Molecular & Integrative Physiology

Newsletter Winter 2008/2009

Greetings from the Head

by Byron Kemper

Greetings from the Department of Molecular and Integrative Physiology (MIP). Phil Best resigned the MIP headship to take a position as associate dean of the College of Liberal Arts and Sciences (interrupted briefly by a tenure as interim dean) and I was appointed head of MIP in December, 2007. Phil guided the department for ten years during the interesting period following the reorganization of Biology into the Schools of Integrative Biology and Molecular & Cellular Biology, and so in many ways was following an uncharted path. About 40% of the present faculty members were recruited during his tenure, and the high quality and vitality of the department are a testament to his strong leadership. He remains an integral part of MIP, continues to teach physiology in the College of Medicine, and provides us valuable advice and assistance from the LAS Dean's office. We are grateful for his outstanding contributions to MIP.

Phil Best receives a plaque of appreciation

With this newsletter, instead of the typical "newspaper reporter" style, we are experimenting with first person articles from members of MIP about their research. In this issue, we have articles from a new faculty member in her third year, Lori Raetzman; the established faculty Benita Katzenellenbogen and Al Feng; and an affiliate in MIP from the Department of Chemistry, Jonathan Sweedler. We also have an article by Milan Bagchi describing a major accomplishment this year, the new national Center for Research in Reproduction and Infertility. We plan to have an annual Fall newsletter (a little late this year) which will be complemented by a newsletter from the School of Molecular and Cellular Biology in the Spring. We hope you enjoy hearing from us. We would love to hear how and what you are doing, so that we can share it with your fellow alumni in next year's newsletter.

These are exciting times for Physiology, which I believe is poised on the edge of a new golden era. Since the discovery of the DNA helix in the 1950s, great advances have been made in molecular and cellular biology and in deciphering the genome. Essentially all the human genes have now been

Burrill Hall

In This Issue

About the Newsletter

The newsletter is an annual publication of the **Department of Molecular & Integrative Physiology** in the School of Molecular and Cellular Biology at the University of Illinois, Urbana-Champaign. It is designed and edited by William Gillespie, MCB Communications Coordinator.

Our alumni are important to us. We want to hear from you. Send us your latest news, and we'll include it in the next newsletter's alumni notes. You can write or email us at the address below.

We also welcome suggestions for future newsletters. If you wish to contribute articles or ideas, please direct correspondence to

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identified, and the function and structure of many of the protein products have been characterized. The challenge now is to determine how all these gene products work together to make a complex living organism and how their dysfunction underlies human disease. Two national initiatives that reflect this challenge are Translation Research (movement of basic research findings to the bedside) and Systems Biology. The term *Systems Biology* is used somewhat ambiguously, but basically refers to combining physiological research in an iterative process with computational and modeling approaches to explain how complex processes in the body work. Physiology is clearly a key discipline in both initiatives, so MIP should be in the center of action in biology at the University of Illinois and flourish during the next ten to twenty years.

Whether we can take advantage of the opportunities awaiting us will depend in part on the resources that are available to us.

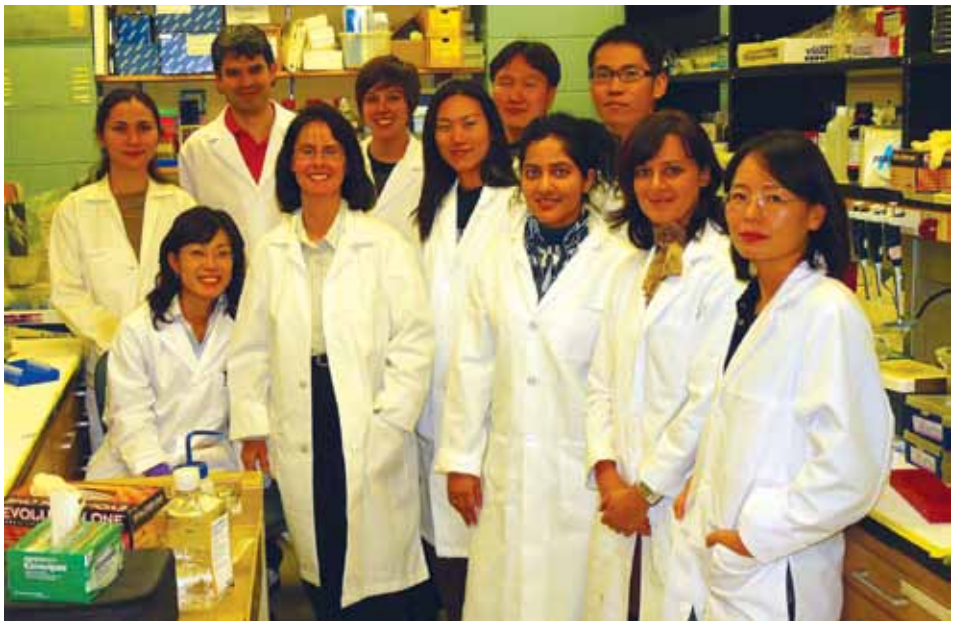
I thought of titling this discussion ***The Privlic University*** to emphasize that direct state appropriations to the University now represent less than 20% of total annual revenues (including research funding). While state funding remains critical for the University and provides a wonderful base for its programs, reaching our common goals of excellence and a brilliant future will require contributions from our alumni and friends, much like private universities—ergo, the chimeric *Privlic University*. Like me, you probably receive dozens (or hundreds) of requests from charities and your alma maters for contributions each year, each of which represents a real need. But consider this: The cost to the University and Department for five years of graduate study for a student today is about $150,000 including stipend, tuition, and fees. It has been estimated that a Ph.D. degree increases lifetime earnings by $1.5 million compared to a baccalaureate degree. If you would consider returning to MIP even just a minimal 1% of the monetary benefits from your doctoral education, total contributions of $165,000 or about $400/yr over a 40-year career would fill the bill. We have great need for support for stipends and travel for graduate students (so that we can attract and support the best), for research to provide needed infrastructure, seed money for new initiatives, and occasional interim support—critical to maintaining momentum in a very tough national funding climate. Elsewhere in this newsletter you will find a donation form. I hope you will consider joining us to provide a brilliant future for MIP. ☐

Research in Breast Cancer and Women's Health Advances

by Benita S. Katzenellenbogen

My research group works at the forefront of biomedical research in reproductive biology and hormone-dependent cancer, and is investigating important interrelationships in the regulation of breast cancer cells by hormones and growth factors, and how changes in signaling by hormones and growth factors impact the effectiveness of endocrine therapies. Persons with breast cancers that are rich in estrogen receptors (ERs), called estrogen receptor-positive breast cancers, are candidates for endocrine therapies, most often treatment with selective estrogen receptor modulators (SERMs) such as tamoxifen or raloxifene, or aromatase inhibitors such as letrozole. These agents act by inhibiting stimulation of breast cancer growth mediated by the estrogen receptor, either by putting the estrogen receptor into an inactive conformation, or by blocking the production of estrogens that bind to and activate the estrogen receptor protein. All forms of endocrine therapies function by interrupting estrogen signaling through the estrogen receptor.

In my lab, postdoctoral scientists Jonna Frasor (now assistant professor in the Department of Physiology at the University of Illinois College of Medicine in Chicago) and Fabio Stossi, Ph.D./M.D. student Daniel Barnett, and graduate student Zeynep Madak-Erdogan have done genome-wide profiling of gene expression in response to treatment of breast cancer and other estrogen target cells (such as bone and uterus) with estrogen and SERMs that have defined the pathways and networks under regulation by these agents. This work has shown that the estrogen receptor is a master regulator of the gene expression and properties of breast cancers, up-regulating survival and proliferation promoting factors, and down-regulating proapoptotic and tumor suppressing factors. Studies by Stossi, Barnett, and Shubin Sheng (Ph.D. 2007) have explored in detail the transcriptional mechanisms underlying gene repression as well as stimulation by the estrogen receptor complex. Graduate students Kyuri Kim and Shweta Bhatt are also studying factors that regulate the turnover and activity of the estrogen receptor and its coregulator partner proteins in cells.



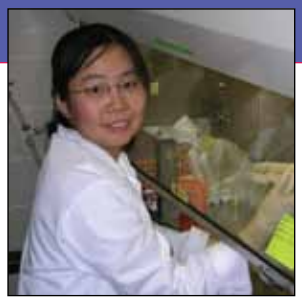
Members of the Katzenellenbogen Lab. Dr. K. is fourth from the left.

Recent work has shown that the estrogen receptor is expressed in two forms, the better-known estrogen receptor alpha as well as the more recently identified estrogen receptor beta. Work by Edmund Chang (Ph.D. 2007) in my lab has documented that estrogen receptor beta is antiproliferative and counters the estrogen stimulation by estrogen receptor alpha. Hence, it is now clear that the effects of estrogens and SERMs in breast cancer will be determined by the levels and ratios of ER alpha and ER beta in different breast cancers. Hence, both estrogen receptors are now being monitored in breast tumors.

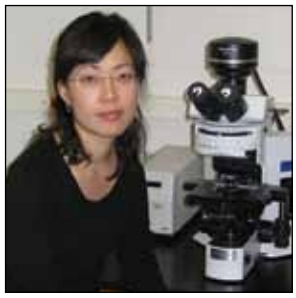
We are also investigating alterations in gene regulation and protein activities that accompany the changes in breast cancer cells when they become resistant to the beneficial activities of SERMs. This work on acquired endocrine therapy resistance, which usually develops at some point during treatment with SERMs, is being spearheaded by Anna Bergamaschi, a new postdoctoral associate in my laboratory. The outcome of Dr. Bergamaschi's research has the potential to improve the selection of breast cancer patients most likely to benefit from endocrine therapies and also provide a new avenue for enhancing the effectiveness of these therapies for treatment of breast cancer.

We are also very interested in reproductive biology and in the improvement of fertility. Work by graduate student Sung-Hee Park is examining the roles of nuclear receptor coregulators in implantation and early stages of pregnancy in animal models using genetically modified, so called knockout, mice. Work by graduate student Zeynep Madak-Erdogan and research assistant Karen Kieser is elucidating the integration of nuclear and extranuclear signaling by estrogen receptors in the actions of estrogens in a variety of estrogen-responsive breast cancer and reproductive cells.

During my career, I have had the pleasure of training forty postdoctoral fellows and thirty-five Ph.D. students. Many of these trainees are leading highly productive careers in academia, research institutes, governmental agencies, and the biotechnology/pharmaceutical industry. Their contributions to the many important advances we have made and the honors accorded my lab are greatly appreciated and I thank them for their hard work, creativity, and friendship. □



Wei Wang



Sunghee Park

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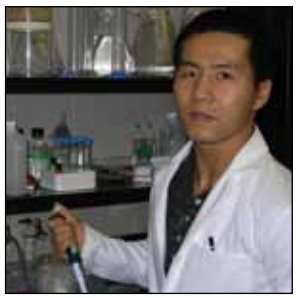


Dr. Yuechao Zhao

Mary Laws

Benita S. Katzenellenbogen is the Swanlund Chair Professor of Physiology and Cell Biology and Professor in MIP, in Cell and Developmental Biology, and the Center for Advanced Studies. She received M.A. and Ph.D. degrees from Harvard University and was a Postdoctoral Fellow with Jack Gorski in MIP for one year. She was one of the initial faculty members in the new College of Medicine at Urbana, being appointed Assistant Professor in MIP in 1971. She has won many awards and honors, which include The Susan G. Komen Breast Cancer Foundation Distinguished Scientist Award, The Breast Cancer Research Foundation Jill Rose Award, The Endocrine Society Roy O. Greep Award Lectureship, and an Honorary Degree (Laurea ad Honorem) from the University of Milan, Italy. In September 2008, she presented the Keynote Lecture at the Nobel Conference on "Recent Advances in Understanding Estrogen Signaling: From Molecular Insights to Clinical Implications" in Stockholm, Sweden. She is a Fellow of the American Academy of Arts and Sciences and served as President of The Endocrine Society (2000-2001). Her research interests are the molecular mechanisms of action of reproductive hormones and their antagonists, and of growth factors in normal cells and in breast cancer and other hormone-responsive cells and tissues.

A New National Center for Research in Reproduction and Infertility

by Milan K. Bagchi

In keeping with the long-standing and rich tradition of research and training in reproductive biology at the University of Illinois, Urbana-Champaign, the National Institute of Child Health and Human Development has awarded funds to create a Center for Research in Reproduction and Infertility on this campus. The five-year award is for $6.8 million from the NICHHD, and substantial matching funds were committed by the School of Molecular and Cellular Biology. It represents the culmination of two years of effort to obtain funding by my colleagues and myself. The goal of this new center is to understand, at molecular and cellular levels, the hormonal mechanisms that regulate embryo implantation and fertility. Implantation is a complex process driven by a cascade of cellular signaling events regulated by maternal hormones. Failure of the fertilized embryo to implant into the uterus is a major cause of infertility, a major public health issue. The scientists at this center will employ innovative investigative strategies to explore the cellular pathways that control maternal-fetal interactions during implantation and to identify factors that underlie infertility in women. The knowledge gained from these studies will

have direct impact on women's health by aiding in development of new molecular diagnostic tools for screening endometrial dysfunction and enabling targeted therapeutic strategies for the treatment of infertility.

A multidisciplinary team of basic and clinical scientists from the UIUC, Emory University School of Medicine (Atlanta, GA), and Baylor College of Medicine (Houston, TX) participates in the research under the Center's program. The UIUC scientists who serve as project leaders in addition to me are Dr. Benita Katzenellenbogen, Swanlund Professor of Molecular and Integrative Physiology, and Dr. Indrani Bagchi, Professor of Veterinary Biosciences. The research team also includes several graduate students who belong to the Molecular and Cellular Biology graduate program. They are: Wei Wang, Sunghee Park, Hatice Kaya, and Sandeep Pawar (not pictured) of Molecular and Integrative Physiology, and Cyril Ramathal of Cell and Developmental Biology. Dr. Yuechao Zhao, a postdoctoral trainee in Molecular and Integrative Physiology, has recently joined the center. Mary Laws is a grad student in Veterinary Biosciences who has collaborated extensively with my lab and contributed to the Center's program. Collectively, these researchers are working to extend the information obtained from basic cell biological studies and unique animal models to the clinical realm to inform the molecular basis of human infertility associated with endometrial dysfunction. The center's program, which serves as a seeding point for the professional development of young scientists wishing to pursue careers in important areas of women's health and infertility research, is an excellent model for the university's current mission of enhancing translational research in biology.

For more information about the Center, go to www.life.uiuc.edu/crri/ □

Milan K. Bagchi is Director of the new National Center for Research in Reproduction and Infertility at UIUC. He joined MIP in 2001 and was promoted to Professor in 2005. He holds a Ph.D. from the University of Nebraska in Chemistry, received postdoctoral training with Bert O'Malley at the Baylor College of Medicine, and was a Senior Scientist and Laboratory Head at the Population Council and The Rockefeller University before joining MIP. His research interest is steroid hormone signaling mechanisms controlling reproduction and development. His research group studies molecular genetic models of reproductive dysfunctions and hormone-dependent breast, endometrial and ovarian cancers.

Romantic Frogs Filter Noise to Hear the Sweet Talk

by Albert Feng

I got excited one day in 1998 when I learned about a species of frog in China: the concave-eared torrent frog. Males of this species have a highly unusual ear morphology, with eardrums lying not on the body surface but at the far end of the ear canals. Curious about the functional significance and the evolutionary origin of ear canals, I began a series of investigations in 2000 in collaboration with my postdoc (Wenyu Lin), and with Professors Peter Narins at UCLA and Junxian Shen at the Chinese Academy of Science, and their students and postdocs. The concave-eared torrent frogs are found in two isolated locations in central China, one of which is the mountain range of Huangshan. There, males can be seen calling nightly from low-lying vegetation on the banks of fast-flowing streams of Taohua Creek during the months of May and June. The frog habitat presents a challenge for sound communication, as the ambient noise is intense and broad-

The research team led by Al Feng (in sunglasses) includes Peter Narins from UCLA (in orange cap), Wenyu Lin from the UIUC (behind Al Feng), and collaborators from the Chinese Academy of Science.

The concave-eared torrent frog (*Odorrana tormota*) that Al Feng and collaborators investigated. The concavity of the ear (behind the frog's eye) is a prominent morphological feature of this species.

band, with peak energy in the range of 2-3 kHz. To communicate acoustically and to avoid masking by the background din, these frogs produce high-pitch vocal signals, with multiple harmonics having energy that extends into the ultrasonic range (up to 128 kHz!). Curious about whether ultrasound is used in communication, or simply represents a byproduct of the frog's sound production system, we performed a series of behavioral and physiological experiments and found that these frogs can hear and communicate with ultrasound, and that the ear is responsible for this perceptual ability. We concluded that the recessed eardrum represents an adaptation to the noisy ambience that allows frogs to detect high frequency sounds to get around the problem of masking by the predominantly low-frequency background din. We subsequently carried out laser vibrometer measurements from the eardrum and found that the eardrum can indeed detect and deliver ultrasound to the ear, but surprisingly only when the Eustachian tubes (the tubes that connect the middle ear cavity with the mouth cavity) are closed. These frogs apparently have a unique cartilage system that can actively open or close their Eustachian tubes at will, through contraction of two sets of muscles, giving them the ability to tune their ears to listen selectively to sounds at low- or high-frequency range. Thus, when the roaring sound of fast-flowing streams is too intense, they can close their Eustachian tubes and listen to the high-frequency (and ultrasonic) components of the vocal signal. The concave-eared torrent frog is the only known animal that can regulate the frequency range of hearing. My colleagues and I additionally found that female torrent frogs also produce ultrasonic calls during the reproductive season. Males are attracted to females' calls and can localize the source with extraordinary precision, in spite of their tiny body size. The localization acuity rivals that of dolphins and barn owls, known to have the highest acuity among all living organisms. I plan to investigate the neural basis of sound localization in the concave-eared torrent frog and believe that this understanding can be utilized to create superior hearing aids. This work has been published in Gridi-Papp *et al.*, *Proc. Natl. Acad. Sci. USA* 105:11014-9 (2008); Shen *et al.*, *Nature* 453:914-6 (2008); and Feng *et al.*, *Nature* 440:333-6 (2006). □

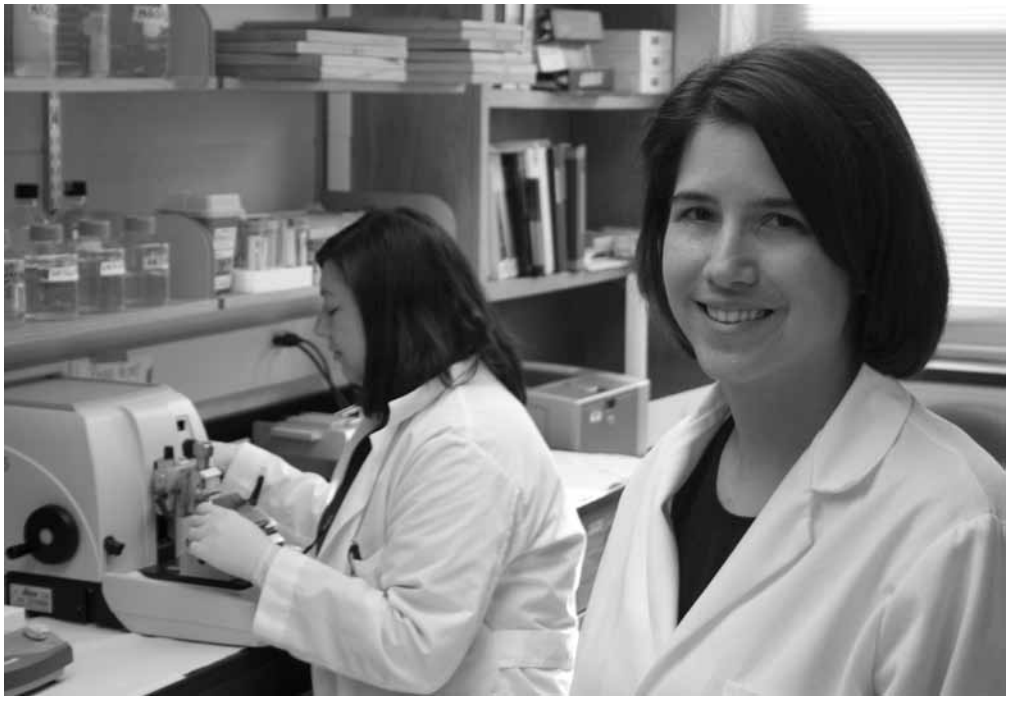
Albert Feng began his higher education in engineering with a B.S. and M.Sc. in Electrical and Biomedical, respectively, Engineering at the University of Miami, and continued combining biology with engineering with Ph.D. thesis studies in Neurobiology & Behavior and Electrical Engineering at Cornell. After postdoctoral stints at UC-San Diego and Washington University, St. Louis, he joined MIP in 1977. He is the Richard and Margaret Romano Professorial Scholar, and is presently Professor of MIP, of Biophysics and Computational Biology, of Neuroscience, of Bioengineering and of the Beckman Institute. Along the way, he served as Head of MIP for five years and as Associate Director of the Beckman Institute. His research interests are neuronal processing of sensory stimuli, focusing on hearing in bats and frogs. In addition to basic science advances, this work led to improved hearing aids which block background noise and present efforts to improve cochlear implants for the hearing impaired.

Signaling Pathways in Pituitary Development

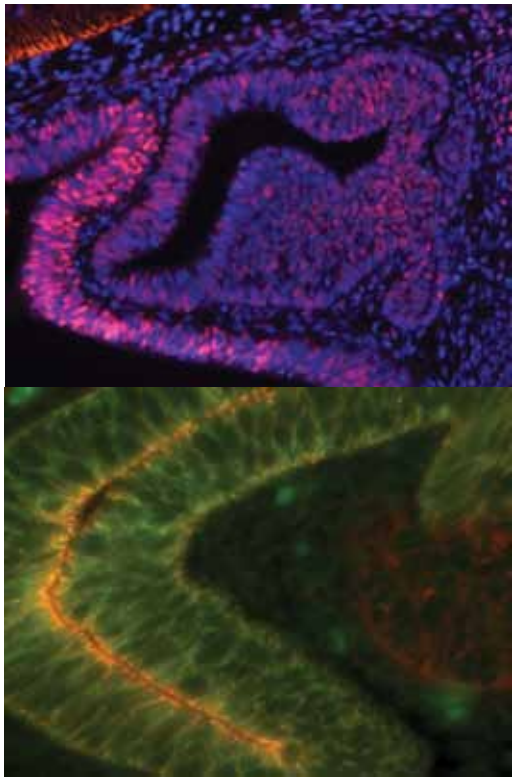
by Lori Raetzman

The pituitary is an endocrine gland that functions as a master controller of growth, reproduction and the body's response to stress. It is estimated that one in five people have an endocrine disruption resulting from too much or too little pituitary hormone secretion. Despite the prevalence of these disorders, relatively little is known about the mechanisms governing the formation of the pituitary gland.

Many processes influence the fate of a pituitary cell, including secreted signaling molecules from the surrounding brain and ectoderm as well as direct contact with cells in these tissues. Over time, these cues can change from directing proliferation to form the pituitary from undifferentiated stem cells in embryonic tissues to directing cell division in the adult organ in response to environmental cues and need, such as during pregnancy. However, in contrast to many differentiated tissues, cell proliferation and the number of cells in the pituitary are not well controlled. As a result, abnormal growth in the pituitary is relatively common with an estimated 25%



Lori Raetzman and graduate student Pamela Monahan.



Top: Hormone producing cells in the developing pituitary must exit the cell cycle before they differentiate. This picture shows many cells that are exiting the cell cycle, as seen by p27 immunostaining (pink color). All cells in the image are visualized by staining the nuclei with DAPI, a dye that fluoresces blue. Bottom: Differential cell adhesion is necessary to form the pituitary during development. This image is a pituitary from a mouse embryo that has been immunostained for E-cadherin in green and N-cadherin in red. Where the two molecules overlap in expression is yellow.

of the population harboring a pituitary tumor. Although benign and frequently undetected, these tumors can negatively impact quality of life. To understand how to prevent or treat these tumors, it is critical that we understand how cell proliferation in the pituitary is regulated and why the regulation is not rigorous. To address this problem, my research focuses on the control of cell division and differentiation during pituitary development and tumor formation. We make extensive use of transgenic "knock-out" mice in which specific regulatory signaling genes are inactive which allows us to assess the role of the disrupted gene in pituitary development.

In the summer of 2005, when I arrived on campus, I was introduced to an eager undergraduate student, Ashley Himes, who has been a great help to my research program. After graduating in 2007, Ashley stayed on in my lab and is currently pursuing a Master's Degree. Ashley's research has shown that Notch signaling plays a key role in pituitary development. Notch is an evolutionarily conserved signaling pathway that directs cell proliferation and differentiation during development of many organ systems. Her studies have illuminated how different targets of Notch signaling have complementary functions in directing pituitary cells to stop dividing and turn into hormone producing cells. We also uncovered a novel role of Notch signaling in directing pituitary cell movement. For these studies, Ashley took advantage of knockout mice lacking genes encoding proteins essential for Notch signaling. This work has recently been accepted for publication in *Developmental Biology*. Studies by a Ph.D. student in the lab, Pamela Monahan, have also further defined how Notch is controlling cell proliferation during pituitary development. We think that Notch signaling may play a role in pituitary tumor formation as well, and hope to explore this idea in the future.

I have a long-standing interest in organogenesis and how formation of cells and connections during development impacts neural and reproductive physiology. I was trained in neurosciences in my thesis studies with Dr. Ruth Siegel and in endocrine and mouse physiology in postdoctoral studies with Dr. Sally Camper. I feel like I've found my home with the Reproductive Biology faculty here in MIP, which also has great strength in neuroscience. The support I have received, both scientifically and personally, has helped me strive for success and I am grateful to be a part of this Department. □

Lori Raetzman majored in Psychobiology at Ripon College in Wisconsin, and received a Ph.D. with Ruth Siegel in Neuroscience at Case Western Reserve University. After five years of postdoctoral work with Sally Camper in Human Genetics at the University of Michigan, she joined MIP in 2005. Her research interests in pituitary differentiation are described in the article above.

New signaling molecules in the brain?

by Jonathan V. Sweedler

What is an analytical chemist doing affiliated with MIP? Not surprisingly, the confluence of these two areas involves neurochemistry. After all, a range of cell-cell signaling molecules are responsible for modulating the activity of the myriad neuronal circuits in our brain. Research in my group focuses on cell-cell signaling in the central nervous system and especially on discovering novel neurochemical pathways. Because neurotransmitters and neuromodulators are so well conserved across metazoa, we use a variety of animal models ranging from mollusks and insects to vertebrates. We characterize these signaling molecules in samples ranging from single cells to entire brain regions.

While we work on neurotransmitters and modulators related to serotonin, peptides and nitic oxide, here I will describe our efforts to characterize one of the most enigmatic group of putative cell-cell signaling molecules in the CNS—d-aspartate (d-Asp) and d-glutamate (d-Glu)—stereoisomers of the classical signaling molecules l-aspartate (l-Asp) and l-glutamate (l-Glu). While extensive research has focused on the role(s) that the more common l-enantiomers of amino acids play in neurotransmission and neuromodulation, recent findings indicate that several d-amino acids are present in both invertebrate and mammalian brains. Of course, though basic biochemistry textbooks state that in higher animals, the building blocks of life are l-amino acids, it appears that in the brain there are exceptions. One established exception is the presence of the d-form of the amino acid serine (d-Ser), which modulates glutamate signaling. Our group, and others, has evidence for the presence of a second d-amino acid, d-Asp, in the nervous systems of a number of animals, and we are now determining its involvement in intercellular signaling.

d-Asp is found in a variety of organs during early stages of animal development. Animal maturation typically coincides with the gradual disappearance of d-Asp except in the pineal gland, the

testes, the pituitary, and some regions of the brain. Using the common neuronal model *Aplysia californica*, we have discovered several subsets of neurons that synthesize d-Asp from l-Asp and selectively uptake d-Asp over l-Asp. In my group, senior scientist Dr. Stanislav Rubkahin, and former Ph.D. graduate students Cory Scanlan and Hai Miao have studied the active transport of d-Asp from neuronal soma to neuronal release sites and its stimulation-dependent release, and we are now determining its effect on postsynaptic neurons. To my surprise, Hai Miao also found that several well-defined neurons have high levels of d-Glu, while its levels in the entire brain appear to be low, indicating that both of these amino acids may have specific functions. Our currrent work is investigating the electrophysiological properties of d-Asp and d-Glu on network activity.

Investigating d-amino acids is challenging as their enantiomers (the l-amino acids) have many of the same physicochemical properties as the d-forms. How do we study chiral amino acids at the single cell level? We have developed several unique approaches to investigate brain chemistry, including methods for isolation of single neurons, individual neurites, as well as biochemical profiling of these structures using chiral microseparations based on a capillary electrophoresis. As shown in the figure on the next page, using a specialized capillary electrophoresis fluorescence detection system, we can detect amino acid amounts down to the attomole level or lower, so that quantitative measurement of enantiomers of these amino acids can be done even in a subcellular structure.

In addition to the research described above on these amino acids, I work with a number of faculty in MIP and other departments at the University of Illinois through an NIH center that I run, the UIUC Neuroproteomics Center on Cell-Cell Signaling, see neuroproteomics.scs.uiuc.edu. ☐

Jonathan Sweedler holds the Eiszner Family Chair in the Department of Chemistry, and has appointments in the Bioengineering Program, MIP, and the Neuroscience Program. He received a Ph.D. degree from the University of Arizona in Chemistry. After postdoctoral training with Dr. Richard Zare and Dr. Richard Scheller at Stanford University, he was appointed Assistant Professor in Chemistry in 1991. He became an affiliate of MIP in 2002. He is the Director of the Carver Biotechnology Center, and is a part-time faculty member in the Beckman Institute's NeuroTech group. Among his many honors are the Heinrich-Emanuel Merck Prize and election as a Fellow in the American Association for the Advancement of Science. His research interest is analytical neurochemistry and focuses on cell-cell signaling in the central nervous system.

Molecular & Integrative Physiology

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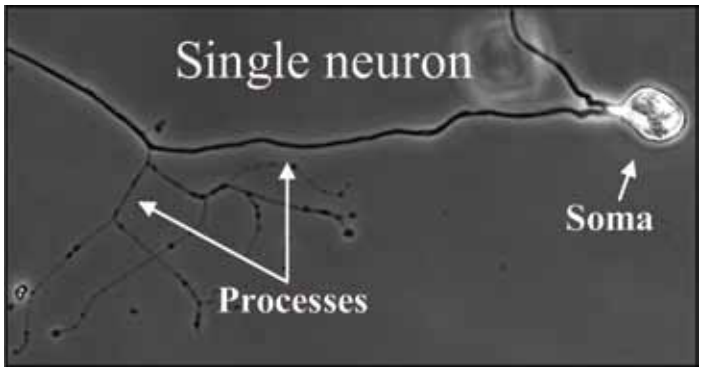
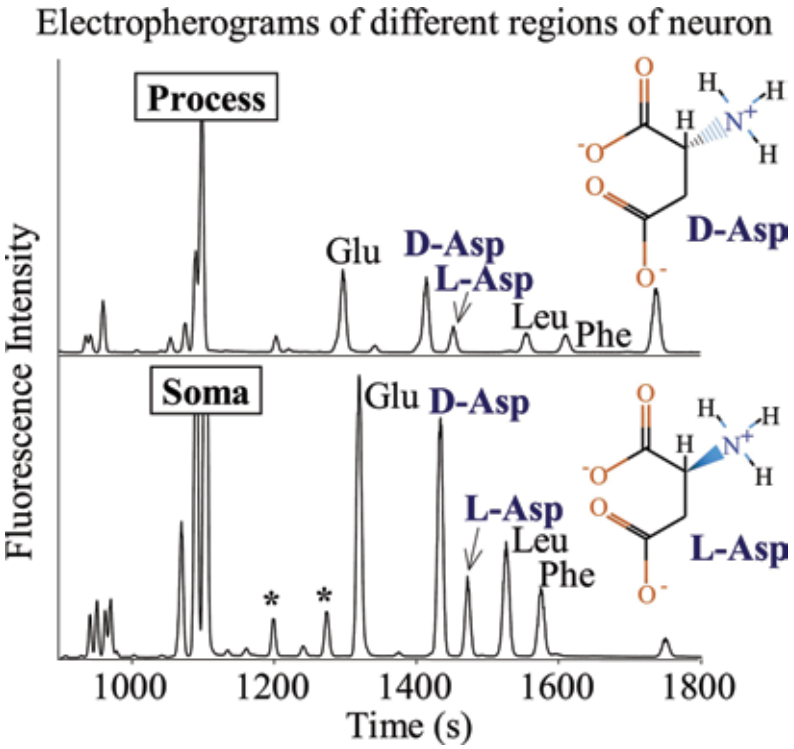
Aplysia californica, with its simpler nervous system and well defined and accessible neuronal networks, is well suited for discovery of the functions of novel cell-cell signaling molecules such as d-Asp and d-Glu.



An image showing a single sensory neuron and its associated neuronal processes.



Electropherograms from the soma and process with the d-Asp and l-Asp peaks labeled; this particular neuron has 3-fold more d-Asp than l-Asp present in its soma and process.

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