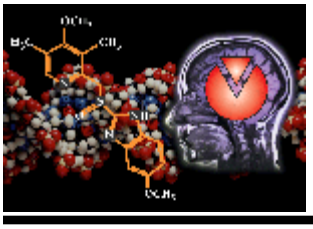


The Pharmacologist

Vol. 51
Number 4
2009
December

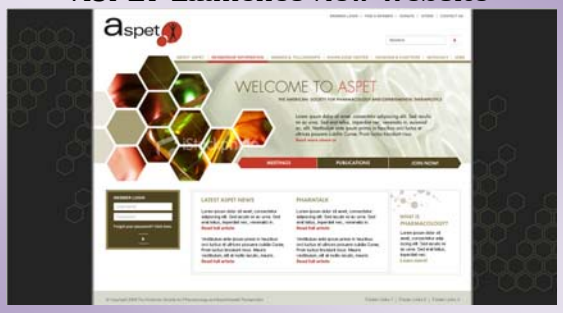
2009 Year In Review

Presidential Torch Passed From Past-President Joe Beavo to President Brian Cox

Awards Winners in 2009

ASPET Participates In Habitat For Humanity in New Orleans

ASPET Launches New Website



ASPET Holds Student/Postdoc Focus Group

Also Inside this Issue:

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Announcements

Please Send In Your 2010 Dues Payment By January 1, 2010.

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YEAR IN REVIEW

As 2009 comes to a close, ASPET would like to thank you for your participation and commitment to the Society! With the help of member contributions, support and participation, we are pleased to announce the following accomplishments made by ASPET this year:

New Website:

2009 saw the launch of ASPET's newly designed website, www.aspet.org. The new design and functionality of the site have allowed us to create lots of new features, including a "President's Blog", where the President of ASPET shares his thoughts with the membership on a variety of issues related to ASPET and pharmacology. We've also improved some of our older features, including the member login pages. As we continue to develop the website, we hope to have many new fun and interactive features so be sure to check back often.

Awards:

In 2009, we awarded 57 Graduate Student and 23 Young Scientist travel awards at the Experimental Biology meeting, all supported by member and corporate donations.

Membership:

Our membership is holding steady in these tough economic times, and 2009 proved to be another successful year in membership recruitment. This year, we have recruited over 450 new members. Many ASPET members are taking an active role in recruiting their students, colleagues and friends into the Society. We hope to continue this growth and encourage greater interest in ASPET and pharmacology in the coming year.

Journals:

The ASPET journals continue to make a strong impact. This year, our journals were given the following Impact Factors:

Journal of Pharmacology and Experimental Therapeutics – 4.309
Pharmacological Reviews – 21.936
Drug Metabolism and Disposition – 3.825
Molecular Pharmacology – 4.711
Molecular Interventions – 8.273

As we wrap up this action-packed year, we have many high hopes for 2010. ASPET is looking forward to expanding our membership base, reaching out to new members in new avenues. Our registration numbers are already up for our Annual Meeting at Experimental Biology 2010 in Anaheim, CA, and we expect great turnout with exceptional science. We hope that you will be a part of all our activities for 2010! Happy New Year!

ASPET ELECTION

The ASPET election for President-Elect, Secretary/Treasurer-Elect, and Councilor will be taking place this month. All Regular, Retired, and Semi-Retired members are eligible to vote. In addition, the following Divisions are holding elections: Division for Behavioral Pharmacology, Division for Drug Metabolism, Division for Integrative Systems, Translational and Clinical Pharmacology, Division for Molecular Pharmacology, Division for Neuropharmacology, and Division for Toxicology. Those of you with email will receive a message when the election opens and will be reminded of your username and password so that you can login to the Members Only section of the web site and vote. This email will also list the divisions in which you are eligible to vote. If you do not have email, you will be sent a paper copy of the election bulletin and a paper ballot and return envelope. You MUST sign the return envelope and print your name legibly in order for your paper vote to be counted. The divisions in which you are eligible to vote will be listed on your address label.

As required by the by-laws, the election site on the web will be open for a minimum of thirty (30) days from the day of notification.

NOMINEES FOR ASPET OFFICE

Candidates for President-Elect

Lynn Wecker

Nancy R. Zahnhiser

Candidates for Secretary/Treasurer- Elect

Terrence J. Monks

Mary E. Vore

Candidates for Councilor

Stephen M. Lanier

Kenneth E. Thummel

NOMINEES FOR DIVISION OFFICE

Division for Behavioral Pharmacology:

Nominee for Chair-Elect

Leonard L. Howell

Nominees for Secretary/Treasurer-Elect

Paul W. Czoty

Walter Koek

Division for Drug Metabolism:

Nominees for Chair-Elect

Hollie Swanson

Nominees for Secretary/Treasurer-Elect

Deepak Dalvie

Aiming Yu

Division for Integrative Systems, Translational, and Clinical Pharmacology:

Nominees for Chair-Elect

Hamid I. Akbarali

Dennis C. Marshall

Nominees for Secretary/Treasurer-Elect

Not Pictured

Alex F. Chen

Andrea Gaedigk

Division for Molecular Pharmacology:

Nominees for Chair-Elect

Randy A. Hall

Rennolds S. Ostrom

Nominees for Secretary/Treasurer-Elect

Carmen W. Dessauer

Val J. Watts

Division for Neuropharmacology:

Nominees for Chair- Elect

Lynette C. Daws

Lian Li

Nominees for Secretary/Treasurer-Elect

Eric L. Barker

Susan L. Ingram

Division for Toxicology:

Nominees for Chair- Elect

William Slikker, Jr

Patricia E. Ganey

Nominees for Secretary/Treasurer-Elect

Todd D. Porter

Not Pictured

Cynthia Ju

There will be no elections this year for the following divisions:

Division for Cardiovascular Pharmacology
Division for Drug Discovery, Drug Development, & Regulatory Affairs
Division for Pharmacology Education

Have you Joined a Division?

Take full advantage of ASPET Membership by joining a Division!!

- **You can participate in creating the scientific program for the annual meeting.**
- **You can network with people in your field at the mixers and divisional programming at the annual meeting.**
- **You can participate in running the division and planning its activities.**
- **You get special notices and newsletters about items and activities of interest in your field.**

ASPET gratefully acknowledges the following individuals who have made contributions over and above dues for 2009:

John J. Abel Award
Christine K. Carrico, PhD

Julius Axelrod Award
Elaine Sanders-Bush, PhD
Lee Eiden, PhD
Arnold J. Eisenfeld, MD
Susan G. Amara, PhD

Karl H. Beyer Student Travel Award
Allen Barnett, PhD
Annette Beyer-Mears, PhD
J. Fred Pritchard, PhD

B.B. Brodie Award
Dennis R. Feller, PhD
Morris S. Zedeck, PhD
David Y. Cooper, MD
H.G. Mandel, PhD
Gopal S. Rao, PhD
Bettie Sue S. Masters, PhD

Joseph P. Buckley Student Travel Fund
Douglas C. Eikenburg, PhD
Balwant N. Dixit, PhD

Thomas F. Burks Student Travel Fund
Robin A. Dodson, PhD
Kenneth D. Wild, PhD
David R. Brown, PhD
James V. Bruckner, PhD
Christine K. Carrico, PhD
David J. Jones, PhD
Frank F. Vincenzi, PhD

P.B. Dews Award
Paul R. Draskoczy, MD
J.D. Leander, PhD
James W. McKearney, PhD
Victor G. Laties, PhD
Jonathan L. Katz, PhD
Jack Bergman, PhD
Claire Advokat, PhD
Alice M. Young, PhD

Early Career Achievement Award Fund
Daniel B. Ellis, PhD
James E. Patrick, PhD

Robert F. Furchgott Student Travel Fund
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Walter R. Dixon, PhD
Siret D. Jaanus, PhD
Robert F. Furchgott, PhD
Eugene Roberts, PhD
Shoji Shibata, MD, PhD
Donald R. Bennett, MD, PhD
Rosemary D. Bevan, BS, MB
Stanley Friedman, MD

IUPHAR Travel Fund
George T. Okita, PhD
Dah H. Ho, PhD
Bhagavan S. Jandhyala, PhD

Harvey B. Haag Student Travel Fund
Allan S. Yard, PhD

Keith F. & Eva K. Killam Student Travel Fund
John F. Bowyer, PhD
Aisar H. Atrakchi, PhD
Merle G. Paule, PhD
David L. Nelson, PhD
Ralph J. Cazort, MD
Anthony J. Hance, PhD
Frank F. Vincenzi, PhD

Benedict R. Lucchesi Lectureshuip in Cardiac Pharmacology
Benedict R. Lucchesi, MD, PhD
Nancy J. Rusch, PhD
Kim Jansen

Members Fund for Graduate Student Travel
Louis A. Barker, PhD
Daniel L. Azarnoff, MD
John R. Hepler, PhD
Bernard P. Salafsky, PhD
Martin D. Green, PhD
Irwin H. Slater, MD
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Michiko Okamoto, PhD
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R. Kelly Hester, PhD
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Joel G. Hardman, PhD
Rita J. Valentino, PhD

Frank G. Standaert Student Travel Fund
Roberto Levi, MD
Donald N. Franz, PhD
Nae J. Dun, PhD

Sustaining Member Fund
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Miendert Danhof, PhD
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Akira Horita, PhD
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Steven E. Mayer, PhD
Louis S. Harris, PhD
David Dime, PhD
Morris D. Faiman, PhD
Stephen H. Koslow, PhD
Richard L. Klein, PhD
Conan Kornetsky, PhD

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Ann F. Welton, PhD
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Jeffrey S. Fedan, PhD
Dennis C. Marshall, PhD
Brian Leyland-Jones, MD
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Kenneth D. Wild, PhD
Earl W. Dunham, PhD
Kenneth E. Moore, PhD
Donald C. Kvam, PhD

Paul M. Vanhoutte Lectureship in Vascular Pharmacology
Stephen T. O'Rourke, PhD
Chao-Yu Miao

Young Scientist Travel Fund
Brian Kobilka, MD
Mark M. Knuepfer, PhD
Alvin H. Gold, PhD
Peter W. Ramwell, PhD
Donald F. Bogdanski, PhD
Susan G. Amara, PhD
David T. Wong, PhD
Achilles J. Pappano, PhD
Ronald G. Coffey, PhD
K.R. Hornbrook, PhD
Junko Sugatani, PhD

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Astellas Foundation
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Your donations help with programming, awards, and other important Society affairs. Making a donation is a great way to demonstrate your commitment to the future of ASPET, pharmacology, and your profession.

Make a donation at www.aspet.org. Be sure to login as a member so that we can make sure to recognize your generous support.

All donations are tax-deductible.

EXPERIMENTAL BIOLOGY 2010 – Anaheim

AM Symposia 9:30 – 12:00 AM Lectures 8:30 – 9:20 PM Symposia 3:00 – 5:30 PM Lectures 2:00 – 2:50

Saturday, 4/24	Sunday AM, 4/25	Sunday PM, 4/25	Monday AM, 4/26	Monday PM, 4/26	Tues AM, 4/27	Tues PM, 4/27	Wed AM, 4/28
Behavioral Pharmacology Society Meeting Day 2	**WIP Walk** **Diversity Mentoring Bkfst** **ISTCP, CVP, DDDRA, NEU** Regenerative pharmacology & stem cell research for tissue and organ repair: State of the art **209**	**ISTCP, CVP, DDDRA, NEU** Applications of stem cell therapies in clinical development & regenerative pharmacology in organ repair 209	**AXELROD LECTURE** Palmer Taylor: Structure Based Drug Design in the Nervous System **Axelrod Symposium** Structure and mechanism in drug enzymes and antimetabolite **209**	**NEUROPHARMACOLOGY DIVISION** Postdoctoral Award Finalists **209**	**NEU, BEH** **RAY FULLER LECTURE** Eric Nestler Transcriptional and epigenetic mechanisms of drug addiction 209 **Ray Fuller Symposium** Epigenetic mechanisms of learning and memory	**BEH, DDDRA, ISTCP, NEU** Epigenetic regulation: concepts and applications in psychiatric, neurological and substance abuse disorders **209**	**TOX, DM, ISTCP** Role of mitochondria in drug hepatotoxicity: A tale of Stress **210C**
2010 Teaching Institute: Simulation in pharmacology education going beyond mannequins. **208**	**DM, ISTCP, TOX** Orphan cytochrome P450 and other drug metabolizing enzymes **210C**	**DM, BEH, DDDRA, DPE, ISTCP** Industrial/academic partnerships: A new era (workshop) **210D**	**ISTCP, NEU** Recent advances in the neuropharmacology of anxiety: Implications for novel therapeutics **210AB**	**BRODIE LECTURE** J. Halpert **2:00 – 3:00** **DRUG METABOLISM** Platform Session & Gillette Award Winners **208**	**TOX, DM** Regulating the regulators: redox regulation, stress response proteins and apoptosis. **210C**	**DIVISION FOR TOXICOLOGY SYMPOSIUM:** ABC transporters, their role in physiology, toxicology and cancer **210C**	**MP, DDDRA, ISTCP, NEU** Sphingosine 1-phosphate signaling as a therapeutic target **208**
Diversity Committee Workshop: Traditional and alternative career paths in rough economic times **210AB**	**BEH, DDDRA, MP, NEU** When the smoke clears, there's more to neuronal nicotinic acetylcholine receptors **210D**	**NEU, DDDRA** Stimulus bias in an allosteric world: Relevance to CNS drug target validation **210AB**	**DPE, BEH, CVP, DDDRA, DM, ISTCP, MP, NEU, TOX** Introduction of drug safety (pharmacovigilance) into curricula **210C**	**DIVISION FOR PHARMACOLOGY EDUCATION SYMPOSIUM:** Making Medical Pharmacology More Clinically Relevant. **210C**	**CVP, MP** New insights about an "old" second messenger, cAMP: Implications for cardiovascular pharmacology **210D**	**DIVISION FOR DRUG DISCOVERY, DEVELOPMENT & REGULATORY AFFAIRS SYMPOSIUM:** Protease-activated receptors: new roles and regulatory Mechanisms. **210D**	**DM, ISTCP, TOX** Protein-protein interactions and modulation of drug metabolism **210AB**
Graduate Student-Postdoc Colloquium Leadership: Skills, styles and self-awareness. **209**	**MP, ASBMB** Spatial and temporal organization of cell signaling **208**	**DDDRA, MP** Receptor-independent activators of G-protein signaling in the nervous system **208**	**MP, NEU** Wnt signaling and development: Conventional and unconventional GPCRs mechanisms **208**	**DIVISION FOR CARDIOVASCULAR PHARMACOLOGY** **Trainee Showcase 210AB** **PAUL VANHOUTTE LECTURE** **W. Campbell** Arachidonic acid metabolites as endothelium-derived hyperpolarizing factors **4:30 – 5:30**	**MP, ASBMB** High-resolution structural approaches to understanding GPCR activation **208**	**DIVISION FOR INTEGRATIVE SYSTEMS, TRANSLATIONAL & CLINICAL PHARMACOLOGY** Award Session **210AB**	
Business Meeting 6:00 – 7:30 pm **Hilton Pacific Ballroom A**	**CVP, DDDRA, ISTCP** New therapeutic approaches to combat arterial thrombosis **210AB**	**DEWS LECTURE** **D. MacMillan** **2:00 – 2:50** **BEH, ISTCP, NEU** In vivo animal modeling in drug discovery and development: Multiple approaches to predict clinical efficacy in CNS disorders **210C**	**DDDRA, MP** Extracellular matrix proteins of the CCN family as therapeutic targets **210D**	**DIVISION FOR BEHAVIORAL PHARMACOLOGY SYMPOSIUM:** Stress, cognitive function and monoaminergic mechanisms in psychiatric disorders **210D**	**ISTCP,BEH, CVP,DDDRA, DM, DPE, MP, NEU, TOX** Integrating genetics, genomics and pharmacology: How the pharma-cogenomics knowledge base catalyzes pharma-cogenomic research and translational medicine **210AB**	**MOLECULAR PHARMACOLOGY DIVISION** Postdoctoral Award Finalists **208**	
Opening Reception 7:30-9:00 **Hilton Sunset Terrace**	**DPE, ISTCP** Applying Web 2.0 technologies in teaching pharmacology: Developing the tool box **Hilton Hotel**		**Best Abstract Completion & Student Post-Doc Mixer** **Hilton Hotel**				

David Sibley Is Next *PharmRev* Editor

Following a search that began last spring, the Board of Publications Trustees Executive Committee selected Dr. David R. Sibley to succeed Dr. Ross Feldman as the next editor of *Pharmacological Reviews*. The journal is the Society's second oldest. It was launched by the Society in 1949 with Dr. Louis S. Goodman serving as its first editor. Dr. Sibley will assume the editorship on January 1, 2010.

The search for Dr. Feldman's successor began in May with a request to all ASPET members to nominate qualified candidates. Approximately 20 distinguished individuals were nominated, and the BPT Executive Committee worked through the summer to complete the selection process.

Dr. Sibley received the Bachelor of Science degree in 1977 from San Diego State University and the Doctor of Philosophy degree in 1982 in physiology and pharmacology from the School of Medicine at the University of California, San Diego. His dissertation was entitled "Ligand Binding Properties of Pituitary D-2 Dopaminergic Receptors".

Dr. Sibley is the Chief of the Section on Molecular Neuropharmacology at the National Institute of Neurological Disorders and Stroke, National Institutes of Health in Bethesda, Maryland.

His extensive editorial activities include serving as Editor in Chief of the *Handbook of Contemporary Neuropharmacology* (Wiley, 2007) and Mini-reviews Editor for *Molecular Pharmacology*. He has held or currently holds various editorial board positions with the journals *Current Molecular Pharmacology*, *Current Psychiatry Reviews*, *Journal of Pharmacology & Experimental Therapeutics*, *Current Neuropharmacology*, *Neuropsychopharmacology*, *Journal of Receptors and Signal Transduction*, *Pharmacology & Therapeutics*, *Neuropharmacology*, *Synapse*, and *Current Protocols in Neuroscience*.

Dr. Sibley has been an ASPET member since 1985 and currently serves as the Society's Secretary/Treasurer. He is Chair of the Julius Axelrod Award Committee and a member of the Finance Committee, the Investment Subcommittee, and the Astellas Award Committee. Past positions with the Society include serving on the Nominating Committee, the Scientific Council, and the Program Committee. He served on the ASPET Division of Neuropharmacology Executive Committee where he held the positions of Secretary/Treasurer and Chair.

Beyond ASPET, he is a Fellow of the American College of Neuropsychopharmacology, where he has served on several committees, and a member of the International Catecholamine Club, the Collegium Internationale Neuro-Psychopharmacologicum, ASBMB, the Society for Neuroscience, and the AAAS.

Prospective *Pharmacological Reviews* authors should note that the manuscript submission process will not change with the change in editors. All submissions will continue to be handled through the journal's online manuscript system. Authors should submit manuscript proposals online at submit-pharmrev.aspetjournals.org. Please read the journal's Instructions to Authors, found online at pharmrev.aspetjournals.org, to prepare a proposal.

New Editorial Board Members

Throughout the year, new members are added to the editorial boards of ASPET's five journals. We will announce new board members in *The Pharmacologist*. Prospective board members are nominated by the editors and must be approved by ASPET's Board of Publications Trustees.

The following individuals were approved by the BPT during the last quarter to serve as new associate editors for the *Journal of Pharmacology and Experimental Therapeutics*:

- **Keith Glaser**, Senior Group Leader and Associate Research Fellow, Abbott Laboratories; Clinical Professor of Pharmacology, Chicago College of Osteopathic Medicine
- **James O'Donnell**, Assistant Vice President and Assistant Dean of Research, West Virginia University

- **Ray Winquist**, Vice President, Pharmacology, Vertex Corp.
- **Arthur Christopoulos**, Professor and NHMRC Senior Research Fellow, Monash University
- **David Gewirtz**, Professor of Pharmacology and Medicine, Virginia Commonwealth University, Medical College of Virginia
- **Yuichi Hattori,** Chairman of Molecular and Medical Pharmacology, University of Toyama
- **Phillip Mayeaux**, Director of Education and Professor of Pharmacology, University of Arkansas for Medical Sciences
- **Domenico Spina**, Reader in Pharmacology and Head of Pharmacology and Therapeutics, Pharmaceutical Sciences Division, King's College, London
- **Michael Williams**, Vice President, Worldwide Discovery Research, Cephalon, Inc.
- **David Weinshenker**, Associate Professor of Human Genetics, Emory University
- **Pat Mantyh**, Professor of Pharmacology, University of Arizona
- **Ben Yerxa**, Executive Vice President and Chief, Research and Development, Inspire Pharmaceuticals
- **Sridhar Mani**, Associate Professor in the Departments of Medicine and Genetics, Division of Oncology, Albert Einstein School of Medicine, was approved as a new member of the *Molecular Pharmacology* editorial board.

New Design for Online Journals

On November 9, ASPET's journals migrated to new web sites. The new look and layout resulted from research and testing on usability conducted by HighWire Press, ASPET's online hosting platform. This work included professional design review by iFactory and a usability-heuristics evaluation from Nielsen/Norman Group. ASPET's journals are among the earliest out of over 1,200 titles to be migrated by HighWire Press to the new site designs.

The new sites are more attractive and easier to navigate. The user interface is a flexible three-column design that places many features at the reader's service without taking attention away from the substantive page content. Features most closely associated with the page content are placed closest to it. The new functionality includes:

- *Abstract preview:* Mouse-over the table of contents and search results page and get an instant pop-up preview of the article abstract, without leaving the page.
- *Figure expansion in place:* Figure and table thumbnails can be enlarged from within the article.
- *Tag-along navigation:* The navigation box follows alongside as you scroll down the article page.
- *Feature hideaway:* Author affiliations, related links, and other article enhancements can be expanded or hidden. Your article enhancement preferences are remembered when you next visit the site.
- *Popular-articles list:* A list of the Most Viewed and Most Cited articles is readily available.
- *Related-articles search:* From within an article, you can click to search for articles by author, keyword, or subject classification.
- *Easier scanning and reading:* Better positioning of the title and abstract, improved text fonts and formatting, plus quick previous/next links to scan by article section make it faster to scan an article online.

As before, reference citations in text are linked to the references, but now the references also link back to where they are cited in the text. Printing a PDF is easier on the new sites—there is no need to close the window frame before printing. The different portions of the PDF viewing screen can be resized to suit the reader's needs. The new sites can be viewed with the web browser on iPhones and other smart phones.

As with any project of this size (ASPET has over 100 years of content on the *JPET* site alone), there have been some glitches. ASPET and HighWire staff have been working to identify and correct problems through extensive quality assurance testing. If you encounter any difficulties while using the online journals, please let us know using the "feedback" buttons located throughout each site.

All ASPET members get online access to the Society's five journals as a member benefit. The ASPET office will gladly help you activate your subscription so you can take advantage of this benefit. Contact us at info@aspet.org.

Public Affairs/ Government Relations

Visit ASPET's new web site at www.aspet.org for updated government and public affairs related matters of interest to pharmacologists. Hit the Advocacy/Policy Updates & News link on the Home Page to sign up for RSS feeds.

And remember to follow news on TWITTER: www.twitter.com/aspet

NIH Appropriations

FY 2010 spending decisions for NIH have yet to be finalized and Congress will likely pass a "minibus" package that will include as many as four appropriations bills including the Labor/HHS spending bill that funds the NIH. NIH's budget increase will fall at or within the range of the House and Senate bills, anywhere from 1.5% to 3.2%, both of which fail to bring the NIH back on track for genuine growth.

While FY 2010 has yet to be resolved, deliberations on the FY'11 budget are well underway within the White House. ASPET joined with many other research advocacy organizations cosigning letters of support to encourage President Obama to continue his commitment "to restore science to its rightful place," and for the historic short-term support for the NIH as evidenced by the $10 billion stimulus funds to the agency through the American Recovery and Reinvestment Act (ARRA). The President's funding decisions for NIH will be made by the end of this year. While the President's decision is not binding to Congressional appropriators, it carries significant influence, particularly this year if NIH is to maintain the research capacity and economic momentum that has been generated by ARRA funding. In November, ASPET asked all its members to contact President Obama at http://www.whitehouse.gov/contact to thank the President for his commitment to science and his inclusion of ARRA funding to help increase NIH's research capacity and to remind him of the need for a sustained commitment to NIH is needed.

As we begin advocacy efforts for FY 2011, it is important that ASPET members contribute to the collective effort of all biomedical research scientists. This effort is more critical than ever. A $1.5 million federal budget deficit is likely to rise significantly higher. A weak economy, health care reform and new spending on the war in Afganistan are creating tremendous pressure to restrict or cut the growth of many spending programs. The Wall Street Journal reported last week that Cabinet agencies are being asked to submit two budgets to the White House. One budget would freeze spending at current levels. The other budget would cut total spending by 5%. And Chairman of the House Appropriations Committee David Obey (D-WI) recently introduced legislation that would increase some taxes to help pay for the war effort. Obey's rationale is that if we are fighting a war in Afganistan, "at least we ought to pay for it, because if we don't then the cost of the Afgan war will wipe out every other initiative that have to try to rebuild our economy. That's what happened with the Vietnam War which wiped out the Great Society. That's what happened with the Korean War. In each case the costs of those wars shut off our ability to afford anything else. I think $900 billion over 10 years is going to put a huge dent in anyone's agenda." 2010 is also an election year raising the specter of deficit politics to an even greater degree.

For additional advocacy and policy information and how you can play a role in helping support a strong NIH, please visit the ASPET website at: http://www.aspet.org/advocacy/

ASPET-Advocacy Outreach Program

ASPET's advocacy outreach program will make a presentation at Vanderbilt on September 30. The purpose of this outreach effort is to educate and train graduate students, post-docs and faculty in pharmacology departments on the importance of grassroots advocacy in support of increased funding for the NIH. The ultimate goal of the outreach program is to 1) develop a cadre of interested individuals who will more effectively advocate on critical issues of science funding and science policy and 2) provide individuals the skills needed to become informed and proactive participants in these issues at whatever institution they may find themselves in the near future. ASPET has visited UT Southwestern, Emory University, and Wayne State for Michigan's Annual Research Colloquium. If there is an opportunity for ASPET to make a presentation in 2009 or 2010 at your institution, contact Jim Bernstein at <jbernstein@aspet.org>.

Summer 2010 Training Opportunity: NIGMS Summer Short Courses In integrative & Organ Systems Pharmacology

The National Institute of General Medical Sciences will again fund four summer short courses that provide specialized training for using intact organ systems and in vivo animal models in the conduct of research. The purpose of each short course is to introduce graduate students, post-docs, and Ph.Ds to the knowledge and skills needed for integrative studies of organ systems and intact animals, and the physiological and biochemical responses of these systems to drugs. These critical skills are in short supply and graduate students and Ph.Ds with these skills are in great demand in both academic and industrial settings. For additional information view:
http://www.aspet.org/Page.aspx?id=175&linkidentifier=id&itemid=175

ASPET-IOSS Fund Application Guidelines

The ASPET-IOSS Fund was created to provide support for graduate students and post-doctoral researchers seeking training in integrative, whole organ systems sciences. The fund is currently supported by Abbott Laboratories, Merck Research Laboratories, Pfizer, and Wyeth Research. The goal is to help augment training of students in this field. For details visit: http://www.aspet.org/Page.aspx?id=175&linkidentifier=id&itemid=175

Mid-Atlantic Pharmacology Society (MAPS)

Annual Meeting Report
November 2, 2009

Morning Session

The annual Mid-Atlantic Pharmacology Society (MAPS) conference was held on Monday, November 2, 2009, at the Temple University Health Sciences Center campus in Philadelphia, PA. The conference was co-hosted by Temple's Schools of Medicine and Pharmacy. Dr. Nae Dun, Professor and Chairman of Pharmacology at Temple Medical School, served as the host for the meeting and Dr. Peter Doukas, Dean of the School of Pharmacy, welcomed all participants. The conference was well attended by students, faculty and industrial scientists from the Delaware Valley area. The theme for this year was **"**Nuclear Receptors: From Evolution of Concept to State-of-the Art Research.**"** The meeting was officially opened by MAPS president Vincent Aloyo, PhD, Drexel University College of Medicine (below left) and Nae Dun, PhD, Temple University School of Medicine (below right).

This year, MAPS was fortunate to have two internationally acclaimed scientists in attendance to deliver the Distinguished Lecture and the Keynote Address. The Distinguished Lecture "*Alternative Approach; From the Swiss Alps to Nuclear Receptors"* was presented by Elwood Jensen, Ph.D, Distinguished University Professor, Vontz Center for Molecular Studies, University of Cincinnati Medical Center. Dr. Jensen began his presentation with a provocative description of how his adventure in tackling the challenges of scaling the Matterhorn at the age of 27, while he was a Guggenheim Fellow working in Zurich, Switzerland, inspired him to be creative and utilize alternative approaches to study the biology of steroid hormone interactions with cells. His pioneering work ultimately led to the discovery of the estrogen receptor in the 1970's. His research proved that estrogen and other hormones exert their effects by binding to a cytosolic protein which then forms a complex with the hormone. This hormone-receptor complex then migrates through the cytoplasm to the cell's nucleus where it can regulate gene expression.

Distinguished Lecturer, Dr. Elwood Jensen (center) being presented with the Distinguished Lecture plaque by Executive Secretary Dr. Jan Kitzen (left) while meeting host Dr. Nae Dun (right) looks on

Dr. Jensen describing his alternative approach to scaling the treacherous north slope of the Matterhorn

Bert W. O'Malley, MD, Tom Thompson Distinguished Service Professor of Molecular and Cellular Biology; Professor and Chairman, Department of Molecular and Cellular Biology, Baylor College of Medicine, presented the Keynote Address on *"Nuclear Receptor Coactivators: Physiology and Pathology."* His presentation reviewed his pioneering work on the molecular mechanisms of steroid hormone action and hormone receptors and coactivators which has had a profound impact on our knowledge of steroid hormones in normal development and in diseases, including cancer. Other speakers included Mitchell A. Lazar, MD, Ph.D; Sylvan H. Eisman Professor of Medicine & Genetics at the University of Pennsylvania, who presented an excellent overview of *"Nuclear Receptors and Metabolism."* One specific topic of interest he described included his recent findings on the peroxisome proliferator activated receptor (PPAR), a fascinating new receptor that is regulated by thiazolidinediones, a new class of anti-diabetes drugs. PPAR is a determinant of adipocyte (fat cell) differentiation, and thus represents a potential clue to the link between obesity and diabetes. His lecture also discussed his research on mechanism of corepressor recruitment, the composition and function of the corepressor complex, and what goes wrong in malignancy, especially myeloid leukemia.

Dr. Bert O'Malley beginning his Keynote Address

George B. Koelle Award

Each year, the organizers of the MAPS meeting honor the memory of the world-renowned local pharmacologist, the late George B. Koelle. The society selects one scientist (usually local) who most closely shares Dr. Koelle's enthusiasm for teaching and conducting outstanding research, to receive the George B. Koelle Award. This year's award was an especially emotional one as the award was presented to the late Dr. Michael Jaye, a molecular biologist at GlaxoSmithKline laboratories. Dr. Jaye's wife Mary Louise Homicki-Jaye and their son Andy Jaye accepted the posthumously awarded plaque.

Koelle Award winner, Dr. Michael Jaye

Dr. John Krawiec, colleague of Dr. Jaye, presenting the Koelle Plaque to Dr. Jaye's son Andy

Luncheon and Posters

The MAPS meeting always allows a generous time for the luncheon. Temple provided a delicious and varied buffet style luncheon that enabled the meeting attendees to enjoy a leisurely lunch while also having plenty of time to interact with students, guest speakers and other scientists, as well as to view the twenty-nine posters included in the poster session.

The poster session was comprised of presentations by undergraduates (9) and graduate students (16) as well as postdoctoral associates (5) from a number of colleges and universities. One student even traveled all the way from Storrs, Connecticut. MAPS councilor Dr. Srinivas Ghatta assembled an adequate number of highly qualified scientists to serve as poster judges so that there was plenty of time for each presenter to discuss their posters with the judges. Several prizes were awarded for the top two best posters in each of these divisions (see winners below). All poster winners received a cash award along with a copy of the textbook Pharmacology and Therapeutics - Principles to Practice, Expert Consult Premium Edition.

Combined poster session (top) and lunch allowed plenty of time for presentations and a leisurely lunch break (below)

Afternoon Session

Dianne R. Soprano, Ph.D Professor, Biochemistry; Fels Institute for Cancer Research and Molecular Biology; Temple University School of Medicine, opened the session with her presentation on *"Retinoic Acid Receptors: Mediators of Retinoid Action"*

Dr. Soprano described her research into the mechanism of action of retinoic acid (RA) at the molecular level. RA exerts its action by the transcriptional regulation of specific genes via a family of nuclear receptors called retinoic acid receptors, RARs, and retinoid X receptors, RXRs. The final presenter of the day was Sunil Nagpal, Ph.D, Director, Nuclear Receptor Biology, Tissue Repair, Wyeth Research (now Pfizer Research), with his presentation titled:*"Liver X Receptor: A Novel Therapeutic Target for Dermal Inflammatory Indications."* Dr. Nagpal described how Liver X receptors (LXRα and β) are liposensors that exert their metabolic effects by orchestrating the expression of macrophage genes involved in lipid metabolism and inflammation. To extend the potential use of LXR ligands, his laboratory explored the possibility of using LXR as a target for dermal inflammatory indications. He presented data demonstrating that an LXR ligand modulates multiple pathways underlying the etiology of skin aging, suggesting that LXR is a novel target for developing potential therapeutics for photoaging and chronological skin aging. His presentation provided new insights into the mechanism of LXR action in keratinocyte differentiation, lipid production and barrier formation, validated LXR as a potential therapeutic target for skin aging as well as atopic dermatitis, and in addition, identified LXR as a first-in-class target for psoriasis indication.

Poster Award Winners:

<u>Undergraduate Division</u> (Awards presented by MAPS councilor Dr. Ellen Walker)

1st Place: Carres Martinez, University of the Sciences of Philadelphia
Title: *Evaluation of MTT and BrdU Assays on Human Melanoma, Breast, and Prostate Cancer Cell Lines after Doxorubicin Treatment*

2nd Place: Kristen Much, Ursinus College
Title: *Mathematical Modeling and Sensitivity Analysis of Antibiotic Resistance*

Graduate Student/Research Associate Division (Awards presented by Dr. James Sidie, Ursinus College)

1st Place: Dafydd Thomas, Temple University School of Medicine
Title: *c-Cbl Negatively Regulates Platelet GPVI Signaling via an Interaction with the Histidine Phosphatase TULA-2 and Syk*

2nd Place: Igor Gurevich, University of Connecticut
Title: *Evidence for a Feedback Loop between Novel NR Coregulator TNIP1 and Retinoic Acid Receptors*

Postdoctoral/Recent PhD Division (Awards presented by MAPS councilor Dr. Robert Willette, GlaxoSmithKline)

1st Place: Daqing Zhang, Temple University School of Medicine
Title: *Hcy-Lowering Therapy Reduced Atherosclerosis and Abrogated Inflammatory Monocyte Differentiation Caused by Hyperhomocysteinemia*

2nd Place: Zhongjian Cheng, Temple University School of Medicine
Title: *Hyperhomocystinemia Aggravated Hyperglycemia-Induced Endothelial Dysfunction Via M-Calpain Activation*

Special Awards:

Past-president of MAPS, Ronald J. Tallarida, PhD, was presented with an award honoring his term of service as president. Many new improvements to MAPS meetings were incorporated during Dr. Tallarida's term as president.

Immediate past-president Dr. Ronald J. Tallarida (right) accepting his award from MAPS councilor Dr. Robert B. Raffa (left)

The final award presentation of the day was a special service award to MAPS Executive Secretary Jan M. Kitzen for his many years of service to the Society. Over the past 16 years Dr. Kitzen has served the Society as treasurer, councilor, vice president and president. During this time he also organized two of the Society's meetings (1993 and 2004).

Jan M. Kitzen (left) accepting the MAPS service award from Robert B. Raffa, PhD, past-president of MAPS and recipient of the Koelle award in 2006

The meeting concluded with a reception for all attendees held in Temple's recently opened new medical school building.

Acknowledgement: MAPS would like to acknowledge Fan Yang, MD/PhD Student, Department of Pharmacology at Temple University School of Medicine, for his willingness to serve as the photographer for the meeting. The Society also expresses its gratitude to MAPS councilor Dr. Carol Beck for obtaining the pharmacology textbooks distributed to all poster award winners.

Abstracts From the MAPS 2009 Meeting:

Category: Undergraduate

Evaluation of MTT and BrdU Assays on Human Melanoma, Breast, and Prostate Cancer Cell Lines after Doxorubicin Treatment. Carres Martinez*, Kathleen Galm, Adeboye Adejare, and Natalia Coleman*. Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, Philadelphia, PA 19104

The efficacy of a drug is partly determined by its ability to be absorbed and metabolized by the cell(s) of interest. Cell proliferation assays are designed to measure the growth and viability of cells based on a cell's ability to absorb and metabolize a particular reagent. Cancer remains the leading cause of death in the world. Over 100,000 estimated new cases of breast and prostate cases have been reported in the US in 2009. Therefore, the re-evaluation of the accuracy of cell proliferation assays in cancer drug discovery is vital for the fight against the overwhelming statistics of reported cases. Doxorubicin is active against many solid tumors, and is one of the most widely used anticancer drugs in current clinical practice. The aim of the present work was to evaluate MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) and BrdU (5-bromo-2`-deoxyuridine) proliferation assays on human breast (MCF-7), prostate (DU-145) cancer and melanoma cell lines (1205Lu) after 24 hours doxorubicin treatment.

***In vitro* Anticancer Properties of Novel Radiosensitizer Analogs.** Marlena Martin*, Zeynep Ates-Alagoz, Natalia Coleman, Aaron Wan, and Adeboye Adejare. Department of Pharmaceutical Sciences, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia, Philadelphia, PA 19104

A series of 9 compounds were designed as novel radiosensitizer analogs using bromonitropropiophenone and bromonitrobenzonitrile as lead compounds. These compounds were then synthesized in our laboratories. The goal of this study was to evaluate *in vitro* anticancer properties of these compounds using different cell lines. The cell lines chosen were MDCK which is a kidney cell line and two cancer cell lines, human prostate cancer (DU-145) and breast cancer (MCF-7). From the series, 6 compounds exhibited potent growth inhibitory effects against MDCK as well as cell both cancer cell lines. Compound 1, the most active of the 6 is an iodosulfone analog. It was tested at 100 µM and 10 µM dose levels on the DU-145 and MCF-7 cell lines. For DU-145 cell line, the treated cells exhibited 10% and 30% survival as compared to control at 100 and 10 µM of drug respectively. For MCF-7 cell line, survival was 7% and 9% respectively. This novel compound was then compared with doxorubicin. It was more active than doxorubicin at the dose level of 10 µM against both carcinoma cell lines at 24, 48, and 72 h time points, but less active at the dose level of 1 µM and less. The target compounds were designed to enhance cytotoxic effects of radiation. However, compound 1 was exhibiting anticancer properties even without the radiation. These results are very encouraging. Future studies include testing the compounds with radiation and *in vivo* studies.

Somatostatin Signaling in Neuronal Cilia Is Critical for Object Recognition Memory. David E. Melnikoff*, Emily B. Einstein[1], Carlyn A. Patterson[1], Beverly J. Hon[1], Kathleen A. Regan[1], Jyoti Reddi[1], Marcus J. Mateer[1], Stefan Schulz[2], Brian N. Johnson[1], and Melanie K. Tallent[1].[1]Dept. of Pharmacology and Physiology, Drexel University College of Medicine Philadelphia, PA 19102; [2]Department of Pharmacology and Toxicology, Friedrich-Schiller-University, D-07747 Jena, Germany

Mature central neurons possess single, non-motile primary cilia of unknown function. In sensory organs and kidney, primary cilia are important signaling organelles. In brain, cilia express a complement of proteins distinct from other neuronal compartments, one of which is the somatostatin receptor subtype SST_3, which exclusively localizes to these structures. We show here that SST_3 is critical for object recognition memory in mice. SST*3* knockout mice are severely impaired in their ability to discriminate familiar from novel objects. Further, systemic injection of an SST_3 antagonist (ACQ090) disrupts recall of familiar objects in wild type mice. *Sst3* knockout mice are not impaired in remembering spatial location of objects. To examine mechanisms of SST_3, we tested synaptic plasticity in CA1 hippocampus. Electrically-evoked long-term potentiation (LTP) was normal in SST*3* knockout mice, while adenylyl cyclase/cAMP-mediated LTP was impaired. The SST_3 antagonist also disrupted cAMP-mediated LTP. Basal cAMP levels in hippocampal membranes were reduced in *sst3* knockout mice compared to wild type mice, although the percentage increase of cAMP by forskolin was

not impaired. Our results show that somatostatin signaling in neuronal cilia is critical for recognition memory, and that signaling via cAMP is a conserved motif of cilia signaling. Neuronal cilia therefore represent a novel non-synaptic compartment crucial for signaling involved in a specific form of synaptic plasticity and in novelty detection.

Mathematical Modeling and Sensitivity Analysis of Antibiotic Resistance. Kristen Much*, Mohammed Yahdi; Ursinus College, Collegeville, PA 19426

Antibiotic resistance has been labeled by the CDC as a top concern that has increasingly become life threatening in hospitals, especially with the emergence of vancomycin-resistant enterococci (VRE). Mathematical models have been shown to be an effective tool to help investigate antibiotic resistance. The goal of this research is to construct a mathematical model of antibiotic resistance in the hospital environment using differential equations, and to conduct a sensitivity analysis to measure the impact of a variety of parameters. A new and elaborate model is introduced that includes three variables—patients with no bacteria, sensitive bacteria, and resistant bacteria, connected through a system of three nonlinear differential equations and twelve parameters, such as fitness cost and the rate of colonization. Realistic ranges of the parameters are determined from recent biological research studies. A computer program (*Mathematica)* is used to produce interactive simulations of the behavior of three variables as the parameters change separately or simultaneously. Equilibrium point analysis is done to describe the impact of parameters on the long term behavior of the spread of the antibiotic resistant infection and provide insight for the best infection prevention measures. Future plans include expanding the model to incorporate multiple drug resistance and stochastic differential equations.

Effect of General Anesthetic 1-Decanol on Temporal Stability of Brainstem Neural Network. Brandon,T.* and J.Sidie; Ursinus College, Collegeville, PA 19426

General anesthetics comprise a diverse array of compounds including fluorinated hydrocarbons, alkyl alcohols, nitrous oxide, barbiturates, xenon; all are characterized by some degree of lipophilicity. The brainstem neural circuit (medullary pacemaker nucleus) responsible for generating the electric organ discharge (EOD) in weakly electric fish is the most stable neural network (coefficient of variation =$2x10^{-4}$) known, in terms of temporal stability. This network was utilized to investigate the potency of the general anesthetic 1-decanol. Transparent knife fish (*Eigenmannia virescens*) are exposed to $1x10^{-4}$ decanol under varying temperature conditions. In addition, the effect of long-term temperature acclimation on anesthetic sensitivity was investigated. Fish were reared at 20°C, 25°C, and 30°C for up to 3 weeks and subsequently tested at these temperatures. The EOD_f is typically 350-450Hz for this species; for an individual fish the frequency is essentially invariant if temperature held constant. EOD signal is fed into NI DAQ device 6251 with 10mHz clock speed. On line signal processing for EOD frequency, standard deviation, coefficient of variation, and frequency interval histogram occurred continuously. CV was sampled over 1000 msec interval. Fish raised at 20°C and tested at 30°C produced maximal anesthetic potency for 1-decanol (EOD_f mean depression = 40-43%). Fish reared at 30°C and tested at 20°C were not as affected by decanol (EOD_f depression =11-19%). Fish reared at 30°C. and tested at 30°C produced EOD_f depression of 35-41%. If EOD_f is reduced (anesthetized state) by lowering temperature 30°C → 20°C, the coefficient of variation increased 0.000095→0.000161. If EOD_f is reduced by exposure to 1-decanol, compared to its value when fish is in deionized water, the cv increases 0.0001→0.0004 over the first 10 minutes of exposure. When fish are allowed to recover in absence of 1-decanol, cv returns to initial value. These data support the view that the pacemaker network's temporal stability is perturbed by anesthetic exposure and that the effect of 1-decanol is greater than the effect of temperature change over these limits. Molecular modeling studies of 1-decanol and related alkyl alcohols (hexanol→undecanol) examined ~80 parameters and revealed no remarkable correlation with anesthetic potency. However, neurobiological analysis of these alcohols demonstrated the importance of chain length (C10-optimal), OH-position (terminal position optimal), degree of saturation (unsaturation decreased potency), fluorinated (decreased potency), diols (ineffective). The aldehyde and carboxylic acid forms exhibit greatly reduced potency.

Supported in part by Merck/AAAS/Ursinus grant.

Responsiveness of microglia in the spinal cord regeneration of *Plethodon cinereus*. Caitlin Cook* and Ellen Dawley. Department of Biology, Ursinus College, Collegeville, PA 19426

Microglial cells are neural support cells that provide immunological assistance for the central nervous system (CNS). Under homeostatic conditions most microglia are found in a resting state, monitoring their local environments. Following CNS injury or infection, microglia become activated and migrate to the site of disturbance. Activated microglia are

phagocytes and clean up damaged neural tissue; this clearance of injured and dead tissue is an early and imperative step for neural regeneration in capable species. *Plethodon cinereus* (eastern red-backed salamanders) are amphibians that have retained the ability to regenerate spinal cord and can also autotomize, or detach, parts of their tails when provoked, making them interesting regenerative organisms for study. The role of microglia in the regeneration of autotomized tails was investigated in *Plethodon cireneus,* focusing on the time of activation, migration, and increased presence of microglia following CNS disturbance. *Lycopersicon esculentum* (tomato) lectin histochemistry was used to visualize the presence of microglia over a series of days following autotomization. Microglia were found in sections closer to the site of autotomization, supporting the expectations that microglia would appear closer to the site of injury to carry out their clearing and regenerative functions. The migration of microglial cells towards the site of autotomization was also visualized using longitudinal sections of tails. Microglial response to injury was noted two days following autotomization and lasted for at least twelve days. There was an elevated expression of microglia between three days post-autotomization until at least six days post-autotomization. Continual investigations may be able to determine approximately how soon after injury microglia respond to the CNS disturbance, when they appear to be most active, and when the number of activated microglia return to normal levels.

Organometallics in Biology: Mössbauer Spectroscopic Studies of the Iron Hydrogenases Model Complexes. Andrey Bilko*, Codrina Popescu, Ursinus College, Collegeville, PA 19426

Iron is the most abundant transition metal in biology, being an essential component of proteins that sustain life processes, from energy generation to DNA synthesis. For many microorganisms the highest yield of chemical energy is offered by the O_2 + H_2 reaction. For instance, *Escherichia coli*, molecular biologists' favorite organism, can generate energy by H_2 oxidation, by using sophisticated catalytic and electron transfer assemblies, called hydrogenases. Iron hydrogenases, which are the focus of this project, catalyze the reversible reaction for the production of molecular hydrogen, according to the equation: $2H^+ + 2e^- \rightarrow H_2$. In the past decade, x-ray crystallography and numerous spectroscopic methods have been used to reveal that the active site of iron-only hydrogenases (H-cluster) contains a 2Fe subcluster bonded to a [4Fe-4S] cluster. While the [4Fe-4S] cluster functions in the electron transport for the reduction of protons, molecular hydrogen is formed at the Fe atoms in the 2Fe-subcluster. This 2Fe subcluster has been the focus of investigation, including the development of model complexes, which mimic the structure and certain properties of the hydrogenases. Recently it has been recognized that all hydrogenase active sites, including the [Fe-Fe]- subcluster are organometallic complexes, namely Fe-carbonyl derivatives. More astoundingly, the dinuclear subcluster is thought to cycle through the Fe(I) state, which has been very rarely seen in chemistry. In the present study, Mössbauer spectroscopy is used to study mononuclear Fe(II), Fe(0), dinuclear Fe(I)Fe(I), and dinuclear Fe(I)Fe(II) compounds in order to establish the effect of ligands on isomer shift and determine parameters hyperfine interactions of the iron sites. This information is interpreted to gain insight into the electronic structure of the models. In particular, Fe(I) compounds with ligands other than the typical organometallic types (i.e. phosphines and CO), which are not known in the chemical literature and are considered highly improbable to occur in enzymes. Understanding the electronic structure of small-molecule Fe(I) compounds will shed light on the structure and mechanism of the hydrogenases.

Neurocognitive Correlates of the Development of Obsessive Compulsive Disorder and Attention Deficit/Hyperactivity Disorder. Amy Hartl*, Avinash Vaidya, Matthew Pall, and Joel Bish, Ph.D. Department of Psychology, Neuroscience Program, Ursinus College, Collegeville, PA 19426

Obsessive Compulsive Disorder and Attention Deficit/Hyperactivity Disorder are neuropsychological disorders characterized by deficient inhibitory capacities. This study examined the relationship between symptoms of OCD and ADHD with the inhibitory capacities of 80 adolescent children and young adults (36 male and 44 female) to determine whether a similar, significant lack of inhibition exists at subclinical levels of these disorders. A further purpose was to determine whether the effect, at subclinical levels, is specific to age group or certain types of inhibition. Twenty-two adolescent children (age 10-16 years) and 58 adults (age 17-23 years) completed self-report measures for OCD and ADHD and performed five computer-generated neurocognitive tasks, including a Color Stroop, an Eriksen Flanker, a Number Stroop, a Go/No-Go, and an Inhibitory Distance task. While a significant positive correlation between OCD and ADHD suggests co-morbidity, group differences for age were found where adults demonstrated significantly more symptoms for both disorders ($p<0.05$). Linear regressions within each age group yielded results showing that, in adolescents, OCD is best predicted by performance on simple response inhibition tasks while ADHD is best predicted by performance on comparative distracter tasks. In adults, performance on more cognitively demanding distracter/response inhibition tasks best predicted OCD, although no significant predictor was found for ADHD. These results suggest that

using neurocognitive tasks to test specific inhibitory abilities may lead to more accurate diagnoses of OCD and ADHD and aid in precise neurocognitive remediation to alleviate some of the developmental symptoms of these common disorders.

The Attachment of Acyclovir to Single Walled Carbon Nanotubes. Greg Lewis* and Mark Ellison. Ursinus College, Department of Chemistry, Collegeville, PA 19426

Purified single walled carbon nanotubes were oxidized through a series of several reactions to produce nanotubes with carboxylic acid functional groups. The carboxylic acid groups of the carbon nanotubes were then converted to acyl chloride groups, using thionyl chloride, before being reacted with the amine group of acyclovir to form amide bonds. Acyclovir is an anti-viral drug which targets the herpes simplex 1 virus. The attachment reaction was performed under varying sets of conditions in order to determine the optimal conditions for attachment. The variable reaction conditions included temperature, solvent, external stimuli and quantities of reactants. In addition to the functionalized carbon nanotubes and the acyclovir, the resultant acid formed during the attachment needed to be neutralized. The attachment of acyclovir to the carbon nanotubes was analyzed using FTIR-ATR spectroscopy. The IR spectra of acyclovir and of acyl chloride functionalized nanotubes were used as comparisons to reacted nanotubes to determine how effective the attachment was. Successfully attached nanotubes showed a spectrum similar to the acyl chloride functionalized nanotubes with major peaks between 3000cm^{-1} and 3500cm^{-1} caused by stretching of both N-H groups and O-H groups. Peaks around 2800cm^{-1} were caused by C-H stretching, and there is a major peak around 1710cm^{-1} indicative of carbonyl stretching. After successful attachment is determined, it is necessary to determine how effectively the amide bond can be broken in order for carbon nanotubes to be effectively used as a delivery system for acyclovir.

On the Dose-Dependent Nature Of Drug Self-Administration Maintained by Progressive Ratio (Pr) Schedules in C57 Mice: A Comparison of Cocaine, Morphine, Fentanyl and Remifentanil. H. Neelakantan*, J. Kim, E.A. Walker, and S.J. Ward. Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA

While cocaine self-administration maintained by progressive ratio (PR) schedule has been shown to be dose-dependent in rats, PR responding for morphine can be relatively independent of the dose. The dose dependent response to cocaine self-administration under a PR schedule is well established in mice; however, it has not been clearly demonstrated for morphine and other opioids. It is important to characterize the PR schedule of self-administration in mice as knock-out mouse self-administration models are often used as investigational tools. To observe if self-administration of morphine and shorter acting opiates was dose dependent in a similar manner to cocaine in C57 mice, intravenous self-administration of cocaine, morphine, and remifentanil and oral self-administration of fentanyl were examined across a range of doses under both an FR1 and PR schedules of drug reinforcement. Response rates maintained by FR1 responding and breakpoints maintained by PR responding were determined, and results indeed demonstrated that while FR1 responding for cocaine and opioids was dose-dependent, opioid self-administration under a PR schedule was relatively independent of dose in C57 mice. Results also suggest that shorter-acting opiates may provide better reinforcers for use in C57 mice to assess the motivational aspect of opioid self-administration. (Supported by NIH CA12909 to EAW)

Category: Graduate Student/Associate

c-Cbl Negatively Regulates Platelet GPVI Signaling via an Interaction with the Histidine Phosphatase TULA-2 and Syk. Dafydd H. Thomas[1*], Carol A. Dangelmaier[2], Jianguo Jin[2], Alexander Y. Tsygankov[3], Satya P. Kunapuli[1,2,4], & James L. Daniel[1,4]. Department of Pharmacology[1], Physiology[2], Microbiology and Immunology[3] and the Sol Sherry Thrombosis Research Center[4], Temple University School of Medicine, Philadelphia, PA

Glycoprotein VI (GPVI) is the major signaling receptor for collagen on the platelet surface. Clustering of this receptor by collagen leads to dual phosphorylation of the ITAM motif found in the intimately associated FcR chain by Fyn and Lyn. Syk is then recruited to the ITAM and undergoes rapid and robust phosphorylation. This leads to a signaling cascade that culminates in the activation of PLC2 followed by calcium mobilization and PKC activation leading to platelet activation. Recently, the adaptor protein and E3 ligase, c-Cbl, has been proposed as a negative regulator of GPVI signaling as potentiation of GPVI functional responses and Syk hyperphosphorylation have been reported in c-Cbl$^{-/-}$ platelets (Dangelmaier et. al. 2005 and Auger et. al. 2003). Therefore, we have investigated the role of the c-Cbl interacting histidine phosphatase, T-cell ubiquitin ligand-2 (TULA-2), in the c-Cbl mediated negative regulation of GPVI signaling. In

murine platelets deficient in TULA-2, we demonstrate enhanced GPVI mediated platelet aggregation and enhanced dense granule secretion, when compared to wild-type platelets. Additionally, a potentiation of calcium mobilization and a prothrombotic phenotype in the ferric chloride thrombosis injury model was observed TULA-2 deficient mice. In TULA-2 and c-Cbl deficient platelets a persistent hyperphosphorylation of Syk was observed following GPVI stimulation in contrast to a peak phosphorylation of Syk followed by dephosphorylation seen in wild-type platelets. Additionally, increased and persistent tyrosine phosphorylation of PLC□2 was observed in TULA-2 and c-Cbl deficient platelets. GST-pulldown experiments using phosphatase inactive TULA-2 demonstrated a GPVI agonist dependent interaction between Syk and TULA-2 while the association of c-Cbl with TULA-2 is constitutive. *In vitro* phosphatase assays indicate that Syk is a substrate for TULA-2. Taken together, these data suggest that c-Cbl negatively regulates GPVI signaling by coordinating the localization of Syk and the histidine phosphatase TULA-2 to allow dephosphorylation of Syk and therefore a reduction in its kinase activity.

Hyperhomocysteinemia Inhibits Endothelial Cell Growth in Hyperglycemia. Pu Fang*, Xiaohua Jiang, Xiaofeng Yang and Hong Wang. Department of Pharmacology, Temple University School of Medicine, PA 19140

Hyperhomocysteinemia (HHcy) is a risk factor for atherosclerosis in diabetic patients. However, the molecular and cellular mechanisms by which HHcy contributes to the development of diabetic vascular disease are not understood. Our previous studies demonstrate that HHcy inhibits endothelial cell (EC) growth. This contributes to endothelial dysfunction and leads to atherosclerosis. Here we study the effect and mechanism of HHcy effect on cultured human umbilical vein endothelial cell (HUVEC) growth in hyperglycemia. We find out that l-homocysteine (L-Hcy, 200 μM) significantly potentiates d-glucose (D-Glu, biologically active form, 30 mM) induced HUVEC growth inhibition, but not in the l-glucose (L-Glu, D-Glu control, can not be metabolized by cells in glycolysis) and mannitol (Man, D-Glu control, effective solute confined largely to the extracellular fluid compartment and contributing to both osmolality and tonicity) groups. Also, we previously report that HHcy with adenosine (Ade) can inhibit HUVEC growth via hypomethylation. Here we find out that L-Hcy (50 μM) with Ade (25 μM) significantly potentiate D-Glu imposed HUVEC growth inhibition. Therefore, we conclude that hypomethylation may be an important biochemical mechanism mediating HUVEC injury in HHcy related diabetes, and potentially contributes to the high prevalence of atherosclerosis in diabetic patients with HHcy.

CD25^{high} T Cells with a Prolonged Survival Inhibit the Development of Diabetes. Y. Yan, J. Mai*, E. Maley, H. Wang, and X-F. Yang. Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA 19140

CD4+CD25^{high}FOXP3+ regulatory T Cells (Tregs), making up 5-10% of peripheral CD4+ T cells, are a unique subset of T cells that have potent immunosuppressive functions and play an essential role in the suppression of autoimmunity. Deficiency in CD28 co-stimulation results in an 80% decrease in the number of Tregs, suggesting that CD28 signal-promoted pathway is critical for Treg survival. However, the mechanism underlying CD28 promoted Treg survival remains unknown. Type I diabetes is an autoimmune disease in which the immune system attacks beta cells of the pancreas resulting in cell death and a decrease in insulin production. Previous reports from our and others' teams showed that Tregs undergo apoptosis via a Bax-dependent pathway and that translationally controlled tumor protein (TCTP) is a Bcl-xL-interacting anti-apoptotic protein that inhibits Bax. In this study we examined two new hypotheses that the progression of diabetes is partially due to the weakened survival of CD25^{high} T cells and that prolonging CD25^{high} T cell survival can maintain Treg suppressive function and inhibit the development of diabetes. To test these hypotheses, a transgenic approach was used to determine whether CD28-upregulated TCTP can prolong the survival of CD4+CD25^{high} Tregs. We find that the TCTP transgene prevents Tregs from undergoing apoptosis induced by interleukin-2 (IL-2) withdrawal, dexamethasone, cyclophosphamide, and anti-Fas treatment *in vitro*. Additionally, TCTP transgenic Tregs express higher levels of FOXP3 than wild-type Tregs and their suppressive activity is maintained. TCTP transgenic Tregs inhibit the development of autoimmune diabetes due to increased survival of suppressive Tregs and decreased expression of pancreatic tumor necrosis factor (TNF)-α. Our results suggest that CD28 signaling promotes Treg escape from thymic negative selection by upregulating TCTP in Tregs and that prolonged survival of Tregs does not attenuate Treg suppressive activity. Our results lead us to propose a new model of "two phase survival" for Tregs, and demonstrate the proof-of-principle that prolonged Treg survival can significantly enhance a new Treg-based therapy in autoimmune diseases.

Three Tier Model for Inflammasome Expression and a New Concept of Inflammation Privilege. Ying Yin,* Fang Liu, Jietang Mai, Xiaohua Jiang, Xinyu Xiong, Michael Jean, Hong Wang, and Xiao-Feng Yang. Department of Pharmacology, Cardiovascular Research Center, Temple University School of Medicine, 3420 North Broad Street, MRB300, Philadelphia, PA 19140

Toll-like receptors (TLRs) and cytosolic nucleotide binding and oligomerization domain (NOD)-like receptors (NLRs) belong to the pathogen-associated molecular patterns' (PAMPs) receptor families (PAMP-Rs) and are initiators of inflammation driven by exogenous PAMPs and endogenous sterile tissue insults. However, the expression profiles of these newly identified TLRs, NLRs, inflammasome components, caspases, and interleukin (IL)-1β in vascular tissues have not been examined thoroughly. To test a new hypothesis that the tissue expressions of components in TLRs/NLRs/inflammasome/caspase-1/IL-1β pathway are differentially regulated at transcriptional levels, we examined the expression profile of those genes by analyzing the data from expression sequence tag (EST) cDNA cloning and sequencing. We made several important findings: (1) among 11 tissues examined, vascular tissues and heart express fewer types of TLRs and NLRs than immune and defense tissues including blood, lymph nodes, thymus and trachea; (2) brain, lymph nodes and thymus do not express proinflammatory cytokines IL-1β and IL-18 constitutively, suggesting that these two cytokines need to be upregulated in the tissues; and (3) based on the expression data of three characterized inflammasomes (NALP1, NALP3 and IPAF inflammasome), the examined tissues can be classified into three tiers – the first tier tissues including brain, placenta, blood and thymus express inflammasome(s) in constitutive status; the second tier tissues have inflammasome(s) in nearly-ready expression status (with the requirement of upregulation of one component); the third tier tissues, like heart and bone marrow, require upregulation of at least two components in order to assemble functional inflammasomes. To further confirm our model, we examined the mRNA levels of inflammasome components in human aortic endothelial cells when stimulated with endotoxin lipopolysaccharide (LPS). Our results indicated that in the presence of LPS stimulation, the mRNA levels of the main inflammasome component including ASC, caspase-1, NALP-1 and NALP-3 are upregulated, which supports our three-tier model. Our original model of three-tier expression of inflammasomes would further suggest a new concept of tissues' inflammation privilege, and provides an insight into the differences among tissues in initiating acute inflammation in response to stimuli.

Tissue Homocysteine Metabolism and Methylation are Regulated by Enzyme Expressions in Human and Mouse Tissues. Natalie C. Chen*[1], Fan Yang[1], Louis M Capecci[1], Ziyu Gu[1], Andrew I. Schafer[2], William Durante[2], Xiao-Feng Yang[1], Hong Wang[1]. [1]Department of Pharmacology and Centers of Cardiovascular Research and Thrombosis, Temple University School of Medicine, Philadelphia, PA, 19140, [2]Department of Medicine, Weill Cornell Medical College, New York, NY 10065, [3]Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, MO 65212

Hyperhomocysteinemia is an independent risk factor of cardiovascular disease and the metabolism of homocysteine involves multiple enzymes. Tissue homocysteine metabolism and its relevance to methylation remain unknown. We established gene expression profiles of 8 homocysteine metabolic and 12 methylation enzymes in 20 human and 19 mouse tissues through bioinformatic analysis using EST clone counts in tissue cDNA libraries. We analyzed the correlations between gene expression and homocysteine, *S*-adenosylhomocysteine(SAH), *S*-Adenosylmethionine(SAM) levels, as well as SAM/SAH ratios in mouse tissues. Homocysteine metabolic and methylation enzymes were classified into two types. The expressions of Type-1 enzymes are positively correlated with tissue Hcy and SAH levels. These include cystathionine β-synthase, cystathionine-γ-lyase, paraoxonase 1, 5,10-methylenetetrahydrofolate reductase, betaine:homocysteine methyltransferase, methionine adenosyltransferase, phosphatidylethanolamine N-methyltransferases and Glycine N-methyltransferase. Type-2 enzyme expressions correlate with neither tissue Hcy nor SAH levels. These include SAH hydrolase, methionyl-tRNA synthase, 5-methyltetrahydrofolate: Hcy methyltransferase, S-Adenosylmethionine decarboxylase, DNA methyltransferase 1/3a, protein S-isoprenylcysteine and HMT. SAH is the only methylation metabolite significantly correlated with homocysteine levels and methylation enzyme expression. We established equations expressing combinatory effects of methylation enzymes on tissue SAH, SAM, and SAM/SAH metabolism. Our study is the first to provide panoramic tissue gene expression profiles and to provide mathematic models of tissue methylation regulation.

Pattern Identification Of Transcriptional Regulation Of Homocysteine-Induced Genes In Monocytes Using Database Mining. Shu Meng[1,2*] , Stephen Ciment[1,2], Michael Jan[1,2,3], Hung Pham[1,2], Xiao-Feng Yang[1,2], and Hong Wang[1,2,3.] [1]Department of Pharmacology, [2]Cardiovascular Research Center, [3]Sol Sherry Thrombosis Research Center, Temple University School of Medicine, Philadelphia, Pennsylvania 19140

Hyperhomocysteinemia (HHcy) is an independent risk factor for cardiovascular disease; however the underlying mechanisms remain unclear. Our recent study showed that HHcy increased inflammatory monocyte/macrophage accumulation in atherosclerotic lesions and accelerated atherosclerosis in Tg-hCBS Cbs-/- Apoe-/- mice fed a high fat diet. To test how homocysteine (Hcy) activates monocytes and which transcription factors are involved in the process, we identified 14 genes whose mRNA levels were up-regulated by Hcy in cultured peripheral mononuclear blood cells (PMBC) or monocyte cell lines via literature search. Using the same strategy, we identified 17 genes and 10 genes that were up-regulated by IL-10 and TNFα, respectively, as the inflammatory responsive gene controls. Four house-keeping genes were randomly selected as the internal controls. We analyzed the occurrence frequency of the binding sites of 32 transcription factors (TF) in promoter region, defined as 1000 bp upstream of the transcription start site. We found that 5 transcription factors, including heat shock factor (HSF), forkhead (FOX), myocyte enhancer factor-2 (MEF2), nuclear factor of activated T-cells (NFAT) and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), have significantly increased frequency in Hcy and TNFα up-regulated genes, compared with that in the housekeeping genes and IL-10 up-regulated genes. Among the 5 TF shared by HHcy and TNFα-induced genes, NFκB and NFAT are well established inflammatory responsive transcription factors. We hypothesize that transcription factors HSF, FOX, and MEF2 are mediator of Hcy-induced inflammatory response in the monocytes. In summary, we identified similar binding patterns of 5 TF in the promoter region of HHcy and TNFα-induced genes in monocytes. HHcy may use similar transcriptional machinery to activate monocytes, which in turn facilitates accelerated atherosclerosis.

Identifying Transcription Factors Mediating Homocysteine Pathology in Human Endothelial Cells. Michael Jan[1,2,3*], Hung Pham[1,2*], Shu Meng[1,2], Stephen Ciment[1,2], Xiao-Feng Yang[1,2], and Hong Wang[1,2,3.] [1]Department of Pharmacology, [2]Cardiovascular Research Center, [3]Sol Sherry Thrombosis Research Center, Temple University School of Medicine, Philadelphia, Pennsylvania 19140

Cardiovascular disease (CVD) and its subsequent complications are the leading causes of death in developed countries. Elevated plasma homocysteine (Hcy) levels have been established as a significant independent risk factor for CVD, though its mechanism remains largely unknown. We have shown previously that Hcy inhibits endothelial cell (EC) growth through DNA hypomethylation and consequent gene expression regulation. In this study, we endeavored to determine the relationship between genes modulated by Hcy in human EC. We compiled a list of genes transcriptionally-regulated by Hcy in human EC from an extensive literature search. The University of Pennsylvania's Transcription Element Search System (TESS) was used to determine transcription factor (TF) binding sites on the genes' putative promoters defined 5000bp upstream of the transcription start site. We found that specific TFs – CCAAT-enhancer-binding protein (C/EBP), glucocorticoid receptor (GR), nuclear factor of activated T-cells (NFAT), and ETS-1/2 – have more binding sites on genes modulated by Hcy as compared to housekeeping controls. We then examined the difference between Hcy-upregulated genes and Hcy-downregulated genes. The upregulated genes had significantly increased binding sites for C/EBP, GR, heat shock factor (HSF), NFAT, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and ETS-1/2, whereas downregulated genes had increased binding sites for C/EBP, GR, and ETS-1/2. In order to study the potential effects of DNA hypomethylation on transcription regulation, we identified CpG islands (DNA methyltransferase binding sites) in the promoter within 2000bp upstream of the transcription start site using the University of Southern California's CpG Island Searcher. TESS was used to analyze transcription factor binding sites in the CpG islands. We found four TFs with significantly increased binding sites in the CpG islands of Hcy-modulated genes – C/EBP, cAMP Response Element Binding Protein (CREB), early growth response protein 1 (EGR-1), and NFAT. Among them, EGR-1 had increased binding sites only in Hcy-downregulated genes, but not in Hcy-upregulated genes. Our data is consistent with the confirmed role of CREB in mediating Hcy pathology and successfully translates our novel bioinformatic approach from screening genetic information to predicting biological function. We show that DNA methylation may be the key mechanism mediating Hcy-modulated gene regulation in EC. Further, C/EBP, EGR-1, and NFAT may be the effector sites for Hcy-induced DNA hypomethylation. Our results and novel methodology provide a systematic approach for elucidating pathways and possible therapeutic targets relevant to Hcy pathology in EC.

Caspase-1 recognizes extended cleavage sites in its natural substrates. Jerry Shen*, Ying Yin*, Jietang Mai, Erin Maley, Hong Wang, and Xiao-Feng Yang. Department of Pharmacology, Cardiovascular Research Center, Temple University School of Medicine, 3420 North Broad Street, MRB 300, Philadelphia, PA 19140

The preferred amino acids in the proteolytic sites have been considered to be similar between caspase-1 and caspase-9. However, the similarity does not support their differential functions since caspase-1 activation leads to inflammatory cell death (pyroptosis) while caspase-9 activation results in non-inflammatory apoptosis. To solve the problem, we tested a new hypothesis that caspase-1 cleavage sites are different from that of caspase-9 cleavage sites. We analyzed the 20 amino acid residues flanking the cleavage sites in 34 caspase-1 and 11 capase-9 experimentally identified substrates. This study has made the following findings: (1) we verified that caspase-1 and caspase-9 shared a 100% stringently conserved aspartic acid residue in the P1 position – however, the structures in the cleavage sites of most caspase-1 substrates are different from that of caspase-9 substrates with respect to *a)* the amino acid residues with frequencies statistically higher than the confidence intervals of the amino acids in human proteins, *b)* the hydrophobic amino acid occurrence frequencies, and *c)* the charged amino acid occurrence frequencies; (2) the amino acid pairs P1-P1' used in the caspase-1 substrates are different from that of caspase-9 substrates; (3) our identified cleavage site patterns are useful to predict 91.4% of cleavage sites of 35 new caspase-1 substrates. Since most caspase-1 substrates are involved in vascular function, inflammation and atherogenesis, our novel structural patterns for the caspases' substrates are significant in developing new detection tools, diagnostics and therapeutics for the pathology in which caspases are involved.

Design and Expression of Recombinant σ-conotoxin GVIIIA. Lisa Hernandez-Cuebas* and Michael White. Drexel University College of Medicine, Department of Biochemistry and Molecular Biology, Philadelphia, PA 19104

Conotoxins (CTX's) are small (≤ 41 amino acids) disulfide-rich peptides found in the venom of predatory cone snails of the genus Conus. There are ~500 species of cone snails, each containing >100 different CTX's, giving rise to >50,000 unique CTX's. Various CTX's are inhibitors of voltage- and ligand-gated ion channels, and provide a rich array of probes for studying these channels. In addition, several CTX's targeted at different channels are in clinical trials as potential therapeutic agents for the treatment of chronic pain. σ-CTX GVIIIA is a 41 amino acid peptide with five disulfide bonds isolated from the venom of Conus geographus. It is a high-affinity competitive antagonist of the serotonin (5-HT) $_{3A}$ receptor, a cys-loop ligand-gated ion channel. σ-CTX GVIIIA can be used to probe the residues involved in ligand recognition by the 5-HT_{3A} receptor. Our goal was to produce a soluble recombinant σ-CTX GVIIIA to be used in structure-function studies, because purifying large quantities of it from the natural source is difficult. We created a periplasmic secretion vector in order to produce soluble recombinant σ-CTX GVIIIA in E. coli. This vector has protein disulfide isomerase A (DsbA) fused to a 6-His tag and small ubiquitin-like modifier (SUMO). We sub-cloned a synthetic σ-CTX GVIIIA gene, optimized for *E.coli* codon usage, into this vector. The fusion protein, DsbA-His-SUMO-conotoxin GVIIIA was expressed in *E.coli* and purified by immobilized metal affinity chromatography (IMAC). The fusion partner (DsbA-His-SUMO) was cleaved by a SUMO specific protease and removed by subtractive IMAC. Mass spectroscopy suggests that the product is σ-CTX GVIIIA. We are in the process of characterizing the properties of this recombinant protein.

Evidence for a Feedback Loop between Novel NR Coregulator TNIP1 and Retinoic Acid Receptors. Igor Gurevich*, Carmen C. Zhang, Charles P. Struzynsky, Brian J. Aneskievich; Dept. of Pharmaceutical Sciences, School of Pharmacy, University of Connecticut, Storrs, CT 06269

Transcriptional control by nuclear receptors (NRs) is mediated not only through their ligands but also through coregulator proteins which act either as coactivators or corepressors of NR activity. In searching for potentially new coregulators, we performed a yeast two-hybrid screen using a human epidermal keratinocyte cDNA library. Here we describe interaction of retinoid receptors with TNIP1, one of the most frequently occurring isolates in our screen. While epidermal keratinocytes express several NRs, retinoid receptors are of particular interest because of their targeting by pharmacologic retinoids used in treatment of epidermal cancers and other hyperproliferative disorders. Thus, the studies of retinoid receptor interaction with coregulators and control over coregulator expression could add to our basic understanding of retinoid receptor activity in such cases. TNIP1 amino acid sequence revealed the presence of two NR boxes suggesting it may be a coregulator. TNIP1 does not interact with RXRalpha but associates with RARalpha and RARgamma in a ligand dependent fashion. RAR-TNIP1 interaction is controlled partially by TNIP1 NR boxes and partially by an extended region in the middle portion of the coregulator not matching any canonical NR Box motifs. As expected from partial reliance on

coregulator NR boxes, RAR-TNIP1 interaction is entirely dependent on the receptor AF-2 domain. While these interaction requirements are suggestive of a coactivator, TNIP1 represses RARalpha and gamma activity in the presence of ligand. This makes TNIP1 an unusual coregulator – a corepressor of agonist bound NRs. Repression is partially relieved by coactivator SRC1, suggesting interference with coactivator recruitment as a mechanism of TNIP1 action. TNIP1 does not associate with histone deacetylase (HDAC) enzymes, suggesting the TNIP1 repression is HDAC-independent. With this atypical function, we sought to determine what might contribute to control of TNIP1 expression. We carried out *in silico* analysis of its promoter to identify putative transcription factor binding sites which predicted several retinoic acid response elements. Transcriptional activation studies revealed that TNIP1 promoter is positively regulated by RARs. EMSA showed RAR binding at distinct sites in the distal portion of TNIP1 promoter. Promoter-luciferase reporter studies confirmed these as response elements. Our findings reveal a potential regulatory feedback loop where TNIP1 expression is increased by RARs which, in turn, attenuates their activity. Such feedback loops between coregulators and their target NRs may serve to buffer cells against extremes of hormone-regulated signaling, such as the presence of toxic ligand levels, or cells being exposed to ligand at inappropriate times.

Species Differences in 5-HT$_{2A}$ Receptor Regulation Following Chronic Agonist and Antagonist Administration. John P. Dougherty*, John A. Harvey, Vincent J. Aloyo. Pharmacology & Physiology, Drexel University College of Medicine, 245 N. 15th St., Philadelphia, PA 19102

The serotonin (5-HT) 2A receptor is a relevant target in numerous diseases and disorders and plays a role in many physiological functions. Transgenic mice may yield novel models for disease, but to use them and improve the therapeutic potential of the 5-HT$_{2A}$ receptor, it is critical to understand how the receptor is normally regulated in the mouse. Current receptor theory states that chronic agonist treatment should result in a decrease in receptor density. This is the case for 5-HT$_{2A}$ receptors in both rats and rabbits. The effect of chronic agonist treatment in mice, however, has not been evaluated. In the current study, adult male C57BL/6J mice received injections of 5-HT$_{2A}$ receptor agonists (lysergic acid diethylamide [LSD] [0.3 µmol/kg or 0.03 µmol/kg], 2,5-dimethoxy-4-iodophenyl-2-aminopropane [DOI] [2.8 µmol/kg]) or vehicle for 8 days. Mice were sacrificed 24 hours after the final injection and their cortices were removed and frozen until assayed. Receptor density was determined through saturation binding assays with [^{3}H]ketanserin. In keeping with results obtained in other species, mice given chronic DOI displayed decreased cortical 5-HT$_{2A}$ receptor density. Similar to findings in rats, chronic LSD-treated mice displayed decreased 5-HT$_{2A}$ receptor density when a 0.3 µmol/kg dose. The lower dose of LSD (0.03 µmol/kg), however, did not alter mouse cortical 5-HT$_{2A}$ receptor density, despite downregulation occurring in rabbits at that dose. In contrast to current receptor theory, which states that chronic antagonist treatment should result in an increase in receptor density, 5-HT$_{2A}$ receptors exhibit a paradoxical down-regulation in rats and rabbits. Chronic treatment with two 5-HT$_{2A}$ receptor antagonists, SR 46349B in the rodent and MDL 11939 in the rabbit, however, results in up-regulation of cortical 5-HT$_{2A}$ receptors. To determine if mice respond similarly to rats or rabbits, we treated mice with MDL 11939 (10 µmol/kg) for 4 days, a dose and duration sufficient to significantly increase 5-HT$_{2A}$ receptor density in the rabbit. No change in cortical 5-HT$_{2A}$ receptor density was observed in mice following chronic MDL 11939 treatment, which suggests a difference in mouse 5-HT$_{2A}$ receptor regulation from other species. Our study is the first to examine the effects of chronic administration of these compounds on 5-HT$_{2A}$ receptor regulation in mice and provides a reference for future studies of 5-HT$_{2A}$ receptor regulation using transgenic mice.

Repeated Exposure to a Stressful Environment Differentially Regulates 5-HT$_{1A}$ and 5-HT$_{2A}$ Receptors. Laura Scarlota*, John A. Harvey, Vincent J. Aloyo. Pharmacology & Physiology, Drexel University College of Medicine, Philadelphia, PA 19102

Serotonin (5-HT) receptors have been implicated in mental disorders including post-traumatic stress, depression, and anxiety. In the current study, we investigated the role of 5-HT$_{2A}$ and 5-HT$_{1A}$ receptors in anxiety by observing the behavioral response of rabbits exposed to a novel stressful environment. Initial placement in an open field elicits head bob behavior in rabbits which can be attenuated by pretreatment with an anxiolytic (5-HT$_{1A}$ partial agonist, buspirone) or a 5-HT$_{2A}$ antagonist (M100907). This suggests open field-elicited head bobs are mediated by inhibition of 5-HT$_{1A}$ and activation of 5-HT$_{2A}$ receptors. The current study provides further support for this hypothesis since a second 5-HT$_{2A}$ receptor antagonist, ketanserin (3µmol/kg) and a full 5-HT$_{1A}$ receptor agonist, 8-OH-DPAT (0.9µmol/kg), also significantly attenuated acute open field head bobs. To measure the effects of chronic stress, 5-HT$_{2A}$ receptor-mediated behavior was compared in rabbits repeatedly placed in the open field (1hr/day for 6 days) to those kept in their home cage. On day 7, a 5-HT$_{2A/2C}$ receptor agonist, 2,5-dimethoxy-4-iodoamphetamine (DOI, 0.3umol/kg), elicited significantly more head bobs in the open field group compared to home cage controls. In both, pretreatment with ketanserin (1µmol/kg) reduced DOI-

elicited head bobs to the same extent suggesting open field exposure causes behavioral sensitization of 5-HT_{2A} receptors. Measurement of frontocortical 5-HT_{2A} receptors by saturation binding with [^{3}H]ketanserin revealed no significant difference between the groups indicating upregulation of 5-HT_{2A} receptors was not responsible for the behavioral effect. To examine the role of 5-HT_{1A} receptors, binding assays using a 5-HT_{1A} receptor antagonist, [^{3}H]MPPF were performed. Open field exposure did not alter either affinity or density as measured with [^{3}H]MPPF. Conversely, assays using an agonist, [^{3}H]DPAT, revealed changes in both parameters, suggesting possible effects on receptor coupling. To measure receptor function, [^{35}S]GTPγS assays were conducted and there was a diminished response to 8-OH-DPAT in the open field group, suggesting 5-HT_{1A} receptors were desensitized which could account for the enhanced behavioral response to DOI. These results have implications not only for anxiety and stress but also for schizophrenia. Since hyperactivity of the 5-HT_{2A} receptor may play a role in affective disorders, and stress can exacerbate symptoms of the disease, the current findings involving reciprocal regulation of 5-HT receptors following stress may lead to future therapeutics targeting both 5-HT_{2A} and 5-HT_{1A} receptors.

Pharmacological Distinctions Between LSD and DOI Elicited Behavior in Rabbits. Schindler EA*, Aloyo VJ, Harvey JA. Drexel University College of Medicine, Department of Pharmacology & Physiology, 245 N. 15th Street, Philadelphia, PA 19102

Hallucinogen-elicited stereotypy has long been used to model human psychosis. In the behavioral model of rabbit head bobs (HBs), both lysergic acid diethylamide (LSD) and 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) elicit HBs. Previously we found lasting tachyphylaxis of DOI, but not LSD, HBs in rabbits recovering from chronic DOI treatment. In order to determine the source of this disparity, we examined the biochemical and behavioral pharmacology of LSD and DOI. Frontocortical tissue of naïve rabbits was used to measure receptor binding affinities through displacement of tritiated ligands, and PI hydrolysis through release of [^{3}H]inositol-4-phosphate. For behavioral studies, rabbits were injected with LSD (0-100nmol/kg) and observed for HBs. Other rabbits were injected with various antagonists 1hr prior to LSD (30nmol/kg) injection. For tolerance studies, rabbits were treated with LSD (30nmol/kg) once daily for eight days, sacrificed two to eight days after last injection, and frontocortical tissue harvested for receptor density and PI hydrolysis analysis. Other groups of LSD-treated animals were challenged with either DOI (300nmol/kg) or LSD (30nmolkg) and observed for HBs. LSD binds to frontocortical serotonin2A (5HT2A) and dopamine1 (D1) receptors with higher affinity than DOI. DOI only has micromolar D1 affinity. Both LSD and DOI induce PI hydrolysis in frontocortical tissue, but only the DOI signal is 5HT2A-mediated. Like DOI, LSD dose-dependently elicits HBs in rabbits, which are blocked by D1 receptor antagonism. In contrast, 1umol/kg of 5HT2A antagonist, ketanserin, blocks DOI HBs, but 10umol/kg is required to inhibit LSD HBs. Chronic LSD treatment, like DOI treatment, leads to frontocortical 5HT2A down-regulation and decreased DOI HBs. Unlike DOI treatment however, neither LSD HBs nor frontocortical PI hydrolysis is decreased in the recovery period after LSD treatment. These findings suggest different pharmacological origins for LSD and DOI HBs. The inability of ketanserin to block LSD-induced PI hydrolysis and the high dose of ketanserin required to block LSD HBs suggest a non-5HT2A mechanism. The 5HT2A down-regulation without behavioral desensitization after chronic LSD treatment further minimizes the importance of 5HT2A. In addition, both LSD and DOI HBs contain a D1 component, but only LSD binds D1 receptors with appreciable affinity. Thus, we suggest that DOI HBs occur through direct 5HT2A and indirect D1 activation, while LSD HBs occur through direct activation of D1 and possibly 5HT2A receptors. This raises the importance of receptor- and enzyme-specific roles in the hallucinogenic effect, which will be the focus of future studies.

Category: Postdoctoral/Recent PhD

Regulatory T Cells Suppress Vascular Inflammation. Zeyu Xiong, Fang Liu*, Hong Wang, Xiao-Feng Yang. Department of Pharmacology, Cardiovascular Research Center, Temple University School of Medicine, 3420 North Broad Street, MRB 300, Philadelphia, PA 19140

The inflammatory autoimmune responses play an important role in accelerating the pathogenesis of atherosclerosis. CD4+CD25^{high}Foxp3+ regulatory T cells (Tregs), which are dependent on interleukin-2 (IL-2) for survival, suppress autoimmune responses. Recent reports indicated that reduction of Tregs is associated with progression of atherosclerosis. However, the mechanism underlying Treg reduction during atherogenesis remains unknown. In this study, we examined a novel hypothesis that insufficient supply of IL-2 in an autoimmune setting may reduce Treg survival by upregulating the expression of pro-apoptotic proteins. We have made several important findings. Bax, a prototypic proapoptotic protein that is induced via a p53-dependent transcriptional mechanism, is upregulated in Tregs but not in

CD4+CD25- effector T cells after IL-2 withdrawal as detected by FACS analysis.. To determine whether upregulated Bax in Tregs is functional in promoting Treg apoptosis, we established a Treg-specific Bax transgenic mouse model (Bax Tg). Treg apoptotic rates, triggered by IL-2 withdrawal in Bax Tg, are significantly increased compared to wild-type mouse Tregs. Higher susceptibility of Tregs to apoptosis during IL-2 withdrawal is associated with downregulated expression of Bax-counteracting, anti-apoptotic translationally controlled tumor protein (TCTP). To determine whether down-regulation of TCTP in Tregs leads to enhanced Treg apoptosis, we constructed a Treg-specific TCTP antisense transgenic mouse model (TCTP-AS Tg). Similarly, Treg apoptotic rates, triggered by IL-2 withdrawal in TCTP-AS Tg, are significantly elevated than that in wild-type mouse Tregs. Reduced survival of Tregs in Bax Tg and TCTP-AS Tg promotes vascular inflammation in the femoral artery induced by cuff placement. Our results have demonstrated for the first time that in addition to inhibiting adaptive immunity, Tregs also suppress acute vascular inflammation, which is mainly constituted by innate immunity and inflammatory mechanisms and that modulation of IL-2-dependent survival pathway in Tregs, regulated by expression of Bax and TCTP, could be used as a new therapeutic approach for inflammatory cardiovascular diseases and atherosclerosis.

Hcy-Lowering Therapy Reduced Atherosclerosis and Abrogated Inflammatory Monocyte Differentiation Caused by Hyperhomocysteinemia. Daqing Zhang [1,3*], Xiaohua Jiang[1], Jodene K Moore[1,7], Remus M Berretta[2], Andrew I Schafer[4], William Durante[5], Warren D. Kruger[6], Steven R Houser[2], Xiaofeng Yang[1,2], and Hong Wang[1,2*]. [1]Department of Pharmacology and Thrombosis Research Center, [2]Cardiovascular Research Center and Temple University School of Medicine, Philadelphia, PA, 19140, [3]Department of Cardiology, Shengjing Hospital of China Medical University, Shenyang, PR. China, [4]Department of Medicine, Weill Cornell Medical College, New York, NY 10065, [5]Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, MO 65212, [6]Division of Population Science, Fox Chase Cancer Center, Philadelphia, PA19111,[7] Department of Systems Biology, Harvard Medical School, Boston MA 02115

Background: We recently reported that hyperhomocysteinemia (HHcy) selectively enriches circulating Ly-6C^{hi} monocytes independent of hyperlipidemia. Here we examined the therapeutic effects of Hcy-lowering on inflammatory monocyte differentiation and atherosclerosis. **Methods and Results:** We established a mouse model of HHcy and hyperlipidemia by crossing cystathionine β-synthase (CBS) and LDLr deficiencies. The *CBS*$^{-/+}$*LDLr*$^{-/-}$ mice were lethally irradiated and reconstituted with bone marrows from EGFP transgenic mice at the age of 8 weeks. Mice were fed a high fat (HF), HF/high methionine (HM) or HF/HM/high vitamin (HV, a high B6/12 and folate diet for Hcy-lowering therapy) at the age of 14 weeks for another 8 weeks. Severe HHcy was induced in mice on HF/HM (Hcy, 275.6 μM) compared with the control mice on HF diet (Hcy, 10.1μM), and abolished in mice on HF/HM/HV diet (39.0 μM). Severe HHcy increased atherosclerotic lesion and enriched Ly-6C^{hi+mid} monocytes subsets in *CBS*$^{-/+}$ *LDLr*$^{-/-}$ mice. Hcy-lowering therapy reduced Ly-6C^{hi+mid} monocytes, which was closely correlated with atherosclerotic lesion (r=0.685, p=0.02). In EGFP chimeric *CBS*$^{-/+}$*LDLr*$^{-/-}$ mice, severe HHcy accelerated atherosclerosis with enhanced BM-derived Ly-6C positive monocyte/macrophage accumulation by morphological analysis. Furthermore, severe HHcy increased BM-derived and resident monocyte accumulation and maturation in aorta by flow cytometry analysis on whole aortic cell suspension. Moreover, BM-derived and resident Ly-6C^{hi+mid} monocyte subset differentiation and Ly-6C^{low} accumulation in aorta were increased in severe HHcy. Importantly, Hcy-lowering therapy significant prevented above phenotypes that HHcy induced lesion, monocyte differentiation on the vessel wall. Meanwhile, severe HHcy increased plasma TNF-α and IL-6 levels, the Ly-6C^{hi+mid} monocytes enriched by Hcy was mainly responsible for TNF- α and IL-6 productions. Using modified Boyden Chamber system, L-Hcy increased THP-1 monocyte transmigration through human aortic endothelial cells. Additionally, sorted Ly-6C^{hi} and Ly-6C^{mid} monocyte subsets exhibited higher transmigration capacities through primary mouse aortic endothelial cells. Finally, L-Hcy enhanced rIFNγ-induced Ly-6C^{hi+mid} monocyte differentiation, which was abolished by SOD plus catalase, and NAD (P) H oxidase inhibitor apocynin. **Conclusion:** Severe HHcy increased inflammatory Ly-6C^{hi+mid} monocyte expansions leading to systemic inflammation. Severe HHcy exacerbated atherosclerosis and enriched BM-derived and resident Ly-6C^{hi+mid} monocytes in the aorta. Hcy-lowing therapy prevented atherogenesis and differentiation of both BM-derived and vessel resident inflammatory monocytes. HHcy-induced inflammatory monocytes differentiation is, at least in part, ascribed to NAD(P)H oxidase mediated superoxide anion production.

Homocystine Induced Apoptosis in Endothelial Cells via Caspase 1 Activation. Hang Xi *[1], Daqing Zhang [1], Andrew I. Schafer [2], William Durante [3], Xiaofeng Yang [1], Hong Wang [1]. [1]Department of Pharmacology, Cardiovascular Research Center, Thrombosis Research Center, Temple University School of Medicine, Philadelphia, PA, 19140, [2] Department of Medicine, Weill Cornell Medical College, New York, NY 10065, [3] Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, MO 65212

Hyperhomocysteinemia (HHcy) is an independent risk factor for cardiovascular diseases (CVD), diabetes and Alzheimer's disease. We have reported previously that homocystine (Hcy) inhibits endothelial cells (ECs) growth and impairs endothelium recovery after injury leading to accelerated atherosclerosis. Here, we reported that Hcy induced apoptosis in human umbilical vein endothelial cells (HUVEC) in the absence and presence of lipopolysaccharides (LPS), a marker of endotoxemia and a powerful risk factor for atherosclerosis. We found that DL-Hcy (0.75~2.25mM) and L-Hcy (0.1~1.25mM) significant reduced cell viability in a dose dependent manner by crystal violet staining assay. L-Hcy (0.5mM) appeared to be more potent and reduced cell viability to 64.3% of control as 100%. DL-Hcy and L-Hcy potentiated LPS (10μg/mL) resulted cell viability reduction dose sensitively. Using Annexin V staining via FACS analysis and TUNEL staining, we found that L-Hcy (0.5mM) induced apoptosis in the absence and presence of LPS. These are associated with increased caspases 1, 8, 9 and 3 activities. Interestingly, caspase 1 activation was observed at 1 hr of Hcy treatment, and lasted till 24 hr. Whereas, caspase 8, 9 activations appeared at 6hr and caspase 3 at 12hr after cells were treated with L-Hcy and LPS. We conclude that Hcy induced EC apoptosis via caspase 1 activation followed by caspases 8, 9 and 3 activations in the absence and presence of LPS. Caspase 1 mediated caspase cascade may mediate ECs apoptosis, contribute to impaired endothelium recovery after injury and accelerated atherosclerosis in HHcy.

Bone Marrow Derived CD34$^+$ Progenitor Cell Therapy Improved Reendothelialization in Cystathionine-β Synthase Deficient Mice. Jun Zhou*[1]; Xiaohua Jiang[1]; Yi Wu[2]; Remus Berretta[3], Steven Houser[3], Warren D. Kruger[4], Andrew I Schafer[5]; William Durante[6]; Xiaofeng Yang[1,2]; Hong Wang[1,2,3]. [1]Department of Pharmacology, [2]Thrombosis Research Center and [3]Cardiovascular Research Center and, Temple University School of Medicine, Philadelphia, PA, 19140. [4]Division of Population Science, Fox Chase Cancer Center, Philadelphia, PA19111. [5]Department of Medicine, Weill Cornell Medical College, New York, NY 10065, [6]Department of Medical Pharmacology and Physiology, University of Missouri, Columbia, MO 65212

Delayed reendothelialization contributes to restenosis after angioplasty. We have reported that hyperhomocysteinemia (HHcy) impaired post-injury reendothelialization leading to increased neointima formation. Here, we examined the effect and mechanism of HHcy on endothelial progenitor cells (EPC), and evaluated the therapeutic role and of bone marrow (BM)-derived CD34$^+$ EPC on reendothelialization using arterial injury in cystathionice-β synthase (CBS) diffident mice. Severe HHcy (Hcy, 140μM) was induced in CBS$^{-/+}$ mice by a high methionine (HM) started at the age of 8 weeks for another 8 weeks. Carotid artery air-dry endothelium denudation procedure was performed at the age of 12 weeks. BM-derived CD34$^+$ EPC from EGFP transgenic mice was transfused (2X10^6 cells/mouse) immediately after carotid artery injury. EPC population was determined by flow cytometry analysis using antibodies against CD34 and VEGFR2. Severe HHcy reduced EPC from 2.13±0.46% in the control mice to 1.19±0.26% in HHcy mice (p=0.02) in the BM. EPCs therapy improved endothelial repair from 50.1±9.3% to 64.5±6.1% in severe HHcy (p=0.006) and from 72.7±10.4% to 79.9±17.2% (P=0.023) in the control mice 7 days after injury. Homocysteine (Hcy, 200-1000 μM) inhibited proliferation and adhesion of primary EPC isolated from human peripheral blood in a dose dependent fashion. In summary, severe HHcy suppresses EPC population in the BM and impairs post-injury endothelial repair. EPC therapy improves post-injury reendothelialization. HHcy suppresses EPCs, at least in part, via inhibiting EPC proliferation and adhesion.

Hyperhomocystinemia Aggravated Hyperglycemia-Induced Endothelial Dysfunction Via M-Calpain Activation Zhongjian Cheng[1*], Xiaohua Jiang[1], Stanislav Sidorov[1], Pu Fang[1], Rosario Scalia, William Durante[2], Xiaofeng Yang[1], and Hong Wang[1], [1]Temple University School of Medicine, Philadelphia, PA 19140, [2]University of Missouri School of Medicine, Columbia, MO 65212

Background: Accumulated evidence demonstrated a strong positive correlation between plasma homocysteine (Hcy) concentrations and cardiovascular mortality in diabetic patients. In this study we examined the effects of hyperhomocysteinemia (HHcy) on hyperglycemia-induced endothelial dysfunction (ED) using a mouse model of type 1 diabetes. Methods and Results: Moderate and severe HHcy (Hcy, 30.2 and 256.4 μM) were induced in male cystathionine beta-synthase (CBS)-deficient mice (CBS$^{+/+}$ and CBS$^{-/+}$) mice fed a high methionine diet (2%). Hyperglycemia was generated by consecutively injections of streptozotocin (STZ, 60 mg/kg/day, i.p., 3 days) in CBS$^{+/+}$ and CBS$^{-/+}$ mice

(glucose, 438.4 and 436.6 mg/dl). Endothelium-dependent relaxation to acetylcholine (ACh) was significantly impaired in the aorta from hyperglycemic and severe hyperhomocystinemic mice. Severe but not moderate HHcy significantly aggravated hyperglycemia-induced ED. Endothelium-independent relaxation to sodium nitroprusside was not changed in all groups. HHcy-potentiated ED in hyperglycemia was completely normalized by preincubation of the aorta with polyethylene glycol superoxide dismutase (PEG-SOD) plus catalase (catalyze the decomposition of H_2O_2), apocynin (an inhibitor of NAD(P)H oxidase) and calpain—calcium-dependent cysteine protease inhibitors (MDL28170, ALLM and calpeptin). Furthermore, we found that μ-calpain activity was significantly increased in the aorta isolated from hyperglycemic and severe HHcy mice, which was synergistically promoted in mice with both hyperglycemia and severe HHcy. High glucose (HG, 25mM, 48 h) incubation also increased μ-calpain activity in the aorta from wild type mice, which is significantly potentiated by Hcy (500 μM). Hcy-potentiated μ-calpain activity was reversed by coincubating the vessels with PEG-SOD plus PEG-calatase or apocynin. Furthermore, Hcy and HG treatment independently and synergistically induced NADPH oxidase activity in aorta and cultured HAEC. Calpain inhibitor MDL28170 coincubation prevented Hcy or/and HG induced NADPH oxidase activation. Finally, urinary level of 8-isoprostane, a vasoconstrictor and antinatriuretic arachionic acid metabolite produced by oxidative stress, was markedly increased in severe HHcy or hyperglycymic mice, which was synergistically enhanced in mice with both conditions. In summary, our study indicates that NADPH oxidase mediated μ-calpain activation contributes to HHcy-induced ED in hyperglycemic condition. Conclusions: HHcy potentiates hyperglycemia-induced ED via μ- calpain activation.

Category: Other

A Novel Method to Measure Cardiomyocyte Hypertrophy by Electrical Impedance. Pu Qin[1], Alexander Alford[1], Thimmaiah P. Chendrimada[1], Teg Pipes[1], John Upson[1], Victoria Ballard[1], Indira Carey[2], Jason Maas[2], Robert Willette[1], Erding Hu[1]. *[1]Heart Failure DPU, Metabolic Pathway CEDD, GlaxoSmithKline, King of Prussia, PA 19406. [2]Roche Applied Biosciences, Indianapolis, IN 46250*

Pathological cardiomyocyte hypertrophy is one of the major underlying mechanisms that cause heart failure. Traditionally, cardiomyocytes hypertrophy is examined by a number of methods such as ^{3}H-thymidine incorporation, cell size by immunostaining, ANP mRNA expression and protein secretion. Recently, a novel assay was developed to examine electrical impedance of cells cultured on 96-well plates. The impedance of electricity flow from anode to cathode on the bottom of the well is proportional to the area that is covered with cells. This assay is currently used to measure cell attachment, proliferation and apoptosis in a label-free and real-time fashion. We hypothesized that this assay can also be used to measure cardiomyocyte hypertrophy. Neonatal rat ventricular myocytes were seeded onto the impedance assay plate. We observed a gradual increase in impedance when these cells are attaching to the plate. The impedance measurements leveled off after about 24 hrs. Upon stimulation with pro-hypertrophic growth factors such as endothelin-1, $PGF_{2\alpha}$ and phenylepherine, impedance measurements further increased which suggested that cells further increased in size. This increase in impedance was dose-dependent and can be blocked by antagonists such as Prazosin. Impedance measurements correlated extremely well with traditional measures of hypertrophy such as ANP mRNA and protein levels which was performed at the end of the study. The EC_{50} of phenylepherine and IC_{50} of Prazosin calculated by all methods were very close to each other and also consistent with published data. In summary, our studies established a novel assay to measure cardiomyocyte hypertrophy in a label-free and real-time manner.

MEMBERS IN THE NEWS

Garret A. Fitzgerald, MD, is one of 65 recently announced new members of The Institute of Medicine (IOM). Election to the IOM is considered one of the highest honors in the fields of health and medicine and recognizes individuals who have demonstrated outstanding professional achievement and commitment to service. New members are elected by current active members through a highly selective process that recognizes individuals who have made major contributions to the advancement of the medical sciences, health care, and public health.

Evan D. Kharasch, MD, PhD has been named interim vice chancellor for research at Washington University in St. Louis. The appointment was effective July 20. As interim vice chancellor, Kharasch will be the chief officer responsible for the University's research mission, overseeing an enterprise that generates more than $500 million for sponsored research from a wide array of funding sources. He will become the institutional official responsible for all compliance programs that oversee the University community's adherence to guidelines governing laboratory animal care and use and research involving human volunteers. His areas of oversight also will include the development of research policies, management of grants and contracts, the continuing education of faculty and staff regarding research regulations, issues related to conflict of interest and research integrity, and intellectual property and technology transfer.

STAFF NEWS

Talia Goldman, has joined ASPET's Journals Department as Editorial Assistant. Talia is responsible for coordinating peer review for JPET, reviewing new submissions for adherence to journal formatting requirements, and posting accepted manuscripts in the journal's Fast Forward section of the website. She also handles emails pertaining to the review and submission process. Talia recently graduated from the University of Maryland, College Park, where she majored in Classics and English.

Laine Cocca, has joined ASPET as the Manager of Accounting Operations. Laine is currently working on bringing ASPET's accounting in-house and will oversee all functions of ASPET's accounting once the new system is in place. Laine comes to ASPET from the American Federation of Teachers, where she spent 5 years in the accounting department. She now brings her skills and expertise to ASPET as we all look forward to an improved accounting process. In her spare time, Laine enjoys watching sports and playing the piano.

Erin Salb, has joined ASPET's Journals Department as Editorial Coordinator for Drug Metabolism and Disposition. Her responsibilities include managing the whole peer review process, including moving papers through the online system, interacting with authors, editors, and readers, posting Fast Forward articles, and communicating with our printing vendor. Erin comes to ASPET from Cadmus Communications, where she was a Journal Production Manager. In her spare time, she enjoys playing softball and plays on several local teams.

Rhonda Frankenfield resigned from ASPET as the Editorial Coordinator for Drug Metabolism and Disposition on November 16, 2010. After 8 years with ASPET, Rhonda is moving on to take some time off work and to help plan her children's weddings. Although she is not currently seeking employment, she hopes to eventually find something closer to her hometown of Frederick, MD. We wish Rhonda all the best and will miss her at the office.

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Your Announcements, Promotions, Achievements, and News

Please send us your news, along with a picture to:

Suzie Thompson, sthompson@aspet.org

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Jacqueline Radwan, Central Michigan Univ
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Joyce Wong, Univ of California - Davis
Wendi Yang, Oberlin College

ASPET notes with sympathy the passing of the following members:

Krishna C. Agrawal, PhD

Ellsworth B. Cook, PhD

Erminio Costa, MD

Ira W. Hillyard, PhD

Gabriel L. Plaa, PhD

Richard F. Riley, PhD

Manjeet Singh, PhD

Paola S. Timiras, MD, PhD

Vincent G. Zannoni, PhD

OBITUARY

Ira W. Hillyard, PhD (1924-2009)

Dr. Ira W. Hillyard, a long-time member of ASPET died Sunday, November 15, 2009.

Ira William Hillyard was born March 23, 1924 in Richmond, Utah, the second child of Neal Jacobsen and Lucille Duce Hillyard. He married Venice Lenore Williams, July 10, 1945 in Logan, Utah. She died, February 20, 1967. He married Norma Larsen, May 1, 1970 in Pocatello, Idaho. He was the father and step-father of five sons (Kevin I. and Eric T. Hillyard; James R., Jesse P. and Ritchie A. Marziale) and six daughters (E. Christine Hillyard; Sharon, Darlene, Charlene, Cynthia, and Kaylene Marziale).

Ira graduated from Idaho State College (Pocatello) in 1949 with a BS in Pharmacy and an interest in drug development research. This led him to graduate programs in the, then, relatively new medical science of Pharmacology. He received an MS in Pharmacology from the University of Nebraska in 1951; and the PhD in Pharmacology and Physiology from the Saint Louis University School of Medicine in 1957. His mentors were Dr. Harald G.O. Holck, at Nebraska, Dr. Erwin Nelson and Dr. Len Procita.

Dr. Hillyard devoted his professional life to the search for new drugs, and to the teaching of effective drug therapy to students of medicine and pharmacy. He conducted successful research programs for The Mead Johnson Company, Evansville, Indiana (1957-1959); The Warner Lambert Research Institute, Morris Plains, NJ (1959-1969), and, The ICN Company, Irvine, CA (1973-1976). His teaching positions were in the School of Medicine of Saint Louis University (1951-1957), and the College of Pharmacy of Idaho State University (1969-1973; 1977-1991). He also served this college as the Director of the Idaho Drug Information and Poison Control Center (1977-1979); as a special assistant to the Dean (1978-1979) and, as its Dean (1979-1986).

Ira also served in the U.S. Navy Hospital Corp during WW II (1943-1946) and, again, during the Korean War (1951-1952). His WW II service was spent with The Fleet Marine Forces in the South Pacific and, more specifically, with the 4th Marine Division where he was a field medic during their engagements against Japan on the islands of Roi/Namur, Saipan, Tinian and Iwo Jima. He was twice wounded and received two Purple Hearts.

Dr. Hillyard was a member of several professional societies and fraternal organizations including: The American Society of Pharmacology and Experimental Therapeutics, The Western Pharmacology Society, The New York Academy of Sciences, The American Association of Colleges of Pharmacy, Sigma Xi, Rho Chi, Phi Delta Chi, Phi Kappa Phi and Phi Lambda Sigma fraternities, The Idaho State Pharmaceutical Association, The Idaho Society of Hospital Pharmacists, The Pocatello Rotary Club, The American Legion and The Military Order of the Purple Heart.

His numerous professional recognitions include listings in: Who's Who in America, Who's Who in the West, The International Who's Who in Medicine and The Outstanding Educators of America. He also received the 1991 Distinguished Pharmacy Alumni Award from Idaho State University and the Pharmacy Teacher of the Year Award, also in 1991. His research and scholarly contributions were presented in numerous oral and written presentations. The latter includes approximately fifteen published reports of his research work, six extensive reviews and two teaching aids (Lecture Guide and Laboratory Manual for teaching pharmacology to pharmacy students).

Submitted by Kevin Hillyard, Sandy, UT

OBITUARY

Gabriel L. Plaa, PhD (1930 – 2009)

Dr. Gabriel Leon Plaa, a prominent educator and toxicologist, died of cancer in Montreal, Canada. He was 79 years of age.

Gabriel L. Plaa was born May 15, 1930 in San Francisco to immigrants from France and thus French was his first language. He graduated from the University of California in 1952 with a B.Sc. in criminalistics. As a veteran of the Korean War, Dr. Plaa returned to the University of California for graduate studies in criminalistics. While attending a course taught by Dr. Charlie Hine, he was given the choice of remaining a graduate student in criminalistics without a stipend, or becoming a graduate student in pharmacology and toxicology with a stipend. Dr. Plaa became a toxicologist, earning his M.Sc. in 1956, and his Ph.D. in 1958 in Comparative Pharmacology and Toxicology with Dr. Charlie Hine as his mentor.

Dr. Plaa was an instructor and assistant professor at Tulane University from 1958-1962, and then was assistant and associate professor at the University of Iowa from 1962-1968. In 1968, Dr. Plaa moved to the University of Montreal where he was Chairman of Pharmacology for 12 years. Over the years, he held other administrative positions at the university including Vice-Dean of Research and Graduate Studies, all the while conducting an active research program. The University of Montreal acknowledged his achievements and named him Professor Emeritus in 1996. In 2003, on the occasion of the 125th anniversary of its founding, the University of Montreal recognized Dr. Plaa as one of the pioneers of the institution.

Dr. Plaa was extraordinarily charitable with his time for the advancement of science nationally and internationally. He served on various scientific committees for the SOT, NIH, ASPET, STC, MRC, NAS, FASEB, WHO, IUPHAR, and IUTOX. He was on the editorial board of nine scientific journals, served as Associate Editor of *TAP, ASPET*, and *CJPP*, and was Editor of *TAP* from 1972-1980. Dr. Plaa was President of the STC (Canada) (1981-1983) and SOT (1983-1984).

Dr. Plaa's research focused on chemical-induced liver injury. With his Ph.D. dissertation, he was the first scientist to study hepatotoxicity using an isolated perfused liver. He made significant contributions in the 1) dose-response characteristics of hepatotoxicity, 2) catecholamines and carbon tetrachloride hepatotoxicity, 3) dye clearance technique for assessing hepatic function, 4) potentiation of haloalkane hepatotoxicity, 5) ANIT-induced cholestasis, 6) the manganese-bilirubin model of cholestasis, and 7) potentiation of chemically- induced cholestasis. Dr. Plaa published 233 peer-reviewed manuscripts, wrote 48 chapters and literature reviews, and edited five books. He received the first Achievement Award from the SOT (USA) in 1967, an award which recognizes promising young scientists. That recognition was affirmed when in 1996 he received the Society's highest award, the Merit Award which recognizes career length contributions to the science and profession of toxicology. In the intervening years he received the Arnold Lehman Award (1981) for his use of sound scientific principles in risk assessment and regulation of chemicals, and the Education Award (1987) for his teaching and training of toxicologists. Similarly in Canada, he received from the STC the VE Henderson Award (1969), the STC Award of Distinction (1984), and was named honorary president of ICT-XI in Montreal (2007).

Dr. Plaa had high expectations, first for himself and then for those he related to; he relayed these expectations with a witty sense of humor that was inspiring and stimulating. Dr. Plaa summarized his scientific career in an article entitled "A four-decade adventure in experimental liver injury" published in *Drug Metabolism Reviews* 29: 1-37, 1997 in which he concluded "the most satisfying 'results' of my research program are not the data or new observations acquired, but the graduate students and fellows with whom I collaborated over a span of nearly 40 years. I am forever grateful for their precious presence and participation in my laboratory." Gabbie's influence in training toxicologists was extraordinary. Two of his Ph.D. students later received Achievement Awards from the SOT (Klaassen and Charbonneau), and five graduate students in the pharmacology-toxicology program during Gabbie's six years at the University of Iowa were later elected Presidents of SOT (Dixon, Gibson, Hook, Klaassen, and McClain).

Dr. Plaa retired from the University of Montreal in 1996. During the last 13 years of his life, he cared for his wife, Colleen, who has multiple sclerosis, much as she cared for Gabbie during his decades in science. Gabbie was also the loving father of eight children, Ernest, Steven, Kenneth, Gregory, Andrew, John, Denise, and David, as well as a grandfather of eight.

Gabbie Plaa had an enormous influence on his children, his "academic children," as well as the entire toxicology community. We all will miss him, but his contributions to society will survive us all.

Submitted by Curtis D. Klaassen, PhD, University of Kansas Medical Center

OBITUARY

Erminio Costa, MD (1924-2009)

Erminio (Mimo) Costa, an expert in the field of neuropsychopharmacology, died Saturday, November 28, from complications of multiple myeloma. Dr. Costa is survived by his wife Ingeborg Hanbaur and sons Michael and Max. His son Robert, passed away on September 1, 2006, from pancreatic cancer.

Dr. Costa was born in Cagliari, Italy and obtained an MD from the University of Cagliari, graduating *magna cum laude* in 1947. This was the start of an enduring career in the fields of pharmacology and neuroscience. He continued his studies at the University, attaining the rank of Associate Professor (in 1948) and Professor of Pharmacology by 1954. In 1956, Dr. Costa joined the Thudichum Research Laboratory in Galesburg, Illinois, and studied under the direction of Drs. Harold Himwich and Murray Aprison in the neurochemistry laboratory. It was here that he was first exposed to clinical psychiatry at a time when chlorpromazine and its analogues became the standard of treatment for patients with schizophrenia. It was also during this period his passion for experimental neuropsychopharmacology was born. While presenting his work at a national meeting in 1958, Dr. Costa first met Dr. Bernard B. Brodie, considered by many to be the father of modern pharmacology. Dr. Brodie subsequently recruited Dr. Costa to the National Institutes of Health where he became first a staff member and then Deputy Chief of the National Heart Institute's Laboratory of Chemical Pharmacology at the National Institutes of Health (NIH). In 1965, Dr. Costa joined Columbia University in New York as Director of Pharmacology of the W. Black Center for the study of Parkinson's disease and three years later was asked to return to NIH, where he founded and for 17 years directed the prestigious Laboratory of Preclinical Pharmacology (LPP) of the National Institutes of Mental Health at St. Elizabeth's Hospital in Washington, D.C.

In 1985 at the age of 61, Dr. Costa founded and became Director of the Fidia-Georgetown Institute for the Neurosciences (FGIN) and Professor in the Departments of Anatomy and Cell Biology and Pharmacology at Georgetown University, Washington, D.C. (1985-1994). Here, he recruited a handful of scientists each with their own expertise to create a program that was truly multi-disciplinary. While each Lab Director was in charge of a research program, Dr. Costa oversaw the efforts and directed an often multifaceted approach to experimental neuroscience. At its height, FGIN employed 65 scientists from all over the world. Prior to the advent of the internet, Dr. Costa and his colleagues implemented a Neuroscience Fax newsletter which was transmitted across the globe in an effort to reinvent how neuroscience findings might be communicated on a faster time scale.

During his career, Dr. Costa mentored numerous young scientists and made significant contributions to the field of neuropharmacology. Along with Dr. Brodie and numerous other eminent scientists, Dr. Costa was one of the founding members of the American College of Neuropsychopharmacology. Along with Professor Philip Bradley, University of Birmingham England, he shared the Chief Editor position for the Journal Neuropharmacology for some 27 years. In 1982, Dr. Costa was elected to the National Academy of Sciences (USA) and he maintained an active presence. Dr. Costa always considered scientific dialogue and rigorous analysis of scientific data to be integral to both the training of junior scientists and the driving force for experimental design. During this time, the ‘Monday morning’ scientific meeting at which current research was presented by a member of the staff, became a tradition that would be carried into the next twenty years of his career. In 1988, together with Nobel Prize Laureates Rita Levi-Montalcini and Gerald Edelman, Dr. Costa founded and directed The International School of Neuroscience in Praglia, Padua, Italy. This school brought cutting-edge neuroscientists to a large audience of graduate students to expose them to the newest advances in the field. In addition to his accomplishments as a leader in the field of neuropharmacology, he championed the cause of neuroscience as a field second to none and without international boundaries. In 1991, Dr. Costa organized the Symposium on Molecular Neurobiology, sponsored by the National Academy of Sciences (USA) and the Academy of Sciences (USSR), held in Kiev, USSR. This effort allowed for the exchange of research data between scientists of the Soviet Union and the United States to foster international dialogue between researchers with similar interests. During his years at NIMH and later as Director of Fidia Georgetown Institute for the Neurosciences, Dr. Costa organized numerous world-renowned symposia and lecture series (the FIDIA Research Foundation Award Lectures in Neuroscience and Fidia Research Foundation Symposium Series). For many years, these were held as symposia satellites to the Annual Meeting of the Society for Neurosciences. From 1991 until 1996, Dr. Costa was a representative of the U.S. National Committee for IBRO. He was the driving force in organizing the "IBRO-SANS-USNC International Neuroscience Course on Neurotransmitter and Receptors" held at Rhodes University, Grahamstown, South Africa (1996).

In 1994, Dr. Costa became McDonnell Visiting Professor in Neurology at Washington University in St. Louis, MO, and Director of the Center for Neuropharmacology at the Nathan S. Kline Institute (NKI) for Psychiatric Research, Orangeburg, NY. In 1996, Dr. Costa was approached by Dr. Boris Astrachan to direct a research program in the Department of

Psychiatry at the University of Illinois Chicago (UIC). At age 72, Dr. Costa rose to the challenge and recruited a team of top scientists including his long-time friend and co-worker, Dr. Alessandro Guidotti. Dr. Costa focused on research into the causes of the psychiatric disease of schizophrenia. His efforts were the first to provide experimental evidence that the origins of schizophrenia might be epigenetic in nature. From 1996 until recently, Dr. Costa directed the Psychiatric Research Institute at UIC and his contributions revealed important insights into our understanding of this insidious disease.

Dr. Costa's enthusiasm and ability to translate scientific hypotheses into successful experiments were contagious for all his collaborators—more than 300 in 60 years, from countries such as China, Japan, Russia, Afghanistan, Pakistan, India, and Nigeria, to a large number of European and Middle Eastern countries. His students always, even years after they had left his laboratories and been appointed to prestigious University positions, greatly valued his mentorship. Dr. Costa had an exceptional lifelong scientific career completely dedicated to discovery in neuroscience. His leadership and fostering of international scientific exchange has had a great impact in modern neuroscience for which he will long be remembered. During his recent retirement party (October 21, 2009), well over one hundred scientists representing every continent attended to honor their mentor. During his long career, Dr. Costa authored over 1,000 manuscripts in prestigious scientific journals.

Dr. Costa had an exceptional lifelong scientific career whose achievements in science, leadership, and fostering of international scientific exchange continue to have a great impact in modern neuroscience. He will be fondly remembered by his former students, collaborators and peers.

Scientific Accomplishments

Dr. Costa scientific achievements, of unique breadth and depth, stem from his innovative and rigorous approach to tackling scientific issues. Dr. Costa was recognized with numerous awards for his contributions over the years, which have always been at the forefront of research in neuroscience and particularly in neuropsychopharmacology. His pioneering studies on serotonin in the human brain (1958) have been and are still followed by numerous other researchers. These scientists subsequently confirmed his initial reports on the multiplicity of serotonin receptors. His studies on serotonin established that this neurotransmitter was a target for the action of antidepressant and antipsychotic drugs. He introduced mass fragmentography as an innovative method that allowed the study of neurotransmitter steady-state levels and turnover rate in discrete rat brain nuclei, an index of specific neuronal system activation. This opened a new path to probe the mechanism of action of psychotropic drugs *in vivo*. In the early 1970's, Dr. Costa revealed the role of cyclic AMP in the transsynaptic induction of tyrosine hydroxylase via a cascade of molecular cytosolic and nuclear events triggered by the activation and nuclear translocation of protein kinase A. These studies were among the first to show a regulatory action of cyclic AMP in the transcriptional activation of a specific gene and currently this mechanism is considered to play an important role in the pathophysiology of depression and in the mechanism of dependence on drugs of abuse. He first proposed and discovered that the $GABA_A$ receptor is the target of anxiolytic benzodiazepines (1974). From these pioneering studies, he explored the mechanisms of $GABA_A$ receptor allosteric modulation and regulation that led to the discovery of the molecular mechanisms underlying benzodiazepine tolerance and dependence. As it applies to benzodiazepines, endogenous peptides, and neurosteroids acting on the $GABA_A$ receptors, his demonstration of drugs acting as allosteric modulators was fundamental to our appreciation of the structural heterogeneity of $GABA_A$ receptors. In addition in the past few years, this discovery was expanded as a conceptual framework to probe the regulation and pharmacology of receptors for other neurotransmitters.

Given the poor results and numerous side-effects associated with current neuroleptics, during the last fifteen years Dr. Costa dedicated his efforts to finding better pharmacological treatments for schizophrenia. Typical for him, he took an innovative path. He and his colleagues established that reelin, an extracellular matrix protein that controls the correct positioning of neurons in laminated structures of the brain, continues to be expressed in the telencephalon and hippocampus of adult mammals where it is synthesized and secreted by GABAergic interneurons. Reelin binds to integrin receptors expressed in dendritic spine postsynaptic densities and as result of this binding, increases protein synthesis locally in dendritic spines, thus implying that reelin plays a fundamental role in synaptic plasticity. In 1998, Dr. Costa and his collaborators discovered that reelin and the enzyme that makes GABA (GAD67) were down-regulated in the brains of schizophrenia patients, a finding in line with the observed neuropil hypoplasticity and decrease in dendritic spine density

in the cortex and hippocampus of these patients. Interestingly, those GABAergic neurons that show reduced expression of reelin and GAD67 also show an increased expression of a DNA-methylating enzyme (DNMT1). These findings suggest that the reelin and GAD67 down-regulation in the brains of schizophrenia patients is associated with hypermethylation of the corresponding promoters of these genes, and furthermore, these studies point to the possibility that an epigenetic mechanism underlies schizophrenia morbidity.

Dr. Costa's exceptional scientific career will have a great impact in modern neuroscience for years to come as he continues to be quoted in scientific journals and his investigations provide the basis for much current experimentation.

Donations for the Erminio Costa Memorial Lecture should be made payable to:
University of Illinois – Department of Psychiatry
Please note-In memory of Dr. Erminio Costa
Mailing Instruction:
Carla R. Ross
Room 551, M/C 912
University of Illinois at Chicago
Department of Psychiatry
1601 W. Taylor
Chicago, IL 60612

Submitted by Drs. Dennis Grayson and Alessandro Guidotti, Department of Psychiatry, University of Illinois Chicago

Proposed Bylaws Change

During the last ASPET Annual Meeting, we held a Student/Postdoctoral Focus group, where we asked many questions about our services and benefits. One of the concerns coming from this group of members included the desire and need to have a separate Postdoctoral category of membership with reduced dues. The focus group brought to our attention the difficulties many Postdoc's face in paying for Regular membership as membership fees usually come out of their own pocket.

Following this focus group, we were also approached by many other members and also some potential new Postdoctoral members who indicated that they also felt ASPET should have this category for Postdoc's as they felt that Regular membership was too expensive for their budget. Lately, many Postdoc's have turned away from joining because they felt the Regular rate of membership was too expensive.

Currently our Postdoctoral members are dispersed among our Student membership category (we allow our student members to stay in this category for two years following graduation if they were a student member for at least one year) and our Regular membership category. Since ASPET does not have a separate Postdoctoral category of membership, we are unable to categorize them and target Postdoc's for the many opportunities, information, and news we have directly related to Postdoc's. This has been an on-going problem for ASPET administrators who have wanted to reach out to Postdoc's for a variety of reasons.

We've listened to these concerns, researched and discussed this at the Fall ASPET Council Meeting and have come up with the following proposed bylaws change for a new Postdoctoral Member category of membership, as well as some changes that will affect the Student category of membership. By creating a new Postdoctoral category of membership, we would be supporting young pharmacologists and postdoctoral fellows, encouraging their membership in the Society, and be able to categorize them in the membership and target them for information and news related directly to Postdoc's.

This proposed bylaws change will be presented to the membership at the Business Meeting at the ASPET Annual Meeting at 6:30PM on April 24, 2010 in Anaheim:

Article II. Members

SECTION 1. Membership Categories

CHANGE

ITEM 6. Student Members. Persons who are enrolled in undergraduate, graduate, or professional degree programs, and who have an interest in pharmacology, are eligible for Student membership, which shall be non-voting. Student members may be proposed later for regular membership or affiliate membership upon meeting the requirements for that membership category. Upon completion of their research doctoral degree, ~~applicants are normally eligible for regular membership but may remain in the Student Member category for no more than two (2) years.~~ student members must upgrade to Postdoctoral membership.

NEW

ITEM 7. Postdoctoral Members. Persons who have received their Ph.D. or equivalent degree in pharmacology or a related field are eligible for Postdoctoral membership. Postdoctoral members will receive the same benefits as Regular members, including the right to vote in ASPET elections. Individuals may remain in the Postdoctoral Membership category for a maximum of five (5) years from the date of receipt of their PhD (or equivalent) degree after which time they must upgrade to Regular Membership.

APS Announces the 2010 Rita Allen Foundation Award in Pain

The Rita Allen Foundation and the American Pain Society announce a call for applications for the 2010 *Rita Allen Foundation Award in Pain*. The RAF and APS may award two grants in the amount of $50,000 annually, for a period of up to three years to those research proposals demonstrating the greatest merit and potential for success.

Candidates must have completed their training and provided persuasive evidence of distinguished achievement or extraordinary promise in **basic science research in pain**. Candidates should be in the early stages of their career with an appointment at a faculty level.

The entire award is to be allocated to projects specifically chosen by the recipient. Overhead is not supported.

Deadlines:
Applications may be submitted online by visiting
http://www.connect2conferences.com/aps4/ws_member/member_login.php

beginning October 1, 2009 and will be due by midnight January 15, 2010. Grant awards will be announced by April 1, 2010. Funds will be awarded for the initial 12 month grant period that will begin upon satisfactory execution of the grant agreement between the RAF and the recipients institution. Applications will be reviewed by a Scientific Advisory Committee of APS and RAF. The committee will not provide a review of unsuccessful applications.

Research Topics:
Proposed research projects should be directed toward the molecular biology of pain and/or basic science topics related to the development of new analgesics for the management of pain due to terminal illness.

General Information:
The application must include a written proposal in English of no more than 7 pages including references and a curriculum vitae including the candidates address and telephone numbers. The candidates application must include letters of support from five people acquainted with the candidates research. At least two of the support letters should come from individuals outside of the candidates institution. In addition, a letter from the appropriate administrators and the Department Chair or Institute Head is required and must demonstrate strong support for the candidates proposed research and career development. The candidate will provide the email contact information for the individuals that support the candidates proposed research. Each individual will be contacted by the online system requesting that their letters of support be uploaded directly into the candidates application.

The candidate should list current and pending research support from all sources. The application process, including the electronic submission of all letters, is online at http://www.connect2conferences.com/aps4/ws_member/member_login.php

Eligibility:
To be eligible for the Rita Allen Foundation Award in Pain the applicant:

- Must demonstrate the strong support of the appropriate administrators and Department Chair or Institute Head
- Candidates should have been on a tenure track for no more than three years and support will be reconsidered if a Rita Allen Foundation Scholar is awarded tenure.
- Must conduct the research and be appointed at an institution in the United States or Canada.

Grant Budget and Grantee Obligations:

- Eligible grant expenses may include Principle Investigator salary but not institutional overhead.
- Recipients are required to submit a 500 word annual progress report and a financial report to the RAF in accordance with the terms of the grant agreement.
- Investigators are required to present an abstract presentation of the sponsored research at a future Annual Meeting of the APS.

For additional information contact APS at 847-375-4715 or info@ampainsoc.org.

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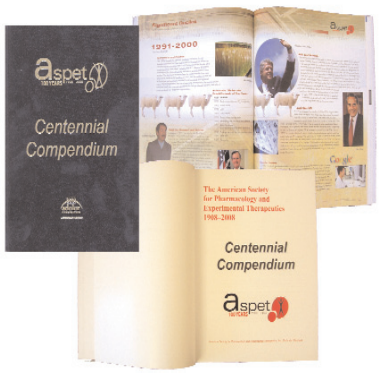

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Experimental Biology is an annual meeting comprised of nearly 13,000 scientists and exhibitors representing six sponsoring societies and 18 guest societies.
General fields of study include anatomy, physiology, biochemistry, molecular biology, pathology, nutrition, pharmacology and immunology. EB 2010 is open to all members of the sponsoring and guest societies and nonmembers with interest in research and life sciences. The majority of scientists represent university and academic institutions as well as government agencies, nonprofit organizations and private corporations.

This multidisciplinary, scientific meeting features plenary and award lectures, pre-meeting workshops, oral and poster sessions, on-site career services and an exhibit floor with an array of equipment, supplies and publications required for research labs and experimental study.

EXPERIMENTAL BIOLOGY 2010 OFFERS:

- Access to 6 collective society meetings in one location with one registration fee
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- Over 400 exhibit booths representing nearly 300 companies
- 4 days of poster sessions with over 5,000 poster displays and author presentations
- Over 90 award programs, of more than $700,000, in travel funding opportunities and poster competitions (awards vary by society)
- Over 65 countries represented annually at the meeting creating a diverse audience
- CME credits available (ASIP sessions only)
- Extensive career development opportunities for students and postdoctoral fellows
- Same registration fees as 2009

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Experimental Biology 2010 - Today's Research: Tomorrow's Health
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Scientific Sessions: ..... Saturday, April 24 – Wednesday, April 28
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Exhibits: ..... Sunday, April 25 – Tuesday, April 27

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(T) 301-634-7010
(F) 301-634-7014
or 301-634-7008
eb@faseb.org
www.experimentalbiology.org

Definitions of Categories of ASPET Membership

Regular Members: Any doctoral level investigator who has conducted and is the primary author on at least one publication of an original study in the area of pharmacology published in a peer-reviewed journal is eligible for membership in ASPET. Exceptions may be made for someone who does not meet the degree requirement but who has made major research contributions to pharmacology. Dues for regular members are $140/year. Regular members must be nominated by one (1) Regular or Retired ASPET member.

Affiliate Members: An investigator who does not meet the requirements for Regular membership because of the lack of a degree or lack of publication is eligible to apply for Affiliate membership. Affiliate members receive all the same member benefits as Regular members except that they may not vote in ASPET elections. Dues for Affiliate members are $105/year. Affiliate members must be nominated by one (1) Regular or Retired ASPET member.

Student Members: Individuals who are enrolled in undergraduate, graduate, or professional degree programs are eligible for Student membership in ASPET. Student members receive all the same benefits as Regular Members except that they may not vote in ASPET elections. Individuals may remain in the Student Member category for up to two (2) years following completion of their research doctoral degree. Undergraduate students pay no dues. Dues for second year and above Student members are $30. Student members must be nominated by one (1) Regular or Affiliate ASPET member.

Sponsors should send an email or letter addressing the applicant's qualifications for ASPET membership directly to the ASPET office (rphipps@aspet.org).

Regular Member Benefits (Dues $140):

- Reduced page charges for corresponding authors to publish in ASPET journals – pay $40/page instead of $80/page and save enough with one four-page article to pay your annual ASPET dues!
- Half-price color fees to publish color figures in ASPET journals.
- Free full-text access to all five online ASPET journals, including all back issues.
- Free subscription to *Molecular Interventions* (print) and *The Pharmacologist (*online).
- Reduced subscription rates for ASPET print journals.
- Reduced registration fees for ASPET meetings.
- Sponsorship of papers at the ASPET meeting.
- Best abstract awards for young scientists at the ASPET meeting.
- Free listing in the FASEB Directory.
- Membership in multiple ASPET Divisions for no additional dues.

Affiliate Members (Dues $105) have all the benefits of Regular Members except they may:

- Sponsor candidates for Student membership only.
- Not sponsor a paper for a non-member at a Society meeting.
- Not vote in Society elections.
- Not hold an elected office in the Society.

Student Members (Dues $30) have all the benefits of Regular Members except they:

- Pay no dues their first year.
- Pay only $30 annual dues thereafter. Undergraduate student members pay no dues and get their first graduate year free.
- Must have their papers at Society meetings sponsored by a member.
- May not vote in Society elections nor hold an elected office in the Society.

2010 Publication Subscription Rates for Members

All Society Members qualify for the following reduced print publication subscription rates:

- *Journal of Pharmacology and Experimental Therapeutics* (Monthly) - $220/year
- *Pharmacological Reviews* (Quarterly) - $89/year
- *Drug Metabolism and Disposition* (Monthly) - $137/year
- *Molecular Pharmacology* (Monthly) - $180/year
- *Molecular Interventions* (Bimonthly) – included with dues

APPLICATION INSTRUCTIONS

Submit the completed Application for Membership form or use the online application form on the ASPET web site at **http://www.aspet.org/membership/apply/.** Submit a current *curriculum vitae* including bibliography for Regular and Affiliate Membership. You may e-mail the CV to the ASPET Membership Coordinator, Robert Phipps, **rphipps@aspet.org**.

Sponsor Statements: Submit a statement(s) of qualifications of the applicant from two Regular/Retired Members of ASPET for Regular Membership or from one Regular/Retired Member of ASPET for Affiliate Membership and Student Membership (Affiliate Members may also sponsor student applicants). In addition to the statement certifying that the applicant is qualified for ASPET membership, sponsors should provide their own current address, phone, fax, and email. It is the responsibility of the applicant to insure that these documents are submitted to the ASPET office.

American Society for Pharmacology and Experimental Therapeutics
9650 Rockville Pike, Bethesda, MD 20814-3995 USA
Phone: 301-634-7060 ♦ Fax: 301-634-7061 ♦ www.aspet.org

Membership Application – TP1209

Please Complete All Sections:

Section 1: Application Details

Application for:

❑ **Regular Membership**

❑ **Affiliate Membership**

❑ **Graduate Student – Expected Date of Graduation:** _____

❑ **Undergraduate Student - Year:** ❑ **Fr** ❑**Soph** ❑**Jr** ❑**Sr**

Section 2: Source

How did you hear about ASPET:

❑ **Meeting** _____

❑ **ASPET Journal** _____

❑ **Mentor** _____

❑ **Other** _____

Section 3: Personal Information

Name:

Institution:

Address:

Telephone:

Fax:

Email:

Section 4: Optional Demographics (Not Required)

Date of Birth: _____

Sex: ❑ Female ❑ Male

Ethnicity:

❑ Asian

❑ Black or African American

❑ American Indian or Alaskan Native

❑ Hispanic or Latino

❑ Native Hawaiian or Pacific Islander

❑ White

❑ Other: _____

The information in this section will be used by ASPET to collate statistics and will be kept private. Completion of this section is voluntary.

Section 5: Sponsor (Must be an ASPET Member)

Name and email of your sponsor:

Please have your sponsor send us a brief letter or e-mail outlining your qualifications for membership in ASPET to the Membership Coordinator , Robert Phipps, (rphipps@aspet.org).

Section 6: Division Selection

Divisions: *Division membership is a benefit of ASPET membership and there is no additional charge to belong to a division. It is highly recommended that you join a division so that you may take full advantage of Society participation. Joining a division allows you to participate in creating the scientific program for the annual meeting, network with people in your field at mixers and divisional programs, and receive special notices and newsletters about items and activities of interest in your field. Be sure to pick a division!*

Indicate primary (1) and as many secondary (X) divisions to which you wish to belong:

___Division for Behavioral Pharmacology
___Division for Cardiovascular Pharmacology
___Division for Drug Discovery, Development & Regulatory Affairs
___Division for Drug Metabolism
___Division for Integrative Systems, Translational, & Clinical Pharmacology
___Division for Molecular Pharmacology
___ Division for Neuropharmacology
___ Division for Pharmacology Education
___Division for Toxicology

Section 7: Curriculum Vitae

Regular, Affiliate, and Graduate Student applicants: Please send your *Curriculum Vitae* (including bibliography) by email to the Membership Coordinator, Robert Phipps (rphipps@aspet.org).

Undergraduate Student Applicants Only:

Current Education :

Expected Degree & Date: School: City/State/Country: Major Field:

Applications are reviewed on a rolling basis. Please DO NOT send payment with your application.
Upon membership approval, you will be sent a dues statement and welcome package.
Student Membership is FREE for the first year, Regular members pay $140, Affiliate Members pay $105.

Call or e-mail the ASPET Membership Department for additional information: 301-634-7135 / rphipps@aspet.org.