

VCU Pharmacology & Toxicology

School of Medicine • Medical College of Virginia Campus

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Chairman's Corner



Dr. Billy R. Martin

Welcome

By Dr. Billy R. Martin

This year has been unique for the department in that we have had challenges, opportunities and successes simultaneously. The Commonwealth of Virginia is experiencing an economic slow down like many other states.

As a result, we have experienced several cuts in our support from the Commonwealth during the year. Fortunately, the department was able to sustain these budget reductions because of strong extramural support for our research program. Actually, our research funding increased 16 percent this year to a total of approximately \$8 million in direct costs. Although our 52 sponsored awards are mainly NIH R01 grants, we have considerable diversity with MERIT awards, a center grant, a program project, senior scientist awards, a training grant and training fellowships. The coming year holds considerable promise as new opportunities appear for our research program.

One of the department's greatest challenges is lack of sufficient high-quality space. The department experienced enormous growth during the past 20 years because of strong leadership and hard work on the part of current and previous faculty. To accommodate this growth, the department accepted space where it was

available. Hence, the department is currently housed in five different locations. Some of our space has more historic than scientific value. However, there is good news. During the past election, a bond referendum for building construction on Virginia's college and university campuses was passed. Virginia Commonwealth University will receive approximately \$77 million during the next five years. Construction that is relevant to the department, both directly and indirectly, includes construction of a new cancer center and a medical science building, along with renovations of West Hospital and Sanger Hall. It is our goal to consolidate the department as much as possible in higher-quality space as these new construction projects are completed.

The department currently has 22 tenured/tenure-eligible faculty members and 19 in collateral positions. I am pleased that Dr. Charlie Cook recently joined our faculty. He is a behavioral pharmacologist with an excellent track record. We continue to press ahead with new faculty recruitments. We have five vacant faculty positions with two searches currently underway. I am excited as the new year approaches because of the opportunities that lie ahead. The department is well positioned to continue its strong record of research and teaching accomplishments. You will have an opportunity to learn about some of our outstanding faculty in this newsletter. I hope you enjoy it. ♦



Dr. Richard Moran

Molecular Pharmacology

By Dr. Richard Moran

The field of molecular pharmacology and toxicology attempts to understand the behavior of drugs and xenobiotics on a step-by-step biochemical and molecular basis. The faculty of the Department of Pharmacology & Toxicology at Virginia

Commonwealth University's Medical College of Virginia Campus apply a rich mixture of techniques and approaches to their research, and selected examples of these approaches follow on the next page.

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Drs. Sarah Jacobs-Helber & Stephen Sawyer

Signal Transduction Cascades In Drug Response

A number of investigators in our department are interested in signal transduction cascades. Drs. Steve Sawyer and Sarah Jacobs-Helber study the downstream intracellular events following activation of the membrane bound erythropoietin (EPO) receptor in erythroid cells by EPO. Recombinant EPO is one of the most important recombinant pharmaceutical agents in the world, amounting to a \$10 billion market in the United States alone for the treatment of renal failure-induced anemias and the anemias secondary to cancer chemotherapy. During his studies at Vanderbilt University, Dr. Sawyer studied the tyrosine kinase activity of the epidermal growth factor receptor and then the signaling downstream of the EPO receptor. Unlike the EGR receptor, EPO did not have an intrinsic tyrosine kinase activity, but rather relied on activation of the cytoplasmic receptor JAK2. Since joining the faculty here at VCU, Dr. Sawyer's group has proven that EPO triggers activation of the STAT transcriptional factor family and also that it activates the PI3-kinase/AKT signaling pathways.

Dr. Steven Grant, an affiliate member of our department, leads an internationally recognized research group that develops new approaches to cancer chemotherapy through the combination of inhibitors of the signal transduction pathways with traditional chemotherapeutic agents. In close collaboration with Dr. Paul Dent, these investigators are using pharmacological disruption of the MAP kinase and JAK/STAT signaling processes to enhance chemosensitivity and radiation responsiveness of human tumor cells.

Analysis of Isoforms of Metabolic Enzymes

Unraveling the toxicology of polycyclic hydrocarbons has been complicated by the remarkable complexity of their hepatic

metabolism. Dr. Joseph Ritter's laboratory took on the challenge of understanding the heterogeneity of the UDP-glucuronyl transferases, the family of hepatic enzymes involved in terminating the carcinogenic threat of the polycyclic hydrocarbons. The different UDP-glucuronyl transferases also are up-regulated differentially by prior exposure of the host to a number of small molecular weight compounds, in a complex pattern that has defied explanation using standard pharmacological or biochemical criteria. Dr.



Dr. Joseph Ritter

Ritter's laboratory has been applying the range of techniques available to define this system at the level of RNA expression, including ribonuclease protection assays (RPAs) and promoter analysis. The transcription of RNA encoding this family of enzymes is a fascinating example of a gene family produced by activation of multiple alternative promoters linking different initial coding sequences to a set of downstream common exons. The first exons of these proteins appear to encode at least a part of the substrate binding sites, so that this differential first exon usage produces proteins with related, but discrete, substrate specificity profiles.

Dr. Moran's laboratory has been studying another problem which was untractable using biochemical approaches, namely how isoforms of the anabolic enzyme folic polyglutamate (fpg) synthetase are made in a tissue-specific pattern in the mouse. Mouse liver and kidney make one isoform while any dividing tissue makes another. These studies were only possible using the techniques commonly used to obtain sequence at the 5' extreme of rare RNA transcripts, namely 5' RACE (rapid amplification of RNA ends), RPAs and genomic DNA analysis. The functional importance of the several transcripts from this single gene in mouse and human tissues was determined using transfection of individual cDNAs into cultured cells that do not express this enzyme, and phenotypic analysis of the resultant cell lines. Dr. Fiona Turner, in Dr. Moran's laboratory, has cloned out the genomic locus for the fpgs gene and found the genetic and epigenetic elements responsible for such an intricate pattern of control of gene expression.

Pharmacogenetics and Pharmacogenomics

It has become increasingly clear that the genetic polymorphisms so common in the human genome are capable of affecting the metabolism of drugs and the responsiveness of individuals to the therapeutic or toxic effects of drugs. The study of this area has given rise to the field of pharmacogenetics. Dr. Joseph Ritter's analysis of the closely related UGT gene products led to the discovery of two commonly occurring allelic variants which

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result in a retardation in the rate of metabolism of the polycyclic hydrocarbons and a resultant increased risk of carcinogenesis in smokers bearing the polymorphism. Dr. Ritter's studies have identified a series of missense alleles for the UGT1A7 gene that encoded proteins of low catalytic activity for conjugating substrates to a form that is readily excreted. A population study demonstrated that a considerable proportion of the population (15 percent) was found homozygous for the low activity allele containing all three missense mutations, UGT1A7*3. These findings suggested a possible role of UGT1A7 in the detoxification and elimination of carcinogenic products in lung and that individuals with low activity might be at increased risk of lung cancers after exposures to polycyclic hydrocarbons. Dr. Ritter's studies exemplify the power of molecular approaches to difficult pharmacological problems: from unraveling the complexity of metabolic profiles by a multigene product family to a classic example of pharmacogenetics.

Receptors and Gene Families

The field of pharmacology has historically led the way in discovering that binding of drugs to receptors initiates the downstream events in drug response. From early on it became clear that receptors for neurotransmitters, hormones and cytokines are heterogeneous in different tissues or even in the same tissue and that the differences in these receptors may have major functional consequences. Using cDNA cloning techniques, Dr. Mary Abood has identified the sequence of all of the receptors for the cannabinoids in different animal species. With this information in hand, it is now possible to study differences in the responsiveness of individual receptor family members in isolation, by expression of recombinant single receptors in bacteria, yeast, or insect cells, or by heterologous expression in non-expressing mammalian cell types. This approach further allows for deletion and site-directed mutagenesis studies for the dissection of the residues and peptides involved in ligand binding, and for the rigorous definition of overlapping specificities of closely related family members.

Drs. Dana Selley and Laura Sim-Selley use molecular approaches to study the mechanisms underlying the acute and chronic effects of psychoactive drugs in terms of cellular mechanisms of drug tolerance and dependence or of agonist efficacy or specificity. Intrinsic to these studies is the use of heterologous expression of neurotransmitter receptors following transfection of cDNAs for the receptors and their cognate signaling proteins in mammalian cells. Such experiments allow dissection of the functional domains of these proteins by the introduction of point or partial deletion mutants of receptors or related signaling proteins that create constitutively active or inactive proteins. For any protein that relies on protein oligomerization or obligate binding partners as intrinsic steps in a signal cascade

such as the neurotransmitters studied by Selley and Sim-Selley, an extremely powerful approach is the use of dominant-negative constructs. Dominant negative constructs are mutant proteins that are nonfunctional but which block ongoing protein-protein interaction required for pathway response. Dominant negative experiments are used to elucidate the functional interaction between ligands and receptors, or between receptors and signaling proteins, or to determine specific steps in the signal transduction pathways that link receptors to alteration in gene expression, cell proliferation or other functional endpoints.

Damage Control

Ionizing radiation and the radiomimetic drugs, such as bleomycin, induce double stranded DNA breaks that are catastrophic for mammalian cells if not repaired. But the formation of



Dr. Larry Povirk

an occasional break in the huge amount of sequence in a mammalian genome sequence and its later religation create an enormous challenge for analysis and reconstruction. Since coming to VCU, Dr. Lawrence Povirk has turned his attention to the precise chemistry of how these DNA strand breaks are repaired, and to defining the molecules that direct this repair. He adapted the technique of ligation-mediated PCR (polymerase chain reaction) to the task of determining the changes in sequence induced at the exact site of repair of DNA strand breaks and the processing of these breaks in human and hamster cell lines. With this background, Dr. Povirk's laboratory team was in the position to apply its expertise to the repair of DNA strand breaks in a simple crude cell extract, taking advantage of the several mutant hamster cells which were known to be missing individual steps in the process. Using recombinant proteins to complement defects in these processes in mutant cell extracts, he is developing a model of the individual proteins in the primary systems to repair these DNA breaks and the backup systems that come into play when the primary systems are impaired.

The Dead and the Undead

Several departmental laboratories study the response of human tumor cells to drugs and radiation. Current work in Dr. David Gewirtz's laboratory is directed toward developing an understanding of the molecular basis for the limited response to the antitumor drugs adriamycin and methotrexate, as well as to ionizing radiation, in p53 wild-type breast tumor cells. Mammalian cells have a complex genetic response to severe DNA damage or to lengthy cell cycle arrest that involves activation of a cascade of killer genes, known as caspases in an

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intricate program known as apoptosis or programmed cell death. Dr. Gewirtz's laboratory in collaboration with Drs.



Dr. David Gewirtz

Shawn Holt and Lynne Elmore in the Department of Pathology have found that human breast cancer cells in culture often do not activate the apoptotic program after exposure to chemotherapy or radiation, but rather enter into a prolonged cell cycle arrest that does not trigger cell death. The prolonged growth is characterized by expression of markers associated with senescence. This response is reminiscent of the behavior of breast tumors in vivo — where individual cells often remain dormant for an extended time period, but ultimately recover, leading to disease recurrence, often 10 or 15 years after initial therapy.

The Unbiased Experiment

When mammalian cells respond to the effects of a drug, a substantial number of proteins change, in part due to the transcriptional response of the cell to the direct and indirect effects of the



Dr. Michael Miles

drug. The traditional approach to such studies, namely to predict what should change based on knowledge of the target of a drug and its conceptualized role in cellular metabolism, has greatly underestimated the complexity of transcriptional response to drug exposure. It has become clear that the response of cells to a drug can be much more widely dispersed than the immediate element of cell metabolism affected directly by the drug. Dr. Michael Miles asks not "Does mRNA X, Y and Z change after drug treatment?" but rather, "What mRNAs change after drug treatment?" a fundamentally unbiased approach. Dr. Miles applies microarray technology, the use of arrays of cDNA or oligonucleotides, to which are hybridized cDNAs complementary to cellular mRNAs, and which are linked to one of two fluorescently labeled dyes. cDNAs from two conditions are then mixed and the overabundance of mRNAs from one tissue is deduced from the predominance of one dye over the other. Current microarrays can allow one to probe for every gene in the yeast genome or the majority of the genes known to be expressed in humans. Commercial arrays are in the making which will allow one to probe for every exon of every gene in the human genomic complement.

Gene Knockout Analysis of Drug Responsiveness

Perhaps one of the most powerful approaches to the determination of the function of a protein is the creation of mice that completely lack the expression of the gene encoding that protein. Such "gene-knock-out" experiments provide information not attainable by almost any other current approach. Several faculty in our department are engaged in the production of gene constructs that allow knock-out mice to be constructed in collaboration with Dr. Jolene Windle of the Department of Human Genetics. Dr. Larry Povirk is using this approach to investigate the involvement of the tyrosyl-DNA phosphodiesterase gene in the early steps in repair of bleomycin-induced DNA damage in collaboration with Drs. Windle and Shirley Taylor. Erin McCarthy, in Dr. Moran's laboratory, is producing constructs to allow deletion of function of the mitochondrial inner membrane folate transporter as a means of determining whether any of the known human genetic deficiency syndromes are the result of mutation in this gene. Also, Dr. Moran's laboratory is producing a variant mouse in which only the downstream promoter of the *fpgs* gene can be used, in an effort to define the role of the upstream promoter during development. ♦

Nobel Prize in Chemistry, 2002



Dr. John B. Fenn receiving the Nobel Prize in Chemistry from King Carl Gustaf of Sweden, Dec. 10, 2002.

John B. Fenn, Professor of Chemistry and Affiliate Professor of Chemical Engineering at VCU received this year's Nobel Prize in Chemistry for his work in the field of mass spectrometry.

"John Fenn's contributions to the science of analyzing proteins moves us one step closer to discovery of important medicines that will help thousands of people one day," said VCU President Dr. Eugene P. Trani. "We are proud to have a life scientist of his caliber on the research faculty at VCU." "Dr. Fenn was instrumental in helping to expand the mass spectrometry facility within our department and we are greatly indebted for his contributions to science" added Dr Billy R. Martin. ♦

Dr. Sandi Welch — School of Medicine Distinguished Mentor Award

At a recent ceremony in the School of Medicine, Sandra Welch, Ph.D., a Professor in the Department of Pharmacology & Toxicology, was honored with the Distinguished Mentor



Dr. Sandi Welch

Award. This award recognizes significant contributions to the career development of others. According to Louis S. Harris, Ph.D., Harvey Haag Professor and Associate Vice President of Health Sciences and past Chair of the department, Sandi has been an exceptional mentor for students of all ages. In addition to her 'formal' mentor relationships with graduate students, she has shared her exper-

tise with elementary school children, high schoolers, and undergraduates. "She is both a patient and a hard taskmaster, but her students are very appreciative of her personal attention." "Dr. Welch is a shining example of a mentor, teacher, researcher and service-involved faculty member," Dr. Earl Ellis added. "Mentee" Dr. Diana Cichewicz couldn't agree more: "She truly cares about her students and her work, and wants to do all that she can to promote learning and scientific achievement. Now, as a post-doc, I strive to be the best I can be to make her proud and to become the type of mentor she is." Sandi also is this year's recipient of the VCU Women in Medicine and Science Professional Achievement Award, and has been honored with Teacher of the Year and Professor of the Year awards. Congratulations. ♦

Dr Laura-Sim Selley — Joseph Cochin Young Investigator Award

Laura Sim-Selley, Ph.D., an Assistant Professor in the Department of Pharmacology & Toxicology, has been awarded

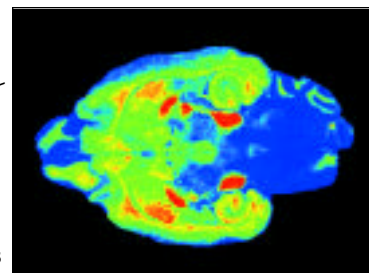


From left: Dr. Dorothy Hatsukami (Outgoing CPDD President), Dr. Billy Martin and Dr. Laura-Sim Selley

the Joseph Cochin Young Investigator Award. Recognizing early career excellence in the science of drug addiction, the award is given annually by

the College on Problems of Drug Dependence (CPDD), the largest and oldest organization for the scientific study of drug

dependence and addictions. Sim-Selley was recognized for her research investigating how specific neurotransmitter receptors in the brain are affected by chronic exposure to drugs, particularly opiates and marijuana. She also is known for her post-doctoral work at Wake Forest University in which she developed a technique that allows researchers to observe the activity level of many of the brain's receptors (see image), a distinct improvement over previous tests that only revealed the receptors' location in the brain. This advance has proven useful in Sim-Selley's own research as well as in the research of others in the field. ♦



New Web Address

The department has a new Web address: www.vcu.edu/pharmtox/ which is presently in operation and functional. Requests to the old address, views.vcu.edu/pharmtox/, will automatically be routed to the new site. You should update your favorites/bookmarks in your browsers to reflect the change.

Focus on Research

Susan Robinson, Ph.D.

Consequences of Prenatal Exposure to Abused Agents



Dr. Susan Robinson

Dr. Susan Robinson, Ph.D., Professor of Pharmacology and Toxicology, joined the department as Assistant Professor in 1981. She obtained her Ph.D. in pharmacology from Vanderbilt University, where she studied mechanisms of action of both “classical” and “atypical” antipsychotic drugs in the laboratory of Dr. Fridolin Sulser. An appointment as staff fellow in the Laboratory of Preclinical Pharmacology, NIMH, under the mentorship of Dr. Erminio Costa, followed her graduate training. While at the NIMH she learned mass spectroscopy and developed an interest in interactions between neurotransmitter pathways in the central nervous system. Her first faculty position was as assistant professor in the Department of Medical Pharmacology and Toxicology at the College of Medicine, Texas A&M University. Dr. Robinson continued her research in neurotransmitter interactions there, with an emphasis on cholinergic neurons and central regulation of the cardiovascular system. For this work, Dr. Robinson received the Lyndon Baines Johnson Research Award of the American Heart Association, Texas Affiliate.

In 1981, Virginia Commonwealth University was, as it is today, a leading site for research in mechanisms and treatment of drug abuse. Although Dr. Robinson joined the Department of Pharmacology & Toxicology at VCU with little interest in the area of drug abuse, it did not take long for her to delve into

this topic. Because she was pregnant at the time, the effects of prenatal exposure to drugs of abuse piqued her interest, albeit in a theoretical way. Dr. Robinson has studied the effects of prenatal exposure to abused solvents, cocaine and nicotine. However, the consequences of in utero opioid exposure have been her primary area of interest.

Methadone maintenance has been a standard treatment for opioid addicts who become pregnant. Although extensive animal testing was conducted on this drug in the late 1960s, no one had ever studied the effect of opioid exposure on cholinergic neurons in the brain of the developing fetus. Moreover, whatever studies had been performed often involved the use of rats, a species that metabolizes methadone much more rapidly than man (or a pregnant woman). By using osmotic minipumps throughout the last two-thirds of gestation, Dr. Robinson and colleagues were able to maintain plasma levels of methadone in pregnant rats at steady-state levels sufficient to result in physical dependence in the newborn pups. This mode of exposure was found to delay the expression of the cholinergic phenotype in the caudate-putamen and disrupt cholinergic neuronal function at later ages. These changes may contribute to neurobehavioral deficits exhibited by children exposed to opioids in utero. Dr. Robinson now is investigating the mechanism behind this effect. She determined that this developmental delay was not due to neonatal withdrawal, but rather was a function of prenatal opioid exposure. Furthermore, buprenorphine, which has recently been approved by the FDA for the treatment of opioid addiction, was found to produce similar effects. In collaboration with Dr. Joan Schwartz at the NINDS, Dr. Robinson also found that prenatal methadone or buprenorphine exposure decreases nerve growth factor content in the caudate-putamen, possibly contributing to the delay in cholinergic development. Most recently, Dr. Robinson has been studying the effects of prenatal opioid exposure on oligodendrocytes and myelination with Dr. Carmen Sato-Bigbee in the Department of Biochemistry and Molecular Biophysics.

In addition to conducting scholarly research, Dr. Robinson also performs service valuable to the research community. She is a member of an NIH study section that addresses disorders which impact specifically the developing brain and spinal cord, and she serves as chair of the VCU Institutional Animal Care and Use Committee. ♦

Focus on Research Focus on Research

Forrest Smith, Ph.D. Mechanisms Underlying Opioid Tolerance



Dr. Forrest Smith

Dr. Forrest Smith, a native of Denver, Col., received his B.S. degree in biology from Abilene Christian University in Abilene, Texas and his Ph.D. with a focus in pharmacology from Texas Tech University Health Sciences Center in Lubbock. In 1990 he began a postdoctoral position with Dr. William L. Dewey in the Department of Pharmacology & Toxicology at Virginia Commonwealth

University. Dr. Smith attained faculty status in 1993 and is currently an Associate Professor in the department. Dr. Smith has actively participated in generating research revenue through both federal and private sources. He has collaborated with Drs. Dewey, Welch, Selley and Sim-Selley in writing the NIDA "Enkephalins: Neuropharmacology and Abuse Potential" that has been funded for more than 25 years, and is a co-principal investigator with Drs. Dewey and Welch on Dr. Martin's Program Project Endogenous Cannabinoids and Brain/Immune Function that was recently funded. In addition, Dr. Smith has received numerous contracts from Purdue Pharma L.P., Southern BioSystems Inc. and Guilford Pharmaceuticals to investigate novel pharmaceutical agents.

Dr. Smith's research has focused on three areas of drug abuse research. The first area has investigated the biochemical pathways that mediate tolerance to the pain relieving properties of morphine. Chronic morphine administration activates two major biochemical pathways in the brain identified as the adenylyl cyclase and the phosphatidylinositol pathways. Highly selective drugs have been developed that inhibit various steps in these pathways. Injecting non-tolerant animals with the inhibitor drugs had no effect on the pain-relieving properties of morphine. However, these drugs completely reversed morphine tolerance for 24-h in some cases. Currently, Dr. Smith is determining in which brain regions the signaling pathways are affected by morphine tolerance. He currently is using PKC knock-out mice and antisense oligonu-

cleotide strategies in an attempt to identify the critical PKC isoforms that are necessary to express morphine tolerance.

Dr. Smith also has focused on understanding the behavioral and biochemical substrates of neonatal opioid tolerance and dependence. Today, many neonates and infants receive fentanyl or morphine by intravenous administration to provide continuous analgesia and sedation during ECMO and mechanical ventilation. These babies are experiencing life-threatening respiratory diseases and are in an intensive care setting for weeks or months. Many of these babies become physically dependent on the infused fentanyl or morphine. Dr. Smith developed a model of neonatal and infant rat fentanyl or morphine tolerance and dependence using implantable Alzet osmotic minipumps. With this model, he demonstrated that juvenile and adult rats exposed to fentanyl as infants were nearly 2.5-times less sensitive to the pain-relieving effects of morphine than their opioid-naïve littermates. This could have profound consequences in the human population of opioid-tolerant babies later in life as they require opioids during surgery or for the treatment of pain. He currently is collaborating with Dr. Laura Sim-Selley to determine the brain regions in which mu-opioid receptor desensitization could be occurring. Another collaboration with Dr. Kurt Hauser (University of Kentucky) is examining the mu-receptors on glial cells that regulate neuronal growth. Finally, babies that become physically dependent are slowly weaned from the fentanyl or morphine, which greatly prolongs their hospital stay. Dr. Smith has been determining whether substituting oral buprenorphine would enable physicians to rapidly terminate the fentanyl or morphine infusions. He has demonstrated that buprenorphine completely blocks fentanyl and morphine abstinence, which might enable these babies to be released earlier from the hospital.

Finally, Dr. Smith is collaborating with Drs. Dewey and Welch on the Program Project to examine the signaling pathways that mediate the behavioral effects of anandamide. Anandamide is naturally produced in our bodies and stimulates the cannabinoid "marijuana" receptor. It is hypothesized that anandamide and delta-9-tetrahydrocannabinol (the active substance in marijuana) have similar, yet also distinctly different, properties that can be detected behaviorally by injecting animals with drugs that inhibit different steps in signal transduction pathways. ♦

Alumni Spotlight

James (Jim) Putney, Ph.D. Class of 1972



Dr. James Putney

VCU in 1969 and began my training in the laboratory of Dr. Joe Borzelleca. My project was to characterize the mechanisms by which drugs pass from the blood into saliva, and involved studies in the whole organism, in perfused salivary glands, and in gland slices incubated *in vitro*. This early training in drug disposition and basic pharmacology by Dr. Borzelleca and other members of Dr. Paul Larson's department was complemented by superb training from the Department of Physiology in the areas of cell physiology and membrane transport. During this time, I developed a close friendship with another graduate student in pharmacology, Frank Goodman, who was working on the actions of drugs and neurotransmitters in smooth muscle. Eventually, through many discussions with Frank and others, I also developed a keen interest in the actions of drugs and neurotransmitters on cells, and became particularly interested in investigating mechanisms which involved Ca^{2+} as a cellular signal.

Upon completing my Ph.D. in 1972, I went to the laboratory of Dr. Paul Bianchi at the University of Pennsylvania to study the role of Ca^{2+} in excitation-contraction and in 1974 I accepted a position as assistant professor in the Department of Pharmacology at Wayne State University, chaired by Bernie Marks. Here I initiated a research program on signal transduction in non-excitabile cells combining my earlier experiences in membrane transport, Ca^{2+} metabolism and salivary glands. During this time, our ideas

Dr. Alfred Burger, my professor of organic chemistry at the University of Virginia, introduced me to the field of pharmacology. Dr. Burger also was instrumental in helping me to apply to, and eventually to be accepted into, three graduate programs in pharmacology; I opted for the Department of Pharmacology at VCU.

I entered a rather small (by today's standards) graduate program in pharmacology at

developed on sources of regulator Ca^{2+} in cells. It soon became evident that the activation of cells by many neurotransmitters involved a biphasic mobilization of cellular Ca^{2+} : release of Ca^{2+} from storage sites within the cell, followed or accompanied by increased entry of Ca^{2+} into cells from the extracellular milieu. My laboratory next turned to attempts at understanding the mechanisms underlying these two fundamental processes.

In 1980, I returned to VCU to continue studying cellular regulation of Ca^{2+} signaling. By this time, the Department of Pharmacology, under Dr. Lou Harris' leadership, as well as the School of Basic Sciences, had grown substantially. I was especially attracted to the nucleus of scientists interested in cellular pharmacology and signal transduction which comprised the cardiovascular division of the department, under the leadership of Ron Rubin. I remained in the department for six years, during which time events transpired which permanently focused and shaped my research career. Soon after my return to Richmond, I was joined by Gillian Burgess who had studied at University College, London, under the tutelage of Don Jenkinson, and who was interested in determining the locus of intracellular Ca^{2+} release in hormone-activated hepatocytes. Gillian developed a method for selectively permeabilizing the plasma membrane of cells so that the free intracellular Ca^{2+} could be rigidly controlled by use of calcium-EGTA buffers. At about the same time, Mike Berridge in Cambridge had developed a theory to explain the ability of neurotransmitters to cause the release of Ca^{2+} from intracellular organelles. He suggested that inositol 1,4,5-trisphosphate (IP₃, a product of phospholipase C) could serve as a second messenger to release intracellular Ca^{2+} . He had convinced Robin Irvine at the AFRC in Babraham to prepare purified IP₃ for testing; subsequently, he proposed to us that our permeable cell preparation would be an ideal system in which to examine the putative actions of this molecule.

What subsequently transpired was one of those truly exciting experiences in science. The IP₃ which Mike Berridge and Robin Irvine sent did, of course, have the activity which Mike had proposed. We were not the only laboratory to whom Berridge and Irvine sent IP₃, and unfortunately we came in second to Irene Schulz in publishing this exciting discovery. As exciting as the

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discovery of IP3 was, it was a failure of IP3 in one context that led to what I would consider our most significant and identifiable contribution to the Ca²⁺ signaling field. In almost all instances, following the release of Ca²⁺ by IP3, there is a subsequent entry of Ca²⁺ into cells across the plasma membrane. Many in the field were disappointed to find that this essential component of the Ca²⁺ signal could not be attributed directly to IP3. In February of 1986, I published a paper in the journal *Cell Calcium* that proposed that this entry was signaled by an unknown messenger produced as a result of the depletion of Ca²⁺ from intracellular stores by IP3. By analogy with a similar arrangement seen with electrical circuitry, this process was called capacitative calcium entry. Despite some initial skepticism, today this concept is widely accepted in the Ca²⁺ signaling field. Embarrassingly, neither we nor a number of other competing laboratories have yet succeeded in identifying this elusive signal.

Shortly after the original article on capacitative calcium entry appeared, I left VCU to pursue research at the National Institute of Environmental Health Sciences. Here, I accumulated and published the proofs for capacitative calcium entry. Recently, we are cloning and expressing putative capacitative calcium entry channels in an attempt to identify these elusive signaling molecules.

My years spent in the department, both as a student and as a young faculty member, were some of the most rewarding and enjoyable of my scientific life. I cannot overstate the support and enriching environment afforded me in the department. It has been a fun ride, and happily it is not over yet. ♦

Footnote: When I think of all of the outstanding scientists who have received their training in the department, it is indeed a challenge to select a single individual for recognition. Our graduates are making outstanding contributions in academia, industry and government, and we are proud of everyone. Given this plethora of talent, it is a special tribute to Dr. Putney to be chosen as the Outstanding Alumnus for 2002 by the MCV Alumni Association. It was obvious from Jim's thesis project that he was destined to be a successful scientist. We were privileged to have Jim return to the department and serve as a faculty member for many years. He was a highly effective educator while he was establishing a national and international reputation. Jim's pioneering research in calcium signaling brought a great deal of prestige to the department. He continues to operate at the forefront of science. We will continue to cheer him on as he continues an exceptional research career. **by Dr. Billy R. Martin**

Graduate Life Now and Then



Dr. Julie Bronder
(Class of '03)

The last 25 years has seen an explosion in the use of technology, particularly with the introduction of personal computers and their subsequent development that has had a great impact on our daily activities. We thought it would be interesting to compare the life of a current graduate student with that of a similar student at the dawn of the computer revolution. Julie Bronder (class of '03) represents today's generation of student and Kimber White (class of '81) reminisces about how things were then.

Kimber White (class of '81) reminisces about how things were then.

Networking

Julie: Thinking of an average weekday, most of us begin, somewhat automatically, by checking our e-mail. Almost daily we receive e-mails regarding visiting seminar speakers and student competitions such as Forbes' Day and Watts' Day.

Communicating with professors about class work through e-mail saves students time by not having to physically search for the professor or play phone-tag with their voicemail. When my mentor was away in Africa, his laptop traveled with him, and over e-mail, we worked on drafts of a paper, sending revised Word documents back and forth between continents within a matter of minutes.



Dr. Kimber White
(Class of '81)

Kimber: Personal computers were nonexistent; punch cards were the norm if you were smart enough to program the mainframe. I still remember when our lab got its first programmable TI hand calculator which used the metal strip to record 15 steps! Most of the time information was passed among fellow students before or after classes or during lunch together at Joe's (great steak sandwiches and fries) or at the Skull and Bones. Reaching advisers

Graduate Life continued from Page 9 ►

when they were away from campus was unheard of, because long distance telephone calls were not allowed. Meeting with professors usually meant sitting on the floor waiting outside their office until showed up, even if you made an appointment.

Presentations

Julie: When I first began graduate school in 1998, I observed students still giving 35 mm slide projector presentations, and watched over the years the phasing out of slide projectors, and the replacement with Power Point presentations, replete with animation and sound effects. It now seems the good old slide projectors are close to being extinct, and perhaps someday will wind up an artifact resting next to the Rubik's cube and Dorothy's ruby slippers in the Smithsonian Museum of American History, gawked at by future generations.

Kimber: Acetate overheads and black and white slides were the standard. If your adviser "had money" you may have been lucky enough to get blue diazo's for your "post doc interviews." Of course, this meant turning in your results to AV several weeks before the meeting. I remember the hours with the razor blade cutting up colored paper, and my fingers, making bar graphs and lining up the text by hand with no spell checker. Use of photographic spray for pasting onto poster board was the next best thing to sliced bread when it came out.

Conferences

Julie: The ease with which we attend scientific meetings is a luxury many of us take for granted. Airline traveling is the choice of transportation, and ticket fares remain relatively inexpensive. Even the posters we carry to these conferences have undergone a significant metamorphosis as well. We now have the equivalent of McDonald's drive-through poster preparation — posters are the product of organizing PowerPoint slides in a program such as Quark Express, and printing them out as one continuous, laminated sheet which is easily rolled up like wrapping paper, and carried in a cardboard tube. Setting up for the poster session involves unrolling the poster and tacking it up with four pushpins.

Kimber: The first thing you learned was to make your poster small enough to carry on the plane with you. You could lose your luggage and stand in front of your poster in wrinkled clothes but the poster must go up. Most of the time, however, the state van was the required mode of transportation with no radio or air-conditioning. It was amazing how many people you could pack into a van before seatbelt laws went into effect. Similarly, you also can pack large numbers of graduate students into one room in order to give them the opportunity to go to a national scientific meeting. You just had to make sure you got up first in order to have hot water and clean towels.

Manuscripts

Julie: A task much more daunting than poster preparation is writing our theses and preparing the figures. Using a typewriter and drawing out graphs by hand is enough to cause any graduate student today to wake up in a cold sweat. Each day we should offer thanks and praise to Microsoft Word and Cricket Graph, not to mention paying homage to PubMed for ease of obtaining references. Once we're online and connected to PubMed, a few keystrokes and two seconds transport us to the multitude of articles that suit our topic or author of choice. The online articles can be downloaded within seconds and printed off the computer. All of this can be achieved within five minutes tops, while the only workout I receive involves sauntering over to the laser printer and impatiently tapping my fingers while waiting for the article to emerge.

Kimber: Typing a thesis which would pass Esther Branch's approval was as tough "THEN" as it is "NOW!" Many a graduate student lived on the money they made typing other people's theses. Or if you were lucky you could bribe your wife or girlfriend into helping with the typing. Some of us resorted to "professionals" who made money on the side offering to type your thesis "at a reasonable cost." Many hours were lost locating references in the stacks of the library, then finding the critical journal you needed missing or "out for binding." If you needed to make a copy, you had to check out the large bound volume of the journal, carry it back to your lab for copying and then return the journal, all within 24 hours.

Colleagues

Julie: I also am struck by the female/male ratio of graduate students and scientists today. Although my lab may not be the most representative sampling pool, I find that out of eleven students, technicians, post-docs and "others," only two Y chromosomes exist in our lab. This was quite impressive to me.

Kimber: There was almost an equal mix of male and female students in my class when I entered the program as a first-year student with 14 other colleagues.

Julie: Despite these notable changes, I am certain the motivation, discipline and dedication of Pharmacology/Toxicology graduate students toward their chosen fields have remained constant throughout the years. The explosion of technology that has advanced science so far over the past decades is sure to continue well into the future, bringing with it more exciting (and somewhat frightening) changes. I wonder what things will have changed in the next 20 years, when my point of view evolves into that of a wise and nostalgic VCU alumna . . . ♦

Pharm•Tox Alumni Connections

For those who will be attending the Society of Toxicology (SOT) meeting March 9-13, 2003 in Salt Lake City, Utah, the Department of Pharmacology & Toxicology will be hosting a welcome reception for all alumni. Location and time to be announced; contact Dr. Kimber White at kwhite@hsc.vcu.edu for more information. If you have recently moved or changed jobs or have never received an e-mail about SOT from Dr. White, please contact him with your new e-mail address.

In the last newsletter, we included a survey to all department alumni asking about your contact with the department, your preferences for an alumni directory, and your ideas for bringing alumni together. Early results showed that:

- 64 percent of respondents work in industry, while 36 percent work in academics or government;
- 91 percent have been in contact with the department over the past year;
- 64 percent have had the chance to recommend the department to prospective graduate students;
- 73 percent expressed willingness to mentor a graduate from the department

If you have not yet responded to this survey, please go to www.vcu.edu/pharmtox/alumni/survey to fill out an online form. Your views are very important to us.

In addition, some of you expressed an interest in attending a reunion of Pharm/Tox graduates at VCU in the upcoming years. We will keep you informed via the newsletter and the Web site about possible reunion plans.

The department would like to create an alumni directory to facilitate communication between graduates of the Pharm/Tox program and to maintain contact information. Please send your updated e-mail address to Dr. Edward Ishac, eishac@hsc.vcu.edu if you would like to be included in the directory.◆

Graduate Corner

The graduate students within our department continue to bring school, state and national recognition and accolades for their research efforts. Congratulations to all students and their advisers. We also are pleased to announce that we have seven new Ph.D. candidates and four certificate students in the department this year. They have come from all over the country to do research here and we are thrilled to have them.

Student Awards

The 2002 Forbes' Day Symposium was held last March. Three students from the department were chosen to give oral presentations: Julie Bronder, George Dalton and Dawn Stoller.

Pharmacology/Toxicology students swept the awards for student presentations at the 2002 Virginia Academy of Science meeting held last May at Hampton University. George Dalton received first place for "Pharmacological Consequences of Activating and Inactivating Mutations in the Rat Mu Opioid Receptor," Dawn Stoller received second place for "Buprenorphine Substitution in the Treatment of Morphine-Dependent Infant Rats" and Ruby Javed received third place for "Involvement of PKC and PKA in Morphine Tolerance but not Physical Dependence in Mice." Randy Abutin was awarded honorable mention for his work on "The Role of Erythropoietin-Dependent and Constitutive Phosphorylation of BAD on Serine 112 in Survival/Apoptosis of Erythroid Cells." This repeats the performance of last year when the students from the department also swept the competition. Congratulations to the students and their advisers.

Jae Wan Lee received the Scholar in Training Award from the American Association for Cancer Research in May, 2002.

First-year Ph.D. candidate, Fraser Orgain won the Most Effective Presenter Award at the School of Medicine's Watt's Day presentations in October. His presentation was "The Interaction of Nicotine and Delta9-tetrahydrocannabinol: A Pharmacological and Genetic Approach."

Latest Graduates

Best wishes to our recent graduates: Lisa Wallace (Ph.D., adviser Dr. Robert DeLorenzo), Ambuja Bale (Ph.D., adviser Dr. John Woodward), Kedar Inamdar (Ph.D., adviser Dr. Larry Povirk), John Andreassi (Ph.D., adviser Dr. Richard Moran), Joseph Contessa (M.D./Ph.D., adviser Dr. R. Schmidt Ulrich), Nitya Chandran (M.Sc., adviser Dr. Robert Balster) and Mike Cassidy (M.Sc., adviser Dr. Dana Selley).

Current Pharmacology & Toxicology Student Organization (PTSO) officers are: Erin McCarthy (president), Julie Bronder (vice president), Erin McCarthy (secretary), Sarah Harvey (treasurer) and Laura Webb (SGA rep) and Dawn Stoller and Joe Contessa (Honor Council reps). If you have questions regarding the PTX Student Organization, PTSO, please contact Erin McCarthy via e-mail at eamccart@mail2.vcu.edu.◆

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Contributions

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