

NEWSLETTER

From dogs and cats *to cows and chicken legs.....*



Bruce Freedman, an Associate Professor in the Department of Pathobiology, was born and raised in the farm country of Lancaster County. From a young age his ambition was to become a veterinarian. However, during the course of a senior honors biology research project at Dickinson College in Carlisle, PA, he started to explore a career in biomedical research and entered a Masters of Science program at The Pennsylvania State University under the guidance of Dr. Roland Leach. There he studied biochemical aspects of a cartilage abnormality called tibial dyschondroplasia in rapidly

growing broiler chickens. This research experience prompted Dr. Freedman to revise his career plans and he applied to the NIH funded Veterinary Medical Scientist Training (VMSTP) program at Penn Vet. A photograph comparing the bones of normal and dysplastic chickens (Fig. 1) became a crucial part of Dr. Freedman's pitch for acceptance when he entered the VMSTP program in 1982. He completed his veterinary training in 1987, and his Ph.D. in Physiology in 1992.

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“Neither rain nor snow, nor sleet or dark of night”.....

After a very snowy season, Penn Vet carries on. We look forward to our annual *Phi Zeta* Student Research Day on Thursday, March 25th. Students are busily planning their talks and poster presentations. This day is set aside to recognize and appreciate our student's academic achievements. Our keynote speaker, Dr. Michael Blackwell, will help us think about the evolving role of veterinary medicine today as we face the global issues of public health, infectious disease, sustainable agriculture, and our ecosystem.

“adapted from Herodotus”



From dogs and cats to cows and chicken legs.. continued from page 1

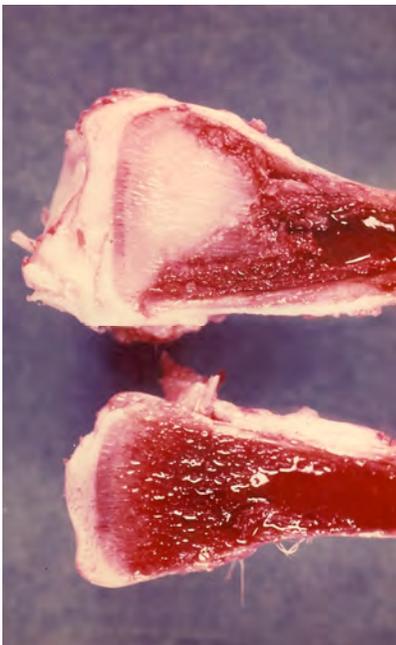


Figure 1. The normal chicken proximal tibiotarsus showing the epiphyseal growth plate and the articular cartilage (bottom). The epiphyseal plate appears as a thin layer of translucent cartilage with numerous capillary tunnels extending from the epiphyseal arteries. The metaphysis is characterized by numerous trabeculae separated by the metaphyseal vessels which ascend the shaft of the bone to the growth plate. A severe dyschondroplastic lesion in the proximal tibiotarsus (top). The lesion, an opaque cartilaginous mass, lies beneath the growth plate and displaces the spongy bone of the metaphysis. The trabeculae extending from the spongy bone appear normal in size but lack the parallel arrangement observed in the normal metaphysis.

From Veterinary Medicine to Pathogen Signaling in Immune Cells

- During the course of studies assessing calcium metabolism during bone growth, Dr. Freedman became interested in the role that this pathway played in regulating many cellular processes. Although he originally focused on calcium-mediated regulation of muscle function, he quickly became interested in the role of calcium and other ions in the regulation of immune cell function. Specifically his dissertation research focused on how these pathways controlled immunity to

pathogens. During postdoctoral training in the Medical School at Penn under the supervision of Dr. Glen Gaulton, Dr. Freedman obtained funding to study the role of potassium channels in the development of a population of lymphocytes, T cells, which provide long lived immunity to infection. He subsequently joined the laboratory of Dr. Michael Kotlikoff, former chair of Animal Biology, as a post-doctoral fellow. In that environment, Dr. Freedman’s work began to focus more closely on how calcium signaling regulated pathogen recognition and protective immune responses.

Dr. Freedman believes that his veterinary medical training provided him with a unique background in comparative medicine that informs his research and offers insights relevant to the treatment of disease. The general objective of his work is to understand how pathogen-induced signaling in lymphocytes and macrophages can be differentially regulated to elicit either a protective response or deleterious pro-inflammatory responses, depending on the specific context in which the pathogen is encountered. Most recently, he has focused on the role that intracellular calcium signaling plays in regulating functional responses to a variety of pathogenic stimuli. For example, he and his collaborator in the School of Medicine, Dr. Ron Collman, found that

different strains of HIV-1, the causative agent of AIDS, elicit distinct signals within their target cells (lymphocytes and macrophages) that influences their ability to infect target cell types. In addition, Dr. Freedman’s group has also found that proteins derived from a wide range of pathogens (including Ebola virus and a variety of pathogenic bacteria) elicit distinct signals within immune cells, affecting subsequent immune cell function.

Dr. Freedman just received a five year NIH grant entitled “Diverse mechanisms of calcium signaling in B lymphocytes” to examine the mechanisms of pathogen-induced calcium signaling in B cells. The goal of these efforts is to visualize proteins directly involved in translating external stimuli into dynamic and functionally specific calcium signals. A cornerstone of this approach has been the application of molecular approaches to modify the expression and function of proteins involved in regulating calcium entry in B cells, in order to precisely define their role in signal transduction. In addition, Dr. Freedman uses techniques such as fluorescence resonance energy transfer (FRET) microscopy, that allow visualization and quantitative measurements of the physical interactions between relevant signaling molecules and patch clamp recording to assay the activity of single calcium channels in immune cells.

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VICE PROVOST’S SPECIAL SEMINAR

On Monday, March 22, 2010 Penn Vet’s Neuroscience Center will co-host the Vice Provost’s Special Seminar in neuroscience in concert with the School of Medicine Neuroscience Center, the Department of Genetics, Intellectual and Developmental Disabilities Research Center (IDDRC), and the Mahoney Institute of Neuroscience featuring a presentation by **Eric J. Nestler, M.D., Ph.D.**, Mount Sinai School of Medicine, director of the Mount Sinai Brain Institute and chair of the Department of Neuroscience. The title of his talk will be “Transcriptional and Epigenetic Mechanisms of Addiction”. The Special Seminar will be held in the BRB II/III auditorium at 4 pm with a reception to follow in the lobby. Contact Dr. Tracy Bale for more information (tbale@vet.upenn.edu). 🐭



Animal Research Information Electronic Submissions (ARIES) System

The **PennERA** team (Electronic Research Administration) is providing optional orientation sessions available to researchers who create, review, or approve animal research protocols. These sessions will provide an overview of the ARIES application, including navigation and other features.

ARIES is the new secure, web-based lab animal protocol submission application that will provide the ability to electronically submit, track, and manage Institutional Animal Care and Use Committee (IACUC) protocol submissions.

To register for a session, go to Knowledge Link at <http://knowledgelinek.upenn.edu/>,

authenticate with your PennKey and PennKey password, then click “Training - Optional” in the left toolbar. When the training list loads, scroll down to the course titled “ARIES - Animal Research Information Electronic Submissions Orientation Sessions – UNIV” and click “Enroll”. If you have any trouble accessing the course, contact aries_help@lists.upenn.edu.

Germ Free Facility--Dr. David Artis Ph.D., Assistant Professor, Department of Pathobiology, has played a critical role in maintaining a germ-free mouse colony at Penn. Because of the challenges in managing such colonies, there are very few universities that have germ-free facilities. Many years ago, Dr. John Cebra, developed a colony at Penn in the Department of Biology, and

since Dr. Cebra’s death David has monitored the facility, and orchestrated the move of the colony from Biology to the Hill vivarium. This germ-free mouse colony is a unique resource for all of the scientists at the University of Pennsylvania.



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When combined with the ability to analyze signal transduction events within individual cells (using imaging techniques available in Dr. Freedman's lab and the Core Imaging Facility in the Veterinary School), these cutting edge approaches will revolutionize the analysis of calcium signaling in cells of the immune system.

Finally, Dr. Freedman has combined high-resolution subcellular imaging with novel technical approaches to dissect the events that influence the duration of calcium signaling, a parameter known to influence gene expression patterns that dictate how immune cells respond to pathogen stimulation. Understanding these events would allow for the development of therapeutic approaches to either modulate aberrant inflammation during autoimmunity or to amplify immune responses to invading microorganisms.

Present and Future - The Veterinary School recently established a high end Core Imaging Facility. Dr. Freedman's long term interest in employing advanced imaging techniques to visualize intracellular signaling responses to pathogens in single cells made him a natural choice to serve as

director of this facility. Dr. Freedman's interest in single cell imaging first took seed in the Kotlikoff lab and was developed further during the summer of 1997, with funding from the Deutscher Akademischer Austausch Diens (DAAD, German Academic Exchange Service) to work in the lab of Dr. Bernd Fleischmann at the University of Cologne, Germany. Dr. Fleischmann's group used high end single cell imaging and patch clamp recording techniques to study intracellular signaling in cardiomyocytes and Dr. Freedman adapted these techniques to his study of lymphocytes. This past year Dr. Freedman took a six month sabbatical at the Mayo Clinic in Rochester, MN. The goal of this sabbatical was to broaden the range of techniques in the lab

and to expand a very productive collaboration initiated several years ago with Dan Billadeau. The focus of this combined effort is to understand signaling pathways that regulate lymphocyte motility critical for trafficking to sites of inflammation where they become activated by pathogens.

Although Dr. Freedman has a great affection for four legged companions, including his two cats and a Chihuahua, he credits a love of science and an affinity for abstract problem solving as his primary motivation for pursuing a career in biomedical research and veterinary medicine. Dr. Freedman's laboratory is located on the 3rd floor of Old Vet Building, Suite 389E and his office is in Suite 368E. ☞

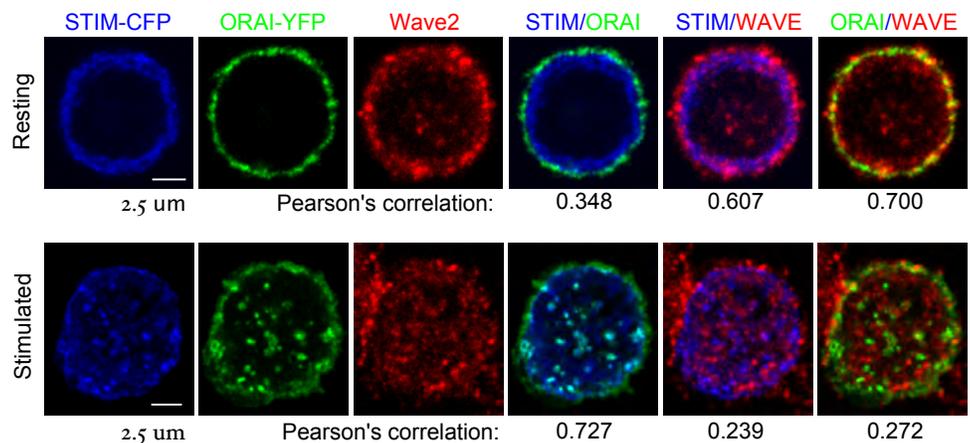


Figure 2. Primary B cells transfected with fluorescently-tagged molecules directly involved in calcium signaling (STIM1-CFP, Orail-YFP), stimulated with thapsigargin to initiate their mobilization and interactions, then stained for the actin cytoskeletal regulator WAVE2 to determine if induced localization was required for their function. Protein localization was visualized in fixed specimens by confocal microscopy and colocalization analyzed using Volocity software. Co-localization was assessed using Pearson's correlation (higher correlation, greater degree of co-localization).

PHI ZETA STUDENT RESEARCH DAY 2010

Thursday, March 25, 2010

The annual *Phi Zeta* Student Research Day will be held on Thursday, March 25, 2010. Participants may register online at:

<http://www.vet.upenn.edu/>

Keynote speaker, Dr. Michael Blackwell, is a former dean of the College of Veterinary Medicine, University of Tennessee. From 1999 to 2000, he served as the Chief of Staff, Office of the Surgeon General. Prior to this Dr. Blackwell served for 20 years as an official of the Food and Drug Administration (FDA). During his interim with the FDA, he covered major mission areas in both human and veterinary medicine. Dr. Blackwell also had more than 15 years of experience as a veterinarian in private practice. This diverse background prepared him to assist with providing solutions to many of today's public health challenges. From 1994 to 1998 he served as the chief veterinarian of the United States Public Health Service (USPHS). In this role he was chief advisor to the Surgeon General of the United States.

Academic awards will be given for oral presentations by students and Fisher Scientific 'best poster' prizes will be awarded.

Organizers

Those participating in organizing the day are Kathryn Michel, Michael Atchison, Margret Casal, John Lewis, Lisa Murphy, Nicola Mason, Phillip Scott, Dean Joan Hendricks, Ashra Markowitz, and Gayle Joseph. Student organizers are Jose Guevara, Ellison Aldrich, Brittany Gregory, Jeffrey Patterson-Fortin, Audra Pompeani Daniel Lantz, Anna Nomura, Haley Anderson, and Alexandra Cantelmo.



Calendar

Monday, March 22, 2010

Vice Provost's Special Seminar
Eric Nestler, MD, PhD
BRB II/III Auditorium 4 PM

Thursday, March 25, 2010

Phi Zeta-Student Research Day
Hill Lobby 12 noon--6 PM

Friday, June 18, 2010

Annual Faculty Research Retreat at New Bolton Center, Kennett Square.
8:30 AM--5:30 PM

Some Recent Awards

Michael Atchison
RO1 AI079002
Title: Control of B cell development by YY1.
7/1/2010-6/30/2015
\$1,250,000

Michael Atchison
RO1 GM082841
Title: Developmental control of enhancer function.
4/1/2010 -3/31/2014
\$1,250,000

James Ferguson
Increasing Economic and Environmental Sustainability of Small and Medium Sized Dairy Farms
USDA/NIFA
1/1/2010 - 12/31/2013
\$396,120

Robert Whitlock,
PA John's Disease Demonstration Herd Penn State University (USDA)
4/19/2009-3/31/2010
\$15,000

András Komáromy
Achromatopsia - Disease mechanisms and cone-directed gene therapy
ARRA Supplement to NIH grant EY-019304
\$84,236

John Wolfe
AAV vector gene transfer to manipulate the pontine micturition circuit. ARRA pilot grant for NIH 3P50DK052620-12S1 (Sam Chacko Prog. Dir)
9/30/09 - 8/31/11 \$119,796

Kendra Bence
Neuronal protein tyrosine phosphatases in metabolism. NIH/NIDDK ARRA supplement to RO1 DK 082417.
12/14/2009-2/28/2010
\$99,928

David Artis
NIH R21 Epithelial cell regulation of intestinal immune homeostasis, 07/15/09-06/30/11,
\$275,000.

AGRICULTURAL SCIENCE

In the summer of 2009, 12 Penn Vet students accompanied six faculty and staff members of the Center for Animal Health and Productivity (CAHP) on a trip to China to visit food animal production facilities as part of their veterinary training. The trip was supported by the Hewlett Award for Innovation in International Offerings at Penn that was awarded to **Dr. Zhengxia Dou**, Associate Professor in the Department of Clinical Studies, New Bolton Center. A USDA grant also provided support for the program.

The two-week trip gave students a unique and eye-opening experience as they toured farms and learned food production basics. They visited research laboratories, attended seminars, and interacted with university faculty, students, as well as local residents. Guided by faculty from Penn and Chinese Universities, our students gained an appreciation of the Chinese systems of animal nutrition, management, and economics and their effects on farm productivity and the environment. They also learned that veterinary medicine involves more than just diagnosis and treatment of sick animals and that future veterinarians must have the necessary knowledge and preparation to play a larger role in the changing world of globalization of food production.

A new Hewlett Award has been granted to Dr. Dou, which will support yet another group of Penn Vet students to travel to China this summer. The new award will help to establish a long-term partnership in research and education with Chinese institutions. Such international, interdisciplinary collaborations will promote a new educational paradigm for Penn Vet's involvement in global issues of sustainable food animal production, environmental protection, and veterinary public health. ♪



Some recent papers



NEMO-binding domains of both IKKalpha and IKKbeta regulate IkappaB kinase complex assembly and classical NF-kappaB activation. Solt LA, Madge LA, **May MJ**.

J Biol Chem. 2009 Oct 2;284(40):27596-608



Insights into Serotonin Signaling Mechanisms Associated with Canine Degenerative Mitral Valve Disease. **Oyama MA**, Levy RJ.

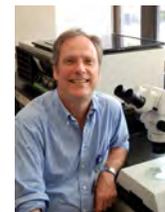
J Vet Intern Med. 2010;24:27-36.

Gene therapy in large animal models of human cardiovascular genetic disease.



Sleeper MM, Bish LT, Sweeney HL. *Inst. Lab Animal Res J.* 50(2): 199-205. 2009

Identification of the nuclear receptor DAF-12 as a therapeutic target in parasitic nematodes. Wang Z, Zhou XE, Motola DL, Gao X, Suino-Powell K, Conneely A, Ogata C, Sharma KK, Auchus RJ, **Lok JB**, Hawdon JM, Kliewer SA, Xu HE, Mangelsdorf DJ. *Proc Natl Acad Sci U S A.* 2009 Jun 9;106(23): 9138-43.



Special Seminar

Thursday, April 29, 2010 - 3 PM
Department of Physiology presents:

Dr. Toni Scarpa, director of the Center for Scientific Review (NIH) DHHS

“Challenges & Opportunities in Peer Review: A Vision for Ensuring its Strategic National Value”

Dunlop Auditorium, Stemmler Hall

RSVP by April 22 to phys@ail.med.upenn.edu

ONE MEDICINE

Penn Vet professor **Gustavo Aguirre** (Clinical Studies PHL) recently spent two weeks traveling to cities throughout Spain presenting lectures to vision-impaired patients. He updated them on the various research treatment avenues currently being explored and indicated how such treatments might ultimately be translated into therapeutic approaches for their hereditary eye diseases. Concerned patients in Pamplona and Madrid were informed of progress in the field of retinal degeneration by Dr. Elena Vecino, a Professor of Cell Biology at the University of the Basque Country and Dr. Aguirre. Dr. Aguirre has been giving these updates annually for the last five years and has developed a considerable rapport with these groups. Dr. Aguirre’s sensitivity to the needs of visually impaired patients is exemplified by his attention to detail. In particular, persons with low vision can differentiate Power Point presentations best on a blue background, so Dr. Aguirre always presents slides with yellow print on a blue backdrop. This obvious concern, coupled with his clear

explanations of ongoing research in Spanish, has endeared Dr. Aguirre to these organizations, and they eagerly await his visits. In addition, Dr. Aguirre presented a research seminar on developing therapies for retinal degenerations at the Center for Biological Investigations (CIB) in Madrid, as well as a second University-wide research seminar on retinal gene therapy at the Bioforo, University of the Basque Country. Dr. Aguirre sustains the long history and importance of translational research at Penn Vet.



David Artis, PhD, Assistant Professor in the Department of Pathobiology, has authored a newly published paper in *Nature* that defines a previously unidentified stem cell-like population that promotes immune responses in the intestine. The findings of the paper have broad implications, as Th2 cells are not only critical for controlling helminth infections, but also promote unwanted immune responses associated with asthma and allergies.

IL25 elicits a multipotent progenitor cell population that promotes TH2 cytokine responses. SA Saenz, MC Siracusa, JG Perrigoue, SP Spencer, JF Urban Jr, JE Tocker, AL Budelsky, MA Kleinschek, T Kambayashi, A Bhandoola, & D. Artis. (2010) *NATURE*, *in press*, Advance Online Publication on www.nature.com/nature

The Steven W. Atwood Library & Information Commons

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- Set-up searches that automatically run on your topic each week?
- Find that elusive full-text article?

To discuss library resources or service topic, just send an email to:

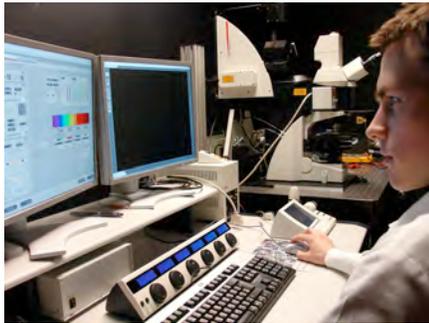
campbell@pobox.upenn.edu

Margaret Grasberger

Lindem will begin work on Monday, March 8, as the new head of the veterinary libraries.

<http://www.library.upenn.edu/vet/>

Penn Vet Imaging Facility...online scheduling



Penn Vet's **Imaging Facility** is located on the third floor of the Hill Pavilion. The core houses a four laser, two-photon/cofocal laser scanning spectral imaging Leica SP5 system on a DM6000 microscope and a two laser Yokagawa CSX-1 spinning disk confocal configured with a Leica DMI4000 microscope. These

instruments will provide capability for fixed specimen, *in vivo* and live cell optical micro-imaging. To inquire about this core facility, please contact Dr. LingLi Zhang at 215 746-0471 or the Department of Pathobiology at 215 746-2046. An online scheduler for the Nikon-E600 wide field fluorescence microscope has been posted. In the electronic version of this newsletter you may follow this link: [Scheduler](#) for the Nikon and for the confocal use this link: [confocal scheduler](#).



The Penn Vet Research Newsletter is distributed quarterly: suggestions, requests, comments, and story ideas should be sent directly to:

resnews@vet.upenn.edu

Office of the Associate Dean for Research

Phillip Scott, Ph.D.

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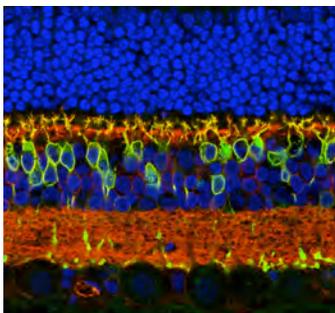
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TO:



Bipolar cell labeling in a canine retina
William Beltran Laboratory