



In this issue:

**Happy 90th
Birthday!
Dr. Domino!**

**Welcome to our
new faculty**

**Natasha Snider
interviews Paul
Hollenberg**

**Drug Discovery &
Development Boot
Camp**

**Masters (MS)
degree program in
Pharmacology**

**Cocaine Esterase-
a life saving drug**

**On-Line
Pharmacology
Course for Nurses**

News

Editor John Traynor
Photographer Denise Gakle
Editorial Assistant DW Liao

Contact Information:
2301 MSRB III
1150 W. Medical Center Dr.
Ann Arbor, MI 48109-5632
Phone: 734-764-8165

Ed Domino - still going strong at 90 years young!

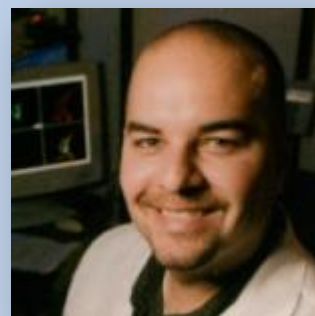


Edward Domino (second left, Professor Emeritus of Pharmacology) celebrated his 90th birthday among family, including several great grandchildren, and friends at the Gandy Dancer on Saturday, December 27th. Ed is still going strong and certainly a force to be reckoned with if his tough questions at departmental seminars are anything to go by! Pictured is Ed with current and former pharmacology faculty members.

Welcome to our new faculty



Michael Holinstat, Associate Professor of Pharmacology. Ph.D. Vanderbilt University.



Paul Jenkins, Assistant Professor of Pharmacology & Assistant Professor of Psychiatry. Ph.D. University of Michigan.

More information about our new faculty members and their research will be in our next edition.

Natasha Snider interviews Paul Hollenberg

What are some of the major changes that occurred in the basic sciences at the Medical School during the 20 years that you served as the pharmacology department chair?



There has been an incredible increase in our knowledge of the basic medical sciences but concomitantly we have learned that there is so much more out there. Within the school there have been major changes in how medical students are taught, particularly to emphasize the

connection from basic science to clinical applications. Another important change is the way we educate graduate students. Twenty years ago each department had its own stand-alone program, and now all graduate programs in the Medical School are part of the Program in Biomedical Science (PIBS) umbrella program that gives students access to many more faculty and research areas. I am pleased that we have played a critical role in the implementation and leadership of this program. Within the department we have emphasized applied pharmacology and offer courses in translational pharmacology and translational research. I see pharmacology as one the most integrative of all the basic biomedical sciences because it takes us from the molecular to the whole animal, including humans. Now that questions and challenges require so much more knowledge and so many more tools, important skills that we need to teach our students are collaboration and networking.

Under your leadership, the Michigan Pharmacology graduate program excelled in the research and career training of our graduate students. What were some of the key activities that helped this aspect? How does the Department ensure that Michigan Pharmacology remains at the forefront of training a strong and diverse scientific workforce?

We provide students with a strong background in all aspects of pharmacology and allow them to make choices about their curriculum and career development opportunities. For example, we offer courses in translational pharmacology, grant writing and research ethics as well as a mandatory biomedical communication course where students learn how to give oral presentations. This has played a key role in our students obtaining positions in academia and industry. We have a very strong base of alumni with more than 280 former PhD students and a similar number of postdocs. Consequently, we have tremendous networking ability in almost any field you can imagine. A large number of our alumni (130+) have already joined our LinkedIn professional networking group. In the future we need to develop bioinformatics and biomedical computing, and systems pharmacology. We will also have to put a greater emphasis on personalized medicine and clinical pharmacology..

You are a leading world expert in the cytochrome P450 enzyme system. What led you to choose this field of research and what are some of the biggest unanswered questions for this field?

Going back to my college days, I was always interested in enzymology and the relationship between the structure and function of enzymes. In those days all we knew was the amino acid contents of enzymes - we knew little about the 2- or 3-dimensional structures of most proteins. When I was a young investigator an area that was just starting to develop was the cytochrome P450s and drug metabolism; the biomedical relevance of this was important to me. I was fortunate to have outstanding students and postdocs plus the resources, and ever improving tools to address important questions. One of the things I point out to graduate students is that in 10 years they will be asking questions and using approaches and tools that may not have existed at the time they



Natasha Snider (PhD, 2009) Assistant Professor- Cell Biology and Physiology, UNC at Chapel Hill

started graduate school. Therefore, we should all continually reinvent ourselves and learn new things - this has been great fun for me. The most enjoyable aspect of my career has been seeing how my trainees have developed outstanding careers.

Future questions relate to the physiological functions of P450s. We need to learn more about their roles in health and disease, and about the functions of their metabolic products, some of which may be in very small quantities. We also need to get a better handle on pharmacogenetics as well as the regulation of the P450s and how we can manipulate their activities to make sure that the drugs are getting to their targets in the right form.

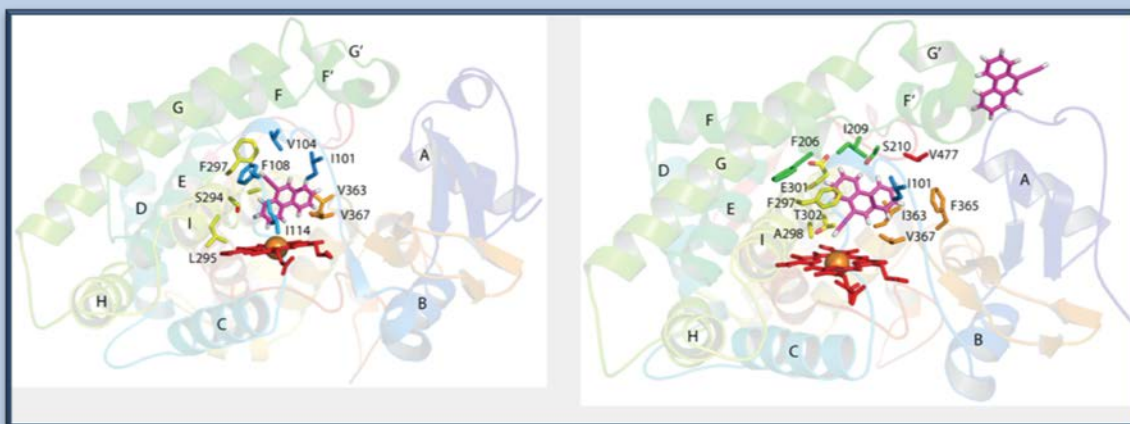
I have often heard you say: “The science is important, but the people doing the science are more important.” Can you comment on the importance of considering the “people factor” in science and research?

The most important thing in life are people. As a department chair you cannot accomplish anything alone. My job has been to figure out how to motivate people and get them to make decisions and take actions that allow the department to move forward. Those decisions have to be based on what is good for the individual and what is good for our Department. It has been great to see what a dedicated group of faculty can do and to see them be successful. I think that the most important thing that we do as basic scientists in a Medical School is

educating and training medical and graduate students, postdocs, and faculty, and helping them to accomplish what they want to do in their life. That has been my philosophy. In addition, I like to treat people the way I would like other people to treat my children - I don't always succeed, but it's what I always try to do.

What are your proudest accomplishments from your tenure as the Chair of Michigan Pharmacology from 1994 to 2014? What is your biggest hope for the future of the Department?

The proudest accomplishment for me has been the development of our graduate program which has contributed greatly to the success of our students and led them to outstanding careers. Over the years, we have played a leadership role in graduate education in terms of direct leadership of PIBS and indirect contributions that have shaped the PIBS program. We have recruited some truly outstanding faculty, some of whom have continued on to become chairs at other institutions; this is important for our Department and the discipline. But in the final analysis, our successful students and postdocs are our most important accomplishment. I would like to see the department continue to provide training to those people who will be the leaders and outstanding researchers in the field of pharmacology. I look forward to working with the department to continue to enhance the training, education and careers of our students, postdocs, and faculty.



Snapshots of the secondary structures of the binary and ternary complexes of 9-ethylphenanthrene (9-EP) and cytochrome P450 2B4 obtained from molecular dynamic simulations and showing the important role of the peripheral 9-EP allosteric ligand in modulating P450 conformations and substrate binding in the active site.

Drug Discovery and Development Boot Camp

Monday, March 16, 2015

The first ever Michigan Pharmacology Drug Discovery Boot Camp was an amazing success! More than 200 colleagues attended - many from other states and institutions. Our keynote speaker was Dr. Rajesh Ranganathan, Director of the NINDS Office of Translational Research.

Congratulations to Drs. Donna Shewach, Harvey Kaplan, and Vince Groppi for planning such a wonderful event!! And many thanks to our students for making Blue Go!



Jim Shayman addressing the bootcamp



Student volunteers at the event



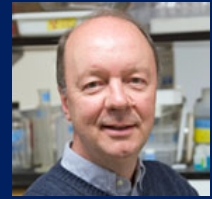
Donna Shewach directing people to the meeting



Vince Groppi, Donna Shewach, and Lori Isom

Masters (MS) degree program in Pharmacology

By Stephen Fisher



Dr. Fisher is Program Director for the MS in Pharmacology. He is Professor Emeritus of Pharmacology and Research Professor Emeritus, Molecular and Behavioral Neuroscience Institute. Dr. Fisher can be reached at skfisher@umich.edu

In 2011, the Rackham Graduate School approved a Master's Degree Program in Pharmacology. At its inception the course was 15 months long, but to better accommodate the needs of prospective students, it was subsequently shortened to 12 months duration. Although it is anticipated that most students will elect to take the course on a full-time basis, an option exists for students to pursue the degree on a part-time basis to accommodate their other personal commitments.

In January of 2014, the first "full" class of MS students (8 in total) matriculated into the program and a second group of students entered in September (fall will be the regular start date for the program in future years).

The goal of the program is to provide training at the graduate level for individuals who desire to enter the Pharmaceutical or Biotech Industries, or those who are planning to enter a career in Government Agencies (such as the Food and Drug Administration) or alternatively, those who desire to obtain a higher degree prior to entry into Medical, Veterinary or Dental Schools or a PhD program. The MS degree program involves a mixture of coursework and independent research. Much of the coursework for the MS degree is the same as that taken by PhD Pharmacology students and includes core courses in Principles of Pharmacology, Autonomic Pharmacology, Endocrine Pharmacology, Molecular Neuropharmacology, Antimicrobial & Cancer Pharmacology, and Cardiovascular Pharmacology. Also,, MS students take a course in Translational Pharmacology and choose an elective in Biochemistry, Cell Biology, Physiology or Translational Research. In addition to the coursework, students are required to select one laboratory in which to pursue a year-long research project. Depending on the student's interests and career goals, this

may take the form of a laboratory research project, or alternatively an in-depth literature survey of a current issue of pharmacological significance. All students are required to write a thesis on their research work and present the results orally to the Department. Our first class of MS students graduated in December. Some are planning careers in medicine or will enter the pharmaceutical industry while others plan to enter PhD programs. We will monitor their progress and wish them well in their future endeavors.



The first MS Pharmacology Graduating Class

More information about our MS program can be found at

<http://medicine.umich.edu/dept/pharmacology/education/masters-program>

Protein-based therapeutic shows efficacy against cocaine toxicity in a human clinical trial

Contributed by Joseph Nichols, Graduate Student (Sunahara/Woods Labs)

Drs. James Woods and Roger Sunahara have developed a protein-based therapeutic to treat cocaine toxicity. Cocaine esterase (CocE), isolated from the bacterium *Rhodococcus sp.* MB1 that grows at the roots of the coca plant, hydrolyses cocaine rapidly enough to significantly decrease cocaine toxicity in an overdose situation. A mutated form of this enzyme developed by Woods and Sunahara took a significant step toward FDA approval late last year when it passed Phase II clinical trials for efficacy.

According to a report released by the Department of Health and Human Services in 2013, cocaine toxicity was responsible for over 40% of all emergency room admittances due to illicit drug use. Currently, emergency room physicians administer benzodiazepines to counter the toxic effects of cocaine and stabilize the patient. Clinicians rely on a strategy of CNS and cardiovascular depression because there is a lack of an FDA approved treatment for cocaine-induced lethality. An alternative approach established in part by Woods and Sunahara is to remove the cocaine from the body as rapidly as possible.

After reaching the circulation, cocaine is hydrolyzed by esterases (Fig 1), mostly butyrylcholinesterase (BChE). If cocaine is broken down more rapidly, then the body's exposure to cocaine decreases proportionally. Of all enzymes known to hydrolyze cocaine, CocE has been found to have the highest rate of cocaine

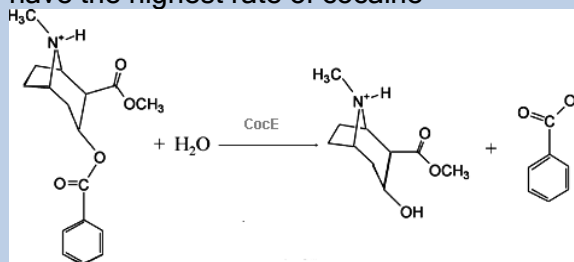


Fig 1. Hydrolysis of cocaine

metabolism, and hydrolyses cocaine 800 times more rapidly than BChE.

Based on its superior kinetics, CocE offered a promising lead as a candidate to reduce cocaine levels in humans. A team of graduate students and post-doctoral fellows developed the protein over several years to prepare it for clinical trials. The Sunahara lab engineered the protein to increase its thermostability and the Woods lab studied the in vivo activity and pharmacology of the CocE mutants to demonstrate their efficacy in rodent and primate animal models. Pre-clinical studies on the CocE mutant enzymes were carried out in collaboration with Reckitt Benckiser Pharmaceuticals Inc., prior to initiation of a successful Phase I trial that commenced in 2010 with the most thermostable mutant, now known as RBP 8000.



Fig 2. Structure of CocE. Mutations providing thermostability are shown in red.

In October 2014 the findings of a Phase II trial that evaluated the efficacy of RBP-8000 were released in the *Journal of Addictive Diseases* (<http://dx.doi.org/10.1080/10550887.2014.969603>). The effect of RBP-8000 at two different doses (100 and 200mg IV) on the pharmacokinetics and pharmacology of cocaine (administered as a 50 mg IV dose) was evaluated in twenty-nine cocaine abusers using a randomized, double-blind, placebo-controlled trial. The study showed that RBP-8000 reduced the concentration of cocaine in plasma by 90%

within 2 minutes of CocE administration and returned cocaine-induced increases in heart rate and blood pressure back to base-line levels significantly quicker than placebo.

Moreover, detectable amounts of CocE were found in the plasma of each trial participant for up to 5 hours. The authors of the study concluded that CocE should be approved for a Phase III trial.

The pioneering work by the Woods and Sunahara research groups has developed a medication that rapidly destroys cocaine in the circulation and will be a life-saving treatment for those overdosing on this drug.

The group is currently working on making very long lasting CocE mutants as a potential medication to treat cocaine addiction.

Other team members who made substantial contributions to the project include Holden Ko (Research Associate Professor), Greg Collins, Emily Jutkiewicz, Diwa Narasimhan (Postdocs), Remy Brim, (PhD 2010), Elin Edwald (PhD 2014), Nhu Truong (PhD 2014), Yong Gong Shi (Research Assistant) and Jimmy Chan (MS 2013).



Joseph Nichols with James Woods and Roger Sunahara (and CocE in the background).

On-Line Pharmacology Course for Nurses Charles B. Smith

Graduate students at the School of Nursing often differ from other students in significant ways. First, the nursing students tended to be older and a few years removed from their undergraduate education. Many of the nursing students have full-time jobs. In addition, some live in distant locations such as Toledo, Kalamazoo, Battle Creek, Grand Rapids, and even Chicago and there are always a significant number from other parts of the world, mostly from Asia but also from

the Middle East. It was extremely difficult for students to take regular courses that require a rich academic background in the biomedical and pharmaceutical sciences, and which met at 8:00 am in the morning in Ann Arbor. Therefore, the School of Nursing asked me to provide a two-term pharmacology course to the special needs of the nursing students by developing an “online” course. This would preserve all of the strengths of the traditional classroom

course without requiring students to visit an actual classroom and listen to an instructor face-to-face.

Pharmacology 659 and 660 Online were developed in the summer of 2008 as a collaborative effort between Pharmacology, the School of Nursing Information Technology Department and the Center for Research on Learning and Teaching. The online courses have two major components, one in which the students through the web-based environment CTools (<https://ctools.umich.edu/gateway>) listen to lectures, obtain lecture notes and practice examinations, and communicate with the teacher and with fellow students in a chat room or via miscellaneous other means. The other component is a “virtual classroom” (VC), provided by Adobe Connect, in which the student “meets” with the instructor(s) and other students in real time.

Each week three or four hours of recorded lectures are made available on CTools. Lectures are split into segments of approximately 15 min in duration that each carries to completion a concept or set of concepts. The student can print a complete set of lecture notes and “play” the recorded lecture sequence as many times as she/he wishes before proceeding to the next segment. The week before a major exam a practice exam is posted on CTools. There are three one hour examinations each term that are taken on-line via the CTools.

One evening each week students and faculty gather online in the VC. Here students talk with each other and with their teachers in real time. Attendance is mandatory. Each session begins with a short quiz based on the material from the preceding week.

Next, two to four student “volunteers” give short “Powerpoint” presentation on topics of clinical significance that are selected to enhance the student’s knowledge of the subject(s) covered during the preceding week. The presentations are extremely popular and the students vie with each other to make outstanding presentations. Presentations are followed by lively discussion

with both questions and clinical observations. For the remainder of the session students ask questions or present accounts of clinical experiences for which they are seeking explanations. Every student has the opportunity to demonstrate her/his expertise!

Students are evaluated by the examinations, attendance at the weekly VC, the weekly quiz and their presentations. Students must complete an on-line anonymous course evaluation. This has proved extremely valuable, providing many constructive suggestions that allow the online courses to continue to evolve.

The main benefits of the on-line course is convenience for nursing graduate students and the fact that the prerecorded lectures can be played repeatedly, especially for students whose first language is not English. As a consequence, student enrollment and student performance has risen sharply compared to the traditional classroom-based course. Students and faculty have attended VC sessions and taken online examinations while traveling to locations around the world, including Mexico City, Bangkok, India, and Jordan. Faculty members have conducted VC sessions from unusual sites such as the Emergency Department at University Hospital and a waiting room at La Guardia Airport!

Over the past forty-plus years, I have taught many students at the University of Michigan, but I have never felt that I knew my students as well as I have come to know the online graduate nursing students. Although I might not recognize them if I passed them on the street, I have a more in-depth understanding of their knowledge, accomplishments, challenges, and personalities than with any other group of students.



Charles (Tad) Smith is Professor of Pharmacology, Medical School and Professor of Nursing, School of Nursing

Alumni News

Namandje Bumpus (Hollenberg Lab, 2008) is the winner of the 2015 Division for Drug Metabolism Early Career Achievement Award by ASPET. **Namandje** was also promoted to Associate Professor of Pharmacology and Medicine, Division of Clinical Pharmacology, Johns Hopkins University School of Medicine and is Deputy to the Associate Dean for Graduate Biomedical Education.

A paper by **Christopher Evelyn** (Neubig Lab, 2009) in Chemistry & Biology entitled “Rational Design of Small Molecule Inhibitors Targeting the Ras GEF, SOS1”, was named the top article for 2014 by the International Chemical Biology Society.

Faculty News

Shaomeng Wang has been elected to National Academy of Inventors.

Jon Maybaum was selected to receive the University of Michigan Medical School 2014 Endowment for the Basic Sciences (EBS).

James Rae was inaugurated as the Thomas H. Simpson Collegiate Professor in Cancer Research on Monday, March 9, 2015.

Margaret Gnegy, Paul Hollenberg, Donna Shewach, and John Traynor have been inducted into The University of Michigan Medical School’s Academy for Educational Excellence and Scholarship.

A paper by **Jorge Iniguez-Lluhi** and colleagues “[Bifunctional Ligands Allow Deliberate Extrinsic Reprogramming of the Glucocorticoid Receptor](#)” published in *Molecular Endocrinology* was highlighted in the “Best of Basic Research, 2014 ” by the Endocrine Society.

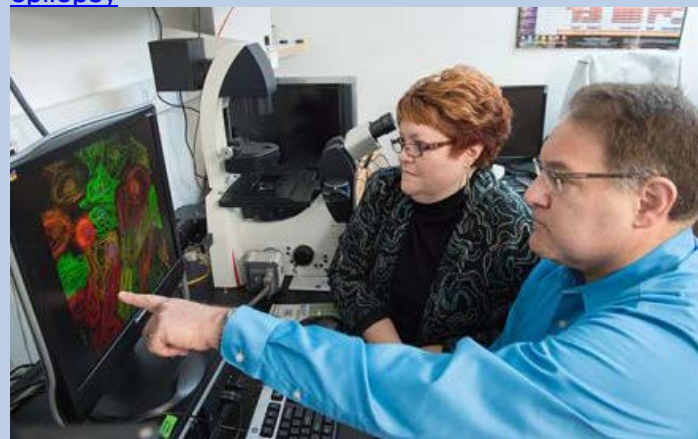
Asim Beg had two papers published in the same February issue of the *Journal of Neuroscience*.

Recent Grants

Lori Isom, (Professor of Pharmacology and Molecular and Integrative Physiology) and **Jack Parent** (Professor of Neurology and Co-Director, EEG/Epilepsy Program) have been awarded a \$3.3 million grant from the [National Institute of Neurological Diseases and Stroke](#) at the NIH. They will lead a team of University of Michigan researchers that will explore the heart-brain connection in sudden death among patients with Dravet syndrome, a type of epilepsy. Their work will use cardiac cells from animals, and brain and cardiac cells developed from human induced pluripotent stem cells. The U-M team’s grant is part of a new “Center Without Walls” that involves scientists in nine groups around the country. All the teams will work on different aspects of SUDEP, or sudden death in epilepsy. The work of the team is also supported by donors including AV Fuel of Ann Arbor and the Dravet Syndrome Foundation. Seed funding was provided by the U-M Center for Organogenesis and Citizens United for Research in Epilepsy.

For further information see:

<http://www.uofmhealth.org/news/archive/201412/brain-heart-connection-u-m-scientists-take-deadly-epilepsy>



Lori Isom and Jack Parent viewing florescent images of adult stem cells

John Traynor and Stephen Husbands (University of Bath) awarded an R01 grant from the National Institute on Drug Abuse to seek medications for the management of polydrug abuse

Omar Mabrouk (Research Investigator) has won a BioFind Award from Michael J Fox Foundation to identify biomarkers in plasma cerebrospinal fluid of Parkinson disease patients.

Student News



Andrew Haak (Neubig Lab) successfully defended his thesis "*Rho/MRTF pathway signaling and small-molecule inhibitor development in systemic sclerosis*", December 2014.



Gianna Hoffman-Luca (Wang Lab) successfully defended her thesis "*Investigation of Resistant Mechanisms of Apoptosis-inducing Anticancer Agents*", December, 2014.



Katherine Ryland (Martens/Lawlor lab) successfully defended her thesis "*The Epigenetic Regulation of KCNA5 in Pediatric Solid Tumors and its Role in Cancer Biology*", March 2015.

Sarah Mikelman, Colleen Carpenter, Isaac Dripps, Ariell Joiner and Kathryn Livingston were awarded travel grants from ASPET to attend the Experimental Biology meeting in Boston, April 2015. Experimental Biology meeting in Boston, April 2015.

Jacob Mahoney (Sunahara Lab) and **Kathryn Livingston** (Traynor Lab) received travel awards from the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) to attend their annual meeting in Melbourne, Australia in December 2014. **Kathryn** won the Best Student Poster Award at the Molecular Pharmacology of GPCRs meeting held jointly with the ASCEPT meeting.

Pharmacology Graduate students volunteered at the Food Gathers Warehouse in January.



Pictured are **Katherine Ryland, Nayiri Kaissarian, Nicole Michmerhuizen, and Zoey Tang**. Also volunteering were **Colleen Carpenter** who took the photograph and **Alex Zestos** (postdoc).

For Daily News Updates

check our webpage:

<http://www.pharmacology.med.umich.edu/Pharmacology/Home.html>

And don't forget to "friend us" on Facebook

<https://www.facebook.com/pages/Michigan-Pharmacology/193058470712533>

If you have news or views you would like to share with alumni, faculty, students and staff, please send information to John Traynor: jtraynor@umich.edu

Regents of the University of Michigan: Michael J. Behm, Mark J. Bernstein, Laurence B. Deitch, Shauna Ryder Diggs, Denise Ilitch, Andrea Fischer Newman, Andrew C. Richner, Katherine E. White, Mark S. Schlissel, *ex officio*. A non-discriminatory, affirmative action employer. © 2015 Regents of the University of Michigan.