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I am delighted to be able to update you on what has happened during the past year. Biological Chemistry is now a participant in the first year of a new Medical School graduate program known as the Program in Biomedical Sciences (PIBS). Approximately 65 students were in the entering class last year. These PIBS students have spent the year doing research in three different laboratories, which can be in any one of several basic science departments within the Medical School. The initial signals indicate that the program has been very successful; David Engelke, who is in our Department, has been the leader of this new effort.

This should also be a very good year for Life Sciences at the University of Michigan as well as Life Sciences within the State. The University has announced a major new initiative which will bring 30 new faculty to campus over the next few years. The State government also plans to put 50 million dollars each year into Life Sciences. This money is part of the tobacco settlement that many states received, and the Governor, in his wisdom, has decided to put these funds toward Life Sciences Research in the State.

As mentioned in last year’s newsletter, the Medical School has also launched the Biological Sciences Scholars Program. This is an effort to bring the most outstanding faculty in the country to the University. Zhaobin Xu is the first of the scholars to join our Department. He is a structural biologist who has gotten off to a terrific start.

Biological Chemistry made two joint appointments this year with scientists in the Chemistry Department. Professors Carol Fierke and Gary Glick have joined our Department, and their research profiles can be found in this newsletter. We are delighted about the closer ties we have developed with the Chemistry Department.

This has been an exciting year for our Department. We continue to actively recruit top level faculty and students. The accomplishments of our faculty have drawn national attention. For example, Rouena Matthews will receive the William C. Rose Award in Biochemistry at the annual meeting of the American Society for Biochemistry and Molecular Biology in Boston, and Michael Marietta was elected to the Institute of Medicine. A more complete list of awards and recognition received by our faculty and students is described later. Lastly, we will be having our annual University of Michigan Biochemistry Reception on June 6 in the Jefferson Room at the Boston Sheraton. I hope you can join us at the first reunion of the millennium.

Jack

Minor J. Cous Professor
Biological Chemistry Chair
Biological Chemistry Department
Updates at the Medical Center

Medical Research Laboratory Facility

The Medical School has announced its commitment to develop a major research facility on the block bounded by Huron Street and Zina Pitcher. Two committees (Facility Planning and Advisory Committees) and several work groups (Programming, Animal Housing & Support, and Support Work Groups) have already been established.

The building will be a 359,000 gross square foot highly-efficient generic bio-medical laboratory building. The concept employs perimeter laboratories and offices with internal laboratory support, thus taking maximum advantage of natural light and view. The typical floor has been developed around two wings. The link will open on the grade level to allow passage between East Huron and Ann Streets, to strengthen pedestrian movement between the Medical Center campus and the Academic campus.

The laboratory space will occupy five floors. The laboratory areas have been designed to provide flexibly-assigned generic modular laboratory space with movable benches, support alcoves which can be used in a variety of ways, a Linear Equipment Room for large common equipment, procedure rooms which can be set up as desired and common support spaces such as glasswash and environmental rooms.

The grade level on the east wing will include the primary building entry (about a half-level up due to the site topography), lobby, conference space, a large commons space and the 300-seat auditorium. A concourse will run north to south the length of the wing, linking these functions and connecting to the proposed north and south bridge connections. A landscaped courtyard space will be developed between the west and east wings.

This project is in its early planning stages and no ground breaking date has been set as well as no completion date. However, the University has acquired all the necessary land and more information should be forthcoming.

Faculty News:

Bernie Agranoff received his fifth annual Faculty Outstanding Service Recognition Award from the Neuroscience Graduate Program in September.

David Aminoff was named Professor Emeritus of Biological Chemistry in August.

Jud Coon continues to be Foreign Adjunct Professor at the Karolinska Institute in Stockholm. He is on the International Advisory Committee for the Thirteenth International Symposium on Microsomes and Drug Oxidations to be held in Stresa, Italy.

Jack E. Dixon gave the John W. Boylan Memorial Lectureship at Mount Desert Island Biological Laboratory in Salisbury, Maine in August and was the Chilton Lecturer in the Biochemistry Department at the University of Texas Southwestern Medical School. He also continues to serve as chair of the Life Science Advisory Committee.

David Engelke was chosen by the Department of Health and Human Services to serve as chairperson of the Cell Development and Function Study Section (6), Center for Scientific Review.

Bob Fuller was promoted from Associate Professor to Professor of Biological Chemistry.

Irwin Goldstein was named Professor Emeritus of Biological Chemistry in December.
George W. Jourdain was named Professor Emeritus of Internal Medicine and of Biological Chemistry.

Michael Marletta was elected to the Institute of Medicine. He also received the Distinguished Faculty Lectureship Award in Biomedical Research from the University of Michigan and was named State of Michigan Scientist of the Year by the Impression 5 Museum.

Lawrence Matthews was named Adjunct Assistant Professor of Biological Chemistry.

Vincent Massey was awarded the Harden Medal of the Biochemical Society and presented the Associated Jubilee Lecture in London and at Leeds last August.

Rowena Matthews was appointed to the Commission on the Advancement of Women in Science, Engineering and Technology. She will receive the William C. Rose Award in Biochemistry at the ASBMB annual meeting in Boston.

Jerry Menon received the University of Michigan 1999 Distinguished Faculty Achievement Award for his contributions in scholarship, teaching and mentorship.

Alex Ninfa was promoted from Associate Professor to Professor of Biological Chemistry. He has served as a member of the Rackham Predoctoral Faculty Selection Committee.

Alan Price (former faculty member, and Assistant Vice President for Research) is Acting Director of the Division of Research Investigations in the Office of Research Integrity, U.S. Public Health Service in Bethesda, Maryland.

Jochen Schacht spoke at the Conference on "Hearing Science for Practicing Otologists" in Beijing, China, in May of 1999 and also gave lectures in several cities during two trips to that country. He received honorary professorships from Hunan Medical University, Changsha, and Tongji Medical University, Wuhan; and was appointed guest professor at the Fourth Military Medical University, Xi'an. In this country he spoke at the Presidential Symposium on "Nitric Oxide" at the recent meeting of the Association for Research in Otolaryngology in (St. Petersburg FL). He is now organizing a symposium on "Pharmacological Treatment of Hearing Disorders" for the European Federation of Otolaryngological Societies to take place in Berlin, Germany. His work on noise-induced hearing loss has been quoted in magazines like Men's Health and Light Cooking.

Michael Uhler received the University of Michigan 1999 Research Scientist Recognition Award.

Bob Zand has been awarded a three-year grant from the National Multiple Sclerosis Society to study posttranslational modifications in normal and MS myelin. He was also appointed as an Associate Editor of the journal, Progress in Polymer Science.

Alumni/ae News:

Carl Aronson (Ph.D. with Zand) is finishing his postdoctoral fellowship at the Naval Research Laboratories and will join Kettering College, Dayton, Ohio, as an Assistant Professor of Physical Chemistry.

Jean-Paul Borg (postdoc with Margolis) has returned to France as an Assistant Professor at the INSERM U119.

Pimchai Chaiyen (Ph.D. with Ballou) is spending a month in the Ballou and Massey laboratories to work on a collaborative project.
James Clemens (Ph.D. with Dixon) is now a postdoctoral fellow working with Larry Zipursky at the University of California, Los Angeles.

Louis DeFilippi (Ph.D. with Hultquist) is now an environmental consultant and this past July started his own company, Louis DeFilippi, LLC.

Barrie Entsch (postdoc with Massey and sabbatical with Ballou) has been promoted to Professor at the University of New England, Armidale, Australia.

George Gassner (Ph.D. with Ballou) is finishing postdoc training at MIT with Steve Lippard and has accepted a position as Assistant Professor at San Francisco State University.

Sandro Ghisla (postdoc with Massey) was the chief organizer of the 13th International Symposium on Flavins and Flavoproteins, held in Konstanz, Germany in September.

Fred Guengerich (postdoc with Coon), Professor of Biochemistry at Vanderbilt University, organized the 10th North American Meeting of the International Society for the Study of Xenobiotics combined with the meeting of the American Chemical Society Division of Chemical Toxicology, held in Nashville last October.

Chris Harris (Ph.D. with Massey) spent a postdoctoral year in Varese, Italy, with Professor Mirella Pilone, and is now with Dale Poulter at the University of Utah in Salt Lake City.

Jennifer Hunt (Ph.D. with Massey and postdoc with Fierke) is now working at Novartis in North Carolina.

Jon Huibregtse (Ph.D. with Engelke) has been recruited to the Institute of Cell and Molecular Biology at the University of Texas at Austin, with an Associate Professor appointment in the Department of Molecular Genetics and Microbiology.

Kuniyo Inouye (postdoc with Coon) is head of the Laboratory of Enzyme Chemistry in the Division of Applied Life Sciences, Graduate School of Agriculture of Kyoto University.

Chung-Liang Kuo (Health Science Research Associate with Coon) recently accepted the position of Database Administrator with GE Aircraft Engines in Cincinnati.

Neocles Leontis (postdoc with Engelke) is a full Professor of Chemistry at Bowling Green University.

Liwu Li (postdoc with Dixon) is now an Assistant Research Scientist in the Infectious Diseases Section of the Department of Medicine at Wake-Forest University in Winston-Salem, North Carolina.

Anthony Lu (postdoc with Coon and recent major benefactor of the Department) spent two weeks at Vanderbilt University last April as Visiting Professor in the Department of Biochemistry.

Deborah Lu (Ph.D. with Menon) is in the biotechnology law clerk program at Pennie & Edmonds LLP, an intellectual property law firm in New York, and expects to start part-time evening law school in the fall. Her work focuses on patent prosecution and opinion work on novel methodologies and therapeutics for biotechnology and pharmaceutical companies, as well as for universities.

Peter Macheroux (postdoc with Massey) now has a faculty position at the ETH in Zurich. He was also a member of the Organizing Committee of the 13th International Symposium on Flavins and Flavoproteins, held in Konstanz in September.
**Tomohiko Machama** (postdoc with Dixon) is now an Assistant Professor in the Department of Pharmacology, Tokyo Metropolitan Institute of Medical Science, in Tokyo, Japan.

**Stephen Mayhew** (postdoc with Massey) has been elected as a member of the Royal Irish Academy, the Irish equivalent of the National Academy of Sciences.

**Susan Miller** (postdoc with Massey) was promoted to Associate Professor with tenure at the University of California, San Francisco.

**Edward Morgan** (postdoc with Coon) is now Professor of Pharmacology at Emory University, where he is Director of the graduate program in Molecular and Systems Pharmacology. Eddie is currently Chair of the Drug Metabolism Division of the American Society for Pharmacology and Experimental Therapeutics. He will be a visiting lecturer here in May, cosponsored by Pharmacology and Biological Chemistry.

**Scott Mulrooney** (postdoc with Williams) is now a Research Assistant Professor in the Department of Microbiology at Michigan State University.

**Daniel Oprian** (Ph.D. with Coon), Professor and Chair of the Department of Biochemistry at Brandeis University, will be the Distinguished Alumni Lecturer in our Department on May 18.

**Mariliz Ortiz-Maldonado** (Ph.D. with Ballou and Massey) will continue in Biological Chemistry as she finishes up various new phases of the project.

**Andrei Raibekas** (postdoc with Massey) is now a senior scientist in the Protein Chemistry Division at Neurotrophic Bioscience Inc. in Toronto.

**Michael Richards** (Ph.D. with Marletta) is a resident in Pediatrics at Washington University Medical School.

**Christopher Rohlman** (Ph.D. with Matthews, and postdoc with Engelke) has advanced to Associate Professor at Pomona College.

**Milton Schlesinger** (Ph.D. with Coon), after 35 years on the faculty of Washington University School of Medicine in St. Louis, became Professor Emeritus as of last July. He had been a Professor in the Department of Molecular Microbiology since 1972. He was recently elected a Fellow of the American Association for the Advancement of Science (AAAS) and was cited for his studies on RNA viruses and the discoveries of lipid modification of proteins and the heat shock response in vertebrate cells. He currently is collaborating with his wife, Sondra, on a history of the virology project.

**Sondra Schlesinger** (Ph.D. with Greenberg) became a Fellow of the AAAS in 1996 and was recently elected Chair of the Medical Sciences division of the AAAS. She is currently Professor of Molecular Microbiology at Washington University School of Medicine. For the past decade she has been involved in developing alpha virus vectors and in this work has been able to learn more about strategies of virus replication. A more recent effort is a study of the history of virology. She has been active as a member of several committees of the American Society for Virology since its inception in 1981 and served as President of the Society in 1992.

**Marcia Steinberg** (Ph.D. with Massey) has joined the Center for Scientific Review (CSR) at NIH as chief of the cell development and function integrated review group (IRG) and as scientific review administrator of the cell development and function study section. As IRG chief, she will supervise seven study sections in the general areas of cell development and function, as well as one study section in
international cooperative projects. She joined the National Science Foundation in 1989 and spent 10 years as a program director in molecular biochemistry before moving to CSR.

**James Stone** (Ph.D. with Marletta) is a resident in Pathology at Brigham and Women’s Hospital, Harvard Medical School in Boston.

**Marc Taylor** (Ph.D. with Massey) now works with Caliper Technologies in Mountain View, California, which concentrates on development of "chips" for nanoliter screening of pharmaceutical libraries.

**Thomas Transue** (Ph.D. with Saper) started a second postdoctoral fellowship in June with Traci Hall at the National Institute of Environmental Health Sciences in the Research Triangle, North Carolina. After a three year postdoctoral fellowship position in Belgium studying unusual heavy-chain antibodies from camels, he is now working at the NIEHS on proteins responsible for recognition of sequences in 3' untranslated regions of mRNA.

**Ted Ueda** (Ph.D. with Coon), Professor of Pharmacology in our Medical School, gave lectures at the faculty of Pharmaceutical Sciences at Osaka University and also at the Osaka National Research Institute of the Ministry of International Trade and Industry.

**Pan-Fen Wang** (postdoc with Williams) is now a research fellow in the laboratory of Dr. George Kenyon, who is Dean of the College of Pharmacy, The University of Michigan.

**Kim White** (Ph.D. with Marletta) is a Senior Scientist at Novartis in Research Triangle Park in North Carolina.

**Yunde Zhao** (Ph.D. with Marletta) is a postdoctoral fellow at the Salk Institute.

**Gregor Zimmerman** (Ph.D. with Taussig) is now at Stanford working in Matt Scott’s laboratory as a Howard Hughes Medical Institute postdoctoral research fellow. He was the Minor J. and Mary Lou Coon Fellowship Awardee last year.

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**Transitions**

**David Aminoff**, Professor of Biological Chemistry, has retired from active faculty status as of August 31, 1999. His undergraduate studies were at Chelsea Polytechnic, London, Great Britain, and he obtained his Ph.D. in Biochemistry from London University in 1949, based on studies undertaken at the Lister Institute of Preventive Medicine. In 1950 he emigrated to Israel, where he participated in two pioneering endeavors over the period 1950-55: the creation of a new Institute for Biological Research, where his research focused on cholera (in anticipation of a potential epidemic resulting from the influx of immigrants from endemic areas), and the setting up of the Marcus Institute for the Fractionation of Blood for the Israeli Red Cross (Magen David Adom) that was established in 1956. This latter venture involved visiting various blood banks and plasma fractionation centers throughout Europe and the States, acquiring the most current information and adapting it to the conditions appropriate to a newly developing country. This mission dovetailed with a year (1995-6) as an Exchange Scientist with Prof. Erwin Chargaff at Columbia University.

From 1957-60, after moving to the U.S., he was a Research Associate at the Public Health Research Institute of New York,
where he developed an assay for viral and bacterial sialidases, detecting free sialic acid in the presence of the bound compound. That assay became extremely popular and earned him the recognition of a Citation Classic. David came to Ann Arbor in 1960 to work with Prof. Saul Roseman at the Rackham Arthritis Research Unit for two years before taking up a position at the Simpson Memorial Institute with a joint appointment in Internal medicine and Biological Chemistry. There he served as the basic science ombudsman/liaison to the clinical discipline, rising through the ranks to become a full Professor in 1980. At the Simpson Memorial Institute he continued his interest in red blood cells, working on the development of a universal blood donor type for transfusion, and studying the mechanism for clearance of senescent erythrocytes from circulation. In recognition of these studies, the University of London bestowed on him the D.Sc. degree, in 1974. He joined the Institute of Gerontology, 1985-91, to further explore mechanisms of cellular aging. David then returned to the Department of Biological Chemistry, where he continues his interests in erythrocytes by collaborating with colleagues within the University and in France, India, and Israel. In addition, he and Dr. Alex Ninfa are continuing to work on the preparation of a universal blood donor.

In view of his distinction, the Regents have named Dr. Aminoff Professor Emeritus of Biological Chemistry.

George W. Jourdain (known to his friends and colleagues as Bill), Professor of Biological Chemistry in the Departments of Internal Medicine and Biological Chemistry in the Medical School, retired from active faculty status as of December 31, 1999 after an outstanding career as a scientist and educator. Bill did his undergraduate work at Amherst College and received a Ph.D. in Microbiology from Purdue University in 1958. He then undertook three years of postdoctoral training in the Rackham Arthritis Research Unit at the University of Michigan with Dr. Saul Roseman. In 1961 he was appointed as an Instructor in the Department of Biological Chemistry and in 1963 was promoted to Assistant Professor. In 1965 he was promoted to Associate Professor and in 1974 to Professor.

His research work focused on the biochemistry of glycoproteins and carbohydrates and on the relationship of carbohydrate-containing macromolecules to the biology of cartilage. Bill’s laboratory is best known for discovering the phosphomannosyl receptor, a molecule that controls the trafficking of lysosomal enzymes. This discovery was a landmark achievement. Additionally, he and his associates developed a method for culture of chondrocytes in alginate beads which simulates the microenvironment of cartilage. This technique has been adopted by investigators worldwide.

Throughout his years in our Department, Bill was a respected and effective teacher of graduate students and medical students. In teaching laboratory courses and our graduate student literature seminar course, he was so stimulating that students were often very enthusiastically caught up in the effort and had to be reminded about their other responsibilities. He has been sought out for advice by colleagues throughout the University and indeed throughout the world, for his special expertise in the biochemistry of glycoconjugates. He served on the Editorial Board of the Journal of Biological Chemistry and on the Physiological Sciences Study Section of the National Institutes of Health. He has held several positions as an officer in the Society for Glycobiology and was President of this group from 1987 to 1989.
Throughout his career, Bill has continued to personally conduct experiments in his laboratory, rather than be content to direct the efforts of technicians and students. He has been a role model for young scientists in training for over three decades. In view of his enduring accomplishments and dedicated service to the University, he has been named Professor Emeritus of Biological Chemistry and Internal Medicine.

Dale L. Oxender, formerly Professor of Biological Chemistry, retired earlier this year from his position as Distinguished Research Fellow in the Department of Cell Biology, Pharmaceutical Division of Warner Lambert-Panke Davis. Dr. Oxender retired from the University of Michigan after a highly productive career as an instructor and scientific investigator. Dr. Oxender then became Vice President for Biotechnology at Parke-Davis.

A native of Michigan, Dale took undergraduate studies at Manchester College in North Manchester, Indiana and received his A.B. degree in chemistry in 1954. Dr. Oxender received his M.S. and Ph.D. degrees in biochemistry from Purdue University in 1956 and 1959, respectively. Upon completion of his doctoral studies, Dr. Oxender accepted a position as an Instructor in the Department of Biological Chemistry in the Medical School at the University of Michigan and collaborated on studies of biological transport with Professor Halvor N. Christensen. Dale held that position until 1963 and was then promoted to Assistant Professor. He became Associate Professor of Biological Chemistry in 1967, and a subsequent promotion to Professor occurred in 1975. Dale served as Director of the Center of Molecular Genetics at the University of Michigan from 1986-1990. Dr. Oxender was vigorous in his research and teaching, and contributed heavily to the present strength of the Department of Biological Chemistry. Dr. Oxender is known internationally for his innovative research contributions in the areas of the biochemistry of proteins, bacterial cell transport, and genetics. Throughout his distinguished career, Dr. Oxender has dedicated himself to improving the state of health and education of society, as well as being a conscientious and effective educator.

After 10 years of service, Dale retired as Distinguished Research Fellow Emeritus at Warner Lambert-Panke Davis. During this time, Dale established a new biotechnology group as well as contributing to the growth of microbiology and biochemistry. On behalf of Parke-Davis, Dale will continue to be responsible for helping to organize the Keystone and the Miami Biotechnology Symposium meetings.

Dale will also continue to hold the title of Professor Emeritus of Biological Chemistry, awarded to him in 1991 by the Regents of the University of Michigan. In awarding this position, the Regents cited Dale's dedicated service as a distinguished scientist and health educator.

Paul A. Sree, Professor of Biochemistry at the University of Texas Southwestern Medical Center and Chief of the Pre-Clinical Science Unit of the Department of Veterans Affairs Medical center in Dallas, died unexpectedly on July 11, 1999, following liver surgery. Paul's undergraduate training in Chemistry was at the University of California in Los Angeles, and his Ph.D. in Comparative Biochemistry was obtained at the University in Berkeley. His extensive postdoctoral studies were with Dr. F. Lipmann at the Massachusetts General Hospital in Boston, Dr. E. Racker at the Public Health Research Institute in New York City, and Dr. F. Lynen at the University of Munich. He joined the faculty in Biological Chemistry at the University of Michigan in 1956, and was here for seven
years before moving to the University of California Lawrence Radiation Laboratory in Livermore and then on to Dallas. He also held the titles of Professor in the Department of Internal Medicine at Southwestern Medical Center and of Research Career Scientist in the VA Medical Center in Dallas.

Paul was a widely recognized expert on intermediary metabolism and enzyme function and a pioneer in developing the concept that enzyme interactions can lead to multienzyme systems with important regulatory properties. For example, one of his recent interests was interactions between sequential enzymes of the Krebs tricarboxylic acid cycle and the possibility that the supramolecular complexes formed may have not only a metabolic role but a structural role in the mitochondria.

Paul and his wife, Oz, had a wide circle of friends in Ann Arbor. He will be remembered by his friends and colleagues not only for his research achievements but also for his warm and enthusiastic personality. He was a fine friend, a splendid teacher, and a dedicated scientist who had a very positive influence on his former students, as well as associates in many parts of the world.

1999 Entering Students

With the Program in Biological Sciences Program implemented, students now enter this program and declare their department affiliation in the following spring and summer.

Degrees Granted

The Department extends its congratulations to the following students who completed their Ph.D. degrees since June of 1998:

Larry Dwayne Adams (Goldman) "Calcium and cAMP-dependent Second Messenger Systems Regulating Nicotinic Acetylcholine Receptor Expression."

Douglas Benson (Franceschi) "Osteoblast-specific Regulation of Bone Sialoprotein Gene Transcription."

James Chester Clemens (Dixon) "Identification of a Novel Signaling Complex that Controls Axon Guidance in Drosophila."

Sean Collins (Uhler) "Compartmentalization of the Cyclic Nucleotide-dependent Protein Kinases and Their Substrates."

Wendy Davis (Peliska) "Mechanistic Characterization of New Inhibitors of DNA Strand Transfer Reactions Catalyzed by HIV-1 Reverse Transcriptase and Nucleocapsid Protein."

John W. Denninger (Marletta) "Structure and Function Relationships in the Soluble Guanylate Cyclase: Activation by YC-1, Carbon Monoxide, and Nitric Oxide."

Kerry Fluhr (Matthews, R.) "Residues that Affect Activation and Deactivation of Cobalamin-dependent Methionine Synthase."

John Christopher Kash (Menon) "Post-transcriptional Control of Lutropin/Choriogonadotropin Receptor in the Ovary: Identification and Characterization of a Receptor-specific mRNA Binding Protein."

Keith Andrew Koch (Thiele) "Essential Transcription Factor-DNA Interactions for the Transcriptional Autoregulation of the Candida Glabrate AMI1 Gene."
Xiao-Dong Liu (Thiele) "Stress Regulation of Heat Shock Transcription Factors."

Mariliz Ortiz-Maldonado (Ballou/Massey) "Insights on the Mechanism of Pseudomonas aeruginosa p-Hydroxybenzoate Hydroxylase from QSAR Studies Using 8-Substituted Flavins."

Shanna McClennen (Scasholtz) "Regulation of Corticotropin-Releasing Hormone Binding Protein Gene Expression."

Robert C. Morshauer (Zuiderweg) "High Dimensionality NMR Experiments with Improved Spectral Resolution Applied to the Complete Structure Determination of the Molecular Chaperone HSC-70 (Heat Shock Cognate 70 KDA) Substrate Binding Domain."

Aileen Nicoletti (Thompson) "Cloning and Characterization of the Human RPE65 Gene: A Model for Regulation of Gene Expression in the Retinal Pigment Epithelium."

Seong J. Noh (Guan) "Structure and Function Analysis of PI8 and the Role of KSR in Muscle Differentiation."

Rafael Perez-Ballestero (Uhler) "Cloning and Characterization of Goldfish and Zebrafish RICH Proteins."

Ramesh Rengan (Omann) "Signaling Actin Polymerization Responses in Hematopoietic Cells."

Kristin Marie Rusche (Marletta) "Studies of the Nitric Oxide Synthase Catalytic and Structural Requirement for α6-Tetrahydro-L-Biopeterin."

Scott Stewart (Guan) "Regulation of Ras.MAP Kinase Signaling Pathways in Mammalian Cells."

Witoon Tiraphon (Kaufman) "Signal Transduction from the Endoplasmic Reticulum to the Nucleus in Mammalian Cells."

Xiaoli Zhan (Guan) "Function and Regulation of Protein Tyrosine Phosphatases in S. cerevisiae Signal Transductions."

Yunde Zhao (Marletta) "Characterization of the Nitric Oxide Sensing Domain of Soluble Guanylate Cyclase."

William Anthony Ziehler (Engelke) "Biochemical and Genetic Analysis of the Structure and Function of the Ribonucleoprotein Enzyme, RNAase P."

Cole Zimmerman (L. Mathews) "Inhibition of SMAD-mediated Activin and the TGF-beta Signaling by Calmodulin."

Gregor Zimmermann (Taussig) "Characterization of the Regulatory Properties of Mammalian Adenylyl Cyclase."

**Distinguished Alumni/ae Lectureship**

As a means to emphasize the importance of the Department's annual Student Award Ceremony, we have instituted the Distinguished Alumni/ae Lectureship. The first Distinguished Alumni Lecture was given last July by Dr. Morris White (Ph.D. 1981 with Christensen), member of the Joslin Diabetes Center and Howard Hughes Medical Institute and Professor of Medicine at Harvard.

This year, the event is special as our distinguished alumni lecture will be part of the Medical School's sesquicentennial celebration. **Dr. Daniel Oprian** (Ph.D. 1980 with Coon), Professor and Chair of the Department of Biochemistry at Brandeis, will be the lecturer on May 18.
Student Awards:

Christensen Award

From left: Michelle Steinhilb, Xiadong Liu, Gregor Zimmerman, Dong Xu, and Yunde Zhou

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 and performance on the Department's preliminary examination. 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 1999 recipient of the award was Heidi Campbell from the Claudia Kent laboratory.

Coon Award

From left: Gregor Zimmerman, Jud Coon, and Susan Coon

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 1999 recipient of this award was Gregor Zimmerman from the Ron Tauessig laboratory.

Dziewiatkowski Award

From left: Dennis Thiele, Xiadong Liu, Todd Damren, Sam Damren, and Nathaniel Damren

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 recipient of the 1999 Award was Xiadong Liu, who trained in the laboratory of Dennis Thiele.

Christman Award

James Gaunt (left) and Michelle Steinhilb (right)

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 1999 recipient of this award was Michelle Steinhilb from the James Gaut laboratory.
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 1999 Murphy Award was presented to Yunde Zhao from the laboratory of Michael Marletta.

Anthony and Lillian Lu Fellowship in Biological Chemistry

From left: Vince Massey, Dong Zu, Anthony Lu, Deborah Lu, Lillian Lu, and David Ballou

The Anthony 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 1999 Anthony Lu Award was presented to Dong Xu from the laboratories of David Ballou and Vincent Massey.

Other Student and Postdoctoral Fellow Awards:

Monsur Dlakic (postdoc with Kerppola) was awarded an American Association for Cancer Research postdoctoral fellowship and a Leukemia Society of America special fellowship.

Kelly Shaffer (undergraduate with Uhler) has been selected to receive a 2000 Pfizer Summer Undergraduate Research Fellowship.

Chad Stasik (undergraduate with Matthews) has been selected to receive a 2000 Pfizer Summer Undergraduate Research Fellowship.
Gifts

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

**Biological Chemistry Endowment Fund**
Minor J. and Mary Lou Coon • G. Robert Greenberg • Ward W. Smith & Cheryl A. Janson • Jack E. Dixon & Claudia Kent • Thomas, Jo-Anna, & Allen Spector • David A. & Evelyn Tyner

**Dominic D. Dziewiatkowski Dissertation Award**
Sam & Jane Ann Damren

**Minor J. and Mary Lou Coon Graduate Student Fellowship in Biological Chemistry**
Vincent Massey • Yoichi & Gail Osawa • Dennis Thiele & Maria Sippola-Thiele

**Anthony and Lillian Lu Fund**
Kun-Liang Guan & Yuli Wang

**Gerard Summer Fellowship Program**

**Other Gifts**
Thanks also to our anonymous donors

We make every attempt to ensure the list is accurate and complete. Please let us know if there are errors. Information about specific gift opportunities is available from:

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**Faculty Profiles**

Ari Gafni, Ph.D
Professor of Biological Chemistry
Director and Senior Research Scientist, Institute of Gerontology

**Summary of Research Interests**

The main research interest in our laboratory focuses on protein folding, and misfolding, mechanisms and on how these processes feature in aging and in age-associated diseases. While the concept that the three dimensional structure of a protein is encoded in its amino acid sequence is a central tenet of contemporary biology, it is still unclear how this information is utilized in directing the polypeptide chain to fold into a unique, biologically active, structure. This problem, often termed "the second half of the genetic code," is of great importance because its solution will allow us to predict structures of proteins from their amino acid sequences (from genetic information), and to engineer more stable, longer lived, proteins by introducing appropriate mutations. This understanding will also open the door for engineering proteins with new structures and functions.

Studies in our laboratory directed at understanding mechanistic aspects of protein folding use the bacterial enzyme alkaline phosphatase (AP) as a model system. These studies have revealed the existence of very slow conformational transitions that occur during AP folding in vitro, reflecting the existence of long-lived, enzymatically-active intermediates in the folding process. The nature of these intermediates is being studied by a variety of biochemical and spectroscopic approaches. Slow conformational transitions have also been found by us to modify some
cellular proteins in old tissues, leading to alterations in their functional properties. We are exploring the molecular basis of these aging-associated processes.

Living cells respond to stressful conditions by elevating the expression of specific proteins termed stress proteins. One class of stress proteins, the molecular chaperones, plays a critical role in assisting newly synthesized proteins to fold in the cell. A major research effort in our laboratory over the last several years has focused on mechanistic aspects of the folding of several proteins as assisted by the bacterial chaperone-protein system GroEL:GroES. Another important function of stress proteins is the protection of cellular proteins against denaturation and aggregation. We are studying how heat-induced denaturation of proteins is inhibited by the low molecular weight heat-shock protein alpha-crystallin. Our studies aim to develop a more detailed understanding of how stress proteins recognize misfolded proteins, bind them tightly to inhibit their aggregation, and how they subsequently release the bound polypeptides in a folding-competent form. The expression of several chaperone proteins has been found to decline significantly during aging and we are exploring the connection between this phenomenon and the increased level of misfolded proteins which accumulate in cells under these conditions.

It is well established that the folded, biologically-active, state of a protein is frequently only marginally stable, and can convert into misfolded products. Some of these misfolded species feature in a number of devastating human diseases where they aggregate, within tissues, to form specific protein deposits called amyloid. The formation of amyloid is the major pathology in Alzheimer's disease, in non-insulin dependent diabetes and in a number of other age-associated diseases; however, little is known about the details of aggregation in the cellular environment. There is strong evidence to implicate early events in this aggregation as key factors in plaque formation. In particular a conversion of the peptide's secondary structure into a predominantly beta-sheet structure is believed to be a crucial step which predisposes the peptide to rapid aggregation. Structural information on early aggregation intermediates is thus of great significance. Current research in our laboratory addresses mechanistic aspects of the tissue-specific production of amyloid deposits, and focuses on the pancreatic peptide amylin, which forms the plaques in late-onset diabetes. We are attempting to elucidate the highly specific molecular interactions which lead to amyloid formation, and which stabilize this structure. Our goal is to identify the reasons for the strong age-relatedness of this deposition and to develop strategies for its inhibition.

**Representative Publications:**
Kim Orth, Ph.D.
Research Investigator,
Biological Chemistry

The bacterial pathogen Yersinia Pestis is the causal agent for the plague or Black Death, which killed over one third of Europe's population in the 15th Century. Although individuals infected with this pathogen, if treated in time, can be cured with modern medicine, epidemic outbreaks of Yersinia still persist. Y. pestis is related to two other pathogens, Y. enterocolitica and Y. pseudotuberculosis, which are causal agents for gastrointestinal disorders. All three of these pathogens contain a 70kb virulence plasmid that encodes machinery required to prevent phagocytosis by the host and to block the host's immune response. As a result, these pathogens can replicate and evade the host's immune system.

One component of this pathogenic machinery is the Type III Secretion System that allows molecules to pass across both the inner and outer bacterial membrane, across the host membrane and into the host cytosol. In the non-infectious state the system is closed with a 'cap' blocking the channel on the outside of the bacterial cell. During infection, the Type III Secretion System opens and acts like a syringe to inject effector molecules into the host cytosol.

A second component of the pathogenic machinery encoded by the virulence plasmid are the effector proteins that are injected into the host cell via the Type III Secretion System. The Yersinia effector proteins or Yops (Yersinia outer proteins) alter specific host signaling systems. The most thoroughly studied Yop is YopH, a potent tyrosine protein phosphatase that was identified by Kun-Liang Guan while he was a postdoctoral fellow in Jack Dixon's lab. YopH dephosphorylates molecules involved in maintaining focal adhesion, thereby disrupting the host's ability to endocytose the infecting pathogen.

Currently our work is focusing on two other effector proteins, YpkA (YopD) and YopJ. YpkA is a serine/threonine kinase that is in an inactive state in the pathogen. Upon translocation across the Type III Secretion System into the host cell, YpkA binds to an activator, localizes to the plasma membrane and alter the cytoskeleton. Recently, we defined this activator to be actin. These observations suggest a novel mechanism that Yersinia uses to disrupt the actin cytoskeleton resulting in an inhibition of phagocytosis of the pathogen. Our future studies will focus on how this phosphorylation event alters the cytoskeletal components and the mechanism of kinase activation by actin.

Previous studies on another effector protein, YopJ, had demonstrated that YopJ could prevent the host from eliciting an immune response and induce apoptosis in the infected cell. As the protein sequence of YopJ gave us no clue as to its function, we put YopJ into a Yeast Two-Hybrid screen to find the protein that YopJ targets in a eukaryotic cell. We identified the target of YopJ as the family of MAP Kinase Kinases. YopJ prevented the activation of these molecules thereby inhibiting all of the MAP Kinase signaling pathways. Careful analysis of the MAP Kinase pathway and the NFkB pathway lead us to hypothesize that an analogous protein in the NFkB pathway would be inhibited by YopJ. Indeed, YopJ inhibited the activation of IKKb, a kinase found in the IKB complex, which is similar to the family of MAP Kinase Kinases. Therefore, we found that YopJ binds to similar proteins thereby inhibiting critical signaling pathways: the MAP Kinase pathways, which control cell growth and regulate the immune inflammatory response and the NFkB pathway, which regulates the immune response, prevents cell death and controls embryonic development.

Our future studies on YopJ include defining the mechanism by which YopJ inhibits these signaling pathways. Preliminary studies
indicate that YopJ is altering the function of signaling complexes upstream and downstream of MAP Kinase Kinase activation. In addition, in collaboration with Dr. ZhaoHui Xu (Dept. of Biological Chemistry), we are interested in solving the crystal structure of YopJ to gain better insight for the activity of this unique family of pathogenic factors expressed in both animal and plant pathogens.


New Faculty

Carol Fierke, Ph.D.
Professor of Chemistry and Biological Chemistry

Catalysis of chemical transformations is the molecular basis of cellular metabolism and regulation. Our goal is to understand the general principles of biological catalysis and molecular recognition. In particular, we are investigating what features of the amino acid or nucleic acid sequence dictate the functional structure and the catalytic potential and specificity of a macromolecule. To answer these questions, we combine mutagenesis and detailed kinetic and thermodynamic analysis with structural analysis. We are currently focusing on delineating the catalytic mechanism of a number of medically important zinc metalloenzymes and ribozymes.

Protein farnesyltransferase (FTase) catalyzes the transfer of a farnesyl group from farnesyl diphosphate (FPP) to substrates such as Ras and nuclear lamins. Since prenylation of Ras is critical for membrane integration and the subsequent transformation of normal cells into cancerous cells by mutant forms of Ras, compounds that inhibit FTase are being investigated as possible antitumor agents. We are investigating the catalytic mechanism, substrate specificity and inhibitor specificity of this enzyme using mutagenesis and kinetic and thermodynamic analysis in light of the high resolution structure of FTase. In particular, we are analyzing the role of residues that interact with either the substrate pyrophosphate or with inhibitors and investigating the functional role of the catalytic zinc ion. A second enzyme, UDP-3-O-acetyl-GlcNAc deacetylase (LpxC) is a zinc metalloenzyme that catalyzes the first committed step in the pathway to form Lipid A, a crucial component of the outer membrane of gram negative bacteria. Inhibitors of this enzyme have antibacterial activity. To further the development of novel antibiotics we are elucidating detailed structure-function relationships in the active site of these proteins using mutagenesis, kinetic analysis, X-ray crystallography, and spectroscopic studies. These experiments should enhance our understanding of the role of proteins in modulating the reactivity of bound zinc and our ability to design potent inhibitors for these enzymes.

Our understanding of biological catalysis and molecular recognition can be tested by the rational design or redesign of an enzyme. To this end, we are redesigning the zinc metalloenzyme, carbonic anhydrase II (CAII), to alter the metal affinity and specificity. These enzyme variants are useful for optimizing a CAII-based biosensor to measure metal ions in complex mixtures such as plasma and seawater. We are also using these specific zinc ion sensors to investigate the intracellular and extracellular regulatory roles of zinc ions. In particular, we are using these tools to evaluate the importance of zinc toxicity as a cause of neuronal injury after stroke, ischemia, seizures, and blunt trauma to the brain. Secondly, we are using protein engineering
methods to develop biosensors to measure the concentrations of environmental toxins, such as heavy metals, arsenate, nitrate and chromate. Finally, we are using "directed evolution" approaches to prepare pyruvate aldolase variants with novel substrate specificities for use as biocatalysts in organic synthetic reactions. Characterization of the structure and function of these novel proteins will provide insights into catalysis, molecular recognition and molecular evolution.

We are also investigating the catalytic modes of ribozymes by determining the structure and mechanism of ribonuclease P (RNase P), a ribonucleoprotein complex that catalyzes the cleavage of tRNA precursors, an essential step in tRNA maturation. We have recently determined the X-ray crystal structure of the Bacillus subtilis P protein (in collaboration with Dr. D. Christianson) and demonstrated that the protein component enhances the catalytic efficiency by interacting with both the P RNA and the leader sequence of pre-tRNA. In the future, we will elucidate the structure of the holoenzyme using crosslinking, crystallography and spectroscopy and probe the catalytic mechanism of hydrolysis, including the role of magnesium, the protein component and specific RNA-RNA interactions, using specifically-modified RNA molecules. Finally, we will investigate the mechanism of yeast RNase P (in collaboration with Dr. D. Engelke) which contains one RNA and multiple protein subunits and chloroplast RNA which is a protein catalyst. These studies are increasing our understanding of the catalytic mechanism of ribozymes in comparison to protein catalysts.

**Representative Publications:**


S Niranjanakumari, T Stams, SM Crary, S.M., DW Christianson, D.W. and CA Fierke "Protein Component of Ribozyme


JE Jackman, CRH Raetz and CA Fierke "UDP-3-O-(R-3-hydroxymyristoyl)N-acetylglucosamine Deacetylase of Escherichia coli is a Zinc Metalloenzyme" Biochemistry 1999, 38, 1902.

JA Hunt, M Ahmed and CA Fierke "Metal Binding Specificity in Carbonic Anhydrase is Influenced by Conserved Hydrophobic Core Residues, Biochemistry 1999, 38, 9054.


Gary Glick, Ph.D.

Prof. of Biological Chemistry
University of Michigan
Medical School

Werner E. Bachmann
Collegiate Prof. of Chemistry
University of Michigan
College of Literature, Sciences,
and Arts

My research group focuses on applying the tools of chemistry to address problems at the chemistry-biology interface. In one research area, we are developing methods to study the structure and folding of DNA and RNA molecules. A key aspect of this work involves the use of chemically-modified nucleotides as probes of structure, function, and folding. For example, we have engineered disulfide cross-links into medium-sized RNAs to probe folding pathways, much in the way disulfide bonds have been used to explore aspects of protein folding. These cross-links have allowed the first structural assessment of an RNA folding transition state which is important for developing mechanistic model of folding.

A second research area is aimed at defining the binding properties of anti-DNA autoantibodies. Anti-DNA autoantibodies are a hallmark of the autoimmune disorder systemic lupus erythematosus. In a process involving antigen recognition, these antibodies mediate the kidney inflammation that results in much of the morbidity and mortality associated with lupus. However, the specific DNA antigens recognized by anti-DNA and the way in which anti-DNA interact with these molecules remains poorly understood. Using binding-site selection experiments we have identified high affinity consensus sequences for several monoclonal anti-DNA autoantibodies and we are now correlating their binding properties and pathogenicity. Not only do these experiments provide knowledge about the pathology of lupus, but they also provide fundamental insight about protein-DNA interactions in general.

The third avenue of research in my laboratory is aimed at developing small molecule agents to treat lupus and other autoimmune disorders. At present, broad-acting immunosuppressive agents are typically employed as therapeutics for lupus and related disorders. However, these drugs produce serious side effects that limit treatment. We have identified a class of pro-apoptotic benzodiazepines that in several animal models, effectively treats autoimmune disease by selectively killing disease-determining lymphocytes. Unlike current therapies, our compounds are not adversely immunosuppressive. Current efforts on this project focus on delineating the signaling pathways that mediate the benzodiazepine-induced death of lymphocytes and how this process leads to disease improvement.

Representative Publications:

E.J. Maglott, S. Deo and G.D. Glick,


Blatt, N.B. and Glick, G.D. Anti-DNA Autoantibodies and Systemic Lupus Erythematosus, Pharmacology and Therapeutics, 1999, 83, 125


J.J. Bedarski, A. Opipari, T. Rao, N.B. Blatt, R.
Biological Chemistry
Sesquicentennial
Alumni/ae Social
Event in Boston, MA

The 2000 meeting of the American Society for Biochemistry and Molecular Biology will be held June 5-9, in Boston, MA. This is a special year as the University of Michigan Medical School celebrates its 150th anniversary. Please plan to join us at this social event. You will be guests of the Department. Chits for drinks will not be required!

DATE:
Tuesday, June 6, 2000

TIME:
6:00 – 8:00 p.m.

PLACE:
Sheraton Boston Hotel

ROOM:
Jefferson Room