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Department of Pharmacological Sciences Research Overview

Four New Faculty Join the Department

Recent Research: Mitochondria

Symposium Honors Dr. Francis Johnson

Graduate and Undergraduate Research Highlights and Awards

Clockwise from above: Crystal structure of MTERF1 • Aristocholic acid-dA adduct • Metaplasia in human pancreatic cancer • Microglia-glioma co-cultures • See pages 3 and 6
Chair’s Message

These are terrific times in the Department. We have grown dramatically and our core now houses more than 20 funded research groups in three centers across the campus. We bring in more than $10 million annually in direct extramural support, and exciting findings are reported regularly in a host of premier journals. Much of the Departmental research space has been recently renovated, creating large open labs that promote cross-group interaction with ready exchange of ideas and approaches.

The NIH-funded, Department-based interdisciplinary Graduate program in Molecular and Cellular Pharmacology trains 40-50 graduate students and links more than 60 faculty from BNL, CHSL, and SBU. Twelve departments, both basic and clinical, participate, ranging from applied math and chemistry to medicine, pediatrics, and neurosurgery. Plans are underway for formation this coming year of the SBU Umbrella Program in Biomedical Sciences and Molecular Medicine, featuring Training Programs in Molecular & Cellular Pharmacology, Neuroscience, and Physiology & Biophysics. This program will offer incoming students new options for integrated training and interactions across a wide spectrum of disciplines.

Our undergraduate major program in Pharmacology is one of only three such in the country and continues to train some of the very best students at SBU, a high fraction of whom go on to medical/graduate school and careers in pharmacological biotechnology.

One of the great features of our faculty and research programs is the breadth of interests and technologies. Department core faculty are addressing key questions in Cancer, Metabolic diseases, Neuropharmacology, Mitochondrial diseases, and Signal transduction using chemical biology, biochemical, cellular, animal model, structural biology, and proteomic and genetic approaches, offering rich opportunities for collaboration and training on multiple levels.

The future undoubtedly presents both opportunities and challenges. Revitalization of the SBU School of Medicine through new leadership and strong philanthropic support is ongoing. We are confident that combined with strong extramural support, even in these relatively difficult times, we will continue to strengthen our research enterprise while delivering high-quality education to postdoctoral fellows, graduate students, medical students, nursing and allied health students, undergraduates, and even high school students!

With best wishes,
Michael A. Frohman

Congratulations to Dr. Holly Colognato on her promotion to Associate Professor and to Drs. Carlos de los Santos and Orlando Schärer on their promotions to Professor in 2011. Congratulations also to Dr. Feng-Qian Li, who was promoted to Research Associate Professor in 2010.
Faculty Awards

Dr. Markus Seeliger received a 2010 New Scholar Award from the Ellison Medical Foundation, a non-profit corporation supporting basic biomedical research on aging relevant to understanding lifespan development processes and age-related diseases and disabilities.

The award provides $100,000 per year for four years. Dr. Seeliger’s research “centers on protein turnover via the ubiquitin-proteasome system, a process intimately involved in disease development.”

This is the second Ellison Foundation award for the department in just two years. In 2009 Dr. Dan Bogenhagen received a Senior Scholar Award for his research on how mitochondrial DNA nucleoid organization promotes age-related mitochondrial dysfunction.

Neurobiology of Disease & Development

David Talmage
Neuregulin functions in cortical development, contributes to abnormal neuroconnectivity (PMID: 20610754)

Stella Tsirka
Microglia/macrophages promote glioma progression (PMID: 21264953)

Molecular Mechanisms of Signaling

Craig Malbon
Dynamics of supramolecular complexes in Wnt signaling (PMID: 20940260)

Feng-Qian Li, Ken Takemaru
Cby and 14-3-3 proteins control trafficking of beta-catenin (PMID: 19940019)

Genome Stability and the Environment

Arthur Grollman, Charles Iden, Francis Johnson, Masaaki Moriya
DNA adducts of aristolochic acid promote base misincorporation (PMID: 19854934)

Mitochondrial Biology

Dan Bogenhagen, Bruce Demple
Novel long-patch DNA repair mechanism in mitochondria (PMID: 18541666)

Cancer Biology

Emily Chen
Cancer stem cell subpopulation enriched by hypoxia/reoxygenation cycles (PMID: 21067584)

Howard Crawford
Key roles of transcription factors in epithelial-mesenchymal transition in pancreatic cancer (PMID: 20160041)
**New Pharmacology Faculty Add Expertise in DNA Repair, Protein Dynamics, Neural Stem Cells and Infectious disease**

In the past two years, Pharmacological Sciences has added four new faculty members in diverse and complementary research areas.

Dr. Bruce Demple joined the faculty from the Harvard School of Public Health in 2009. Dr. Demple was recruited as part of the SBU Consortium for Inter-Disciplinary Environmental Research (CIDER), a multi-departmental initiative to tackle “challenges that stem from the complex interactions between humans and the natural world.” Dr. Demple’s research is driven by trying to understand how cells defend against damaging molecules that are endogenous to cells but also produced by environmental agents. Drawn to SBU by both the ongoing research in the medical school and the opportunities afforded by CIDER, Dr. Demple is “happy with the colleagues and the prospects for collaboration at SBU” that he has encountered since arriving.

The department has also welcomed three junior members to its faculty. Dr. Dr. Markus Seeliger, who joined in the fall of 2009, studies the role of protein plasticity and dynamics in the promiscuity of kinase inhibitors and the regulation of the ubiquitin system. Key questions in his research group concern the regulation of kinase activity, including how active and inactive conformations are stabilized and how these states interconvert. A new research area concerns the age-related changes in the substrate spectrum of ubiquitin ligases.

MCP graduate students Liz Louie, Jason Hall, Cindy Leiton and Jason Quinones at the Celebrating Diversity and Academic Excellence conference held in May 2011.
Dr. Adan Aguirre arrived shortly after Dr. M. Seeliger in January 2010. Dr. Aguirre’s lab investigates the cellular and molecular mechanisms that regulate the transition of undifferentiated neural progenitor cells, or neural stem cells, into specialized neural cells during normal development. His group is examining how these mechanisms function in pathological situations when microenvironments are modified.

Both Dr. M. Seeliger and Dr. Aguirre are supported by the NIH K99/R00 Pathways to Independence Award program, the purpose of which is “to increase and maintain a strong cohort of new and talented NIH-supported independent investigators” by facilitating their transition from mentored postdoctoral fellow to independent researcher.

Since November 2010, Dr. Jessica Seeliger has been building her research program on membrane biogenesis in the human pathogen *Mycobacterium tuberculosis*. Her lab focuses on the design and application of chemical tools to study lipid biosynthesis and transport processes. The inhibition of these processes could provide novel avenues for antibacterial therapy.

Dr. J. Seeliger appreciates the support she has received from her pharmacology colleagues as she starts her lab. “I also have great colleagues in chemistry who work on TB. My lab is in West Campus, so it’s easy for me to interact with faculty in biochemistry and microbiology. That proximity has already helped with collaborations and general cross-pollination.”
Recent Research: Germline Development and Transcriptional Regulation in Mitochondria

Elena Yakubovskaya and collaborators in the lab of Dr. Miguel Garcia-Diaz published their work on the mitochondrial transcriptional regulator MTERF1 last year in Cell. Drawing on structural and biochemical data, they showed that MTERF1 mediates transcriptional termination taking advantage of a DNA binding mechanism that involves helix unwinding and base flipping.

Further studies revealed that the pathogenic mitochondrial DNA mutations G3249A and G3244A, which underlie the rare neuromuscular disorder, Kearns-Sayre syndrome, interfere with recognition of the target sequence and lead to termination defects.

These results “suggest a link between mitochondrial disease and the regulation of mitochondrial transcription.” (Cell, 2010, 141, 982,993. PMID: 20550934)

In March of this year, Huiyan (Winnie) Huang, members of Dr. Michael Frohman’s lab and their collaborators at the University of Kentucky published in Developmental Cell on a link between mitochondrial phospholipase D (MitoPLD) and an RNAi-based defense mechanism used to protect spermatocytes from transposons.

Prior work had uncovered a role for MitoPLD in supporting mitochondrial fusion by generating the lipid signal phosphatidic acid (PA) on the mitochondrial surface. In the current work, PA was shown to recruit a PA phosphatase, Lipin 1b, whose activity converted the PA into diacylglycerol to promote mitochondrial fission, suggesting a new model for mitochondrial homeostasis.

PA was then shown to be necessary for the association of mitochondria with nuage, a specialized germline structure required for the generation of piRNAs, a third form of RNAi that prevents genomic damage by transposons during development. (Dev. Cell, 2011, 20, 376-387. PMID: 21397848)
Francis Johnson Symposium – 80 Years Young

In October 2010, the department, along with the chemistry department, honored Dr. Francis Johnson with a day-long symposium to commemorate his 80th birthday. Dr. Johnson is the founding vice-chairman of the department of pharmacological sciences and was recruited from the Dow Eastern Research Laboratory to SBU in 1973 by Dr. Arthur Grollman, the founding chair. Among his many diverse accomplishments, highlights include:

- One of the most quoted reviews in organic chemistry, on two rules that describe the conformational behavior of unsaturated organic molecules
- First use of carba-nucleoside mimics to study nucleoside excision repair and to explore a biological problem using a model system
- Co-founding (with Dr. R.C. Gupta) of Chem-Master Int. Inc., a company devoted to custom synthesis for academic researchers and the pharmaceutical industry
- Ongoing development by Chem-Master Int. of treatments for inflammation, colon cancer, brain cancer, periodontitis, rosecea, and acute respiratory distress syndrome.

Dr. Johnson’s current research involves studies on the aristolochic acids, which are plant-derived potent cumulative nephrotoxins that cause an upper urothelial cancer. In addition to his ongoing teaching, he has mentored over 35 Ph.D. graduate students, several of whom returned to speak in his honor. “Dr. Johnson continues to inspire his students through his excitement about science and his genuine care and concern for all the people who have circulated through his laboratory. I remain lifelong friends with my Johnson lab mates,” says David Walt, Ph.D. ‘79. Dr. Johnson is grateful to his students and colleagues and especially his wife Marta, for their continuing support.

Medical Pharmacology Education Receives a Makeover

Changes are afoot for medical and dental pharmacology education in the School of Medicine starting fall 2011. General pharmacology (Pharm I) will continue to be taught simultaneously to both medical and dental students.

However, the second segment (Pharm II) will be integrated with the systems-based medical curriculum. A separate Pharm II course is being designed for the dental students.

Says course director Paul Fisher, “Reorganization provides an unusual opportunity to tailor different offerings for medical versus dental students, and to work closely with other medical and dental faculty to specifically integrate pharmacology teaching into other aspects of the year two curriculum.”

Over the past year, Dr. Fisher, Dr. Paul Richman, Dr. Steve Vitkun and Vice Dean for Undergraduate Medical Education Latha Chandran have overseen the redesign with additional input from other SBU medical educators.
Structurally Disordered Proteins Give Up Their Conformational Secrets

by Onika Murray

Jim McCann has always had a flair for taking on daunting riddles with repose. As an undergraduate, he was able to solve the trickiest questions on exams, an ability that set him apart. Here at SBU, Jim continues to distinguish himself as a fourth-year doctoral candidate in the Molecular & Cellular Pharmacology graduate program. After receiving his B.E. in Chemical Engineering at The Cooper Union in 2007, he joined Dr. Mark Bowen’s lab in the Department of Physiology & Biophysics, where he has been applying single-molecule techniques to protein structure determination.

Earlier this year, Jim was first author on a publication in *Structure*, “Domain Orientation in the N-terminal PDZ Tandem from PSD-95 is Maintained in the Full-length Protein.” Given that this title might baffle the average person, Jim amiably explained the goal of his project. “We wanted to figure out the orientation of PSD-95, a protein about which very little is known structurally because of its ‘intrinsically disordered’ protein classification. PSD-95 is a dynamic protein that continually shifts between an ordered and disordered state, so our single-molecule FRET technique has allowed us to figure out its domain orientation as well as its low-energy structure.”

These results also have connections to health, as PSD-95 has been implicated in a plethora of neurological diseases, such as autism, schizophrenia and Alzheimer’s. Jim’s work provides the first insights into the structure of PSD-95, which would provide an important guide in drug design for this class of neurological disorders.

Jim is also second author on an article in the April 2011 issue of *Structure*. The paper, entitled “Beyond the Random Coil: Stochastic Conformational Switching in Intrinsically Disordered Proteins,” dealt with verifying the lowest-energy configuration of PSD-95. Last September, the department recognized Jim for his work with a 2010 Van der Kloot Research Award, which is given for excellence in research scholarship.

Jim plans to complete his degree next spring, but his future career plans are otherwise still up in the air. “I’m really uncertain about what the next phase will be. I’m deciding whether to take the industry or academia route.” We can guess, though, that wherever he goes, Jim will continue to solve difficult riddles.
On June 6 the MCP graduate students gathered for their 8th Annual Graduate Students’ Symposium. This event is organized and run entirely by the students themselves, and this year was led by student representative Victoria Fischer. Students Vinal Patel, Luisa Escobar-Hoyos, Cindy Leiton, Ken Lee, Tiffany Tsui, Ifeanyi Obiorah, and Christopher Eyermann gave wonderful talks that displayed the breadth and depth of their ongoing research.

“Since I joined the MCP program, today’s presentations had the most variety of topics, from neurons to glia, to biochemistry and molecular biology. I thought it was by far the best representation of the variety of areas our program faculty are involved in, compared to previous years,” said Ifeanyi Obiorah.

The David L. Williams Memorial Travel Award is given annually in memory of one of the department’s “founding fathers,” Dr. David L. Williams. This year’s recipient was Jim McCann who will use the award to attend the Annual Biophysical Society Meeting in 2012. Wahida Ali was recognized as the award’s runner-up.

Every year the students vote on a distinguished professor to give the keynote seminar. This year, Dr. Mark Zervas of Brown University discussed his work on determining how the temporal and spatial deletion of Tsc1 and mTOR dysregulation during brain development causes neurological disease in tuberous sclerosis. The MCP students joined Dr. Zervas for lunch and discussions about life after the Ph.D., career options, and funding politics. The students were grateful for his insight and perspective on academic and industry careers.
Pharmacology Undergraduates Pursue Medical Research
by Wahida Ali

The pharmacology program at Stony Brook is an attractive major for scientifically minded undergraduates for many reasons. When faculty member Dr. Jessica Seeliger spoke to students earlier this year, she took an informal poll on their motivation for choosing the pharmacology program. “I was surprised—and impressed—by how many of them cited their interest in research as a deciding factor.”

In addition to rigorous coursework, pharmacology majors must write a research thesis, an experience that introduces them to the bench and provides context for their classroom learning. With only around 25 students per year, the program is also attractive for the personal attention and guidance students receive from director Dr. Bob Watson and administrator Janice Kito.

Senior Victoria Pisarevskaya has enjoyed diverse research experiences as a pharm major. As a member of the SBU honors program WISE (Women In Science and Engineering), Victoria started research as a freshman, working in the bioengineering program on designing a transdermal vaccine patch. Her research interest took a very different turn after a summer internship working with children with autism piqued her interest in human psychological research. Upon returning to school in the fall, Victoria discovered the SBU Cody Center, a leading center for the diagnosis and therapy of pediatric autism. In her current research with Dr. Eli Hatchwell (Dept. of Pathology), she is designing DNA chips with the goal of examining copy number variations in the brains of autistic patients.

In 2010, Victoria was an author on two papers in the *European Journal of Neuroscience* and *Progress in Neuropsychopharmacology and Biological Psychiatry* resulting from her research at SBU. After graduation, she hopes to pursue an M.D./Ph.D. with a specialty in pediatric oncology.

The department graduated 17 pharmacology baccalaureates on a sunny morning this May. Simon Tong received the Sir James Black Award for Excellence for achieving “the highest overall scholastic excellence in course work and a senior research project.” Simon worked with Dr. Francis Johnson on the zinc-binding properties of drugs and will pursue a Ph.D. in chemistry at SBU.

Lisa Malone received the Jean M. Devlin Award for displaying “the greatest potential for making significant future contributions to the pharmacological sciences.” Lisa did her thesis research on structures of kinase-inhibitor complexes with Dr. Markus Seeliger. She will pursue a masters degree in biotechnology at Albany College of Pharmacy and Health Sciences starting this fall.

Victoria Pisarevskaya (see right) sent her classmates on their way with a rousing speech. “I, along with my fellow graduates, can’t help but feel blessed for this amazing opportunity to fill our minds with the invaluable knowledge that will allow us to go on and excel… to be the agents of positive change.”

Undergraduate program director Dr. Bob Watson (Far right) with students from the pharm laboratory class Arjun Tara, Rana Said, Victoria Pisarevskaya, Miti Gandhi, Rubayyah Alamgir and in back, Brian Lebedinski, Mark Shehata, and James Jungwon Park.
Molecular & Cellular Pharmacology Welcomes Five Ph.D. Candidates for 2011

This fall the graduate program in Molecular and Cellular Pharmacology introduces five students to the department. They bring with them diverse scientific interests and experiences that include EGFR signaling in breast cancer, bacterial growth response to antibiotics, and the development of liposomes for drug delivery.

MCP Class of 2011

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<tr>
<th>Name</th>
<th>University/Institution</th>
<th>Major</th>
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<tbody>
<tr>
<td>Matthew Burak</td>
<td>University of Rhode Island Kingston</td>
<td>Chemical Eng.</td>
</tr>
<tr>
<td>Julie-Ann Cavallo</td>
<td>Fordham University / UMDNJ</td>
<td>Biology / Biomed Sci</td>
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<tr>
<td>Stephanie Chapelliouen</td>
<td>William Paterson University</td>
<td>Biotechnology</td>
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<tr>
<td>Megan Cosgrove</td>
<td>SUNY Geneseo</td>
<td>Biochemistry</td>
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<td>Grace Tan</td>
<td>Vassar College</td>
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Undergraduates in Pharmacology Garner Top University Honors

Pharmacology majors Leah Noroña and Micahel Pulkoski-Gross were both awarded the 2011 Undergraduate Recognition Award for Academic Excellence. This University honor is “given for academic accomplishments that go beyond the classroom experience.” Both juniors are pursuing research with pharmacology faculty: Leah with Dr. Miguel Garcia-Diaz and Michael with Dr. Markus Seeliger.

“Mike has shown great dedication in the lab,” says Dr. Seeliger, “and that work has already paid off—he will be a co-author on our upcoming paper on kinase-ligand structural studies.”

Congratulations to the Undergraduate Class of 2011

Leah also received a SBU 2011 Minority Access to Research Careers Fellowship, which provides tuition and stipend support to outstanding undergraduates committed to a career in biomedical research.

Pharm Happy Hour!
Top: Sherry Peng, Qun Gao, Grace Chen, Richard Bennett, Markus Seeliger,
Bottom: Devi Evanayake, Yelena Altshuller, Mary Lou Previti, Ken Lee, Jason Quinones
A Fresh Face for the Department of Pharmacological Sciences

The department will have a renewed presence on the internet starting Fall 2011. Over the past half year, Dr. Markus Seeliger and director of IT Paul Stern, along with Dr. Orlando Schärer and MCP graduate student Jason Hall, have overseen the complete redesign of the department webpage.

Input from other members of the department was largely voluntary, but also incentivized: a department-wide image competition helped quickly build an inventory of research-related graphics. The award-winning images from MCP graduate students Cindy Leiton and Freyja McLenahan are shown below.

Coming soon: the new and improved www.pharm.stonybrook.edu