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# Sanders-Bush, Wecker, and Cox Elected to ASPET Council

Elaine Sanders-Bush

## ASPET members elected Elaine Sanders-Bush as President-Elect, Lynn Wecker as Secretary/Treasurer-Elect, and Bryan F. Cox as Councilor.

Lynn Wecker

Bryan F. Cox

Elaine Sanders-Bush, Professor of Pharmacology at Vanderbilt University School of Medicine in Nashville, Tennessee, will assume the duties and responsibilities of President-Elect in July of 2005.

Lynn Wecker, Professor and Chair of Pharmacology at the University of South Florida in Tampa, Florida, will become Secretary/Treasurer-Elect in July 2005. Dr. Wecker has chaired the Program Committee for the past six years.

Bryan F. Cox will assume the position of Councilor in July. Dr. Cox is Director of the Department of Integrative Pharmacology at Abbott Laboratories in Abbott, Illinois. He has served on the Program Committee and is a past Chair of the Division for Drug Discovery, Development and Regulatory Affairs

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## Contact ASPET


Phone: 301-634-7060 FAX: 301-634-7061

Email: info@aspet.org

Mailing Address:
9650 Rockville Pike
Bethesda, Maryland 20814-3995



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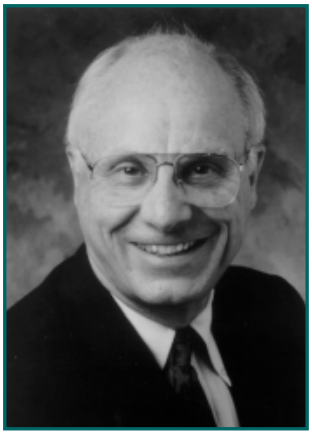
## ASPET AWARD WINNERS FOR 2005



# Kenneth E. Moore, Ph.D.

### *Torald Sollmann Award*

Dr. Kenneth E. Moore, Professor and Chair Emeritus of the Department of Pharmacology and Toxicology at Michigan State University is the recipient of the 2005 Torald Sollmann Award. The Award was established by Wyeth Research to commemorate the pioneering work in America of Dr. Torald Sollmann in the fields of pharmacological investigation and education. Dr. Moore was selected for this Award because of his outstanding and productive research career, his devotion to the teaching of pharmacology, and his unparalleled service to ASPET.

Dr. Moore's creative research has provided new insights into the actions of drugs with brain neurotransmitters. His four decades of research on brain catecholamine systems have included pioneering studies on the development of denervation supersensitivity in the central nervous system and on the biochemical mechanisms of action of psychomotor stimulants such as amphetamine. For the last three decades his work has focused on hypothalamic dopamine systems, characterizing the responses of these neurons to pharmacological, endocrinological, and environmental manipulations. Using neurochemical methods that he and his colleagues developed or refined, Dr. Moore demonstrated that hypothalamic dopaminergic neurons differ in many fundamental ways from the "classic" nigrostriatal and mesolimbic dopaminergic neurons.

Dr. Moore had a primary role in developing pharmacology curricula for students in the three colleges of medicine at Michigan State University and co-authored, with Richard Rech, one of the first educational textbook in psychopharmacology (*Introduction to Psychopharmacology*, 1971). He was Chair of the Department of Pharmacology and Toxicology for 14 years. His outstanding service to Michigan State University was recognized in 1998 when Dr. Moore was awarded the Distinguished Faculty Award, one of the highest honors a faculty member can be given. Dr. Moore has held many leadership positions during more than 30 years of service to ASPET, including Secretary-Treasurer, Chair of the Board of Publications Trustees, and President of the Society.

**Dr. Moore will give the Torald Sollmann Lecture, titled "Pharmacology: Not Just a Job," on Sunday, April 3, at 1:30 pm in Room 3 of the San Diego Convention Center.**

# Randy Hall, Ph.D.

### *John J. Abel Award*

Randy Hall, Ph.D., of the Emory University School of Medicine Department of Pharmacology is the recipient of the 2005 John J. Abel Award, sponsored by Eli Lilly. Dr. Hall receives the John J. Abel Award as an outstanding young investigator for his contributions that have helped shape the field of pharmacology.

Dr. Hall received his Ph.D. from the University of California at Irvine, where he studied the regulation of ionotropic glutamate receptors. In 1994, Dr. Hall moved to the Vollum Institute in Portland, Oregon, to do a post-doctoral fellowship studying receptor trafficking and phosphorylation. Dr. Hall continued his post-doctoral training in 1996 at Duke University, where he studied the signaling and regulation of adrenergic receptors. In 1999, Dr. Hall joined the Department of Pharmacology at Emory University School of Medicine. Dr. Hall has been a pioneer in characterizing non-traditional mechanisms of signaling by G-protein-coupled neurotransmitter receptors, as well as studying the regulation of classical G protein-mediated signaling by receptor-associated scaffold proteins. More recently, his laboratory has also studied the physical interactions between receptors which can regulate receptor properties and allow for cross-talk between different neurotransmitter systems.

Dr. Hall has received a Howard Hughes Medical Institute Post-Doctoral Fellowship, a Faculty Development Award from the PhRMA Foundation, and the W.M. Keck Foundation Distinguished Young Scholar in Medical Research Award.

## Donald P. McDonnell, Ph.D.

### *Pharmacia-ASPET Award in Experimental Therapeutics*

Dr. Donald McDonnell, Ph.D., of the Duke University Medical Center is the recipient of the 2005 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. McDonnell received his Ph.D. in 1987 from the Baylor College of Medicine, where he became an Assistant Professor in the Department of Cell Biology. He moved to Ligand Pharmaceuticals and then to Duke University Medical School. He is currently Director of Graduate Studies, Pharmacology and Cancer Biology, Professor of Medicine, and the Glaxo Wellcome Professor of Molecular Cancer Biology. Dr. McDonnell received ASPET's J.J. Abel Award in 1999.

Dr. McDonnell's research has been pivotal in the studies that indicated that the structure of nuclear receptors is influenced by the nature of the bound ligand and that cells are able to distinguish between these different conformations. This relationship between receptor structure and function, subsequently confirmed by others using crystallography, is the basis for many drug discovery programs. As his research career progressed, Dr. McDonnell turned his attention to defining the role of estrogens in breast cancer and to determining why some tumors were resistant to the antiestrogen, tamoxifen, and why all responsive tumors eventually fail tamoxifen therapy. This work has led to the discovery of GW5638, a drug that inhibits the growth of Tamoxifen resistant tumors in mouse models and which is now being evaluated in clinical trials for metastatic breast cancer. These and subsequent pioneering studies led to the feasibility of targeting the receptor-ligand interface as a target for new drug discovery. Recently, his work has extended beyond estrogens and includes studies on the molecular pharmacology of the progesterone and androgen receptor and of several orphan nuclear receptors.

## J. Victor Nadler, Ph.D.

### *ILAE Epilepsy Research Award*

J. Victor Nadler, Ph.D., Professor in the Department of Pharmacology and Cancer Biology and in the Department of Neurobiology at Duke University Medical Center, is the recipient of the 2005 ASPET-Epilepsy Award. The Award is sponsored by ASPET and the International League Against Epilepsy and donated by Pfizer. The award is to recognize and stimulate outstanding research leading to better clinical control of epileptic seizures.

Dr. Nadler received his Ph.D. in Pharmacology from Yale University. He completed postdoctoral training in the Department of Psychobiology at the University of California, Irvine, where he was then promoted to Assistant Research Psychobiologist.

Dr. Nadler's research interests include mechanisms of epileptogenesis and of excitatory neurotransmission in the mammalian brain. His most noteworthy contributions include the initial identification of glutamate and aspartate as transmitter candidates in the hippocampus, the development of the kainic acid model of epilepsy, and the discovery of mossy fiber sprouting as a mechanism of hyperexcitability in temporal lobe epilepsy. Dr. Nadler is credited with introducing the concept that the development or strengthening of recurrent excitatory circuits is a causative factor in the lesional epilepsies.

Dr. Nadler has received a Research Career Development Award, a Javits Award, and numerous research grants from NINDS. He is author or coauthor of more than 120 original publications, as well as many reviews and book chapters. In addition, he serves or has served on NIH study sections and the editorial boards of *Hippocampus*, the *Journal of Neuroscience*, *Cellular and Molecular Neurosciences*, and *Epilepsy Advances*. In addition to his research, Dr. Nadler is deeply involved in medical education at Duke Medical School. He served as the course director for Medical Pharmacology, currently directs the integrated Body and Disease

course, co-chaired the Curriculum Committee, and served as the leader of curricular initiatives in basic science. Dr. Nadler is a member of ASPET, the American Epilepsy Society, the Society for Neuroscience, and the International Society for Neurochemistry.

**The Award Winners will receive their awards at the Awards Ceremony**
**Saturday, April 2**
**7:00 – 7:30 pm**
**Marina D in the San Diego Marriott**

### Graduate Student Travel Award Winners

Kalindi Bakshi (City Univ of New York)
Joseph M. Breier (Boston Univ Sch of Med)
Kathryn A. Brown (Univ of Iowa)
Melissa A. Burmeister (Louisiana State Univ HSC)
Jason O. Burnette (Med Col of Georgia)
Mary Lolis Garcia Cazarin (Univ of Kentucky)
Anuran Chatterjee (Med Col of Georgia)
Tooba Cheema (Univ of Michigan)
Curtis Robert Chong (Johns Hopkins Univ Sch of Med)
Michael D. Davis (Univ of Virginia)
John H. Dubinion Jr. (Univ of Pittsburgh)
Alejandro Dunnick (Med Univ of South Carolina)
Vaidehee Deshpande (Univ of Texas at Austin)
Ankur V. Dnyanmote (Univ of Louisiana at Monroe)
Jill Marie Donelan (Tufts Univ)
Chris Evelyn (Univ of Michigan, Ann Arbor)
Bradford D. Fischer (Univ of North Carolina at Chapel Hill)
Ying Fu (Univ of Michigan, Ann Arbor)
Srinivas Ghatta (North Dakota State Univ)
Aditya A. Goel (Univ of The Pacific)
Eric Gross (Med Col of Wisconsin)
Amer C. Hakam (Univ of Houston)
Joachim Hartmann (Texas Tech Univ HSC)
Yi Jing (West Virginia Univ)
Ashley C. Jones (Washington State Univ)
Prasad R. Joshi (Univ of Alaska Fairbanks)
Tony K.L. Kiang (Univ of British Columbia)
Ranjita Kokje (Univ of Mississippi)
Laura M. Kreckler (Med Col of Wisconsin)
Sangderk Lee (Univ of Virginia)
Tiangang Li (Northeastern Ohio Univ Col of Med)
Yun Liu (Oklahoma Univ HSC)
Jean Lanette Lord (Univ of Arizona)
Jennifer Losapio (St Louis Univ Sch of Med)
Aditi Marwaha (Univ of Houston)
Rebecca Miller (Univ of Missouri)
Tim Mitin (Tufts Univ Sch of Med)
Tanvi Modi (Univ of Louisville)
Prabhakara Reddy Nagareddy (Univ of British Columbia)
Wei Ni (Michigan State Univ)
Demian F. Obregon (Tulane HSC)
Erik R. Olson (Northeastern Ohio Univ Col of Med)
Bladimir J. Ovando (Univ of Buffalo)
Oné R. Pagan (Cornell Univ)
Prasad Narayan Paradkar (Univ of Buffalo)
Damon Poburko (Univ of British Columbia)
Kirsten M. Raehal (Ohio State Univ)
Gautham K. Rao (Michigan State Univ)
Marcia Reinhart (Univ of Oxford)
Kamakshi Sachidanandam (Univ of Georgia)
Rajarshi Sengupta (Univ of South Florida)
Rajkumar Sevak (Univ of Texas HSC)
Ryan C. Smith (Creighton Univ Med Ctr)
Prajakta Anilkumar Sonalker (Univ of Pittsburgh)
Jeremiah Stitham (Dartmouth Med Sch)
Lorraine N. Sunday (UCI)
Christopher K. Taylor (Creighton Univ Sch of Med)
Manish M. Tiwari (Univ of Arkansas for Med Sci)
Okechukwu T. Ukairo (Duquesne Univ)
Kristy L. Wagner (Penn State Univ)
Hong Wang (Michigan State Univ)
Kellie J. White (Purdue Univ)
Clare Wilhelm (VA Med Ctr)
Eric Williamson (Med Univ of South Carolina)
Renee Wong (Med Univ of South Carolina)
Yanling Xu (UCI)
Yang Xu (Univ of Washington)
Yi Zhang (Univ of Tennessee HSC)

### SURF Travel Award Winners

Tobi N. Callaghan (Univ of Kansas Med Ctr)
Edward G. Haberli II (Univ of New England)
Ryan Paolino (Univ of New England)
Tara Verville (Univ of New England)

# ASPET AWARD WINNERS FOR 2005

## Young Scientist Travel Award Winners

Anthony J. Baucum (Univ of Utah)
Kelly A. Carrigan (Univ of North Carolina at Chapel Hill)
Thirunavukkarasu Chinnasamy (Univ of Pittsburgh)
Marcus Delatte (McLean Hosp/Harvard Med Sch)
Amy M. Deveau (Univ of New England)
Bill Fantegrossi (Emory Univ)
Rayna J. Gonzales (UCI)
Anjelica L. Gonzalez (Baylor Col of Med)
Chris Hague (Emory Univ Sch of Med)
Erin Heinzen (Univ of North Carolina at Chapel Hill)
RHP Hilgers (Med Col of Georgia)
Liming Jin (Johns Hopkins Univ)
Emily M. Jutkiewicz (Univ of Michigan Med Sch)
Yugesh Kharel (Univ of Virginia)
Bernard Le Foll (NIDA)
Aurea Elizabeth Linder (Med Col of Georgia)
Charles W. Locuson (Univ of Minnesota)
Brett M. Mitchell (Baylor Col of Med)
Joseph Fomusi Ndisang (Univ of Saskatchewan)
Jeffrey J. Olearczyk (Med Col of Georgia)
Cláudia Ramos Rhoden (FFFCMPA, Brazil)
Jason R Richardson (Emory Univ)
Terrilyn A. Richardson (Emory Univ)
Sanjoy Roychowdhury (Univ of Iowa)
Deepak R. Thakker (Novartis Inst for BioMed Res)
Zhimin Tong (University of Texas at Austin)
Rodney A. Velliquette (Northwestern Univ)
Zhengyuan Xia (Univ of British Columbia)
Li Zhang (Univ of Pennsylvania Sch of Med)

## ASPET thanks its generous sponsors for EB '05

### Educational Grants for Scientific Programming

Avanti Polar Lipids
Espirion Therapeutics, a Division of Pfizer Global R&D
Hoffman-La Roche
Merck Research Laboratories
Pfizer, Inc.
Wyeth Research

### ASPET Awards

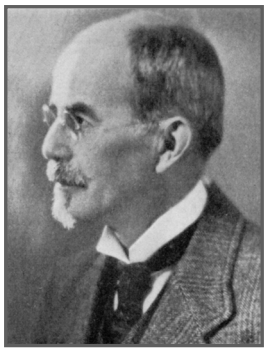
Wyeth Research (Torald Sollmann Award)

Eli Lilly and Company (John J. Abel Award)

Pfizer, Inc. (ILAE Epilepsy Research Award)

# CALL FOR AWARD NOMINATIONS FOR 2006

## JOHN J. ABEL AWARD



The John J. Abel Award in Pharmacology, supported by Eli Lilly and Company, was established to stimulate fundamental research in pharmacology and experimental therapeutics by young investigators. The annual Award consists of $2,500, a plaque, and travel expenses for the winner and spouse to the award ceremony at the annual meeting of ASPET.

Nominees for this award shall not have passed their **thirty-ninth birthday on April 30** of the year of the Award. The candidate need not be a member of the Society; however, a nomination must be made by an ASPET member, and no member may nominate more than one candidate a year. The Award shall be made for original, outstanding research in the field of pharmacology and/or experimental therapeutics. Independence of thought, originality of approach, clarity and excellence of data presentation are important criteria. Candidates shall not be judged in comparison with the work of more mature and experienced investigators. Quality rather than the number of contributions shall be emphasized. It shall be the responsibility of the sponsor to make clear the contribution of the candidate to any jointly authored reprints and manuscripts and the originality and independence of the candidate's research. Selection will be made by the J.J. Abel Award Committee, appointed by the President of ASPET.

Nominations shall be accompanied by six (6) copies of each of the following:

1. Summary that describes the importance of the candidate's work.
2. Each of six published articles or manuscripts accepted for publication that are a representation of the candidate's work.
3. Brief biographical sketch of the candidate.
4. Candidate's *curriculum vitae* and bibliography.

Nominations for this Award must be received no later than **September 15, 2005** by the Executive Officer, American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, Maryland 20814-3995.

### Winners of the John J. Abel Award

| | | | | | |
|---|---|---|---|---|---|
| 1947 | George Sayers | 1966 | Lewis S. Schanker | 1985 | P. Michael Conn |
| 1948 | J. Garrott Allen | 1967 | Frank S. LaBella | 1986 | Gordon M. Ringold |
| 1949 | Mark Nickerson | 1968 | Richard J. Wurtman | 1987 | Lee E. Limbird |
| 1950 | George B. Koelle | 1969 | Ronald Kuntzman | 1988 | Robert R. Ruffolo, Jr. |
| 1951 | Walter F. Riker, Jr. | 1970 | Solomon H. Snyder | 1989 | Kenneth P. Minneman |
| 1952 | David F. Marsh | 1971 | Thomas R. Tephly | 1990 | Alan R. Saltiel |
| 1953 | Herbert L. Borison | 1972 | Pedro Cuatrecasas | 1991 | Terry D. Reisine |
| 1954 | Eva K. Killam | 1973 | Colin F. Chignell | 1992 | Frank J. Gonzalez |
| 1955 | Theodore M. Brody | 1974 | Philip Needleman | 1993 | Susan G. Amara |
| 1956 | Fred W. Schueler | 1975 | Alfred G. Gilman | 1994 | Brian Kobilka |
| 1957 | Dixon M. Woodbury | 1976 | Alan P. Poland | 1995 | Thomas M. Michel |
| 1958 | H. George Mandel | 1977 | Jerry R. Mitchell | 1996 | John D. Scott |
| 1959 | Parkhurst A. Shore | 1978 | Robert J. Lefkowitz | 1997 | David J. Mangelsdort |
| 1960 | Jack L. Strominger | 1979 | Joseph T. Coyle | 1998 | Masashi Yanigasawa |
| 1961 | Don W. Esplin | 1980 | Salvatore J. Enna | 1999 | Donald P. McDonnell |
| 1962 | John P. Long | 1981 | Sydney D. Nelson | 2000 | William C. Sessa |
| 1963 | Steven E. Mayer | 1982 | Theodore A. Slotkin | 2002 | Steven A. Kliewer |
| 1964 | James R. Fouts | 1983 | Richard J. Miller | 2003 | David S. Bredt |
| 1965 | Eugene Braunwald | 1984 | R. Peter Guengerich | 2004 | David P. Siderovski |
| | | | | 2005 | Randy Hall |

# CALL FOR AWARD NOMINATIONS FOR 2006

## THE PHARMACIA-ASPET AWARD IN EXPERIMENTAL THERAPEUTICS

The Pharmacia-ASPET Award in 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. The award is supported in perpetuity by a gift from Pharmacia. The winner will receive a $2,500 honorarium, a bronze medal, and travel expenses for the winner and spouse to the award ceremony at the ASPET annual meeting.

There are no restrictions on nominees for this award. The Award shall be made on the basis of published reprints, manuscripts ready for publication, and a two-page summary of the candidates accomplishments and qualifications for the award. Selection will be made by the Pharmacia-ASPET Award Committee, appointed by the President of ASPET.

Nominations shall be accompanied by six (6) copies of each of the following:

1. Two (2)-page summary that details the importance of the candidate's work.
2. Each of six articles published or ready for publication by the candidate that have direct bearing on the Award.
3. Brief biographical sketch of the candidate.
4. Candidate's *curriculum vitae* and bibliography.

Nominations for this Award must be received no later than **September 15, 2005** by the Executive Officer, American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, Maryland 20814-3995.

**Winners of the ASPET Award for Experimental Therapeutics**

| | | | | | |
|---|---|---|---|---|---|
| 1969 | John A. Oates | 1982 | William H. Prusoff | 1995 | Henry I. Yamamura |
| 1970 | Joseph R. Bertino | 1983 | Marcus M. Reidenberg | 1996 | Robert F. Furchgott |
| 1971 | Elliot S. Vesell | 1984 | Sir James Black | 1997 | Michael M. Gottesman |
| 1972 | Francois M. Abboud | 1985 | Louis Lemberger | 1998 | Phil Skolnick |
| 1973 | Dean T. Mason | 1986 | Alan C. Sartorelli | 1999 | Yung-Chi Cheng |
| 1974 | Leon I. Goldberg | 1987 | Albrecht Fleckenstein | 2000 | Saloman Z. Langer |
| 1975 | Mackenzie Walser | 1988 | Jean-Francois Borel | 2001 | George R. Breese |
| 1976 | Louis Lasagna | 1989 | Benedict R. Lucchesi | **Became Pharmacia-ASPET Award in Experimental Therapeutics** | |
| 1977 | Allan H. Conney | 1990 | Albert Sjoerdsma | | |
| 1978 | Attallah Kappas | 1991 | Theophile Godfraind | 2002 | Darryle D. Schoepp |
| 1979 | Sydney Spector | 1992 | James W. Fisher | 2003 | William C. DeGroat |
| 1980 | Sanford M. Rosenthal | 1993 | V. Craig Jordan | 2004 | Philip Needleman |
| 1981 | David G. Shand | 1994 | Susan B. Horwitz | 2005 | Donald McDonnell |

## GOODMAN AND GILMAN AWARD IN RECEPTOR PHARMACOLOGY

The Louis S. Goodman and Alfred Gilman Award in Drug Receptor Pharmacology, contributed by GlaxoSmithKline, was established to recognize and stimulate outstanding research in pharmacology of biological receptors. Such research might provide a better understanding of the mechanisms of biological processes and potentially provide the basis for the discovery of drugs useful in the treatment of diseases. The award is presented biennially in even years and consists of an honorarium of $2,500, a plaque, and travel expenses for the winner and spouse to the award ceremony at the ASPET annual meeting.

There are no restrictions on the nominees for this award. However, nominations must be made by a member of ASPET, and no member may nominate more than one candidate a year. The award is to be made on the basis of the research contributions described in published work or submitted manuscripts and a summary of those contributions described in the letter of the individual who nominates the candidate. Selection will be made by the Goodman and Gilman Award Committee, appointed by the President of ASPET.

Nominations shall be accompanied by six (6) copies of each of the following:

1. Summary that details the importance of the candidate's work.

2. Each of six articles published or ready for publication that have direct bearing on the award.
3. Brief biographical sketch of the candidate.
4. Candidate's *curriculum vitae* and bibliography.

Nominations for this Award must be received no later than **September 15, 2005** by the Executive Officer, American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, Maryland 20814-3995

**Winners of the Goodman and Gilman Award in Drug Receptor Pharmacology**

| | | | | | |
|---|---|---|---|---|---|
| 1980 | Solomon H. Snyder | 1988 | Ronald M. Evans | 1996 | Elliott M. Ross |
| 1982 | Pedro Cuatrecasas | 1990 | Alfred G. Gilman | 1998 | David Garbers |
| 1984 | Robert F. Furchgott | 1992 | Paul Greengard | 2000 | Melanie H. Cobb |
| 1986 | Robert J. Lefkowitz | 1994 | Jean-Pierre Changeux | 2002 | Lee E. Limbird |

## BERNARD B. BRODIE AWARD IN DRUG METABOLISM

The B. B. Brodie Award in Drug Metabolism has been established to honor the fundamental contributions of Bernard B. Brodie in the field of drug metabolism and disposition. The Award is presented biennially in even years to recognize outstanding original research contributions in drug metabolism and disposition, particularly those having a major impact on future research in the field. The B. B. Brodie Award is sponsored by the Division for Drug Metabolism, and funds to support the award come from members' contributions.

The award consists of a $2,000 honorarium, a commemorative medal, and travel expenses to the award ceremony at the annual meeting. A lecture, delivered by the awardee at the annual meeting, describing appropriate research accomplishments and their future direction, will be published in *Drug Metabolism and Disposition*.

There are no restrictions on institutional affiliation, and a candidate need not be a member of the Society. The only restriction for the Award is that supporting research accomplishments must not be used to win any other major award. Only one nominator is necessary, although more are acceptable, and the nominators need not be members of ASPET. Selection of an awardee will be made biennially by the B.B. Brodie Award Committee, appointed by the President of ASPET, with input from the Division for Drug Metabolism.

Nominations shall be accompanied by six (6) copies of each of the following:

1. Selections and comments on the outstanding papers.
2. Nominating letter and no more than five supporting letters detailing accomplishments of the nominee.
3. Brief biographical sketch of the candidate.
4. Candidate's *curriculum vitae* and bibliography.

Nominations for this Award must be received no later than **September 15, 2005** by the Executive Officer, American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, Maryland 20814-3995.

**Winners of the Bernard B. Brodie Award in Drug Metabolism**

| | | | | | |
|---|---|---|---|---|---|
| 1978 | James R. Gillette | 1988 | Wayne M. Levin | 1999 | Marion W. Anders |
| 1980 | Minor J. Coon | 1990 | Daniel M. Ziegler | 2000 | Bettie Sue Masters |
| 1982 | Donald M. Jerina | 1994 | Paul R. Ortiz de Montellano | 2002 | Eric F. Johnson |
| 1984 | Gilbert J. Mannering | 1996 | Anthony Y.H. Lu | 2004 | Thomas L. Poulos |
| 1986 | Daniel W. Nebert | 1997 | Ronald W. Estabrook | | |

# P. B. Dews Award for Research in Behavioral Pharmacology

ASPET's Division of Behavioral Pharmacology sponsors the P. B. Dews Award for Research in Behavioral Pharmacology to recognize outstanding lifetime achievements in research, teaching and professional service in the field of Behavioral Pharmacology and to honor Peter Dews for his seminal contributions to the development of behavioral pharmacology as a discipline. The biennial award is supported by an endowment made possible by contributions from Aventis, Centre de Recherche Pierre Fabre, Eli Lilly, Harvard University, International Life Sciences Institute Caffeine Committee, Merck (San Diego), Pepsi Cola Company, Pfizer Central Research and Pfizer Global Research and Development, Pharmacia, Wyeth-Ayerst Research, and ASPET members.

The Award consists of $750, a plaque, and travel expenses to the award ceremony at the ASPET annual meeting. The recipient will be invited by the Chair of the Division of Behavioral Pharmacology to deliver a special lecture on this occasion. The lecture will be published subsequently in an appropriate ASPET-sponsored publication

There are no restrictions on nominees for this award. Nominations may be made by members of ASPET or of any relevant scientific society. Selection will be made by the P.B. Dews Award Committee, appointed by the President of ASPET with input from the Division for Behavioral Pharmacology.

Nominations shall be accompanied by six (6) copies of each of the following:

1. Description of the candidate's major contributions, including scientific, teaching and professional achievements.
2. Candidate's *curriculum vitae* and bibliography.
3. List of the candidate's trainees.
4. Each of five major publications.
5. Brief biographical sketch of the candidate.

Nominations for this Award must be received no later than **September 15, 2005** by the Executive Officer, American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, Maryland 20814-3995.

**Winners of the P. B. Dews Award**

| | | | |
|---|---|---|---|
| 2002 | William H. Morse | 2004 | Joseph V. Brady |

## 2005 NIH Director's Pioneer Award
## Call for Nominations

The National Institutes of Health announces the 2005 NIH Director's Pioneer Award, a key component of the NIH Roadmap for Medical Research. The award supports scientists of exceptional creativity who propose pioneering approaches to major challenges in biomedical research.

The program is open to scientists at all career levels who are currently engaged in any field of research, interested in exploring biomedically relevant topics, and willing to commit the major portion of their effort to Pioneer Award research. Women, members of groups that are underrepresented in biomedical research, and individuals in the early to middle stages of their career are especially encouraged to nominate themselves. Awardees must be U.S. citizens, non-citizen nationals, or permanent residents.

In September 2005, NIH expects to make 5 to 10 new Pioneer Awards of up to $500,000 in direct costs per year for 5 years.

The streamlined self-nomination process includes a 3- to 5-page essay, a biographical sketch, a list of current research support, and the names of three references. Submit nominations on the Pioneer Award Web site **between March 1 and April 1, 2005.**

http://nihroadmap.nih.gov/pioneer

# Changes Proposed to ASPET's Bylaws

The following changes to the bylaws will be proposed by ASPET Council for consideration at the Annual Business Meeting on April 3, 2005. If these changes are approved at the Business Meeting, they will be distributed to the general membership for a vote. Deletions are shown as strikeouts in ~~red~~ and additions are shown in **bolded blue.** With the exception of Article II. Section 1. Item 3 (Retired Members), the changes to the existing articles are intended to codify actual practice, to include in the bylaws a requirement for the Council to meet, and to define a quorum for the Business Meeting and the Council meeting. The additions to the bylaws are designed to bring them into accordance with the IRS requirements for a 501(c) (3) organization. The change in the requirements for Retired Member status would not apply to those members already in Retired status.

## CHANGES TO EXISTING ARTICLES

### Article II. Members

**Section 1. Membership Categories**

**Item 3. Retired Members** Any member of the Society who has been a **Regular or Affiliate** member for 30 years or who has retired because of disability ~~or age~~ may, upon approval of the Council, be relieved from the annual assessment while retaining the privileges of membership.

### Article III. Officers

**Section 2. Council**

The management of the Society shall be vested in a Council consisting of the President, **who shall chair the Council**, the President-Elect, the immediate Past President, the Secretary/ Treasurer, the Secretary/Treasurer-Elect, the immediate Past Secretary/Treasurer, and three other Councilors. The Executive Officer, the Chair of the Board of Publications Trustees, and other individuals as may be approved by Council shall be *ex officio* members of the Council without vote. ~~Five voting members of the Council shall constitute a quorum~~

### Article IV. Nomination and Election of Officers and Elected Committee Members

**Section 1. Nomination and Election Process**

**Item 2. Nominating Committee** The Nominating Committee shall consist of the Secretary/Treasurer of half of the Divisions on a rotating basis, the ASPET immediate Past President to serve as non-voting chair, and the Chair of the Program Committee **as an *ex officio* member without vote.**

### Article VII. Meetings

**Item 2. Business Meetings** A Business Meeting of the membership shall be scheduled at the regular, annual scientific meeting of the Society. Other business meetings of the Society may be held at times and places determined by the Council. Members of the Society shall be notified at least four weeks in advance of the time and place of such meetings. **One hundred members shall constitute a quorum for the transaction of business.**

**Item 3. ~~Quorum~~ Council Meeting There shall be a Council meeting at the annual meeting and at other times and places as determined by the Council. Five voting members of the Council shall constitute a quorum.**

## ADDITION OF NEW ARTICLES

### Article X. Conflict of Interest

**Any Council member, officer, employee, or committee member having an interest in a contract or other transaction or determination presented to the Council or a committee for recommendation, authorization, approval or ratification shall give a prompt, full and frank disclosure of his/her interest to the council or committee prior to its acting on such contract or transaction. The body to which such disclosure is made shall thereupon determine, by majority vote, whether the disclosure**

**shows that a conflict of interest exists or can reasonably be construed to exist. If a conflict is deemed to exist, such person shall not vote on, nor use his/her personal influence on, nor participate (other than to present factual information or to respond to questions) in the discussion or deliberations with respect to such contract, transaction or determination. Such person may not be counted in determining the existence of a quorum at any meeting where the contract, transaction, or determination is under discussion or is being voted upon. The minutes of the meeting shall reflect the disclosure made, the vote thereon and, where applicable, the abstention from voting and participation, and whether a quorum was present.**

### Article XI. Nondiscrimination

**The officers, employees, and persons served by this corporation shall be selected in a non-discriminatory manner which respect to age, sex, race, national origin, and political or religious opinion or affiliation.**

## ASPET Annual Business Meeting
## Sunday, April 3
## 6:00 pm – 7:00 pm
## San Diego Marriott Hotel
## Marriott Hall 2

## Student-Mentor Mixer
## Immediately Following
## in Marriott Hall 3

# The Pharmacology Education Partnership: Improving High School Biology and Chemistry

Rochelle D. Schwartz-Bloom, Ph.D.
Professor of Pharmacology
Department of Pharmacology & Cancer Biology, Duke University Medical Center

## Introduction

The Pharmacology Education Partnership (PEP) is a curriculum we developed for high school biology and chemistry teachers, providing them with tools to teach biology and chemistry principles using pharmacology topics (e.g., drugs of abuse). This partnership between Duke University Medical Center and the North Carolina School of Science and Math (NCSSM) was funded by a Science Education Drug Abuse Partnership Award from the National Institute on Drug Abuse. The major premise of our project was that high school students might learn basic concepts in biology and chemistry better if the material was presented in the context of something interesting and relevant to their own lives. Forty-seven teachers across the US were trained to use the curriculum in their classrooms (a second project is ongoing with ~220 teachers being trained across the US). The PEP project includes several components such as curriculum design, science content, and professional development. The PEP project has been tested in 3500 students nationally and has demonstrated significant achievement in high school biology and chemistry in those classrooms using the PEP modules. The results of the study were published in the Journal of Research in Science Teaching (Schwartz-Bloom and Halpin, 2003). Below, several of the features and our findings are summarized.

## The PEP Modules

Initially, we developed four pharmacology modules that were field-tested by 47 teachers throughout the US. [In our ongoing project, we have developed two additional modules.] The current curriculum involving all six modules is online at www.thepepproject.net and is available to the public. Briefly, each module focused on a pharmacologic topic that integrates biological and chemical principles. The modules also integrated other subjects appropriate to the topic, such as mathematics, public policy, psychology, and social sciences. Each pharmacology module consisted of 1) a set of learning objectives, 2) an inquiry-directed student handout (problem-based learning approach), 3) a teacher's guide with background science content (containing answers to student questions) and illustrative graphics, 4) a glossary of terms, 5) a resource list, and 6) student hands-on or "minds-on" activities and assessment strategies (these were developed by the teachers at the workshop and then they were added to the modules).

The six modules developed for the PEP curriculum are summarized in Table 1 (below).

**PEP Curriculum Modules**

| Module Title | Module Content |
|---|---|
| 1. Acids, Bases, and Cocaine Addicts | acid-base chemistry, molecular structure, circulatory system, membrane transport, cocaine formulations, addiction biology |
| 2. Drug Testing: A Hair-Brained Idea | acid-base chemistry, molecular structure, cellular structure, anatomy, biology & chemistry of hair, nicotine, cocaine, heroin, racial ethics |
| 3. How Drugs Kill Neurons: It's Radical! | oxidation-reduction, oxygen radicals, neuron structure, neurochemistry, cell death, methamphetamine, neurodegenerative diseases |
| 4. Military Pharmacology: It Takes Nerves | covalent bonding, enzyme action, autonomic nervous system, physiology, behavior of gases, chemical warfare, Middle East & Japan current events/history |
| 5. Why Plants Make Drugs for Humans | plant cell structure, acid-base chemistry, molecular structure, membrane transport, tobacco industry chemical "tricks" |
| 6. Steroids and Athletes: Genes Work Overtime | chemistry of testosterone, molecular structure, muscle cell anatomy and physiology, DNA structure, transcription and protein synthesis, androgenic/anabolic steroids, drug testing |

The PEP modules were designed as supplements to provide teachers with alternate ways of teaching basic concepts already covered in their existing curricula. There is no prescribed method for using the modules, thus providing the flexibility that teachers need so that they can incorporate the content in a way that fits their own teaching styles and time constraints.

## The PEP Website

The six modules can be found online at our website, www.thepepproject.net. The PEP website for teachers and students is one of the highlights of the project. Its high quality graphics and animations, combined with the interactive nature of the various components, make it a unique and fun educational tool. An example of one of the screens from the PEP website is shown in Figure 1. The science content for Module 5 ("Why Do Plants Make Drugs for Humans") is on the left panel, and a figure that accompanies the text is on the right panel. This particular figure is animated on the website; the user clicks on the thumbnail image and the animation starts automatically. The animation shows how acetylcholine and nicotine bind to an acetylcholine receptor to open sodium channels and produce a current across the membrane. Other features in the PEP website include a pop-up glossary and a section for students called, "What Did I Learn?" In this section, students engage in interactive quizzes that assess content knowledge for each of the modules.

**Figure 1**


## Professional Development: The Workshops

The 47 teachers recruited to participate in the PEP project attended a one week professional development workshop at Duke University. We used a "wait-listed" control design; 22 teachers attended the workshop and field-tested the modules the following year; the second year, the remaining 25 teachers attended the workshop ("wait-listed" controls) and then field-tested the following year. During the workshop, teachers learned basic pharmacology principles that apply to biology and chemistry concepts. Also teachers worked in groups to develop supplemental classroom activities (both inquiry-based and non-inquiry based) for each module. Using a pretest/posttest design, we found that teacher knowledge of biology and chemistry concepts (20 true/false questions) increased at the end of the 1 week workshop (as expected) and was maintained for at least one year (Figure 2). In our ongoing project, the

professional development includes the same instruction in a full day workshop at the National or North Carolina Science Teachers Association meetings or in a Distance Learning workshop over 3 weeks—data from the 220 teachers participating supports our previous findings; teachers' knowledge increased at the end of the one-day or the Distance Learning workshops and as before, knowledge was retained throughout the school year.

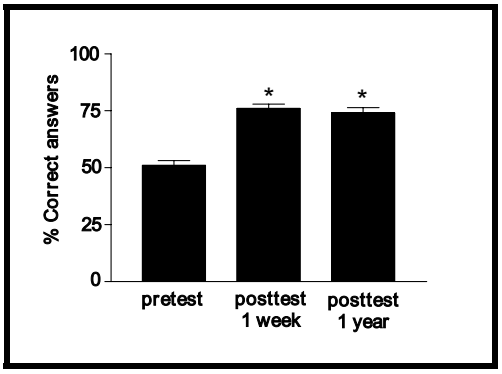



**Figure 2**

The professional development is an important component of the PEP curriculum. Analysis of the data revealed that student performance in biology and chemistry classes whose teachers attended the workshop was significantly better than that in classes whose teachers did not attend the workshop (Schwartz-Bloom and Halpin, 2003).

### Field-testing the Curriculum

At the workshops, the teachers were instructed to incorporate the modules into their standard curriculum in a way that fit their own teaching styles and time constraints. Teachers field-tested the modules in their classrooms of beginning or advanced biology or chemistry—all four years were represented. At the end of the school year, we tracked the number of modules used by each teacher. Six of 47 teachers did not use any modules, and of those who did use modules, 28 used more than one module. In our ongoing project, we tracked the online usage of the modules by both teachers and students online; for the 2003-2004 school-year, we have had hundreds to thousands of hits on each module by both teachers and students.

### Evaluation of the Curriculum

At the end of the year of field-testing, students (~3500 total, from both the control and experimental groups) were administered a 20-item multiple choice test of basic biology and chemistry principles ("basic knowledge") and an 8-item test of their knowledge about drugs ("advanced knowledge"). Statistical analysis of the data collected using hierarchical linear modeling revealed that the use of the PEP modules was a significant predictor of better performance in both biology and chemistry classes compared to standard curricula in which no modules were used (Schwartz-Bloom and Halpin, 2003). The more modules used, the better the students performed (i.e., a "dose-response" effect) in both the basic and advanced knowledge categories (Figure 3); there were gains of up to 28 percentage points when 4 modules were used compared to no modules. Other predictors of improved scores included the course level (i.e., advanced placement) and course type (i.e., chemistry vs biology). The student year ($9^{th}/10^{th}$ vs $11^{th}/12^{th}$ grades) did not predict better scores. The degree of improvement obtained by using the modules is considerably greater than that reported in several science education studies of standards-based instructional practices (Von Secker and Lissitz, 1999; Kahle et al., 2000). We are in the process of analyzing data from our current study from ~13,000 students across the US.

> Topics on drugs and drug abuse are probably highly relevant and meaningful to high school students.

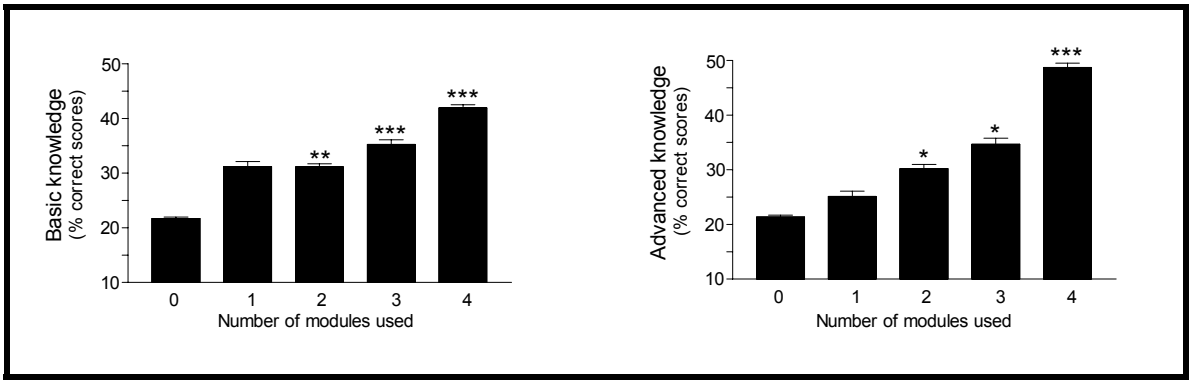



**Figure 3**

Performance of all students on questions of "basic knowledge" and "advanced knowledge" depending on the number of modules used during the course. Data are the mean ± S.E.M. scores from biology and chemistry students in basic and advanced classes. Hierarchical linear modeling (HLM) revealed that the number of modules was a significant predictor of student scores. (Schwartz-Bloom and Halpin, 2003)

In addition, we found that biology students increased performance on the chemistry questions, and chemistry students increased performance on biology questions when at least two modules were used. The findings supported our hypothesis that not only would biology students learn biology better, but they also learned chemistry better (and vice versa).

## Conclusions

The substantial gains in biology classes on chemistry questions, and vice versa, highlights the usefulness of pharmacology topics, which have an inherently integrative nature, in science education. In addition, the real-world relevance of the content in the modules may have been a major factor in the successful outcome of this study. Topics on drugs and drug abuse are probably highly relevant and meaningful to high school students. If such topics can help capture student interest in science, then other features of science education reform may be more effective. One of the ultimate goals in science education is to help students use science to be critical thinkers and make good decisions in their daily lives (Yiping, 1996). It remains to be determined whether a program such as the one we developed will help teenagers make intelligent decisions about drug use. Nevertheless, the approach we have taken using pharmacology topics should be applicable to many areas of science that are parts of students' daily lives.

## References

Kahle, J.B., Meece, J., & Scantlebury, K. (2000). Urban African-American middle school science students: does standards-based teaching make a difference? *Journal of Research in Science Teaching*, 37:1019-1041.

Schwartz-Bloom, R.D. & Halpin, M.J. (2003). Integration of pharmacology topics into high school biology and chemistry classes improves student performance. *Journal of Research in Science Teaching*, 40: 922-938.

Von Secker, C.E. & Lissitz, R.W. (1999). Estimating the impact of instructional practices on student achievement in science. *Journal of Research in Science Teaching*, 36:1110-1126.

Yiping, Y., et al., (1996). Within-class grouping: A meta-analysis. *Reviews of Educational Research,* 66:423-458.

# Experimental Biology/IUPS 2005 ✸ Public Policy Workshops & Symposia

Open to All EB/IUPS Registrants

## Let's Get Integrative: Finding Jobs in Industry

**Saturday, April 2, 3:00-5:30 pm, Room 3**

Good jobs are available for scientists with a background in integrative organ system biology. Find out what skills are needed and what opportunities exist. Industry representatives discuss prospects for those trained in the use of intact organ systems and *in vivo* animal models. Meet scientists from Abbott Laboratories, Amgen, Cypress Biosciences, Merck Research Laboratories, and Wil Research Laboratories and learn about opportunities in these companies.

## Big Science Ahead: W[h]ither the PI?

**Sunday April 3, 10:30 am – 12:00 noon, Room 6A/B**

What is the role of the individual scientist in a "big science" world? How do we train/compensate/ evaluate scientists who participate in multidisciplinary or interdisciplinary research teams? As funding increases for biomedical research shrink, what is the future of the PI? Can existing PIs maintain the current model of training several young scientists who themselves seek to become PIs? If not, what will those scientists do, and how will we continue to be able to attract "the best and the brightest" to the life sciences?

- Susan Swain, President and Director, Trudeau Institute
- Norka Ruiz Bravo, Deputy Director for Extramural Research, National Institutes of Health
- Mary F. Lipscomb, professor and chair, Department of Pathology, Univ. of New Mexico School of Medicine

## Trans-national Impacts of Animal Welfare Regulation

**Sunday, April 3, 3:15-5:15 pm, Room 29C**

- Introduction/overview: What are the issues?—Kevin Kregel, Univ. of Iowa
- New European animal welfare standards: Potential impact and concerns—Anne-Dominique Degryse, Centre de recherche Pierre Fabre
- International animal welfare standards and the pharmaceutical industry—David P. Brooks, Glaxo Smith Kline
- A view from the bench: The future of international collaborations—Pontus Persson, Humboldt Univ.
- Tempering the process: The in's and out's of oversight—Joseph R. Haywood, Michigan State Univ.
- Questions/panel discussion

## AAI Public Affairs Session

**Sunday, April 3, 12:30-2:30 pm, Room 26 A/B**

## Developing and Implementing a Communications Strategy: The Basics for the Basic Scientist

**Monday, April 4, 3:15-5:15 pm, Room 29C**

*Part 1 – Identifying and Refining Your Research Message*
Rosie Mestel, *Los Angeles Times* Science/Medical Writer

*Part 2 – Disseminating Your Research Message*
Gale Davy, Executive Director, Wisconsin Association for Biomedical Research and Education
Robert Nellis, Research Communications Director, Mayo Clinic
Mayer Resnick, Communications Officer, American Physiological Society

*Q&A Session and Wrap-Up* Hannah Carey, University of Wisconsin School of Veterinary Medicine

## How To Prevent Institutional Shutdowns: Safeguarding Your Human Subjects Research Program

**Tuesday, April 5, 12:00 noon-1:30 p.m., Room 17A**

- How accreditation can safeguard and improve the research enterprise—S.R. Smith, California Western School of Law
- Perspective of a Human Research Protections Officer on institutional shutdowns—M. Keane, Univ. of Minnesota
- Perspective of a researcher on how to navigate institutional roadblocks to human subjects research—R.W. Bianco, Univ. of Minnesota
- Panel discussion

# DIVISION SESSIONS AT EB/IUPS '05

## Division for Behavioral Pharmacology Symposium: Preclinical Assessment of Pain and Analgesic Drugs

Monday, April 4, 3:00 – 5:30 pm, Convention Center, Room 5A
Chair: S. Steve Negus

Preclinical models of acute pain. Edward J. Bilsky, *Univ. of New England*
Preclinical models of inflammatory pain. Todd W. Vanderah, *Univ. of Arizona*
Preclinical models of neuropathic pain. Michael R. Brandt, *Wyeth Disc. Res., Princeton, NJ*
Targeting pain-suppressed behaviors in preclinical models of pain and analgesia. S. Steve Negus, *McClean Hospital, Harvard Med. Sch.*
Use of fMRI for drug development in pain and analgesia. David Borsook, *McClean Hospital, Harvard Med. Sch.*

## Division for Cardiovascular Pharmacology Graduate Student and Postdoctoral Scientist Best Paper Competition

Monday, April 4, 3:00 – 5:30 pm, Marriott Hotel, Marina D
Chair: John C. Kermode

Graduate Student Presentations:

Contribution of $cPLA_2$ and $PLD_2$-regulated Akt activation to Ang II-induced vascular smooth muscle cell growth during injury. Fang Li. *Univ. of Tennessee Hlth. Sci. Ctr.* (Advisor: Kafait Malik)
Activation of estrogen receptor alpha protects the in vivo rabbit heart from ischemia-reperfusion injury. Erin A. Booth. *Univ. of Michigan Med. Sch.* (Advisor: Ben R. Lucchesi)
Mn-SOD deficient mice exhibit increased oxidative stress and vascular dysfunction with aging. Kathryn A. Brown. *Univ. of Iowa Col. of Med.* (Advisor: Frank M. Faraci)
Cloning and identification of the porcine A1 adenosine receptor mediating a novel mitogenic action of adenosine in coronary artery smooth muscle cells. Jianzhong Shen. *Univ. of Missouri-Columbia* (Advisors: Michael Sturek (now Indiana Univ. Sch. of Med.) and Peter Wilden)

Postdoctoral Presentations:

Role of sphingosine kinase in endothelial barrier protection. Melissa L. Brannen. *Univ. of Illinois at Chicago* (Advisors: Denise Goodman, Children's Memorial Hospital, and Dolly Mehta, Univ. of Illinois at Chicago)
Epoxyeicosatrienoic acid-dependent TRPV4 activation increases spontaneous transient outward current frequency in cerebral arterial smooth muscle. Scott Earley. *Univ. of Vermont Col. of Med.* (Advisor: Joseph Brayden)
Antioxidant N-acetylcysteine (NAC) attenuates PKC-β2 and connective tissue growth factor (CTGF) overexpression and myocardial hypertrophy in diabetic rats. Zhengyuan Xia. *Univ. of British Columbia (*Advisor: John H. McNeil)

## Division for Clinical Pharmacology Symposium: Pharmacological Rationale for COX-2 Adverse Effects: Scientific and Regulatory Lessons Learned?

Tuesday, April 5, 3:00 – 5:30 pm, Convention Center, Room 5B
Chairs: David A. Flockhart and Darrell R. Abernethy

The cardiovascular biology of cyclooxygenase-2. Garret A. Fitzgerald, *Univ. of Pennsylvania* and Alastair J.J.Wood, *Vanderbilt Univ. Sch. of Med.*

## Division for Drug Discovery, Drug Development & Regulatory Affairs Symposium: Therapeutic Agent-Device Combinations

Monday, April 4, 3:00 – 5:30 pm, Convention Center, Room 4
Chair: Tom J. Parry

Preclinical development of drug-coated stents. Gregory A. Kopia, *Cordis Corp., Warren, NJ*
Clinical development of drug-coated stents. Pedro A. Lemos, *Univ. of Sao Paolo, Brazil*
Stem cell therapy for cardiac diseases. Guilherme Silva, *Texas Heart Inst., Houston*
Regulation of combination device products. Mirjam van Werven, *Cordis Corp., Miami Lakes, FL*

## Division for Drug Metabolism Workshop: Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) and the Scientific Community: An Interactive Workshop

Monday, April 4, 3:00 – 5:30 pm, Marriott Hotel, Marina E
Chairs. Timothy S. Tracy and David S. Riddick

Navigating PharmGKB: Hands-on experience. Teri E. Klein, *Stanford Univ.*
PharmGKB: What can it do for me? Russell B. Altman, *Stanford Univ. Med. Ctr.*
Pharmacogenetics of CYP2C9 inhibition and activation. Timothy S. Tracy, *Univ. of Minnesota*
Pharmacogenetics of FMO1 and FMO3. Ronald N. Hines, *Med. Col. of Wisconsin*
N-acetyltransferase pharmacogenetics and adverse reactions to sulfonamides. Craig K. Svensson, *Univ. of Iowa Col. of Pharmacy & Hlth. Sci.*

## Division for Molecular Pharmacology Postdoctoral Awards Finalists

Tuesday, April 5, 3:00 – 5:30 pm, Marriott Hotel, Marina E

## Division for Neuropharmacology Symposium: The Ten Commandments of Pharmacology: Does Functional Selectivity/Agonist Trafficking Make Nothing Sacred?

Tuesday, April 5, 3:00 – 5:30 pm, Convention Center, Room 2
Chair: Richard B. Mailman

Introduction: Are pharmacology's ten commandments still viable? How functional selectivity affects teaching and research. Richard B. Mailman, *Univ. of North Carolina at Chapel Hill*
Evidence and mechanisms of ligand-dependent functional selectivity in GPCRs from a structural perspective. Harel Weinstein, *Weill Med. Col., Cornell Univ.*
Conformational changes at the dimer interface are associated with receptor activation. Jonathan A. Javitch, *Columbia Univ. Col. of Physicians and Surgeons*
Is functional selectivity an artifact of in vitro systems? Bryan L. Roth, *Case Western Reserve Univ. Sch. of Med.*
Classifying drugs and receptors: Past, present, and future. Michael Spedding, *Inst. de Recherches Servier, Suresnes, France*
Message in a model: Receptor theory as a tool for studying functional selectivity. Arthur Christopoulos, *Univ. of Melbourne, Parkville, Victoria, Australia*
Functional selectivity: Is it real and does it affect drug discovery? Keith J. Miller, *Bristol-Myers Squibb*
Panelists:
David R. Sibley (*NINDS, NIH),* William P. Clarke (*Univ. of Texas Hlth. Sci. Ctr. at San Antonio),* Mark von Zastrow (*UCSF),*David E. Nichols (*Purdue Univ. Sch. of Pharm. & Pharmaceut. Sci),* Richard B. Mailman (*Univ. of North Carolina at Chapel Hill Med. Sch.),* Brian K. Kobilka (*Stanford Univ. Med. Ctr.)*

## Division for Systems and Integrative Pharmacology Symposium: 20 Years of Calcium Imaging: A Revolution in Cell Physiology to Dye For

Tuesday, April 5, 3:00 – 5:30 pm, Convention Center, Room 5A
Chairs: Ismail Laher and Harm J. Knot

Keynote Lecture: Calcium as a master switch. Roger Y. Tsien, *UCSD Sch. of Med.*
Calcium and striated muscle. W. Jonathan Lederer, *Univ of Maryland*
Calcium regulates cell secretion. Ole H. Petersen, *Univ. of Liverpool*
Calcium and smooth muscle contraction. Mark T. Nelson, *Univ. of Vermont*
Calcium regulates endothelial cell function. Wolfgang F. Graier, *Univ. of Graz, Austria*

## Division for Toxicology Symposium: Role of Mitochondria in Toxic Oxidative Stress

Tuesday, April 5, 3:00 – 5:30 pm, Convention Center, Room 4
Chair: Marc W. Fariss

Role of mitochondrial vitamin E in toxic oxidative stress. Marc W. Fariss, *Univ. of Colorado Hlth. Sci. Ctr.*
Role of mitochondrial DNA in toxic oxidative stress. Ben Van Houten, *NIEHS, NIH, Research Triangle Park, NC*
Role of cardiolipin in toxic oxidative stress. Sten Orrenius, *Karolinska Inst., Stockholm, Sweden*
Role of mitochondrial aconitase in toxic oxidative stress. Manisha Patel, *Univ. of Colorado Hlth. Sci. Ctr.*
Role of mitochondrial uncoupling protein 2 in pathogenesis of type 2 diabetes. Catherine B. Chan, *Atlantic Vet. Col., Univ. of Prince Edward Is.*

## Online Usage Soars

Average monthly use of ASPET's online journals in 2004 was almost double that of 2003. *JPET* continued to show strong growth with a 96% increase in hits. This followed a 94% increase from 2002 to 2003. *Molecular Pharmacology* and *Drug Metabolism and Disposition* hits increased by 82% and 98%, respectively, when comparing 2003 and 2004 usage data. The previous year's increases were 54% and 51%, respectively. *Pharmacological Reviews* jumped 69%, and *Molecular Interventions* grew 114% in 2004. These journals' hits increased by 20% and 26%, respectively, in 2003.

Several actions helped provide greater exposure for the journals. In 2002, ASPET signed an agreement with EBSCOhost Electronic Journals Service (EJS) that allowed bibliographic information to be posted on the EJS site with links to ASPET's sites. This information is similar to that found at PubMed and Medline. EBSCO is the largest U.S.-based subscription agent, and the EJS site serves as a portal for many of its customers. ASPET journals' bibliographic information is also available at the web site of Infotrieve, a document-delivery service. Infotrieve serves primarily corporate clients but is available to everyone.

The biggest boost by far came from being indexed by Google in the summer of 2004. Earlier that year ASPET signed an agreement allowing Google to crawl the journal sites so they can be fully indexed. Google quickly outpaced PubMed and Medline in referring users to ASPET's journals. This has been the case for other scientific journals as well. Likewise, Yahoo refers more users to the Society's journals than the NIH sites.

Three statistics gauge online journal usage. "Total completed requests" is the number with which most people are familiar. It reports the hits to a site. Every time that any page on the site receives a hit, it is counted here.

The number of "distinct files requested" shows the breadth of material being used. Of course, this number should rise as new articles are added. However, growth on the ASPET sites has risen by a greater percentage than the number of files added each year. For instance, *JPET* rose by 48% in 2004, and *DMD* rose by 105% with the other journals falling between those numbers. This statistic shows that a wide range of articles is being accessed.

Last, the number of "distinct hosts" using the sites is an indication of the number of users. A single IP address (the "hosts" being counted) may represent an entire company or institution, so an IP address may represent thousands of people. It is significant that the number of distinct hosts using the five journals grew between 48% (for *MolPharm*) and 137% (for *Molecular Interventions*) during 2004. The number of distinct hosts ranges from 1,855 reading *Molecular Interventions* to 19,538 reading *JPET*.

## Archival Issue Update

Although taking longer than expected, work to make all back issues of ASPET's journals available online is progressing. When the complete collection of back issues was shipped for scanning last summer, the expected completion date was early 2005. Automated scanning of the back issues took longer than anticipated, and the early volumes of *JPET* had to be scanned manually. The nearly 100-year-old pages were too brittle for the machines, and foldout pages scattered throughout the early volumes required special handling.

The good news is that scanning was completed in February. Currently large PDF files created for each volume are being broken down into individual articles. "Meta data" including the title, byline, abstract, and bibliographic citation information for each article will be keyed. After going through quality assurance, the articles will be put online. Completion of the project is anticipated by July.

## *"Congratulations—Your Paper Is Published!"*

In February, ASPET began a new alerting service for its authors. All *JPET*, *Molecular Pharmacology*, and *DMD* authors are automatically alerted by email of publication in the "Fast Forward" publish-ahead-of-print section of the journal web site. Manuscripts are posted as Fast Forward articles soon after acceptance, and they are considered officially published when they appear on the site.

Because postings can occur at irregular intervals, the alerting service saves authors from having to check the site repeatedly. ASPET's

online manuscript review system automatically emails all authors for whom the system has an email address. Authors can register with the system through the *JPET*, *MolPharm*, or *DMD* web sites. Go to the journal site, click on "Submit a Manuscript," and then click on "Create a new account."

ASPET's journals are the first to provide this alerting service through Bench>Press, the online manuscript system from HighWire Press. ASPET staff members came up with the idea and worked with HighWire Press to implement it.

## NIH Public Access Policy

On February 3, the NIH published the final version of its policy for enhanced public access to NIH-funded research. The full text of the policy is available at the NIH web site (**http://www.nih.gov/about/publicaccess/index.htm**). In brief, the policy intends to provide free access to peer-reviewed manuscripts resulting from NIH-funded research through PubMed Central, the NIH open access publication site. The archive is also intended to help the NIH manage its research portfolio.

As they say, the devil is in the details, and the NIH policy is no exception. Since being announced, a number of policy details are puzzling authors and publishers. Memos and other communications coming from the NIH have provided conflicting information, adding to the confusion. Some details have been worked out while others remain to be resolved.

Some of the policy's details and procedures are expected to evolve and change over time. This article attempts to cover the main points and discuss how they may impact ASPET's publications program. The information provided below comes from the NIH web site and publications- and library-based listervs. David Lipman at the National Library of Medicine answered a number of questions presented to him by John Sack at HighWire Press on behalf of HighWire's publishing partners, and I have drawn on those discussions as well.

***Voluntary or not?*** Contrary to memos from some NIH program heads, the policy states: "Though the NIH anticipates that investigators will use this opportunity to submit their manuscripts, sending electronic copies is voluntary and will not be a factor in the review of scientific progress." That many at the NIH understand the policy to be mandatory raises concerns. Grantees may feel pressured to comply.

That many at the NIH understand the policy to be mandatory raises concerns.

***What papers are covered by the policy?*** Some memos have said that only research articles resulting from NIH grants that are active as of May 2, 2005 (the implementation date of the policy) will be accepted. David Lipman at the NLM has said "…we'll take submissions on papers accepted after May 2 even if the NIH grant is no longer active." The system has not been budgeted to handle non-NIH-funded research, so papers funded through other sources should not be deposited. However, the NIH is looking for funding to allow other research articles to be included in the system.

Only manuscripts that have been accepted for publication in a peer-reviewed journal may be deposited. The policy calls for the final, accepted, peer-reviewed manuscript to be submitted. Editorials, commentaries, opinion pieces, and descriptive literature review papers are not covered by the policy.

***Does the author deposit the manuscript?*** Yes…and no. Grantees can have third parties make submissions for them. However, the third party proxy will need information and interaction outside the scope of a publisher, compositor, or online journal host. Some journals have said they will deposit accepted manuscripts on behalf of their authors. The NIH has said that this will not be possible, at least in the beginning. Submitters will need the following information to use the web-based submission system:

- The name and email address of the PI on the paper
- The grant ID(s) associated with the paper
- The title of the journal publishing the paper
- The title of the article for submission identification (not necessarily the final title)
- The delay period after publication for public release of the paper
- The files associated with the paper (text, figures, supplemental data)

The NIH system will tag the manuscript using XML (a computer mark-up language) and convert it to a PDF file. The NIH-processed version of the manuscript will be sent back to the submitter for approval. There are concerns that this version will be confused with author proofs sent from the publisher. The two could be sent to the author around the same time.

***NIH Version vs. Journal Version.*** The fully formatted, copyedited, and corrected version will appear on the journal web site. The NIH policy will create a second version of each article supported by NIH funding. The NIH version will not be copyedited. It is unclear just what corrections an author will be able to make once the paper is submitted to the NIH system. Some publishers may supply copies of the final version to the NIH, but this is an additional expense for the publisher. ASPET and others asked the NIH to provide a link to the final version instead of posting the manuscript. The NIH rejected this idea.

It seems possible for a manuscript submitted to the NIH system to not be matched with the final publisher's version because of changes made during copyediting or during page proofs. Similar but not identical versions may cause confusion, and in some instances, real problems for researchers and other readers. There do not appear to be any safeguards to prevent an author from intentionally or unintentionally reinserting into the NIH version of a manuscript over-hyped/over-broad conclusions or other questionable statements excised during peer review. Apparently it is up to the author to make sure the two versions match.

***What about copyright?*** This is one of the more contentious issues of the policy. In the NIH's words, "Authors and/or their institutions should ensure that their PMC [PubMed Central] submissions are consistent with any other agreements, including copyright assignments that they may have, or enter into, with publishers or other third parties." If an author transfers copyright to the publisher, which is the case for ASPET's journals and most others, the publisher holds copyright. Depending on the publisher's policy, authors may not be permitted to deposit manuscripts with PMC under any condition; they may deposit and release the article to the public after a delay specified by the publisher, or the author may deposit and release the article whenever the author wishes.

Before depositing a manuscript, authors should check with their publishers to make sure that they are not violating copyright. The NIH has a right to use articles that result from research funded by the NIH. The question being debated by some publishers and their lawyers is what the NIH may do with those materials. One view is that public dissemination is not allowed without permission of the copyright owner.

**Look for changes in copyright forms in the coming months.**

Look for changes in copyright forms in the coming months. Some publishers are likely to grant back to authors the right to deposit the manuscript with PMC. With that, the publisher may also define when the manuscript may be released to the public.

***What is the delay period?*** The NIH encourages submitters to make their work freely available as soon as possible but no later than 12 months. The policy states that the clock starts ticking from the "official date of final publication." This is another area of confusion. The publish-ahead-of-print version constitutes official publication because the work is publicly available. At times, the NIH has defined official publication as the version that appears in a journal issue. Dr. Lipman concedes "The policy document is a bit ambiguous as to the details of the earliest possible point of release…." Look for further clarification in the future.

Authors will not have to supply an actual release date when they submit their manuscripts. They will only need to signify the delay period. Based on article bibliographic data deposited by publishers to PubMed/Medline, the NIH knows when an article has been published. Their system will set the clock ticking based on the deposit of that data.

***What is ASPET's position on the delay period?*** ASPET makes all of its online journal content freely available after 12 months. The Society has not made a decision as to how soon accepted manuscripts from its journals may be released through PMC. An obvious concern for ASPET and many other societies and publishers is the effect that free access through the NIH will have on subscription sales. There are several hotly contested points of view on this topic. Some feel that free access will have no impact. Their reasoning is that libraries must have full journal content, not just the NIH-funded research. And, the final publisher's version is desired—sometimes necessary—because of errors caught in copyediting. Some journals already release manuscripts after a short or no delay.

**ASPET makes all of its online journal content freely available after 12 months.**

On the other hand, the library community has been vociferous in supporting open access in general and the NIH policy specifically. Some librarians see it as a solution to rising subscription prices and clearly think they will be able to cut subscriptions. If a significant

number of articles from a journal are free immediately at PubMed Central, a library may decide that it can use inter-library loan or document delivery to get the remaining content and do without a subscription.

***Free access for all sounds great—why oppose it?*** Many society publishers like ASPET feel that the NIH policy is unnecessary because our journals make their content freely available after 12 months. The NIH policy creates a duplicate system that takes money away from research to serve needs that are already being met by journals such as ASPET's. The policy makes no distinction between journals that make content freely available and those that do not. Because journals like ASPET's release the final, formatted, copyedited, and corrected version of all articles, the journal web sites arguably do a better job than providing raw manuscripts through PubMed Central.

The NIH policy creates a duplicate system that takes money away from research to serve needs that are already being met by journals such as ASPET's.

Neither those for or against the NIH policy can guarantee the outcomes they predict. We can be sure, however, that if subscription cancellations accelerate, there will be no way to replace that income and no going back. Two of ASPET's journals have run at a loss for many years. In most years, income from other journals or investments has covered the losses. We cannot be sure that will always happen as seen during recent years when the stock market performed poorly. The low-priced journals of not-for-profit society publishers are at particular risk from the NIH policy, and some could cease publication. Because these journals are reasonable priced and make their content freely accessible after a reasonable amount of time, the NIH policy is unnecessary and risky.

We will keep ASPET's members informed of the evolving details and procedures related to the policy as well as any impact on the Society's journals.

# Public Affairs/ Government Relations

## EB'05 Teaching Institute

Attendees at the Experimental Biology 2005 meeting in San Diego are invited to attend the ASPET Teaching Institute program, Let's Get Integrative: Finding Jobs in Industry. The session will be held on Saturday, April 2, from 3:00-5:30 p.m. in Room 3 of the convention center.

Attendees will hear from industry representatives about opportunities that exist for those individuals trained in the use of intact organ systems and *in vivo* animal models. For those scientists with a background in integrative organ system biology, there are good jobs available. Find out what skills and background are needed and what opportunities exist. Industry representatives will visit the breakout groups and discuss what needs and skills they look for when recruiting in integrative organ system biology and what opportunities exist within their companies. Meet scientists from Abbott Laboratories, Amgen, Cypress Biosciences, Merck Research Laboratories, and Wil Research Laboratories.
http://www.aspet.org/public/meetings/eb05.html

## ASPET, ASCPT, SOT Congressional Briefing on Dietary Supplements

On January 31 and February 1, ASPET, together with the American Society for Clinical Pharmacology and Therapeutics, and the Society of Toxicology, held congressional staff briefings on the subject of "Botanical Dietary Supplements: Scientific Perspectives and Public Health Pitfalls." The briefings were sponsored by Senator Richard Durbin (R-Ill) and Reps. Henry Waxman (D-CA) and Susan Davis (D-CA). Speakers included Jason D. Morrow from Vanderbilt University, Steven Kliewer from the University of Texas Southwestern Medical Center and George A. Burdock of The Burdock Group. You can view the PowerPoint presentations by the speakers at http://www.aspet.org/public/public_affairs/pa_botanical_res.html.

The ASCPT has also published a position statement on dietary supplement safety and regulation (*Clin Pharmacol Ther* 2005;77:113-22). The ASCPT states that enhanced oversight of dietary supplements is essential to increase consumer safety and offers five recommendations that provide mechanisms by which oversight and safety can be enhanced. Read the ASCPT position statement at
http://www.ascpt.org/govaffairs/position_statements/index.htm

## NIH Conflict of Interest Regulations Impact NIH Scientists and Professional Societies

On February 3, the NIH released new regulations governing NIH employee's collaborative arrangements with industry. For details on the regulations and some questions it raises, see the ASPET primer on NIH Conflict of Interest Rules at http://www.aspet.org/public/public_affairs/pa_nih_coi2005.html. For NIH scientists, the new regulations make it necessary to notify their ethics officers at the earliest time possible, of any possible award or service to a professional society to determine what, if any, possible conflict might exist. The main determination appears to be what is allowable under "outside activity" or "official duty" as an NIH employee. NIH has stressed that employees seek guidance as soon as they consider serving the professional society in any manner. This includes service to professional societies' boards of directors or standing committees, or as editors of journals or service to editorial boards. As a general rule, NIH scientists should not be involved in any fiduciary or other capacity that has any input into budget making decisions of the professional society.

NCCAM National Center for Complementary and Alternative Medicine

## NCCAM's New Strategic Plan Released

The NCCAM 5-year strategic plan for 2005-2009 was released at a recent meeting of the National Advisory Council for Complementary and Alternative Medicine. To order a printed copy of the plan, or to view it online, visit
http://nccam.nih.gov/about/plans/2005/index.htm

## Medicines for You Revised

NIGMS has revised Medicines for You, a lay-language flyer that describes the science of pharmacogenetics and answers questions about pharmacogenetics research. Visit http://www.nigms.nih.gov/medsforyou/index.html

## NIGMS Biomedical Beat

NIGMS has just launched a new electronic newsletter featuring recent research advances supported by the Institute. This digest, called Biomedical Beat, will initially be produced on a monthly basis. The first issue describes the NIGMS role in supporting basic research that led to a powerful new painkilling drug, a new approach to engineering carbohydrates for research and possibly medical applications, and the discovery of a long-sought gene regulator. The short pieces contain links to additional information, and some have accompanying images. An expanded version of the material is available online at http://www.nigms.nih.gov/biobeat

## News from FASEB

The FASEB Federal Funding report for FY2006 was released on January 19. Read the report at http://www.faseb.org/opa/fund2006/fedfund2006.pdf. ASPET members can also read FASEB's Washington Update for biweekly news from Capitol Hill at http://www.faseb.org/opa/washington/.

**Plan Now to Attend EB '2006**
**Moscone Convention Center**
**San Francisco, CA**
**April 1-5, 2006**

**For more information, visit:**
**www.faseb.org/meetings/eb2006**

# Division Election Results for 2005

## Division for Drug Discovery, Drug Development & Regulatory Affairs

Ronald L. Dundore
Chair-Elect

Michael F. Jarvis
Secretary/Treasurer-Elect

## Division for Molecular Pharmacology

Robert A. Nicholas
Chair-Elect

Lee M. Graves
Secretary/Treasurer-Elect

## Division for Drug Metabolism

Laurence S. Kaminsky
Chair-Elect

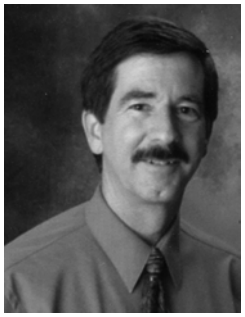
Jeffrey Stevens
Secretary/Treasurer-Elect

## Division for Systems & Integrative Pharmacology

R. Clinton Webb
Chair-Elect

Lori A. Birder
Secretary/Treasurer-Elect

## Division for Toxicology



James P. Kehrer
Chair-Elect

Alan R. Parrish
Secretary/Treasurer-Elect

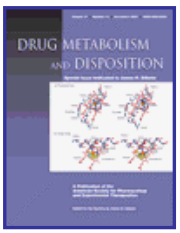
# Division for Drug Metabolism

## PharmGKB Workshop at EB '05

Bring your wireless-capable laptops and "log-in" to the pharmacogenetics "wireless workshop" sponsored by the Drug Metabolism Division and the National Institute of General Medical Sciences. The "wireless workshop" will be held on Monday afternoon (April 4) from 3:00pm to 5:30pm in Marina Ballroom E of the Marriott Hotel (next to the convention center and home to ASPET headquarters). The workshop is formally entitled "Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) and the Scientific Community: An Interactive Workshop." Participants will be able to log on to the PharmGKB database and learn how to access the data, deposit data and explore the benefits of the PharmGKB database. In addition to interactive presentations by PharmGKB personnel, non-PharmGKB researchers will be presenting their data, interactively demonstrating how they deposited their data into the database and the ease of access. Wireless access points (and electrical connections) will be available so bring your laptop and be a part of this novel, interactive workshop. The topics and participants for the workshop are as follows:

- *Navigating PharmGKB: A hands-on experience*. Teri E. Klein, Stanford University
- *PharmGKB: What can it do for me?* Russell B. Altman, Stanford University Medical Center
- *Pharmacogenetics of CYP2C9 inhibition and activation.* Timothy S. Tracy, University of Minnesota
- *Pharmacogenetics of FMO1 and FMO3.* Ronald N. Hines, Medical College of Wisconsin
- *N-acetyltransferase pharmacogenetics and adverse reactions to sulfonamides.* Craig K. Svensson, The University of Iowa

## James R. Gillette Best Paper Awards for 2004




The Drug Metabolism Division is pleased to announce the 2004 James R. Gillette Best Paper Award winners. One award each was given for the best paper published in *Drug Metabolism and Disposition* in the category of Pharmacokinetics/Transporters and the category of Drug Metabolism. The Award winning papers are:

Pharmacokinetics/Transporters category

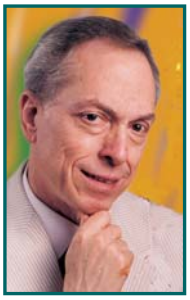
**Nagata Y, Kusuhara H, Hirono S, Endou H, Sugiyama Y**. Carrier-mediated uptake of $H_2$-receptor antagonists by the rat choroid plexus: involvement of rat organic anion transporter 3. *Drug Metab Dispos* 32(9):1040-7, 2004.

Drug Metabolism category

**McConn DJ II, Lin YS, Allen K, Kunze KL, Thummel KE.** Differences in the inhibition of cytochromes P450 3A4 and 3A5 by metabolite-inhibitor complex-forming drugs. *Drug Metab Dispos* 32(10):1083-91, 2004.

James R. Gillette Best Paper Award winners will present their work during the Drug Metabolism Division's platform session
on
Wednesday, April 6, 2005
in
Room 11B of the San Diego Convention Center

## MEMBERS IN THE NEWS



**Solomon H. Snyder**, **M.D.,** Professor and Director of the Department of Neuroscience at Johns Hopkins University School of Medicine, was named a recipient of the 2005 National Medal of Science in the Biological Sciences by President George W. Bush. This award is the nation's highest honor for science and technology and honors individuals in a variety of fields for pioneering scientific research that has led to a better understanding of the world around us, as well as to the innovations and technologies that give the United States it global economic edge, according to a press release from the White House. The award was established in 1959 and is administered by the National Science Foundation. Scientists are recognized not only in the biological sciences, but also in the behavioral and society sciences, engineering, physical sciences, and mathematics. The honorees will receive their awards at a White House ceremony on March 14, 2005.

**Ho-Leung Fung, Ph.D.,** Professor of Pharmaceutical Sciences at the University of Buffalo, State University of New York, has been named the Editor-in-Chief of *The AAPS Journal,* an online, open-access publication covering the topics of drug discovery, development and therapy. Dr. Fung takes over this position from another ASPET member, Wolfgang Sadee, the founding Editor-in-Chief of the publication. Dr. Fung is a Fellow and former President of the American Association of Pharmaceutical Sciences (AAPS).

**Kathleen M. Giacomini, Ph.D.,** Professor and Chair of the Department of Biopharmaceutical Sciences at the University of California, San Francisco, was named by former HHS Secretary Tommy Thompson to serve on the National Advisory General Medical Sciences Council. The Council, which meets three times a year, is composed of leaders in the areas of research funded by the National Institute of General Medical Sciences (NIGMS) and functions as the second tier of peer review for research and research training grant applications assigned to NIGMS. Dr. Giacomini's research focuses on the transport of drug molecules in and out of cells, as well as pharmacogenetic variation in drug response. She served as a member of the Editorial Board for the *Journal of Pharmacology and Experimental Therapeutics* from1998 – 2000.

## STAFF NEWS

**Richard Dodenhoff, ASPET Journals Director**, will be appearing on-stage as Dwight Eisenhower and other characters in this year's Hexagon production Hexagon at 50: With Levity and Jesting for All." Hexagon, Inc. is a non-profit, all volunteer membership organization that produces "DC's only original, political, satirical, musical comedy revue" to benefit charities in the Washington, DC area. In the 50 years since its first production, Hexagon has contributed more than $3 million to local charities. The production runs throughout the month of March. Guest celebrities from Congress and the local news media appear nightly as "news anchors." Rich has been active in Hexagon for several years, working behind the scenes on costumes and in the box office. This is his first year "in front of the lights."

Can you spot the REAL Ike?

# NEW MEMBERS

## REGULAR MEMBERS

**Myles Akabas**, Albert Einstein College of Medicine, Dept of Physiology and Biophysics
**Kelly Carrigan**, University of North Carolina, Dept of Psychology
**Dayue Duan,** University of Nevada School of Medicine, Dept of Pharmacology
**Emir Duzic**, Cephalon, Inc., Molecular & Cellular Pharmacology
**Joseph Garner**, Advanced Product Enterprises LLC
**Anuja Ghorpade**, University of Nebraska Medical Ctr, Dept of Pharmacology
**Robert Hadley**, University of Kentucky College of Medicine, Dept of Molecular & Biomedical Pharmacology
**Shelley Hooks**, Univ of Georgia College of Pharmacy, Pharmaceutical & Biomedical Sciences
**Joanne Ingwall**, Brigham and Women's Hospital, NMR Laboratory for Physiological Chemistry
**Yugesh Kharel**, Univ of Virginia, Dept of Pharmacology
**Gordon Kirby**, University of Guelph, Dept of Biomedical Sciences
**Bjorn Knollmann**, Georgetown University Medical Center, Dept of Pharmacology
**Ralph Laufer**, Merck Research Laboratories, IRBM P. Ageletti, Italy
**Bernard Le Foll**, National Institute on Drug Abuse, Preclinical Pharmacology Section
**Malath Makhay**, Neurogenetics, Inc.
**Donald McDonnell**, Duke University Medical Center, Dept of Medicine
**Bruce McEwen**, The Rockefeller University
**Lance McMahon**, University of Texas, HSC, Dept of Pharmacology
**Masao Miwa**, University of Shizuoka, Dept of Biochemistry
**Elke Perloff**, BD Biosciences Discovery Labware
**Jennifer Perry**, Nat'l Inst of Environmental Hlth Sciences, Laboratory of Pharmacology and Chemistry
**Mark Reilly**, Central Michigan University, Dept of Psychology
**Terrilyn Richardson**, Emory University, Dept of Pharmacology
**Motohiko Sato**, Louisiana State University HSC, Dept of Pharmacology & Experimental Therapeutics
**Maxim Soloviev**, WIL Research Laboratories, Inc.
**Jeffrey Staudinger**, University of Kansas, Dept of Pharmacology & Toxicology
**Raman Venkataramanan**, University of Pittsburgh Sch of Pharmacy, Pharmaceutical Sciences & Pathology
**Francisco Villarreal**, University of California Medical Center, Dept of Cardiology
**Li Zhang**, University of Pennsylvania School of Med, Dept of Pharmacology
**Lingzhi Zhang**, University of California, San Diego, Dept of Pharmacology

## AFFILIATE MEMBER

**Savita Patil,** R.C. Patel College of Pharmacy, Karvand Naka, India

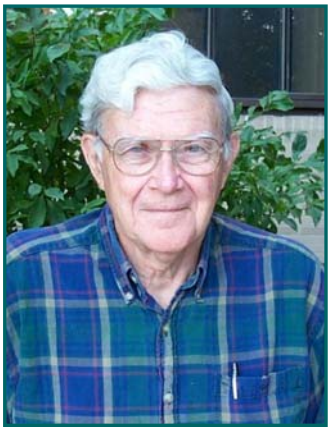
## GRADUATE STUDENT MEMBERS

**Cordelia Barrick**, University of North Carolina, Dept of Toxicology
**Curtis Chong**, Johns Hopkins University School of Med, Dept of Pharmacology
**Ziva Cooper**, University of Michigan, Dept of Pharmacology
**Michael Davis**, University of Virginia, Dept of Pharmacology
**Vaidehee Deshpande**, University of Texas College of Pharmacy, Dept of Toxicology
**Alejandro Dunnick**, Medical University of South Carolina, Dept of Pharmaceutical Sciences
**J. Fowler**, University of North Carolina, Dept of Psychiatry
**Cody Fox**, Des Moines University, Dept of Physiology & Pharmacology
**Ying Fu,** University of Michigan, Dept of Pharmacology
**Mary Garcia-Cazarin**, University of Kentucky Medical Center, Dept of Pharmacology
**Erica Gipson**, University of Nevada School of Medicine, Dept of Pharmacology
**Aditya Goel,** Univ of the Pacific Thomas J Long School of Pharmacy, Dept of Physiology & Pharmacology
**Heather Good**, Drexel University College of Medicine, Dept of Pharmacology & Physiology
**Jason Guichard**, Medical University of South Carolina, Dept of Biomedical Sciences
**Amy Herrold**, Loyola University, Center for Hip and Knee Surgery
**Tony Kiang**, University British Columbia, Faculty of Pharmaceutical Sciences

## NEW MEMBERS

**Ranjita Kokje**, University of Mississippi, Dept of Pharmacology
**Laura Kreckler**, Medical College of Wisconsin, Dept of Pharmacology
**Sangderk Lee**, University of Virginia, Dept of Pharmacology
**Jean Lord,** University of Arizona, Dept of Phamacology & Toxicology
**Livia Machado**, University of Georgia College of Pharmacy
**Abdallah Mahmoud**, Mansoura University Faculty of Pharmacy, Kafr El-Badmas, Dorgham Dept, Egypt
**Christopher Means,** University of California, San Diego, Dept of Pharmacology
**Tim Mitin,** Tufts University School of Medicine, Dept of Pharmacology & Experimental Therapeutics
**Ryan Monfeli,** Medical University of South Carolina, Dept of Pharmaceutical Science
**Nicole Moore,** Duke University, Dept of Pharmacology
**Kelly O'Connell**, Creighton University, Dept of Pharmacology
**Margaret Panning**, SUNY Upstate Medical University, Dept of Pharmacology
**Marcia Reinhart,** University of Oxford, Dept of Pharmacology
**Sharif Rumjahn**, University of Nevada School of Medicine, Dept of Pharmacology
**Gilandra Russell,** University of Louisville, Dept of Pharmacology/Toxicology
**Kamakshi Sachidanandam**, Medical College of Georgia, Dept of Clinical Pharmacology
**Patrick Shaw,** Michigan State University, Dept of Pharmacology & Toxicology
**Lorraine Sunday,** University of California College of Medicine, Dept of Pharmacology
**Jennifer Tichenor**, University of Nevada School of Medicine, Dept of Pharmacology
**Robert Tomko**, University of Pittsburgh, Dept of Pharmacology
**Jasmine Vittori**, University of Nevada School of Medicine, Dept of Pharmacology
**Katerina Vrzalikova,** University of Palacky Faculty of Med, Laboratory of Molecular Pathology
**Eric Wauson,** University of North Carolina, Dept of Pharmacology
**Eric Williamson**, Medical University of South Carolina, Dept of Pharmaceutical Sciecnes
**Jonathan Wojtkowiak,** Wayne State University, Dept of Pharmacology
**Renee Wong,** Medical University of South Carolina, Dept of Pharmaceutical Sciences
**Yang Xu,** University of Washington, Dept of Pharmaceutics
**Hushan Yang**, Baylor College of Medicine, Dept of Pharmacology
**Yuanyuan Zhang**, University of Kentucky, Graduate Center for Toxicology

**UNDERGRADUATE STUDENT MEMBERS**
**Jennifer Edwards**, Michigan State University, Dept of Pharmacology & Toxicology
**Troy McEachron**, Arizona State University, Dept of Microbiology
**Karla Paulsen**, University of California, Santa Barbara, Marine Science Institute
**Enyinnaya Uwaekwe**, Voorhees College, Dept of Biology



## Bert Nicholas La Du, Jr. , M.D., Ph.D.
## 1920 – 2005

Dr. Bert N. La Du, Professor Emeritus of Pharmacology at the University of Michigan, died January 30, 2005. Dr. La Du was President of ASPET from 1978-1979.

Born in Lansing, Michigan, Bert Nichols La Du, Jr. received his Bachelor of Science degree in Chemistry from Michigan State College in 1943 and earned an M.D. from the University of Michigan Medical School in 1945. After an Internship at Rochester General Hospital in Rochester, New York, and a year as a Teaching Assistant in the Michigan State Department of Biochemistry, he joined the Department of Biochemistry at the University of California in Berkeley, where he received his Ph.D. degree in 1952.

From 1950 until 1963, Dr. La Du was associated with the National Institutes of Health, stationed first as a Surgeon at Goldwater Memorial Hospital Research Service in New York, and the National Heart Institute, and later as Medical Director of the National Institute of Arthritis and Metabolic Diseases. After a sabbatical year at the Galton Laboratory of University College in London, Dr. La Du became Chairman of the Department of Pharmacology at New York University in 1963.

Dr. La Du moved from New York to Michigan in 1974, where he served as Chairman of the Department of Pharmacology at the University of Michigan from 1974-80, and then returned to full-time research and teaching in the Department. He retired officially in 1989 and became Professor Emeritus of Pharmacology. In retirement, he continued to be an active, funded investigator with recent grants from the Michigan Life Sciences Corridor Fund and a research contract with the University of Texas.

Throughout his scientific career, Dr. La Du's primary research interests were the biochemistry of drug metabolism and pharmacogenetics. He was an early leader of research on human inborn errors of amino acid metabolism. He is recognized internationally as one of the "founding fathers" of pharmacogenetics. For the past 35 years Dr. La Du's research has focused on the effects of heredity on drug metabolism and response. He made major contributions to the understanding of genetic variants of the serum cholinesterase enzymes in those human individuals who are unusually susceptible to the actions of succinylcholine. In recognition of his pioneering work, the 1st International Conference on Paraoxoanases: Basic and Clinical Directions of Current Research was held in Ann Arbor at the University of Michigan in April 2004.

Dr. La Du is survived by his wife of 58 years, Catherine Shilson La Du; his sister, Carol; four daughters, Libby, Mary, Anne and Jane; six grandchildren and one great-grandchild.

**ASPET notes with sympathy the passing of the following members:**

**Julius C. Allen**

**Domingo M. Aviado**

**Julius Axelrod**

**Allan D. Bass**

**Aldo N. Corbascio**

**Edward D. Freis**

**David Kupfer**

**Bert N. La Du**

**Edward Majchrowicz**

**W. Leigh Thompson**

**Vernon G. Vernier**

# New England Pharmacology Society

The 33rd annual meeting of the New England Pharmacologists was hosted by the Department of Pharmacology at the University of New England College of Osteopathic Medicine (UNECOM) on January 28 and 29, 2005 in Portland, Maine. Drs. David Mokler, Edward Bilsky and Amy Davidoff organized the meeting, and Dr. Richard Reese (Chairman of the Department of Pharmacology at UNECOM) welcomed the attendees during Friday's opening session. The meeting was noteworthy in that this was the first meeting held in Portland when it did not snow!!

Dr. Wolfgang Sadée, recovering from eye surgery, still provided the first keynote address.

Over 100 attendees participated in two days of scientific discussions and presentations. There was good representation from the major pharmacology programs throughout the New England region, as well as from the pharmaceutical/biotech industry. **Dr. Wolfgang Sadée**, the Felts Mercer Professor of Medicine and Pharmacology at Ohio State University, gave a very thought provoking keynote address entitled **"Pharmacogenomics – An Imperative for Improved Drug Therapy."** The presentation stimulated much discussion throughout the meeting. On Saturday afternoon the meeting closed with an equally interesting talk by **Dr. Douglas Sawyer**, Associate Professor of Medicine, Boston University School of Medicine entitled **"Translating Clinical Toxicology of Chemotherapeutics Into Preventive Medicine."**

Two poster sessions with 33 posters and two oral sessions with 16 talks given by undergraduate and graduate students and postdoctoral fellows filled the Friday afternoon and Saturday morning session. Graduate student awards were given out during the banquet on Friday evening. Student awardees were Yan Ma from Dartmouth Medical School, Siripan Phattanarudee from Massachusetts College of Pharmacy and Health Sciences, Kirk M. Bertelsen from Tufts University School of Medicine, Kristen Barbee from the University of New England College of Osteopathic Medicine, Patricia C. Rose from the University of Vermont College of Medicine and Jeffery R. Simard from the Boston University School of Medicine.

The meeting was generously supported by a grant from ASPET and contributions from the Department of Pharmacology at Dartmouth Medical School and the University of New England College of Osteopathic Medicine.

Dr. Doug Sawyer gave the Saturday keynote address entitled "Translating Clinical Troxicology of Chemotherapeutics into Preventive Medicine."

Kristen Barbee (Univ. New England) presents her research to Dr. Joyce DeLeo (Dartmouth Hitchcock Medical Center) during one of the poster sessions.

Students discussing their research during the Saturday Morning break.

The graduate student and post-doctoral award winners being recognized at the awards ceremony. The awardees are (from left to right) Siripan Phattanarudee from Massachusetts College of Pharmacy and Health Sciences, Yan Ma from Dartmouth Medical School, Kirk M. Bertelsen from Tufts University School of Medicine, Kristen Barbee from the University of New England College of Osteopathic Medicine, Patricia C. Rose from the University of Vermont College of Medicine, and Jeffrey R. Simard at the Boston University School of Medicine.

★ Award Winner

**Corticotropin-Releasing Factor Disrupts Prepulse Inhibition in the Rat: The Role of Central CRF-1 and 2 Receptors.** I.C Arrillaga-Romany and R.P. Hammer, Jr., Tufts University School of Medicine, Boston, MA

Social stress has been associated with the onset and relapse of schizophrenic symptoms, including deficits in sensorimotor gating which can be measured by a loss of normal prepulse inhibition (PPI), which is believed to involve a hyperactive mesolimbic dopamine system. Corticotropin-releasing factor (CRF) is released during stress and regulates levels of central monoamines, including dopamine. Moreover, elevated levels of CRF have been reported in the CSF of schizophrenic patients, suggesting that CRF overactivity could be responsible, at least in part, for the onset of schizophrenia symptoms. Two CRF receptors (1 and 2) exist in the CNS, both expressed in various brain regions which contribute to PPI. Recent work in mice suggests that these two receptors may have opposing effects on PPI. The present study assessed the effect of centrally administered human//rat (h/r) CRF (1.0 ug or 3.0 ug) alone or in combination with antisauvagine-30 (ASV-30, 10 ug), a selective CRF-2 receptor antagonist, on percent PPI in male Sprague Dawley rats. PPI levels following intracerebroventricular CRF +/- ASV-30 infusions were compared to baseline PPI assessed before and after cannulation surgery. CRF- induced grooming and locomotion were also assessed following drug infusions to ensure the successful delivery of the peptide into the CNS. Rats administered 3.0 ug, but not 1.0 ug, of h/r CRF displayed significant disruption in PPI compared to baseline. This disruption was neither enhanced nor diminished by the addition of ASV-30 (10ug) to the h/r CRF, which suggests that the CRF-2 receptor may play a minimal role in this response. Overall, the results demonstrate that CRF can disrupt PPI in the rat and highlights the potential role of CRF and the CRF-1 receptor in the mechanism underlying stress-induced sensorimotor gating deficits. *This work was supported by USPHS Award MH066954.*

**Targeting Pain-suppressed Behaviors in Preclinical Assays of Pain and Analgesia: II. Effects of Morphine on Acetic Acid-Suppressed Locomotor Activity in Mice.** K. Barbee[1], G.W. Stevenson[2], S. S. Negus[2] and E.J. Bilsky[1], [1]Department of Pharmacology, University of New England, Biddeford, ME; [2]ADARC, McLean Hospital-Harvard Medical School, Belmont, MA

Effective management of pain continues to be a clinical challenge. Industry and academic laboratories have invested significant resources into identifying novel targets, synthesizing small molecule drug candidates, and performing preclinical/clinical assessments of lead candidates. The introduction of novel pharmacotherapies has, however, been rather limited, with several advanced-stage candidates failing in phase III clinical trials. One potential limitation in the drug discovery process is the manner in which drug candidates are tested in preclinical models of nociception, with an emphasis being placed on pain-evoked behaviors in rodents. Our laboratories are developing assays that focus on pain-suppressed behaviors that may complement traditional methods. We present results that compare the effects of i.p. acetic acid on a pain-evoked behavior (writhing) and a pain-suppressed behavior (locomotor activity-LMA) in two strains of mice (ICR and C57BL/6J). Acetic acid (0.18-0.56%) produced concentration- and time-dependent increases in writhing and decreases in LMA. The potency of acetic acid was similar for both effects, but decreases in LMA lasted longer than increases in writhing. Also, a high concentration of 1% acid induced less writhing than lower concentrations. Morphine produced a dose-related restoration of LMA at doses that did not stimulate LMA in control animals. These doses also reduced the number of abdominal writhes in a dose-dependent fashion. We are currently testing a number of other analgesic drugs, along with drugs that produce false positives, in this assay. These studies, along with companion assays assessing acetic acid-induced suppression of feeding behavior, may help improve the predicative reliability of preclinical antinociceptive assays.

★**Stimulation Of P-Gp Mediated Transport & Expression By Flutamide *In Vitro***. Kirk M. Bertelsen, Lisa L.von Moltke, & David J.Greenblatt,Tufts University School of Medicine, Boston MA

**Aims:** Steroid receptor antagonists, such as tamoxifen (TAM) or mifepristone (MFP), display significant inhibition of the ABC transport protein P-glycoprotein (P-gp) *in vitro*. To date, interactions between androgen receptor antagonists have yet to be described. Given their common use as treatments for prostate cancer, interactions between androgen receptor antagonists and P-gp may be important.
**Methods:** Two *in vitro* models of drug transport were used to assess the effects of flutamide (FLU) on drug transport. Possible modulation of P-gp expression was also investigated.
**Results:** Acute FLU treatment stimulated transport of Rho-123 in Caco-2 monolayers ($P_{App(B\rightarrow A/A\rightarrow B)}$ Control: 5.8+/-1.2, 100.0 µM FLU: 10.5+/-1.0). These observations were confirmed using a Rho-123 retention assay within LS180V cells. As positive controls, TAM and MFP displayed inhibition in both models. After 72-hour incubation with LS180V cells, only FLU resulted in enhanced immunoreactivity of P-gp after Western blot analysis.
**Conclusions:** In contrast to TAM and MFP, these data suggest that FLU stimulates P-gp activity and expression. Whether *in vitro* models used in these studies are representative of prostate tissues remains unclear. Nonetheless, considering that MDR1 expression

within prostatic neoplasms remains a clinically significant issue, the stimulatory effects noted with FLU on P-gp function and expression may have clinical implications.

**Changes in the Regulation of the Human MCL1 Transgene in Mice Suggest that MCL1 Deregulation Plays a Role in the Enhanced Susceptibility to Tumorigenesis.** K.E. Braley, M. A. Pierce, R. W. Craig, Dartmouth Medical School, Hanover, NH

Mice that are transgenic for the pro-viability BCL2 family member MCL1 demonstrate increased B and T cell survival, and develop lymphoma at high frequency but with long latency. We set out to understand how transgene expression is regulated in hematolymphoid cells from these mice, with the ultimate goal of being able to manipulate MCL1 expression and thereby influence cell survival and potentially tumorigenesis. Using primary cells explanted from the spleen and bone marrow, we examined the effects of the phorbol ester PMA as well as the cytokine IL-6, agents known to increase MCL1 expression in cultured cell lines. Our results show that IL-6 resulted in an increase in expression of the MCL1 transgene cells, and that this occurred along with the activation of STAT3. Additionally, blocking IL-6 with a neutralizing antibody resulted in a decrease in MCL1 expression. Reduced transgene expression was associated with reduced cell viability, as assayed by apoptotic morphology and TUNEL staining. Interestingly as the mice aged and became more prone to tumor development, MCL1 inducibility by IL-6 was lost, and therefore apoptosis could no longer be induced by blocking IL-6. These findings suggest that deregulation of MCL1 may be an early step that contributes to the susceptibility of these mice to tumorigenesis.

**Acute and Long-term Neurobiological Effects of MDMA (Ecstasy) on the Hippocampus.** J. Cunningham[1], J. Raudensky[1], Gary Gudelsky[2], J. Tonkiss[1], B.K. Yamamoto[1], [1]Boston University School of Medicine, Boston, MA; [2]University of Cincinnati College of Pharmacy, Cincinnati, OH

MDMA ((±)3,4-methylenedioxymethamphetamine) is a widely abused recreational psychostimulant known to cause selective damage to serotonin (5HT) neurons in the CNS. These effects are particularly evident in the hippocampus, the area of the CNS most associated with learning and memory and an area that receives major 5HT input from the raphe nucleus. Previous studies have shown that methamphetamine, a similar amphetamine analogue, produced a gradual and significant increase in GLU levels within the hippocampus and a decrease performance in cognitive tasks.

To evaluate the effects of MDMA on extracellular hippocampal glutamate concentrations, male Sprague-Dawley rats administered a neurotoxic dose regimen of MDMA (10mg/kg q 2hr X 4; i.p.) and extracellular glutamate was measured in the hippocampus by in vivo microdialysis. Results showed a 3-fold gradual increase in basal glutamate concentrations that remained elevated 12 hours after the final injection of MDMA. To assess the long-term effects of MDMA on learning and memory, preliminary behavioral data (n= 4/saline or MDMA treatment) from a Morris Water Maze task collected 17 days after MDMA administration suggest that MDMA produces deficits in spatial learning. Future studies will examine if the elevated concentrations of glutamate produce excitotoxicity to the hippocampus. *Supported by DA07427 and DA16866.*

**A Rapid Screening Technique for Ligand Gated Ion Channel Modulators.** S.S. Downing, T.T. Gibbs, Boston University School of Medicine, Boston, MA

Electrophysiology is the gold standard of functional assays, but conventional methods are laborious and time consuming. As electrophysiological assays become high throughput, better methods are needed to accurately determine and quantitate the effect of allosteric modulators on the agonist response. We present a novel, agonist independent method for the rapid screening of ligand gated ion channels which expedites the processes of drug sample preparation and data accumulation and reduction. This method relies on a set of well characterized receptor mutants that increase receptor gating without affecting receptor binding. The modulator efficacy at the native receptor is determined from a single measured data point at the mutant receptor by using an allosteric transition model. This method reduces the 28000 solutions needed to screen 1000 potential drug candidates against 28 different $GABA_A$ receptor subtypes using conventional electrophysiological techniques to 1028. We have developed a sensitive assay based on this method which quickly identifies low efficacy modulators of ion channels. We validated this approach for the modulation of the $\alpha1\beta3\gamma2$ $GABA_A$ receptor by diazepam, flurazepam, zolpidem and DMCM. The modulator effect at the native receptor was determined by the model, which relates the efficacy measured in the assay to the energetics of modulator interaction at the native receptor. The savings in time and labor by significantly reducing the number of drug samples and electrophysiological measurements demonstrate the benefit of this approach. In addition, this method provides a convenient way to rapidly evaluate the screening results.

**Social Stress Increases Fos Expression in Ventral Tegmental Area Neurons Innervating the Nucleus Accumbens**. S. Fanous, E.M. Nikulina, RP Hammer, Tufts University School of Medicine, Boston, MA

Psychostimulants increase dopamine neurotransmission within the mesocorticolimbic system; their repeated administration causes sensitization to their effects, thought to be related to addiction. Repeated social defeat stress (SDS) induces cross-sensitization. The mesocorticolmbic circuit includes the ventral tegmental area (VTA) and its target, the nucleus accumbens (NAc), both significantly involved in sensitization and functionally responsive to SDS, exhibiting increased Fos expression. This projection may be important in cross-sensitization. Our laboratory found that repeated SDS exposure in rats induces significant increases in Fos-like immunoreactivity (Fos-LI) in the NAc shell 7 days after stress exposure. The present study examined the effect of repeated SDS in rats on Fos-LI in VTA neurons innervating the NAc shell. Rats received iontophoretic application of the retrograde tracer fluorogold to the NAc shell 7 days prior to SDS. SDS consisted of 30 min exposure to an aggressive resident rat once daily for 5 consecutive days. Control animals were handled on these days. Double-label immunohistochemistry for Fos-LI and fluorogold was used to detect functionally activated VTA neurons projecting to the NAc shell. In the experimental group, 72% of VTA neurons exhibiting Fos-LI displayed fluorogold labeling, in comparison to 40% in the control group, indicating that VTA neurons functionally activated after repeated SDS innervate the NAc shell. Changes in Fos expression in the VTA-NAc projection after social stress may represent cellular changes underlying cross-sensitization.

**Genomic Loss at the SPRY2 Locus (13q21.2-q22) in Human Ovarian Carcinoma.** D.M. Ferris[1], Lynne Hiorns[2], N. Johnston[1], A. Feeley[1], Brian Leyland-Jones[3], R. Perez[1], [1]Dartmouth Medical School, Hanover, NH; [2]Oxford University, Oxford, UK; [3]McGill University, Montreal, Quebec, Canada

Sprouty is a negative regulator of receptor tyrosine kinase (RTK) signaling during development, discovered in *Drosophila*. Human Sprouty (SPRY) proteins inhibit the Ras/mitogen-activated protein (MAP) kinase pathway during development, normal cell growth, and proliferation. Emerging data from our and other laboratories suggest that SPRY proteins are candidate tumor suppressors. SPRY2 gene, mRNA and protein were assayed in six human ovarian carcinoma cell lines. The gene and mRNA were present in all, with five of six exhibiting a single base change from wild type. Sprouty2 protein was observed in four of six cell lines. In addition, tumor tissue from twelve patients with advanced ovarian carcinoma was subjected to comparative genomic hybridization, which revealed a genomic loss of 13q21.2-q22 in ten out of twelve samples. The SPRY2 locus is within this region, and subsequent amplification of homogenized DNA from these samples showed potential copy loss. Laser capture microdissection (LCM) was used to dissect tumor from stroma to amplify the DNA separately. PCR shows a specific 120bp SPRY2 amplicon in all samples, in both tumor and stroma. Together, these data are consistent with the hypothesis that SPRY2 is a tumor suppressor. Ongoing studies will focus on quantitating copy number, verifying genomic integrity, and determining the potential function of the sequence variant.

**Conserved Structural Motifs Mediate Metal-Induced Destabilization of Rhodopsin**. S. Gleim, A. Stojanovic, J. Hwa, Dartmouth Medical School

Neurodegenerative R*etinitis pigmentosa* (RP) can be characterized by missense rhodopsin mutations, rhodopsin instability and misfolding, rod cell death, retinal degeneration and blindness. Recently, zinc and copper have emerged as a common factor in aggregate development and progression of neurodegenerative disorders such as Alzheimer's and ALS. We have identified and characterized two conserved metal coordination motifs, involving $His^{100}$ in the first intradiscal loop and $His^{195}$ in the second, localized among a cluster of RP mutations. Treatment of purified wild-type rhodopsin with zinc or copper demonstrated a loss of thermostability (UV/Vis) similar to that observed with mutations $His^{100}$Phe and $His^{195}$Phe where metal coordination is lost. Simultaneous disruption of both sites further destabilizes rhodopsin while eliminating the effect of metal addition. Native interactions of these histidine residues are thus critical for rhodopsin stability, and are interrupted by zinc coordination and/or a subset of RP mutations. These results may in part explain variable disease progression observed in patients with identical mutations. Intradiscal zinc coordination may also be a potential therapeutic target. *Supported by grants from the Department of Pharmacology and Toxicology, Dartmouth Medical School (JH), the Karl Kirchgessner Foundation (JH) and the PhRMA Foundation (AS).*

**Methamphetamine-induced Spectrin Proteolysis and Dopamine Depletions in the Substantia Nigra.** T. Hatzipetros and B.K. Yamamoto, Boston University Medical School, Boston, MA

We have demonstrated that during a neurotoxic methamphetamine (METH) regimen, glutamate in the substantia nigra (SN) is acutely increased in the presence of $D_2$ antagonism. These findings suggest that $D_2$ antagonism after METH may produce excitotoxic cell

damage in the SN. To test the hypothesis that $D_2$ antagonism after METH is toxic to SN cells, we measured dendritic spectrin immunoreactivity and dopamine (DA) tissue content 14 days after METH administration. Spectrin, a scaffolding protein, can be proteolyzed under conditions of NMDA receptor activation, increased intracellular calcium, and activation of calcium-dependent proteases. The results show that METH (10 mg/kg i.p. q 2 hrs X 4) significantly decreased spectrin immunoreactivity in the SN by 27 %. Haloperidol (0.5 mg/kg/day i.p. X 5 days) after the acute repeated METH administration slightly exacerbated this decrease. DA content in the SN was not affected by METH alone but was decreased by 24 % in rats treated with haloperidol after METH. These results indicate that METH may cause excitotoxic cell damage in the SN and that $D_2$ antagonism may exacerbate this damage. Moreover, sub-chronic haloperidol administered after METH appears to produce a loss of DA in the SN but it is unclear if this is related to excitotoxicity. Regardless, these data have clinical implications such that the use of haloperidol as a treatment for METH overdose may be contra-indicated. *Supported by DA07606 and DAMD 17-99-1-9479*

**Gene Expression Analysis Following Lumbar Nerve Root Injury Identifies Genes Associated with Low Back Pain: Emphasis on Sex Differences in Pain Sensitivity**. M.L. LaCroix-Fralish[1], F.Y. Tanga[2], J.N. Weinstein[2], J.A. DeLeo[1,2], [1]Dartmouth Medical School, Hanover, NH; [2]Dartmouth-Hitchcock Medical Center, Lebanon, NH

Low back pain with radiculopathy has a major impact on human health worldwide. Microarray gene analysis holds great promise for screening novel targets for physiological and persistent pain modulation. Considerable evidence exists for sex differences in pain. Women typically report lower pain thresholds as compared to men and have an increased incidence of many painful diseases. The purpose of the present study was to determine if there are genes that are differentially regulated in males and females after nerve root injury. A rat model of lumbar radiculopathy (loose chromic gut ligation of the L5 dorsal/ventral nerve roots) was used for these studies. We analyzed gene expression in lumbar spinal cord homogenates from Sprague-Dawley male (n=2) and female (n=2) and Holtzman female (n=2) rats at two time points (7 days and 14 days) following L5 nerve root ligation using the Affymetrix RAE230A GeneChip. The groups of genes from each strain/sex that were significantly (± 2-fold change) changed from time-paired sham surgical control animals (n=2/group) were determined using the Affymetrix MAS v5.1 analysis software. The expression patterns of several genes of interest were subsequently confirmed using RT-PCR. The resulting data represent genes that are coordinately regulated in the lumbar spinal cord of male Sprague-Dawley rats following L5 nerve root ligation at two time points post-nerve root ligation. Further analysis based on sex in the Sprague-Dawley female group uncovered potential genes that are associated with sex differences in tactile sensitivity following L5 nerve root ligation. *Support Contributed By: NIH/NIAMS, Bristol-Myers Squibb/Zimmer Orthopedics Foundation*

**High-Dose Methamphetamine Activates the Striatonigral Pathway to Increase Striatal Glutamate**. K.A. Mark and B.K.Yamamoto, Boston University Medical School, Boston, MA

Methamphetamine (METH) is neurotoxic to dopamine (DA) terminals in the striatum. METH-induced increases in DA and glutamate (GLU) are responsible for this long-term damage. METH increases DA directly via reverse transport, however this is not the case for GLU release. We hypothesize that METH-induced increases in GLU is mediated by (1) activation of the direct GABAergic striatonigral pathway, (2) subsequent decreased nigrothalamic GABA activity, (3) consequent disinhibition of thalamocortical activity and (4) ultimately increased corticostriatal GLU release.

Previous studies using *in-vivo* microdialysis have showed that METH (10mg/kg x4; 2hr;i.p.) increases GABA release in the substantia nigra, pars reticulata (SNr) by 50%. Furthermore, METH decreased downstream nigrothalamic GABA activity by 30% as measured by microdialysis in the ventromedial thalamus (VM). It has been shown that neurons in the SNr are tonically inhibited by GABA via postsynaptic GABA-A receptors, therefore we hypothesize that perfusion of a GABA-A receptor antagonist into the SNr will prevent METH-induced decreases in GABA release in the VM. Our results show that intranigral perfusion of the GABA-A antagonist, bicuculline (BIC, 10μM) attenuated the METH-induced decreases in GABA release in the VM. In addition, GABA-A-receptor blockade in the SNr attenuated the METH-induced increases in striatal GLU release and DA depletions. These data provide the first evidence that METH activates the direct striatonigral GABAergic/GABA-A pathway to decrease nigrothalamic GABA transmission and disinhibit corticostriatal GLU transmission. *Support Contributed By: DA07606 and DAMD 17-99-1-9479*

**Levothyroxine Upregulates P-glycoprotein Independent of the Pregnane X Receptor.** T. Mitin, L.L. von Moltke, M.H. Court, D.J. Greenblatt, Tufts University School of Medicine, Boston, MA

P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) constitute a physiologic barrier in the intestine for many of the same substrates. Their expression can be influenced by nuclear Pregnane X receptor (PXR), which acts as a receptor for various endobiotics

and xenobiotics. However, P-gp and CYP3A4 are not identical in anatomic localization, suggesting unique as well as shared regulatory mechanisms of gene expression. We used established human colon carcinoma cell lines (LS180V and Caco-2) and measured mRNA and protein levels in cells after exposures to levothyroxine (L-T4), triiodo-L-thyronine (L-T3) and rifampin. Results indicate that L-T4, L-T3 and rifampin can upregulate the expression of P-gp mRNA and protein in LS180V cells, but only L-T4 and L-T3 can produce the same effect in Caco-2 cells, which are relatively lacking in PXR. In addition, L-T4 and L-T3 did not affect the expression of CYP3A4 in either cell line. We conclude that P-gp, but not CYP3A4, can be upregulated by thyroid hormones in vitro by a PXR-independent mechanism. Considering the widespread prescription use of L-T4 preparations in the older adult population, these results may be important for the clinical consideration of drug-drug interactions mediated by P-glycoprotein.

**Interactions Between Mu and Kappa Opioid Agonists in Assays of Schedule-Controlled Responding and Thermal Nociception in Rhesus Monkeys: A Dose-Addition Analysis.** S. S. Negus, S. McWilliams, G. W. Stevenson, McLean Hospital, Harvard Medical School, Belmont, MA

Studies of drug interactions may provide insight into mechanisms of drug action and contribute to the development of safer and more effective medications. For example, mu opioid receptor agonists such as morphine are widely used as analgesics, but their utility is limited by undesirable side-effects such as high abuse potential. Agonists at kappa opioid receptors also produce antinociception, but kappa agonists do not produce morphine-like side effects. This suggests that a combination of mu and kappa agonists may produce analgesia with fewer undesirable effects than mu agonists alone. Accordingly, the purpose of this study was to evaluate behavioral effects produced by combinations of a mu agonist (fentanyl) and a kappa agonist (U69,593) in rhesus monkeys. Results were evaluated with dose-addition analysis, which permits quantification of drug interactions as super-additive (synergistic), additive or sub-additive. Fentanyl, U69,593 and their combinations were tested in two behavioral procedures. Sedative effects were examined in an assay of schedule-controlled responding, in which food reinforcement was available under a fixed-ratio 30 schedule. Antinociception was examined in a warm-water tail-withdrawal procedure. Both fentanyl and U69,593 produced a dose-dependent decrease in response rates in the assay of schedule-controlled responding and a dose-dependent increase in thermal antinociception. Drug interactions were additive or sub-additive for both effects. Implications of these findings will be discussed.

**The Prostacyclin Receptor Induces Vascular Smooth Muscle Cell Differentiation Through the cAMP/PKA Pathway**. A.P. Nomikos, K.M. Fetalvero, B.L. Merenick, R.J. Wagner, R.J. Powell, J. Hwa, K.A. Martin, Dartmouth Medical School, Hanover, NH

Recent studies of COX-2 inhibitors suggest that the balance between thromboxane and prostacyclin is a critical factor in cardiovascular homeostasis. Disruption of prostacyclin signaling by genetic deletion of the receptor or by pharmacological inhibition of COX-2 is associated with increased atherosclerosis and restenosis after injury in animal models, and adverse cardiovascular events in clinical trials (Vioxx®). We studied mechanisms of prostacyclin action on human vascular smooth muscle cells (VSMC) in culture. These cells exhibit a dedifferentiated, migratory, proliferative phenotype, similar to what occurs following arterial injury. We report that the prostacyclin analog iloprost induces differentiation of VSMC from this synthetic, proliferative phenotype, to a quiescent and contractile phenotype. Iloprost induced a dose-dependent expression of contractile protein markers of differentiation, including MHC, calponin, and □-actin, as determined by western blotting and RT-PCR analysis. Iloprost also induced expression of the cyclin dependent kinase inhibitors $p21^{cip}$ and $p27^{kip}$, and inhibited proliferation. Iloprost activated cAMP/PKA signaling in human VSMC, and the cell permeable cAMP analog 8-Br-cAMP mimicked the iloprost-induced differentiation. Rp-8Br-cAMPs, an inhibitor of PKA, inhibited the iloprost effects, suggesting that iloprost induces VSMC differentiation via $G_s$ activation of the cAMP/PKA pathway. These studies reveal regulation of VSMC phenotype as another potential mechanism for the cardiovascular protective effects of prostacyclin.

**Effect of Arsenite on CYP3A4 in Cultured Human Hepatocytes.** T.L. Noreault[1,2], V. Kostrubsky[3], S. Wood[2], R. Nichols[1,2], S. Strom[4], H. Trask[1,2], S. Wrighton[5], J. Jacobs[1,2], P. Sinclair[1,2], J. Sinclair[1,2], [1]Dartmouth Medical School, Hanover, NH; [2]Veterans Administration Medical Center, White River Junction, VT; [3]Pfizer, Ann Arbor, MI; [4]University of Pittsburgh Medical Center, Pittsburgh, PA; [5]Lilly Research Laboratories, Indianapolis, IN

Arsenic is a naturally occurring, worldwide contaminant implicated in numerous human pathological conditions, including cancer and several forms of liver disease. A contributing factor to these disorders may be the alteration of cytochrome P450 levels by arsenic. CYP3A4, a major CYP in humans, is involved in the metabolism of half of all currently used drugs. Here, in primary cultures of human hepatocytes, we assessed the effects of acute arsenite exposure on CYP3A4, as well as transcription factors involved in CYP3A4 expression. The concentrations of arsenite used in these studies were non-toxic and failed to elicit an oxidative response. Treatment of hepatocytes with arsenite in the absence or presence of CYP3A4 inducers, rifampicin or phenobarbital, caused dramatic decreases in CYP3A4 mRNA, protein and activity. PXR protein was detected in both the cytosol and nucleus. Interestingly,

rifampicin did not cause the nuclear translocation of PXR, even though CYP3A4 mRNA was induced. Furthermore, arsenite failed to alter mRNA or protein levels of PXR and Sp1. Surprisingly, arsenite significantly decreased nuclear levels of RXR protein. These results suggest that arsenite inhibits both basal and induced CYP3A4 transcription in primary human hepatocytes, by decreasing the nuclear receptor RXR.

**Differential Effects Of The Cannabinoid Receptor Agonist, WIN 55,212-2, On Lamina I And Lamina V Spinal Trigeminal Nucleus Caudalis Neurons.** Akiko Ogawa[1] and Ian D.Meng[2], [1]Department of Neurology, University of California, San Francisco, CA; [2]Department of Physiology, University of New England, College of Osteopathic Medicine, Biddeford, ME

Direct application of cannabinoids to the spinal or medullary dorsal horn inhibits lamina V nociceptive neurons. The present study compared the effect of the cannabinoid receptor agonist, WIN 55,212-2 (WIN-2) on the activity of lamina I and lamina V spinal trigeminal nucleus caudalis (Vc) neurons. Using extracellular single unit recording in anesthetized rats, activity evoked by a contact thermode was measured before and after local application of WIN-2 to the brainstem. Fast and slow heat ramps were used to differentiate between activity evoked primarily by Aδ and C primary afferent fibers, respectively. In lamina V neurons, WIN-2 (1 μg/μl and 2 μg/μl ) attenuated activity evoked by fast heat, slow heat and cooling ($P<0.05$). In contrast, WIN-2 (1 μg/μl and 2 μg/μl ) attenuated activity evoked by slow heat and cooling ($P<0.05$), but not fast heat in lamina I neurons. These results demonstrate that WIN-2 has differential effects on Vc neurons depending on their laminar location. In separate experiments, the effect of intrathecal administration of WIN-2 to C1 on head withdrawal latencies produced by fast heat, slow heat and cooling of the lateral face was assessed in lightly anesthetized rats. WIN-2 (200 μg and 300μg, $P<0.01$) increased face withdrawal latencies for slow heat and cooling, but not for fast heat stimulation. Taken together, these results indicate that WIN-2 inhibition of the behavioral reflex may result from inhibition of lamina I neurons. *Supported by: DA014548.*

**Influence of Inflammatory Molecules on Humbilical Cord-derived Mast Cells (hCBMC) Expression of Corticotrophin-Releasing Hormone (CRH) Receptor-2 and Toll-like Receptor-2.** L. Oleson, N. Papadopoulou, D. Kempuraj, T.C. Theoharides, Tufts University Sackler School of Graduate Biomedical Sciences, Boston, Massachusetts

CRH, which normally regulates the hypothalamic-pituitary-adrenal axis and typically is thought to be anti-inflammatory, has recently been found outside the brain where it exerts proinflammatory effects, possibly through mast cells. However, it is not known whether CRH receptors (CRH-R) are present on human mast cells, which also express CRH. In this study, we used RT-PCR and immunocytochemistry to investigate whether hCBMCs express CRH-R and whether this expression is influenced by the presence of inflammatory molecules IL-1α/β, IL-4, or lipopolysaccharide (LPS). We found that hCBMCs express the CRH-R1α and R2 isoforms and that stimulation with LPS greatly induced CRH-R2 expression. Moreover, hCBMCs first primed with IL-4 for three weeks prior to stimulation with IL-1α exhibited greater CRH-R2 expression than nonprimed cells. Fluorescent immunocytochemistry (ICC) in hCBMCs confirmed the increase of R2 expression in IL-4 treated cells. The expression of CRH-R on human mast cells represents a link between the immune and nervous systems. Furthermore, mast cells are also known to express toll-like receptor 2 (TLR-2), which is important in host defense response to microbial ligands. IL-1 treatment greatly induced TLR-2 expression in hCBMCs, suggesting that cytokines could stimulate hCBMCs to respond to both CRH and bacterial triggers. These results implicate CRH and its related peptides in inflammatory conditions affected by stress.

★**Cataleptic And Locomotor Effects Of Acute And Chronic Gamma-Hydroxy Butyrate (Ghb) And Its Precursors In Mice.** S. Phattanarudee, L.S. Quang, T.J. Maher, Massachusetts College of Pharmacy and Health Sciences, Boston, MA

This study investigated the acute and chronic effects of the "date-rape" drug GHB and its precursors gammabutyrolactone (GBL) and 1,4-butanediol (1,4BD) on locomotor activity and catalepsy in male Swiss Webster mice. Acute equimolar doses of GHB (100-300 mg/kg; i.p.), GBL (83-248 mg/kg) and 1,4BD (87-261 mg/kg) were compared. Other mice received GHB, GBL or 1,4-BD for 14 days, and locomotor activity was determined periodically. Mice also received GHB, GBL or 1,4BD for 14 days and cataleptic behavior determined periodically. While GHB (100) increased locomotion, higher doses of GHB, and all doses of GBL and 1,4BD caused acute hypolocomotion. However, hypolocomotion on days 6 and 14 was attenuated. Additionally, on day 15 while GHB (300) administered to naïve mice caused marked hypolocomotion, this effect was shorter-lived in mice pre-exposed to GHB (200), however, such effect was not shown from GBL and 1,4BD. All agents produced catalepsy (peak onset at 20-30 min) on day 1. GHB produced a tolerance to the catalepsy, but this did not occur with GBL or 1,4BD. This study demonstrated the hypolocomotor activity and cataleptic effects of GHB, GBL and 1,4BD when administered acutely. Chronic GHB led to the development of tolerance to both hypolocomotion and cataleptic responses, however chronic GBL and 1,4BD appeared to develop less tolerance to hypolocomotion, but not to catalepsy.

**p53-Dependent Pathways in Retinoic Acid and Cisplatin Response in TGCTs.** A.M. Pike, J.S.Kerley-Hamilton, M.Spinella, Dartmouth Medical School, Hanover, NH

Testicular germ cell tumors (TGCTs) are one of the few solid tumors routinely cured with cisplatin-based chemotherapy. The NT2/D1 cell line is highly malignant but can be induced to differentiate and lose tumorigenicity with all-*trans* retinoic acid (RA). Microarray analysis was performed on NT2/D1 cells and a derived RA-resistant line (NT2/D1-R1) that is co-resistant to cisplatin. Retinoic acid and cisplatin have distinct gene expression profiles in NT2/D1 and NT2/D1-R1 cells. In general a similar but restricted set of genes was regulated by RA in NT2/D1-R1 cells compared to NT2/D1 cells. In contrast, the expression profiles with cisplatin were entirely distinct between the cell lines. Interestingly, many of the overlapping RA and cisplatin target genes in the sensitive line were known p53 target genes. TGCTs express high levels of wild-type p53 that is otherwise commonly mutated in over 50% of human cancers. Cisplatin target gene activation was markedly reduced or prevented in the presence of siRNA to p53 suggesting p53 plays an important role in cisplatin mediated responses. In addition, RA induction of p21, GDF15, and PLK2 was partially p53 dependent. The data suggests that the dramatic curability of TGCTs in response to cisplatin may be due to a hyper-transcriptional response dominated by p53 activation. The studies also suggest that de-regulation of p53 may participate in the dual resistance to RA and cisplatin in NT2/D1-R1cells.

**Effects of Stress and Methamphetamine on Glutamate Function in the Hippocampus.** J. Raudensky, J. Cunningham, J. Tonkiss, B.K. Yamamoto, Boston University School of Medicine, Boston, MA

Stress has been shown to precipitate drug-seeking behavior and alter the effects of drugs of abuse. The hippocampus contains high amounts of glucocorticoid receptors and is therefore vulnerable to stress. Previous studies indicate that acute restraint stress elevates extracellular glutamate (GLU) concentrations in the hippocampus, an effect that is attenuated by adrenalectomy. In addition, methamphetamine (METH) also increases extracellular GLU in the hippocampus as measured via *in vivo* microdialysis. Excitotoxicity associated with increases in extracellular GLU may be damaging to the hippocampus and attenuation of these increases in extracellular GLU may be protective.

The hippocampus is also an important structure for learning and memory. To evaluate the effects of stress and METH on hippocampal-dependent learning and memory, Morris Water Maze (MWM) performance was evaluated in rats after exposure to a ten day chronic unpredictable stress (CUS) regimen followed by repeated METH administration (7.5mg/kg; 2hr X 4; i.p.). Preliminary results indicate a METH-induced deficit in MWM performance that is attenuated by prior exposure to stress. Ten days of CUS also increased protein concentrations of glial glutamate transporter GLT-1 (EAAT2) in the hippocampus by 15%. Ongoing studies are testing the hypothesis that increases in EAAT2 may attenuate the METH-induced increases in extracellular GLU in the hippocampus, thereby affording protection against the potential excitotoxic effects of GLU. *Support Contributed By: NIGMS Award T32GM008541; DA07606*

**Inhibition of PC5 Expression Leads to Decrease in CCK Secretion and Upregulation of PC1, PC2 and CCK Expression in STC-1 Cells.** N.A. Reynolds, A. Blum, M.C. Beinfeld, Tufts University School of Medicine, Boston, MA

Cholecystokinin (CCK) is a peptide that is involved in key processes throughout the gut and brain. It is derived from a precursor that is modified as it travels through the secretory pathway. The length of CCK made varies and depends on points of endoproteolytic cleavage during processing. One of the enzymes thought to be important for endoproteolytic cleavage is Prohormone Convertase 5 (PC5). In this study, the role of PC5 in processing CCK was further investigated. A murine intestinal cell line, STC-1, was transfected with plasmids encoding for mRNA that acts as siRNA targeted against the PC5 gene. CCK secretion was measured by radioimmunoassay. Expression of PC5 and CCK were measured by real time PCR and immunoblotting. Expression of other PCs present in STC-1 cells was also measured. CCK levels were reduced in transfected STC-1 cells compared to controls. PC5 mRNA and protein levels were also reduced while the level of PC2 protein, PC1 and CCK mRNA appeared to increase. This may represent a compensatory mechanism in which expression of PC1, PC2 and CCK is promoted to compensate for loss of PC5. The results from this study further support that PC5 is important in processing of CCK and that loss of expression of one PC results in upregulation of other PCs and even the substrate itself.

**Effects Of Diuretic Treatment On The Neurobehavioral Toxicity Of Gamma-Hydroxybutyrate (Ghb).** R. Sarangarajan, S. Nualpring, S. Phattanarudee, T.J. Maher, Massachusetts College of Pharmacy and Health Sciences, Worcester and Boston, MA

GHB, a metabolite of GABA, is suggested to function as a neurotransmitter / neuromodulator in the central nervous system. In addition to its recently approved use in the treatment of cataplexy associated with narcolepsy, GHB is a well-known drug of abuse and

implicated in cases of drug-facilitated sexual assault. Treatment of toxicity associated with GHB overdose includes supportive therapy to maintain respiratory and cardiovascular function until the drug is largely eliminated. The current study investigated the use of diuretics to enhance renal excretion of GHB as a method to reduce GHB toxicity. Male CD-1 mice weighing 20-26 grams were treated with a fixed dose of GHB (1400 mg/kg) in combination with vehicle (V), furosemide (F;40 mg/kg) or mannitol (M; 2g/kg) (intraperitoneal). The rotarod (ROTO) performance and presence of righting reflex (RR) were determined as indicators of GHB toxicity. The duration of impairment for V, F and M are as follows (ROTO= 176, 236, and 212 min; RR= 101, 143, and 135 min), demonstrating that treatment with either diuretic significantly increased the duration of impairment for both tests compared to V. In contrast to expectation, the increase in GHB toxicity manifested by the prolongation of the neurobehavioral impairment is most likely the result of increase in brain GHB concentration due to significant reduction of extracellular fluid volume by diuretic action.

**3,4-Methylenedioxymethamphetamine and Brain Mitochondrial Function.** N.E Sparling[1], J.M. Brown[1], A. Darvesh[2], G. Gudelsky[2], and B.K. Yamamoto[1], [1]Boston University School of Medicine, Boston, MA; [2]University of Cincinnati, Cincinnati, OH

3,4-Methylenedioxymethamphetamine (MDMA), "Ecstasy", is an abused amphetamine analog which targets the serotonin (5HT) system. Past studies indicate that mitochondrial function and energy metabolism are altered following high doses. Cytochrome oxidase (mitochondrial complex IV) rapidly decreases after MDMA or methamphetamine (METH). Additionally, the provision of substrates for the mitochondrial electron transport chain (ETC) attenuates the long-term dopamine depletions produced by high dose METH treatment. METH also decreases complex II-III activity in the striatum. Based on these results, we hypothesized that the provision of energy substrates will block MDMA-induced 5HT depletions and that MDMA will decrease mitochondrial ETC activity.

MDMA (10mg/kg q 2hrs x 4) or saline was injected into male Sprague-Dawley rats. Reverse dialysis of either ubiquinone (100 µM) or nicotinamide (1 mM) during the injections of MDMA blocked the depletions of 5HT in the striatum when measured 5 days later. Reverse dialysis of nicotinamide also attenuated the 5HT depletions in hippocampus. Complex I-III activity in the striatum decreased by 46% at 12h and 17% at 24h compared to saline controls. Complex II-III activity was also decreased in the striatum by 34%, 12h after MDMA. These results suggest that MDMA compromises mitochondrial electron transport chain function through an inhibition of complexes I-III and II-III and that the provision of energy substrates is neuroprotective against the MDMA-induced 5HT depletions. *Supported by DA07427, DA16866 & NIGMS Award T32GM008541*

★**Targeting Pain-suppressed Behaviors in Preclinical Assays of Pain and Analgesia: I. Effects of Morphine on Acetic Acid-Suppressed Feeding in Mice.** G.W. Stevenson[1], K. Barbee[2], E. Bilsky[2], S.S. Negus[1], [1]ADARC, McLean Hospital-Harvard Medical School, Belmont, MA; [2]Department of Pharmacology, University of New England, Biddeford, ME

Pain increases the occurrence of some behaviors (e.g. withdrawal responses, writhes) and decreases others (e.g. feeding, locomotion). Most preclinical assays measure pain-evoked behaviors, and analgesics are tested for their ability to reduce these behaviors. However, drugs that produce motor impairment may act as "false positives" in these assays. Moreover, clinical medicine (especially veterinary medicine) relies heavily on measures of pain-suppressed behaviors to assess pain states and analgesic efficacy. We sought to develop an assay of pain-suppressed behavior, because 1) true analgesics would be expected to increase behavior, whereas motor impairing drugs would not, and 2) a preclinical assay of pain-suppressed behavior might model important aspects of clinical pain. Our study proceeded in 3 steps: 1) identify conditions that produced stable feeding in mice, 2) assess the ability of a commonly used chemical noxious stimulus (i.p. acetic acid injections) to suppress feeding, and 3) assess the ability of a well-established analgesic (morphine) to restore pain-suppressed feeding. Mice were given access to a dish containing 8ml Ensure liquid food (0-100% in water) during daily sessions (7.5-120 min). Levels of consumption were dependent on both Ensure concentration and session duration. Acetic acid (0.10 – 0.56%) produced a time- and concentration-dependent decrease in Ensure consumption. Morphine (0.1 – 1 mg/kg) potently prevented acid-suppressed feeding. The effects of morphine were time-dependent, selective for acid-suppressed feeding, and naltrexone-reversible. Studies with other compounds are ongoing. These results suggest that assays of pain-suppressed behaviors may complement assays of pain-evoked behaviors in preclinical studies of pain and analgesia.

**Molecular, Biochemical, and Genetic Analysis of the Human Prostacyclin Receptor.** J. Stitham[1], K. Fetalvero[1], A. Blount, Jr.[1], E. Arehart[1], S. Kennedy[2], T. MacKenzie[2], D. Belloni[2], W. Noll[2], and John Hwa[1], [1]Dartmouth Medical School, Hanover, NH; [2]Dartmouth-Hitchcock Medical Center, Lebanon, NH

Polymorphisms are emerging as important determinants of disease progression and drug therapy. The human prostacyclin receptor (hIP) plays important protective roles within the cardiovascular system (anti-thrombotic and pro-vasodilatation). Initial genetic screening of the general population (CPHS#14888): 119 healthy individuals from 3 different ethnic groups (Caucasian, African American, and Asian) and 40 persons with hyper-coagulability disorders revealed 11 polymorphisms within the hIP receptor: 4 non-

synonymous mutations (V25M, R212H, S319W, E354D) and 7 synonymous mutations (G27, L33, V53, L186, R212, S328, T373). No unique polymorphisms were detected within the hyper-coagulable group, but various ethnic propensities were identified in the general population (V25M & S319W are exclusive to African Americans, while R212H & E354D are limited to Asians). Binding and activation assays revealed a functional deficit in the R212H mutant receptor. Further screening (coronary artery disease group) revealed a novel non-synonymous R212C mutation with functional deficiencies, as well as another unique synonymous R212 mutation (CGT). Such results exposed an emerging propensity towards R212 mutations (CGC codon) within the important third cytoplasmic loop of the hIP, and evidence from the SNP database supports this observation in numerous other GPCRs. Such polymorphisms may have an impact on disease responses to GPCR-targeted drugs. *Funded by NIH-NHLBI, AHA-SDG (JH), & AHA-PDF (JS)*

**The $CCK_B$ Receptor Regulates Catecholamine Exocytosis.** M.B. Tagen and E.N. Pothos, Tufts University School of Medicine, Boston, MA

Dopamine is a catecholamine neurotransmitter that is extensively colocalized with the peptide cholecystokinin (CCK) in the CNS. In the present study, we considered the possibility whether $CCK_A$ or $CCK_B$ receptors expressed on dopamine neuronal terminals in the CNS or catecholamine-releasing chromaffin cells in the periphery directly regulate evoked neurotransmitter release. We used carbon fiber amperometry to measure electrically-evoked dopamine release from acute coronal brain slices of $CCK_AR$ -/- and $CCK_BR$ -/- mice and their respective wildtypes. The slices from $CCK_BR$ -/- mice exhibited significantly larger spike amplitudes and numbers of dopamine molecules released compared to the $CCK_BR$ +/+ mice in the nucleus accumbens shell and the dorsal striatum. Amperometry performed on cultured adrenal chromaffin cells showed that the catecholamine quantal size in $CCK_BR$ -/- cells (but not the $CCK_AR$ -/- cells) was increased. These results indicate that the $CCK_BR$ plays an important role in inhibiting stimulated dopamine neurotransmission in areas of the CNS controlling motivation and reward, possibly through a decrease in quantal size.

**Characterization of Neuroimmune Activation in Morphine-Tolerant Neuropathic Rats.** V.L. Tawfik[1], N. Nutile-McMenemy[1,2], J.A. DeLeo[1,2], [1]Dartmouth Medical School, Hanover, NH; [2]Dartmouth-Hitchcock Medical Center, Lebanon, NH

Neuroimmune activation, characterized by glial activation and cytokine expression, has previously been shown to contribute to the development of neuropathic pain and also participates in morphine tolerance. In this study, we characterized the temporal and dose-response relationships of morphine tolerance and neuroimmune activation in neuropathic pain. Rats received an L5 spinal nerve transection and the development of tactile allodynia was monitored using 2 and 12 g von Frey filaments. An osmotic pump delivering saline, 1 or 10 mg/kg morphine sulfate s.c or saline, 5 or 20 nmol/hr morphine sulfate i.t. was implanted on day 6 after L5 transection (n = 6/group/time point). Spinal cord was harvested on days 9, 12 and 20 after surgery and processed by real-time RT-PCR for determination of GFAP and ITGAM expression (astrocyte and microglial markers, respectively) as well as cytokines IL-1β and IL-6. Development of tolerance to both doses of morphine (as evidenced by increased sensitivity to mechanical stimuli) occurred though the central route hastened tolerance. In addition, transcriptional alterations in GFAP, ITGAM, IL-1 and IL-6 were further enhanced after i.t. compared with s.c. morphine treatment. We hypothesize that i.t. delivery of morphine activates glial cells and cytokine expression by recruitment of both transcriptional and translational processes leading to a robust neuroimmune activation that plays a key role in opioid tolerance development in neuropathic pain.

**Eph A/Ephrin A Interactions in Neurovascular Cultures.** J. teRiele, D. Damon, University of Vermont, College of Medicine, Burlington, VT

Vascular sympathetic innervation determines blood pressure and flow, and contributes to cardiovascular disease. The present study investigates the role of ephA/ephrinA interactions in determining this innervation. Neurovascular cultures were used to determine if vascular-derived ephrinA modulates the growth or guidance of sympathetic axons. Reverse transcription-polymerase chain reaction (RT-PCR), western, and immunohistochemical analyses show that ephA4 is present in sympathetic neurons. RT-PCR and western analyses indicate the presence of ephrinA1 in adult and neonatal arteries of the rat. Exogenous ephrinA1 (1 □g/cm$^2$) decreases NGF (1 ng/ml)-induced axon growth; in the absence of ephrin A1 growth is significantly greater (48.8 $\pm$ 6.7 mm) than in the presence of ephrinA1 (26.3 $\pm$ 5.7 mm; $p < 0.05$, unpaired t-test). To determine if vascular smooth muscle (VSM)-derived ephrinA modulates sympathetic axon growth or guidance, the effects of VSM were studied. VSM, like ephrinA1, inhibits NGF (50 ng/ml)-induced axon growth; growth in the presence of VSM (123 $\pm$ 36 mm) is less than that in the absence of VSM (427 $\pm$ 54 mm; $p < 0.05$, unpaired t-test). In preliminary studies, inhibition of EphA/EphrinA interactions reduce the effects of VSM on axon growth. These data indicate

that ephrinA ligands (VSM) and EphA receptors (neurons) are present and functional in neurovascular co-cultures, and suggest that ephA/ephrinA interactions play a role in sympathetic axonal growth and guidance to blood vessels.

**AIDA, a Selective Group I mGluR Antagonist, Potentiates the Anticonvulsant Effect of Lorazepam in Mice.** L. P. Volak, J.M. Reddi and J. M. Fahey, Tufts University School of Medicine, Boston, MA

Ionotropic and metabotropic glutamate receptors have been implicated in the development of benzodiazepine tolerance in mice. Several studies have shown that mGluR agonists and antagonists can modulate $GABA_A$ receptors *in vitro* as well as *in vivo*. In this study, we examined the effect of a Group I mGluR antagonist, AIDA, and a Group III mGluR agonist, L-AP4, on the locomotor and anticonvulsant effects of the classic benzodiazepine, lorazepam, in male CD-1 mice. AIDA, L-AP4, or vehicle was administered with lorazepam or vehicle 90 min prior to open-field activity monitoring and pentylenetetrazole-induced seizure activity testing. Neither AIDA nor L-AP4 had a significant effect on the reduction in movement due to lorazepam as assessed by the distance traveled, number of rears, and number of stereotypies in open-field analysis. The ability of lorazepam to increase the pentylenetetrazole-seizure threshold was potentiated by AIDA, but not L-AP4. The differential effect of AIDA on lorazepam's anticonvulsant activity compared to its lack of an effect on locomotor activity may result from a specific interaction of AIDA with type 1 benzodiazepine receptors, which may mediate the anticonvulsive effects of classic benzodiazepines. These data suggest that AIDA antagonism of Group I mGluR can cause a downstream effect on $GABA_A$ receptors and may be effective as a dual therapy to reduce benzodiazepine tolerance after chronic administration.

**Role of the Xenobiotic Receptor PXR in Acetaminophen Hepatotoxicity.** K.K. Wolf[1], S.G. Wood[2], B.W. Walton-Strong[1], K. Yasuda[6], L. Lan[6], P.R. Sinclair[1,2], S.A. Wrighton[3], E.H. Jeffery[4], R.M. Evans[5], E.G. Schuetz[6], J.F. Sinclair[1,2], [1]Dartmouth Medical School, Hanover, NH; [2]VA Medical Center, White River Junction, VT; [3]Lilly Research Laboratories, Indianapolis, IN; [4]University of Illinois, Urbana, IL; [5]Howard Hughes Medical Institute, La Jolla, CA; [6]St. Jude Children's Research Hospital, Memphis, TN

The pregnane X receptor (PXR) is a key regulator of many xenobiotic-metabolizing enzymes. To investigate if PXR has a role in acetaminophen (APAP) toxicity, we examined APAP hepatotoxicity and metabolism in wild-type and *PXR(-/-)* mice in a C57BL/6 background. *PXR(-/-)* mice were less sensitive to APAP hepatotoxicity than wild-type mice. Hepatic cytochrome P450 (CYP) 2E1 levels were identical in the two mouse lines. CYP3A protein levels were elevated 2.5-fold in *PXR(-/-)* mice. CYP1A2 levels were decreased 3-fold. These findings suggest that PXR is a positive modulator of CYP1A2 expression and that CYP1A2 contributes to the development of APAP hepatotoxicity. No significant differences in APAP metabolism were observed between wild-type and *PXR(-/-)* mice, as measured by the plasma levels of glucuronide, sulfate, and glutathione-conjugated metabolites. APAP uptake was 47% greater in wild-type mice compared to *PXR(-/-)* mice. APAP was not a substrate of the transport protein MDR1. Our finding that APAP hepatotoxicity is decreased in *PXR(-/-)* mice shows that PXR is an important modulator of APAP hepatotoxicity, possibly through up-regulation of CYP1A2 expression and increased APAP absorption.

**Synthetic Triterpenoids Induce the Cytoprotective and Anti-inflammatory Protein Heme Oxygenase 1 *in vitro* and *in vivo***. M Yore, K Liby, D Royce, T Honda, G.W. Gribble and M.B. Sporn, Dartmouth Medical School, Hanover, NH

Synthetic oleanane triterpenoids are pleitrophic agents with numerous actions and efficacy in a broad spectrum of diseases. 1[2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oyl]imidazole (CDDO-Im) is a novel synthetic triterpenoid synthesized by our laboratory which is currently undergoing preclinical evaluation as a cancer therapeutic in phase one clinical trials. Here we report new findings pertaining to the cytoprotective and anti-inflammatory abilities of this compound. In the current study, we examined the effects of CDDO-Im on microsomal heme oxygenase 1 (HO-1). HO-1 oxidizes heme to CO, biliverdin, and ferrous iron. The enzyme is of clinical interest as the biliverdin and bilirubin produced by the enzyme are potent antioxidants and are involved in a manifold of protective physiological situations. CDDO-Im potently induced HO-1 in a dose and time dependent manner both *in vitro* and *in vivo*. *In vivo* induction occurs in numerous organs when the compound is administered either orally or parentally. To assess HO-1 enzymatic activity induced by CDDO-Im the formation of bilirubin was measured from *in vivo* and *in vitro* specimens. HO-1 induced by CDDO-Im, dose-dependently increased bilirubin levels; this induction was blocked by Zinc Protoporphyrin IX, a competitive antagonist of HO-1. Further structure function analysis of CDDO-Im identified the carbonyl group at position 12 essential for this activity. Further investigations into the activity of CDDO-Im and its potential clinical applications are ongoing.

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2. Statement and signatures from two sponsors for Regular membership and from one sponsor for Affiliate/Student membership.*
3. *Curriculum vitae* (include bibliography) for Regular and Affiliate membership.

*A letter or e-mail may be sent by the sponsor to the Membership Coordinator (rphipps@aspet.org) in lieu of the sponsor's signature and statement of qualifications of the applicant on the form. Call or e-mail the ASPET Membership Department for additional information: (301) 634-7135 / rphipps@aspet.org

For on-line submission, go to http://www.aspet.org/public/membership/memberapplform_ia_1003.pdf

## Future Meetings

Experimental Biology '06
San Francisco, CA
Saturday-Wednesday
April 1-5, 2006
(AAA, APS, ASIP, ASBMB, ASNS, ASPET)

Experimental Biology '07
Washington, DC
Saturday-Wednesday
April 28-May 2, 2007
(AAA, APS, ASIP, ASBMB, ASNS, ASPET)

🏆 ASPET's Centennial 🏆
Experimental Biology '08
San Diego, CA
Saturday-Wednesday
April 3-9, 2008