

Feature Story: Katharine Dexter McCormick and the Pill



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- 2014 Election Nominees
- Program grid for ASPET Annual Meeting at EB 2014
- Holiday Gift Ideas for Pharmacologists
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- MAPS Chapter Meeting abstracts (online only)

*Katharine Dexter McCormick
(Courtesy of the Santa Barbara
Historical Museum)*

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2014 Dues Notices

Please check your mail and email inbox for your 2014 Dues notice. You can mail your payment or renew online at

www.aspet.org

no later than January 1, 2014.



Dear ASPET members,

It is hard to believe that the year is nearly over. At our fall Council meeting, we had a very dynamic strategic planning discussion. The three focus areas were: enhancing membership, education, and the future of ASPET. Over the next few months, we will be rolling out new initiatives that evolved from those discussions. We would appreciate hearing your thoughts on these topics or other issues related to ASPET.

As the year ends, we would also like to get your help with two other efforts. Following on the membership discussion at our Council meeting, I'd like to remind you about our Member-Get-A-Member campaign (<http://www.aspet.org/membership/member-get-a-member/>). The more you recruit, the more chances you have to win a prize. Also, the top recruiters will be recognized at the ASPET Annual Meeting at EB 2014 and in the March issue of *The Pharmacologist*. Please take the time to recommend students or junior colleagues as members. Also, let's encourage people who are "practicing pharmacology without a license" to join up. A lot of our colleagues currently doing pharmacology research may not consider themselves to be pharmacologists. Let's get them into our community.

We also are working hard to endow some of our major awards (Abel, Axelrod, Goodman & Gilman, and Sollmann). Please help us meet our goal of making these awards a permanent fixture of ASPET to recognize the giants in our field. Additionally, a number of funds for student and young scientist travel and member services would benefit from your contributions. All donations can be made at <http://www.aspet.org/donate/>. I would like to specifically point out the generous matching pledge of \$30,000 toward the Goodman & Gilman Award from an anonymous donor, which will double your contribution to allow us to more rapidly meet our goal on that award.

By now, I hope that you have submitted your work to next year's EB 2014 meeting. We have a very exciting program and also will have joint sessions with the Chinese Pharmacological Society (CNPHARS). See you in San Diego!

Sincerely,

Rick Neubig

Your Donations Are Needed to Endow:



Current
Goodman & Gilman
Endowment Fund

John J. Abel Award

Donate now at <http://www.aspet.org/awards/aspnet/abel/#Abel-Endowment-Fund>

Julius Axelrod Award

Donate now at <http://www.aspet.org/awards/aspnet/axelrod/#Axelrod-Endowment-Fund>

Goodman and Gilman Award in Receptor Pharmacology

Donate now at <http://www.aspet.org/awards/aspnet/goodman-gilman/#Goodman-Gilman-Endowment-Fund>

Torald Sollmann Award

Donate now at <http://www.aspet.org/awards/aspnet/sollmann/#Sollmann-Endowment-Fund>

Donate to these important awards and watch the endowments grow!
Thank you for your support!

2013 Year in Review

by Suzie Thompson

What a year 2013 has been! In April, we held an exceptional Joint Annual Meeting with the British Pharmacological Society at Experimental Biology. Despite the tumultuous start of the meeting this year in Boston, we had record attendance, with 1,173 ASPET members attending the meeting and an overall 14,593 attendance for the whole meeting. We awarded 83 Graduate Student Travel Awards, 32 Young Scientist Travel Awards, and three SURF Fellow Awards. Our program this year was packed with cutting-edge science and leading speakers in our field. We also had an incredible turnout for the GPCR Colloquium, which was held as a satellite meeting to our main Annual Meeting. If you haven't already, be sure to take a look at our program for 2014 (<http://www.aspet.org/EB2014/program/>), when we will be meeting in San Diego along with the Chinese Pharmacological Society (CNPHARS). We expect next year's meeting to be another fantastic one.

The ASPET journals continue to be leaders in the field of pharmacology. This year, we teamed up with the British Pharmacological Society and Wiley to bring you a joint open access journal, *Pharmacology Research & Perspectives*. Be sure to check it out at www.pharmacolresperspect.com. The ASPET journals also got social this year. Each of the journals is on Facebook and Twitter (<http://www.aspet.org/publications.aspx>), so you can follow us and get updates about new issues, articles of interest, and other fun facts. The editors are all working hard on bringing you the best journals for 2014, so be sure to submit your papers and keep reading.

Membership is also doing well. We have had more new Regular Members join ASPET this year than we have had in the past six years. Also, our retention rate is great with over 85% renewing their membership.

We hope to continue to grow the Society and attract more members who are doing research in pharmacology and experimental therapeutics, and we hope that you will continue to do your part to keep our membership strong. Please tell a friend, colleague, or student about ASPET, and spread the word about our member driven programming at EB, our exciting science policy efforts, our travel awards and support for students, and much more. Currently, ASPET is running a Member-Get-A-Member program in which we are rewarding members for their recruitment efforts. For more information about this program, visit <http://www.aspet.org/membership/member-get-a-member/>.

It has been a fantastic year, and we thank you for being a part of our important Society. As you may know, ASPET is currently going through a re-branding process. We will be launching a new look, brand, logo, and tagline in 2014. As the field of pharmacology changes, ASPET is also changing to better fit the needs of our members and those who are doing research in pharmacology and experimental therapeutics. We hope to attract new members and enhance our membership benefits to our current members through this process. We have some exciting things planned for 2014, so we hope that you will renew your membership (if you haven't already) and get ready for an amazing 2014!

As always, we would love to hear your feedback, so please be sure to tell us how we can help make your membership as beneficial as possible!

Wishing you a happy, healthy, and successful new year!

—The ASPET Staff



Save the Date:
**Joint Annual Meeting of ASPET &
 the Chinese Pharmacological Society**
April 26 - 30, 2014, San Diego, CA

**To Register and submit your Late-Breaking
 Abstract, visit us at
www.experimentalbiology.org**

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Get Started Today!

- Tell a friend, colleague or student about the benefits of membership
- Encourage them to fill out an application form online at: www.aspet.org
- Tell them to enter Marketing Code: MGM and provide your name in the sponsor field
- Once they are approved for new membership and their dues payment has been made, you will receive credit for your recruitment efforts
- If you have any questions about this program, please contact the membership department at membership@aspnet.org or call (301) 634-7060

By helping us recruit new members, you will be contributing to the growth and sustainability of ASPET. A growing ASPET means great recognition for the field of pharmacology, more resources and support for our members, and a louder voice with policy makers.

For more program details, visit:

<https://www.aspet.org/membership/member-get-a-member/>

2013 Contributions

ASPET gratefully acknowledges the following individuals who have made contributions for 2013:

John J. Abel Award in Pharmacology

Louis Barker
Allan Conney
Joann L. Data
Robin A. Dodson
James Fujimoto
James Halpert
Kenneth Jacobson
Ronald Kuntzman
John Lazo
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Bernard B. Brodie Award in Drug Metabolism

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Drug Metabolism Early Career Achievement Award

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Richard Okita
Kenneth Thummel

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Goodman and Gilman Award in Receptor Pharmacology Fund

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Goodman & Gilman Award in Receptor Pharmacology

Endowment Fund



Consider your year-end donations now: Donate to the Goodman and Gilman Award in Receptor Pharmacology Endowment Fund. An anonymous donor will match donations up to \$30,000 for this award endowment fund, making your contribution go twice as far.

https://www.aspet.org/cvweb_aspet/goodman-gilman.shtml

Graduate Student Travel Fund

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 Michiko Okamoto
 Achilles Pappano
 Robert Pechnick
 Stephanie Watts
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 Richard Ye
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Harvey B. Haag Student Travel Fund

Louis Harris

IUPHAR Travel Fund

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 William Slikker

Benedict R. Lucchesi Lectureship in Cardiac Pharmacology

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 Mitchell Steinberg
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Note: This list reflects contributions received as of December 6, 2013.

Thank you to our 2013 Corporate Contributors

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 National Board of Medical Examiners

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 Med Associates Inc.

2014 Elections

The ASPET election for President-Elect, Secretary/Treasurer-Elect, and Councilor will take place this month. All Regular, Postdoctoral, and Retired members are eligible to vote. In addition, the following Divisions are holding elections: Division for Drug Metabolism (page 233); Division for Integrative Systems, Translational and Clinical Pharmacology (page 233); Division for Molecular Pharmacology (page 234); Division for Neuropharmacology (pages 235-236); and Division for Toxicology (page 237). Members may vote online by logging into the Members-Only section of ASPET.org and selecting "Vote in the 2014 ASPET Election" on the Member Homepage. View the 2014 Election bulletin at http://www.aspet.org/uploadedFiles/Members_Only/Election_Bulletin/2014-Bulletin-final.pdf.

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. The election opened on December 2, 2013 and will close on January 15, 2014.

Nominees for President-Elect:



Ken Thummel
Candidate's Statement:

As many of you are well aware, ASPET has been experiencing a number of external and internal pressures that will shape its future and relevance to the lives of its members and to the US public. Much of this change has been driven by a reduction in funding for biomedical research, as well as growing pressures on academic institutions and the pharmaceutical industry to reduce infrastructure costs with

evolving changes in healthcare reimbursements. There is also growing concern among ASPET's youngest members over the opportunities and sustainability of a career in the pharmacological sciences. Thus, the need for ASPET and what it has to offer is greater than ever. It can be a champion of quality healthcare by fostering the development of innovative and personalized therapeutics. It can be at the forefront of public education about the benefits and risks of pharmacological interventions for the treatment of disease and how balance between the two can be optimized. In close partnership with other professional societies, it can be a knowledgeable, national spokesman when questions arise in the public domain about the need for continued investment in biomedical research and the long-term benefits that the public can derive from that investment. In addition, it can be an advocate for sustained investment in graduate and postdoctoral education and innovation in how the next generations of pharmacologists are trained, ensuring them a fulfilling and productive career. If elected President of ASPET, I will work tirelessly to advance this agenda. I believe that my extensive background as an academic research scientist and educator, and as someone with leadership experience and who is interested in public policy, has prepared me well for this endeavor.



Scott Waldman
Candidate's Statement:

It has been an honor and pleasure helping to advance our Society and the discipline as Chair of the Scientific Program Committee and a Member of Council. I am humbled to have been nominated for the position of President of ASPET. In that context, our discipline of pharmacology is experiencing an unprecedented time of contrasts and paradoxes. Emerging technologies have yielded extraordinary discoveries in molecular mechanisms underlying disease. In contrast, we find ourselves in an era of fiscal constraint that compromises opportunities to translate those discoveries into new algorithms for disease prediction, prevention, and cure. Beyond this hard economic landscape, the integration of diagnostics and therapeutics into clinical management paradigms holds the promise of tailored treatments for individuals and their diseases. Paradoxically, the very relevance of our discipline, whose core concepts embody the creation of those personalized approaches, demonstration of their safety and utility, and optimization of their application in patients and populations, is being challenged in academic, public, and private sectors. These environmental challenges frame the essential role of ASPET as the voice of pharmacology, establishing strategies that advance the discipline locally and nationally. In that context, I believe the role of the ASPET President is to collaborate with members and leaders to maximize the value of the society, sustain the discipline, advance the science, and create opportunities for individual career growth.

As President, I will advance the discipline through well-established and familiar mechanisms. For example, as Chair of the Scientific Program Committee, I have the remarkable opportunity to showcase cutting-edge content for the Annual Meeting, offering our members unique opportunities for exposure to the latest scientific advances, to meet experts pioneering technologies evolving the discipline, and for global advancement of our science through international partnerships, for example with the British Pharmacological Society and the Chinese Pharmacological Society. Organizationally, as a member of ASPET Council, I have the honor of working with outstanding leaders to advocate nationally for the importance of pharmacology through the Government Affairs Committee, and in collaboration with our sister organizations in FASEB, to sustain and expand research support that forms the lifeblood of our discipline. Moreover, as both a scientific contributor and Council member, I take great pride in our portfolio of scientific journals, which serves as the reigning voice of the discipline, the vehicle that disseminates the most impactful pharmacologic research, the forum for interdisciplinary discourse, and the conveyance for local and national policy related to pharmacology.

In this challenging environment, beyond these traditional mechanisms, I will lead the organization into the future employing creative

Scott Waldman Candidate's Statement (continued)

strategies that maximize membership value and grow the discipline. Reflecting inwardly on members, our future is the next generation of committed pharmacologists, and I will work diligently to develop organizational strategies that support career development. For example, innovative mentoring programs that match successful career pharmacologists with nascent practitioners can maximize the likelihood of success. Similarly, organizational roadmaps can provide clear pathways to Society ladders of responsibility, creating (inter)national leadership experiences required for career advancement. Further, I will establish scientific divisions as incubators for the next generation of leaders by creating mandates that recognize and cultivate talent, provide divisional leadership opportunities, and promote scientific contributions to the Annual Meeting to create depth and breadth in a leadership pool that ensures and secures the future. Additionally, I will enhance award and grant programs that, in part, fill the gap created by government austerity to provide a lifeline to trainees and young faculty struggling to establish a career foothold. Moreover, I will work with our Society experts to define the contemporary portfolio of essential core concepts differentiating pharmacology from other disciplines, disseminate those concepts at our Annual Meetings and in our journals, provide best practices for pharmacology education, and advocate for the essential nature of pharmacology in undergraduate and graduate curricula, in order to re-affirm the central relevance of the discipline. Finally, I will work to engage program directors in government agencies and the biopharmaceutical community, and journal editorial leadership, and secure their participation in our Annual Meeting, to create opportunities for interactions with young scientists that enhance career success. In addition to this internal focus on member value, I will lead the organization in developing strategies that reflect outwardly, championing the central nature of basic and applied pharmacology in therapeutic discovery, development, regulation and application to academia, biopharmaceutical, regulatory, and funding communities. Beyond these agencies directly linked to our discipline, I will drive outward organizational strategies to educate citizens as key stakeholders in the benefits and deliverables of pharmacology in the context of emerging experimental therapeutics that prevent and cure disease.

It is true that pharmacology, like all of modern science, is under duress. However, where there are challenges, there also are opportunities to evolve, succeed, and even grow, in the context of leadership with vision and strategy to navigate that course. As President, I look forward to the opportunity to work with ASPET leaders and members to develop that vision and strategy and continue evolving the organization and discipline.

Nominees for Secretary/Treasurer-Elect:



Haian Fu

Professor, Department of Pharmacology; Director, Discovery & Developmental Therapeutics Program, Winship Cancer Institute; Director, Emory Chemical Biology Discovery Center, Emory University, Atlanta, GA



Dennis Marshall

Executive Director, Medical Affairs, Ferring Pharmaceuticals Inc.

Nominees for Councilor:



Margaret Gnegy

Professor of Pharmacology; Associate Chair of Pharmacology; University of Michigan Medical School



Alan Smrcka

Louis C. Lasagna Professor in Experimental Therapeutics; Professor of Pharmacology and Physiology; Professor of Biochemistry and Biophysics; Professor at the Aab Cardiovascular Research Institute, University of Rochester School of Medicine

HAVE YOU JOINED A DIVISION?

Take full advantage of ASPET Membership by joining a Division!

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



Annual Meeting



ASPET ANNUAL MEETING AT EB 2014 PROGRAM GRID

San Diego, CA (All rooms listed are in the Convention Center unless otherwise noted.)
AM Symposia 9:30 – 12:00; AM Lectures 8:30 – 9:20; PM Symposia 3:00 – 5:30; PM Lectures 2:00 – 2:50

Lectures

Divisional Programming

Social

Business

	Saturday, 4/26	Sunday AM, 4/27	Sunday PM, 4/27	Monday AM, 4/28	Monday PM, 4/28	Tues AM, 4/29	Tues PM, 4/29	Wed AM, 4/30	Wed PM, 4/30
Behavioral Pharmacology Society Meeting Marriott Marquis & Marina, TBD 8:00 AM – 6:00 PM Separate pre-registration required	JULIUS AXELROD AWARD LECTURE Seasons of the lives of scientists: The journey from training to careers in discovery to service for society Lee Limbird 8:30 AM – 9:20 AM Room 2	PHARMACOLOGY EDUCATION DIVISIONAL PROGRAMMING: Addressing prescribing errors through medical student education & assessment S.K. Rajasekaran, D. Nierenberg 3:00 PM – 5:30 PM Room 5B	J.J. ABEL AWARD LECTURE TBA 8:30 AM – 9:20 AM Room 2	J.J. ABEL AWARD LECTURE TBA 8:30 AM – 9:20 AM Room 2	B.B. BRODIE AWARD LECTURE TBA 2:00 PM – 2:50 PM Room 5A	DM Role of (drug) transporters in imaging in health & disease B. Steiger, Y. Sugiyama 9:30 AM – 12:00 PM Room 5A	ISTCP DIVISION YOUNG INVESTIGATOR AWARDS PLATFORM SESSION 3:00 PM – 5:30 PM Room 5A	RAY FULLER LECTURE AMPA Receptor Potentiation: Implications for the Discovery of Medicines for Treatment-Resistant Depression Jeffrey Wilkin 8:30 AM – 9:20 AM Room 2	DDD/DM, TOX Improving maternal therapeutics: Drug metabolism & transport during pregnancy & lactation M. Isoherranen, H. Swanson, D. Morrison 3:00 PM – 5:30 PM Room 3
2014 Teaching Institute: Practical technologies for effective teaching R. Hayslett, C. Davis 12:00 PM – 2:30 PM Room 3	BEH, NEU, TOX Animal models of polydrug abuse P. Czoty, R. De la Garza 9:30 AM – 12:00 PM Room 4	CNPHARS LECTURE: Target-net based drug discovery for Parkinson's disease treatment by HTS/HCS Guan-Hua Du 2:00 PM – 2:50 PM Room 5A	ISTCP, CVP, TOX Fetal programming of adult cardiovascular disease M. Choppell, A. Marshall 9:30 AM – 12:00 PM Room 4	P.B. DEWIS AWARD LECTURE TBA 2:00 PM – 2:50 PM Room 4	NEU, CVP, DDD, MP Transporters in glial cells as new therapeutic targets L. Almurizatoro 9:30 AM – 12:00 PM Room 4	TOXICOLOGY DIVISION SYMPOSIUM: Macrophages and tissue injury: Agents of defense or destruction D. Laskin 3:00 PM – 5:30 PM Room 5B	TOX, BEH, ISTCP, NEU Scientists vs. street chemists: The toxicity of designer marijuana L. James, J. Moran 9:30 AM – 12:00 PM Room 3	ISTCP, CVP, DDD, MP, TOX Targeted/individualized therapy: Approaches for the future translational pharmacologist J. Paul 3:00 PM – 5:30 PM Room 5A	
Graduate Student-Postdoctoral Colloquium: Success skills for all careers S. Ingram 2:45 PM – 5:15 PM Room 2	DPE, BEH, CVP, DDD, DM, ISTCP, MP, NEU, TOX Career opportunities beyond the bench: Education as a viable path J. Reuben, K. Marcadante 9:30 AM – 12:00 PM Room 5A	CNPHARS, DDD Drug discovery in China and the United States J. Glowa, Y. Zhang 3:00 PM – 5:30 PM Room 5A	DPE, BEH, CVP, DDD, DM, ISTCP, MP, NEU, TOX Collaborative role of pharmacology in education of health care professions S. Anandru, R. Theibald 9:30 AM – 12:00 PM Room 5A	BEHAVIORAL PHARMACOLOGY DIVISION SYMPOSIUM: Making the right choice: Translational use of choice procedures in understanding the neurobiology and development of pharmacotherapies for drug addiction M. Banks, M. Nader 3:00 PM – 5:30 PM Room 4	ISTCP, CVP, DDD, MP 12-lipoxygenase & disease: New insights into regulation & inhibition of a critical enzyme M. Holinstat 9:30 AM – 12:00 PM Room 2	DDD DIVISION SYMPOSIUM Productive Public Private Partnerships for Pharmacological Progress J. Lazo 3:00 PM – 5:30 PM Room 4	DM, DDD, ISTCP, TOX "Target-site" drug metabolism & transport R. Fazi 9:30 AM – 12:00 PM Room 5A	NEU, BEH, CVP, DDD, ISTCP, MP Future therapies for chronic pain: Focus on novel non-opioid targets B. Greenwood-Van Meerveld 3:00 PM – 5:30 PM Room 4	

ASPET ANNUAL MEETING AT EB 2014 PROGRAM GRID

Saturday, 4/26	Sunday AM, 4/27	Sunday PM, 4/27	Monday AM, 4/28	Monday PM, 4/28	Tues AM, 4/29	Tues PM, 4/29	Wed AM, 4/30	Wed PM, 4/30
<p>ASPET Business Meeting 6 PM – 7:30 PM Ballroom 208/C</p>	<p>DDD, MP Drug discovery against protozoal pathogens <i>M. Philips</i> 9:30 AM – 12:00 PM Room 5B</p>	<p>MP, CVP, DDD, ISTCP New insights derived from cell specific knockout of heterotrimeric G-alpha proteins <i>F. Murray, P. Insel</i> 3:00 PM – 5:30 PM Room 2</p>	<p>TOX, DDD, DM, ISTCP, MP Drug-induced idiosyncratic reactions and immunotoxicity <i>J. Utrecht</i> 9:30 AM – 12:00 PM Room 5B</p>	<p>NEUROPHARMACOLOGY DIVISION POSTDOCTORAL AWARD FINALISTS 3:00 PM – 5:30 PM Room 2</p> <p>NEU SCIENTIFIC PROGRAMMING MTG 5:45 PM – 7:30 PM Room 2</p>	<p>CVP, MP Not just a glue: Pharmacology, physiology & pathology of transglutaminases <i>S. Warts, E. Bakker</i> 9:30 AM – 12:00 PM Room 3</p>	<p>CARDIOVASCULAR DIVISION TRAINEE SHOWCASE 2:30 PM – 4:30 PM Room 3</p> <p>TBA 4:30 PM – 5:30 PM Room 3</p> <p>CVP SCIENTIFIC PROGRAMMING MTG Room 3</p>	<p>MP, DDD Chemical biology in drug discovery <i>H. Fu, H. Chen</i> 9:30 AM – 12:00 PM Room 4</p>	<p>CVP, ISTCP, MP, TOX Hydrogen sulfide: From physiological messenger to pharmacological target <i>N. Konogy, U. Sen</i> 3:00 PM – 5:30 PM Room 2</p>
	<p>TOX, CVP, ISTCP, MP Therapeutic potential of targeting oxidative stress pathways <i>P. Meyeux, C. Wu</i> 9:30 AM – 12:00 PM Room 3</p>	<p>NEU, DDD, ISTCP, MP Emerging technologies in neuropeptide research: Identification & validation of neuropeptide systems as therapeutic targets <i>S. Clark</i> 3:00 PM – 5:30 PM Room 4</p>	<p>BEH, ISTCP, NEU, TOX Sleep disruptions associated with neuropsychiatric & degenerative disorders: Implications, preclinical models & development of novel pharmacotherapies <i>R. Gould, C. Jones</i> 9:30 AM – 12:00 PM Room 3</p>	<p>CVP, ISTCP, TOX Mitochondrial fragments: A novel mediator between inflammation & cardiovascular disease <i>R. Webb, C. Ferreira Wenceslau</i> 3:00 PM – 5:30 PM Room 3</p> <p>TOX EXECUTIVE COMMITTEE/SCIENTIFIC PROGRAMMING MTG 5:45 PM – 7:30 PM Room 3</p>	<p>ISTCP, DM, TOX Emerging integrative approaches to predicting host response to antimicrobials <i>N. Bumpus</i> 9:30 AM – 12:00 PM Room 5B</p>	<p>MP, CVP, DDD, ISTCP Inhibitory GPCRs as therapeutic targets for obesity and type 2 diabetes <i>M. Kimpfe</i> 3:00 PM – 5:30 PM Room 2</p>	<p>DDD, CVP, ISTCP, MP Arginase as an emerging therapeutic target <i>R. Carlowell</i> 9:30 AM – 12:00 PM Room 5B</p>	
<p>Opening and Awards Reception 7:30 PM – 9:30 PM Center Terrace</p>		<p>Student/Postdoc Best Abstract Competition 6:30 PM – 8:30 PM Marriott Marquis & Marina, TBD</p> <p>Student/Postdoc/ Mixer 9:00 PM – 11:30 PM Marriott Marquis & Marina, TBD</p>		<p>Past Presidents' Dinner 6:00 PM – 9:00 PM Marriott Marquis & Marina, TBD</p> <p>BEH/NEU Mixer 7:30 PM – 9:30 PM Marriott Marquis & Marina, TBD</p> <p>DDD/DPE/ISTCP MIXER 7:30 PM – 9:30 PM Marriott Marquis & Marina, TBD</p> <p>DM/TOX Mixer 7:30 PM – 9:30 PM Marriott Marquis & Marina, TBD</p> <p>MP Mixer 7:30 PM – 9:30 PM Marriott Marquis & Marina, TBD</p>		<p>CVP MIXER 6:30 PM – 8:00 PM Marriott Marquis & Marina, TBD</p>		<p>Closing Reception 6:00 PM – 8:00 PM Marriott Marquis & Marina, TBD</p>

BEH= Behavioral Pharmacology; CNPHARS=Chinese Pharmacological Society; CVP=Cardiovascular Pharmacology; DDD=Drug Discovery & Development; DM=Drug Metabolism; DPE=Pharmacology Education; ISTCP=Integrative Systems, Translational & Clinical Pharmacology; MP=Molecular Pharmacology; NEU=Neuropharmacology; TOX= Toxicology



Important Things to Remember

Important Dates:

February 21, 2014:

Late Breaking Abstract Submission Deadline

February 21, 2014:

Early Registration Discount Deadline

March 21, 2014:

Hotel Reservation Deadline

March 21, 2014:

Cancellation Deadline

April 11, 2014:

Child Care Registration Deadline

Noteworthy at EB:

Child Care - Camp EB will be available each day of the meeting, so you don't have to worry about leaving the kids at home.

Room Share Board - Find someone with similar interests to share a room with for the meeting. Visit the EB website for details.

WIP Into Shape - Women in Pharmacology networking walk

Give a Day of Service to San Diego - Friday, April 25 - 4th annual day of service by ASPET members

Wednesday Reception - Stay for the afternoon sessions on Wednesday. Enjoy one more night in San Diego at a reception hosted by ASPET.

Important Links for the ASPET Annual Meeting at EB 2014:

General Information:

<http://www.aspet.org/EB2014/>

Program Information:

<http://www.aspet.org/EB2014/program/>

Travel Award Information (Students and Postdocs):

<http://www.aspet.org/awards/travel/>

EB 2014 Official Website:

<http://www.experimentalbiology.org/>

EB 2014 Registration Information:

<http://experimentalbiology.org/2014/Attendees/Registration.aspx>

Late-Breaking Abstract Submission:

<http://www.abstractsonline.com/submit/login.asp?mkey=%7B5B9D1EBB%2D5EEF%2D4E8E%2D9FFA%2D641686838541%7D>

EB 2014 Housing Information:

<http://experimentalbiology.org/2014/Attendees/Housing.aspx>

Camp EB Childcare:

http://www.accentregister.com/events/ch_events.asp?eld=6432



Improving maternal therapeutics: Drug metabolism and transport during pregnancy and lactation

Wednesday, April 30, 2014, 3:00 – 5:30 p.m. • San Diego Convention Center, Room 3

CHAIRS



Nina Isoherranen
University of Washington



Hollie Swanson
University of Kentucky
Medical Center



Donald Mattison
Risk Sciences International

SUMMARY

Use of prescription and over the counter drugs is very common during pregnancy, but due to changes in drug metabolism and transport during pregnancy, the dosing of drugs cannot be directly extrapolated from non-pregnant women or men. Increased scrutiny by the FDA and NIH on therapy of pregnant women has resulted in a considerable increase in the amount of research generated in the area of drug disposition during pregnancy. This symposium is designed to cover the area of drug disposition during pregnancy and highlight the breadth of tools that are currently used to investigate drug disposition during pregnancy.

Supported by funding from:



Canadian Alliance for the Safe and Effective Use of Medications in Pregnancy and Breastfeeding

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

For more information:

dmattison@risksciences.com

To register:

www.aspet.org/EB2014

AGENDA

General overview

Nina Isoherranen, University of Washington



Prediction of drug disposition during pregnancy by PBPK modeling and simulation

Jashvant Unadkat, University of Washington



Mechanisms of CYP2D6 regulation during pregnancy

Junior Speaker: Young Jeong, University of Illinois - Chicago



Adaptive changes in liver and intestinal metabolism and transport function in pregnancy and lactation

Mary Vore, University of Kentucky



Addressing pregnancy-associated changes in pharmacodynamics and pharmacokinetics of anti-malaria drugs

Joel Tarning, Mahidol University

Panel discussion

Moderator: Donald Mattison, Risk Sciences International

Holiday Gifts for Pharmacologists

Products from around the Web and ASPET.org

Still haven't found that perfect gift for your friends, colleagues, or students? We've put together a list of fun gift ideas for your fellow scientists.



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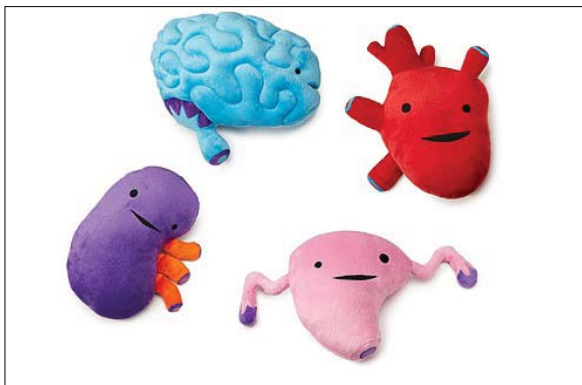
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MOLECULE JEWELRY

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<http://molecularmuse.etsy.com>



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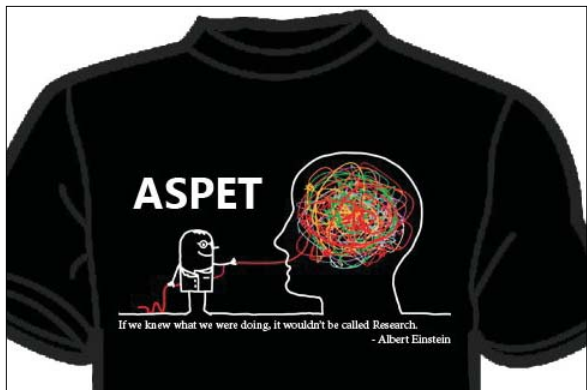
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\$15.00 for members; \$17.00 for nonmembers

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PHUTURE PHARMACOLOGIST T-SHIRT

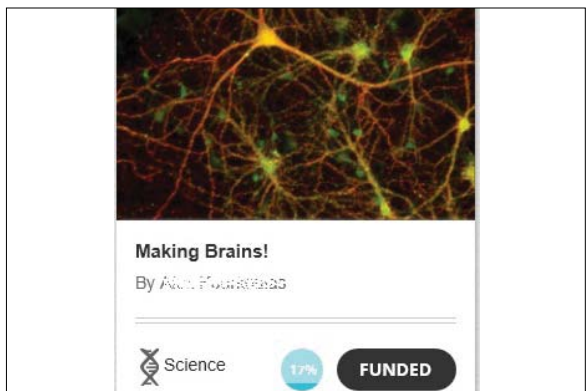
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Katharine Dexter McCormick and the Pill

by Rebecca J. Anderson, Ph.D.

On January 3, 1957, Katharine Dexter McCormick wrote to Margaret Sanger, "I think we have gained the oral contraceptive we have been seeking and now it must be implemented as fully as possible. Nothing else matters to me, now that we have got the oral contraceptive" (1). History remembers Margaret Sanger as the iconic founder of Planned Parenthood and the person who coined the term "birth control." But Katharine McCormick? Today, she is rarely mentioned with more than a footnote. Yet, McCormick was the driving force and certainly the most colorful character behind the Pill.

Katharine Dexter was born in 1875 in Dexter, MI, the town founded by her grandfather. At 15 and after the death of her father, Katharine and her mother moved to Boston, where both sides of her family had deep, aristocratic roots. As teenagers, Katharine and her brother traveled extensively throughout Europe. She spoke fluent French and German, but she preferred taking science courses and aspired to become a surgeon. In an early display of her no-nonsense, laser-focused approach to problem-solving, Katharine critically evaluated the science curricula at local colleges including Harvard and Radcliffe—discarding them all as inadequate. She finally settled on the Massachusetts Institute of Technology because its laboratory facilities impressed her. Despite educational and social barriers that discouraged women from attending college and seeking a science degree, Katharine spent three years studying to fulfill the prerequisites for official admission and easily passed her entrance exams. Four years later, she received her bachelor's degree in biology, the only woman in her class and the first woman ever to receive a science degree from MIT. She was 28 years old.

In 1904, Katharine married Stanley McCormick after an erratic, on-again-off-again courtship. Stanley was the youngest son of Cyrus McCormick, the inventor of the mechanized reaper, which had made the McCormicks fabulously wealthy. Katharine abandoned her plans to attend medical school when her new in-laws disclosed a carefully guarded family secret. Although Stanley showed talent as an artist and junior executive in his father's International Harvester company, he was afflicted with a mental illness that was also present, to a greater or lesser extent, in his siblings. Various diagnosed by the medical community as manic-depression, catatonia, dementia praecox, and schizophrenia, Stanley's precise ailment is hard to classify according to the current DSM-V criteria. Regardless, he indisputably exhibited sporadic unruly and violent behavior that seemed to be provoked by the sight of women. Consequently, all women (nurses, household staff, and even Katharine) were kept out of his view, and he was legally declared insane in 1909.

Shortly after their marriage, Katharine moved Stanley to Riven Rock, a peaceful 87-acre estate owned by the McCormick family in Santa Barbara, CA, and spared no expense (including a large medical and household staff) to care for him. For the next few decades, Katharine's primary residence was her mother's fashionable Boston townhouse. She spent her summer holidays at her mother's Swiss chateau and made at least one visit each year to Riven Rock—a 5-day journey by train. Over the years, Katharine hired a series of full-time physicians to care for Stanley. The first was Gilbert V. Hamilton, a young



At left: Katharine Dexter McCormick (Courtesy of the Santa Barbara Historical Museum). **At right: Margaret Sanger** (Courtesy of the Library of Congress)

but forward-thinking psychiatrist and authority on sexual behavior. She built a fully equipped primate laboratory at Riven Rock and funded Hamilton's primate experiments on sexual behavior—the first such facility in the world—hoping that the research might lead to a breakthrough treatment for Stanley. Among Hamilton's collaborators was Robert Yerkes, a pioneering primate behaviorist who spent six months at Riven Rock conducting experiments in Hamilton's lab (2). Hamilton also published his studies on the Riven Rock primate colony (3) and later summarized his work dealing with human sexuality in a landmark book, *A Research in Marriage* (1929), the first of its kind published in the U.S. One of Hamilton's associates was a young and eager Alfred Kinsey.

Katharine avidly read medical journals, followed the latest trends in mental healthcare, and consulted the best clinicians in the U.S. and Europe. When psychoanalysis provided little benefit to Stanley, she turned to the emerging field of neuroendocrinology. Through her scientific reading and training, she became convinced that a biochemical imbalance was responsible for Stanley's mental illness. In 1927, Katharine funded a proposal by Roy Hoskins and created the Memorial Foundation for Neuro-Endocrine Research, the first in the country to research the influence of hormones on mental illness, particularly schizophrenia. The Foundation's offices and animal research were housed at Harvard Medical School, and the principal human studies were conducted at Worcester State Hospital for indigent mental patients. Hoskins was the Foundation's director for 20 years, and the Foundation published 350 studies, but none of them helped Stanley.

An early and ardent feminist

Starting when she was a student at MIT and continuing through the early years of her commuter marriage, Katharine devoted much of her time to women's suffrage. Although she was a close confidant of Carrie Chapman Catt, Ida Tarbell, and other leaders in the suffrage movement, Katharine kept a low profile. She did not want the press to associate her feminist activities with the Dexter and McCormick family names or Stanley's infirmity. With white gloved, Victorian gentility, Katharine was the national suffrage group's planner, strategist, scribe, and organizer—skills that she employed pragmatically and effectively to all the social causes

she advocated. And as the sole heir to the Dexter family fortune of \$10 million after her brother's early death from tuberculosis, she also generously financed those causes. The suffragettes systematically implemented a state-by-state lobbying campaign that was largely crafted by Katharine, and after passage of the 19th Amendment (women's suffrage) in 1920, she helped to found the League of Women Voters.

Katharine met Margaret Sanger in 1917, just a few years after Sanger began her fight to legalize contraception. (The 1873 Comstock Act prohibited pornography, abortions, and contraception, and many states had enacted supplemental laws that prohibited distribution of information and devices for contraception.) Sanger (one of eleven children) particularly wanted to improve the plight of impoverished women like her mother, who were entrapped in tenements by the Industrial Revolution, but Katharine saw contraception as the key to freedom for all women. By 1921, Katharine and Sanger had struck a mutually beneficial alliance. Katharine was impressed with Sanger's charisma and unflagging commitment to birth control. Sanger, in turn, saw Katharine as representative of a new generation of feminists, who provided an entrée into high society and access to new financial resources for the birth control movement. Katharine also possessed impressive scientific knowledge, a commitment to science, and a professionalism that defied the stereotype that women were emotional, irrational, and subjective.

Katharine smuggled a year's supply of diaphragms past customs officials for four straight years.

Conscious of Catholic-dominated Boston, which strongly opposed birth control in all forms, Katharine continued to keep a low profile. But she worked hard behind the scenes, attracting funds and many sympathizers for Sanger's nationwide activities. Katharine and Sanger also planned, published, and distributed a number of pamphlets on contraception—activities that were illegal—and Katharine underwrote the cost of publication.



Gregory Pincus in his laboratory with one of his experimental rabbits (Courtesy of University of Massachusetts Medical School Archives, Lamar Soutter Library, University of Massachusetts Medical School, Worcester, Massachusetts)

When a New York court ruled that physicians could prescribe contraceptives when medically necessary (creating an exception to the Comstock Act), Sanger recruited sympathetic physicians and opened the first American birth control clinic in January 1923 in Brooklyn, NY. Availability of contraceptives was severely restricted in the U.S., and demand for diaphragms (the only female-controlled contraceptive) outstripped supplies. Once again, Katharine came to the rescue. During her annual European holiday in July 1922, she went on a spending spree for the latest fashions and, posing as a French or German scientist,

met with manufacturers in Rome, Milan, and Paris to buy hundreds of diaphragms. She then hired local seamstresses to sew the diaphragms into her new wardrobe and packed the clothes into eight steamer trunks. Using this ruse, she smuggled a year's supply of diaphragms past customs officials for four straight years. When the needs at Sanger's clinic grew beyond the supplies that Katharine could safely smuggle in her clothes, she bribed a ship's captain to transport the contraband in cosmetics cases to a Canadian port. Liquor smugglers then carried the diaphragms across the border in their whiskey crates to warehouses managed by Sanger's husband in the Prohibition-thirsty United States.

For 20 years, Katharine corresponded intermittently with Sanger. She continued reading the latest medical research in psychiatry, endocrinology, neuroscience, and birth control and provided some funds for contraceptive research through Sanger's Planned Parenthood Federation, but her attention and funding focused primarily on neuroendocrine research and finding a cure for Stanley. When Stanley died in 1947, Katharine inherited his estate, tripling her already considerable wealth. She ended her support for neuroendocrine research and shifted all her energies to finding "a fool-proof contraceptive" (4).

After concluding the complicated probate of Stanley's estate, Katharine wrote Sanger in October 1950 and asked her to identify the best prospects for contraceptive research and the greatest need for financial support. Katharine was not interested in funding academic or basic research. She wanted to support scientists who could develop a tangible product. Sanger suggested Gregory Pincus, an expert in hormonal biology.

Pincus, Hoagland, and Chang



Hudson Hoagland and Gregory Pincus, shortly after founding the Worcester Foundation for Experimental Biology (Courtesy of University of Massachusetts Medical School Archives, Lamar Soutter Library, University of Massachusetts Medical School, Worcester, Massachusetts)

ratory he devised chemical and mechanical means to entice rabbit sperm to fertilize eggs and then coaxed the conceptuses to grow and divide for a short period. He published this landmark *in vitro* fertilization work in 1936 (5). Although it was a brilliant and widely heralded achievement, Pincus's research was also highly controversial, and his faculty appointment was not renewed.

Hudson Hoagland, a graduate school classmate, arranged for Pincus to join the biology department at Clark University in nearby

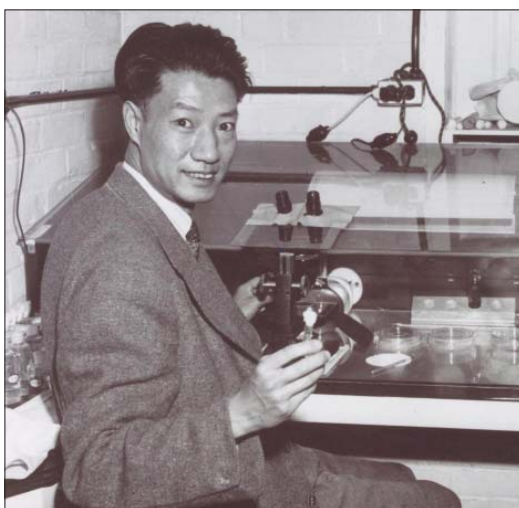
Gregory Pincus was born in 1903 and initially followed in the footsteps of his father and two uncles, who were accomplished agronomists. After majoring in agriculture at Cornell, Pincus shifted his interests during graduate school at Harvard to genetics, and thereafter, a lifelong fascination with reproduction. He joined the Harvard faculty, and in the laboratory he devised chemical and mechanical means to entice rabbit

Worcester, MA. In 1944, Hoagland and Pincus co-founded the Worcester Foundation for Experimental Biology, where they could devote full time to research according to their own impeccable standards and without interference from academic administrators. In its early years, the independent, private, nonprofit research institution operated on a shoestring budget. The scientists performed their own clerical and custodial chores. Pincus took care of the laboratory animals, Hoagland mowed the lawn, and Mrs. Hoagland kept the books. In addition to his brilliant intellect, Pincus was a hustler and a sociable charmer, captivating everyone with his stories and anecdotes on medical research. He easily attracted grants from federal agencies and commissions from drug companies for experimental studies. The Worcester Foundation soon earned a reputation for independent and unbiased research, and thanks to Pincus, an expertise in reproduction.

When Sanger recommended Pincus, Katharine was already familiar with his work, having read his articles on the use of hormones to control fertility in rabbits. Her first step, in 1950, was to visit her old friend Hudson Hoagland, a schizophrenia researcher who had collaborated with Hoskins's Neuro-Endocrine Research Foundation at Worcester State Hospital. Katharine was not impressed with the Worcester Foundation's barebones laboratory facilities, and she did not learn much about the ongoing research projects at this first meeting, but Hoagland promised to send her the details.

A few months later, in early 1951, Sanger invited Pincus to a dinner with several of her gynecology friends and asked his opinion on the feasibility of finding a medicinal product for birth control. Sanger and Katharine wanted an oral contraceptive—a pill that was cheap, plentiful, and easy to use. Until Sanger asked, Pincus had never considered contraceptive research, but he said it was possible, explaining that "such an undertaking would require money to purchase all of the material, engage staff, and obtain thousands of rats and rabbits" (4). All Sanger could offer at that time was a paltry \$2,500, but the idea intrigued Pincus. Back at the Foundation, he dug out a scientific article published in 1936 by investigators at the University of Pennsylvania. They reported that ovulation could be prevented in rabbits by injecting progesterone (6). Using that observation as a starting point, Pincus and Min-Chueh Chang followed up on Sanger's suggestion and began their first contraceptive studies in April 1951.

Pincus had met Chang while on sabbatical in England, where Chang was a graduate student at Cambridge University. In the aftermath of World War II, Chang had difficulty returning to China, and Pincus offered him a position at his new Foundation in Worcester. Chang became a leading authority on mammalian reproduc-



Min-Chueh Chang in his laboratory at the Worcester Foundation (Courtesy of University of Massachusetts Medical School Archives, Lamar Soutter Library, University of Massachusetts Medical School, Worcester, Massachusetts)

tion, and his skills harmonized perfectly with Pincus's own laboratory expertise. But unlike Pincus, Chang preferred the lab to socializing and spent long hours and weekends expertly handling the delicate reproductive specimens.

Under a \$3,400 stipend from the Planned Parenthood Federation, Chang soon confirmed the University of Pennsylvania results, injecting progesterone to inhibit ovulation in rabbits and also in rats. With those results in hand, Pincus and Chang approached Planned Parenthood for additional funds in January 1953, but the Federation board balked at the idea. They did not see how studies on rats and rabbits could benefit women. Katharine, who had made donations to Planned Parenthood and specifically earmarked her money for contraceptive research, intervened and browbeat the board into approving Pincus's request. But she was frustrated at the Federation's indifferent handling of contraceptive research, "when the need is so urgent" (1). She decided it was time to get directly involved.

Commissioning the Pill

On June 7, 1953, Katharine and Sanger met with Pincus and Hoagland at the Worcester Foundation. At a scant five feet, Sanger was a petite, stylish, sweet-faced woman whose appearance and manner was "never so beautiful that women didn't like her but attractive enough so that men wanted to give her money" (7). Conversely, men actually feared Mrs. McCormick. Although she was sensitive to people's feelings and never raised her refined, matronly voice, she rarely smiled and, according to one biographer, was "a woman more strange and powerful than fiction could ever invent" (4). Katharine's imposing, ramrod frame stretched to nearly six feet, and the Worcester scientists had never met anyone like her. She immediately asked to tour the labs and review the scientists' resumes. Then, she interrogated them about their views on contraception and birth control. Pincus was amazed at her scientific knowledge. She knew the field, spoke the language, and conversed with him no differently than an exchange between two research scientists.

Pincus passed Katharine's stringent examination, and at the end of the meeting, she handed him a check for \$20,000 for start-up activities. He doubted that much would come from this line of research, but he immediately realized Mrs. McCormick represented a potential bonanza in research money, which he took great care to groom. A week later, Katharine returned to the Worcester Foundation with her lawyer and again met with Pincus and Hoagland. She had drafted a contract, and they quickly agreed to terms for the operation, decision making, and timelines of the project. Pincus could not give Katharine a precise timetable, but he estimated the project would take 10–12 years. She gave him another check for \$20,000, and Pincus agreed to make improvements in the laboratory facilities; they settled on a first year budget of \$70,000. With the stroke of Katharine's pen, targeted development of an oral contraceptive had officially begun. And she told Pincus to be quick about it. Katharine and Sanger were both in their 70s.

To handle the clinical side of the project, Pincus turned to John Rock, who was already a legend in gynecology and obstetrics. Although Sanger was initially suspicious of Rock, a practicing Catholic, Katharine was impressed by his personal charm, humility, and unyielding professionalism. They were both Boston Brahmins and also shared a strong belief in the freedom of women to govern their own bodies. Rock explained, "I separated biology from theology quite early in my life and never confused them again" (4).

Rock had a thriving practice at several Harvard-affiliated hospitals including the Free Hospital for Women in Brookline on the outskirts of Boston. The ultimate caregiver, Rock oozed self-confidence, poise, and a commanding presence. His patients loved him. Rock also gave lectures on human sexuality to the Harvard medical students, including a run-down on the known forms of contraception, although dispensing such information violated Massachusetts' anti-birth control law. Rock had also pushed to the edge of legality by opening the first Rhythm Clinic in the U.S., teaching Catholic women how to calculate the fertile period in their menstrual cycle to avoid pregnancy. However, after years of meticulous data analysis, Rock concluded that there were too many variables in a women's menstrual cycle to make rhythm a reliable method for birth control.

Much of Rock's practice focused on assisting infertile women who wanted children. However, to help them, he realized that he needed to pinpoint and understand the one-to-two day interval when ovulation occurs. For 14 years, Rock and his associates collected and studied surgical specimens from women who had undergone hysterectomies for other medical reasons. He consulted frequently with Pincus, the young Harvard faculty member who was an expert in *in vitro* rabbit fertility. Rock announced his success in 1944, the first report of *in vitro* fertilization and cell division of human ovarian eggs (8). Photographs and microscope slides from this research effort remain the only specimens of early human conceptuses in existence.

The two collaborators lost touch after Pincus moved to Worcester, but they reunited by chance at a scientific conference in 1952. To Pincus's surprise, Rock had already injected women with progesterone and estrogen. Rock's goal was to "reset" the menstrual cycle of women with idiopathic sterility (due either to inconsistent ovulation, repeated miscarriages, or undiagnosable endometriosis). A large portion of these infertile women became pregnant within four months of stopping the hormonal treatments—a phenomenon that became known as the "Rock rebound." Of course, Rock knew that the progesterone/estrogen regimen mimicked the high endogenous hormonal levels that naturally prevent ovulation in pregnant women; his treatment was producing a "pseudo-pregnancy." Therefore, although Rock intended to overcome infertility and induce ovulation (by strategically stopping the hormone regimen), he knew that progesterone/estrogen blocked ovulation as long as it was injected—a contraceptive effect.

At Pincus's urging, Rock tried progesterone alone in a new series of infertile women (like Pincus and Chang were doing in animals). Rock's progesterone-only experiment was ongoing at the time that Katharine commissioned the Worcester Foundation in 1953. Four of the 30 women who received the progesterone injections became pregnant a few months after stopping treatment—the Rock-rebound phenomenon. Unfortunately, regardless of how high a dose Rock used, he could not achieve a complete "pseudo-pregnancy" effect; 15% of the women showed signs of ovulation during treatment. Also, progesterone had to be injected. In short, progesterone did not meet Katharine and Sanger's directive of an effective, easy-to-use, *oral* contraceptive.

The age of steroids

Katharine, Pincus, and Rock were fortunate that they began their quest for an oral contraceptive at a time when steroid chemistry was one of the hottest topics in pharmaceutical research. In the 1940s, Russell Marker discovered a way to synthesize progesterone using a starting material extracted from a Mexican yam. He subsequently

founded Syntex Corporation in Mexico to produce tons of progesterone, which various drug companies used as a starting material to synthesize the lucrative new anti-inflammatory steroid, cortisone. They also synthesized progesterone analogs (which were called progestins to distinguish them from the natural hormone) for use in treating infertility and menstrual disorders such as endometriosis.



Carl Djerassi (Courtesy of the Library of Congress)

Through his endocrine studies of fertilization, Pincus had become quite knowledgeable about steroid chemistry and worked as a consultant to Syntex and other pharmaceutical firms. When Rock's progesterone study fell short of Katharine's goal, Pincus wrote to his pharmaceutical contacts and asked if they had anything under development that might be a more potent and orally active progestin. Two replied that they did. Carl Djerassi, a young chemist at Syntex, and Frank B. Colton, a steroid chemist at G. D. Searle & Co., had been synthesizing progestins for potential use in treating rheumatoid arthritis and menstrual disorders. (Developing an oral contraceptive was the furthest thing from their minds. Drug companies shunned the notion of a hormonal contraceptive, viewing it as unprofitable and, because of strong religious opposition, a public relations quagmire.)

The progestin synthesis campaigns followed logically from earlier work by steroid chemists. In 1938, Hans Inhoffen and Walter Hohlweg at Schering installed a triple bond (acetylene) substituent on ring D, producing an orally active steroid. In 1944, Maximilian Ehrenstein, a University of Pennsylvania chemist, removed the C-19 methyl group of progesterone, producing the more potent "19-nor progesterone." In the early 1950s and working independently, Djerassi and Colton discovered that the triple bond acetylene substituent on ring D of this 19-nor progesterone increased the steroid's potency eight-fold and was orally active.

Throughout 1953, Searle, Syntex, and other drug companies sent hundreds of structurally related progestins to Pincus. Chang methodically tested them for efficacy and safety in his rat and rabbit experiments (9). He quickly narrowed the leads to Djerassi's norethisterone (S-759) from Syntex and Colton's norethynodrel (SC-4642) from Searle. Both were 19-nor progesterones with the triple bond substituent on ring D and differed only by the position of a double bond in ring A.

Rock-solid clinical trials

By 1954, Pincus and Chang were confident that S-759 and SC-4642 were the right compounds for Rock to test in women. In this Phase I clinical trial, Rock recruited most of the 50 women from the Free Hospital clinic in Brookline. He administered one of the two progestins for several menstrual cycles and then stopped treatment, hoping for the "Rock rebound." But this time, Rock also intensively examined and carefully charted the women to

determine whether the compounds truly stopped ovulation.

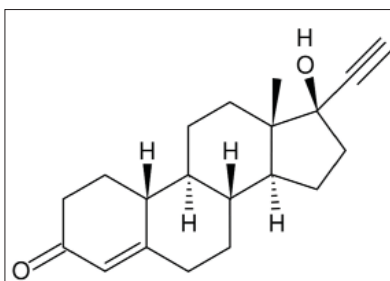
From the beginning, Pincus realized that Mrs. McCormick would not be a typical financial sponsor. She kept a close eye on the Worcester team's work and was unrelenting in her demand for details. Every two weeks, she received a detailed progress report from Pincus, in addition to her daily phone conversations and frequent visits to the foundation's laboratories. Pincus never felt entirely comfortable with Katharine and chafed at the amount of time he was required to spend with her. But he always responded promptly to her questions and requests and developed a sincere admiration for her. Every six months, Katharine, Pincus, and Hoagland met to review the project's expenses and to discuss the budget for the next six months. Regardless of the costs, Katharine always authorized payment and approved the budget, once she was satisfied with their answers. She understood the realities of research, and they were making rapid progress, but she still pushed the researchers to work faster and was frustrated by anything she perceived as a delay.

In 1955, Rock was nearing mandatory retirement at Harvard and its affiliated hospitals. The Free Hospital customarily granted limited space to retired staff as a courtesy, but in Rock's case it was essential for the hospital to keep him engaged as a "consultant." He generated a large share of the hospital's patients. Even so, the dilapidated and cramped retirement quarters he was assigned were unsuitable to continue his practice and the clinical contraceptive research. Calling those facilities a "hovel," Katharine bought a building directly across the street from the Free Hospital and gave Rock \$100,000 for renovations. Near the end of Rock's first clinical trial, some of the 50 participants were drawn from his patients at the new, appropriately named Rock Reproductive Clinic.

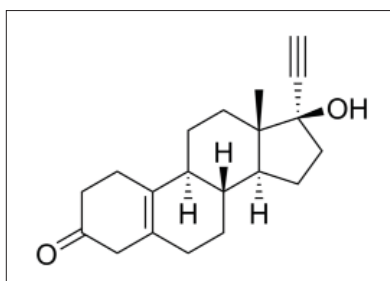
In early 1955, the first trial with SC-4642 and S-759 was still ongoing, but the results already confirmed Rock's earlier findings with injected progesterone. About 15% of the women exhibited rebound pregnancies after treatment was stopped. More importantly, the oral compounds inhibited ovulation in all of the women during treatment (10). Rock had demonstrated Proof of Concept, and Pincus was now certain that they could develop the kind of pill that Sanger and Katharine had specified.



Celso-Ramon Garcia (left), John Rock (right), and Gregory Pincus, reviewing their oral contraceptive data in 1957 (Courtesy of University of Massachusetts Medical School Archives, Lamar Soutter Library, University of Massachusetts Medical School, Worcester, Massachusetts)



Syntex's S-759, norethisterone (Norgestrel®)



Searle's SC-4642, norethynodrel (Enovid®)



Edris Rice-Wray (Courtesy of Henrylee Marlo)

But Rock took his time. He moved with thoughtful caution through every step of testing these new progestins. He discussed the risk factors at length with each of his volunteers, instinctively employing high safety standards despite no regulatory requirements at that time for informed consent. He also insisted on reproducing the initial findings and collecting additional safety data on the two progestins (now called Phase II trials), before starting definitive, large-scale trials. However, he was tempting fate if he continued these increasingly high-profile clinical trials in Massachusetts. His dissemination of contraceptive advice to patients, his lectures on contraception to medical students, and his small Phase I clinical trial had not raised suspicions, but they were all illegal activities. He faced up to five years in prison and fines of \$1,000 for each instance in which contraceptive advice or aids were supplied.

After considering various alternative locations, the Worcester team settled on Puerto Rico. Although the island was predominantly Catholic, its laws were more forgiving about contraception. Also, Rock and Pincus knew local investigators who were birth control advocates and qualified to conduct the trials: Celso-Ramon Garcia and Edris Rice-Wray. Still, they camouflaged their true intentions, describing the project as a study of the physiology of progesterone in women, rather than as a study of contraception. Rock made frequent trips to Puerto Rico, closely monitored all of the trial patients' health records, and personally examined the tissue samples.

Retrospectively, Katharine always called the first Puerto Rican trial a "flop." It suffered from poor record keeping, noncompliant volunteers, and interference from Catholic-oriented senior officials at the University of Puerto Rico. Garcia then recruited twenty medical students and nurses for a second trial, which ran smoothly until a Catholic faction at the testing hospital stonewalled the project. Nevertheless, by late 1955, the combined data from Rock's Phase I trial and the Puerto Rican volunteers justified launching the large Phase III trials. But first, the Worcester team needed to decide between SC-4642 and S-759. There were multiple conferences in Puerto Rico, Brookline, and Worcester. They checked and rechecked their own data as well as the data generated by Syntex and Searle. Rock leaned on Pincus for critical statistical data to determine which of the two compounds had fewer side effects. Rock and Garcia reviewed the medical findings, blood tests, and reproductive tissue samples from the volunteers. In the end, Rock relied on his experienced instincts to select Searle's SC-4642.

The third (and pivotal) clinical trial in Puerto Rico was conducted by Rice-Wray at a government housing project in Rio Piedras, a suburb of San Juan, and began in April 1956. Most of the participants were Catholic, but they were also practical in their attitudes toward child-bearing: choosing the evil of birth control over the evil of not being able to feed another child. The Catholic

Church hierarchy reacted by admonishing parishioners from the pulpit, and the Catholic Social Workers Guild warned in a television broadcast that the drug was dangerous. Consequently, about 10% of the women dropped out of the trial, and all of them became pregnant. After that, Rice-Wray never had a problem recruiting volunteers. They flocked to the clinic asking for the drug, not just the indigent population, but schoolteachers and the social workers themselves. And no one dropped out.

During the trial, the investigators discovered a small impurity of mestranol, a synthetic estrogen, in one batch of SC-4642. Searle revamped production to remove it, and Rice-Wray observed that the pure progestin produced a higher incidence of undesirable breakthrough bleeding during the menstrual cycle, rather than at the end. Further analysis revealed that traces of mestranol had been present in the original effective batches of SC-4642, and its unintended presence probably accounted for the better performance of SC-4642 compared to S-759. Going forward, Searle deliberately formulated the SC-4642 tablets with 1.5% mestranol.

At their semiannual budget meetings, Katharine was pleased with the investigators' impressive results but constantly urged them to go faster. Day-by-day, the progress seemed to be "slow as molasses" (4). The six-month budgets had now swelled to more than \$100,000 to cover the laboratory testing and expanded clinical trials. But after reviewing the results and being satisfied with Pincus's answers, Katharine simply nodded to her attorney, and he knew what to do. Hoagland and Pincus could only stare with awe at the generosity of their benefactor.

Katharine and the Worcester team felt the Rio Piedras trial, although thriving, would not be sufficient to satisfy the Food and Drug Administration. They set up another Puerto Rican site at Humacao, where they duplicated the Rio Piedras protocol. They also established a clinical site in Haiti at the invitation of the island's ruler, "Papa Doc" Duvalier.

It was amazing that so many women—an estimated 500,000—suddenly had menstrual disorders requiring treatment, women who had never seemed to have menstrual problems before.

Gaining approval

Prior to the Puerto Rican trials, Rock had never given progestin to women for more than six cycles. He was confident that short term treatment was safe, but to address longer-term safety questions, the Worcester team incorporated additional endpoints into their Phase III clinical protocol, looking specifically at birth defects, long-term fertility, and the ratio of boy-to-girl births. To their relief, when subsequent pregnancies occurred within four months in 85% of the women who stopped the Pill in order to get pregnant, boys and girls arrived in equal numbers, and no birth defects afflicted any of the infants. At the end of the first nine months of the clinical trial (47 women-years of experience), none of the women suffered any serious problems.

In 1957, Searle submitted Rock's data in an application to the FDA to license SC-4642 (Enovid®) for regulating the menstrual cycle. At that time, drug companies only needed to submit data demonstrating a drug's safety and purity. FDA approved Enovid for menstrual disorders with minimal debate. Searle executives were still waffling about licensing Enovid for the contraceptive indication, but the significance of this initial regulatory approval was not missed by Katharine. She told Sanger, "Of course this use of the oral contraceptive for menstrual disorders is leading inevitably to its use against pregnancy...a very happy and fortunate course" (1). She was now 83 and increasingly in pain from arthritis. Pincus and Rock were both concerned about her obviously delicate health, but she brushed them off.

At their next budget review, Pincus reported that drug companies were approaching him for information. (In 1957, Syntex's S-759 was also approved for treatment of menstrual disorders and marketed under a license to Parke-Davis as Norlutin®.) It was amazing that so many women—an estimated 500,000—suddenly had menstrual disorders requiring treatment, women who had never seemed to have menstrual problems before. (The drug's label included a warning that Enovid prevented ovulation and pregnancy, which amounted to free advertising for Searle.) Searle heard rumors that doctors were already prescribing Enovid to prevent pregnancies. As sales surged, Searle's executives suddenly became supportive.

Still, Rock was biding his time and closely monitoring the women, hesitant to declare that Enovid was safe for oral contraceptive use. His best guess of the dose that would ensure freedom from pregnancy was 10 mg. He knew that dose was safe, because he had administered up to 300 mg to his "Rock rebound" patients. But Rock and Katharine knew that those who opposed birth control would exaggerate any suspected adverse reactions. When the clinical database reached 10,000 menstrual cycles, Rock was finally convinced that they had collected a sufficient burden of proof on the drug's safety. Not a single woman in the Puerto Rican and Haitian trials had developed either blood clotting problems (which were later shown to be associated with the Pill when combined with smoking) or any signs of cancerous changes.

In the summer of 1959, Katharine, her lawyer, Pincus, Rock, and representatives from Searle held a series of meetings to discuss the strategy for licensing Enovid as an oral contraceptive. They had checked the data innumerable times for accuracy and could answer any question about side effects, long-term administration, and costs. On October 29, 1959, Searle submitted the application to the FDA, with results from 897 women, 801.6 woman-years of use, and 10,427 menstrual cycles. The results could not have been more definitive. Some women had been taking the Pill for five years with no significant adverse reactions. And no one who took the Pill as directed became pregnant.

But Searle's application raised an unprecedented regulatory issue: the FDA had never been asked to evaluate a drug that was intended for long-term use in healthy people. The agency was certainly also aware of the strong opposition of the Catholic Church and other conservative groups. The mandated FDA review time was 90 days, but because the agency was not empowered to require efficacy data, FDA officials often took advantage of an administrative loophole to extend the review time by 6 months, hoping drug companies would use the time to provide more information and strengthen the evidence for a drug's therapeutic benefits. Although Pasquale DeFelice, the designated FDA medical reviewer, admitted that Enovid had been tested more

extensively than any drug in the FDA's history, "we were in no hurry to put the FDA stamp of approval on it" (4). DeFelice exercised the extension provision, twice. Rock was outraged at the unwarranted delays, and Searle's medical director requested a hearing.

For their spokesperson at this historic showdown, Searle designated Rock, whose knowledge, expertise, reputation, and pedigree were undisputed. On a frigid day in December 1959, Rock and Searle's medical director met with DeFelice in his FDA office, a wooden building constructed as a temporary barracks during World War I. The young medical reviewer had not yet been board-certified in gynecology and was no match for Rock, a towering figure in both physical and intellectual stature. Yet, despite Rock's deft answers to every FDA concern, DeFelice remained entrenched. He required Searle to provide additional laboratory data on 500 women to examine a possible relationship between Enovid use and blood clotting. Rock already knew from his own analysis that there was no relationship, and Searle's tests confirmed it. In addition, in a maneuver that predated the FDA's Advisory Committee system, DeFelice sent the data to 61 professors of obstetrics and gynecology, asking for their recommendations. Twenty-six recommended approval of the birth control pill; fourteen were unable to make a decision. Of the 21 who disapproved, two cited religious objections, but the other 19 professors gave no rationale, scientific or otherwise.

On May 11, 1960, Searle received official notification that Enovid had been approved as the first oral contraceptive, almost seven years to the day after Katharine, Sanger, Pincus, and Hoagland met to initiate the project. In the summary of the approval letter, deputy FDA commissioner John L. Harvey wrote, "Although we recognize the presence

of moral issues, they do not come within the jurisdiction of the Food and Drug Administration" (4). Searle and Syntex supplied the progestins to Pincus, Chang, and Rock for the preclinical and clinical studies, but no other drug company support and no government funds were used to develop the Pill. Katharine McCormick singlehandedly financed the entire effort, an estimated \$2 million (\$16 million in today's currency), and she gladly could and would have put up ten times that much if necessary.

The celebrations at the Worcester Foundation went on all day, with champagne and food paid for by Katharine. *The New York Times* called approval of the Pill, "the most sweeping socio-medical revolution in history" (1). Despite regulatory approval, many states still prohibited the sale of contraceptives, and views on their use remained polarized. The day after the Pill's approval, Pincus told Katharine that doctors were receiving threats and warned her that since she had been mentioned in the newspapers as patroness of the project, her life might be in danger as well. That evening, Katharine and her secretary boarded a train out of Boston under assumed names headed for an undisclosed location. Despite the threats, public acceptance of the Pill was rapid, and in the 1960s use of all forms of birth control expanded. One-by-one, the state laws came off the books. Ironically, the last anti-birth control law to fall was a Massachusetts statute, which was declared discriminatory and unconstitutional by the U.S. Supreme Court in 1972.

Katharine Dexter McCormick died on December 28, 1967 at the age of 92. At that time, 18 progestin/estrogen products had been approved as oral contraceptives, and the Pill was being taken by more than six million American women.

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New Editorial Board Members

Dr. Ravi Iyengar has been named an Associate Editor to *The Journal of Pharmacology and Experimental Therapeutics*. Dr. Iyengar is the Dorothy H. and Lewis Rosenstiel Professor with the Department of Pharmacology and Systems Therapeutics at the Icahn School of Medicine at Mount Sinai, New York, NY. With **Dr. Darrell Abernethy** and **Dr. Donald Mager**, Dr. Iyengar will be responsible for manuscripts submitted to *JPET*'s new section on Quantitative Systems Pharmacology.

Dr. Kenneth E. Thummel joined *Molecular Pharmacology* as an Associate Editor. Dr. Thummel is a Professor and the Milo Gibaldi Endowed Chair of the Department of Pharmaceutics, School of Pharmacy, at the University of Washington, Seattle, WA.

Dr. Graeme Milligan will succeed **Dr. Laura Bohn** as the Minireviews Editor for *Molecular Pharmacology* in January 2014. Dr. Milligan is the Gardiner Professor of Biochemistry at the University of Glasgow, Glasgow, Scotland.

Journals Department Staff Changes

Jill Filler, ASPET's Managing Editor, retired on October 3 after nearly 12 years with ASPET. She has been succeeded by **Dianne King-McGavin** who joined ASPET on November 1 as the Peer Review Manager. Dianne has held positions with the Biophysical Society and the American Society for Nutrition.

Also on November 1, **Cassie Wood** returned from maternity leave. Cassie is the Editorial Coordinator for *JPET*.

See the Staff News section on page 227 for more information about these ASPET staff members.

PR&P Launches First Issue

Pharmacology Research & Perspectives completed its first issue on October 23. *PR&P* is jointly published by ASPET, the British Pharmacological Society (BPS), and John Wiley & Sons, Inc. Articles are published on a continuing basis and then grouped into an issue. Issues will be designated bimonthly.

PR&P utilizes cascading reviews in a manuscript transfer program from ASPET's primary research journals and the two journals of the BPS. The journal also publishes new submissions. *PR&P* is an entirely open-access journal and can be freely accessed at <http://www.PharmacolResPerspect.com>.

The journal recently announced that it will include the publication of negative findings including preclinical papers that show a hypothesis is incorrect or papers on drugs that have failed in early clinical development. *PR&P* also invites manuscripts that provide drug discovery reviews (strategy, hypotheses, and data resulting in a successful thera-

peutic need), frontiers in translational medicine (drug and target validation for an unmet therapeutic need), and pharmacological hypotheses (reviews that are oriented to inform a novel hypothesis).

Dr. Michael J. Curtis serves as the Editor-in-Chief, and **Dr. Darrell R. Abernethy** is the journal's Deputy Editor. To learn more about the scope of *PR&P* and submit a manuscript, visit <http://www.PharmacolResPerspect.com>.

ORCID

ASPET has implemented the use of ORCID IDs for our manuscript submission and tracking system, Bench>Press. As described on the ORCID website, <http://www.orcid.org>, ORCID "provides a persistent digital identifier that distinguishes you from every other researcher and, through integration in key research workflows such as manuscript and grant submission, supports automated linkages between you and your professional activities ensuring that your work is recognized." The use of ORCID IDs helps disambiguate authors with similar names and provides a consistent record for authors who change names or use variations of the same name (e.g., Joe Smith, J. Smith, J.A. Smith, and Joseph Smith).

There is no charge to register with ORCID, and the Bench>Press implementation is designed to be unobtrusive and easy. When you register at ORCID, you can link your record to your publications, affiliations, grants, and patents. You have the option of providing biographical information as well. Publications can be added manually or by importing records from a number of databases such as the ANDS National Collections Registry in Australia, Europe PubMed Central, Scopus, ResearcherID, and CrossRef.

This new feature was added in mid-November for ASPET's journals. Although ORCID IDs are just starting to appear, they are being rapidly adopted by publishers and funding agencies. Including them in ASPET's journals will be an asset for our authors. To register with ORCID, go to <http://www.orcid.org>.

Social Bookmarking

Social bookmarking was added to ASPET's journals on September 4. Social bookmarking is a personal knowledge management tool that allows users to save and categorize a personal collection of bookmarks and share them with others. Readers can alert their colleagues to articles of interest through 11 social media sites: CiteULike, Connotea, Delicious, Digg, Facebook, Google+, LinkedIn, Mendeley, Reddit, Technorati, and Twitter. When you see an article that you think is of interest to your colleagues, you can tell them about it using social bookmarking. This feature is available to all readers of ASPET's journals. Links to the 11 social media sites appear at the end of the abstract view and full-text HTML view of each article. For the PDF version, the links are in the column to the left of the PDF in the expandable list under "Social Bookmarking."



Can Congress Avoid Sequestration in FY 2014?

With the December 13 deadline days away, it remains to be seen, at the time of this writing, if the House and Senate budget conference committee will be able to arrive at a negotiated settlement that bridges the differences between the Republican and Democrat budgets and avoids sequestration for FY 2014. If the committee fails – a likely proposition, it would mean that House and Senate leadership will have to cobble together a funding bill by January 15 or face another government shutdown.

The budget conference committee has met just twice, with little to show other than opening statements and both sides of the aisle suggesting that sequestration must be avoided for FY 2014. There seems to be a bipartisan consensus that sequestration was a bad way to cut spending and it should not be repeated in FY 2014. There is a very real sense on Capitol Hill that there are, in the words of House Budget Committee Chair Paul Ryan (R-WI), "...smarter ways of cutting spending-whether you're Republican or Democrat." And House Appropriations Chair Hal Rogers (R-KY) together with the 12 Chairs of all the Appropriations Subcommittees sent a letter on November 18 urging the Budget Conference Committee to as quickly as possible arrive at an agreement that provides for adequate spending levels for FY 2014. Concerned that the Budget Conference Committee might fail, the Appropriations Chair's letter notes that "failure to reach a budget deal to allow Appropriations to assemble funding for FY 2014 will reopen the specter of another government shutdown...the probability of governance by continuing resolution based on prior year outdated spending needs and priorities...the current sequester and the upcoming second sequester in January would result in more indiscriminate across the board reductions that could have negative consequences on critically important federal programs, especially on national defense." So there does seem as if Congressional leaders want to stop sequestration and return to the regular order of the appropriations process. However, the issue remains how and will they actually arrive at a deal that addresses these issues?

While there may be some window for optimism that NIH will avoid sequestration, the threat persists until Congress changes it. If the Budget Conference Committee can't come to some agreement, then it is possible Congressional leadership may continue to fund the government after January 15 with another Continuing Resolution (CR). Keep in mind, however, that if there is a full-year CR for FY 2014 at the FY 2013 funding levels, then there would be a sequester since the CR would exceed the budget caps established under the 2011 Budget Control Act (BCA). A more favorable outcome would be some sort of agreement that allows for the higher Senate spending levels or having Congress amend the BCA to allow for higher spending caps. Hopefully, as you read this, the outcome of these deliberations is resolved more favorably for NIH.

Science Advocates

With some momentum, the biomedical research community responded in a robust way to alert Congress of the dangers sequestration poses to the NIH. ASPET members have written to members of

the budget conference committee at the urging of ASPET President Richard Neubig's letter. (See page 216.)

ASPET also joined many other organizations in cosigning a community sign-on letter to the House-Senate budget conferees, urging Congress and the Administration to "work responsibly on a FY 2014 budget agreement that replaces sequestration with a balanced plan that recognizes the significant cuts already made to discretionary programs, preserves the nation's investment in medical research, and protects the health of the American people." And through an effort led by the Association of American Medical Colleges, ASPET asked our own graduate students and postdoctoral trainees to contact their Members of Congress to provide their perspectives about the future of biomedical research and its importance to all of us. As of November 8, almost 2,500 individuals wrote to their Congressional delegation.

Also, 200 medical school deans and teaching hospital CEOs expressed "grave concern" about sequestration's impact on NIH in a letter to Congress. The Deans and CEOs letter further expressed the concern that cuts to NIH "...threaten current and emerging basic research opportunities across the country, as well as the clinical studies that are essential to bringing scientific discoveries from the bench to the bedside" and that these cuts, "... will discourage young people from careers in medical research, risking the loss of the next generation of innovators and their ideas."

The Science Coalition, comprised of scientific research organizations, also recently published a report that highlighted the 100 companies that grew out of an investment of just \$330 million in federal research funding (<http://www.sciencecoalition.org/pr.php?id=568>) and the negative impact that \$95 billion in federal research and development cuts could have over the next decade.

FASEB issued an e-action alert to rally the community to tell Congress to work together to restore funding cuts for NIH, NSF, and other science agencies to pre-sequestration levels and agree on a fiscal year 2014 budget that sustains the prior investment in research. FASEB also wrote to members of the Budget Conference Committee asking that funding for NIH be restored. You can read the FASEB letter on page 218.

The Rita Allen Foundation and the American Pain Society Announce the 2014 Rita Allen Foundation Award in Pain

The Rita Allen Foundation (RAF) and American Pain Society (APS) may award two grants in the amount of \$50,000 annually, for a period of up to three years to those research proposals demonstrating the greatest merit and potential for success. Eligible candidates will have completed their training and provided persuasive evidence of distinguished achievement or extraordinary promise in basic science research in pain. Candidates should be in the early stages of their career with an appointment at faculty level. The deadline for applications is January 17, 2014. For further details, please visit <http://www.americanpainsociety.org/about-aps/awards/rita-allen-foundation-award-in-pain.html> or contact APS at 847-375-4715 or info@americanpainsociety.org.



Council

October 23, 2013

Richard R. Neubig
President
Michigan State University

Dear ASPET member:

Annette E. Fleckenstein
President-Elect
University of Utah

As you are well aware, last week Congress finally resolved its differences allowing the federal government to re-open through January 15 and the nation's debt ceiling limit to be raised through February 7.

John S. Lazo
Past President
University of Virginia

For most federally funded grantees this resolution, however temporary, is good news. However, for all of us in the NIH community one thing has not changed yet is not discussed as much: The NIH remains underfunded and is facing another round of serious sequestration cuts.

Sandra P. Welch
Secretary/Treasurer
Virginia Commonwealth University

As part of the budget agreement noted above, a new bipartisan Congressional budget commission has been set up that will try to bridge the \$90 billion that separates the House and Senate FY 2014 budget resolutions. Frankly, there is no reason for optimism that Congress will arrive at a "grand bargain" deal that includes all of the spending, tax, and entitlement issues that need to be addressed by the December 13 deadline. However, NIH is funded at the current sequestration level through January 15. In spite of their opposition to sequestration, Democrats agreed to that funding level before the shutdown and as a compromise to help end the shutdown. So regardless of the political dynamic of which political party won or lost the political fight, sequestration remains for FY 2013 and threatens again in FY 2014 (mid-January).

Paul A. Insel
Secretary/Treasurer-Elect
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Past Secretary/Treasurer
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University of Texas Health Science
Center – San Antonio

John D. Schuetz
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St. Jude Children's Research Hospital

That is the bad news.

Kenneth E. Thummel
Councilor
University of Washington

Here is some good news.

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Democrats may have conceded sequestration for FY 2013, but they hate it. They are well aware of the damage it is doing to the NIH and the entire federal research enterprise. Significantly, over the past year we have seen many Republicans, including appropriators, publicly state that cuts to domestic discretionary spending have gone too far. While sequestration has done its damage, our community has effectively educated many in Congress and the public about the consequences of continued cuts to NIH. ASPET members have played their part in bringing greater awareness to members of Congress and the public. Many of you have contacted your Congressional representatives to let them know how these cuts are impacting your institution. There have been countless numbers of opinion pieces in local papers written across the country by leaders in academic medicine, industry, and rank and file bench scientists (including some ASPET members) informing local media about sequestration's impact. Never have so many in Congress on both sides of the partisan aisle been more aware of the problem or of the need to fix it. That is not to suggest this will be easy. The politics of these discussions will be difficult. However, momentum is on our side. ASPET members have an opportunity to play their part in rolling back sequestration in FY 2014.

Brian M. Cox
FASEB Board Representative
Uniformed Services University
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Scott A. Waldman
Program Committee
Thomas Jefferson University

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The budget conference commission intends to finish all FY 2014 spending bills by December 13. This is not an easy task given how charged the political environment is in Washington. While many in Congress want sequestration rolled back, others do not.

Given the difficult situation that NIH is in, it is easy to forget that NIH enjoys bipartisan support. But sequestration is law and if Congress does not act to pass legislation to avoid it in FY 2014, NIH will be greatly impacted. We must continue to make our case in support of NIH to all Members of Congress.

The following Members of Congress have been appointed to the bipartisan conference commission:

- Rep. Tom Cole (R-OK)
- Rep. Tom Price (R-GA)
- Rep. Diane Black (R-TN)
- Rep. James Clyburn (D-SC)
- Rep. Nita Lowey (R-NY)
- Sen. Ron Wyden (D-OR)
- Sen. Bill Nelson (D-FL)
- Sen. Debbie Stabenow (D-MI)
- Sen. Bernie Sanders (I-VT)
- Sen. Sheldon Whitehouse (D-RI)
- Sen. Mark Warner (D-VA)
- Sen. Jeff Merkley (D-OR)
- Sen. Chris Coons (D-DE)
- Sen. Tammy Baldwin (D-WI)
- Sen. Tim Kaine (D-VA)
- Sen. Angus King (I-ME)
- Sen. Chuck Grassley (R-IA)
- Sen. Mike Enzi (R-WY)
- Sen. Mike Crapo (R-ID)
- Sen. Lindsey Graham (R-SC)
- Sen. Rob Portman (R-OH)
- Sen. Pat Toomey (R-PA)
- Sen. Ron Johnson (R-WI)
- Sen. Kelly Ayotte (R-NH)
- Sen. Roger Wicker (R-MS)

If you reside in the Congressional district and/or state of the above mentioned budget conference commission members, it is important you contact these individuals. Your message should be brief, asking that NIH be funded at pre-sequestration levels for FY 2014 to help sustain biomedical research. Note how years of flat funding and sequestration have impacted scientific opportunity and progress, are causing young investigators to leave research, and threaten America's leadership in biomedical research.

To reach your Congressional delegation, visit: <http://www.aspet.org/Page.aspx?id=216>. However, all ASPET members need to reach out to their Congressional delegation. Your Members of Congress can be reached via email directly through their websites.

Congress needs to hear from all members of the science community, so encourage your colleagues to act too. These efforts by our community really can help raise Congressional awareness about NIH's value and help us avoid sequestration in FY 2014. If you do contact Congress or have any questions, please let us know by contacting ASPET's government affairs director, **Jim Bernstein** at jbernstein@aspnet.org.

Sincerely,



Richard R. Neubig
President



FASEB

Federation of American Societies
for Experimental Biology

Representing Over 110,000 Researchers

301.634.7000
www.faseb.org

9650 Rockville Pike
Bethesda, MD 20814

November 07, 2013

The Honorable Patty Murray
U.S. Senate
Washington, DC 20510

The Honorable Paul Ryan
U.S. House of Representatives
Washington, DC 20515

Dear Chairwoman Murray and Chairman Ryan:

As you begin conference negotiations on the fiscal year (FY) 2014 budget, we urge you to replace sequestration with an alternative deficit reduction plan that allows for sustained investment in the nation's research and science agencies. Sequestration has dealt a devastating blow to an enterprise already suffering from underfunding and previous budget cuts, and the impact is being felt in labs and research institutions across the country. Critical research has not been done, a generation of young researchers is being driven away by the lack of career opportunities, senior investigators are leaving research altogether, and prior investments in science are being undermined.

While the opportunities to develop new therapies for many diseases are unprecedented, years of flat-funding, inflation, and \$1.7 billion in cuts due to sequestration have reduced the National Institutes of Health's (NIH) ability to support innovative research. In constant dollars (adjusted for inflation), the FY 2013 budget for NIH was at its lowest level since FY 2000. At the current level, NIH can fund only one in six grants, leaving many outstanding research programs without support. The price of continuing on this path will be the abdication of U.S. leadership in biomedical research. Between 1999 and 2009, the U.S. share of the global investment in research and development declined from 38 to 31 percent.

Scientists and engineers funded by the National Science Foundation (NSF) have made important discoveries leading to the invention of revolutionary new technologies, including 3-D printing, digital wireless telecommunications, stronger bulletproof vests, and computer-aided design and manufacturing. Sequestration reduced the NSF budget by \$375 million, and as a result, the agency funded 1,000 fewer promising research grants. Any additional cuts to NSF will further erode the research and training programs that produce the scientific advances needed to keep our nation globally competitive and protect our standard of living.

Research programs supported by federal agencies including NIH, NSF, the Department of Energy Office of Science, the Department of Agriculture, and the Department of Veterans Affairs are essential for improving our understanding of diseases, increasing crop production, harnessing new energy sources, protecting against bioterrorism, and addressing the unmet needs of our veteran population. Furthermore, the federal investment in these agencies is a critical source of new innovations in health care, agriculture, and technology; it is the kind of investment that no individual company or private entity could afford to undertake on its own.

This summer the Senate Appropriations Committee approved FY 2014 bills for NIH and NSF that are very similar to [FASEB's recommendations](#). These funding levels will support modest growth for these critical agencies and are a first step toward reversing the harm from the FY 2013 sequestration cuts. FASEB respectfully requests that you work together to reach a bipartisan deficit reduction solution that recognizes the significant cuts that have already been made to discretionary programs and ensures the sustainability of the nation's research enterprise.

Sincerely,

Margaret K. Offermann, MD, PhD
FASEB President

cc: Members of the Conference Committee

The American Physiological Society • American Society for Biochemistry and Molecular Biology • American Society for Pharmacology and Experimental Therapeutics
American Society for Investigative Pathology • American Society for Nutrition • The American Association of Immunologists • American Association of Anatomists
The Protein Society • Society for Developmental Biology • American Peptide Society • Association of Biomolecular Resource Facilities
The American Society for Bone and Mineral Research • American Society for Clinical Investigation • Society for the Study of Reproduction • The Teratology Society
The Endocrine Society • The American Society of Human Genetics • Environmental Mutagenesis and Genomics Society • International Society for Computational Biology
American College of Sports Medicine • Biomedical Engineering Society • Genetics Society of America • American Federation for Medical Research
The Histochemical Society • Society for Pediatric Research • Society for Glycobiology • Association for Molecular Pathology

Meet the 2013 ASPET Washington Fellows!



ALEX J. BREWER, III
Baylor College of Medicine

Alex was born in Arkansas, but raised in Houston, TX. He earned a B.S. in chemical and bio-molecular engineering from Rice University and is currently a graduate student in the Department of Pharmacology at Baylor College of Medicine.

His laboratory seeks to identify new medications for the treatment of substance use disorders by investigating medications already approved by the FDA for other indications in studies similar to phase 1 clinical trials. His particular dissertation project focuses on studying a potential drug combination and its effects on the subjective and reinforcing effects produced by cocaine use in cocaine dependent individuals. Alex's research interests lie within science and technology policy, pharmaceutical development, and clinical trials. Alex has observed firsthand the types of scientific breakthroughs and their subsequent benefits to public health that can be achieved with cooperation between policymakers, the public, and the scientific community, and he wants to help ensure that scientific progress will continue to be made for the benefit of society.



MELISSA GEYER
University of Illinois
College of Medicine

Melissa was born and raised in Woodbridge, VA, a suburb of Washington D.C. She is a graduate student in the Pharmacology Department at the University of Illinois at Chicago. Her dissertation research focuses on the role end-binding protein play in regulation of endothelial barrier function in lung.

Between earning her B.S. in genetic engineering from Cedar Crest College and graduate work at UIC, she worked extensively with preclinical research projects as a Project Manager in San Diego, CA. She also worked as a Technician at the University of Michigan investigating the role of tissue plasminogen activator in acute ischemic stroke using mouse models. Through the ASPET Washington Fellows program, she hopes to gain greater exposure to the scientific community to facilitate networking. She also hopes the program provides her with opportunity to develop her interest in science policy and to learn more about governmental public policy.



DEBRA COOPER, Ph.D.
University of Texas
Medical Branch at
Galveston

Debra was born and raised in Houston, TX. She went to Duke University in North Carolina to pursue her B.S. in psychology. Following that, she went on to graduate school at Emory University in Atlanta, GA,

where she studied the effects of the enzyme dopamine beta-hydroxylase on cocaine mediated behaviors and neurochemistry. While pursuing her doctorate, she also obtained an HHMI funded Certificate in Translational Research. In the spring of 2013, she defended her thesis and received a Ph.D. in neuroscience from Emory University. She is currently a postdoctoral fellow at the University of Texas Medical Branch in Galveston, TX. Her research focuses on how the serotonin system shapes behavioral responses to reinforcers. Debra believes that effective advocacy backed by sound scientific research is necessary for maintaining a strong federal research program.



COLIN HIGGINS
University of Iowa

Colin was born in Omaha, NE, and raised across the Missouri River in Council Bluffs, IA. He discovered molecular pharmacology while an undergraduate, studying allosteric modulators of neuronal nicotinic acetylcholine receptors at Grinnell College, where he

earned a B.A. in biological chemistry with a concentration in neuroscience. He is currently a fourth-year Ph.D. candidate in medicinal chemistry at the University of Iowa. Colin's dissertation project focuses on structural models of allosteric inhibition of regulators of G protein signaling with an eye toward generating novel therapeutic agents for neurological disorders. His research interests include neuropharmacologic enhancement and the structural underpinnings of allostery. Colin is concerned with the public's perception of the value of scientific inquiry and how scientists can improve awareness for the importance and impact of their work.



PRASAD KRISHNAN, Ph.D.
Pennsylvania State University

Prasad is a postdoctoral scholar at Penn State University at University Park. His research is focused on the role of Ppar beta/delta in prevention of cancers like skin and prostate. His work also involves understanding

the mechanism of liver toxicity of environmental toxicant like PFOS. Prasad was born and raised in India where he received his B.S. in pharmacy and M.B.A. in marketing. He later moved on to the LSU Health Sciences Center, in Shreveport, LA, for a Ph.D. program in the Department of Pharmacology, Toxicology and Neuroscience. His Ph.D. thesis was on breast cancer prevention with a natural product, citrus auraptene. As a graduate student, he served as the department student representative of the South Central Chapter of the Society of Toxicology, and was part of SOT's Career Resources and Development committee and Mentoring Subcommittee. Prasad currently serves as the Chair of Penn State Postdoctoral Society. He believes ASPET's Washington Fellows Program is the need of the time to effectively advocate for increasing funding for advancing biomedical research.



STEPHANIE A. MATHEWS, Ph.D.
National Institute on Alcohol Abuse and Alcoholism (NIH)

Stephanie was born in Wisconsin and raised in Louisville, KY. She received her B.S. in agricultural biotechnology from the University of Kentucky and her M.S. and Ph.D. in pharmacology

and toxicology from the University of Louisville. Her dissertation research was aimed at studying the impact of impaired S-adenosylmethionine metabolism and its effects on interferon-alpha antiviral signaling, with relevance to the hepatitis C virus. Stephanie was actively involved in promoting science education and recruiting underrepresented minorities to STEM fields throughout her college career. In 2011, she became a Federal Government Non-FTE Fellow at NIH, and her current research is aimed at investigating the immune mechanisms contributing to alcohol-induced liver injury. Stephanie plans to use her diverse scientific background to advocate for biomedical research funding and communicate with policymakers about the need for improving science education for K-12 schoolchildren and implementing programs aimed at encouraging and supporting underrepresented minorities pursuing higher education in STEM fields. She believes the ASPET Washington Fellows Program will provide her with a unique and valuable opportunity to learn more about policymaking and put into practice her passion for advocating for increased science funding and promoting the necessity of biomedical research.



ANDREW R. STOTHERT
University of South Florida

Andrew, a native of Galveston, TX, grew up in Omaha, NE. He graduated from Nebraska Wesleyan University where he earned a Bachelor of Science degree in biology. Next, he received a Master of Science degree in medical science from the

University of South Florida. Currently, he is working towards his Ph.D. in molecular medicine and neuroscience from the University of South Florida. Andrew works in the Byrd Alzheimer's Institute, studying neurological disorders such as Alzheimer's disease and glaucoma. His current projects focus mainly on the role of molecular chaperones and how they interact with proteins leading to pathological conditions associated with disease. His chaperones of interest are Grp94, an ER chaperone responsible for the sequestration of mutant forms of myocilin during glaucoma, and Hsc70, a co-chaperone playing a significant role in Tau regulation during Alzheimer's disease. Andrew believes that the ASPET Washington Fellows Program will provide an invaluable opportunity to gain the skills necessary to advocate for increased funding for scientific research.



CHRISTOPHER L. MOORE
University of Arkansas for Medical Sciences

Born in Virginia and raised in Nebraska and Iowa, Christopher received a B.S. in ecology and evolutionary biology from the University of Arizona and an M.S. in pharmaceutical QA/RA from the Temple University School of Pharmacy. Chris-

topher is a Ph.D. candidate in pharmacology at the University of Arkansas for Medical Sciences in Little Rock, AR. His research focus is scaffolding protein mediated control of blood pressure in cerebral arteries and its relation to hypertension and stroke. Prior to starting doctoral studies, he worked in drug discovery at Parke-Davis and Pfizer Pharmaceuticals, where his work focused on pre-clinical behavioral pharmacology of psychotherapeutics. Christopher believes participation in the ASPET Washington Fellows Program provides a unique opportunity to learn science advocacy and public policy skills necessary to ensure public support and funding for research.



Creating and Maintaining a Social Media Presence: Articles of Interest

For those of you who have embraced social media, we have compiled a handful of tips, tricks, and other helpful information to maximize your experience with these tools.

Twitter feature lets you DM (direct message) those not following you

<http://mashable.com/2013/10/15/twitter-direct-messages/>

Have you ever wanted to send a message directly to someone, one that Twitter won't post all over your feed? While that feature has been a staple of Twitter, tweeters are now discovering that they have the ability to send a direct message to more than just their Twitter followers.

The beginner's guide to the hashtag

<http://mashable.com/2013/10/08/what-is-hashtag/>

The hashtag (#) isn't just a Twitter phenomenon. Read on for its uses across other social media platforms and what you can do with a hashtag on each platform.

How to optimize your profile photos across social media

<http://mashable.com/2013/10/03/social-media-profile-photos/>

Here's a handy little article that gives you the sizes of profile photos for several different social media outlets. While that information is really just a couple of Google searches away, it's handy to have it all written out in one article.

Facebook Graph Search now lets you find comments, posts

<http://mashable.com/2013/09/30/facebook-graph-search-conversations/>

In addition to searching for people, places, and groups, you can now search content that people post on Facebook. You will be able to search if your Facebook friends posted about certain topics on their Timeline. If you use it properly, this feature can be a great way to start or join in on a conversation on Facebook.

4 ways to improve your Twesume

<http://mashable.com/2013/09/21/twesume/>

Students and postdocs, check this out. Have you ever given any thought to supplementing your multiple-page CV with 140 characters or less of text?

Twitter unveils Emergency Alert System

<http://mashable.com/2013/09/25/twitter-alert-system/>

This is a test. This is only a test. If this had been an actual emergency, you would have seen posts in 140 characters or less on your screen detailing an emergency situation. Read on for details on how to set up this important feature to be more aware of emergency situations.

Typo in your Facebook status? Just hit the new 'Edit' button

<http://www.nbcnews.com/technology/typo-your-facebook-status-just-hit-new-edit-button-8C11270151>

Finally, Facebook allows the grammar police to have some peace of mind. Have you ever posted something on Facebook and then looked at it on your Timeline or news feed, wishing for a mulligan or perhaps deleting the post entirely? If so, this article is a must read for you. Enjoy typing away, because you can now edit your Facebook posts.

Your Facebook 'Like' is now protected by the U.S. Constitution

<http://mashable.com/2013/09/18/facebook-like-protected-speech/>

Yes, "liking" a page or a post on Facebook actually constitutes protected speech. Read the article for the intriguing details.

The beginner's guide to HootSuite

<http://mashable.com/2013/09/18/hootsuite-beginners-guide/>

Hootsuite helps you manage your Facebook and Twitter content, as well as content from other social media platforms. It also allows you to schedule your posts ahead of time, keep track of your posts, keep track of people who mention you on social media, and keep track of those who you follow.

7 things you didn't know Bitly could do

<http://mashable.com/2013/09/16/bitly-tips-and-tricks/>

Bitly, a URL (a.k.a. Web address) shortener that comes in handy for sites like Twitter that allow posts of a finite number of characters, can actually track social media posts and compile statistics for you, in addition to a whole host of other things.

More tips on social media and electronic resources can be found online at: <http://www.aspet.org/knowledge/social-media-and-other-electronic-resources>.



Book Review

by Christine K. Carrico, Ph.D.

Stiff: The Curious Lives of Human Cadavers

Author: *Mary Roach*

Stiff: *The Curious Lives of Human Cadavers*, by Mary Roach, is a well-researched, often humorous if somewhat macabre, look into the use (and misuse) of human corpses. In search of her material, Ms. Roach travels from the University of Tennessee Anthropological Research Facility to the Wayne State University crash test lab to a crematorium in Haikou, China to a start-up composting company in Sweden and numerous research and burial facilities in between in search of her subjects. There isn't much you won't know about cadavers, although there is probably much you would rather not know when you finish this book.

The book starts out ("The human head is of the same approximate size and weight as a roaster chicken") in a laboratory setting where plastic surgeons are practicing facial reconstruction on isolated cadaver heads. From the surgery lab, the author visits a gross anatomy lab at UCSF and subsequently attends the memorial service for the human cadavers used in the lab, a very touching and respectful event. As with all of her chapters, she goes in depth into the history of the use of cadavers as it relates to the topic of that chapter. And if the current reality often seems grim, historical fact is far worse. Roach also talks to the people involved and tries to capture what they are thinking about as they work with human remains.

Roach visits the University of Tennessee Anthropological Research Facility where scientists study how bodies decay in an attempt to improve the ability to define time and mechanism of death for forensic purposes. This "lab" is actually an outdoor field when cadavers are subjected to a variety of weather conditions and the process of decay is carefully recorded. She visits the Crash Test Dummy Lab where scientists study tolerance limits in impact studies on human cadavers in an attempt to design more protective vehicles. She visits ballistics labs where research is conducted on how to design bullets that have more "stopping" and less "killing" power. She interviews someone who studies the effects of impact on bodies retrieved following airplane crashes to figure out what might have caused

the crash. She discusses alternatives to the use of cadavers. One of her more humorous riffs is on the use of gelatin "thighs" to measure bullet impact craters.

I confess that I had to take a break about half way through the book, not because it wasn't interesting reading, but because I found the body count, so to speak, unnerving. Given my reactions as a mere reader, it is perhaps not surprising that the author herself seems to become somewhat more moralistic in the later chapters. Of course, these are the chapters that deal with historical experiments to prove or disprove crucifixion theories (how crucifixion actually kills someone), live burial (how to determine death before the stethoscope and EEG), the search for the soul (weighing bodies immediately before and after death), human cannibalism (let's not go there), guillotining (how long does an isolated head continue to "live"), to name just some of them. The end of the book becomes more interesting as she explores alternative "ways to end up." These include a Swedish movement towards organic burial (human composting), water cremation, and plastification. Roach ends the book with her own personal views on her ultimate disposition.

In addition to her meticulous researching the topic, the author injects just enough humor (sometimes very corny humor) into the reading to keep it from being overwhelmingly grim. I suppose when you are dealing with a topic such as this, a sense of humor is an absolute requirement. One thing that left a lasting impression on me was that all of the people she talked to and with whom she interacted exhibited great respect for the cadavers and the people they had been. Even if one only read this book for its historical perspective, it is a worthwhile read (probably best done around Halloween).



Hey Grad Students and Postdocs! Want some extra cash?

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

Interviews with ASPET Members

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



MICHAEL W. WOOD, Ph.D.
AstraZeneca Pharmaceuticals LP
ASPET Regular Member

Who or what have been the greatest influences throughout your career?

I have been very fortunate throughout my career. I have had the opportunity to work alongside very talented and insightful scientists on many discovery teams, and those team members have been a positive influence on me. Working within an atmosphere of diligent competence and creative vision, it is hard to not stretch yourself to be your best. Of course, there were many teachers, instructors, and professors that poured their souls into their vocation, and those people left lasting imprints on me as well. One of my earliest inspirations was a high school chemistry teacher that devoted considerable effort to making the subject matter as interesting as possible. She frequently paced through the classroom during her lectures and I remember vividly the day she caught me napping and dumped the remainder of her glass of water on my head. I made sure to remain attentive after that.

What drew you to AstraZeneca Pharmaceuticals?

The initial attraction of industrial drug discovery at AZ was the notion that I could invent a treatment for some aspect of human suffering. That allure hasn't faded, and I remain as attracted to identifying treatments as ever. Discovering and developing novel candidate therapies is a massive team effort, and it is not a simple task, either. In the face of very challenging odds, it is critical to be surrounded and encouraged by talented and dedicated people focused on the same goal. As the pharmaceutical industry continues to change, the composition of the discovery teams has been changing. Now, industrial drug discovery teammates are not necessarily even working under the same roof (particularly at AZNeuro – see www.azneuro.com). Despite the ongoing evolution of how drug discovery is being done, the mission remains important and my teammates are as inspiring as ever.

What do you like to do for fun?

I have a wonderful family and they are a greatest source of joy in my life. I like to play music and read as well.

How would the people in your office describe you?

To be honest, I don't really want to imagine how my colleagues view me. I would rather keep propagating the internal delusion that I am a friendly, collaborative and productive member of the team.

How has membership in ASPET benefitted you and your career?

The single most valuable benefit of ASPET membership is the personal relationships that have sprouted from my participation. Working on the Program Committee and the Neuropharmacology Executive Committee has been a terrific experience. The committee members have such deep scientific knowledge and have all been very generous with their time. ASPET membership has been a career boost as well. I've made some key connections that have enabled collaborations that would not have happened without ASPET meetings.

What advice would you offer to aspiring pharmacologists?

Frankly, I worry about this question. I really enjoy pharmacology as an applied science. It's such a complex and integrated discipline, and I have been very fortunate to secure employment in my preferred field throughout my career. However, the employment ecosystem has changed and continues to change. When I left graduate school, there were limited choices for next steps, and those options were understood by all pretty well. Pure academic research and applied research within large corporations were the two chief options for career development. Biotechnology was building rapidly as an established third option. It seems to me now that the field of options has expanded considerably and the lines between the major pathways have blurred. Federal funding for scientific research has dropped off sharply, pharmaceutical companies have been laying scientists off en masse, and the sources of capital have shifted focus away from biotechnology companies. These change drivers don't make it easy for an aspiring pharmacologist. But I see a much more diverse array of possibilities now. The presence of cure-hunting scientists as a component of patient advocacy groups appears to be on the rise, contract research organizations are contributing more to the search for therapies than ever, and the formation of new biotechnology companies still continues. Academic drug discovery is another avenue that appears to be building as well. All of these represent alternatives to the major pathways of the past. Nonetheless, I know that it can be difficult for aspiring pharmacologists to find a venue to build their craft. My hope is that, as often happens after a decline, we will witness a resurgence in investment in pharmacology to the level that it deserves.



CLAUDIO ZANETTINI, Ph.D.
University of Texas Health Science Center
ASPET Postdoc Member

What sparked your interest in pharmacology?

Pharmacology is an important part of our everyday life; we wake up in the morning and have a good cup of Italian espresso coffee (at least I do!), we feel light headed when hiking at high altitudes, or we might enjoy a cold beer while listening to a local folk band at a house concert. Substances and drugs are all around us, and they affect our behavior. Pharmacology explains how each of these substances (i.e. caffeine, oxygen levels, alcohol) produce their effects and can help us understand why we choose to consume one substance instead of another (e.g., a cold beer instead of a soda at the concert). The most fascinating aspect of pharmacology is that it provides answers that are remarkably simple, orderly, and quantitative. The activity of drugs can be described and predicted by mathematical functions (i.e., receptor theory), regardless of their mechanism of action or effects, and this is true for caffeine, oxygen, and alcohol, as well as any other substance...this amazed me. Of course enthusiasm is not always sufficient, and I have been very lucky to work with great behavioral pharmacologists (Dr. Lisa R. Gerak and Dr. Charles P. France in the Department of Pharmacology at the University of Texas Health Science Center at San Antonio [UTHSCSA] and Dr. Steven R. Goldberg at IRP/NIDA section) who have supported and encouraged my interest in pharmacology.

What do you find most challenging about your work?

I have encountered many challenges in this work. First, I moved to a different country to pursue my career. I have explored unknown scientific fields, sometimes with few pharmacological tools available, and our answers are rarely definitive and we must continue to question everything. However, I believe that those challenges make this career worthwhile. This work has given me the opportunity to visit and live in wonderful places here in the U.S. and to interact with and learn from great people. Moreover, every day is different from the day before, with new questions and solutions to find.

Tell us about your most favorite experiment/study with which you have been involved.

I am really enjoying the work that I have been doing at UTHSCSA with Drs. Gerak and France. In some of our current projects, we are investigating *in vivo* mechanisms that might account for benzodiazepine tolerance and dependence using a combination of quantitative pharmacology and functional analysis of behavior. We have recently shown that benzodiazepine tolerance does not alter the interaction between drugs acting at benzodiazepine sites on GABA_A receptors; moreover, by employing two types of quantitative pharmacological analyses (Schild Plot and Lew and Angus nonlinear regression) to behavioral data, we demonstrated that the apparent affinity of flumazenil at the benzodiazepine site does not change as a consequence of tolerance. Beyond the specific results of this study, I remain awed by the reliability with which we can study mechanism of action of drugs using the right combination of pharmacological and mathematical tools and operant behavior.

What might someone be surprised to know about you?

In Italy, we have the best soccer players in the world. We won four world cups, two Italian teams are in the top ten for most UEFA Champions League titles, and almost everyone in Italy plays or follows soccer. I said almost because I know at least one person that it is not even slightly interested in soccer...me! There are so many other interesting activities in the world that we have to select from; for me, there was not enough time for soccer. But I swear that I am Italian!

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

Good experimental ideas often arise from interactions with colleagues, and solid science is enhanced by comments and suggestions of peers. ASPET is a great society because it provides young scientists like me with networking opportunities and occasions for meeting and interacting with leading pharmacologists. For example, I was a recipient of the Young Scientist Travel Award which gave me the opportunity to present my work at EB 2013 in Boston and to talk about science with other members of the Behavioral Pharmacology Division of ASPET. I am also thankful to have a chance to tell you about myself and my enthusiasm for pharmacology in this interview.

What do you see in store for the future of pharmacology? How do you see the science advancing?

Technological advancement is allowing us to identify targets, discover new pharmacological tools, and determine effects and mechanism of action of drugs faster and more reliably. We generate enormous amounts of scientific data, more than ever before, and the current challenges are to increase access to and analyze relevant information while decreasing redundant efforts. Over the next few years, I expect to see a tremendous increase in informational tools, databanks/shared repositories, and collaborations between the pharmaceutical industry and academia in order to increase speed and reduce costs associated with the discovery and development of novel drugs. I also look with great interest at the new online platforms for discussing science and interacting with peers; I believe that they have the potential to spark new ideas and increase the quality of science, and I would not be surprised to see more of the projects develop.

I am, however, also aware of the risk of such advancement, such as the possibility of confusing science and technology. B.F. Skinner was a forward-thinking scientist whose studies contributed to the birth of behavioral pharmacology, and his views on the interaction between science and technology mirror my own. More than 50 years ago, Dr. Skinner said, "Nor should we allow ourselves to become enamored of instruments of research. We tend to think of the scientist in his observatory or laboratory, with his telescopes, microscopes, and cyclotrons. Instruments give us a dramatic picture of science in action. But although science could not have gone very far without the devices which improve our contact with the surrounding world, and although any advanced science would be helpless without them, they are not science itself."



ANDREA BOYD TRESSLER, B.S. Case Western Reserve University ASPET Graduate Student Member

What influenced your decision to pursue an education in pharmacology?

Junior year at Spelman College, I took a toxicology class. It was my first introduction into pharmacology, and I was fascinated with the pathways of drug metabolism. I wanted to learn more about

how drugs interacted with the body, and my advisor encouraged me to pursue a Ph.D. in pharmacology.

What do you find most challenging about your studies?

The most challenging part of my studies is staying motivated when my research becomes stagnant or when experiments don't work. However, when a key experiment finally works and I get the answers to the question I am asking, it makes it all worth it.

Tell us about your most favorite experiment/study with which you have been involved.

Right now part of my project is looking at how tumor cells die when treated with chemotherapeutic drugs. I find uncovering the cell death pathways underlying chemotherapeutic efficacy very fascinating. Also, it is very exciting knowing that what I'm doing will make an impact in the field of cancer research.

Outside of pharmacology, what are some of your other interests or hobbies?

When I'm not in lab, I spend my time catching the latest movie or going to one of the many great restaurants in Cleveland. Cleveland is also home to a very impressive arts scene, so I enjoy visiting art galleries, seeing off Broadway shows at Playhouse Square, or listening to the Cleveland Orchestra.

How would the people in your program at Case Western Reserve University describe you?

The people in my program would describe me as hardworking, persistent, and a people person. I'm willing to help fellow students with anything, whether it involves discussing experimental findings or listening to a practice presentation with a colleague.

How are you hoping that membership in ASPET will benefit your career and interest in pharmacology?

My membership to ASPET so far has given me great opportunities to network and make potential collaborations by providing travel funds to attend conferences. The people I have met through ASPET have been very eager to help me in any way possible, ranging from advice on how to obtain funding to what I should look for in a postdoc mentor. I hope that my continued membership will connect me to great researchers that I can work with as a postdoc and throughout my career. I hope that it will continue to increase my access to cutting edge research and scientists that will help my love of pharmacology grow.

Members in the News



The work of **Julie Blendy, Ph.D.**, professor of pharmacology at the University of Pennsylvania's Perelman School of Medicine, was recently written about on *BioScienceTechnology.com* and *ScienceCodex.com*. Dr. Blendy has been performing research in mouse models, trying to pinpoint the molecular path that hastens the time it takes for an anti-depressant to work. The transcription factor cAMP response element-binding protein (CREB) is thought to play a role in the long-term effects of antidepressants,

as it regulates the expression of many genes that have been implicated in depression and antidepressant response. CREB deficient mice show antidepressant like-responses and rapid response to antidepressant treatments in a variety of behavioral tests. However, following deletion of CREB, a related protein, CREM (cAMP response element-modulator) is upregulated. To determine whether upregulation of CREM expression was sufficient to recapitulate the phenotype seen in CREB-deleted mice, Dr. Blendy's lab overexpressed the CREM activator, CREMt, in the hippocampus of wildtype mice. They found that overexpression of CREMt was sufficient to recapitulate the accelerated antidepressant response and the increase in hippocampal neurogenesis seen following hippocampal CREB deletion. These findings are the first evidence that CREMt in the brain can play a role in the behavioral responses to antidepressant treatment. Future work delineating CREMt targets responsible for this accelerated antidepressant response could provide unique therapeutic targets for depression.

Dr. Blendy has been a member of ASPET since 2006 and is a member of the *Molecular Pharmacology* Editorial and Advisory Board.

<http://www.biosciencetechnology.com/news/2013/09/path-makes-antidepressants-act-quicker-discovered>

http://www.sciencecodex.com/pinpointing_molecular_path_that_makes_antidepressants_act_quicker_in_mouse_model-119353



William B. Campbell, Ph.D. recently received the Distinguished Service Award from the Medical College of Wisconsin. The award, presented at the College's convocation ceremony on September 18, 2013, is the highest faculty honor presented at the Medical College of Wisconsin. Dr. Campbell, professor and chair of the Medical College of Wisconsin's Department of Pharmacology and Toxicology, is a renowned expert on the regulation of arterial pressure. He is a previous recipient of ASPET's

Paul Vanhoutte Award in Vascular Pharmacology (2010) and was presented with the 2013 PhRMA Foundation Award in Excellence at the ASPET Annual Meeting at Experimental Biology 2013 in Boston, MA. <http://www.wauwatosanow.com/userstoriessubmitted/224045741.html>



In October, **P. Jeffrey Conn, Ph.D.**, Professor and Director of the Vanderbilt University Program in Drug Discovery, wrote an article entitled "United effort is our best hope" for The Tennessean regarding the 2013 Academic Drug Discovery and Life Science Tennessee combined conference held in Nashville, TN. Dr. Conn, co-founder of the Academic Drug Discovery Consortium, wrote about the aim of the conference which was to stimulate collaborative efforts between academia and industry in bio-

medical research and ultimately produce more successful and cost-effective drug development processes. The article is no longer available, but information about the Academic Drug Discovery Consortium can be found online at: <http://www.addconsortium.org/>.

Dr. Conn serves as a delegate to the International Union of Basic and Clinical Pharmacology (IUPHAR). He is a previous recipient of Pharmacia-ASPET Award for Experimental Therapeutics and the ASPET-Astellas Award in Translational Pharmacology, having received both in 2007.



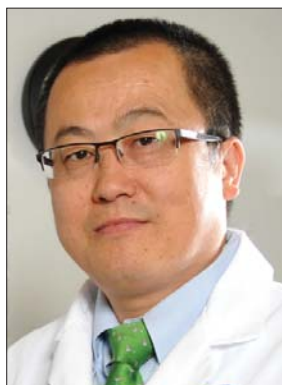
In mid-October 2013, **Evan Kharasch, M.D., Ph.D.**, was elected to the Institute of Medicine of the National Academy of Sciences. Dr. Kharasch serves as the Vice Chancellor for Research at Washington University in St. Louis. He is also the Director of the Division of Clinical and Translational Research and Russell D. and Mary B. Sheldon Professor in the Department of Anesthesiology, in the School of Medicine. Additionally, he holds an appointment as Professor in the Department of Biochemistry and Molecular Bio-

physics, and in the Washington University Pain Center.

"Kharasch leads the university's initiative on research innovation and entrepreneurship, which aims to maximize public benefit from the university's fundamental research discoveries. His office also oversees the continuing education of faculty and staff regarding research regulations as well as issues related to conflict of interest, research integrity, intellectual property and technology transfer. His research interests include basic, translational and clinical pharmacology, with an emphasis on mechanisms and clinical aspects of drug disposition, interactions, toxicity and pharmacogenetics. His studies are aimed toward a better understanding of individual differences in response to drugs and optimization of therapy."

A full write-up of the honor received by Dr. Kharasch can be found of the Washington University School of Medicine's Department of Anesthesiology website: http://anest.wustl.edu/about/news/kharasch_elected_to_institute_of_medicine.

Dr. Kharasch was previously a member of the Clinical Pharmacology, Pharmacogenomics & Translational Medicine Division Executive Committee. He has been a member of ASPET since 1984.



Ji Li, Ph.D., Assistant Professor in the Department of Pharmacology and Toxicology at the University at Buffalo School of Medicine and Biomedical Sciences, was part of a team at Yale University who developed a small molecule that can limit damage to the heart by ischemia when the heart becomes infarct. The molecule, MIF20, that was shown to "increase migration inhibitory factor (MIF) action through it's receptor."

"The research shows that the small-molecular MIF agonists may offer a novel

approach in selected clinical settings to compensate for age-related or genetic deficiencies in the way that the AMPK responds to ischemic injury, the researchers conclude."

The study, published in *Circulation*, came from research that had been going on since 2007 when Dr. Li was on the faculty at Yale.

Dr. Li has been a member of ASPET since 2010. http://www.buffalo.edu/ubreporter/research/news.host.html/content/shared/university/news/ub-reporter-articles/stories/2013/JiLi_ischemia.detail.html



Charles D. Nichols, Ph.D., Associate Professor in the Department of Pharmacology and Experimental Therapeutics at the Louisiana State University Health Sciences Center, recently led a research team that developed of a new genetic research technology to study behavior and cell function in fruit flies (<http://esciencenews.com/articles/2013/09/05/lsuhsc.researchers.develop.new.system.better.study.behavior.cell.function>). Dr. Nichols, a member of the Neuropharmacology Division's Executive Committee, was also featured in the

news in mid-October 2013 for heading another research team which "found that activation of serotonin 5-HT_{2A} receptor proteins potently blocks TNF-alpha induced inflammation" (<http://www.sciencedaily.com/releases/2013/10/131003111157.htm>). This powerful new anti-inflammatory mechanism "could lead to the development of new oral medications for atherosclerosis and inflammatory bowel disorders."



Emily E. Scott, Ph.D., Associate Professor in the Department of Medicinal Chemistry at the University of Kansas, was featured in the September 2013 issue of *Findings Magazine*, a publication of the National Institute of General Medical Sciences. The feature piece tells how Dr. Scott's interest in marine biology eventually led her to study cytochromes P450 and work on trying to block the reaction of CYP2A13 converting nicotine-derived nitrosamine ketone into two cancer-causing molecules. Dr. Scott is

currently a member of the *Drug Metabolism and Disposition* Editorial Board and serves as Associate Editor of *Pharmacological Reviews*. She was the recipient of the 2011 Division for Drug Metabolism Early Career Achievement Award. <http://publications.nigms.nih.gov/findings/sept13/hooked-on-heme.asp>



As it is very difficult to publish "negative" results in science, **Crista Royal, Ph.D.**, of Evans, GA came up with the idea to co-found the *Journal of Negative Results (JNegRes)* along with Andrew Harmon of Richmond, KY. Even if experiments do not generate the desired outcome, negative results are still useful results. This kind of information is invaluable to research, but up to now -- unpublishable. Dr. Royal's team believes all findings should be shared. Sharing negative results as well as positive ones

would help refine our collective knowledge and bring our ideas closer to the actuality of how the universe works. Each negative result, as well as each positive result, brings us closer to the truth.

JNegRes will provide free public access to ideas, data, and experiments that have had negative results, have been disproven, or, have had sufficient experiments done to demonstrate that the hypothesis tested is likely incorrect. It will also publish the results of studies that have sufficient data showing them to be unprofitable under contemporary conditions. Dr. Royal came up with the idea of a *Journal of Negative Results* when in graduate school at the Medical College of Georgia, now Georgia Regent's University, in Augusta, GA. "Out of 10 projects I worked on in grad school, seven had negative results and the results were never published..." she said.

Dr. Royal is currently adjunct faculty in biology at Augusta Technical Institute and plans to continue teaching part-time while starting the journal. The *Journal of Negative Results* will launch on October 1, 2014. *JNegRes* will be accepting article submissions throughout the coming year as they program the *JNegRes.org* website. They will need reviewers prior to launch as papers arrive in each discipline. For more information, email Crista@JNegRes.org.

Dr. Royal has been an ASPET member since 2007. She was a 2010 and 2011 recipient of the ISTCP Division's Graduate Student Best Abstract Award at the ASPET Annual Meeting at Experimental Biology.



During the American Heart Association's (AHA) High Blood Pressure Research 2013 Scientific Sessions, held September 11 – 14, **R. Clinton Webb, Ph.D.**, chair of the Department of Physiology at Georgia Regents University's Medical College of Georgia, was awarded the Irvine Page-Alva Bradley Lifetime Achievement Award from the AHA Council on High Blood Pressure Research. The award celebrates his achievements in the field of hypertension. Dr. Webb's research focuses on

"how contraction and relaxation of blood vessels is altered and can be improved in hypertension." He is currently a member of the ASPET Division for Cardiovascular Pharmacology Executive Committee and serves as chairperson of the Division's Awards Committee. <http://phys.org/wire-news/140535414/webb-receives-lifetime-achievement-award-for-hypertension-resear.html>

Staff News



Jill Filler "officially" retired after almost 12 years as Managing Editor of the ASPET journals on October 3, 2013, but worked part-time from home until Cassie Wood returned from her maternity leave. It was a wonderful way for Jill to transition into retirement, no alarm clock, no rush-hour traffic and still enough time to embark on her post-retirement pursuit of "doing lunch." That is going so well that she has joined a gym with a pool and replaced work clothes with workout clothes. She has lists of chores to accomplish, trips to take, and people to visit (thanks to several journal colleagues who shall remain anonymous). Jill says, "It was fascinating to be part of the incredible changes in scientific publishing from when I first began (before the journals were even online), and it is wonderful now to catch up with the continued developments from my computer, on my deck, in the sun, with my mug of coffee."



Ashlee Laughlin joined ASPET as the Administrative Assistant in September 2013. She is responsible for handling core office functions as well as assisting with the organization of the Executive Office. Ashlee comes to ASPET after serving as Staff Assistant at the American University, Washington College of Law in the Office of Special Events & Continuing Legal Education. She received her B.A. in communications from Salisbury University and has since pursued an MBA in digital and social media at New England College. Ashlee enjoys blogging, and reading fashion magazines in her spare time.



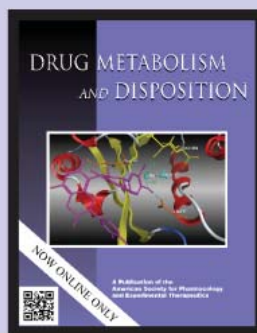
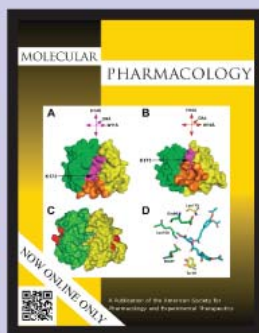
Dianne King-McGavin joined ASPET as Peer Review Manager in November 2013. She is responsible for the oversight of the peer review process for ASPET's journals. Dianne comes to ASPET from the American Society for Nutrition, where she acted as Production Manager for their three journals. Before that, Dianne was the Publications Manager for the Biophysical Society.

Dianne enjoys hiking and running and when she can find the time, reading. When she's not travelling, which she also loves, she's daydreaming about all the places she wants to visit.



Cassie Wood, *JPET's* Editorial Coordinator, and her husband Mike welcomed a baby boy on August 17, Samuel Elliott. He goes by Sam, Sammy, or Samuel, and loves looking at stars, the sound of birds, and grabbing everything within reach, especially long hair. After several weeks of maternity leave, Cassie is now back at the office.

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Daniel Jones, Indiana Wesleyan Univ
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Haojie Zhu, Univ of Michigan College of Pharmacy
Matthew Beckman, Augsburg College
Aramandla Ramesh, Meharry Medical College
Svetlana Tikunova, Univ of Houston
Yoshitaka Kawaraguchi, Nara Medical Univ, Japan
Yamini S Bynagari, Univ of California-San Francisco
Hao Chen, Univ of Tennessee Health Science Center
Mei Hong, South China Agricultural Univ, China
Inaki Troconiz, Univ of Navarra, Spain

Regent Laporte, Ferring Research Institute
Maria Tejada-Simon, Univ of Houston
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Werner Hollriegl, Baxter Innovations GmbH, Austria
Raymond Perez, Univ of Kansas Clinical Research Center
Paul Emmerson, Eli Lilly
Nour-Eddine Rhaleb, Henry Ford Hospital
Vibhudutta Awasthi, Univ of Oklahoma Hlth Science Ctr
Michael Aaron Frohman, Stony Brook Univ
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Mate Erdelyi, Univ of Gothenburg, Sweden
Ju Hyun Kim, LG Life Sciences, South Korea

Felicia Gooden, Univ of Cincinnati
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Carlos Baez-Pagan, Univ of Puerto Rico
Courtney Donica, Univ of Texas MD Anderson Cancer Center
Wenyan Han, Univ of Tennessee Health Science Center
Zhihong Peng, Univ of Notre Dame
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Lisha Kuang, Univ of Kentucky
Steven Chang, Washington Univ-St. Louis
Vishal Yadav, West Virginia Univ Health Sciences Center
Yang Chen, Virginia Commonwealth Univ

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Andy Tsai, Tzu Chi Univ, Taiwan
Monica Soto Velasquez, Purdue Univ
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Karla Claudio-Campos, Univ of Puerto Rico
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Mahend Brahadeesh, JSS Medical College, India
Goutham Vasam, North Dakota State Univ
Hari Priya Vemana, Western Univ of Health Sciences
Yewande Okunoren-Oyekenu, Univ of Leicester, United Kingdom

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Ishani De, Univ of Wisconsin - Madison
Swapnil Shewale, Wake Forest Univ
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Amal El Daibani, Univ of Toledo
Samar Rezaq, Brody School of Medicine at East Carolina Univ
Gina Marrone, Weill Cornell Graduate School of Medical Sciences
Surendra Sharma, Post Graduate Institute of Medical Education and Research, India
Yuxiao Wang, Univ of Georgia

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Vivekkumar Dadhania, Univ of Louisiana at Monroe, College of Pharmacy
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Rosemary Poku, Florida A&M Univ
Mengxi Sun, Univ of Kansas
Clark Sims, Univ of Arkansas for Medical Sciences
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Ademola Oyagbemi, Univ of Ibadan, Nigeria
Cathryn Stevenson, Marshall Univ - Joan C. Edwards School of Medicine

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Lee Leavitt, Univ of Utah
Danielle Zajac, The Ohio State Univ
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Promotions, Appointments, Awards, and other Achievements...

We want to hear all about it!



Get Featured in the Members in the News Section of **The Pharmacologist!**

Share your news with fellow ASPET Members!

Contact Gary Axelrod at gaxelrod@aspet.org

In Sympathy

ASPET notes with sympathy the passing of the following members:

Carmine Paul Bianchi

Allan H. Conney

Ronald W. Estabrook

Nancy K. Mello

Obituaries

Carmine Paul Bianchi (1927 – 2013), Founding Member of Mid-Atlantic Pharmacology Society (MAPS)



The Scientific Community of Philadelphia lost a loyal member on August 13 with the passing of Carmine Paul Bianchi, Ph.D., age 86, emeritus professor and former chairman of pharmacology at the Thomas Jefferson University College of Medicine. Paul joined ASPET in 1966 and was a founding member of the Mid-Atlantic Pharmacology Society (MAPS).

Paul was born in Newark, NJ, but grew up in Maplewood, NJ, where he joined the army at age 18. He served as a surgical sergeant technician at Ft. Dix Army Hospital (1945 – 46). He received a bachelor's degree in chemistry from Columbia University (1950), and a master's and doctoral degree in physiology and biochemistry from Rutgers University (1956). Paul obtained an NIH fellowship (1956 – 58) and was a visiting scientist there under Dr. Abe Shanes from 1958 – 59. His muscle studies began as he became an associate member of the Institute for Muscle Disease of New York (1959 – 62). He joined the

Pharmacology Department at the University of Pennsylvania (1961 – 76), leaving as a tenured professor to assume the chairmanship and tenured professorship in pharmacology at Thomas Jefferson University. He stepped down as chairman in 1987 but retained his professorship until he retired, as emeritus professor in 1999.

Paul wrote, or contributed, to three books and some 200 scientific papers in his field of research. His primary interests were the role of calcium ions in nerve and muscle action and the importance of ion channels in pharmacology and drug action. Paul was gregarious in nature, and enjoyed attending and/or presenting papers at national and international scientific meetings. At Temple University, he was a frequent visitor to our seminars and served often as external examiner of our graduate students' thesis defense. On the personal side, Paul loved to cook bouillabaisse and the Thanksgiving turkey. His faith was a strong element of his productive life; he was an Elder at the Swarthmore Presbyterian Church. Surviving Paul are his second wife, Eleanor, and daughters Margaret, Alison Edwards, Judith Bianchi, and Jocelyn Agalone, four grandchildren and one great-grandchild. Paul will be missed by all.

Submitted by John J. O'Neill, Ph.D., Professor Emeritus, Temple University

Allan H. Conney (1930 – 2013), Former ASPET President, Pioneer of Cytochrome 450 Induction



We note with regret the passing of Allan H. Conney, the William M. and Myrle W. Garbe Professor of Cancer and Leukemia Research at Rutgers University. Dr. Conney was born in 1930 in Chicago, IL and obtained a B.S. degree in pharmacy from the University of Wisconsin in 1952. He also received his Ph.D. from Wisconsin, working with Professors James and Elizabeth Miller. During his thesis, he did some of the first experiments demonstrating the induction of what we now know as cytochromes P450.

During postdoctoral work at the NIH, he continued to gain insight into drug metabolism. From 1960 – 1987, he was affiliated with Burroughs-Wellcome and Hoffman-LaRoche and made major contributions in basic research in drug metabolism, providing

some of the early evidence for multiple forms of cytochrome P450 and their catalytic selectivity. He also demonstrated cytochrome P450 induction in humans and stimulations of cytochrome P450 activity by chemicals. His collaborative studies with Dr. Donald M. Jerina of the NIH on polycyclic aromatic hydrocarbons established much of what is now termed the bay region/diol epoxide pathway. He also began a research program on cancer prevention, which he continued after moving to Rutgers University in 1987 as the founding Chairman of the Department of Chemical Biology, a post he held for another 15 years.

In 1982, he was elected to membership in the National Academy of Sciences. He served as President of ASPET in 1983 – 1984. Allan Conney published 538 primary articles, reviews, and book chapters. For a further account of his work, see *Annu. Rev. Pharmacol. Toxicol.* **43**:1-30, 2003.

Written by F. Peter Guengerich and Anthony Y. H. Lu

Ronald Winfield Estabrook (1926 – 2013), Pioneer in the Study of Cytochrome P450s



On August 5, 2013, Ronald W. Estabrook, Ph.D., M.D. (honoris causa) died in Dallas at the age of 87. His renowned scientific career focused largely on the study of cytochrome P450s and drug metabolism. Ron was born in Albany, NY, and at the age of 17 (1943) joined the U.S. Navy, training in the V-12 program at Princeton. Upon graduation from Officer Training School as an ensign (1945), Ron served on a submarine chaser and minesweeper, the latter in minefields of Okinawa and Japan. Upon discharge, Ron attended Rensselaer Polytechnic Institute, graduating with a degree in biology in 1950. He took his graduate training at University of Rochester, supervised by Prof. Elmer Stotz and received his Ph.D. in 1954, with a dissertation entitled "Studies on the Cytochromes in Heart Muscle Extracts." This work set the stage for more than 55 years of important research studying hemoproteins. Stotz was a well-recognized investigator in the study of hemoproteins and directed Ron to postdoctoral training with Britton Chance at the University of Pennsylvania.

After three years of postdoctoral training in the Chance laboratory where he mastered modern techniques of spectroscopy, Ron became a visiting research fellow in the Molteno Institute, Cambridge University in the laboratory of David Kielin. Kielin had named the hemoproteins in mitochondria as "cytochromes." Ron's training by Stotz, Chance, and Kielin set the stage for his independent career. In 1959, Chance recruited him to Penn as Assistant Professor of Physical Biochemistry, and subsequently he achieved the rank of Professor in 1965. It was during this period that Ron made a series of discoveries that solidified his reputation as a pioneer and leader in the study of cytochrome P450s. With his colleagues Otto Rosenthal and David Cooper, he reported the role of a P450 in adrenocortical microsomes in 21-hydroxylation of steroids as a terminal mixed-function oxidase. He showed that this reaction required a P450 using the recently established photochemical action spectrum technology of Warburg. This work was reported in three landmark papers in 1963. In 1967, with colleagues Herbert Remmer and John Schenkman, Ron reported roles of P450s in hepatic microsomes in drug metabolism, including optical measurement of substrate binding. Over the rest of his exceptional experimental career, Ron and colleagues from around the world made many key discoveries on P450s and drug metabolism.

In 1968, his career changed abruptly. Ron accepted an offer to become Chairman of Biochemistry at the University of Texas Southwestern Medical Center in Dallas. He was also named Virginia Lazenby O'Hara Professor of Biochemistry. He continued his important research in Dallas, while at the same time establishing one of the

major biochemistry departments in the world. In 1973, his role at UT Southwestern became more complex with his appointment as Dean of the Graduate School of Biomedical Sciences. In 1977, having made the essential steps for establishing the outstanding graduate school which exists at UT Southwestern, he returned to his roles as an investigator and department chair. He served as Chair until 1982 and as an active investigator until 2006 when he became Emeritus Professor.

During his almost 50 years as an independent investigator, Ron trained a large number of young scientists, many of whom are leaders in the study of drug metabolism around the world. Beyond these, Ron hired six young faculty members who became chairmen of biochemistry departments: Bettie Sue Masters (Medical College of Wisconsin), Russ Prough (University of Louisville), Tom Smith (Howard University), Mike Douglas (University of North Carolina), Mike Waterman (Vanderbilt University), and Lou Hersh (University of Kentucky).

Ron received numerous awards recognizing his accomplishments, far too many to name here. As a result we mention those of particular distinction. At University of Texas Southwestern, he was named Cecil H. and Ida M. Green Endowed Professor of Biochemistry in 1990. In 2006, he was named Ashbel Smith Emeritus Professor, and in 2008, one of the six educational colleges for medical students at UT Southwestern was named Estabrook College. Of particular note was being elected to the Institute of Medicine in 1975 and the National Academy of Sciences in 1979. He was the first member of NAS at UT Southwestern, which has now had about 30 members. In 1997, he received the ASPET Bernard B. Brodie Award in Drug Metabolism and the FASEB Distinguished Scientist Award. He worked tirelessly to encourage young scientists in the area to take leadership in the Drug Metabolism Division. He also served as President of the International Society for the Study of Xenobiotics from 1988 – 89.

For those who have attended scientific meetings with Ron, one memory that we all carry away was his penetrating questions of the speakers' research. The last meeting that he attended, the North American Regional ISSX meeting in October 2012 in Dallas, he was still asking such questions. Ron was a true pioneer in our understanding of many aspects of P450 and drug metabolism. He will be remembered by all who met him. Our research has surely been enriched and has prospered from his participation. We are grateful we had a chance to know him as a scientist and a friend.

While the above summarizes the exceptional accomplishments of Ron Estabrook as an investigator and leader in biochemistry, his most admirable accomplishment is his commitment to his family. Ron and his wife June have been well known throughout the world as a close and supportive couple. Their family consists of four children, seven grandchildren, and five great-grandchildren. When one looks for mentors and examples of a well-lived life, professionally and personally, Ron Estabrook is a worthy model.

Submitted by Russell A. Prough, Ph.D. and Michael R. Waterman, Ph.D.

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Division News

Behavioral Pharmacology Division

News

Awards

The **Peter B. Dews Award** for achievement in behavioral pharmacology for 2014 is under review by the selection committee. The past award winners were: 2002 William H. Morse; 2004 Joseph V. Brady; 2006 Leonard Cook; 2008 Charles R. Schuster; 2010 Donald E. McMillan; and 2012 James E. Barrett.

People on the Move

Larry Carter was promoted to Director of Clinical Development at Jazz Pharmaceuticals and will be moving to the Bay area.

Dr. David C. U'Prichard is the Part-time CSO and member of the Board of Managers of BioMotiv L.L.C. (Cleveland). He also serves as a President of Druid Consulting L.L.C., consulting to the pharmaceutical and biotechnology industries from his base in Philadelphia, PA, and as a partner at Druid BioVentures L.L.P. (Philadelphia). Dr. U'Prichard is Chairman of the Executive Board of Stratified Medicine Scotland, a national academic-industry consortium supported by the Government of Scotland.

Dr. Kayode D.S. Bamitale has recently been awarded a one year postdoctoral Fellowship in the School of Laboratory Medicine and Medical Sciences, Doris Duke Medical Research Institute, Nelson R. Mandela School of Medicine, University of KwaZulu - Natal, Durban, South Africa, effective October 1,

2013. Dr. Bamitale was a Senior Lecturer and Acting Head of Department of Medical Pharmacology and Therapeutics, Obafemi Awolowo University Ile - Ife, Nigeria from February 1, 2011 - July 31, 2013. He pioneered the newly created department. He has been a member of the society since 2005.

Scientific Advances

Michael Swedberg has done some work over past several years on "special senses" to create models to assess safety pharmacology issues on the visual and auditory systems. His group is using two-choice operant models to control for resistance to non-specific side effects. Recently, an auditory model was presented complementing a previously published visual disturbance model. These models show promise for specifically addressing special senses, avoiding motor and motivational bias.

<http://www.sciencedirect.com/science/article/pii/S0006899310000995>;
<http://www.sciencedirect.com/science/article/pii/S0006899313004150>

The following is a strategy paper authored by Dr. Swedberg for abuse liability from an industry standpoint, which may be of interest:

http://journals.lww.com/behaviouralpharm/Abstract/2013/09000/A_proactive_nonclinical_drug_abuse_and_dependence.8.aspx

One' Pagan is a pioneer in the area of behavioral pharmacology using planaria. His recent work has explored the relationship of nicotine or cocaine in regenerating planarians: <http://www.ncbi.nlm.nih.gov/pubmed/23684614>

Cardiovascular Pharmacology Division

News

Incoming Officers for 2014

Dr. David B. Averill, Professor in the Department of Basic Sciences at The Commonwealth Medical College, and **Dr. Fadi T. Khasawneh**, Assistant Professor of Pharmaceutical Sciences at Western University of Health Sciences, will begin their terms as Chair and Secretary/Treasurer, respectively, of the Cardiovascular Division on July 1, 2014.

Cardiovascular Division at the ASPET Annual Meeting at Experimental Biology 2014

Symposium help: The Cardiovascular Pharmacology Division has added the webpage "Submitting a Symposium for EB": http://www.aspet.org/Cardiovascular_Pharmacology/submitting-a-symposium-for-EB/

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

Trainee Showcase: The Cardiovascular Pharmacology Division is privileged to once again sponsor the Trainee Showcase for Cardiovascular Science during the ASPET Annual Meeting at EB 2014. This will be held on Tuesday, April 29 from 2:30 – 4:30 p.m., in Room 3 of the San Diego Convention Center. Come in support of the trainees of cardiovascular pharmacology.

Symposia: Please plan to attend one of our three exciting symposia. They span from studies in mitochondrial fragments ("Mitochondrial fragments: A novel mediator between inflammation and cardiovascular disease") and hydrogen sulfide ("Hydrogen sulfide: From physiological messenger to pharmacological target"), to transglutaminases ("Not just a glue: Pharmacology, physiology and pathology of transglutaminases"). Scheduling can be found on ASPET's EB program Web page: <http://www.aspet.org/eb2014/Program/>.

The Cardiovascular Pharmacology Division Scientific Programming Meeting will be held on Tuesday, April 29 from 5:45 - 6:30 p.m. in Room 3 at the San Diego Convention Center and will adjourn to the Cardiovascular Pharmacology Division mixer. The mixer will be held on that same Tuesday, April 29, from 6:30 - 8:00 p.m. at the San Diego Marriott Marquis and Marina.

The Paul Vanhoutte Distinguished Lecture, now a fully endowed lectureship, will be given at the ASPET Annual Meeting at EB 2014.

Getting You Involved!

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

Drug Metabolism Division

Division Election

Nominees for Chair-Elect:



Deepak Dalvie



Emily Scott

Nominees for Secretary/Treasurer-Elect:



Robert Foti



Swati Nagar

Integrative Systems, Translational and Clinical Pharmacology Division

Division Election

Nominees for Chair-Elect:



Michael Holinstat



Pamela Hornby



Qingyu Stephanie Zhou

Nominees for Secretary/Treasurer-Elect:



Ben T. Green



Wael Mohamed

Molecular Pharmacology Division

Division Election

Nominee for Chair-Elect:



Greg Tall

Nominee for Secretary/Treasurer-Elect:



Joe Blumer

News

LinkedIn

We are pleased to announce a new group on LinkedIn just for those interested in molecular pharmacology. This group will serve as a great place to connect with other members, see upcoming events, start a scientific discussion, or troubleshoot a laboratory method. If you already use LinkedIn, just click on the link below. If you are new to LinkedIn, you will first need to create a free account and then join our group.

ASPET Molecular Pharmacology group on LinkedIn: <http://www.linkedin.com/groups/ASPET-Molecular-Pharmacology-Division-5092933>

Upcoming Conferences and the ASPET Annual Meeting at Experimental Biology 2014

The Keystone Symposia entitled "G Protein-Coupled Receptors: Structural Dynamics and Functional Implications" will take place March 30 — April 4, 2014 at Snowbird Resort, Snowbird, UT. The scientific organizers are **Christopher G. Tate** and **Fiona H. Marshall**. For more information and to register go to <http://www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1250>.

The FASEB Summer Research Conference entitled "G Protein-coupled Receptor Kinases: From Molecules to Diseases" will focus on recent advances in our understanding of the mechanism of action of G protein-coupled receptor kinases (GRKs), their physiological functions, and their role in pathological conditions. This SRC will take place on June 8, 2014 in Steamboat Springs, CO. Go to <https://www.facebook.com/events/146567978885912/> for more information.

The Gordon Research Conference on "Phosphorylation & G-Protein Mediated Signaling Networks" will focus on the regulation of kinases and G Proteins in normal, pathological, and synthetic systems. This GRC will take place on June 15 — 20, 2014 at the University of New England in Biddeford, ME. Organizers are **Melanie H. Cobb** and **Carman W. Dessauer**. For more information and to apply to attend go to <http://www.grc.org/programs.aspx?year=2014&program=phosphor>.

Additionally, we hope to see you all at the 2014 ASPET Annual Meeting at Experimental Biology April 26 — 30 in San Diego, CA!

Summary of the 2013 GPCR Retreat

The 14th annual joint meeting of the Great Lakes GPCR Retreat and the Club des Récepteurs à Sept Domaines Transmembranaires du Québec (GPCR Retreat) was held October 17 — 19 at the Wyndham Playhouse Square, in Cleveland, OH. The retreat is an annual joint meeting that rotates through locations in the United States and Canada surrounding the Great Lakes. This was the first time the meeting was held in Cleveland. Case Western Reserve University hosted the meeting and the organizing committee included **David Lodowski**, **Marvin Nieman**, and **Paul Park**. The conference has a rich history of supporting graduate student and post-doctoral trainees, emphasizing networking between senior researchers and trainees. Over 153 attendees from the United States, Canada, and beyond attended the meeting, including more than 70 graduate students and postdoctoral fellows. In keeping with the tradition of encouraging and advancing trainees, four trainees were selected from their research abstracts to present talks during the conference; **Shanna Bowersox** of Carnegie Mellon University, **Stéphanie Clément** of McGill University, **Katherine Lee** of the University of Western Ontario, and **Rabindra Shivanaraine** of the University of Toronto. Eight trainee posters were also selected to receive a cash prize: **Henry Dunn** of the Robarts Research Institute/Western University, **Guillaume Bastin** of the University of Toronto, **Michael Goren** of Weill Cornell Medical College, **Etienne Khoury** of McGill University, **Vincent Lam** of the University of Toronto, **Daniel Shiwarski** of Carnegie Mellon University, **Chinmay Surve** of the University of Rochester, and **Allison Whited-Holt** of Case Western Reserve University.

The Conference began on Thursday evening with President Barbara Snyder of Case Western Reserve University, who gave opening remarks welcoming the attendees to Cleveland. **Roger Sunahara** introduced the Hyman Niznik memorial keynote speaker, 2012 Nobel Laureate, **Brian Kobilka**. The keynote, "Structural insights into G protein coupled receptor signaling," detailed recent advances in β 2-adrenergic structure, highlighting the structural basis for receptor activation upon agonist binding, receptor allostery, and partial agonism. The evening continued with the first of two poster sessions and a welcome dinner before adjourning for the evening.

The Friday morning began with the "Hubert Van Tol Symposium on Animal Models," chaired by **Stephen Ferguson** of the Robarts Research Institute of Western University. The symposium included the following

talks: "Genetic approaches to understand oligomerizations of GPCRs" by **Krzysztof Palczewski** of Case Western Reserve University; "Proteinase-stimulated signaling in vitro and in vivo: A GPCR-enzyme partnership" by **Morley Hollenberg** of the University of Calgary; "Protective effect of the RGS2-eIF2B binding domain (RGS2eb) against pathological cardiac hypertrophy" by **Katherine Lee** of the University of Western Ontario; and "GRK2 inhibition in the failing heart – nearing translation" by **Walter Koch** of Temple University. This was followed by the next symposium "GPCR Signaling in Vision," which was chaired by **Paul Park** of Case Western Reserve University's Department of Ophthalmology. The symposium included the following presentations: "Targeted design of signaling-biased arrestins" by **Vsevolod V. Gurevich** of Vanderbilt University; "Molecular chaperones in the biogenesis and quality control of rhodopsin" by **Michael Cheetham** of the UCL Institute of Ophthalmology, UK; and "Supramolecular architecture of the rhodopsin-transducin complex" by **Andreas Engel** of Case Western Reserve University.

After lunch, the symposia continued with the "Biophysical Studies of GPCRs," chaired by **David Lodowski** from the Center for Proteomic and bioinformatics at Case Western Reserve University, which included talks from **Reinhard Grisshammer** of the National Institutes of Health, "Structure of the agonist-bound neurotensin receptor NTS1"; **Scott Prosser** of the University of Toronto, "Understanding the role of ligands on GPCR activation by NMR"; **Shanna Bowersox** of Carnegie Mellon University, "Cell-autonomous tuning of opioid sensitization by substance P"; **Rabindra Shivnaraine** of the University of Toronto, "Probing the receptor-G protein interaction in live cells using dual-color fluorescence correlation spectroscopy (DCFCS) and Forster resonance energy transfer (FRET)"; and **Stanley Opella** of the University of California, San Diego, "Structure, dynamics, and function of unmodified GPCRs in phospholipid bilayers under physiological conditions." After a short break, the symposia continued with a discussion on "Translational GPCR Research," chaired by **Rick Neubig** from Michigan State University, who also presented "Attacking challenging drug targets: Gene transcription downstream of GPCRs"; followed by presentations from **Thomas Facklam** of BioMotiv L.L.C., "From hit to the clinic"; and **Michel Bouvier** of the Université de Montréal, "Translating basic discoveries into drug discovery programs." The three presenters then held a roundtable discussion detailing the interface between aca-

ademic science and the drug development process. The evening continued with the second of the two poster sessions and the conference dinner.

The Saturday morning symposia began with a discussion of "Non-Canonical GPCR Signaling," chaired by **Terry Hébert** of McGill University. This symposium included presentations by **Xiaoping Du** of the University of Illinois, Chicago, "Crosstalk between GPCR and integrins"; **Jean-Pierre Vilardaga** of the University of Pittsburgh, "Noncanonical GPCR signaling mechanisms"; **Stéphanie Clément** of McGill University, "Biased signaling and allosteric modulation of the Angiotensin II type 1 receptor"; and **Jonathan Stamler** of Case Western Reserve University, "Signaling through GPCRs by S-nitrosylation." The final symposium, "GPCR Action inside the Cell," was chaired by **Marvin Nieman** of the Department of Pharmacology at Case Western Reserve University and included presentations by **Neil Grimsey** of the University of California, San Diego, "Ubiquitin and intracellular signaling by GPCRs"; **Bruce Allen** of the Université de Montréal/Montreal Heart Institute, "Intracrine GPCR signalling in the adult cardiomyocyte"; **Jean Luc Parent** of the University of Sherbrooke, "Functional cooperativity from an interaction between a GPCR and the intracellular synthase of its agonist"; and **Nevin Lambert** of Georgia Health Science University, "Movement of Gs between plasma membrane receptors and intracellular compartments."

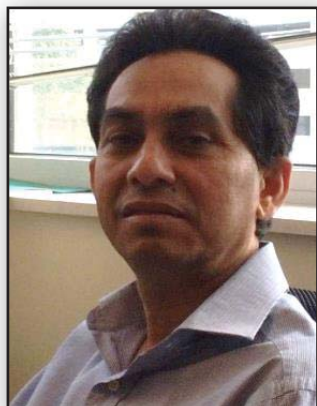
Acknowledgements: The 2013 GPCR retreat organizing committee would like to thank the following financial supporters: the Molecular Pharmacology Division of ASPET, Art Robins Instruments, Berthold Technologies, Case Western Reserve University (School of Medicine, Ophthalmology and Visual Sciences, Pharmacology, and Proteomics), CHU Sainte-Justine Research Center, DiscoverX, McGill University, NIGMS, Photon Technology International, Robarts Research Institute, University of Michigan, University of Ottawa (Faculty of Medicine, Brain and Mind Research Institute), University of Rochester, and University of Toronto (Leslie Dan Faculty of Pharmacy, Pharmacology & Toxicology), as well as acknowledging Nancy Vitale and Jonathan Volpe of the Case Western Reserve University Department of Ophthalmology and Visual Sciences for their essential organizational assistance.

Contributed by David Lodowski, Ph.D., Case Western Reserve University

Neuropharmacology Division

Division Election

Nominees for Chair-Elect:



Anil Kumar



Beverley Greenwood-Van Meerveld



Harel Weinstein

Nominees for Secretary/Treasurer-Elect:



Michael Wood



Wael Mohamed

News

Society for Neuroscience 2013 Annual Meeting

Our Neuropharmacology Mixer at the SfN was a great success. It was held on Sunday, November 10, from 6:30 — 8:00 p.m. at Hilton Bayfront hotel in San Diego, CA. Approximately 100 people attended the event.

Neuropharmacology Division Secretary/Treasurer **Lakshmi Devi** spoke about joining ASPET and being part of Neuropharmacology Division. Attendees liked how the mixer gave them an opportunity to meet people and network within a cozier setting at a big meeting. We hope that this get-together spurred a lot of camaraderie and future symposia submissions.

Pictures from the Mixer at Neuroscience 2013



Pharmacology Education Division

News

Travel Awards for Pharmacology Educators – Application Deadline is Monday, January 6, 2014

Funds for meeting travel can be difficult to find these days — can we help? Each year, the Division for Pharmacology Education sponsors up to three travel awards for primary or secondary division members to attend the ASPET Annual Meeting at Experimental Biology. Awards can be up to \$1,000 towards the costs of attending the meeting. Preference is given to those presenting an education abstract at EB 2014. Details are available on the Division website: <http://www.aspet.org/Education/Pharmacology-Educators-Travel-Award/>. Travel award recipients will be notified by the end of January and will be recognized at the DPE Scientific Programming Meeting on Sunday, April 27, from 5:45 – 7:30 p.m. at the ASPET Annual Meeting at EB 2014.

Academy of Pharmacology Educators – Application deadline is Monday, January 6, 2014

The purpose of the Academy of Pharmacology Educators is to provide a means to recognize individuals who have made exemplary contributions to pharmacology education in one or more of the following areas: student-teacher interaction, innovative contributions, scholarly endeavors, and/or professional development and service. Application is by self-nomination. Details are available on the Division website: <http://www.aspet.org/Education/Academy/>. New Academy members will be notified by the end of January and will be honored at the DPE Scientific Programming Meeting on Sunday, April 27, from 5:45 – 7:30 p.m. at the ASPET Annual Meeting at EB 2014.

Career Ladders

Depending on your career stage, promotion and tenure committees typically like to see involvement and/or recognition at the national or international level. How does this happen? How do you become involved? ASPET's Division for Pharmacology Education is willing to be a part of your career.

Have you considered developing a proposal for an education session or volunteering to serve on a committee? Or download the criteria to apply for the Academy of Pharmacology Educators, and create a plan/schedule to apply in the future! If you are interested in becoming involved with educational programs at ASPET, email DPE Chair **Carol Beck** (carol.beck@jefferson.edu), DPE Secretary-Treasurer **Robert Theobald, Jr.** (RTheobald@atsu.edu), or DPE Program Committee Representative **Jayne Reuben** (jreuben@ghs.org). You can also talk to us during EB 2014 at the DPE Scientific Programming Meeting on Sunday, April 27, from 5:45 – 7:30 p.m. or the DPE/DDD/ISTCP Mixer on Monday, April 28, from 7:30 – 9:30 p.m.

Join and participate in our LinkedIn group for interesting discussions about Pharmacology Education:

<http://www.linkedin.com/groups/ASPET-Pharmacology-Education-Division-5033126>

Division for Pharmacology Education Symposia at Experimental Biology 2014

Jayne S. Reuben (Univ. of South Carolina School of Med-Greenville) and **Karen Marcante** (Medical Col. of Wisconsin and Children's Hospital of Wisconsin) will co-chair a session on "Career opportunities beyond the bench: Education as a viable path" on Sunday, April 27, from 9:30 a.m. – 12:00 p.m. **Senthil K. Rajasekaran** (Oakland Univ. William Beaumont Sch. of Med.) and **David W. Nierenberg** (Dartmouth-Hitchcock Med. Ctr.) will chair the DPE Division Symposium on "Addressing Prescribing Errors through Medical Student Education and Assessment" on Sunday, April 27, from 3:00 – 5:00 p.m. **Robert J. Theobald, Jr.** (Kirksville Coll. of Osteopathic Med.) and **Sandra Carlin Andrieu** (LSUHSC New Orleans Sch of Dentistry) are co-chairing a session on "Collaborative role of pharmacology in the education of healthcare professions" on Monday, April 28, from 9:30 a.m. – 12:00 p.m. For more information on the Division's programming at the ASPET Annual Meeting at EB 2014, please visit: <http://www.aspet.org/eb2014/program/>.

Save the Dates

DPE Scientific Programming Meeting: Sunday, April 27, 5:45 – 7:30 p.m.
DPE/DDD/ISTCP Mixer: Monday, April 28, 7:30 – 9:30 p.m.

Toxicology Division

Division Election

Nominees for Chair-Elect:



Gary Rankin



William Slikker

Nominee for Secretary/Treasurer-Elect:



Lauren Aleksunes

Chapter News

Upstate New York Pharmacology Society

Third Annual Meeting Scheduled



The Upstate New York Pharmacology Society (UNYPS) Chapter of ASPET will hold its 3rd Annual Scientific Meeting on Monday, May 19, 2014 at the University at Buffalo Center for the Performing Arts in Buffalo, NY. The theme of the scientific meeting is *Development and Disease across the Lifespan*.

The Keynote Speaker will be **Burns C. Blaxall Ph.D., FAHA**, pharmacologist and Professor of Pediatrics at the University of Cincinnati Children's Hospital.

Dr. Blaxall is Director of Translational Science at the Heart Institute of the Cincinnati Children's Hospital Medical Center. The Heart Institute integrates research and clinical programs and is making significant progress towards the ultimate goal of eliminating heart disease. Dr. Blaxall's research accomplishments have enabled iden-

tification of molecular pathways leading to heart failure and, importantly, to the discovery of next generation therapies that offer protection against the disease. Dr. Blaxall's keynote presentation is entitled "New Approaches to an Old Disease: Therapeutic Discovery for Heart Failure."

Additional invited international scientists addressing the theme *Development and Disease across the Lifespan* include **Vincent Tropepe Ph.D.**, Associate Professor of Cell and Systems Biology at the University of Toronto. Dr. Tropepe's presentation title is "Dopamine Modulation of Brain and Behavioural Development in Zebrafish." Select graduate students from the participating institutions will present oral research reports as part of the Presidential Symposium. In addition, postdoctoral fellows as well as junior scientists, will give platform presentations. Poster presentations will feature scientific research conducted by attending undergraduate students, graduate students, and postdoctoral fellows. Prizes at all levels of poster presentation will be awarded. The UNYPS business meeting will be held afterwards.

Mid-Atlantic Pharmacology Society

Summary from the 2013 Annual Meeting



The Annual meeting of the Mid-Atlantic Pharmacology Society was held at the University of the Sciences on Monday, October 7, 2013 in Philadelphia, PA. This

year's meeting, with the theme of *G protein-coupled receptors: Current Thoughts and New Directions*, brought together about 95 scientists and trainees from academic institutions and the pharmaceutical industry throughout the Mid-Atlantic region. From the 29 abstracts submitted by graduate, undergraduate, and postdoctoral trainees, two trainees were selected to present oral presentations: **Brittany Ebersole** from the Penn State College of Medicine presented "Palmitoylation of the dopamine D2 receptor and its effect on trafficking," and **Rebecca C. Robinson** from Temple University presented "A cannabinoid receptor 2 agonist increases regulatory T-cells and inhibits graft rejection *in vitro* and *in vivo*." Other trainees presented their research posters to judges, with the following students receiving prizes for their research presentations: **Marguerite K. McDonald** of Drexel University received first prize in the postdoc division; **Cassandre Cavanaugh** of Drexel University, **Harshini Neelatakantan** from Temple University, and **Melissa Manners** from Drexel University received first, second, and third prize, respectively, in the graduate student division. Undergraduate presenters received participation awards for this year because of the limited number of entries in this division.

In addition to viewing research posters, meeting attendees were able to listen to state of the art presentations from a number of experts in the area of G protein-coupled receptors. Despite a last minute schedule change necessitated by the government shutdown, attendees were first welcomed by **Dr. Heidi Anderson**, new Provost for the University of the Sciences, and **Dr. Diane Morel**, 2013 President of MAPS. Research presentations in the morning session by **Dr. Lawrence (Skip) Brass** of the University of Pennsylvania on "How the platelet signaling network shapes the hemostatic response to injury and contributes to heart attacks and strokes"; **Dr. Michael P. Holinstat** of Thomas Jefferson University on "The newly identified oxylipin, 12-HETrE, regulates platelet function and thrombosis in a GPCR-dependent manner"; and **Dr. Madhu Chintala** on "Discovery and development of voropaxar, a novel PAR-1 antagonist for the treatment of atherothrombosis" provided an in depth view of GPCRs in cardiovascular disease. Following presentation of the George B. Koelle award to **Dr. Scott Waldman** of Thomas Jefferson University in honor of his contributions to pharmacology research, teaching and mentorship of trainees, and lunch, meeting attendees then heard presentations on GPCRs in neuroscience from **Dr. Mary Abood** of Temple University on "Cannabinoid receptors: Inside and out" and this year's keynote speaker, **Dr. Lakshmi Devi** from Mt. Sinai and the Icahn School of Medicine on "Big science on a modest budget: Lessons from deorphanizing a hypothalamic G protein-coupled receptor involved in body weight regulation." Attendees wrapped up a very collegial and educational meeting with a networking reception and awards ceremony for winners of the poster competition.

Appendix

Abstracts presented at the 2013 MAPS Annual Meeting, October 7, 2013

The role of MeCP2 in pain and its regulation by microRNAs

Melissa Manners¹, Rehman Qureshi², Yuzhen Tian¹, Ruby Gao¹, Zhaolan Zhou³, Ahmet Sacan², Seena Ajit¹; ¹Department of Pharmacology & Physiology, Drexel University College of Medicine, Philadelphia, PA 19102; ²School of Biomedical Engineering, Science & Health Systems, Drexel University, Philadelphia, PA 19104; ³Department of Genetics, University of Pennsylvania School of Medicine, Philadelphia, PA 19104

Decreased pain perception is commonly reported in children with Rett syndrome (RTT). Nearly all cases of RTT are caused by mutations in methyl-CpG-binding protein 2 (*MECP2*), suggesting that normal *MeCP2* function is important in modulating pain. One mutation observed in RTT resulting in decreased pain sensitivity is in amino acid T158, located in the methyl-CpG binding domain of *MeCP2*. Transgenic mice with this mutation have reduced *MeCP2* binding to methylated DNA, decreased protein stability, and a phenotype resembling RTT. We are assessing mechanical and thermal sensitivity in *MeCP2* T158A mice to determine the role of this mutation in the development and maintenance of pain. Expression studies of *MeCP2* in dorsal root ganglion (DRG) and spinal cord (SC) from rodent models of inflammatory and neuropathic pain showed that *MeCP2* mRNA and protein increased in DRG but decreased in SC from neuropathic pain model. Chromatin immunoprecipitation sequencing is being pursued to study how differential binding of *MeCP2* to chromatin can induce crucial gene regulatory changes in pain state. Protein expression can be regulated by microRNAs (miRNAs). Our profiling study of rat DRG from neuropathic pain model showed a decrease in expression of 15 miRNAs that are predicted to bind the *MeCP2* 3' untranslated region (3'UTR), thirteen of which were upregulated in the cerebellum of *MeCP2*-deficient mice. We validated miRNA binding to the 3'UTR of mouse *MeCP2* and miRNA profiling of DRG from T158A mice is ongoing. Multiple independent approaches are being pursued to elucidate the role of *MeCP2* in pain.

Resistance of the CRPS patients to the analgesic effect of ketamine is associated with dysregulation of the endogenous opioid system

Botros Shenoda*¹, Guillermo Alexander², Sabrina Douglas¹, Rehman Quershi³, Ahmet Sacan³, James Barrett¹, Robert Schwartzman² and Seena Ajit¹; ¹Department of Pharmacology & Physiology, ²Neurology, Drexel University College of Medicine, Philadelphia, PA 19102; ³School of Biomedical Engineering, Science, and Health Systems, Drexel University, Philadelphia, PA 19104

Complex Regional Pain Syndrome (CRPS) is a chronic neuropathic pain condition characterized by severe pain beyond the area of injury. The non-competitive NMDA receptor blocker ketamine is known to be effective in relieving pain in patients with CRPS. Only moderate to severely afflicted CRPS patients, for whom all other treatments have failed, are considered for ketamine treatment. The analgesic effect of ketamine is not observed in all patients and thus, a subset of patients is reported to be treatment-resistant. The mechanism of action of ketamine is not well understood but the analgesic effect of ketamine is suggested to be mediated through the modulation of the endogenous opioid system. We investigated microRNA expression in whole blood from responders and non-responders to ketamine therapy and observed differential expression of twenty three microRNAs. Some of these microRNAs are predicted to target mRNAs of genes in the endogenous opioid pathway. The expression of the proopiomelanocortin (POMC), a precursor of several biologically active peptides with roles in pain, was found to be significantly higher in the blood of the non-responders. However the level of beta-endorphin was significantly lower in these patients. No significant difference in the level of adrenocorticotrophic hormone (ACTH), an alternative product of the POMC, was observed between responders and non-responders. Our data suggests that dysregulation of the endogenous opioid system may be an underlying mechanism leading to ketamine resistance in some patients. Aberrant microRNA signature in these patients may contribute to this dysregulation and could serve as biomarkers for predicting treatment response.

Improving homology modeling of GPCRs using restrained simulated annealing method

Rajan Chaudhari*¹, Andrew J. Heim¹ and Zhijun Li¹; ¹Department of Chemistry and Biochemistry, University of the Sciences, Philadelphia, PA 19104

G protein-coupled receptors (GPCRs) are the top ranked drug targets in pharmaceuti-

cal industry because of their ability to induce a wide variety of cellular responses. Structural information of such drug targets plays an important role in accelerating the drug discovery process. Recent advances in X-ray crystallographic techniques have greatly facilitated the determination of GPCR crystal structures. Still homology modeling remains an important tool for studying GPCRs. A challenge in applying homology modeling techniques to GPCRs is to improve the quality of the structural models given the low sequence identity between the target and the template proteins. In this study, we aim to address this challenge through restrained simulated annealing approaches. We first identified a set of conserved restraints between the template and the target protein. We then applied them to the homology model using restrained simulated annealing methods. As a proof of concept, we were able to improve the homology model of the human beta 2 adrenergic receptor (PDB ID 2RH1) based on the low sequence identity template of the anabaena sensory rhodopsin (PDB ID 1XIO) by ~2.5Å°. The result suggested that our proposed approach is helpful in improving homology models of GPCRs constructed based on template of low sequence identity.

The role of miRNA regulation in inflammation-related depression

Cassandra Cavanaugh*, Brian Platt, Baktisha Alla, Janet Clark; Department of Pharmacology & Physiology, Drexel University College of Medicine, Philadelphia, PA 19102

Significant clinical data suggest that inflammation contributes to depression. Using a Bacille Calmette Guerin (BCG) -induced model of inflammation-related depression we have shown that animals exhibit an acute sickness response, chronic elevation in circulating pro-inflammatory cytokines and a chronic depressive phenotype as assessed using various behavioral assays following a single dose of BCG. In addition, we have discovered that 10 to 30% of mice administered BCG show the sickness response and chronic elevation of pro-inflammatory cytokines but are resilient to developing a depressive phenotype. In an effort to understand the neurobiological processes that are altered by chronic inflammation and lead to a depressive phenotype, or result in resilience, we have studied changes in miRNA expression in hippocampal tissue from saline control, BCG-resilient and BCG-susceptible mice. We have identified 12 miRNAs in the BCG-susceptible samples and 4 miRNAs in the BCG-resilient samples whose expression are significantly altered. Using the TargetScan prediction database we have identified potential target genes that may be modulated by these miRNAs and are biologically interesting with regard to mood disorder. Circadian locomotor output kaput (Clock) is a transcription factor involved with maintaining circadian rhythms and this gene may potentially be upregulated by mmu-miR-412 and down-regulated by mmu-miR-203. The G-protein-coupled receptor 55 (GPR55) may be potentially regulated by miR-412; the demethylase *jarid1c* may be regulated by mmu-miR-540-3p; and the hypocretin 2 receptor (*hcrt2*) may be regulated by miR-203. Using a luciferase assay system we have now confirmed that these miRNAs can interact with the 3'UTR for the respective genes listed above. Studies are underway to determine if these miRNAs can modulate the expression of the respective potential target proteins in cultured cells. We are also currently assessing protein levels of potential target genes in hippocampal samples from BCG-susceptible and saline control mice using western analyses. Preliminary data for Clock shows 50% less protein in BCG-susceptible samples as compared with saline controls. These data suggest that miR-412 and miR-203 may regulate Clock expression and that BCG may alter Clock expression in BCG-susceptible mice through changes in miRNA expression further suggesting that circadian rhythms may be disrupted in this model of inflammation-related depression.

Palmitoylation of the dopamine D2 receptor and its effect on trafficking

Brittany Ebersole*, Matthew Woll, and Robert Levenson; Penn State College of Medicine, Hershey, PA 17033

The dopamine D2 receptor (D2R) is a G-Protein Coupled Receptor (GPCR) involved in a variety of cellular pathways, including those responsible for cognition, emotion, and reward. The D2R has previously been shown to be palmitoylated. Palmitoylation is the addition of a 16-carbon fatty acid palmitate to cysteine residues of proteins by enzymes called protein acyltransferases (PATs). In mammals, 23 potential PATs (containing a common zDHHC domain) have recently been described. While palmitoylation appears to affect trafficking of a variety of GPCRs, the functional significance

of D2R palmitoylation is unknown. The goals of the current study are to 1) verify the palmitoylation of the D2R employing a novel non-isotopic palmitoylation detection technique and determine the site(s) of palmitoylation within the D2R, 2) identify the PAT(s) that contribute to palmitoylation of the D2R, and 3) determine whether palmitoylation plays a role in D2R trafficking. Using bioorthogonal click chemistry, D2R palmitoylation was verified in HEK cells stably expressing the D2R. Yeast two-hybrid screening and co-immunoprecipitation techniques were used to identify several PATs (zDHHC3, zDHHC4, and zDHHC8) that interact with the D2R. Overexpression of these enzymes resulted in increased D2R palmitoylation. Additionally, click chemical analysis of various D2R mutants led to the identification of the C-terminal cysteine (C443) as the primary site of D2R palmitoylation. Deletion of C443 from the D2R led to a significant decrease in D2R palmitoylation as well as a reduction in cell surface expression. **Keywords:** dopamine D2 receptor; palmitoylation; protein acyltransferases; bioorthogonal click chemistry; yeast two-hybrid; co-immunoprecipitation.

Phosphatidylinositol 3-kinases (PI3K) signaling plays an important role in 5-aminolevulinic acid (ALA)-induced protoporphyrin IX (PpIX) accumulation in human breast cancer cell lines

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A major metabolic change exhibited by many tumor cells is the abnormality in heme synthesis. Tumor cells have been found to produce more protoporphyrin IX (PpIX), a fluorescent precursor of heme synthesized in mitochondria, than surrounding normal cells presumably due to changes in the expression and activity of heme synthetic enzymes. Tumor accumulation of PpIX can be further increased by exogenous administration of 5-aminolevulinic acid (ALA), the first product in heme synthetic pathway. This is because exogenous ALA will bypass the feedback inhibition imposed by heme on the synthesis of ALA, leading to the overproduction of PpIX. Although enhanced tumor accumulation of PpIX, either inherently or following the administration of ALA, has been explored for tumor detection and treatment, the mechanism involved in enhanced ALA-PpIX accumulation in tumor cells is still poorly understood.

By profiling ALA-mediated PpIX production in a panel of human breast cancer cells with varied genotypic and phenotypic background, we have found enhanced PpIX production in most of these cell lines. Because altered phosphatidylinositol 3-kinases (PI3K) pathway signaling has been commonly found in human breast cancers, we are interested in understanding whether/how modulating PI3K signaling affects the ALA-PpIX production. PI3K pathway signaling can be stimulated pharmacologically by growth factors or genetically by overexpressing human epidermal growth factor receptor (Her2, ErbB2). We found that insulin treatment and overexpression of ErbB2 in MCF10A human breast epithelial cells significantly enhanced ALA-PpIX production, which can be effectively inhibited by PI3K pathway inhibitors including BEZ235 and lapatinib. Western blot analysis indicates that ErbB2 overexpression as well as insulin and BEZ treatments modulated the expression of enzymes involved in heme synthesis. These results strongly suggest that PI3K signaling plays an important role in regulating ALA-PpIX synthesis. Furthermore, the glycolysis inhibitor 2-deoxyglucose decreased the ALA-PpIX production, suggesting a link between attenuated mitochondria bioenergetic function and reduced ALA-PpIX production.

Selective CB2 receptor activation ameliorates EAE by reducing Th17 differentiation and immune cell accumulation in the CNS

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CB2, the cannabinoid receptor expressed primarily on hematopoietic cells and activated microglia, mediates the immunoregulatory functions of cannabinoids. The involvement of CB2 in EAE has been demonstrated by using both endogenous and exogenous ligands. We showed previously that CB2 selective agonists inhibit leukocyte rolling and adhesion to CNS microvasculature and ameliorate clinical symptom in both chronic and remitting-relapsing EAE models. Here we showed that Gp1a, a highly selective CB2 agonist, with a four log higher affinity for CB2 than CB1, reduced clinical scores and facilitated recovery in EAE in conjunction with long term reduction in demyelination and axonal loss. We also established that Gp1a affected EAE through at least two different mechanisms, *i.e.*, an early effect on Th1/Th17 differentiation in peripheral immune organs, and a later effect on the accumulation of pathogenic immune cells in the CNS, associated with reductions in CNS chemokine and adhesion molecule expression. This is the first report on the *in vivo* CB2-mediated Gp1a inhibition of Th17/Th1 differentiation. We also confirmed the Gp1a-induced inhibition of

Th17/Th1 differentiation *in vitro*, both in non-polarizing and polarizing conditions. The CB2-induced inhibition of Th17 differentiation is highly relevant in view of recent studies emphasizing the importance of pathogenic self-reactive Th17 cells in EAE/MS. In addition, the combined effect on Th17 differentiation and immune cell accumulation into the CNS, emphasize the relevance of CB2 selective ligands as potential therapeutic agents in neuroinflammation.

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Discriminative stimulus effects of mephedrone

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The synthetic drug Mephedrone (MEPH) is a newly emerged recreational drug which increases dopamine (DA) and serotonin (5-HT) release, inhibits DA and 5-HT synaptic uptake and produces serotonergic, but so far, not dopaminergic deficits. The purpose of this study, was to characterize a distinct pharmacological profile for MEPH and to establish both high and low doses as discriminative stimuli. A behavioral two-choice drug discrimination assay was utilized to examine the subjective and discriminative properties of Mephedrone. We hypothesize that MEPH will produce discriminative stimulus effects based upon multiple component cues of DA and/or 5-HT. MEPH should share discriminative stimulus effects with other drugs that alter the DA, 5-HT and NE systems. So far, an array of psychostimulants, DA, NE and 5-HT agonists were used to test the hypothesis for low dose MEPH (0.5 mg/kg) as a stimulus. We found low dose MEPH to fully substitute for 5HT agonists tested and partially substitute for low doses of DA agonists tested. Although we already we see that low dose MEPH is an established discriminative stimulus which shares stimulus effects of DA and 5-HT agonist, the composite pharmacological profile appears to be a unique composition of DA, 5-HT and NE activation.

Bicyclo-helptane 2-amines as σ_2 receptor ligands: Potential use as anticancer agents

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Sigma2 (σ_2) receptors have been found to be over-expressed in a variety of human tumor cell lines. Activation of these receptors is believed to induce apoptotic cell death via multiple pathways. Ligands acting on this receptor have also been proposed to be chemosensitizers. We therefore began to investigate discovery of novel selective compounds for this receptor. Several selective σ_2 receptor ligands were discovered in our lab through the NIMH-Psycho Active Drug Screening Program which determined binding affinities. K_i values for displacement of [³H] DTG for σ_2 receptor ranged from 5.5 to 16 nM, and for σ_1 receptor were > 10,000 nM, making these ligands some of the most selective for σ_2 receptor over σ_1 as well as other receptors. We then began to investigate the effects of co-administering these ligands and DNA-damaging drugs such as doxorubicin on cancer cell lines. Assessment of cytotoxicity of these compounds was conducted using the human pancreatic adenocarcinoma cell line PANC-1 which is known to over-express the σ_2 receptor and the MTT viability assay. Efficacy of these ligands was compared to structurally similar compound with no σ_2 receptor affinity to support our belief that the observed activity was in part due to binding to the σ_2 receptor. In a comparison, the selective compound had profound cytotoxicity compared to the non-selective ligand. In addition, we found that co-administering the σ_2 receptor ligands with doxorubicin led to synergistic effects in reducing viability of the cells. Our studies suggest that σ_2 receptor binding induces cell death, and synergistically increases the sensitivity of PANC-1 cells to doxorubicin.

Investigation of *in vitro* ligand bias at the human kappa-opioid receptor (hKOPR)

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Ligand bias or functional selectivity is the ability of an agonist to differentially activate the G protein pathway or the beta arrestin pathway and has been described for both the delta opioid and mu opioid receptors (Rivero G et al. 2012; Audet N et al. 2012). We are interested in characterizing ligand bias at the KOPR due to the proposed G protein-mediated analgesic effects and beta arrestin-mediated dysphoric effects that occur upon receptor activation (Bruchas M et al. 2007 and McLaughlin JP et al. 2004). These data suggest that the development of a compound with little beta arrestin recruitment but full G protein activation would be of great interest in the search for a non-addictive analgesic. To this end, we have examined 21 KOPR ligands for the ability to recruit G proteins

via [³⁵S]GTPγS binding and receptor internalization in the on-cell western (OCW) assay as a measure of beta arrestin recruitment. Mouse neuroblastoma (N2A) cells were stably transfected with the HA-tagged human kappa opioid receptor (hKOPR) and at least eight doses of each kappa agonist was tested, ranging from 0.01 nM – 10 μM. EC50 and Emax values of each ligand in both functional end points were determined from dose-response curves. We then used the Ehlert method described in Griffin MT et al. (2007) to quantify ligand bias using the endogenous peptide for the KOPR, dynorphin A, as the reference compound. We found that etorphine, ICI-199441 and pentazocine were G protein biased, whereas nalbuphine, xorphanol, butorphanol, ti-fluadom, salvinorin A and enadoline were identified to be arrestin biased. Nalorphine, β-FNA, bremazocine, EKC, dynorphin B, dynorphin A, U50,488H, U69,593, MOM-salvinorin B, nalfurafine and spiradoline were all found to be balanced compounds. It is our hope that we can translate these findings to an *in vivo* mouse model to further the understanding of KOPR activation and ligand bias. *This work was funded by NIH grants DA007237 and DA017302.*

Mechanisms of activation of dopamine D₁ receptors by rotigotine: A route to novel Parkinson's disease drugs

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Rotigotine is a dopamine agonist used as symptomatic therapy of Parkinson's disease (PD). Although most clinically approved agonists target dopamine D₂-like receptors, activation of D₁ receptors by full intrinsic activity agonists has been shown to have efficacy in PD equal to levodopa. The D₂-selective drug rotigotine is unique in that it has high D₁ intrinsic activity and that unlike the available selective full D₁ agonists (e.g., dihydrexidine or SKF81259), it does not contain the catechol moiety that is known to cause rapid metabolism and poor bioavailability. Thus, understanding the molecular mechanisms by which rotigotine activates the D₁ receptor may provide leads to novel D₁ agonists. To investigate the molecular interactions between the D₁ receptor and rotigotine, we made mutations to alanine in highly conserved transmembrane 5 serines (S5.42^{199A}, S5.43^{199A}, and S5.46^{202A}), as well as in transmembrane 6 aromatic amino acids (F6.51^{288A} and F6.52^{289A}) that are involved in receptor activation and ligand interactions. S5.42A and S5.43A mutations greatly decreased the affinity and receptor activation mediated by rotigotine, whereas S5.46A mutation did not cause any significant change. This suggests that hydrogen bond formation occurs between the hydroxyl group of rotigotine and S5.42 and/or S5.43, but not S5.46. Similarly, the F6.51A mutation decreased the affinity of rotigotine to a far greater extent than F6.52A mutation suggesting that hydrophobic/aromatic interactions with F6.51 are particularly important. Aromatic ring conservative mutations (F6.51Y and F6.51W) were made to restore the hydrophobic/aromatic interactions at the position of F6.51, and they partially restored the loss of affinity and intrinsic activity caused by F6.51A mutation confirming the critical role of F6.51 in rotigotine interaction.

These receptor-ligand interaction data provided a basis for the possible docking pose of rotigotine to the D₁ receptor homology model based on the human β₂-adrenergic receptor. The docking simulation demonstrates that the hydroxyl group of rotigotine may form critical bifurcated hydrogen bond with S5.42 and S5.43, and the thiophene group of rotigotine may form critical hydrophobic/aromatic interactions with F6.51. This contact map between the D₁ receptor and rotigotine indicates that rotigotine may be used as a new scaffold for D₁ receptor agonists with high D₁ intrinsic activity.

Anti-allodynic, conditioned rewarding, and reinforcing effects of morphine in the presence of paclitaxel-induced peripheral neuropathy in male and female C57Bl/6 mice

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Clinical management of severe acute and chronic pain with prescription opioids remains a challenge due to concerns about opioid-induced dependence and addiction. Sex-differences in pain sensitivity, opioid analgesia, and reinforcing effects of opioids are observed in rodents. The purpose of our study is to test the hypothesis that the presence of paclitaxel-induced chronic peripheral neuropathy will differentially alter the sensitivities of male and female mice to morphine-induced anti-allodynic, conditioned rewarding, and reinforcing effects. Saline (control) or the chemotherapeutic agent paclitaxel (8 mg/kg) were administered on days 1, 3, 5, and 7 in different groups of male and female mice in order to induce allodynia. In the first experiment, effects of morphine (2.5-10 mg/kg) in reversing paclitaxel-induced mechanical allodynia were determined using the Von Frey filament assay. Next, the conditioned rewarding effects of morphine (0.3-10 mg/kg) were assessed in control and paclitaxel-treated male and female mice using the conditioned place preference procedure. Lastly, mice were

implanted with indwelling catheters and trained to self-administer morphine under a progressive ratio schedule of reinforcement. Once stable responding was achieved, mice were treated with saline or paclitaxel to determine the effects of paclitaxel treatment on the reinforcing effects of morphine (0.01-0.1 mg/kg/inf). Morphine produced significant anti-allodynic effects in both males and females with increased potency in male versus female mice. Paclitaxel treatment significantly enhanced sensitivity to the conditioned rewarding effects of morphine compared to the controls in both male and female mice. Finally, paclitaxel treatment produced a significant upward shift in the dose-response curve for morphine self-administration - an effect that was significantly pronounced in male versus female mice. The cumulative recordings from the self-administration sessions displayed marked differences in the pattern of drug-taking behavior in the paclitaxel versus control male mice. These results suggest that the reward-related behavioral effects of the prescription opioid morphine are altered by the presence of paclitaxel-induced peripheral neuropathy with male mice displaying greater sensitivity to these effects compared to female mice. Overall, these results may have implications for the understanding of potential sex differences in the clinical management of pain and the gender-dependent abuse liability of prescription opioids in humans. *Supported by R01 CA129092.*

Arylbicycloheptylamines: Novel conformationally restricted uncompetitive NMDA receptor antagonists

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Uncompetitive N-Methyl-D-aspartic acid receptor (NMDAR) antagonism is an important pharmacological strategy in the treatment of various neurodegenerative diseases including Alzheimer's disease and dementia. One promising class of NMDAR antagonists is the arylcycloalkylamine, represented by the anesthetic ketamine and illicit drug phencyclidine. To further probe the structure activity relationship of this promising class, a series of conformationally restricted arylbicycloheptylamines were designed using a pharmacophore based approach. Syntheses of the target compounds were performed in several steps using standard procedures. NMDAR affinity (K_i) was determined via competitive binding studies using ³H-MK-801 in rat brain. K_i values ranged from low nM to low μM. Although affinity was generally reduced for the rigid bicycloheptylamines relative to cyclohexane counterparts, significant NMDAR affinity was retained. Consistent with existing pharmacophore models, the exo-diastereomers in which the phenyl ring occupies the axial position exhibited ~ 2-4 fold greater affinity for NMDAR than their endo-counterparts. Several of the target compounds displayed *in vitro* protection against NMDA and KA induced cell damage. Similarly, many target compounds possess *in vivo* neuroprotection. While some of the compounds exhibited toxicity, the results suggest toxicity can be reduced relative to neuroprotective efficacy.

A cannabinoid receptor 2 agonist increases regulatory T-cells and inhibits graft rejection *in vitro* and *in vivo*?

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Cannabinoids are known to have anti-inflammatory and immunomodulatory properties. Cannabinoid receptor 2 (CB2) is expressed mainly on leukocytes and is the receptor implicated in mediating many of the effects of cannabinoids on immune processes. We have previously reported that a CB2-selective agonist, O-1966, inhibits the Mixed Lymphocyte Reaction (MLR), an *in vitro* correlate of graft rejection, through the CB2 receptor. This inhibition was found to occur mainly via a direct effect on T-cells. The present study sought to determine mechanisms for the immunosuppressive action of O-1966 and to test its efficacy in blocking acute skin graft rejection in mice. Treatment with O-1966 increased IL-10 release in MLR culture supernatants. An increase in the percentage of regulatory T-cells (Tregs) was observed in MLR cultures and pretreatment with anti-IL-10 resulted in a partial reversal of the inhibition of proliferation and blocked the increase of Tregs. The ability of O-1966 treatment to block rejection of skin grafts *in vivo* was also tested. Mice received skin grafts from a histoincompatible donor animal, and the time to graft rejection was determined. Compared to mice that received the vehicle, mice that received O-1966 treatment had significantly prolonged graft survival and an increased percentage of Tregs in the spleen. The spleen cells from O-1966-treated mice had reduced proliferation in an MLR and an increased percentage of Tregs in culture. Together, these data support the potential of this class of compounds as useful therapies to be used alone, or in combination with standard therapies, to prolong graft survival in transplant patients. *This work was supported by Temple University Tobacco Settlement Fund and NIDA grants DA13429, DA06650, and T32-DA07237.*

Substantial enantiomer-specific differences in the neurochemical and behavioral actions of the synthetic cathinone mephedrone

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Synthetic cathinones are an emerging group of amphetamine-derivative compounds gaining popularity in abuse in the United States and around the world. Of the growing number of synthetic cathinones, mephedrone (4-methylmethcathinone) is one of the most commonly abused. Mephedrone is a non-specific monoamine transporter substrate that produces psychostimulant effects like those observed with amphetamine and MDMA. Similar to amphetamines and cathinones, mephedrone has a chiral center and exists stably as two enantiomers, R-mephedrone (R-MEPH) and S-mephedrone (S-MEPH). While several investigations have identified the effects of stereochemistry on neurochemistry and behavior of similarly structured psychostimulants, no investigation has been performed on mephedrone. We provide the first investigation into the neurochemical and behavioral differences of R-MEPH and S-MEPH across multiple endpoints. R-MEPH and S-MEPH were found to have similar effects on dopamine transporter uptake inhibition and dopamine release, while S-MEPH was more potent in producing serotonin transporter uptake inhibition and release. Locomotor activity was evaluated in acute and repeated, intermittent paradigms, with R-MEPH producing significantly greater ambulation and stereotypy than S-MEPH across multiple doses. Additionally, only R-MEPH produced locomotor sensitization. Conditioned place preference assays determined R-MEPH, but not S-MEPH, produces place preference. Additionally, S-MEPH but not R-MEPH attenuated thermal nociception in the hot plate test, and pretreatment with naloxone did not attenuate S-MEPH effects. Taken together, this data illustrates stereospecific actions of mephedrone on neurochemistry and behavior and warrants further study.

Differential GPCR signaling kinetic signatures associated with ligand gradient sensing

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CXCR4, a chemokine G protein-coupled receptor, is essential for migration of select neuronal, cardiovascular, and hematopoietic cells, as well as metastatic breast cancer cells whereby CXCR4 dysregulation promotes a migratory and invasive phenotype. Normally following SDF (CXCL12) activation, CXCR4 is rapidly phosphorylated by GRKs, a key step in initiating adaptor recruitment, which promotes receptor desensitization and receptor trafficking to endocytic sites. Previously we identified Arf6 as a novel regulator of the SDF-CXCR4 axis, whereby it inhibits trafficking of activated CXCR4 from the cell surface, and potentiates CXCR4 signaling to membrane-delineated ERK. Here we characterized a phosphorylation mechanism by which Arf6 delays CXCR4 trafficking, and identified that Arf6 leads to sustained ERK signaling kinetics specifically upon SDF gradient sensing, which requires Shp2 phosphatase. Specifically, we assessed 1) Arf6 effects on CXCR4 phosphorylation by mobility shift assay, 2) differential ERK activation kinetics, by uniform versus gradient SDF stimulation methods, 3) the role of Arf6 and Shp2 in sustained ERK kinetics and migration by siRNA and inhibitor approaches, and 4) signaling kinetic signatures associated with SDF gradient sensing for migratory and proliferative machinery by microarray. Our results demonstrate that constitutively active Arf6-QL inhibits SDF-dependent CXCR4 phosphorylation, which is unaltered by receptor deglycosylation or by phosphatase inhibition with okadaic acid. Additionally, SDF gradient sensing leads to sustained ERK kinetics, in contrast to transient ERK activity upon uniform SDF stimulation. Furthermore, this differential CXCR4 signaling to sustained ERK is inhibited by Arf6 siRNA. Similar to growth factor receptors, both sustained ERK and migration requires Shp2, as indicated by inhibition with Shp2 siRNA and PHS1. Interestingly, signaling kinetic signatures associated with SDF gradient sensing by CXCR4, suggest that migratory machinery are promoted, whereas proliferative machinery are inhibited as measured by microarray analysis. These data support a working model that Arf6 modulates CXCR4 phosphorylation, leading to delayed trafficking of CXCR4 to endocytic sites and sustained CXCR4 signaling to a novel Shp2-ERK pathway and previously unidentified migratory machinery. These data have implications on metastatic breast cancer cells known to have elevated Arf6. *These studies were supported by NIH grant GM-097718, PA Department of Health grant SAP4100057688, and USciences start-up funds.*

A novel GPCR pathway is required for migration of metastatic breast cancer cells

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The research presented here supports a model whereby a CXCR4-Arf6-ERK pathway is critical to the mechanism of CXCR4 dysregulation in metastatic breast cancer cells. CXCR4 is a chemokine G protein-coupled receptor essential for select neuronal, car-

diovascular, and hematopoietic cell migration towards SDF (CXCL12), and is now recognized to promote cancer metastasis. Dysregulation of the SDF-CXCR4 axis in nonmotile primary tumor cells confers an aberrant migratory capacity and promotes metastatic homing of tumor cells to distal SDF-expressing organs. Metastasis is the major cause of mortality in cancer patients, therefore these findings have led to vigorous attempts to identify molecular factors that contribute to CXCR4 dysregulation in cancer. Previously we identified Arf6 as a novel regulator of the SDF-CXCR4 axis, whereby it enhances both CXCR4 cell surface levels and CXCR4 signaling to membrane-delineated ERK. Here we identified a novel Arf6-ERK pathway required for migration of metastatic breast cancer cells. Specifically, we determined the steepness and duration of SDF gradient that is associated with robust signaling to cortactin, an actin-binding protein that promotes migration and invasion. Utilizing this defined gradient, we assessed the effects of mutational or GEF-mediated Arf6 activation, siRNA-mediated Arf6 knockdown, and MEK inhibition on CXCR4-mediated migration in response to co-stimulation with SDF and collagen, as measured by transwell motility assays. Our results demonstrate that in noninvasive MDA-MB-361 and MDA-MB-468 cells, Arf6 activation unmask a migratory phenotype which is blocked by MEK inhibition. Additionally, in highly invasive MDA-MB-231 and BT-549 cells, the migratory phenotype is blocked by Arf6 siRNA and MEK inhibition with PD98059, U0126, or DN-MEK1. Migration is rescued by siRNA-resistant Arf6 expressions constructs, and correlates with localization of ERK to pseudopodial extensions. These responses are specific to CXCR4-mediated migration as suggested by blockade with CXCR4 antagonist or neutralizing antibody, AMD3100 and 12G5 respectively, and no change of cell adhesion or FBS-mediated migration. These results provide insight into the role of a novel CXCR4-Arf6-ERK pathway in regulating SDF-mediated migration, and support the model that Arf6 is critical to the mechanism of CXCR4 dysregulation in metastatic breast cancer cells. *These studies were supported by NIH grant GM-097718, AFPE sponsored AACR New Investigator grant, and USciences start-up funds.*

Detection and determination of functional adenosine receptors on renal fibroblasts

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Adenosine is an inflammatory signaling molecule produced from the degradation of adenosine triphosphate (ATP) or cyclic adenosine monophosphate (cAMP) that acts as a dynamic signaling molecule through activation of the G-protein coupled receptor (GPCR) P1 purinoceptor family that contain A₁, A_{2a}, A_{2b}, and A₃ adenosine receptor (AR) subtypes. Adenosine levels are increased in renal tissue of Diabetic Nephropathy patients compared to healthy controls, and *in vivo* streptozotocin induced diabetes models. Kidney fibrosis of the interstitial space is a hallmark of end stage renal disease (ESRD) where patients are exclusively dependent on dialysis to maintain renal protein clearance. Accumulation of fibrotic proteins throughout the kidney is a major pathology associated with Diabetic Nephropathy due to increased fibroblast proliferation and matrix protein production by myofibroblasts. To date adenosine signaling has not been investigated in renal fibroblasts. This investigation focused on the identification and relative expression of A₁, A_{2a}, A_{2b}, and A₃ adenosine receptors and quantified the effects of receptor activation and blockade on intracellular cAMP levels. Quantitative real time PCR was used to identify that adenosine A₁ receptor expression was low and adenosine receptor A_{2b} was more highly expressed while A_{2a} and A₃ were undetectable. To determine if these receptors were functional, fibroblasts were treated with adenosine or 5'-N-Ethylcarboxamidoadenosine (NECA), an adenosine agonist specific to all adenosine receptor subtypes. Both compounds induced intracellular cAMP, with NECA (IC₅₀=23.94uM) more potent than adenosine (IC₅₀=38.06uM). Cells pretreated with specific A₁ and A_{2b} receptor agonists or antagonists, before NECA or adenosine activation, examined which receptor contributes to the total cAMP response seen with adenosine or NECA stimulation. When cells were pretreated with the A_{2b} receptor antagonist 8-[4-[4-(4-Chlorophenyl)piperazine-1-sulfonyl]phenyl]-1-propylxanthine (BAY-603), the cAMP response was blocked in both adenosine and NECA stimulated cells. Conversely, cells pretreated with an A₁ receptor specific agonist 2-Chloro-N-cyclopentyl-2'-methyladenosine (MeCCPA) also had decreased cAMP. Finally, renal fibroblasts stimulated with the A_{2b} agonist 2-[[6-Amino-3,5-dicyano-4-[4-(cyclopropylmethoxy)phenyl]-2-pyridinyl]thio]-acetamide (BAY60-653) had increased mRNA expression of TGF β , Fibronectin, and α 5MA, markers of a myofibroblast phenotype and fibrosis. Overall these data identify adenosine receptor A₁ and A_{2b} as the two subtypes mediating adenosine signaling in renal fibroblasts. The totality of A₁ and A_{2b} receptor activation through adenosine or NECA results in increased intracellular cAMP signaling and stimulation of A2B results in increased transcription in fibrotic markers. Taken together, this data highlights that functional adenosine receptor A1 and A2B subtypes can influence intracellular cAMP levels and transcription of fibrotic genes.

Kappa opioid receptor agonist-induced neurite outgrowth: studies on underlying mechanisms

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Kappa opioid receptor (KOPR), a G protein-coupled receptor, acts through Gi/o and β -arrestin pathways to produce different cellular functions. KOPR has been shown to be involved in neurite outgrowth and stem cell differentiation. Previous studies from our lab showed that in Chinese hamster ovary (CHO) cells stably transfected with human KOPR, U50,488H induced internalization but etorphine did not. In this study, we used Neuro2a mouse neuroblastoma cells stably transfected with the hKOPR (N2A-3HA-hKOPR) to examine whether KOPR activation promoted neurite outgrowth in these cells. U50,488H and etorphine bound to KOPR in N2A-3HA-hKOPR membranes with Ki values of 3.1 and 0.7nM, respectively, indicating that etorphine has 4X higher affinity than U50,488H. Cells were treated with agonists for 10 min followed by incubation in serum-free medium for 24h and cells were stained with β III-tubulin and Hoechst33258 to reveal neurite structure and nuclei, respectively. Nuclear staining allowed quantitation of cell number. Images under microscope were captured. Neurite length/ neuron was quantified with the NIH neurite-trace Image J software. We found that U50,488H at 0.1, 1 and 10 μ M significantly enhanced neurite outgrowth by 24.3%, 27.3% and 45.9%, respectively. Etorphine at 1 μ M increased neurite length by 10.8%, but not at 0.1 or 0.01 μ M, demonstrating that etorphine is much less efficacious than U50,488H. We then examined if there are difference between the two agonists in the mechanisms underlying neurite outgrowth. U50,488H- and etorphine-induced neurite outgrowth were inhibited by pretreatment with the KOPR antagonist norBNI for 10min, indicating KOPR-mediated effect. In addition, pretreatment with pertussis toxin (50 μ g/ml, 1h) blocked U50,488H- and etorphine-induced neurite outgrowth, demonstrating the involvement of Gi/o proteins. Knockdown of β -arrestin2 by siRNA enhanced the effect of both U50,488H and etorphine in inducing neurite outgrowth, while knockdown of β -arrestin1 did not have effect, indicating that β -arrestin 2 plays a regulatory role in reducing the Gi α -mediated response. These results indicate that both agonists induce neurite outgrowth via KOPR and Gi/o protein, but not through β -arrestins. (Supported by NIH grant DA17302.)

Treatment induced microRNA modulation in complex regional pain syndrome

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MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression through the degradation or post-translational repression of target messenger RNAs. Correlations between altered expression patterns of miRNAs and disease states are now well established. The stability of miRNAs in body fluids and their dysregulation in a number of diseases indicate their utility as potential biomarkers and may offer insight into novel therapeutic intervention strategies. Complex regional pain syndrome (CRPS) is a chronic neuropathic pain condition that predominantly occurs after an injury, affecting one or more extremities. CRPS patients experience chronic pain and inflammation beyond the initial injury that can be severely debilitating. Treatments, particularly in moderate-severe cases, provide little relief. Ketamine, a widely used anesthetic, is one of the treatment options being pursued for CRPS. In this study, we examined the changes of 758 miRNAs in the blood of 19 CRPS patients before and after ketamine treatment, using Taqman low-density array cards. Twenty three miRNAs were differentially expressed between responders and non-responders before ketamine treatment, suggesting that miRNA signature profiles may be potentially beneficial in predicting treatment outcome. Five miRNAs were differently expressed after treatment in patients who responded to ketamine. Correlational studies of inflammatory markers, selected medical conditions and other clinical parameters are also being performed. The development of miRNA biomarkers will be an exceptionally valuable tool for stratifying patients in clinical trials and in assisting physicians in choosing treatment options.

Development of nanoparticles displaying LyP-1 peptides for targeted cancer drug delivery

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LyP-1 (CGNKRTRGC) is a cyclic 9-amino acid peptide discovered through bacteriophage display selection. Its receptor protein, p32/gC1qR/HABP1, is significantly expressed on the surface of tumor lymphatic cells and tumor-associated macrophages. Fluorescein

labeled LyP-1 has been shown to localize with its receptor in tumor lymphatic vessels accumulating preferentially in hypoxic/nutrient-deprived areas of tumors. Linear and cyclic LyP-1 peptides of wild type and negative control (CGEKRTRGC) sequences were synthesized using standard Fmoc solid phase peptide synthesis and the N terminus was then coupled with N₃-PEG₄-COOH prior to cleavage to facilitate copper-free click chemistry reactions. Post cleavage oxidations of the LyP-1 peptides were performed in solution using iodine (3 eq/peptide) followed by conjugation with bis-dibenzocyclooctyne DBCO-PEG₄-DBCO linker. Purifications were carried out under slightly acidic conditions (1% AcOH/H₂O) due to the acid sensitivity of the remaining DBCO moiety. The purity and the chemical identity of the products were verified by RP-HPLC and ESI-MS as well as MALDI-TOF respectively. The compounds with a free DBCO group were then conjugated with nanoparticles bearing azido groups on their surface. These nanoparticles, were Polystyrene-PEG block copolymers and a Vitamin E stabilized core were made by flash nanoprecipitation having an azido and fluorescent dye labeled surface. We are currently synthesizing new nanoparticles with FITC and Cy5 labeling to conjugate onto LyP-1 peptides for *in vitro* cellular uptake experiments using the MDA-MB-231 human breast cancer cell line as well as for *in vivo* studies.

β -adrenergic receptor-mediated transactivation of epidermal growth factor receptor decreases cardiomyocyte apoptosis through differential subcellular activation of ERK1/2 and Akt

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β -adrenergic receptors (β AR) are critical regulators of cardiac function whose dysregulation during heart failure are associated with diminished function. However, β AR-mediated EGFR transactivation has been shown to relay cardioprotection via unknown mechanisms. We hypothesized that acute β AR-mediated EGFR transactivation in the heart promotes differential subcellular activation of ERK1/2 and Akt, promoting cell survival through modulation of apoptosis. To test this hypothesis, C57BL/6 mice underwent acute i.p. injection with isoproterenol (ISO) \pm AG1478 (EGFR antagonist) to assess the impact of β AR-mediated EGFR transactivation on phosphorylation of ERK1/2 (P-ERK1/2) and Akt (P-Akt) in distinct cardiac subcellular fractions. Increased P-ERK1/2 and P-Akt were observed in cytosolic, plasma membrane and nuclear fractions following ISO stimulation. Whereas the P-ERK1/2 response was EGFR-sensitive in all fractions, the P-Akt response was EGFR-sensitive only in the plasma membrane and nucleus, results confirmed in primary rat neonatal cardiomyocytes (RNCM). β AR-mediated EGFR-transactivation also decreased apoptosis in serum-depleted RNCM, as measured via TUNEL as well as caspase 3 activity/cleavage, which were sensitive to inhibition of either ERK1/2 (PD184352) or Akt (LY-294002) signaling. Caspase 3 activity/cleavage was also sensitive to inhibition of transcription, which, with an increase in nuclear P-ERK1/2 and P-Akt in response to ISO, suggested that β AR-mediated EGFR transactivation may regulate apoptotic gene transcription. An Apoptosis PCR Array identified *tnfsf10* (TRAIL) to be altered by ISO in an EGFR-sensitive manner, which was confirmed via ELISA measurement of both membrane-bound and soluble TRAIL levels. These results demonstrate that β AR-mediated EGFR transactivation induces differential subcellular activation of ERK1/2 and Akt leading to increased cell survival through the modulation of caspase 3 activity and apoptotic gene expression in cardiomyocytes. Further understanding the downstream consequences of these effects in response to β AR-mediated EGFR transactivation could lead to improved therapies for the treatment of heart failure.

Exosomes carry biomolecular signatures reflecting inflammation-induced cellular alterations and alleviate thermal pain sensitivity in mice

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Chronic inflammatory pain is a systemic condition accompanied by altered expression of circulating RNA and proteins. We have previously shown that patients with a debilitating chronic pain disorder, Complex Regional Pain Syndrome (CRPS), have measurable increases in circulating cytokines and dysregulated expression of 18 miRNAs. Exosomes are small vesicles that transport a source specific signature of proteins, mRNAs, and miRNAs through bodily fluids. These novel mediators of intercellular communication are being explored for therapeutic and biomarker utilities. In this study, we profiled exosomal miRNAs from CRPS patient serum and determined that miRNAs altered in this chronic pain state are trafficked by exosomes.

To determine the global effects of inflammation on exosomal content, we used RAW 264.7 mouse macrophage-derived exosomes, to quantify changes in miRNA, mRNA and cytokine levels after stimulation with lipopolysaccharides (LPS). Expression profiling of macrophage-derived exosomal miRNA revealed differential expression of 15 of the 281 detectable miRNAs after LPS stimulation. Several cytokines that mediate inflammation were elevated in exosomes secreted by LPS-stimulated cells. Next-Gen sequencing of exosomal RNA showed alterations in both innate and adaptive immune system pathways. Exosomes from LPS-treated macrophages were sufficient to cause NF- κ B activation *in vitro* and to reduce paw edema after a single intraplantar injection in a mouse model of inflammatory pain. Additionally, macrophage-derived exosomes reduce thermal hyperalgesia 24 h after induction of inflammatory pain. Overall, our data suggests that macrophage-derived exosomes are immunoprotective, and that exosomal content reflects cellular alterations due to inflammation and pain.

GPCR-G_s-mediated cyclic AMP signaling for neurogenesis, growth arrest, and cell survival is parcellated among the cAMP sensors NCS/Rapgef2, Epac, and PKA

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Upon exposure to ligands that activate G_s-coupled GPCRs causing cAMP elevation, dividing neuroendocrine cells differentiate (cease proliferation and extend neurites), and are also protected from programmed cell death upon serum withdrawal. We have used the PC12 cell high-throughput cell strain NS-1 to screen for ligand/GPCR combinations that mediate signaling for differentiation. We found that they include members of both family A and family B GPCRs (e.g. dopamine via the D₁ receptor; PACAP via the PAC1 receptor; and VIP through the VPAC₁ and VPAC₂ receptors). However, there are also G_s-linked GPCRs that, unlike, for example, PACAP, activate some aspects of neuronal differentiation but not others, such as the β_2 -adrenoceptor for norepinephrine and epinephrine. These results (unpublished and see Emery and Eiden, *FASEB J*, **26**:3199-3211; Emery et al., *Mol Pharm*, **83**:95-105; Emery et al., *Science Signaling*, **6**:ra51) imply that GPCR-G_s signaling initiated by cAMP must proceed through independent signaling through multiple cAMP sensors downstream of adenylate cyclase. Recently, we demonstrated the existence of a linear signaling cAMP-dependent pathway initiated by PACAP leading to ERK activation through Rap1, B-Raf and MEK, and not requiring any known cAMP sensor. We named the required cAMP sensor activity the neurogenic cAMP sensor, or NCS (Emery and Eiden, *FASEB J*, **26**:3199-3211). Subsequently we identified the NCS as the protein product of the Rapgef2 gene and showed that PACAP-dependent ERK activation and neurogenesis require NCS/Rapgef2 but not Epac or PKA (Emery et al., *Science Signaling*, **6**:ra51).

We now report that in NS-1 cells, PACAP-dependent growth arrest requires Epac but not NCS/Rapgef2 or PKA. Both PACAP and a selective Epac agonist, 8-CPT-2'-O-Me-cAMP, cause growth arrest in NS-1 cells. Inhibition of Epac blocks growth arrest in

response to either agent. Furthermore, we found that stimulation of Epac leads to the activation of both Rap1 and the MAP kinase p38. Surprisingly, these two downstream effectors of Epac appear to be arranged in separate signaling pathways: inhibition of Rap1 did not affect p38 phosphorylation or vice versa, and Epac-dependent growth arrest required the activity of p38, but not Rap1. Thus, in NS-1 cells, cAMP-dependent growth arrest is wholly dependent on Epac-p38 signaling and does not require NCS/Rapgef2-ERK or PKA-CREB activity. We now intend to explore possible roles of the recently identified Epac/p38 signaling pathway for growth arrest in the contexts of neural development and neuronal replenishment, via progenitor cell differentiation, throughout the lifespan.

Divergent effects of CB2 receptor agonism on learning and memory in naïve versus stroked mice

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We have recently demonstrated that treatment with a CB2 agonist was protective in a mouse middle cerebral artery occlusion model of cerebral ischemia/reperfusion injury. The present study aimed to determine whether these protective effects of CB2 agonism would extend to a mouse photothrombosis (PT) model of permanent ischemia and determine associated alterations in inflammation. In addition, we determined whether the PT model induces alterations in learning and memory behavior that are also prevented by CB2 receptor activation. In Experiment 1, untreated mice were exposed to PT stroke and inflammatory markers were measured. In Experiment 2, mice received a subchronic treatment regimen of the CB2 selective agonist O-1966 or vehicle 1 hr prior to and 2 and 5 days following induction of PT injury and infarct size and inflammatory markers were assessed at 24h and 7 days post injury. In Experiment 3, mice received subchronic O-1966 or vehicle paired with PT injury, sham injury, or no manipulation (naïve mice). Learning and memory effects of injury and O-1966 treatment were assessed on days 6 and 7 using a novel object recognition task and an operant acquisition and retention procedure. Photothrombosis was associated with a significant infarct size and inflammatory response, and these effects were attenuated by O-1966. PT was also associated with significant learning and memory impairments on days 6 and 7 post-injury, and these deficits were reversed with O-1966 treatment. Surprisingly, sham-operated mice receiving O-1966 treatment showed a significant learning deficit compared with vehicle treated sham mice, and this effect of O-1966 was also observed in operationally naïve mice. Therefore it appears that O-1966 effects on learning and memory are dependent upon the inflammatory state of nervous tissue. Our current working hypothesis is that in non-stroked animals, CB2 activation of astrocytes alters neuronal signaling in learning and memory regions of the CNS, thereby impairing cognitive processes, while in the presence of inflammation the role of microglia and their regulation by CB2 receptor agonism prevails.

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