

**Boston...
Here we come!**

In this issue:

- 2013 Award Winners
- Election Results
- **AZT: A Rational Drug Ahead of its Time,**
by Rebecca J. Anderson, Ph.D.
- 2012 P.B. Dews Award Lecture,
by James E. Barrett, Ph.D.
- International Collaboration article,
*by John S. Lazo, Ph.D. and Philip
Routledge, M.D.*

ASPET Vacancy Announcement

Executive Officer

The American Society for Pharmacology and Experimental Therapeutics (ASPET) invites applications from dynamic and dedicated individuals seeking to fill the position of Executive Officer with service beginning as soon as August 1, 2013. ASPET is a non-profit scientific society with more than 5,000 members who are employed in academia, industry, foundations and the government, or are students and postdoctoral fellows. ASPET members are active in a wide array of activities including conducting basic and clinical pharmacological research designed to develop new medicines and therapeutic agents that fight existing and emerging diseases, as well as educating the next generation of pharmacologists and other health professionals. ASPET is located in Bethesda, Maryland on the campus of the Federation of American Societies for Experimental Biology (FASEB), of which ASPET is a founding member.

The Executive Officer reports directly to the ASPET Council and is responsible for implementing financial, scientific, publication, membership, educational, and other programs and policies approved by the Board. The responsibilities of the individual in this position include but are not limited to the following:

- Oversees all operations, programs and initiatives of ASPET including managing an office of 14 staff who carry out the day-to-day activities of ASPET
- Works closely with the Director of Accounting, Membership and Subscriber Services, senior ASPET staff, the Treasurer and the Finance Committee, which are responsible for the financial operations of the ASPET to develop and maintain the budget
- Interacts with and supervises the Publications Director and staff to ensure efficient publication of ASPET's journals, the Government and Public Affairs officer to promote advocacy activities, and the Director of Marketing to promote the society through the use of the website and social media
- Develops new programs and initiatives in conjunction with the ASPET Council and directs outreach, fundraising, and educational programs
- Is responsible for ASPET's scientific meetings and coordinates activities of all ASPET Council meetings committees, Divisions and all committees.
- Represents ASPET in public and private venues

Qualified candidates should have a record of achievement and leadership in academic, industrial, governmental, association and/or other not-for-profit organizations, prior executive/administrative experience, and a demonstrated ability to conceptualize and implement new projects. An advanced degree in science and knowledge of pharmacology are highly preferred. Excellent communication, interpersonal and management skills are required.

Please send a letter of application, including a statement of interest and a résumé or curriculum vitae by April 12, 2013

to FASEB/ASPET Human Resources
9650 Rockville Pike, Bethesda, MD 20814
or email materials to resumes@faseb.org.

Please visit our website at <http://www.aspet.org> for more information about ASPET.

President's Corner



Comings and Goings

Dear ASPET Members,

We are fast approaching the 2013 ASPET Annual Meeting, which will be held in Boston at Experimental Biology 2013 on April 20-24. This year, we are also meeting with the British Pharmacological Society, the premier pharmacology society in the U.K. formed in 1931. We have an exciting program planned which you will not want to miss: the Sir James Black Lecture features 2012 Nobel Laureate in Chemistry Robert Lefkowitz, the Julius Axelrod Award Lecture by Gavril W. Pasternak speaking on "No pain, big gain: Truncated mu opioid receptor splice variants as drug targets," and the John J. Abel Award lecture given by Arthur Christopoulos, "Reciprocal relationships: The yin and yang of GPCR allostery." We have fabulous sessions that should be attractive to students, postdoctoral fellows, academic faculty, and scientists in biotechnology and pharmaceutical organization. For our students and fellows, we have a Graduate Student Colloquium on "Introducing the Individual Development Plan: A key to success," a symposium on "Translating pharmacology into career choices in the pharmaceutical and biotechnology industry," and a workshop on the "Art of item writing (NBME style) and basics of assessment." There are many symposia, including ones on "Cognitive enhancers for the treatment of neuropsychiatric disorders," "Emerging technologies for delivering neurotherapeutics across the blood-brain barrier," "Epigenetic control of drug metabolism and transport," "Transcription factors as therapeutic drug targets," sleep apnea, apolipoprotein E, stem cells, and systems pharmacology. There will be numerous opportunities for you to meet old friends and make new ones. I hope to see you at our Annual Meeting at EB 2013.

Some of you may know that our Executive Officer for the last 16 years, Christie Carrico, has decided to retire later this year. Christie truly has made an indelible mark on our society, recruiting and maintaining a remarkable staff in the main office and helping to build it into the premier pharmacological organization in the world. She has been the heart and soul of ASPET, overseeing our financial and education mission, ensuring members of Council, the Board of Publication Trustees, divisions, and committees fulfill their responsibilities in a timely manner. Her outstanding professionalism places ASPET in a fabulous position to move forward nationally and internationally during this exciting time in pharmacology. We have identified a search committee that will begin the process of identifying our next Executive Officer. As we proceed, I hope to provide you with additional information about our progress. Please feel free to communicate any advice or names of candidates to Rick Neubig (rneubig@umich.edu) or me (lazo@virginia.edu). I also hope you will join me in celebrating Christie's many accomplishments at our meeting in Boston.

Sincerely,

John S. Lazo

*Meet the Leaders of ASPET
Exhibit Hall, Booth 432
April 21-23, 12:00PM - 2:00PM*

Leaders Include:

| | |
|-------------------------------------|-----------------------------------|
| <i>Annette E. Fleckenstein, PhD</i> | <i>Richard R. Neubig, MD, PhD</i> |
| <i>Charles P. France, PhD</i> | <i>John D. Schuetz, PhD</i> |
| <i>Paul A. Insel, MD</i> | <i>Kenneth E. Thummel, PhD</i> |
| <i>Michael F. Jarvis, PhD</i> | <i>Lynn Wecker, PhD</i> |
| <i>John S. Lazo, PhD</i> | <i>Sandra P. Welch, PhD</i> |
| <i>Edward T. Morgan, PhD</i> | |

*Please check our website or the booth
for a full schedule of leaders at the booth.*

Contents

NEWS

| | |
|------------------------------------|----|
| President's Corner | 3 |
| 2013 Election Results | 5 |
| 2013 ASPET Award Winners | 6 |
| ASPET Annual Meeting at EB 2013 | |
| Important Dates and Information | 10 |
| Proposed Bylaws Change | 10 |
| Full Program | 12 |
| Activities for Students & Postdocs | 27 |
| 4th GPCR Colloquium | 28 |

FEATURES

| | |
|--|----|
| International Collaboration | 30 |
| <i>by John S. Lazo, Ph.D. and Philip Routledge, M.D.</i> | |
| AZT: A Rational Drug Ahead of its Time | 31 |
| <i>by Rebecca J. Anderson, Ph.D.</i> | |
| 2012 P.B. Dews Lecture | 35 |
| <i>given by James E. Barrett, Ph.D.</i> | |

DEPARTMENTS

| | |
|--|-----|
| In Sympathy | 45 |
| Obituary: Peter Dews | 45 |
| <i>written by W.H. Morse</i> | |
| Journals | 49 |
| Science Policy | 51 |
| Book Review: State of Wonder by Ann Patchett, | 54 |
| <i>reviewed by Christine K. Carrico, Ph.D.</i> | |
| In the Spotlight: Interviews with ASPET Members | 55 |
| Members in the News | 58 |
| Staff News | 59 |
| New ASPET Members | 60 |
| Division News and Election Results | |
| Behavioral Pharmacology | 62 |
| Cardiovascular Pharmacology | 63 |
| Drug Metabolism | 64 |
| Integrative Systems, Translational and Clinical Pharmacology | 64 |
| Molecular Pharmacology | 66 |
| Neuropharmacology | 66 |
| Toxicology | 67 |
| Chapter News | |
| Upstate New York Pharmacology Society | 68 |
| Great Lakes | 68 |
| Mid-Atlantic Pharmacology Society | 69 |
| Membership Information | 71 |
| Membership Application | 72 |
| <u>APPENDIX (ONLINE ONLY)</u> | |
| MAPS 2012 Annual Meeting Abstracts | A-1 |

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Postmaster: Send address changes to: *The Pharmacologist*, ASPET, 9650 Rockville Pike, Bethesda, MD 20814-3995.

2013 Dues Notices

If you haven't already done so, please pay your 2013 dues. You can mail in your payment or renew online at:
<https://www.aspet.org/login.aspx>

2013 Election Results

ASPET is pleased to announce the following election winners:



PRESIDENT-ELECT

Annette E. Fleckenstein, Ph.D.

Dr. Fleckenstein joined ASPET as a Student Member in 1993 and has been a Regular Member since 1996. As a student member, she received several travel awards including in 1998 a James A. Bain Young Scientist Travel Award to attend the 13th International Congress of Pharmacology. She served on the Committee on Women in Pharmacology from 1999 – 2002. She also served as Secretary/Treasurer for the Division for Neuropharmacology in 1999 and on the Division Executive Committee from 1998 – 2001. Dr. Fleckenstein was elected ASPET Secretary/Treasurer in 2007 and served on the ASPET Council from 2006 – 2009. As Secretary/Treasurer, she chaired the Finance Committee and served on the Investment Subcommittee from 2006 – 2009. She was reappointed to the ASPET Finance Committee as an at-large member in 2010. While on Council, Dr. Fleckenstein chaired the Astellas Awards Committee and served as the Council liaison to the Division for Behavioral Pharmacology. Dr. Fleckenstein is also a member of the Society for Neuroscience, the College on Problems of Drug Dependence, the American College of Neuropsychopharmacology, and the International Drug Abuse Research Society.



SECRETARY/TREASURER-ELECT

Paul A. Insel, M.D.

Dr. Insel has been a member of ASPET since 1978. He was a member of the Program Committee from 1992 – 1999, serving as Chair from 1996 – 1999. He served on the Experimental Biology Program Theme Committee from 1994 – 1996 and chaired the Signal Transduction Theme Committee. He was then a member of the EB Program Committee from 1997 – 1999. From 1999 – 2006, Dr. Insel represented ASPET on the Experimental Biology Board, chairing it from 2000 – 2006. Dr. Insel was also a member of the Program Committee for the 2002 IUPHAR Congress. Dr. Insel was on the Abel Award Committee from 1992 – 1993 and on the ASPET Awards Committee in 1995. He was elected to the Nominating Committee in 1995. Dr. Insel was a member of the Editorial Board of *Molecular Pharmacology* from 1983 until he became its Associate Editor in 2000 and Editor in 2003 – 2006. He was also Associate Editor of *the Journal of Pharmacology and Experimental Therapeutics* from 1998 – 2001 and currently serves as Associate Editor of *Pharmacological Reviews*, a position he has held since 2000. He is an Associate Editor of the *British Journal of Pharmacology*, Editor of the *Annual Review of Pharmacology and Toxicology* and Co-head of Faculty of 1,000 in Pharmacology and Drug Discovery. Dr. Insel was elected as a Fellow of the American Association for the Advancement of Science, the American Society of Clinical Investigation, and Association of American Physicians. He is also a member of the American Society for Cell Biology, the Endocrine Society, the American Society for Biochemistry and Molecular Biology, the American Physiological Society, and the American Heart Association Basic Science Council.



COUNCILOR

John D. Schuetz, Ph.D.

Dr. Schuetz has been a member of ASPET since 2005. He served as the Chair of the Division for Toxicology in 2010 – 2011 and has been a member of the Division Executive Committee since 2009. He was a member of the Program Committee from 2010 – 2012. Dr. Schuetz was appointed to the Editorial Board for *Drug Metabolism and Disposition* in 2003 and has been an Associate Editor since 2005. Dr. Schuetz also belongs to the American Association for Cancer Research, and American Association for the Study of Liver Diseases, the American Association for the Advancement of Science, the Alliance for Cell Signaling, the International Society for the Study of Xenobiotics, the American Society for Microbiology, and the American Society for Biochemistry and Molecular Biology.



**Meet the ASPET Washington Fellows
And Learn About this Exciting New Program
Exhibit Hall, Booth 432**

April 21 & 22

1:00 PM – 2:00 PM



2013 ASPET Award Winners



Julius Axelrod Award **Lee E. Limbird, Ph.D.**

Dr. Lee Limbird, Professor of Biochemistry and Dean of the School of Natural Sciences at Fisk University has been named recipient of the 2013 Julius Axelrod Award in Pharmacology by the American Society for Pharmacology and Experimental Therapeutics (ASPET). Dr. Limbird is recognized for her major contributions to research and her outstanding leadership and mentorship to several generations of graduate students. The Julius Axelrod Award, named after the 1970 Nobel Prize winner in Physiology or Medicine, is given to recognize outstanding scientific contributions in research and mentoring in pharmacology. The Award was established to honor the memory of the eminent American pharmacologist who shaped the fields of neuroscience, drug metabolism, and biochemistry.

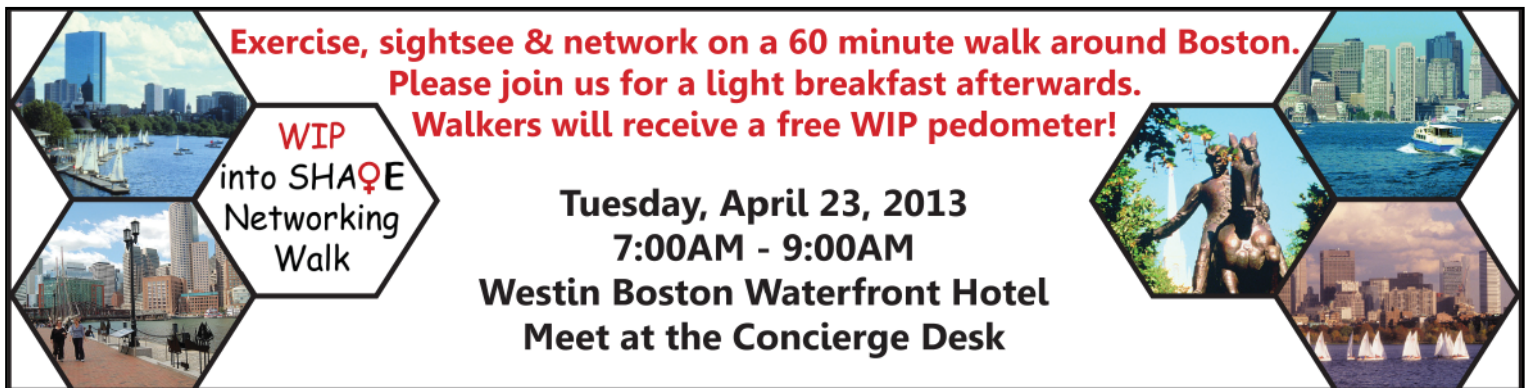
Dr. Limbird obtained her Bachelor's degree in Chemistry from the College of Wooster in Ohio and earned her Ph.D. from the University of North Carolina. After postdoctoral research at Duke University, she joined the Department of Pharmacology at Vanderbilt University, where she would chair the department and later serve as Vanderbilt University Medical Center's first Associate Vice Chancellor for Research. She represented Vanderbilt on numerous state academic partnerships. In 2005, she joined Meharry Medical College as Vice President for Research and Chair of the multidisciplinary Department of Biomedical Sciences. Dr. Limbird would move to Fisk University in 2008.

Since her post-doctoral fellowship at Duke under Nobel Laureate Robert Lefkowitz, Dr. Limbird's research career has focused on G-protein coupled receptors. Her research on alpha-2 adrenergic receptors is considered pioneering and showed how those specific receptors relate to regulation of blood pressure, sedation, pain suppression, and opioid drug action. She has also devised strategies for selective manipulation of these receptors, opening up opportunities for therapeutic development.

In addition to her many significant research discoveries, Dr. Limbird is credited with many for bringing Vanderbilt's Department of Pharmacology to its leading position. Her devotion to Vanderbilt's academic excellence, mentoring and nurturing of students, postdocs, and young faculty are legendary and extend to offering personal support for many student related activities including travel to meetings. While at Vanderbilt, she developed a partnership with Meharry's Department of Pharmacology to catalyze interactions between the two departments.

Dr. Limbird has been a recipient of many awards including ASPET's John Jacob Abel Award for young investigators and the Goodman and Gilman Award for Receptor Pharmacology. She has served on numerous NIH review committees and has been active in ASPET serving as Councilor, Secretary/Treasurer, and in other leadership capacities. She has received many teaching awards given by the graduate students themselves, and many of her own doctoral and postdoctoral students are among the most successful in academia and industry.

Dr. Limbird will be presented the ASPET-Julius Axelrod Award in Pharmacology on Saturday, April 20 at the ASPET Business Meeting/Awards Ceremony of the Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics/Experimental Biology (EB) 2013 Meeting in Boston, MA. The ASPET Business Meeting and Awards Ceremony will take place at the Boston Convention Center, Room 107AB from 6:00 – 7:30 PM immediately followed by the Opening Reception. Dr. Limbird will give the 2014 Julius Axelrod Lecture. The 2013 Julius Axelrod Award Lecture will be given by last year's recipient, Gavril W. Pasternak, Ph.D., of Memorial Sloan Kettering Cancer Center. Dr. Pasternak will deliver a lecture titled, "No pain, big gain: Truncated mu opioid receptor splice variants as drug targets," on Sunday, April 21 from 2:00 – 2:50 PM in Room 107AB in the Boston Convention Center.



Exercise, sightsee & network on a 60 minute walk around Boston.
Please join us for a light breakfast afterwards.
Walkers will receive a free WIP pedometer!

WIP
into SHAQE
Networking
Walk

Tuesday, April 23, 2013
7:00AM - 9:00AM
Westin Boston Waterfront Hotel
Meet at the Concierge Desk

The graphic features a central text area with a white background and black text, surrounded by a collage of six hexagonal images showing various Boston landmarks and waterfront views. The images include the city skyline, a harbor with sailboats, a statue of a figure on a horse, and a view of the waterfront with buildings and water.



John Jacob Abel Award
Arthur Christopoulos, Ph.D.

Arthur Christopoulos, Ph.D., Professor of Pharmacology at Monash University and Principal Research Fellow of the National Health and Medical Research Council of Australia, is the recipient of the 2013 John J. Abel Award, sponsored by Pfizer. Dr. Christopoulos receives the John J. Abel Award as an outstanding young investigator in recognition of his fundamental contributions to the field of analytical pharmacology and the study of G protein-coupled receptors, notably in his work on allosteric modulation and biased signaling of GPCRs.

Dr. Christopoulos is one of the world's leading receptor pharmacologists. His key contributions to the field have been the dissemination of the concept of GPCR allosterism and the development of assays and analytical procedures that facilitate the detection, validation, and quantification of allosteric drug effects and ligand-based signaling. This work has had a major impact on modern GPCR focused drug discovery.

Dr. Christopoulos received his Ph.D. from the Victorian College of Pharmacy at Monash University in Australia. Following his postdoctoral training at the University of Minnesota, he returned to Australia and established his own laboratory with a view to develop analytical pharmacology techniques to address many of the preclinical challenges of modern drug discovery. More recently, his work has turned to understanding the structural basis underlying allosteric modulator effects at GPCRs as well as overcoming translational bottlenecks in progressing modulator-focused drug discovery programs.

He is the highest-ranked Australian based scientist in the disciplines of pharmacology and toxicology. Additionally, Dr. Christopoulos also serves on the editorial board of eight international journals, including *Molecular Pharmacology*, *the Journal of Pharmacology and Experimental Therapeutics*, and *Pharmacological Reviews*.

Dr. Christopoulos will be presented the 2013 John J. Abel Award on Saturday, April 20 at the Business Meeting/Awards Ceremony of the Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics/Experimental Biology (EB) 2013 Meeting in Boston, MA. The ASPET Business Meeting/Awards Ceremony will take place at the Boston Convention Center, Room 107AB from 6:00 – 7:30 PM immediately followed by the Opening Reception. Dr. Christopoulos' John J. Abel Award Lecture is titled, "Reciprocal relationships: The yin and yang of GPCR allostery" and will be delivered on Monday, April 22 from 8:30 – 9:20 AM in Room 107C at the Boston Convention Center.



Pharmacia-ASPET Award for Experimental Therapeutics
Richard R. Neubig, M.D., Ph.D.

Dr. Richard R. Neubig, Professor in the Department of Pharmacology, Co-director of the Center for Chemical Genomics, and Director of the Center for the Discovery of New Medicines at the University of Michigan, is the recipient of the 2013 Pharmacia-ASPET Award for Experimental Therapeutics. The Pharmacia-ASPET Award for Experimental Therapeutics is given annually to recognize and stimulate outstanding research in pharmacology and experimental therapeutics—basic laboratory or clinical research that has had, or potentially will have, a major impact on the pharmacological treatment of disease. This award is funded by an endowment from Pharmacia (now Pfizer) and by ASPET.

Dr. Neubig earned his dual degrees from Harvard and undertook an internal medicine residency at the University of Michigan. After that he was appointed as Assistant Professor in the Department of Pharmacology. He quickly established himself as an international authority on the biochemistry and pharmacology of the alpha2-adrenergic receptor. As a result of these important scientific contributions, Dr. Neubig attained full professorship only 10 years after assuming a faculty position. He is considered one of the pioneers in the investigation of the biophysics of adrenergic receptors and GPCRs in general. More recently, Dr. Neubig has contributed a series of critical reports proving that the set of proteins directly regulating G protein signaling (RGS molecules) regulates signaling in intact cells. For these and other important contributions, Dr. Neubig is widely considered to be one of the leading authorities on RGS proteins both nationally and internationally.

Together with colleagues, he helped establish the Center for Chemical Genomics (CCG) where investigators across the University have isolated several novel compounds that could lead to the development of novel therapeutics. The success of the CCG was recognized by the University when it named him the Director of the Center of Discovery of New Medicines.

Dr. Neubig is President-elect of ASPET and has been active in the International Union of Basic and Clinical Pharmacology. He is co-founder of the Great Lakes GPCR Retreat, an annual meeting that has gained international stature and is now considered one of the field's most informative and intense conferences focusing on GPCR signaling. He has also made significant contributions to education and mentorship. He has contributed to graduate and medical school curriculum and serves as course director or co-director of several courses. He has served as thesis advisor for over 60 graduate students.

Dr. Neubig will be presented the Pharmacia-ASPET Award on Saturday, April 20 at the Business Meeting/Awards Ceremony of the Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics/Experimental Biology (EB) 2013 Meeting in Boston, MA. The ASPET Business Meeting/Awards Ceremony will take place at the Boston Convention Center, Room 107AB from 6:00 – 7:30 PM immediately followed by the Opening Reception.



Robert R. Ruffolo Career Achievement Award in Pharmacology

Pancras C. Wong, Ph.D.

Dr. Pancras C. Wong, Senior Research Fellow at Bristol-Myers Squibb Company, is the recipient of the 2013 Robert R. Ruffolo Career Achievement Award in Pharmacology. The award was established in recognition of the contributions made to drug discovery and development by Dr. Ruffolo, former President of Research and Development at Wyeth Pharmaceuticals, and is given to recognize the scientific achievements of scientists who are at the height of their careers and who have made significant contributions to any area of pharmacology. Dr. Wong has dedicated 30 years to drug discovery research and has co-discovered two breakthrough medicines in two different therapeutic areas.

After receiving his Ph.D. at the University of Minnesota, Dr. Wong began his pharmaceutical career as a Senior Research Pharmacologist in Hoechst-Roussel Pharmaceuticals. He joined the DuPont Company in 1983 to conduct research in hypertension and heart failure.

While at DuPont, Dr. Wong played an integral role in the discovery of receptor subtypes for angiotensin II, AT1 and AT2, the characterization of the biological functions of these receptor subtypes, and the identification of losartan as a selective AT1 receptor antagonist. Losartan is now marketed under the trade name Cozaar.

At Bristol-Myers Squibb, Dr. Wong conducts research focused on developing new antithrombotic drugs. The research goal was to discover novel oral anticoagulants with improved safety, efficacy, and ease of use compared with warfarin, the standard of care. Dr. Wong's work contributed to the development of apixaban to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Recently, apixaban has been approved for this indication in the U.S., Europe, Japan, and Canada.

Dr. Wong has published over 150 papers and book chapters. He was selected as a recipient of the American Chemical Society Award for Team Innovation in 1997 and the Ondetti & Cushman Award for Scientific Innovation from Bristol-Myers Squibb in 2011. He has been a longstanding member of ASPET and is an elected Fellow of the American Heart Association.

Dr. Wong will be presented the Robert R. Ruffolo Career Achievement Award in Pharmacology on Saturday, April 20 at the Business Meeting/Awards Ceremony of the Annual Meeting of the American Society for Pharmacology and Experimental Therapeutics/Experimental Biology (EB) 2013 Meeting in Boston, MA. The ASPET Business Meeting/Awards Ceremony will take place at the Boston Convention Center, Room 107AB from 6:00 – 7:30 PM immediately followed by the Opening Reception.



Torald Sollmann Award in Pharmacology

William L. Dewey, Ph.D.

William L. Dewey, Ph.D., Professor and Chair of the Department of Pharmacology and Toxicology at the Virginia Commonwealth University, is the recipient of the 2013 Torald Sollmann Award. The Award was established to commemorate the pioneering work in America of Dr. Torald Sollmann in the fields of pharmacological investigation and education. Dr. Dewey was selected for this award because of his outstanding and productive research career; his significant contributions to medicine utilizing education, research, and service; and his unparalleled service to ASPET and the discipline it represents.

Dr. Dewey earned his Ph.D. from the University of Connecticut. Upon completion of his postdoctoral work at the University of North Carolina, he was offered a position there as Assistant Professor of Pharmacology. In 1972, he was recruited to VCU, where he has served numerous positions including Vice Chair for Research, Dean of the School of Basic Health Sciences, Associate Provost, and Vice President for Research and Graduate Studies. His distinguished research has pioneered approaches to understand mechanisms of substance abuse, including significant findings on the mechanism of action of opioid agonists and antagonists and the cannabinoids. His collaborative research helped discover that an increase in endogenous opioids occurred in sudden infant death syndrome (SIDS) and led to the development of therapeutics for the treatment of SIDS and other diseases with centrally induced respiratory depression. In addition to his opioid work, his research has contributed significantly to pharmacology and our understanding of the mechanisms of tolerance to marijuana.

In addition to his excellent mentoring of dozens of doctoral and postdoctoral trainees, Dr. Dewey's contributions to pharmacology education are nationally recognized. He is the founder, President and Treasurer of The Friends of the National Institute on Drug Abuse, a coalition of over 100 organizations which advocates for research, treatment, and prevention of substance abuse. He served as President of ASPET and tirelessly contributed to numerous other leadership roles within the society for many years, including chairing the Centennial Celebration Committee. He is a past President of the Federation of American Societies for Experimental Biology (FASEB) and twice was elected to lead the College on Problems of Drug Dependence. As appointed Chairman of the Virginia Biotechnology Research Act Study Committee, he played a major role in the passage of the act and served as the first Vice President of the Virginia Biotechnology Research Park.

Dr. Dewey will be presented the Torald Sollmann Award on Saturday, April 20 at the Business Meeting Awards Ceremony of the Annual Meeting/ of the American Society for Pharmacology and Experimental Therapeutics/Experimental Biology (EB) 2013 Meeting in Boston, MA. The ASPET Business Meeting/Awards Ceremony will take place at the Boston Convention Center, Room 107AB from 6:00 – 7:30 PM immediately followed by the Opening Reception.



Benedict R. Lucchesi Distinguished Lectureship in Cardiac Pharmacology

Andre Terzic, M.D., Ph.D.

Andre Terzic, M.D., Ph.D., Professor of Medicine and Pharmacology, Marriott Family Endowed Professor in Cardiovascular Diseases, and Director of the Center for Regenerative Medicine at the Mayo Clinic, is recipient of the 2013 Benedict Lucchesi Award in Cardiac Pharmacology. The biennial award was established by the American Society for Pharmacology and Experimental Therapeutics to honor Dr. Lucchesi's lifelong scientific contributions to our better understanding and appreciation of pharmacological treatment and prevention of cardiovascular disease and for his mentoring of many cardiovascular pharmacologists. The Awards Committee selected Dr. Terzic in recognition of his scientific leadership as an international leader in cardiac pharmacology.

A native of Paris (France), Dr. Terzic received medical and graduate education at the Universities of Belgrade, Paris, and Illinois (Chicago), followed by fellowship training at the French National Institutes of Health, Thomas Jefferson University, and the Mayo Clinic. Dr. Terzic would become the youngest faculty with dual academic rank of Professor in Medicine and Pharmacology at the Mayo Clinic and its inaugural director of Regenerative Medicine.

Dr. Terzic has made landmark contributions in our understanding of cardioprotective and cardioregenerative strategies. His early career contributions began with pioneering studies into the mechanisms by which ATP-sensitive potassium channels bring about cardioprotection. His laboratory leads the world in discoveries of the principles by which these ion channels mediate cardiac protection and how to therapeutically target them to prevent cardiac injury. Dr. Terzic's more recent efforts in regenerative science have drawn international attention representing cutting-edge translational research. He has led efforts in the development of next generation cardiovascular regenerative therapies, including the first-in-man clinical trial using organ-specified stem cells for heart repair. His scientific success is matched by his outstanding mentorship and dedication to the scientific and medical community.

Dr. Terzic will be presented the Benedict Lucchesi Award at his lecture. Dr. Terzic's lecture is entitled "Regenerative cardiac pharmacology: The next frontier," and will be presented on Tuesday, April 23, 2013 from 4:30 – 5:30 PM in Room 107AB of the Boston Convention Center, Boston, MA.



ASPET Division for Drug Metabolism Early Career Achievement Award

Nina Isoherranen, Ph.D.

Dr. Nina Isoherranen, Associate Professor in the Department of Pharmaceutics at the University of Washington, is the recipient of the 2013 Drug Metabolism Early Career Achievement Award. The Award was established by ASPET's Division for Drug Metabolism to recognize excellent original research by early career investigators in the area of drug metabolism and disposition.

Dr. Isoherranen received her Bachelor's and Master's of Science degrees from the University of Helsinki. After earning her Ph.D. in Pharmaceutical Sciences from the Hebrew University in Jerusalem, Israel, she continued her training as a postdoctoral fellow at the University of Washington, joining the Department of Pharmaceutics as an Acting Assistant Professor and soon after as Assistant Professor.

Dr. Isoherranen's work has centered on characterizing the complex drug-drug interaction scenarios involving inhibitory metabolites and multiple-P450 inhibitors; understanding of the expression, activity, and physiological importance of CYP26 enzymes in retinoic acid metabolism; and the role of drug metabolizing enzymes during pregnancy and fetal development. She has established herself as a leader and pioneer in the prediction of complex drug-drug interactions.

Dr. Isoherranen is committed to the advancement of education and training of graduate students, professional Pharm.D. students, and postdoctoral fellows, as well as supporting the progress of the drug metabolism field. She has been honored with many awards, among them the Kaye Innovation Award from the Hebrew University, Young Investigator Award from the American Epilepsy Society, and the Distinguished Ph.D. Student prize from the Hebrew University.

Dr. Isoherranen's lecture, titled "The biochemistry and clinical significance of CYP26 enzymes in regulating retinoic acid homeostasis," will be presented on Monday, April 22 from 2:00 – 2:50 PM in Room 108 of the Boston Convention Center.



**Opening and Awards Reception
Directly following the ASPET Business Meeting
Saturday, April 20, 2013
Boston Convention Center, SW Lobby**



Annual Meeting

Important Annual Meeting Information

Important Dates

March 22, 2013: Deadline for Discounted Hotel Reservations. Reserve your housing at <http://registration3.experientevent.com/ShowEXB131/>. Need to share a room for the meeting? Visit the EB Room Share Board at <http://experimentalbiology.org/eb/pages/roomshare/roomsharing.asp>.

April 5, 2013: Child Care Registration Deadline. Camp EB will be available each day of the meeting, so you don't have to worry about leaving the kids at home! Register for Camp EB at: http://www.accentregister.com/events/ch_events.asp?eld=6364.

Important Links

Program Information: <http://www.aspet.org/EB2013/program/>

Registration: <http://experimentalbiology.org/EB/pages/Registration.aspx>

Boston Convention & Exhibition Center and City Guide: http://www.massconvention.com/bcec_attendee_guide.html

Important Reminders

Use the **EB Itinerary Builder*** to create your schedule for the meeting: <http://experimentalbiology.org/EB/pages/Itinerary-Builder-Program.aspx>

EB Mobile App* - to help you organize your schedule and check sessions on your mobile device. Download at <http://www.experimentalbiology.org>.

***Note:** At time of publication, the EB Itinerary Builder and EB Mobile App were not yet available. Check the aforementioned Web pages for updates.

Give a Day of Service to Boston - Friday, April 19. For the past four years, ASPET members attending the ASPET Annual Meeting at EB 2013 have spent a day volunteering in the local communities of the host city: In 2009, we built homes with Habitat for Humanity in the Upper 9th Ward in New Orleans; in 2010, 2011, and 2012, we prepared and served meals to homeless residents of Pasadena, Washington, DC, and San Diego, respectively. The Behavioral Pharmacology Division of ASPET is again sponsoring a volunteer opportunity at EB 2013 in Boston. We will spend Friday, April 19, helping **Cradles to Crayons** provide children living in homeless or low-income situations in Boston with the essential items they need to thrive. Further details will follow to those who express an interest in volunteering. If you plan to join us, please contact Charles P. France at france@uthscsa.edu, 210-567-6969 (voice), or 210-567-0104 (fax).

Follow ASPET's tweets and Facebook posts during the meeting. On Twitter, our program-related posts will have the hashtag #EB2013. We encourage you to use #EB2013 and #ASPET13 on Twitter in your discussions about the ASPET Annual Meeting at EB 2013.

At the ASPET Booth

Visit the ASPET booth, #432, at the Boston Convention Center. There, you can sign up for membership, get information about ASPET membership and activities, pick up a FREE luggage tag and EB 2014 Save the Date gift, and shop at the ASPET Store.

Meet the ASPET Leadership! Get to know some members of Council, Journal Editors, and other leaders of the society.

Meet the ASPET Washington Fellows! These graduate students, postdoctoral trainees, and young researchers will be available at the ASPET booth.

Information for the Business Meeting: Proposed Bylaws Change

The following proposed change to an ASPET bylaw will be voted on by members at the Business Meeting, Saturday, April 20, 6:00 PM at the Boston Convention Center:

Currently, applicants for Regular, Affiliate and Postdoctoral membership in ASPET must be sponsored by a Regular member. As the reach of the society increases, it has become increasingly difficult for individuals who wish to be members to find a sponsor in their institution/country. Staff attempts to find members in their institutions, but often end up referring the applications to Division chairs or other members for approval. Essentially, this approval depends on the CV and bibliography of the applicant to ascertain that they meet the minimum criteria for membership. This same review is also done at the staff level. Council voted in October to eliminate the criterion for sponsorship by an ASPET member with the proviso that the same level of document review be done at the staff level.

Existing Bylaw: SECTION 2. Nomination of Members

Proposal of Nominees. Nominees for membership shall be proposed by one regular member of the Society. Nominations may be submitted at any time during the year. Review of applications by the Executive Office shall occur on a regular basis.

Proposed Bylaw change: SECTION 2. Application for Membership

Applications for membership may be submitted at any time during the year. Review of applications by the Executive Office shall occur on a continual basis for Regular, Affiliate, and Postdoctoral membership. Applications for student membership must be accompanied by a statement from an ASPET member or the applicant's research advisor or department chair indicating that the student is training in pharmacology and is a student in good standing.

American Society for Pharmacology and Experimental Therapeutics

Visit us at Booth #432

At the ASPET Store this year:

- ASPET T-shirts
- New Kid's T-shirts
- Baseball Caps
- Stuffed Donkeys
- Ornaments
- Historical Compendiums



Meet the ASPET Leadership!

Members of Council, Journal Editors, and other Society Leaders will be available at the ASPET booth between 12PM and 2PM each day! Be sure to stop by to chat with them, ask questions, and to share your thoughts and ideas!

Check the booth for a detailed schedule.

Also at the ASPET Booth:

- Sign up for new membership and get 50% off dues for 2013
- Students get FREE membership
- Get information about all of ASPET's activities and member benefits
- Pick up your FREE ASPET luggage tag
- Pick up your FREE EB 2014 Save the Date gift



2013 Annual Meeting Program

Friday, April 19

Behavioral Pharmacology Society Meeting

Westin Boston Waterfront, Commonwealth Ballroom B/C; 6:00 PM – 11:00 PM

Saturday, April 20

Behavioral Pharmacology Society Meeting

Westin Boston Waterfront, Grand Ballroom E; 8:00 AM – 6:00 PM

2013 Teaching Institute: Training Models for Undergraduate Pharmacology: US/UK Perspectives

Boston Convention Center, Room 108; Noon – 2:30 PM

Chair: Nick J. Goulding, Barts and the London Sch. of Med. and Dentistry

Setting an agenda for undergraduate pharmacology

Nick J. Goulding, Barts and the London Sch. of Med. and Dentistry

Undergraduate degrees in the UK: Where are we going?

Susan Brain, King's Col. London

Educating the next generation of in-vivo pharmacologists: Meeting the needs of industry and academia

David Lewis, Univ. of Leeds, Sch. of Biomed. Sci.

Pharmacology for undergraduates: The Duke model

Rochelle D. Schwartz-Bloom, Duke Univ. Med. Ctr.

Toward an integrated undergraduate pharmacology curriculum

Robert Watson, State Univ. of New York at Stony Brook

Panel Q & A: Future prospects for undergraduate education in pharmacology: An agenda for ASPET and BPS

Graduate Student Colloquium: Introducing the Individual Development Plan: A Key to Success

Boston Convention Center, Room 107C; 2:00 PM – 5:00 PM

Chair: Lynn Wecker, University of South Florida

As Yogi Berra once said, "You got to be careful if you don't know where you're going, because you might not get there." Although Yogi was likely not thinking about a scientific career when he made that statement, the concept of the Individual Development Plan (IDP) as a tool to help individuals assess their skills, interests and values, has been used in the business and governmental sectors for some time, and has now permeated academia. Simply put, the IDP is typically used to identify professional goals and objectives, assess one's skill set relative to these goals, and develop a plan (both short-term and long-term) to acquire the skills required to achieve these goals. Most resources would agree that the IDP is currently recognized as the best practice in promoting professional development, and is recognized as an important, valuable and beneficial tool for professionals at all career stages with all types of goals. It also serves as a communications tool, enabling graduate students to communicate their long and short term goals with their mentors. Creating an IDP at the beginning of graduate school can lead to more effective time management and use of resources, and more focused efforts, targeted towards achieving career goals.

This colloquium will begin with a brief overview of ASPET's new mentoring program and will quickly move into a synopsis of the steps used to create an IDP. You will learn how to map out your general career trajectory, match your skills and strengths with your career choices, and identify areas for development that build upon your current strengths. Once the process and steps are presented, attendees will begin to create their own IDP and should expect to have a solid first version by the time they complete the workshop, keeping in mind that the IDP is a 'living document' that continuously evolves throughout one's career.

Individual Development Plan: A key to success

Lynn Wecker, Univ. of South Florida

Career Path Speakers:

Gunther Kern, AstraZeneca, Boston

Federico Bernal, NCI/NIH

Maja Köhn, European Molecular Biology Laboratory, Heidelberg

Stephani Sutherland, Freelance Science Writer, Scientific American MIND and

Pain Research Forum

Myron Toews, Univ. of Nebraska Med. Ctr.

Mary Jeanne Kallman, Covance Labs.

Introduction to ASPET mentoring program

Remy Brim, Bioethics Dept./NIH

Break-out session group leaders:

Myron Toews, Univ. of Nebraska Med. Ctr.

Christine K. Carrico, ASPET

Ann Hanna-Mitchell, Univ. of Pittsburgh Sch. of Med.

Mary Jeanne Kallman, Covance Labs.

Harriet Kamendi, AstraZeneca

Susan Ingram, Oregon Hlth. & Sci. Univ.

ASPET Business Meeting

Boston Convention Center, Room 107AB; 6:00 PM – 7:30 PM

ASPET Opening and Awards Reception

Boston Convention Center, SW Lobby; 7:30 PM – 9:30 PM

Sponsored by the National Board of Medical Examiners and by Pharmacology Research & Perspectives

Sunday, April 21

Diversity Mentoring Breakfast

Westin Boston Waterfront, Revere; 7:30 AM – 9:30 AM

Workshop: Art of Item Writing (NBME style) and Basics of Assessment

Westin Boston Waterfront, Grand Ballroom E; 9:00 AM – 12:30 PM

ASPET gratefully acknowledges the educational grant from the National Board of Medical Examiners for supporting this workshop.

Sponsored by the Division for Pharmacology Education

Chairs: Agata P. Butler, Nat'l. Board of Med. Examiners and Senthil Kumar Rajasekaran, Oakland Univ. William Beaumont Sch. of Med.

Reflecting world-wide shifts toward integrative curricula, this workshop focuses on writing MCQ exams for basic science courses that assess the application of knowledge to clinical situations and interpreting the data obtained from student performance. Following an introduction to the topic, three 60 minute sessions will be conducted to:

- 1) provide guidance and hands-on training in constructing and critiquing case-based assessment items;
- 2) help to understand the basics of exam item analysis and the ways one can interpret the results; and
- 3) discuss hot topics in medical education, including potential teaching and assessment methods for educational research.

Introduction to the workshop: Importance of correct item writing and current trends in recognizing educational research
Senthil Kumar Rajasekaran, Oakland Univ. William Beaumont Sch. of Med.

Developing high-quality multiple-choice test items for basic sciences
Mark Raymond, National Board of Medical Examiners

Setting pass/fail standards: Discussing item analysis
Mark Raymond, National Board of Medical Examiners

Hot topics in medical education research
Lynn Crespo, Univ. of South Carolina Sch. of Med., Greenville

Orthostatic intolerance: Insights into pharmacologic, physiologic and gender issues

Boston Convention Center, Room 106; 9:30 AM – Noon

Sponsored by the Divisions for Cardiovascular Pharmacology & Integrative Systems, Translational and Clinical Pharmacology

Chairs: Julian Stewart, New York Med. Col. and Amy Arnold, Vanderbilt Univ. Sch. of Med.

Standing up from a supine or seated position depends on rapid cardiovascular adaptations that are driven by an interplay of autonomic, volume and hormonal mechanisms. The inability of these mechanisms to adequately compensate for changes in posture results in orthostatic intolerance. A growing number of disorders have been associated with orthostatic intolerance and all are more prevalent in women. This symposium will explore the underlying physiologic mechanisms, gender difference and current pharmacologic targets for both acute and chronic forms of orthostatic intolerance, including syncope, fatigue, and postural orthostatic tachycardia syndrome.

Vasovagal syncope: putative triggers and pharmacological and physiological approaches to management
Roger Hainsworth, Univ. of Leeds

Neural and non-neural control of orthostatic intolerance: implications for sex differences
Qi Fu, Texas Healthy Presbyterian Hosp. Dallas

Identifying sympathetic nervous system abnormalities in orthostatic intolerance
Elisabeth Lambert, Human Neurotransmitter Lab.

Ehlers Danlos Syndrome, joint hypermobility and orthostatic intolerance
Peter Rowe, Johns Hopkins Children's Ctr.

Hypo-osmolality pressor stimulus is linked to transient receptor potential vanilloid 4 (TRPV4) in the portal region
Junior Speaker: Tu Mai, Vanderbilt Univ.

Loss of muscle sympathetic nerve activity and blood pressure phase synchronization in postural vasovagal syncope
Junior Speaker: Christopher E. Schwartz, New York Med. Col.

Novel functions for cyclic nucleotide phosphodiesterases and their implications for pharmacological intervention

Boston Convention Center, Room 107AB; 9:30 AM – Noon

Sponsored by the Divisions for Molecular Pharmacology; Cardiovascular Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; & Neuropharmacology

Chair: Marco Conti, UCSF

Phosphodiesterases (PDEs), the enzymes that degrade and inactivate cyclic nucleotides, are considered critical components in cellular homeostasis, and the design of PDE inhibitors occupies a prime role in pharmacology. The discovery of several new genes and numerous variants has broadened the applications of PDE pharmacology. Genetic models and selective inhibitors have uncovered a host of new functions that can be ascribed to a specific PDE isoform. This session will focus on how the integration of specific PDE variants into macromolecular complexes with receptors, channels and kinases provides novel insights into the generation of signaling microdomains and the specificity of cellular responses to external cues.

Domain structure and interactions in cyclic nucleotide phosphodiesterases: An atomic view of PDE regulation
Jayvardhan Pandit, Pfizer Global R&D, Groton Labs.

Novel insights into the mechanism of action of beta-adrenergic antagonists: Modulation of PDE4-beta-adrenergic receptor complexes
Wito Richter, UCSF

Phosphodiesterases and cyclic nucleotide compartments in the regulation of cardiac function
Rodolphe Fischmeister, Univ. de Paris-Sud XI, France

PDE inhibitors and the treatment of airway inflammation
Clive Page, King's College, London

Post translation regulation of PDE10 and the implication in their physiological role in the CNS and in drug discovery
Nicholas Brandon, AstraZeneca, Cambridge

Correlating structure and function of drug metabolizing enzymes: An ongoing challenge

Boston Convention Center, Room 107C; 9:30 AM – Noon

Sponsored by the Divisions for Drug Metabolism & Toxicology

Chairs: Emily Scott, Univ. of Kansas and Eric Johnson, Scripps Res. Inst.

The diversity and flexibility of many of the active sites of human drug metabolizing enzymes with different ligands makes correlations between structure and function an ongoing challenge. The design of specific inhibitors of certain cytochrome P450 enzymes requires knowledge of the enzyme structure and the ability to integrate biophysical and computational approaches to understand function. This symposium will explore the ways that cytochrome P450 enzymes are being used as drug targets by exploring the use of traditional (NMR) and newer (structure-based ADMET) methods to predict metabolism.

Cytochrome P450 Structure: Common themes and variations on the theme
Eric Johnson, Scripps Res. Inst.

Investigations of human cytochrome P450 enzymes with solution NMR

Emily Scott, Univ. of Kansas

Predicting ligand interactions with metabolizing enzymes: An in silico structure-based approach

Maria Miteva, Univ. Paris Diderot

Novel pharmacoenhancer cobicistat: Discovery and development of a CYP3A inhibitor

Lianhong Xu, Gilead Sci., Inc.

Physical interactions among NADPH-cytochrome P450 reductase, CYP1A2, and CYP2B4 in the endoplasmic reticulum

Junior Speaker: John Connick, LSUHSC New Orleans

Cognitive enhancers for the treatment of neuropsychiatric disorders

Boston Convention Center, Room 108; 9:30 AM – Noon

Sponsored by the Divisions for Behavioral Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; & Neuropharmacology

Chairs: Kathleen M. Kantak, Boston Univ. and Roger D. Spealman, Harvard Med. Sch.

There is a current trend of exploring cognitive-enhancing therapeutic drugs as treatments for a number of neuropsychiatric disorders, including Alzheimer's disease, schizophrenia, anxiety and drug addiction. This session will review novel preclinical research currently being done to discover new drug targets across a spectrum of disorders. Findings show a striking similarity in the drug targets that have been examined across multiple neuropsychiatric disorders and it now seems likely that the discovery of safe and effective cognitive-enhancing therapeutic drugs for one disorder may translate to other disorders with neurocognitive deficits.

Targets for cognitive-enhancing pharmacotherapy

Joseph G. Wettstein, F. Hoffmann-La Roche Ltd.

Translational approaches to cognitive enhancing drugs for neuropsychiatric disorders

Trevor W. Robbins, Univ. of Cambridge

Novel cholinergic-based therapeutic strategies for Alzheimer's disease and age-related memory decline

Alvin V. Terry, Georgia Hlth. Sci. Univ.

Therapeutic uses of cognitive enhancers in rat and monkey models of drug addiction

Brid Á Nic Dhonnchadha, Boston Univ.

Neuroplasticity in rodent models of fear extinction and use of cognitive enhancers

Gary B. Kaplan, VA Boston Healthcare System

Summary and discussion

Kathleen M. Kantak, Boston Univ. and Roger D. Spealman, Harvard Med. Sch.

Emerging technologies for delivering neurotherapeutics across the blood-brain barrier

Boston Convention Center, Room 109A; 9:30 AM – Noon

Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology; Cardiovascular Pharmacology; Drug Discovery and Development; & Neuropharmacology

Chairs: Nisha Nanaware-Kharade, Univ. of Arkansas for Med. Sci. and Eric C. Peterson, Univ. of Arkansas for Med. Sci.

The blood brain barrier is vital for CNS homeostasis and the preservation of neuronal integrity. It also plays a role in the pathology and progression of a broad spectrum of CNS disorders, including Alzheimer's disease, ALS, Parkinson's disease as well as presenting a challenging barrier to delivering drugs into the CNS. This symposium will highlight some of the new technologies developed for delivering drugs across the BBB, including neurosurgical techniques, chemical-based strategies that modify the physicochemical properties of the drug, and biotechnology-based strategies which "trick" the endogenous BBB transporters.

Anatomy and physiology of the blood brain barrier (BBB) with special emphasis on transport of biologicals across the BBB and insights into the development of in vitro BBB model

Eric Shusta, Univ. of Wisconsin-Madison

Principles for targeting tight junction proteins and functions

Maria Balda, Univ. Col. London, Inst. of Ophthalmology

Intranasal drugs, biopharmaceuticals and stem cells bypass the blood-brain barrier to treat Alzheimer's, Parkinson's, stroke, brain tumors, PTSD, TBI and other CNS disorders

William H. Frey, Regions Hosp.

Gene delivery across the blood brain barrier for treating neurological disorders

Brian Kaspar, Nationwide Children's Hosp.

JULIUS AXELROD AWARD LECTURE

Boston Convention Center, Room 107AB; 2:00 PM – 2:50 PM

Gavril W. Pasternak, Memorial Sloan-Kettering Cancer Center

No pain, big gain: Truncated mu opioid receptor splice variants as drug targets

Introduction: Kim Neve, VA Med. Ctr.

JULIUS AXELROD SYMPOSIUM: Expanding the repertoire of G-protein coupled opioid receptor targets

Supported by the John V. Croker Fund

Boston Convention Center, Room 107AB; 3:00 PM – 5:30 PM

Chair: Gavril W. Pasternak, Memorial Sloan-Kettering Cancer Center

Alternative pre-RNA splicing of the mu opioid receptor gene: Insight into complex mu opioid actions

Ying-Xian Pan, Memorial Sloan-Kettering Cancer Center

Opioid receptor heteromers: New pharmacology and new therapeutic possibilities

Lakshmi A. Devi, Mount Sinai Sch. of Med.

Biased agonism and trafficking: Discriminating opioid drug actions by receptor endocytosis

Mark Von Zastrow, UCSF

Translating pharmacology into career choices in the pharmaceutical and biotechnology industry

Boston Convention Center, Room 106; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Pharmacology Education; Drug Discovery and Development; & Integrative Systems, Translational and Clinical Pharmacology

Chairs: Janet Clark, Drexel Univ. Col. of Med. and other chair TBD

The integration of pharmacology into the complex fabric of drug discovery and development emphasizes just how critical the discipline is to evaluating a compound, assessing its therapeutic potential, evaluating liabilities and then integrating all of this into making a decision about progression into humans. Leading pharmacologists in the various specialty areas of expertise that contribute to the drug discovery and development process will discuss how their pharmacological specialties contribute to the process and share how they determined their career paths.

Educational initiatives in pharmacology for a career in the pharmaceutical or biotechnology industry

James Barrett, Drexel Univ. Col. of Med.

Pharmacology in target identification and validation

Peter Hutson, Shire Pharmaceut.

Pharmacogenetics in drug discovery and development

David Stone, Merck Res. Labs.

Pharmacoepidemiology: Studying drugs in populations

Sean Hennessy, Perelman Sch. of Med. at the Univ. of Pennsylvania

Clinical pharmacology and the development of drugs

Darrell Abernethy, FDA, Annapolis

Epigenetic control of drug metabolism and transport

Boston Convention Center, Room 107C; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Drug Metabolism; Drug Discovery and Development; Integrative Systems, Translational and Clinical Pharmacology; Molecular Pharmacology; & Toxicology

Chairs: Aiming Yu, Univ. at Buffalo, SUNY and Yoichi Osawa, Univ. of Michigan

The importance of genetic factors in the control of drug metabolism is well recognized; however there is also increasing evidence that drug-metabolizing enzymes and transporters are regulated by epigenetic factors such as DNA methylation, histone modification, and noncoding RNA mechanisms. This session will introduce new findings on epigenetic regulatory mechanisms in drug metabolism and transport and the impact of epigenetic factors on the pharmacological and toxicological effects of drugs and their implications in therapy.

Overview of genetic and epigenetic mechanisms underlying variable drug metabolism and drug response

Magnus Ingelman-Sundberg, Karolinska Inst., Stockholm

Chromatin modification in control of drug metabolism during liver development

Xiaobo Zhong, Univ. of Kansas Med. Ctr.

Role of epigenetic mechanisms in differential regulation of the dioxin-inducible CYP1A1 and CYP1B1 genes

Oliver Hankinson, UCLA David Geffen Sch. of Med.

Noncoding RNAs in post-transcriptional control of drug metabolism and transport

Aiming Yu, Univ. at Buffalo, SUNY

Long noncoding RNAs and transcription of cytochrome P450s in mouse liver during maturation

Junior Speaker: Lai Peng, Univ. of Connecticut

Innate immunity and cardiovascular disease: Unfolding the therapeutic potential of toll-like receptors

Boston Convention Center, Room 108; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Cardiovascular Pharmacology & Integrative Systems, Translational and Clinical Pharmacology

Chairs: R. Clinton Webb, Georgia Hlth. Sci. Univ. and Styliana Goulopoulou, Georgia Hlth. Sci. Univ.

Toll-like receptors (TLRs) are pattern recognition receptors that activate the innate immune response. In addition to exogenous infectious ligands, TLRs sense certain endogenous molecules that are released during host tissue injury/death. Activation of TLRs leads to the activation of NF- κ B and the production of pro-inflammatory cytokines that may have both beneficial (repair) and detrimental (inflammation) effects on the host. TLRs are expressed not only in immune cells but also in cardiac and vascular tissue, suggesting that TLRs may be a link between innate immunity, inflammation, and cardiovascular disease. This session will address newly discovered TLR-associated molecular pathways that are involved in the genesis of endothelial dysfunction and cardiovascular remodeling characterizing various cardiovascular pathologies. The therapeutic potential of TLR manipulation will be discussed.

Danger, tissue injury and immunity

Polly Matzinger, NIAID, NIH

Toll-like receptors in gestational hypertension

Brett Mitchell, Texas A&M Hlth. Sci. Ctr.

Innate immune mechanisms in viral myocarditis

Jesus Vallejo, Baylor Col. of Med.

Toll-like receptors: Therapeutic targets in cardiovascular disease?

Claudia Monaco, Imperial Col. London

The influence of methadone on toll-like receptor 4 and human mu opioid receptor expression

Junior Speaker: Summer Dodson, Oklahoma State Univ.

Chronic Toll-like receptor 9 activation mediates heightened vascular contractility via attenuated NOS activity in isolated aortic segments

Junior Speaker: Cameron McCarthy, Georgia Hlth. Sci. Univ.

Therapeutic approaches for erectile dysfunction (ED) and benign prostatic hyperplasia (BPH): Present & future

Boston Convention Center, Room 109A; 3:00 PM – 5:30 PM

Sponsored by the British Pharmacological Society; and the ASPET Divisions for Cardiovascular Pharmacology; Drug Discovery and Development; & Integrative Systems, Translational and Clinical Pharmacology

Chair: Selim Cellek, Cranfield Univ., Bedfordshire

Despite the successful pharmacological agents such as PDE5 inhibitors, alpha blockers and 5-alpha reductase inhibitors, erectile dysfunction and benign prostatic hyperplasia remain difficult-to-treat diseases. The aim of this symposium will be to provide an evidence-based overview of the novel pharmacological agents, stem cell, and gene therapy approaches that have recently been developed for the two diseases. In addition, the session will open a debate on the use of PDE5 inhibitors in both erectile dysfunction and benign prostatic hyperplasia as well as their use for other indications.

Pathophysiological link between ED and BPH

Selim Cellek, Cranfield Univ., Bedfordshire

Soluble guanylate cyclase activators for ED

Peter Sandner, Bayer HealthCare AG, Wuppertal

PDE5 inhibitors for treatment of BPH

Arthur Burnett, Johns Hopkins Hosp.

Novel therapeutic approaches to ED and BPH

Michael O'Leary, Harvard Med. Sch.

Use of PDE5 inhibitors in indications other than ED and BPH

Ian Eardley, Leeds Royal Infirmary

Student/Postdoc Best Abstract Competition

Westin Boston Waterfront, Grand Ballroom AB; 6:30 PM – 8:30 PM

ASPET/BPS Student & Postdoc Mixer

Westin Boston Waterfront, Harbor Ballroom I; 9:00 PM – 11:30 PM

Monday, April 22

JOHN J. ABEL AWARD LECTURE

Boston Convention Center, Room 107C; 8:30 AM – 9:20 AM

Arthur Christopoulos, Monash Univ.

Reciprocal relationships: The yin and yang of GPCR allostery

Introduction: Stephen Lanier, Med. Univ. of South Carolina

Advancing discoveries from the academic laboratory to the market

Boston Convention Center, Room 106; 9:30 AM – Noon

Sponsored by the Divisions for Drug Discovery and Development & Pharmacology Education

Chair: Robert Leadley, Schoolcraft Col.

As pharmaceutical companies continue to merge and downsize their basic research efforts in many therapeutic areas, there is an increasing need and interest for academic investigators to think entrepreneurially about their discoveries. This symposium will help guide investigators through the various steps leading to commercialization of their research by covering topics such as intellectual property protection, private and public funding opportunities, regulatory requirements, and the steps required to move a discovery out of the lab and into the marketplace.

Intellectual property protection: What, when, and how to protect and share your discovery

Weston Gould

Regulatory hurdles from bench to bedside

Ronald L. Dundore, InfaCare Pharmaceut. Corp.

What to know when working with Technology Transfer Offices

Ronald J. Shebuski, Cardiovascular Research Consulting, LLC

Licensing: Do you have what they really want?

Chris Vlahos, Lilly Res. Labs.

Novel dynamics of cAMP: Towards new therapeutic interventions through compartmentalized signaling networks

Boston Convention Center, Room 107AB; 9:30 AM – Noon

Sponsored by the British Pharmacological Society & the ASPET Division for Molecular Pharmacology

Chair: Martina Schmidt, Univ. of Groningen and Marc Peters-Golden, Univ. of Michigan Med. Sch.

The discovery of cAMP transformed the understanding of cellular regulation by providing not only the second messenger concept, but also the discovery of G proteins, G protein-coupled receptors (GPCRs), and the conceptual roots of compartmentalized signaling. Spatiotemporal dynamics in the subcellular distribution of cAMP signaling networks likely determine the net outcome of cAMP in chronic disorders. This session will explore the spatiotemporal dynamics of compartmentalized cAMP signaling and the roles of adenylyl cyclases, A-kinase anchoring proteins, G protein-coupled receptors, and protein kinase A as possible drug discovery targets.

Cyclic nucleotide signaling in subcellular compartments

Manuela Zaccolo, Univ. of Oxford, Balliol Col.

Adenylyl cyclase as orchestrators of cAMP microdomains

Dermot M.F. Cooper, Univ. of Cambridge

Cell signalling in space and time

John. D. Scott, Univ. of Washington

Higher order protein complexes and phospholipid interactions in GPCR signaling

John Tesmer, Univ. of Michigan

Dysregulation of cAMP networks in fibrotic lung disease

Marc Peters-Golden, Univ. of Michigan Med. Sch.

Developing Pharmacological Probes Targeting exchange protein directly activated by cAMP

Junior Speaker: Xiaodong Cheng, Univ. of Texas Medical Branch

Modulation of the cAMP pathway by Pseudomonas aeruginosa quorum sensing molecules

Junior Speaker: Leigh Stoddart, Univ. of Nottingham Med. Sch.

New kids on the block: Organic cation transporters and plasma membrane monoamine transporter in neurodegenerative, psychiatric and addictive disorders

Boston Convention Center, Room 107C; 9:30 AM – Noon

Sponsored by the Divisions for Neuropharmacology; Drug Metabolism; Integrative Systems, Translational and Clinical Pharmacology; Molecular Pharmacology; & Toxicology

Chair: Lynnette C. Daws, Univ. of Texas Hlth. Sci. Ctr. at San Antonio

In addition to the traditional high affinity transporters for biogenic amines which are the targets for many CNS drugs, organic cation transporters and plasma membrane monoamine transporters have been recently discovered to transport biogenic amines in the brain as well. This symposium will address the significant role of these “newer” transporters in regulation of biogenic amine neurotransmission as it relates to their

- 1) distribution and cellular location in brain;
- 2) ability to transport biogenic amines, even in the presence of the high-affinity transporters for these neurotransmitters;
- 3) neuroprotective actions;
- 4) sensitivity to regulation by corticosterone and stress and implications for drug abuse and psychiatric disease; and
- 5) potential as targets for the development of improved therapeutics to treat psychiatric, addictive and neurodegenerative disorders.

Plasma membrane monoamine transporter: Structure, function, and therapeutic potential for mental illness

Joanne Wang, Univ. of Washington

Neurotoxicity in animal models of Parkinson's disease is mediated by the organic cation transporter-3

Kim Tieu, Plymouth Univ., Peninsula Sch. of Med. and Dent.

Organic cation transporters and the plasma membrane monoamine transporter: Uncovering novel targets to treat depression

Lynette C. Daws, Univ. of Texas Hlth. Sci. Ctr. at San Antonio

Role of organic cation transporter-3 in stress effects on cocaine reinstatement

Paul J. Gasser, Marquette Univ.

Impaired monoamine and organic cation uptake in choroid plexus in mice with targeted disruption of the plasma membrane monoamine transporter (Slc29a4) gene

Junior Speaker: Haichuan Duan, Univ. of Washington

Role of the coagulation cascade in tissue injury and disease

Boston Convention Center, Room 108; 9:30 AM – Noon

Sponsored by the Divisions for Toxicology & Integrative Systems, Translational and Clinical Pharmacology

Chair: James P. Luyendyk, Michigan State Univ.

The coagulation cascade comprises a highly regulated network of serine proteases terminating in the generation of the enzyme thrombin. Exposures spanning hepatotoxic drugs to inhaled particles have been shown to cause activation of the coagulation cascade, and coagulation cascade activation is now believed to not merely be the consequence of tissue injury, but a critical mechanism of disease progression and toxicological response. This session will explore various components of the coagulation cascade and the role they play in staph infection, ischemia/reperfusion kidney injury, nephrotoxicity, heart failure and liver disease.

Host prothrombin and fibrinogen are critical determinants of pathogen toxicity and host tissue damage following S. aureus infection

Matthew J. Flick, Cincinnati Children's Hosp.

Fibrinogen: A biomarker and therapeutic candidate in kidney damage

Vishal S. Vaidya, Harvard Med. Sch.

Contribution of coagulation proteases to the vascular inflammation in sickle cell disease

Rafal Pawlinski, UNC, Chapel Hill

Liver let die: Coagulation decides

James Luyendyk, Michigan State Univ.

Fatty acid activation of G protein-coupled receptors: Basic and clinical perspectives

Boston Convention Center, Room 109A; 9:30 AM – Noon

ASPET gratefully acknowledges the educational grants from the Institut de Recherches Servier and Janssen Research & Development, LLC for supporting this symposium.

Sponsored by the ASPET Division for Molecular Pharmacology

Chairs: Graeme Milligan, Univ. of Glasgow and Celia Briscoe, Janssen

This session will review what is known about the expression, function and regulation of members of the G protein-coupled receptor family shown to be receptors for free fatty acids. The speakers will also address the pharmacology and mode of binding, both orthosteric and allosteric, of selected ligands, the state of validation of each receptor as a potential therapeutic target and the progress to date of translating the basic molecular knowledge of these receptors into clinically useful drugs.

Overview of the free fatty acid receptor family and the enigma of GPR120

Celia Briscoe, Janssen

Developing novel ligands for free fatty acid receptors

Graeme Milligan, Univ. of Glasgow

GPR40 as a potential target for the treatment of type 2 diabetes

Vincent Poitout, Univ. of Montreal

GLPG0974, a selective FFA2 antagonist: a promising approach for treatment of neutrophil driven disorders?

Johan Beetens, Galapagos NV

Phosphorylation and internalization of short splicing variant of the omega 3 fatty acid sensor, GPR120

Junior Speaker: Omar Sanchez-Reyes, Universidad Nacional Autónoma de México

Canadian Society for Pharmacology & Therapeutics (CSPT) Trainee Oral Presentations

Boston Convention Center, Room 109B; 9:30 AM – 12:00 PM

Chair: Fiona Parkinson, CSPT

Introduction

Fiona Parkinson, CSPT

Pharmacogenomics of vincristine-induced neurotoxicity in pediatric cancer patients

Ursula Amstutz, Univ. of British Columbia

Characterization of the vascular phenotype of the equilibrative nucleoside transporter 1 knockout mouse

K. Arielle Best, Western Univ.

Genetic and clinical determinants of CYP3A4 activity in patients using 4 β -hydroxycholesterol as an in vivo probe

Inna Ying Gong, Western Univ.

Tricyclic compounds inhibit the OATP1A2 transporter

Jennifer Lu, Univ. of Montreal

Therapeutic use of eNOS/Caveolin-1 antagonistic peptides for endothelial dysfunction and atherogenesis

Arpeeta Sharma, Univ. of British Columbia

Pharmacogenetics of warfarin safety and effectiveness in children

Kaitlyn Shaw, Univ. of British Columbia

Decreased nuclear receptor activity mediates downregulation of drug metabolizing enzymes in chronic kidney disease through epigenetic modulation

Thomas Velenosi, Western Univ.

Surgery-induced inflammation reduces morphine distribution into cerebrospinal fluid

Yan Wang, Dalhousie Univ.

CANADIAN SOCIETY FOR PHARMACOLOGY AND THERAPEUTICS AWARD RECIPIENT LECTURES

Boston Convention Center, Room 109B; 1:30 PM – 4:30 PM

Chair: Fiona Parkinson, CSPT

Senior Investigator Award Recipient

Rachel Tyndale, Univ. of Toronto, Toronto

Piafsky Young Investigator Award Recipient

Bernard Le Foll, Univ. of Toronto, Toronto

Distinguished Service and Education Award

Jean Gray, Halifax, Nova Scotia

DRUG METABOLISM DIVISION EARLY CAREER ACHIEVEMENT AWARD LECTURE

Boston Convention Center, Room 108; 2:00 PM – 2:50 PM

Nina Isoherranen, Univ. of Washington

The biochemistry and clinical significance of CYP26 enzymes in regulating retinoic acid homeostasis

Introduction: Ken Thummel, Univ. of Washington

Drug Metabolism Division James Gillette Award & Platform Session

Boston Convention Center, Room 108; 3:00 PM – 5:30 PM

Impact of development and genetic variation on human hepatic CYP2B6 expression and activity

Andrea Gaedigk, Children's Mercy Hospital & Clinics

Differences in the catalytic properties of CYP2B6s between common marmoset and human

Shizuo Narimatsu, Okayama Univ

The effect of obesity and development on in vitro hepatic metabolism

Gina Danielson, Univ. of Minnesota

Transport by OATP1B1 and OATP1B3 enhances cytotoxicity of EGCG and certain substituted quercetins

Yuchen Zhang, Univ. of Kansas Med. Ctr.

Evidence for epigenetic regulation of UGT1A1 protein expression and activity in healthy human livers

Umit Yasar, Tufts Univ. Sch. of Med.

Active site gating controls substrate selectivity in cytosolic sulfotransferases A and spinophilin

Ian Cook, Albert Einstein Col. of Med.

James Gillette Best Paper Award: The Role of FcRn in the disposition, metabolism and pharmacokinetics of soluble non-crosslinking immune complexes

Hamsell Alvarez, Merck Res. Labs.

James Gillette Best Paper Award: Vitamin D receptor activation enhances Benzo[a]pyrene metabolism via CYP1A1 expression in macrophages

Presenting Author: Shigeyuki Uno Nihon Univ. Sch. of Med.

Neuropharmacology Division Postdoctoral Scientist Award Finalists

Boston Convention Center, Room 106; 3:00 PM – 5:30 PM

Keynote Speaker: Lakshmi Devi, Mount Sinai Sch. of Med.

Cannabinoid 1 receptor as therapeutic target in preventing chronic epilepsy

Robert Di Maio, Univ. of Pittsburgh

Dimerization of G-protein coupled Receptors (GPCRs) in Appetite Regulation and Food Reward

Harriet Schellekens, Univ. Col. Cork Sch. of Pharmacy

GPR158 and GPR179: a subfamily of orphan GPCRs as a new class of G protein signaling modulators

Cesare Orlandi, Scripps Res. Inst.

Increased plasma ammonia concentration contributes to methamphetamine-induced blood-brain barrier damage

Nicole A. Northrop, Univ. of Toledo Col. of Med.

Amphetamine and methamphetamine differentially regulate biophysical properties of dopamine transporter

Kaustuv Saha, Univ. of Florida

Cross-talk between beta and alpha2 adrenergic receptors in sympathetic neurons relies on protein kinase A and spinophilin

Christopher M. Cottingham, Univ. of Alabama at Birmingham

Keynote Address: How to do big science on a modest budget: lessons from deorphanizing a G protein-coupled receptor

Lakshmi Devi, Mount Sinai Sch. of Med.

Molecular Pharmacology Division Postdoctoral Award Finalists

Boston Convention Center, Room 107AB; 3:00 PM – 5:30 PM

Keynote Speaker: Brian Kobilka, Stanford Univ. Sch. of Med.

Identification of substituted benzazepines as functionally selective ligands of the D1 dopamine receptor

Jennie Conroy, NINDS/NIH

Development of a membrane anchored chemerin receptor agonist as a novel modulator of inflammation

Jamie Doyle, Tufts Medical Center

Non-Canonical Signaling by GPCR-Arrestin-G β γ Ternary Complexes

Vanessa Wehbi, Univ. of Pittsburgh Sch. of Med.

Keynote Address: Probing G protein coupled receptors: a few of my favorite experiments

Brian Kobilka, Stanford Univ. Sch. of Med.

Drug Discovery and Development Symposium: Gliobiology: emerging concepts in neural-glia interactions in chronic disease

Boston Convention Center, Room 107C; 3:00 PM – 5:30 PM

Chair: Michael F. Jarvis, AbbVie

Reciprocal interactions between motor neurons and surrounding astrocytes in ALS

John Weiss, Univ. of California, Irvine Sch. of Med.

Spinal cord neural-glia interactions in chronic pain

Ru-Rong Ji, Duke Univ. Med. Ctr.

Regulation of myelination by action potentials and an introduction to neuron-glia interactions

R. Douglas Fields, NICHD/NIH

Regeneration-related axon and Schwann cell interactions

Doug Zochodne, Univ. of Calgary

Spinal cord neural-glia interactions in chronic pain

Anindya Bhattacharya, Janssen Pharmaceut. Co. of Johnson & Johnson

Local Ca²⁺ signals in the endothelium: Key regulators of vascular function and dysfunction

Boston Convention Center, Room 109A; 3:00 PM – 5:30 PM

Sponsored by the Division for Cardiovascular Pharmacology

Chairs: Mark T. Nelson, Univ. of Vermont and Robert M. Bryan, Jr., Baylor Col. of Med.

Endothelial cell Ca²⁺ is broadly accepted as a key regulator of endothelial cell-dependent dilation of small arteries. Recent studies using sophisticated Ca²⁺ imaging techniques have shown that endothelial cells experience local changes in Ca²⁺ under physiological conditions, the frequency and nature of which determine their effect on endothelial cell function. This session will focus on localized endothelial cell Ca²⁺ signals mediated by two pathways: Ca²⁺ influx through Transient Receptor Potential (TRP) channels and inositol trisphosphate (IP₃)-mediated Ca²⁺ release from intracellular stores. Understanding these Ca²⁺ signaling mechanisms in the endothelium is a critical first step in identifying the cause for endothelial cell dysfunction in vascular disorders such as hypertension.

Conducted vasodilation in resistance arteries: Ca²⁺ signaling between endothelial cells

Steven S. Segal, Univ. of Missouri

TRPA1-induced endothelial calcium signals and vasodilation

Scott Early, Colorado State Univ.

Differential regulation of SK and IK channels during endothelium dependent hyperpolarization

Kim A. Dora, Univ. of Oxford

Elementary TRPV4 Ca²⁺ signals regulate endothelium dependent vasodilation

Swapnil K. Sonkusare, Univ. of Vermont

Endothelial Ca²⁺ wavelets and myoendothelial feedback

Donald G. Welsh, Univ. of Calgary

Alteration of endothelial CaMKII in AngII-induced hypertensive mice

Junior Speaker: Chimene Charbel, Montreal Heart Inst.

Behavioral Pharmacology and Neuropharmacology Divisions Joint Mixer

Westin Boston Waterfront, Grand Ballroom D; 6:00 PM – 8:00 PM

Molecular Pharmacology Division Business Meeting and Mixer

Westin Boston Waterfront, Burroughs; 7:00 PM – 9:00 PM

Pharmacology Education, Drug Discovery and Development, & Integrative Systems, Translational and Clinical Pharmacology Divisions Joint Mixer

Westin Boston Waterfront, Carlton; 7:30 PM – 9:30 PM

Y.E.S. Young Experimental Scientist Mixer

Westin Boston Waterfront, Galleria; 9:00 PM – 11:00 PM

*21 & older must have ID to receive drink tickets

Tuesday, April 23

WiP into Shape Networking Walk

Westin Boston Waterfront Hotel, 7:00 AM – 9:00 AM. Meet at the concierge desk.

Pharmacology Education Division Program: The future of Ph.D. education in biomedicine: U.S. and European perspectives

Westin Boston Waterfront Hotel, Grand Ballroom E; 9:30 AM – Noon

Chair: Jane A. Mitchell, Imperial Col. London

PhD training in the USA: present and future

Joey V. Barnett, Vanderbilt Univ. Med. Ctr.

PhD education in the UK: why change?

Nick J. Goulding, Barts and the London Sch. of Med. and Dentistry

Standards of PhD education: the ORPHEUS perspective

Michael Mulvany, Aarhus Univ. Graduate Sch. of Hlth. Scie., Denmark

Research funder perspective: PhD graduate attributes – future needs

Alison Hall, NIGMS/NIH

Roundtable discussion

Acetaminophen induced hepatotoxicity: Lessons learned during the last four decades investigating mechanisms of toxicity

Boston Convention Center, Room 106; 9:30 AM – Noon

Sponsored by the Divisions for Toxicology; Drug Discovery and Development; Drug Metabolism; & Pharmacology Education

Chairs: José E. Manautou, Univ. of Connecticut and Hartmut Jaeschke, Univ. of Kansas Med. Ctr.

2013 marks the 40th anniversary of the publication of the pioneering work of Brodie and co-workers in the Journal of Pharmacology and Experimental Therapeutics demonstrating the role of drug metabolism and protein covalent binding in acetaminophen-induced hepatotoxicity. While this work paved the way for toxicological investigations aimed at elucidating the mechanism of acetaminophen toxicity, the precise mechanism of liver toxicity has eluded investigators. This session will highlight what is known 40 years after the initial publication of Brodie's paper, including the role of biotransformation, the role of mitochondria and oxidant stress, the hepatoprotective effects of Vanin-1, the use of acetaminophen plasma protein adducts as diagnostic markers in acetaminophen-induced hepatotoxicity.

Acetaminophen biotransformation and reactive intermediate toxicity: How did we get here?

Steven Cohen, Massachusetts Col. of Pharm. and Hlth. Sci.

Mitochondria – oxidant stress and other signaling events associated with acetaminophen hepatotoxicity in mice and humans

Hartmut Jaeschke, Univ. of Kansas Med. Ctr.

Role of Vanin-1 in acetaminophen hepatotoxicity: Regulation of thiol homeostasis and immune response to liver injury

José E. Manautou, Univ. of Connecticut

Acetaminophen plasma protein adducts: Diagnostic markers and disease mechanisms in mice and humans

Laura James, Univ. of Arkansas for Med. Sci.

Induction of neuronal nitric oxide synthase (nNOS) in livers of mice treated with toxic doses of acetaminophen

Junior Speaker: Rakhee Agarwal, Univ. of Arkansas for Med. Sci.

A "reductionist" approach to cardiovascular disease: Inorganic nitrate to nitrite to NO

Boston Convention Center, Room 107AB; 9:30 AM – Noon

Sponsored by the British Pharmacological Society

Chairs: Amrita Ahluwalia, Queen Mary Univ. and David Lefer, Emory Univ. Sch. of Med.

While previously considered inactive oxidative metabolites of endogenous nitric oxide (NO) synthesis, inorganic nitrate and nitrite are now known to be reduced back to NO to provide an alternative source of NO under certain conditions. There is growing evidence that this pathway can act as a rescue pathway in situations where the normal healthy endogenous synthesis of NO has been compromised. This session will discuss the therapeutic potential of this pathway and the clinical studies that have translated much of the basic science into therapeutics.

Inorganic nitrite—a metabolite with a mission!

Mark Gladwin, Vascular Medicine Inst.

Nitrite therapy in heart failure: Mechanisms and therapeutic potential

David Lefer, Emory Univ. Sch. of Med.

The red blood cell nitrite reductase: A therapeutic target in hypertension

Amrita Ahluwalia, Queen Mary Univ. of London

Dietary nitrate/nitrite and pulmonary hypertension

Reshma Baliga, Barts & The London Med. Sch., London

Purinergic transmission in visceral function and sensation

Boston Convention Center, Room 107C; 9:30 AM – Noon

Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology & Molecular Pharmacology

Chairs: James J. Galligan, Michigan State Univ., Hamid Akbarali, Virginia Commonwealth Univ.

Purines are primary neurotransmitters controlling GI motility, secretion and blood flow as well as contributing to control of bladder sensation and function. They also play an important role in visceral sensation and pain mechanisms. This session explores in detail the various aspects of purine function with a focus on the development of new therapeutic approaches to modulating purine mechanisms as a strategy to treat GI and bladder functional disorders.

Multiple purinergic neurotransmitters in the abdominal viscera

Violeta Mutafova-Yambolieva, Univ. of Nevada

Purinergic control of gastrointestinal secretion

Fivos Christofi, Ohio State Univ.

Purinergic synaptic transmission in the enteric nervous system and control of gut motility

James J. Galligan, Michigan State Univ.

Purinergic signaling in visceral pain mechanisms

Christopher Keating, Univ. of Sheffield

Voltage-gated ion channel blockers as potential analgesic agents

Boston Convention Center, Room 108; 9:30 AM – Noon

Sponsored by the Divisions for Drug Discovery and Development & Neuropharmacology

Chair: Michael F. Jarvis, AbbVie

Voltage-gated ion channels play an integral role in the regulation of membrane ion conductance, neurotransmitter release, and cellular excitability in neurons. Several nonselective sodium channel blocking drugs have reduced chronic pain in human trials. Recently discovered gain and loss of function mutations of one particular sodium channel isoform implicate this channel as a modulator of nociceptive sensitivity. Inhibition of low-voltage activated (T-type) and high-voltage active (N type) calcium channels leads to analgesia through modulation of neuronal membrane excitability and neurotransmitter release. These results will be discussed in the context of developing new small molecule channel modulators as potential analgesic agents lacking the addictive and analgesic tolerance potential of opioids.

Structure and function of voltage-gated sodium channels at atomic level

William A. Catterall, Univ. of Washington

Chasing men on fire: Sodium channels and pain

Steve Waxman, Yale Univ. Sch. of Med.

Novel means of targeting T-type calcium channels to treat pain

Gerald Zamponi, Univ. of Calgary

Antinociceptive pharmacology of small molecule sodium channel blockers

Michael F. Jarvis, Abbott Labs.

Discovery and early clinical development of potent and selective small molecule Cav2.2 calcium channel blockers

Simon Tate, Convergence Pharmaceut.

Transcription factors as therapeutic drug targets

Boston Convention Center, Room 109A; 9:30 AM – Noon

Sponsored by the Divisions for Molecular Pharmacology; Drug Discovery and Development; & Toxicology

Chairs: Theresa M. Filtz, Oregon State Univ. Col. of Pharmacy and Mark Leid, Oregon State Univ. Col. of Pharmacy

Transcription factors are the proximal regulators of gene expression that control the nature of a cell — what type of cell it is, what it can become, how it responds — as well as the regulators of aberrant responses, growth and proliferation in diseases as varying as neoplastic transformation to cardiac hypertrophy to insulin resistance. Targeting transcription factors in disease should provide a highly selective means to manipulate cell response, function, growth and proliferation, but in general, transcription factors are considered to be difficult drug targets. The discovery that nuclear hormone receptors respond to endogenous small molecules has led to the realization that it might be possible to target transcription factors with small molecules. This session explores varying approaches in interrupting or mimicking the protein-protein and protein-DNA interactions that underlie the basic activity of transcription factor proteins.

Regulating the regulators: Transcription factor control by post-translational modification

Mark Leid, Oregon State Univ.

Activation of p53 tumor suppression by MDM2 antagonists

Lyubomir T. Vassilev, Hoffmann-La Roche, Inc.

Small molecule transcriptional modulators: Structure and mechanism

Anna Mapp, Univ. of Michigan

Synthetic strategies for targeting protein-protein interactions

Paramjit Arora, New York Univ.

Therapeutic applications of zinc finger nucleases

Edward Rebar, Sangamo BioSciences, Inc.

Canadian Society for Pharmacology & Therapeutics (CSPT): Practical Pharmacology

Boston Convention Center, Room 109B; 9:30 AM – 11:30 AM

Chair: Richard B. Kim

CSPT: Women and Pregnancy: Safety, Efficacy, Ethics and Research Needs in Pharmacology

Boston Convention Center, Room 109B; 1:00 PM – 5:00 PM

Chair: David Knoppert, Children's Hlth. Res.Inst., London, Ont.

Opening remarks

David Knoppert, Children's Hlth. Res.Inst., London, Ont.

Pharmacokinetics and gender differences

Donald R. Mattison, Risk Sci. Intl.

Impact of Pregnancy on maternal pharmacokinetics of medications

Mary F. Hébert, Univ. of Washington

Pharmacokinetics and Bioequivalence – evaluating the risks

Gideon Koren, Univ. of Toronto

Gender barriers in policy and regulation

Martha Nolan, Society for Women's Hlth. Res.

Removing risks to prescribing in pregnancy: next steps in research and regulation. Panel discussion

Moderated by Donald R. Mattison, Risk Sci. Intl.

Closing remarks

David Knoppert, Children's Hlth. Res.Inst., London, Ont.

Cardiovascular Pharmacology Division Trainee Showcase

Boston Convention Center, Room 107AB; 2:30 PM – 4:30 PM

Sestrin2 is cardioprotective against ischemia/reperfusion injury by promoting LKB1-mediated AMPK activation

Alexander Morrison-Nozik, Univ. at Buffalo (SUNY)

Pregnane X receptor mediates dyslipidemia Induced by the HIV protease inhibitor amprenavir in mice

Robert Helsley, Univ. of Kentucky

Heterogeneity of ATP-sensitive K⁺ channels in cardiac myocytes: Enrichment at the intercalated disk

Miyoun Hong, New York Univ. Sch. of Med.

Genetic deletion of the TRPC3 channel blunts the development of angiotensin II-induced hypertension in mice

Asif Pathan, Univ. of Arkansas for Med. Sciences

Angiotensin II receptor blockade, but not ACE inhibition, reduces nocturnal hypertesion and natriuresis in autonomic failure patients with low renin activity

Amy Arnold, Vanderbilt Univ.

Aged eNOS^{-/-} mice display increased APP expression, microglial activation, and impaired spatial memory

Susan Austin, Mayo Clinic

BENEDICT R. LUCCHESI DISTINGUISHED AWARD LECTURE IN CARDIAC PHARMACOLOGY

Boston Convention Center, Room 107AB; 4:30 PM – 5:30 PM

Andre Terzic, Mayo Clinic

Regenerative cardiac pharmacology: The next frontier

Introduction: Nancy Rusch, Univ. of Arkansas for Med. Sci.

Negative symptoms of schizophrenia: Neuronal circuit, translation and future directions

Boston Convention Center, Room 106; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Drug Discovery and Development; Behavioral Pharmacology; & Neuropharmacology

Chairs: Ruggero Galici, Bristol-Myers Squibb and Leslie Jacobsen, Bristol-Myers Squibb

Negative symptoms are a primary cause of disability in schizophrenia, comprising restricted affect, lack of motivation and asociality. These diverse symptoms are not fully explained by the current understanding of the pathophysiology of schizophrenia. This session will bring together preclinical and clinical scientists to summarize the current knowledge on negative symptoms of schizophrenia and to discuss promising treatments and future directors for translational assays and model development.

Negative symptoms: Clinical features and prospects for treatment

Brian Kirkpatrick, Scott & White Healthcare

Emotion and motivation deficits in schizophrenia: The behavioral and neural substrates of negative symptom

Ann Kring, Univ. of California, Berkeley

Pharmacotherapies for negative symptoms of schizophrenia

Leslie Jacobsen, Bristol-Myers Squibb

Modeling negative symptoms of schizophrenia in animals

Athina Markou, UCSD

Integrative Systems, Translational and Clinical Pharmacology Division Hot Topics: A (r)evolution in drug discovery & therapy: From organs on a chip and 3D biomimetics to regenerative pharmacology

Boston Convention Center, Room 107C; 3:00 PM – 5:30 PM

Chairs: George J. Christ, Wake Forest Sch. of Med. and Sitta Sittampalam, NIH Ctr. for Translational Therapeutics

Rapid fabrication of architecturally-correct human tissues in vitro by 3D bioprinting: Function follows form

Sharon Presnell, Organovo Inc.

Microscale engineering of tissues and organs

Linda Griffin, MIT

Human Organs-on-Chips

Don Ingber, Harvard Med Sch/Children's Hosp

Silk: A multifunctional biomaterial with applications for controlled drug delivery, tissue repair and engineering 3D tissues

D. Kaplan, Tufts Univ.

Toxicology Division Symposium: The mitochondrion as a toxicological and pharmacological target

Boston Convention Center, Room 108; 3:00 PM – 5:30 PM

Chair: Rick G. Schnellmann, Med. Univ. of South Carolina

New methods to identify changes in mitochondrial function

Craig C. Beeson, Med. Univ. of South Carolina

MitoQ and prevention of mitochondrial dysfunction

Victor Darley-Usmar, Univ. of Alabama, Birmingham

Mitochondrial etiology of Alzheimer's and Parkinson's disease

Douglas C. Wallace, Children's Hosp. of Pennsylvania

Drugs that target mitochondrial biogenesis accelerate the recovery of cellular and organ function

Rick G. Schnellmann, Med. Univ. of South Carolina

Behavioral Pharmacology Division Symposium: The opioid-cannabinoid connection: A translational, behavioral perspective

Boston Convention Center, Room 109A; 3:00 PM – 5:30 PM

Chairs: Margaret Haney, Columbia Univ. Col. of Physicians and Surgeons and Ziva D. Cooper, Columbia Univ. Col. of Physicians and Surgeons

The endogenous cannabinoid system: an emerging target to treat opioid and cannabinoid dependence

Aron H. Lichtman, Virginia Commonwealth Univ.

Pharmacological and neurobiological studies investigating opioid and endocannabinoid interactions in rodent models of stress-induced analgesia

David Finn, Natl. Univ. of Ireland, Galway

Pharmacological evidence for opioid modulation of the reinforcing effects of CB1 receptor agonists in non-human primates

Zuzana Justinova, NIDA, IRP, NIH

Naltrexone alters marijuana's analgesic and intoxicating effects in daily marijuana smokers

Ziva D. Cooper, Columbia Univ. Col. of Physicians and Surgeons

The potential clinical efficacy of cannabinoid agonists in treating opioid-dependent patients

Adam Bisaga, NYS Psychiatric Inst.

Cardiovascular Pharmacology Division Mixer

Westin Boston Waterfront, Grand Ballroom D; 6:00 PM – 8:00 PM

Drug Metabolism and Toxicology Divisions Joint Mixer

Westin Boston Waterfront, Commonwealth Ballroom A; 7:00 PM – 9:00 PM

Wednesday, April 24

NORMAN WEINER LECTURE

Boston Convention Center, Room 107C; 8:30 AM – 9:20 AM

David E. Clapham, Boston Children's Hospital, HHMI, Harvard Med. Sch.

Novel ion channels and their regulation

Introduction: Andre Terzic, Mayo Clinic

Apolipoprotein E: A protein at the intersection of vascular and neurodegenerative disease biology

Boston Convention Center, Room 106; 9:30 AM – Noon

Sponsored by the Divisions for Neuropharmacology & Cardiovascular Pharmacology

Chairs: Cheryl Wellington, Univ. of British Columbia and Michael Wood, AstraZeneca Pharmaceuticals

Apolipoprotein E (ApoE) isoform variability has been identified as an important risk factor of Alzheimer's disease and as well as shown to influence the risk of cardiovascular disease. ApoE is a multifunctional and polymorphic protein synthesized and secreted by liver, brain, and tissue macrophages. The molecular mechanisms underlying ApoE as a risk factor for disease remain largely unknown. This program will examine evidence for potential ApoE involvement in several disease settings, including atherosclerosis, restenosis, Alzheimer's disease, and traumatic brain injury. A roundtable discussion will conclude the session by examining how the current knowledge of ApoE disease biology can be exploited in the search for new drugs to treat these disorders.

Molecular basis for differential effects of apolipoprotein E isoforms on lipoprotein metabolism

Michael C. Phillips, Univ. of Pennsylvania Sch. of Med.

Vascular contributions to the pathogenesis of Alzheimer's disease

Richard Mayeux, Columbia Univ. Med. Ctr.

ApoE isoform-specific ApoE/A β complex levels: potential mechanism(s) for AD risk, novel AD biomarker and therapeutic target

Mary Jo LaDu, Univ. of Illinois at Chicago

From concussion to dementia: A key role for apolipoprotein E in the central nervous system

Cheryl Wellington, Univ. of British Columbia

Roundtable Discussion

Michael Wood, AstraZeneca Pharmaceuticals

The 5-HT_{2C} receptor: A new target for multiple therapeutics

Boston Convention Center, Room 109B; 9:30 AM – Noon

Sponsored by the British Pharmacological Society and the ASPET Divisions for Molecular Pharmacology & Neuropharmacology

Chair: Lora Heisler, Univ. of Cambridge

The 5-HT_{2C} receptor is implicated in a wide variety of behaviors and physiological processes via action in the CNS. 5-HT_{2C} receptor activation provides a tonic influence over the release of various neurotransmitters and neuropeptides and has been implicated in depression, anxiety, schizophrenia, reward, glucose homeostasis, and energy balance, to name a few. With the advent of more advanced genetic technology and more selective 5-HT_{2C} receptor compounds, a greater understanding of the functional role and potential therapeutic application of the 5-HT_{2C} receptor has begun to be realized. This session will look at insights into the 5-HT_{2C} receptor, that allow for a better understanding of their potential for the treatment of a number of prevalent conditions, including depression, obsessive-compulsive disorder, schizophrenia, drug addiction, obesity and type 2 diabetes.

A bioinformatics approach to 5-HT_{2C} receptor modulation of behavioral patterns

Laurence Tecott, UCSF

The effect of Htr2c post-transcriptional modification on 5-HT_{2C} receptor regulated behaviour

Anthony Isles, Cardiff Univ. Sch. of Med.

A novel treatment for obesity: The 5-HT_{2C} receptor agonist lorcaserin

Steven Smith, Sanford-Burnham Med. Res. Inst.

5-HT_{2C} receptor agonists: A mechanistically new target for type 2 diabetes treatment

Lora Heisler, Univ. of Cambridge

5-HT_{2C} Receptor agonist anorectic efficacy potentiated by 5-HT_{1B} Receptor agonist co-application; an effect mediated via augmented pro-opiomelanocortin neuron activation

Junior Speaker: Barbara Doslikova, Univ. of Cambridge

New roles for signaling by G protein beta/gamma subunits

Boston Convention Center, Room 107C; 9:30 AM – Noon

Sponsored by the Divisions for Molecular Pharmacology; Cardiovascular Pharmacology; & Neuropharmacology

Chair: Alan Smrcka, Univ. of Rochester Sch. of Med.

Heterotrimeric G protein beta/gamma subunits were discovered more than 30 years ago as essential components of the GPCR signal transduction machinery. More current studies have shown that instead of (in addition to) serving a scaffolding role, these components of the GPCR complex also play an important role in downstream signaling, implying a potential role as therapeutic targets. This session will explore their potential role in development, angiogenesis, parkinsonism, inflammation, heart failure, subcellular signaling, and neural circuitry.

Pharmacological targeting of Gbg subunits: Mechanisms and outcomes

Alan Smrcka, Univ. of Rochester Sch. of Med.

Translocation of Gbetagamma subunits to subcellular compartments

N. Gautam, Washington Univ. Sch. of Med.

Distinct roles for individual G bg isoforms in neurological signaling circuits

Janet Robishaw, Weis Ctr. for Res.

Scaffolding of Gbg by WD40 repeat proteins

Songhai Chen, Univ. of Iowa

G protein betagamma subunits in regulating trafficking and assembly of signaling complexes

Terry Hébert, McGill Univ.

Pharmacological enhancement of wakefulness

Boston Convention Center, Room 107B; 9:30 AM – Noon

Sponsored by the Divisions for Behavioral Pharmacology; Integrative Systems, Translational and Clinical Pharmacology; & Neuropharmacology

Chair: Jeff Witkin, Eli Lilly and Co.

This symposium will investigate the clinical need for wake promoting agents for the treatment of sleep apnea, shift work and other conditions of fatigue. Both the pharmacological mechanisms that can impact wakefulness, cognitive augmentation, and their side effects, and new pharmacological mechanisms underlying wake-promoting neurobiology will be addressed.

Introduction to wake promotion

Dale M. Edgar, Eli Lilly and Co.

Physiological control systems for wakefulness

Luis De Lecea, Stanford Univ.

Modafanil (Provigil) as a wake-promoting agent

Jeff Vaught, Former CSO/Executive VP Cephalon

Histamine H₃ Receptor Inverse Agonism

Jean-Charles Schwartz, Bioprojet

Metabotropic glutamate receptors as targets for wake promotion

Keith A. Wafford, Eli Lilly and Co.

Signals activating pancreatic stem cells and beta cell regeneration

Boston Convention Center, Room 108; 9:30 AM – Noon

Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology & Molecular Pharmacology

Chair: Thomas M. Wilkie, UT Southwestern Med. Ctr. at Dallas

Complex physiology drives beta cell expansion in diabetes and pregnancy. Recent discoveries demonstrate the integration of metabolic cues, neural processing and efferent signaling involved in the stimulation of beta cell expansion in diabetes. This session will explore the use of pregnancy as a model for the hormonal stimulation of beta cell expansion, hypothalamic control of islet cell function, the role of RGS proteins in the pancreas as biomarkers of beta cell expansion, and the use of stem cells as human beta cell progenitors.

Integrated pathways for type 2 diabetes from mouse genetics and genomics

Alan Attie, Univ. of Wisconsin

Small molecule screens in beta cell lines for beta cell expansion

Bridget Wagner, Broad Inst. of Harvard & MIT

Mapping the specific neuronal connections between the central nervous system and the endocrine pancreas

Christopher J. Rhodes, Univ. of Chicago

hESCs and iPSCs differentiation to pancreatic endocrine lineage

Shuibing Chen, Weill Cornell Med. Col.

The pharmacology of natural products

Boston Convention Center, Room 109A; 9:30 AM – Noon

Sponsored by the Divisions for Behavioral Pharmacology; Drug Discovery and Development; Drug Metabolism; Integrative Systems, Translational and Clinical Pharmacology; & Toxicology

Chairs: Craig Hopp, NCCAM, NIH and John Williamson, NCCAM, NIH

The use of natural products by the public for the treatment of illness has steadily increased. Most of these products have not been proven to be clinically efficacious. Recent studies have highlighted pathways involved in the beneficial actions of natural products, involving inflammatory, immunomodulatory, cell proliferative, and anti-oxidant targets, as well as assorted pharmacokinetic mechanisms. This session will highlight scientifically based studies underlying the efficacy of cranberry juice for the treatment of urinary tract infections, anti-inflammatory mechanisms of omega-3-fatty acids, the pharmacological actions of cocoa extract, the pharmacology of phytoestrogens, and the potential for using tetra-hydro-palmatine to treat drug abuse.

Cranberry: Role in prevention of bacterial adhesion

Amy Howell, Rutgers, the State Univ. of New Jersey

Novel pro-resolving mechanisms and omega-3 fatty acids

Charles Serhan, Brigham and Women's Hosp. and Harvard Med. Sch.

Natural product's potential for drug abuse treatment

David Y.W. Lee, Harvard Med. Sch.

Pharmacological effects of cacao flavanols: From receptors to clinical endpoints

Francisco Villarreal, UCSD Sch. of Med.

Prevention of estrogen carcinogenesis by botanical dietary supplements for women's health

Judy L. Bolton, Univ. of Illinois at Chicago

Panel Discussion (Questions for Speakers and NCCAM)

Peripheral mechanisms of opioid analgesia

Boston Convention Center, Room 106; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Neuropharmacology; Behavioral Pharmacology; & Molecular Pharmacology

Chair: Kelly A. Berg, Univ. of Texas Hlth. Sci. Ctr.

While opioids are a key drug class for the treatment of pain, their CNS effects with the attendant legal and social issues cause significant drawbacks. One approach to eliminate these drawbacks is to target opioid receptors located on primary sensory neurons that mediate pain neurotransmission in the periphery. This symposium will discuss the roles of peripheral delta opioid receptors (DOR) and kappa opioid receptors (KOR) in the molecular mechanisms involved in pain regulation. The potential role of DOR-KOR heteromerization and interactions with arrestin in the mechanisms underlying peripherally restricted opioid analgesia will be discussed. Results from in vitro experimental strategies and molecular/computational modeling will be integrated with ex vivo and in vivo findings in peripheral sensory neurons to generate insight in the significance of opioid receptors in peripheral mechanisms of opioid analgesia.

Current status of pain therapeutics

Ken Hargreaves, Univ. of Texas Hlth. Sci. Ctr. San Antonio

Molecular determinants and thermodynamics of opioid receptor signaling

Marta Filizola, Mount Sinai Sch. of Med.

6'GNTI is a G protein-biased kappa opioid receptor agonist that inhibits arrestin recruitment

Jonathan Javitch, Columbia Univ. Med. Ctr.

DOR-KOR heteromer-mediated signaling and antinociception in primary sensory neurons

William P. Clarke, Univ. of Texas Hlth. Sci. Ctr. San Antonio

Sleep apnea: A sleeping giant in disease pathologies

Boston Convention Center, Room 107B; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Integrative Systems, Translational and Clinical Pharmacology; Behavioral Pharmacology; Cardiovascular Pharmacology; & Neuropharmacology

Chairs: Issy Laher, Univ. of British Columbia and Najib Ayas, Univ. of British Columbia

Sleep apnea is a common disease that is characterized by repetitive episodes of asphyxia and is recognized as an independent risk factor for cardiovascular morbidity and mortality. This symposium will summarize the currently available information on the cardiovascular, metabolic and other consequences of sleep apnea, pharmacological and non-pharmacological management strategies for sleep apnea, and the use of different animal models to study sleep apnea.

Sleep apnea for non-experts

Najib Ayas, Univ. of British Columbia

Animal models of sleep apnea

Vsevolod Polotsky, Johns Hopkins Univ.

Sleep apnea as a risk factor for cardiovascular diseases

T. Douglas Bradley, Univ. of Toronto/Mount Sinai Hosp.

Sleep apnea and type 2 diabetes

Esra Tasali, Univ. of Chicago Med. Ctr.

Biomarkers in sleep apnea

Atul Malhotra, Brigham and Women's Hosp. and Harvard Med. Sch.

Stem cells: Pharmacology and therapeutics

Boston Convention Center, Room 108; 3:00 PM – 5:30 PM

Sponsored by the British Pharmacological Society-Young Scientists and the ASPET Divisions for Integrative Systems, Translational and Clinical Pharmacology & Behavioral Pharmacology

Chairs: Daniel Reed, Imperial Col. London and Jane A. Mitchell, Imperial Col. London

The application of stem cells in pharmacology is quickly gathering momentum and pharmacology is of great importance for the optimal use of stem cells in regenerative medicine. This session, organized by the Young Scientists Group of the British Pharmacological Society, will address how and why pharmacology is important in stem cell research and vice versa. Speakers will address how stem cells can be used in cardiovascular pharmacology and the treatment of cardiovascular disease, the pharmacologic mobilization and activation of endogenous stem cells and stem cell progenitors, the role of stem cells in neuroprotection, and the use of stem cell derived cells as model systems for screening.

Introduction to stem cells in pharmacology

Daniel Reed, Imperial Col. London

Stem cells as a platform for biotherapeutic drug safety screening

Jane A. Mitchell, Imperial Col. London

Stem cells: the future of therapy for pulmonary hypertension

Duncan J. Stewart, Ottawa Hosp. Res. Inst.

Cell based solutions for cardiovascular disease

Doris A. Taylor, Texas Heart Inst.

Microfluidic and materials approaches to determining cell fate

Armon Sharei and Janeta Zoldan, MIT

Bioinformatic analysis of microglia-neural stem cell interactions: a role for wnt5a

Junior Speaker: Maya Woodbury, Boston Univ. Sch. of Med.

Systems biology answering pharmacological questions

Boston Convention Center, Room 109A; 3:00 PM – 5:30 PM

Sponsored by the Divisions for Toxicology & Integrative Systems, Translational and Clinical Pharmacology

Chairs: Rick Neubig, Univ. of Michigan and John Lazo, Univ. of Virginia Sch. of Med.

While the paradigm of one-drug-one-target has led to important advances in therapeutics, it is becoming clear that the complex interplay of biological systems can greatly influence the response of a drug. Moreover, drugs often exploit multiple targets within an organism. A more complete understanding of all of the interacting elements of a signaling pathway, transcriptional network, or neural circuit may be necessary to accurately predict the response to a given drug. Complex biological interactions such as redundancy and feedback have important implications for both acute responses and the development of resistance. The availability of large data sets of protein structure and interactions, genomic variations, and compound actions permit a more thorough analysis of such questions. Leading researchers in this new and rapidly developing area will discuss how the use of complex systems approaches can be used to explore mechanisms of drug resistance, design novel therapeutic agents, and predict efficacy.

P4 Medicine: How a systems approach will revolutionize medicine

Leroy Hood, Inst. for Systems Biol.

Network models in cancer pharmacology

Dana Pe'er, Columbia Univ.

Practical applications of systems biology in the pharmaceutical industry

Bruce Gomes, Novartis Inst. for BioMedical Res., Inc.

Metabolic network analysis to predict therapeutic responses

Jason Papin, Univ. of Virginia

SIR JAMES BLACK LECTURE

Boston Convention Center, Room 157ABC; 2:00 PM – 2:50 PM

Robert J. Lefkowitz, Duke Univ. Med. Ctr.

Molecular mechanisms of biased agonism at 7 transmembrane receptors

Introduction: Humphrey Rang, British Pharmacological Society

Note: This lecture and session are part of a colloquium on G-Protein Coupled Receptors which continues Wednesday evening and Thursday. While this lecture and session are open to any EB registrant, attendance at the poster session, dinner, and remainder of the colloquium Wednesday evening and Thursday requires separate registration.

Colloquium Symposium: Bridging the efficacy divide: Novel molecular insights driving biased ligand drug discovery

Boston Convention Center, Room 157ABC; 3:00 PM – 5:30 PM

Chairs: Arthur Christopoulos, Monash Univ., Victoria and Robert J. Lefkowitz, Duke Univ. Med. Ctr.

Biased ligands: Developing better drugs through selective signaling at GPCRs

Jonathan Violin, Tevana Inc.

Ligand-biased signaling under the light of BRET

Michel Bouvier, Univ. of Montréal

Allosteric modulation of endogenous metabolites: Implications for on- and off-target drug action and bias

Patrick M. Sexton, Monash Univ., Victoria

Moving from biased signaling to functional (physiological) bias

Andrew Tobin, Univ of Leicester

The atypical antipsychotic clozapine induces 5-HT2AR-mediated signaling and behavioral events in a beta-arrestin2-independent but Akt-dependent manner

Junior Speaker: Cullen Schmid, The Scripps Res. Inst.

For the remainder of the G-Protein Coupled Receptors Program, view pages 28-29.

ASPET Closing Reception

Boston Convention Center, Ballroom Foyer; 6:00 PM – 8:00 PM

Activities for Students & Postdocs

Saturday, April 20

Graduate Student Colloquium: Introducing the Individual Development Plan: A Key to Success

Boston Convention Center, Room 107C
2:00 PM – 5:00 PM

ASPET Business Meeting

Boston Convention Center, Room 107AB
6:00 PM – 7:30 PM

ASPET Opening and Awards Reception

Boston Convention Center, SW Lobby
7:30 PM – 9:30 PM

Sunday, April 21

Diversity Mentoring Breakfast

Westin Boston Waterfront, Revere
7:30 AM – 9:30 AM

Student/Postdoc Best Abstract Competition

Westin Boston Waterfront, Grand Ballroom AB
6:30 PM – 8:30 PM

ASPET/BPS Student & Postdoc Mixer

Westin Boston Waterfront, Harbor Ballroom I
9:00 PM – 11:30 PM

Monday, April 22

Behavioral Pharmacology and Neuropharmacology Divisions Joint Mixer

Westin Boston Waterfront, Grand Ballroom D
6:00 PM – 8:00 PM

Molecular Pharmacology Division Business Meeting and Mixer

Westin Boston Waterfront, Burroughs
7:00 PM – 9:00 PM

Pharmacology Education, Drug Discovery and Development, & Integrative Systems, Translational and Clinical Pharmacology Divisions Joint Mixer

Westin Boston Waterfront, Carlton
7:30 PM – 9:30 PM

Y.E.S. Young Experimental Scientist Mixer

Westin Boston Waterfront, Galleria
9:00 PM – 11:00 PM

*21 & older must have ID to receive drink tickets

Tuesday, April 23

WiP into Shape Networking Walk

Westin Boston Waterfront Hotel, 7:00 AM – 9:00 AM
Meet at the concierge desk.

Cardiovascular Pharmacology Division Mixer

Westin Boston Waterfront, Grand Ballroom D
6:00 PM – 8:00 PM

Drug Metabolism and Toxicology Divisions Joint Mixer

Westin Boston Waterfront, Commonwealth Ballroom A
7:00 PM – 9:00 PM
Wednesday, April 24

ASPET Closing Reception

Boston Convention Center, Ballroom Foyer
6:00 PM – 8:00 PM

Saturday, April 20 – Wednesday, April 24

All in the Convention Center

FASEB Internet/Cyber Cafés

.....Hall and North Lobby

FASEB Resume Critique/Career Counseling & myIDP

Sunday, April 21 – Wednesday, April 24

.....Hall B

Message Center/Free Literature

.....Lobby, near registration area

Career Development Sessions

The following are pharmacology related career development sessions that will be offered at the ASPET Annual Meeting at Experimental Biology 2013:

Graduate Student Colloquium: Introducing the Individual Development Plan: A Key to Success

Saturday, April 20 (*see information in column to the left*)

Diversity Mentoring Breakfast

Sunday, April 21 (*see information in column to the left*)

Translating pharmacology into career choices in the pharmaceutical and biotechnology industry

Sunday, April 21; Boston Convention Center, Room 106; 3:00 PM – 5:30 PM

Advancing discoveries from the academic laboratory to the market

Monday, April 22; Boston Convention Center, Room 106; 9:30 AM – Noon

FASEB Career Development Seminars and Workshops

Sunday, April 21 – Wednesday, April 24

All seminars and workshops will be held in the EB 2013/FASEB Career Center located in Hall B of the Boston Convention Center.

For full descriptions of these FASEB workshops, please visit:

http://www.faseb.org/Portals/0/MARC/PDFs/EB2013_Seminar_Descript_1%2004%2013.pdf

To view a scheduling grid of these FASEB workshops, please visit:

http://www.faseb.org/Portals/0/MARC/PDFs/EB2013_Seminar_Grid_1%2004%2013.pdf

4th GPCR Colloquium



Wednesday, April 24 - Thursday, April 25

Boston Convention and Exhibition Center, Room 157ABC, Boston, MA. Posters will be located in Room 156ABC.

A satellite program to the joint ASPET/BPS Annual Meeting at EB 2013

Organizers: Laura Bohn, Ph.D., The Scripps Research Institute, Scripps Florida
Roger Sunahara, Ph.D., University of Michigan Medical School
Graeme Milligan, Ph.D., University of Glasgow, College of Medical, Veterinary and Life Sciences

Sponsored by the ASPET Divisions for Neuropharmacology, Molecular Pharmacology, Drug Discovery and Development, & Toxicology, and the British Pharmacological Society

Please visit <http://www.aspet.org/Meetings/GPCR2013/> to register for the meeting.

Program

Wednesday, April 24:

1:00 PM Registration open
2:00 PM – 2:05 PM Welcome and introduction to the 4th GPCR Colloquium and Sir James Black Honorary Lecture
2:05 PM – 2:55 PM **Sir James Black Honorary Lecture**
Molecular mechanisms of biased agonism at 7 transmembrane receptors
Robert J. Lefkowitz, Duke University

Bridging the efficacy divide: Novel molecular insights driving biased ligand drug discovery

Sponsored by the Divisions of Molecular Pharmacology & Neuropharmacology

Session Chairs: Arthur Christopoulos and Robert J. Lefkowitz

3:00 PM – 3:35 PM *Biased ligands: Developing better drugs through selective signaling at GPCRs*
Jonathan Violin, Trevena, Inc.
3:35 PM – 4:10 PM *Ligand-biased signaling under the light of BRET*
Michel Bouvier, Université de Montréal
4:10 PM – 4:45 PM *Allosteric modulation of endogenous metabolites: Implications for on- and off-target drug action and bias*
Patrick M. Sexton, Monash University
4:45 PM – 5:20 PM *Moving from biased signaling to functional (physiological) bias*
Andrew Tobin, University of Leicester
5:20 PM – 5:30 PM *The atypical antipsychotic clozapine induces 5-HT_{2A}R-mediated signaling and behavioral events in a beta-arrestin2-independent but Akt-dependent manner*
Junior Speaker: Cullen Schmid, The Scripps Res. Inst.

Official end of ASPET's Annual Meeting at Experimental Biology 2013.

Attendance at the poster sessions, dinner and remainder of the Colloquium on Wednesday evening and Thursday requires separate registration.

5:30 PM – 8:30 PM Open Registration; POSTER PRESENTATIONS; DINNER (Buffet- 6:30 PM) for GPCR symposium (Poster awards if prizes can be raised; **Sponsorship needed, Please contact Christie Carrico or Laura Bohn.**)

Thursday, April 25:

8:00 AM – 8:30 AM Registration Open, Coffee
8:30 AM – 9:20 AM **Allosteric modulators: Enhancing the selectivity and potency of current therapeutics**
Allosteric modulators for improving CNS therapeutic targets
Jeff Conn, Vanderbilt University

Report from the MLPCN GPCR probe development

Session Chair: Laura Bohn

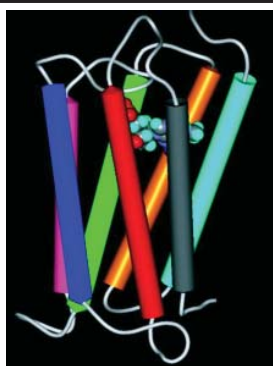
9:25 AM – 10:05 AM *Introduction to the MLPCN and an update on Sphingosine1Phosphate receptor drug development*
Hugh Rosen, The Scripps Research Institute
10:10 AM – 10:35 AM *The chemistry behind CNS drug development*
Jeff Aubé, University of Kansas
10:40 AM – 11:05 AM *An industry perspective on GPCR drug discovery*
Chris Felder, Eli Lilly and Company
11:05 AM – 11:20 AM COFFEE BREAK

Location, location, location: Diverse signaling as a function of context (within the cell)

11:20 AM – 11:55 AM *Receptor trafficking determining receptor signaling*
Mark von Zastrow, University of California, San Francisco

- 11:55 AM – 12:20 PM *Signaling from the nuclear membrane: Metabotropic glutamate receptor, mGluR5, triggers unique signaling cascades from inside the cell*
Karen O'Malley, Washington University
- 12:20 PM – 1:30 PM LUNCH: Provided
- Structure and function: Emphasis on context and drug design**
Session Chair: Roger Sunahara
- 1:30 PM – 2:10 PM *An update on GPCR structure and drug development*
Roger Sunahara, University of Michigan Medical School
- 2:15 PM – 2:40 PM *X-ray structures for the predictive generation of GPCR drugs*
Fiona Marshall, Heptares Therapeutics
- 2:45 PM – 3:05 PM *Cannabinoid ligands gaining entry*
Patricia Reggio, University of North Carolina, Greensboro
- Transient or transformative: Receptor oligomerization finds its way**
- 3:10 PM – 3:40 PM *The prevalence, maintenance and relevance of GPCR oligomerization*
Graeme Milligan, University of Glasgow
- 3:45 PM – 4:10 PM *5HT2AR-mGluR interactions and implications in schizophrenia*
Javier González-Maeso, Mount Sinai School of Medicine
- 4:10 PM Adjournment

Corporate Sponsors include: **Discover_{Rx}**



4th GPCR Colloquium

Wednesday, April 24 – Thursday, April 25



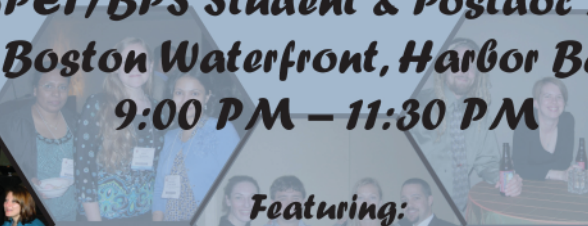
**Held as a satellite meeting to the ASPET
Annual Meeting at Experimental Biology 2013
Boston, MA**



For more information and to register for the 4th GPCR Colloquium, please visit: <http://www.aspet.org/Meetings/GPCR2013/>.

ASPET/BPS Student & Postdoc Mixer
Westin Boston Waterfront, Harbor Ballroom J
9:00 PM – 11:30 PM

Featuring:
Dessert Stations
Two Free Drinks
DJ & Dancing



International Collaboration

A Vital Component of Scientific Progress

by John S. Lazo, Ph.D., ASPET President and Philip Routledge, M.D., British Pharmacological Society President

Alexander Fleming, a Scotsman, is credited with the discovery of penicillin in 1928, and Howard Florey (an Australian pharmacologist and pathologist), Ernst Chain (a German-born biochemist), and their colleagues with identifying its potential role as an antibacterial agent. Reducing this proposal to practice, however, only occurred when the Englishman, Norman G. Heatley traveled to the U.S., and scientists in Merck and Company and E.R. Squibb and Sons eventually became involved collaboratively. Production was facilitated by the large-scale deep fermentation process designed by the American engineer, Margaret Hutchinson Rousseau. An American chemist, John C. Sheehan, then successfully synthesized penicillin in 1957, laying the foundation for the future production of many effective penicillin analogues (1). As a result of these individuals and their international collaborations, perhaps the most important class of life-saving antibiotics are now available to millions of people worldwide. This is only one of numerous examples of how joint international ventures advance pharmacology.

The American Society for Pharmacology and Experimental Therapeutics (ASPET) has long demonstrated its commitment to promoting international collaboration. In 1929, the society was involved with other FASEB organizations in hosting the Thirteenth International Physiological Congress (held in Boston), and when the First International Pharmacological Meeting was held in Stockholm, Sweden, in August 1961, ASPET members were well represented among the 1,500 delegates. Five years later, ASPET was involved in the founding of the International Union of Pharmacology (IUPHAR), now called the International Union of Basic and Clinical Pharmacology (2).

The British Pharmacological Society (BPS), with over 3,000 members from 60 countries worldwide, considers itself to be a truly international organization. Like ASPET, BPS is a member of IUPHAR. The BPS was also involved in the founding of the Federation of European Pharmacological Societies (EPHAR) in 1990 and the European Association of Clinical Pharmacology and Therapeutics (EACPT) in 1993.

Good communication internationally between learned scientific societies stimulates the collaborative links that can accelerate the development of pharmacological agents from conception to clinical use. Our members believe that the only way to grow is to experiment. We are delighted that our two societies have therefore decided to jointly launch an open access online-only journal *Pharmacology Research & Perspectives (PR&P)*. This journal will publish original research and reviews in pharmacology, clinical pharmacology and therapeutics, perspectives on these topics, and articles on education related to these areas. The open access approach will allow a rapid and efficient publication process to be followed by access via PubMed Central immediately after publication. We will begin accepting manuscripts for *PR&P* in April 2013, and we warmly welcome Dr. Mike Curtis, a longstanding BPS member as the journal's first editor.

The history of penicillin illustrates the importance of interdisciplinary teams in advancing science. We are therefore pleased that the launch of *PR&P* will occur at Experimental Biology 2013 in Boston, when pharmacologists, anatomists, biochemists, nutritionists, pathologists, physiologists, as well as scientists from many other disciplines will be meeting to share ideas and hopefully develop new and productive collaborations, achieving together what they could not do alone.

References

1. Parnham MJ and Bruinvels J, editors (1987) *Selections from Discoveries in Pharmacology*, Elsevier, Amsterdam.
2. Parascandola J (2007) A Brief History of ASPET on Its Centennial Anniversary, *Molecular Interventions* 7:288-30.

Join us for the ASPET Closing Reception
Boston Convention Center, Ballroom Foyer
6:00 PM – 8:00 PM

Featuring:
Italian & Asian Food Stations
Open Bar
Two Caricature Artists



Feature Article

AZT: A Rational Drug Ahead of its Time

by Rebecca J. Anderson, Ph.D.

When Francis Collins, Director of National Institutes of Health (NIH), announced the new National Center for Advancing Translational Sciences (NCATS), he pointed to the development of the early antiretroviral drugs to treat acquired immunodeficiency syndrome (AIDS) as an example of the successes that he hopes NCATS will emulate in conquering other complex diseases (1). The urgency in addressing the devastating AIDS epidemic in the 1980s rallied an unprecedented partnership between a greatly incongruent cluster of stakeholders: academia, patient advocates, philanthropists, industry, and the government. Among all those stakeholders, the laboratories and clinics at NIH played a central role. They characterized the human immunodeficiency virus (HIV) and committed vast resources to antiretroviral research and AIDS clinical trials, which facilitated the launch of the first generation of AIDS drugs in an amazingly short period of time.

Among the goals that Collins is now championing at NCATS is "rescuing and repurposing" drugs that have already undergone preclinical development and human safety testing at pharmaceutical firms. He hopes that academic researchers will be able to discover new therapeutic properties of old compounds, short-circuit the transition to clinical trials, and ultimately, salvage them as useful new drugs. Eight companies (Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Pfizer, and Sanofi) are contributing compounds from their archives for the pilot program. To justify this initiative, Collins again pointed to the AIDS experience in the 1980s and the repurposing of azidothymidine (AZT), a compound that Jerome Horwitz had originally synthesized as a drug to treat cancer.

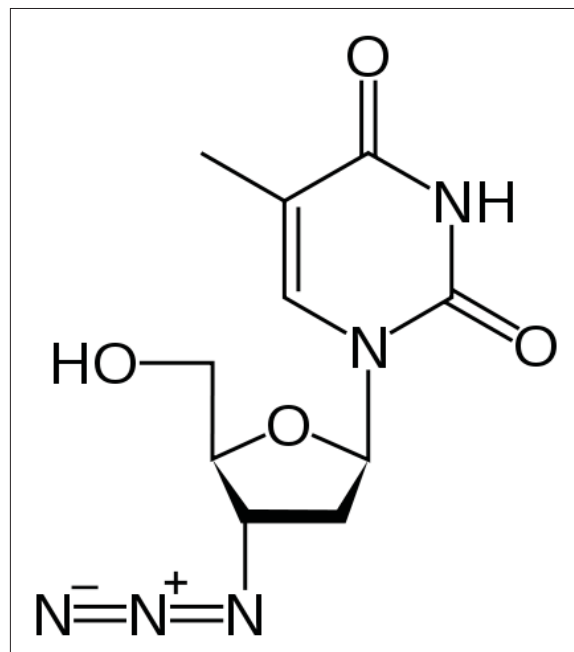


Figure 1. The chemical structure of azidothymidine (AZT).

The Michigan Connection

Jerome Horwitz was born in Detroit on January 16, 1919, the son of a businessman who sold poultry. As a teenager, Horwitz decided he did not want to spend his life cleaning out chicken coops and was inspired to pursue a different career after reading *Microbe Hunters*, the 1926 classic about groundbreaking scientists written by University of Michigan professor Paul de Kruif. "A light bulb went on. I knew what I wanted to do" (2). High school football injuries exempted Horwitz from military service during World War II, and he earned his bachelor's (1942) and master's (1944) degrees in chemistry from the University of Detroit. In 1948, he received his Ph.D. in chemistry from the University of Michigan. Horwitz's first job was at the Illinois Institute of Technology, where he helped develop solid rocket fuels for the Navy, but "I didn't enjoy working with explosives" (2).

In 1956, he joined the Detroit Institute of Cancer Research as a research associate and spent the rest of his career working in oncology. His two young daughters, both of whom would later marry physicians, asked him why he went into research. "I told them I wanted a career in which, with some luck and lots of work, I might have a chance to make a difference" (3). At a time when scientists were randomly picking compounds off the shelf to see if any might work against cancer, Horwitz was among the first to apply rational drug design. "We thought, how could we design a compound that would inhibit the duplication of cancer cells?" (4)

Using thymidine (one of the naturally occurring nucleosides of DNA) as a starting point, Horwitz and his colleagues synthesized a group of chemical analogs, one of which was AZT. Horwitz thought that cancer cells would phosphorylate the modified thymidines and try to incorporate them into a new strand of DNA. He had hoped that the false nucleotide would prevent addition of the native nucleotides, terminating the DNA chain and blocking cell proliferation. Unfortunately, when Horwitz's team tested the compounds in leukemic mice, they saw no activity. "It was frustrating because the theory seemed right. We had this very interesting set of compounds waiting for a disease to cure" (3). But he was also realistic. "There are far more disappointments in research than causes for celebrations" (5). Horwitz published the dismal results in 1964 and moved to more promising lines of research (6).



Figure 2. Dr. Jerome Horwitz in his Wayne State University laboratory. (Courtesy of Walter P. Reuther Library, Wayne State University)

Meanwhile, George Hitchings and Gertrude Elion had been searching for antagonists of nucleosides at Wellcome Research Laboratories in North Carolina since the 1940s. They created analogs of purines and pyrimidines that successfully targeted bacterial and parasitic infections and cancer. Most notable was their discovery of 6-mercaptopurine, for which they were later recognized with a Nobel Prize. Their talented research group also developed acyclovir for genital herpes, the first antiviral drug approved by the Food and Drug Administration (FDA). But in general, they were less successful in suppressing viruses than in finding antibacterial and anticancer drugs.

Acyclovir, which was launched in 1982, broke an eight-year drought in new product approvals at Burroughs Wellcome, a company privately owned at that time by the British Wellcome Foundation, Ltd. Unfortunately, acyclovir's lackluster initial sales (due to the FDA's strict limitations on its use and fierce competition for the herpes market) did little to help the company's bottom line. Although the Wellcome Foundation remained profitable, the lack of a major product introduction in nearly a decade had severely squeezed the company's profit margins (7). They desperately needed a blockbuster.

In 1981, the chemists at Wellcome Research Laboratories prepared a series of deoxythymidines using synthetic methods published in the 1970s by two research groups led by Ronald Glinski and Tai-Shun Lin (8, 9). One compound, 509U81, proved to be active in their microbiological screens. Although 509U81 was inactive against a wide variety of DNA and RNA viruses, it had notable antibacterial activity in animal models of *Escherichia* and *Salmonella* infections. With only a small amount of compound available, safety assessment was limited to a two-week oral dose-range-finding toxicology study in rats. That preliminary study turned up no "red flags," but the toxicologists cautioned that further safety studies should be conducted (10).

When a virus was determined to be the causative agent of AIDS in 1984 (originally termed HTLV III or LAV and later, HIV), the Wellcome researchers redirected their considerable virology expertise to tackle this new target. In October 1984, they hosted a series of seminars in Research Triangle Park by HIV pioneers Françoise Barre-Sinoussi, Robert Gallo, and Samuel Broder, who catalyzed the company's discovery and development efforts. The Wellcome scientists obtained mouse retrovirus samples from Kent Weinhold at nearby Duke University and set up a plaque reduction assay, infecting murine FG-10 cells with the retrovirus to form plaques. They began by screening representative compounds, such as acyclovir, from their established drug development programs. They also invited Wellcome's senior organic chemists to contribute 10-20 compounds representative of their synthetic expertise. Among the twelve compounds furnished by the chemists on November 2, 1984, was 509U81. When technicians examined the FG-10 cells treated with 509U81 in their assay, they discovered no plaques in any of the 18 plates. None at all. 509U81 had completely prevented the mouse retrovirus from forming plaques. Even before they could reproduce their results, rumors began circulating throughout the company, causing feverish activity (10).

The results were confirmed, but the scientists tempered their enthusiasm because the plaque reduction assay was based on a mouse retrovirus. 509U81 might behave differently against HIV, a human retrovirus, which the Wellcome scientists were not equipped to handle. In fact, at that time few researchers had the expertise to evaluate compounds for HIV activity, and no standard assays existed. To further characterize the compound's effects, the Wellcome group arranged to have 509U81 tested in HIV assays developed by Broder (National Cancer Institute), Weinhold (Duke), and Gerald Quinnan (FDA). When these laboratories each reported that 509U81 inhibited HIV in their assays, Burroughs Wellcome launched the largest and most aggressive drug development effort in its 100-year history (10).

The Wellcome chemists synthesized or purchased analogs of 509U81 to extend the structure-activity-relationships of the chemical series, but none of those compounds was superior as an antibacterial or antiviral agent. At the same time, the chemists began producing numerous batches of 509U81 for toxicology and other preclinical development studies. Although the toxicology studies (conducted according to Good Laboratory Practices and needed to support the initial clinical trials) received the team's top priority, compound supply was limited. To conserve drug, the team conducted the multi-dose, GLP toxicology studies without benefit of the usual preliminary dose-range-finding experiments. The high dose levels selected for both the rat four-week study (10-fold the estimated human dose) and the dog two-week study (six-fold the anticipated human dose) were also dictated by compound availability. The final reports of these rat and dog toxicology studies were signed a mere ten weeks after the first animal had been dosed, and the first Phase I clinical trial began a few days later.

This was the last time that the preclinical toxicology studies were completed ahead of the clinical trials they were meant to support, as the chemists scrambled to produce sufficient drug supplies to keep up with the drug's development. They needed large amounts of thymidine, a key starting material, and searched worldwide for producers. Using a lot of "out-of-the-box" creative thinking, they continued to explore new synthetic routes, evaluating and optimizing chemical production based on the three synthetic methods published by Horwitz, Lin, and Glinski (6, 8, 9). NIH alleviated the near-term crisis by donating 40 kg of thymidine, and the Wellcome facilities at Research Triangle Park, North Carolina and Dartford, UK, began scaling up production. In October 1985, they completed the final reaction steps on many small batches to produce 15 kg of clinical-grade material. The chemists in North Carolina stopped briefly to mark this milestone with a celebration that featured a huge cookie frosted with the compound's chemical structure and melting point (10).

The Wellcome chemists also synthesized the major metabolic product of 509U81, a glucuronide, to support the clinical program. This metabolite would be used as the HPLC marker for assaying drug concentrations of 509U81 in the clinical samples. However, *de novo* synthesis was laborious, and the chemists found it easier to supply the required assay marker by isolating and purifying the glucuronide from the urine of monkeys dosed with 509U81.

Also in October 1985, Wellcome Research Laboratories and their research collaborators published the results of their initial laboratory findings (11). The article generated intense interest around the world. In Michigan, Jerome Horwitz saw the news of this breakthrough and recognized the chemical structure of 509U81, which was published in the research paper. It was, in fact, AZT, the same compound he had synthesized twenty years earlier. He was happy that his thymidine analogs were finally showing some pharmacologic activity, even if not as anticancer drugs. He told reporters, "If these chemicals provide a first generation of treatments against AIDS and leads for even better therapies, then our purpose will have been served" (4).

The First Clinical Trials

On July 3, 1985, as soon as the first GLP toxicology reports were signed, the first patient received AZT in the Phase I trial, which was conducted at the National Cancer Institute and Duke University under Burroughs Wellcome sponsorship. The 19 AIDS patients in this trial received one of four dose regimens for six weeks (two weeks intravenously and four weeks orally) to assess AZT's safety, bioavailability, and pharmacokinetics.

Although AZT had a relatively short half-life, it was well absorbed, crossed the blood-brain barrier, and was well tolerated. In addition, when the data were analyzed in January 1986, the investigators also saw hints of the drug's therapeutic efficacy in some patients: increased CD4 cell counts (circulating helper-inducer T-lymphocytes), clearance of fungal infections, weight gain, and a loss of the virus in cultured peripheral blood mononuclear cells (12).

Encouraged by these results and knowing that hundreds of people were dying each week from AIDS, Burroughs Wellcome jumped immediately to a placebo controlled, double blind trial in severely ill AIDS patients. (Conventional drug development takes a more cautious approach, assessing investigational drugs in a series of Phase II dose-optimization and safety trials before launching a definitive, blinded trial, but AIDS patients and their attending physicians were desperate.) According to Kathryn Pattishall, the Burroughs Wellcome clinicians felt this was "the most vigorous test to determine [the drug's] therapeutic index. If it proved to be effective in the most severely ill patients while exhibiting manageable adverse effects, then it might be more beneficial in patients with milder forms of the disease" (10). The blinded Phase II clinical trial began in February 1986 and enrolled AIDS patients at 12 university medical centers in the United States. The protocol specified treating the randomized patients with either AZT or placebo in a blinded fashion for 24 weeks (13).

Because of ethical concerns, the high safety risk of this fast-tracked trial, and the public pressure generated by the reaction to the recently published initial laboratory results, Burroughs Wellcome appointed an independent Data Safety and Monitoring Board (DSMB) to oversee the trial. This board of medical, ethical, and statistical experts was charged with examining the safety and efficacy data every two months and, based on their findings, making recommendations on whether or not Burroughs Wellcome should proceed with the trial.

The investigators completed enrollment of 282 AIDS patients in June 1986. By the end of the summer, the DSMB noted a significant improvement in the patients treated with AZT. Compared to the placebo group, the AZT-treated patients had increased CD4 cell counts, gained weight, and had improved neurological function. AZT also decreased the level of HIV-associated p24 antigen circulating in the patients' blood and significantly decreased their opportunistic infections. Best of all, the DSMB noted that fewer deaths were being reported in the AZT group than in the placebo group (13). Due to the staggered enrollment, some patients had been treated for only 10 weeks, and yet the drug was unquestionably beneficial. On September 19, 1986, the DSMB recommended that Burroughs Wellcome terminate the trial because of the significantly lower mortality rate in the AZT-treated group. They felt it was unethical to continue treating some patients with a placebo, when AZT clearly prevented death. Taking the DSMB's advice, Burroughs Wellcome stopped the trial and offered AZT to all patients in the placebo group. Most of them accepted. The investigators continued to treat and monitor the patients beyond the original 24-week trial period, collecting long-term mortality data.

This Phase II trial had been well designed, enrolling only patients who met narrow criteria for disease status and progression. The uniform and comparable groups permitted an unbiased assessment of AZT's effects, and the results were unequivocal. But the patients in this small trial could not be considered representative of AIDS patients in general. To confirm the trial's results and also to accommodate a wider range of patients who were desperate for treatment, Burroughs Wellcome launched a compassionate use program in October 1986. Over the next six months and in conjunction with the NIH, the company dispensed AZT free of charge to any AIDS patient who wanted it and met minimal criteria. Approximately 4,800 patients took advantage of the program, and they represented a good cross-section of the general AIDS population (10).

Medical reviewers at the FDA had been working closely with Burroughs Wellcome throughout the clinical investigations, monitoring the progress of the trials and reviewing the results. By early 1987, they were satisfied that AZT was effective and had a reasonable side effect profile. On March 19, 1987, AZT became the first antiretroviral AIDS drug approved by the FDA, a short 21 months after the first patient had been dosed. At that time, the six-month toxicology studies in rats and monkeys were still in progress, and the other safety assessments that are traditionally required prior to regulatory approval (one-year toxicity studies in rats and monkeys, carcinogenicity studies in rats and mice, and developmental and reproductive studies in rats) had just begun (10).

Gaining Momentum

In Michigan, Jerome Horwitz was elated when he learned about the clinical trial results. He had not been involved with any of the AIDS research or AZT development activities, but in his own way, he had fulfilled the goal he had described to his daughters many years before—to make a difference. "AZT is finally able to do some good, to prolong life and improve the quality of life for AIDS patients. It's not a cure—few viruses can

be cured—but it's offering hope to a lot of people" (3). For the next decade, AZT remained the primary weapon in clinicians' armamentarium for combatting AIDS.

Following AZT, researchers investigated a number of other nucleoside analogs, hoping to repeat the success of the Burroughs Wellcome team. And again, Horwitz's early research pointed them in the right direction. Of the first four antiretroviral drugs approved by the FDA for AIDS, three of them had been first synthesized in Horwitz's laboratory in the 1960s: AZT, dideoxycytidine (ddC), and stavudine (d4T). Horwitz never patented those compounds and never profited from them, but years later, Burroughs Wellcome donated money to Wayne State University's cancer institute to establish a chair in his name (14).

Jerome Horwitz continued to lead an active cancer research group. He was named director of the chemistry division at the Detroit Cancer Institute in 1965 and joined the Wayne State University faculty in 1967. In 1970, he became scientific director of WSU's Michigan Cancer Foundation (now the Barbara Ann Karmanos Cancer Institute) and was named chairman of the institute's chemistry department in 1973. Horwitz created a solution called X-Gal, which is widely used to detect the presence of β -galactosidase. In 2003, Wayne State licensed to a pharmaceutical company several compounds that Horwitz developed for treating solid tumors, and he received the first royalty check in his long career at age 86. He retired in 2005—still supported by research grants and actively working in his laboratory until the last day (15). He died last year at his home in Bloomfield Township, MI, at the age of 93. Among the tributes that followed his death, one captured the course of his career best by describing Horwitz as "one of academe's most under-recognized inventors"(2).

References

1. Collins FS (2011) Reengineering translational science: the time is right, *Science Translational Medicine* **3**(90), p. 90cm17.
2. Woo E (Sept. 26, 2012) Jerome Horwitz, Wayne State medical researcher who developed anti-AIDS drug, dies at 93. *The Detroit News*.
3. People Magazine (Dec. 22, 1986) AZT, the anticancer drug he developed 22 years ago, is now our best hope in the battle against AIDS. *People Magazine*.
4. New York Times (Sept. 19, 1986) A failure led to drug against AIDS. *New York Times*.
5. University of Detroit Mercy (Fall 2008) Jerome P. Horwitz's drug research makes global medical history. *Spiritus Magazine*.
6. Horwitz JP, Chua J, and Noel M (1964) Nucleosides. V. The monomesylates of 1-(2'-Deoxy- β -D-lysofuranosyl)thymine. *J Organic Chem* **29**(7): 2076-2078.
7. McInnis D (June 19, 1983) Herpes: Burroughs Wellcome sees its treatment as a way to cure profit ills. *New York Times*.
8. Glinski RP, Khan MS, Kalmas RL, and Sporn MB (1973) Nucleoside synthesis. IV. Phosphorylated 3'-amino-3'-deoxythymidine and 5'-amino-5'-deoxythymidine and derivatives. *J Organic Chem* **38**:4299-4305.
9. Lin TS and Prushoff WH (1978) Synthesis and biological activity of several amino analogues of thymidine. *J Med Chem* **21**:109-112.
10. Pattishall KH (1993) Discovery and development of zidovudine as the cornerstone of therapy to control human immunodeficiency virus infection, in *The Search for Antiviral Drugs* (Adams J and Merluzzi VJ, eds.) pp. 23-43.
11. Mitsuya H, Weinhold KJ, Furman PA, St. Clair MH, Lehrman SN, Gallo RC, Bolognesi D, Barry DW, and Broder S (1985) 3'-azido-3'-deoxythymidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro. *Proc Natl Acad Sci* **82**:7096-7100.
12. Yarchoan R, Weinhold KJ, Lyerly HK, Gelmann E, Blum RM, Shearer GM, Mitsuya H, Collins JM, Myers CE, Klecker RW, et al. (1986) Administration of 3'-azido-3'-deoxythymidine, an inhibitor of HTLV-III/LAV replication, to patients with AIDS or AIDS-related complex. *Lancet* **327**(8481): 575-580.
13. Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, Leedom JM, Groopman JE, Mildvan D, Schooley RT, et al. (1987) The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *N Engl J Med* **317**:185-191.
14. Vitello, P (Sept. 20, 2012) Jerome Horwitz, AZT creator, dies at 93. *New York Times*.
15. Wayne State University (July 27, 2005) Dr. Horwitz retires at 86 after historic career. *Prognosis*.



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P.B. Dews Award Lecture

Behavioral and Pharmacological Determinants of Pharmacological Plasticity

by James E. Barrett, Ph.D.

Lecture Given at Experimental Biology 2012 by the P.B. Dews Lifetime Achievement Award Recipient

Introduction

Behavioral pharmacology has generally been defined as the experimental study of the effects of drugs on behavior and of the ways in which behavior affects drug action. The first part of this definition is reasonably straightforward and appears to occupy the predominant focus of many currently engaged in behavioral pharmacology research. The latter portion of this definition, however, has been frequently overlooked as well as underappreciated. Yet, evaluating the ways in which behavioral antecedents and consequences affect drug action broadens the spectrum and dimensions of pharmacology and also contributes significantly to our understanding and appreciation of the contribution of behavior to determining the pharmacological effects of drugs. Since the initial experiments conducted by P.B. Dews demonstrating that the behavioral effects of a drug depended on the schedule of reinforcement, behavioral pharmacologists steeped in the tradition of the experimental analysis of behavior have been profoundly influenced and intrigued by the powerful effects of environmental variables that control behavior and on the manner in which those variables may modulate drug action.



James E. Barrett, Ph.D.

In his initial landmark study (Dews, 1955) which established the foundation for the discipline of behavioral pharmacology, pentobarbital increased the rate of key peck responding of pigeons under a fixed-ratio schedule of food reinforcement at doses that markedly reduced responding maintained under a fixed-interval schedule of reinforcement. Surprisingly, the effects of pentobarbital on these behaviors were not uniform – as might have been expected – but depended on the schedule of reinforcement that maintained responding. Although Dews discussed the sensitivity of behavior to the effects of pentobarbital, he emphasized use of the "techniques" of schedules of reinforcement to detect the behavioral effects of drugs. This emphasis on schedule-controlled behavior as a determinant of the effects of drugs is a theme that runs throughout much of Dews's subsequent work on drugs whether he was discussing the specific effects of drugs under many different experimental conditions or whether he was elucidating more global concepts such as addiction (Dews, 1973), analgesia (Dews, 1974), or neurotransmitters (Dews, 1975). His penetrating insight, together with his expansive and often poetic description of the principles and concepts underlying the contribution of schedule-controlled behavior to pharmacology, have been inspirational to many and were posited with a perspective that foreshadowed many findings that were to be supported experimentally in the years to follow. Thus, it is appropriate that this article summarizes a considerable amount of research on the behavioral effects of drugs that has embraced Dews's emphasis on the importance of schedule-controlled behavior and on the role of the environment in contributing to those effects. Concepts such as the environmental context in which behavior is occurring, along with an examination of prior behavioral and pharmacological experience, have been studied and seen to greatly influence drug effects. In what are now multiple instances, these conditions have been demonstrated to completely reverse the "typical" actions of many drugs, particularly those that are abused. These findings have implications for a more thorough understanding of variables affecting drug abuse and also for arriving at a more detailed understanding of behavioral influences on neuropharmacological and epigenetic mechanisms contributing to those effects. The results of studies summarized here provide a strong recognition and appreciation of Dews's emphasis on the remarkable contribution of behavior as a determinant of drug action, an emphasis that leads to the general conclusion that not only is behavior malleable or modifiable (i.e., "plastic") but, perhaps somewhat unexpectedly, so are the effects of drugs.

Schedules of Reinforcement Using Noxious Stimuli

Advances in science and the elucidation of certain principles are frequently made following the introduction of a new technique or the introduction of a new technology. This was the case following the introduction and emphasis on schedules of reinforcement as a means to establish and maintain behavioral performances that provided objective methods for analyzing many complex processes (Ferster and Skinner, 1957). This was also the case when it was demonstrated that the effect of a behavioral consequence such as the delivery of a response-produced electric shock does not uniformly result in a suppression of responding (i.e., punishment) but can, under some conditions, actually maintain high levels of responding that result only with its presentation. Convenient dichotomies sometimes allow for a certain orderliness and regularity but, on occasion, may neglect or mask certain fundamental principles about the relationships between behavior and the environment. For example, it seems quite reasonable that food should maintain or increase behavior when it follows a response and that a noxious electric shock that follows a response should result in a decrease in responding. However, Kelleher and Morse (1968a) and McKearney (1968) demonstrated in a striking set of experiments conducted with squirrel monkeys that the noxious stimulus of electric shock could function as a reinforcer, maintaining behavior in much the same way as other reinforcing events. Byrd (1969) conducted similar experiments with comparable outcomes in cats. Several studies that followed these initial experiments demonstrated that the same electric shock can maintain behavior that results in its presentation, serving as a reinforcer, while, in the same animal under a different component of a multiple schedule, can suppress behavior, functioning as a punisher (Barrett and Glowa, 1977; Kelleher and Morse, 1968a). Similarly, the same event – electric shock in one experiment (Barrett and Spealman, 1978) and cocaine in another (Spealman, 1979) – has been shown to maintain

behavior that *terminates* its presentation while also serving simultaneously under a different stimulus condition to *maintain* responding. Under some conditions, it has been possible to demonstrate that two different responses of squirrel monkeys can be simultaneously maintained with one response (a chain pulling response) *terminating* the delivery of electric shock while a second response (a lever press) is maintained by the *presentation* of the very same shocks terminated by the first response (Barrett and Stanley, 1980a).

These several experiments which focused primarily on schedules of reinforcement using noxious stimuli, while seemingly enigmatic, provided compelling data that broadened the interpretation of the nature and scope of reinforcement, focused attention on the importance of the behavioral history of the subject, and further emphasized the powerful contribution of schedules of reinforcement to the shaping and maintenance of behavioral performances. They also opened new avenues to develop complex behavioral performances to explore the importance of these variables in the field of behavioral pharmacology and to expand the focus on topics such as the nature of the reinforcing event, the influence of the context in which behavior occurred and the role of behavioral history.

Environmental Events and Behavioral Consequences

Early experiments using squirrel monkeys demonstrated that the nature of the event controlling behavior did not appear to be as significant as the schedule of reinforcement in determining the effects of certain drugs such as amphetamine and chlorpromazine (Kelleher and Morse, 1964). These results were surprising to some because it seemed that the effects of a drug might differ depending on whether responding was maintained by food or, alternatively, by the termination of a noxious electric shock. Nevertheless, the study by Kelleher and Morse reaffirmed the importance of schedule-controlled behavior to drug action that was first described by Dews (1955). Many of the early studies pointing to the importance of schedules of reinforcement as well as to other determinants of drug action were summarized in a now classic publication by Kelleher and Morse (1968b) that remains to this day an important contribution to the literature in behavioral pharmacology.

Subsequent studies with squirrel monkeys responding under fixed-interval schedules of food- or shock-presentation examined the effects of a wider range of drugs such as morphine, alcohol and chlordiazepoxide, (Barrett, 1976; McKearney, 1974). These experiments demonstrated differential drug effects depending on whether food or shock was the consequent event. Under these conditions, alcohol and chlordiazepoxide increased food-maintained responding but decreased comparable rates and patterns of responding maintained by shock (see Figure 1 for the effects of chlordiazepoxide). Morphine, however, increased responding maintained by shock presentation while decreasing food-maintained responding (McKearney, 1974). Cocaine and amphetamine, as might have been expected based on the earlier study by Kelleher and Morse (1964), increased responding regardless of whether it was maintained by shock or by food (Barrett, 1976; McKearney, 1974), and chlorpromazine decreased responding under both conditions (McKearney, 1974). Thus, it appears that some drugs do indeed produce different effects depending on the specific consequence that maintains responding (Barrett and Katz, 1981). Based on these studies, it appears that anxiolytic and sedative-hypnotic drugs decrease responding maintained by the delivery of a noxious shock, whereas these drugs appear to increase responding maintained by the delivery of food; in contrast, the μ opioid receptor agonist morphine produces the opposite effects, increasing responding maintained by shock while decreasing food-maintained responding. Psychomotor stimulants, on the other hand, appear to produce increases in responding maintained by either event, whereas drugs such as chlorpromazine reduce responding under both conditions.

There are a number of striking aspects to these studies. One noteworthy point is that these experiments studied squirrel monkeys responding under a multiple schedule of food and shock reinforcement. Under this schedule, the two maintenance events were occurring within the same experimental session under different stimulus conditions and both events maintained comparable rates and patterns of responding (see Figure 1). This latter point is another feature emanating from Dews's work emphasizing the schedule-controlled rate and temporal pattern of responding as an important feature contributing to the behavioral effects of drugs (e.g., Dews and Wenger, 1977). Because Dews demonstrated the dependency of drug effects on reinforcement schedules with a single reinforcer, for any valid comparison of the effects of drugs on responding maintained by different consequent events, it is critical that those different events maintain comparable rates and patterns of responding. This was the case in the original publication by Kelleher and Morse (1964) and was also the case in the experiments just described. A second point is that the majority of these results were obtained when responding was maintained solely under fixed-interval schedules and the effects differ under other schedules of reinforcement. For example, when responding was maintained under fixed-ratio schedules of food or stimulus-shock termination, the effects of ethanol, pentobarbital, and chlordiazepoxide were similar under both of these maintenance conditions (Katz and Barrett, 1978). Therefore,

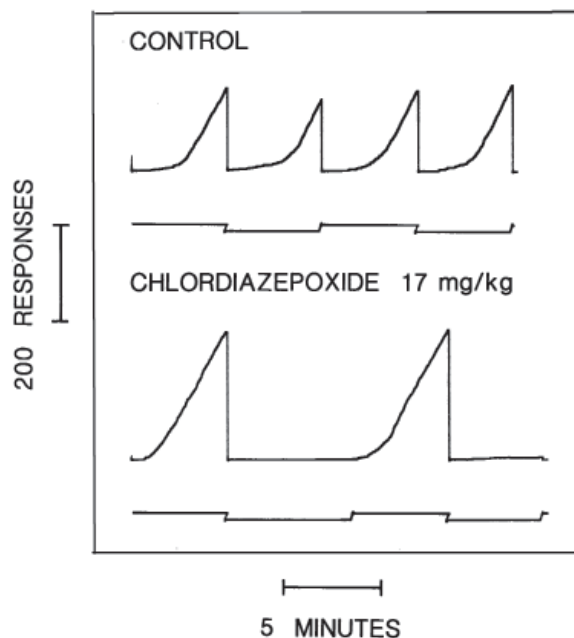


Figure 1. Cumulative response records showing selective effects of chlordiazepoxide on performances of squirrel monkeys maintained under a multiple fixed-interval schedule by food or shock presentation. Ordinate: Cumulative responses; Abscissa: Time. The response pens reset to base following the delivery of food or electric shock at the completion of each fixed interval. The lines beneath each cumulative record were displaced during the shock-presentation component and each component was associated with a distinctive visual stimulus. Control performances show comparable rates and patterns of responding under the food- and shock-presentation schedules. Chlordiazepoxide increased responding maintained by food but nearly eliminated responding during the shock-presentation schedule. (From Barrett and Witkin, 1986, used with permission.)

it may be the case that responding under fixed-interval schedules is more sensitive to drug effects that depend on the type of maintaining event than is the case with other schedules. In another experiment with responding of squirrel monkeys maintained under second-order schedules of intramuscular cocaine injection or food presentation, cocaine, chlordiazepoxide, and chlorpromazine did not affect responding differently depending on the maintaining event (Valentine et al., 1983). The use of second-order schedules of reinforcement in these studies was unique in that the event maintaining responding – either cocaine or food presentation – was delivered only at the end of the experimental session where it was paired with a visual stimulus; responses throughout the session produced the stimulus according to a schedule, and responding was maintained throughout by the visual stimulus that only occurred at the end of the session with the administration of cocaine or food. Thus, taken as a whole, these studies indicate that, under certain schedules of reinforcement, the type of event that maintains responding can play an important role in determining the effect a particular drug will have on behavior. However, the schedule of reinforcement is also a significant factor in the determination of those effects as these differences were primarily demonstrated under fixed-interval schedules.

In many respects, the outcomes of studies described in this section are not unreasonable nor should they be surprising. They would appear to be consistent with Dews's perspective of the importance of the environment and of behavioral consequences and the role they play in behavioral pharmacology. In addition, it would indeed be surprising if a particular drug had effects that were uniform across a wide range of behaviors and consequent events. Selectivity of drug effects is important under a wide range of conditions and can be crucial under others. For example, it is important that drugs targeting anxiety, depression, schizophrenia, or drug abuse be relatively devoid of effects on behaviors other than those targeted for treatment. This has often been a formidable challenge for the development of drugs in the area of neuropsychopharmacology where the effort has been on targeting key symptoms while not affecting other behaviors that are a critical part of the behavioral repertoire.

Environmental Context

Behavior, more often than not, occurs in a complex environment where multiple factors may be converging and where both proximal and remote influences can play an important role in governing that behavior. The environmental context in which behavior is occurring can also exert a powerful influence on the behavioral effects of a drug. In one experiment (McKearney and Barrett, 1975) responding of squirrel monkeys was maintained by food presentation in one component of a multiple schedule, whereas in the alternate component, associated with a different visual stimulus, there were no scheduled consequences for responding (extinction). Subsequently, responding maintained by food was

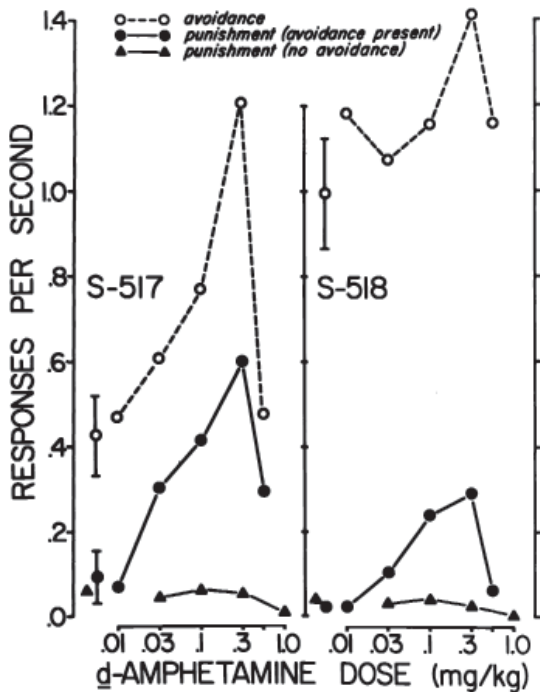


Figure 2. Effects of d-amphetamine on responding under the multiple avoidance-punishment schedule. Ordinate: responses per second; Abscissa: log dose. Unconnected points with brackets indicate mean control rates of responding + one standard deviation. Triangles refer to punished responding during the multiple punishment-extinction schedule (no avoidance schedule in effect). Filled circles refer to punished responding (avoidance schedule in effect), and open circles represent avoidance responding during the multiple punishment-avoidance schedule. d-Amphetamine increased punished responding only when the avoidance schedule was in effect during the alternate component of the multiple schedule. (From McKearney and Barrett, 1975, used with permission.)

suppressed by the delivery of electric shock (punishment); responding in the extinction component was not affected by this change in the schedule. Under these conditions, d-amphetamine only decreased punished responding (Figure 2, triangles), a result that has been replicated repeatedly in a number of species and experimental situations. In addition, there were no effects on responding during the extinction component (data not shown). Subsequently, an avoidance schedule was introduced during the component in which responding previously had no consequences. After rates of responding stabilized, d-amphetamine now produced substantial increases in punished responding in the other schedule component (Figure 2, filled circles) and also increased responding maintained by the avoidance schedule (Figure 2, open circles). Thus, under one experimental condition or context, d-amphetamine had no effect on punished responding but when the context in which that behavior alternated with avoidance behavior, dramatic increases occurred in punished responding.

Similar rate-increasing effects of d-amphetamine on punished responding were obtained in a study in which responding of squirrel monkeys was maintained under a multiple schedule. In one component, responding was maintained under a fixed-interval schedule of shock presentation and, in the alternate component, food-maintained responding was suppressed (punishment) by the same shock that maintained responding in the other component (Barrett, 1977). The effects of d-amphetamine on punished responding under these schedule conditions could reflect induction from the rate-increasing effects on shock-maintained responding that would reflect an interaction between the two components of the schedule. Such contextual interactions where changes in the schedule of reinforcement in one component of a multiple schedule produce changes in behavior in the alternate component where the conditions have not changed have been reported often in the behavioral literature (e.g., 'behavioral contrast') by a number of investigators (Reynolds, 1961a, b; Spealman, 1976). Rarely, however, have these been seen in the behavioral pharmacology literature (but see Barrett and Stanley, 1980b). Nonetheless, these findings indicate that the behavioral effects of drugs can be significantly influenced not only by the more immediate consequences of behavior, as suggested by Dews, but also by more remote influences such as those occurring in a different environmental context.

Recent studies examining the social context of drug self-administration in non-human primates have the potential to extend our understanding of the role of social factors in drug

abuse (Nader et al., 2012). These experiments, conducted when monkeys are housed in a social environment, offer the possibility of elucidating several variables that exist within a unique but experimentally controlled social situation such as social rank, gender difference, drug history, and the imposition of stress. The manipulation and examination of the influence of these variables within a social context may yield unique insights into the role of these factors in initiating, maintaining, and modulating the self-administration of abused drugs, particularly as studies on behavioral and pharmacological history, as well as contextual factors, are subjected to experimental analysis.

Behavioral History

Analyses of the determinants of the behavioral effects of drugs, as summarized above, have generally focused on those more immediate factors governing behavior such as the schedule of reinforcement and the environmental context in which behavior is occurring. However, there are a number of instances in which historical factors have been shown experimentally to contribute to current behavior and to the effects of drugs. Studies in both rodents and humans have shown that a *history* of responding under one schedule of reinforcement can produce enduring effects on responding subsequently maintained under a different schedule (e.g., Wanchisen et al., 1989; Weiner, 1964). A number of studies using rats and pigeons also have demonstrated that reinforcement history can alter the effects of drugs such as methadone and *d*-amphetamine (Egli and Thompson, 1989; Nader and Thompson, 1987; 1989; Poling et al, 1980; Urbain et al., 1978). Although some of these studies examined drug effects when rates of responding were different, possibly contributing to the outcome due to rate-dependent effects, the finding that there are potential historical influences on behavior and on drug effects was significant in expanding the number of variables experimentally demonstrated to contribute to the behavioral effects of drugs (see Nader et al., 1992).

Historical influences on drug effects in squirrel monkeys were obtained (Barrett, 1977) in an experiment similar to the one described above where the introduction of an avoidance schedule in one component of a multiple schedule changed the effects of *d*-amphetamine on punished responding (McKearney and Barrett, 1975). In this study, responding of squirrel monkeys was initially established under a punishment schedule in which food-maintained responding was suppressed by the delivery of shock. The effects of *d*-amphetamine were as expected, i.e., responding was either not affected or was decreased (Figure 3, left panel). The punishment schedule was then removed and an avoidance schedule was introduced. Under this condition, as in the McKearney and Barrett (1975) study, responding was established and maintained by the postponement of electric shock delivery. After several weeks of avoidance training, the avoidance schedule was removed and the punishment schedule was reintroduced; punished responding was allowed to stabilize under the punishment condition for several weeks. At this point, punished responding was now substantially increased with *d*-amphetamine (Figure 3, right panel). The increases in punished responding in monkeys with a history of shock avoidance are clear in the cumulative response records of performances shown in Figure 4. Following exposure to the avoidance schedule, increasing doses of *d*-amphetamine now produced large increases in punished responding with subject MS-12 (left panel). The same doses of *d*-amphetamine only decreased punished responding in subject MS-21 with no history of responding under the avoidance schedule (right panel). Thus, a temporally distant history of responding under the avoidance schedule was sufficient to substantially alter

the effects of *d*-amphetamine, producing a qualitatively different effect of this drug on punished responding. These effects of prior and ongoing experience as determinants of the effects of *d*-amphetamine on punished behavior were confirmed and extended by Bacotti and McKearney (1979).

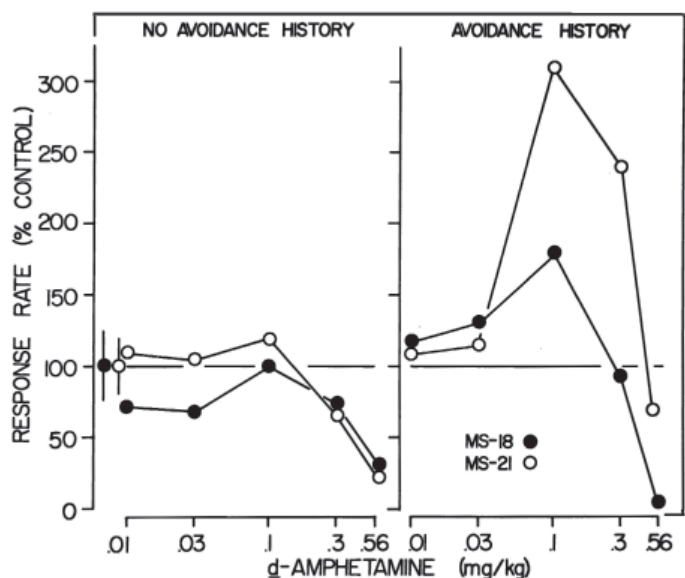


Figure 3. Modification by behavioral history of the effects of *d*-amphetamine on punished responding of squirrel monkeys. Responding was maintained under a five-minute fixed-interval schedule by the presentation of food; each 30th response during this component produced an electric shock which suppressed responding (punishment). The panel on the left shows the effects of *d*-amphetamine on punished responding prior to training under an avoidance schedule in which responding postponed the delivery of electric shock. The panel on the right shows the effects of *d*-amphetamine on these same monkeys after they were exposed to the avoidance schedule. Note that the history of avoidance responding produced a substantial modification of the effects of *d*-amphetamine. (From Barrett, 1987, used with permission.)

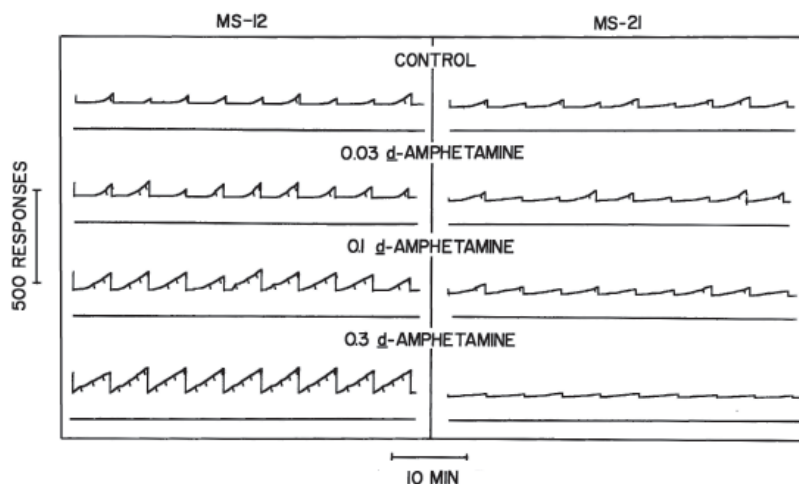


Figure 4. Dependence of the effects of *d*-amphetamine on behavioral history. Cumulative response records from experiments shown in the dose-response curves of Figure 3. Squirrel monkeys were studied under a five-minute fixed-interval schedule of food presentation where every 30th response during the interval produced shock, resulting in a suppression of responding. Subject MS-12 (left panel) had prior exposure to a shock-avoidance schedule whereas subject MS-21 (right panel) had no prior history with that schedule. *d*-Amphetamine increased punished responding only with those monkeys having prior experience under the avoidance schedule. Ordinate: Cumulative responses; Abscissa: Time. The response pens reset following the delivery of food at the completion of each fixed interval. (From Barrett, 1977, used with permission.)

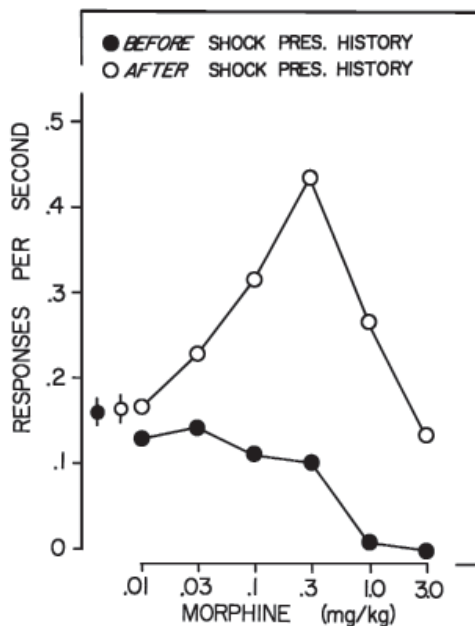


Figure 5. Behavioral history modifies the effects of morphine. Effects of morphine on performances of squirrel monkeys responding under a shock-avoidance schedule before and after exposure to a schedule where responding was maintained by response-produced shock. Note that prior to the exposure to the shock presentation schedule, morphine only decreased avoidance responding, whereas following exposure to the shock presentation schedule, morphine now produced large increases in responding under the avoidance schedule. (Adapted from Barrett and Stanley, 1983, used with permission.)

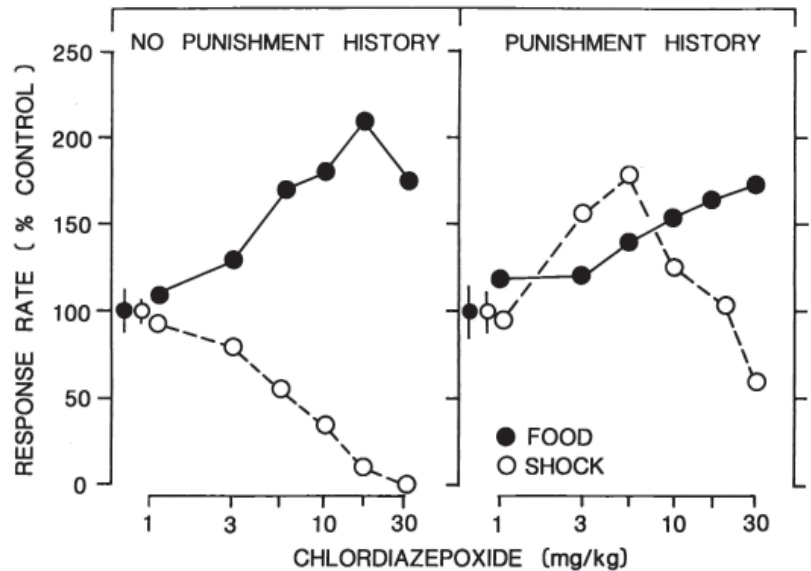


Figure 6. Modification of the effects of chlordiazepoxide by behavioral history. Effects of chlordiazepoxide on responding of squirrel monkeys maintained under a multiple fixed-interval schedule of food or shock presentation (see Figure 1). Dose-response curves on the left were determined prior to a history of punished responding, whereas those on the right were obtained after training under a schedule where food-maintained responding was punished. Note that chlordiazepoxide's effects on shock-maintained responding were reversed following the punishment history. (Barrett and Witkin, 1986, used with permission.)

Subsequent studies indicated that the effects of drugs other than *d*-amphetamine could also be reversed by behavioral history. For example, a history of responding under a fixed-interval schedule of shock presentation reversed the rate-decreasing effects of morphine on avoidance responding (Barrett and Stanley, 1983, Figure 5); these effects of morphine also occurred when responding was concurrently maintained by the schedules of response-produced shock and shock avoidance (not shown). In addition, the rate-decreasing effects of chlordiazepoxide on responding maintained by electric shock can be reversed in monkeys with a history of punished responding (Figure 6). That the effects of drugs such as cocaine (see below), *d*-amphetamine, morphine, and chlordiazepoxide can produce different outcomes depending on behavioral history is of interest, for it suggests that the behavioral effects of these drugs which are often abused can depend quite critically on prior consequences of behavior.

Several experiments were conducted to further examine the conditions potentially contributing to the effects of behavioral history. In one experiment (Barrett and Witkin, 1986), the role of the avoidance schedule was examined by first determining the effects of *d*-amphetamine on punished responding. One monkey of a pair was then exposed to an avoidance schedule where responding postponed the delivery of shock. A second monkey was "yoked" to this monkey. The yoked monkey received the same shocks that were not avoided by the "lead" monkey. Thus, the yoked monkey received the same intensity and temporal distribution of shocks but had no control over their delivery. When the punishment schedule was reintroduced, *d*-amphetamine increased responding in those monkeys with an avoidance history (Figure 7, filled circles) but had no effect or only decreased responding in the yoked subjects (Figure 7, filled squares). Thus, the avoidance schedule and the contingencies arranged by that procedure are the significant factors in contributing to the behavioral history.

Further studies were conducted to determine whether the response that was trained under the avoidance schedule had to be the same as that under the punishment schedule. The question was whether the avoidance response could be trained using one response manipulandum with punished responding maintained using a different manipulandum. One way of looking at this question was whether it was sufficient to have a behavioral history of shock avoidance even with a response that differed from that which was subsequently punished. To examine this question, squirrel monkeys were trained under a shock avoidance schedule using a chain-pulling response. Lever pressing was established with food as a

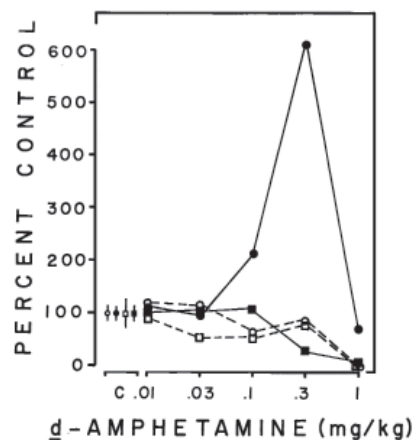


Figure 7. Effects of *d*-amphetamine on punished responding before and after exposure to either an avoidance schedule or to a schedule of response-independent shocks (yoked procedure). Open symbols represent the effects of *d*-amphetamine on punished responding before exposure to an avoidance schedule (circles) or, in separate monkeys, prior to the response-independent delivery of shocks not avoided by the monkey responding under the avoidance schedule (squares). Filled symbols show the effects of *d*-amphetamine following exposure to the avoidance schedule (circles) or on subjects after receiving the yoked, response-independent shock history (squares). Exposure to the avoidance schedule was essential for modifying the effects of *d*-amphetamine on punished responding. (Adapted from Barrett and Witkin, 1986, used with permission.)

reinforcer and the effects of cocaine examined under a schedule in which lever pressing was punished (Tatham et al., 1993). The results were comparable to those obtained when the same response was maintained throughout; i.e., cocaine produced increases in punished lever pressing even though the history of avoidance responding was established using a chain-pulling response. Thus, these results indicate that the history of shock avoidance, even though established with a different behavioral response, still has a substantial effect in diametrically changing the effects of a drug from decreases to increases in the likelihood of a response.

In a further effort to evaluate the role of the shock postponement or avoidance schedule, responding of squirrel monkeys was initially maintained under a differential-reinforcement of low-rate schedule (DRL) where responding within a certain period of time postpones the delivery of food (Tatham and Barrett, 1993). The rationale behind this study was that perhaps the behavior of postponing a consequent event may alter the pharmacology of cocaine. Following training under the DRL schedule, monkeys were then exposed to the punishment procedure and the effects of cocaine were determined. Under those conditions, cocaine did not produce increases in punished responding. However, when those animals were subsequently training under the avoidance schedule and cocaine effects were re-determined, increases in punished responding occurred. Thus, this study provides another example, in addition to that of Barrett and Witkin (1986) and Tatham et al. (1993), where the avoidance schedule appears to be critical in establishing this particular pharmacological plasticity of drug effects on punished responding related to behavioral history.

Drug-Behavior Interactions and Pharmacological History

There are now a number of instances where the administration of a drug under a particular set of experimental conditions produces a behavioral effect that is opposite that typically obtained. In most instances, these effects have been shown to persist even when those initial conditions are removed. These experiments provide further examples of the 'plasticity' of the pharmacological effects of drugs on behavior and add a further dimension to our understanding of the many determinants of drug action. As one example of this drug-behavior interaction, Brady and Barrett (1986) studied the effects of morphine on squirrel monkeys responding under a multiple fixed-interval schedule where responding in each of the two components terminated a visual stimulus in the presence of which shocks could occur. During one of these components, every 30th response also produced shock and responding was suppressed (punishment). In contrast to the previous literature on the effects of morphine on punished responding, this drug produced large increases in punished responding under the multiple schedule, effects that persisted when the effects of morphine were examined under the single schedule of punished responding alone (Figure 8). Morphine was then examined in another set of subjects under the punishment schedule alone and did not increase punished responding (Brady and Barrett, 1986). However, when subjects were subsequently trained under the multiple schedule and administered morphine, increases in punished responding occurred and again persisted when its effects were re-examined under the punishment condition alone (data not shown). These and similar studies suggest that the combined exposure to a drug and a specific behavioral experience can produce dramatic differences in drug effects that persist even when the original conditions that induced those effects are removed.

Although these experiments on drug-behavior interaction history are similar in many respects to those discussed previously as contextual determinants, there are other instances in which the effects of pharmacological history alone have been shown to affect the actions of a drug. In one set of experiments, Glowa and Barrett (1983) showed that the effects of pentobarbital on punished responding of squirrel monkeys maintained under a schedule of stimulus-shock termination depended on whether those monkeys had previously received morphine under these schedule conditions. In monkeys without prior exposure to morphine, pentobarbital increased responding, whereas in monkeys with prior morphine experience pentobarbital produced decreases in responding. These findings suggest that the behavioral effects of drugs may depend on previous experience with other drugs, even when those drugs are from a different pharmacological class.

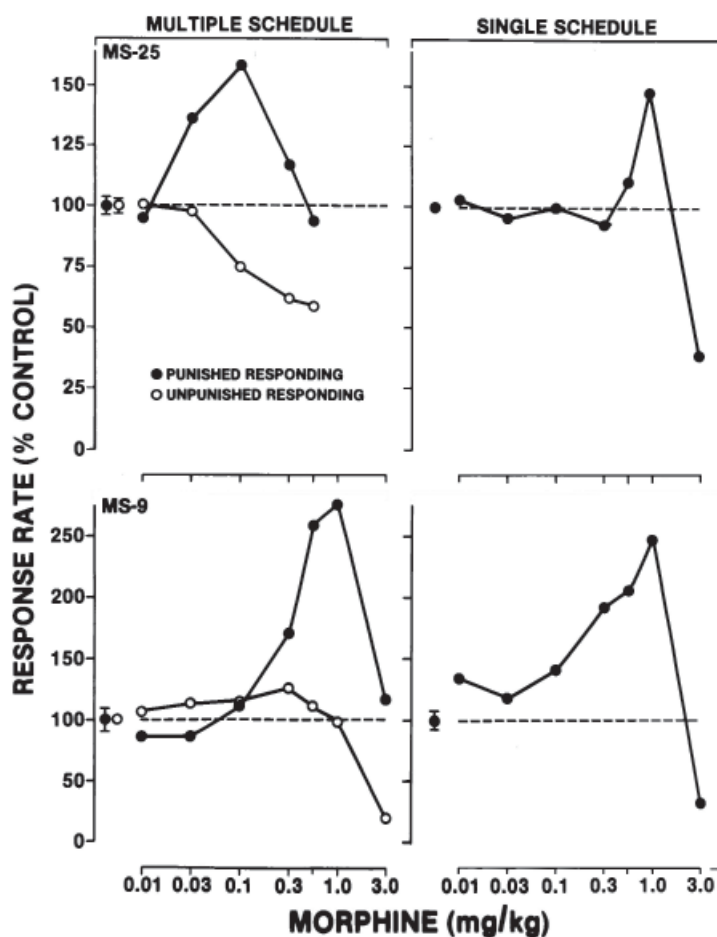


Figure 8. Dose-response curves for two squirrel monkeys under multiple- and single-schedule conditions in which responding was maintained under a fixed-interval stimulus-shock termination schedule; the first response after five minutes terminated a visual stimulus in the presence of which shocks could occur. During one component of the multiple schedule, every 30th response produced a shock which suppressed responding during that component (punishment). The effects of morphine were studied under the multiple schedule and subsequently under the single schedule of punishment alone. In contrast to the effects of morphine on punished responding in the absence of these conditions, morphine increased punished responding. Thus contextual or historical factors can dramatically affect morphine's effects on behavior. (Brady and Barrett, 1986, used with permission.)

The importance and impact of pharmacological history has also been seen in drug discrimination experiments in which prior drug history has been shown to enhance or diminish the discriminative stimulus effects of drugs that have multiple neuropharmacological actions. Findings from drug discrimination studies indicate that prior pharmacological experience appears to be capable of 'biasing' the subjective effects of drugs, thereby enhancing or diminishing the discriminative stimulus effects of drugs with multiple pharmacological effects (Barrett and Olmstead, 1989). Studies in humans have also reported a relationship between prior drug experience and later use and/or addiction (Haertzen et al., 1983). Other studies have examined the role of drug history in self-administration experiments and have demonstrated that pharmacological history can affect the potential for a drug to be self-administered (e.g., Bergman and Johanson, 1985; Falk and Tang, 1989; Panlilio et al., 2013; Shinday et al., 2013; Young et al., 1981). For example, Hiranita et al. (2013) have shown that rats that previously self-administered cocaine will also self-administer σ_1 receptor agonists (σ_1 Rs). However, without that history, σ_1 R agonists were not self-administered. Of interest, is the additional finding in this study that the reinforcing effects of the σ_1 R agonists were not mediated by dopamine receptor systems; dopamine receptor antagonists, which blocked cocaine self-administration, did not block the self-administration of the σ_1 R compounds. In addition, there were no changes in dopamine levels in the nucleus accumbens shell at doses of the σ_1 R agonists that were self-administered. These studies taken as a whole provide a compelling perspective on the powerful effects of prior behavioral experience and pharmacological history on the effects of abused drugs. As Falk (1983) once commented, "Pharmacological structure does not imply motivational destiny" (p. 320).

Summary and Conclusions

Peter Dews has had a significant and enduring influence on the field of behavioral pharmacology. This influence is based not only on his establishing its origins, blending the two disciplines of the experimental analysis of behavior and pharmacology, but also on how that field developed following his initial studies and how it has matured throughout the past near 60 years. Many of the themes and implications regarding the role and importance of the environment and of the influence of schedule-controlled rates and patterns of responding on drug action have served to guide research for many years, allowing the field to develop following the principles of an experimental and quantitative discipline closely and beneficially aligned with both pharmacology and the experimental analysis of behavior. This article serves as a reminder of just how prescient Dews was in his framing of the scope and importance of behavioral pharmacology and how far the current emphasis seems to have drifted from those early concepts which addressed intriguing and fundamentally important questions about the behavioral determinants of drug action that remain unresolved to this day.

The collective findings summarized in this manuscript, representing the contributions of many individuals, may have certain implications not only for formulating issues fundamental to an analysis of the behavioral effects of drugs but also to increasing our understanding of drugs of abuse and abuse liability. One striking aspect of the many studies summarized in this manuscript is the observed "pharmacological plasticity," that is, the multiple ways in which drugs can affect behavior. This plasticity is intimately linked to the schedule of reinforcement, to behavioral consequences, to the environmental context and to behavioral and pharmacological history. It is important to appreciate that all these factors contribute eventually to historical influences on behavior and on the effects of drugs. An experimental or an environmental context in which events occur and produce behavioral consequences becomes part of that individual's repertoire and governs future behavior. As we have seen here, these influences can play an overwhelming role in the effects of drugs.

The effects summarized here have been seen predominantly with a wide variety of abused drugs from different pharmacological classes. If certain drugs are abused due to their effects on behavior, and those behavioral effects are related to past behavioral experience or to experience with a particular drug, then such historical factors become exceedingly important in our understanding of the etiology of substance abuse and in the development of various approaches undertaken for treatment and prevention strategies. A better understanding of those behavioral and pharmacological factors may generate novel approaches for 'immunizing' individuals against the effects of drugs having abuse liability and for the development of potential pharmacological interventions. Although seemingly remote at the present time, it remains quite clear that both behavioral and pharmacological variables can influence the effects of abused drugs in striking and significant ways as suggested throughout this paper.

A related point has evolved from the studies demonstrating the importance of behavioral history in determining the effects of abused drugs. In the majority of the studies described in this manuscript, the behavioral performances were comparable prior to and following the interpolated procedure that was responsible for modifying drug effects. Thus, although the ongoing rate and pattern of responding can be an important influence on the effects a drug will have on behavior, it is not all determining. A number of abused drugs can reveal "sequestered" or residual influences on behavior that are not otherwise evident in ongoing behavior. Prior behavioral experience can leave residual effects that are not manifested in ongoing behavior and are observed only following the administration of a particular drug. The nature of those residual influences remains unclear at the present time and in need of clarification.

It is becoming increasingly possible to probe more deeply into "structural plasticity" associated with exposure to drugs of abuse that may yield further insight into changes occurring at the molecular and epigenetic level. For example, Robinson and Kolb (2004) have demonstrated that exposure of rats to amphetamine, morphine, cocaine, or nicotine produces persistent alterations in dendritic structure and on dendritic spines on cells in brain regions such as the nucleus accumbens. These authors suggest that this plasticity in CNS structure following exposure to abused drugs may be responsible for some of the factors related to addiction and may also be related to behaviorally-driven influences as well. Similarly, Nader et al. (2006) have demonstrated long-term decreases in dopamine D2 receptor availability in rhesus monkeys following a one-year period of cocaine self-administration suggesting that the plasticity induced by these changes in CNS activity are long lasting. Finally,

Damez-Werno et al. (2012) have reported that repeated exposure to cocaine produces epigenetic modifications in chromatin that can be viewed as "epigenetic scars" suggesting another approach to addressing and clarifying some of the issues related to both the pharmacological and behavioral factors that may provide new insights into the molecular neurobiology of drug addiction.

It is quite clear that the marriage of the experimental analysis of behavior and pharmacology has been an active and vibrant field, only a portion of which is summarized in this manuscript. The field of behavioral pharmacology has frequently been criticized for its emphasis on overt schedule-controlled behavior to the exclusion of other variables and hypothetical mechanisms. However, knowledge of the pharmacology and neuropharmacological mechanisms and molecular biology of abused drugs, while of unquestionable importance, does not provide a complete account of the behavioral effects of drugs of abuse. As Dews once said, "A drug is obviously essential for drug addiction, as are Mycobacteria for tuberculosis ...[but] ...knowledge of the pharmacology of abused drugs will not tell us all we need to know about addiction" (Dews 1973, p. 37). The point is that behavioral analyses continue to demand far more attention than has been the case in recent years. Indeed, the enduring legacy to Dews's many contributions will be in a continued analysis of, and appreciation for, the importance of environmental influences on the effects of drugs on behavior and of the importance of behavioral pharmacology to the broader discipline of pharmacology.

Acknowledgements

There are many individuals to thank for providing me with the behavioral history and the experimental context that allowed me to pursue the majority of the studies described in this manuscript leading to the receipt of this award. The influences of Peter B. Dews, W.H. Morse, R.T. Kelleher and J.W. McKearney were pivotal and profound in the shaping of my behavior and in the development of my career. It is especially meaningful to have been the recipient of this award in light of the influence that Peter's experimental and conceptual contributions had on my career. My postdoctoral experience with Jim McKearney at the Worcester Foundation for Experimental Biology was exceedingly important in providing a rich and exciting repertoire of behavioral and pharmacological opportunities that were really the precursor of much that followed. I would also wish to thank the many students who contributed to these studies and to my career as well. Many are mentioned in the body of the text and in the references; what can never be conveyed in writing is the mixture of excitement, surprise, and enjoyment we had in developing these and other studies. It simply would not have been possible to approach the recognition that has led to the receipt of this award without their substantive contributions, both experimentally as well as with their enduring friendships. We all derived a collective satisfaction that we were potentially contributing to the foundation of behavioral pharmacology that was initiated by Peter and his colleagues. I would also like to thank my wife, Maura, who has throughout been extremely understanding and supportive of the many activities that are part of one's career. Finally, it especially sad that in the same year that this Award was received, Peter passed away. There is an obituary by W.H. Morse published in this issue of *The Pharmacologist* as well as an "In Memoriam" published in *The Behavior Analyst* (Barrett, 2013).

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References

- Bacotti AV and McKearney JW (1979) Prior and ongoing experience as determinants of the effects of d-amphetamine and chlorpromazine on punished behavior. *J Pharmacol Exp Ther* **211**:80-85.
- Barrett JE (1976) Effects of alcohol, chlordiazepoxide, cocaine and pentobarbital on responding maintained under fixed-interval schedules of food or shock presentation. *J Pharmacol Exp Ther* **196**:605-615.
- Barrett JE (1977) Effects of d-amphetamine on responding simultaneously maintained and punished by presentation of electric shock. *Psychopharmacology* **54**:119-124.
- Barrett JE (1985) Modification of the behavioral effects of drugs by environmental variables, in *Behavioral Pharmacology: The current status*, (Seiden LS and Balster RL, eds.) pp. 7-22, Alan R. Liss, Inc., New York.
- Barrett JE (1987) Nonpharmacological factors determining the behavioral effects of drugs, in *Psychopharmacology: The Third Generation of Progress* (Meltzer HY, ed.) pp. 1493-1501. Raven Press, New York.
- Barrett JE (2013) Peter B. Dews, In Memoriam. *The Behavior Analyst*, in press.
- Barrett JE and Glowa JR (1977) Reinforcement and punishment of behavior by the same consequent event. *Psychol Rep* **40**:1015-1021.
- Barrett JE, Glowa JR and Nader MA (1989) Behavioral and pharmacological history as determinants of tolerance- and sensitization-like phenomena in drug action, in *Psychoactive Drugs* (Goudie A and Emmett-Oglesby M, eds.) pp. 181-219, Humana Press, Clifton, New Jersey.
- Barrett JE and Katz, JL (1981) Drug effects on behaviors maintained by different events, in *Advances in Behavioral Pharmacology* (Thompson T, Dews PB and Kim WA, eds.) vol. 3, pp. 119-168, Academic Press, New York.
- Barrett JE and Olmstead SN (1989) Spiroxatrine as a discriminative stimulus: Effects depend upon pharmacological history. *Drug Dev Res* **16**:365-374.
- Barrett JE and Spealman RD (1978) Behavior simultaneously maintained by both presentation and termination of noxious stimuli. *J Exp Anal Behav* **29**:375-383.

- Barrett JE and Stanley JA (1980a) Maintenance of responding by squirrel monkeys under a concurrent shock-postponement, fixed-interval shock presentation schedule. *J Exp Anal Behav* **34**:117-129.
- Barrett JE and Stanley JA (1980b) Effects of ethanol on multiple fixed-interval fixed-ratio schedule performances: Dynamic interactions at different fixed-ratio values. *J Exp Anal Behav* **34**:185-198.
- Barrett JE and Stanley JA (1983) Prior behavioral experience can reverse the effects of morphine. *Psychopharmacology* **81**:107-110.
- Barrett JE and Witkin JM (1986) The role of behavioral and pharmacological history in determining the effects of abused drugs, in *Behavioral Analysis of Drug Dependence* (Goldberg SR and Stolerman IP, eds.) pp. 195-223, Academic Press, New York.
- Bergman J and Johanson CE (1985) The reinforcing properties of diazepam under several conditions in the rhesus monkey. *Psychopharmacology* **86**:108-113.
- Brady LS and Barrett JE (1986) Drug-behavior interaction history: Modification of the effects of morphine on punished behavior. *J Exp Anal Behav* **45**:221-228.
- Byrd LD (1969) Responding in the cat maintained under response-independent electric shock and response-produced electric shock. *J Exp Anal Behav* **12**:1-10,
- Damez-Werno D, LaPlant Q, Sun H, Scobie KN, Dietz, DM, Walker IM, Koo, JW, Vialou VF, Mouzon E, Russo SJ and Nestler EJ (2012) Drug experience epigenetically primes *Fosb* gene inducibility in rat nucleus accumbens. *J Neurosci* **32**:10267-10272.
- Dews PB (1955) Studies on behavior. I. Differential sensitivity to pentobarbital of pecking performance in pigeons depending on the schedule of reward. *J Pharmacol Exp Ther* **113**:393-401.
- Dews PB (1973) The behavioral context of addiction. *Bayer-Symposium IV, Psychic Dependence*, pp. 36-46, Springer-Verlag, Berlin.
- Dews PB (1974) What is analgesia?, in *Narcotic antagonists* (Braude MC, Harris LS, May EL, Smith JP and Villarreal, eds.) pp. 235-243, Advances in biochemical psychopharmacology, vol. 8, Raven Press, New York.
- Dews PB (1975) Neurotransmitter balances and behavior, in *Neurotransmitter balances regulating behavior* (Domino EF and Davis JM, eds.) pp. 125-133, NPP Books, Arlington, Massachusetts.
- Dews PB and Wenger GR (1977) Rate-dependency of the effects of amphetamine, in *Advances in Behavioral Pharmacology* (Thompson T and Dews PB, eds.) vol. 1, pp. 167-227, Academic Press, New York.
- Egli M and Thompson T (1989) Effects of methadone on alternative fixed-ratio fixed-interval performance: Latent influences of schedule-controlled responding. *J Exp Anal Behav* **52**:141-153.
- Falk JL (1983) Drug dependence: Myth or motive? *Pharmacol Biochem Behav* **19**:385-391.
- Falk JL and Tang M (1989) Schedule-induced chlordiazepoxide intake: differential effect of cocaine and ethanol histories. *Pharmacol Biochem Behav* **33**:393-396.
- Ferster CB and Skinner BF (1957) *Schedules of Reinforcement*. Appleton-Century Crofts, New York.
- Glowa JR and Barrett JE (1983) Drug history modifies the behavioral effects of pentobarbital. *Science* **220**:333-335.
- Haertzen CA, Kocher TR and Miyasato K (1981) Reinforcement from the first drug experience can predict later drug habit and/or addiction: Results with coffee, cigarettes, alcohol, barbiturates, minor and major tranquilizers, stimulants, amarijuana, hallucinogens, heroin, opiates and cocaine. *Drug and Alcohol Dependence* **11**:147-165.
- Hiranita T, Meueu M, Soto PL, Tanda G and Katz JL (2013) Self-administration of cocaine induces dopamine-independent self administration of sigma agonists. *Neuropsychopharmacology* **38**:605-615.
- Katz JL and Barrett JE (1978) Ethanol, pentobarbital and chlordiazepoxide effects in squirrel monkeys responding under fixed-ratio food presentation and stimulus-shock termination schedules. *Psychopharmacology* **56**:153-155.
- Kelleher RT and Morse WH (1964) Escape behavior and punished behavior. *Fed Proc* **23**:808-817.
- Kelleher RT and Morse WH (1968a) Schedules using noxious stimuli. III. Responding maintained with response-produced electric shocks. *J Exp Anal Behav* **11**:819-838.
- Kelleher RT and Morse WH (1968b) Determinants of the specificity of the behavioral effects of drugs. *Ergeb Physiol Biol Chem Exp Pharmacol* **60**:1-56.
- McKearney JW (1968) Maintenance of responding under a fixed-interval schedule of electric shock presentation. *Science* **160**:1249-1251.
- McKearney JW (1974) Effects of d-amphetamine, morphine and chlorpromazine on responding under fixed-interval schedules of food presentation or electric shock presentation. *J Pharmacol Exp Ther* **190**:141-153.
- McKearney JW and Barrett JE (1975) Punished behavior: Increases in responding after d-amphetamine. *Psychopharmacologia* **41**:23-26.
- McKearney JW and Barrett JE (1978) Schedule-controlled behavior and the effects of drugs, in *Contemporary research in behavioural pharmacology* (Blackman DE and Sanger DJ eds.) pp. 1-68, Plenum Press, New York.

Nader MA, Czoty PW, Nader SH and Morgan D (2012) Nonhuman primate models of social behavior and cocaine abuse. *Psychopharmacology* **224**:57-67.

Nader MA, Morgan D, Gage HD, Nader SH, Calhoun TL, Buchheimer N, Ehrenkauffer R and Mach RH (2006) PET imaging of dopamine D2 receptors during chronic cocaine self-administration in monkeys. *Nat Neurosci* **9**:1050-1056.

Nader MA, Tatham TA and Barrett JE (1992) Behavioral and pharmacological determinants of drug abuse. *Ann NY Acad Sci* (The Neurobiology of Drug and Alcohol Addiction) vol. 654, pp. 368-385.

Nader MA and Thompson T (1987) Interaction of methadone, reinforcement history and variable-interval performance. *J Exp Anal Behav* **48**:303-315.

Nader MA and Thompson T (1989) Interaction of reinforcement history with methadone on responding maintained under a fixed-interval schedule. *Pharmacol Biochem Behav* **32**:643-649.

Panlilio LV, Zanettini C, Barnes C, Solinas M and Goldberg SR (2013) Prior exposure to THC increases the addictive effects of nicotine in rats. *Neuropsychopharmacol* advance online publication, February 6, 2013; doi:10.1038/npp.2013.16.

Poling A, Krafft K, Chapman L (1980) d-Amphetamine, operant history, and variable-interval performance. *Pharmacol Biochem Behav* **12**:559-562.

Reynolds GS (1961a) Behavioral contrast. *J Exp Anal Behav* **4**:57-71.

Reynolds GS (1961b) An analysis of interactions in a multiple schedule. *J Exp Anal Behav* **4**:107-117.

Robinson TE and Kolb B (2004) Structural plasticity associated with exposure to drugs of abuse. *Neuropharmacol* **47**:33-46.

Shinday NM, Sawyer EK, Fischer BD, Platt DM, Licata SC, Atack JR, Dawson, GR, Reynolds DS, and Rowlett JK (2013) Reinforcing effects of compounds lacking intrinsic efficacy at $\alpha 1$ subunit-containing GABAA receptor subtypes in midazolam- but not cocaine-experienced rhesus monkeys. *Neuropsychopharmacol* advance online publication, January 16, 2013; doi:10.1038/npp.2012.265.

Spealman RD (1976) Interactions in multiple schedules: The role of the stimulus reinforce contingency. *J Exp Anal Behav* **26**:79-93.

Spealman RD (1979) Behavior maintained by termination of self-administered cocaine. *Science* **204**:1231-1233.

Tatham TA and Barrett JE (1993) Shock avoidance but not DRL history reverses the behavioral effects of cocaine on punished behavior. *Behav Pharmacol* **4**:159-166.

Tatham TA, Gyorda AM and Barrett JE (1993) Generalization of behavioral history across responses in the reversal of the effects of cocaine and d-amphetamine on the punished responding of squirrel monkeys. *Behav Pharmacol* **4**:61-68.

Urbain C, Poling A, Millam, J and Thompson T (1978) d-Amphetamine and fixed-interval performance: effects of operant history. *J Exp Anal Behav* **29**:385-392.

Valentine JO, Katz JL, Kandel DA and Barrett JE (1983) Effects of cocaine, chlordiazepoxide and chlorpromazine on responding of squirrel monkeys under second-order schedules of IM cocaine injection or food presentation. *Psychopharmacology* **81**:164-169.

Wanchisen BA, Tatham, TA and Mooney, SE (1989) Variable-ratio conditioning history produces high- and low-rate fixed-interval performance in rats. *J Exp Anal Behav* **52**:167-179.

Weiner H (1964) Conditioning history and human fixed-interval performance. *J Exp Anal Behav* **7**:383-385.

Young AM, Herling S and Woods JH (1981) History of drug exposure as a determinant of drug self-administration, in *Behavioral pharmacology of human drug dependence* (Thompson T and Johanson CE, eds.) NIDA Research Monograph No. 37, pp. 75-89, U.S. Government Printing Office, Washington, D.C.

Celebrating the Life of Peter Dews



Please join us to celebrate the life of Peter Dews (1922-2012), whose life and work contributed greatly to the development of behavioral pharmacology as a discipline.

Tuesday, April 23, 2013

Harvard Club (Bartlett Room), 374 Commonwealth Avenue, Boston, MA

6:30 - 9:00 p.m.

RSVP is required. If you would like to attend, please email Danielle Jordan at djordan@aspet.org.

In Sympathy

ASPET Notes with Sympathy the Passing of the Following Members:

| | | | |
|----------------------|----------------------|-------------------|---------------|
| John P. Bunker | Peter B. Dews | Jerome J. Kamm | Roger Sevy |
| Virginia E. Davis | Benjamin D. Fremming | Richard D. Levere | Yung J. Sohn |
| Salvatore J. DeSalva | Leo R. Goldbaum | John C. McGiff | Ralph D. Tanz |

Obituary

Peter B. Dews (1922-2012)

Peter Dews died on November 2, 2012, after several years of declining health. He is widely recognized as the single individual most responsible for the emergence of behavioral pharmacology as an experimental science concerned with the rigorous assessment of the behavioral effects of drugs. From the time of his first experiments on scheduled-controlled behavior, Dews understood that the sequential scheduling procedures he was using in elucidating the pharmacology of central nervous system (CNS) drugs had general significance for all behavioral phenomena, including many aspects of biomedical sciences. It was through a series of fortunate circumstances and wise decisions on the part of Dews that this Englishman with no formal training in anything to do with behavior became a powerful advocate for an awareness of behavior as a part of biology, and of the need for biological scientists to have an understanding of behavior in physical as opposed to subjective terms.



Peter Dews was born in the north of England, in Yorkshire, and lived there until his mid-twenties. He had very good schooling in the fundamentals of mathematics, physical sciences, and the English language before going to the University of Leeds to study medicine. This early experience, coupled with his original, independent temperament, is reflected in his educational philosophy that one good introductory course is sufficient to prepare a student to begin independent, individual study – very different from the way the same material is taught repeatedly in high school, college and graduate school in the United States. Dews treated postdoctoral fellows as he would like to be treated – to be provided with adequate resources and then left alone to use them.

In medical school, Dews liked physiology and pharmacology the best of all subjects. After finishing his internship in 1945 and not wanting to be a junior person in the Department of Physiology at Leeds, he became a Demonstrator and then Lecturer in the newly established sub-department of Pharmacology under W.A. Bain. Bain had in his possession a large quantity of a potent extract from marijuana (itself a story of serendipity), and Dews began studying the actions of "red oil" on the behavior of laboratory animals with no success at all. However, from that time Dews had an interest in the behavioral effects of drugs. (For more details see Dews, 1997.)

When J.H. Burn came to Leeds to fill in for an unavailable external examiner, he met Dews and invited him to spend the summer of 1946 at Oxford. While there, Dews and J.D.P. Graham studied the diverse pharmacological effects of the antihistamine pyrilamine, a report of which appeared in the first volume of the *British Journal of Pharmacology*. Two years later, Burn suggested Dews as a possible alternative to replace the original candidate for a fellowship position at Burroughs Wellcome in Tuckahoe, New York.

Dews came to the United States in 1948 and spent two years as a research fellow at Burroughs Wellcome. He did collaborative research on the histamine liberator 48-80, and conducted an independent study on the effects of various psychomotor stimulants and convulsants on what he termed "voluntary activity" in mice. During this time, he realized that he was interested in the CNS effects of drugs on behavior, but was still unsure about how to proceed. While at Leeds, he had sought advice from other pharmacologists on ways to study behavior in experimental animals, but nothing that was suggested (Pavlovian conditioning, learning in mazes) seemed suitable to Dews for determining quantitative dose functions. In the 1940s, there was literally no interest among pharmacologists in the United Kingdom in the behavioral effects of drugs, and even Dews himself, when studying the varied pharmacology of antihistamines, never considered investigating the "drowsy" effects reported in man.

Before coming to New York, Dews took a vacation in Switzerland and stopped in Paris at the laboratory of Daniel Bovet to visit with Bernard Halpern, another antihistamine researcher. Their friendship was renewed a year later when Halpern came to New York en route to attend the fall meeting of the American Physiological Society in Minneapolis, and to give a lecture at the Mayo Clinic. When Halpern suggested that Dews accompany him to Minnesota, Dews hastily changed his vacation plans and did so. At the Mayo Clinic, Charles Code, Halpern's host, had a research interest in histamine and antihistamines, and during their first casual conversation, Code asked Dews if he would like to work at the Mayo Clinic, saying that he knew of Dews's antihistamine paper.

In 1949, Peter married Grace Miller, also employed at Burroughs Wellcome, and after fulfilling his commitment there, moved in 1950 to the Mayo Clinic. He worked on the effects of cortisone, ACTH, and adrenalectomy on anaphylaxis in the Section on Physiology with Code, which formed the basis of his Ph.D. in Physiology from the University of Minnesota. The person at the Mayo Clinic who most influenced Dews was the biostatistician, Joseph Berkson, with whom he worked in 1952 as a Research Associate in the Division of Biometry and Medical Statistics. His interest in statistical analysis and estimating error took form then and continued throughout his career, particularly when he later turned his attention to risk assessment in behavioral toxicology.

In 1952, Otto Krayer, at that time seeking someone interested in the CNS to fill a position in his Department of Pharmacology at Harvard, came to Rochester to give a Mayo Foundation Lecture. Earl Wood, who had previously been in Krayer's department, knew that Dews had written a paper on voluntary activity in mice, and suggested Krayer meet him. When they met, Dews (now seven years past his medical degree and on leave from a permanent position in Pharmacology at Leeds) accepted Krayer's offer of an Instructorship.

From the 1930s, B.F. Skinner had been interested in the effects of drugs on behavior, saying the brain could be "unlocked with a molecule better than with a scalpel." After Skinner returned to Harvard from Indiana in 1948, he periodically telephoned Krayer asking if any of his staff members were interested in drugs affecting behavior. Immediately after Dews arrived, Krayer suggested that he go over to Cambridge to see Skinner. Dews met Skinner in his office and then Skinner's associate, Charlie Ferster, showed Dews around the research laboratory. There were more than a dozen set-ups where the pecks of pigeons inside enclosed picnic boxes were being recorded cumulatively in time on paper tracings. Dews had never heard of B.F. Skinner and he didn't know what he and Ferster were studying, but Dews instantly recognized the paper tracings as the equivalent of slope kymograph recordings, and that the procedures that produced them could be what he had been looking for: a way to measure the effects of graded doses of a drug on a quantitative aspect of behavior in continuous time. As Ferster walked around showing the experiments that were going on in the different chambers, he understood that Dews appreciated what he was seeing even without specific knowledge of what the experiments were about. He invited Dews to come back and make injections in the middle of sessions to see what would happen. When such treatments resulted in an interesting change in the pattern of the cumulative response record it constituted an experiment for Ferster. Ferster thought it was wonderful to have Dews coming over and altering schedule performances with injections of pentobarbital, antihistamines, LSD, and the marijuana derivative synhexyl. Single observations on all these drugs are reported in figures in "Schedules of Reinforcement" (1957). It took Dews a little longer to establish to his satisfaction that this was a worthwhile approach for studying the effects of drugs. He did this by chronically treating pigeons with sodium bromide and seeing that their altered performances were related to the bromide blood level.

Ferster gave Dews all the components for several set-ups and helped him put them into operation in the Department of Pharmacology to study the effects of drugs on schedule-controlled performances in the pigeon. Pigeons were not a species used in pharmacological research, but Krayer gave this venture and its subsequent expansion his full support. Krayer championed the extension of pharmacology to other fields as strongly as Skinner championed the wider application of behavioral techniques. Krayer tried to make the professional situation for every member of his department as good as could be, which Dews fully appreciated. In every way, Krayer encouraged this rather unusual type of behavioral research as part of pharmacology, even to reading and commenting on drafts of manuscripts, a helpful but humbling experience for authors. Dews was also outstanding in giving editorial help, and it was a pleasure to get his good advice about manuscripts. If he thought a sentence wasn't quite right, he rewrote it and always made it better. Here and there he would scratch out one word and substitute another that had just the right nuance. He had a very good sense for using words. For example, in 1947, in characterizing the antagonistic properties of drugs such as atropine and antihistamines, Dews employed the term "agonist," a very early, if not the first, use of this word in a pharmacological context to designate the substance against which a specific antagonist is effective.

In his initial experiment, Dews followed Ferster's advice and studied pecking in pigeons where a brief presentation of food followed a peck under two different scheduling conditions. The drug he chose to study was pentobarbital, and its effects on the rate and pattern of pecking were dose-dependently related to the two schedules. (Later he commented that with some other drugs the results would not have been so clear and may have discouraged his continuing this type of research.)

This first experiment influenced Dews profoundly. He realized that he had, at last, quantitative assay procedures for studying the effects of drugs on behavior in a pharmacologically rigorous way. Perhaps equally importantly, he appreciated the positive advantages of Skinner's general approach of studying behavior in an isolated, controlled space without extraneous influences, and describing it in objective physical terms. In subsequent experiments, he used scheduling procedures to study how behavioral effects of drugs were related to the established psychological concepts of motivation and discrimination by varying the degree of food deprivation and the complexity of stimuli. He also continued studies on different scheduling conditions. Neither traditional psychological explanations of behavior nor the pharmacological classification of drugs as stimulants or depressants appeared to be useful in interpreting the details of his results. Generalizing from the combined specific findings in these experiments, Dews concluded that the behavioral effects of drugs depended predominantly on the behavior engendered by the controlling scheduling conditions and could be changed by changing the scheduling conditions. Later, a relation between ongoing behavior and magnitude of drug effect was shown quantitatively for many drugs.

From the start, Dews regarded behavioral pharmacology as a discipline of pharmacology exemplified by rigorous assessment of the effects of drugs on objectively quantifiable behavior, and distinguished it from more clinically oriented psychopharmacology. When *the Journal of Pharmacology and Experimental Therapeutics* established specific field editors to oversee publications in various fields of pharmacology, Dews became the field editor for behavioral studies and in that capacity further influenced the direction of research in behavioral pharmacology. The Division of Behavioral Pharmacology within the American Society for Pharmacology and Experimental Therapeutics has ensured the perpetuation of the Dews legacy by

establishing an award in his name to be given biennially. The most recent recipient of that award, James E. Barrett, has written a scholarly review of the experimental work of Dews and his formative influence on the field of behavioral pharmacology (Barrett, 2006).

Dews joined the Department of Pharmacology at the Harvard Medical School in January 1953, was promoted from Instructor to Associate Professor, and in 1962 was appointed Stanley Cobb Professor of Psychiatry and Psychobiology, assuming wider responsibilities in the Department of Psychiatry. He continued to conduct collaborative experiments on behavioral pharmacology, physiology, and toxicology as before, but from the early 1960s, his major independent research was the quantitative study of schedule-controlled performances. He regarded Skinner's early work and Ferster and Skinner's scheduling procedures as the most significant influences on his career, and a recurring theme in his many reviews and essays was the recognition of how the ongoing behavior of life is controlled by its sequential interplay with environmental happenings.

Dews did not enjoy giving formal lectures, nor were they charismatic, yet his impromptu speaking was elegant and effective, with a delightful quality of improvisation. Lectures in pharmacology given to Harvard medical students by the same individuals were similar year to year, except those of Dews. For example, when lecturing on antiepileptic drugs, which patients take all their lives, Dews once gave a mini-lecture on the importance of physicians working with patients to establish an effective therapeutic dose with minimal side effects for chronically administered drugs. The next year his lecture changed to emphasize neurophysiological aspects of epilepsy. Fortunately, many of the off-the-cuff remarks Dews made at symposia and meetings were preserved in published commentaries, which have the flavor of insightful originality and the use of apt analogies that characterized his impromptu speaking. These writings contrast with the discussion sections of his experimental papers, which never went beyond carefully-worded, logical inferences of the results.

Dews's ability to quickly and wisely discern and clearly express the gist of complex situations made him highly effective on committees at Harvard and nationally. He served on Harvard committees continuously for some thirty-five years, and nationally on committees relating to mental health, drug dependence, social behavior, brain research, pharmacology, toxicology, space science, and evaluations of training and research programs. He said that he liked committee work and found it relaxing, taking him away from the rigor of laboratory experiments.

In contrast to his active participation in committees, Dews's habitual manner in conducting laboratory research was solitary. He preferred to do the actual work of some experiments himself, and visiting dignitaries were often surprised to find the Professor doing the work of a technician. He never ever spoke about any research that he was conducting independently until it was completed and he had studied the data sufficiently to make some logical conclusions about the results.

For many years, Dews directed a successful National Institute of Mental Health training program for Biological Training in the Behavioral Sciences. He supported collaborations on research in different fields only if the joint research conformed to the accepted standards of each separate field. He believed most research should be conducted with the internal cohesion of a limited context, but that the results of such research took on a greater validity when they could be usefully applied to other areas of research. Understandably, he often cited the successful use of scheduling procedures from psychology in conducting pharmacological studies and the reciprocal influence from studies with drugs in showing the role of ongoing behavior itself as a psychological principle. He felt strongly that medical students should be taught a rational perspective on behavior and behavioral pharmacology. Starting in the late 1950s, one of the twelve student laboratories in pharmacology at Harvard was on the effects of drugs on behavior.

Dews was elected to the American Academy of Arts and Science and the Institute of Medicine, and was a member of a dozen professional societies (pharmacology, physiology, toxicology, neuroscience, and psychology). He served for fifteen years as the director of educational activities for the International Brain Research Organization. He enjoyed the fellowship of professional colleagues and attended many scientific meetings. Traveling for Dews was exploring where tourists never go, using public transportation, getting to know the local culture, and speaking the local language as much as possible. This robust adventurous spirit was also evident in the leisure activities Dews liked best: bicycling, swimming, hiking, and camping with his family.

Dews equaled the behaviorists Watson and Skinner in his disdain for mentalistic and subjective explanations of behavior. Like Skinner, he championed the wider understanding and appreciation of the concept of schedule-controlled behavior, in particular emphasizing in a non-polemic way its importance in other areas of science. After Skinner's death, Dews became the most eloquent advocate for the objective study of behavior as an experimental science and for understanding it in the context of physically defined concepts.

Peter Dews is survived by his wife Grace; daughter Pamela Rentschler; sons, Kenneth, Alan, and Michael; a sister, Jean Hilditch, in England; nine grandchildren, and a great-grandchild.

written by W.H. Morse

References

- Barrett JE (2006) Behavioral determinants of drug action: The contributions of Peter B. Dews. *J Exp Anal of Behav*, **86**: 359-370, 2006.
- Dews PB (1997) Why did behavioral pharmacology develop so late? *European Behavioural Pharmacology Soc Newsletter*, 2-7, June.
- Ferster CB and Skinner BF (1957) *Schedules of Reinforcement*. Appleton-Century-Crofts, Inc., New York.

ASPET

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DMD Adds Editorial Board Members

Twelve researchers were approved by the Board of Publications Trustees to serve on the *Drug Metabolism and Disposition* Editorial Board:

Lauren M. Aleksunes, Assistant Professor, Pharmacology and Toxicology, Rutgers University

Michael D. Cameron, Assistant Professor and Associate Director of DMPK, Translational Research Institute at Scripps Florida

Cuiping Chen, Director of Pharmacokinetics and Clinical Pharmacology, Depomed

Moshe Finel, University Researcher and Group Leader, Center for Drug Research, University of Helsinki

Robert S. Foti, Scientist, Department of Pharmacokinetics and Drug Metabolism, Amgen

Bruno Hagenbuch, Professor of Pharmacology, Toxicology, and Therapeutics, University of Kansas

Wojciech Krzyzanski, Associate Professor of Pharmaceutical Sciences, University at Buffalo, SUNY

Xingrong Liu, Senior Scientist, Drug Metabolism and Pharmacokinetics, Genentech

Donald E. Mager, Department of Pharmaceutical Sciences, University at Buffalo, SUNY

Qingcheng Mao, Associate Professor of Pharmaceutics, University of Washington

Jeffrey Staudinger, Associate Professor of Pharmacology and Toxicology, University of Kansas

Mitchell E. Taub, Boehringer Ingelheim Pharmaceuticals, Inc., Nonclinical DMPK

The Board of Publication Trustees appreciates the commitment of these researchers to DMD, and the Society and is grateful for their service.

BPT Sets Terms for Editorial Board Members

A term-limit policy for the members of ASPET's editorial boards went into effect at the beginning of 2013. Under the new policy, which was approved by the Board of Publications Trustees, Associate Editors and editorial board members for *DMD*, *JPET*, and *Molecular Pharmacology* may be appointed for renewable three-year terms. Terms begin on January 1 of the year in which the board members are appointed. The policy states that Editors have sole discretion on the renewal or nonrenewal of appointments, which should be done within one month of the term's expiration. As in the past, Editors also have the authority to terminate these appointments at any time.

The duties of *Pharmacological Reviews* Associate Editors are different from those serving the other ASPET journals, so that board is not covered by the new policy. The *Pharmacological Reviews* editorial board representatives from the British Pharmacological Society and the Scandinavian pharmacological societies already have term limits.

The policy provides a mechanism for ensuring the continued excellence and efficacy of the editorial team for each ASPET journal.

ASPET, BPS, and Wiley to Launch New Journal

In partnership with the British Pharmacological Society and John Wiley & Sons, Inc., ASPET will publish a new online-only open-access peer-reviewed journal named *Pharmacology Research & Perspectives*. *PR&P* will open for submissions in April 2013. The journal will publish original research, reviews, and perspectives in all areas of preclinical and clinical pharmacology, therapeutics, education, and related research areas.

Pharmacology Research & Perspectives will take advantage of cascading reviews from the other journals published by ASPET and the BPS. Cascading reviews allow scientifically rigorous articles that do not meet the priority objectives of the other journals to be referred to *PR&P* for publication. A referred manuscript with its associated files and reviewer comments will be forwarded to *PR&P* for consideration. The authors of referred papers do not have to start the review process from the beginning, saving time and effort. *PR&P* will also welcome de novo submissions.

Pharmacology Research & Perspectives will be overseen by a management committee with representatives from the three organizations. The journal will have an Editor-in-Chief and a Deputy Editor, each serving for three years. The Deputy Editor will succeed the Editor-in-Chief.

The first Editor-in-Chief, chosen by the BPS, is Dr. Michael J. Curtis, Ph.D., King's College London. Dr. Curtis has extensive editorial experience, serving as Editor-in-Chief of the *Journal of Pharmacological and Toxicology Methods* and Reviews Editor for the *British Journal of Pharmacology*, among other positions.

The first Deputy Editor was chosen by ASPET. The name of the Deputy Editor will be announced by the time of ASPET's annual meeting. Selection of subsequent Deputy Editors will alternate between the BPS and ASPET.

James Barrett, Chair of the Board of Publications Trustees notes that "ASPET is pleased to be working with the British Pharmacological Society and Wiley to launch this exciting new open-access journal, *Pharmacology Research & Perspectives*. The journal builds on the long-standing excellence of the publications associated with the two scientific societies and joins enthusiastically with Wiley in this new endeavor that will provide additional options for scientists and a forum for new directions in the discipline of pharmacology."

"The publication of *Pharmacology Research & Perspectives* puts the ASPET-BPS-Wiley alliance at the forefront of open-access publishing in pharmacology. I am confident the expertise and insight of Mike will ensure we are able to realize the full potential of this exciting opportunity," comments Professor Philip Routledge, BPS President.

Deborah Dixon, VP, Publishing Director, Wiley comments "We are extremely pleased to be partnering with two prestigious organizations to publish this new open-access journal in pharmacology. It will provide authors worldwide with a high-quality publishing option that will be fast and efficient."

All articles in *PR&P* will be published as fully open access under a Creative Commons License on the Wiley Online Library and deposited in PubMed Central immediately upon publication. There will be a publication fee, payable by authors on acceptance of their articles. The publication fee will be discounted for ASPET and BPS members. Authors affiliated with or funded by an organization that has a Wiley Open Access Account can publish without directly paying any publication charges.

The journal expects to publish its first issue in the autumn of 2013.

Like Us! Follow Us!

ASPET's journals launched a social media presence earlier this year on Facebook and Twitter to meet the varying preferences for information delivery. These social media options are offered in addition to email alerts and RSS feeds. These Facebook pages and Twitter feeds also address the needs of those who want to keep up with the journals but who do not necessarily follow news about the society.

Each journal has its own Facebook page and Twitter feed:

| | |
|--|---|
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The Facebook pages and Twitter feeds will be used to:

- Announce new issues
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- Alert readers to minireviews, perspectives, and special sections
- Announce additions to the Editorial Boards
- Alert users to changes in the Instructions to Authors
- Announce new Impact Factors when they come out each year
- Keep followers informed of other changes, updates, and news about the journals

"Like" the journals on Facebook and follow the Twitter feeds to be aware of the latest in content, journal policies, and other important information.



by Jim Bernstein

Budget Cuts Loom as Congress Considers Final FY 2013 Spending Bills; Biomedical Research Community Speaks Out about Spending Cuts to NIH Budget

As you read this newsletter, you will know Congress has fixed, delayed – again, or allowed sequestration to happen on March 1. Developing talks in late February also indicated that Congress may move or restructure the automatic spending cuts so that they will be part of the upcoming talks concerning expiration of the Continuing Resolution (CR) on March 27 and final resolution of the FY 2013 spending bills. The CR has been funding government agencies since October 1, the start of FY 2013.

For many weeks, thousands of biomedical researchers, patient advocates, and academic and medical institutions have continually informed Members of Congress how destructive sequestration or any potential spending cuts would be in future budget negotiations over FY 2013 to NIH and other federal science agencies.

ASPET has been active on several fronts, with members making Congressional visits, contacting their Congressional delegation, and joining coalition efforts to give greater force to a broad community of pharmacologists and other biomedical scientists.

ASPET's Washington Fellows have been coming to Capitol Hill since late February and will continue to make almost forty visits to Congressional offices through early April. There is universal agreement about NIH's mission and broad acceptance that such funding needs to be preserved, but it is difficult in this political and economic environment to find a way to avoid cuts.

In mid-February, ASPET also co-signed two community-wide coalition letters. A letter sent from *Nondefense Discretionary United* was sent to all Members of Congress and the White House. The NDD letter urges the President and Congress to adopt a "balanced" approach to deficit reduction that does not include additional cuts to domestic discretionary programs like the NIH. The NDD letter noted spending on domestic discretionary programs represented just 3.4 percent of the country's Gross Domestic Product in 2011, and under the funding caps established Budget Control Act of 2011 that raised the debt ceiling, by 2021 NDD programs will decline to just 2.5 percent of GDP, the lowest level in at least 50 years. Another important effort was led by the *Ad Hoc Group for Biomedical Research*. This letter was specific to NIH funding (the Ad-Hoc Group's mission is to increase NIH funding). You can read the Ad-Hoc letter on pages 53-54.

White House Details Impact of Sequestration

These efforts came at the same time the White House released specific information on how sequestration would impact NIH, FDA, and other federal agencies.

The White House estimated that mandatory cuts would mean about a 5% reduction for all non-defense programs. But since these spending cut targets must be met in the remaining seven months of the (FY'13) fiscal year, the real percentage reduction would be approximately 9% for non-defense programs. (Defense programs would receive an effective cut of 13%.) The White House release further states that NIH would be:

"...forced to delay or halt vital scientific projects and make hundreds of fewer research awards. Since each research award supports up to seven research positions, several thousand personnel could lose their jobs. Many projects would be difficult to pursue at reduced levels and would need to be cancelled, putting prior year investments at risk. These cuts would delay progress on the prevention of debilitating chronic conditions that are costly to society and delay development of more effective treatments for common and rare diseases affecting millions of Americans."

And the White House release further notes that for FDA, which faces a cut of about \$319 million including user fees, new drug approvals at the Center for Drug Evaluation and Research (CDER) would:

"...face delays in translating new science and technology into regulatory policy and decision-making, resulting in delays in new drug approvals. The FDA would likely also need to reduce operational support for meeting review performance goals, such as the recently negotiated user fee goals on new innovative prescription drugs and medical devices."

While it will have little impact, it was still encouraging to hear the President in his State of the Union address being outspoken in support of science and research:

"If we want to make the best products, we also have to invest in the best ideas. Every dollar we invested to map the human genome returned \$140 to our economy. Today, our scientists are mapping the human brain to unlock the answers to Alzheimer's; developing drugs to regenerate damaged organs; devising new material to make batteries 10 times more powerful. Now is not the time to gut these job-creating investments in science and innovation. Now is the time to reach a level of research and development not seen since the height of the Space Race."

What's Next?

Regardless of how sequestration plays or played out, several looming deadlines also make it certain NIH will face continued threats of budget cuts.

March 27, as mentioned above, is the date the current Continuing Resolution (CR) expires. Congress must pass another CR or finalize spending bills for the fiscal year or the government will shut down. Will additional cuts be part of any deal that completes FY 2013 spending bills?

April 15 is a budget deadline for both the House and Senate to pass their budgets for FY 2014. The Senate expects to pass a budget for the first time in four years, if for no reason this year than they won't get paid if they don't. But House and Senate budget resolutions are only broad guidelines and have no

real force. Tax and spending decisions are made by different committees. Regardless, tight spending caps put pressure to reduce spending further. The House Republican leadership has said that in the absence of sequestration, the budget they will adopt will eliminate the deficit in 10 years.

And on May 19, the debt ceiling suspension will be lifted. The House and Senate had earlier agreed to this date to avoid a government default early this year. This will be a particularly difficult time. Remember back in August 2011, Congress at the last minute agreed to raise the debt ceiling limit but put in place sequestration as a means to make Congress act on significant deficit and debt reduction. House Republicans agreed to suspend the debt ceiling limit until this date with the expectation that there would be additional spending cuts, beyond what was already agreed to in 2011.

ASPET Advocacy Outreach

ASPET members are reminded that the Advocacy Outreach Program is designed to develop awareness in graduate students, postdocs, and faculty of the need for enhanced biomedical research advocacy. The discussion/presentation provides an overview of the political and economic environment impacting NIH funding and the skills needed to allow scientists-advocates to help influence the debate. There is no financial obligation to your institution or department. The ultimate goal of the outreach program is to 1) develop a cadre of interested individuals who will more effectively advocate on critical issues of science funding and science policy and 2) provide individuals the skills needed to become informed and proactive participants in these issues at whatever institution they may find themselves in the near future. ASPET has visited UT Southwestern, Emory University, Wayne State for Michigan's Annual Research Colloquium, University of Louisville, Vanderbilt University Medical Center, and Drexel University College of Medicine. Upcoming visits include the University of South Florida and the University of Buffalo.

Nondefense Discretionary (NDD) United Letter Sent to All Members of Congress and the White House, Co-signed by ASPET

February 11, 2013

Dear Representative:

The undersigned organizations and institutions, which represent patients, scientists, health care providers, and industry, are gravely concerned about the impact of continued cuts, including sequestration, funding shortfalls in fiscal years 2013 and 2014, and the threat of additional cuts to offset the debt ceiling, on medical research supported by the National Institutes of Health (NIH), and the subsequent negative consequences for the health of all Americans.

At a time when we should be investing more in medical research, we have continued to shrink our investment to a point where we are sacrificing real opportunities for discovery of new innovations and medical advances. Declining funding also is eroding our position as the world leader in research and discovery. The NIH serves to improve the health and quality of life for all Americans and spur job creation and economic growth. There is no doubt; the impact of the proposed cut on NIH-funded research will be immediate and devastating. The Senate Budget Committee estimates that sequestration would result in a 5.1 percent reduction in FY 2013 discretionary spending. In a recent interview, NIH Director Francis Collins, M.D., Ph.D., described the impact of sequestration as a "profound and devastating" blow at a time of unprecedented scientific opportunity. Sequestration will come at the end of a decade that has seen the NIH budget fall by nearly 20 percent after inflation, and on top of an estimated \$900 billion in spending cuts mandated by the Budget Control Act over the next ten years. The impact of sequestration would be exacerbated because it would occur in the middle of the fiscal year, forcing researchers to immediately incur drastic budget cuts and abandon potentially life-enhancing research.

The undersigned groups and institutions also are concerned that continued cuts will negatively affect job creation and seriously jeopardize America's leadership in medical research. An analysis released in April 2012 by the Federation of American Societies for Experimental Biology (FASEB) notes that that biomedical research enterprise supports a significant workforce, such that, "the impact on employment and local economies will be immediate and severe." A March 2012 report from United for Medical Research estimates a 7.8 percent reduction in the NIH budget will "result in 33,000 fewer jobs across the U.S. and a \$4.5 billion decrease in economic activity." In May 2012, Research!America warned that sequestration will negatively impact U.S. competitiveness just as other nations are aggressively boosting their investments in research and development.

If we are to address the health challenges of an aging and increasingly diverse population, and remain a vibrant force in the global economy, America needs more investment in medical research, not less. We respectfully urge Congress and the Administration to work together on a solution that preserves the nation's investment in medical research and the health of the American people.

Sincerely,

Academic Pediatric Association
AcademyHealth
Academy of Radiology Research
Ad Hoc Group for Medical Research
Adult Congenital Heart Association
AIDS Alliance for Women, Infants, Children, Youth and Families
The AIDS Institute
Albert Einstein College of Medicine of Yeshiva University and
Montefiore Medical Center
Alliance for Aging Research
Alpha-1 Association
Alpha-1 Foundation
American Academy of Child & Adolescent Psychiatry
American Academy of Developmental Medicine and Dentistry
American Academy of Neurology
American Academy of Pediatrics

American Association for Cancer Research
American Association for Dental Research
American Association for the Study of Liver Diseases
American Association of Colleges of Nursing
American Association of Colleges of Osteopathic Medicine
American Association of Colleges of Pharmacy
American Association of Multi Sensory Environments
American Association of Oral and Maxillofacial Surgeons
American Brain Coalition
American Chemical Society
American College of Cardiology
American College of Neuropsychopharmacology
American College of Radiology (ACR)
American Congress of Obstetricians and Gynecologists
American Federation for Aging Research
American Gastroenterological Association

American Geriatrics Society
American Heart Association
American Lung Association
American Neurological Association
American Pediatric Society
American Physiological Society
American Psychiatric Association
American Psychological Association
The American Society for Cell Biology
American Society for Gastrointestinal Endoscopy
American Society for Microbiology
American Society for Pharmacology & Experimental Therapeutics
American Society for Reproductive Medicine
American Society of Clinical Oncology
American Society of Hematology
American Society of Nephrology

American Society of Pediatric Nephrology
American Society of Transplantation - AST
The American Society of Tropical Medicine and Hygiene
American Sociological Association
American Thoracic Society
American Tinnitus Association
American Urogynecologic Society
Arthritis Foundation
Associated Medical Schools of New York (AMSNY)
Association for Applied Psychophysiology & Biofeedback
Association for Clinical Research Training
The Association for Frontotemporal Degeneration
Association for Patient-Oriented Research
Association for Prevention Teaching and Research
Association for Psychological Science
Association for Research in Vision and Ophthalmology
Association of Academic Health Centers
Association of Academic Health Sciences Libraries
Association of American Cancer Institutes
Association of American Geographers
Association of American Medical Colleges
Association of American Universities
Association of Independent Research Institutes
Association of Medical School Pediatric Department Chairs
Association of Minority Health Professions Schools
Association of Public and Land-grant Universities
Association of Schools of Public Health
Asthma and Allergy Foundation of America
AVAC: Global Advocacy for HIV Prevention
Baylor College of Medicine
Beth Israel Deaconess Medical Center, Boston
Biophysical Society
Boonshoft School of Medicine of Wright State University
Boston University
Brigham and Women's Hospital
BrightFocus Foundation
Brown University
CADASIL Together We Have Hope Non-Profit Organization
Case Western Reserve University
Cedars-Sinai Health System
Central Michigan University College of Medicine
Charles R. Drew University of Medicine and Science
Child Neurology Society
The Children's Hospital of Philadelphia Research Institute
Christopher & Dana Reeve Foundation
City of Hope
Cleveland Clinic Foundation
Clinical Research Forum
Coalition for Imaging and Bioengineering Research
Coalition for the Advancement of Health Through Behavioral and Social Sciences Research (CAHT-BSSR)
Coalition for the Life Sciences
Coalition to Promote Research (CPR)
College on Problems of Drug Dependence
Columbia University Medical Center
Conference of Boston Teaching Hospitals
The Consortium of Academic Centers for Integrative Medicine
Consortium of Social Science Associations (COSSA)
Cooley's Anemia Foundation
COPD Foundation
Cornell University
Council on Governmental Relations
Creighton University
Crohn's & Colitis Foundation of America
Cure Alzheimer's Fund
Cystic Fibrosis Foundation
Dana-Farber Cancer Institute
David Geffen School of Medicine at UCLA
Digestive Disease National Coalition
Drexel University College of Medicine
Drugs for Neglected Diseases Initiative
Duke University School of Medicine
Emory University
The Endocrine Society
Epilepsy Foundation
EPSCoR/IDeA Foundation

Exceptional Parent
Federation of American Societies for Experimental Biology (FASEB)
Federation of Associations in Behavioral & Brain Sciences
Foundation for Biomedical Research
Foundation for Integrative AIDS Research (FIAR)
Friends of NIDA
Friends Research Institute, Inc.
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Geisel School of Medicine at Dartmouth
Genetics Society of America (GSA)
The Gerontological Society of America
Health Sciences South Carolina
Heart Rhythm Society
Hepatitis B Foundation
Herbert Wertheim College of Medicine
HIV Medicine Association
HIV Prevention Justice Alliance (HIV PJA)
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International Cancer Advocacy Network (ICAN)
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International Foundation for Functional Gastrointestinal Disorders
International Rectal Microbicide Advocates
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JDRF
Jeffrey Modell Foundation
Joint Advocacy Coalition of ACRT, APOR, CRF, & SCTS
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Loyola University Stritch School of Medicine
Lupus Foundation of America
Lupus Research Institute
March of Dimes
Massachusetts General Hospital
Massachusetts Institute of Technology
Massachusetts Neuropsychological Society
Mayo Clinic
McLean Hospital
MdDS Balance Disorder Foundation
Medical College of Wisconsin
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Medical University of South Carolina College of Medicine
Medicines for Malaria Venture – MMV
Meharry Medical College
Melanoma Research Alliance
The Methodist Hospital System
The MetroHealth System
Michigan State University
Morehouse School of Medicine
The Mount Sinai Medical Center
National Academy of Neuropsychology
National Alliance for Eye and Vision Research
National Alliance on Mental Illness
National Alopecia Areata Foundation
National Area Health Education Center Organization
National Association of State Alcohol and Drug Abuse Directors
National Marfan Foundation
National Multiple Sclerosis Society
National Organization for Rare Disorders (NORD)
National Osteoporosis Foundation
National Primate Research Centers
National Women's Health Network
NephCure Foundation
Northeastern University
NYU Langone Medical Center
The Ohio State University Wexner Medical Center
Oregon Health & Science University
Pancreatic Cancer Action Network
Parkinson's Action Network
Partners HealthCare
Penn Medicine
Penn State College of Medicine
Population Association of America/Association of Population Centers
Pulmonary Hypertension Association
Project Inform
Prostate Cancer Foundation

Research!America
The Research Institute of Nationwide Children's Hospital
Rutgers, The State University of New Jersey
Saint Francis Hospital and Medical Center, Hartford, CT
Saint Louis University
San Francisco AIDS Foundation
Scleroderma Foundation
SIU School of Medicine
Sjögren's Syndrome Foundation
Sleep Research Society
Society for Behavioral Neuroendocrinology
Society for Clinical and Translational Science
Society for Computers in Psychology (SCIP)
Society for Maternal-Fetal Medicine
Society for Neuroscience
Society for Pediatric Research
Society for Personality and Social Psychology (SPSP)
Society for Psychophysiological Research (SPR)
Society for Research in Psychopathology
Society for Women's Health Research (SWHR)
Society of Biological Psychiatry
Society of Gynecologic Oncology
Society of Hospital Medicine
Society of Mathematical Psychology
Society of Multivariate Experimental Psychology
Spaulding Rehabilitation Hospital
St. Joseph's Hospital and Medical Center
Stanford University School of Medicine
Stony Brook University
Stony Brook University School of Medicine
SUNY Upstate Medical University
Temple University School of Medicine
Texas A&M Health Science Center College of Medicine
Treatment Action Group (TAG)
Tufts Medical Center
Tufts University
Tufts University School of Medicine
Tulane University
Tuskegee University College of Veterinary Medicine, Nursing & Allied Health
UNC School of Medicine
Unite 2 Fight Paralysis
United for Medical Research
University at Buffalo
The University of Alabama at Birmingham
University of California, Irvine
University of California, San Francisco
University of Illinois Chicago College of Medicine
The University of Iowa
University of Kentucky
University of Maryland
University of Massachusetts Medical School
University of Michigan Medical School
University of Minnesota Medical School
University of Missouri-Kansas City School of Medicine
University of Nebraska Medical Center
University of New Mexico
The University of North Carolina at Chapel Hill
University of Oklahoma Health Sciences Center
University of Pittsburgh School of Medicine
University of Rochester
University of Rochester School of Medicine and Dentistry
University of South Dakota Sanford School of Medicine
University of Tennessee
University of Vermont College of Medicine
University of Washington
University of Wisconsin School of Medicine and Public Health
University Professors of Neurology
US Hereditary Angioedema Association
Vanderbilt University
Virginia Commonwealth University
Wake Forest School of Medicine
Washington University in St. Louis
Wayne State University School of Medicine
Western Michigan University School of Medicine
Yale School of Medicine

Book Review

by Christine K. Carrico, Ph.D.

State of Wonder

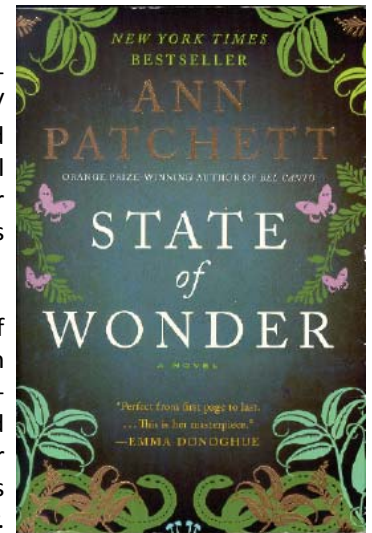
State of Wonder by Ann Patchett, prize-winning author of Bel Canto, takes place primarily in the Brazilian jungle and purports to be about pharmacology. Marina Singh started out her career as an OB/GYN. Following a horrendous error during a Caesarean delivery while in her residency, she retreated to the relative safety of bench research in pharmacology for a small pharmaceutical company (Vogel Pharmaceuticals). While I initially wished that the protagonist had elected pharmacology as her chosen career rather than as a second best to medicine, it became clear later in the book why this transition from bedside to bench was important to the plot.

The story begins with Dr. Singh receiving notification that her colleague, Anders Eckman, has died of a fever in Brazil while on company business. Company business, it turns out, was to attempt to pin down the research progress of an eccentric and egotistical company scientist pursuing a drug that allowed women in one indigenous tribe to bear children until the ends of their lives. Dr. Swenson had been in the Amazon for over five years; no one knew exactly where, since she refused to disclose her location, refused to call when she did visit civilization, and failed to respond to any written requests for research updates. Dr. Singh is selected by the board of Vogel Pharmaceuticals to complete Dr. Eckman's mission, since 15+ years earlier, she had done her OB/GYN training under Dr. Swenson. Eckman's widow also begs her to go and find out exactly what happened to her husband. So with vaccinations updated and an ample supply of Lariam to protect her from malaria, Marina Singh heads to Manaus, Brazil to first attempt to make contact with the illusive Dr. Swenson, obtain details on Anders Eckman's death, and yes, get the highly important research progress report.

Manaus is suffocatingly hot, Marina's luggage gets lost, she suffers terrible side effects from the Lariam, and Dr. Swenson's apartment is occupied by a feckless young Australian couple whose main function seems to be to keep people from contacting Dr. Swenson. Barbara and Jackie Bovender are, respectively, a "writer" and a surfer, and they appear to freeload around the world looking for inspiration and the perfect wave. They set out to entertain Marina, while at the same time attempting to dissuade her from waiting for Dr. Swenson to return to Manaus. After many diversions, digressions, and evasions, Marina Singh finally meets Dr. Swenson and heads back up the Rio Negro with her and a young deaf and blind boy named Easter to begin life with the Lakashi tribe.

Put to work analyzing blood levels of the wonder drug that allows pregnancy at any age, Marina realizes that she is doing exactly what Vogel needs – verifying research results. She also observes many ancient tribal women in advanced stages of pregnancy. Talking to one of Dr. Swenson's colleagues, she learns that the drug also has other highly beneficial and salutious effects, including the prevention of malaria. It is interesting reading about Marina's assimilation into the tribe and her gradual recognition that the error that she made as a resident could have been made by anyone. There is a lot of introspection on her part, there being little else to do in the jungle, including the status of her romantic relationship with Mr. Fox, the president of Vogel Pharmaceuticals. Eventually, Barbara Bovender shows up with Mr. Fox, who has come to find Marina since none of her letters have reached him. This presents a moral dilemma for Marina since by now the ethical downsides of lifelong childbirth are apparent. Barbara, meanwhile, tells of a nightmarish adventure that she and Mr. Fox had coming up river. This eventually leads to Marina learning the truth of Dr. Eckman's death. There are sufficient plot twists and turns involving Dr. Swenson, the young boy Easter, and Dr. Eckman's death, to keep the reader interested throughout the book.

While there are good descriptions of the undesirable effects of Lariam, there is little description of the possible pharmacology behind a drug that prevents malaria as well as allows women to bear children their entire lives. Even the drug delivery system (chewing the bark directly on the trees) is bizarre. As an adventure novel this is a good book that will capture your attention and keep you reading, but in the end it is a book about a pharmacologist, not about pharmacology.



Calling all bookworms!

If you have recently read a pharmacology- or science-related book, fiction or non-fiction, that you found interesting enough to share with your peers, we invite you to write a book review of it for *The Pharmacologist*. For further information, please contact **Gary Axelrod** at gaxelrod@aspet.org or **301-634-7916**.

In the Spotlight

Interviews with ASPET members

Our members come from a diverse array of backgrounds, pharmacological interests, and career levels. "In the Spotlight: Interviews with ASPET members" picks three ASPET members from each category of membership (Regular, Postdoc, and Student) to interview for each issue of The Pharmacologist. Get to know your fellow members:

Brian M. Cox, Ph.D., Uniformed Services University of the Health Sciences - Regular ASPET Member

Who or what have been your greatest influences in your work?



My initial experiences in pharmacology were substantially influenced by two very different pharmacologists. As an undergraduate student at Chelsea College, London, I learned a lot from Mary Lockett, who was then the Department Head. She was in many ways a remarkable woman, outwardly a prim and proper product of pre-war Britain (that is pre-World War II) but in her own unique way she was an iconoclast. Her lectures were delivered at speed but were often interspersed with interesting graphic details, memorably including her personal simulations of the motor and functional impairments associated with major neurologic disorders. In particular her enactment of the motor symptoms of tertiary syphilis greatly engaged her students, if only because it seemed so incongruous. She was a skilled experimentalist who personally worked in the lab almost every day on complex procedures using anesthetized cats in studies on the regulation of kidney function. She expected her students to get into the lab and conduct experiments even while

they were just beginning to learn the science. It was an excellent way to get a lot of experience with a very wide range of procedures. I also gained a unique insight into academic politics and the art of defending territory. Space at Chelsea was limited. With expanding programs, the administration talked of taking away a lab from the department to make an office for another department. Mary Lockett moved a mouse colony into the adjacent room, relying on the vagaries of ventilation in an old Victorian building to make the disputed room un-inhabitable by any but those who could tolerate a strong mouse odor; the pharmacology department retained the space. Mary Lockett eventually moved to the University of Western Australia in Perth to head the pharmacology department there. She died in 1982, but she is apparently still remembered since the UWA web site indicates that in 2008 an academic scholarship was named in her honor.

My Ph.D. mentor was Marta Weinstock in the department of pharmacology at St. Mary's Hospital Medical School, London. It was in her lab that I first became interested in the actions of opiate drugs and the receptors that mediate their effects. Marta was also an adventurous experimentalist – any good idea was worth testing experimentally, preferably that same day; an approach that would drive today's animal research oversight committees crazy. Soon after I graduated, Marta moved to Israel, first to Tel Aviv, and then later to head the department of pharmacology in the Hebrew University of Jerusalem, where she had a significant influence on experimental pharmacology in Israel over many years, and she is now a professor emeritus. I still often meet people in the USA who have worked or trained with Marta in Israel.

My first faculty position was back at Chelsea College London, teaching pharmacology to pharmacy and science undergraduates, as well as contributing to a productive Master's program set up to train pharmacologists to work in the then rapidly expanding UK pharmaceutical industry. In a one-year course, students were required to conduct lab experiments three days a week throughout the year, and the faculty was expected to make sure that these experiments "worked." Soon after I returned to Chelsea, Michael Ginsburg became the department head, and it was from him that I learned that while a physiological approach to pharmacology offered an important "big picture" understanding of the effects of drugs, a more complete understanding of how drugs worked and influenced physiologic function required knowledge of the underlying biochemistry. Michael persuaded me to start studying the biochemical basis of opiate drug tolerance and dependence, and it was these studies that eventually resulted in my move to the USA. Avram Goldstein happened to be in the audience at a meeting organized by Hans Kosterlitz where I presented studies that we had conducted on the effects of recently discovered protein synthesis inhibitors on morphine tolerance. After the talk, Avram invited me to come to Stanford for a sabbatical year, an offer I was delighted to be able to take up.

Working with Avram Goldstein was also a major formative experience. By the time I joined his group, he had established a large team (at least by UK standards) to identify and characterize opiate drug receptors, as a necessary first step on the way to solving the heroin addiction problem. (Avram liked to think big.) It was a new experience to have several colleagues also working on the same problem, and the opportunity to learn to work cooperatively on a problem was valuable. Avram was also a very critical thinker; he encouraged novel approaches to problems but challenged all ideas, requiring that you had marshaled your arguments and presented them as clearly and cogently as possible. Avram recruited excellent scientists from around the world, and he encouraged open-ended wide-ranging discussions. In summer, lab meetings were frequently spent around the big swimming pool at chez Goldstein, and Avram's wife, Dody, herself an excellent scientist with an independent program in alcohol research, sometimes dropped by. The years I spent working with Avram at Stanford were some of the most productive of my life. He was a towering figure in the discipline (figuratively and literally), and it was a great learning experience. Avram died last year after long debilitating illness; a special edition of *Molecular Pharmacology* honoring his life and services to pharmacology will be published this spring with contributions from several colleagues who worked with him over many years.

These distinguished scientists had the greatest influence early in my career as a pharmacologist, but I have been fortunate to work in various ways over many years with a large number of wonderful faculty colleagues, and with students, postdocs, visiting fellows, laboratory technicians, and research collaborators from a wide range of backgrounds. Each in their own way has left a mark. I owe many a debt of gratitude to all of these people for the insights that I have gained from them.

What drew you to Uniformed Services University (USU)?

I needed a job. Having stretched out my sabbatical from London University for almost eight years, I realized that I had burned too many bridges to return, but with three young children, I now needed a more secure job than relying on research funding alone. While at Stanford, I had met Lou Aronow, who had been recruited from Stanford to become the founding chair of pharmacology at USU. He was now building up the department and seeking new faculty with experience in neuropharmacology, and he invited me to move to USU. At that time, research at USU was funded very largely from internal Department of Defense funds. The opportunity to work in new labs in a new department in a new medical school with most of the research funding available internally was attractive. I also liked the Washington area; if I could not live in northern California, then the DC area was an attractive alternative. Of course, the generous internal research funding did not last very long; within a year of my arrival, it became necessary to seek extramural funding to maintain a working laboratory.

What advice would you offer to aspiring pharmacologists?

First, become an expert in a significant research area, but read widely and be prepared to employ new techniques throughout your career. Then develop the interpersonal skills that will make you an effective collaborator who is sought out by other investigators; in the future, innovations with major impact on the progress of pharmacology are more likely to come from interactive research teams with multiple investigators covering several areas of technical expertise than from single investigator labs.

What might someone be surprised to know about you?

There are no surprises; what you see is what you get.

How many years have you attended the ASPET Annual Meeting at EB?

My attendance at ASPET meetings goes back way before the establishment of the EB meeting. In addition to the large inter-society meeting organized by FASEB, then known as the FASEB spring meeting, ASPET also held a single society summer meeting, usually held in different universities across the country. I think I attended my first ASPET meeting in the spring of 1974, and I have attended many ASPET, FASEB, and later EB meetings since then.

What is your favorite part about the ASPET Annual Meeting at EB?

We have some great plenary lectures; these provide an excellent opportunity to keep up-to-date in areas outside your own expertise, a great help if you have to give lectures in these areas. But beyond the science, the opening reception and the division mixers are both enjoyable and very important parts of the meeting, providing a venue to meet old friends as well as new recruits to the discipline who are attending an ASPET meeting for the first time, and these occasions also offer another opportunity to form new collaborations.

Do you have any suggestions for ASPET regarding anything in the organization in which you would like to see improvement?

There are many things about the EB meeting that are not entirely under the control of ASPET; major changes also require the support of the other societies participating in EB, so effecting substantial change is a challenge for a small society like ASPET. We are now facing a period when funding for travel to general meetings is likely to become even more constrained. The ASPET leadership has to work with EB to try to restrain the apparently ever-increasing costs of attending meetings, and in addition to find additional ways to support the travel to the meetings of younger pharmacologists who now seldom have access to institutional travel funds.

When you leave your lab for the final time, what do you hope to have accomplished in your career? Please be as specific as possible.

Survival, mainly. More seriously, I enjoy teaching and am proud of the fact that over many years across two continents, in three medical schools and one school of pharmacy, I have helped train several thousand physicians, quite a few pharmacists, and a good number of scientists now working in pharmacology research in academia or the drug industry or other areas where they use their pharmacology expertise. In the research arena, I was fortunate to be in the right place at the right time to participate in the discovery of endogenous opioids, and more recently, I have been privileged to work in a large collaborative project established to respond to the increasing number of military and civilian head injuries, seeking to develop better diagnostics, to understand the mechanisms underlying brain injury, and to develop novel therapies that might facilitate recovery. Throughout my career, I have really enjoyed the opportunity that a career in the biomedical sciences provides to meet and work with brilliant people from around the world.

Amy C. Arnold, Ph.D., University of Vanderbilt - ASPET Postdoc Member



What sparked your interest in pharmacology?

My first experience with pharmacology was during my graduate studies in a laboratory that used a unique approach to integrate pharmacology with whole animal physiology methods. It was during this time that I became interested in how drugs acting within the central nervous system can modify cardiovascular function. I was also encouraged during this time to become actively involved in ASPET. This interest in pharmacology research and service has continued during my postdoctoral fellowship in clinical pharmacology.

What do you find most challenging about your work?

The most challenging part of my career thus far has been learning effective time management in order to strike a good balance between work and having a fulfilling personal life. Part of achieving this balance for me has been learning to say no when needed, taking a few minutes each day to focus on relaxation, and maintaining weekly gatherings with good friends.

What do you like to do for fun?

During my free time, I like to participate in athletic activities to relieve stress and have fun, such as volleyball, kickboxing, pilates, and yoga. I also really like to travel and to explore new destinations.

How would others in the lab at which you work describe you?

Hopefully other members of my laboratory would describe me as hard working, optimistic, collaborative, and supportive.

How has membership in ASPET benefitted you and your career thus far?

During my training, I have been able to take advantage of numerous outstanding benefits that ASPET provides for young investigators. These opportunities include graduate student and postdoctoral travel awards to attend Experimental Biology, oral presentation of research in division trainee showcases, co-chairing a scientific symposium, and participation in division committees. My service on the Executive Committee for the Division of Cardiovascular Pharmacology has been particularly rewarding for networking with renowned investigators and for making active contributions to the discipline.

What are your career goals or aspirations in pharmacology?

My long-term career goal is to manage a successful independent laboratory with academic research focused on the neural mechanisms of hypertension. This research would ideally consist of both basic science and clinical research using integrative pharmacology and physiology methods. I also hope to help further the discipline by advocating for pharmacology education and by encouraging future young scientists to become involved in the society.

Jason M. Kehrl, B.S., University of Michigan - ASPET Graduate Student Member



What sparked your interest in pharmacology?

Growing up, I experienced the pain that chronic mental health issues can impose upon those who are afflicted and their families. Several of my family members suffer from mood disorders and others are dependent on alcohol and nicotine. After coming out, this background made me even more acutely aware to the substance abuse that runs rampant in the gay community. One example stands out in my mind in particular. During my years as an undergraduate at Illinois Institute of Technology in Chicago, there was a prominent man who was the head of a local nonprofit. During a methamphetamine high, he ran over a cab driver. To me this exemplified the unique burden mental health and addiction can place on an individual. As compared to most any other type of illness, many people see those suffering a mental illness as having a character defect or vilify the person based upon actions they take while ill. These experiences are what drive my interest in neuropharmacology and what led me to join the Neuropharmacology division of ASPET.

What do you find most challenging about your studies?

Research is a roller coaster with good days and periods of nothing working. Given my B.S. in computer science, I was much more accustomed to regular incremental progress where there is a clear reason for your code not working. So, accepting the ride and enjoying it has been a major challenge.

What is or was your most favorite experiment/study with which you have been involved?

Clinically prescribed drugs have unwanted side effects in addition to their beneficial effects. Reducing drug side-effects will reduce healthcare costs and increase patient quality of life. Roughly 75% of patients on medication for a chronic condition stopped treatment due to side effects. Not taking a prescription as directed is associated with \$289 billion in annual healthcare costs and causes over 100,000 deaths per year. Given this background, my favorite experiment to-date involved testing a commonly used clinical drug and showing in a genetically altered mouse that we could maintain the on-target effects while minimizing the off target side effects. The hope is that the alteration made to these mice could be mimicked pharmacologically, allowing for drugs with reduced side effects. Unfortunately, the work has yet to be published, so I cannot share any further details.

What drew you to the University of Michigan?

Three main reasons drew me to the University of Michigan. First, Ann Arbor is a great location. For a town of its size, there is great diversity. During my visit, I went dancing at a massive gay bar that is right near campus, saw guys walking downtown holding hands and several interracial couples. Being out and coming from a big city, this diversity was very important to me. Second was the broad research opportunities through the PIBS program so that I could still do rotations in wet and dry labs to decide what subject matter was most appealing for my dissertation. And last, but certainly not least, was a personal interaction with Dr. Rick Neubig. I had not been provided his personal phone number, but I looked it up in the phone book and called him on the weekend I had to declare my decision. At the time, I was still debating between Michigan and another top tier school. While I reached his machine, within a few hours I had a phone call back from him apologizing for the delay, as he had been out birding that morning. Regardless really of the content of our conversation, the level of respect, interest, and time taken to discuss my questions had me sold on attending Michigan.

Tell us about some of your hobbies.

Haha. Well I like to run small businesses. That counts right? After college, I started a mobile DJ business and currently headline Revel (<http://revelannarbor.wordpress.com/tag/ann-arbor/>), a bimonthly queer costume party in Ann Arbor. I am also a landlord with four tenants and rent parking spaces for Michigan football home games. I am a Senior Project Advisor at Nexecon Consulting Group (<http://nexeconconsulting.com/>), a student run organization that tackles strategic questions for companies within the Detroit metro area. I also really enjoy learning in areas outside of the sciences and am currently brushing up on my Spanish and want to learn Mandarin next.

What are your career goals or aspirations in pharmacology?

Given my love of both pharmacology and business, I really want to work at the interface of health/science and business. I aspire to become a trusted consultant to drug development and/or healthcare companies and focus on improving both patient outcomes and a company's bottom line.

Members in the News

Brian Hoffman



(Courtesy of Brian B. Hoffman)

Brian B. Hoffman is currently a Professor of Medicine at Harvard Medical School and a physician in the VA Boston Healthcare System. He has had a long-standing interest in adrenergic pharmacology and has recently completed *Adrenaline*, a book about the history of adrenaline.

Adrenaline was discovered in 1894 and quickly made its way out of the lab into clinics around the world. In this engrossing account, Brian Hoffman examines adrenaline in all its capacities, from a vital regulator of physiological functions to the subject of Nobel Prize-winning breakthroughs. Because its biochemical pathways are prototypical, adrenaline has had widespread application in hormone research leading to the development of powerful new drugs. Hoffman introduces the scientists to whom we owe our understanding, tracing the paths of their discoveries and aspirations and allowing us to appreciate the crucial role adrenaline has played in pushing modern medicine forward. He also investigates the vivid, at times lurid, place adrenaline occupies in the popular imagination, where accounts of its life-giving and lethal properties often leave the realm of fact.

Additional information is available at the publisher's website: <http://www.hup.harvard.edu/catalog.php?isbn=9780674050884>.

Rick Neubig



ASPET President-elect **Richard R. Neubig, M.D., Ph.D.**, will become professor and chairperson of the Michigan State University Department of Pharmacology and Toxicology, effective July 1, 2013. Dr. Neubig, whose research deals with G proteins and their receptors, will be heading to Michigan State after 20 years at the University of Michigan as professor of pharmacology, associate professor of internal medicine, and director of the Center for the Discovery of New Medicines.

Twelve ASPET Members Elected as 2012 AAAS Fellows

In October 2012, the AAAS Council elected 701 members as AAAS Fellows, 12 of whom are members of ASPET. These individuals were recognized for their contributions to science and technology at the Fellows Forum held on February 16, 2013 during the AAAS Annual Meeting in Boston, MA. Congratulations to the following ASPET members who were elected as 2012 AAAS Fellows:

Section on Biological Sciences

Patrick J. Casey
Lakshmi A. Devi
Bruce A. Freeman
William Plunkett
Alvaro Puga

Section on Medical Sciences

Dan Mark Roden

Section on Neuroscience

Peter Jeffrey Conn
Ronald B. Emeson

Section on Pharmaceutical Sciences

Paul F. Hollenberg
Marilyn Emily Morris
David E. Smith
Lynn Wecker

Share your news...

Awards,

Promotions,

Achievements

Share your accomplishments with *The Pharmacologist* and with the ASPET community.

Send information and pictures to gaxelrod@aspnet.org.



Staff News

ASPET Executive Officer Christine K. Carrico, Ph.D. Announces Retirement



Christine K. Carrico, Ph.D., ASPET Executive Officer, has announced her plans to retire this summer. She will have been at the helm of ASPET for 16 years. A search committee has been established and the ad for the job appears on page 2 of this issue of *The Pharmacologist*. When asked her plans for retirement, Christie indicated that the first thing will be sleeping past 5:45 AM. She plans to take some time to reflect on what she wants to do with this next stage of her life and get the non-ASPET aspects of her life "in order." A longer retrospective of her time at ASPET will appear in the June issue.

ASPET Staff Holiday Season Celebration

On Wednesday, December 12, ASPET Staff celebrated the Holiday season with a luncheon at Mrs. K's Toll House in Silver Spring, MD.



Clockwise from bottom left, ASPET Staff members Rich Dodenhoff, Crystal Ledger, Alan Poland, Jim Bernstein, Gary Axelrod, Christie Carrico, Suzie Thompson, Bobby Phipps, Danielle Jordan, Cassie Wood, Ron Hanks, and Matthew Hilliker.

Keep in Touch...

**Have you moved?
Changed your email address?
Changed jobs?**

Keep us informed of changes to your contact information so you don't miss out on any important ASPET News!

Email us at membership@aspet.org

New ASPET Members

Regular Members

Patrick U. Agbasi, Federal Univ of Technology, School of Health Technology, Nigeria
James W. Aiken, Keystone Symposia on Molecular & Cellular Biology
Abu-Bakr Al-Mehdi, Univ of South Alabama
H Babaei, Tabriz Univ Med Sciences, Iran
Douglas A. Bayliss, Univ of Virginia
Raymond G. Booth, Northeastern Univ
Amber V. Buhler, Pacific Univ Oregon
William A. Coetzee, New York Univ School of Medicine
Bimal N. Desai, Univ of Virginia
Leslie L. Devaud, Pacific Univ School of Pharmacy
Leslie Dickmann, Amgen
Kim Eberle-Wang, Springside Chestnut Hill Academy
Wenke Feng, Univ of Louisville School of Medicine
Hugh M. Fentress, Fisk Univ
Ibragim Gaidarov, Arena Pharmaceuticals
Arturo E. Gonzalez-Iglesias, Florida State Univ
Marion K. Gordon, Ernest Mario School of Pharmacy, Rutgers Univ
Fredric Gorin, Univ of California-Davis
Jose Ernesto Groning, CVS Pharmacy
Klara Gyires, Semmelweis Univ, Hungary
Ki Baik Hahm, CHA Univ, South Korea
Alison H. Harrill, The Hamner Institutes for Health Sciences
David A. Hartman, Aptiv Solutions
Kurt F. Hauser, Virginia Commonwealth Univ
Ralf Hausmann, RWTH Aachen Univ, Germany
Paiboon Jungsuwadee, Roosevelt Univ College of Pharmacy
Leonid Kagan, Rutgers Univ
Mikhail Kalinichev, Adxex Therapeutics
Roongpetch Keowkase, Srinakharinwirot Univ Faculty of Pharmacy, Thailand
Eun-Hee Kim, CHA Univ, South Korea
Yun Ping Lim, China Medical Univ College of Pharmacy, Taiwan
Aurea E. Linder, Univ Federal de Santa Catarina, Brazil
Jianxi Liu, Purdue Pharma LP
Hong Lu, SUNY Upstate Medical Univ
Vinay S. Mahajan, Harvard Medical School
Jeff S. McDermott, Eli Lilly and Co.
Wael M. Mohamed, Menoufiya Faculty of Medicine, Egypt
Anush Oganessian, Univ of Washington
Pil-Hoon Park, Yeungnam Univ, South Korea
James P. Pearson, Ironwood Pharmaceuticals, Inc.
Gabriela K. Popescu, Univ at Buffalo
Nicole H. Purcell, Univ of California-San Diego
Lauren C. Purington, Albany College of Pharmacy and Health Sciences
Deepa A. Rao, Pacific Univ
Yong Ren, Pfizer
David H. Rominger, Trevena Inc
Michael Saporito, Melior Discovery Inc
Timothy J. Searl, Northwestern Univ, Feinberg School of Medicine
Arun K. Shukla, Duke Univ Medical Center
McHardy M. Smith, Univ of the Sciences
Patricio Soares-da-Silva, Univ Porto Faculty Medicine, Portugal
Brendan D. Stamper, Pacific Univ
Catia Sternini, UCLA David Geffen School of Medicine
Dawn Thompson, William Harvey Research Institute
Richard B. van Breemen, Univ of Illinois College of Pharmacy
Jin Xu, Memorial Sloan-Kettering Cancer Center
Akinori Yanaka, Univ of Tsukuba, Japan
Oksana Zayachkivska, Lviv National Medical Univ, Ukraine

Affiliate Members

Kaza Ahluwalia, Chandigarh, India
Selina F. Darling-Reed, Florida A&M Univ
Mohamed E. Ebadat, National Org for Drug Control and Research (NODCAR), Egypt
Leslie Goldstein, NYIT College of Osteopathic Medicine (NYCOM)
Hailemichael Z. Hishe, Mekelle Univ-CHS, Ethiopia
Krithika Lingappan, Baylor College of Medicine
Siripan Phattananurudee, Chulalongkorn Univ Faculty of Pharmaceutical Sciences, Thailand
Hiranmayi Ravachandran, Anna Univ, India
Saeed A. Sheikh, King Saud Univ College of Medicine, Saudi Arabia
Heidi A. Schwanz, Boston Univ

Postdoctoral Members

Federico C. Beasley, Univ of California-San Diego
Milu Cherian, St Jude Children's Research Hospital
Jun Deng, Univ of Kentucky
Jonathan W. Dickerson, Vanderbilt Univ
Mohamed Elmahdy, Ohio State Univ
Andrew C. Emery, NIMH, NIH
Silja I. Freitag, Queen's Univ, Canada
Rabea Graepel, Univ of Calgary, Canada
Jin Boo Jeong, Univ of Maryland
Nakpangi A. Johnson, AstraZeneca
Stefan M. Kolata, NIH
Yue Liu, Northeastern Univ
Kimberly M. Lovell, Scripps - Florida
Nicholas M. Mordwinkin, Stanford Univ
Irene Paterniti, Univ of Messina, Italy
Gaurav D. Patki, Univ of Houston
Christna J. Schier, Virginia Commonwealth Univ
Kathryn B. Smedlund, Univ of Toledo College of Medicine
Ernesto Solis, Virginia Commonwealth Univ
Devki Sukhtankar, Univ of Michigan
Evita van de Steeg, TNO, The Netherlands
Camilla F. Wenceslau, Georgia Regents Univ
Derek S. Wilkinson, National Institute on Drug Abuse, NIH
Hye Sook Yoon, Mayo Clinic
Faisal Zaidi, Univ of Toyama, Japan
Lei Zhou, The Scripps Research Institute

Graduate Student Members

Mouhamed S. Abdel-Maksoud, Sinai Univ, Egypt
Oreoluwa O. Adedoyin, Univ of Kentucky, College of Pharmacy
Mohannad A. Almikhlafl, Massachusetts College of Pharmacy and Health Sciences
Amirah Aly, Northeastern Univ
Malay Bhowmik, Hamdard Univ, India
Praveen K. Bommareddy, Long Island Univ

Melanie V. Brady, Fisk Univ
 Michela Campolo, Univ of Messina, Italy
 An T. Dao, Univ of Houston
 Rania A. El Fawal, Zagazig Univ Hospitals, Egypt
 Mahmoud E. El-Daly, Univ of Calgary Faculty of Medicine, Canada
 Ahmed F. El-Wakeil, Sinai Univ, Egypt
 Daniel E. Felsing, Univ of Florida
 Joseph C. Grieco, Univ of South Florida, Byrd Alzheimer's Research Institute
 Allyson N. Hamlin, Univ of Cincinnati College of Medicine
 Candice N. Hatcher, Virginia Commonwealth Univ
 Michael P. Hayes, Univ of Iowa
 Elizabeth Holly, Tufts Univ
 Danielle E. Hooker, Emory Univ
 Nazar Hrytsevych, Lviv National Medical Univ, Ukraine
 Benjamin A. Hughes, Medical Univ of South Carolina
 Loretta O. Iniaghe, Univ of Benin, Nigeria
 Anthony C. Johnson, Univ of Oklahoma Health Sciences Center
 Nene Kalu, Johns Hopkins School of Medicine
 Kristin Lewis, Ohio State Univ
 Anita Li, Florida Institute of Technology
 Yiwei Liu, Auburn Univ
 Kerise A. Lyttle, Hokkaido Univ Graduate School of Medicine, Japan
 James J. Mahoney, Univ of Houston - Baylor College of Medicine
 Jasmine M. Miller-Kleinhenz, Emory Univ
 Rehab M. Mohamed, Suez Canal Univ Faculty of Pharmacy, Egypt

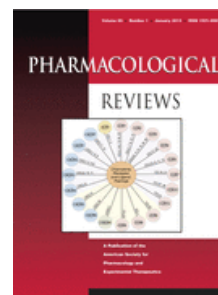
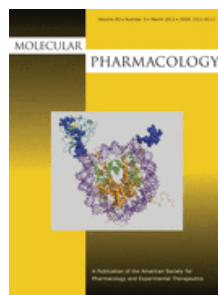
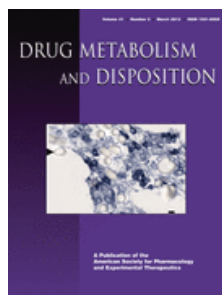
Saroj Nepal, Yeungnam Univ, South Korea
 Jenny Nguyen, Western Univ
 Olaitan J. Olanipekun, Obafemi Awolowo Univ, Nigeria
 Marie Onakomaiya, Dartmouth Univ, Geisel School of Med
 Bharti R. Patel, Univ of Rochester, School of Medicine and Dentistry
 Chad A. Pope, Univ of Connecticut
 Irena Pshyk-Titko, Lviv Medical Univ, Ukraine
 Kesa V. Randell, Florida Agricultural & Mechanical Univ
 Luiza Rusu, Univ of Illinois-Chicago
 Alex Sandweiss, Univ of Arizona
 Joel M. Schrock, Weill Cornell Graduate School
 Kayle Shapero, Boston Univ
 FNU Shikha, Texas Tech Univ Hlth Science Ctr
 Neha Singh, North Dakota State Univ
 Hannah M. Stoveken, Univ of Rochester
 Lokraj Subedee, JSS Medical College, India
 Francesca Toselli, Univ of Queensland, Australia
 Jennifer T. Triplett, Florida A&M Univ
 MaKendra L. Umstead, Emory Univ
 Sara J. Weaver, Univ of Wisconsin Madison
 Senny Wong, Univ of Nevada-Reno
 Olivia Yu, Univ of California-San Diego
 Yuchen Zhang, Univ of Kansas Medical Center
 Cuiqing Zhao, Univ of Louisville
 Fouad A. Zouein, Univ of Mississippi Medical Center

Undergraduate Student Members

Ahmed G. Ahmed, Rutgers Univ
 Matthew Cheung, Rutgers Univ
 Eun Jung Kim, Rutgers Univ Ernest Mario School of Pharmacy
 Michael J. Krueger, Univ of Wisconsin-Stout

Joab O. Odera, Winston-Salem State Univ
 Eva Y. Pan, Rutgers Univ
 Parin Patel, Rutgers Univ.
 Nicole M. Sayers, Univ of Arizona

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Division News

Behavioral Pharmacology Division

Division Election Winners

Chair-Elect:



Jeffrey Witkin

Secretary/Treasurer-Elect:



Lisa R. Gerak

News

Election Results

Dr. Jeffrey M. Witkin, Senior Research Advisor for Psychiatric Drug Discovery at Eli Lilly and Company, has been elected Chair-Elect of the Division for Behavioral Pharmacology. **Dr. Lisa R. Gerak**, Assistant Research Professor in the University of Texas Health Science Center-San Antonio's Department of Pharmacology, has been elected Secretary/Treasurer-Elect of the Division. Drs. Witkin and Gerak will assume their respective roles as division officers on July 1, 2013.

Behavioral Pharmacology Division Symposia at Experimental Biology

Highlights of some of our programming at the ASPET Annual Meeting at Experimental Biology include the following:

Kathleen M. Kantak and **Roger D. Spealman** will co-chair a symposium on "Improving cognitive deficits associated with neuropsychiatric disorders: Role for cognitive enhancers and behavioral interventions." There is a current trend of exploring cognitive-enhancing therapeutic drugs as treatments for a number of neuropsychiatric disorders, including Alzheimer's disease, schizophrenia, anxiety, and drug addiction. Each presents with co-occurring neurocognitive changes that are central to many of the maladaptive behaviors characterizing each disorder. The primary objective of this symposium is to provide a current overview of preclinical research being done with cognitive-enhancing therapeutic drugs across a spectrum of disorders.

Ziva Cooper and **Margaret Haney** will co-chair a symposium on "The opioid-cannabinoid connection: A translational, behavioral perspective." Over the last decade, findings from molecular to clinical studies have strengthened the evidence supporting the modulatory relationship between opioid and cannabinoid systems. This symposium will draw upon behavioral studies across species that have probed the nature of this interaction, and will explore how the relationship is being harnessed to investigate novel pharmacological approaches for cannabinoid and opioid dependence.

Jeff Witkin will chair a symposium on "Pharmacological enhancement of wakefulness." Increase in wakefulness is sought by people in modern industrial societies and laborers across the world. The symposium will evaluate the clinical need for wake-promoting agents as in sleep apnea, shift work, and other conditions of fatigue. Moreover, pharmacological mechanisms will be identified that can impact wakefulness, cognitive augmentation, and their side-effects.

Community Outreach Activity at Experimental Biology

Lastly, the Behavioral Pharmacology Division of ASPET is again sponsoring a volunteer opportunity at EB 2013 in Boston. We will spend Friday, April 19, 2013, helping **Cradles to Crayons** provide children living in homeless or low-income situations in Boston with the essential items they need to thrive. For those who are interested, further details and contact information for the volunteer opportunity can be found on page 10 in this issue of *The Pharmacologist*.

Cardiovascular Pharmacology Division

Division Election Winners

Chair-Elect:



David B. Averill

Secretary/Treasurer-Elect:



Fadi T. Khasawneh

News

Election Results

We are pleased to announce that **Dr. David B. Averill**, Professor in the Department of Basic Sciences at The Commonwealth Medical College, has been elected Chair-Elect of the Division. **Dr. Fadi T. Khasawneh**, Assistant Professor of Pharmaceutical Sciences at Western University of Health Sciences, has been elected Secretary Treasurer of the Division. Congratulations to these two individuals who have been long-term supporters of the CV Division. Drs. Averill and Khasawneh will assume their respective roles as division officers on July 1, 2014.

Symposium Help

The Cardiovascular Pharmacology Division has added a "Submitting a Symposium for EB" Web page:

http://www.aspet.org/Cardiovascular_Pharmacology/submitting-a-symposium-for-EB/.

This helpful site lists symposia that have been sponsored by the Division since 2005, a sample of symposium proposal, guidelines, and timelines. We hope this will enable the submission of many proposals to the Division. Our thanks to **Dr. Nan Kanagy** and Mr. Gary Axelrod for making this happen.

EB 2013: Be There!

The Cardiovascular Pharmacology Division is privileged to once again sponsor the Trainee Showcase for Cardiovascular Science during EB. This will be held on Tuesday, April 23 from 2:30 – 4:30 PM in Room 107AB at the Boston Convention Center. Come in support of the trainees of cardiovascular pharmacology.

Please plan to attend one of our three exciting symposia. They span from studies in the human ("Insights into pharmacologic, physiologic and gender issues"), to new view of inflammation in the vasculature ("Innate immunity and cardiovascular disease: Unfolding the therapeutic potential of toll-like receptors") and calcium signaling in the endothelium ("Local Ca²⁺ signals in the endothelium: Key regulators of vascular function and dysfunction"). Scheduling can be found on the EB website, <http://www.aspet.org/eb2013/program/>.

The Cardiovascular Pharmacology Division Business meeting will be held on Tuesday, April 23 from 5:45 – 6:45 PM in room 107AB at the Boston Convention Center and will adjourn to the division's mixer, which will be held from 6:00 – 8:00 PM on Tuesday evening in the Westin Boston Waterfront, Grand Ballroom D.

Getting You Involved!

What would be helpful to you to see on the Cardiovascular Pharmacology Division's website? Please contact Stephanie Watts, wattss@msu.edu, with ideas and comments. We are always looking for ways to improve and serve you better.

Have you joined a Division?

Take full advantage of ASPET Membership by joining a Division!

- Participate in creating the scientific program for the annual meeting.
- Network with people in your field at mixers and divisional programming at the annual meeting.
- Participate in running the division and planning its activities.
- Receive special notices and newsletters about items and activities of interest in your field.

Drug Metabolism Division

Division Election Winners

Chair-Elect:



Larry C. Wienkers

Secretary/Treasurer-Elect:



Mary Paine

News

Election Results

Dr. Larry C. Wienkers, Senior Director of the Department of Pharmacokinetics & Drug Metabolism at Amgen Inc., has been elected Chair-Elect of the Division. **Dr. Mary Paine** of the University of North Carolina-Chapel Hill Eshelman School of Pharmacy, has been elected Secretary/Treasurer-Elect of the Division. Drs. Wienkers and Paine will assume their respective roles as division officers on July 1, 2014.

Integrative Systems, Translational and Clinical Pharmacology Division

News

ISTCP Pharmacology Symposia at Experimental Biology

The Integrative Systems, Translational and Clinical Pharmacology Division is sponsoring four full symposia and a special HOT TOPICS symposia on breakthrough technologies at the April EB meeting. In addition, the division is also co-sponsoring 12 symposia with other ASPET divisions and in conjunction with the British Pharmacology Society Young Scientists, ISTCP is pleased to sponsor a symposium on "Stem cells: Pharmacology and therapeutics."

Below are highlights of the ISTCP developed symposia:

Emerging technologies for delivering neurotherapeutics across the blood-brain barrier (BBB), Sunday, April 21, 9:30 AM – Noon
Chairs: Nisha Nanaware-Kharade, Univ. of Arkansas for Med. Sci. and Eric C. Peterson, Univ. of Arkansas for Med. Sci.

The blood brain barrier (BBB) plays an important role in the pathology and progression of a broad spectrum of central nervous system (CNS) disorders. Normally, it isolates the CNS from the general circulation and provides a unique anatomical and physiological protection. However, it stands as the major obstacle in clinical translation of many promising macrotherapeutics due to their inability to cross this formidable barrier. Over the past decade, many ingenious strategies have been developed to deliver neurotherapeutics across the BBB. The symposium will highlight some of these cutting edge technologies including design features essential for biotherapeutics to surpass the BBB. Leading scientists in the field of BBB will discuss various challenges for drug delivery across the BBB.

The symposium will a) provide an overview of the BBB, especially vascular pathobiology and potential transport pathways for biotherapeutics along with associated challenges, b) describe the current technologies developed to deliver macrotherapeutics across the BBB, c) identify challenges associated with the development of these BBB drug delivery systems, and d) discuss the translation of these methodologies from animal models to patients.

Purinerbic transmission in visceral function and sensation, Tuesday, April 23, 9:30 AM – Noon
Chair: James J. Galligan, Michigan State Univ., Hamid Akbarali, Virginia Commonwealth Univ.

Purines are neurotransmitters and paracrine signaling molecules in multiple organ systems including the gastrointestinal tract and the bladder. As primary neurotransmitters, purines control gastrointestinal motility, secretion and blood flow, and they also contribute to bladder function. Purines are also involved in visceral sensation and pain mechanisms. Because of the central importance of purinerbic signaling in visceral organs, there is a substantial effort to develop drugs which can intervene in purinerbic mechanisms as a strategy for the treatment of gastrointestinal and bladder functional disorders and pain. The symposium will include discussion of the controversy of the chemical nature of purinerbic transmitter in the gut and bladder, role of purines in initiating and modulating secretion, polarity of the projections of purinerbic nerves in the enteric nervous system and functional targeting of the calcium channel subtypes that control purine release, and the role of purines in pain mechanisms.

Signals Activating Pancreatic Stem Cells and Beta Cell Regeneration, Wednesday, April 24, 9:30 AM – Noon

Chair: Thomas M. Wilkie, UT Southwestern Med. Ctr. at Dallas

The speakers will describe new therapeutic approaches to help control the complex physiology driving beta cell expansion in diabetes and development. Recent discoveries demonstrate the integration of metabolic cues, neural processing and efferent signaling that stimulates beta cell expansion in diabetes. Developing therapeutics requires diverse expertise in the fields of metabolism, neural control of feeding behavior and energy homeostasis, pancreas physiology, in vitro differentiation of ES and/or iPS cells, and cell replacement therapies. Speakers in the symposium are Allan Attie, Bridget Wagner, Chris Rhodes, Shuibing Chen, Tom Wilkie, and Lola Reid.

Sleep apnea: a sleeping giant in disease pathologies, Wednesday, April 24, 3 PM – 5:30 PM

Chair: Issy Laher, Univ. of British Columbia; Co-chair: Najib Ayas, Univ. of British Columbia

Sleep apnea is a common disease that is characterized by repetitive episodes of asphyxia, with moderate to severe disease affecting 9% of males and 4% of females; about 80% of patients are thought to be clinically undiagnosed. Sleep apnea is recognized as an independent risk factor for cardiovascular morbidity and mortality. Major risk factors for sleep apnea include obesity, male gender, smoking, increasing age, abnormalities of craniofacial morphology and postmenopausal status in women. Obesity, in particular, is a highly prevalent finding among patients with obstructive sleep apnea (OSA) and as the prevalence of obesity rises, the prevalence of OSA is expected to increase as well. This condition has been linked to serious long-term adverse effects such as hypertension, metabolic dysregulation and cardiovascular disease. Although the mechanism for the initiation and aggravation of cardiovascular disease has not been fully elucidated, oxidative stress and subsequent endothelial dysfunction play major roles. Animal models, which have the advantage of being free of comorbidities and/or behavioral variables (that commonly occur in humans) allow invasive measurements under well controlled experimental conditions, and as such are useful tools in the study of the pathophysiological mechanisms of sleep apnea. This symposium will summarize (i) currently available information on the cardiovascular, metabolic, and other consequences of sleep apnea, (ii) management strategies (pharmacological and non-pharmacological), and (iii) common experimental approaches useful in sleep apnea in different animal models.

This year, the ISTCP Division will be presenting a special “HOT TOPICS” session on breakthrough technologies, on Tuesday, April 23, 3:00 PM – 5:30 PM: A (r)evolution in drug discovery & therapy: From Organs on a chip and 3D biomimetics to regenerative pharmacology

Chair: George J. Christ, Wake Forest Sch. of Med.; Co-chair: Sitta Sittampalam, NIH Ctr. for Translational Therapeutics

New technologies and research paradigms are being rapidly applied to the pharmacological arena with the overall goal of increasing both the efficiency of the drug discovery process and the safety and efficacy of the resulting therapeutics. Moreover, the parallel development of novel biomaterials, drug discovery and delivery systems/vehicles is increasing the range of potential therapeutics that can be utilized. This symposium will provide a cutting edge look at these new developments. The goal is to review their implications for developing new insights into drug action, as well as providing improved, potentially curative (regenerative pharmacology) therapies for the treatment of tissue and end organ disease/dysfunction. Speakers: Sharon Presnell, Linda Griffith and Don Ingber.

Keynote speaker: Chris Austin, Director, National Center for Advancing Translational Science (NCATS)

Future Symposia Discussion at the ISTCP Business Meeting

The general body meeting for the ISTCP Division will be held on Monday afternoon, April 22. In order to identify current and emerging areas of research, the ASPET Programming Committee has decided to shorten the time for symposia submission. As such, we plan devote time at the business meeting to identify symposia topics for the 2014 EB meeting. We encourage our members to put forth topics of interest and to attend and present these ideas at the business meeting. The proposals do not need to be refined. We will be looking for new ideas for symposia, and this meeting will help identify further areas for symposia submissions. This is an excellent opportunity for junior members to become symposia chairs. Further information will be forthcoming via email.

Graduate Student and Postdoctoral Poster Competition

The ISTCP Division graduate student and postdoctoral poster competition will be held on Sunday evening, April 21, 6:30 – 8:30 PM. The ISTCP Division thanks all the judges who volunteered for this event. This year we had 20 members offer to judge!

ASPET Integrative Research Award in Pharmacology

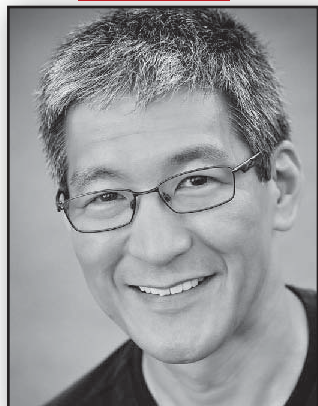
This year, ASPET made five awards to graduate and postdoctoral trainees who are involved in active research projects that involve *in vivo* pharmacology or are focused on organ systems as an integral part of their research efforts. The ASPET-IRP Awards were highly competitive with 108 applications received. Predoctoral students receive stipends totaling \$22,000 in direct costs; postdoctoral trainees will receive a stipend of \$32,000 in direct costs. The ASPET-IRP Award is for one year and concludes December 31, 2013.

Congratulations to **Sarah C. Petersen**, Washington University School of Medicine and **Nicolette A. Louissaint**, Johns Hopkins University – ISTCP Postdoctoral Members!

Molecular Pharmacology Division

Division Election Winners

Chair-Elect:



Roger K. Sunahara

Secretary/Treasurer-Elect:



Qin Wang

News

Election Results

Dr. Roger K. Sunahara, Associate Professor of Pharmacology at the University of Michigan Medical School's Department of Pharmacology, has been elected Chair-Elect of the Division. **Dr. Quin Wang**, Associate Professor at the University of Alabama-Birmingham Department of Cell, Developmental and Integrative Biology, has been elected Secretary/Treasurer-Elect of the Division. Drs. Sunahara and Wang will assume their respective roles as division officers on July 1, 2014. Congratulations to our new division leadership, and thank you to all nominees who were asked to run on the ballot.

Molecular Pharmacology Division Program Highlights for Experimental Biology

The Molecular Pharmacology Division is again sponsoring or co-sponsoring a wide variety of programming for the ASPET Annual Meeting at EB 2013, including the GPCR Colloquium, which complements the diverse interests of the MP membership. The MP Executive Committee would especially encourage members to attend the MP Division Postdoctoral Award Finalist session on Monday afternoon of the meeting. This competitive session will be chaired by recent Nobel Laureate **Brian Kobilka, M.D.**, who will also give the keynote address entitled "Probing G protein coupled receptors: A few of my favorite experiments." That evening, all members are invited to the annual business meeting/mixer, which will highlight our top graduate student posters and postdoctoral finalists. We will also have an opportunity to finalize any "last minute" symposium proposals some members may submit for the 2014 meeting as well as socialize with colleagues and friends. We hope to see you there in Boston.

Recent Honors or Awards given to Molecular Pharmacology Division Members

2012 Nobel Prize in Chemistry

Robert J. Lefkowitz, M.D., Duke University, HHMI Investigator
Brian Kobilka, M.D., Stanford University School of Medicine

2012 Queen Elizabeth II Diamond Jubilee Medal (in recognition of contributions to Canada)

Susan P.C. Cold, Ph.D., FRSC, FCAHS, Queens University

2012 American Heart Association Kenneth M. Brinkhous Young Investigator Prize in Thrombosis

Michael Holinstat, Ph.D., Thomas Jefferson University

2012 Society of Toxicology Undergraduate Educator Award

Sidhartha D. Ray, Ph.D., FACN, Manchester University

2012 American Association for the Advancement of Science Fellow

Carmen Dessauer, Ph.D., University of Texas Health Science Center at Houston

2013 John Jacob Abel Award

Arthur Christopoulos, Ph.D., Monash University

2013 Pharmacia-ASPET Award for Experimental Therapeutics

Richard R. Neubig, M.D., Ph.D.,

2013 Julius Axelrod Award

Lee E. Limbird, Ph.D., Fisk University

2013 Benedict R. Lucchesi Distinguished Lectureship in Cardiac Pharmacology

Andre Terzic, M.D., Ph.D., Mayo Clinic

2013 ASPET Division for Drug Metabolism Early Career Achievement Award

Nina Isoherranen, Ph.D., University of Washington

Neuropharmacology Division

News

Neuropharmacology Division Highlights for Experimental Biology

With the 2013 meeting of ASPET fast approaching, Neuropharmacology Division members are encouraged to support our junior members by attending the student and postdoctoral sessions.

The **Best Student/Postdoctoral Abstract Competition** will be held on the evening of Sunday April 21, from 6:30 – 8:30 PM at The Westin Boston Waterfront, Grand Ballroom AB. This is always a great event! Come and meet these enthusiastic young investigators and learn about their exciting research, while enjoying a cocktail reception.

The competition for the **Best Postdoctoral Scientist Award** will be held on the afternoon of Monday April 22, from 3:00 – 5:30 PM at the Boston Convention Center, Room 106. The Executive Committee selected six finalists from an impressive group of applicants. The finalists are:

Dr. Christopher M. Cottingham, University of Alabama at Birmingham, for his work on *cross-talk between beta and alpha2 adrenergic receptors in sympathetic neurons and its reliance on protein kinase A and spinophilin*

Dr. Robert Di Maio, University of Pittsburgh, for his work on *the cannabinoid 1 receptor as therapeutic target in preventing chronic epilepsy*

Dr. Nicole A. Northrop, University of Toledo College of Medicine, for her work on *the contribution of increased plasma ammonia concentration to methamphetamine-induced blood-brain barrier damage*

Dr. Cesare Orlandi, Scripps Research Institute, for his work on *GPR158 and GPR179, a subfamily of orphan GPCRs and a new class of G protein signaling modulators*

Dr. Kaustuv Saha, University of Florida, for his work on *differential regulation of the biophysical properties of the dopamine transporter by amphetamine and methamphetamine*

Dr. Harriet Schellekens, University College Cork School of Pharmacy, for her work on *the role of dimerization of G-protein coupled Receptors (GPCRs) in appetite regulation and food reward*

In addition to presentations by our **Postdoctoral Scientist Award** finalists, we are pleased to announce that the keynote address will be given by **Professor Lakshmi Devi**. She will share her insights on "How to do big science on a modest budget: lessons from deorphanizing a G protein-coupled receptor." Dr. Devi is Professor of Pharmacology and Systems Therapeutics, Psychiatry and Neuroscience, at Mount Sinai School of Medicine. She is the Associate Dean for Academic Enhancement and Mentoring as well as Director of the Interdisciplinary Training in Drug Abuse Research Program. Throughout her career, she has been interested in several lines of research, including receptor dimerization, regulation of peptide biosynthesis and opiate addiction. She studies mechanisms underlying opiate and cannabinoid receptor activation using a combination of classic and modern techniques in molecular pharmacology as well as biochemical, cell biological, pharmacological and behavioral approaches.

Social Events at Experimental Biology

Catch up with old friends and make new ones at the Neuropharmacology Division Mixer, held jointly with the Behavioral Pharmacology Division this year. The mixer will be on Monday evening, April 22, from 6:00 – 8:00 PM, in the Westin Boston Waterfront, Grand Ballroom D.

Toxicology Division

Division Election Winners

Chair-Elect:



Debra Laskin

Secretary/Treasurer-Elect:



Heather E. Kleiner-Hancock

News

Election Results

Dr. Debra Laskin, Professor and Chair of Pharmacology & Toxicology at Rutgers University's Ernest Mario School of Pharmacy, has been elected Chair-Elect of the Division. **Dr. Heather E. Kleiner-Hancock**, Assistant Professor in the Department of Pharmacology, Toxicology & Neuroscience at the Louisiana State University Health Sciences Center in Shreveport, LA, has been elected Secretary/Treasurer-Elect of the Division. Drs. Laskin and Kleiner-Hancock will assume their respective roles as division officers on July 1, 2014.

Chapter News

Upstate New York Pharmacology Society

Spring 2013 Meeting

Frontiers in Neuropharmacology

May 13, 2013, Center for the Arts, University at Buffalo

"Frontiers in Neuropharmacology" is the title and theme of the second annual meeting of the Upstate New York Pharmacology Society to be held Monday May 13, 2013 at the Center for the Arts of the University at Buffalo.



Dr. David Sibley

Dr. David R. Sibley, senior investigator of the Molecular Pharmacology Division of the National Institute of Neurological Disorders and Stroke, will deliver the keynote address. Dr. Sibley plans to present outcomes of his latest research on novel screening approaches to identify dopamine receptor modulators. Compounds with high affinity and selectivity for dopamine receptor subtypes are targets for the development of medications with application in diverse clinical settings. Scientific advances have identified viable pharmaceutical targets and medical chemistry efforts have helped identify small molecules for clinical advancement.

Dr. Lynn Wecker (University of South Florida), **Dr. Margaret Gnegy** (University of Michigan), and **Dr. Stephen Traynelis** (Emory University) will also speak as invited guests at the "Frontiers in Neuropharmacology" symposium.

For updates on program, registration, and abstract submission, please visit: <http://www.aspet.org/UNYPS>.

Great Lakes Chapter

26th Annual Scientific Meeting: Updated Program

*Friday, June 14, 2013
The Searle Conference Center
Rush University Medical Center, Chicago, IL
1725 W. Harrison St.
Professional Building
Chicago, IL*

Poster Session (8:30 – 10:30 AM)

Vendor Exhibit (8:30 AM – 12:00 PM)

Great Lakes Young Investigator Symposium (10:45 – 11:45 AM)

Career Workshop (Lunch & Learn) (12:00 – 1:00 PM)

Symposium (1:00 – 4:15 PM)

"Functional microRNA in disease: novel opportunities for pharmacology"

Keynote Address: Chunxiang (Kevin) Zhang (Rush University)

MicroRNAs in Cardiovascular disease: current progress and challenges

Speakers:

Zain Paroo (University of Illinois at Chicago)

Regulating the microRNA machinery

Gianpiero Di Leva (The Ohio State University)

MicroRNA roles in tumorigenesis and chemotherapy resistance

Jonathan Maher (Abbott Laboratories)

MicroRNAs as biomarkers of safety and efficacy in drug discovery and development

Poster Awards & Business Meeting (4:15 – 5:00 PM)

For updates on the program, registration, and abstract submission, visit <http://www.aspet.org/GLCMeeting/>.

Mid-Atlantic Pharmacology Society

Mid-Atlantic Pharmacology Society 2012 Fall Meeting Report: Epigenetic Targets and Novel Therapeutics



The 2012 MAPS annual meeting, "Epigenetic Targets and Novel Therapeutics," was hosted by GlaxoSmithKline (GSK), on Thursday, October 25, 2012 at the Collegeville, PA site. Epigenetics is a rapidly evolving field and has potential applications to pharmacology and drug development. The speakers were selected to cover the range of the study of epigenetics, from the most basic research, to translational studies, to applications of epigenetics, to drug development in oncology.

In addition to the speakers, two individuals submitting abstracts reporting research related to epigenetics were invited to give 10-minute oral presentations. The 10-minute presentations were given by **Andrey Finegersh**, University of Pittsburgh School of Medicine, and **Dr. Seena Ajit**, Drexel University College of Medicine.

Approximately 150 scientists and students from the Delaware Valley participated in the 2012 meeting, representing our largest attendance in recent MAPS history. In addition to the invited speakers, research was presented in 24 posters and two 10-minute invited talks.

The day began with poster set-up and judging. By category, there were eight undergraduate student posters, 10 graduate student/research associate posters, and three postdoctoral researcher posters. Three additional posters were presented but not judged. MAPS Councilors **Sri Ghatta, Ph.D.** and **Michael Holinstat, Ph.D.** organized the judges. Posters remained up throughout the day for viewing by attendees. Check-in for attendees who were not presenting or judging started one hour later; these attendees could view posters, enjoy a light breakfast, and visit exhibits by sponsors Covance, EMD Millipore, and Nanostring Technologies.

The meeting began with greetings from MAPS president **Carol L. Beck, Ph.D.** and welcomes from GSK host **Dash Dhanak, Ph.D.** and organizer **Robert Willette, Ph.D.**

This year's keynote speaker was **C. David Allis, Ph.D.**, from the Rockefeller University. Dr. Allis was introduced by **Jim Smothers, Ph.D.**, a former postdoctoral trainee in his lab and currently the Director of Oncology Global Business at GSK.

In his keynote address, "Beyond the Double Helix: Varying the Histone Code," Dr. Allis spoke about the epigenetic landscape, focusing on histone variants and how mutations in specific genes coding for histones have recently been linked to some cancers such as pancreatic cancers and childhood brain tumors. He also spoke about the protein Daxx, which is an apoptosis mediating protein in the cell death pathway, but also has a more recently identified role as an H3.3-specific histone chaperone. Mutations in DAXX have been identified in some patients with pancreatic neuroendocrine tumors. These mutations could make Daxx no longer compatible to complex with H3.3.

Before breaking for lunch, the **George B. Koelle Award** was presented. MAPS presents this annual award to honor the memory of the world-renowned and pioneering local pharmacologist, the late George B. Koelle. MAPS selects one scientist (usually local) who most closely shares Dr. Koelle's enthusiasm for teaching and conducting outstanding research. This year's recipient was **Dr. Robert N. Willette**: *in vivo* cardiovascular pharmacologist, mentor, and educator. In addition to organizing this year's scientific sessions, Dr. Willette is also a past president of MAPS. Over the course of his career, first at Smith-Kline Beecham and continuing at GlaxoSmithKline, Dr. Willette's research has added to our understanding of the cardiovascular system. He has mentored and encouraged many young scientists in industry and academia. **Diane Morel, Ph.D.**, MAPS Vice President, presented the award on behalf of MAPS.

Presentation of the Koelle Award was followed by lunch and additional time to view posters and sponsor exhibits.

The second speaker was **Johnathan Whetstone, Ph.D.**, Harvard/Massachusetts General Hospital, with his talk titled, "Looking through the Eyes of Histone Demethylases: the Biological Impact of Lysine Methylation." He spoke about the impact of chromatin and modulating factors on gene expression, cell cycle, chromosome stability, and DNA damage response. In particular he looked at the enzyme JMJD-2 and its role in regulating DNA replication. Increases in this enzyme resulted in faster s-phase through the redistribution of chromatin.

Andrey Finegersh, M.D./Ph.D. student, University of Pittsburgh School of Medicine, gave an invited 10-minute talk about his research, "Acute ethanol alters histone composition at model gene promoters in mouse cerebral cortex." His research looks at the impact of ethanol on histone composition in the mouse cerebral cortex model (CCx). They treated mice with ethanol and then examined the cerebral cortex after six hours. They concluded that acute ethanol altered histone composition in CCx genes which are targets of ethanol.

Moving one step closer towards translation of the research to the clinic, **Peter Tummino, Ph.D.**, GlaxoSmithKline, presented "A Second Generation of Epigenetic Agents for Oncology." His talk focused on the role of nucleosomes, epigenetic proteins, and the histone code in oncology. In particular, he spoke about EZH2 target genes linked to prostate, breast, and lung lymphoma when mutated. They developed GSK126, which is a potent and selective EZH2 inhibitor. He also spoke of BET reader proteins which directly regulate transcription, and BET inhibitors which silence MYC in hememalignancies.

The second invited 10-minute talk was presented by **Seena Ajit, Ph.D.**, Drexel University College of Medicine, about the "Role of Histone deacetylase inhibitor (HDACi) in Pain." Their studies revealed that their HDACi actually induced pain in mice models and is thus pro-nociceptive. They also discovered that HDACi can induce pro-inflammatory mediators through the up-regulation of IL-1 β .

The final speaker of the day took the topic into the future with **Victoria Richon, Ph.D.**, Epizyme, on the topic of "Targeting Chromatin Modifying Enzymes in Cancer: Lessons Learned and Path Forward." She spoke about DOT1L, a histone methyltransferase, and its role in MLL rearranged leukemia. Cutaneous T-cell lymphoma is highly sensitive to epigenetic treatments, and therefore this target is very important. DOT1L complexes with AF10 and A17 proteins to read and initiate transcription and is associated with this particular leukemia. They hypothesized that a DOT1L inhibitor could return cell differentiation to normal levels as opposed to leukogenesis. They developed EPZ004777, and found it to be highly selective for DOT1L. It only targets

MLL rearranged cells meaning only these leukocytes, and is well tolerated by patients. These drugs represent the next generation of drugs and are some of the first to specifically apply epigenetic research into molecularly targeted drugs.

After concluding remarks, the meeting adjourned to move to the location of the awards ceremony and networking reception. Poster session organizers Michael Holinstat and Sri Ghatta introduced the award winners from the poster session. First place winners received a trophy and \$300, and second place winners received a trophy and \$150. The awards were concluded with one name drawn from among the names of all presenters to receive a gift certificate for a future poster printing, compliments of Slidemakers, Inc. Attendees then enjoyed refreshments while networking, socializing, and congratulating the winners.

We look forward to our next meeting in 2013 and to another opportunity to discuss and communicate about the sciences and disciplines involving pharmacology!

Note: Abstracts presented at the 2012 Mid-Atlantic Pharmacology Society Meeting can be found on pages A-1 - A-7 in the online-only appendix of this issue of *The Pharmacologist*.

Poster Session Winners:

Undergraduate Category:

First Place: John J. Kim, Johns Hopkins University

Second Place: Rohit Dasgupta, Johns Hopkins University

Acknowledgements

The Mid-Atlantic Pharmacology Society would like to thank the following companies and organizations for providing financial and other forms of support for the meeting:

- American Society for Pharmacology and Experimental Therapeutics (ASPET)
- Covance
- EMD Millipore
- GlaxoSmithKline, Cancer Epigenetics DPU, Oncology R&D
- Nanostring Technologies
- Slidemakers, Inc.

Graduate/Research Associate Category:

First Place: Harshini Neelakantan, Temple University School of Pharmacy

Second Place: Sarah Dobreniecki, University of the Sciences, Philadelphia

Postdoctoral Researcher Category:

First Place: Anastasia Wyce, GlaxoSmithKline

Special Thanks to:

- Poster session judges
- Sri Ghatta and Michael Holinstat for organizing the poster session and judges
- Joe Lin for photography
- Temple graduate student Margaret Sperow for helping at the Registration Desk
- Donna DeVillars for administrative assistance with GSK arrangements
- Gary Axelrod, Ronzo Hanks, and Bobby Phipps in the ASPET office
- Andrew Glibicky, Jefferson graduate student, for notes on the scientific sessions



Clockwise, starting in the center: David Allis, Johnathan Whetstine, Peter Tummino, Victoria Richon, Talking science at the reception, Diane Morel presents Koelle award to Robert Willette, Rohit Dasgupta explains poster to Ellen Walker. PHOTOS: Joe Lin.

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Appendix

Abstracts presented at the 2012 Mid-Atlantic Pharmacology Society Meeting

INVITED ORAL PRESENTATIONS*

Invited Oral Presentation #1

Acute ethanol alters histone composition at model gene promoters in mouse cerebral cortex

Andrey Finegersh^{1,2} and Gregg E. Homanics, PhD^{2,3}; ¹Medical Scientist Training Program, ²Department of Pharmacology & Chemical Biology, and ³Department of Anesthesiology, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15261

BACKGROUND: Ethanol (EtOH) consumption contributes to 3.5% of deaths and \$235 billion in societal costs annually in the United States. Acute EtOH is associated with changes in gene expression in the cerebral cortex (CCx); however, no studies have correlated EtOH-induced changes in gene expression to altered histone modifications at gene promoters in CCx.

METHODS: Eight-week-old, male C57Bl/6J mice were treated with 3 g/kg EtOH (i.p.) or an equivalent volume of saline and sacrificed 6 hours after injection; the CCx was immediately removed and flash frozen. We examined global levels of histone modifications in CCx using Western blot. RT-qPCR and chromatin immunoprecipitation (ChIP) were used to study epigenetic reprogramming at model genes whose expression was altered by EtOH in CCx. A commercially available PCR array was used to identify changes in expression of chromatin modifying enzymes.

RESULTS: We identified a 25% increase in global histone subunit H3 tri-methylated at lysine 4 (H3K4me3) ($p < 0.05$) in EtOH-treated mice in CCx; there was no change in global H3K27me3 or histone subunit H3 acetylated at lysine 9 (H3K9ac) or 14 (H3K14ac). Next, we investigated whether changes in histone modifications are present in genes whose expression is altered by acute EtOH in CCx. EtOH was associated with ~20% decreased expression of glutamic acid decarboxylase 1 (GAD1) ($p < 0.05$) and ~75% - 100% increased expression of metallothionein 1 (MT1) ($p < 0.05$), MT2 ($p < 0.01$), and early growth response 1 (Egr-1) ($p < 0.05$) in CCx. Using ChIP, we found that EtOH decreased the association of the GAD1 promoter with H3K9,14ac ($p < 0.05$) and H3K27me3 ($p < 0.05$). For our model up-regulated genes, EtOH increased the association of the MT2 promoter with H3K4me3 ($p < 0.05$) and decreased the association of the MT1 promoter with H3K27me3 ($p < 0.05$). Finally, we used a PCR array to show that acute EtOH decreases expression of the histone acetyltransferase (HAT) Csrp2bp ($p < 0.01$), histone deacetylase 11 ($p < 0.05$), and Esco2 ($p < 0.01$) and increases expression of the HAT Kat2b ($p = 0.056$) in CCx.

CONCLUSIONS: Acute EtOH alters histone composition at model genes whose expression is up- or down-regulated by EtOH in CCx. While we have yet to identify a uniform epigenetic program induced by EtOH, we show that EtOH increases global H3K4me3 and alters the expression of histone modifying enzymes in CCx.

Invited Oral Presentation #2

Role of Histone deacetylase inhibitor in pain

Seena Ajit, Kathryn Capasso, Yuzhen Tian, Rehman Quershi, Ahmet Sacan, Huijuan Hu, James Barrett; Pharmacology & Physiology, Drexel University College of Medicine, Philadelphia, PA, 19102

Chemotherapy-induced peripheral neuropathy is a major dose-limiting factor in the use of chemotherapeutic agents, with patients unable to complete full or optimal treatment. Histone deacetylase inhibitors (HDACi) are a new class of chemotherapeutic drugs. They bring about epigenetic alterations by acetylation of the histone proteins in chromatin and play an important role in the regulation of gene expression. Two recent studies showed that HDACi can alleviate inflammatory pain. A novel HDAC inhibitor from Johnson and Johnson (JNJ) is currently in phase 2 clinical trials as a chemotherapeutic agent. The goal of the study was to investigate the role of JNJ HDACi in pain and the underlying molecular mechanisms. Subcutaneous administration of JNJ HDACi in 8-week-old male C57BL/6 mice followed by behavioral assays including tactile allodynia and mechanical hypersensitivity showed that this HDACi induce pain and is thus pronociceptive. Spinal cord (SC), dorsal root ganglion (DRG), and blood samples were collected 7 days after administration of JNJ HDACi or vehicle. Gene expression studies of key epigenetic regulators showed upregulation of both RNA and protein for Hdac9 and Hdac11 in SC and DRG respectively. To gain further insight on molecular mechanisms and to explore a potential biomarker strategy, we profiled microRNAs (miRNAs) in blood and SC. miRNAs are small non-coding RNA that binds to the 3' untranslated region of mRNAs to induce gene silencing. We observed differential expression of miRNAs in both blood and SC samples from JNJ HDACi treated samples compared to the control. To further elucidate the mechanisms underlying the development of pain, we investigated if JNJ HDACi can activate NF- κ B using a reporter cell line. Our results showed a dose and time dependent activation of NF- κ B by JNJ HDACi. We also observed an upregulation of IL-1 β in treated cells compared to control. Thus our studies indicate that this JNJ HDACi can induce proinflammatory mediators. Global gene expression profiling studies of SC are ongoing and this data will be used to elucidate the miRNA-mRNA correlations to obtain insight into pathway alterations.

**About the invited oral presentations: The judges were asked to review all of the submitted abstracts related to the theme of the meeting (epigenetics) and select two outstanding abstracts. The authors of the selected abstracts were asked to forego a poster presentation and to present a 10 minute oral presentation of their research as part of the symposium*

UNDERGRADUATE STUDENT DIVISION

Abstract #1

G6PD Diagnostic: A Point-of-Care Diagnostic to Detect Glucose-6-phosphate dehydrogenase (G6PD) Enzyme Deficiency to Improve Treatment of Malaria

Rohit Dasgupta^{1,2}, Vikram Rajan¹, Joy Ukaigwe¹, Hannah Jiam¹, Uma Mohan¹, Pranay Rao¹, Martin Kang¹, Jordan Mandel¹, Renu Kondragunta¹, Anne Le MD¹, Robert Allen, PhD¹, Michelle Wobker, PhD², Graham Simpson, PhD³; ¹Johns Hopkins University, Baltimore MD 21218; ²GlaxoSmithKline R&D, Collegeville PA 19426; ³GlaxoSmithKline R&D, Research Triangle Park, NC 27709; ⁴GlaxoSmithKline R&D, Stevenage, UK SG1 2NY

Tafenoquine is a new anti-malarial drug being developed by GlaxoSmithKline (GSK), in partnership with Medicines for Malaria Venture (MMV), for treatment of *P. vivax* malaria. It is believed to be superior to existing treatments (such as primaquine) due to its single-dose formulation and ability to prevent relapse. A drawback with primaquine and tafenoquine is potential toxicity in patients with a hereditary condition known as glucose-6-phosphate dehydrogenase (G6PD) deficiency. Approximately 400 million people are estimated to have some degree of G6PD deficiency, most of these people living in areas having a history of endemic malaria. In these patients, primaquine and tafenoquine can cause hemolysis of red blood cells and, in extreme cases, could be fatal. There is thus a need for a sensitive point-of-care (POC) diagnostic which can be used to screen patients' suitability to receive tafenoquine or primaquine. We have developed a simple POC diagnostic for detection of G6PD deficiency based on a color change proportional to the activity of G6PD in red blood cells. The chemical reaction for our diagnostic test is based on a previously published enzymatic reaction that produces an

orange color dye derived from WST-8, one of the reagents in the reaction. We have designed a unique filter device used to transform the measurement reading of the WST-8 test from a qualitative color gradient to a binary measurement. The filters are preset at certain wavelengths corresponding to the color that specific quantities of G6PD activity produce through the chemical reaction. Our current prototype also uses a stamp device to apply reagents to the testing material before the application of blood. This test can be used on whole blood and the result can be read in under 30 minutes. Our methods demonstrate a path for the development of simple and inexpensive diagnostic assays that may be useful for detecting G6PD deficiency in remote settings.

Abstract #2

The acquisition of methylation at Dlk1-DMR

Abigail Hochman, Tamara L. Davis; Department of Biology, Bryn Mawr College, Bryn Mawr, PA 19010

Mammals inherit one allele of each gene from each parent. The majority of genes express both copies equally, however in genomic imprinting, only the allele inherited from a specific parent is expressed. Changes in chromatin structure, including DNA methylation, in which a methyl group is covalently bonded to the nucleotide cytosine, allow the transcriptional machinery to distinguish between the parental alleles and identify the allele to be expressed. Imprinted domains are clusters of coordinately regulated imprinted genes located next to or near one another.

One such cluster is the Dlk1-Gtl2 imprinted domain, which contains three differentially methylated regions (DMRs): Dlk1-DMR, IG-DMR, and Gtl2-DMR; and several genes, including Dlk1 and Gtl2. My research is focused on the gene Dlk1 and the Dlk1-DMR. Dlk1 has been identified as a tumor suppressor gene and plays an important role in development and the Notch signaling pathway. The Dlk1-DMR is heavily methylated on the paternal allele, while methylation is absent on the maternal allele, and studies show that only the paternal allele is expressed.

We seek to establish when during development DNA methylation is acquired at the Dlk1-DMR and ultimately compare it with the acquisition of DNA methylation at the Gtl2-DMR. Because Dlk1 and Gtl2 are located so closely together, it is expected that they will acquire methylation at similar times, suggesting coordinate control. Our research shows that Dlk1-DMR is substantially methylated on the paternal allele in five day neonatal mouse liver tissue, while the maternal allele lacks methylation.

Abstract #3

Acquisition of paclitaxel resistance is associated with a more aggressive and invasive phenotype in prostate cancer

John J. Kim^{1,2}, Bo Yin¹, Christhunesa S. Christudass¹, Naoki Terada¹, Krithika Rajagopalan¹, Danielle Y. Lee⁵, Ben Fabry⁶, Takumi Shiraishi¹, Robert H. Getzenberg¹, Robert W. Veltri¹, Steven S. An^{3,4,5,*} & Steven M. Mooney^{1,*}; ¹James Buchanan Brady Urological Institute, Department of Urology; ²Department of Biomedical Engineering, Whiting School of Engineering, The Johns Hopkins University School of Medicine, Baltimore, MD 21287; ³Johns Hopkins Physical Sciences in Oncology Center, ⁴Johns Hopkins In Vivo Cellular and Molecular Imaging Center, ⁵Department of Environmental Health Sciences, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD 21205; ⁶Physiology Program, Harvard School of Public Health 665 Huntington Avenue, Boston, MA 02115

BACKGROUND: Drug resistance is a major limitation to the successful treatment of advanced prostate cancer (PCa). Patients who have metastatic, castration-resistant PCa (mCRPC) are treated with chemotherapeutics. However, these standard therapy modalities culminate in the development of resistance.

METHODS: Molecular and biophysical methods were employed to characterize a classic mCRPC cell line (DU145) and investigate the functional changes in vitro and in vivo that corroborate in the development of drug resistance.

RESULTS: Compared with the parental DU145, its paclitaxel-resistant cell line (DU145-TxR) was highly invasive and motile *in vitro* and exercised greater cell traction forces. DU145-TxR cells showed an abnormal nuclear morphology with extensive chromosomal content. Strikingly, the CSK of DU145-TxR cells exhibited a more fluid-like behaviour with a faster rate of remodeling than that of the parental cells. DU145-TxR cells showed a discrete loss of keratins but a distinct gain of ZEB1, Vimentin and Snail, suggesting an induction of epithelial-to-mesenchymal transition.

CONCLUSIONS: These findings demonstrate, for the first time, that paclitaxel resistance in PCa is associated with a trans-differentiation of epithelial cell machinery that enables more aggressive and invasive phenotype and portend new strategies for developing novel biomarkers and effective treatment modalities for PCa patients.

Abstract #4

Determining residues that influence ligand specificity in the dihydrofolate reductase enzyme family

Michael Little, Emily Egbert, Seema Patel and Nina M. Goodey; Department of Chemistry and Biochemistry, Montclair State University, Montclair, NJ 07043

The importance of Dihydrofolate reductase (DHFR) arises from its function in DNA biosynthesis and cell replication as inhibition of DHFR can adversely affect cell growth. Understanding factors that influence DHFR homolog inhibitor specificity is critical for the design of compounds that selectively target DHFRs from pathogenic organisms over the human homolog. In an earlier article that used a quantitative analysis to predict residues away from the active site that play a key role in ligand specificity in the DHFR enzyme family, residues H38, A39, I86, W85, Q84, T125, F126, and Y127 were identified as potential specificity determinants. To validate these predictions, we have purified DHFR variants with altered residues at these positions and determined the effects of mutations on ligand specificity. Mutated *B. Strearothermophilus* (H38N, A39Y, I86A, W85L, Q84A, T125A, F126L, and Y127A) genes have already been expressed and purified. Binding constants to select ligands (Trimethoprim, Raltitrexed, Pyrimethamine) have been measured by equilibrium binding titrations using a Fluoromax-4 fluorescence spectrometer. Comparisons on ligand binding profiles of the mutants to those of the wild type enzyme have revealed that the mutated amino acid positions do influence ligand selectivity. We are currently determining k_{cat} values for the mutant and wildtype DHFR to determine effects of the mutations on turnover rates. Further comparison of ligand specificity of double mutants is currently in progress to investigate synergy between the different positions in ligand binding specificity.

Abstract #5

Effect of cannabidiol and morphine in a mouse model of chemotherapy-induced neuropathic pain

Mak Sarich, Harshini Neelakantan, Ellen A. Walker, Sara Jane Ward; Temple University School of Pharmacy, Philadelphia, PA 19140

A common and debilitating side effect of chemotherapy is peripheral neuropathy (CIPN). CIPN leads to discomfort in the extremities, particularly burning pain and allodynia in the hands and feet. Opioids are the most widely prescribed pain reliever for CIPN, but they are subject to abuse and users develop rapid tolerance to dose. Viable drugs that are an alternative to morphine for pain relief are cannabinoids. Research in rat models shows that the cannabinoid agonist, WIN 55,212-2, reverses chemotherapy-induced peripheral neuropathy. Cannabidiol, an allegedly indirect CB-agonist, is a viable drug for pain relief due to its non-rewarding and non-dysphoric analgesic effects. Our laboratory has recently sought to determine the effectiveness and mechanisms of CBD in CIPN reversal and prevention in C57Bl/6 mice, and to examine alternative assays to stimulus-evoked withdrawal for studying pain behaviors. It was hypothesized that CBD could both prevent and reverse CIPN while morphine would only reverse CIPN. CIPN was induced in mice by treatment with the chemotherapeutic agent paclitaxel. Mice induced with CIPN that were treated with cannabidiol showed prevention and reversal of mechanical allodynia in Von-frey filament assays. Mice treated with morphine only showed reversal. Allodynia assays showed that CBD treatment of CIPN was blocked by the serotonin 5-HT1A antagonist WAY 100635. Alternate assays were performed to examine whether other behaviors were affected by CIPN aside from traditional nociceptive measurements. These included feeding, social interaction, and anxiety behaviors. It was hypothesized that CIPN would produce non-elicited nociceptive behaviors: diminished feeding, increased aggression, diminished social interaction, and increased anxiety. Home-cage feeding studies showed no change in food consumption in mice treated

with paclitaxel compared to saline treated mice. In a progressive ratio operant feeding assay, paclitaxel treated mice showed diminished feeding under select conditions. In a plus-maze assay studying anxiety, paclitaxel treatment did not change overall exploratory behavior, but increased time spent on the open arm. In a social interaction experiment, mice with CIPN observed increased aggression and decreased sniffing behavior. It was concluded that CBD can prevent or reverse behavioral toxicity in CIPN. This likely works at least in part through the activation of 5HT1A receptors. Paclitaxel-induced neuropathy also alters other behaviors in C57Bl/6 mice, but this is less significant than changes observed in other pain behaviors.

Abstract #6

Allelic distribution of histones in liver tissue at the promoter, CpG island and upstream of DMR regions of *Rasgrf1*

Sarah Schnellbacher, Tamara L. Davis; Bryn Mawr College, Bryn Mawr, PA 19010

Rasgrf1 is monoallelically expressed in mouse liver tissue. To determine which epigenetic regulatory features of *Rasgrf1* are responsible for paternal imprinting, we isolated chromatin from neonatal mouse liver associated with permissive and inhibitory histone modifications H3K4me2, H3K9ac, H3K9me3, and H3K27me3. Through qPCR and quantitative analysis, we measured the distribution of histone modifications on the parental alleles shedding light on which regulatory regions of *Rasgrf1* are important in maternal silencing. Inconsistent histone modification distributions on the region upstream of the differentially methylated region (uDMR) and promoter suggest that these regulatory regions have little influence on imprinting patterns. Paternally distributed histone modifications in the CpG rich DMR recommend that histone modifications in the DMR may be responsible along with DNA methylation in the DMR on the paternal chromosome for paternal expression and maternal silencing.

Abstract #7

A Novel Arf6—ERK pathway is required for migration of metastatic breast cancer cells

Jacqueline Freed[^], Corena V. Shaffer[^], and Catherine C. Moore, [^] = co-first authors; Department of Pharmaceutical Sciences, University of the Sciences, Philadelphia, PA, 19104

The research presented here supports a model whereby Arf6 is critical to the mechanism of CXCR4 dysregulation in metastatic breast cancer cells. CXCR4 is a chemokine receptor essential for select neuronal, cardiovascular, and hematopoietic cell migration towards SDF (CXCL12), and is now recognized to promote cancer metastasis. Dysregulation of the SDF-CXCR4 axis in nonmotile primary tumor cells confers an aberrant migratory capacity and promotes metastatic homing of tumor cells to distal SDF-expressing organs. Metastasis is the major cause of mortality in cancer patients, therefore these findings have led to vigorous attempts to identify molecular factors that contribute to CXCR4 dysregulation in cancer. Previously we identified Arf6 as a novel regulator of the SDF-CXCR4 axis, whereby it enhances both CXCR4 cell surface levels and CXCR4 signaling to membrane-delineated ERK. Here we identified a novel Arf6—ERK pathway required for migration of metastatic breast cancer cells. Specifically, we determined the steepness and duration of SDF gradient that is associated with robust CXCR4 signaling to cortactin, an actin-binding protein with known involvement in cancer cell migration and invasion. Utilizing this defined gradient, we also identified we assessed effects of mutational or GEF-mediated Arf6 activation, siRNA-mediated Arf6 knockdown, and MEK inhibition of CXCR4-mediated migration in response to co-stimulation with SDF and collagen, as measured by transwell cell motility assays. Our results demonstrate that in noninvasive MDA-MB-361 and MDA-MB-468 cells, Arf6 activation unmasks a migratory phenotype which is blocked by MEK inhibition with PD98059 and U0126. Additionally, in highly invasive MDA-MB-231 cells, siRNA-mediated knockdown of endogenous Arf6 and MEK inhibition with PD98059 and U0126 significantly reduce the migratory phenotype. These responses are specific to CXCR4-mediated migration as suggested by blockade with a CXCR4 antagonist or neutralizing antibody, AMD3100 and 12G5 respectively, and no change of cell adhesion or FBS-mediated migration. These results provide insight into the role of a novel Arf6—ERK pathway in regulating CXCR4-mediated migration, and support the model that Arf6 is critical to the mechanism of CXCR4 dysregulation in metastatic cancer cells. These studies were supported by NIH grant GM-097718, AFPE sponsored AACP New Investigator grant, and start-up funds from USP.

Abstract #8

Effects of prenatal alcohol exposure on internal capsule axons and corticothalamic neurons

K. Waits, J. Alacci, C. Howard, J. Weber, C. Favero; Ursinus College, Collegenille, PA 19426

Fetal Alcohol Spectrum Disorder (FASD) is the term used for both cognitive and physical abnormalities resulting from prenatal alcohol exposure. Timing and amount of exposure determines the severity of these conditions. Reciprocal connections between the cortex and thalamus are responsible for sensation and perception. Impairments of these neurons and their axons are presumed to be the underlying cause of sensory integration issues seen in humans with FASD. In order to study the effects of prenatal ethanol exposure, Swiss Webster mouse embryos were exposed to ethanol *in utero* during embryonic days (E) 12.5 to (E) 14.5 and analyzed at postnatal day (P) 0. Observations and analysis was on (P) 0 because the thalamocortical axons (TCAs) and corticothalamic axons (CTAs) should have reached their destinations, specifically the cortex or thalamus. Nissl staining was used to examine the cytoarchitecture of the brain. Using immunohistochemistry, specifically the antibody T-box brain 1 (Tbr1), corticothalamic cell fate and number were analyzed. In order to count corticothalamic neurons within the layers V and VI of cortex, binning analysis was used. The cross-sectional area of axon bundles was measured in the internal capsule of caudal sections. These studies may provide insights about the underlying cellular phenomena resulting in deficits in sensory processing in FASD.

GRADUATE STUDENT/ RESEARCH ASSOCIATE DIVISION

Abstract # 9

Metabolic engineering of *Escherichia coli* and *Saccharomyces cerevisiae* for production of vitamin A

Sarah Dobreniecki, Melissa G. Marko, Jennifer Anthony & John Porter; University of the Sciences, Department of Biological Sciences, Philadelphia, PA, 19104

Vitamin A is an important dietary micronutrient that plays an essential role in vision, immunity, growth and embryonic development. It is estimated that vitamin A deficiency is a public health problem in over 120 countries that can lead to blindness, cornea ulceration, and impaired resistance to infection. Vitamin A cannot be synthesized by humans, and must be obtained by ingestion of provitamin A foods. If the intake of these compounds is inadequate, then supplementation is required. Current production methods have been deemed insufficient because chemical synthesis is very difficult, and there is limited availability of provitamin A compounds from natural sources. Our work focuses on engineering *Escherichia coli* and *Saccharomyces cerevisiae* to produce large quantities of vitamin A. We utilize strains engineered to produce increased levels of the terpenoid precursors, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP). Taking the engineered strains, we have introduced carotenoid genes (*crtE*, *crtB*, *crtI*, and *crtY*) from *Pantoea ananatis*, and have successfully produced the vitamin A precursor, β -carotene. In addition, a β -carotene dioxygenase synthesized from *Mus musculus* and codon-optimized for *E. coli* was introduced into this strain to produce all-*trans* retinol.

Abstract #10

Metabolic engineering of monoterpene in *E. coli* and its effect on breast cancer cell lines

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Terpenoids are a large diverse class of naturally occurring organic chemicals, which are used extensively for their aromatic and pharmaceutical qualities. One such terpenoid is perillyl alcohol that has potential anti-cancer activity. It is derived from plant extracts (i.e. mint, cherries and celery seeds), where it is produced *via* the mevalonate pathway.

Our work focuses on engineering the bacterium *Escherichia coli* to produce large quantities of terpenoids, including perillyl alcohol and its derivatives. The genes involved in the perillyl alcohol biosynthetic pathway include geranyl pyrophosphate synthase (GPPS), limonene synthase (LS), a cytochrome P450 alkane hydroxylase (*ahpG*), a ferredoxin reductase (*ahpH*), and a ferredoxin (*ahpI*). In our lab, we have successfully cloned the codon-optimized versions of gpps from *Picea abies*, the limonene synthase gene from *Mentha spicata* and *ahpH*, *ahpG* and *ahpI* from *Mycobacterium* sp. into *E. coli*. We describe construction of the perillyl alcohol biosynthetic pathway for expression in *E. coli* and extraction and production of the pathway intermediate limonene detected via GC-MS. When the combination of these genes was expressed in *E. coli*, a monoterpene similar in structure to perillyl alcohol was produced that was determined to be *cis-p-mentha-2,8, dien-1-ol*. The *cis-p-mentha-2,8, dien-1-ol* inhibited the cell proliferation of MCF-7 and MDA-MB-231 breast cancer cells by nearly 60%. The growth experiments performed to determine toxicity levels of pathway expression in *E. coli* showed that there was no additional metabolic burden to the cell. We performed directed evolution of this monoterpene biosynthetic pathway using random mutagenesis to create a library of derivatives of perillyl alcohol. The library was screened to identify any mutants that were effective against the two breast cancer cell lines- MCF-7 and MDA-MB-231 via cell viability assay and cell proliferation assay. We found that a pool of 15 clones together was able to inhibit the proliferation of MDA-MB-231 cells by 62.7% and inhibit the growth of MCF-7 cells by 21.5%. Current work is being done to identify the mutant that is responsible for the antiproliferative activity in breast cancer cell lines.

Abstract #11

ARF6 and Shp2 phosphatase regulate CXCR4 phosphorylation and signaling to ERK

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CXCR4, a chemokine G protein-coupled receptor, is essential for select neuronal, cardiovascular, and hematopoietic cell migration towards its ligand SDF. It has also been determined to be a major co-receptor for HIV-1 entry, and CXCR4 gene mutations lead to WHIM syndrome, an immunological disease. More recently, CXCR4 has been implicated in cancer and is now recognized to play a critical role during metastasis. Primary non-motile tumor cells with dysregulated SDF-CXCR4 axis adopt migratory phenotype and metastasize to distal SDF-expressing organs. Metastasis is the major cause of mortality in cancer patients, therefore it is important to identify the machinery that regulates CXCR4 in tumor cells. Normally, following SDF stimulation, CXCR4 is rapidly phosphorylated by G protein-coupled receptor kinases (GRKs) or protein kinase C (PKC). CXCR4 phosphorylation initiates adaptor recruitment, promoting receptor uncoupling from G proteins leading to receptor desensitization, and promoting receptor trafficking to sites of endocytosis leading to receptor downregulation. Previously we identified ARF6 as a novel regulator of SDF-CXCR4 axis, whereby it inhibits removal of CXCR4 from cell surface following agonist stimulation, and potentiates CXCR4 signaling to membrane-delineated ERK. Here we addressed mechanism by which ARF6 regulates CXCR4 trafficking. Specifically, we assessed effects of time, SDF dose, de-glycosylation, serine/threonine/tyrosine phosphatase inhibitors on CXCR4 phosphorylation, and the ability of ARF6 to modulate CXCR4 phosphorylation. Here, we demonstrated that ARF6 inhibits CXCR4 phosphorylation in a dose- and time-dependent manner, and upon CXCR4 de-glycosylation. ARF6 inhibition of CXCR4 phosphorylation is unaltered in presence of phosphatase inhibitors OA and PTP1B. We also assessed the effects of PTP1B, and siRNA-mediated ARF6 and Shp2 knockdown on ERK signaling, upon gradient SDF sensing. We identified a novel gradient SDF→CXCR4→Shp2→sustained ERK pathway, and demonstrated that Shp2 is differentially regulated upon SDF gradient sensing. These data provide further insight into the mechanism by which CXCR4 is regulated, and support a working model that ARF6 and Shp2 modulate CXCR4 phosphorylation and signaling in metastatic cancer cells, leading to dysregulated termination of CXCR4 signaling and trafficking of CXCR4 to endocytic sites. These studies were supported by NIH grant GM-097718, and start-up funds from USP.

Abstract #12

Cocaine synergism with alpha agonists in rat aorta: computational analysis reveals an action beyond reuptake inhibition

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Cocaine was administered to isolated rings of rat thoracic aorta, alone and also in combination with three different adrenoceptor agonists: phenylephrine, methoxamine, and norepinephrine. At doses where cocaine alone produced no vasoconstriction, it potentiated the vasoconstriction produced by all three adrenoceptor agonists — a clear indication of synergism between cocaine and these agents. Higher doses of cocaine in combination with alpha adrenoceptor agents gave an inverted-U shaped (hormetic) dose-effect curve, i.e., dose-related relaxation at higher doses. This is likely due to cocaine's multiple mechanisms of actions. The hormetic dose-effect relation was analyzed using computational methodology based on dose equivalence to derive the unknown second component of action that causes relaxation. This relaxing component, possibly related to activation of myosin light chain phosphatase, was quantified as a dose-effect curve. Most important is the synergism between cocaine and alpha-adrenoceptor stimulation which cannot be explained as an action due to reuptake inhibition. Further, this interaction is present at doses that may be physiologically relevant and which therefore might contribute to the vasoconstriction and hypertension associated with cocaine use.

Abstract #13

Recombinant nucleosomes. A codifiable substrate template for drug discovery in epigenetics

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In eukaryotes, the nucleosome core particle, comprised of nucleic acid and histone protein, is the building block of chromatin, the repository of genetic information. Histone methyltransferases methylate lysine and arginine residues in the N-terminal 'tails' of histones, and this activity is linked to changes in chromatin structure. Naturally occurring nucleosomes possess complex patterns of modifications on the N-terminal tails of histones. To reduce complexity and discover fundamental principles of the substrate preferences of histone-modifying enzymes, a system for the production of homogeneous, unmodified recombinant human nucleosomes and modified counterparts was established. These nucleosomes are distinct from natural isolates, because homogeneity is achievable at a given site, and the effect of modification can be studied in isolation or in combination with other modifications. Conflicting accounts of the specific activity of the histone 3 methyltransferase WHSC1 exist in the literature based in part on the use of peptides as substrates. We have determined the substrate preference of WHSC1 using recombinant human polynucleosomes which possess defined marks at positions H3K18 and H3K36 of histone 3. We conclude by quantitative means, that WHSC1 produces a dimethyl mark on histone H3 at lysine-36, to the exclusion of other possibilities which have been reported in the literature, notably H3K4 and H4K20. The availability of functional recombinant "designer" nucleosome substrates improves our capability to determine substrate specificity and kinetic parameters for methyltransferases, and promote drug discovery efforts for GSK targets that modify or read chromatin.

Abstract #14

Effects of cannabidiol (CBD) versus morphine in acute and chronic pain-stimulated and -depressed preclinical models in mice

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In order to increase the predictive validity of preclinical pain studies, recent research has started to focus on concurrent assessment of the effectiveness of potential analgesics using both pain-stimulated and -depressed behavior. In the current set of studies, we investigated the antinociceptive and anti-allodynic effects of CBD (a potential 5HT1A agonist) in comparison to the standard μ -opioid agonist morphine using acute and chronic pain-stimulated and -depressed rodent models. We hypothesized that while morphine will be more effective than CBD in the acute nociceptive assays, CBD will more effective in chronic models of peripheral neuropathies. In the first set of experiments, the antinociceptive effects of morphine (0.32-10 mg/kg) and CBD (5-20 mg/kg) were determine using acetic acid (0.4% conc.)-stimulated stretching and acetic acid-depressed

conditioned operant responding for liquid food in mice. The results showed that morphine produced significant dose-dependent antinociception in the acute pain-stimulated and –depressed behavioral assays while CBD produced no significant antinociception or alteration of operant responding. Additionally, we tested combination effects of morphine and CBD in these assays. The results revealed that while CBD enhanced the antinociceptive effects of morphine in acetic acid-stimulated stretching, CBD blocked the effects of morphine in the acetic acid-depressed feeding assays. In the second set of experiments, the ability of morphine (2.5-10 mg/kg) and CBD (2.5-10 mg/kg) to both prevent and reverse mechanical allodynia were investigated using a model of chemotherapy (paclitaxel, 8mg/kg)-induced peripheral neuropathy (CIPN) in mice. The results demonstrated that while both morphine and CBD were effective in reversing paclitaxel-induced mechanical allodynia, only CBD robustly prevented the onset and development of allodynia associated with paclitaxel treatment in mice. Further, we concurrently assessed the effectiveness of CBD versus morphine using a CIPN-induced place-conditioning procedure. The results indicated that paclitaxel treatment increased the sensitivity of mice to CBD and morphine-induced place-conditioning effects. These results support the clinical observation that opioids are relatively more potent analgesics in the treatment of acute pain but are less effective in the treatment of chemotherapy-induced neuropathic pain. Further, the results provide evidence for cannabidiol to be used as a potential prophylactic for paclitaxel-induced neuropathic pain without associated abuse potential. (Supported by R01 CA129092)

Abstract #15

Ultraviolet radiation (UVB)-induced migration of skin dendritic cell subsets is mediated through TGF- β signaling

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Ultraviolet radiation (UVB) is the leading cause of skin cancer worldwide. UVB also modulates certain inflammation driven cutaneous pathologies such as delayed type hypersensitivity and contact hypersensitivity through actions on skin resident dendritic cell (DC) subsets. Transforming Growth Factor- β 1 (TGF- β 1) is a potent immunoregulatory cytokine in the skin microenvironment. Here, we show that TGF- β 1 is required for UVB induced activation and migration of dendritic cells to the skin draining lymph nodes. We irradiated skin of Skin Hairless (SKH1) mice with UVB in the presence or absence of SB431542, a small molecule inhibitor of the TGF- β 1 type I receptor and measured lymph node migration of skin dendritic cell subsets at acute time points. Topical inhibition of TGF- β 1 pathway with SB431542 suppressed the migration of skin dendritic cell subsets, primarily CD103+ CD207+ and CD207- DC populations to the lymph nodes in response to UVB irradiation. In addition, in an *ex vivo*, skin explant assay for the migration of dendritic cells, UVB induced DC migration into culture media was suppressed with topical inhibition with SB431542. In mice expressing a dominant negative receptor for TGF- β in CD11c+ dendritic cells (CD11c-T β RII DNR), UVB induced migration of DC subsets- CD103+ CD207+ and CD207- was suppressed directly linking TGF- β signaling in DCs to UVB induced migration of DCs. Treatment with SB431542 also suppressed UVB-induced Interferon γ (IFN γ) secretion as well as the effector differentiation of T lymphocytes within the lymph nodes. Consistent with decreased activation within the lymph nodes, SB431542 decreased UVB activation of the skin infiltrating CD4 and CD8 lymphocytes after acute treatments and in UVB-induced skin tumors. Together, these data show that the TGF- β 1 signaling pathway is important for the initiation of the inflammatory response to UVB irradiation of the skin, mediated primarily through the dendritic cells.

Abstract #16

Prolactin promotes differentiation of breast cancer cells through suppression of CK5 by a BCL6 dependent mechanism

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Prolactin (PRL) is a critical regulator of normal growth, development, and differentiation of breast epithelia. While PRL has been shown to promote mammary tumorigenesis, accumulating evidence also supports a role for PRL in maintaining breast cancer cell differentiation. A principal signaling mediator of PRL, Stat5, promotes differentiation of human breast cancer cells *in vitro*. In addition, active Stat5 is an independent favorable prognostic marker, and loss of active Stat5 is associated with increased risk of tamoxifen therapy failure in breast cancer patients. Progesterone has recently been shown to increase a basal cell-like CK5-positive population in luminal breast cancer cell lines. These progesterone-induced CK5-positive cell populations are quiescent, therapy-resistant, and have tumor-initiating capability, indicating that they represent a progenitor/cancer stem cell population. We now report that PRL can counteract the synthetic progestin R5020 (Pg) induced increase in the CK5 population in luminal breast cancer cells. PRL suppresses the population of CK5 positive cells both *in vitro* and *in vivo*. These CK5+ cells were chemoresistant, indicating that PRL may sensitize tumors to therapy. We further report that Pg is a potent inducer of BCL6, an oncogene and transcriptional repressor that has been shown to be critical for the inhibition of terminal differentiation of germinal center B-cells and for the maintenance of leukemia initiating cells. We and others have demonstrated that basal levels of BCL6 are rapidly suppressed by PRL in breast cancer cells, and BCL6 is expressed during early pregnancy, when reproductive hormones such as Pg are elevated. We now report that PRL is capable of suppressing not only basal levels of BCL6 but also the robust induction of BCL6 by Pg. BCL6 induction was required for Pg-induction of CK5 positive cells based on shRNA-mediated knockdown of BCL6. Immunohistochemistry on clinical breast cancer specimen revealed that BCL6 and CK5 expression are significantly correlated in progesterone receptor positive, premenopausal patients. We propose that PRL prevents Pg-induced CK5 positive progenitor cell induction through a mechanism that involves suppression of Pg-induced BCL6. These opposing effects of PRL and Pg may have important implications for drug responsiveness of breast cancer.

Abstract #17

Long residence time inhibition of EZH2 in activated PRC2

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EZH2/PRC2 catalyzes transcriptionally repressive trimethylation of histone H3 at lysine 27 and has been associated with hematologic cancer. Activating mutations in EZH2 at Tyr641 and Ala677 identified in non-Hodgkin lymphomas result in hypertrimethylation at H3K27. Interestingly, EZH2/PRC2 is activated by H3K27me3 and this activation is proposed as a mechanism for self-propagation of gene silencing. Recent work has identified GSK126 as a potent, selective and SAM competitive inhibitor of EZH2 that decreases global H3K27 trimethylation in mutant lymphoma cell lines. Here we show that activation of PRC2 by an H3 peptide trimethylated at K27 is primarily an effect on catalysis (k_{cat}) with no effect on substrate binding (K_m). Additionally, GSK126 is shown to be a time-dependent inhibitor of the activated form of EZH2 specifically, but rapidly reversible using non-activated EZH2. Overall inhibition constant (K_i^*) values for GSK126 were determined to be as low as 100 pM and appear to be driven by slow dissociation of inhibitor from the activated enzyme. The data suggests that activation of EZH2 results in an enzyme conformation which possesses greater affinity for GSK126. We speculate that the slow dissociation from activated EZH2/PRC2 is at least partly responsible for the high degree of inhibitor selectivity and anti-proliferative activity observed in lymphoma cell lines.

Abstract #18

Dissecting the mechanism of enhanced aminolevulinic acid-mediated protoporphyrin IX accumulation in tumor cells

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A major metabolic change exhibited by many tumor cells is the abnormality in heme synthesis. Tumor cells have been found to produce more protoporphyrin IX (PpIX), a fluorescent precursor of heme, than surrounding normal cells likely due to changes in the expression and activity of heme synthetic enzymes. Tumor accumulation of PpIX is further increased by exogenous administration of 5-aminolevulinic acid (ALA), the first product in heme synthetic pathway. This is because exogenous

ALA can bypass the negative feedback inhibition imposed by heme on the synthesis of PpIX, leading to the overproduction of PpIX and other heme precursors. Although enhanced tumor accumulation of PpIX, either inherently or following the administration of ALA, has been explored for tumor detection and treatment, the mechanism involved in enhanced ALA-PpIX accumulation in tumor cells is still poorly understood.

By comparing the expression level of genes encoding heme synthetic enzymes between tumor and normal tissues in more than 900 breast cancer patients, we have found that most enzyme genes involved in heme synthesis are overexpressed in tumor tissues than in normal tissues. By profiling ALA-mediated PpIX production in a panel of human breast cancer cells with varied genotypic and phenotypic background, we have found enhanced PpIX production in most of these cell lines. These results suggest that enhanced ALA-PpIX production is likely due to multiple genetic abnormalities.

Because many oncogenic transformations stimulate protein kinase signaling pathways, thereby we first started to determine how modulating kinase signaling affects ALA-PpIX production. We found in various breast cancer cell lines that EGFR inhibitor gefitinib, EGFR/Her2 inhibitor lapatinib and PI3K inhibitor BEZ235 decreased ALA-PpIX production in a dose-dependent manner. However, MEK inhibitor PD325901 as well as chemotherapeutic agent docetaxel had a little effect on ALA-PpIX fluorescence. These results suggest that receptor tyrosine kinase and its downstream PI3K signaling are involved in regulating ALA-PpIX production. More importantly, these data indicate that ALA-PpIX fluorescence can be used to predict therapeutic response to these molecular-targeted agents.

POSTDOCTORAL RESEARCHER DIVISION

Abstract # 19

Combinatorial genome-wide targeting of NFkB and C/EBPβ during the early phase of liver regeneration in ethanol-fed rats

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The central objective of this study is to identify the effects of a chronic ethanol diet on the patterns of genome-wide binding of two key transcriptional regulators, NFkB and C/EBPβ, during the early phase of liver regeneration after partial hepatectomy (PHx). The complexity of the regeneration process involves interactions of multiple transcription factors in the activation and regulation of target genes. Transcription factors activated within 1 to 6 hrs after PHx are involved in regulating expression of genes that are associated with homeostasis and stimulating cells to reenter cell cycle and proliferate. We employed Chromatin Immunoprecipitation followed by Roche NimbleGen ChIP-ChIP microarray platform to detect NFkB targets, and ABI SOLiD ChIP-seq platform to detect C/EBPβ targets, in liver samples obtained at 6h following PHx. We performed dynamic pattern analysis to identify gene sets with correlated binding evolution of NFkB and C/EBPβ. Our results indicated that targeting by C/EBPβ alone is the dominant aspect in both ethanol and isocaloric pair-fed carbohydrate control groups. Within this pattern, C/EBPβ binding at a significant number of gene promoters were novel in the ethanol group. However, a similar number of targets showed common C/EBPβ binding without NFkB binding between the two dietary groups. These sets were enriched for processes regulating cell cycle, transcription, cell proliferation, cell death, apoptosis. We found subtle patterns reflecting combinatorial post-PHx binding in both the factors. For eg: in control data set, a group of genes transiently binding to NFkB targets followed by C/EBPβ binding at 6hr time point were associated with processes such as cell proliferation, protein transport, chemical homeostasis, regulation of fatty acid metabolic process etc. Relatively fewer genes were targeted by both NFkB and C/EBPβ at 6h post PHx. The majority of these genes showed altered binding activity in the ethanol group. Based on these results, we conclude that chronic ethanol effects are mediated through individual as well as combinatorial targeting by key transcriptional regulators during liver regeneration. Research support: NIH AA018873 and AA017261.

Abstract #20

C/EBPβ mediated genome-wide combinatorial transcriptional regulatory dynamics during early onset of liver regeneration and chronic alcohol intake

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The primary objective of this study is to characterize effects of chronic alcohol consumption on genome-scale transcriptional regulatory network dynamics during the early phase liver regeneration after 70% partial hepatectomy (PHx) at 6h post 2/3rd PHx in the rat. Rats were fed liquid diet containing 36% of total calories derived from ethanol for 5 weeks, controls were pair-fed an isocaloric liquid diet with carbohydrate replacing ethanol. Genome-wide binding targets C/EBPβ were detected by ABI SOLiD sequencing approach and qPCR validation. Our results indicate significant differences in the binding profiles of C/EBPβ in chronic ethanol samples compared to isocaloric controls, at baseline as well as in response to PHx. Major component of the difference consisted of missing binding activity in the chronic ethanol group, for baseline as well as PHx induced activity. Pathway analysis of these gene sets revealed several cellular processes such as regulation of cell proliferation, regulation of cell cycle, lipid biosynthetic process, response to hormone stimulus, lipid catabolic process, MAPK signaling pathway. C/EBPβ was detected during liver regeneration at the gene promoters of key regulatory pathways such as (1) positive regulation of cell cycle, regulation of programmed cell death, regulation of cAMP biosynthetic process, positive regulation of RNA metabolic process, MAPK signaling pathway etc common to chronic ethanol and control groups; (2) mitochondrion, negative regulation of cell death, Insulin signaling pathway, cell adhesion etc showing missing activity in the ethanol group (3) regulation of transcription, protein kinase activity, VEGF signaling pathway etc showing novel binding in the ethanol group. We employed qPCR to validate a limited set of genomic loci with missing increase in C/EBPβ activity in the ethanol group. We used our PAINT and TRANSFAC bioinformatics software to predict combinatorial regulatory modules containing co-localized binding sites for NF-κB, STAT3, cFos, cJun, C/EBPα and C/EBPβ, on key genes promoter regions, e.g., Mt1a, G0s2, iNOS, Sod2, etc. This indicates potential for C/EBPβ to coordinate with other key transcriptional regulators active during early phase of liver regeneration. Based on these findings, we propose that significant reduction of genome-wide binding activity of C/EBPβ underlies chronic alcohol-mediated deficiencies in liver regeneration response to PHx. Research Support: NIH AA018873 and AA017261.

Abstract #21

Prospects for bromodomain inhibitors in solid tumors

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The bromodomain and extra-terminal (BET) family of proteins, including Brd2, Brd3, Brd4, and BrdT, are chromatin reader proteins that bind acetylated lysines in the N-terminal tails of histones via their tandem bromodomains. We have developed a panel of selective inhibitors (I-BETs) that bind to BET proteins and disrupt their interaction with histones. BET inhibitors have been shown pre-clinically to possess anti-proliferative activity in multiple hematologic malignancies. Here we will describe the activity and sensitivity profile of GSK I-BET compounds in preclinical models of solid tumors.

Abstract #22

EZH2 Inhibition as a Therapeutic Strategy for Lymphoma with EZH2 Activating Mutations

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In eukaryotes, epigenetic post-translational modification of histones is critical for regulation of chromatin structure and gene expression. EZH2 is the catalytic sub-unit of the Polycomb Repressive Complex 2 (PRC2) and is responsible for repressing gene expression through methylation of histone H3 on lysine 27 (H3K27). EZH2 over-expression is implicated in tumorigenesis and correlates with poor prognosis in multiple tumor types. Additionally, somatic heterozygous mutations of Y641 and A677 residues within the catalytic SET domain of EZH2 occur in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL). The Y641 residue is the most frequently mutated residue, with up to 22% of GCB (germinal center B-cell) DLBCL and FL harboring mutations at this site. These lymphomas exhibit increased H3K27 tri-methylation (H3K27me3) due to altered substrate preferences of the mutant enzymes. It is unknown whether specific, direct inhibition of EZH2 methyltransferase activity will be effective in treating EZH2 mutant lymphomas. Herein, we demonstrate that GSK126, a potent, highly-selective, S-adenosyl-methionine (SAM)-competitive, small molecule inhibitor of EZH2 methyltransferase activity, decreases global H3K27me3 levels and reactivates silenced PRC2 target genes. GSK126 effectively inhibits the proliferation of EZH2 mutant DLBCL cell lines and dramatically inhibits the growth of EZH2 mutant DLBCL xenografts in mice. Together, these data demonstrate that pharmacological inhibition of EZH2 activity may provide a promising treatment for EZH2 mutant lymphoma.

Abstract #23

Sensitive and simultaneous profiling of hundreds of transcripts from a single cell on the nCounter platform

Mike Krouse, Brian Birditt, Jim White, Lucas Dennis, Rich Boykin, Gary Geiss, Philippa Webster; Presented by Paul Rasmussen on behalf of Nanostring Technologies R&D; Nanostring Technologies, Seattle, WA 98109

Abstract not published per request of the presenters.

Abstract #24

A noncanonical role of the cellular retinol-binding protein 1 (CRBP1) controls the ovarian malignant phenotype

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Altered retinoid homeostasis and signaling have been found in many cancers such as ovarian, breast, and prostate cancer. A consistent loss of CRBP1 (cellular retinol-binding protein 1), a protein with well documented roles in cellular vitamin A homeostasis, has been detected in early ovarian and other epithelial malignancies, suggesting a role of this protein as a possible tumor suppressor. Therefore, we used the inducible GeneSwitch™ system to tightly-regulate CRBP1 expression in the human ovarian carcinoma cell line NIH-OVCA3, in order to determine CRBP1's effect on the tumorigenic phenotype under vitamin A sufficient and vitamin A deficient conditions. Although induction of CRBP1, under vitamin A sufficient conditions, did not significantly alter the tumorigenic phenotype, we discovered that vitamin A depletion essentially eliminated the ability of our model ovarian cancer cell line to grow in a substrate independent manner and markedly reduced tumor formation in immunocompromised (SCID) mice. Remarkably, induction of CRBP1 restored both the ability to clone in soft agarose and form tumors in SCID mice, reduced reactive oxygen species (ROS), and significantly increased expression of CD133, a marker related to ovarian cancer stem cells. Microarray analysis of anchorage independent cells revealed up-regulation of genes related to WNT signaling, migration/invasion, cell cycle, angiogenesis, and stem cell biology following CRBP1 induction under vitamin A deficient conditions. These results suggest that a noncanonical role of CRBP1, related to ROS signaling and cancer cell "stemness," can control the ovarian malignant phenotype.

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