

department of
Pharmacology
newsletter



University of Michigan Medical School

One Hundred and Nine Years of Pharmacology Science

Summer 2000

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Dear Colleagues and Friends:

I am very pleased to send you this issue of the Department of Pharmacology Newsletter. The past year has been an extremely busy and exciting time for us. In May, we had an NIH Site Visit for our Pharmacological Sciences Training Program which went very well, based on the feedback we have received so far. In addition, the Department completed an internal review, which was directed by Dr. Margaret Gnegy, and in June, we had our first external review of the department since March 1989. That also went very well.

Since the last newsletter, there have been changes in key posts within the Medical School. Allen Lichter, M.D., who had previously been Chair of Radiation Oncology, was named permanent Dean after serving a brief period as the Interim Dean. Steve Goldstein, Ph.D., from our own Department of Surgery, was named Associate Dean for Research after a lengthy and thorough search. The search for a Director of the Bioinformatics continues in the Medical School. The University, with significant participation by the Medical School, is aggressively seeking the best candidate for the Director of its Life Sciences Institute, which

became a reality when the Regents and President Bollinger approved its formation this past Fall. The University of Michigan Health System has committed \$150 million with another \$50 million commitment by the University to the development of this Institute. The goal of this institute is to enhance education, basic research, and translational research in the life sciences at the University. The research themes for the Institute include: biocomplexity, chemical and structural biology, genomics and complex genetics, and cognitive neuroscience. The Medical School hopes to recruit 30-40 new faculty to the University through this program, and new research space of 350,000 square feet will be constructed over the next 3 1/2 years to accommodate them. Additionally, the State of Michigan has committed \$50 million a year for the next 20 years from the State's tobacco settlement to provide funding for competitively awarded research proposals in the State. Obviously, this creates numerous opportunities for our faculty and the development of new or expanded research collaborations in which we plan to be heavily involved.

The research enterprise in the Department of Pharmacology continues to grow and prosper with

continuing increases in overall funding from the National Institutes of Health. Total annual direct research expenditures exceeded \$5 million last year. The faculty in the Pharmacology Department has also continued to play leadership roles in the development and implementation of the Program in Biomedical Sciences (PIBS), our new program for combined graduate student recruitment. The first class recruited through this program matriculated last Fall and six members of that class indicated Pharmacology as their primary department choice. The changes in our curriculum that were implemented as a result of PIBS have been very well received by the students. This was also a banner year for the department in that 10 students successfully defended and earned their Ph.Ds. In fact, Elaine Tanhehco, a student in Ben Lucchesi's laboratory, was the 200th student to earn a Ph.D. from our department.

Faculty members continue to fill leadership roles as sequence coordinators in the Medical School curriculum. Our teaching programs have been greatly enhanced by the development of course websites that students have found to be very convenient and helpful.

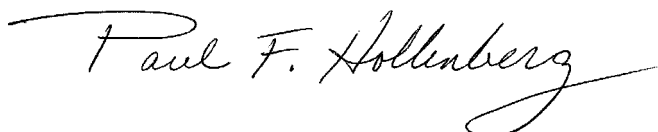
In the latest U.S. News and World Report the Department of Pharmacology is ranked 8th in the country for its doctoral and professional program and is one of only two biomedical science programs at the University of Michigan ranked in the top 10. Our young faculty continue to do well in obtaining new grant funding and we enjoy strong support from the Medical School for our innovative diversity initiatives with undergraduate and graduate students. This past summer 7 students participated in our Charles Ross Minority Summer Research Program.

With regard to the recruitment of new faculty, it gives me great pleasure to announce the recruitment of Jorge Iniguez-Lluhi and Roger Sunahara. Jorge earned his Ph.D. while working in the laboratory of Al Gilman, Nobel Laureate, at Southwestern Medical School in Dallas; while Roger was a postdoctoral fellow with Dr. Gilman and then joined the faculty at Southwestern Medical School as an Assistant Professor. Both faculty members were recruited under the auspices of the Biological Sciences Scholars Program of the University. Jorge's appointment as Assistant Professor was effective June 15 and we are excited that he has joined the department. Roger's appointment will be effective sometime toward the end of this year and we are equally excited about his joining our ranks.

We would again like to acknowledge the alumni and faculty contributions to the department and its programs over the past year. These contributions are very important to our teaching and research programs and contribute to the continued success of the department. An honor roll of past contributors is included on the back page of this newsletter.

I would also like to thank the people who joined us at this year's Annual Alumni Social Hour held at the Joint Meeting of ASPET and ASBMB in June, which included a symposium honoring Wendell Weber for his many contributions as a teacher and researcher. I am happy to announce that we had a fantastic social hour this year with more than 75 attendees. I am looking forward to another great get together in Orlando next year and will get the details out to you next March. Until then, remember to stay in touch and let us know if you have any announcements that you would like included in the next newsletter. If any of you are planning on attending the Medical School Sesquicentennial Celebration this Fall, please let us know and plan to attend Jay Goodman's seminar as this year's Outstanding Alumnus recipient.

Sincerely,



Paul F. Hollenberg, Ph.D.
Maurice Seevers Collegiate Professor and Chair of Pharmacology

Appointments and Promotions

- HELEN A. BAGHDOYAN** was appointed as Professor of Pharmacology, without tenure, effective August 1, 1999. Her primary appointment is in the Department of Anesthesiology. Prior to joining the University of Michigan, Dr. Baghdoyan was a Professor of Anesthesia and Pharmacology at Pennsylvania State University College of Medicine.
- PAUL D. BOUCHER**, a Research Fellow in the laboratory of Donna Shewach, was appointed as a Research Investigator in the Department of Pharmacology effective August 1, 1999.
- MEI-CHUAN KO**, a Postdoctoral Fellow in the laboratory of James H. Woods, was promoted to Research Investigator effective June 1, 1999.
- JERRY A. STITZEL** was appointed as an Assistant Research Scientist in the Department of Pharmacology effective July 1, 1999. He received his Ph.D. in Biology from Johns Hopkins University in 1992. He was previously a Research Associate in the Institute for Behavioral Genetics at the University of Colorado in the laboratory of Allen C. Collins.
- QIN WANG** was appointed as a Research Investigator in the laboratory of Rick Neubig effective October 25, 1999. She obtained her M.D. in Medical Genetics from West China University in Chengdu, China in 1988 and until recently was an Assistant Professor at the Weiss Center for Research at Pennsylvania State College of Medicine.

Honors and Awards

- RAYMOND E. COUNSELL** and **MARC A. LONGINO** were presented with a 1999 Inventor Recognition Award by the University of Michigan for their Hepatocyte-Selective Oil-in-Water Emulsion patent.
- STEPHEN K. FISHER** was appointed Deputy Chief Editor of the Journal of Neurochemistry.
- LORI L. ISOM** received an award from the Distinguished Faculty and Graduate Student Seminars Program in the Rackham School of Graduate Studies for her symposium on the "Structure of Voltage-Gated Ion Channels Involved in Human Disease."
- BENEDICT R. LUCCHESI** was appointed as an Editor of the British Journal of Pharmacology.
- JYOTI MALHOTRA**, a Postdoctoral Scholar in the laboratory of Lori Isom, received the Roche Bioscience Prize for the outstanding poster presentation at the Advances in Ion Channel Research meeting last March.
- RICHARD R. NEUBIG** served as chair of the Pharmacology Study Section, Center for Scientific Review, at the National Institutes of Health for the period July 1, 1999 through June 30, 2000.
- MARSHAL SHLAFER** has been elected as a representative and member on the Basic Science Academic Review Board for a three year period effective August 1, 1999 and ending July 31, 2002. Marshal was also chosen as a recipient of the Winter 1999 Medical Student Award for Teaching Excellence, which recognizes the top two faculty in Components I and II each term.
- MARTHA J. SOMERMAN** was elected Vice President of the American Association of Dental Research. She was also appointed to the Editorial Board of the Journal of Periodontology and the NIH-NIAMS Program Project Review Study Section on November 19, 1999.
- JAMES H. WOODS** was nominated by the Executive Council of ASPET to take the lead in starting a new Division of Behavioral Pharmacology.

REBECCA MCLAUGHLIN celebrated 20 years of service at the University of Michigan where she has been a member of the Department of Pharmacology in the research laboratory of James H. Woods.

Coming and Going

TERRANCE BARRETT joined the laboratory of Benedict Lucchesi as a Research Fellow effective November 1, 1999. He received his Ph.D. in Pharmacology at the University of British Columbia in Vancouver, Canada in 1999 under the supervision of Michael Walker.

RICK BROSCOE completed his Research Fellowship in Jim Woods' laboratory on November 30, 1999 and accepted a position with MPI Research in Mattawan, Michigan.

SONYA COAXUM also joined the laboratory of Benedict Lucchesi as a Research Fellow in September 1, 1999. Sonya earned her Ph.D. in Pharmacology at Meharry Medical College in Nashville, Tennessee. She is a former Charles Ross Summer Research Fellow.

MICHAEL HLUBEK completed his Research Fellowship in the laboratory of Ron Holz on January 7, 2000 and accepted a position as Production Leader at the Air Force Drug Testing Lab at Brooks Air Force Base in Texas.

FEI LI, a Postdoctoral Fellow in the laboratory of Lori Isom accepted a position in Internal Medicine effective April 13, 2000.

YOSHIHIRO MORISHIMA was appointed as a Research Fellow in the laboratory of Bill Pratt on March 20, 1999. He received an M.D. and Ph.D. in Medicine and Biochemistry in 1989 and 1993, respectively, from Osaka City University Medical School in Japan.

LESLIE PARSELS rejoined the Department of Pharmacology as a Research Fellow in the laboratory of Jon Maybaum effective August 23, 1999. Leslie recently completed a Postdoctoral Fellowship at Yale University prior to returning to Ann Arbor.

MARK REILLY completed his Research Fellowship in the laboratory of Jim Woods effective June 30, 1999 and accepted a position in the Psychology Department at Arizona State University in Tempe.

LEI SUN was appointed as a Research Fellow in the laboratory of Ron Holz effective October 25, 1999. She received her Ph.D. in Biochemistry from the Institute of Basic Medical Sciences in Beijing, China in 1998.

HAUILING ZHONG joined Rick Neubig's laboratory as a Research Fellow effective July 19, 1999. He received his Ph.D. in Physiology from Wayne State University in 1997.

Faculty Presentations

RAYMOND E. COUNSELL and MARC A. LONGINO

- Third International Conference on Isotopes, "Synthesis and Evaluation of a Radioiodinated Phospholipid Ether Analog (NM-404) for Diagnostic Imaging of Prostate Cancer." Vancouver, BC, September 6, 1999.
- American Association of Pharmaceutical Scientists, 14th Annual Meeting, "Development and Assessment of a Surface Modified Nanoemulsion for CT Lymphography," New Orleans, LA, November 1999.

EDWARD F. DOMINO

- Society for Research on Nicotine and Tobacco, "Tobacco smoking increases gating of irrelevant and enhances attention to relevant tones but at a cost," San Diego, CA, March 6, 1999.
- Basic Science Research Laboratories, Fujisawa Pharmaceutical Company, Ltd., "Seminar on the Cholinergic System and Alzheimer's Disease—The Role of the Nicotinic Cholinergic Receptors," Osaka, Japan, April 1, 1999.
- Kawanishi Pharma Research Institute, "Seminar on Preclinical Studies of New Antiparkinsonian Agents in MPTP-Induced Hemiparkinsonism," Osaka, Japan, August 24, 1999.
- Invited Chairperson, Round Table on Nicotinic Receptors in Addiction, International Symposium on Neuronal Nicotinic Receptors from Structure to Function, Venice, Italy, October 1–4, 1999.
- American Neurophysiology Society Meetings, "Topographic EEG Gender Similarities and Differences in Response to Tobacco Smoking," St. Louis, MO, November 1, 1999.

Faculty Presentations continued...

LORI L. ISOM

- Organized and Chaired, "Sodium Channel B Subunits as Cell Adhesion Molecules: Homophilic and Heterophilic Interactions," Experimental Biology Meeting 1999, Washington DC, April 20, 1999.
- Roche Bioscience, "Sodium Channel B Subunits have Dual Roles: Channel Modulation and Cell Adhesion," Palo Alto, CA, October 18, 1999.
- DuPont Pharmaceuticals, "Sodium Channel B Subunits have Dual Roles: Channel Modulation and Cell Adhesion," Wilmington, DE, November 17, 1999.
- Organized a National Conference on Voltage-Gated Ion Channels in the Era of the Human Genome Project this past Spring. The Symposium was held at the University of Michigan in the Michigan League on April 9-10, 2000. Speakers at the event included William Catterall, Ph.D. (University of Washington), Barry Ganetzky, Ph.D. (University of Wisconsin), Robert Kass, Ph.D. (Columbia), Stephen Waxman, M.D., Ph.D. (Yale), Miriam Meisler, Ph.D. and Phil Andrews, Ph.D. (University of Michigan), and Jeffrey Thomas, Maggie Johns, Brian Moldover, and Charles Taylor (Warner-Lambert/Parke-Davis).

BENEDICT R. LUCCHESI

- Department of Cell Biology Distinguished Lecturer Series, University of Medicine and Dentistry of New Jersey, "Reperfusion Injury Activated Complement Directly Modifies Myocardial Function and Tissue Viability," Stratford, NJ, May 3, 1999.
- Department of Pharmacology and Toxicology, Medical College of Wisconsin, "Views of Myocardial Reperfusion Injury: Fact or Fiction," First Annual Harold F. Hardman Lectureship Series, Milwaukee, WI, May 14, 1999.

MARTHA J. SOMERMAN

- IADR/AADR Annual Meeting, "Biologically Active Molecules in Cementum," March 1999.
- Scientific Workshop, "Enamel Matrix Components in Formation, Mineralization and Regeneration of Dental Tissues," Norway, September 24-29, 1999.
- 11th International Conference on Periodontal Research, "Wound Healing – Biological Concepts with Impact on Periodontal Regeneration," Göteborg, Sweden, June 17-19, 1999.

WENDELL W. WEBER

- College of Pharmacy, University of Arizona, "Populations and Polymorphisms," Tucson, AZ, March 11, 1999.
- Department of Pathology, Medical College of Wisconsin, "Pharmacogenetics," Milwaukee, WI April 23, 1999.
- Rhone-Poulenc Rorer Pharmaceuticals, Scientific Education Network, "Pharmacogenomics," San Diego, CA, June 10 – 12, 1999.

JAMES H. WOODS

- European and Behavioral Pharmacology Society, "Alcoholism Models in Primates," September, 1999.
- Department of Psychiatry, Johns Hopkins Medical School, "Cocaine and the HPA Axis," October, 1999.
- Department of Pharmacology, Wayne State University, "Cocaine and the HPA Axis," December, 1999.

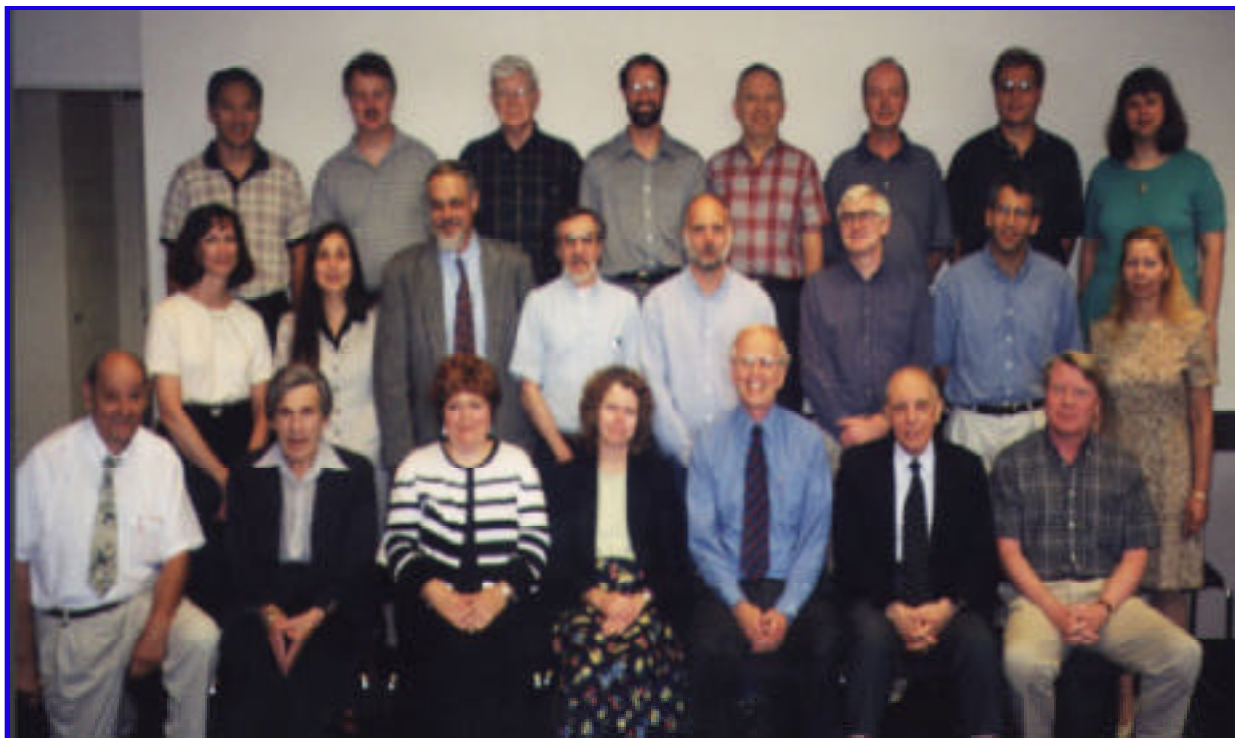
They Shall be Heard

ADA Guide to Dental Therapeutics. Somerman MJ, Seven chapters (Respiratory Concerns; Corticosteroids; Antifungals; Desensitizing Agents; Neoplastic Disorders; Tobacco Cessation; Musculoskeletal/Connective Tissue Associated Drugs) out of 31. Ed: SG Ciancio, ADA Publishing Col., Inc., Feb. 1998; Updated 1999.

Somerman MJ, Hollinger JO. *Bioengineering Oral Tissues.* In: Primer on the metabolic bone diseases and disorders of mineral metabolism, eds. M. Favus, *et al*, Chapt. 86, 465-468, 1999.



Department of Pharmacology Faculty



Front row: Ed Domino, Vince Zannoni, Lori Isom, Margaret Gnegy, Paul Hollenberg, Benedict Lucchesi, Rob Simpson Second row: Donna Shewach, Helen Baghdoyan, Tad Smith, Bill Mancini, Marshal Shlafer, John Traynor, Jon Maybaum, Ute Kent Third row: Yoichi Osawa, Jerry Stitzel, Bert LaDu, Rick Neubig, Gerald Levy, Steve Fisher, Marc Longino, Mary Bittner.

New Grant Awards

The following sponsored research projects were funded January 1, 1999, through December 31, 1999:

Astra Zeneca

BENEDICT R. LUCCHESI, "Prevention of Arterial Thrombosis/Rethrombosis by Intravenously Administered Platelet P2Y₁-Receptor Antagonist," 03/01/99-12/31/00.

JAMES H. WOODS, "Ventilatory Function in Rhesus Monkeys," 07/01/00-12/31/00.

Friskies

MARTHA J. SOMERMAN, "Continued Investigations on Mechanisms Regulating Resorption and Repair in Feline Neck Lesions," 05/06/99-05/05/02.

LXR Biotechnology, Inc.

BENEDICT R. LUCCHESI, "Myocardial Repurfusion Injury," 01/01/99-06/30/00.

Monsanto Company

BENEDICT R. LUCCHESI, "Assessment of Drug-Induced QT Prolongation," 10/14/99-05/1/00.

National Institutes of Health

LORI L. ISOM, "Functional Modulation of Sodium Channels by Tenascin-R," 01/01/00-02/28/00.

WILLIAM B. PRATT, "Steroid Receptor Transformation," 12/01/99-11/30/04.

DONNA S. SHEWACH, "Gemzar: Mechanisms of Cytotoxicity and Radiosensitizations," 07/01/99-6/30/03 and (Ted Lawrence-P.I.), "Radiosensitization by Gemcitabine," 04/01/99-03/31/02.

MARTHA J. SOMERMAN. "Interdisciplinary Workshop on Oral Health and Quality of Life, 09/30/99-09/29/00; (Giannobile-P.I.), "Gene Therapy for Reconstructing Periodontal Tissues," 12/01/99-11/30/04; and (Franceschi-P.I.), "Gene Therapy Approach for Engineering Craniofacial Bone," 12/01/99-11/30/04.

GAIL D. WINGER, "Stimulants, Depressants and Hallucinogens as Reinforcers," 08/01/99-08/31/04.

National Science Foundation

LORI L. ISOM, "Regulation of Sodium Channel Density and Localization in Polarized Cells," 08/15/99-07/31/03.

Novartis

JAMES H. WOODS (with Mei-Chuan Ko), "Evaluation of the Anti-hyperalgesia Efficacy of Various Antagonists, 11/01/99-09/30/00.

Elsa U. Pardee Foundation

DONNA S. SHEWACH (with Medical College of Ohio), "Enhancement of Drug Cytotoxicity by Increasing Gap Junctional Intercellular Communications," 09/30/99-10/01/00.

Pfizer

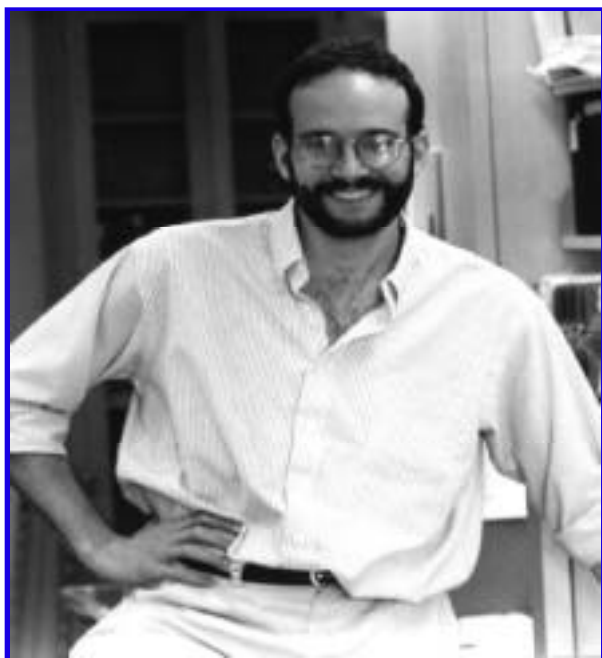
MEI-CHUAN KO (with James H. Woods), "Evaluation of Anti-hyperalgesic Efficacy of the Pfizer B₂ Antagonist," 02/10/00-08/10/00.

Warner-Lambert

GAIL D. WINGER, "Evaluation of Pregabalin as a Blocker of Cocaine," 12/01/00-08/31/00.

Wyeth-Ayerst Laboratories

JAMES H. WOODS, "Evaluation of the Reinforcing Effects of Sedative Compounds," 04/01/99-04/01/00.

From the Laboratory of Jorge A. Iñiguez-Lluhí, Ph.D.**FOCUS ON RESEARCH**

The Pharmacology Department welcomed its newest faculty member, Jorge A. Iñiguez-Lluhí, as Assistant Professor of Pharmacology on June 15, 2000. Dr. Iñiguez-Lluhí received his Ph.D. in Pharmacology from the University of Texas Southwestern Medical School in Dallas in 1994. His graduate work in the laboratory of Dr. Alfred G. Gilman focused on G protein signaling. Most recently, he completed his postdoctoral training in the laboratory of Keith R. Yamamoto at the University of California, San Francisco studying signaling and transcriptional regulation by the glucocorticoid receptor. In the following paragraphs, Dr. Iñiguez-Lluhí describes the research interests that he plans to pursue at the University of Michigan.

Research Interests for the Laboratory:

A fundamental property of living cells is their ability to sense cues in their environment, process the information they embody and respond in a physiologically and developmentally appropriate manner. The types of cellular responses mounted during normal and pathologic conditions are ultimately dependent on the accurate expression of a large array of independent genes. The establishment and maintenance of such gene expression programs relies on the complex interplay between specific transcription regulatory factors, the signals they respond to and the regulatory genomic sites where they act.

Our interests lie in understanding the molecular basis for the regulatory transactions that transcription factors engage in as they assemble in the vicinity of specific genes and how these operations are integrated to yield the final transcriptional output. We focus on members of the Intracellular Receptor (IR) superfamily as well as other transcription factor classes as paradigms to explore these issues. IRs constitute a large group of transcription regulators including key mediators of metabolism, reproduction, growth and differentiation and its members mediate the effects of steroid and thyroid hormones and other signaling molecules. Upon agonist binding to a C-terminal ligand-binding domain (LBD), IRs are recruited to specific genomic sites via a central DNA binding domain. Once within the vicinity of a target gene, IRs deploy latent transcriptional regulatory functions and in conjunction with other sequence-specific factors, they nucleate the assembly of multiprotein complexes that activate or repress transcription of nearby promoters. By taking advantage of complementary *biochemical*, *genetic*, *structural* and *molecular biological* approaches we are exploring A) the basic mechanisms of transcription, B) the molecular basis of specific functional interactions among transcription factors and C) how these elements of *genomic regulatory logic* are assembled to give rise to the complex patterns of gene expression in an intact developing tissue.

Determinants and mechanism of transcriptional activation.

Many of the functional properties of IRs can be recapitulated in model organisms such as the yeast *Saccharomyces cerevisiae*. We have exploited the genetic tools available in this organism to define the critical transcriptional activation determinants within the N-terminal regulatory region of the Glucocorticoid Receptor (GR). Through an unbiased genetic screen for mutant receptors with altered transcriptional potential we found that the *hydrophobic* character of critical residues within a short 16 amino acid region is essential for transcriptional activation.

By providing a link between structure and function, these mutants constitute invaluable tools to study both genetically and biochemically the mechanism of action of this domain. Recently, we have exploited these mutants to identify components of the cellular machinery that interpret the activation signal emanating from this region of the receptor. We found that DRIP 150 directly interacts with the N-terminal region of GR and mediates some of its functions. This protein is a specific subunit of a recently described protein complex implicated in transcriptional activation by multiple regulators. We are examining the biochemical and structural properties of this interaction and exploring its functional consequences.

Molecular basis and regulation of transcriptional synergy.

The DNA regulatory regions of a particular gene determine the specific pattern of its expression and invariably contain binding sites for a variety of transcription factors, often in multiple copies. Functional interactions between multiple regulators often yield a more than additive or synergistic output but the mechanisms that enable or control such synergy are not fully understood. I recently identified a novel protein motif responsible for the control of synergy. These short motifs are found in steroid receptors and other regulators such as the proto-oncogenes *cMyb* and ETS-1. When disrupted, transcriptional synergy is greatly enhanced. This occurs without alterations in DNA binding or in the intrinsic activation potential of the regulators. Deletions of *cMyb* encompassing the synergy control motif possess enhanced transcriptional activity and are the most common transforming alteration of this proto-oncogene. We are interested in the mechanism of action of these motifs since they represent a higher order element of the genomic regulatory logic. We are using them as probes to identify and understand the molecular basis for the mechanisms that control the outcome of functional interactions among transcription factors.

Probing regulatory interactions in the context of an intact tissue.

At a higher level of organization, we are interested in examining how individual transcription factor regulatory interactions contribute to the establishment of gene expression programs in the context of an intact mammalian animal or tissue. Current mouse knock-out or knock-in approaches however, are labor intensive and can be limited since an essential role of the gene of interest during development could preclude analyses in mature organs, and functional redundancy could demand multiple mutations before the emergence of a phenotype.

We are interested in developing alternative genetic approaches to assess the transcriptional and developmental consequences of regulatory proteins at the tissue level. The remarkable regenerating potential of the adult liver and recent advances in both gene targeting and liver stem cell research offer the possibility to use this organ as a genetically accessible experimental system to overcome some of these problems. Furthermore, this tissue is a primary target of glucocorticoids and thus ideally suited to study the consequences of altering individual functional surfaces of the glucocorticoid receptor. In conjunction with novel tools to monitor genome-wide expression, these methods may allow us to examine the contributions of any particular factor to the regulation of gene batteries during normal physiologic function or during regeneration and disease.

The combination of basic studies of fundamental mechanisms of cell regulation with manipulation of whole animal systems is likely to be an essential component of the emerging functional genomics era. By applying innovative approaches, we envision participating in the daunting but increasingly approachable tasks of revealing how the basic elements of genomic regulatory logic are assembled into the higher order structure and hierarchy of genome-wide *cis*-regulatory networks.

The Laboratory of Jerry Stitzel, Ph.D



Dr. Jerry A. Stitzel received his bachelor's degree in Molecular, Cellular, and Developmental Biology and Biochemistry from the University of Colorado in Boulder. He earned his Ph.D. from Johns Hopkins University in Baltimore, Maryland, and then returned to the University of Colorado where he completed his postdoctoral work at the Institute for Behavioral Genetics in the laboratory of Dr. Allan Collins.

Dr. Stitzel's major focus is the use of genetics as a tool to explore the biological basis for individual variability in response to nicotine for a variety of physiological and behavioral measures in mice. While in the Collins' laboratory, Dr. Stitzel began studies to identify naturally occurring molecular variations for the genes that encode the various receptor subunits of the nicotinic acetylcholine family in mice. This work led to the identification of an assortment of mouse strain-specific alleles for several of the nicotinic receptor subunit genes. Subsequent genetic analyses demonstrated that segregation of the strain-specific alleles for

the nicotinic receptor $\alpha 7$ subunit gene were highly predictive of individual variability in the brain region-specific expression of the nicotinic receptor that binds α -bungarotoxin with high affinity. Dr. Stitzel also found that the alleles of $\alpha 7$ were associated with individual differences in sensitivity to nicotine in mice. These studies were the first to demonstrate that genetic heterogeneity of a specific nicotinic receptor subunit gene was associated with individual differences in nicotinic receptor expression and sensitivity to nicotine. The work on the nicotinic receptor $\alpha 7$ subunit has led to the identification of an unusual isoform of $\alpha 7$ that arises from a combination of alternative splicing and RNA editing. This isoform provides the first evidence that the $\alpha 7$ subunit is alternatively spliced in brain and is the only demonstration to date of editing of a nicotinic receptor RNA. Studies are currently underway to determine the functional significance of this unique isoform.

Additional studies by Dr. Stitzel have shown that the strain-specific alleles of the nicotinic receptor subunit genes for $\alpha 4$, $\alpha 5$, and $\alpha 6$ also co-segregate with individual differences in sensitivity to nicotine in distinct mouse populations. The alleles for $\alpha 4$ have recently been shown to be highly predictive of individual variation in nicotinic receptor function in mouse brain as measured by nicotine-stimulated R^{+} efflux from synaptosomal preparations.

Dr. Stitzel was recruited to the University of Michigan by the recently formed University of Michigan Tobacco Research Network headed by Dr. Kenneth Warner of the School of Public Health. At the University of Michigan, Dr. Stitzel intends to continue his work on the identification and characterization of naturally occurring nicotinic receptor subunit variation. These studies will hopefully lead to a better understanding of the role of distinct nicotinic receptor subtypes in modulating various behavioral and physiological responses to nicotine. Dr. Stitzel also expects to expand his genetic studies to identify genes other than those of the nicotinic receptor subunit family that contribute to individual variations in nicotine sensitivity.

NewStudents

René Bernard, B. S., Biology, Apotheker, Universitat Regensburg, Regensburg, Bavaria, Germany

Tigwa Davis, B. S., Biology, Morehouse College, Atlanta, GA

Anwar Dunbar, B. S., Biology, Johnson C. Smith University, Charlotte, NC

Jennifer Harrell, B. S., Biochemistry/Molecular Biology, Dickinson College, Carlisle, PA

Emily Jutkiewicz, B. S., Bio-psychology, Tufts University, Medford, MA

Elizabeth Lapoczka, B. S., Biology, Ashland University, Ashland, OH

NewGraduates

Jordan Scott Fridman, “Divergent Phenotypes Induced by Expression of BCL-XS: Cytokinetic Effects and Death without Caspases.” Mentor: Jonathan Maybaum. Jordan has accepted a postdoctoral position at the Cold Spring Harbor Laboratory in New York. He joined the laboratory of Dr. Scott W. Lowe where he is studying drug resistance and cell death in lymphoma using genomics and *in vivo* models of B-cell lymphoma.



Using a tetracycline-regulated expression system, we have shown that expression of bcl-XS is able to elicit divergent, phenotypic responses in different cell lines. In K12 rat colon carcinoma cells, we observe two phenotypic responses. A small fraction of cells undergo spontaneous programmed cell death while the majority of cells undergo a form of cytosclerosis. This stasis is the result of a redistribution of cells out of the S-phase, and into the G1-phase of the cell cycle. Expression of bcl-XS also decreased the viability of K12 cells, as demonstrated by a log decline in clonogenic survival and, this decrease is not prevented by caspase inhibition. Expression of bcl-XS was determined to be sufficient to induce acute cell death in 3T3 cells and the manner in which these cells die is both morphologically and biochemically different from Fas/CD95 induced apoptosis. These data suggested that cytochrome *c* was being released from the mitochondria and should therefore trigger the activation of pro-caspase-9 and apoptosis. However, the lack of caspase activation was determined to be due to a unique phenomenon also caused by expression of bcl-XS, depletion of cellular cytochrome *c*. *In vitro* pro-caspase activation assays proved that addition of exogenous cytochrome *c* to cytosolic extracts prepared from bcl-XS expressing 3T3 cells is sufficient to trigger ³⁵S-pro-caspase-9 processing.

Furthermore, transient transfection experiments showed that cell death induced by bcl-XS is not inhibited by dominant negative caspase 9, but that cell death induced by bax or bak expression is inhibited. Consequently, bcl-XS must kill 3T3 cells through a pathway that does not require liberation and/or action of bax/bak nor through a caspase-dependent pathway.

Elizabeth R. Glaze, “Role of BrdU in Enhancing the Effect of BCNU in D54 Human Glioma Cells: Evidence that the Mechanism Involves the Formation of New BCNU-Induced DNA Lesions”. Mentor: William R. Mancini. Liz has accepted a postdoctoral position in the Department of Pharmacology at the University of Pennsylvania. She is working in the laboratory of Dr. Trevor Penning where she is studying dihydrodiol dehydrogenase-induced DNA damage in stable transfectants exposed to polycyclic aromatic hydrocarbons.



The prognosis of patients with gliomas is poor. Hence, most clinicians use a combination of drugs to increase the tumor cell kill in patients with this disease. One protocol, which uses a thymidine analog, BrdU, to increase the effect of radiation, can enhance the survival time of patients from 1 year to 2 years. We determined that BrdU will also sensitize tumor cells to the alkylating agent, BCNU, which is widely used

to treat this type of cancer. Furthermore, we have evidence suggesting that the mechanism by which sensitization is occurring involves the formation of BCNU-induced DNA adducts.



Daniel Allan Hamstra, “Gene Dependent Enzyme/Prodrug Therapy for Head and Neck Cancer.” Mentors: Jonathan Maybaum and Alnawaz Rehemtulla. Dan is an MSTP student and will be finishing Medical School at the University of Michigan.

5-Fluorouracil (5-FU) and methotrexate (MTX) are two of the most active single agents in the treatment of head and neck cancer (HNC). Therefore, we evaluated two Gene Dependent Enzyme Prodrug Therapies (GDEPT) to localize high-doses of MTX or 5-FU to the tumor site through the *in situ* activation of systemically administered non-toxic prodrugs.

To study the cytosine deaminase (CD) / 5-fluorocytosine (5-FC) GDEPT an orthotopic animal model of head and neck cancer was utilized. Treatment of animals bearing CD-expressing tumors with the maximum tolerated dose of either 5-FU or radiotherapy (RT) had no impact upon tumor growth or animal survival even when 5-FU/RT were administered concomitantly. In contrast, treatment with 5-FC resulted in a greater than two-fold increase in time of survival which was enhanced by the addition of concurrent RT. In order to improve upon the CD / 5-FC GDEPT we next compared the bacterial and yeast CD enzymes for their ability to convert 5-FC to 5-FU. CD derived from *S. cerevisiae* had a 250-fold higher capacity to convert 5-FC to 5-FU than its bacterial counterpart, and this resulted in both a 30-fold lower IC_{50} for 5-FC *in vitro* and a markedly enhanced “bystander effect.” *In vivo* the yeast enzyme resulted in a significant decrease in tumor growth rate following treatment with 5-FC and a 60% rate of long-term survivors, while there were no long-term survivors for the animals bearing tumors expressing bacterial CD. These studies suggest a role for GDEPT in the treatment of locally advanced head and neck cancer.



Thomas Gregory Hullinger, “Role of Osteopontin in Skeletal Metastasis.” Mentor: Martha J. Somerman. Tom accepted a position with Parke-Davis (Pfizer) in Ann Arbor, in the laboratory of Dr. Sótirios K. Karathanases.

The ability of prostate and breast cancer cells to preferentially metastasize to bone and have pronounced effects on the structure and function of the skeleton is well recognized yet mechanisms governing these processes have not been firmly established. This dissertation has focused on the role of bone matrix adhesion proteins in targeting of tumor cells to bone and the response of bone to tumor cell invasion. Bone matrix proteins were demonstrated to support attachment of prostate cancer cells and evidence was provided to suggest that the bone matrix adhesion proteins osteopontin (OPN) and bone sialoprotein (BSP) mediate this attachment process. Expression of $\alpha_v\beta_3$, a cell surface integrin receptor for OPN and BSP, was correlated with tumor cell attachment. In addition, tumor cell attachment to bone proteins was abolished with a blocking antibody to the integrin $\alpha_v\beta_3$. Furthermore, OPN and BSP are known to contain an arginine-glycine-aspartic acid (RGD) domain which mediates cell attachment and competition experiments with RGD peptides blocked attachment of tumor cells to bone proteins. Collectively these results indicate that OPN and BSP promote the attachment of prostate cancer cells and suggest that bone associated adhesion molecules play an important role in the recruitment of prostate cancer cells to bone.

The osteolytic response of bone to tumor cell invasion is due in part to the ability of tumor cells to up-regulate OPN mRNA in osteoblasts, where OPN has been shown to promote osteoclast activity. Secretory products from osteolytic but not osteoblastic tumor cell lines were demonstrated to up-regulate OPN in osteoblasts. Signal transduction studies demonstrated that both PKC and the MAP kinase cascade were involved in the OPN response. Bone homing tumor derived factors known to up-regulate OPN were assessed for their effects on OPN transcription. Promoter studies revealed that TGF β activated OPN transcription via a Hox binding element; whereas, bone morphogenic protein2 activation of OPN transcription involved the same Hox binding element and a putative Smad binding element.

Daniel Allan Linseman, “Muscarinic Receptor Signaling to the Non-Receptor Tyrosine Kinases Focal Adhesion Kinase and Activated CDC42HS-Associated Kinase-1.” Mentor: Stephen K. Fisher. Dan has accepted a position as an Associate Investigator at the University of Colorado in the laboratory of Dr. Kim Heidenreich in the Department of Pharmacology. The principal research focus of Dr. Heidenreich’s laboratory is the elucidation of signal transduction pathways which regulate neuronal apoptosis.

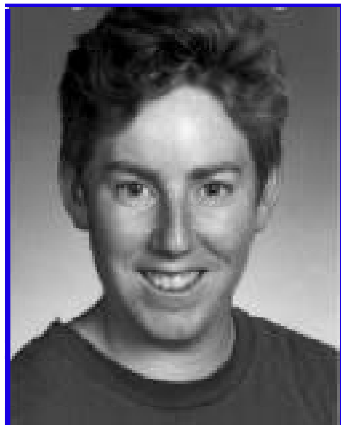


Cholinergic transmission is a crucial element of cognitive function in the CNS. Deficits in muscarinic cholinergic receptor (mAChR) signaling contribute to the pathophysiology of Alzheimer’s disease. The signal transduction pathways which link receptor stimulation to changes in synaptic plasticity are presently unclear. Tyrosine kinase activity is required for neuronal growth cone remodeling and for long term potentiation/depression, two *in vitro* models of learning and memory. Focal adhesion kinase (FAK) and activated Cdc42Hs-associated kinase-1 (ACK-1) are non-receptor tyrosine kinases which are highly expressed in brain. Recently, both FAK and ACK-1 have been postulated to regulate synaptic changes in the CNS. Therefore, the principal objectives of this thesis were to determine if mAChRs expressed in neuronal cells signal to these kinases and to elucidate the signaling pathways involved.

Stimulation of mAChRs on SH-SY5Y human neuroblastoma cells elicits neurite outgrowth and a marked increase in the tyrosine phosphorylation of FAK, which depends on an intact actin cytoskeleton, but does not require phosphatidylinositol 4,5-bisphosphate (PIP₂)-derived second messengers. Maintenance of agonist-sensitive PIP₂ pools is a prerequisite for FAK signaling and this lipid may facilitate protein:protein interactions (e.g., vinculin:talin) which localize FAK to sites of cytoskeletal remodeling. Two small molecular weight GTPases that regulate actin cytoskeletal dynamics, Rho and Cdc42, are also necessary for FAK signaling. Although in fibroblasts Rho has been shown to modulate PIP₂ synthesis, inhibition of Rho Cdc42 function in SH-SY5Y cells attenuates FAK signaling independently of effects on PIP₂ content.

Activation of mAChRs also induces an enhanced tyrosine phosphorylation and increased kinase activity of ACK-1. Agonist-stimulated ACK-1 phosphorylation is blocked by inhibition of Cdc42 function, but unlike FAK, does not require an intact cytoskeleton. PIP₂ second messengers are not necessary for mAChR signaling to ACK-1, but rather, a novel PKC-dependent negative feedback loop is observed.

The results are the first to document a role for either PIP₂ or Cdc42 in FAK signaling and to demonstrate activation of ACK-1 following stimulation of a receptor coupled to neurite outgrowth. The data support a role for FAK and ACK-1 in growth cone remodeling and reveal several potential targets for modulating the activities of these tyrosine kinases.



Kim Melinda McGinnis, “Calcium, Calmodulin, and Calcium/Calmodulin Dependent Kinase and Phosphatase: Roles in Neuronal Cell Death.” Mentor: Margaret E. Gnegy. Kim has accepted a Postdoctoral Fellowship in the Molecular Neurogenetics Unit at Massachusetts General Hospital.

Changes in intracellular Ca^{2+} concentration are an essential signaling mechanism for many neuronal processes including neurotransmitter release, long-term potentiation, and gene transcription. The Ca^{2+} binding protein calmodulin (CaM) is a calcium-activated switch that activates numerous enzymes with diverse functions. In carbachol-treated SK-N-SH human neuroblastoma cells, CaM translocates from the membrane to the cytosol. I showed that the CaM translocation is due to release of Ca^{2+} from the intracellular stores. Pretreatment with the intracellular Ca^{2+} (Ca^{2+}_i) chelator BAPTA, but not the non-specific Ca^{2+} -channel antagonist Ni^{2+} prevents carbachol-mediated

CaM translocation. Thapsigargin, which increases Ca^{2+}_i through emptying the intracellular stores, activates PKC α and induces CaM translocation. Exposure to K^+ , which increases Ca^{2+}_i through influx of extracellular Ca^{2+} (Ca^{2+}_e), leads to neither PKC α activation nor CaM translocation. Calcium source selectivity is increasingly recognized as an important factor in Ca^{2+} mediated signal transduction. Alterations in Ca^{2+} homeostasis have been implicated in the onset of cell death that is linked to neurodegenerative diseases. I show that exposing SH-SY5Y cells to 5 mM Ca^{2+}_e leads to activation of the Ca^{2+} dependent cysteine protease calpain and induces necrosis. Blockade of Ca^{2+} channels with Ni^{2+} prevents Ca^{2+}_e -mediated calpain activation. Conversely, depletion of Ca^{2+}_e with 2 mM EGTA activates caspase-3-like proteases and induces apoptosis. EGTA-mediated activation of caspase-3-like proteases can be interrupted by restoration of Ca^{2+}_e . The fates of CaM-dependent kinase and phosphatase in neuronal cells undergoing apoptosis were also examined. I showed that CaM kinase inhibition potentiates thapsigargin-mediated cytotoxicity through a caspase-dependent pathway. Ca^{2+} /CaM-dependent protein kinase IV (CaMK IV) is fragmented during apoptosis at different sites by calpain and caspase-3. I found that these cleavage sites fall within the kinase catalytic domain. CaMK activity decreases in SH-SY5Y cells and cerebellar granule neurons undergoing apoptosis. The loss in activity precedes loss of viability. Conversely, inhibition of the CaM-dependent phosphatase calcineurin protects against thapsigargin-mediated apoptosis. Calcineurin is also fragmented during apoptosis. Purified calcineurin is cleaved by digestion with purified caspase-3 to a 45 kDa fragment.

The fragmentation occurs at a site such that the regulatory domain is cleaved from the catalytic domain. The phosphatase activity of purified calcineurin increases as a result of caspase-3 digestion. The activity loses its CaM-dependency, consistent with the loss of the regulatory domain. Work in this thesis clarifies the effects of changes in Ca^{2+} concentration in protease activation and the roles of CaM-dependent kinases and phosphatase in neuronal apoptosis.



James E. Novak, “Inositol Homeostasis and Phosphoinositide Signaling During the Neuronal Differentiation of NT2 Cells.” Mentor: Stephen K. Fisher. Jamie is a third-year Medical Student in the University of Michigan Medical School and a member of the Medical Scientist Training Program.

Although dysfunctional inositol homeostasis and phosphoinositide signaling in central nervous system (CNS) neurons have been implicated in neuropsychiatric disease, the study of inositol biochemistry in pure, human neuronal populations has been hindered by the lack of a suitable cell model. The goal of this thesis was to use the NT2-N neuronal cell system to test the hypotheses that: (i) differentiated neurons attain a high concentration of inositol as result of changes in inositol transport, and that (ii) neuronal differentiation is associated with specific and functional change, in the expression of phosphoinositide signaling proteins.

Inositol transport, in turn, is regulated by signaling molecules in NT2-N neurons. Inositol uptake is refractory to modulation by most second messengers, although hypertonic stimulation of uptake may be mediated by p38 mitogen-activated protein kinase. Volume-sensitive inositol efflux, in contrast, is stimulated by protein kinase C activation and by elevation of the cytosolic Ca^{2+} concentration but is blocked by Cl^- channel inhibitors.

In summary, neuronal differentiation of NT2 cells was associated with: (i) a ten-fold increase in inositol concentration consistent with increased uptake and decreased efflux, and (ii) a five-fold increase in the rate of inositol lipid hydrolysis consistent with increased expression of $\text{G}_{q/11}$ and PLC- β 1/4.

Quintin Pan, “1,25-Dihydroxyvitamin D_3 Regulation of *c-myc* Expression and HL-60 Cell Differentiation: A Role for PKC β and HOXB4.” Mentor: Robert U. Simpson. Quintin is applying to Medical School.

The focus of this dissertation was to determine the mechanism by which 1,25-(OH) $_2\text{D}_3$ regulates *c-myc* expression and the importance of PKC β in HL-60 cell differentiation.

The importance of PKC β levels and activation in 1,25-(OH) $_2\text{D}_3$ promotion of HL-60 cell differentiation was investigated. Increase in PKC β levels and promotion of cell differentiation was observed to be maximal at 48-72 hours of continuous 1,25-(OH) $_2\text{D}_3$ treatment. Cells treated with six hours of 1,25-(OH) $_2\text{D}_3$ followed by absence of hormone for 66 hours showed a significant increase in PKC β levels. However, this six hour treatment protocol was not sufficient to fully promote cell differentiation. These results suggest that 1,25-(OH) $_2\text{D}_3$'s genomic action to increase PKC β levels is not sufficient to fully promote terminal cell differentiation. Therefore, it was hypothesized that continuous treatment with 1,25-(OH) $_2\text{D}_3$ is required and that the hormone must also activate PKC β to fully promote cell differentiation. Ionomycin was used to increase diacylglycerol and intracellular calcium levels. These actions of ionomycin were shown to activate the increased levels of PKC β by 1,25-(OH) $_2\text{D}_3$. Cell differentiation promoted by ionomycin in 1,25-(OH) $_2\text{D}_3$ pretreated cells was similar to differentiation promoted by continuous 1,25-(OH) $_2\text{D}_3$ treatment. This suggests that 1,25-(OH) $_2\text{D}_3$ has increased enough *de novo* synthesis of PKC β , if activated, after six hours to fully promote cell differentiation. These results suggest that 1,25-(OH) $_2\text{D}_3$ must have a genomic action to increase PKC β levels and a nongenomic action to provide cofactors to activate PKC β in order to fully promote HL-60 cell differentiation.

The roles of three putative protein-binding sites in the *c-myc* gene were examined. 1,25-(OH) $_2\text{D}_3$ was demonstrated to enhance nuclear protein binding to MIE1, MIE2, and MIE3. Specificity studies indicated that these 1,25-(OH) $_2\text{D}_3$ inducible proteins are capable of binding to three different MIE sites; however, with different affinities. Next, the physiological relevance of these MIE binding sites in the regulation of *c-myc* was determined. 1,25-(OH) $_2\text{D}_3$ was able to down-regulate CAT expression with the wildtype promoter. The ability of 1,25-(OH) $_2\text{D}_3$ to inhibit CAT expression was significantly decreased with a MIE1 deletion construct. Furthermore, deletion of MIE1, MIE2, and MIE3 completely rendered 1,25-(OH) $_2\text{D}_3$ ineffective at controlling CAT expression. These results indicate the MIE1, MIE2, and MIE3 binding proteins are required and may interact cooperatively to block *c-myc* transcriptional elongation during HL-60 cell differentiation.

In summary, this dissertation provided new insights into the regulation of *c-myc* expression and the importance of PKC β in 1,25-(OH) $_2\text{D}_3$ promotion of HL-60 cell differentiation. Delineating these molecular cellular events has increased our knowledge of the processes involved in terminal differentiation. This dissertation brings us a better understanding of the mechanisms involved in terminal differentiation of a cancer cell and may provide the basis for novel therapeutic approaches to combat cancer.





Scott Douglas Sorensen, “A Role for Phosphoinositides in the Regulation of Muscarinic Cholinergic Receptor Endocytosis.” Mentor: Steven K. Fisher. Scott accepted a postdoctoral position with Dr. P. Jeffrey Conn at Emory University.

The central nervous system contains a high density of muscarinic cholinergic receptors (mAChRs) that have been implicated in a number of neuropsychiatric disorders. The M_3 subtype of mAChR couples through $G_{a/11}$ to the activation of phosphoinositide-specific phospholipase C (PLC) and hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) to form two second messengers, diacylglycerol (DAG) and inositol trisphosphate, which regulate the protein phosphorylation state as well as Ca^{2+} homeostasis within the cell. Given the central role that protein phosphorylation and Ca^{2+} homeostasis play in neuronal physiology, the regulation of this signaling pathway assumes major importance. A common

regulatory response to the prolonged agonist occupancy of the mAChR, as well as many other G-protein coupled receptors (GPCR), is the endocytosis of these receptors to a compartment distinct from that of the plasma membrane. The purpose of this thesis is two-fold: (i) to investigate the functional status of the internalized mAChR and (ii) to gain mechanistic insights into GPCR endocytosis by determining the role that phosphoinositides play in facilitating receptor endocytosis.

Incubation of SH-SY5Y neuroblastoma cells with the muscarinic agonist, Oxotremorine-M, resulted in the endocytosis of mAChRs as well as the alpha subunit of $G_{a/11}$ into a vesicular (V_1) fraction. Addition of the agonist also resulted in an increased formation of DAG in the V_1 , but this increase persisted when mAChR endocytosis was blocked. ^{32}P phosphoinositide labeling studies and direct enzyme assays indicated a limited capacity of the V_1 to synthesize PIP_2 . The latter may account for the limited ability of internalized mAChRs to activate PLC.

A role for phosphoinositides in the endocytosis of mAChRs was investigated via pretreatment of SH-SY5Y cells with either wortmannin (WT), LY-294002, or phenylarsine oxide (PAO). Inclusion of each of these chemically distinct inhibitors of phosphatidylinositol 4-kinase (PI4K) blocked agonist-induced mAChR endocytosis. Furthermore, PAO-mediated inhibition of both mAChR endocytosis and phosphoinositide synthesis could be fully reversed by inclusion of the bifunctional thiol, 2,3-dimercaptopropanol. WT-, LY-294002-, and PAO-sensitive PI4K activity was found primarily in vesicular and cytosolic fractions, consistent with the distribution of PI4Kb. These results indicate that phosphoinositide synthesis regulates mAChR endocytosis and that a WT-sensitive PI4K, such as PI4Kb, is required. However, overexpression of PI4Kb did not effect mAChR endocytosis indicating that PI4Kb is not rate-limiting.

The phosphoinositide requirement for GPCR endocytosis was further investigated utilizing 1321N1 astrocytoma cells, which possess PLC-coupled mAChRs and adenylyl cyclase-linked β -adrenergic receptors (β -AR). Addition of WT alone reduced phosphatidylinositol phosphate (PIP) and PIP_2 labeling and partially (30%) inhibited β -AR internalization. However, addition of Oxotremorine-M to WT-pretreated cells led to a further reduction of PIP_2 , but not of PIP, and to a substantial inhibition (>70%) of β -AR endocytosis. These results point to a general requirement for phosphoinositides, and PIP_2 in particular, in GPCR endocytosis.

Elaine Jean Tanhehco, "Modulation of Myocardial Complement Expression by Inflammatory Stimuli." Mentor: Benedict R. Lucchesi. Elaine accepted a position as a postdoctoral fellow in the laborator of Andrew H. Lichtman, M.D., Ph.D., in the Department of Pathology at Brigham and Women's Hospital, Harvard Medical School. She will be studying T-cell differentiation and trafficking in various disease states.

Complement activation mediates tissue destruction in a variety of cardiomyopathies. Delineating what influences this process may unveil potential pharmacologic targets.

Preconditioning refers to the ability of brief periods of ischemia to protect the heart from a subsequent, prolonged ischemic event. This effect is thought to be accomplished by opening of ATP-sensitive potassium (K) channels. Both ischemic preconditioning or treatment with K channel openers significantly decrease complement expression by the reperfused rabbit isolated heart and in an in vivo model of ischemia and reperfusion. The reduction of local complement generation may be one mechanism by which preconditioning protects the ischemic heart.

Free radicals function as mediators of the inflammatory response and can also initiate gene expression. Isolated hearts exposed to reactive oxygen species exhibited increased complement mRNA levels and MAC protein production. Isolated hearts treated with cocaine also increased complement generation via an anti-oxidant sensitive mechanism, supporting the premise of free radical-stimulated tissue complement expression. Heparin attenuated cocaine-induced membrane attack complex (MAC) formation, suggesting that this may be the mechanism by which it protects the ischemic heart.

Individual complement components, as well as the MAC, can trigger intracellular signaling pathways without causing cell death. Isolated hearts subjected to regional ischemia and reperfusion developed significantly smaller infarcts when pretreated with a sublytic concentration of human plasma.

The present work indicates that complement can act both as a damaging and beneficial element in myocardial ischemia/reperfusion injury. Tissue complement may serve as a possible site for therapeutic regulation by anti-ischemic agents, while the signaling pathways triggered by sublethal complement attack could be exploited for future development.



Awards/Presentations

LEE KOETZNER won a Student Award from the Division of Neuropharmacology for his paper entitled "Antagonism of Cocaine by Immunization: Operant Behavior in the Rhesus Monkey." He also received a Graduate Student Travel Award from ASPET to attend the Experimental Biology 1999 Meeting in Washington DC, from April 17–18, 1999.

JAMES NOVAK, presented a poster entitled "Neuronal Differentiation of NT2 Cells Alter Expression of Phosphoinositide Signaling Components," at the Society for Neuroscience Meeting in Miami, Florida, from October 23–28 1999.

ELAINE TANHEHCO received a Graduate Student Travel Award to attend the Experimental Biology 1999 Meeting held in Washington D.C. from April 17–18, 1999.

Symposia/Colloquia

Pharmacological Sciences Training Program Symposium

The Nineteenth Annual PSTP Graduate Student Symposium was held on April 10, 1999 in the William H. Dow Laboratory at the University of Michigan. The keynote speaker was Gary M. Bokoch, Professor of Immunology and Cell Biology at the Scripps Research Institute in La Jolla, California. The title of his talk was, "Running with the PAK; p21-Activated Kinase as an Effector of Rac/Cdc 42 GTPase Signaling."

The Twentieth Annual PSTP Graduate Student Symposium was held on March 18, 2000. The keynote speaker for this year was John W. Huggins, Chief of Viral Therapeutics at the United States Army Medical Research Institute for Infectious Diseases. The title of his talk was, "Antiviral Therapy of Smallpox and Monkeypox: The Emerging Threat of Viral Bioterrorism."

Pharmacology Research Colloquium

The past two Pharmacology Research Colloquia with participating students from the Medical College of Ohio, Michigan State University, Wayne State University, and the University of Michigan were held on June 25, 1999, at the University of Michigan and more recently, at Michigan State University on Friday, June 23, 2000.

Pharmacology Retreat

On September 16, 1999, the department held its third annual retreat at the Waldenwoods Conference Center in Heartland, Michigan, just north of Ann Arbor. The retreat was organized by Lori Isom and provided a relaxed and informal setting for students, faculty, postdocs, and senior research staff to interact both scientifically and socially. An excellent series of short talks by the faculty was followed by a very stimulating round table discussion involving both students and faculty.

Modern History of Our Department

After many old and new deadlines for the Modern History of the University of Michigan Department of Pharmacology, there is light at the end of the tunnel. The book is about 90% in rough draft form. If anyone has not submitted a chapter, vita, and/or photographs please send them as soon as possible to Ed Domino in the Department with a final deadline of Dec. 1, 2000.

Department Summer Student Programs

Since 1997, the Department of Pharmacology has participated in the Gerald J. Dalton/Vincent G. Zannoni Summer Undergraduate Research Program sponsored through ASPET. Last year, the participants in the summer program included:

Seth Beebe, Junior, Biopsychology, University of Michigan
Heathe Carleton, Junior, Microbiology, University of Michigan
Jarin Chun, Junior, Pharmacy Program, University of Michigan
Charles Fan, Freshman, General Studies, University of Michigan
Danielle Mills, Sophomore, Biochemistry, University of Michigan
Dimitriy Nikolayevskiy, Junior, Biochemistry, University of Detroit
Timothy Tran, Senior, Microbiology, University of Michigan

ASPET and Charles Ross Summer Fellows 1999



*Front row: Jarin Chun, Tigwa Davis, Chibuzor Nwankwo, Nneka Okwuanga, Timothy Tran, Danielle Mills
Second row: Dimitriy Nikolayevskiy, Charles Fan, Victor Feldbaum, Nate Reid, Benjamin Asfaw*

The Department of Pharmacology web page has a new URL (<http://www.med.umich.edu/pharm/>) and has recently been updated. Among the changes are a new layout, more information about our current teaching and curriculum, and rapidly growing sections on the department's history and descriptions of the University of Michigan Medical Center, the University, and Ann Arbor. Photographs are being added to just about all the main sections to add some pizzazz. If you have suggestions, comments, or links you think we might add, please get in touch with Dr. Marshal Shlafer (mshlafer@umich.edu). Updates are coming frequently, so visit often!

1999 Charles Ross Fellowships

This past year was an extremely successful year for our minority summer research fellowship program. With the expanded financial support received from the Medical School's Diversity and Career Development Program and the on-going Summer Research Opportunities Program in the Rackham Graduate School, we provided nine outstanding would-be scientists with an opportunity to study and do research in the various laboratories within the Department of Pharmacology. In the nine years since we established this unique program, we have provided 29 summer fellowships to these young individuals in the hope that they might select biomedical research, and in particular Pharmacology, as a career choice. If you would like to help us in sustaining this endeavor, please feel free to make a financial contribution to this worthy program. Contributions should be made out to the University of Michigan and sent to the Department of Pharmacology in care of Dennis Ondreyka.

BENJAMIN A. ASFAW

Benjamin is a graduate student at Wayne State University Medical School. He received his B. S. in Psychology from Johns Hopkins University in 1993. He plans to take a leave of absence from Medical School so that he can pursue a Masters degree in the Health Management and Policy Program in the School of Public Health at the University of Michigan. Benjamin's research project was on the "Effects of Nicotine and Tobacco Smoking on the Topographic EEG" in the laboratory of Ed Domino.

OLYNTHIA CHANCY

Olynthia was a freshman/sophomore from Michigan State University. She grew up in the Detroit/Ypsilanti area and plans on obtaining a degree in the field of medical technology, physiology, zoology, chemistry or biochemistry. She then hopes to be fluent enough in French to study abroad to experience a different way of life and then eventually move on to medical school specializing in obstetrics and gynecology. Olythia conducted her research project in the laboratory of Jon Maybaum.

ANGELA COTTINGHAM

Angela is a junior in Mechanical Engineering at the University of Michigan. She worked on two research projects studying gender and nicotine; and race and nicotine with Ed Domino.

The biotransformation of tobacco-containing chemicals is mediated by various cytochrome P450 microsomal enzymes located throughout the human body. One specific P450 microsomal enzyme is produced by the CYP2A6 gene located on human chromosome 19q13.1-13.2. To date there are three known CYP2A6 alleles, of which one is the wild type and the other two are null or inactive. Persons with the null or inactive alleles are less likely to smoke tobacco; those with the active allele are more likely to smoke. These CYP2A6 genetic differences not only affect tobacco smoking behavior, but also the activation of specific tobacco N-nitrosamines which cause cancer. It is hypothesized that African American tobacco smokers, who also have a greater incidence of lung cancer, have more active forms of CYP2A6 than other races and, therefore, are more extensive activators of nitrosamines such as 4-(methyl-nitrosamine)-1-(3pyridyl)-1-butanone (NNK). The purpose of this project was to test this hypothesis and to develop suitable phenotyping/genotyping techniques as rapid screens for predicting the degree of susceptibility to tobacco-associated cancers.

TIGWA DAVIS

Tigwa did his undergraduate work at Morehouse College. He was accepted by the Medical School's Program in Biomedical Sciences (PIBS). He plans on obtaining a Ph.D. in Pharmacology. His summer fellowship was in the laboratory of Lori Isom.

Control of the cell surface density and localization of voltage-gated Na⁺ channels is a critical aspect of neuronal function and development. The threshold for action potential generation and the frequency of firing of neurons depend critically on localized cell surface density and the functional properties of Na⁺ channels. Myelination of axons, both

1999 Charles Ross Fellowships

central and peripheral, permits rapid saltatory conduction of action potentials through a cooperation between the axon itself and specialized glial cells which envelope the axon with multiple insulating layers: oligodendrocytes in the central nervous system, and Schwann cells in the peripheral nervous system. The exposed axonal membrane at interruptions in the myelin sheath, known as nodes of Ranvier, contain locally high concentrations of voltage-gated Na^+ channels, the membrane proteins which are responsible for initiation and propagation of the action potential. We have shown that the auxiliary subunits of voltage-gated Na^+ channels contain extracellular cell adhesion molecule domains. These proteins do not form the ion-conducting pore of the channel yet have significant modulatory effects on channel gating voltage-dependence of channel activation and inactivation, as well as the levels of channel protein expressed at the plasma membrane. Recent experiments have shown that an extracellular matrix protein secreted by oligodendrocytes during the early phases of myelination, tenascin-R, functionally modulates Na^+ channel α_1 and β_2 subunits. Experiments to characterize these interactions in detail were performed as part of Tigwa's summer project.

JEANETTE HASLETT

Jeanette is a junior in the Cellular and Molecular Biology program at the University of Michigan. She hopes to go to medical school after finishing her degree and views this fellowship as a valuable learning experience in her development. Jeanette's research project was in the laboratory of Donna Shewach.

Two major interests of investigators in the Cancer Pharmacology Program are the study of cell killing by nucleoside analogs and the enhancement of cell killing by X-irradiation. The nucleoside analogs require activation within the cancer cell by phosphorylation to nucleosides that then interfere with DNA synthesis to cause cell death. Jeanette focused on exploring methods of enhancing drug activation, both by biochemical manipulation of existing enzymes in the activation pathway, and by using gene transfer techniques to express enzymes not normally present in humans, but which are superior activators of the nucleoside analogs. Such gene transfer techniques can be used in cultured cells to overcome drug resistance.

CHIBUZOR NWANKWO

ChiChi was a sophomore in the pharmacy program at Texas Southern University. She conducted her research in the laboratory of Ben Lucchesi.

NNEKA OKWUANGA

Nneka is a sophomore in the pharmacy program at Texas Southern University. She also conducted her research in the laboratory of Ben Lucchesi.

DOMINGO PEREZ

Mingo received his B.S. in Biochemistry and Toxicology in 1999 from Eastern Michigan University. He plans on attending graduate school and feels that this program provided him with an excellent opportunity for hands-on experience and prepared him for his future educational and professional goals. Mingo carried out his research project under the guidance of Ben Lucchesi.

Myocardial damage occurs both during the ischemic phase when blood flow to regions of the heart is diminished or absent, and during the reperfusion phase when blood flow is increased again as a result of drug treatment and/or angioplasty. Mingo used animal models for analyzing the pathophysiological basis for myocardial injury and the pharmacological protection of the ischemic heart have been designed to investigate the role of endogenous complement in ischemia/reperfusion injury. His preliminary data showed plasma-derived complement to be responsible for much of the tissue damage associated with reperfusion injury, however, the role that tissue complement plays has not been determined.

Alumni Steering Committee/Outstanding Alumnus Award

Attendees for this year's Alumni Steering Committee included Robert Gussin, Gerard Gebber, James Gibb, Irene Glowinski, Serrine Lau, John Lazo, Mitch Steinberg and Mike Vasko. The meeting was held on Friday, October 1, 1999, coinciding with the University of Michigan Medical School's kick-off activities for the Sesquicentennial Celebration. Allen Lichter, the newly appointed Dean of the Medical School met with the committee to discuss the many challenges that the Medical School and its departments will be facing over the next few years as well as the recent announcement of the Life Sciences Initiative and its impact on the School, the University, and the State of Michigan.

The recipient of the 1999 Outstanding Alumnus Award was Stephen G. Holtzman, Professor in the Department of Pharmacology at Emory University School of Medicine. Dr. Holtzman received his Ph.D. in 1969 under the mentorship of Julian Villarreal. His lecture was on "Acute Opioid Dependence".

Alumni News

MICHAEL BRANDT, a former Research Assistant in the laboratory of James Woods, received the Wyeth-Ayerst Young Psychopharmacologist Award.

IRENE GLOWINSKI has left the Office of Scientific Review, at the National Institute of General Medical Sciences (NIGMS), for a position as Associate Director of Operations, Communications and Policy in the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases.

JAY GOODMAN was elected President of the Society of Toxicology.

CHARLENE MCQUEEN was appointed as Councilor for the Society of Toxicology.

JOHN McNEILL has been awarded the first "Ken Bowman Award for Cardiovascular Research" by the Institute of Cardiovascular Sciences, University of Manitoba, where he gave a lecture entitled "Vanadium as an insulin-enhancing agent: Effects on models of hypertension, cardiomyopathy and diabetes," on September 8, 1999. The award is presented for lifetime achievement in cardiovascular research.

RAYMOND W. RUDDON was promoted to the position of Corporate Vice President of Science and Technology at Johnson and Johnson effective February 1, 2000. He joined the Johnson & Johnson Corporate Office of Science & Technology in September 1997, as Director, Science & Technology with support responsibilities for the Pharmaceutical Sector, including the areas of diagnostics and biotechnology. Since graduating from the University of Michigan, Ray has served as Director of the Biology Masters Program at the National Cancer Institute, returned to the University of Michigan as Chairman of the Department of Pharmacology, and then served as Professor of Oncology and Director of the Eppley Institute for Cancer Research at the University of Nebraska Medical Center.

MAXINE STITZER received the Brody-Schuster Award from the Division of the American Psychological Association for Psychopharmacology and Drug Abuse.

The Department of Pharmacology would like to extend its thanks and appreciation to **GRACE W. GRAY** (Ph.D., 1951) for the donation of her Michigan Doctoral hood and academic gown to the department. After 45 years of teaching and research in pharmacology, Grace retired 15 years ago from the University of Minnesota to devote more time to pursue her life's interest in the natural world such as wilderness preservation, the environment, population control, and human lifestyles.

ROBERT Z. GUSSIN, After a very distinguished 25-year career with Johnson & Johnson, Bob Gussin, Corporate Vice President of Science and Technology, retired from Johnson & Johnson on February 1, 2000.

After joining the Corporation in 1974 as Executive Director of Research at McNeil Laboratories, Bob rose to Vice President, Scientific Affairs there before assuming his Corporate role as Chief Technical Officer in 1986. Throughout his career Bob has been known for his pioneering instincts and for the enthusiastic leadership he has brought to Johnson & Johnson's pursuit of new research-based products and technologies. In dealing with the scientific aspects of major internal projects, interacting with academic and other outside research organizations, and in making recommendations about the acquisition of technologies and products, Bob's inquisitiveness, high energy, advocacy and perseverance have served the Corporation well on numerous occasions. He has been a superb representative of Johnson & Johnson, whether serving as a spokesperson in the public arena on scientific issues, or interfacing with the scientific community on research and development matters. In this role, Bob has been Chair of the Department of Pharmacology's Alumni Steering Committee since its inception, serving the committee and the department in exemplary fashion over the past ten years. The department would like to congratulate Bob on his retirement and thank him for his outstanding service over the years.



EDWARD F. DOMINO, Professor of Pharmacology at the University of Michigan Medical School, retired from active faculty status on August 31, 1999.

Born in Chicago, Professor Domino received four academic degrees from the University of Illinois: Bachelor of Science degrees in 1947 and 1948, a Master of Science in Pharmacology in 1951, and a Doctor of Medicine in 1951. From 1951 to 1953, he alternated between the roles of Intern at Presbyterian Hospital in Chicago and Instructor in Pharmacology at the University of Illinois College of Medicine.

In 1953, Professor Domino joined the faculty of the University of Michigan at the rank of Instructor in Pharmacology. He was promoted to Assistant Professor in 1954, to Associate Professor in 1958 and to Professor of Pharmacology in 1962. During many of the years that he served the University of Michigan, he held a concurrent appointment at the Lafayette Clinic in Detroit where he was the Director of the Laboratory of Pharmacology and of the Michigan Neuropsychopharmacology Research Program from 1967 to 1981, and Director of Clinical Psychopharmacology from 1981 to 1983. From 1984 to 1986, he held the title of Clinical Professor in the Department of Psychiatry at Wayne State University School of Medicine.

Professor Domino's numerous research activities have been in the broad field of neuropsychopharmacology with its implications in anesthesiology, gerontology, neurology, psychiatry, and toxicology. He has published more than 300 original research articles in peer-reviewed journals and has authored or edited a dozen scientific books. He has served brief terms as a visiting professor at a number of universities, both in the United States and abroad. He has served on the editorial boards of approximately 20 scientific journals.

As a teacher at the University of Michigan, Professor Domino has played a major role in the pharmacology courses for second- and fourth-year medical students and also for medical students in the Neurosciences Program. Further, he has taught in the pharmacology course in the Dental School and in programs for interns and residents at the University Hospitals. He has served as mentor to graduate students pursuing Ph.D. degrees in pharmacology and to a very large number of postdoctoral fellows from around the world.

The Regents named Dr. Domino Professor Emeritus of Pharmacology in recognition of his years of distinguished teaching and research. We are pleased that Dr. Domino is continuing his involvement in research and teaching as an active emeritus faculty member.

DEPARTMENT OF PHARMACOLOGY HONOR ROLL

Every name listed on the Department of Pharmacology Honor Roll is further evidence of growing participation and support of the research and teaching missions of the department. And, every new name and every increased gift from a graduate, faculty member, or friend is one more reason why the Department of Pharmacology at the University of Michigan can look forward to the next millenium with enthusiasm.

In recognition of these gifts over the past three years, we would like to acknowledge the generosity of our friends, faculty, and alumni listed below:

Edward Alpert	Alexander Kandel	Raymond Ruddon
Donald Bennett	Glenn Kiplinger	Donna Shewach
Arthur Cohen	Guim Kwon	James Shayman
Raymond Counsell	Bert La Du	Martha Somerman
Joseph Cranston, Jr.	John Lazo	Mitchell Steinberg
Frank DeFilippes	Karen Leach	Paula Stern
Laura DeForge	Susan Mattano	Janice Stickney
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Paul Hollenberg	Paul Quinn	Gail Winger & James Woods
Ronald Holz	Lora Rikans	Vincent Zannoni
K.R. Hornbrook	Joseph Romson	Morris Zedeck

Please update us on your current position and research and let us know about any changes in your address and telephone number, either present or forthcoming. Your announcements and comments are most welcome.

Name _____ Year of Graduation _____ Ph.D. M.S. M.D.
(circle)

Title _____

Organization _____

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Phone (business) _____ (home) _____

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