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LETTER FROM THE CHAIR

Dear Graduates, Friends and Colleagues,
“It’s the people!”

I’m sure you have seen that phrase before, but it’s one that came immediately to mind when I sat down to think about this year’s Newsletter and what makes the Department of Biological Chemistry at the University of Michigan so outstanding. This year the numbers of people in the Department, both students and faculty, have increased significantly. Fifteen new Ph.D. students and five new faculty joined the Department in the fall.

Our Graduate Admissions Committee chaired last year by Debra Thompson and Alex Ninfa and this year by Ruthann Nichols and Ben Margolis has been very successful in attracting new, very high caliber graduate students to the Department. This success in recruiting results from a collective and cooperative effort by our students, faculty and staff. Last year Mohamed Abazeed and this year Rebecca Haeusler have been the student representatives on the Graduate Admissions Committee, and along with the other

committee members, they have been particularly helpful in deciding which students to invite for recruiting visits and in hosting the visiting students during recruiting weekends. Elizabeth Goodwin does a superb job staffing our graduate office which permits our program to thrive.



The Class of 2009 (since I’m sure they will all finish in five years) has a great deal of spirit and considerable acting tal-

ent. These were on display at the midnight campfire gathering at the Departmental retreat in August and in the skit presented at the holiday party in December. You can see pictures of your new academic siblings on page 5 of the newsletter and pictures of departmental activities on our new web site. You will find one of Professor Ballou that is worth a visit to this site.

Our new faculty members about whom you will read more in this issue are Suzanne Admiraal, Ming Lei, Neil Marsh, Patrick O’Brien, and Matthew Young. Neil Marsh, who has been at the University of

BIOLOGICAL CHEMISTRY STAFF

2 William L. Smith, PhD
Chair

Robert Fuller, PhD
Associate Chair

Jackie Benson
Staff Support

June Bialecki
Assistant to the Chair

Julie DeFilippo
Grants Manager

Bob Elliot
Equipment & Supplies Supervisor

Beth Goodwin
Graduate Program Coordinator

Mary Grapp
Finance Manager

Patricia Haines
Staff Support

Sharon Hoffman
Human Resources Manager

Jonathan Kufahl
System Administrator

Merlis Nolan
Department Administrator

Sandra Ridella
Staff Support

Jessica Viskup
Computer Systems Specialist

Michigan for eight years, holds an appointment in the Department of Chemistry, and we were very pleased that he accepted the offer of a joint appointment in Biological Chemistry. Matt Young is jointly appointed in the Bioinformatics Program. In addition to these five people, Janet Smith from Purdue University spent the year transitioning to Ann Arbor and is now situated in the Life Sciences Institute with a faculty appointment in Biological Chemistry. These new faculty enhance our strengths in structural enzymology, protein processing and folding, signal transduction and regulation of gene expression.

About seven years ago, thirteen departments and programs conducting biomedical research on the University of Michigan campus—both from the Medical School and LS&A School--initiated a joint graduate student recruiting program called the Program in Biomedical Sciences (PIBS). Dave Engelke has served admirably as director of this program. About 70 students enter through PIBS yearly and are free to rotate through two or three of the some 350 participating laboratories before selecting a Ph.D. mentor. Most of the students now in the laboratories of Biological Chemistry faculty have entered through PIBS. However, experience with PIBS has indicated that at least some students with a more chemical bent do not apply to this program. In part as a response to this and in part because of the developing interface among Chemistry, Medicinal Chemistry and Biological Chemistry, a freestanding

interdisciplinary Ph.D. program in Chemical Biology has been initiated. This program is administered through the Rackham Graduate School and Gary Glick and Bruce Palfey are co-directors. The number of students in Chemical Biology is expected to ramp up from about 10 the first year to about 20 per year in four or five years. When steady state is reached, we expect there will be on the order of 100 students in the program with perhaps as many as half of them training in the laboratories of Biological Chemistry faculty. We are excited about the prospects of this program because this is an important, emerging area of the biosciences. Moreover, the University of Michigan, with its strengths in Biological Chemistry, Chemistry and Medicinal Chemistry, is well placed to become the top Chemical Biology program in the country. Provost Paul Courant and Medical School Dean Allen Lichter have been very supportive in the development of this program. You can learn more about the Chemical Biology program at : www.chembio.umich.edu.

We currently have 45 faculty members in the Department. We were ranked 12th in NIH funding last year among biochemistry departments in this country, which is down two or three slots from a year ago, and we look to begin improving this ranking as new faculty come on board and initiate their programs. However, our established faculty continue to be

exceptionally productive and well-recognized as you will read about on the following pages.

And finally, three important items. First, I hope you will take the time to visit our new Departmental web page (www.biochem.med.umich.edu); web pages are always under construction, but I believe we have a nice framework that will last for some time and that you will find informative and easy to navigate. Second, let me thank all of those alumni(ae), faculty and staff who have provided financial donations to the department.

These monies are an ever more important factor in supporting our activities and maintaining Biological Chemistry at Michigan as a Department that we can all be exceptionally proud of. And finally a reminder that our University of Michigan Biological Chemistry Mixer is scheduled for the ASBMB-Experimental Biology meeting in San Diego on April 3, 2005. I look forward to having all of you who are planning to attend this meeting stop in for refreshments and say hello.

With best wishes for the coming year,



William L. Smith

FACULTY NEWS

Phil Andrews continues his five year endeavor developing proteomic technology under the State of Michigan's Life Sciences Corridor with the \$11.9 million grant from the National Center for Research Resources (NCR), a branch of the NIH. This continues to make Michigan a national leader for research and development in the field of proteomics.

Jud Coon is Guest Editor with O. Hayaishi, R. Estabrook, L. Que, and S. Yamamoto of a special issue of Biochemical and Biophysical Research Communications to celebrate the 50th anniversary of the discovery of oxygenases. (Osamu Hayaishi is a "Michigan graduate" with an honorary Doctor of Science Degree awarded in 1980 with the recommendation of our Department.) Jud is a member of the Board of Directors of the Society for the Study of Cytochromes P450 and also of the International Organizing Committee for the Conference on Cytochromes P450—Biochemistry, Biophysics, and Bioinformatics, to be held in Dallas.

Jack Dixon, Chair of our Department 1991-2001, and now Dean for Scientific Affairs at the University of California, San Diego, will receive the ASBMB 2005 Merck Award for his scientific achievements.

David Engelke received the 2004 Distinguished Faculty Lectureship Award in Biomedical Research from the Medical School for his outstanding contributions to the University in the areas of teaching, research and service. He presented his lecture in May 2004 entitled, "Retrieving Genetic Information: Thinking Outside the Line."

Carol Fierke will become the Chair of the Chemistry Department on March 1, 2005. She was elected President-Elect for 2005-2006, and President for 2007-2008 of the Biological Chemistry Division of

the American Chemical Society. She also received the Academic Women's Caucus 2005 Sarah Goddard Power Award, an honor given to individuals who have worked for the advancement of women.

Kun-Liang Guan received a Faculty Recognition Award for 2003-2004. This award acknowledges Kun-Liang's extraordinary achievements in the areas of teaching, scholarly research, mentorship and service to the University. He was also named the Halvor Christensen Collegiate Professor in the Life Sciences.

Tom Kerppola provided information for a press release on a new U-M technology which makes it possible to see ubiquitin proteins inside living cells. Citation: PNAS published October 5, 2004, 1-1073/pnas 0404445101.

Martha Ludwig has been given one of the University's highest honors by being named the J. Lawrence Oncley Distinguished University Professor of Biological Chemistry. Larry Oncley, who was a member of the National Academy of Sciences, President of the Biophysical Society, and editor of the Society's major publication, The Biophysical Journal, retired in 1980 as Professor Emeritus of Biological Chemistry and of Chemistry at the University of Michigan, and died in July of last year.

Rowena Matthews was elected to the Institute of Medicine because of her major contributions to the advancement of medical sciences. Rowena is a leading authority in understanding how vitamin-containing enzymes function in the body. Her work bridges basic biochemical research and its clinical applications to metabolic disease in humans.

FACULTY NEWS

Brian Ross was elected as President-Elect of the Society for Molecular Imaging and will assume the Presidency at the annual meeting in Cologne, Germany in September 2005 until the 2006 meeting.

Janet Smith has been named the Margaret Hunter Collegiate Professor in the Life Sciences.

4 **Bill Smith** delivered the J.J. Berzelius Lecture last November in Stockholm at the Karolinska Institute. The prestigious lectureship was founded in connection with the 200th anniversary of the birth of Berzelius, who was not only a prominent chemist but also one of the founders of the Karolinska Institute. Bill also lectured at the RIKEN Structural Biology Symposium on Lipid-Mediator Related Proteins from Basic Science to Clinical Application in Hyogo, Japan. He is a Member of the ASBMB Council and will serve through the present year.

David Turner was awarded the prestigious Wilson Foundation Grant. Only one is given per university in any given year. The proposals are pre-selected by the Biomedical Research Council of the Medical School and are then forwarded to the Wilson Foundation for consideration. Only innovative, cutting-edge research is funded.

Robert Zand is serving as a member of the Jordi-Folch Pi Award Committee of the American Society of Neurochemistry. He was re-elected to a second term as President of the University of Michigan Chapter of Sigma Xi, the Scientific Research Society.

Bill Lands, formerly Professor in this Department, who later worked at the National Institute on Alcohol Abuse and Alcoholism, where he was Director of the Basic Research Program (1990-1997) and then served as

Senior Scientific Advisory to the Director (1997-2002), has very generously established a lectureship. The William E.M. Lands Lectureship on the Biochemical Basis for the Physiology of Essential Nutrients is expected to advance biochemical education at Michigan and to encourage students to look at molecular mechanisms in the health consequences of dietary food choices.

ALUMNI/AE NEWS

Xinxin Ding (Ph.D. with Coon), Professor of Molecular Genetics and Toxicology at SUNY Albany and Senior Scientist at the Wadsworth Center of the New York State Department of Health, is Secretary/Treasurer Elect of the Drug Metabolism Division of ASPET.

Cathy Luschinsky Drennan (Ph.D. with Ludwig) received a Presidential Early Career Award for Scientist and Engineers, the nation's highest honor for scientists and engineers who are at the beginning of their career. She was also a co-recipient of the 2004 Edgerton Faculty Achievement Award from MIT, the highest honor MIT gives to a junior faculty member.

Fred Guengerich (Postdoc with Coon), Professor of Biochemistry and Director of the Center in Toxicology at Vanderbilt University, will receive the 2005 William C. Rose Award of the ASBMB. He has also received the American College of Toxicology President's Distinguished Service Award and the Sidney P. Colowick Faculty Research Award at Vanderbilt University that is given for excellence in research that serves as a platform for discovery in diverse research areas.

Dan Oprian (Ph.D. with Coon), the Louis Bessie Rosenfeld Professor and Chairman of the Department of Biochemistry at Brandeis University, spent a sabbatical leave in Cambridge, England, at the MRC Laboratory of Molecular Biology. He worked with Gebhard Schertler on the crystallization of rhodopsin, and they were able to crystallize recombinant rhodopsin

(purified from transfected COS cells grown in monolayer) and collect a complete set of data from the microfocus beam at Grenoble.

Julian (Bill) Peterson, (Ph.D. with Coon) and his wife, Dr. Sandra Graham, both on the faculty of the Department of Biochemistry at the University of Texas Southwestern Medical Center, are chairing the local organizing committee for the 14th International Conference on Cytochromes P450 to be held in Dallas in June.

Feng Shao (Ph.D. with Dixon) is now a postdoctoral fellow with Dr. Marc Kirschner at Harvard Medical School.

Tony Tranguch (Ph.D. with Engelke) continues to be a member of the screen actors guild and practice clinical psychiatry in midtown Manhattan.

Keith Wilkinson (Ph.D. with Williams) and his wife Linda were the guests of Irwin Rose for the awarding of his Nobel Prize. Professor Rose acknowledged that Keith's work, while a postdoc with him, was crucial in the award of the Prize.

Qing-Yu Zhang (Ph.D. with Menon) has been promoted to Research Scientist 4 at the Wadsworth Center of the New York State Department of Health. She will be directing a chemical genomics core.

DISTINGUISHED GRADUATE LECTURESHIP



Our fifth annual Biological Chemistry Student Awards Ceremony and Distinguished Graduate Lecture was held on June 9, 2004. Dr. Colleen Hayes (Ph.D. with Goldstein) presented a lecture entitled "The Vitamin D Endocrine System and Autoimmune Disease." She is a Professor at the University of Wisconsin-Madison. Her research focuses on diseases of the immune system to understand the molecular mechanisms that regulate immune system development and function. Specifically, mouse disease models are used to study how the vitamin D hormone, 1,25-dihydroxyvitamin D3 inhibits multiple sclerosis. She also studies how mutations in the receptor for B cell activating factor of the tumor necrosis factor family (BAFF) disrupts B lymphocyte development and causes common variable immunodeficiency disease.

NEW STUDENTS JOIN PH.D. CANDIDATES



Jared Chrispell (Thompson) is from Kingston, New York and received his B.S. in Biochemistry from SUNY, Buffalo, New York in May, 2003. Jared was awarded a position on the Human Genetics Training Grant in June, 2004.



Junyu Xiao (Xu) is from Wangkui, People's Republic of China and received his B.S. in Biochemistry from Peking University in Beijing, People's Republic of China. Junyu was a recipient of the Mingde Scholarship for four consecutive years while at Peking University.

2005 GRADUATE STUDENT AWARDS

Christensen Award



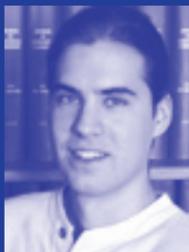
The Halvor N. and Mary Christensen Award for Ph.D. Graduate Study in the Department of Biological Chemistry is presented annually to a second-year student on the basis of academic record. This award is given in memory of Professor Halvor N. Christensen, who was Chair of the Department from 1955-1970, and his wife Mary. The 2004 recipient of the award was Becky Haeusler, whose mentor is Dave Engelke.

Christman Award



The Adam A. and Mary J. Christman Award is presented to a third-year Department student who is judged to be the most outstanding in that class. The award is dedicated to the memory of Professor and Mrs. Christman. The 2004 recipient of the award was Mohamed Abazeed, whose mentor is Bob Fuller.

Coon Award



The Minor J. and Mary Lou Coon Award is given to the student who best exemplifies overall excellence in research, teaching, and service. This award is given in honor of Professor Minor J. (Jud) Coon, who was Chair of the Department from 1970-1990, and his wife Mary

Lou. The 2004 recipient of the award was Robert Pejchal, whose mentor was Martha Ludwig

Dziewiatkowski Award

The Dziewiatkowski Award, which is offered to the student who submits the most outstanding Ph.D. Dissertation during the previous academic year, is given in memory of the late faculty member, Professor Dominic D. (Jay) Dziewiatkowski. The 2004 recipient of the award was Hao Zhou, whose mentor was Dennis Thiele.

Anthony and Lillian Lu Award



The Lu Award is presented annually to a student on the basis of academic background, achievement in the graduate program, and potential as a scientist, with preference for a student who is a non-U.S. citizen. The 2004 recipient of the award was Qian Yang, whose mentor is Kun-Liang Guan

Lee Murphy Memorial Prize



The Lee Murphy Memorial Prize is presented 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. The 2004 recipient of the award was Huiira Chong, whose mentor is Kun-Liang Guan.

STUDENT NEWS

Mohamed Abazeed (Fuller) recently received the Rackham Predoctoral Fellowship Award which is one of Rackham's most prestigious fellowships and is awarded for outstanding research and academic excellence. He also holds a position on the Human Genetics Training Grant.

Adam Avery (Vojtek) holds a position on the Cellular Biotechnology Training Program.

Scott Berger (Miller) holds a position on the Immunology Training Grant.

Daniel Coughlin (Engelke) achieved a position on the Pharmacological Sciences Training Program.

Jared Chrispell (Thompson) was awarded a position on the Human Genetics Training Grant.

Rebecca Haeusler (Engelke) was awarded a place on the Genetics Training Program.

Chung-Han (Joe) Lee (Guan) holds a position on the Cellular Biotechnology Training Program.

Kuei Lee (Ross) holds a position on the Cellular Biotechnology Training Program.

Brian Moore (Xu) was awarded a position on the Molecular Mechanisms of Microbial Pathogenesis Training Program.

June Pais (Fierke) continues as an NSF Fellowship holder.

Leah Parkinson (Fuller) was awarded a position on the Cellular Biotechnology Training Program.

Lance Rider (Fierke) was awarded a position on the Chemical Biology Interface Training Program.

Pamela Wong (Gafni) was awarded a position on the Molecular Biophysics Training Grant.

DOCTOR OF PHILOSOPHY DEGREE GRANTED

The Department extends its congratulations to the following students who have completed their PhD degrees between April 1, 2003 and December 10, 2003.

Jennifer M. Blanchette (Fuller)

"Characterization of Saccharomyces cerevisiae trans Golgi Network Protein Trafficking Events Using Cell-Free Systems." Jennifer is conducting research in the laboratory of Dr. Min Han at the University of Colorado, Boulder where she is studying developmental signaling in the nematode, *C. elegans*.

E. J. Brace (Fuller)

"Role of Soi3p in Localization of the Processing Protease Kex2p to the trans-Golgi Network Through Assembly of Vacuolar ATPase." E.J. will be joining Anne Vojtek's lab while interviewing for post-doctoral positions in the field of neurobiology.

Huiira Chong (Guan)

"Mechanisms of Regulating the Raf/MAPK Signaling Pathway." Huiira is a Research Fellow at the Life Sciences Institute.

Jeremy J. Day-Storms (Fierke)

"RNA-Protein Interactions in Prokaryotic and Eukaryotic Ribonuclease P." Jeremy is a research fellow with Patrick O'Brien in our Department.

Elise Manning Hondorp (Matthews)

"Oxidative Stress Inactivates Cobalamin-Independent Methionine Synthase in Escherichia coli." Elise will continue her work in Rowena Matthew's lab in the Life Science Institute and pursue a post-doctoral research position.

David Michael Karnak (Margolis)

"Biochemical and Structural Studies of the LIN-2 and 7 (L27) Dimerization Domain: Linking Proteins Important in Cell Polarity." Dave is a Research Fellow in the Department of Obstetrics and Gynecology with Steven Domino at the University of Michigan.

Robert Pejchal (Ludwig)

"Structural Studies of Methylenetetrahydrofolate Reductase and Cobalamin-Independent Methionine Synthase: Back-to Back Enzymes in One-Carbon Metabolism." Rob will continue work in the laboratory of Martha Ludwig while arranging a post-doctoral position.

Suzanne Admiraal

Dr. Suzanne Admiraal joined the Department of Biological Chemistry as an Assistant Professor in September of 2004. She hails from western New York and earned

her undergraduate degree in biochemistry at Calvin College in Grand Rapids, MI. She did graduate research in the laboratory of Dr. Daniel Herschlag in the Biochemistry Department at Stanford University, where she investigated the transition state and mechanisms of phosphoryl transfer from ATP. After completing her Ph.D. in 1999, she began collaborative postdoctoral studies supervised by Dr. Chaitan Khosla at Stanford University and Dr. Christopher Walsh at Harvard Medical School. In these laboratories she studied how substrates are covalently loaded and subsequently processed by rifamycin synthetase, a multi-protein assembly line responsible for biosynthesis of the backbone of the antitubercular antibiotic rifamycin.

Suzanne's current research focuses on the biosynthesis of two classes of structurally diverse molecules called polyketides and nonribosomal peptides. These molecules serve a variety of functions, such as defense and signaling, for their microbial producers, and in other organisms they often elicit serendipitous biological responses, including antibiotic, antiviral, and antitumor activities. The biosynthesis of many polyketides and peptides occurs on modular protein assembly lines known as polyketide synthases (PKS) and nonribosomal peptide synthetases (NRPS), respectively. Each protein module within a multimodular assembly line directs the addition of a single substrate monomer to the elongating polyketide or peptide chain. Each module may also contain active sites for substrate modifica-

tion. For example, after each condensation reaction joining a new acetate-derived monomer to a growing polyketide chain, a PKS module causes the resulting β -carbonyl to undergo all, part, or none of a reductive cycle of β -ketoreduction, dehydration, and enoyl reduction. Likewise, an NRPS module may contain active sites that catalyze epimerization, methylation, or cyclization of its amino acid monomer, in addition to peptide bond formation. Several biosynthetic assembly lines have been successfully reprogrammed to make novel molecules. Research in Suzanne's laboratory aims to uncover general principles for assembly line functioning and reprogramming by studying the biochemical mechanisms of several prototypes. These studies may ultimately facilitate the development of enzymatic or chemoenzymatic routes to useful molecules.

Ming Lei

Dr. Ming Lei joined the Department of Biological Chemistry as an Assistant Professor in November of 2004. Ming received his B.S. in Physics

from Tsinghua University in Beijing, China. After he obtained his M.Sc. in Physics from McGill University he went to Harvard University to pursue his graduate degree in Biophysics in Dr. Stephen Harrison's laboratory, where he performed the structural studies of p21-activated protein kinase (Pak) by X-ray crystallography. In the course of this work he discovered that unlike other protein kinases Pak is kept in an inactive state by homodimerization and activated by interactions with GTP-liganded forms of Cdc42 or Rac, a process important for cytoskeletal actin assembly and cellular morphology. After completing

his Ph.D. in 2001, Ming began his postdoctoral researches on telomere ends protection in Dr. Thomas Cech's lab at University of Colorado at Boulder. Telomeres are higher order nucleoprotein complexes that cap the ends of chromosomes and play essential roles in conferring genome stability and cell proliferation capacity in all eukaryotes. Changes in telomere functions and the associated chromosomal abnormalities have been implicated in human aging and cancer. He solved the crystal structures of the DNA-binding domains of POT1 (protection of telomeres 1) proteins from both fission yeast and human cells complexed with their telomeric single-stranded substrates. The structures explain the molecular basis of telomeric DNA sequence recognition by POT1 and provide an atomic-resolution model for chromosome end-capping and insights into how POT1 proteins coat the entire single-stranded region of the telomere.

Ming's lab continues to study the molecular basis of the mechanism of telomere end protection and the regulation of telomere length in humans. One of Ming's interests is the molecular architecture of the single-stranded region (G-overhang) of the telomere. In human cells, the G-overhang is 100 - 400 nt long, and capable of binding up to about 30s POT1 molecules. It is unknown whether the POT1-G-overhang complex forms a compact higher-order structure or simply adopts a bead-on-string-like extended flexible conformation. The preliminary results of Ming's lab indicated that the G-overhang binds to its binding protein, POT1, forming a helical, higher order complex (T-helix). Research in Ming's lab aims to characterize the protein-DNA and protein-protein interactions of the T-helix with the final goal of solving the three-dimensional crystal structure of the entire T-helix. Another project is to study a multi-subunit complex (telosome), which forms the protective cap of the telomere

and contributes to a regulatory network for telomere length regulation. Core members of this complex include TRF1 and TRF2, which bind directly to double-stranded telomeric DNA, and POT1, which binds to the single-stranded DNA at the telomere terminus. The lab will study the interactions among the components of telosomes and their roles in telomere maintenance, employing a variety of biochemical, biophysical and structural approaches to dissect and reconstitute these interactions in vitro. These studies are expected to lead to novel insights into telomere architecture and how it is maintained and regulated in human cells.

Neil Marsh

Dr. Neil Marsh joined the Department of Biological Chemistry as Associate Professor in September of 2004. He holds a joint appointment in the

Chemistry Department, where he has been a member of the faculty since 1995. Neil is originally from England and took his undergraduate degree in Natural Sciences from the University of Cambridge. He continued his studies in Cambridge, where he earned his Ph.D. in Biochemistry working with Dr. Peter Leadlay. His thesis research centered on the structure and mechanism of the vitamin B12-dependent enzyme, methylmalonyl-CoA mutase, an enzyme important in fatty acid metabolism. After completing his Ph.D., Neil joined Dr. Craig Townsend's laboratory at the Johns Hopkins University as a postdoctoral fellow. There he studied how enzymes synthesize β -lactam antibiotics, which include the clinically important penicillins and cephalosporins. In particular, his research focused on clavamate syn-

thase, an enzyme that, remarkably, catalyzes three separate oxidative transformations in the biosynthesis of clavulanic acid, which is a potent inhibitor of β -lactamase enzymes that are responsible for antibiotic resistance.

Neil began his independent research career first as a senior scientist at Cambridge University, where he held a prestigious Royal Society Research Fellowship for five years before moving back to the USA to join the faculty of the University of Michigan. His research has centered on the mechanisms by which enzymes generate and control free radicals. He is best known for his work on glutamate mutase, which is one of a group of adenosylcobalamin (coenzyme B12) enzymes that catalyze unusual carbon skeleton isomerizations. These enzymes are interesting because the reactions they catalyze have no counterpart in conventional organic chemistry, and they provide valuable model systems with which to elucidate the general principles by which enzymes harness extremely reactive radical species towards productive catalysis. More recently Neil and his group have begun to investigate the mechanism of another radical enzyme, benzylsuccinate synthase. This enzyme catalyzes a remarkable reaction – the addition of toluene across the double bond of fumarate to give benzylsuccinate. This is the first step in the anaerobic metabolism of toluene by various bacteria, and Neil's group hopes that understanding the mechanism of this enzyme may lead to new approaches in bio-remediation.

A newer interest in his laboratory is the design of proteins using unnatural amino acids. Currently, his group is focused on building "Teflon" proteins using extensively fluorinated analogs of hydrophobic amino acids to pack the inside of the protein. He expects that such proteins

may exhibit useful new properties such as increased thermal stability, resistance to unfolding in organic solvents, and resistance to degradation by proteases. Teflon proteins may also exhibit novel protein-protein interactions and provide model systems to test theories of protein folding.

Patrick O'Brien

Dr. O'Brien joined the Department as an Assistant Professor in September 2004. He received his B.S. in Biology and Chemistry from Santa Clara University

where he completed his Honors Thesis on lipid dynamics within human erythrocyte membranes. He obtained his Ph.D. in Biochemistry with Prof. Dan Herschlag at Stanford University, where he studied the catalytic mechanism of E. coli alkaline phosphatase. In the course of this work he discovered that this well-known phosphatase also catalyzes sulfatase and phosphodiesterase reactions. This observation of 'catalytic promiscuity', the ability of a single active site to catalyze multiple types of chemical transformations, helps to explain the evolutionary diversification of enzymes. Indeed distant relatives of alkaline phosphatase are known to be biological sulfatases and phosphodiesterases, raising the possibility that the promiscuous activities of alkaline phosphatase might have aided in the divergent evolution of these enzymes. The widespread existence of catalytic promiscuity among modern-day enzymes and the many examples of enzyme superfamilies suggest that biochemical pathways might have evolved, and continue to evolve, by the optimization of pre-existing promiscuous activities.

(See the December 2003 issue of Chemical & Engineering News for a discussion of catalytic promiscuity.)

After completing his doctoral work, Pat moved across the country to pursue post-doctoral studies in Prof. Tom Ellenberger's lab at Harvard Medical School, where he focused on the question of how 3-methyladenine DNA glycosylases locate and initiate repair of cytotoxic 3-methyladenine lesions. As these lesions form spontaneously in the cell and are potent blocks of DNA replication, it is not surprising that prokaryotes and eukaryotes independently evolved enzymes that function as 3-methyladenine DNA glycosylases. Although there are substantial differences between these enzymes (for example, the human enzyme does a much better job of discriminating against undamaged DNA and the *E. coli* enzyme has a unique ability to remove alkylated pyrimidines), both utilize base-flipping mechanisms that allow them to identify chemically damaged bases via their weakened base-pairing.

Pat's lab at the University of Michigan continues to study enzymes involved in DNA repair and replication, using a variety of biochemical, biophysical, and structural techniques to reconstitute and dissect these pathways *in vitro*. Current projects include studying the catalytic mechanism of DNA ligases. Human cells have three DNA ligases that are responsible for repairing different types of broken DNA and Pat seeks to understand the biochemical basis for this specialization. The DNA ligase reaction involves formation of covalent enzyme-AMP and AMP-DNA intermediates, raising the question of how multiple chemical transformations are carried out within a single active site. The lab is also studying enzymatic base-flipping, in which a nucleotide is extruded from the DNA duplex. Base-flip-

ping is a critical component of most reactions involving a duplex DNA substrate, including base excision repair and DNA methylation, because it allows access to a base moiety that is normally hidden within the double helix. More generally, Pat is interested in the dynamics of protein-protein and protein-nucleic acid interactions within multi-component DNA repair and replication complexes and plans to use both *in vitro* biochemistry and structural biology to understand how multi-step, multi-enzyme DNA repair pathways are coordinated.

Matthew Young



Dr. Young joined the University as an Assistant Professor in Biological Chemistry and the Bioinformatics Program in December of 2004. He earned both his B.A. and

Ph.D. degrees from Wesleyan University in Connecticut. Working in the laboratory of David Beveridge, he applied and refined computational chemistry techniques, such as molecular dynamics simulations, to investigate sequence-dependent molecular structure and dynamics in nucleic acids. He then spent three years as a postdoctoral fellow (Damon Runyon Cancer Research Foundation) in the laboratory of John Kuriyan at the Rockefeller University in New York City, where his work focused on the Src family of proto-oncogene proteins. He utilized computational modeling to investigate the structural basis for the allosteric regulation of catalytic activity in this family of enzymes, testing hypotheses by engineering protein mutants with altered regulatory properties. He continued his work in California when the Kuriyan lab moved to the University of

California, Berkeley. In Berkeley he largely concentrated on another proto-oncogenic signaling protein, one that is the molecular target of novel anti-cancer therapies, the Abl tyrosine kinase. With use of x-ray crystallography, he structurally characterized inhibitor complexes of the Abl protein, including a number of mutant Abl proteins that have emerged in patients receiving anti-leukemia therapy. While at Berkeley he was awarded a Burroughs Wellcome career award at the scientific interface.

Matt's current research will continue to integrate computational and experimental techniques to study problems in protein kinase regulation and cell signaling. Protein kinases represent one of the fundamental components of cell signal cascades that propagate signals for fundamental cellular processes including growth, differentiation, and metabolism. In higher organisms, hundreds of diverse protein kinases have evolved different molecular mechanisms to regulate the signaling states of distinct but often co-existing signaling pathways. In an example of regulation in a family of proteins Matt is currently studying the Cyclin Dependent family of Kinases (CDKs), which have evolved to require the binding of additional proteins, the cyclins, in order to activate their catalytic activity. Some examples of additional molecular mechanisms that have evolved to regulate catalytic activity in protein kinases include the interactions of additional domains with the catalytic core, phosphorylation-stabilized conformational transitions the binding of external inhibitory proteins, and protein kinase localization. His goal is to understand these regulatory mechanisms from a structural perspective, using the CDK family as a model.

From a computational approach, he employs molecular modeling approaches based upon atomic resolution chemical potential energy functions that are capable of describing detailed molecular properties of the proteins under study. Historically carried out largely on supercomputers, these simulations are now routinely carried out on clusters composed of pc-class computers linked together. Among other things, this modeling approach is used to describe the molecular motions of proteins in an *in vitro* environment. Coupling these models with x-ray crystallography and *in vitro* enzymatic assays enables him to study regulatory mechanisms from a protein dynamics, structure, and activity based perspective.

We are extremely grateful to all of the individuals (and in some cases their organizations) whose recent gifts and donations have provided valuable discretionary funds to support a wide range of Departmental activities.

Ward W. Smith and Cheryl A. Janson

Claudia and Jack Dixon

G. Robert and Susan A. Greenberg

Karen Christensen Grey

Minor J. Coon

Audrey F. Seasholtz

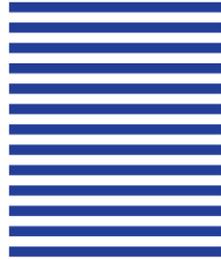
Jane Ann Damren

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University of Michigan Medical School
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