

NEWSLETTER

Mitochondrial Biology in Disease.....
the mechanisms of mitochondrial-nuclear cross-talk



Narayan G. Avadhani is a professor of biochemistry in the Department of Animal Biology, School of Veterinary Medicine. He received a BSc (Hons) degree from the Karnatak University, Dharwar, India, in Chemistry and Physics in 1962 and worked for two years in the Department of Defense, India, as a Junior Scientific Officer before

pursuing his graduate studies in the Department of Chemical Technology (currently renamed the Institute of Chemical Technology), University of Bombay in Mumbai in 1964. After receiving a Ph.D. degree he carried out three years of post-doctoral research in the Department of Physiology and Biophysics at the University of

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12th ANNUAL BIOMEDICAL POSTDOCTORAL RESEARCH SYMPOSIUM

The 12th Annual Biomedical Postdoctoral Research Symposium will be held on November 4th, 2013 in the BRB II/III Auditorium and Lobby at 421 Curie Boulevard, Philadelphia, PA 19104. The symposium will include: Poster sessions and oral presentations research talks by BPP postdocs and awards for the best posters and oral presentations. The keynote lecture will be delivered by [Dr. Bruce Alberts](#) of

UCSF, recent past editor-in-chief of Science, former president of the National Academy of Science, and an original author of 'Molecular Biology of the Cell'. If you have any questions, please contact Adam Walker, Chair of the BPC Symposium Committee, at bpc.symposium@gmail.com, or the Office of Biomedical Postdoctoral Programs at bppevent@mail.med.upenn.edu.

Fall 2013

The fall semester is underway at Penn Vet.....

- There is a new associate vice provost for research and executive director of the Center for Technology Transfer, **John S. Swartley**, Ph.D.

- Penn Vet welcomed a new assistant dean of advancement, alumni relations and communications, **Carol Pooser**.

- **NIH** has granted universities an 11th hour reprieve. There will be a delay of one year in implementing proposed changes to project by project accounting on awards. The revised NIH guidance is available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-120.html>.

- **30 Penn science graduate students** visited Washington DC to meet with members of Congress to discuss how reduced NIH funding is negatively impacting the ability of Penn research laboratories to train students, perform basic science, and develop new medical treatments.

2013 SUMMER RESEARCH TRAINING FOR STUDENTS at PENN VET



Jonah Binstock, a senior at Haverford College, is planning to enter veterinary medicine after graduation. He looked at cell migration and wound healing for his project in Dr. Sue Volk's laboratory.



High School Student **Aditi Ahuja** worked in Dr Nicola Mason's laboratory to evaluate Her2/neu expression in canine osteosarcoma.



Mara Kraenzlin V'16 worked in Dr. James Lok's laboratory to learn about a parasitic nematode *Stongyloides stercoralis* in comparison to the free living nematode, *Caenor-habditis elegans*. She will also assist in a study of gene regulation during the infective process by *S. stercoralis*.

Summer training programs provide mentorship and infrastructure for veterinary students, high school students, visiting scholars, and undergraduate and graduate students to attain research laboratory experience, including technical and conceptual skills in performing hypothesis-based research. A range of students find their way to a Penn Vet laboratory. They may be participants in the Merial/NIH Summer Program, or the NIH *Clinical and Translational Science Award (CTSA)* program, or students from nearby colleges and universities. These students eagerly secured summer slots in laboratories at Penn Vet to pursue their research interests. Many summer students are from the NIH/**Merial Summer Program**, designed to expose students to all phases of biomedical research. Penn Vet students and faculty mentors in the 2013 Merial Program were: Lisa Brody (Dr. Margret Casal); Drew DeLong (Dr. L. Soslowsky); Ashley Klein (Dr. Robert Greenberg); Kelly Giffear (Dr. Bernard Shapiro); Sam Gilbert (Dr. Kurt Hankenson); Julie Lee (Dr. Mark Haskins); Risa S Lisle (Dr. M Granato); Andrea Moffitt (Dr. J Baur); Marc Myers (Dr. Kurt Hankenson); Katelyn MacGillivray (Dr. B Freedman); Scott Pandya (Dr. Brett Kaufman); Klaudia Polak (Dr. Urs Giger); Amanda Samuels (Dr. R. Harty); Sarah Schoenhut (Dr. Tracy Bale); Julie Soohoo (Dr. Makoto Senoo); Anne Staudenmaier (Dr. Erica Miller); Rebecca Stevens (Dr. N. Mason). Chelsea Del Alcazar (Dr.

Lachian Smith); and Scott Petesch (Dr. Charles Vite).



Alexis Leanza, Summer Intern (CTSA), Class of 2015 Swarthmore College, worked in Dr. C. López's laboratory on determining the role of neutrophils and interleukin -10 in the immune response to respiratory viral infection.



Cristhian Cadena worked in the laboratory of Dr. Carolina López where he studied the role of defective viral genome mutations on their

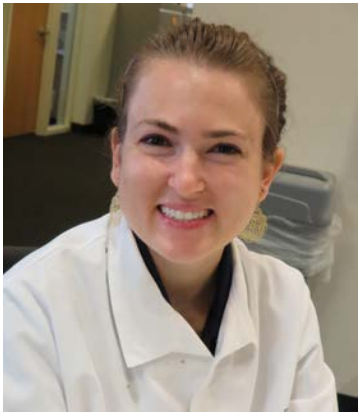
"We were very impressed that some of the Merial Students from last year returned this summer to continue working on their research project", said Dr. Margret Casal, Department of Clinical Studies Philadelphia.

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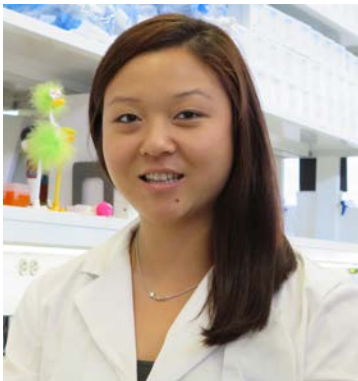
SUMMER RESEARCH AT PENN VET continued



Scott Pandya, V'16 worked with Dr. Brett Kaufman on a project to determine the role of PIF1 in the maintenance of muscle mitochondrial respiratory complex I activity.



Sarah Schoenhut, V'16 worked in Dr. Tracy Bale's laboratory doing research on the neural circuitry behind resiliency to pre-pubertal stress in mice.



Julie Lee V'15 worked with Dr. Mark Haskins this summer and her project involved an analysis of the variation in mannose-6-phosphorylation by AAV versus RV gene therapy in mucopolysaccharidosis--a genetic metabolic disorder of animals and children.



Ashley Klein V'16 studied the effects of multidrug resistance (MDR) transporter inhibition on the reproductive organs of schistosomes using MDR-inhibiting drugs and RNAi knockdown. Ashley worked in Dr. Robert Greenberg's laboratory.

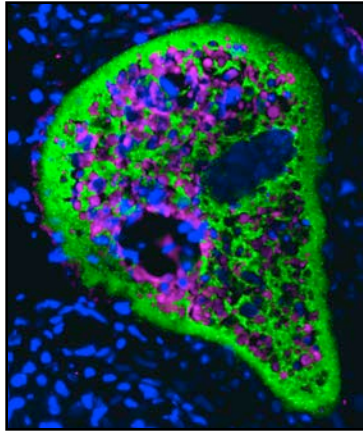


Michael Levenson, V'15 worked with Dr. Nicola Mason in the development and performance of a Phase II/III clinical trial combining palliative radiation with a modified Her2/neu expressing *Listeria monocytogenes* vaccine. He developed an iPad app for client communication and data collection associated with both phase I and phase II clinical trials using this vaccine approach.

Penn Vet faculty-mentored summer research projects reveal new possibilities for motivated students. A laboratory experience may bring unexpected discoveries and open a new door along a rewarding career pathway. Students participate in weekly seminars, and present their work in oral, poster, and written presentations. Being part of a summer program on the Penn Campus exposes a student to a wide variety of research topics.



Anne Staudenmaier, V'15, a NIH/ Merial summer student and recipient of the Morris Student Scholar Award for summer research. She studied the immune response in the common raccoon, *Procyon lotor*, to modified live canine distemper and feline panleukopenia vaccines under Erica Miller, D.V.M.



IgT, a fish mucosal immunoglobulin, surrounds a ghost-like *Ichthyophthirius multifiliis*, a skin parasite of rainbow trout. The parasite is stained in magenta, IgT is stained in green and the cell nuclei are stained with DAPI (blue). Scale bar represents 20 μ m. Image courtesy of D. Gomez and J. O. Sunyer.

Dr. J. Oriol Sunyer and his laboratory won 1st place in the Postdoctoral Fellow category of Perelman School of Medicine's first annual "Art in Science" competition. This image was also selected for the *Image of the Day* in "The Scientist".

HAVE YOU UPDATED YOUR FEDS PAGE RECENTLY?

Faculty Expertise Database System is our database in which to enter and update biographical information that provides content for faculty and researcher webpages, CVs, key words, and publications. LINK: [FEDS Vet Login](#)

Data entry questions | New Bolton Center: Pam Salsbury salsbury@vet.upenn.edu
610-925-6320

Data entry questions | Uploading citations | PubMed link help: Margy Lindem mlindem@pobox.upenn.edu
215-898-8895

General web questions: Carole Luke caluke@vet.upenn.edu
215-746-1395

RECENT AWARDS

(direct costs)

Thomas Parsons

PA Soybean Promotion Board
Anticipating the next welfare challenge: Environmental enrichment of gestating sows
\$10,000 2/28/2013 - 2/28/2014

Igor Brodsky

NIH Ro1 Modulation of Inflammation Activation by Yersinia.
\$985,000 8/1/13-7/31/17

Lisa Murphy

FDA U18
Method validation and comparison for the detection of mycotoxins in novel animal
\$450,000 9/1/13-7/31/18

J Oriol Sunyer

USDA-NIFA
Role of fish immunoglobulin IgT in skin and gill mucosal immune and protective responses
\$ 352,899 11/01/13-10/31/16

Anna S. Kashina

NIH/GM
Ro1 Molecular Mechanisms of Protein Arginylation
\$868,832 09/01/13-05/31/17

Leszek K. Kubin

NIH/HLB
Ro1 Upper airway control during disrupted and misaligned sleep
\$738,000 08/01/13-5/31/16

Ellen Puré

CRI(Cancer Research Institute) CLIP Award. Adoptive T cell therapy targeted to tumor stromal to treat lung cancer
\$200,000 7/1/13-6/30/15

Ellen Puré

CRI(Cancer Research Institute) Fellowship Award
Regulation of inflammatory and immune response to pancreatic cancer by FAP+ stromal cells
\$60,000 8/1/13-7/31/15

Charles Vite

Natl. Niemann-Pick Disease FDN Fellowship of the cats
\$100,000 9/01/13-8/31/15

Calendar

January 23, 2014 Research Resources Orientation for Faculty

More information later ~ Save the Date

March 11, 2014 Phi Zeta Student Research Day

Mark your calendars ~ Save the Date

RECENT PAPERS



Z Xu, D Parra, D Gomez, I Salinas, Y-A Zhang, LV Gersdorff, Jorgensen, RD Heinecke, K Buch-mann, S LaPatra, and **JO Sunyer** (2013) Teleost skin, an ancient mucosal surface that elicits gut-like immune responses *PNAS USA* 110 (32): 13097 -13102.

The study was also featured in the "highlights" section of the September issue of [Nature Reviews Immunology](#)



A Chopra, ME Murray^{3,4}, F Byfield, M Mendez, R Halleliuyan, D Restle, D Raz-Ben Aroush, PA Galie, K Pogoda, R Bucki, C Marcinkiewicz, GD Prestwich, T Zarembinski, CS Chen, **Ellen Puré**, JY Kresh, and PA

Janmey (2013) Augmentation of integrin-mediated mechanotransduction by hyaluronic acid (2013) *Biomaterials*, in press



Bigg PW, Baldo G, **Sleeper MM**, **O'Donnell PA**, Bai H, Rokkam VR, Liu Y, Wu S, Giugliani R, **Casal ML**, **Haskins ME**, and Ponder KP (2013) Pathogenesis of mitral valve disease in mucopolysaccharidosis VII dogs. *Mol. Genet. Metab.*

epub ahead of print.



Sweeney E, Roberts D, Lin A, Guldberg R & **Jacenko O** (2013) Defective endochondral ossification-derived matrix and bone cells alter the lymphopoietic niche in Collagen X mouse models. *Stem Cells Dev.* epub ahead of print.

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Illinois, Urbana-Champaign. He joined the Department of Animal Biology in 1972 as a Research Associate, and was promoted to Assistant Professor of Biochemistry (Tenure Track) in 1973. He became a full Professor in 1983 and was awarded the Harriet Ellison Woodward Chair in 1989. He has served the School in a number of administrative capacities, including Director of Summer Research Program for Professional Students, Head of Laboratories of Biochemistry, Director of Mari Lowe Center for Comparative Oncology and Chair of the Department of Animal Biology. His research during his early years at Penn was focused on the characterization of basic mechanisms of mitochondrial transcription and translation and transcriptional regulation of Cytochrome c Oxidase genes. For the past 20 years his research has focused on mitochondrial-nuclear cross-talk, mitochondrial oxidative and chemical stress, and mitochondrial dysfunction in cancer and degenerative diseases.

Mitochondrial stress modulates nuclear gene expression and induces metabolic and phenotypic changes:

The Avadhani group discovered a retrograde signaling mechanism in mammalian cells through which mitochondrial genetic (mitochondrial DNA (mtDNA) mutations and reduced mtDNA content), metabolic (drugs and chemicals) and respiratory stress (ROS) conditions are communicated to the nuclear compartment. Specifically, they found that genetic or metabolic changes

induced perturbations in the mitochondrial transmembrane potential, resulting in an increase in steady state cytosolic calcium levels and the consequent activation of calcineurin and a number of Ca²⁺ dependent factors. This retrograde signaling cascade affects the expression of >120 nuclear genes involved in a multitude of cellular processes and can promote tumorigenesis in immortalized skeletal myocytes. Studies over the past 10 years show that retrograde signaling is propagated through the activation of a novel calcineurin dependent NFkB that requires IKBβ, Ca²⁺ activated C/EBPδ, NFAT and CREB transcription factors and hnRNPA2, a transcriptional coactivator. In addition, recent studies show that hnRNPA2 is a novel HAT (histone acetyl transferase) protein. Retrograde signaling also plays a critical role in telomere maintenance and epithelial to mesenchymal transition in breast cancers and contributes to aging, age-related degenerative diseases, and other types of cancer. Translational studies on the use of synthetic small molecules for controlling or aborting the signaling in animal models are currently underway.

Mitochondria are the hot spots of drug metabolism and toxicity, a possible evolutionary slip:

Mammalian mitochondria contain well over 1500 proteins, and excepting the 13 polypeptides coded by mtDNA, are imported from the cytoplasm. In early experiments Dr. Avadhani observed that cytochrome P450 proteins (CYPs) that are normally targeted to the endoplasmic

reticulum (ER) and which play a crucial role in drug metabolism and drug-induced toxicity can also localize to mitochondria. Paradoxically, ER targeted CYPs 1A1, 1B1, 2E1, 2B1, 2D6 and 3A4 lack canonical mitochondria targeting signals. To resolve this issue, Avadhani's laboratory identified novel chimeric targeting sequences that drive bimodal targeting of the same primary translation products to multiple cellular locations. Mitochondrial targeting of CYPs is specifically activated by phosphorylation or site specific cytosolic endo-protease processing. As mtDNA is the direct and preferential target of wide ranging carcinogens, his findings suggest that ROS production by mitochondrially targeted CYP may contribute to cellular toxicity and other pathophysiological processes. Ongoing studies show that mitochondrial CYP2E1 plays a major role in alcohol induced liver toxicity, and that mitochondrial CYP2D6 plays a role in MPTP (a contaminant in synthetic cocaine) induced Parkinson's disease. If confirmed, this would be a paradigm shift in our understanding mechanisms of drug induced neuronal toxicity. Finally, he has shown that mitochondrial CYP1A1 and CYP1B1 play a role in BaP and TCDD induced mitochondrial dysfunction and possibly in cigarette smoke induced bone loss. In extension of these studies, Dr. Avadhani's group is collaborating with Drs. Serge Fuchs from Penn Vet and Anil Rustgi at Penn's Perelman School of Medicine to investigate the roles of Ahr regulated CYP1 family genes in cigarette smoke

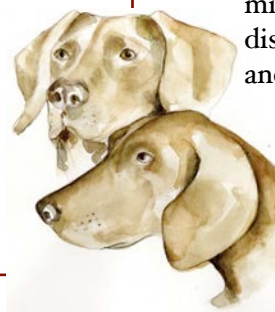
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AVMA LIFETIME EXCELLENCE
IN RESEARCH AWARD



Gustavo Aguirre, VMD, PhD

Dr. Gus Aguirre, professor in the Department of Clinical Studies Philadelphia, was awarded the **2013 AVMA Lifetime Excellence in Research Award** on August 3rd, at the AVMA/Merial-NIH Veterinary Scholars Symposium held at Michigan State. Dr. Aguirre was acknowledged for his more than four decades of research on degenerative retinal diseases affecting both dogs and humans. His research has been directed towards identifying the genetic causes of inherited blindness, identifying the mechanisms linking mutation to disease, and developing treatment approaches.



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induced inflammation and pancreatitis, which is a precursor for pancreatic cancer.

A novel cAMP independent mitochondrial PKA targets cytochrome c oxidase dysfunction:

Structure and function of cytochrome c oxidase (CcO) has been a focus of study in the Avadhani laboratory for more than 20 years. CcO, a highly regulated electron transfer chain complex, is a pace-setter of mitochondrial OXPHOS activity and is a highly sensitive target of oxidative and nitrosative stress. His group has demonstrated that three CcO subunits (CcO I, IV1 and Vb) are selectively degraded by hypoxia and myocardial ischemia-reperfusion (IR) injury and that subunit degradation coincided with high mitochondrial ROS production. Although previous studies suggest that CcO does not produce ROS under normoxia or hypoxic conditions, Avadhani's group has shown that the increased ROS observed during hypoxia or myocardial ischemia results from electron spillage from dissociated respirosome complexes. Moreover, their studies demonstrate that increased mitochondrial PKA-mediated phosphorylation of CcO subunits under hypoxic and IR conditions targets them for selective degradation by mitochondrial LON, an ATP dependent protease which is also activated under these pathophysiological conditions. Dr. Avadhani and coworkers have recently demonstrated that such PKA activation is dependent on mitochondrial ROS, which potentially activates PKA by dissociating the catalytic subunit of PKA from AKAP anchored complex.

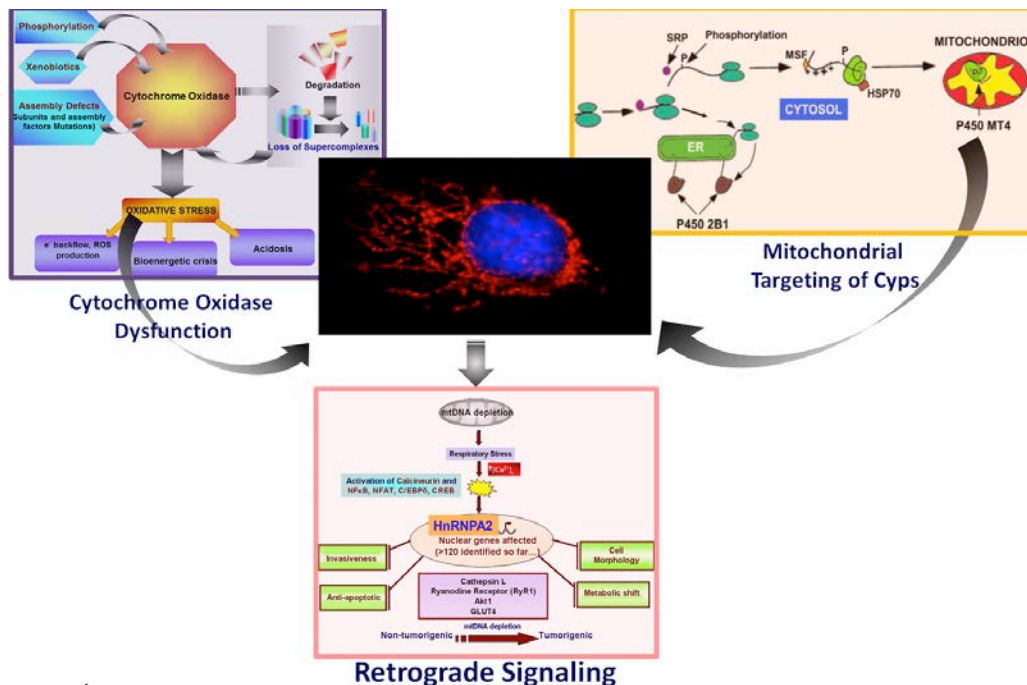
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A Modern Eye Trunk Show to benefit canine cancer research at The University of Pennsylvania School of Veterinary Medicine will feature the complete lines of Claire Goldsmith Eye Wear and Classic 1940's to 1970's Sunglasses of Oliver Goldsmith on **Thursday, November 14th, 2013** from 2-7 pm, 3419 Walnut Street, Philadelphia, 215 386 5953.




DIETER SCHIFFERLI VISITS UNIVERSITIES IN CHINA

Dieter Schifferli, Dr. Med. Vet, Ph.D., an associate professor in the Department of Pathobiology, recently toured China, where he participated in the Cold Spring Harbor Asia Conference on "Yersinia" in Suzhou, and presented talks at four academic institutions: Zhejiang University, College of Animal Sciences, Hangzhou; Huazhong Agricultural University, College of Veterinary Medicine, Wuhan; Yangzhou University, College of Veterinary Medicine; Jiangsu Academy of Agricultural Sciences, Institute of Veterinary Medicine, Nanjing.



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PKA inhibitors and mitochondria targeted antioxidants (Mito-Q and Mito-CP) selectively block the activation of this PKA and markedly reduce IR damage to the myocardium. Currently collaborative efforts with Dr. B. Kalyanaraman, Medical College of Wisconsin, Milwaukee are underway for the design and synthesis of mitochondria targeted PKA and LON inhibitors as possible therapeutic agents against ischemic heart damage.

The research in Dr. Avadhani’s laboratory is funded by grants from NIH Institutes, NIAAA, NIGMS and NCI. His laboratory is located at r89 E VET. 

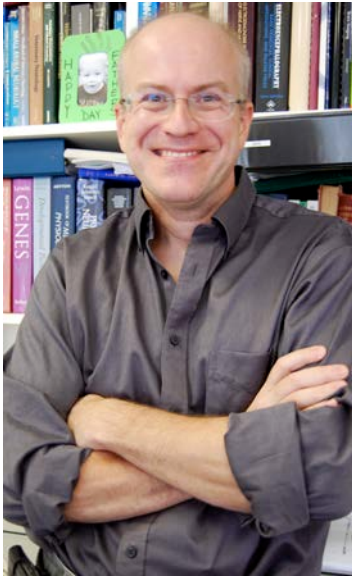
Selected Publications

1. Biswas, G. Adebajo, O., Freedman, B., Anandatheerthavarada, H. Vijayasathy, C., Zaidi, M. Kotlikoff, M. and Avadhani N. Retrograde Ca2+ signaling in C2C12 skeletal Myocytes in response to mitochondrial genetic and metabolic stress: A Novel mode of Inter-Organelle crosstalk. *EMBO J.* 18:522-533, (1999).
2. Biswas, G., Srinivasan, S., Anadhatheerthavarada, H. K., and Avadhani, NG., Dioxin-mediated tumor progression through activation of mitochondria-to-nucleus stress signaling. *Proc. Natl. Acad. Sci., USA*, 105: 186-191 (2008).
3. Boopathi E, Srinivasan S, Fang JK, Avadhani NG., Bimodal protein targeting through activation of cryptic mitochondrial targeting signals by an inducible cytosolic endoprotease, *Mol Cell.* 32:32-42 (2008).
4. Prabu, K. *et al.*, Protein Kinase A mediated phosphorylation modulates cytochrome c oxidase function and augments hypoxia and myocardial ischemia related injury. *J. Biol. Chem.* 281:2061-2070, (2006).
5. Iqbal, J., Li, S., Cao, J., Yuen, T., Lu, P., Bab, I., Leu, N., Srinivasan, S., Wagage, S., Hunter, C., Nebert, DW., Zaidi, M., and Avadhani, N., Smoke carcinogens cause bone loss through the Aryl hydrocarbon receptor and induction of CYP1 enzymes. *Proc. Natl. Acad. Sci. USA.* 110:11115-20 (2013).
6. Guha M, Srinivasan S, Ruthel G, Kashina AK, Carstens RP, Mendoza A, Khanna C, Winkle TV and Avadhani NG. Mitochondrial retrograde signaling induces epithelial-mesenchymal transition and generates breast cancer stem cells. *Oncogene* 2013 (In Press).



SCIENCE CAFÉ ...Nicola Mason, an assistant professor, Departments of Clinical Studies Philadelphia and Pathobiology, will discuss “Hunting with the Hounds: How Dogs Lead the Way in the Search for Effective Cancer Therapies” at the Oct. 22 Science Café. Scholars illuminate thought-provoking issues in the “hard” and “soft” sciences in a series of free public forums—the Penn Science Café and its sister lecture series, the Penn Lightbulb Café at 6 pm (email: bryangm@upenn.edu (215) 898.8721) [World Cafe Live Upstairs](#), 3025 Walnut St., are free and open to the public.

Research in Niemann-Pick Type C Disease Acknowledged



In August, Charles Vite, D.V.M., Ph.D., associate professor in the Department of Clinical Studies Philadelphia, attended the “Ride for Adam” in Schnecksville, PA. He received a plaque for his research on Niemann-Pick Type C

disease (NP-C) from the **Race for Adam Foundation**, a volunteer non-profit organization dedicated to funding research projects to find a treatment and cure for NP-C and related neurodegenerative disorders. The foundation is named in honor of Adam Recke. The Recke family along with 1000 bikers raised money and awareness for the treatment of NP-C. Additionally, Dr. Vite received recent awards from the **Ara Paresghian Medical Research Foundation** and the **Support of Accelerated Research- SOAR**, funding his research on Niemann-Pick type C disease.

Roszell BR, Tao JQ, Yu KJ, Gao L, Huang S, Ning Y, Feinstein SI, **Vite CH**, Bates SR. Pulmonary abnormalities in animal models due to Niemann-Pick type C1 (NPC1) or C2 (NPC2) disease. *PLoS One*. 2013 Jul 2;8(7):e67084. PubMed PMID: 23843985

The **Penn Vet Research Newsletter** is distributed quarterly. Suggestions, requests, comments, and story ideas should be directed to:

resnews@vet.upenn.edu

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During the government shutdown, Penn’s Office of Research Services (ORS) asks that investigators continue to submit proposals to ORS in compliance with currently listed due dates. ORS will review proposals to make sure they are ready to go, but will then hold the system to system submission until Penn receives notice that agency electronic systems are fully operational.

TO: