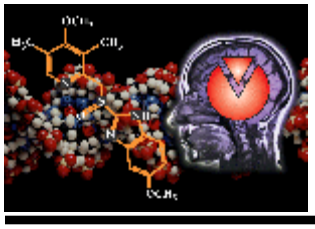

The Pharmacologist

Vol. 50
Number 4
2008
December

2008: Year In Review

ASPET Celebrates 100th Anniversary

Presidential Torch Passed From President Minneman to President Beavo

ASPET 100th Birthday Party in the Gaslamp District – San Diego

ASPET Attends Clinical Pharmacology & Therapeutics - Quebec

Award Winners in 2008

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News

Features

Announcements

BE SURE PAY YOUR 2009 MEMBERSHIP DUES BY JANUARY 1, 2009!!

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YEAR IN REVIEW

As 2008 comes to a close, ASPET would like to thank you for your participation in the Society and making our Centennial year the best year yet! With the help of member contributions, support and participation, we are pleased to announce the following accomplishments made by ASPET this year:

Centennial Celebration:

2008 marked ASPET's 100th Anniversary and we celebrated in a huge way!

At this year's Annual Meeting in San Diego, we threw a huge outdoor birthday party in the Gaslamp District. The street festival was attended by over 750 members, friends, and staff. The party was packed with live music, great food, drinks, and street entertainers, including a mime, a stilt-walker, and caricature artists. There was dancing, door prizes, and lots of fun.

Outstanding science was also featured in our special Centennial symposia at the Annual Meeting. Topics included Cocaine Abuse, Schizophrenia, Obesity, and other hot topics in science. One special symposium featured ASPET's Nobel Laureates, who shared their career experiences with students.

We also commemorated our 100th Anniversary by creating a collection of interesting articles about ASPET and pharmacology. The Centennial Compendium was given to all ASPET members who attended our annual meeting. The compendium is now on sale online at www.aspet.org, along with other special Centennial memorabilia including, t-shirts, hats, and waterbottles.

As part of our Centennial celebrations, we hosted a reception at the Clinical Pharmacology and Therapeutics meeting in Quebec this summer. ASPET was honored and recognized by CPT and IUPHAR for our achievements over the past 100 years.

Awards:

In 2008, we awarded 87 Graduate Student and 25 Young Scientist travel awards at the Experimental Biology meeting, all supported by member and corporate donations. In honor of our Centennial, we increased the number of travel awards this year.

Membership:

Our membership is growing, and 2008 proved to be another successful year in membership recruitment. This year, we have recruited close to 500 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 next year.

As we wrap up this action packed year, we have many high hopes for 2009. ASPET is looking forward to expanding our membership base, reaching out to new members in new avenues. We are also working on updating our website to make it more user-friendly for our members. We expect another great Annual Meeting in New Orleans in April, and we hope that you will be a part of all our activities for 2009! Happy New Year!

ASPET gratefully acknowledges the following individuals who have made contributions over and above dues for 2008:

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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 Cardiovascular Pharmacology, Division for Drug Discovery, Drug Development & Regulatory Affairs, Division for Drug Metabolism, Division for Molecular Pharmacology, 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

James R. Halpert

Kim A. Neve

Candidates for Secretary/Treasurer- Elect

Bryan F. Cox

Edward T. Morgan

Candidates for Councilor

Richard R. Neubig

Mariana Morris

ELECTION 2008

NOMINEES FOR DIVISION OFFICE

DIVISION FOR CARDIOVASCULAR PHARMACOLOGY

Nominee for Chair-Elect

John C. Kermode

Nominees for Secretary/Treasurer-Elect

D. Bruce Averill

Hemal Patel

DIVISION FOR DRUG DISCOVERY, DRUG DEVELOPMENT & REGULATORY AFFAIRS

Nominees for Chair-Elect

Robert J. Leadley

Kenneth D. Tew

Nominees for Secretary/Treasurer-Elect

Anindya Bhattacharya

Timothy A. Esbenshade

DIVISION FOR DRUG METABOLISM

Nominees for Chair-Elect

Xinxin Ding

J. Steven Leeder

Nominees for Secretary/Treasurer-Elect

R. Scott Obach

Emily E. Scott

DIVISION FOR MOLECULAR PHARMACOLOGY

Nominees for Chair-Elect

No Picture Available

J. David Port

Rennolds S. Ostrom

Nominees for Secretary/Treasurer-Elect

Shelley Hooks

No Picture Available

James E. Porter

ELECTION 2008

DIVISION FOR TOXICOLOGY

Nominees for Secretary/Treasurer-Elect

Jeffrey Staudinger

Courtney E. Sulentic

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

Division for Behavioral Pharmacology
Division for Clinical Pharmacology, Pharmacogenomics & Translational Medicine
Division for Neuropharmacology
Division for Pharmacology Education
Division for Systems & Integrative Pharmacology

G-Protein Targets Colloquium

April 17 – 18, 2009

New Orleans, LA

Organized by Alan V. Smrcka, PhD and Theresa M. Filtz, PhD

This is a satellite meeting to Experimental Biology 2009

Sponsored by: ASPET's Division for Molecular Pharmacology

Co-Sponsored by: The American Society for Biochemistry and Molecular Biology

Preliminary Program: Friday, April 17

Theme I: Effector Structure and Mechanism for Regulation

Mechanism of PLC Activation by G Protein
T. Kendall Harden, Univ of North Carolina

RhoGEF Structure/Function
John J.G. Tesmer, Univ of Michigan

Molecular Basis for K^+ Channel Regulation by Gβγ
Diomedes E. Logothetis, Mt Sinai Sch of Med

Theme II: Novel G Protein Effectors and Regulatory Mechanisms

G12/G13 Activation of Adenylyl Cyclase
Lily Jiang, Univ Texas Southwestern Med Ctr

A Novel Signaling Mode for α_{1A}-Adrenergic Receptors
Marcos E. Milla, Roche

Talk Selected from Abstracts

Theme III: Effector Scaffolding

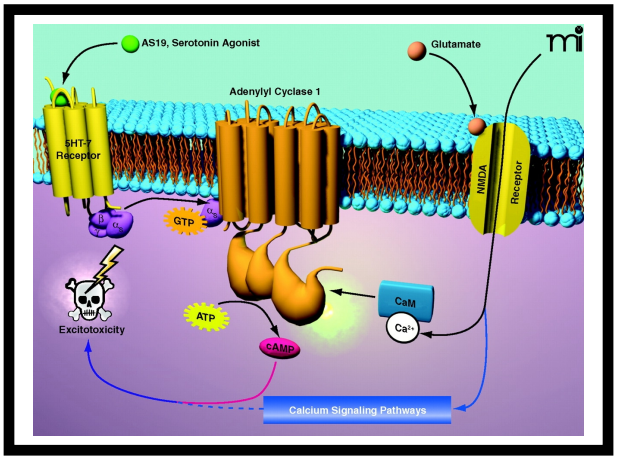
Adenylyl-Cyclase-AKAP Interactions
John D. Scott, Univ of Washington

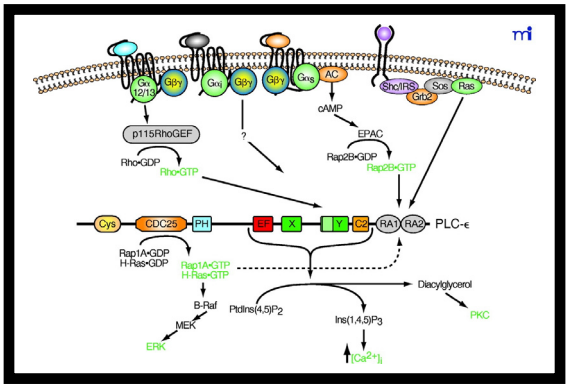
Molecular Chaperones for Kir3 Channel Assembly
Terry Hebert, McGill Univ

Talk Selected from Abstracts

Special Lecture on G Protein BRET Methods: Application to G Protein Effectors

Use of BRET to Monitor G Protein Conformational Changes
Michel Bouvier, Univ of Montreal





Preliminary Program: Saturday, April 18

Theme IV: Effector Cell Physiology and Pharmacological Targeting

RhoGEF Regulation in Cells
Phillip B. Wedegaertner, Thomas Jefferson Univ

Epac in cAMP-Dependent Physiology
Martina Schmidt, Univ Groningen

Pharmacological Targeting of AC
Yoshihiro Ishikawa, UMDNJ-New Jersey Med Sch

Small Molecule Targeting of Gβγ–Effector Interactions
Alan V. Smrcka, Univ of Rochester

Talk Selected from Abstracts

Theme V: Physiological Roles of G Protein Effector Systems *in vivo*

Adenylyl Cyclase and Longevity/Physiology
Stephen F. Vatner, UMDNJ-New Jersey Med Sch

PLC Regulation in the Heart
Elizabeth A. Woodcock, Baker Med Res Inst

PI3 Kinase γ in Neutrophil Function
Dianqing (Dan) Wu, Yale Univ

Plenary Lecture:

G Proteins and G Protein Targets
Heidi Hamm, Vanderbilt Univ

For More Information on Programming and to Register:
http://www.aspet.org/public/meetings/meetings.html

American Society for Pharmacology and Experimental Therapeutics at Experimental Biology 2009 – NEW ORLEANS

All rooms listed are in the San Diego Convention Center unless otherwise noted.

Sun – Tues AM Symposia 9:30 – 12:00; AM Lectures 8:30 – 9:20; PM Symposia 3:00 – 5:30; PM Lectures 2:00 – 2:50; Wed symposia 8:00 – 10:30 AM

Saturday, 4/18	Sunday AM, 4/19	Sunday PM, 4/19	Monday AM, 4/20	Monday PM, 4/20	Tues AM, 4/21	Tues PM, 4/21	Wed AM, 4/22
Behavioral Pharmacology Society Meeting Day 2			**WIP Into Shape Walk**		**ASPET/APS Women in Pharmacology & Physiology Workshop** Pathways to Leadership: Developing Critical Skills *A.Del Tredici, H. Brevig, B. Alexander* Room 346		
G-Protein Targets Colloquium Day 2 *A. Smrka, T. Filtz* Hilton, Grand Salon 3 & 6	**RAY FULLER LECTURE** **8:30– 9:20** Room 206 **Ray Fuller Symposium** Mechanisms of Nicotine Addiction *H. Lester* Room 206	**IUPHAR LECTURE** **2:00 – 2:50 pm** Room 206 CPPTM, DM, MP, ASBMB Metabolomics in the Search for Biomarkers for Human Diseases *F. Gonzalez, R. Kim* Room 207	**JULIUS AXELROD LECTURE** **8:30-9:20** Room 206 **Julius Axelrod Symposium:** The Neurotransmitter End Game: Structure, Function & Regulation of Neurotransmitter Transport *R. Blakely* Room 206	MOLECULAR PHARMACOLOGY DIVISION Postdoctoral Award Finalists *M. Bouvier* Room 206	TORALD SOLLMANN LECTURE 8:30-9:20 Room 206 All Divisions All Presidents' Symposium on Integrative Pharmacology *D. Marshall, W. Fleming* Room 206	NEU, BEH, SIP, TOX Neuroplastic & Neurode-generative Changes Associated with Drug Abuse & Addiction *J. Cadet* Room 210	MP Virally-encoded G Protein Coupled Receptors as New Drug Targets? *R. Leurs* Room 210
2008 Teaching Institute Threading New Concepts into Existing Curriculum: Experiences with Genomics *G. Dunaway* Room 207	EDU, CVP, SIP Integrating Basic Sciences & Patient Care in a Core Clerkship Curriculum *A. Wilson-Delfosse* Room 208	PHARMACOLOGY EDUCATION DIVISION Using Medical Simulation to Enhance Pharmacology Education Through-out the Undergraduate Curriculum *J. Szarek* Hilton - Melrose	EDU/SIP, DDDRA Regenerative Pharmacology: The New Pharmacology *G. Christ, J. Strandhoy* Room 209	DRUG DISCOVERY, DEVELOPMENT & REGULATORY AFFAIRS DIVISION New Insights into Pain Signaling Pathways *A. Bhattacharya, M. Jarvis* Room 208	TOX, DM Exposure to Environmental Agent Alters Epigenetic Homeostasis *M. Costa, M. Vore* Room 208	CLINICAL PHARMACOLOGY, PHARMACOGENOMICS & TRANSLATIONAL MEDICINE DIVISION Translational Clinical Pharmacology Research: Emerging Frontiers *R. Kim* Room 207	CPPTM, DDDRA, SIP, WIP Therapeutics in Auto-immunity: Treatment Successes and Side Effects as a Tool of Elucidating Pathogenic Pathways *C. Paronis, C. Weyand* Room 207
Diversity Committee Workshop: ASPET Travel Fellows: Lessons Learned Along the Way *G. Torres* Room 208	CVP. ASBMB AMPK as a Novel Therapeutic Approach for the Treatment of Metabolic Disorders & Heart Disease *K. Walsh, B. Viollet* Room 207	CVP, CPPTM, SIP The Serotonin Transporter: Not Just for Neurons Anymore *A. Linder, S. Watts* Room 206	MP, CPPTM, CVP, DDDRA SIP, ASBMB MicroRNAs as Biological Effectors & as Pharmacological Targets in the Cardiovascular System *J.D. Port* Room 207	CARDIOVASCULAR PHARMACOLOGY DIVISION Junior Scientists' Competition Benedict Lucchesi Distinguished Award Lecture Room 210	DDDRA, MP Discovery & Development of Oligonucleotide Therapeutics *T. Parry* Room 207	SYSTEMS & INTEGRATIVE PHARMACOLOGY DIVISION Young Investigator Platform *D. Bylund, D. Marshall* Room 208	SIP, CVP, DDDRA, MP Endothelial Progenitor Cells & Cardiovascular Disease – From Bench to Bed Side *A. Chen* Room 208

Saturday, 4/18	Sunday AM, 4/19	Sunday PM, 4/19	Monday AM, 4/20	Monday PM, 4/20	Tues AM, 4/21	Tues PM, 4/21	Wed AM, 4/22
Graduate Student-Postdoc Colloquium Mentoring: It Goes Both Ways *S. Lindsey* Room 209	NEU, BEH, DDDRA, MP, SIP Advances in Down Syndrome Neuroscience Research: Implications for Alzheimer's Disease, Dementias, & Other Cognitive Disorders *T. Esbenshade, A. Costa* Room 210	TOX, DM, MP Generating Proteomic Diversity in Xenobiotic Biotransformation with Alternative RNA Splicing *C. Omiecinski* Room 208	TOX, CPPTM, CVP, DM The Role of Nuclear Receptors in Lipid Homeostasis *J. Pascussi, C. Omiecinski* Room 208	TOXICOLOGY DIVISION Nrf2 and the Regulation of ARE-dependent Xenobiotic Response *Q. Ma* Room 209	DM, CPPTM, DDDRA, SIP, TOX Targeting Drug Metabolizing Enzymes for Effective Chemopreventive Approaches *H. Swanson, E. Scott* Room 209	DRUG METABOLISM DIVISION Early Career Achievement Award Lecture Room 209 Platform Session: Biotransformation & Drug Transport *K. Thummel, T. Kocarek* Room 209	NEU, CVP, MP, SIP, TOX Gases as Neuromodulators in Sensing: From Nitric Oxide to Hydrogen Sulfide *A. Kawabata/P. Moore* Room 206
Business Meeting 6:00 – 7:30 pm	DDDRA, SIP A Renaissance in Marine Pharmacology: Preclinical Curiosity to Clinical Reality *K. Glaser, A. Mayer* Room 209	BEH, DDDRA, NEU, **SIP** Emerging Approaches to Treatment of Alzheimer's Disease *R. Strong, G. Gerhardt* Room 210	BEH, NEU, SIP The Role of Insulin & Leptin in Drug Addiction & Mood *C. France, L. Daws* Room 210	BEHAVIORAL PHARMACOLOGY DIVISION Pharmacological Imaging in Behavioral Pharmacology & Drug Development *L. Howell, M. Nader* Room 207	NEU, BEH, MP ASBMB Receptor Signaling & Regulation in Neuropsychiatric Research *L. Bohn* Room 210	NEUROPHARMACOLOGY DIVISION Postdoctoral Scientist Award Finalists Room 206	DM, CPPTM, DDDRA Regulation of Xeno-biotic Metabolizing Enzymes in Humans: Implications for the Propagation of Health & Disease *C. Falany, M. Runge-Morris* Room 209

Important Dates to Remember:

Early Registration Deadline: February 9, 2009
Late Breaking Abstracts Deadline: February 25, 2009
Housing Reservation Deadline: March 10, 2009

For more information, visit:

www.eb2009.org

www.aspet.org

The View from the Executive Office— Interviews with ASPET's Executive Officers

There have been four executive officers throughout ASPET's first 100 years. It's unusual for an organization celebrating its centennial to find all of its executive officers still living. Dr. William L. Dewey, Chair of ASPET's Centennial Committee, began interviewing the executive officers in 2006 to record their memories of the Society and how it changed during each one's tenure. The fourth in a series of four interviews concludes with Christine K. Carrico, PhD.

Christine K. Carrico, PhD
Executive Officer, 1997 - Present

WLD: When did you start to work for ASPET?
CKC: I started this job in August of 1997.
WLD: I know that you have a Ph.D. degree in pharmacology. Were you a member of ASPET prior to assuming this position?
CKC: I have been a member of the Society since 1980.
WLD: How do you think the Society has changed since 1980–1981 for a member?
CKC: It's become more responsive to the members. I think it is a lot more interactive with the membership. Unfortunately, I don't think it's grown significantly, but we are continuing to work on that. It has grown in terms of staff because we have brought publication of the journals in house, and so three-fourths of the staff are totally devoted to journals.
WLD: What is the size of the staff now?
CKC: The size of the staff now is 16.
WLD: Are they all full time?
CKC: One is three-quarters time. They work on journals, public affairs, education, meetings, membership, and everything else. It seems like it's a reasonably large staff, but we're actually pretty lean when you compare it to other FASEB societies in terms of what we do versus who we have to shepherd things in this office.
WLD: One of the roles of this office is to communicate between the membership and the Council, that is, the president and the other leadership. How do you see that interaction?
CKC: The job of this office is to serve the leadership and the members and to keep the Society operating with minimum attention from the volunteers elected to office, and to help the elected officers accomplish their goals. I know there are plenty of small societies that are run by the officers sort of out of their lab or their office, but they certainly don't publish five journals, they don't have an annual meeting of the scope that we have, and they don't have public affairs outreach programs of the scope that we have. The staff is here to do what membership and the leadership want done and to make things happen. I have been involved in two different organizations, one of which was totally staff driven and the other of which was totally volunteer driven. ASPET leans more toward the independent staff driven model, but I don't think this is a staff driven organization. I think it's very much a member driven organization. The staff may do a lot of the leg work, the background work, and the implementation work, but the ideas come from the members. I think I have a good relationship with most of my presidents and my Council, and I think they value my input so I can make suggestions about the things I think should happen or need to happen, and they listen. They shoot them down sometimes, and sometimes they accept them. Part of my job is to put the ideas out there to get people thinking about them, and most of the time, unless there is a major financial reason for it, I don't care if they accept it or don't accept it. It's meant to be something for them to think about.

WLD: The decisions that are made are the responsibility of the individual elected to office, but they serve a total term of three years. If that person is elected and has any sense, they know that very soon, possibly before the thing they had an idea about could be carried out, they will be gone. Maybe the next person will care about similar issues or concentrate on something they want to do. So the real success and stability and continuity of this organization is in this office, and maybe in another sense the leadership is really here and it should be.

CKC: The institutional memory is here clearly. One of the things I did was to create an information handbook that we send out to the newly elected Council members. This book has some of the history and information on all the things we do. We have seen this problem with FASEB without continuity and strong leadership in the executive office—kind of wandering around and not knowing where to go. I think that certainly we've provided that anchor. For example, Jim Bernstein presents the Public Affairs Committee with some ideas that he thinks will be of interest to them, and they may say pharmacologists don't care about that. We come up with suggestions for the annual meeting or suggestions for new programs or budget suggestions; again, these are based on, as you pointed out, our experience since we work on these things every day. So we know where some of—or most of—the skeletons are and what some of the problems are, and we think about what some of the solutions may be.

WLD: This is your paid job, and the elected people get paid for a job that is for something else.

CKC: I know. They keep reminding us.

WLD: The officers are not paid for what they are doing, yet they take their responsibilities very seriously. At times it must be difficult for both groups: the paid employees and the volunteers. Could you comment on that?

CKC: The interaction is between the volunteers and the paid leadership, if that is what you want to call us. Part of my job is to keep the volunteers out of trouble, and fortunately I have never been in the situation, or come up against a situation, where there was a legal issue with major implications because they didn't listen to me. I guess if there were I would still keep trying to convince him or her of what it could mean, either legally or financially.

WLD: Wouldn't one think that the expertise here is much more than what the volunteer has?

CKC: I think I would try to bring in a real expert like a lawyer or a banker or a professor from a university to meet with everybody and mediate if it was serious enough, but most issues are not quite in that situation.

WLD: Do you perceive a problem with the number of members?

CKC: I think that the membership number continues to be an issue.

WLD: What do you think your office can do or the elected people can do to increase membership? Is anything wrong with 4,000 members or whatever it is? Or do we need a 15,000 membership? What are your feelings about that?

CKC: I would like to see us grow slowly. I don't think we need to be a 15,000 member organization. I mean, in a sense we are growing and our membership number is staying steady. Approximately 25% of our members are retired, and we lose track of a significant portion of them. Plus, we tend to lose a larger number of the members from industry as they move around; we lose track of them, and don't have a way to contact them. But, we are getting a lot of new members. The fact that we are maintaining a reasonable, steady state I think is a good sign that we are getting new members. When Bud Kline was here, he made a real push to increase the student member base, and we went from something like 25 students to almost 1,000 students over three years. Two years ago council decided—and I think this was a reasonable decision—that students should pay some dues after their first year. Partly this was because the students were getting all the benefits of regular members and not paying anything. Plus, students can apply for travel awards and don't have to pay anything in dues.

WLD: Is it a concern that they would have no commitment?

CKC: Council figured that a $25 or so dues signifies a commitment to the Society. The numbers of student members then dropped back to about 400, but I still think that is still a pretty healthy student membership. So those numbers have kind of changed over the last few years. The problems with our membership go beyond just the membership numbers in the Society. They go to the fact that the pharmacology departments are disappearing. The people who may be doing pharmacology and might be considered members of ASPET possibly did not get a degree in pharmacology, may not be in the Pharmacology Department, and may not think of themselves as pharmacologists, and don't perhaps realize the benefits that could be derived from belonging to ASPET. There are a whole bunch of other societies, e.g. Society for Neuroscience, Society of Toxicology. The argument that I hear from a lot of people is that they already belong to another society, and I say that is good but I belong to five and you might consider joining ASPET since one belongs to different societies for different reasons. If you are a cancer researcher, you probably belong to AACR for your research, but if you have to teach in a pharmacology course outside the cancer area, then you would benefit by belonging to ASPET because that is where you are going to hear what is going on in the rest of the discipline and increase the opportunity for interaction with your colleagues. You may not belong to ASPET because it is the hottest place to hear cutting edge research in your area, but you belong to ASPET because you are a pharmacologist.

WLD: Are you suggesting that there is more than one way to look at the role of ASPET? One could be its role to the membership, which could be exactly the same for all members, but also could be somewhat different for each member. A second could be the role of ASPET to pharmacology as a discipline, and third its role to groups of pharmacologists such as departments of pharmacology. How do you see ASPET interacting with departments of pharmacology? Do you think the relationship of ASPET to departments may be more important in the future when some are challenging the need for pharmacology departments in at least some schools? What about the interaction with the chairs?

CKC: Yes, the Chairs' group takes the lead on what the role of the pharmacology departments will be in the medical and other professional schools. Certainly if they have an initiative and if they have a role for us and ask us to participate, we would consider it. I think that the Chair's group is in the best position to deal with the medical schools and the deans. Where we come in, I think, is to provide education. I wish we had resources to educate undergraduate students about what pharmacology is and why it is a field they should consider as a discipline for graduate school. That would provide the students with information on what pharmacology departments or physiology departments or whatever do in terms of research. Hopefully we can do some of this education as part of the centennial. One of our goals is to educate the general public about how valuable pharmacology is as a discipline. I think *Molecular Interventions* has served a very useful function. We are hoping that, if we can find the right person to hire, we are going to be able to get it out more broadly so the people who are not pharmacologists can get their hands on it and can be more informed about our discipline.

WLD: Do you sell *Molecular Interventions* to magazine stores and to city and county libraries?

CKC: No, not at this time, but we would like to consider doing this.

WLD: Back to the number of members; is there anything wrong with ASPET being a 4,000 member organization 10 years from now?

CKC: Not as long as it is 4,000 active, involved members or even 2,000 involved members. I have been through Councils where the emphasis was to get as many members as possible. Everybody on Council was supposed to go out and recruit five members, and that didn't work because these members, by and large, didn't renew. I watched Council during Ken Moore's presidency, where they shifted their emphasis from the position of growth of new numbers to one where they felt it was really important that we provide the best possible services for the members we have even if we don't grow.

WLD: Another question is whether you are comfortable with the size of the current office staff. Do you think it should be more?

CKC: I have mixed feelings about it. We are in the process of trying to hire a membership marketing person to identify and get new members and try to make sure we keep the members that we have. [Editor's note: Subsequent to this interview, ASPET hired Suzie Thompson as Member Services Marketing Manager.] We need to determine just what it is that members want from the Society. As I said earlier, we are trying to get *Molecular Interventions* into public libraries and other places, and we don't have staff to do that sort of thing. Twelve to fifteen is an ideal size staff for working together. Above that one could begin to get factions and things like that. I'm lucky to have wonderful staff people. My senior staff, Rich Dodenhoff, Jim Bernstein, and Harry Smith [and now Suzie Thompson], are all real team players, really good to work with, and know their fields. I turned the journals over to Rich. I don't know a lot of the details about the day-to-day operations of any of our journals because I don't need to. But having said that, I don't think we can do much more with the size staff that we have. We are pretty much stretched about as thin as we can go.

WLD: In general, is the mechanism—not the personnel—but the mechanism between the leadership of ASPET and the needs of the staff acceptable?

CKC: Yes.

WLD: If you needed more staff or anything else that had a cost, I expect you would try to convince Council that you needed it. Would you be asked to discuss it with the appropriate committee and have them bring it to Council for discussion? Is the mechanism in place satisfactory?

CKC: Yes. That is not a problem at all.

WLD: Should there be a liaison person between the Council and the executive office or would that person be in the way?

CKC: That is what I am.

WLD: I was hoping you would say that.

CKC: Now I have to say, Rich, Harry, [Suzie,] and Jim all attend the Council meetings. As senior staff, if the Council has questions about the journals, they better ask Rich if they want the best answer, or on public affairs, ask Jim. I encourage any of my staff if they want to, or feel they have to, or have a concern with me that they can't deal with me personally, they should feel free to go to the president or any other Council member. In fact, this is in our procedures manual. The president comes in once a year and meets with the staff without me there.

WLD: The bottom line is that you are pretty satisfied with the mechanism in place for this type of thing**.**

CKC: Yes.

WLD: Meetings. There used to be two meetings a year. The concern arose that the fall meetings were getting too small. Attendance was about 800. There are scientific societies that are very happy to have 200 people at a meeting, yet ASPET was less than happy with 800 people at a meeting. They felt it was a failure. The question was asked, should we really do a meeting in the fall and also do one in the spring? It was decided to stop the fall meetings in 1992. Is there a reason to consider going back to two meetings a year?

CKC: The problem with really small meetings is that you lose money on them, and you can't afford to lose too much money. The non-journal part of the Society does not take in enough money to be self-supporting.

WLD: Is it better to have a very high powered meeting for 200 people that doesn't make money or have a larger, possibly less impact, meeting for 2,000 people that does make money?

CKC: I think the answer is yes. We put on maybe one small meeting a year in addition to the annual meeting. It's usually highly focused like GPCR or RGS proteins or pharmacogenomics, for example. We are lucky if we get 150 people to those, and sometimes they break even, and sometimes they make a little money; frequently they don't. Council has always felt, as has the Program Committee, that those meetings are worth doing even if we don't make money. At some point, however, you need have a meeting where you make some money for the Society.

WLD: Isn't it true that we lost a lot of money on the IUPHAR Congress through no fault of our own?

CKC: Yes, every one said it was a wonderful meeting and it was. There were about 2,000 people total. Unfortunately, the budget was for about 4,000. When we budget for these smaller meetings, we budget to break even; we don't budget to make a profit. We are happy if we break even, and we don't charge the meeting budget for any of the staff time or anything else that's involved, which is significant. Unfortunately, you sometimes can't get the organizers to understand that you can't always be losing money no matter what the perception is of the value of the meeting. Often they feel that they've absolutely got to have a particular meeting no matter what the costs are. I think that there is a place for both small and large meetings organized by the Society, but neither should put a burden on all other activities of the Society.

WLD: Are societies and other scientific organizations too dependant on money these days? I guess some people out there think some societies have millions of dollars in the bank. Of course today, millions of dollars is not what it was in 1985, and yet when they think of their own finances, they don't have millions of dollars in the bank. Why does ASPET need so much money?

CKC: The main purpose of having money in the bank is to guarantee the stability of the organization, so you will continue to have journals and our other benefits to members in the event of a financial catastrophe, such as a cancelled annual meeting. For instance, if you publish in *JPET*, the financial stability provides the resources so that it will continue to be there for you to publish and for people to cite your publications. If you present your experimental findings at the Experimental Biology Meeting because the physiologists and the biochemists are there, it is important for ASPET to continue to be a part of that meeting. Without such stability pharmacologists would not continue to be a part of it. In terms of reserves in the bank, the recommendation is that you should have at least a year's budget in the bank. Another reason for having reserves is that if they are making money for you, you can use that money to provide more services for the members or to expand programs. That is how ASPET functions. Much of our revenue comes from our journals. The rest of it comes from income from our reserves. When we got into financial trouble a couple of years ago, it was due to the fact that income from our reserves decreased so dramatically. We had to actually go into the corpus of the reserves. The numbers are there for you to do that once or twice, but that's not a trend that you want to continue. We made a lot of tough decisions so that we didn't continue to drain the reserves.

WLD: Isn't one of the reasons that it is important to have financial security is to keep people of quality working for the organization? The essence of ASPET is having someone like yourself on the staff who can make things happen. I think that if the Society lost that, then they have absolutely nothing. I don't hear that expressed enough. I think that people who are elected to office understand that.

CKC: I'm not sure that all of the members do. Some of them clearly do, and I'm sure anybody that's been part of the BPT for the last seven years, understands that. Rich has not only increased the circulation, increased the quality, and the timeliness, but he's decreased the cost dramatically, and if we lost him in that position, that would be a problem.

WLD: I agree. If he's worried about not having a salary next year due to the lack of reserves, then he's going to go somewhere that he has a guaranteed salary.

CKC: So, that's another reason why money is important.

WLD: Now let me ask about the major objectives of the Society. Why do we need to continue the Society? What activities are beneficial to members in their overall professional activities?

CKC: Meetings, journals, public advocacy for issues that are important to pharmacologists, and educational programs to maintain the pipeline come to mind.

WLD: Do you think they changed over the years?

CKC: I think so. Several years ago when Tony Mazzaschi was here, we had a very active public affairs program. After Tony left, that went somewhat into hiatus. For a while we had no one, then there was a half time person, then we had no one. That used to be one of the hardest things for the Council to understand. Since we belonged to FASEB, they wondered why we needed our own public affairs person. Now with Jim Bernstein handling this area, they are saying, we have Jim; what do we need FASEB for? The answer is that FASEB may not be interested in all of the issues most important to us or cannot reach consensus in many of the areas that are critical to pharmacologists, such as animal research, organ systems and integrated pharmacology, herbal medicine, dietary supplements, those sorts of things. FASEB is probably not going to take a position on those. If for example, the Chairs group (AMSPC) were to identify a congressional strategy for pharmacology departments, and if we were to get involved in that, that would be clearly an ASPET issue, and Jim would spend a huge amount of time on it, just as he has with the integrative and organ systems pharmacology initiative. I think what has changed is that we have become more proactive than we used to be.

WLD: Would you agree that the four major activities of the Society are journals, meetings, education, and advocacy, and all but advocacy have remained the same over the years?

CKC: Probably so. Education may have decreased over the years, so I think that we are ramping that up because it used to be that you didn't have to worry too much about educating the next generation. Due to changing opinions in medical schools and elsewhere, it appears to be more of a need again.

WLD: Another thing that has changed is that decades ago, there weren't as many societies as there are today. So when a pharmacologist wanted to present his/her data, the obvious place to present it was at an ASPET-sponsored meeting. That may or may not be true today with all the newer and more specialized meetings. How do you feel ASPET, representing a large discipline, should respond to that challenge?

CKC: As I said, when I talk to people, I always make the argument that we belong to different societies for different reasons. I hear a lot of feedback from the people who find that the neuroscience meeting is just too big for them anymore. Our meeting doesn't attract as many people or as many members as I would like it to and it varies from year to year, but I think our programs have gotten much better with the divisional structure orientation in our meetings. I don't know how you go about marketing our meeting more widely than we do. That's one of the reasons why I said to Council, if I can have one more staff person, I think that person would market our small meetings. I believe we could have more than 150 people for most of them, but we just don't get that much interest. I'm sure there are marketing opportunities out there for them. I just don't know what they are and how to take advantage of them. I guess some people find EB sort of overwhelming and too big. Of course, I always went to them as the Federation Meeting, but I always liked them because I wasn't limited to going just to pharmacology. I think the participating societies' executive officers do the best job they can to avoid conflicting programming. The more societies that get involved—and often there are seven at any meeting—the harder it is to do that. There used to be an EB programming committee, but they voted to disband themselves because they thought that others were doing their job.

WLD: How about FASEB? What are the advantages and disadvantages of ASPET being an organization within FASEB?

CKC: Well, I would say that they probably would vary depending on the views of the FASEB leadership, both elected and paid. There are lots of benefits to being here on campus. There are the interactions with other executive officers, there are other journal people, lots of things that you don't have to worry about, that you'd have to worry about if you were out there on your own—mail delivery and human resources. I think that the argument that we are getting our money's worth of belonging to FASEB because of all their public affairs activities needs to be examined carefully on a regular basis. FASEB is into a growth mode, and they want to acquire all these new societies. The more societies they have, the harder it's going to be for them to identify areas where they can have an impact on advocacy and can achieve consensus because FASEB is a consensual organization. Nobody argues that their lobbying for NIH is not valuable and certainly they do that well, but so do lots of other groups out there. Whereas in the past it was always a given that we belong to FASEB because of what they do in public affairs, I think that now we need to look at this carefully. FASEB is increasing its dues from $25,000 or $30,000 for the Society to $60,000, and the question is whether we are going to still feel that it is a bargain at this new price.

WLD: Let me put this dollars thing into perspective. As I remember it in the late 80s, $60 of the $65 of an ASPET member's dues went to FASEB. Then it went down to $10. How much will it cost per member when the cost for the Society goes to $60 per year?

CKC: $20.

WLD: It will be 20 dollars out of…

CKC: $140 or so.

WLD: It's still a lot of money.

CKC: Right. We did a calculation about four years ago, and at that point each member cost us about $450. And at that time, they were paying $65 in dues.

WLD: Help me understand. Are you saying that for each member, who was paying $65 a year in dues, the Society provided $450 worth of value to that member?

CKC: That's if you take the operating budget of the Society and divide it by the number of members. You can say $20 comes out of member's dues to go to FASEB, but that $20 actually comes out of ASPET's budget to go to FASEB. If Council feels like it's really worth it and ASPET's members are benefiting, then that's fine.

WLD: Don't we have two Board members representing us on the FASEB Board?

CKC: No, FASEB recently changed its bylaws so that we only have one voting representative, and one non-voting representative, who ASPET pays to send to the meetings. The organization is pretty much run by the Executive Committee because the Board has gotten so big. Again, because of this focus on growth, FASEB is run by its executive leadership: its president, past president, president-elect, executive director, and chief financial officer. ASPET's Council has not always been entirely satisfied with the way FASEB has responded to concerns we have raised.

WLD: How do we get representation in the Executive Committee? Have we had anyone run for president of the FASEB Board?

CKC: At least one member ran. The president is elected by the FASEB Board members. It's a self-nomination process, and I think any Board member is able to run as long as they have been on the Board for at least a year. Essentially they have to be willing to run. To improve the communication with our FASEB Board representative, we have now decided that our FASEB Board rep will stay on Council during his/her time on the FASEB Board, which gives some of them a five-year term. I suspect knowing that, some of our folks will not be interested in making that long a commitment. I think it's like any election in that the people who are elected are the ones who seem to be the best known or the ones that speak up the most or who have published the most.

WLD: How about your impressions of how the activity in the Society today relates to the objectives of John Jacob Abel in 1908?

CKC: I'll have to confess that I don't know what his objectives were. The Articles of Incorporation, which were written in about 1930, have a mission statement. ASPET had to have that information because the Society had to incorporate when it took over *JPET* from J.J. Abel. The mission statement basically says the objectives are to provide education and the ability for scientists to present their research and interact. I think that we are meeting them pretty well.

WLD: Do you feel that we are positioned to continue to do that in the future, and is there any reason why we shouldn't be able to? What are the stumbling blocks that we have to overcome?

CKC: There are challenges. Open access publishing is going to be one of them. To date, we have not been adversely affected by either the move to all electronic publishing or by the open access move on the part of NIH and others. Partly, that's because Rich and Brian Cox, and Ken Harden before him, as chairs of the BPT, have been fairly thoughtful and had foresight. We moved our subscription models to ones that would not so heavily hurt us if individuals and institutions only wanted online subscriptions. The BPT basically made the decision last year that as soon as a manuscript is accepted, before it is copyedited or formatted, it will go online in all its unformatted glory and anybody can access it who wants to at no cost. The formatted, copyedited version with all the references and tables will be the copy of record, and it is the citable one. It is under access control for a year. The raw manuscript stays available the entire time, so we now have open access journals, by definition. The issue is, and my prejudice is showing here, that open access for NIH is not just about open access; it's about control. It has less to do with whether or not the public should be able to see these journals without paying for them. So, no matter what the scientific publishing community does, it will not satisfy NIH. And being NIH, they have a lot of power, so that will continue to be a challenge for us.

WLD: Is the reason that it will be a challenge the financial aspect? As you said, 50% or more of our income is from journals.

CKC: Easily.

WLD: Is *JPET* or any other of our journals going to go away? It's been around almost 100 years.

CKC: I don't think so. And *Drug Metabolism and Disposition* has an extremely loyal following. *Molecular Pharmacology* is a very highly regarded journal and has a very high impact factor. *Pharmacological Reviews* is one of only two archival review journals out there in pharmacology. So, I think that our journals will continue to exist although it is not clear in what format exactly, nor clear they will continue to make money for us. There is no decrease in submission of manuscripts; in fact, it's the opposite. A second potential concern is a decrease in attendance at meetings due to a decrease in grants. I've been around long enough, working with NIH, to know that grant cycles go up and down. Right now we are in a tight funding cycle, and money is going to be tight, and so probably meeting attendance is going to go down for a while.

WLD: What's the best part of this job and what is the worst?

CKC: The best part is working with the members and the officers, interacting with them. I've known a lot of these people for years, and that's one of the reasons I love the annual meeting because I get to see those people. And as I say, I have an absolutely wonderful staff.

I think the best part of the job is for all of us really just doing things that work well and that the members seem to benefit from and enjoy and appreciate. The first year we did the online election and it actually didn't bomb and everything came out alright gave us a really good feeling. And we went to online dues payment to make it easier for people to just click from the web site and pay their dues. We had $50,000 in dues payments in the first three days, which benefited us in that we had that money quicker and members didn't have to remember to stamp the envelope and return it. I think it benefited the members, the staff, everyone. As more people get comfortable with online programs, I think that more and more people will use our online features. Another fun part is implementing new things that will make the Society more efficient and more responsive, and make the members happy.

WLD: Is each day different with some good and some bad mixed in?

CKC: One of the reasons that I decided to leave NIH was that, while I wasn't exactly bored with my job, there was a tediousness to it. Here the elections are routine and recurring. *The Pharmacologist* is recurring although each issue is a new challenge, but that's about all that is repetitive. The Council meetings, even though they happen twice a year, are never the same because there are always different things that are coming up in Council, and different people are involved. So it's a new and different challenge almost every day. I think that in a way we have set ourselves up differently with our divisions. I think it makes it very important that we keep our divisions happy, and I have no problem with that because I think that the divisions are what really revitalized ASPET. I think that's the most important thing that has happened to ASPET in the last 20 years in terms of moving the organization forward.

WLD: And when was that?

CKC: October of '98 is when Council had the retreat that sanctioned the creation of many divisions. We had the divisions of Drug Metabolism and Neuropharmacology before that.

WLD: Didn't we have those way back in the 80s?

CKC: Right, and one or two sections. Council decided to basically empower the divisions at that point by giving them a budget and giving them better programming slots and various things. Then we did a survey to find out that if we were to create new divisions, what would people like to see? We created two or three at that point, and then another two later, and so on. Now we have 10.

WLD: It should be exciting for you to see that develop, a real feeling of accomplishment.

CKC: It is and sometimes it's like having 10 kids ranging from the autistic to the child prodigy. They keep us on our toes. If a division doesn't feel that they are getting to do the things that they want to do, they might just say, "Well, you know we've got like 1,000 members and we will just go and form our own society." I'm not really worried about that happening because I think we provide them with very good service. Council gives them a budget, and within that budget they can do with it what they want. But it keeps us honest.

WLD: Is there anything else that you can think of that I should have asked you**?**

CKC: When am I retiring?

WLD: No, that's not possible. The answer is never.

CKC: I don't know. That's the answer.

WLD: Thank you so much, really, it was great.

CKC: Oh well, thank you.

WLD: I hope this is going to be useful to the members and the readers.

Journals

PubMed Central Delivery for Funded Authors

Effective with the first issues of 2009, ASPET will deliver journals articles funded by the NIH, the Wellcome Trust, the Howard Hughes Medical Institute, and the six agencies of the Research Council UK to PubMed Central on behalf of authors. This will fulfill the deposit requirements of these funders. Articles authored by NIH employees will be deposited on their behalf as well.

The ASPET Board of Publications Trustees approved this service for authors during its meeting in October. PubMed Central requires testing of sample files before they will accept deposits. The new service for ASPET's authors was not announced sooner because we did not know how long the process would take to implement. Approval to start with the January issues was given on December 8.

Authors should note that new funding citation requirements have been implemented for ASPET's journals. These are given in the Instructions to Authors for each journal. Articles to be delivered to PubMed Central will be identified based on a funding footnote. The footnote must follow a prescribed format if the authors cite funding from any of the agencies listed above. Authors must provide their grant number(s) if they cite funding from these agencies. Intramural funding of NIH employees' work must be noted in a footnote as well. The wording is given in the Instructions to Authors and follows wording required by the NIH for its intramural researchers.

Articles funded by the NIH will have a 12-month embargo period at PubMed Central. The BPT voted to allow a six-month embargo period for papers funded by the Wellcome Trust, HHMI, and the RCUK, in compliance with those organizations' requirements. Articles from *JPET*, *Molecular Pharmacology*, and *DMD* continue to be freely available in manuscript form immediately upon acceptance from their respective journal's web site as *Fast Forward* articles.

If your article was funded by any of these agencies and published in an ASPET journal issue prior to January 2009, you must still deposit the manuscript version yourself with PMC to be in compliance with these funding agencies' requirements.

RSS Feeds Available

ASPET's five journals now offer RSS feeds. RSS stands for "really simple syndication" and is a web feed XML format that contains either a summary of content from an associated web site or the full text. RSS feeds notify users of updated content on their favorite websites without them having to go to the site. RSS can also be used to syndicate information from one Web site to another. Feeds can be downloaded to a PDA, a personal web page, or a computer desktop. A feed reader is necessary, but there are many available for free.

The feed options for all ASPET's journals include the current issue and the last three issues. For *Pharmacological Reviews*, *DMD*, and *Molecular Pharmacology*, there are also feeds for Fast Forward (publish ahead of print) articles. *JPET* offers all of these plus feeds by table of contents subject headings. Feeds provide the article title, authors, abstract, and a link to the article at the journal's web site. RSS feeds are free to all. Access to full-text articles is by subscription. All ASPET members get access to the five ASPET journals as part of their Society membership. Members have to activate their subscriptions to use them. Contact info@aspet.org for instructions to activate your subscription or to get your user name and password if you forget them.

RSS feeds can be used to supply content to web sites. This is done by putting a "widget" on the site. Web sites that show continuously updated information such as news headlines and weather reports use widgets that get their data from RSS feeds. Content that is syndicated in this way can reach a greater number of people and gain more exposure. That's one of the goals for ASPET's RSS feeds.

Emailed tables of contents and emailed content alerts will continue to be provided. RSS is an additional option rather than a replacement.

Click on the orange RSS button located on each journal's homepage to find links to feed readers and instructions for signing up for RSS feeds.

Public Affairs/ Government Relations

NIH and FDA Funding Status

Congress continues to work toward completion of an economic stimulus package that President-elect Obama could sign after he takes office. The new Congress is expected to reconvene on or around January 6. A short term stimulus package might also be passed shortly. This will include immediate relief for food stamp recipients, unemployment and Medicaid beneficiaries. Another economic stimulus package, most likely well in excess of $600 billion, will be considered this winter. This second stimulus package will aim to boast economic infrastructure, education, green technology, etc. The second stimulus package could be an opportunity for NIH to receive at least $1 billion in additional funding. This funding would provide immediate support to several thousand competitively awarded research grants.

In the last 12 months Congress has had three opportunities to flat-fund FDA or allow inflation-only increases. Each time FDA was given special consideration and enhanced funding. $150 million was added to the FDA's budget through the 2008 supplemental bill. And another $150 million was addressed to the agency's base through passage of the FY'09 Continuing Resolution. The above increases were on top of a $145 million increase to the FDA that Congress provided this December. FDA is still seriously under-funded but for the first time it appears that Congress has accepted that FDA cannot carry out its mission adequately without a significant increase in funding. With these increased funds Congress has provided guidance on how these and additional resources could be used. They include a host of food safety issues and 1) use new science and analysis to improve the safety of medical products, 2) develop and implement quantitative decision-making tools to assess the safety and effectiveness of drugs, biologics, and devices, 3) enhance science programs across the agency and establish mechanisms to access the best scientific knowledge and expertise to modernize its regulatory science, 4) strengthen FDA capacity to support emerging areas of science, 5) upgrade FDA science capacity by providing more training and professional development support for FDA science staff.

Evolution Symposium at Experimental Biology 2009

"The Evolution of Creationism" is the subject of the EB Public Affairs Symposium to be held at EB'09 in the New Orleans Convention Center on Monday, April 20, 2009 from 5:00-6:30 pm. Confirmed speakers include notable experts on the subject including: Barbara Forrest, Southeastern Louisiana University, author of Creationism's Trojan Horse; Ken Miller, Brown University, author of Finding Darwin's God and other books on the battle over teaching evolution; Eugenie Scot, Executive Director of the National Center for Science Education, and author of Evolution versus Creationism (a second edition of which is soon to be published); and Judge John E. Jones, the Federal Judge who presided at the landmark Kitzmiller v. Dover, PA trial in 2005 that was the first direct challenge brought in US federal courts against a school district that required the presentation of intelligent design as an alternative to evolution. The plaintiffs successfully argued that intelligent design is a form of creationism and that the school board policy violated the Establishment Clause of the First Amendment. Judge Jones' decision has sparked considerable response from both supporters and critics. Some of the subjects to be covered include how supporters of intelligent design use academic freedom and "teach the controversy" principles to advance their agenda and what the future holds for science education.

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 developing programs (see above) that provide training of students in this field. For application information visit:
http://www.aspet.org/public/public_affairs/pa_ioss.html.

Training Opportunity: NIGMS Summer Short Courses in Integrative & Organ Systems Pharmacology

The National Institute of General Medical Sciences will once again fund four summer short courses that provide specialized training for using intact organ system and in vivo animal models in the conduct of research. The purpose of each short course is to introduce graduate students, post-docs and PhDs 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. Graduate students and PhDs with these skills are in great demand in both academic and industrial settings. Summer Short Courses in Integrative and Organ Systems Science are available at Michigan State University, University of California at San Diego, University of Nebraska Medical Center, and the University of North Carolina at Chapel Hill. Please view: http://www.aspet.org/public/public_affairs/pa_NIGMS_shortcourse_awards.html.

NIGMS Global Alliance for Pharmacogenomics Expands

An announcement of five new collaborative projects in the Global Alliance for Pharmacogenomics can be viewed at: http://www.nigms.nih.gov/News/Results/RIKENII_11102008.htm.

FASEB News

FASEB has published "Building Electronic Bridges to Bionics: The Basic Science of Neural Prosthetics," the latest edition in FASEB's Breakthrough in Bioscience series. This article explores the cutting-edge science of neural prosthetics, from cochlear implants to artificial retinas to bionic limbs, and describes the roots of these devices in centuries of fundamental research. To obtain a free copy of these publications, visit the Breakthroughs in Bioscience web site http://opa.faseb.org/pages/Publications/breakthroughs.htm or contact FASEB's Office of Public Affairs at (301) 634-7650. The new article may be accessed here: .http://opa.faseb.org/pdf/BuildingElectronicBT.pdf.

FASEB also launched a new website to provide the research community with information and resources on animal rights extremism www.animalrightsextremism.org.

FASEB has also updated the online data compilation related to education and employment of biological and medical scientists. The site contains presentations of data taken from national surveys and aims to foster an informed discussion on topics related to the training and career development of biomedical researchers. FASEB encourages others to use the graphs and resources available in publications and presentations of their own. The site can be accessed at: http://opa.faseb.org/pages/PolicyIssues/training_datappt.htm.

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Have you moved, changed jobs, or graduated?
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rphipps@aspet.org

Division for Neuropharmacology & Behavioral Pharmacology

The Division for Neuropharmacology & Behavioral Pharmacology co-hosted a Social/Mixer at this year's *Society for Neuroscience* meeting in Washington, D.C. on November 16, 2008. The mixer featured light hors d'oeuvres and a cash bar. ASPET members and non-members alike enjoyed an evening of networking and socializing with colleagues and students. The mixer was open to anyone with an interest in neuropharmacology, and it gave younger scientists a chance to meet more established scientists in the field. Non-member attendees were encouraged to apply for membership in ASPET and in the division. As a result of the *Society for Neuroscience* meeting, ASPET signed up 83 new member applications.

Pictures from the Mixer are below:







Mid-Atlantic Pharmacology Chapter
Abstracts from the 2008 Annual Meeting:

The PAM-1 Aminopeptidase Regulates Centrosome Dynamics to Ensure Anterior-Posterior Axis Specification in One-Cell *C. elegans* embryos. Pauline Greene, Sara Marshall, Lauren Brady* and Rebecca Lyczak. Ursinus College, Collegeville PA, 19426.

The formation of an anterior-posterior axis in early *C. elegans* embryos is a process dependent on a series of events triggered by the sperm donated centrosome. We have identified a puromycin-sensitive aminopeptidase (PAM-1) that is involved in this process. PAM-1 regulates centrosome movement, which is crucial to normal polarity establishment at the one cell stage. In *pam-1* mutants, the sperm pronucleus/centrosome complex (SPCC) fails to contact the posterior cortex. As a result, polarity is not established, and pseudocleavage (a sign of polarity) never occurs. By inactivating the motor protein dynein heavy chain (*dhc-1*) and its regulator *lis-1* which act to move the centrosome away from the cortex, the *pam-1* mutant phenotype can be reversed and polarity and pseudocleavage are restored. Quantitative analyses of wild type and mutant embryos along with confocal microscope images show that RNA interference to inactivate *dhc-1* or *lis-1* can reverse the *pam-1* mutant phenotype. Thus, PAM-1 regulates polarity by positioning the centrosome at the posterior pole. Additionally, we are constructing a double mutant homozygous for a meiosis arresting phenotype, *mat-1*, in addition to the *pam-1* phenotype, to provide further evidence that PAM-1 ensures the interaction between the posterior cortex and centrosome that is necessary for proper polarity development.

Investigating the Role of the Puromycin Sensitive Aminopeptidase PAM-1 in the *Caenorhabditis elegans* Meiotic Spindle Apparatus. Christopher Reeves*, Rebecca Lyczak. Department of Biology, Ursinus College, Collegeville PA, 19426.

The understanding and characterization of temperature-sensitive (TS) embryonic lethal mutants in *Caenorhabditis elegans* are crucial to furthering knowledge of developmental biology. It has been shown previously that the puromycin-sensitive aminopeptidase PAM-1 is required in the early *C. elegans* embryo for certain developmental characteristics, including the proper specification of the anteroposterior (AP) axis and timely exit from meiosis. The *pam-1* mutant embryo is also known to possess chromosomal segregation defects in mitosis and meiosis. We hypothesize that the meiotic spindle apparatus is affected by the loss of PAM-1 and contributes to the observed chromosome segregation defects in *pam-1* mutant embryos. Visualization of the meiotic spindle apparatus was made possible by the use fluorescence microscopy in conjunction with nematode strains possessing GFP and mCherry fusion constructs on tubulin and histone proteins. A control pattern of spindle behavior in wild type embryos has been accomplished and we have begun collecting data on *pam-1* mutant embryos. Early time-lapse fluorescence photography results indicate that the meiotic apparatus translates excessively during divisions and tubulin activity may not cease at the appropriate time after meiosis II; further investigation is necessary to establish any definitive spindle defect.

Neurobiological Studies of the Binding of the General Anesthetic 1-Decanol to Serum Albumin. Matthew Bell,* James Sidie. Ursinus College, Collegeville, PA 19426.

The molecular mechanisms which underlie general anesthesia are not well understood, and a greater understanding could lead to safer and more effective use of general anesthetics. Many diverse compounds, including xenon, medium chain-length primary alkanols, diethyl ether, and halothane, produce anesthesia. Serum albumin is the most common vertebrate blood protein (6 x 10^{-4} M in humans). Albumin is able to bind a wide variety of ligands, including fatty acids. It can also bind to medium chain-length primary alkanols that are known anesthetic agents (octanol- undecanol); this binding should reduce the potency of the general anesthetics. Decanol was examined in this study of the effect of serum albumin and pH on anesthetic potency. Transparent knife fish were used as a model system; a stable sinusoidal electric organ discharge (EOD) is generated by a pacemaker nucleus in the medulla. The fish are exposed to varying concentrations of the anesthetic and bovine serum albumin, at pHs 6-10. Depression of EOD frequency (a measure of anesthetic potency) was recorded for twenty minutes while the fish bathed in anesthetic solution. EOD frequency then recorded for another 20 minutes with the fish in deionized water to monitor extent of recovery. Decanol and bovine serum albumin (BSA) were varied 10^{-4}-10^{-5}M. There is no discernable effect of pH on the binding of decanol by BSA when both compounds are present in equimolar concentrations. However, as the concentration of albumin was decreased and the anesthetic concentration was held constant the anesthetic effect increased. If decanol concentration is held constant at 5x10^{-5} M and BSA concentration is varied (0, 0.5 x10^{-5}, 1 x10^{-5}, 2.5 x10^{-5},

5 x10^{-5} M) then the anesthetic effect is diminished as a function of BSA concentration (26, 21, 22, 17, 11 % EOD frequency depression). This means that at equimolar concentrations (1x10^{-4} or 5x10^{-5} M) of decanol (ligand) and BSA the anesthetic potency (EOD frequency depression) is diminished by approximately 50%. In light of literature claims that BSA has 2-12 fatty acid binding sites, we would have expected a greater drop in anesthetic potency. Future experiments will examine the docking (binding) of octanol and decanol with BSA targets.

Investigation of the Microtubule-Associated Protein PTL-1 as a Target of the Puromycin-Sensitive Aminopeptidase PAM-1 in the *Caenorhabditis elegans* Embryo. Brett Godoy*, Kate Susman, and Rebecca Lyczak. Department of Biology, Ursinus College, Collegeville, PA 19426.

In *Caenorhabditis elegans,* the puromyocin-sensitive aminopeptidase PAM-1 has been shown to play a key role in embryonic meiotic exit and anterior-posterior (AP) axis determination. Mutations in *pam-1* lead to delays in meiotic exit and AP axis formation, which results in the production of excessive amounts of dead embryos. Despite the implication of PAM-1 in early embryonic axis specification, the mechanism by which it acts is currently unknown. We believe that PAM-1, which is the *C. elegans* homolog of human puromycin-sensitive aminopeptidase, is involved in protein degradation and that a buildup of PAM-1 target protein(s) plays a role in the observed abnormal embryonic development and increased probability of lethality. The protein PTL-1 is a microtubule-associated protein homologous to the human Tau protein, which has been shown to form polymeric aggregates in Alzheimer's Disease. Work in other systems suggests that Tau may be a target of a puromycin-sensitive aminopeptidase in humans. Thus, we hypothesize that PTL-1 may be a PAM-1 target in *C. elegans*. We propose that the buildup of PTL-1 in *C. elegans* embryos leads to some of the observed phenotypic abnormalities in *pam-1* mutants. To test this hypothesis, we have created a *pam-1; ptl-1* double mutant strain and we propose to observe the resultant phenotype. We have also used RNA interference to inactivate the *ptl-1* gene in *pam-1* mutants. In both cases, we expect to see a rescue of some of the *pam-1* phenotypes, particularly those that depend on proper microtubule function. We plan to tag the spindle apparatus with GFP to visualize the AP axis and observe the pinching of polar bodies to measure the timing of meiotic exit. Overall, we hope to determine whether PTL-1 is a target of PAM-1 and what role it plays in bringing about delayed meiotic exit and inhibiting axis formation in *pam-1 C. elegans* mutants.

Acetylcholinesterase Mutants Are Sensitive to Oxidative Stress in the Nematode, *Caenorhabditis elegans.* [1]Laura Gurenlian*, [1]Julie Bodkin, [1]Michael Cafarchio, [1]Aakash Shah, [2]Alicia N. Minniti, [2]Nibaldo C. Inestrosa, and [1]Rebecca Kohn. [1]Dept. of Biology, Ursinus College, Collegeville, PA, 19426, [2]Fac. de Cs. Biologicas P. U. Católica de Chile, Santiago, Chile.

Neurodegenerative diseases such as Alzheimer's can be devastating. Research has linked both oxidative stress and acetylcholinesterase (AChE) activity to Alzheimer's. Oxidative stress is caused by radicals that attack the DNA of the cells causing them to commit suicide. When oxidative stress targets the nervous system, the neurons begin to degrade and are no longer able to transmit signals properly. AChE is responsible for breaking down acetylcholine, a neurotransmitter. When acetylcholinesterase activity is inhibited too much acetylcholine is transmitted, causing paralysis. We are investigating the link between oxidative stress and AChE to determine if these two processes are acting synergistically. We are performing our studies in the model organism, *Caenorhabditis elegans*, a small nematode with a nervous system that is similar to that of humans. Embryos of AChE double mutants, *ace-2; ace-1*, which lack 95% of normal AChE activity, and wild type embryos were placed on plates and allowed to grow for five days. These plates included paraquat, which induced an oxidative stress environment, and 5-fluoro-2'-deoxy-uridine (FUDR), a chemical that prevents the worms from laying new embryos. After five days the percentage of adults and the percentage of embryos hatched were determined. In both strains there was a general trend for there to be a decrease in the percentage of adults and embryos hatched as paraquat increased, however, no statistically significant data was obtained. These data suggests that the double AChE mutant is no more sensitive to oxidative stress than the wild type during both the adult and the embryonic stages. However, an AChE triple mutant, *ace-2, unc-13; ace-1* was also tested and this mutant was significantly more sensitive to oxidative stress than the wild type during the larval and adult stages. The protein UNC-13 regulates the release of neurotransmitters and so a mutation in this gene would counteract the affect of the *ace-1* and *ace-2* mutations. This mutant also appears to be resistant to oxidative stress during the embryonic stage as the percentage of embryos hatched was not only significantly higher than the wild type but was independent of the concentration of paraquat. We are currently acquiring data for an *unc-13* mutant to determine if UNC-13 is singularly responsible for this outcome or if it is the combination of the three mutations. Preliminary data for the *unc-13* mutant suggests that UNC-13 is solely responsible for an oxidative protective mechanism during the embryonic stage. However, additional trials and testing still needs to be conducted in order to substantiate and validate this conclusion.

Using BTBR T$^+$ *tf*/J Mice as a Model for Complete Callosal Agenesis. Sarah Beltrami*, Joel Bish. Department of Neuroscience, Ursinus College, Collegeville, PA 19426.

Agenesis of the corpus callosum (ACC) is characterized by the partial to complete absence of a corpus callosum in the brain, a white matter tract which connects the two hemispheres. The corpus callosum, though not the only interhemispheric structure, is crucial for sensory information transfer between the hemispheres. As a result of this neurological defect, behavioral, cognitive, and physical impairments frequently occur. There is currently no effective treatment for this disorder, but symptomatic therapies have shown some promise. Mice within the strain of BTBR T$^+$ *tf*/J completely lack a corpus callosum, therefore displaying the most severe ACC phenotype. The objective of this study was to utilize these mice, and their appropriate control C57BL/6J mice, to determine if environmental enrichment could act as a therapy to improve their impairments. Post enrichment, C57BL/6J mice showed more exploration, improved spatial memory, and a slight improvement in bimotor dexterity compared to nonenriched mice. BTBR T$^+$ tf/J mice also improved in spatial memory and bimotor dexterity, but not in exploration. These measures were determined using an open field task, Morris Water Maze, and peg running task, respectively. A learning effect was apparent in both strain but not an enrichment affect, though enrichment appears to be necessary for the retention of progress. BTBR T$^+$ tf/J mice explore less of their environment compared to C57Bl/6J mice regardless of enrichment.

The Molecular Mechanisms of Targeting COP9 Signalosome as Potential Antitumor Therapy. Maria Demarco*, Fan Jiang, Dong Zhang. Oncology Division, Wyeth Research, Pearl River, NY 10965 (*Summer Intern from UMBC).

Ubiquitin (Ub) is a 76 amino acid small protein, which can be covalently conjugated to the lysine residues of different proteins. The modifications of proteins by Ubiquitin could regulate a variety of biological processes, including protein degradation, intracellular localizations, and protein-protein interaction.
The specificity of ubiquitination is provided by ubiquitin ligases, which physically interact with target substrates. The SCF (SKP1-CUL1-F-box protein) ubiquitin ligase controls cell size, proliferation, and survival, and its regulation has been implicated in aberrant cellular growth and tumorigenesis. SCF complexes have a central role in cell cycle progression, cellular growth, and differentiation by targeting oncogenic proteins for degradation and cancer-associated mutations. Within the SCF complex, the F-box protein contributes to the substrate recognition, while Cullin-1 functions as a scaffold protein to bring together the substrates and E1 and E2 enzymes.
Cullin-1 belongs to a family of proteins, called Cullin, which can be modified by the covalent attachment of the ubiquitin-like protein NEDD8 to a conserved Lys residue in the cullin homology domain. Neddylation enhances the cullin-dependent ubiquitin-ligase activity by facilitating the recruitment of ubiquitin-loaded E2s. Alternatively, NEDD8 can be removed (deneddylation) by the COP9 signalosome (CSN) decreasing the recruitment/ activation of E2s. One of the COP9 subunits, CSN subunit 5 (CSN5) is thought to be the enzyme that deconjugates the Nedd8 modification from the Cullin subunit of the SCF E3 ligase.
At Wyeth Oncology, we have shown that inactivation of CSN5 reduces the viability of many cancer cell lines while has marginal effects on non-transformed human cells. However, it is still unknown whether these effects on viability are solely due to the CSN5 subunit or to the entire COP9 signalosome. To address this question, we downregulated CSN2 (another subunit in COP9) to identify other possible subunits involved in the viability defects. In addition, we have also attempted to investigate the potential molecular mechanism behind the survival effects on cancer cells when COP9 signalosome is inactivated.

Comparison of Human Liver Microsomes, Cytosol, Suspended Hepatocytes, and Plateable Hepatocytes for Prediction of Human Metabolism. Jessica Schwartz*[1,2], Wei Lu[1] and William DeMaio[1]. [1] Wyeth Research, Drug Safety and Metabolism, Collegeville, PA 19426 (work performed at Wyeth), [2] University of Maryland, Baltimore County, Dept. of Chemical Engineering, Baltimore, MD 21250.

The recently issued Metabolites in Safety Testing (MIST) guidance recommends toxicological evaluation of disproportionate human metabolites, those representing greater than 10% of the parent compound at steady state where equivalent exposure cannot be demonstrated in animal studies. Therefore, it is desirable to predict human metabolism well before its first study in humans to ensure timely drug development. The purpose of this work was to compare three different in vitro systems for their ability to predict the in vivo human metabolism of three compounds: troglitazone (TGZ), abacavir (ABV), and clozapine (CLZ). The three in vitro systems studied were: microsomes fortified with their respective cytosol, plateable hepatocytes, and suspended hepatocytes. These three compounds were chosen because their metabolism has already been documented. They were incubated in the three in vitro systems, and their metabolism was

determined by LC/MS analysis. Our results indicated that the plateable hepatocytes were more capable of generating the major metabolites than the other in vitro systems, due in part to the fact they are capable of generating metabolites for up to 5 days, resulting in a higher yield of metabolites. It has been suggested that the use of plateable hepatocytes should be routinely used at the predevelopment stage with other in vitro systems to provide a more accurate prediction of human metabolism. The value of plateable human hepatocytes to predict in vivo human metabolism has been demonstrated with these compounds and should be evaluated with more compounds.

Induction of Cytochrome P450 Genes in Human Hepatocytes by a New Chemical Entity. Tchatchouang, C.*[1], Kubik, J., Xiang, Q., Enoru, J., and Yengi, L. Wyeth Pharmaceuticals. Collegeville, PA, 19426, [1]University of Maryland, Baltimore County MD 21250.

The ability of a new chemical entity (NCE) to induce cytochrome P450 (CYP) isozymes in human hepatocytes was investigated to determine whether it has the potential to cause induction-mediated drug-drug interactions in humans.

Human hepatocytes from three donors were plated in collagen-coated 12 well plates and treated with three concentrations of the NCE for 48 hours. Induction of CYP1A2, CYP2B6, CYP2C9 and CYP3A4 by the compound was evaluated both at the mRNA and enzyme activity levels.

The compound did not affect CYP1A2 mRNA or enzyme activity, but appeared to upregulate expression of CYP2B6, CYP2C9 and CYP3A4 mRNA and CYP2B6 and CYP3A4 enzyme activities (Table 2). Induction of CYP3A4 activity appeared to be significant, suggesting that this compound may induce CYP3A4 in vivo. Therefore, a clinical drug interaction study is recommended.

How Skin Ages: Exploring the Role of the Nuclear Receptor LXRbeta in the Skin. *Casey M. Daniels[1, 2] Qi Shen[2], Wei Wang[2], Catherine C. Thompson[2]. [1]University of Maryland, Baltimore County, Baltimore, MD 21250, [2]Wyeth Research, Women's Health & Musculoskeletal Biology, Collegeville, PA 19426.

The skin is the largest organ in the human body and is essential for protection from dehydration and infection. As skin ages its function deteriorates, increasing susceptibility to damage and disease. The epidermis is the outermost layer of the skin, comprised of keratinocytes at various stages of differentiation. Here we examine the role of Liver X Receptor beta (LXRbeta) in mouse epidermis, to help determine whether LXRbeta is a therapeutic target for improving the integrity and function of aged skin. A member of the nuclear receptor superfamily, LXRbeta is a transcription factor that regulates specific genes in response to ligand binding. LXRbeta is highly expressed in the skin, and LXR ligands induce the expression of genes that are important for skin function, such as those that regulate lipid metabolism. To use mouse skin as a model, we first asked whether the molecular changes observed in aged human skin are observed in the mouse. Since reduced cell proliferation and increased cell differentiation are characteristic of aged human skin, we used immunohistochemical staining to compare these processes in young and aged mice. As expected, the epidermis from older mice was thinner than in the young mice, and preliminary results indicated that cell proliferation was decreased. In addition, there was increased expression of a terminal differentiation marker (filaggrin) and decreased expression of keratin 14, indicating an increase in keratinocyte differentiation. To examine the role of LXRbeta in the skin, we performed a similar analysis using LXRbeta "knockout" mice. As in aged skin, the epidermis of LXRbeta knockout mice appears thinner than that of age-matched wild type mice, and showed decreased cell proliferation as well as increased differentiation. Together, these results suggest that mouse skin undergoes the same age-related molecular changes as human skin and that a deficit in LXRbeta resembles the aging process. Our results suggest that LXRbeta is a potential therapeutic target for skin aging and warrants further investigation, as aged skin is an unmet medical need of increasing importance in the aging population.

Dynamic Mass Redistribution Profiles of hCB2 Receptor Agonist and Inverse Agonist Stimulation. Brian Murray*, John R. Mabus, Christopher M. Flores and Ellen E. Codd. Analgesics Team, Johnson & Johnson Pharmaceutical Research and Development, Spring House, PA 19477.

Epic technology (Corning), using an optical biosensor to monitor dynamic mass redistribution (DMR), is useful for evaluating G-protein coupled receptor (GPCR) signaling. In this study, cannabinoid receptor type 2 (CB2) signaling was studied in Chinese hamster ovary (CHO) cells recombinantly expressing human CB2. Cells were plated in 384-well Epic plates 24 hr prior to the experiment, at 5,000 cells/well in DMEM F12 in the presence of G418. After overnight incubation at 37^{o}C at 5% CO_2, the media in the wells was removed, the wells rinsed, and the media replaced with HBSS buffer

containing 20 mM HEPES and 0.1% BSA. The plate was equilibrated for 50 minutes in the Epic instrument before initiation of the experiment. DMR readings were then commenced at 43 sec. intervals, with ten readings taken as a preaddition baseline and 100 readings taken following the addition of vehicle or ligand to the plate. The DMR was averaged over replicate wells (typically 12 or 24 in number), the time of maximum signaling was determined, and the resulting concentration-response data analyzed using non-linear regression in GraphPad Prism. Concentration dependent signaling was observed for several CB2 agonists and inverse agonists. Signaling induced by the agonists CP 55,940, WIN 55212-2 and L-759,656 was positive (pDMR), whereas signaling induced by the inverse agonists AM 630 and SR-144528 was negative (nDMR). The potencies obtained for agonists were in the nanomolar range, in the order of WIN 55212-2 ≡ L-759,656 > CP 55,940, and were similar to potencies previously obtained in assays of GTPγS binding or inhibition of forskolin stimulated cAMP accumulation. Treatment with pertussis toxin (200 ng/mL) overnight abolished both agonist- and inverse agonist-induced signaling, suggesting $G_{i/o}$ mediation of both signals. The present studies highlight the potential of this assay system to elaborate novel cellular information regarding ligand directed signaling for diverse ligands, without the need to differently manipulate the signaling state of the cells. Studies using pharmacologic tools to elucidate the cellular pathways responsible for agonist and inverse agonist DMR signaling are ongoing.

Evaluation of Candidate Learning Mechanisms of Chemotherapy-Induced Retrieval Deficits in a Mouse Autoshaping Procedure. John J. Foley* and Ellen A. Walker. Department of Pharmaceutical Sciences, Temple University School of Pharmacy, 19140.

Previous studies in our laboratory have shown retrieval deficits in mice in an autoshaping procedure after acute administration of 5-fluorouracil alone and combined with methotrexate (Foley et al, 2008). The purpose of the present studies was to investigate whether these effects may be attributable to state-dependent learning and/or conditioned taste aversion. In our first experiment, mice were pre-exposed to Ensure solution over a period of five days to familiarize the mice with the Ensure solution and prevent conditioned taste aversion before undergoing a two-day autoshaping procedure. On Day 1 of the procedure, mice were injected with saline control or 3.2 mg/kg methotrexate and 75 mg/kg 5-fluorouracil, and placed within operant chambers to measure acquisition of a behavioral response. On Day 2, mice were placed back into the chambers to measure retention and/or retrieval of that previously learned response. We chose this combination because it has produced the greatest retrieval deficits in our published results to date. Pre-exposure to Ensure did not alter the performance of either the saline-treated or drug-treated mice. The mice injected with saline still performed significantly better on Day 2 than Day 1 and the mice injected with the combination of methotrexate and 5-fluorouracil showed a deficit on Day 2 relative to Day 1. These results are consistent with our previous findings and demonstrate that the deficits we reported did not result from a conditioned taste aversion to a novel stimulus. We also examined 5-fluorouracil in a state-dependent learning paradigm. The phenomenon of state-dependent learning refers to the retrieval of information acquired in the same context or physiological state that was present when the organism first learned or encoded the task (Overton, 1974). In five separate groups of mice, we injected: 1) saline prior to the Day 1 and Day 2 sessions (Sal-Sal); 2) 5-fluorouracil prior to the session on Day 1 and saline prior to the session on Day 2 (5FU-Sal); 3) 5-fluorouracil after the Day 1 session and saline prior to the session on Day 2 ([post-5FU]-Sal); 4) saline prior to the session on Day 1 and 5-fluorouracil prior to the session on Day 2 (Sal-5FU); and 5) 5-fluorouracil prior to the Day 1 and Day 2 sessions (5FU-5FU). The timing of the 5-fluorouracil injection impacted performance on Day 2 but not Day 1. The fact that we observed retrieval deficits on Day 2 in the 5FU-Sal and 5FU-5FU groups but a lack of retrieval deficits for the mice that received 75 mg/kg 5-fluorouracil prior to the session on Day 2, the Sal-5FU group, suggests that state-dependent learning is not the predominant learning phenomenon impacted by this agent. Taken together, these data suggest that conditioned taste aversion and state-dependent learning do not explain the retrieval deficits observed. Rather, the chemotherapeutic agents we studied cause memory and/or retrieval impairments in mice by others mechanisms such as hippocampal disruptions. Further studies are planned to further elucidate these phenomena.

TRPA1 Mediates the Noxious Effects of Natural Sesquiterpene Deterrents. Jasmine Escalera*, Christian A. von Hehn, Bret F. Bessac, Michael Sivula, and Sven-Eric Jordt. Department of Pharmacology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06520.

Plants, fungi and animals generate a diverse array of deterrent natural products that induce avoidance behavior in biological adversaries. The largest known chemical family of deterrents are terpenes characterized by reactive α,β-unsaturated dialdehyde moieties, including the drimane sesquiterpenes and other terpene species. Deterrent sesquiterpenes are potent activators of mammalian peripheral chemosensory neurons, causing pain and neurogenic inflammation. Despite their widespread synthesis and medicinal use as desensitizing analgesics their molecular targets remain unknown. Here we show that isovelleral, a noxious fungal sesquiterpene, excites sensory neurons through

activation of TPRA1, an ion channel involved in inflammatory pain signaling. TRPA1 is also activated by polygodial, a drimane sesquiterpene synthesized by plants and animals. TRPA1-deficient mice show greatly reduced nocifensive behavior in response to isovelleral, indicating that TRPA1 is the major receptor for deterrent sesquiterpenes *in vivo*. Isovelleral and polygodial represent the first fungal and animal small molecule agonists of nociceptive TRP channels.

Repeated administration of the neurokinin- 3 (NK-3) receptor antagonist SB222200 enhances subsequent behavioral responses to cocaine. Chinwe A. Nwaneshiudu* and Ellen M. Unterwald. Dept. of Pharmacology and Center for Substance Abuse Research, Temple University School of Medicine.

Studies indicate that NK-3 receptors localized in the substantia nigra and VTA acutely modulate activity of dopaminergic neurons and dopamine outflow to the striatum and prefrontal cortex, brain regions that mediate locomotive behavior and reward. The long-term effects of NK-3 receptor modulation on dopaminergic activity presently have yet to be addressed. Therefore, the purpose of this study was to determine if prior repeated administration of the NK-3 receptor antagonist SB 222200 alters dopamine- mediated hyperactivity. Adult male CD-1 mice were injected daily with SB 222200 (5, 10 mg/kg, s.c.) or vehicle for 5 days. Seven days after SB 222200 administration, animals received either saline, cocaine (20 mg/kg, i.p.) or the selective D1 receptor agonist SKF 82958 (0.125, 0.25 mg/kg, i.p.), and activity was monitored for up to 90 mins. The brains of a separate group of animals were harvested after SB 222200 administration, and membranes from the striatum were incubated with ^{3}H SCH 23390 (0.1-8nM) in presence or absence of fluphenazine in order to measure dopamine D1 receptor density. Results show that mice injected with SB 222200 for 5 days had significantly enhanced hyperactivity, mainly stereotypic activity, when challenged with cocaine 7 days later compared to vehicle treated mice. In addition, administration of SB 222200 resulted in enhanced hyperactivity after a SKF 82958 challenge 7 days later, which was also stereotypic activity. Concurrent data from ^{3}H SCH 23390 binding studies showed a 20% increase in dopamine D1 receptors in the striatum of animals injected with SB 222200. These data suggest that prior blockade of NK-3 receptors by SB 222200 enhances subsequent dopamine- mediated behaviors possibly as a result of neuroadaptations involving dopamine D1 receptors in the striatum. These findings may implicate a role of NK-3 receptors in regulating long-term plasticity of dopamine neurotransmission.

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Metabolism of Tienilic acid and its isomer in rat and characterization of metabolites by LC/MS/MS. Sarah Tsay*[1,2] and John C. L. Erve[1]. [1] Wyeth Research, Drug Safety and Metabolism, Collegeville, PA 19426, [2] University of Maryland, Baltimore County, Dept. of Biochemistry, Baltimore, MD 21250.

Tienilic acid (Ticrynafen, TA) is a urocosuric diuretic drug that was launched in Europe in 1976 and later in the United States in 1979. By 1980, however, idiosyncratic hepatotoxicity in patients taking TA resulted in its withdrawal from the market. Although no hepatotoxic effects were observed with TA in preclinical animal studies, a contaminant representing a positional isomer where the thiophene is attached at C3, tienilic acid isomer (TAI), was found to be directly hepatotoxic. These observations indicated that slight structural changes in a molecule could have a profound impact on toxicology. Although TA and TAI have been investigated extensively, much of that work focused on reactive metabolite formation. The purpose of the present study was to use modern analytical techniques that were not available at the time of the original preclinical studies to re-examine the metabolism of TA and TAI in rat. To this end, rats were dosed p.o. with 30 mg/kg TA or TAI with bile and urine collected over 24 hours. Urine and bile samples were chromatographed using ultra performance liquid-chromatography (UPLC) and mass spectrometry was performed using a quadrupole orthogonal time-of-flight mass spectrometer. Differences in the resulting chromatograms of TA and TAI were striking and indicated that TAI underwent more extensive metabolism than TA. Several previously unidentified metabolites were also characterized by mass spectrometry in this study. Overall, this investigation has revealed that TAI undergoes more extensive metabolism than TA and in light of the recognized hepatotoxic properties, our observations support a metabolism based structure-toxicity relationship. Based on the present findings, we have initiated *ab initio* calculations that will attempt to rationalize the disparate behavior of TA and TAI based on molecular electronic factors.

Modulation of Cocaine-Induced Activity by Intracerebral Administration. Jordan Trecki* and Ellen Unterwald. Temple University School of Medicine, Philadelphia, PA 19140.

The role of chemokines in immune function is clearly established. Recent evidence suggests that these molecules also play an important role in the CNS. The chemokine CXCL12 has been identified in several regions of the adult rat brain including the substantia nigra, ventral tegmental area and caudate putamen. CXCR4, a receptor activated by CXCL12, is

expressed by dopaminergic neurons in the substantia nigra. The present study tested the effects of intracranial injections of CXCL12 on cocaine-induced locomotion and stereotypic activity in adult male Sprague Dawley rats. Results demonstrate that intracerebroventricular administration of CXCL12 (25 ng/4 µl) 15 minutes prior to cocaine (20 mg/kg, IP) produced a significant potentiation of both ambulatory and stereotypic activity as compared to cocaine alone. The effects of CXCL12 were blocked by administration of the selective CXCR4 antagonist, AMD 3100. Administration of CXCL12 into specific brain regions was performed to further understand the site of action of CXCL12. Administration of CXCL12 (25 ng/0.5 µl) bilaterally into the ventral tegmental area 15 minutes prior to cocaine (20 mg/kg, IP) significantly potentiated cocaine-induced ambulatory activity, whereas microinjections of CXCL12 into the caudate putamen selectively increased stereotypy. Conversely, administration of CXCL12 into the lateral accumbens shell resulted in an inhibition of cocaine-stimulated ambulatory activity. No alterations in ambulatory or stereotypic activity were observed following CXCL12 administration into the core of the nucleus accumbens. These results demonstrate that CXCL12 can modulate the behavioral effects produced by cocaine in a brain region-specific manner.

The Role of GSK3 In Cocaine Conditioned Reward. J.S. Miller* and E.M. Unterwald. Dept. of Pharmacology, Center for Substance Abuse Research, Temple University School of Medicine, Philadelphia, PA 19140.

Glycogen synthase kinase-3 (GSK3) is a critical mediator for a number of intracellular signaling systems. Originally isolated from skeletal muscle, this enzyme is widely expressed in all tissues with abundant levels in the brain. The activity of GSK3 is regulated by a number of kinases, with activation occurring via tyrosine phosphorylation and subsequent inactivation via serine phosphorylation. Studies from our laboratory indicate that pharmacological inhibition of GSK3 attenuates cocaine-induced locomotion in mice. Here, we investigated the role of GSK3 inhibition in cocaine-conditioned reward using a conditioned place preference paradigm. To assess the role of GSK3 inhibition on the development of cocaine conditioned reward, a 4-day unbiased conditioned place preference procedure was used in which adult male CD-1 mice were administered saline or cocaine (10 mg/kg, i.p.) and paired to alternate sides of the conditioning chamber for 30 minutes. Preference scores were determined in a drug-free state with animals having access to both sides of the conditioning chamber. Pretreatment with the selective GSK3 inhibitor SB 216763 (2.5 mg/kg, i.p.) 5 minutes prior to cocaine significantly attenuated the development of cocaine-induced place preference as compared to pretreatment with vehicle, indicating a reduction in the rewarding properties of cocaine. A similar unbiased 8-day conditioned place preference procedure was used to determine the role of GSK3 inhibition in maintaining cocaine place preference. Following testing for the initial expression of cocaine preference (day 9), mice were treated for 2 days (days 9 and 10) with vehicle or SB 216763 (2.5 mg/kg, i.p.) in their home cages and the maintenance of cocaine preference was assessed on day 11. Under these conditions, SB 216763 significantly attenuated the maintenance of cocaine conditioned reward as compared to vehicle treatment, indicating that inhibition of GSK3 enhanced the extinction of cocaine-induced place preference. These results indicate that GSK3 serves an important role in cocaine-conditioned reward and is a critical intracellular signaling protein for the development and maintenance of cocaine-induced place preference.

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A Novel Histidine Tyrosine Phosphatase, TULA-2, Associates with Syk and Negatively Regulates GPVI Signaling in Platelets. 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, 19140.

Glycoprotein VI (GPVI) is the primary platelet receptor for collagen signaling. Following damage to the vascular endothelium, the GPVI receptor interacts with the exposed sub-endothelial collagen. This interaction initiates a signaling cascade involving phosphorylation of the dual ITAM motif of the FcRγ chain by Fyn and Lyn, followed by the recruitment, phosphorylation and activation of Syk. This leads to the eventual activation of PLCγ2 and the liberation of calcium from intracellular stores to cause platelet activation. While a lot is known about the activation processes involved in GPVI signaling less is known about its negative regulation. The T-cell ubiquitin ligand (TULA) family of proteins have been implicated in the negative regulation protein tyrosine kinase (PTK)-dependent signaling pathways. More recently, it has been shown the TULA family member, TULA-2, exhibits phosphatase activity towards PTKs, including Syk, and this activity is responsible for the negative regulation of T-cell receptor signaling (Mikhailik et. al. 2007, Agrawal et. al. 2008). Thus, we investigated the role of TULA-2 in the negative regulation of the GPVI signaling cascade. We show that TULA-2 is expressed in both human and murine platelets. Deletion of TULA-2 in murine platelets manifests itself functionally as enhanced aggregation in response to the GPVI agonist convulxin as well as enhanced dense granule secretion when compared to wild type platelets. No difference was witnessed in response to the PAR4 agonist AYPGKF. TULA-2

deficient platelets also exhibit sustained hyperphosphorylation of Syk at tyrosines 525 and 526 as well as hyperphosphorylation of PLCγ2 at tyrosines 753 and 759, indicative of enhanced kinase and phospholipase activity respectively. GST-pulldown experiments suggest that Syk and TULA-2 are able to associate in resting and convulxin stimulated platelets and *in vitro* phosphatase assays demonstrate that TULA-2 can dephosphorylate Syk at tyrosines 525 and 526. Taken together, these data suggest that TULA-2 is a negative regulator of GPVI signaling and this is mediated by an association of TULA-2 with Syk, allowing the dephosphorylation of Syk at catalytically important tyrosine residues.

Repeated Exposure To a Stressful Environment Sensitizes the 5-HT$_{2A}$ Receptor. Laura Scarlota*, John A. Harvey, Vincent J. Aloyo. Department of Pharmacology & Physiology, Drexel University College of Medicine, 245 N. 15th Street, Philadelphia, PA 19102.

Serotonin (5-HT) receptors are involved in regulation of the stress response. One stressor, novel environment exposure, is mediated by 5-HT$_{2A}$ receptors as measured by rabbit head-bob behavior. Our goal was to determine if repeated exposure to the open-field modifies 5-HT$_{2A}$ receptors and behavior. New Zealand rabbits were observed in an open-field chamber for an hour, once daily for 6 days. Twenty-four hours after the last exposure to the open-field, rabbits were treated with the 5-HT$_{2A/2C}$ agonist, DOI (0.3µmol/kg). The open-field group had significantly more DOI-elicited head-bobs than home cage rabbits. Pretreatment with the 5-HT$_{2A}$ antagonist, ketanserin (1µmol/kg), significantly attenuated DOI-elicited head-bobs in rabbits exposed to the open-field by 65% compared with saline. These results demonstrate that chronic open-field causes behavioral sensitization of the 5-HT$_{2A}$ receptor. To determine if this behavior corresponds to an increase in 5-HT$_{2A}$ receptor density, rabbits were sacrificed and frontal cortex were obtained. Receptor density was measured by saturation binding using [^{3}H]ketanserin. There was no significant difference in the density of open-field or home cage rabbits suggesting down-stream mechanisms or secondary receptor systems may be responsible for behavioral sensitization. Further experiments showed the 5-HT$_{1A}$ agonist, 8-OH-DPAT, attenuates acute novelty-elicited head-bobs, thus future studies will examine the role of 5-HT$_{1A}$ receptors in the DOI response. Since aberrant signaling of the 5-HT$_{2A}$ receptor has been implicated in affective disorders and stress has been shown to exacerbate these disorders, the current findings involving stress-induced sensitization of the 5-HT$_{2A}$ receptor may have relevance in understanding neural mechanisms of these conditions.

Pharmacological Characterization of Serotonin Receptors in Mice. Dougherty JD*, Aloyo VJ, Harvey JA. Department of Pharmacology & Physiology, Drexel University College of Medicine, 245 N. 15th Street MS488, Philadelphia, PA 19102.

The serotonin (5-HT) 2A and 2C receptors are therapeutically-relevant targets for many disorders and physiological functions. Mice, rats, and rabbits are all used in an effort to elucidate the numerous roles of these receptors, and mice provide a particularly promising model for gaining a richer behavioral, pharmacological, and biochemical understanding of 5-HT$_2$ receptors through use of the wide array of available transgenic strains. To make full use of this model, we first must know its pharmacological profile and compare the mouse with other models. Our study was performed to provide a profile of the basic properties of this receptor.
Adult male C57Bl/6 mice were sacrificed, their cortices removed and frozen until assayed. 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors were examined using ^{3}H-ketanserin and ^{3}H-mesulergine, respectively. Scatchard analysis demonstrated that ^{3}H-ketanserin bound with high affinity (Kd = 0.45nM) and a density comparable to that observed in other species. ^{3}H-mesulergine also bound with high affinity (Kd = 0.3nM), but with a density approximately 1/10 of that observed in other species. Further analysis of 5-HT$_{2A}$ receptors using ^{3}H-ketanserin revealed that the highly-selective 5-HT$_{2A}$ antagonists, spiperone and MDL 11939, showed very high affinity for the mouse 5-HT$_{2A}$ receptor. In contrast, the highly-selective 5-HT$_{2C}$ antagonists (SB 206553 and RS 1022221) showed a very low affinity for the mouse 5-HT$_{2A}$ receptor. Our study demonstrates that 5-HT$_{2C}$ receptor contribution to binding in mouse cortex is minimal and mice offer an excellent model for examining the 5-HT$_{2A}$ receptor.

Ligand-Dependent Behavioral Recovery after Pharmacological Treatment in the Rabbit. Schindler EA*, Aloyo VJ, Harvey JA. Department of Pharmacology & Physiology, Drexel University College of Medicine, 245 N. 15th Street MS488, Philadelphia, PA 19102.

Serotonin2A (5HT2A) receptors signal through phosphatidylinositol (PI) hydrolysis and are associated with head movement behavior. The literature typically reports correlations in the density-signal-behavior relationship, but some find discordance among measures as well. Many of these studies are limited by the use of a single probe drug. Thus, in this study we measured changes in 5HT2A receptor density, PI hydrolysis signaling, and drug-elicited head bobbing behavior

using various agents. Rabbits were given daily injections of 5HT2A/2B/2C agonist DOI (3umol/kg) or saline for eight days. One to eight days after the last injection, some animals were sacrificed and frontocortical tissue harvested for receptor density and PI hydrolysis analysis. Other animals were first challenged with either DOI (300nmol/kg) or LSD (30nmol/kg), watched for head bobs for 60 minutes, and then sacrificed for receptor density analysis. One day after chronic treatment, 5HT2A receptor density, 5HT- and DOI-induced PI hydrolysis, and LSD-, and DOI-elicited head bobs were significantly reduced as compared to controls. In the days following cessation of drug administration, all measures returned to control levels, except DOI-elicited head bobs, which remained significantly reduced throughout the 8 day recovery period. These findings confirm the density-signal relationship for 5HT2A receptors, but reveal a ligand-dependent discordance in behavioral recovery. Pharmacological differences between LSD and DOI may address this asymmetry. For instance, LSD appears to remain bound to the 5HT2A receptor longer than DOI. The two agents also exhibit functional selectivity at 5HT2A receptor signaling, which will be the focus of future studies.

Serotonin Receptor Agonists Improve Motor Function Following Spinal Transection in Adult Rats. Elizabeth A. Dugan*, Nicole Amato, Katina Hanford, Michael Sabol, Stacy Jacob-Vadakot, Marion Murray, Jed S. Shumsky. Drexel University College of Medicine, Philadelphia, PA 19121

We studied the effects of administration of serotonin (5-HT) receptor agonists as a potential pharmacologic treatment for spinal cord injury. The loss of descending 5-HT projections contributes to locomotor deficits that follow complete thoracic spinal cord transection. Serotonin receptors in lumbar spinal cord respond by proliferating, providing a pharmacological target for 5-HT receptor agonists to improve motor deficits. We administered quipazine, a 5-HT_2 receptor agonist, and *m*CPP, a more selective 5-HT_{2C} receptor agonist to adult spinalized rats and found that hindlimb motor function improved from almost complete paralysis (BBB score = 0-1) to extensive movements around two or three joints with occasional sweeping (BBB score = 6-8). Both agonists also produced deleterious behavioral side effects such as hindlimb tremors and elements of the serotonin syndrome. Dose response curves where used to determine optimal doses for each agonist that improved hindlimb function while minimizing side effects. To identify the receptors that mediate the locomotor and behavioral side effects, we co-administered quipazine or *m*CPP with various 5-HT receptor antagonists. We found that a combination of 5-HT_{2A} (MDL 11,939) and 5-HT_{2C} (SB 206,553) receptor antagonists completely reversed both the improvements in locomotor function and hindlimb tremors elicited by either quipazine or mCPP. 5-HT_{2A} (but not the 5-HT_{2C}) receptor antagonist blocked the effects of quipazine. Neither antagonist alone blocked the locomotor improvements elicited by mCPP, but the 5-HT_{2C} (and not the 5-HT_{2A}) receptor antagonist blocked hindlimb tremors. Thus, the 5-HT_{2A} receptor plays a role in mediating hindlimb function following adult spinal transection and that the 5-HT_{2C} receptor contributes to these effects.

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Modulation of Nitric Oxide Production in Human EA.hy926 Cells as Measured by 3-Amino, 4-aminomethyl-2',7'-difluorofluorescein Dyes. Lauren D'Angelo* and Diane Morel. Department of Pharmaceutical Sciences, University of the Sciences, Philadelphia, PA 19104.

Human EA.hy926 cells, a hybridoma of human umbilical vein endothelial and A549 cells, were chosen as a model to study modulation of endothelial nitric oxide synthase (eNOS) activity because of their retention of endothelial morphology and function as well as superior growth characteristics. The fluorescence of nitric oxide (NO)-specific difluorofluorescein dyes, DAF-FM and DAF-FM-DA (^{RT} Calbiobiochem) was used to monitor extracellular and intracellular NO production, respectively, as an index of eNOS activity. Specificity and sensitivity of the assay were validated using a spontaneous NO donor, detaNONOate after labeling of cells with 5 μM of the intracellular form or co-incubation with 1 μM of the extracellular form of DAF-FM. DAF FM fluorescence was linear for both (r^2 of 0.98 and 0.89, respectively) with increasing amounts of NO. The limit of detection for the intracellular form was ≤ 34 nM NO and 68 nM NO for the extracellular form. Basal cell-mediated NO production was negligible; however, cellular oxidative stress, induced by BSO pretreatment and measured by dichlorofluorescin fluorescence, increased intracellular NO to about 50 nM; this was further enhanced by co-incubation with 100 uM H_2O_2. In contrast, pretreatment with vitamin C or co-incubation with 5-30 μM menadione increased cellular oxidative stress but reduced intracellular NO production. In the presence of tiron, a cell permeable SOD mimic, both basal and menadione-reduced intracellular NO production was enhanced. Cell pretreatment with tiron had no effect. Neither cell pretreatment with sepiapterin, a substrate in tetrahydrobiopterin synthesis, nor co-incubation with arginine, the substrate for eNOS, had any effect on NO production. A competitive inhibitor of eNOS, L-NAME, at 3-100 μM reduced basal NO production by ~35 %. In summary, EA.hy926 cells exhibit little to no basal NO production as measured by DAF FM dyes. However, this apparent NO production can be enhanced by certain forms of oxidative stress.

Similarities and Differences Between Pain and Itch Using Formalin-Induced Nociception and GNTI-Induced Excessive Scratching Models in Mice: Behavioral and Neuroanatomical Evidence. S. Inan*, N. J. Dun and A. Cowan. Department of Pharmacology and Center on Substance Abuse Research,Temple University School of Medicine, Philadelphia, PA 19140.

Pain and itch are two different sensations. The aim of the study was to establish similarities and differences between pain and itch using formalin-induced nociception and kappa opioid antagonist-induced excessive scratching in mice. Male, SW mice (25-30 g, n=8-10) were randomly selected. The neuroanatomical localization of neurons in the dorsal horn of the spinal cord, activated by pain and scratching, was detected using c-fos immunohistochemistry (IHC). Formalin (5%, 20 µl) or saline was injected s.c. to the dorsal side of the right hind paw. Other groups of mice were administered 5′-guanidinonaltrindole (GNTI, 0.3 mg/kg, s.c.) or saline to the back of the neck. C-fos IHC was performed in lumbar (for pain) and cervical (for scratching) spinal sections obtained at 2 h. Next, we investigated if intradermal (i.d.) pretreatment (at -10 min) with lidocaine (2%, 0.1 ml) antagonizes pain and scratching. Mice were injected i.d. with lidocaine (to the right hind leg) or saline. Formalin or saline was then injected and the time spent licking the right hind paw was recorded at 0-10 min and 20-35 min. For scratching, mice were pretreated i.d. with lidocaine (behind the neck) or saline and then challenged with GNTI or saline. The number of neck-directed scratches was counted for 30 min. Also, c-fos IHC was performed on the spinal cord sections mentioned above to examine effects of pretreatment with lidocaine on c-fos expression elicited by pain and scratch sensations. We found that (a) neurons activated by pain are located on the medial side of the superficial and deeper layers whereas neurons activated by scratch are located on the lateral side of the superficial layer of the dorsal horn, (b) lidocaine antagonizes responses to both pain and scratch and (c) lidocaine antagonizes c-fos expression evoked by both stimuli. Our results indicate that pain and scratch stimuli activate different neuron groups in the dorsal horn and argue for the comprehensive clinical testing of lidocaine as an antipruritic.

Serum and Glucocorticoid-Regulated Kinase Mediates Hypertension and End Organ Damage in DOCA-Salt Hypertension. Christine G. Schnackenberg[1], Melissa H. Costell*[1], Bao Hoang[2], Graham Duddy[3], Robert N. Willette[1]. [1]Department of Investigative & Cardiac Biology, [2]Discovery Technology Group, GlaxoSmithKline, King of Prussia, PA, 19406, [3]Discovery Technology Group, GlaxoSmithKline, Harlow, United Kingdom.

Serum and glucocorticoid-regulated kinase 1 (SGK1) plays an important role in mediating mineralocorticoid receptor stimulated sodium reabsorption. We have previously shown that SGK2 can compensate for renal sodium reabsorption in the absence of SGK1. Therefore, we tested the hypothesis that SGK1 and SGK2 contribute to the hypertension and end organ damage during DOCA-salt hypertension. The systolic blood pressure, cardiac, and renal responses to DOCA-salt hypertension or SHAM were determined in $sgk1^{-/-}$, $sgk2^{-/-}$ double knockout (DKO, n=20) and homozygous wildtype littermates (WT, n=19). During baseline conditions DKO had lower body weight and systolic blood pressure, and higher water intake and heart rate compared to WT. After 11 weeks of DOCA-salt hypertension, genetic ablation of SGK1 and SGK2 significantly attenuated the hypertension (192 ± 8 vs. 158 ± 6 mmHg), microalbuminuria (9.9 ± 2.1 vs. 5.0 ± 1.7 mg/day), left ventricular hypertrophy, renal fibrosis, protein deposition, and glomerular hypertrophy (3.3 ± 0.2 vs. 1.7 ± 0.3 total renal score), and morbidity and mortality (6/11 vs. 1/9 deaths). Absence of functional SGK1 and SGK2 shifted the pressure-natriuresis curve to the left and increased the slope, indicating improved renal function and reduced salt-sensitivity. These results suggest that SGK1 and SGK2 contribute to the cardiovascular and renal pathophysiology of DOCA-salt hypertension.

Identification of Cells with Cardiomyogenic Potential in Human Blood. Christian H. James*, Pu Qin, Laurie Mackenzie, Ming Gui, Bryan E. Hoffman, Scott D. Gardner, Jay M. Edelberg and Victoria L.T. Ballard. GlaxoSmithKline, King of Prussia, PA, 19406

The discovery of cardiac stem cells in recent years has led to great interest in the development of therapeutic strategies that target these endogenous cell sources for cardiovascular repair. It is most important to optimize these new therapies for the treatment of older individuals who have the highest prevalence of cardiovascular disease. While most studies have focused on the use of bone marrow-derived cells, the development of strategies targeting blood-borne stem cells may facilitate the widespread application of cardiac regenerative therapies. To determine whether blood is indeed a source of cardiac stem cells, we developed a high density culture assay to assess the cardiomyogenic potential of peripheral blood mononuclear cells (PBMCs) isolated from healthy human volunteers (age = 23-35y, n=10). Baseline analysis revealed expression of the stem cell genes oct-3/4 and c-kit in whole blood as well as PBMCs. PBMC culture however resulted in a complete downregulation of the stem cell markers (d7, c-kit = 19% of d0, oct-3/4 = <1% of d0). Strikingly, this decline

coincided with induction of expression of cardiac structural genes, including α-and β-myosin heavy chain and cardiac troponin T. The increase in cardiac Troponin in these cultures was confirmed by flow cytometry (~25% Troponin+ cells by d7). Additionally, factors important for embryonic cardiomyogenesis, including Activin-A and BMP-4, further increased cardiac gene and protein expression levels by >2-fold. Based on these results, we examined potential age-associated changes in circulating stem cell populations. Q-RTPCR analysis of gene expression in blood samples from young (age = 23y±2.1, n=20) and old (age = 69y±5.0, n=40) subjects was performed. Notably, oct-3/4 expression levels were maintained in the older population, while c-kit expression decreases with age (38.0% decrease vs. young, P=0.006). These findings thus demonstrate that human blood contains a population of pluripotent stem cells with the potential to generate cardiomyocytes in vitro. Moreover, targeting the age-associated decline in the c-kit+ stem cell population may provide novel therapeutic strategies to promote cardiac stem cell repair mechanisms in older individuals.

Post-Treatment with Hypoxia-Inducible Factor Proline Hydroxylase (HIF-PH) Inhibitor Improves Cardiac Function Through Promoting Angiogenesis in the Rat After Myocardial Infarction. Weike Bao*, Connie Erickson-Miller, Kevin J. Duffy , Jennifer L. Ariazi, Shufang Zhao, Rosanna Mirabile, Sheri Moores, Beat M Jucker, John Lepore, Tianli Yue, Robert N. Willette. GlaxoSmithKline, King of Prussia, PA, 19406.

Background: Hypoxia inducible factor (HIF) is a transcriptional factor regulating genes that play roles in angiogenesis, erythropoiesis, and proliferation/survival. We hypothesized that stabilization of HIF by GSK360A, a novel, orally active prolyl hydroxylase inhibitor, protected the heart following myocardial infarction (MI) through promoting angiogenesis.
Methods and Results: Lewis rats were subjected to myocardial infarction and randomized to treatment with 360A (30 mg/kg/d, oral, for 4 weeks, n=18) or vehicle (n=17) starting 48 h after MI. MI significantly reduced ejection fraction (EF, %) from 71 in the sham group to 43, 38, 37 and 32 in the vehicle group at 48 h, 2 weeks, 4 weeks and 3 months, respectively, after MI. In contrast, EF at 2 and 4 weeks following MI in 360A-treated group were similar to the level at 48 h after MI (45%), and significantly higher than that in vehicle group ($p<0.01$ at both time points) suggesting that 360A abolished progressive cardiac dysfunction induced by MI. Moreover, EF was still significantly improved at 3 months compared to the vehicle group (36±1.0% vs. 32±1.2%, $p<0.05$). The improved cardiac function was accompanied by an increased level of erythropoietin and hemoglobin. In addition, 360A attenuated left ventricular end diastolic pressure and pulmonary edema. Histological analysis revealed that 360A significantly attenuated right ventricular hypertrophy and increased α-SMA staining in the MI hearts suggesting that 360A increase mature vessels and improve the angiogenesis.
Conclusion: These results suggest that HIF-PH inhibitors may provide a novel approach for treatment of chronic heart failure.

Role of the Serotonin Receptor 1B in the Induction of Apoptosis in Breast Cancer. *Diane Hansali-Delpy[1], Mauricio Reginato[1] & Bradford Jameson[1]. [1]Drexel University College of Medicine, Department of Biochemistry & Molecular Biology Philadelphia, PA 19102.

Serotonin is primarily thought of as a neurotransmitter. But only 5% of the body's serotonin is in the central nervous system. Our data demonstrate that the serotonergic pathways are functionally present in Breast Cancer cells.

We have characterized the mRNA encoding the various serotonin receptors in MCF-10A (immortalized from normal tissue), MCF-7 (estrogen positive), and MDA-MB-231 (estrogen negative). The data were compared to normal epithelial cells (HMEC). The 'machinery' for responding to serotonergic signals was present in all of the cell types at different level. We charcoal-filtered the sera in order to grow the cells in the absence of exogenously added serotonin. Because charcoal-filtering removes other small molecules, we added back serotonin to the media to find out if any of the transcriptional changes were related to the serotonin pathway. There is clearly a feedback pathway in all of these cells that transcriptionally respond to the presence or absence of serotonin.

When cultured in monolayer, all cell lines tested are highly sensitive to the selective inhibition of the 1B receptor, independently of their $5HT_{1B}$ transcription level.
But when the same MCF-10A are cultured in 3D matrigel and form acini they become resistant to the inhibitor; while erbB2 over expressing MCF-10A die with the same exposure. In MCF-7, withdrawal of the serotonergic signal through the 1B receptor seems to result in cell-cycle arrest then induction of programmed cell death.

Collectively these data suggest that serotonergic pathways may offer new therapeutic targets in the design of treatment strategies for combating breast cancer.

Differential Responsivity to the Behavioral Effects of Cocaine in Mice Lacking the Delta Opioid Receptor. Karen A. Pescatore and Ellen M. Unterwald. Temple University School of Medicine, Department of Pharmacology, Center for Substance Abuse Research, Philadelphia, PA, 19140.

Previous behavioral and pharmacological evidence suggest that opioid receptors are involved in the rewarding and locomotor activating effects of cocaine. To examine the functional role of the delta opioid receptor (DOR), the present experiments used DOR knockout mice, produced by deleting exon 2 of mouse gene DOR-1 (Zhu et al., 1999). Using DOR knockout as well as wild-type mice, cocaine-induced reward and locomotor behavior were assessed. Specifically, to assess cocaine reward, a conditioned place preference procedure was used in which mice were injected with cocaine (10 mg/kg ip) on Days 1 and 3 and confined to one side of the two-sided chamber. On alternating days, animals were injected with saline and confined to the other side of the chamber. This procedure was repeated for a total of four days. On the day following the last conditioning day, animals were tested for the establishment of place preference. Results indicate that cocaine-induced place preference was attenuated in DOR knockout mice. Given that DOR agonists can stimulate locomotion, the locomotor activating effects of cocaine in DOR knockout mice were compared to wild-type mice. Acute administration of cocaine induced greater locomotor activity and stereotypy compared to saline; however, there were no significant differences between genotypes. Although the acute effects of cocaine did not differ between DOR knockout and wild-type mice, it was also of interest to examine the effect of cocaine administration and the development of behavioral sensitization, the results of such assessments are discussed. These results indicate that the delta opioid receptor may be involved in the rewarding effects of cocaine, but not its acute locomotor activating effects.

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Factors Affecting Cannabinoid CB1 Receptor Modulation of Reinforcement Processes. Sara Jane Ward[1]*, Rebecca G. Hamby[1], Marisa B. Rosenberg[1], Linda Dykstra[2] and Ellen A. Walker[1]. [1]Department of Pharmaceutical Sciences, Temple University 19140, [2]Department of Psychology, The University of North Carolina, Durham, NC 27514.

Cannabinoid CB1 antagonists have promising therapeutic potential as anti-obesity and anti-addiction compounds. For example, pharmacological antagonism or genetic invalidation (knockout, or KO) of CB1 receptors decreases the reinforcing properties of sucrose, heroin, alcohol, and nicotine in laboratory animals. The CB1 receptor antagonist SR141716, a.k.a. Rimonabant, improves weight loss in obese humans and decreases relapse to cigarette smoking in clinical trials. However, several questions regarding the role of CB1 receptors in reinforcement remain unanswered. The present series of experiments characterized and compared factors affecting CB1 receptor modulation of reinforcement processes, including: 1) the reinforcement behavior being modeled; 2) the role of the reinforcer type (palatable sweet food, palatable non-sweet food, cocaine); 3) CB1 receptor antagonism versus KO; and 4) the sex of the experimental subject. Male and female C57Bl/6 wild type and CB1 KO mice were trained to self-administer vanilla Ensure, corn oil, and cocaine under fixed ratio and progressive ratio schedules of reinforcement. For pharmacological antagonism studies, mice were pretreated with 1.0 – 10.0 mg/kg SR141716 or vehicle. Results revealed that several factors impact the extent to which CB1 receptors modulate reinforced behavior. CB1 receptor antagonism and KO modulated reinforcement behavior across several self-administration models, including acquisition, motivation, and relapse behavior. While CB1 receptor antagonism and KO attenuated Ensure and drug reinforcement, the reinforcing properties of corn oil were only weakly affected by CB1 modulation. Although the majority of SR141716 effects closely mirrored the effect of CB1 KO in our studies, SR141716 attenuated motivated behavior in some assays that were not affected by CB1 KO. Lastly, reinforcement behaviors were more robustly decreased in female versus male CB1 knockout mice. Taken together, these studies demonstrate that the type of reinforcer, pharmacological manipulation versus genetic invalidation, and sex impact the role of CB1 receptors in reinforced behavior.

This work was supported by grants F32-DA01931 (SJW), R01-DA002749 (LAD), and R01-DA014673 (EAW).

Ceftriaxone, Beta-Lactam Antibiotic and Glt1 Activator, Attenuates Acute and Senstized Locomotor Responses to Amphetamine. Bruce A. Rasmussen,[1,2]* Ellen M. Unterwald,[2,3] and Scott M. Rawls[1,2]. [1]Department of Pharmaceutical Sciences, Temple University, School of Pharmacy, Philadelphia, PA, 19140; [2]Center for Substance Abuse Research, Temple University, Philadelphia, PA, 19140; [3]Department of Pharmacology, Temple University, School of Medicine, Philadelphia, PA, 19140.

A variety of disorders such as psychostimulant addiction, are regulated by glutamate, a neurotransmitter rapidly cleared by uptake via the glutamate 1 (GLT1) transporter. Because antibiotics with beta lactam structure such as ceftriaxone

(CFT), upregulate GLT1 we hypothesized that CFT would alter locomotor responses to amphetamine (AMP). Male adult rats (N=8 for all groups) were treated with CFT (200mg/kg) or saline (Sal) on days 1-5. On days 6-8 pretreatment with either CFT or Sal continued followed by an injection of either AMP (2mg/kg) or saline. On day 13 all groups were challenged with AMP (2mg/kg). There were no significant acute or sensitized effects of CFT administered alone. In contrast, CFT partially blocked and the development of sensitized locomotor responses in stereotypy and ambulation. CFT also partially attenuated the acute effects of AMP in both responses. Chronic treatment with CFT did not alter NMDA receptor levels. Current work is examining the effect of CFT on GLT1 protein regulation. These results suggest therapeutic potential for drugs with beta lactam structure in treating psychostimulant abuse.

Supported in part by T32 DA07237 (EMU/BAR)

Spider Venom 163 as a Novel Pharmacological Tool. M. Mori, R. Peri, L. He, Q. Shan, D. Chen, R. Arias, M.R. Bowlby, J. Dunlop. Neuroscience Discovery, Wyeth Research, CN8000, Princeton, NJ 08543.

Background and Study Objectives: TRPM channels have emerged as potential therapeutic targets for their ability to modulate calcium and magnesium influx during pathological (stroke and pain) and physiological conditions. To date, no specific pharmacological inhibitors of the TRPM2 channels are available; our aim was to identify such inhibitors.

Methods: HEK293 cells expressing TRPM2, TRPM7 and TRPM8 channels were tested in Fluorometric Imaging Plate Reader (FLIPR), patch clamp electrophysiology and in cell death assays.

Results: We screened a small library of spider venom toxins in FLIPR on TRPM2 channels and in a panel of ion channels to test for specificity of action. We identified the spider venom 163 (SP-163) as a specific reversible inhibitor of TRPM2 channels. 10 µg/ml of SP163 blocked ~85% of the TRPM2 currents. SP-163 was selective against the related TRPM7 channel and channels from the Nav (1.2, 1.5, 1.7, 1.8), HCN (1 and 2), KCNQ (2, 3, 5) and hERG families. Staining with propidium iodide showed that 1 hour exposure to 1.1 µg/ml crude SP-163 did not alter cell viability.

Summary/Conclusions: SP163 is a novel TRPM2 channel blocker which can specifically block ADPR and H_2O_2-activated TRPM2 currents. Therefore it can potentially be used as a pharmacological tool to assess TRPM2 channel function.

The Endogenous Nitrated Fatty Acid 9-Nitro-Oleate Stimulates Nociceptive Sensory Nerves via The Activation of TRPA1 Channels. TE Taylor-Clark*, W Bettner, BJ Undem. Johns Hopkins School of Medicine, Baltimore, MD 21224.

Introduction: Nitro-oleate is a fatty acid that has been found in esterified form in phospholipids comprising plasma membranes. Nitro-oleate can presumably be released from the membrane via the action of specific phospholipases. Nitro-oleate is formed following the nitration of oleic acid (either free or esterified), which can occur downstream of the endogenous production of peroxynitrite during oxidative stress. Oxidative stress is associated with a wide range of visceral pathophysiologies that have inappropriate nociceptive sensory nerve activation. Nitro-oleate is capable of forming covalent modification of cysteine residues via the Michael reaction. These types of covalent modifications of cysteine residues on the nociceptive sensory nerve ion channel TRPA1 have been shown to gate the cation channel pore, leading to nociceptor activation. We therefore hypothesize that 9-nitro-oleate (9-OA-NO2) will activate TRPA1 channels.

Methods and results: 9-OA-NO_2 (0.03-30µM) activates HEK cells stably transfected with human TRPA1 channels (hTRPA1-HEK) as shown by Fura 2AM calcium imaging. 9-OA-NO2 (0.03-100uM) has no effect on non-transfected HEK cells or HEK cells stably transfected with human TRPV1 channels. In addition, oleic acid (0.1-100µM) failed to activate hTRPA1-HEK cells. The activation of hTRPA1-HEK cells by 9-OA-NO_2 (3µM) was not inhibited by the NO scavenger carboxy-PTIO (1mM) but was partially inhibited by the reducing agent dithiothreitol (1mM). Using acutely dissociated mouse vagal sensory neurons, we have shown that 9-OA-NO2 (10µM) robustly activates approximately 40% of wild-type neurons in our Fura 2AM calcium imaging assay (these neurons also responded to TRPA1 agonist allyl isothiocyanate and to the TRPV1 agonist capsaicin). However, in vagal neurons dissociated from TRPA1-/- mice, 9-OA-NO_2 responses were reduced by approximately 90% compared to wild-type. In an ex vivo vagally innervated mouse lung preparation, 9-OA-NO_2 evoked action potential discharge from capsaicin-sensitive C-fiber nerve terminals, but not capsaicin-insensitive vagal afferent nerves.

Summary: 9-nitro-oleate is a potent endogenously produced activator of TRPA1 channels and is capable of activating sensory nerves in a TRPA1-dependent manner. Nitration of oleic acid (thus forming the TRPA1 agonist OA-NO_2)

represents a mechanism by which oxidative stress can modulate nociceptor activity, either immediately or after subsequent phospholipase activation events.

A Possible Role of Fetal/ Embryonic Cells in the Mechanisms of Signal Transduction. Godfrey Caesar*, 209 West 137th St., NY., NY 10030.

Ultimate aging and death has the following stages, birth to maturity, to aging and death. The following processes may be included, i.e Hormonal control, limited cell division, gene/s mutation, protein cross linkage, and free radicals.

Put another way aging is a process of a general system/s failure which eventually cripples a person to the point of death. Members of the same species, more so of genetic similarity have similar life expectancies. The embryo – fetus which develops into a person who dies from "natural old age", must be wholesome in nature (not disease/s) prone. Therefore, such embryonic/fetal cells can be used as a form of gene therapy to compensate for the immunological breakdown (internal body defenses) or genetic defect/s (mutation, alteration or loss of protective gene/s), and thus help to prevent disease in various parts of the human body.

These cells are transgenic and may help the prolongation of life with a minimum of disease. The eventual outcome of the mechanisms of signal transduction is an alteration in cellular activity and changes in the program of genes expressed within the responding cell.

Wholesome embryonic/ fetal cells can help regulate gene/s expression for the benefit of the individual. i.e. survival of the fittest. Embryonic sheep or pig extracts may be useful. Med. Hyp. (2002), 58 (5) 371-373 help explain the possible genetic origin and possible prevention of at least some diseases, and Nature vol 444, 14th Dec, 2006, 894-898 helps explain the genetic mechanism of no sensation of pain in some individuals.

(+/-)TC-5619 Produce a Profound Desensitization of Alpha-7 Nicotinic Receptor Activated Currents In Vitro. F. Jow, M.R. Bowlby,* T. Lock, R. Peri, D. Kowal, A. Nencini, S. Haydar, C. Ghiron, G. Tertsappen and J. Dunlop. Neuroscience Discovery, Wyeth Research, Princeton, NJ 08543.

Alpha-7 (α7) nicotinic acetylcholine receptor (nAChR) agonists are promising therapeutic candidates for the treatment of cognitive dysfunction associated with a variety of disorders including schizophrenia and Alzheimer's disease, and a number of selective agonists have now been disclosed. TC-5619 has recently been identified as a potent and full agonist at the α7 nAChR. In this study we have examined the effect of (+/-)TC-5619 on α7 nAChR agonist-evoked currents in stably expressing GH4C1 cells. The α7 nAChR agonist activity of (+/-)TC-5619 was confirmed in a FLIPR based assay measuring agonist activation of calcium flux. In electrophysiological experiments, sequential application of increasing concentrations of acetylcholine to GH4C1/α7 cells produced a concomitant concentration-dependent increase in the magnitude of evoked currents (EC_{50} = 30 μM). Interestingly, sequential application of (+/-)TC-5619 to GH4C1/α7 cells resulted in small currents in the presence of low drug concentration and no subsequent response when higher concentrations of compound were applied. Cells treated with low concentrations of (+/-) TC-5619 were also found to be unresponsive to subsequent addition of acetylcholine, suggestive of a profound and long-lasting receptor desensitization to these low drug concentrations. This desensitization could be reversed by PNU-120596, a strong Type-II PAM of α7. Potent α7 nAChR agonist activity of (+/-)TC-5619 could be demonstrated by treating individual cells with a single concentration of drug (EC_{50} = 0.11 μM; E_{max} = 0.76). Similarly, a number of closely related (+/-)TC-5619 analogs were found to be potent α7 receptor agonists but only when evaluation of each concentration of drug was restricted to a single cell. In contrast, a series of unrelated α7 nAChR agonists, representing diverse chemotypes, e.g., SEN12333, were found to produce a similar concentration-dependent increase in evoked currents when applied sequentially to the same cell, as was observed with acetylcholine. These results suggests unique properties of (+/-)TC-5619 with respect to α7 nAChR desensitization when compared with other selective α7 agonists.

Strategies for Assessment of State-Dependent Inhibition of Voltage-Gated Sodium Channel NaV1.7. Chen, H., Zhang, H., Tseng, E., Shan, Q., Shen, R., Lou, Z., Peri, R*., Kaftan, E., Kennedy, J., Dunlop, J., Mayer, S., and Bowlby, M.R. Wyeth Research, Discovery Neuroscience, Therapeutic Area, Princeton, NJ.

Voltage-gated sodium channel Nav1.7 is expressed in dorsal root ganglion (DRG) neurons. Genetic evidence shows that people with loss of function mutations are insensitive to pain and gain of function mutations are hypersensitive to pain, implicating inhibition of Nav1.7 as a strategy for pain management. Pharmaceutical sodium channel screening strategies

employ a combination of optical and electrophysiological assays. Using a recombinant human Nav1.7 cell line we describe here an optimized 384 well membrane potential FLIPR assay and planar electrophysiological IonWorks assays to identify Nav1.7 blockers with a moderate to high throughput. Compounds from 16 different chemical series and a standard (imipramine) were used in this validation. Using IonWorks Quattro compounds with state-dependent inhibition of Nav1.7 can be identified. State-dependent inhibition protocols can also be used to investigate the effects of these compounds on selectivity channels Nav1.5 and Nav1.2 . Our results show a good pharmacological correlation of FLIPR results with electrophysiological data obtained in IonWorks.

Whole Blood PAI-1 mRNA is a Biomarker of CCR2 Inhibition in Macrophage Recruitment and Atherogenesis. Pu Qin[1*], Alan Olzinski[2], Laurie MacKenzie[1], Roberta Bernard[2], Carla Cornejo[2], Patricia Welch[4], Steve Clark[4], Jessica Schroeck[4], Scott Gardner[4], Greg Turner[2], Beat Jucker[2], Clark Sehon[3], Erding Hu[1], Jay Edelberg[1] and Peter Gough[2]. [1]Translational and Regenerative Medicine, [2]Biology, [3]Chemistry, Metabolic Pathway CEDD, Molecular Discovery Research, GlaxoSmithKline, King of Prussia, PA 19406.

Chemokine (C-C motif) receptor 2 (CCR2), a GPCR predominantly expressed by monocytes and macrophages, is important in monocyte recruitment to sites of inflammation including atherosclerotic plaque through binding to chemokine Monocyte Chemoattractant Protein 1 (MCP-1). Based on the correlation between reduced MCP-1/CCR2 activity and decreased vascular inflammation and atherosclerosis, CCR2 antagonists are being developed for the clinical treatment of atherosclerosis. In order to facilitate the clinical development of a CCR2 antagonist we sought to identify and validate potential blood-borne biomarkers of pharmacologic CCR2 inhibition. An initial *in vitro* transcriptomic study identified 558 genes in primary human monocytes regulated by MCP-1 for >2 fold. Subsequent Taqman analysis demonstrated that PAI-1 mRNA was both consistently induced by MCP-1 (3-fold) and was specifically down regulated by CCR2 inhibitor, GSK1344386B (4-fold reduction). *In vivo* studies in a thioglycollate (TG) induced peritonitis model with huCCR2 knock-in mice showed PAI-1 mRNA expression in whole blood is upregulated by TG (3-fold at 6 hr). Pre-treatment with CCR2 inhibitor before TG resulted in a dose-dependent reduction of this PAI-1 upregulation (maximal 90% reduction vs. TG). Importantly, the whole blood PAI-1 levels showed a significant correlation with TG-induced peritoneal monocyte recruitment ($r=0.88$, $p<0.05$). To further test its utility as a biomarker of CCR2 antagonism, whole blood PAI-1 levels were measured in huCCR2 knock-in ApoE$^{-/-}$ mice treated with a combination of Angiotensin II and high-fat diet to accelerate atherosclerosis. Mice treated with CCR2 antagonist for 5 weeks had 35% lower whole blood PAI-1 mRNA levels compared with vehicle treated controls ($p<0.05$), correlating with a 17% reduction in aortic root atherosclerotic lesion size ($p<0.05$). Overall, these significant correlations between whole blood PAI-1 mRNA and macrophage recruitment and atherosclerosis highlight the potential utility of PAI-1 mRNA to serve as a robust blood-borne biomarker in translational studies of CCR2 inhibition.

TRPV4 Currents Recorded from Freshly-Isolated Guinea-Pig Urothelial Cells. Xiaoping Xu*, Zuojun Lin, Earl Gordon, Irina M Lozinskaya, Yifeng Chen, Kevin S Thorneloe. Metabolic Pathways CEDD, GlaxoSmithKline, King of Prussia, PA, 19406.

Introduction: TRPV4 is expressed in both smooth muscle and urothelial cells of the urinary bladder and has been shown to modulate bladder function. We therefore investigated the electrophysiological properties of TRPV4 expressed in the urothelium.

Methods: Single urothelial cells were freshly isolated from guinea pig urinary bladder with collagenase. Conventional whole-cell patch-clamp was used to record membrane currents, and isolated urothelial cells were collected for Taqman analysis using a wide-bore patch pipette.

Results: Taqman analysis of the urothelial cells confirmed their identity, with a high expression of the urothelial-selective marker uroplakin 1a, along with TRPV4. The TRPV4 agonist, GSK1016790A, activated TRPV4 currents in the freshly isolated guinea-pig urothelial cells that were completely inhibited by ruthenium red (5 μM). The EC_{50} for GSK1016790A was determined to be 11 nM, with an averaged current density of -79±35 pA/pF and 168±40 pA/pF (n=5) at -60 mV and + 60 mV, respectively, using 10 nM GSK1016790A. In addition, TRPV4 currents in urothelial cells were activated by hypotonic extracellular solution (240 mOsm) and by arachidonic acid (10 μM). In these guinea-pig urothelial cells, under the same experimental conditions, the TRPV1 agonist capsaicin (10 μM) did not activate any current.

Conclusions: We demonstrate for the first time that TRPV4 channels are functionally expressed at the plasma membrane of freshly-isolated urothelial cells from guinea-pig, whereas TRPV1 currents were not detectable. These data further

support a functional role for TRPV4 in urothelial cell physiology, and represent the first ionic current measurements obtained from freshly-isolated urothelial cells.

Biological Characterization of Latrophilin-2 and its Genetic Association with Hypertension. Christopher Knouff[a], David J. Behm[b], Kijoung Song[a], Yifeng Chen[c], Quinn Lu[d], Katie Freeman[c], Michael McQueney[c], Tom Sweitzer[d], GENECARD investigators[e], Ruth McPherson[f], Abby Sukman[d], Matthew Burns[d], James Fornwald[d], Dawn Waterworth[a], Robert Willette[b], Vincent Mooser[a], Alan Olzinski[b]. [a]Genetics Division, [b]Metabolic Pathway Center of Excellence for Drug Discovery, [c]Discovery Target Genetics, and [d]Biological Reagent and Assay Development GlaxoSmithKline, King of Prussia, PA and Research Triangle Park, NC. [e]See poster for complete listing, [f]Division of Cardiology, University of Ottawa Heart Institute, Ottawa, ON, Canada.

Introduction: In two population based studies, SNPs within the *LPHN2* gene, encoding latrophilin-2, were associated with hypertension. Latrophilin-2 is a large family B, G-protein coupled receptor that binds to the black widow-spider vertebrate venom alpha-latrotoxin, a toxin which can cause severe hypertension in humans.

Purpose: The purpose of this study was to characterize the biology of LPHN2 in relation to hypertension.

Results: Taqman data demonstrated that the *LPHN2* gene is highly expressed in the vasculature of human tissue. A cell-based assay system (FLIPR) was developed to evaluate latrophilin-2 function demonstrating increased Ca+ signaling with addition of toxin. siRNA for LPHN1 and LPHN2 was then used to evaluate specificity of the receptor. Furthermore, since alpha-latrotoxin is known to form pores in cell membranes, we constructed a non-pore forming mutant of alpha-latrotoxin. Both the wild and mutant reagents mediated contraction of rat mesenteric arteries and raised blood pressure (~40 mmHg) in rats.

Conclusion: Taken together, these clinical, genetic, biochemistry and pharmacology data converge towards latrophilin-2 playing a role in regulating blood pressure.

MEMBERS IN THE NEWS

Linda S. Birnbaum, PhD, has been appointed Director of the National Institute of Environmental Health Sciences (NIEHS). Dr. Birnbaum, who is currently a Senior Advisor at the Environmental Protection Agency (EPA), where she served for 16 years as Director of the Experimental Toxicology Division, will begin her new role in January 2009. Dr. Birnbaum is a past Chair of ASPET's Toxicology division and has served on the Program committee.

Brian M. Cox, PhD, past Chair of Pharmacology at Uniformed Services University School of Medicine (USUHS), was honored on November 13th by USUHS. A symposium was held in his honor. Sessions at the symposium included "Opioids and other drugs of addiction" and "Neuropharmacology and neurologic disorders." A celebratory dinner followed the symposium. Dr. Cox is the current President-Elect of ASPET, has served as the Chair of the Board of Publications Trustees, and has been involved with many ASPET committees.

Susan B. Horwitz, PhD, Distinguished Professor at Albert Einstein College of Medicine of Yeshiva University, Falkenstein Professor of Cancer Research, and Co-Chair of the Department of Molecular Pharmacology, has received the American Cancer Society's highest honor, the Medal of Honor for Clinical Research, for her outstanding contributions in the fight against cancer. Dr. Horwitz is an internationally recognized molecular pharmacologist who has made major contributions to our understanding of antitumor drugs. Her pioneering research in identifying the mechanism of action of Taxol®, as an inhibitor of cell division due to its interaction with microtubules, led to clinical trials of this drug in the mid-1980s. Taxol® is now involved in the first line of treatment in many cancers, including ovarian, breast and non-small cell lung cancer. The drug has been administered to more than one million patients. Dr. Horwitz has won numerous awards, including the ASPET Award for Experimental Therapeutics.

V.C. Jordan, PhD, DSc, Vice President and Research Director for Medical Sciences and the Alfred G. Knudson Chair of Cancer Research at the Fox Chase Cancer Center, has received two honorary awards from professional societies that recognize his pivotal role in the development of the selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene. Dr. Jordan has been elected as an Honorary Member of the Royal Pharmaceutical Society of Great Britain and has also received what is considered to be the highest honor in medicine in the United Kingdom, an Honorary Fellowship of the Royal Society of Medicine.

(This announcement was originally published in ASBMB Today)

Albert Sjoerdsma, MD, PhD, a 51-year member of ASPET and recipient of the 1977 Harry Gold Award in Clinical Pharmacology and the 1990 Award for Experimental Therapeutics, is the subject of a new biography-memoir*, Starting with Serotonin: How a High-Rolling Father of Drug Discovery Repeatedly Beat the* Odds ($27.50, Improbable Books, www.improbablebooks.com). Richly detailed and well-researched, *Starting with Serotonin*, by award-winning journalist and lawyer Ann G. Sjoerdsma, Dr. Sjoerdsma's daughter, relates the scientific journey of a bench-to-the-bedside pioneer who is often referred to as the Father of Clinical Pharmacology.

STAFF NEWS

Crystal Wygal, joined ASPET on November 24th as the temporary Meetings Assistant. She will be assisting Nancy White in planning and organizing the Annual Meeting in New Orleans. She will be involved with updating databases, planning and booking space for special events, and much more. Crystal will be with ASPET until the end of April and will be attending the Annual meeting. In her spare time, Crystal loves painting, making jewelry and other crafts. She has a special interest in Medieval history.

ASPET WELCOMES THE FOLLOWING NEW MEMBERS:

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ASPET notes with sympathy the passing of the following members:

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Edward J. Walaszek

Billy R. Martin, PhD
1943 - 2008

Billy R. Martin, husband, father, friend and world renowned scientist and educator died at his home on June 8, 2008. Billy was born in Kernersville, North Carolina on April 25, 1943. He earned an AB in Chemistry and a Ph.D. in Pharmacology from the University of North Carolina at Chapel Hill. His loyalty to that institution lasted throughout his life and was only surpassed by his devotion to his family and his friends.

For his doctoral dissertation, Billy performed seminal work to show that the pronounced tolerance to delta-9-tetrohydrocannabinol was a pharmacological tolerance in the neurons of the central nervous system and not a metabolic or distributional tolerance, which had been hypothesized. He continued his training in cannabinoid pharmacology at the University of Uppsala in Sweden and at Oxford University in England. He became an Assistant Professor of Pharmacology at Virginia Commonwealth University in 1976 and rose through the ranks to become full Professor in 1987 and Chair of the department in 2000.

Billy was universally recognized as one of the top pharmacologists in the field of cannabinoid research and added significantly to our knowledge of the mechanism of action of nicotine and other drugs of abuse. He characterized the dependence liability of cannabinoids and, with the leading chemists in the field as collaborators, carried out an extensive investigation of the structure activity relationships of these interesting compounds. His methodology for the characterization of the pharmacological profile of cannabinoids has been used by most scientists working in this field. It clearly is the standard of practice.

Billy carried out the definitive pharmacological, cellular and molecular investigations of the first identified endogenous cannabinoid, anandamide. He demonstrated that tolerance developed and a withdrawal syndrome existed following the cessation of its chronic administration. He demonstrated and characterized the existence of two types of cannabinoid receptor and recently presented evidence of a third receptor.

He combined receptor binding assays with classical pharmacological models in whole animals to characterize the reinforcing effects of nicotine and similar compounds. He, along with other chemists as collaborators, did an exhaustive structure activity relationship which provided a much better understanding of the nicotinic receptor and defined the structural requirements for nicotinic agonists and antagonists.

Billy published over 400 papers, chapters and reviews. His scholarly work was very well funded throughout his career. He earned a MERIT award, and was the principal investigator on a center grant and a program project grant studying various aspects of the pharmacology of cannabinioids. He also earned an RO1 grant to characterize the acute and chronic effects of abused drugs taken by inhalation and other grants to study nicotine. The list of his collaborators from this and other countries is most impressive. He served as chair of study sections, as field editor for The Journal of Pharmacology and Experimental Therapeutics and was elected president of two international scholarly organizations, The College on Problems of Drug Dependence (CPDD) and The International Cannabinoid Research Society (ICRS).

Billy was honored by his university with their awards of scholarship and overall excellence, by the Commonwealth of Virginia as its outstanding scientist, by CPDD with the Nathan B. Eddy Award and by ICRS by the Mechoulam Award. Billy was a distinguished neuropharmacologist and friend who will be missed by numerous scientists throughout the world but most by those of us who had the pleasure to work with him daily for many years.

Prepared by William L. Dewey, PhD, Virginia Commonwealth University.

Norman J. Uretsky, Ph.D.
1941 – 2008

Professor Norman J. Uretsky, age 67, passed away on 20 September, 2008, in Columbus, OH. Dr. Uretsky was born in New York City on April 29, 1941. He obtained his B.S. in Pharmacy from the College of Pharmacy at The Columbia University and his Ph.D. in Pharmacology from the University of Chicago. He was the first Postdoctoral Fellow of Dr. Leslie L. Iversen, in the Department of Pharmacology, University of Cambridge, England (1968-1970). Dr. Uretsky was an Assistant Professor in pharmacology at Harvard Medical School prior to joining the faculty of the College of Pharmacy at The Ohio State University in 1977. At The Ohio State University, he taught a variety of pharmacology courses to professional, non-professional, and graduate students. Dr. Uretsky received numerous awards for his distinguished teaching during his career, including the Miriam Balshone Teaching Award from the College of Pharmacy in 1983 and 1986, and the Distinguished Teaching Alumni Award from The Ohio State University in 1997. He was named the Charles H. Kimberly Professor in Pharmacy by The Ohio State University Board of Trustees in 1991. Although he retired in 2004, Dr. Uretsky continued teaching pharmacology to students in the College of Pharmacy. He served on several advisory editorial boards including The Journal of Pharmacology and Experimental Therapeutics and on study sections of the NIH.

Dr. Uretsky authored over 83 research publications. Dr. Uretsky's discovery on the effects of 6-hydroxydopamine (6-OHDA) on noradrenaline-containing neurons while working in Dr. Iversen's laboratory was a pioneering contribution to the understanding of the role of this compound in producing a "chemical sympathectomy" in vertebrate brain, and was published in Nature. His studies on the effect of 6-OHDA on brain catecholamine metabolism, spontaneous motor activity and amphetamine induced hyperactivity in rats, were again published in Nature. These studies indicated that 6-OHDA produced a rapid degeneration of catecholamine-containing nerve terminals in the central nervous system. Dr. Uretsky not only studied regional effects of 6-OHDA on catecholamine containing neurons in rat brain and spinal cord, but also showed that α-methyldopa inhibited tyrosine hydroxylase activity in the striatum. The collaboration of Dr. Uretsky with Dr. Duane D. Miller and Dr. Lane J. Wallace at the Ohio State University resulted in designing and synthesizing numerous dopaminergic and glutamatergic receptor agonists and antagonists, and extensive number of structure-activity relationship and functional studies were carried out to gain insight as to which species is better suited for interaction with the receptor and pharmacological activity. Dr. Uretsky discovered that the activation of D_1 and D_2 dopaminergic receptors and AMPA/kainate excitatory amino acid receptors in the nucleus accumbens is required for the stimulation of MK801-mediated locomotor activity. He also demonstrated that activation of dopaminergic receptors in the nucleus accumbens caused the stimulation of locomotor activity and glutamatergic transmission. However, an increase in glutamate in the nucleus accumbens is neither sufficient nor necessary to produce a stimulation of locomotor activity. His research team demonstrated for the first time that free 3-nitrotyrosine itself, in the absence of direct oxidative events, can elicit potent neurodegenerative effects *in vivo,* suggesting that 3-nitrotyrosine may have a causal role in striatal neurodegeneration.
Another focus of Dr. Uretsky's research was to understand the mechanism of actions of drugs of abuse, with special emphasis on psycostimulant drugs such as amphetamine and cocaine. In addition to being addicting, these drugs also have sensitizing effects in a manner that certain of their effects increase when the drug is taken repeatedly. Dr. Uretsky was interested in evaluating how addiction and sensitization occur. He focused this area of his research in the specific regions of the brain (nucleus accumbens and ventral tegmental area). These areas utilize neurotransmitters such as dopamine, GABA and glutamate. His research also dealt with neurotransmitter interactions in response to drugs like amphetamine and cocaine. He was interested in determining how the nature of these interactions change in animals, which have experienced repeated drug exposures. Dr. Uretsky's research findings will provide basic and clinical scientists with a better understanding of behavioral and neurochemical mechanisms.

Dr. Uretsky was a humble and unpretentious person. He advised us "to help others without any expectation". He believed that a team of researchers with clear understanding is needed to make any project succeed. He combined science, a robust sense of humor, and administrative skills in a manner that gained him admiration and respect from his peers and students. Despite suffering from cancer, Dr. Uretsky was able to share his own experience of fighting with this disease with his students in the classroom. Even in last stages of his life, he remained affectionate, encouraging and inspiring to those who knew him. He taught his students and postdocs to be independent. He rarely asked us how things were going, but he was often next to us in the laboratory and always ready to listen to us or help us. We can pay him a tribute if we fulfill his dream of focusing on pharmacological aspects of neurodegenerative diseases and pharmacological actions of

drug abuse for which he has already initiated the first step, and combine this knowledge with molecular approaches to advance the understanding of drug action and treatment for neurodegenerative diseases.

He was a great teacher. All those who knew him will fondly remember him not only because he was a scholar, but a true teacher and mentor with compassion and genuine concern for his students. He served a perfect example of the following quote:

“A good teacher is like a candle - it consumes itself to light the way for others.”

In addition to being a scientist, Dr. Uretsky was devoted to his family: wife Ella, daughter Karen, son Michael, and daughter-in-law Donna. Memorial contributions may be directed to The Norman J. Uretsky Memorial Fund, The Ohio State University, College of Pharmacy, 500 W. 12th Avenue, Columbus, OH 43210-1291, USA.

Prepared by Tahira Farooqui, The Ohio State University.

Edward J. Walaszek
1927 - 2008

We are saddened by the loss of Professor Edward J. Walaszek, PhD; MD honoris causa.

Edward Walaszek, 81, passed away October 12, 2008. He is survived by his wife, Sophie Walaszek, son Edward Walaszek Jr., and daughter Sheila Walaszek. He is also survived by his sisters Adeline Ignarski and Estelle Palka, and his grandsons Alex and Kevin Walaszek.

Ed was born July 4, 1927 in Chicago, Illinois. He graduated from the University of Illinois (1945-49; B.Sc.; Pharmacognosy) and the University of Chicago (1950-53; Pharmacology) where he attained his PhD under the mentorship of Drs. Kelsey and Geiling. He received a USPHS Postdoctoral Fellowship to do research at the University of Edinburg (1953-55) with Professor Sir John Gaddum.

In 1955, Dr. Walaszek became an Assistant Professor of Biochemistry and Neurophysiology at the University of Illinois Medical School. He then was recruited to the University of Kansas Medical School in 1957 and rapidly moved through the academic ranks as an Assistant Professor (1957-59), Associate Professor (1959-62), Professor (1962-64) and Professor and Chairman (1964-92). He also served as Guest Research Worker (1961) at the Laboratorie de Pathologie et Therapeutique Generalis, Faculte de Medicine in Paris with professor Minz. During his 28 years as Chairman of the Department of Pharmacology, Toxicology, and Therapeutics, he developed the Department from a small Department to one that had national and international recognition in both research and education.

Professor Walaszek's research focused on neuropharmacology and he established a close working relationship with Professor Ed Smissman, Chair of the Department of Medicinal Chemistry at the University of Kansas Lawrence campus. Together they published many seminal papers on structure activity relationships of drugs. He was one of the early researchers to use radioactive labeled drugs as tracers of biological activities and was the first to describe the mechanism of experimental catatonia induced by bulbocapnine.

Professor Walaszek's greatest pride was the development of the Computer Assisted Teaching Systems (CATS) pioneered in the Department during the early 1970s. At one time the computer programs, with courses in medicine, nursing, and graduate studies, were used in 54 medical schools in the United States and in 10 foreign countries. In July of 1991, he presented a computer program that used Chinese characters at the University of Singapore.

Dr. Walaszek received numerous awards and honors including: Research Career Development Award (1961 to 1964), Research Career Award (1963 to 1964), Rector's Medal for Lectureship from University of Helsinki (1965), Recognition Medal from the Hungarian Academy of Sciences (1972), Medal from the Polish Academy of Sciences (1975), Medal from the Polish Pharmaceutical Industry "POLFA" (1977), Honorary Membership in both the Hungarian and Finnish Pharmacology Societies, and was listed in Who's Who in America and Who's Who in the World. He also received the Executive Vice-Chancellor's Award for Distinguished and Devoted Service to the University of Kansas Medical Center

(1974), Foreign Member, Finnish Academy of Sciences and Letters (1979), Chancellor's Award for Excellence in Teaching (1980), Caduceus Medallion for Innovative Basic Medical Sciences Teaching, Vanderbilt University (1982), and, his most treasured honor, Doctor of Medicine and Surgery, MD honoris causa, University of Helsinki (1990).

Professor Walaszek was a member of many Scientific Societies and served on numerous National Committees, International Committees, Educational Committees and Local Committees often serving as an officer including chairman of many these committees. He has published numerous scientific papers in renowned journals and often was invited as a guest speaker at institutions and Scientific meetings. He also served as a consultant to several pharmaceutical companies. The Department graduated its 100th student the year that Professor Walaszek resigned as Chairman. He, for many years, was strong leader in pharmacology research and education. He most certainly will be missed as a leader, mentor, researcher, educator, and most of all as a friend.

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

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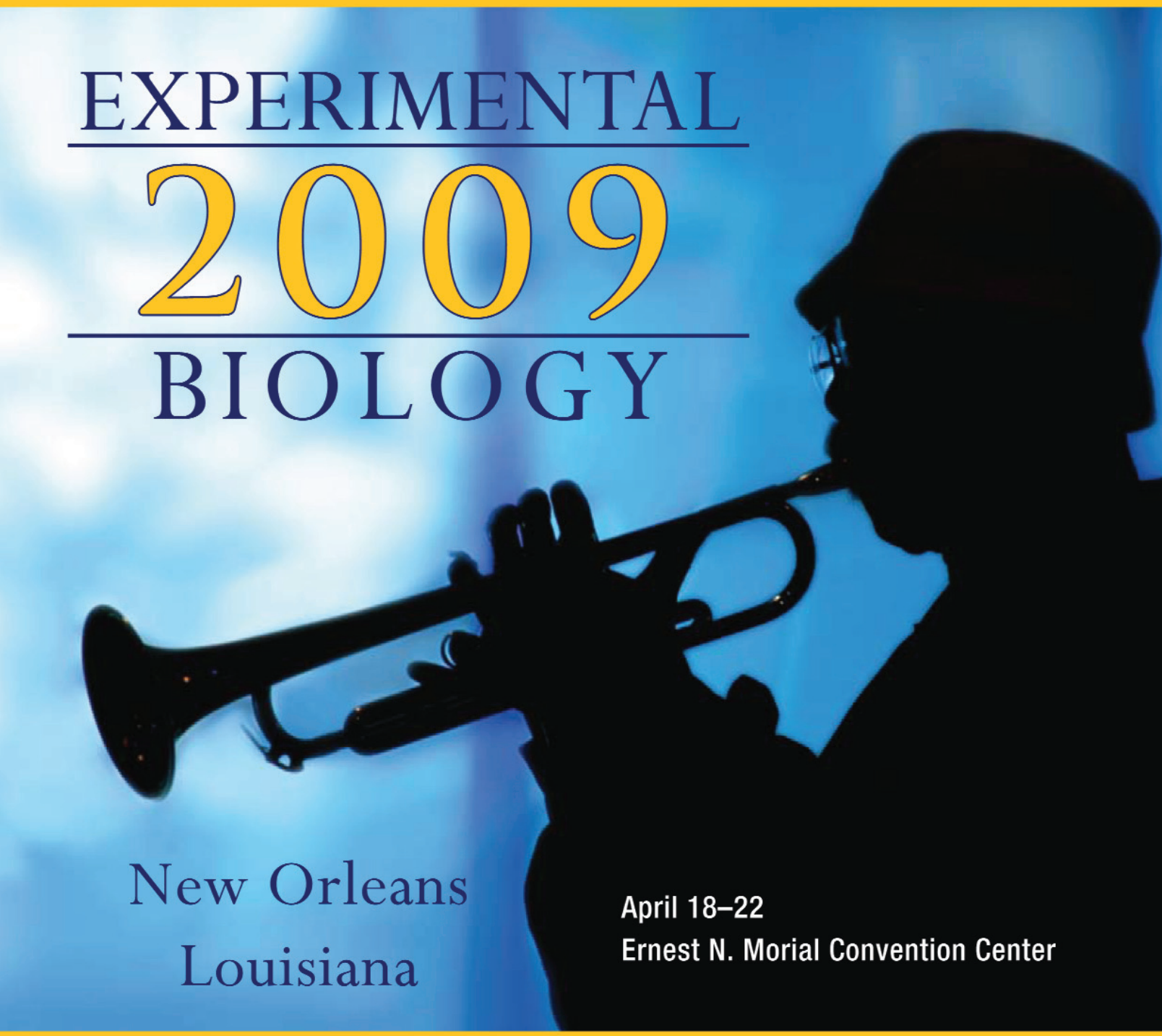

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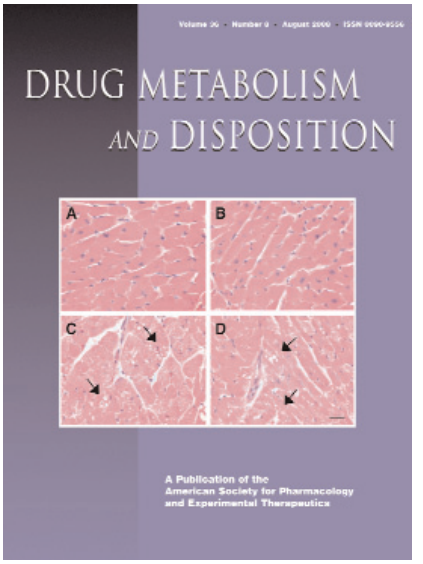

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- May not vote in Society elections nor hold an elected office in the Society.

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