NEWSLETTER

Respiratory failure is a leading cause of chronic morbidity and mortality...*after spinal cord injury*

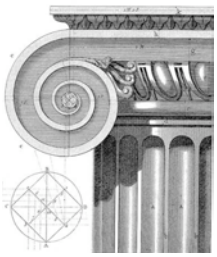
Dr. Frank J. Golder is an Assistant Professor of Anesthesiology (tenure-track) in the Department of Clinical Studies – Philadelphia. In 1992, Dr. Golder received a Bachelor of Veterinary Science (B.V.Sc., New Zealand's VMD equivalent) at Massey University, New Zealand. After an internship the following year, he moved to the US to pursue specialist training in Veterinary Anesthesiology at UC Davis, CA. Dr. Golder completed his residency in 1997 and was certified by the American College of Veterinary Anesthesiologists.

continued on page 2

Summertime.....

We have just concluded our 2010 annual faculty research retreat on the beautiful grounds of New Bolton Center at Kennett Square. The weather was ideal and the large turnout of faculty, postdocs and graduate students made for a good time. Faculty co-chairs Bruce Freedman and Mark Oyama along with their committee designed a unique program of paired clinician-basic scientist presentations exemplifying the current trends in translational research at Penn Vet. Our Marshak Lecturer, Dr. Chand Khanna from the National Cancer Institute of NIH gave an inspiring talk. To top the day off, Dr. Mark Oyama was awarded the Pfizer Award for Research Excellence.

A new system to manage your references--you can no longer use eRA commons after July



NIH is now providing **Commons users** with a more efficient, accurate and user-friendly way to manage their professional bibliographies, associate publications with their grant awards, and ensure compliance with the NIH Public Access Policy. If not already established, principal investigators must establish a "My NCBI account" to gain access to "My Bibliography". The account must be linked to eRA Commons accounts. And, as of October 22, Commons will no longer display citations previously entered by the PI. To read about this in detail go to: My NCBI Tool to Replace eRA Commons for Bibliography management (NOT-OD-103): http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-103.html

continued from page 1.....Dr. Frank Golder

He then enrolled in a Ph.D. program at the University of Florida, Gainesville, FL, where he investigated the effects of spinal cord injury (SCI) on the neural control of breathing in rats. Upon completion of his Ph.D., Dr. Golder was a post-doctoral fellow in the laboratory of Dr. Gordon S. Mitchell, Ph.D., at the University of Wisconsin, Madison, where he investigated experimental approaches to improve breathing after spinal cord injury in rats. In 2006, Dr. Golder joined the faculty at Penn, where he contributes to the Anesthesia service at VHUP and pursues his research interest in spontaneous and evoked mechanisms of respiratory motor plasticity after cervical spinal cord injury.

SCI and respiratory failure

At least half of all human SCI patients have concurrent respiratory dysfunction (e.g., an inability to cough, sigh, or generate large inspiratory volumes), and respiratory failure is a leading cause of chronic morbidity and mortality after SCI. Most SCIs are anatomically incomplete and there is a capacity for functional plasticity of residual neural tissue, which contributes to spontaneous motor recovery below an injury. However, mechanisms of spontaneous recovery are typically incomplete. Therefore, identifying and developing therapeutic agents to improve recovery (i.e., breathing) after SCI has the potential to improve survival and quality of life. Dr. Golder's primary research goal is to identify candidate molecules that can elicit plasticity of spared spinal pathways, strengthen respiratory motor recovery, and improve breathing in spinally injured people and, by extension, veterinary patients.

Effects of experimentally-induced cervical SCI on breathing

Dr. Golder began investigating the effects of cervical SCI on breathing during his Ph.D. studies. He initially described the effects of an incomplete high cervical SCI on respiratory motoneuron activity and breathing in adult rats. He demonstrated that rats utilize a higher respiratory frequency and lower tidal volume (the volume of air inhaled and exhaled at each breath during rest) to maintain normal ventilation[1]. He also demonstrated that one-sided SCI alters respiratory motor output to **both** sides of the spinal cord and to brainstem respiratory motoneuron pools **above** the lesion[2], revealing novel and unexpected mechanisms controlling respiratory motor output after SCI.

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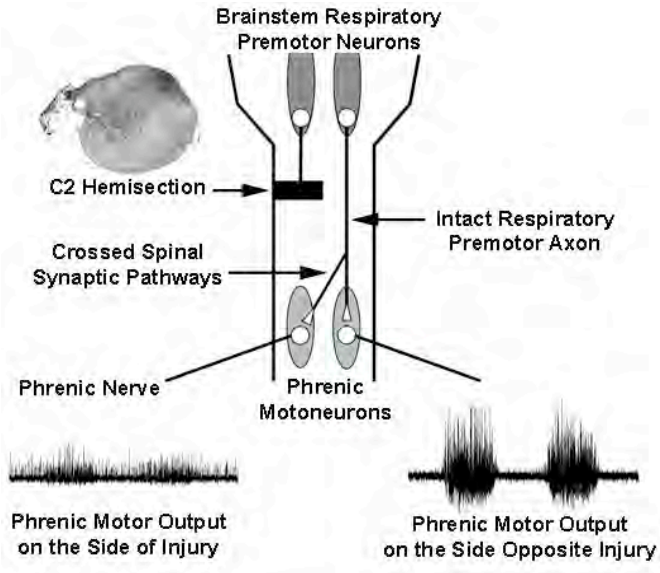

Figure 1. Schematic representation of the caudal brainstem and cervical spinal cord demonstrating the effects of C2 spinal hemisection on phrenic motoneuron activity at 8 weeks post-injury. C2 spinal hemisection initially paralyzes the hemidiaphragm on the side of injury. Over time, modest spontaneous motor recovery develops *via* strengthening of residual cross spinal synaptic pathways that convey premotor drive across the spinal midline caudal to the injury. Phrenic bursts are analogous to inspiration in an awake animal. Pauses between bursts are analogous to expiration. Phrenic burst amplitude correlates to tidal volume in awake animals. This injury creates a rapid shallow breathing pattern due to the loss of motor output on the side of injury. Identifying therapeutic agents to strengthen this spontaneous recovery could improve breathing after spinal cord injury.

Dr. Frank Golder's research continued from page 2

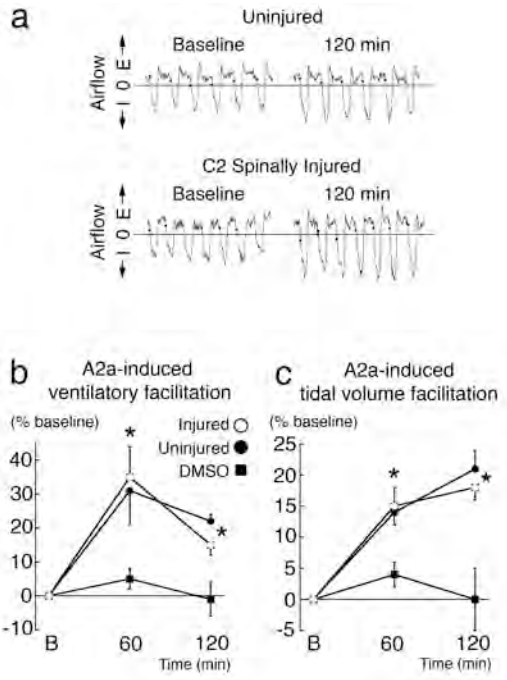

Figure 2. An A2a receptor agonist increases tidal volume in uninjured and spinally injured unanesthetized rats. (a) Representative airflow traces (I = inspiration, E = expiration) measured in a whole-body plethysmograph from an uninjured (upper trace) and C2 spinally hemisected rat (lower trace) at 8 weeks post-injury, during baseline breathing and 120 min after intraperitoneal administration of the A2a receptor agonist. (b & c) Average data for percentage change from baseline values in pulmonary ventilation (frequency x tidal volume) and tidal volume after A2a receptor agonist delivery (uninjured: closed circles; injured: open circles) or vehicle (DMSO; square). The A2a receptor agonist elicited long-term facilitation of ventilation that was primarily a result of increased tidal volume. * significantly different from groups ($p<0.05$); data are mean ± SEM.

A video from the US National Institutes of Health **(NIH)** in Washington DC offers biomedical researchers a view of the peer-review process in grant applications. The NIH's Center for Scientific Review (CSR) released **'The NIH Peer Review Revealed'** (see http://go.nature.com/UJfkfi)

In addition, a small amount of spontaneous respiratory motor recovery develops over time (~ 8 weeks) **below** the level of injury following cervical SCI in rats. This recovery develops *via* strengthening of spared spinal pathways that cross the spinal midline below the injury, activating phrenic motoneurons, which innervate the diaphragm. Although this modest motor recovery was not enough to improve tidal volume, it was necessary to accommodate large inspiratory volumes (such as exertional breathing and sighs)[3]. Collectively, these early experiments characterized the effects of experimentally-induced cervical SCI on breathing and identified a functional role for spontaneous, albeit weak, respiratory motor recovery.

Therapeutic strategies to improve breathing after SCI

During his post-doctoral fellowship, Dr. Golder hypothesized that the partial respiratory motor recovery observed after cervical SCI in rats could be strengthened using a known stimulus for spinal synaptic plasticity, namely exposure to intermittent hypoxia[4]. He found that short bouts of intermittent hypoxia augmented synaptic pathways to phrenic motoneurons below the injury, thereby improving tidal volume. Intermittent hypoxia elicits phrenic motor facilitation (and presumably tidal volume facilitation) by increasing spinal synthesis of the neurotrophin BDNF, resulting in activation of its receptor, TrkB[5]. Although intermittent hypoxia is limited as a therapeutic tool by its adverse effects, these studies identified TrkB agonists as candidate molecules to improve breathing after SCI. Thus, the Golder lab is currently investigating the use of small and highly diffusible BDNF mimetics.

Adenosine 2a receptor agonists as novel therapeutics for ventilatory control disorders

Adenosine 2a (A2a) receptor agonists can mimic BDNF by *transactivating* TrkB receptors. Dr. Golder hypothesized that these agonists would therapeutically elicit phrenic motor facilitation and improve breathing. In a series of experiments[6], he demonstrated that spinal delivery of A2a receptor agonists transactivated TrkB receptors near phrenic motoneurons, which in turn elicited long-lasting (hours) phrenic motor facilitation. A2a receptor activation also increased tidal volume for up to 48 hours after SCI. These novel findings demonstrated that small, highly permeable drugs

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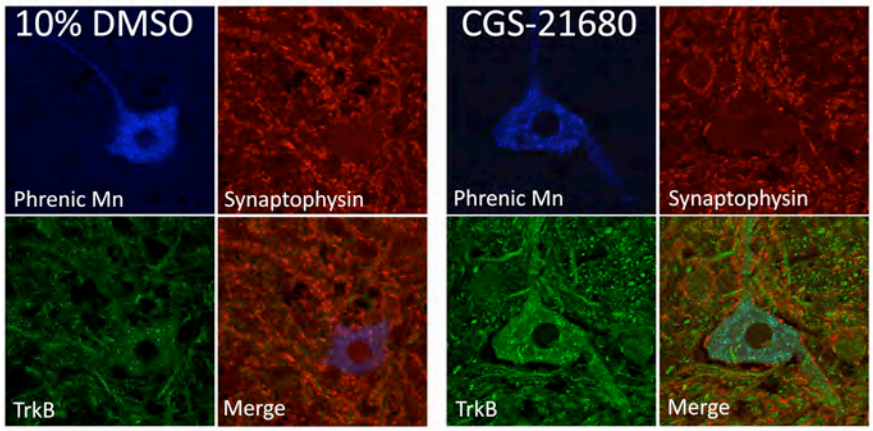

Figure 3. Intrathecal administration of the A2a receptor agonist, CGS-21680, increased TrkB expression within phrenic motoneurons in an injured rat at 1 month post-injury. Left: Confocal microscopic images of a phrenic motoneuron (Phrenic Mn; blue) with TrkB protein (green) and synaptophysin (red) immunoreactivity harvested from a rat that received vehicle control. Right: Similar image from a rat that received intrathecal CGS-21680.

may provide an effective therapeutic strategy in the treatment of human and veterinary patients with ventilatory control disorders, such as obstructive sleep apnea, or respiratory insufficiency after spinal injury. Dr. Golder's most recent studies have aimed at identifying the cellular mechanisms responsible for A2a-induced respiratory motor recovery[7], and, in collaboration with Dr. Houlé at Drexel University, evaluating the efficacy of A2a receptor agonists at improving function in other non-respiratory systems affected by SCI (i.e., nociception and locomotion). Through the use of a wide variety of *in vivo* and *ex-vivo* techniques, Dr. Golder's laboratory is able to fully evaluate the effects of spinal injury models and novel therapeutic strategies on breathing.

Furthermore, his training as a basic scientist and a veterinarian permits a unique systems-wide approach to interpreting data and understanding the translational implications (efficacy and safety) to the whole animal.

Dr. Golder's research is funded by the Craig H Neilsen Foundation and the National Institute for Neurological Disorders and Stroke/NIH, NS060929. His laboratory is located in the newly renovated 3rd floor section of Rosenthal Building and his office is in Room 390EB.

Selected publications

1. Golder, F.J., Reier, P.J., Davenport, P.W. & Bolser, D.C. Cervical spinal cord injury alters the pattern of breathing in anesthetized rats. *J Appl Physiol* 91, 2451-2458 (2001).

2. Golder, F.J., Reier, P.J. & Bolser, D.C. Altered respiratory motor drive after spinal cord injury: supraspinal and bilateral effects of a unilateral lesion. *J Neurosci* 21, 8680-8689 (2001).

3. Golder, F.J., et al. Respiratory motor recovery after unilateral spinal cord injury: eliminating crossed phrenic activity decreases tidal volume and increases contralateral respiratory motor output. *J Neurosci* 23, 2494-2501 (2003).

4. Golder, F.J. & Mitchell, G.S. Spinal synaptic enhancement with acute intermittent hypoxia improves respiratory function after chronic cervical spinal cord injury. *J Neurosci* 25, 2925-2932 (2005).

5. Baker-Herman, T.L., et al. BDNF is necessary and sufficient for spinal respiratory plasticity following intermittent hypoxia. *Nat Neurosci* 7, 48-55 (2004).

6. Golder, F.J., et al. Spinal adenosine A2a receptor activation elicits long-lasting phrenic motor facilitation. J *Neurosci* 28, 2033-2042 (2008).

7. Golder, F.J. Spinal NMDA receptor activation is necessary for de novo, but not the maintenance of, A2a receptor-mediated phrenic motor facilitation. *J Appl Physiol* 107, 217-223 (2009).

Responsible Conduct of Research RCR

There are new standards for RCR training as of January 24th 2010. RCR training is required for undergraduates, graduate students, and postdoctoral fellows funded by the National Science Foundation (NSF) and for graduate students and postdoctoral fellows and faculty funded by NIH training grants and career awards. For details: http://www.upenn.edu/research/rcr/

RENOVATED LAB SPACE

Penn Vet Faculty move into new space

A long-standing plan to build Penn Vet's regenerative medicine program has come to fruition with the completion of renovations on the third floor of Rosenthal Building and Old Vet Quad (OVQ). The 8,350 square foot space includes: five tissue culture rooms; five procedure rooms; two equipment areas; 45 work stations for students and technicians; and one cold room. In addition, a conference room and faculty offices are located in OVQ. 295 linear feet of laboratory bench space has provided greatly improved work space for two Penn Vet faculty members, **Drs. Frank Golder (Department of Clinical Studies PHL) and Ralph Meyer (Department of Animal Biology)**.

Drs. Golder and Meyer are the first to move into the new laboratories. Penn Vet's faculty expertise in germ and stem cell biology is supported and facilitated by the new space. The new space will accommodate six principal investigators in total. In the emerging initiative of regenerative medicine, the School foresees recruitment of two new faculty members with research interests in either 1) neural stem cells, neurodegenerative disease, 2) the role of mesenchymal stem cells in treating osteoporosis, or 3) transdifferentiation of pluripotent stem cells in the treatment of diabetes.

Dr. Golder's long-term goal is to determine the cellular, neuro-chemical, and molecular basis of the functional plasticity of phrenic motoneurons that innervate the diaphragm. (see feature article on page 1). Dr. Meyer is interested in the environmental, genetic and epigenetic basis of non-obstructive male infertility. Current research in his lab is focused on functions of poly (ADP-ribose) (PAR) metabolism mediated by specific poly(ADP-ribose) polymerases (PARP enzymes) in DNA repair and chromatin remodeling events that take place in germ cell development. Using genetic mouse models of a disrupted PAR pathway, an exciting new mechanism of PAR, PARP and poly(ADP-ribose) glycohydrolase (PARG) dependent spermatid nuclear reorganization that is known to be essential for male gametogenesis was recently discovered in Dr. Meyer's lab.

Funding for renovations

The renovation costs were funded by the Pennsylvania Tobacco Settlement, FRES Facility Renewal Funds, and funds from the Vice Provost for Research.

Ralph Meyer in his new office

RECENT PAPERS

Kenney EM, Rozanski EA, Rush JE, deLaforcade-Buress AM, Berg J, **Silverstein DC,** Montealegre C, Jutkowitz LA, Adamantos S, Ovbey DH, Boysen SR, Shaw SP. Incidence and prognostic significance of multiple organ dysfunction in dogs with abdominal sepsis. *JAVMA* ,2010; 236(1):83-87.

Shaohua Chang, Cristiano Mendes Gomes, Joseph A. Hypolite, James Marx, Jaber Alanzi, Stephen A. Zderic, Bruce Malkowicz, Alan J. Wein, and **Samuel Chacko**. Detrusor overactivity is associated with downregulation of large-conductance calcium- and voltage-activated potassium channel protein. *Am J Physiol Renal Physiol*, 2010; 298: F1416 - F1423.

Mouse MOV10L1 associates with Piwi proteins and is an essential component of the piRNA pathway. Zheng K, Xiol J, Reuter M, Eckardt S, Leu NA, McLaughlin KJ, Stark A, Sachidanandam R, Pillai RS, and **Wang PJ**. *Proc Natl Acad Sci U S A*. In press. June 2010

THE 2010 SAUL WINEGRAD AWARD FOR OUTSTANDING DISSERTATION

Dr. Jacqueline Perrigoue is the 2010 recipient of the Saul Winegrad Award for an outstanding dissertation. Jackie, a recent graduate, was a PhD student in the laboratory of Dr. David Artis, Department of Pathobiology. While at Penn, as a member of the **Immunology Graduate Group**, Jackie was a highly respected and well-liked student. Her thesis was entitled "Initiation and regulation of type 2 immunity and inflammation at mucosal sites" for which she received the prestigious Winegrad Award upon graduation from the University of Pennsylvania. She is now a postdoctoral associate in Dr. David Wiest's lab in the Immune Cell Development and Host Defense Program at Fox Chase Cancer Center.

2010 PHI ZETA STUDENT RESEARCH DAY AT PENN VET

Phi Zeta Student Research Day is held annually to acknowledge scholarly achievement of VMD and VMD/PhD students at Penn Vet. The annual event showcases excellence in our student research and academic achievements at Penn Vet. The 2010 program, held on March 25, featured six oral presentations by students (basic and clinical research), selectively chosen by a faculty panel of judges. Outstanding presenters of abstracts received awards of excellence following their oral presentations. The keynote address was delivered by **Dr. Michael Blackwell**, former dean of the University of Tennessee College of Veterinary Medicine and former Chief Veterinarian of the United States Public Health Service (USPHS). As chief veterinarian, Dr. Blackwell was a chief advisor to the Surgeon General of the United States from 1994-1998. There was *standing room only* for his inspirational talk. The dual degree oral presenters, and awards, respectively, were **Gregory Rak** (1st Place), **M Noelle Knight** (2nd Place), and **Catrina King** (3rd Place); and the VMD oral presenters were **Sarah Ward** (1st Place), **Kristina Simone** (2nd Place) and **Breanna Caltagarone** (3rd Place). 'Best Posters Prizes' were awarded to **Abigail Shearin** (1st Place), **LaTasha Crawford** (2nd Place), and **Sarah Cannizzo** (3rd Place. The annual Phi Zeta Student Research Day provides an opportunity and a meeting place for students, residents, and faculty to connect and enhance collaborations and communication between the basic and clinical researchers and to hear about the exciting research taking place in the School of Veterinary Medicine.

MARK HASKINS a PLENARY SPEAKER at MPS MEETING IN AUSTRALIA

Dr. Mark Haskins, Department of Pathobiology, was a plenary speaker on June 24th at the 11th International Symposium on Mucopolysaccharide and Related Diseases entitled "Translating Research into Clinical Reality" in Adelaide, Australia. His talk "Looking Forward from Looking Back" was a complement to the program that focused on areas of newborn screening, prognostics, understanding pathology and therapeutic options.

RECENT AWARDS

Charles Vite
Safety, Performance, and Efficacy of a Seizure Advisory System in Dogs with Epilepsy. A pilot. Neurovista Corporation. 3/1/10-2/29/12 $209,179

Charles Vite
ERT in KRABBE Disease in Dogs
Shire FDN. Human Genetic Therapies
12/15/08-4/1/12 (additional funding awarded in May 2010) $262,378

Kathryn Rook
Evaluation of Cytokine Production in the Diseased and Normal Skin and Peripheral Blood of Canine Patients Diagnosed with Cutaneous Epitheliotopic T-Cell Lymphoma, Pilot grant: *Amer. Col. of Vet. Derm.*
6/1/10-5/31/11. $9,000

Paula Henthorn
Validation of a SNP Haplotype Associated with Mastiff Cystine Stone Formation for Use in Genetic Testing. AKC-Canine Health Foundation. 4/1/10-12/31/10 $12,952

Nicola Mason
Canine Hereditary Cancer Consortium: From Bark to Bedside. Translational Genomics Research Inst.9/30/09-8/31/10 $99,009

Bruce Freedman
NIH R01-AI 060921, Novel Mechanisms of Ca2+ Signaling in B Lymphocytes,
2/1/10-01/31/15 $1,250,000

David Artis
R21 - Functional biology of intestinal epithelial cells in food allergy. 4/1/10-3/31/12 NIH $389,125

David Artis
ARRA supplement to R01 Functional biology of IL-25 during helminth infection
4/19/10-3/31/11 NIH $124,851

Mark Siracusa
F32 - Dissecting innate immunity to helminth parasites $150,234 NIH

Sherrill Davison
Dept of Agriculture grant "Maintenance of membership laboratory requirements"$50,000

Ron Harty
R21 - Innate Immune Defenses Against Filoviruses NIH $275,000 6/1/10-5/31/12

Mark Haskins
R01 - Gene therapy for alpha-mannosidosis.
NIH $250,000 4/15/10-3/31/12.

Tracy Bale
R01 NIH - Early Pregnancy stress programming of offspring emotionality
7/1/10--6/30/15 $1,250,000

Tracy Bale: R01 NIH Early gestation as a sensitive period to stress in sex-dependent neurodev. 7/1/10--6/30/15 $1,250,000

Peter Dodson
NSF: Early history of horned & duck billed dinosaurs: discoveries in Gansu China $137,500
7/1/10-6/30/2014

Serge Fuchs
R01 NIH - Interferon responses in myeloid leukemia
7/1/10--6/30/15 $1,037,500

J-P Saint-Jeannet
R01 - NIH Control of Neural Crest Development in Xenopus
7/1/10--6/30/15 $1,250,000

PJ Wang
R03 - NIH Modeling human male infertility in mice
7/1/10 - 6/30/12 $100,000

Makoto Senoo
NIH - SDRC pilot
p63 in normal epidermal development & pathogenesis -- $35000 - 7/1/10-6/30/11

Bernard Shapiro
R01 - NIH - Hormonal imprinting predetermines developmental expression of cytochrome P450s. 7/1/10--6/30/15
$1,037,500

Frank Golder
The role of phrenic motoneuron gap junctions in respiratory recovery after SCI. Univ. Res. Foundation (UPENN) $45,660 2010

Dean Richardson
Grayson-Jockey Club
In vivo gene therapy for treatment of Laminitis.
4/1/2010-3/31/2012
$119,865

Ray Sweeney
Grayson-Jockey Club
Rapid PCR Diagnosis of Eq Botulism Types A, B and C
4/1/2010-3/31/2012
$33,665

Kurt Hankenson
IOA Bingham Trust Pilot grant
Notch Signaling in Bone Regeneration
$50,000 7/1/10--6/30/11

Brett A. Kaufman
Regulation of mitochondrial DNA stability and expression by transcription factor TFAM.
$44,000 Univ Res Foundation UPENN
8/1/10-7/31/11

Frank Luca
Tumor suppressor-dependent regulation of mRNA localization in yeast. $50,000
Univ Res Foundation UPENN
8/1/10--7/31/11

HONORS and AWARDS

Mark Oyama, Clinical Studies PHL, is the winner of the 2010 Pfizer Prize for Research Excellence shown with **Dean Joan Hendricks** and **Sharon Campbell** from Pfizer at the recent faculty retreat.

The **American Society for Cell Biology** has awarded the 2010 Early Career Life Scientist Award to **Anna Kashina**, Department of Animal Biology, School of Veterinary Medicine, University of Pennsylvania.

The **Morris Animal Foundation** Veterinary **Student Scholars (VSS) program** awarded stipends to **Mariam Kamal** and **Benjamin Golas** for their clinical or basic animal health and/or welfare research projects entitled: "Parasitic Threats to Sumatran Rhinos, Elephants and Tigers in Way Kambas National Park" (Kamal) and ""Analysis of Ascorbic Acid Supplementation Via Water for Black and Rufous Sengi (Rhynchocyon-petersi)"(Golas). The Veterinary Student Scholars (VSS) program gives veterinary students hands-on involvement in research early in their career so they will consider entering a field where they are so critically needed.

Annual Faculty Research Retreat...June 18, 2010

On June 18 the weather was ideal and the setting sublime. Faculty, postdocs, residents and graduate students gathered on the grounds of New Bolton Center campus for the **annual faculty research retreat**. Dean Hendricks opened the program of 'paired' faculty presentations by **Dean Richardson** and **John Gearhart**; **Nicola Mason** and **Michael May**; **András Komáromy** and Jackie Tanaka; **Lillian Aronson** and **Christopher Hunter**; and **Shelley Rankin** and **Dan Morris**. Chand Khanna (NIH/NIC) delivered the Marshak Lecture. Phillip Scott, Associate Dean for Research thanked the organizing co-chairs Bruce Freedman and Mark Oyama for their efforts and organization of a unique program.

The Penn Vet Research Newsletter

is distributed quarterly: suggestions, requests, comments, new publications and story ideas should be sent directly to:

resnews@vet.upenn.edu

Phillip Scott, PhD

Associate Dean *for* Research

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