doing extremely well. We were very pleased to see them here and we hope we can see them again soon.

I am sorry to announce to those of you who haven't heard that **Anita Roberts**, one of my very best students, finally succumbed in her battle against gastric cancer. Although given only a couple of months to live, she battled the disease for a period of three years and was an inspiration to all of us. Anita was one of the most marvelous human beings I have ever had the pleasure of knowing and I know all of you who knew her feel the same.

I love to hear from all of you. Please do not hesitate to send any kind of communication you can. Although you may not hear from me, I want you to know that I appreciate hearing from any and all of you.



Perry Frey
Lab

The Frey lab is in transition. Since the last Newsletter report, **Glen Hinckley** and **Phil Schwartz** completed their Ph. D. requirements and received their degrees. Glen is a postdoctoral researcher in the College of Engineering, and Phil will do his postdoctoral work with Vern Schramm at the Albert Einstein College of Medicine. Postdoctoral associates **Kaisheng Huang** and **Elham Behshad** have moved on to permanent positions at Amgen and Incyte, respectively. One of our lab anchors, **Frank Ruzicka** formally retired, but he continues part-time as a Senior Scientist Emeritus. **Susan Yang** is continuing as a postdoctoral associate, and is job hunting this year. **Alejandro Yevenes** has joined the lab as a postdoctoral associate and is working on phosphoketolase. Alejandro received his Ph. D. degree in the laboratory of our long-time friend and associate Emilio Cardemil at the University of Santiago. **Ab Arab-**

shahi and **Dawei Chen** continue as Scientists in our research program.

We have welcomed additions to the families of lab members and recent alumni in Madison. Glen and Michelle Hinckley are proud parents to Everett Ariosto Hinckley. Adrian Hegeman and Ericka welcomed their daughter Sylvia Sanders Hegeman. Alejandro and Paola Yevenes recently celebrated the birth of their second daughter, Daniela, and their first daughter Belen is very excited about her new sister. The Yevenes family is very happy in Madison.

The new book on "Enzymatic Reaction Mechanisms", on which Perry and Adrian have been working for some years, in their spare time, is being published by the Oxford University Press and will be out in January of 2007. Adrian and Perry feel a sense of accomplishment, as well as relief that it is finally in print.

This will be the last year of research in the Frey lab. Perry has been planning for the past five years to retire after 2007. Perry did not submit applications for renewal of the grants that have supported research in the lab for the past 37 years because of his plans for retirement. In preparation for a soft landing, recruitment of graduate students was halted after Phil Schwartz entered the group, so Phil is the last graduate student to receive his Ph.D. in the Frey lab. Alejandro Yevenes will be the last postdoctoral associate in the group and will leave sometime in 2007. Through attrition, the size of the group has been contracted so that during 2007 all of the lab members will leave for other opportunities. Retirement for Perry is planned for the end of the year.

Perry has felt honored each time a graduate student or postdoctoral associate chose to enter

the lab, and he has thoroughly enjoyed all of his interpersonal interactions with students, post-doctoral associates, and scientists in the Frey lab and in other labs of the Department of Biochemistry and those of his collaborators. The research completed by the students and other researchers in the lab has given Perry great satisfaction and pleasure, and he wishes all of his former associates every success and pleasure with their future careers. Perry has also been honored to work with colleagues in Biochemistry on many collaborative research projects, all of which have enriched his professional life. In retirement, Perry will pursue interests that he has had to defer because of the demands of his career in biochemical research. However, he will keep a hand in Biochemistry and continue with a few activities in professional organizations.



**Laura Kiessling
Lab**

Exciting times have come to the Kiessling lab over the past year. The "star" headline goes to **Matt Allen** (who also works in the Raines lab) for winning an NIH K99/R00 Award – one of 58! – to make a successful transition from mentored post-doc to junior faculty member. This means, however, that Matt will be here less than a year now.

The Stem Cell Lounge became an official entity of the lab, located on the east side. Within this lounge, we find **Joe Klim**, **Ratmir Derda**, **Lingyin Li**, and **April Weir**.

Joe Klim passed his preliminary examination over the summer. Joe also adopted hobbies of rowing and playing drums in a concert band.

Ratmir attended the Gordon Conference located in beautiful Switzerland and brought back chocolate snacks for everyone. When not performing ingenious experiments, Ratmir likes to D.J. and represents the Stem Cell Lounge at the Cardinal.

Lingyin, a fourth year chemistry graduate student, traveled to China over the summer and affectionately brought back many gifts for the group. She also revealed her secret talent of being an exceptional pianist, and throws a great barbeque.

April has made it to her second year of graduate school alive, despite the threat of tetanus from an accident regarding the Christmas ornament. She is continuing the tap dance training she began in preschool and has also adopted jazz and ballet dancing.

Team B-Cell was born to balance out the Stem Cell Lounge. This group consists of

Rachael Carpenter and **Adam Courtney**. This west-side team (only half the size of the Stem Cell Lounge) has a large fan following, making it a force to reckon with in the group.

Adam continues to perfect the art of western blotting, and play hockey for the biochemistry team, following his Canadian upbringing.

Rachael remains the strong female voice needed to keep the male-dominated lab in balance, and the unofficial morning coffee maker. She hopes to begin agility training this summer with her standard schnauzer, Bryn.

New PhD holder **Erik Puffer** enjoys long walks on the beach, quiet evenings at home, and deep philosophical conversations regarding the meaning of life.

Not to be left out, Team Galf insists that they were the original "team" of the group. Team Galf includes **John May** and **Todd Gruber**, two grad students possessing the uncanny ability to talk longer at sub-group meetings than everyone else combined! **Emily Dykhuizen**, **Becca Splain**, and new post-doc **Raja Annamalai** round out the team.

Todd has returned to the Kiessling lab after his spring internship in San Diego. He walked out of all of our lives and thought he could march right back as if nothing had happened.

Team "everybody else" includes **Eric Underbakke** and **Jack Borrok**.

Jack enjoys listening (and singing along) to the Decemberists, and feeding baby guppies to his ferocious fish, Gaylord Nelson. He has also initiated the first Kiessling lab poker tournament.

Eric has gotten everyone in the lab, except April and John May, addicted to the show, *Battlestar Galactica*. There is no change in Eric's status as the go-to person and the know-it-all in the lab.

Richard Grant, **Margaret Wong**, and post-docs **Jiyoung Chang**, and **Yimin Zhu** work, as Eric does, on protein modification.

Erin McElroy and **Grace Jiarpinitnun** work with Jack, Eric and Richard and Yimin on chemotaxis and signaling.

David Peal has earned his PhD and requires that everyone first address him by saying, "Dr. Peal, I am a mere underling and wish your almighty wisdom."

Post-doc **Christine Brotschi** returned to Switzerland to work in pharma research and development.

The Kiessling group welcomes **Eric Kanugh**, the new undergraduate in the lab. Also new are Joe's guppies, Nebby and Tammy and the 6 offspring that have been born, and Eric's *Betta splendens*, Fighting Bob. New to the Chemistry department are graduate students **Aim Tongpenyai**, **Shane Mangold**,

Samira Musah and undergraduate **Pun Wangkanont**.

Love has certainly been in the air in the Kiessling lab as Eric Underbakke is now married to Dipa Sashital and Jack Borrok is married to Roxanne Mitchell. John May will soon be married to Kelly Gorres, as they have recently gotten engaged.

While we had some new additions, the Kiessling lab has also had to say goodbye to friends **Jessica Hollenbeck**, **Coby Carlson** and **Brendan Orner**. All were post-docs in the laboratory, or as we say, the lab elders. Jessica is now an assistant professor at Trinity University in Texas while Coby is a researcher at Invitrogen. Brendan is an assistant professor in Singapore.

Although changes are inevitable, the Kiessling group remains close and is an awesome force in the Biochemistry department. We won the Christmas ornament contest of 2005, took first place in Egg Drop 2006 (thanks to the engineering genius of April and Rachael), and placed in the Halloween costume contest with Todd's Mexican wrestling alter ego, La Vaca Furiosa.

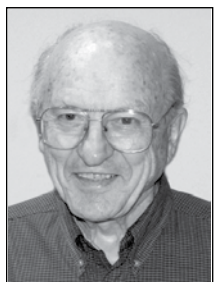


**Judith Kimble
Lab**

Since our last newsletter in April, 2006, three graduate students have moved on to their next steps in life. **Beth Thompson** began her postdoc in September 2006 in the laboratory of Dr. Sarah Hake in Berkeley, California. **Dan Hesselson** defended his thesis in June, was married October 8 in a wonderful ceremony here in Madison, and began his postdoc in the laboratory of Dr. Didier Stainier in San Francisco. **Liana Lamont** decided to punt on her postdoc for the time

being, and instead is exploring other options, including teaching chemistry and editing a journal in education. The new people are settling in, and the lab continues to be a fun place to do science. This is obviously the short version, so please stop in to say hello and get really caught up if you are in the neighborhood!!

Here are some new email addresses:
bethompson@calmail.berkeley.edu,
daniel.hesselson@ucsf.edu



**Henry Lardy
Lab**

Greetings from the Lardy Lab!

Cards and letters from past colleagues added cheer to our holiday period. Our current workers list is the same as last year and we are still working on exciting new steroids. More about that next year.

The Biochemistry Department created a Henry Lardy Professorship and appointed Ron Raines to it. Ron has a joint appointment as a Professor of Biochemistry and Chemistry as does his wife Laura Kiessling—both are excellent chemists. Laura holds the Laurens Anderson Professorship. Many of you will recall that Andy was my first graduate student after having served in the Air Force during World War II.

Our lab has been without grant support during the past two years but we are now assured of support beginning in February. Our most recent paper acknowledges support, not from NIH, but from **Myron Mehlman** who has contributed generously to our work. Available funds will be good news to **Nancy Kneer** who, in sympathy with our budget problem, reports only a small fraction of the hours she works. **Dr Padma Marwah** published a paper (*Bioorganic & Medicinal Chem*) in which she described the synthesis of 62 new steroids. That is one way to keep her bibliography number to a minimum. **Dr Ashok Marwah** and I have studied the conversion of known natural steroids to new metabolites in

living rats. Caring for animals in Biochem is not as convenient as it was before a Dean took our space to create more offices.

As time races by there are always sad events to report. **Bert Pressman** died as a result of an auto accident in June. **Dave Garbers** suffered a fatal heart attack this autumn. **Jack Gorski**, an Emeritus Professor of Biochemistry, with a joint appointment in Animal Sciences, died a few months ago. **Marion Wagner** quit smoking about 25 years ago but it was not soon enough to prevent the appearance of lung cancer that she fought bravely for many months. Throughout that time Marion was cheerful and frank about the limited time she had left before losing the

battle. Her last weeks were spent at Hospice- a beautiful care center donated to the city by a local family. Marion enjoyed the many visitors up to her last day.

Both Annrita and I are enjoying good health, are outdoors a lot, and proud of our fantastic Grandchildren. I missed the Biochem meeting in San Francisco this last year because our plane returned to Madison for repairs. We could not have reached the meeting until after our Poster day, so I cancelled. I hope to see you in Washington DC in April of this year.

We wish you a very good New Year and invite you to visit!



**John Markley
Lab**

Comings and goings:

Anne Lynn Gillian-Daniel joined the lab as an administrative assistant and is doing a great job attending to details and helping us meet deadlines. **Greg Zorntezzer** completed his Ph.D. then stayed on briefly as a postdoc with Brian Fox and John to complete studies of the dynamics of acyl acyl carrier protein. Greg recently moved to a postdoctoral position in Michael G. Katze's lab at the University of Washington, Seattle. **Liya Wang** completed his Ph.D and has taken a postdoctoral position in Edgar Spalding's lab here in Madison. **Young Kee Chae** arrived from Seoul with his family to spend a sabbatical in the lab. Young Kee will be working as a senior member of our metabolomics team. **Ed Mooberry** seems to be enjoying retirement and continues to help us out on high-pressure issues. Budget constraints at NMRFAM have forced us to downsize the facility staff. This sadly led to departures of long term facility members **Frits Abildgaard** and **Heike Blad**.

News from former lab members:

Liz Farr sent word that she is working at an accounting firm in Albuquerque. She has a CPA license and is working on a degree as Certified Valuation Analyst with the goal of a career in estate planning. Her eldest step-daughter made Liz a grandmother last October! She sends her greetings. **John Newman** reported that New York City and his job are treating him well. John is an Associate in Biotechnology at Merrill Lynch in the Big Apple. Congratulations to **Rob Tyler**, who is at the Medical College of Wisconsin, on receiving an American Heart Postdoctoral Fellowship. **Jürgen Schleucher** recently sent greetings from Umeå, Sweden, along with a copy of a Ph.D. thesis from one of his students, who followed up

on work Jürgen carried out at NMRFAM. Jürgen reported that he is now a homeowner and keeps busy running projects on structural biology and plant isotopomer investigations.

Meetings:

John's travels this year included two retirement parties: one in April the day before the ENC at Pacific Grove in honor of Gerd LaMar, retiring from UC, Davis and one at Stanford in October in honor of Oleg Jardetzky. There were three trips to Canada: to Banff for the advisory board meeting for the Human Metabolome Project, to Edmonton for a metabolomics conference, and to Toronto for talks in the Pharmacy department and at Mitsu Ikura's group retreat (where John was invited to speak about the "Early Days of Protein NMR Spectroscopy", proving how ancient he is). In Toronto, John saw **Fleming Hansen**, who is a postdoc in Lewis Kay's lab. John, **Qiu Cui**, and **Ian Lewis** attended the Metabolomics Society Meeting in Boston. They stayed at a B&B one block from the apartment where John lived for 2 years as a graduate student. At the meeting, they were pleased to see **Jasna Fejzo** and **Mike Reily**, who now work for branches of the same company. Another talk was at the First Annual Structural Biology and Molecular Biophysics Workshop, University of Nebraska Medical Center. John, **Eldon Ulrich**, **Jürgen Doreleijers**, and **Jikui Song** attended the ICMRBS meeting in Göttingen in August. John combined a Gordon conference in Aussois, France, with talks in Evry and Montpellier, where he visited **Cathy Royer** an old collaborator from UW. A Far East trip took John to Beijing for the international structural genomics meeting. Also at that meeting were



Dmitiry Vinarov and **Qin (Kate) Zhao** now representing Promega. In Beijing, they were royally entertained by **Jinfeng Wang** from the Academia Sinica and her husband Zhenxi Wang and by **Bin Xia**. Then John flew to Tokyo for a meeting of the Worldwide Protein Data Bank (BMRB is a new member) and to Sapporo for two talks followed by a weekend excursion to hot springs and volcanoes in southern Hokkaido.

Other News:

CESG celebrated its 100th structure with a cruise on Lake Mendota (see the photo). CESG and NMRFAM partnered to put on two highly successful workshops. The workshop on "NMR Data Collection and Processing" (organized by **Anne Lynn**, **Milo Westler**, **Marco Tonelli**, **Klaas Hallenga**, and **Frits**) brought in 11 guest speakers from five countries and 37 attendees from 4 countries, including former lab members **Josh Kurutz** (Univ. of Chicago), **Wen-Jin (Winston) Wu** (Academia Sinica, Taipei), and **Enrique Melendez** (Univ. of Puerto Rico). The workshop on "Wheat Germ Cell-Free Protein Production" (organized by **Dmitiry** and **Carrie Loushin-**

Newman brought in 7 outside speakers and 26 hands-on attendees from 8 countries. The attendees learned all the steps involved in going from DNA to protein *in vitro*. Similar workshops will be held in 2007: contact us for details if you are interested.

Diane Sheehan had a show of her weavings at the new Watrous Gallery in the new Overture Center, mostly pieces produced on her new Jacquard looms that run on compressed air and are computer controlled (one at her studio at home and one in the Department of Environment, Textiles and Design, where she continues to teach).

Milestones:

Claudia and **Gabriel Cornilescu** have a daughter Ioana born 10/21/2006. **I-jin ("Jo") Lin** and Jeng-Ya Yeh have a new baby girl, Heidi, born 11/7/2006; with Zoe this makes two daughters. They are living in the Portland Oregon area. Congratulations to **Zsolt Zolnai** and Nevena Lucic who married last fall; Nevena has landed a residency in internal medicine at Methodist Hospital in Brooklyn, New York.



**Julie Mitchell
Lab**

It's been a very busy year for us. **Sarah** and **Omar** are both doing prelims. **Sarah**, **Raman** and **Steve** have all been working on papers, and **Roummel** had two accepted. Roummel decided not to go to Louisville and stayed on as a Research Scientist. Sarah's paper is on recursive structures within biological pathways, Raman's on

time-dependent models of uranium reduction, Steve's on predicting hot spots in protein-pro-



tein interfaces, and Roummel's on methods for clustering and optimization of protein docking predictions.

We've also had a lot of undergrads work with us this year. Steve worked with three students, **Corina Prieto**, **Yinka Lesi** and **Brandon Wanta**. Corina looked into incorporating flexibility into hot spot predictions, Yinka and Bran-

don on engineering new hot spots into protein interfaces. Steve is now going into the lab to test these experimentally. **Mariko Hasebe** has been working with Sarah on categorizing the dynamic behavior of recursive motifs in biological pathways. Finally, **Laura LeGault** has been working with several of us toward the design of web-based services for protein docking.



**James Ntambi
Lab**

Greetings from the Ntambi lab!!

2006 has been one of both continuity and change for the Ntambi lab as we persist in trying to understand various aspects of carbohydrate and lipid metabolism using the stearoyl CoA desaturase-1 (SCD1) deficient mouse as a model.

Early this year, Dr. **Weng Chi Man** relocated to Phoenix, AZ after receiving her Ph.D degree in December 2005. She later successfully found a post-doc position at the medical school of Stanford University with Dr. Bertha Chen, studying the molecular basis of diseases involving changes in connective tissues such as stress urinary incontinence and female pelvic floor dysfunction, with the long-term goal of developing treatment for the patients.

In May, **Caroline Otzelberger** from University of Hohenheim, Germany joined our lab to complete her research thesis for her "Diploma" degree. "Diploma" is an academic degree in Germany that resembles a Masters

degree in the United States. For the last part of her Diploma degree, she is required to do research on a small project for a period of six to eight months and present her results in a form of a written thesis back home at the Nutritional Sciences department. Here in our lab, she's been working on determining whether SCD1 deficiency alone in the liver can account for the enhanced insulin signaling observed in the global SCD1 deficient mice.

As for other members of the lab—Dr. **Makoto Miyazaki**, Dr. **Matt Flowers**, Dr. **Xueqing Liu**, **Harini Sampath**, and **Kiki Chu**—each of us are continuing our research in our respective projects including the regulation of SCD1 by nuclear receptors and dietary fats, role of SCD1 in inflammation, and generation and characterization of various tissue-specific SCD knockout mice. **Cora Holt** our undergraduate student continues to work with various members of the lab to enhance her knowledge through first-hand laboratory experience. **Thezin Chonyi** is a hard-working high-school student who spends after school hours learning lab techniques.

Last, but certainly not least, our mentor Dr. **James Ntambi** continues to juggle between many tasks, which consist of providing guidance to his students, speaking about SCD at various conferences around the world, and taking students on a 3-week long study-abroad program during the Winter break each year studying health and nutrition topics in the developing country of Uganda, Africa. His international work, and the program in Africa in particular, are described on page 13.

We hope that you have enjoyed reading about us in this issue and wish you all the very best in your endeavors.





**George Phillips
Lab**

This year marks the sixth year that the Phillips Laboratory has been in operation in Madison. Things are really moving along now, including the graduation of Wisconsin Ph.D. students **Dr. Byung Wu Han** (now a postdoc at The Scripps Research Institute with Prof. Ian Wilson, **Dr. Euiyoung Bae** (currently evaluating postdoctoral opportunities), and **Dr. Jason McCoy** (now a Genome Sciences Training Program Postdoc in the Phillips Lab).

The crystallography team associated with the Center for Eukaryotic Structural Genomics, led by **Dr. Craig Bingman** and also comprising **Dr. Ed Bitto**, **Dr. Jason McCoy**, bioinformaticians **Dr. Xiaokang Pan** and **Dr. Gary Wesenberg**, graduate student **Elena Levin**, technician **Louise Meske**, computer systems administrators **Bryan Ramirez** and numerous enthusiastic and energetic UW undergrads have deposited about seventy-five protein structures in the Protein Data Bank and are really cranking in terms of getting unique proteins crystallized, solved, refined, and their functional relevance defined.

No one can keep up with them and their new discoveries. Computational studies related to structural bioinformatics are also in full swing. Postdocs **Dr. Dimitry Kondrashov** and **Dr. Demian Riccardi** are busy connecting theoretical predications of protein motions to reality, graduate student **Ryan Bannen** is busy studying connections between sequence, structure, and dynamics. **Roman Aranda**, along with **Elena Levin** has been making experimental movies of myoglobin in action, setting world records for the generation of time-resolved atomic coordinates on the 100 picosecond time scale! We also welcome two new students to the Phillips laboratory family, **Chris Bianchetti** (a cajun, we love his cooking) and **Aram Chang** (who cooked up some new crystals on his first try) from the UW Biophysics program, who will be working on new projects connecting protein structure, dynamics, and function. If you read this and have been in the Phillips laboratory in a previous life, drop in sometime, or at least keep us posted on your whereabouts.



**Wes Pike
Lab**

From modest beginnings here at the University of Wisconsin in July of 2001, the Pike laboratory has transitioned into a full-fledged member of the Department of Biochemistry. We can say with some certainty that we have made our final laboratory move – not only to this university but to great digs on the 5th Floor of the New Biochemistry Addition where we now have considerable space and, importantly, future room to grow. Several members of the department call this space the “Penthouse”. I can only say we do have a nice view of the lake, although a recent Bacteriology addition has obscured some of this grandeur (not that we spend a lot of time looking out the window). The laboratory has gone through considerable growth as well as ebb and flow over the past few years since the last report. We have integrated a number of graduate students as well as postdocs and research assistants into the laboratory, and have graduated several as well. Aside from the ongoing research that we have in place in the areas of vitamin D and bone, perhaps most exciting are some of the new research areas into which our current research has led us.

Since coming to Madison, we have thus far taken on the training of 6 Biochemistry graduate students, **Lee A. Zella**, **Sungtae Kim**, **Jackie Fretz**, **Mark Meyer**, and most recently, **Rob Nerenz** and **Katie Bishop**.

Lee Zella completed her Ph.D. degree in August of this year, and has elected to stay on as a Research Associate. **Sungtae Kim** completed his degree in November, and has taken a new position at the Salk Institute in America's most beautiful (and expensive) city, San Diego. We are anticipating that **Mark Meyer** and **Jackie Fretz** will complete the work for their doctoral degrees sometime this summer. Both of them have published papers under their “belts” and we expect additional studies to emerge soon. Both **Rob** and **Katie** are the newcomers to the laboratory and are faced with taking Preliminary Exams this coming spring. Their research projects are going very well, however, and thus we expect their Prelim proposals to be well outlined, well thought out and successfully defended. **Dr. Hironori Yamamoto**, a Research Associate from Japan who helped us move from Ohio to Madison, and **Dr. Makoto Watanuki**, an orthopedic surgeon also from Japan, joined us several years ago. Both have completed successful training programs here in Madison and have returned to their home country. **Miwa Yamazaki**, a Visiting Scientist from Professor Keichi Ozono's laboratory at the University of Osaka, Japan also joined us at that time. Unfortunately, Miwa recently left us for home as well. All of us thoroughly enjoyed Hironori, Makoto and Miwa's stays in Madison

and their important contributions to the laboratory; they are missed greatly and will not be forgotten. Thus, we now represent a highly undiversified laboratory. On the upside, Dr. **Melissa Martowitz** recently joined us as a Research Associate, having completed a Ph.D. degree with Dr. Emory Bresnick in the Department of Pharmacology here at the University. Melissa was interested in the role of upstream enhancers in the regulation of β -globin gene expression and her transition to the study of the mechanism of the regulation of RANKL gene expression by the vitamin D hormone has been a relative easy one. As a Research Associate, Lee plans to pursue, among other things, a characterization of the new regulatory regions within the vitamin D receptor gene that she has discovered.

Our research continues to focus on the biological and molecular actions of steroid hormones in the regulation of calcium homeostasis. Of course, these studies focus primarily on the actions of the vitamin D receptor, but also on the actions of both the estrogen and androgen receptors as well as the glucocorticoid receptor. Surprisingly, our research has also led us into studies of target genes for the hormone PTH as well as the inflammatory cytokines such as IL-1, IL-6 and TNF α and the cytokine oncostatin M. In brief, new genes have been identified that are key to the calcium homeostatic actions of the vitamin D hormone in the intestine, kidney and bone. These include the calcium ion channels TRPV5 and TRPV6 as well as the essential osteoclastogenic factor RANKL. Using chromatin immunoprecipitation coupled to DNA microarray hybridization (termed ChIP-chip), Mark and Makoto identified and characterized the molecular mechanism whereby 1,25(OH) $_2$ D $_3$ regulates the expression of the intestinal calcium channel TRPV6. Surprisingly, this gene is regulated by at least 5 different DNA sequences, and Mark continues to explore their utilization in not only intestinal cells but bone cells as well. A more recent success has been the application of ChIP to studies in the mouse intestine and kidney in vivo. At another level, Sungtae and Miwa screened the RANKL gene locus, identified and then characterized the enhancers located upstream of the RANKL gene that mediated the actions of 1,25(OH) $_2$ D $_3$. Interestingly, these enhancers were discovered to be located enormous distances upstream of the start site of RANKL transcription, opening up an exceptionally fertile area of novel research that

is now in the hands of Melissa, Rob and Katie. Lee used this technique of ChIP-chip screening to identify the regulatory elements located in the vitamin D receptor gene that mediate autoregulation by 1,25(OH) $_2$ D $_3$. This regulatory puzzle has existed since the mid 1980's when we first discovered that the vitamin D receptor autoregulated its own expression. As with the above findings, these regulatory regions were found to be located within introns of the vitamin D receptor gene over 30 kilobases downstream of the transcriptional start site. This discovery has prompted a new approach by Lee towards characterizing the regulatory regions of the vitamin D receptor gene. Finally, similar studies by Jackie led to the identification of novel regulatory elements within the LRP5 gene, a gene which represents a co-receptor for the Wnt signaling pathway that functions in osteoblast differentiation and regulation. Jackie continues this work as well as the research she has focused upon for the past several years aimed at delineating mechanisms whereby RANKL activates the process of osteoclast formation. While many additional projects are ongoing, these findings represent the major focus of our current efforts.

Of course, I have left out perhaps the most important change in our staff. Dr. **Rupa Shevde**, who accompanied me to the University of Wisconsin from the University of Cincinnati and was instrumental in not only setting up the laboratory but keeping it running smoothly for the past 5 years, left last year to take a position as Senior Scientist and Group Leader at WICELL Institute. As many of you know, WICELL specializes in advancing the development of the human embryonic stem cell technology pioneered originally by Dr. James Thomson and now frequently in the national news. Rupa has long wanted to work in a different research setting where her numerous strengths could be put to a greater challenge and this seems to be emerging as the right place. She now teaches the WICELL course in stem cell technology and a short course on "how to" in human embryoid body development. It is an exciting time, and Rupa gets to meet scientists from all over the planet who come to be trained in the art. Perhaps her most interesting challenge is as an advocate for science in Wisconsin public middle schools and high schools, where she works to excite the next generation of scientists. This type of work speaks to her greatest strengths. Nevertheless, we miss her greatly in the laboratory.

Finally, new happenings are occurring on the personal front. Lee Zella was just married in January, 2007, and has changed her name to Lee Ann Short. Mark Meyer is planning on getting married, although his life changing event is scheduled for July. We wish them long and prosperous lives together with their chosen partners.

In closing, I am very happy to be here in the Department of Biochemistry at the University of

Wisconsin. Our new laboratory, new students, and the excellent research environment created by the faculty of this department are likely to ensure our success here in the future. We thank Hector DeLuca for the role he played in getting us here. While we have much to accomplish in the next few years, we are confident that this will be the place to do it!



Ron Raines
Lab

The Raines lab is in a dynamic steady-state, with eight people leaving the group in 2006 and eight others joining the group. You can see all 25 of us at "work" in the most recent cartoon by our artist in residence, Annie Tam.

Departures.

Four graduate students successfully defended their Ph.D. theses in 2006. **Kim Dickson** is now an Assistant Professor at Macalester College in St. Paul, Minnesota. **Bryan Smith** is a Scientist at Deciphera Pharmaceuticals in Lawrence, Kansas. **Steve Fuchs** is a postdoctorate at the University of North Carolina in Chapel Hill, and **Eugene Lee** will leave shortly for postdoctoral work at Caltech.

Three postdoctorates also left us. **Jason Horng** is now an Assistant Professor at the National Tsing Hua University in Hsinchu, Taiwan. **Thimmalah Govindaraju** (a.k.a., Govind) is a Humboldt Fellow in Dortmund,

Germany. **Moushumi Paul** is a Scientist at the USDA in her home town of Philadelphia.

Arrivals.

We are delighted that five graduate students joined the Raines lab in 2006: **Jimmy Hernandez** and **Mike Levine** in biochemistry, **Nadia Sundlass** in biophysics, **Sayani Chattopadhyay** in organic chemistry, and **Amit Choudhary** in physical chemistry. Mike and Nadia (like Rebecca Turcotte) are also in the M.D./Ph.D. program.

In addition, two postdoctorates crossed the Atlantic Ocean to join us: **Daniel Gottlieb** from Dortmund, Germany and **Eddie Myers** from Bristol, England.

Thomas Baumann both arrived and departed in 2006, spending a few months with us as an "interdoc". Thomas has now returned to complete his doctoral work with Stefan Bräse in Karlsruhe, Germany (who sent us interdoc Christine Schilling in 2005).

Couplings.

Steve Fuchs and Erin Mettert (Kiley lab) got married in 2006. **Kelly Gorres** and John May (Kiessling lab) expanded a long-standing intergroup collaboration by announcing their engagement.

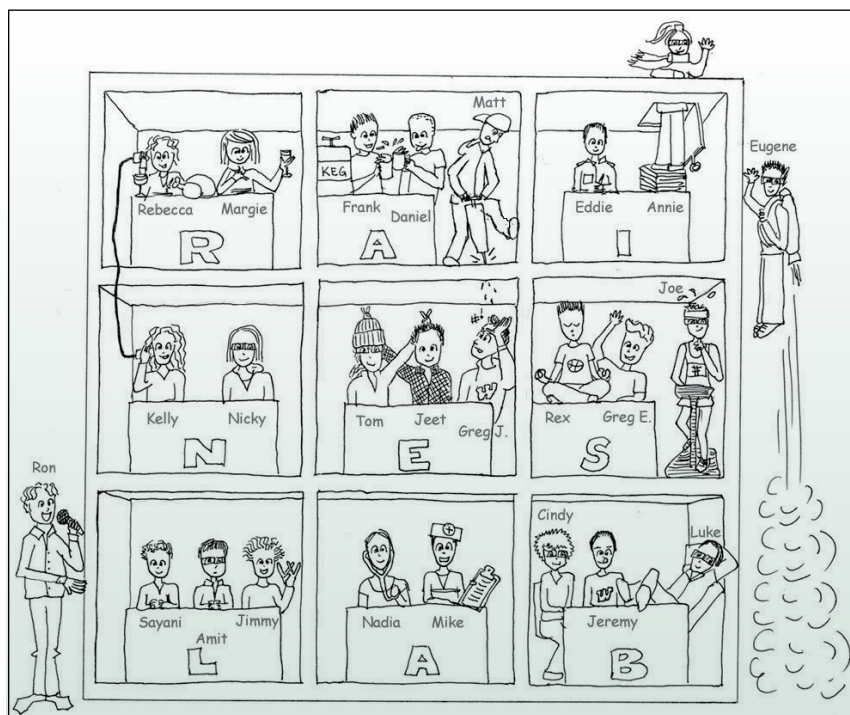
Progeny.

Rex Watkins and his wife Natalie brought Emilyn into the world. **Frank Kotch** and his wife Stefanie created Andrew.

Armchair Sports.

Though new to the "sport", Daniel captured the 2006 championship in the Raines lab Fantasy Football League, defeating sports veteran Rebecca Turcotte in the final round.

Contact Us! As always, we are happy to welcome lab alumni to drop in for a visit and update us on life after the Raines lab. Or, see us at the March 2007 ACS meeting in Chicago. Otherwise, please send us an e-mail, and visit our lab website for more news: www.biochem.wisc.edu/raines.





Bill Reznikoff
Lab

It is with mixed emotions that I write my lab's news this year. Cathy and I are really looking forward to our BIG move to West Falmouth, Massachusetts this summer, BUT, we love Madison and we have many great friends here. We will miss living here. Within the Department it is very, very tough for me. I cannot imagine a better place to have grown my career. Of course the facilities, research opportunities and University support have been great. But it is the friendships, colleagues and the special scientific openness that I shall miss the most. Thank you all very much. Of course my lab members will be especially missed. They are and have been great. Currently the lab members include: **Deb Hug**, who keeps the lab functioning; **Igor Groyshin**; postdocs **Agata Czyz** and **Soheila Vaezslami**; and my last Wisconsin graduate student, **Rich Gradman**. **Chris Adams** defended this year, trekked around South America with Olivia and is now a Stanford post-doc.

This year has been great on the research front. In a collaboration with John Marko (now at Northwestern), Chris Adams set up a single molecule system for studying Tn5 transposition. We were uncertain whether the work would just result in phenomenally beautiful pictures or whether we would also make fundamental discoveries. I think that we have made important discoveries. A big thing that we discovered is that transposase forms catalytically inactive complexes with non-specific DNA that are likely important in the biology of Tn5 transposition. How does transposase "find" transposon DNA in a veritable sea of other DNA sequences? At least for short distances the transposon ends are found through a direct transfer mechanism. How does non-specific DNA participate in transposition regulation? The non-specific DNA is a sink that inactivates the bulk of the transposase.

We are also back in the crystallography business. This has involved a collaboration between us (primarily Agata Czyz with help from Igor Groyshin) and Dima Klenchin in Ivan Rayment's lab. The goal is to explain why having a 5' phosphorylated non-transferred strand has a huge positive impact on strand transfer. Simplistic biochemistry would not predict an effect, but the structure demonstrates that the phosphate is likely important for moving the non-transferred end out of the way of the incoming target DNA. Agata and Dima hopefully will also show us, for the first time, a transposition complex with a bound transposition inhibitor.

In addition to performing crystallography, Agata is using small molecule diketoacid inhibitors to study the details of how transposase works. This has been a longstanding project in collaboration with Daria Hazuda's group at Merck. It amazes me how 6 chemically similar inhibitors can have such different modes of action.

Rich and Igor have had a very fruitful collaboration using genetic and biochemical analyses to map out transposase residues important for target capture. The results make a beautiful and somewhat surprising picture since residues away from the previously proposed target binding region have the biggest effects.

Soheila's interests are in performing a saturated genetic / biochemical analysis of all transposase residues predicted to make DNA end sequence contacts. This work should make a major contribution to our structure function studies of the transposase.

My goals next year are to: set up a small lab at the MBL in Woods Hole in order to continue Tn5 studies, and to study the eating patterns of Striped Bass and Blue Fish by fishing in the waters around Woods Hole. Who knows, maybe the latter will turn into a genomics project.



Doug Weibel
Lab

We moved into 473 Biochemistry Addition—formerly Anant Menon's lab—in July and have been busy building a lab, collecting data, and recruiting lab members over these past months. Let me introduce the current cast:

Basu Bhattacharyya hails from Madison—he graduated from UW-Madison in 2005 where he was a double major in biochemistry and Spanish. Basu is currently a senior research assistant in the group and is in the transition between his undergrad and graduate education.

Charlie Burns is a sophomore at UW-Mad-

ison majoring in biochemistry and Spanish. He grew up in Crystal Lake, IL and bears a striking resemblance to Liam Gallagher from the British band Oasis.

Matt Copeland is a first year graduate student in biochemistry who grew up in Baltimore, MD. Matt received his BS in biochemistry from McDaniel College in Maryland where he played lacrosse (and led the team as captain) and collected a large number of accolades.

Corinne Lipscomb is a first year graduate student in chemistry who hails from Springfield,

IL. Corinne received her BS in chemistry from Manchester College in Indiana where she also studied French and ran cross-country and track. As an undergraduate student she studied organic chemistry in Paris.

Sean McMaster hails from Kenosha, WI and is a freshman majoring in biochemistry and mathematics.

Joseph Molinda is a sophomore at UW-Madison majoring in biochemistry. Joe played college football during his freshman year. (Attention faculty: Joe can be hired out to move heavy lab equipment. I charge only \$50/hr.)

Hannah Tuson is a first year graduate student in biochemistry. Hannah grew up in Yorktown Heights, NY and received her BS in biochemistry from Lafayette College in Pennsylvania where she ran track and collected a number of honors.

Doug Weibel is the PI. You can read more about him in the article located earlier in this issue of the newsletter.

You can expect to see great science coming from this group of talented (and athletic and linguistic) scientists in the near future.



**Marv Wickens
Lab**

In the Wickens group, we work on how mRNAs are regulated in animals. The biological impact of regulation at the mRNA level now is incontrovertible. The control of translation, mRNA stability and localization are important mechanisms that help determine when, where and how much protein a gene produces.

Many of the same proteins control mRNAs in embryos and the nervous system, and likely in other somatic tissues as well. We want to know how these regulators work, and what they do in biology. We already know that the repressors have vital roles in stem cells and learning and memory, and we are hoping to get a biochemical understanding of how they operate.

We focus primarily on proteins that bind to and control mRNAs: some repress, and some activate. Over the last year, a trio of young scientists in the lab, **Aaron Goldstrohm**, **Daniel Seay** and **Brad Hook**, took a major step forward by identifying key molecular interactions

that underlie repression. Starting with the yeast *S. cerevisiae*, the threesome identified a specific contact between a repressor bound to the mRNA and to a specific protein in a large repression complex. From there, they showed that this mode of control likely was conserved throughout the animal kingdom.

Aaron and Brad are post-docs and continue to focus on protein-mediated repression. In recognition of the importance of his contributions, Aaron was recently awarded the **Paul Boyer Award**, given to an outstanding post-doctoral fellow in the department. He'll be giving a departmental seminar this spring, and I am already at work on embarrassing stories for his introduction.

Daniel moved on recently to study biological rhythms with Mike Young at Rockefeller. During his last months in the lab, Daniel opened up a new and exciting area concerning the function of non-coding RNAs and intergenic transcrip-

tion. He still has a few experiments to do, but the end is in sight, even if it is crowded by the bustle of Manhattan streets.

Since I last wrote, **Amy Cooke** and **JJ Chritton** joined the lab; both are now second year students. JJ is trying to extend our biochemical analysis to translational repression *in vitro*. We hope to recapitulate various forms of protein-mediated control in the test tube – the classic biochemist’s approach – with an aim to identifying the key components and dissecting their functions. Amy has been working with the same group of regulatory proteins, but focusing on how they control mRNAs during early development — and how that connects molecularly to what they do in adults. Her work has united her with oocytes and embryos of the South African clawed toad, which I am sure she will come to love (however frustrated they now periodically make her).

RNA-protein interactions also are vital in regulation, as they determine which mRNAs are controlled. **Laura Opperman**, a grad student, has learned a great deal about how one particular class of repressors that bind mRNAs recognize their particular targets. The remarkable thing is the degree to which the interaction is modular and rationally manipulable, at least by Laura. She has now expanded her work from yeast to frogs, and then to mammalian cells. She would like to use rationally designed proteins to target specific mRNAs for control at will. **Craig Stumpf** focuses on the specificities and functions of RNA binding repressors in the worm *C. elegans*. **Leah Gross**, an undergrad, works with Laura to learn the rules of RNA recognition.

Jae Eun Kwak and **Labib Rouhana**, both grad students, have been focusing on activators of mRNAs, and on a family of proteins that add poly(A) to mRNAs in the cytoplasm. We discovered this enzyme initially in *C. elegans*, in collaboration with Judith Kimble; since then, we have identified counterparts in many other species, including humans. We now know a great deal about how these poly(A) polymerases act and are controlled, and are exploring their biological functions in *Xenopus* and *Drosophila*. Labib has identified a positive-feedback loop in which the activator actually activates its own mRNA.

Along the way, Jae Eun has identified yet another, new class of polymerases — these add poly(U), not poly(A), to their substrates. We are dying to know what RNAs they control and how.

Jacque Baca, a grad student, is studying how proteins that recognize double-stranded RNAs contribute to mRNA control, and how they interface with other regulators. She has been focusing on *C. elegans*, and appears poised to approach these issues.

Fonda and **Sinziana**, two undergrads, help support the entire research enterprise by preparing media, and buffers, and doing the glassware.

Marv Wickens, a professor, no longer even remotely red-haired continues in much the same way as he always has. You can find him in his office, enjoying the conversations with the people who actually get things done in the lab, fretting over some issue — scientific, meta-scientific, or otherwise — or being helped by **Carol** to remain on track and semi-in control and on time, or wondering how his son, **Zach**, really is doing, or how those barnyard animals got loose in the lab again. For those of you who remember Zach as a little red-haired bundle in Marv’s lap, that was 18+ years ago, and Zach has just begun college at Macalester in the Twin Cities! Hard to believe. Indefatigable, time.

I will not try to recapitulate all the highlights of our illustrious alumni — there just are too many good things going on. I will say that visiting my ex’s is wonderful. I had the great pleasure of in situ observations of three ex-students, **Dave Zarkower** and **Vivian Bardwell**, at the University of Minnesota, and **Jeff Collier**, a brand spanking new faculty member at Case Western in Cleveland. A visit to **Sunnie Thompson**, now in University of Alabama, is on deck. Here in Madison, **Mike Sheets** and **Catherine Fox** are thriving in the Biomolecular Chemistry Department — and their young son Max is thriving even more, though he has lost Zach, a favored babysitter.

I am really tempted to say something about all of you here, because I love thinking about how all of you are doing, and picturing you again in my mind’s eye, not just in the lab but off doing your own adult (or pseudo-adult) thing. But that is not practical here. There are those of you scattered around the globe and those in courtrooms, those in the Senate and those doing post-docs, those who have joined faculties, and those who are losing them, like me. You know who you are.

Suffice it to say that I would love to hear from you, and even more, to see you. Come by sometime, or drop an email, or a photo. You are always here anyway, even if you don’t know it.

Faculty Email & Telephone Numbers

Rick Amasino.....	amasino@biochem.wisc.edu	608/265-2170
Aseem Ansari	ansari@biochem.wisc.edu	608/265-4690
Alan Attie.....	attie@biochem.wisc.edu	608/262-1372
Sebastian Bednarek.....	bednarek@biochem.wisc.edu . . .	608/263-0309
Sam Butcher.....	butcher@biochem.wisc.edu	608/263-3890
Margaret Clagett-Dame .	dame@biochem.wisc.edu	608/262-3450
Mo Cleland.....	cleland@biochem.wisc.edu	608/262-1373
Mike Cox	cox@biochem.wisc.edu	608/262-1181
Betty Craig.....	ecraig@wisc.edu	608/263-7105
Hector DeLuca	deluca@biochem.wisc.edu	608/262-1620
Brian Fox	bgfox@biochem.wisc.edu	608/262-9708
Perry Frey.....	frey@biochem.wisc.edu	608/262-0055
Paul Friesen	pfriesen@wisc.edu	608/262-7774
Colleen Hayes	hayes@biochem.wisc.edu	608/263-6387
Hazel Holden	hazel_holden@biochem.wisc.edu	608/262-4988
Ross Inman	rbinman@wisc.edu	608/262-9881
Laura Kiessling.....	kiessling@chem.wisc.edu	608/262-0541
Judith Kimble	jekimble@wisc.edu	608/262-6188
John Markley	markley@nmrfam.wisc.edu	608/263-9349
Tom Martin	tfmartin@wisc.edu	608/263-2427
Julie Mitchell	mittchell@biochem.wisc.edu	608/263-6819
Rebecca Montgomery	rimontgomery@wisc.edu	608/262-6773
Dave Nelson.....	nelson@biochem.wisc.edu	608/263-6879
James Ntambi	ntambi@biochem.wisc.edu	608/265-3700
Ann Palmenberg.....	acpalmen@wisc.edu	608/262-7519
George Phillips.....	phillips@biochem.wisc.edu	608/263-6142
Wes Pike	pike@biochem.wisc.edu	608/262-8229
Ron Raines	raines@biochem.wisc.edu	608/262-8588
Ivan Rayment.....	ivan_rayment@biochem.wisc.edu	608/262-0437
Tom Record	record@chem.wisc.edu	608/262-5332
George Reed.....	reed@biochem.wisc.edu	608/262-0509
Bill Reznikoff.....	reznikoff@biochem.wisc.edu . . .	608/262-3608
Mike Sussman	sussman@biochem.wisc.edu	608/262-8608
Doug Weibel.....	weibel@biochem.wisc.edu	608/890-1342
Marvin Wickens	wickens@biochem.wisc.edu	608/262-8007
Chris Wiese.....	wiese@biochem.wisc.edu	608/263-7608

Emeritus

Julius Adler	adler@biochem.wisc.edu	608/262-3693
Laurens Anderson	landers2@facstaff.wisc.edu	608/262-3041
Helmut Beinert	hbeinert@facstaff.wisc.edu	608/263-6357
Robert Burris	burris@biochem.wisc.edu	608/262-3042
Alfred E. Harper	harp3600@attbi.com	
Paul J. Kaesberg		608/262-2205
Henry Lardy.....	halardy@facstaff.wisc.edu	608/262-3372
Roland R. Rueckert.....	rrruecke@facstaff.wisc.edu	608/262-6949
Heinrich K. Schnoes		608/262-0650
John W. Suttie.....	suttie@biochem.wisc.edu	608/262-2247

If you have questions or information please feel free to contact us.

<http://www.biochem.wisc.edu>

Department of Biochemistry
University of Wisconsin–Madison
433 Babcock Drive
Madison, WI 53706-1544 USA

Phone: 608/262-3040

FAX: 608/262-3453

Change of Address, Information, and General Inquiries

Cheryl Adams Kadera
(608) 262-9835

E-mail: adams@biochem.wisc.edu

IPiB Graduate Program (Information and Applications)

Flavia Arana (608) 265-2281

E-mail: graduateadmissions@biochem.wisc.edu

Undergraduate Program/Internships

Dan Barnish (608) 265-9846

E-mail: undergraduateprogram@biochem.wisc.edu

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Janice Carberry (608) 262-7129

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UNIVERSITY OF WISCONSIN-MADISON

433 Babcock Drive

Madison WI 53706-1544 USA

