You will immediately note that instead of receiving the Departmental Newsletter in March or April as in the past, it is being changed to near year-end. When many alumni attended the Departmental reception at the spring ASBMB meeting, it made sense to put the newsletter together prior to this meeting but most alumni have now opted for smaller, summer time meetings instead of the larger society meeting.

First, an update on the Department. As of this writing, there are 48 faculty with appointments in Biological Chemistry. Included in this number are 21 faculty members for whom the Department is completely responsible for space and salary support, and another 27 faculty with joint appointments in centers, institutes or other departments for whom we have lesser financial responsibilities. About two thirds of these individuals have their tenure homes in Biological Chemistry. In addition to our faculty, the Department has 35 graduate students in the Biological Chemistry Ph.D program. There are also three students in the Cellular and Molecular Biology Ph.D. program, eight in the Chemical Biology program and five in the Biophysics program who are training in laboratories of our faculty.

Early this year Dr. Ursula Jakob from the Department of Molecular, Cellular, and Developmental Biology in LS&A became jointly appointed in Biological Chemistry. Ursula’s interests are in protein folding and processing and her studies mesh with those of a number of other Departmental faculty. You might want to take a look at her 2008 Cell paper that describes how household bleach functions through a novel redox mechanism to kill bacteria. We continue to move forward with hiring with the goal of reaching 25 “wholly owned” faculty within the next few years. We are actively conducting national searches for a new assistant professor and a senior faculty member to fill the prestigious Lu Professorship.

Like everyone else who has struggled through the recent recession (I read where it was over but have not seen the evidence), the department faces significant financial challenges. Fortunately, our faculty have been aggressive and successful in seeking NIH funds – both traditional R01’s and American Recovery and Reinvestment Act (ARRA) stimulus grants. The medical school mandates and the faculty strive to cover at least half of their salaries on grants—a big change from just a few years ago—and to generate indirect costs.
sufficient to cover the facilities and administrative costs of running a complex research enterprise like ours. In addition, our undergraduate course offerings generate significant tuition revenue. With the help of many faculty who have been willing to take on larger teaching responsibilities—Dave Ballou is a notable example—we have come close to operating in the black this past year.

I hope you enjoy reading the recent goings on in the Department in the following pages. In these pages you will find updates on faculty and students, a remembrance of Biological Chemistry graduate and Nobel laureate Marshall Nirenberg, information on our four endowed lectures, and more. I also hope that you will keep us informed, and through us, your former friends and colleagues, of special happenings in your careers. Please feel free to send me a note (smithww@umich.edu), and I will make sure that all relevant information is included in next year’s newsletter. Alternatively, you can send us an update at the Alumni and Friends page on our new and improved BioChem website (http://www.biochem.med.umich.edu).

Let me close by thanking Jud Coon in particular for all the work he puts in to making sure that we have a high quality and informative newsletter each year. Enjoy!

Best wishes for the upcoming year and regards,

Bill
A fine example of philanthropy at work is the Lee Murphy Memorial Prize, one of six graduate student awards in the Department of Biological Chemistry. Since 1985, this prize has been given annually to the graduate student deemed by the Student Awards Committee to embody the highest ideals of scientific integrity and to have published a highly significant paper or series of papers. The award is named in honor of Lee A. Murphy, an alumnus of the department (Ph.D., 1978) who conducted research in the laboratory of Irwin Goldstein on the isolation and purification of lectin. Lee died suddenly of a brain hemorrhage on September 26, 1983, and an endowment was established in his name shortly thereafter. In 2009 the department received a generous gift from Kevin J. Murphy to grow the prize endowment even larger.

As noted elsewhere in this newsletter, the 2010 Lee Murphy Memorial Prize awardee is Zhonghua Yan, a graduate student in Ruma Banerjee’s laboratory. Yan is elucidating the role of redox remodeling in the adaptive immune system needed to promote T cell activation and proliferation. Yan demonstrated that regulatory T cells that function to suppress autoaggressive T cells and to keep autoimmune responses in check interfere with the process of redox remodeling. He thus identified a previously unknown immunosuppressive mechanism. Yan’s first paper was published in Nature Chemical Biology, was highlighted in a News and Views article, was the subject of a press report released by the UM Medical Center and elicited, within a month of publication, two invitations to write review/perspective articles in this emerging area of immunology. In response to these invitations, Yan authored a “Current Opinions” piece on this subject, which was published in Biochemistry.

We extend our sincere thanks to all those who have given to the Lee Murphy Memorial Prize endowment and look forward to many more years of awarding this prize to the very best of our graduate students.
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The Department of Biological Chemistry relies upon the philanthropic generosity of donors to fund many aspects of its operations. Gift funds are essential to supporting activities beyond our basic operations. From endowed professorships and lectureships, to graduate student fellowships, seminar speakers, and gifts in direct support of research, donations help make the department an intellectually exciting and vibrant community. As a benefactor of the Department of Biological Chemistry, we ask that you consider directing your gift one of several ways:

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For 2010 charitable deductions and credits, the IRS has ruled that credit card gifts are deductible only in the year the bank processes the transaction. To be processed for tax year 2010, credit card gifts by mail must reach the University by December 15th; OR you may call (888) 518-7888 (toll free) or (734) 647-6179 (local), 9 AM - 4 PM EST, between December 15th and 31st, 2010 to donate over the phone. Please have the information requested on the enclosed gift card on hand for your call. Your gift by check must be postmarked by December 31, 2010.

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In Memoriam | Remembering Marshall Nirenberg

Marshall Nirenberg, our Department's most celebrated graduate, died January 20 of this year at the age of 82 of intestinal cancer. In this newsletter, I write what we have learned about his graduate student days in Ann Arbor in 1952–57. I urge readers who knew Marshall during those years to send me (agranoff@umich.edu) or Jud Coon (mjcoon@umich.edu) relevant observations or anecdotes that can be added to our Departmental file. I also add my personal reminiscences.

I last saw Marshall in December of 2008, at a meeting of the American College of Neuropsychopharmacology in Scottsdale, AZ, which he attended as the spouse of his neuroscientist wife, Dr. Myrna Weisman. Fortunately for the attendee. Marshall was persuaded to give a special lecture, in which he described the sequence of events by which he unraveled the messenger RNA code that determines the amino acid sequence of proteins. A close approximation of that exciting talk can be found in his Trends in Biochemical Sciences article as well as in his Nobel Lecture.

I met Marshall in 1957, when he first came to NIH, where we overlapped until my wife Ricky and I left Bethesda for Ann Arbor in the fall of 1960. Marshall remained at NIH for his entire career despite offers to move elsewhere (more about that below). He said that he preferred doing research to writing grant proposals, and was content in the NIH intramural program. We chatted briefly at various scientific meetings over the years, as well as during my sabbatical at NIH in the late 1980's.

Marshall received a B.S. in Biology and Chemistry from the University of Florida at Gainesville in 1948, and an M.S. in Zoology in 1952, having written a thesis on ecological and taxonomic aspects of the caddis fly. He applied for graduate training to the Department 1952, in the final years of Howard Lewis' 32-year reign as Chair. His application was apparently judged to be marginal, and I understand that he was admitted on a probationary status. In 1955, during the period that Marshall pursued his thesis research, Halvor Christensen became the Departmental Chairman, and took on the task of reinvigorating the Department by new faculty appointments, with an emphasis on research. Marshall completed his doctoral thesis entitled "Heterogeneous Systems in Ascites Tumor Cells" under the mentorship of James F. Hogg, then an assistant professor. Marshall's thesis committee, in addition to Jim Hogg, consisted of Adam Christman, Merle Mason, and Lila Miller, all of the Department, F. F. Blicke, Professor of Pharmaceutical Chemistry, and W. J. Nungester, Professor of Bacteriology. His Ph.D. was granted on April 15, 1957, and shortly thereafter Marshall moved on to Bethesda as a Cancer Society Fellow in the NIH laboratory of Hans DeWitt Stetten. He initially studied metabolism of Ehrlich ascites cells, then purified enzymes related to the degradation of γ-hydroxybutyrate with Bill Jacoby, with whom he published several papers. Marshall then met Gordon Tomkins, a brilliant and knowledgeable investigator, who offered him an NIH position after his fellowship ended, with freedom to pursue his own research interests. Marshall and I knew each other from chance encounters in the enormous Building 10, in the library, or evenings at the NIH cafeteria where unmarried post-docs tended to eat dinner, often between ongoing experiments. I found him to be somewhat quiet, but not reluctant to venture an opinion, and to possess a good sense of humor. I recall an informal research presentation he presented to a weekly noon biochemical journal club organized by Giulio Cantoni, well-known for his pioneering work on methylation. As I recall, Marshall proposed novel approaches to the study of intermediary metabolism of Ehrlich ascites tumor cells. As we were leaving the room, the biochemist Seymour Kaufman said to me, "You know, if one of those cockamamie ideas of Marshall's ever works, he'll be famous!" It may have been somewhat of a backhanded compliment, but nevertheless was prescient of Marshall's future.

The first time I saw Marshall after my move to Ann Arbor in 1960 was in August 1961, in Moscow at the fifth Congress of the International Union of Biochem-
istry (IUB). I digress here to describe the circumstances of this Congress, which were unusual. The USA and USSR were in the midst of the Cold War. Fifteen months earlier, a US high altitude U2 spy plane had been shot down while monitoring Soviet nuclear arms activity. To his eventual embarrassment, President Eisenhower announced that the U2 was an off-course weather plane. Khrushchev had withheld the news that the pilot was alive, having parachuted out at a survivable altitude, and that enough of the crashed plane was recovered for the Russians to identify its spyware. In addition, four months before the Congress, Yuri Gagarin, a Soviet cosmonaut, orbited the earth in Vostok 1 and returned safely. The streets of Moscow were still covered with placards bearing his portrait. It would be eight years before the US moon shot got us back into the space race. There were nervous jokes among the Western European and American attendees about being followed or rooms that might have been bugged. To my recollection there were no major political mishaps. Nevertheless, attendees with travel or accommodation issues had to deal with the stolid, humorless representatives of Intourist, the official (and only) Soviet travel agency. Our passports were collected and were not returned until the close of the meeting.

The meeting venue and accommodations consisted of Moscow University classrooms and student dormitories, and both were marginally functional. A major problem in the research presentation sessions was that the Soviet slide projectors were non-zoom and designed for large lantern slides, while most of us had brought 35 mm slides. Consequently, speakers had to refer to miniscule images projected on to what appeared to be bedsheets, the combination of which demoralized the presentations. Attendance of the individual sessions dwindled. Like most of the presenters, Marshall was disappointed that his striking discovery would go unnoticed. I saw him outside meeting rooms, and he dispiritedly suggested taking a break and visiting the mausoleum in Red Square, where the refrigerated remains of both Lenin and Stalin were on display. I later learned that shortly thereafter, Francis Crick had invited Marshall to present his finding in Crick’s plenary session, thus giving Marshall’s work the crucial exposure it deserved. His message: polyU stimulates formation of polyphenylalanine! The elucidation of the code had begun. Heinrich Matthaei and Marshall had prepared 20 tubes, each containing all 20 amino acids in which only one amino acid was radio-labeled. The mixtures were added to cell-free homogenates to which a purported messenger RNA was added. According to a backstory, prior to performing his fateful experiment, Marshall asked Gordon Tompkins to suggest what he might use as an inactive control RNA, whereupon Tomkins suggested polyU. That was lucky, since UUU codes for phenylalanine, the least soluble of the amino acids, as is its polymer. Since a TCA precipitate was used in the early experiments to separate the polypeptides from the labeled amino acid precursor, even a very short radiolabeled polyphenylalana-

nine polymer would be insoluble, and thus be detected.

Bad luck apparently temporarily befell the laboratory of Marshall’s competitor, the celebrated biochemist, Severo Ochoa. PolyA, used in a comparable experiment, codes for lysine. Unfortunately for them, TCA does not precipitate polyllysine. The competition between Nirenberg and Ochoa has been described as a David and Goliath struggle. It would have been easy for Marshall to rest on his laurels, having already shown that a code existed. Instead, he pursued identification of the other triplet codons over the next five years until the functions of each were established. He recognized that as the novice in this contest, he could ill afford mistakes. He writes: “From the beginning I vowed never to cut corners or reduce the vigor with which experiments were done to win the competition.” Marshall had spoken about his graduate training with Jim Hogg, and of his gratitude for Hogg’s stress on thorough and rigorous experiments, and confirmation by repetition of positive results. Hogg was delighted and tickled by his former student’s fame. In a letter to Marshall in January 1962, he wrote:

Dear Marsh,

In view of the very extensive recent publicity, we are considering putting a sign on our house, as follows “Painted by Marshall V. Nirenberg, AD 1953.” Would you please send us a letter of authentication? We could then perhaps obtain a tax exemption as an historical site.

The letter goes on to refer to a rift between Marshall and Halvor Christensen that went unexplained. Looking into this matter, I learned that Marshall had been offered a faculty position in the early 1960’s by the Chair of another University of Michigan department, had accepted the offer, then reneged, unfortunately after his name had been written into a major grant proposal, and presumably having led to other unfortunate consequences for that department’s prospective faculty search process. Christensen, embarrassed by the behavior of one of his department’s graduates, attempted in vain to get Marshall to reconsider and fulfill his obligation. Taking into consideration the intense competition to define the triplet code as he did and with great care to avoid errors, and also taking into account the resources he was receiving from his NIH colleagues, who foresaw him as NIH’s first Nobel laureate, most would forgive him today. In fact, he was eventually awarded an honorary degree from UM in 1965. In the end, he brought great honor to our Department as well as to the entire University.

After completing his spectacular work on the universal code for protein synthesis Marshall began to con-
sider new research horizons, and was attracted to neuroscience. At that time, neuroscience research was blossoming on many fronts. Molecular biologists, behaviorists, geneticists, and even physicists became entranced with the molecular basis of brain function, especially memory, using a number of animal models, including fruit flies, rodents, fish, sea slugs, and many others. Others examined single cells or brain slices to study neuronal model systems. Marshall looked into a number of neuroscience-related research avenues, and settled on cultured neuroblastoma cells for a starter. He continued to make important contributions on a variety of neurobiological themes for an additional 45 years, until his death in January.

Marshall Nirenberg last visited the University in May, 1997, as a speaker in a Neuroscience symposium held in the Rackham Amphitheatre organized jointly by the Mental Health Research Institute (now the Molecular and Behavioral Neuroscience Institute) and the Department. The event was cosponsored by the Warner Lambert Company and the Biomedical Research Council of the UM Medical School.

One last recollection — in 1976, Marshall and I found ourselves with a free evening in Hamburg during the tenth IUB Congress, and we had dinner together at a fish restaurant. We reminisced about our years at NIH, and about neuroscience, which we both now shared as a common interest. As for dinner, I recommended the Seetzhunge, a Baltic variant of Dover sole. It was truly delicious. Every time I ran into Marshall thereafter, he greeted me by first recollecting that wonderful evening.

I feel privileged to have known one of the greatest scientists of the twentieth century.

1. Nirenberg, M. 2004 Historical review: Deciphering the genetic code - A personal account. TIBS 29: 46-54
2. Nirenberg, M. Nobel Lecture 1968
3. Nirenberg, M. W. and Matthaei, J. H. 1961 The dependence of cell-free protein synthesis in E. coli upon naturally occurring or synthetic polyribonucleotides. PNAS 47: 1588-160a
Dr. Ruma Banerjee has been elected to the Council of the American Society for Biochemistry and Molecular Biology (ASBMB), whose primary function is to advise and work with the President of the society. ASBMB publishes *Journal of Biological Chemistry, Molecular & Cellular Proteomics*, and *Journal of Lipid Research*; additionally, its monthly members magazine, *ASBMB Today*, covers society news, committee activities, member achievements and news of interest to its 12,000 members. ASBMB’s Minority Affairs Committee works to increase cultural diversity in the fields of biochemistry and molecular biology by increasing participation, visibility and status of minorities within the scientific community. Dr. Banerjee also serves on ASBMB’s Public Information Task Force, whose goal is to foster scientific literacy and enhance public trust in the scientific research enterprise.

Dr. Banerjee also joined the editorial board of *Antioxidant and Redox Signaling*, the premier journal in the field of Redox Biology.

**Yali Dou** received the 2010 American Association for Cancer Research Gertrude B. Elion Cancer Research Award for her project “Targeting MLL in acute myeloid leukemia.” In BioChem her focus, using a combination of biochemical, cellular, and genetic analyses, is to analyze the structure, function, and regulation of MLL complex; study the cross-talks between MLL and other histone modifying activities such as histone acetyltransferase and histone ubiquitinase; and elucidate the mechanism of MLL deregulation (deletion, amplification and translocation) in leukemogenesis.

A consortium of BioChem faculty and one faculty member from Internal Medicine/Microbiology and Immunology (Bob Fuller, PI; Kathleen Collins, David Engelke, Ruma Banerjee, Carol Fierke, Aaron Goldstrohm, Tom Kerppola, Ming Lei, Stephen Ragsdale and Anne Vojtek) recently obtained an NIH equipment grant for a fluorescence microscope system that will have a number of advanced features for imaging and analysis of live cells and fixed samples. The widefield inverted microscope will feature a motorized stage with environmental control and continuous autofocus for extended, multi-spot time lapse imaging of both cultured animal cells and microbial cells. A computer-driven laser system will permit cell photoablation, 405 nm photoactivation of photoactivatable fluorescent proteins, and photobleaching of yellow, green and red fluorescent proteins for FRAP (fluorescence recovery after photobleaching) and FLIP (fluorescence loss in photobleaching) experiments. Rapid Z-axis stepping by a piezo Z-stage will make it possible to obtain Z-stacks rapidly for fast 4D imaging coupled with deconvolution. A rapid (1 ms) excitation filter switcher coupled with an image emission splitter will make it possible to obtain, simultaneously, images with two different emission filters for rapid 4D FRET (fluorescence resonance energy transfer) microscopy. The system will also feature a state-of-the-art Photometrics Evolve512 backthinned, cooled EMCCD camera which will provide high sensitivity and signal to noise. This imaging system will provide a flexible platform for both high sensitivity and high resolution for imaging static and dynamic samples.

**Irwin Goldstein** was scheduled to deliver a series of lectures last April in the Biochemistry Department at the University of Norway in Oslo. Irwin recalls “Several days before I was to leave, there was a volcanic eruption in Iceland. The volcanic ash cloud enveloped a good part of Europe and it became apparent that I could not leave the United States. The dates for my lectures had been set many months before in a lecture series in Glycobiology and the coordinator, Prof. Ute Kringle, was extremely upset to learn that I could not leave the US for Norway. Then I learned, to my amazement, that it would be possible for me to deliver my lectures by video conferencing. And so...
on the appointed days, a crew from the Medical School's IT group came into my office and set up the television communication system which not only allowed me to present my two lectures, but also permitted students to ask questions! This was to me a miracle of communication. But then, this is the twenty first century and nothing should have surprised me.”

Aaron Goldstrohm was awarded an Edward Mallinckrodt Jr. Foundation Grant, providing up to three years of support to study the enzyme Nocturnin. Nocturnin degrades messenger RNAs and controls diet-induced obesity, a rapidly growing health epidemic. Dr. Goldstrohm’s team aims to understand Nocturnin’s molecular function with the hope of using this information to target the enzyme to control obesity. Dr. Goldstrohm earned his doctorate at Duke University, and pursued his postdoctoral work at the University of Wisconsin–Madison.

We are pleased to welcome Ursula H. Jakob, as an Associate Professor without tenure in the Department of Biological Chemistry. Dr. Jakob currently also holds an appointment as Associate Professor with tenure in the Department of Molecular, Cellular and Developmental Biology. She received her Ph.D. in Biochemistry in 1995 under the direction of Dr. J. Buchner in the Biophysics and Physical Biochemistry Department at the University of Regensburg, Germany. As a DFG-sponsored Postdoctoral Fellow, she performed her postdoctoral training with Dr. James Bardwell in the Biology Department at the University of Michigan.

Author of over 45 peer-reviewed publications in such top-flight journals as Science, the Journal of Biological Chemistry, and the Proceedings of the National Academy of Science, Dr. Jakob performs research on the biochemistry of redox regulation and oxidative stress. Her laboratory is presently focusing on the function and 3-dimensional structure of recently identified heat shock proteins. Prior to becoming a member of the University of Michigan faculty, she discovered the redox-regulated chaperone Hsp33. Her discoveries reported in Cell (1999) helped establish the field of re-
dox-regulation of protein function. Her findings gave protein unfolding, long known to cause protein inactivation, a new role by showing that it causes the activation of Hsp33 (Ilbert et al., NSMB, 2007). Dr. Jakob's studies have provided significant conceptual advances in the areas of thiol chemistry, metal biology, chaperone function, and protein folding. Hsp33-like zinc-centers were long considered to be redox-inert and structural, but they are now recognized as potential targets of reactive oxygen species and are found in numerous redox-regulated proteins. One very significant discovery published in Cell (2008) was the finding that hypochlorous acid, the active ingredient of household bleach, exerts its antimicrobial function at least in part by causing the oxidative unfolding of key bacterial proteins. Dr. Jakob has also developed several innovative techniques that can be used to provide an in vivo snapshot of the thiol status of proteins (PNAS, 2008). These tools provide biologists with an unprecedented ability to directly detect, monitor, and quantify the effects of oxidative and nitrosative stress in vivo.

Dr. Jakob's discoveries in redox-biology have enabled her to answer fundamental questions about redox-regulation and the role oxidative damage plays in host defense and aging. And we could not be more delighted to call her one of our own.

In the search for cancer inhibitors, researchers are shedding light on the enzyme telomerase. Here at BioChem, HHMI Early Career Scientist Ming Lei investigates an important aspect of how cells control the length of telomeres, the structures located at the ends of chromosomes. Telomere length is reduced in aging and in tumor cells, so understanding its control is important. Lei's work focuses on the protein, Fbx4, which keeps the telomeres operating correctly. It starts with the enzyme telomerase, which affects the caps, or telomeres, at the end of a chromosome. Telomeres shorten over time. But telomerase prevents this from happening, making the cell immortal. If cancer is triggered in the cell, the presence of telom-
erase leads to the growth of the cancer. Telomerase is kept in control by the protein TRF1, which keeps the telomeres operating correctly. But another protein, Fbx4, can bind to TRF1 and degrade it, causing the telomeres to lengthen. Now, researchers have discovered, a third protein, TRF2, can step in and override Fbx4 by binding to TRF1 first and preventing Fbx4 from attaching to it. This finding paves the way for developing a drug that acts like TRF2, keeping everything in check and stopping the first domino from falling. “In 90 percent of cancers, no matter what caused the cancer to form, it needs telomerase activity to maintain the cell. Without telomerase, the cell will die. Our work is key to understanding a detailed mechanism for how these molecules interact and how to design a drug to block Fbx4,” reports Lei. The results of his study appeared in a February issue of *Developmental Cell*.

**Rowena Matthews,** G. Robert Greenberg Distinguished University Professor emerita has been elected to the American Philosophical Society, the oldest learned organization in the United States. The APS was founded in 1743 by Benjamin Franklin to promote useful knowledge in the sciences and humanities. Today the Society has 987 members; Matthews is one of only 35 new members elected this year.

**Steven Ragsdale** was elected as a Fellow of the American Association for the Advancement of Science for his “studies of complex metalloenzymes that catalyze challenging reactions in anaerobic organisms.” Election as a Fellow of AAAS is an honor bestowed upon members by their peers. Fellows are recognized for meritorious efforts to advance science or its applications. Dr. Ragsdale was recognized for his contributions at the Fellows Forum on 20 February 2010 during the AAAS Annual Meeting in San Diego.

Following that, Ragsdale launched into a three year collaboration with **Eric Zuiderweg,** Jeff Martens and **Jeanne Stuckey.** The NIH funded study, “Elucidation of the role of the heme regulatory motif in heme oxygenase-2,” focuses on heme oxygenase and its role in oxygen sensing.

Each year the Dean of the University’s Medical School chooses a select number of faculty to recognize those “who demonstrate exceptional accomplishment in the areas of teaching, research, clinical care and community service.” This year Dean James O. Wooliscroft selected five faculty members for his award, and BioChem’s own **Raymond C. Trievel, Jr.** is among them. Trievel earned his doctorate at the University of Pennsylvania, and conducted his postdoctoral studies at the National Institutes of Health. Dr. Trievel’s special interest is the chemical and structural biology of enzymes that covalently modify histones, transcription factors, and other nuclear proteins.

“My current research focuses on elucidating the molecular mechanisms underlying the specificities of histone methyltransferases and demethylases and on developing new assays and reagents to characterize these enzymes.” Also of note is that Trievel was named the recipient of the 2010 Etter Early Career Award from the American Crystallographic Association. The Etter award recognizes outstanding achievement and exceptional potential in crystallographic research demonstrated by a scientist at an early stage of their independent career. The award was established in 2002 to honor the memory of Professor Margaret C. Etter (1943–1992), who was a major contributor to the field of organic solid-state chemistry.

Hsp70s (70 kDa heat shock proteins) maintain cellular homeostasis by orchestrating protein folding, protein refolding, protein transport and protein targeting. Changes in expression of these chaperones are associated with pathologies, classically heat shock, but also cancer and protein-folding diseases. Hsp70s favor the native folding of proteins by disentangling misfolded polypeptides by ATP-driven cycles of substrate binding and release. **Erik Zuiderweg’s** group has lately reached a milestone in understanding how ATP binding in the

*Continued on page 25*
Endowed Lectures

2009 Irwin J. Goldstein Lectureship in Glycobiology

Ajit Varki, M.D.

Sialic Acids: A Hot-Spot in Human Evolution and Disease

Ajit Varki, M.D. is Distinguished Professor in the Departments of Medicine and Cellular & Molecular Medicine, Co-Director of the Center for Academic Research & Training in Anthropogensy (CARTA), Co-Director of the Glycobiology Research and Training Center, and Associate Dean for Physician-Scientist Training at the University of California, San Diego, (UCSD). Dr. Varki received basic training in Physiology, Medicine, Biology, and Biochemistry at the Christian Medical College, Vellore, India, and at the University of Nebraska, and Washington University in St. Louis. Dr. Varki also has training and board certification in internal medicine, hematology, and oncology.

Dr. Ajit Varki's research interests focus on a family of cell surface sugars called sialic acids, and their roles in biology, evolution and disease. Currently active projects are relevant to the roles of sialic acids in microbial infectivity, the regulation of the immune response, the progression and spread of tumors, and the unique aspects of human evolution. His group is particularly intrigued having discovered multiple differences in sialic acid biology between humans and our closest evolutionary cousins, the great apes. These differences are a signature of the events that occurred during the last few million years of human evolution, and appear relevant to understanding several aspects of human physiology and disease.

Dr. Varki is an elected member of the Institute of Medicine (IOM), National Academy of Sciences, which is both an honorific society and an advisory body on health and health policy matters. His memberships also include the American Academy of Arts and Sciences, the American Society for Clinical Investigation, and the Association of American Physicians. Dr. Varki is the recipient of the 2005 Karl Meyer Award in Glycobiology, which is presented in recognition of an active leader who has made significant and ongoing contributions to knowledge in the field of glycobiology.

2009 William E.M. Lands Lectureship on the Biochemical Basis for the Physiology of Essential Nutrients

Richard J. Wurtman, M.D.

Administering Phosphatide Precursors Increases Synaptic membrane, Dendritic Spines, and probably, Brain Synapses?

Richard J. Wurtman, M.D. is Cecil H. Green Distinguished Professor of Neuropharmacology, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology. Dr. Wurtman received his M.D. in 1960 cum laude from Harvard Medical School. Dr. Wurtman’s research areas include Neurotransmitters, Phospholipids and Neuronal Membranes, Neurodegenerative Diseases, Nutrition, Melatonin and the Pineal Gland, and Appetite Disturbances. He currently serves on the Editorial Boards of Brain Research, Integrative Psychiatry and Journal of Molecular Neuroscience.

Dr. Richard Wurtman’s talk described the ability of three circulating nutrients – uridine, DHA, and choline – consumed together, to promote synaptogenesis. New synapses continue to form in the human brain throughout the lifespan, by the coupling of a postsynaptic cellular organelle, a dendritic spine, with a terminal bouton on a presynaptic neuron. The spines and the synapses they form are principally composed of synaptic membrane, which is characterized by particular phosphatide species and specific proteins (e.g., synapsin-1; synaptophysin; PSD-95; GluR-1). Consuming the three nutrients increases brain levels of these phosphatides and proteins, the numbers of hippocampal dendritic spines, and, very likely, synapses. In contrast processes that diminish the
numbers of functional dendritic spines – e.g., amyloid plaques in Alzheimer’s disease – are known to impair synaptogenesis.

Biosynthesis of the phosphatides in synaptic membrane requires glucose, uridine, a PUFA (e.g., DHA), and choline: Uridine is the brain's major source of UTP and CTP; DHA is a component of the diacylglycerol (DAG) molecules preferentially utilized for phosphatide synthesis; and choline, a metabolically-expensive molecule, is needed to form both phosphatidylcholine [PC] and the neurotransmitter acetylcholine [ACh]. DHA and/or its PUFA precursor linolenic acid is an essential nutrient obtainable only from the diet; uridine and choline must be obtained both from foods and from endogenous synthesis in the liver.

These three nutrients readily cross the blood-brain barrier and are then enzymatically converted to the intermediates in phosphatide synthesis. Importantly, the enzymes that catalyze the conversions all exhibit low affinities for these substrates. Increasing brain levels of uridine, DHA, or choline in rats or gerbils causes parallel increases in UTP/CTP, DHA-containing DAG, and phosphocholine. These increases, in turn, elevate brain levels (per brain or per cell) of PC and of the other major phosphatides in synaptic membrane. And perhaps surprisingly, administering the three phosphatide precursors also selectively increases the above synaptic proteins; hippocampal dendritic spines; and, probably consequently, neurotransmitter release and cognitive performance. All three precursors act in part by increasing the substrate-saturation of a rate-limiting low-affinity enzyme. However one of them – uridine – also acts via a second mechanism: it and its nucleotide products activate brain P2Y receptors, which promote neuronal differentiation.

2010 Martha L. Ludwig Lectureship in Structural Biology

David R. Davies, Ph.D.

Fifty Years of Protein Structure: From Myoglobin to the Innate Immune System

David R. Davies, Ph.D. is Cecil H. Green Distinguished

Professor, Laboratory of Molecular Biology, Molecular Structure Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

Dr. Davies received his Ph.D. in Physical Chemistry at Magdalen College in Oxford, England.

Dr. David Davies is a distinguished structural biologist who traces his career to the inception of biological crystallography. A native of Wales, Dr. Davies obtained a Ph.D. in physics at Oxford University and performed postdoctoral research in small-molecule crystallography with Professor Linus Pauling at Caltech. His work in structural biology began in 1955 as a visiting scientist with Alex Rich in the Mental Health Institute at NIH where he undertook X-ray diffraction studies of RNA complexes and reported the first structure of a G-quartet. Shortly thereafter, Dr. Davies' interest shifted to protein structure, and he joined Sir John Kendrew in the Medical Research Council Laboratory at Cambridge, England, where he helped determine the crystal structure of myoglobin at atomic resolution, an accomplishment that earned Dr. Kendrew the Nobel Prize in Chemistry. Dr. Davies then returned to the United States and rejoined the NIH as the chief of the Section on Molecular Structure in the Laboratory of Molecular Biology at the National Institute of Diabetes, Digestive, and Kidney Diseases. Over the course of the next 40 years, Dr. Davies made seminal contributions to our understanding of protein structure. Most notably, he pioneered the field of structural immunology and provided the first crystal structures of intact immunoglobulins. In recent years, his research has focused on retroviruses and the innate immune system. In 1994, Dr. Davies' group reported the first crystal structure of HIV integrase, which has emerged as a major target for antiviral drug design. His most recent work has centered on the structure and function of Toll-like receptors in innate immunity, culminating in the structure of the Toll-like receptor 3 in complex with double-stranded RNA in 2008.

Continued on page 17
Dr. Michael O’Donnell is an HHMI Investigator and Anthony and Judith Evnin Professor at the Rockefeller University. He received his Ph.D. degree at the University of Michigan for his work with Charles Williams, Jr., on electron transfer in the flavoprotein thioredoxin reductase. He performed postdoctoral work on Escherichia coli replication with Arthur Kornberg and then on herpes simplex virus replication with Robert Lehman, both in the Biochemistry Department at Stanford University. Dr. O’Donnell was a member of the faculty of Cornell University Medical College, New York City, before moving to Rockefeller. He was recently elected to membership in the National Academy of Sciences.

The elegant structure of duplex DNA suggests that the replication process would be simple. Duplication of the chromosomes, however, requires numerous proteins acting together to unwind and replicate the two strands of duplex DNA. Dr. O’Donnell’s laboratory studies these replication mechanisms with the goal of understanding how the protein gears act together to make copies of DNA and how they function with repair and recombination factors to ensure that those copies are accurate.

Over the years, research from Dr. O’Donnell’s lab has provided an overview of how the replication machine functions in Escherichia coli, and several of its features have been found to be common to yeast and humans. A circular protein, which he and his colleagues refer to as a sliding clamp, completely encircles duplex DNA, acting as a mobile tether to hold the replication machine to the chromosome as it functions. The sliding clamps of prokaryotes β and eukaryotes (PCNA) have similar structure and function. Dr. O’Donnell solved the structures of these ring-shaped proteins in collaboration with John Kuriyan’s laboratory (now at the University of California, Berkeley) and showed that they comprise six domains organized on a dimer or trimer surface. Once on DNA, the clamp binds the replication machinery and slides along behind it, constantly holding it to the chromosome for long distances.

To become attached to DNA, sliding clamps require a multiprotein clamp loader machine that uses ATP to open the circular clamp and place it onto DNA. The detailed workings of how these clamp loaders function have been one of the lab’s aims in both prokaryotic γ and eukaryotic (RF-C) systems. Biochemical studies by Dr. O’Donnell’s group, combined with crystal structure information from Dr. Kuriyan’s laboratory, show that these clamp loaders are circular heteropentamers of crescent-shaped subunits that act like a hand with fingers; ATP binding powers the hand to manipulate the ring-shaped clamp onto DNA, and ATP hydrolysis allows the ring to close. Understanding the process by which two DNA polymerases cooperate with one clamp loader and a hexameric ring-shaped helicase to simultaneously synthesize both strands of duplex DNA is a project that has also held Dr. O’Donnell’s fascination over the past few years. He and his colleagues have learned about three point switches between primase, the clamp loader and DNA polymerase and the processes by which sliding clamps are recycled and regulated. New and recent studies into other, accompanying processes include how the replication machinery interfaces with proteins in repair, DNA damage checkpoint paths and recombination. For example, the sliding clamps interact directly with MutS and MutL, and the O’Donnell lab is studying how it functions in mismatch repair. The β and PCNA clamps also bind several other proteins, indicating that these clamps and clamp loaders are at the center of many DNA metabolic processes. Dr. O’Donnell’s lab is initiating a project on the role
of these proteins in recombinative repair in which the replication fork encounters a lesion that must be fixed by recombination and repair proteins. Scientists had widely anticipated that a replication fork would collapse upon encountering a lesion, but Dr. O'Donnell's group found that this is not the case. Instead, blocks on the lagging strand are bypassed entirely by the replication machinery. Further, the replication fork helicase itself is capable of encircling either one of two strands, and in the latter mode it is capable of branch migration of Holliday junctions, making it a likely candidate as a central actor in recombinative repair of a stalled replication fork.

The O'Donnell lab is also studying how replication origins are activated for DNA synthesis, with the expectation that studies in the yeast system will lead to information on overall control of chromosome replication.

At the lecture Dr. Williams warmly welcomed Dr. O'Donnell back to the department for an exciting lecture "Obstacles to replication and mechanism used by a replisome to circumvent them."

Dr. Steven P. Gygi's research focuses on the large-scale identification and characterization of proteins by mass spectrometry and sequence database searching. One of the most dramatic developments in biological research during the past decade has been the shift from the analysis of individual genes and proteins to the comprehensive analysis of biological systems and pathways. This has been enabled by the emergence of automated, high-throughput genomic technologies and their application to sequence complete genomes to measure gene expression on a genome-wide scale. Currently, no comparably powerful technology is available for the analysis of biological systems on the protein level. However, proteins are the most significant class of biological effector molecules, and a complete model of a biological process cannot be established without knowledge of the identity, function and activity state of the proteins involved. Dr. Gygi is committed to the formulation of technologies for the rapid, sensitive, quantitative and comprehensive analysis of protein expression profiles in complex biological samples, ultimately in whole cell lysates.

Dr. Gygi has authored more than 150 publications. He has been the recipient of several awards including a National Institutes of Health post-doctoral training grant (1997-2000), the Gulf Oil Outstanding Achievement in Biological Sciences Award (2003), the Fanconi Anemia Research Fund Discovery Award (2007), and the John and Virginia Kaneb Fellows Award (2008).
Redox Signaling and Disease

17 September 2009
10:30 am - 5:00 pm
Forum Hall, Palmer Commons

Sponsored by the Department of Biological Chemistry 
& the University of Michigan Medical School Office of Research

Ruma Banerjee, Ph.D., University of Michigan
Toren Finkel, M.D., National Institutes of Health
Mark Gladwin, M.D., University of Pittsburgh
Chuan He, Ph.D., University of Chicago
Ursula Jakob, Ph.D., University of Michigan
Leslie Poole, Ph.D., Wake Forest University
Nicholas Tonks, Ph.D., Cold Spring Harbor

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For registration
Annual Student Awards | 2009 & 2010

The Minor J. and Mary Lou Coon Award

Awarded annually to the student who exhibits overall excellence in research, teaching, and service to the department. This award honors Professor Jud Coon, former Chair of the department, and the late Mary Lou Coon who have provided the gift that supports this award.

2009 Awardee: Donald Raymond
Mentor: Janet Smith

2010 Awardee: Ryan Evans
Mentor: Audrey Seasholtz

The Lee Murphy Memorial Prize

Awarded annually to the student who embodies the highest ideals of scientific integrity and who has published a paper or a series of papers judged most significant by the Awards Committee. This award is named in honor of Lee Murphy, an alumnus of this department.

2009 Awardee: Bin Zhao
Mentor: Kun-Liang Guan

2010 Awardee: Zhonghua Yan
Mentor: Ruma Banerjee

The Dzwiewatkowski Award

Dedicated to the memory of the late faculty member, Dominic D. (Jay) Dzwiewatkowski, this award is offered to the student who has submitted the most outstanding Ph.D. dissertation during the last academic year.

2009 Awardee: Rebecca Fagan
Mentor: Bruce Palsey

2010 Awardee: Stacie Bulfer
Mentor: Ray Trievel
The Halvor N. and Mary M. Christensen Award

Presented to a second-year student on the basis of academic record. This award is given in honor of the late Mary M. and Professor Emeritus Halvor N. Christensen who served as Chair of Biological Chemistry from 1955–1970. Mary and Halvor Christensen generously provided the original gift that supports this annual award, and their daughter Karen Christensen-Gray has also generously donated funds to support this award.

2009 Awardee: Jennifer Gehret
Mentor: Janet Smith

2010 Awardee: Curtis R. Powell
Mentor: Daniel Goldman

The Adam A. and Mary J. Christman Award

Presented to a third-year student judged to be the most outstanding in that class. The Christman Award is named in memory of former long-time faculty member Professor Adam Christman.

2009 Awardee: Ashley Reinke
Mentor: Jason Gestwicki

2010 Awardee: Jennifer Gehret
Mentor: Janet Smith

The Anthony and Lillian Lu Award

Presented to a student on the basis of academic background, achievement in the graduate program, and potential as a scientist. This award is made possible by the Lu Family who have generously provided the gift that supports this annual award.

2009 Awardee: Li Yi
Mentor: Stephen Ragsdale

2010 Awardee: Zhonghua Yan
Mentor: Ruma Banerjee
Pancreatic Islet Amyloid Polypeptide Membrane Binding and Permeabilization
Mentor: Ari Gafni, Ph.D.

Jared D. Chrispell. November 17, 2009
Characterization of RPE65 and RDH12, Two Enzymes Associated With Retinal Dystrophy and Retinoid Processing
Mentor: Debra A. Thompson, Ph.D.

Feng Wang. November 24, 2009
Structural Analyses of Telomere Associated Proteins
Mentor: Ming Lei, Ph.D.

Tushar Menon. December 1, 2009
Regulation of Androgen-Responsive Transcription by the Chromatin Remodeling Enzyme CHD8
Mentor: Daniel A. Bochar, Ph.D.

Abigail E. Wolfe. December 11, 2009
Kinetic Mechanism for Binding and Flipping of Damaged Bases by Alkyladenine DNA Glycosylase
Mentor: Patrick J. O’Brien, Ph.D.

Stacie L. Bulfer. February 5, 2010
Structure, Mechanism and Regulation of Homocitrate Synthase
Mentor: Raymond C. Triever, Ph.D.

Samuel G. Gattis. April 19, 2010
Mechanism and Metal Specificity of Zn-dependent Deacetylases
Mentor: Carol A. Fierke, Ph.D.

Li Yi. April 28, 2010
Characterization of the Redox Switches in Human Heme Oxygenase-2 and a Human Heme-Responsive Potassium Channel
Mentor: Stephen W. Ragsdale, Ph.D.

Jay N. Pieczynski. August 6, 2010
Regulation of Apical Polarity Complexes
Mentor: Benjamin L. Margolis, M.D.
Siyan (Stewart) Cao received his Bachelor's Degree in Biological Science from Zhejiang University, China, in 2008. He joined Dr. Randal Kaufman's lab in 2009 and the focus of his research is endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) in the function and homeostasis of mammalian intestinal epithelial cells (IEC). He uses several genetic mouse models with mutations in UPR-associated genes, including eukaryotic translation initiation factor 2A (eIF2A), double-stranded RNA-activated protein kinase (PKR), and activating transcription factor 6 (ATF6), to characterize the function of these genes in IEC under normal conditions and upon stresses, e.g. infection and radiation. He also uses mouse models and cell culture systems to investigate how ER stress is induced in IEC by inflammatory signals commonly found in intestinal lumen and whether this cellular stress can be alleviated by chemical chaperones.

Manila Hada received her Bachelor of Science degree from Kathmandu University in Dhulikel, Nepal in July 2007. Manila’s research in Dr. Roland Kwok’s laboratory is in the area of neuroblastoma cancer, which is diagnosed in new born and young children. The tumor develops during embryogenesis or after birth from sympathoadrenal stem cells. Recent studies from Kwok’s laboratory indicate that the DNA repair mechanism in neuroblastoma cells may be defective leading to tumor development. To test this hypothesis, Kwok’s laboratory has employed a neural crest stem cell model to test whether alteration of the expression of the DNA repair factors in neural crest stem cells would disturb the sympathoadrenal lineage development leading to tumor formation.

Jenna Hendershot received her Bachelor of Science from Grand Valley State University in Allendale, Michigan in 2009. Jenna’s research with Dr. Pat O’Brien involves studying human Alkyldenine DNA Glycosylase (AAG), a 33 kDa monomeric protein responsible for initiating repair of a wide variety of alkylated and deaminated purine lesions in DNA. Crystal structures have revealed that AAG uses nucleotide flipping to rotate lesioned bases out of the DNA duplex into its active site where the flipped-out lesion is fully inserted into a deep pocket, stacked between the aromatic side chains of tyrosine-127 and tyrosine-159. Currently Jenna is examining the binding of site-directed AAG mutants, Y127W and Y159W, to a naturally fluorescent 1,6-ethenoadenosine (eA) lesion to investigate the mechanism of nucleotide flipping. Replacement of active site tyrosines with tryptophans provides an opportunity to monitor conformational changes in the protein and investigate the tolerance of the binding pocket to changes in volume.

Swathi Krishnan obtained her Bachelor’s degree in Biotechnology from PSG College, India. Swathi’s research in Dr. Ray Triewel’s lab involves the structural and biochemical characterization of lysine demethylases (KDMs). KDMs and lysine methyltransferases are enzymes that dynamically control methylation of various proteins and have been shown to be important in a number of biological processes and in diseases like cancer. The Triewel lab aims to better understand how these enzymes function. Swathi’s work focuses on determining the crystal structure of enzymes in the JMJ2 class of KDMs that demethylate lysine residues of histone H3. Her research also focuses on developing and optimizing biochemical assays that can help characterize the catalytic parameters of these enzymes.

Libya Mansour received both her Bachelor and Master of Science degrees at the University of Nevada, Las Vegas and joined the University of Michigan in the Summer of 2008. In the laboratory of Dr. Georgios Skiniotis she studies the structure of large molecular protein complexes using electron microscopy. Her thesis research involves the structural characterization of the single pass, transmembrane lepin receptor (L-R). L-R and its ligand lepin are key players in regulating food intake and energy expenditure. Defective signaling in the lepin/L-R system can lead to obesity, hyperinsulinaemia, type 2 diabetes and tumorigenesis. As such, both stimulation and inhibition of the lepin receptor have applications in disease treatment, with the intracellular as well as the extracellular parts of the receptor representing significant drug targets. However, these pharmacological approaches have been hampered by the absence of structural information regarding the lepin/L-R complex. The Skiniotis Lab employs single-particle electron microscopy followed by computational image processing which allows for building 3D models of dynamic macromolecular assemblies in their natural physiological state.

Claudia Alejandra McDonald received her Bachelor of Science degree from Washington State University in Pullman, Washington in 2001. After completing her degree Claudia worked as a technician in academic laboratories, a medical center, and a biotech company. Claudia then went on to complete her Master of Science degree at San Francisco State University in San Francisco, California. In 2009, she began her Ph.D. studies at the Stanford University School of Medicine, where she is currently a graduate student in the laboratory of Dr. Robert A. Behrens. Her research focuses on the structural and functional characterization of the RASopathies, a group of genetically related disorders characterized by developmental delay, mental retardation, and tumors. Her work involves the use of structural biology techniques, such as X-ray crystallography and cryo-electron microscopy, to elucidate the molecular mechanisms underlying these diseases.
Francisco, California in 2008. Claudia also cofounded a proteomics software company, Proteome Solutions, prior to starting the doctoral program in Biological Chemistry at the University of Michigan. Claudia’s research in Dr. Bruce Palfrey’s laboratory is in the area of enzymology. Claudia is interested in studying the mechanism of a tRNA modifying enzyme named TrmFO. TrmFO is a tRNA methylating flavoenzyme that uses methylenetetrahydrofolate as its 1-carbon donor instead of the common S-adenosylmethionine and uses the flavin as the reductant. Claudia is also interested in studying the kinetic and chemical mechanism of TrmFO.

Joe Micucci received his Bachelor of Science in Biochemistry and Molecular Biology from the Pennsylvania State University in December 2007. While working in Dr. Dan Bochar’s lab, Joe focuses on several aspects of CHARGE syndrome, a complex developmental disorder that arises from point mutations within the Chd7 gene encoding an ATP-dependent chromatin remodeling enzyme. Joe’s project aims to characterize the chromatin remodeling capability of CHD7 by in vitro biochemical assays and to monitor in vivo effects of CHD7 depletion by quantitative PCR and chromatin immunoprecipitation in a mouse model of CHARGE syndrome concentrating on neurogenesis and inner ear development.

Curtis Powell received his Bachelor of Science degree from Brigham Young University-Idaho in April 2008. Here at the University of Michigan, Curtis joined Dr. Daniel Goldman’s laboratory, studying retinal regeneration using zebrafish. The retinal regenerative capacity of zebrafish has been attributed to Muller glia. Upon retinal injury, Muller glia follow a timeline of dedifferentiation, proliferation, and differentiation, ultimately regenerating all retinal cell types and restoring retinal function. As we understand the mechanism whereby Muller glia carry out their regenerative role, novel insights are gained in the field of regenerative medicine. Curtis’s current research is designed at understanding the role of APOBEC2, which he has found to be necessary for retinal regeneration.

Amber Smith received her Bachelor of Science from the University of California at Santa Cruz in 2008. In Dr. Janet Smith’s laboratory, Amber is studying the mechanism of pyridoxal 5’ phosphate, a heteromeric glutamine amidotransferase through structure using crystallography.

Mark Taylor received his Bachelor of Science in Biochemistry and Biophysics from the University of Michigan, Ann Arbor in June 2007. Mark’s research in Dr. Patrick J. O’Brien’s lab focuses on DNA repair, specifically the human DNA ligase I protein. DNA ligase I catalyzes the final nick-sealing step of DNA replication and some DNA repair pathways. Because of its function in DNA replication and repair, inhibition of DNA ligase I remains a potential strategy by which to aid chemotherapeutics in combating cancer. Currently, Mark is determining the overall kinetic mechanism of human DNA ligase I in order to better understand how potential inhibitors affect the complex 3-stage reaction mechanism.

Jamie Van Etten received her Bachelor of Science from the College of Charleston, South Carolina in 2007. Jamie’s research with Dr. Aaron Goldstrohm involves work with human PUF proteins. PUF (Pumilio and FBF) proteins are highly conserved, sequence-specific RNA binding proteins. They bind 8-12 nucleotide sequence elements in the 3’ untranslated region of target mRNAs via a conserved RNA binding domain. It is thought that all PUFs repress translation via several processes; deadenylation and degradation of mRNA targets and/or inhibition of translation, and that they act in concert with co-repressor proteins to control stability and translation of target mRNAs. Humans possess two distinct PUFs, PUM1 and PUM2, which are enriched in the brain, germline, and stem cells. Jamie is interested in characterizing the mechanisms by which PUFs regulate mRNA lifespan in human cells using techniques designed to measure mRNA stability and PUF-dependent repression.

Cody Vild earned his Bachelor of Science degree from Carnegie Mellon University in Biological Sciences with a minor in Chemistry in May 2008. Cody is involved in research in Dr. Zhaoxi Xu’s laboratory in the area of structural and biochemical analysis of Endosomal Sorting Complexes Required for Transport (ESCRT) proteins. ESCRT proteins are protein complexes that are responsible for membrane trafficking, and have been found to play important roles in Multivesicular Body (MVB) biogenesis, retroviral budding and cytokinesis. Defects in this highly conserved pathway lead to various disease states such as cancer and improper neurological development. Studies have shown that an ATPase associated with various cellular activities (AAA) Vps4, interact with ESCRT proteins to regulate their function. At least four proteins (Did2, Ist1, Vta1, and Vps60) have been shown to regulate Vps4 activity by interacting with Vps4 directly or indirectly by interacting with each other. In the Xu lab, they seek to understand how these proteins can regulate Vps4 by obtaining 3-D structures of these various proteins complexed together. By understanding the allosteric regulation of Vps4, they hope to gain insight on how Vps4 can regulate ESCRT function.
Gerwin Westfield received his Bachelor of Science degree from the University of Michigan in Ann Arbor, MI in April 2009. Gerwin's research in Dr. Georgios Skiniotis' laboratory is involved with determining the structure of chromatin remodeling and modifying complexes. Chromatin remodelers are macromolecular complexes involved in insertion, sliding, and removal of nucleosomes in tightly packed chromatin. Chromatin modifying enzymes place different modifications (acetylation, methylation, ubiquitination) on histone tails within the nucleosome. The Skiniotis laboratory uses electron microscopy as a tool to characterize the architecture of these macromolecular complexes. Generating 3D reconstructions of these complexes helps determine the relationship between their structure and function.

Chase A. Weidzana received his Bachelor of Science from the University of Rochester, Rochester, New York in 2009. Chase's research with Dr. Aaron Goldstrohm involves work with a founding PUF family member, Drosophila Pumilio (Pum), which partners with corepressors Brain Tumor (Brat) and Nanos (Nos) to induce repression of Hunchback (Hb) mRNA. Binding to the Nanos-Response Element (NRE) in the Hb 3'UTR, Pum creates an anterior-posterior gradient of Hb protein which confers correct body patterning in the developing Drosophila embryo. Chase's over-arching goal is to characterize the mechanism of Pumilio regulation. To study this, he has developed an assay which measures Pum repression. Using this assay, he aims to test the existing models of Pum repression using multiple techniques which evaluate Pum's effect on mRNA stability and translation. He also plans to verify proposed corepressors as well as identify new ones. These methods will hopefully divulge the mechanism of Puma action, and reveal new insight into post-transcriptional gene regulation.

Noah Wolison received his Bachelor of Science from Brandeis University in 2008 where he researched propionate kinase in the lab of Gregory Petsko and Dagmar Ringe. Currently, Noah is working in Dr. Carol Fierke's lab on the specificity and metal switching of HDAC8. In doing so, Noah is trying to identify the deacetylosome (the set of proteins in the cell which are deacetylated) and determine how HDAC8 is able to utilize multiple metals in its active site to perform its catalytic mechanism. The determination of this information will lead to a better understanding of the events initiating a number of diseases ranging from cancer to Alzheimer's disease.

Faculty News continued from page 13

nucleotide-binding domain regulates protein-substrate binding in the substrate-binding domain, i.e. the allosteric mechanism of the chaperone. Using the latest NMR methods and equipment, they unveiled marked differences in the conformations and dynamics of Hsp70’s in different states. The work, published last year, is also somewhat of a milestone of NMR - fruitful study of proteins as large as 70 kDa by NMR is still not very common. Zuiderweg’s group capitalizes on its insights in the Hsp70 mechanism by aiding Jason Gestwicki’s group in Biological Chemistry and Pathology in the discovery of small-molecule modulators of the Hsp70's for treatment of the above-mentioned diseases.

Student News & Achievements

One of Stacie Bulfer’s publications in JBC was highlighted as a Paper of the Week, representing the top 1% of papers reviewed in terms of impact and significance to the field.

Ryan Evans was awarded a prestigious Rackam Predoctoral Fellowship for 2010-2011. This fellowship includes tuition, stipend, and grad care health insurance for three terms.

Jennifer Gehret was awarded a Young Scientist Travel Award from the American Crystallographic Association to attend its 2010 Annual Meeting.

Donald Raymond was awarded the Pauling Prize for the Overall Best Poster at the 2010 American Crystallographic Association Conference held in Chicago.

Amber Smith was awarded a Ruth L. Kirschstein National Research Service Award by the National Institutes of Health. The Individual Predoctoral Fellowship will provide funds for tuition, fees, health insurance, and training related expenses.

Noah Wolison was awarded a 2010 National Science Foundation Graduate Research Fellowship. Selection is based upon each student’s outstanding abilities and accomplishments, as well as their potential for achieving high levels of success in their future academic and professional careers.
Almost all activities of the cell are regulated and propagated by cell signaling networks. One prominent signaling mechanism used by cells is that of protein phosphorylation. As a post-translational modification, phosphorylation can activate, inactivate, or work in concert with other signaling mechanisms to manipulate the activity of many important enzymes having broad ranging results on gene transcription, metabolic function, and in extension, many larger cellular phenomena, such as regulation of the cell cycle. The cyclin-dependent kinases (CDKs) are a prime example of signaling enzymes which integrate multiple signaling inputs to propagate a signal directly affecting and deciding the cell fate. One activity of CDK2 is to enable the progression of the cell cycle from G1 phase to the S phase by phosphorylating key inhibitors of the cell cycle. Given this important role, the activity of CDK2 is strictly controlled by a variety of allosteric activators and inhibitors as well as activating and inhibiting phosphorylations on a variety of residues, in addition to possible regulation by other factors. To understand how this regulation is achieved, we are studying how the fundamental reaction mechanism is carried out during the complete catalytic cycle of the activated CDK2 complex, and how the structural changes caused by binding of CDK2's regulatory agents result in altered CDK2 phosphorylation activity.

This figure shows the electrostatic potential of a crystal structure of a transition state mimic of CDK2 as viewed from the perspective of the target protein substrate in the active site of the kinase. The importance of this structure is that compared to other structures of the active CDK2 complex, the kinase is trapped "in the act" of phosphorylating a protein substrate, permitting direct observations of how the active site features of CDK2 are achieving efficient catalytic activity. In fact, this transition state mimic reveals previously unknown attributes of the CDK2 catalytic cycle, including the transient binding of a second catalytic Mg2+ ion in the active site and the resulting structural consequences of this binding, further investigated by computer simulation. Previous structures of many active protein kinases have indicated that some bind a single Mg2+ while others bind two. These recent data suggest that the transient binding of a second, catalytically essential, Mg2+ is a general mechanism for many protein kinases. While there may be similarities in the catalytic details of phosphoryl transfer that are conserved between divergent protein kinases, the regulatory strategies employed by the cell to regulate these kinases are vastly different. Further, the relative rates of different steps of the protein kinase catalytic cycle are known to vary between different protein kinases and regulation can be achieved when external factors alter these rates. One way CDK2 appears to be regulated is by altering the affinity of the second catalytic Mg.

Douglas Jacobsen

Douglas Jacobsen is a Bioinformatics student in Matthew Young's laboratory.
Fred Guengerich (postdoctorate with Jud Coon), Professor of Biochemistry and Director of the Center in Molecular Toxicology at Vanderbilt School of Medicine, was presented with the R.T. Williams Distinguished Scientific Achievement Award at the recent International ISSX meeting held in Istanbul. Fred is currently Interim Chair of the Vanderbilt Department of Biochemistry.

Paul Hollenberg (Ph.D. with Jud Coon), the Maurice H. Severs Collegiate Professor and Chair of the University's Department of Pharmacology, has been inducted as a member of the 2010 class of Fellows of the American Chemical Society. The Fellows Program was developed by the ACS Board of Directors to honor members of the American Chemical Society "for outstanding achievements in and contributions to Science, the Profession, and the Society". The Fellow designation is bestowed on ACS members who have achieved excellence in two defined areas - scientific/professional accomplishments and outstanding service to the ACS. This year's 192 new Fellows, like the first 163 ACS Fellows, represent academia, industry, and government. The American Chemical Society is the world's largest scientific society with more than 161,000 members. Paul was a co-founder of Chemical Research in Toxicology, the premiere journal in the field of toxicology, and played a leading role in the American Society for Pharmacology and Experimental Therapeutics (ASPET).

Anthony Lu (postdoctorate with Jud Coon and very well known to the Department for his generous support of the Anthony and Lillian Lu Annual Student Award) was honored at the 18th International Symposium on Microsomes and Drug Oxidations held in Beijing in May. The meeting was dedicated to Anthony for his outstanding research, devoted service to the scientific community, and invaluable efforts in mentoring the younger generation of scientists. He retired from his position as Executive Director of Drug Metabolism at Merck in 1997 and then joined Rutgers University as an Adjunct Professor in the Department of Chemical Biology. He was among the first researchers in the pharmaceutical industry to apply basic cytochrome P450 knowledge in the search for and development of drug candidates with superior properties, and he was a pioneer in the use of modern in vitro approaches to study drug metabolism, drug residues, and toxicity. That work has had immense practical value in drug development and regulation, and was instrumental in the setting of standards by the Food and Drug Administration for regulation of veterinary medicine.

Deborah Lu (Ph.D. with Jerry Menon) visited the Department last May to attend our annual award presentations and represent her family as donors of the Lu Annual Graduate Student Award. She was invited to meet with interested students to talk about alternative careers, in particular intellectual property law. After her postdoctoral fellowship at Harvard Medical School and the Skirball Institute for Biomolecular Medicine, Deborah decided to pursue a career involving science writing. She then proceeded to work for an intellectual property boutique law firm as a law clerk and attended Fordham University School of Law during the evening. Deborah is now a shareholder (a corporate equivalent to a partner) at Vedder Price P.C., a general practice law firm in New York. She has reminded us of two other graduates of our Department who have made similar career choices. Ken Chahine (Ph.D. with Dan Goldman) is a patent attorney at Business, Scientific and Legal Consulting at NextGenMedicine, LLC, and Visiting Professor of Law at the University of Utah S.J. Quinney College of Law. Eric Baude (Ph.D. with Mike Uhler) is currently a patent attorney with Brinks Hofer Gilson and Lione in Ann Arbor, Michigan. After a postdoctoral fellowship with Dr. David Garbers at the University of Texas Southwestern, Eric obtained his J.D. with Honors from Chicago-Kent College of Law. He was corporate counsel at Pfizer Inc. from 2001 to 2007 and then moved to the intellectual property law firm of Brinks Hofer Gilson and Lione. His work focuses on Biotechnology patent drafting and prosecution, portfolio management, and freedom-to-operate analyses. This October, he presented a seminar entitled "The Impact of New U.S. Biosimilar Law on IP Strategy" for the Danish Patent and Trade Mark Office in Copenhagen, Denmark.

Peter Zaphiropoulos (Ph.D. with Jud Coon) has been promoted to Professor in Molecular Biology in the Department of Biosciences and Nutrition at the Karolinska Institute in Stockholm. His research is focused on providing a better molecular understanding of the role of Hedgehog signaling in cancer development. This pathway, originally identified in Drosophila, is one of the major developmental cascades, and its deregulation may result in cancerous transformation, with the first example being the most common form of skin cancer, basal cell carcinoma. He and his colleagues are now addressing regulatory mechanisms of Hedgehog signal transduction that implicate microRNA molecules as well as mRNA variants of signaling components. For clinical models of the Hedgehog signaling-mediated events, the childhood cancers of medulloblastoma and rhabdomyosarcoma are being investigated, with the ultimate goal being the development of future therapeutic interventions.