Department of Biological Chemistry

Newsletter 2002

University of Michigan Medical School

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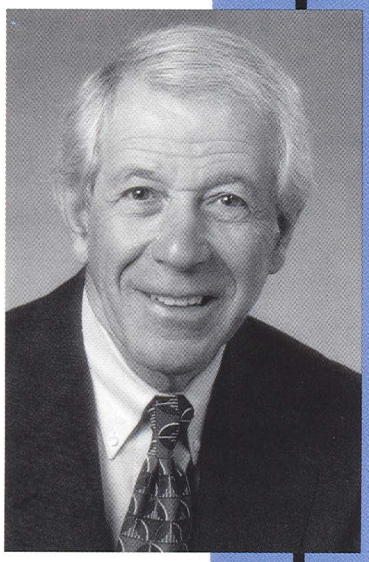
Letter from the Interim Chair



When my sons and a friend asked me what I had learned about life upon reaching the biblical age of three score and ten, I hesitated for a moment and then replied, "Expect the unexpected, for it most surely will occur." Little did I realize that my own words were prophetic: Here I am, plucked from retirement, to become the Interim Chair of our Department of Biological Chemistry, although I continue to work in my lab almost every day.

As you all know, Jack Dixon retired from the Chair after ten years of inspired leadership to become Director of the recently-formed Life Sciences Institute. Jack's tenure was marked by outstanding gains for the Department, and we wish him much success in his new role. The search for his successor continues. The search committee, headed by Paul Hollenberg, Chair of Pharmacology, is composed of nine members including Claudia Kent and Dennis Thiele from our Department; it is actively involved in the task of identifying additional new Chair candidates.

The Department continues its status as a strong entity pursuing vigorous programs of research, teaching and service with the establishment of new courses and research collaborations with colleagues both from within and outside our School. Noteworthy are our initiatives in bioinformatics and proteomics.

Should you return for a visit to Ann Arbor you would not recognize our campus. A new Life Sciences Institute Building, located next to the Power Plant, is well on its way, and ground breaking for a new Biomedical Sciences Research Building located in the space occupied by the Neuroscience building on Huron Street occurred just this April.

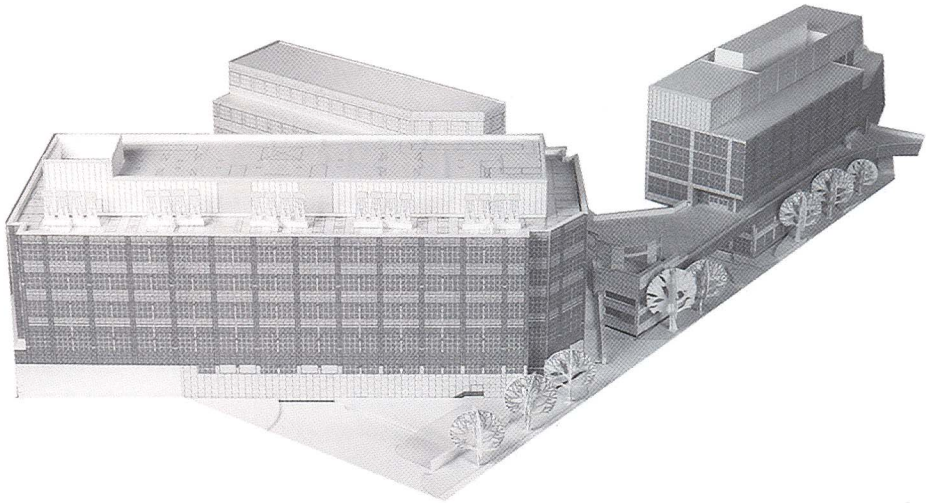
I hope that you will enjoy reading in this Newsletter about the involvement of three of our faculty members, Jack Dixon, Martha Ludwig, and Phil Andrews, in some exiciting scientific developments that will benefit our Department as well as strengthen science elsewhere in the State of Michigan.

Irwin Goldstein

Irwin J. Goldstein, Ph.D.
Professor and Interim Chair
Department of Biological Chemistry

Life Sciences Institute Update

"The Life Sciences movement is gaining momentum at the University."



I am very pleased to bring you up to date on the progress of the new Life Sciences Institute. As you may already know, the Institute is a new interdisciplinary research facility being built on the Ann Arbor campus as a physical and intellectual bridge between central campus and the medical center. Its core emphases will be on genomics and complex genetics, and structural, computational and chemical biology, as well as cell biology and related areas. The building completion date of September 2003 is right on track. Once completed, the Life Sciences Institute will hire 20 to 30 world-class researchers in a variety of disciplines from outside the University of Michigan, as well as offering fellowships and research sabbaticals to University of Michigan faculty who wish to work at the Institute.

Along with the Institute, there will be two other buildings and a 1,100-space parking garage. The Science Instruction Center is a four-story building atop the parking garage. This building will house classrooms and labs for the new Life Sciences curriculum. The Commons Building, a 99,000-square-foot space, will house offices, conference space, and retail and dining facilities, including a food court. The University's bioinformatics core will be here as well.

Even though the physical building is not yet complete, the Life Sciences movement is gaining momentum at the University. I am pleased to announce that the first annual Life Sciences Symposium, led by Zhaohui Xu, is to be held May 9 in the Ford Auditorium in the University Hospital. This year's theme is "The Structural Biology of Cell Signaling" and will feature talks by Jonathan Goldberg, John Kuriyan, Harvey Lodish, Roderick MacKinnon, Yigong Shi, and Zhaohui Xu. This symposium will highlight recent developments and provide an opportunity for students and scientists from around the state to learn from prominent scientific leaders.

I am also happy to announce that Elizabeth Barry, U-M's Associate Vice President and Deputy General Counsel, has been named as the Institute's Managing Director. Liz will undertake the day-to-day responsibilities for the building, staffing, and operation of the Institute. Liz has a very diverse background in administration and finance as well as legal expertise. She will add breadth to the Institute, playing a key role in fund raising and outreach programs. Her traits are sure to be an asset to the Institute, and I look forward to her joining us in April.

If you would like to read more, please check out our website at *http://www.lifesciences.umich.edu.*

—Jack E. Dixon

Michigan Life Sciences "Corridor" Launched

A novel major initiative has been launched with funding provided from the State of Michigan settlement of the tobacco litigation. The Michigan Life Sciences Corridor (MLSC), administered by the Michigan Economic Development Corporation, plans to use $1 billion of these funds over a period of 20 years to "promote life sciences research and business development." Support for research is available to scientists joining in collaborative projects, to biotechnology companies, and to major institutions. Development of shared infrastructure and technology transfer are important goals of the program. The concept of a "corridor" indicates that institutions and companies across the state will work as partners in basic research, collaborative research, and commercial development.

As part of the MLSC, the major universities, along with the van Andel Institute in Grand Rapids, have been

...continued page 3, "Corridor"

"Corridor" continued...

funded to develop infrastructure and capabilities in several areas. These are Animal Models, centered at van Andel Institute, Genomic Technologies (WSU), Biological Information (UM), Structural Biology (MSU), and Proteomics (UM). The infrastructure development is expected to provide unique facilities to researchers state-wide and will open new opportunities to faculty, students and trainees in our department.

Several faculty in Biological Chemistry have been involved in the planning and development of the infrastructure initiatives. Part of the funding allocated to the Structural Biology center is for building and maintenance of facilities for x-ray diffraction at the Advanced Photon Source located at Argonne National Laboratory outside Chicago. The expectation is that the number and complexity of systems that can be studied by x-ray groups in Michigan will be significantly enhanced by securing access to synchrotron x-ray sources. Martha Ludwig has spearheaded this effort, which will provide new beamlines for crystallographers from the Michigan institutions. Other departmental crystallographers involved in the project are Mark Saper, Jeanne Stuckey, and Zhaohui Xu.

With $10 million funding for the initial two years, optics and experimental stations will be built to accommodate a full range of protein crystallography experiments. Our partners in the construction and operation of the facility are Northwestern University crystallographers and beamline scientists. Full development of the Argonne operations will add four more experimental stations and will include additional institutional partners. The Michigan investment will provide capabilities for advanced structural studies and unique opportunities for research and training.

Part of the support for structural biology will provide local facilities and consultation for structure determination in Ann Arbor. A Laboratory for Analysis of Macromolecular Structure, with Dr. Jeanne Stuckey as manager, is assisting faculty and students in Biological Chemistry and other departments in sequence modification, cloning and expression, crystallization, and x-ray structure determination.

Other aspects of the Structural Biology Center will be equally important for scientists in Biological Chemistry. Funds have been allocated for the acquisition of an ultra-high-field NMR spectrometer, to be located in East Lansing. Erik Zuiderweg has had a leading role in the design and development of this facility. Rowena Matthews, as former Chair of the Biophysics Research Division, has been involved in development of new labs and methodologies for the study of single molecules, again supported in part by funds from the Michigan Corridor.

—Martha L. Ludwig

Michigan Proteome Consortium

The Michigan Proteome Consortium (MPC) is a multi-institution initiative dedicated to the development and delivery of state-of-the-art high throughput proteome technologies to academic and industrial investigators across the State of Michigan. MPC has nodes at four major research institutions in the state of Michigan. Each node functions as part of the Consortium to provide services to both academic and industrial investigators. It is administered by the Senior Director, Philip Andrews, and a Steering Committee, with the help of a Scientific Advisory Committee. The four primary core services are: Proteome Mapping, High-Throughput Yeast Two-Hybrid Screening, Protein Microarrays, and Proteome Informatics. The Consortium also employs 17 highly skilled staff members to support proteomics research. Detailed information on the Cores and the services may be obtained at *www.CTAalliance.org*.

The Proteome Mapping Laboratory is distributed between two sites, one at Michigan State University and the other at University of Michigan. The Director, Philip Andrews, is at the University of Michigan, and the Associate Director, Brett Phinney, is at Michigan State University. The two sites act as a single laboratory to provide a broad range of proteome mapping services to investigators. The Proteome Mapping Laboratory is focused on provision of high-throughput proteomics services, although pilot and feasibility projects are also supported. Services offered include: LC MS and LC MS/MS, analysis of protein complexes, mapping sites of post-translational modifications, 2D gel electrophoresis and image analysis, and protein expression profiling by D electrophoresis and by 2D LC MS/MS. Areas of particular expertise include analysis of membrane proteins, bacterial pathogens, and tumor and tissue samples as well as mapping sites of post-translational modifications.

The Proteome Informatics Core provides software development, database, and bioinformatics support for the MPC and its clients. The Proteome Informatics staff consists of four full-time software engineers and programmers for software and database development. The PRIME information management system (prime.proteome.med.umich.edu) is developed and supported by this group. Additional computational support is provided by the Michigan Center for Biological Information (*www.CTAalliance.org*), Brian Athey, Director.

Services provided by the High-Throughput Yeast Two-Hybrid Core under the direction of Russell Finley at Wayne State University include screening all the pair-wise interactions between large sets of proteins (up to 10,000) as well as more traditional library screening and provision of reagents for yeast two-hybrid screening. The Core occupies 1,000 sq. ft. of renovated lab space at Wayne State University.

The Protein Microarray Core, directed by Brian Haab and located at the VanAndel Research Insitute, is scheduled for services in 2003 and will provide custom and stock protein microarrays for researchers.

—Philip C. Andrews

What's Happening & Updates

Faculty News

Dave Ballou will participate in a collaborative research project with Barrie Entsch from the University of New England in Aruisdale NSW, Australia. Barrie will join Dave and Vince Massey for an extended period beginning in January 2003. They are long-term collaborators.

Jud Coon is on the International Advisory Committee for the Symposium on Microsomes and Drug Oxidations to be held in Sapporo, Japan next July. The International Conference on Cytochrome P450 held in La Grande Motte, France, last September was dedicated to him in recognition of his contribution to the advancement of biochemical, biophysical and biological research on P450.

David Engelke retired as Chair of the Cell Development and Function 6 Study Section.

Claudia Kent was selected as Co-Chair of the Program Committee for the 2003 ASBMB National Meeting.

Benjamin Margolis received the University's Faculty Recognition Award.

Jerry Menon received a Merit Award from the National Institutes of Health for his ongoing studies on structure/function studies of luteinizing hormone receptor. The award provides support for 10 years.

Larry Oncley, Professor Emeritus of Biological Chemistry and Professor Emeritus of Chemistry, recently moved to Cape Cod (*email, jloncley@verizon.net*). Two years ago, at the time of his 90th birthday, the Biophysics Research Division named the J. Lawrence Oncley Conference Room in his honor. He was elected to the Natural Science Hall of Fame, newly established by Southwestern College, Winfield, Kansas, and last October attended the inaugural induction ceremonies that honored, as the initial membership, ten outstanding scientists graduated by the college during the previous 115 years of its history.

Todd Porter, formerly Assistant Professor in our Department, is Associate Professor in the Division of Pharmaceutical Sciences, University of Kentucky College of Pharmacy in Lexington. He received the Faculty Appreciation Award from the Graduate Students in Toxicology last year for his efforts on their behalf.

Dennis Thiele received the University's Distinguished Faculty Achievement Award for 2001.

Zhaohui Xu received a 2001 PEW Scholars Award. The PEW Charitable Trust awards are granted to young investigators who show outstanding promise in the basic and clinical sciences.

Alumni/ae News

Eric Baude (Ph.D. with Uhler) has taken a position as Patent Counsel with Pfizer in Ann Arbor. Previously, he was a patent attorney with Townsend and Townsend and Crew LLP in San Francisco.

Faye Bradbury (Ph.D. with Menon) has accepted a position in the Stuctural Biology Section at Pfizer Global Research in Ann Arbor.

P imchai Chaiyen (Postdoc with Ballou) continues to work on flavoproteins at Mahidol University in Bangkok. She is collaborating with Dave Ballou and Vince Massey and occasionally visits to carry out research experiments. She will be sending two Thai students to our department in the next few years.

James Clemens (Ph.D. with Dixon) has been named a Helen Hay Whitney Fellow and is currently a postdoctoral fellow in Larry Zupursky's laboratory at University of California, Los Angeles.

Carl Correll (Ph.D. with Ludwig) is currently Assistant Professor of Biochemistry and Molecular Biology at the University of Chicago. Carl's postdoctoral fellowship with Tom Steitz at Yale introduced him to the world of RNA structure and recognition. His independent research continues in this area, with studies of the maturation of rRNA and protein recognition of conserved features in ribosomes.

Paul Craig (Ph.D. with Dekker) is on a sabbatical leave from his faculty position at Rochester Institute of Technology and is spending a year in the Supercomputing Center at University of California, San Diego.

William Dean (Ph.D. with Coon), Professor of Biochemistry and Molecular Biology at the University of Louisville School of Medicine, is a member of the Board of the European Platelet Group, which holds meetings in Germany. He has also been active in the American Heart Association serving on consortium peer review committees and has been a member of the Ohio Valley Affiliate Research Committee.

Xinxin Ding (Ph.D. with Coon) is Associate Professor in the Department of Biomedical Sciences, School of Public Health, State University of New York at Albany. He and his wife **Qing-Yu** (Ph.D. with Menon) both have the title of Research Scientist at the Wadsworth Center of the New York State Department of Health.

...continued page 5, Alumni/ae

Alumni/ae News Continued...

Catherine Drennan (Ph.D. with Ludwig) was a postdoctoral fellow with Doug Rees at CalTech and in 1999 was appointed Assistant Professor of Chemistry at MIT. Her postdoctoral and independent research has dealt with structure-function relationships in complex metalloenzymes, primarily carbon monoxide dehydrogenase and B_{12}-dependent ribonucleotide reductase. Cathy is a Searle Fellow and the Cecil and Ida Green Career Development Assistant Professor of Chemistry.

Paul Engel (Postdoc with Massey), now chair of Biochemistry at the University College Dublin, has been elected to the Royal Irish Academy.

Jon Friesen (Postdoc with Kent) is now an Assistant Professor in the Chemistry Department at Illinois State University in Normal, Illinois. Jon continues to study eukaryotic cytidylyltransferases.

Fred Guengerich (Postdoc with Coon), Professor of Biochemistry and Director of the Center in Toxicology at Vanderbilt University, was given the Earl Sutherland Prize for Achievement in Research from Vanderbilt last year.

Gordon Hassing (Ph.D. with Goldstein) has retired from the Procter & Gamble Company after working for them since 1969. He served in a number of research and R&D management assignments, both in the United States and Europe.

Dennis Koop (Postdoc with Coon and then Assistant Professor in our Department), now Professor of Physiology and Pharmacology at the Oregon Heath Science University, has been serving as Chair of the Drug Metabolism Division of the American Society for Pharmacology and Experimental Therapeutics.

James MacDonald (Postdoc with Kent) is a Scientist at the John P. Robarts Research Institute in London, Ontario, where he works on signaling adaptor proteins.

Peter Macheroux (Postdoc with Massey) has accepted a Full Professorship at a new German University, International University, Bremen, Germany.

Graham Moran (Visiting Research Postdoc with Ballou) is an Assistant Professor in the Chemistry Department at the University of Wisconsin, Milwaukee. He is studying various oxygenases involving pterins.

Marco Muda (Postdoc with Dixon) is now a Senior Principal Investigator at Serono Reproductive Biology Institute in Randolph, Massachusetts.

Kim Orth (Postdoc with Dixon) is now an Assistant Professor at the University of Texas Southwestern Medical. Kim recently had two papers in *Science*.

Yoichi Osawa (Ph.D. with Coon), Associate Professor of Pharmacology at the University of Michigan, received the Henry Russel Award, which recognizes exceptional scholarship and teaching ability of the University's junior faculty members.

Young Seo Park (Postdoc with Kent) is an Assistant Professor in the Department of Food and Bioengineering, Kyungwon University, South Korea.

Steve Pernecky (Postdoc with Coon), who has been promoted to Associate Professor of Chemistry at Eastern Michigan University, is spending a sabbatical leave in the University of Michigan Pharmacology Department.

Andrei Raibekas (Postdoc with Massey) has taken a position with Amgen in California.

Sondra Schlesinger (Ph.D. with Greenberg) and **Milton Schlesinger** (Ph.D. with Coon), both in the Department of Molecular Microbiology, Washington University School of Medicine, have become involved in various aspects of the history of virology. The Sloan Foundation has sponsored a Website on the history of structural virology that can be viewed at *http://medicine.wustl.edu/virology*.

Chris Vlahos (Ph.D. with Dekker) works for Eli Lilly and has been elected to the editorial board of the Journal of Biological Chemistry. He also co-chaired and spoke at a session of the American Society of Pharmacology and Experimental Therapeutics Meeting in April.

Ronald White (Postdoc with Coon) has been promoted to Vice-President of Drug Metabolism and Pharmacokinetics at the Schering-Plough Research Institute. He is also an Adjunct Associate Professor of Chemical Biology at Rutgers University and lectures occasionally in the Chemistry graduate program at Princeton.

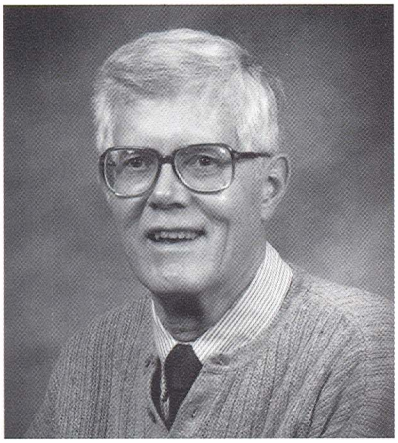
New – Alumni/ae Website

We would like to stay in touch with our Alumni/ae. Please visit our Alumni/ae website at

http://www.biochem.med.umich.edu/biochem/alumni_form.html

We look forward to hearing from you soon!

Transitions



Donald E. Hultquist, Ph.D.
Professor of Biological Chemistry

Donald E. Hultquist, Professor of Biological Chemistry, retired from the University on August 31, 2001 after serving on the faculty of the Medical School for his entire academic career.

Don was born, raised, and educated in up-state New York. He received a B.S. in Chemistry and a Ph.D. in Biochemistry from the University of Rochester, isolating and studying lactoperoxidase during his doctoral research. His postdoctoral research with Paul Boyer at the University of Minnesota and UCLA focused on phosphohistidine chemistry.

He joined the faculty of the University of Michigan in 1964, becoming Full Professor in 1979. In his research laboratory, he mentored nine Biological Chemistry doctoral students as well as a large number of students in undergraduate, medical, and interdisciplinary graduate programs. His research focused on the catalysis of oxidation-reduction reactions in red blood cells and on the functioning of antioxidant systems. Previously unrecognized hemeproteins, copper proteins, reductases, and proteases were isolated, chemically characterized, and studied with regard to biological function and medical significance. Particular recognition was awarded him for characterizing the methemoglobin reduction system and the system by which riboflavin prevents oxidative damage in tissues. He has lectured and conducted research in Japan as a Fellow of the Japan Society for the Promotion of Science.

Don developed highly successful innovations in teaching. He taught the first undergraduate biochemistry course in our Department and coupled this with a research-based enrichment seminar. For second-year Inteflex students, he designed and taught a medical biochemistry course which stressed active student participation. For medical students, he developed and taught a pre-matriculation summer course and set up a clinical correlation program in which 4th-year medical students taught 1st-year students. For M.D./Ph.D. students, he designed individualized programs and then encouraged the School to apply for funding for a combined M.D./Ph.D. Program. These efforts in teaching, led to his receiving the University's Outstanding Teaching Award.

Don has also been an effective administrator. He served for one year as the acting director of the CMB Graduate Program and for 13 years as director of the medical biochemistry and molecular & cell biology courses. From 1996 to 2000, he was Associate Chair of the Department of Biological Chemistry and administrator of its graduate program. In administration, as in teaching and research, he proved to be a dedicated student counselor and advocate.

The Regents have recognized his academic achievements by naming him Professor Emeritus of Biological Chemistry.

Symposium to Honor Donald E. Hultquist

"Cellular Oxidation"

June 15, 2002

The Department will be honoring Donald Hultquist on the occasion of his retirement from the Department after 37 years of research, administration, and teaching. The symposium acknowledges his contributions to the fields of hemeproteins, phosphoproteins and protection from oxidative damage. The symposium features lectures by Nobel Laureate Paul Boyer, Harvard hematologist Frank Bunn, and University of California-San Francisco chemist Paul Ortiz de Montellano.

For More Information
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On the Web

To find out what's new in the Biological Chemistry Department, visit our website at

http://www.biochem.med.umich.edu/

In Memoriam —

Lewis D. Stegink, Professor of Pediatrics and Biochemistry at the College of Medicine, University of Iowa, died last October 19 of complications resulting from Parkinson's Disease after a distinguished and productive career as a scientist and teacher.

He received his undergraduate degree at Hope College and Ph.D. degree from our Department in 1963 with his thesis work in Jud Coon's laboratory. Lew was a dedicated teacher of medical and graduate students at Iowa and widely known for his research on biochemical nutrition, which led to his receiving the Mead Johnson Award of the American Institute of Nutrition. He was the first to purify the β-hydroxy-β- methylglutaryl-CoA cleavage enzyme and developed a microenzymatic method for quantitative analysis of acetyl groups in amino acids and proteins. His research interests included biochemical changes occurring during normal and abnormal development of the human infant, the toxicity of monosodium glutamate, D-methionine, and aspartame, parenteral nutrition, and placental transfer and absorption of amino acids and peptides. He was a member of numerous editorial boards and national committees dealing with nutritional science. Lew will be greatly missed by his family and colleagues.

New Students Join Current Ph.D. Candidates

Andrew Andrews is from Raleigh, North Carolina. He received his M.S. in Microbiology at North Carolina State University.

Jennifer Aurandt is from Toledo, Ohio. She received her B.S. in Chemistry from Bowling Green University, Toledo, Ohio. She was given an Undergraduate Research Award, Elliot Blinn Memorial Scholarship and Rising Junior Scholarship.

Michael Begley is from Melrose, Massachusetts. He received his B.A. in Biochemistry at Middlebury College in Vermont. While there he received Departmental Honors, College Scholar Award, and Outstanding Senior Biochemist Award.

Katherine Hicks is from Endwell, New York. She received her B.S. in Biochemistry from Bucknell University in Lewisburg, Pennsylvania. She belonged to a number of honor societies and participated in the Merck Corporation's Summer Internship Program.

Anthony Ludlam is from Livonia, Michigan. He received his B.S. in Biochemistry from Michigan State University.

Narinporn Pattaramanon is from Nakhon Phanom, Thailand. She received her B.S. in Biochemistry from Chulalongkorn University in Bangkok, Thailand. She received First Class Honors, Gold Medal in Biochemistry, Outstanding Student Award, and Tab Nilanthi's Outstanding Graduate Award.

Robert Pejchal is from Framingham, Massachusetts. He received his B.A. and B.S. in Biochemistry and Biology from Brandeis University, Waltham, Massachusetts.

Mattabhorn Phimphilai is from Muang, Thailand. She received her M.D. and Clinical Sciences degrees from Chiangmai University, Chiangmai, Thailand as well as passing her Thai Board of Medicine from the Royal College of Internal Medicine. She was honored by Awards for Best Student in Medical Sciences, Best Medical Student in Anatomy, Best Medical Student in Academics, and Academic Medal Award for Outstanding Medical Student.

KunYoo Shin is from Bundanggu, Sungnam, Republic of Korea. He received his B.A. in Agricultural-Chemistry and his M.S. in Biochemistry from Korea University.

Rebecca Taurog is from Mendota Heights, Minnesota. She received her B.A. in Biochemistry and her B.S. in Biology from Brandeis University. While there she was a Howard Hughes Undergraduate Summer Fellow.

Minfeng Zhu is from Nanjing, China. He received his B.S. in Biochemistry from Nanjing University. He received a Renming Scholarship, Elite Scholarship, and second prize for the Basic Science Forum Student Essay Contest while attending Nanjing University.

Degrees Granted

The Department extends its congratulations to the following students who have completed their Ph.D. degrees since May of 2001.

Diane Hall (Matthews)
"Mapping the Interactions Between *Escherichia Coli* Flavodoxin and Its Physiological Partners, Flavodoxin Reductase and Cobalamin-Dependent Methionine Synthase." As a member of the Medical Scientist Training Program, Diane will be returning to medical school to complete her clinical training.

John Stansberry (Uhler)
"Biochemical and Functional Analysis of cGMP-Dependent Protein Kinases from *C. elegans*." John is currently doing a postdoc with Dr. Claudia Kent in our department.

Michelle Steinhilb (Gaut)
"Analysis of the Alzheimer's Disease Amyloid Precursor Protein (AAP) in the Secretory and Endocytic Pathway." Michelle will conduct post-doctoral research on α–synuclein-induced neurodegeneration in Drosophila in the laboratory of Dr. Mel Feany in the Department of Pathology at Harvard Medical School.

Travis Hiroshi Tani (Matthews)
"Transitions Between the Gut and the Gutter: A Global Examination of the Regulon Controlled by the Leucine Responsive Regulatory Protein (LRP) in *Escherichia Coli*." Travis will be pursuing a position in industry.

Distinguished Alumni/ae Lectureship

Dr. Sidney Strickland (left), Claudia Kent and Jack Dixon

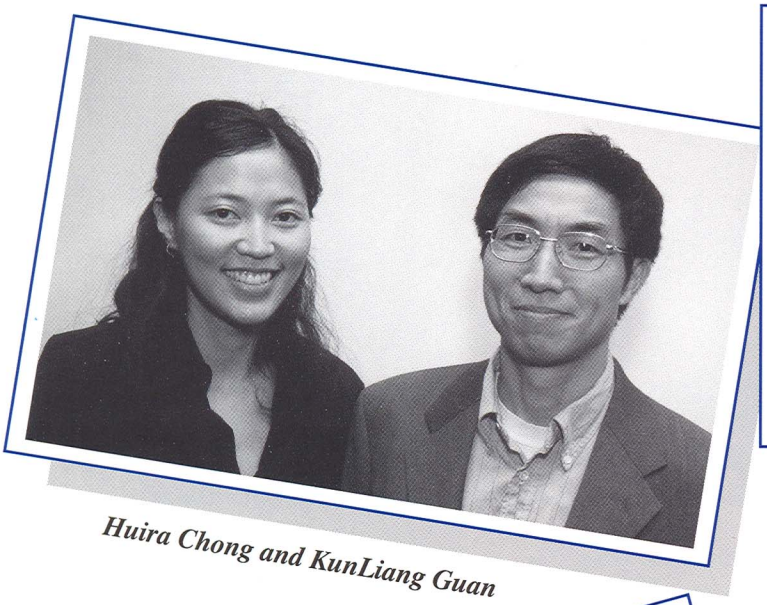
Our third annual Distinguished Graduate Lecture, along with our Student Awards Ceremony, was held in May, 2001. Dr. Sidney Strickland was our Distinguished Graduate, and he presented a lecture entitled "Life, Death, and Regeneration in the Mammalian Nervous System: Roles for Proteases and the Extracellular Matrix."

Sid received his Ph.D. from the Department after carrying out his thesis work in the laboratory of Vince Massey. He performed postdoctoral work at the Rockefeller University with Dr. Edmund Reich, where he was introduced to the plasminogen system. Sid was Professor of Pharmacological Sciences at SUNY Stoney Brook for a number of years before moving back to the Rockefeller University as a Professor of Neurobiology and Genetics as well as Dean and Vice-President for Graduate and Postgraduate Studies.

Strickland's current research focuses on the role of extracellular proteolysis in the nervous system. For example, his laboratory has investigated the connection between tissue plasminogen activator (tPA) and cell death in the hippocampus, and has found that cell death involves plasmin-mediated degradation of laminin, a component of the extracellular matrix. In an extension of this work, the Strickland lab is investigating the role of tPA in the progression of Alzheimer's disease. The laboratory also studies the role of tPA in the peripheral nervous system, and has found that plasmin-mediated fibrin degradation has a protective effect after injury to the sciatic nerve.

The 2002 Student Award Ceremony and Distinguished Graduate Lecture was presented on May 16, 2002. The lecturer was Dr. Mark Adams (Ph.D. with Oxender) of Celera Genomics. Dr. Adams has played a major role in the genome sequencing studies at Celera. He received his Ph.D. in 1990.

Student Awards

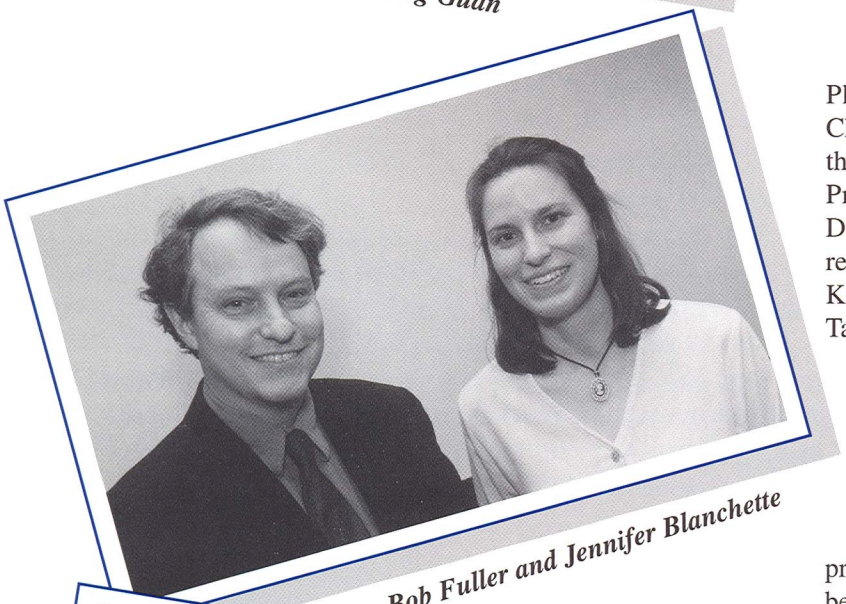


Huira Chong and KunLiang Guan

Ron Taussig (left) and Peter Clapp

— Christensen Award —

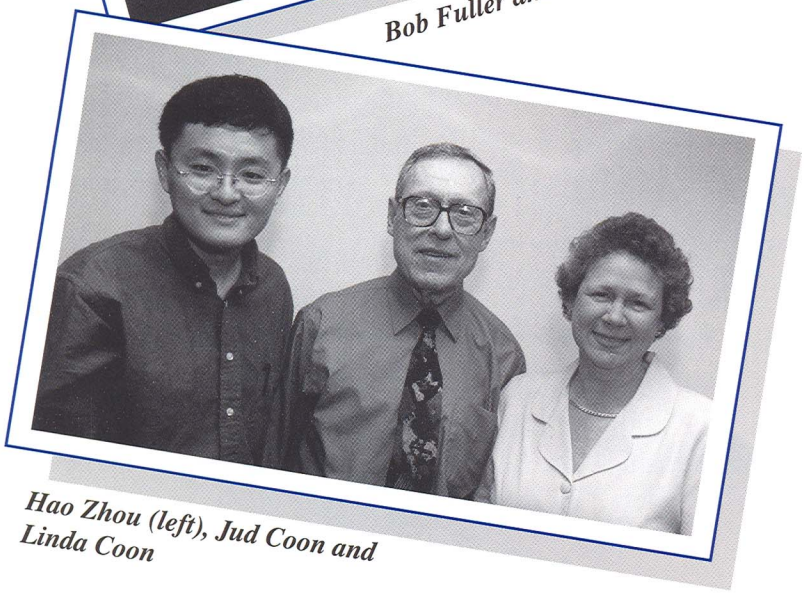
The Halvor N. and Mary M. Christensen Fellowship for Ph.D. Graduate Study in the Department of Biological Chemistry is presented annually to a second-year student on the basis of academic record. This award is given in honor of Professor Halvor N. Christensen, who was Chair of the Department from 1955-1970, and his wife Mary. The 2001 recipients of the award were Huira Chong, whose mentor is KunLiang Guan and Peter Clapp, whose mentor was Ron Taussig.



Bob Fuller and Jennifer Blanchette

— Christman Award —

The Adam A. and Mary J. Christman Fellowship 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 2001 recipient of the award was Jennifer Blanchette, whose mentor is Bob Fuller.



Hao Zhou (left), Jud Coon and Linda Coon

— Coon Award —

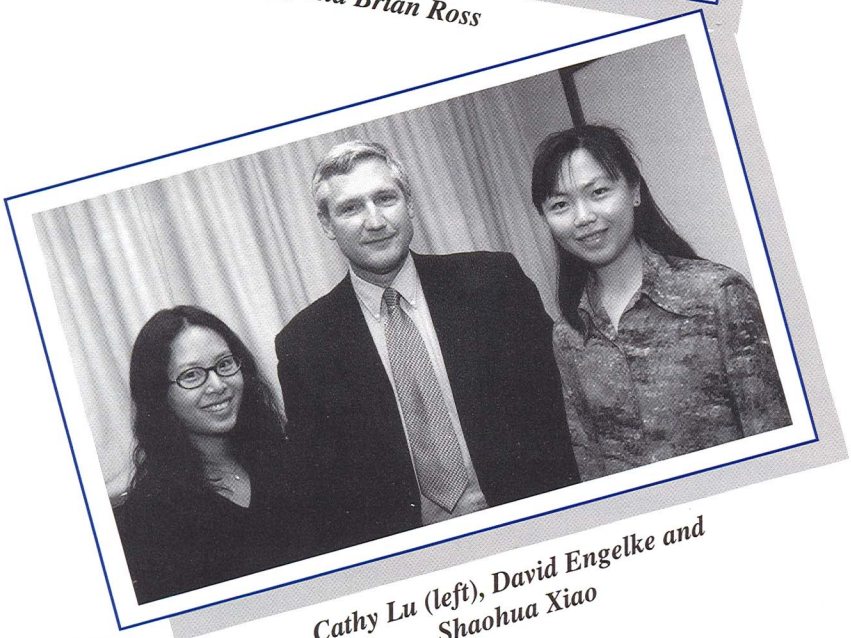
The Minor J. and Mary Lou Coon Award is given to the student who best exemplifies overall excellence in research, teaching and service. This award is given in honor of Professor Minor J. (Jud) Coon, who was Chair of the Department from 1970-1990, and his wife Mary Lou. The 2001 recipient of the award was Hao Zhou, whose mentor is Dennis Thiele.

Student Awards

Lauren Stegman (left) and Brian Ross

— Dziewiatkowski Award —

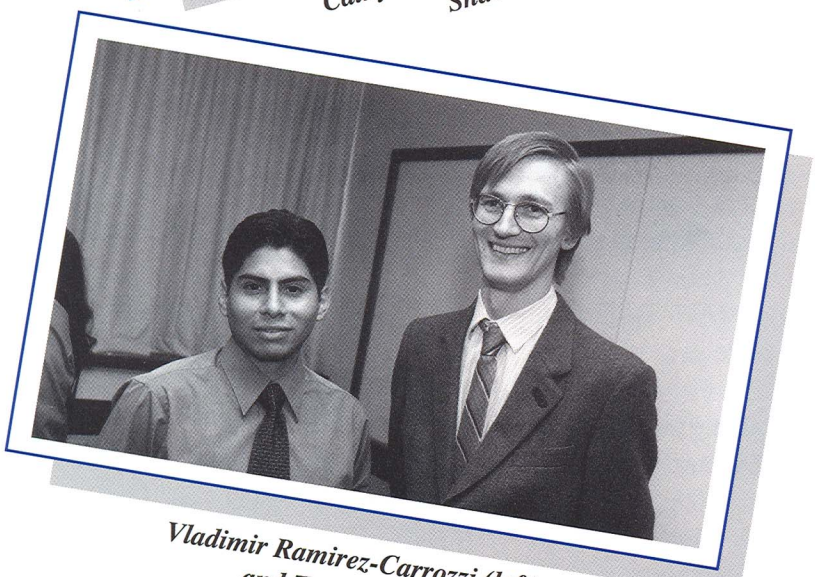
The Dziewiatkowski Award, which is offered to the student who submits the most outstanding Ph.D. Dissertation during the previous academic year, is given in memory of the late faculty member, Professor Dominic D. (Jay) Dziewiatkowski. The 2001 recipient of the award was Lauren Stegman, whose mentor is Brian Ross.



Cathy Lu (left), David Engelke and Shaohua Xiao

—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 to a student who is a non-U.S. citizen. The 2001 recipient of the award was Shaohua Xiao, whose mentor is David Engelke.

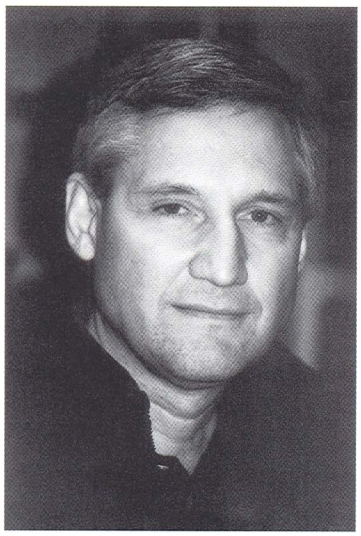


Vladimir Ramirez-Carrozzi (left) and Tom Kerppola

— Lee Murphy Memorial Award —

The Lee Murphy Memorial Award 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 2001 recipient of the award was Vladimir Ramirez-Carrozzi, whose mentor is Tom Kerppola.

Faculty profiles



David R. Engelke, Ph.D.
Professor of Biological Chemistry

My lab continues to study the biosynthesis of small RNAs in eukaryotes. Most experiments are carried out in yeast to take advantage of genetic and molecular experimental tools, but recent experiments have also addressed potential clinical uses of small nucleic acids.

tRNA Genes in Yeast - One area of investigation is the chromatin structure of actively transcribed genes and the mechanism by which transcription factors control that structure. We recently found that small, RNA polymerase III transcription units influence the structure and transcriptional activity of the surrounding chromatin in the yeast genome, and can act as negative regulatory elements (silencers) of neighboring genes. Current evidence suggests that silencing involves subnuclear localization of tRNA genes and is not related to other forms of transcriptional silencing in yeast. We are investigating the mechanism of this regulation using genetic, biochemical, and cytological approaches.

tRNA Biosynthetic Pathway - One of the earliest and most interesting enzymes in the tRNA biosynthetic pathway is RNase P, which is composed of both a catalytic RNA subunit and protein "cofactors." The bacterial enzymes have only a single small, dispensable protein subunit, but the nuclear enzyme has twenty times as much protein, split into nine essential subunits. Multiple lines of evidence suggest that the entire early tRNA biosynthetic pathway, including RNase P, may be localized to the nucleoli, where it is coordinated with ribosomal RNA processing. We are investigating the interaction of the RNase P subunits with this pathway, as well as attempting to create a three-dimensional structural model of the interaction of this complex enzyme with pre-tRNA substrates.

Expression of Potential Therapeutic RNAs in Human Cells - Several classes of small RNAs are under intense scrutiny as potential therapeutic agents. In particular, short double stranded RNAs known as "small interfering RNAs" (siRNAs) have recently been shown to effectively inhibit expression of corresponding mRNA sequences. We have developed expression cassettes to allow expression of these small RNAs and localization to different compartments of human cells. Nuclear siRNA expression is particularly effective in attacking endogenous and viral gene products, and we intend to study the pathway.

Selection of Diagnostic RNA Aptamers -Nucleic acid "aptamers" are ligands selected from a random sequence library. With sufficient selective pressure, it is possible to derive aptamers that bind to virtually any molecule or surface – far exceeding the limits of antibody selection. In addition, nucleic acids can easily be labeled with fluorescent dyes, radionuclides, or affinity tags, making aptamer ligands an attractive potential source of diagnostic and affinity reagents. The laboratory is currently selecting and testing a number of such reagents as tools in the characterization of RNP complexes.

In addition to research and teaching, I continue as Director of the Program in Biomedical Sciences (PIBS), the cooperative recruiting, admissions, and first year graduate program. The program has grown to serve 13 Ph.D. programs with the addition of the new, interdepartmental Bioinformatics Program and the central campus Department of Molecular, Cellular, and Developmental Biology (MCDB, half of the old Biology Department). With resources from the Medical School we have also been able to set up a service to provide career development information and contacts to students and postdoctoral fellows. Our aim for the future is to continue to provide services, while maintaining the autonomy and strength of the individual training programs.

Recent Publications:

Houser-Scott, F, Xiao, S, Millikin, CE, Zengel, JM, Lindahl, L and Engelke, DR. Interactions among the protein and RNA subunits of *Saccharomyces cerevisiae* nuclear RNase P. *Proc. Natl. Acad. Sci.* USA. 99:2684-2689 (2002)

Paul, CP, Good, PD, Winer, I, and Engelke, DR. Effective expression of small interfering RNAs in human cells. *Nature Biotech.* 29:505-508 (2002)

Srisawat, C and Engelke, DR. RNA affinity tags for purification of RNAs and RNP complexes. in press in *Methods* (2002)

Xiao, S, Scott, FH, Fierke, CA and Engelke, DR. Eukaryotic RNase P: A Plurality of Ribonucleoprotein Enzymes. in press in *Annu. Rev. Biochem.* (2002)

Ruthann Nichols, Ph.D.
Associate Professor
of Biological Chemistry

Peptides are critical messengers and regulators of animal behavior, development, and physiology; thus, their aberrant synthesis or signaling can result in dysfunction or death. I am interested in how peptides act in biological processes, for instance, how myotropins transmit and modulate muscle contractility. Myotropic peptides affect the frequency of spontaneous contractions of muscles in the cardiovascular system, gastrointestinal tract, and reproductive tissue and are likely to affect a wide range of processes from heartbeat to satiety to fertility. A goal of my research is to identify molecules involved in myotropin synthesis and signaling in order to design agonists and antagonists for basic and applied research.

Frequently, peptide structures and signal transduction pathways are conserved between invertebrates and vertebrates; thus, research in an experimentally versatile organism like *Drosophila melanogaster* can provide insight into how peptides act in humans. *D. melanogaster* is a powerful system for peptide research because behavior and physiology can be combined with biochemistry, genetics, and molecular biology techniques in an animal species whose generation time is short and whose genome is sequenced.

Research in my laboratory focuses on four myotropins: flatline, FaRPs, myosuppressin, and sulfakinin. We isolated the naturally occurring peptides and characterized the genes encoding each peptide to understand the role(s) of these myotropins in biology. In addition, we developed bioassays to explore the effects of these myotropins on *in vivo* and *in vitro* heart rate, and gut and oviduct motility. We named the *D. melanogaster* C-type allatostatin (AST) peptide flatline (FLT) because it stops heart rate, an effect that is long lasting but limited to a narrow developmental time period. FLT decreases gut contractions, but its effect on gut is not as dramatic as on heart. The human somatostatin/galanin/opioid receptor is homologous to *D. melanogaster* A-type AST receptor; no human C-type AST homolog has been identified. We will delineate FLT structure-activity relationship (SAR) and design agonists and antagonists to investigate function and isolate a receptor(s). In addition, we will generate mutants to establish FLT function(s).

Drosophila myosuppressin (DMS) decreases heart rate; however, unlike FLT, DMS acts throughout the life cycle and its effect is reversible. DMS evokes a potent and long lasting decrease in the frequency of contractions of the gut. Although DMS and FMRFamide-related peptides (FaRPs) are structurally related, the effect of FaRPs on heart and gut muscle contractions is not comparable to DMS. We will determine if DMS acts through tissue-specific receptor subtypes in heart and gut to better understand its signal transduction pathway. In addition, we will generate mutants to establish DMS function(s).

Drosophila sulfakinin (DSK) increases heartbeat, but decreases gut contractions. Sulfakinin peptides are similar in structure and activity to the human brain-gut peptides cholecystokinin and gastrin. DSK requires a sulfated tyrosine to stimulate heartbeat, however, nonsulfated DSK is more effective in gut tissue. We will determine DSK SAR to produce agonists and antagonists and unfold the mechanism of how this peptide works in heart and gut. In addition, we will generate mutants to establish DSK function(s). A long-term goal is to apply our results to understand the roles of these unique myotropins in human biology.

Recent Publications:

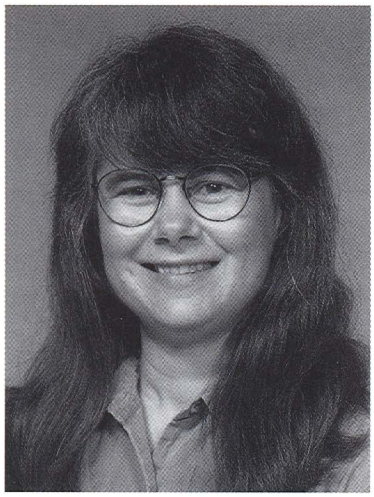
Richer, S., Stoffolano, J.G., Jr., Yin, C-M. and Nichols, R. Immuno-localization of dromyosuppressin (DMS) and effects of DMS and benzethonium chloride on crop contractions in *Phormia regina* (Meigen). *J. Comp. Neurol.* 421:136-142. (2002)

Merte, J. and Nichols, R. Roles of *Drosophila melanogaster* FMRFamides in physiology: redundant or diverse? *Peptides* 23:209-220. (2002)

Merte, J. and Nichols, R. *Drosophila melanogaster* myotropins have unique functions and signaling pathways. *Peptides* 23:757-763. (2002)

Price, M.D., Merte, J., Nichols, R., Koladich, P.M., El-Meniawi, F.A., Tobe, S.S. and Bendena, W.G. Drosophila melanogaster flatline gene encodes a myotropin homolog of Manduca sexta allatostatin. *Peptides* 23:787-794. (2002)

Faculty profiles



Geneva M. Omann, Ph.D.
Associate Professor
of Biological Chemistry

My research efforts are centered on understanding cell signaling by G-protein coupled receptors. We are also interested in inflammation and the immune system, so the bulk of our work has focused on G-protein coupled receptors in the human neutrophil. As part of the "innate" immune system, in contrast with the antibody-producing cells of the "adaptive" immune system, neutrophils constitutively express on the cell surface receptors for bacterial peptides that can immediately respond to a bacterial infection. There are also receptors on the neutrophil that bind inflammatory mediators released from injured tissues. Thus neutrophils are the first type of cell to respond to injury and infection and are responsible for initiating an extensive series of events that result in inflammation followed by eventual wound healing and infection resolution. Many of the symptoms of inflammatory diseases, including rheumatoid arthritis and acute respiratory distress syndrome, result from excessive activation of neutrophils and we hope the knowledge generated by our studies will aid in the design of better anti-inflammatory drugs for controlling such diseases.

A prominent receptor on neutrophils that mediates the cells response to bacterial infections is the N-formyl peptide receptor. N-formyl peptides are short peptides released by bacteria. The receptors are G-protein coupled receptors that mediate migration of cells to the site of an infection and induce the release of proteases, hydrolases and bactericidal peptides that all function to kill the bacteria. We are studying the relationship between the kinetics of the N-formyl peptide-receptor binding characteristics and receptor processing events and cellular responses. We have synthesized fluorescently labeled N-formyl peptides that are used to measure the kinetics of N-formyl peptide binding to receptors on intact cells using a technique called flow cytometry. This method allows the accumulation of large data sets with high time resolution from which kinetic rate constants for the binding and processing events can be calculated. Using a variety of techniques, the responses produced by the N-formyl peptides are quantified. These responses include cytoskeletal activation, protease release, oxidant production, and signaling events such as calcium elevation and phospholipid metabolism. We have noted that different N-formyl peptides produce differing levels and kinetic patterns in the responses they induce, even though they all bind to the same site on the receptor. In collaboration with investigators from the Department of Chemical Engineering, we are creating mathematical models that link the binding events and responses in an effort to better understand how cellular responses might be regulated by controlling the kinetic events that occur at the receptor.

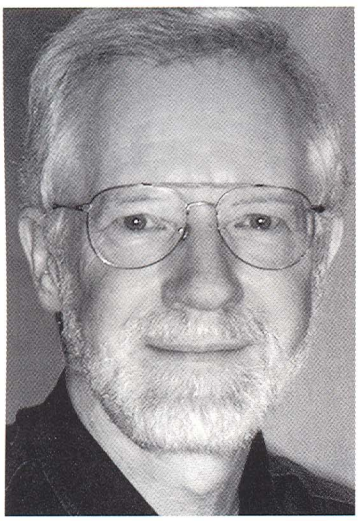
In collaboration with investigators from the School of Public Health, we have been studying the interaction between the immune system and environmental contaminants. We have focused on problems in the Great Lakes region related to mercury and polychlorinated biphenyls. We have measured the levels of these contaminants in immune tissues of lake trout taken from the Great Lakes. In addition, we have performed laboratory studies on thymocytes taken from lab-reared lake trout. Our studies show that concentrations of mercury found in fish taken from the field are sufficient to induce cell death in thymocytes in laboratory studies. In addition, we have shown that environmental contaminants and endogenous stress factors, such as cortisol, interact to produce greater immunotoxicity. We are continuing studies to understand the mechanisms of these phenomena in lake trout.

Recent publications:

Riccobene, TA, Omann, GM, and Linderman, JJ. Modeling activation and desensitization of G-protein coupled receptors provides insight into ligand efficacy. *J. Theor. Biol.* 200:207-222, 1999.

Sweet, LI, Passino-Reader, D, Meier, PG, and Omann, GM: Xenobiotic-induced apoptosis. Significance and potential application as a general biomarker of response. *Biomarkers* 4: 237-253, 1999.

Waller, A, Pipkorn, D, Sutton, K, Linderman, JJ, and Omann, GM: Validation of flow cytometric competitive binding protocols and characterization of fluorescently labeled ligands. *Cytometry* 45:102-114, 2001.



Jochen Schacht, Ph.D.
Professor of Biological Chemistry
in Otolaryngology
Scientific Director, Kresge Hearing
Research Institute

In the mammalian cochlea, a few thousand sensory cells (about 3,500 inner hair cells, to be more precise) process and analyze sounds of a frequency spectrum ranging from 200 – 18,000 Hz. The cochlea can process stimuli with greater sensitivity and over a greater energy range than any other sensory organ. My laboratory has been fascinated by the inner ear for nearly 30 years, striving to understand biochemical processes in auditory function and pathology. Two examples will illustrate our approach.

Aminoglycoside antibiotics (e.g., gentamicin and streptomycin) were discovered almost sixty years ago and are still commonly used worldwide. They are effective and inexpensive, making them the drugs of choice in developing countries. They are, however, "ototoxic," having the potential to cause hearing loss through the destruction of hair cells. We have developed the hypothesis that these drugs catalyze the formation of free radicals based on their ability to form redox-active metal complexes. Evidence from *in-vitro* studies points to a reaction mechanism involving unsaturated fatty acids as electron donors. While pursuing the details of the reaction, we began testing this hypothesis *in vivo*.

Treatment of mice with aminoglycosides indeed caused lipid oxidation in the cochlea establishing the link between our *in-vitro* model and ototoxicity *in vivo*. Consistent with a free-radical-induced pathology, antioxidants protected both cochlear structure and function from aminoglycoside damage. Salicylate was one of the effective compounds, suggesting that ototoxicity might be prevented by aspirin, whose active component is salicylate. This suggestion is being tested in a clinical trial conducted by colleagues in China, a country with a very high use of aminoglycosides. Initial results suggest that we might indeed be able to prevent aminoglycoside-induced hearing loss, thereby alleviating the major cause of preventable deafness in the world today.

Another project that has long occupied my laboratory follows a similar *in-vitro* to *in-vivo* evolution, in this case at the level of basic auditory function. Intracellular free calcium in cells of the inner ear is regulated by both IP3-mediated and calcium-induced calcium release, and we could show in isolated single cells that calcium signals are attenuated by the nitric oxide/cyclic GMP/protein kinase G pathway. An intriguing finding was a prominent calcium response to neuromodulators in the "supporting cells" of the inner ear, non-neural cell types that have no known role in the activity of the cochlea except to provide structural support. Measurements in isolated cells showed that changes in intracellular calcium alter cell stiffness, probably by influencing the arrangement of microfilaments and microtubules. Auditory processing is a mechanical transduction event in which sound induces vibrations of the cochlear neuroepithelium. Since changes in supporting cell stiffness will influence the mechanical properties of the neuroepithelium, we now postulate that calcium transients in supporting cells constitute a "tuning" mechanism of the auditory transduction process. Next we would like to test how exactly the physiological processing of sound is affected - a task that will keep us and our collaborators busy for a while.

Our research would be impossible without extensive collaborations. We are fortunate to work at the Kresge Hearing Research Institute, where fourteen laboratories in different disciplines research auditory function and dysfunction. Beyond the Institute, we have frequently collaborated with colleagues in Biological Chemistry and other departments on campus. But our "hearing community" extends beyond the U of M. Over the years we have carried out joint projects with research groups in the United States, Germany, Sweden, England, France, Japan and China.

Such collaborations bring with them a lot of travel. Fortunately, I enjoy traveling, even outside of my professional activities. And I never travel without camera and binoculars, so that I will not miss the beauties of other cultures and the birds that inhabit those countries.

Katrina Ward Hope Moves to Dean's Office After Years of Dedication to Our Department

After 21 years of superb service to our Department, Katrina Ward Hope has accepted the position of Administrator for Basic Science Departments in the office of the Dean of the Medical School. At a departmental reception recently held to honor Katrina for her achievements as Administrator in Biological Chemistry, several faculty commented on her many talents and achievements. She profoundly redirected the office to make it more efficient and responsible to the demands of a growing and rapidly changing scientific department. Several years ago she received the University's first Distinguished Service Award as part of a Staff Recognition ceremony. She was cited for her "strengths of cooperation, collegiality, fairness, diplomacy, caring, teamwork, and for her high aspirations." We wish Katrina much continuing success in her new challenging position.

Donations and Gifts

We are extremely grateful to all of the individuals and companies whose gifts and donations have provided valuable discretionary funds to support a wide range of Departmental activities.

The following funds, programs, awards, and fellowships are available if you would like to have your contribution to the Department of Biological Chemistry designated more specifically.

- Biological Chemistry Endowment Fund
- Dominic D. Dziewiatkowski Dissertation Award
- Minor J. and Mary Lou Coon Graduate Student Fellowship in Biological Chemistry
- Anthony and Lillian Lu Fund
- Vincent Massey Collegiate Professorship in Biological Chemistry

To find out more about gift opportunities to the Department, please contact:

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Biological Chemistry

Department of Biological Chemistry Newsletter

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