

NEWSLETTER

Squamous cell carcinoma is the most common oral cancer in humans and cats.... and the feline disease shares similarities with its human counterpart.



Dr. John R. Lewis is an Assistant Professor of Dentistry and Oral Surgery, Department of Clinical Studies PHL and Associate Director of Mari Lowe Center for Comparative Oncology. After obtaining his BS in biology from Bucknell University in 1993 and his VMD from the

University of Pennsylvania in 1997, Dr. Lewis signed on with a progressive small animal practice in Clayton, North Carolina. It was here where he first felt the frustration of practitioners everywhere in dealing with feline oral squamous cell carcinoma (SCC). Although surgery

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WHAT'S NEWSWORTHY IN EYE RESEARCH

On October 16, 2009, **András M. Komáromy** Dr.Med.Vet., Ph.D., Assistant Professor of Ophthalmology, Department of Clinical Studies Philadelphia and member of the Eye Research Group, joined the Association for Research in Vision and Ophthalmology (ARVO) board members and volunteers in Washington, DC to meet with members of Congress and their staffs and present them with vital information regarding vision research and its profound effects on the millions of people who suffer from eye diseases. In an effort to educate legislators on the crucial need for continued funding of medical research, which has such significant results, ARVO members met with their respective representatives and made personal appeals for their support of such appropriations to make the case for translational vision research.

As 2009 closes we can reflect on the many achievements of our faculty: publications highlighting our advances in basic, clinical and translational medicine, stimulus funds from NIH (> \$4M), and an increase in overall grant funding from \$30M in 2008 to \$32M in 2009. However, the challenges we face in the coming year will be substantial. Faculty funded by NIH will deal with significant changes in the format of grant applications and a reduction in the number of resubmissions, and funding from all sources is likely to become more competitive. We can respond to these challenges by being proactive: writing grants earlier to obtain critical feedback from our colleagues prior to submission, highlighting our research strengths to expand our funding sources, and using the extensive resources in Penn's biomedical community to employ the most innovative techniques in our research. Please contact me or Gayle Joseph to let us know how we can be of assistance in meeting these upcoming funding challenges.

Phillip Scott

LESLIE KING--GRANTS EDITOR at Penn Vet.



Leslie King received her Ph.D. degree in Immunology and Microbiology from Duke University and carried out her post-doctoral studies with Dr. Jonathan Ashwell at the National Cancer Institute,

National Institutes of Health. She came to the University of Pennsylvania School of Medicine (SoM) for a second post-doctoral fellowship in 1996, working in the laboratory of Dr. John Monroe, Department of Pathology and Laboratory Medicine. While working with Dr. Monroe her research focused on the antigen receptor-induced signaling pathways involved in differential induction of tolerance in immature lymphocytes and activation in more mature lymphoid populations. There she honed her grant writing skills and discovered she actually enjoyed the process! In 2007, Leslie joined Penn Vet as the first Grants Editor for the School and has been successfully working with principal investigators ever since.

When she is not editing grants, Leslie enjoys spending time with her husband Mickey Marks (SoM faculty member), her beautiful tweenage daughter Jennifer, and their two rescue pups, McKenzie and Beethoven.

If you are interested in working with Dr. King on your next proposal, please contact Phil Scott via email at psscott@vet.upenn.edu. To discuss grant strategy, you may contact Dr. King directly at lking@vet.upenn.edu. It is required that you provide a rough draft of your proposal 4 weeks prior to the deadline. Please note that Dr. King will also assist faculty with non-NIH grants and the importance of early drafts of your proposal applies here as well. Leslie King's office is located at 216 Rosenthal Building.

NIH APPLICATION CHANGES FOR FY2011 FUNDING

Enhanced review criteria to be used by reviewers in their assessment of scientific and technical merit

Biographical Sketch changes--a new personal statement will be incorporated. Limit the list of selected peer-reviewed publications to no more than 15

One additional page will be allowed for Specific Aims. For resubmission and revision applications for most programs, the introduction will be limited to one page

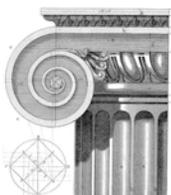


Shortened page limits on NIH grants are announced for due dates on or after **January 25, 2010**

Background and Significance, Preliminary Studies/Progress Report, and Research Design and Methods will be consolidated into a new single section called Research Strategy divided into 3 parts

Resources section will be changed to require a description of how the scientific environment will contribute to the probability of success of the project

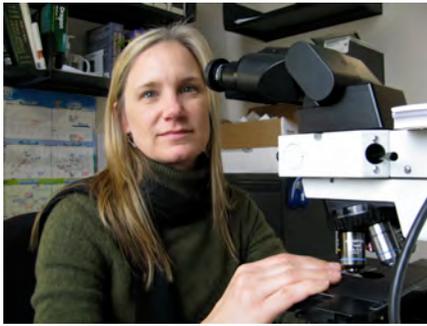
IF YOU HAVE A COLLABORATOR providing a biosketch for your application...they must also follow the guidelines!



For NIH detailed guidelines go to:

<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-016.html>

HISTOLOGY SERVICE AT PENN VET



Dr. Elizabeth Mauldin

Elizabeth Mauldin, DVM, is an Assistant Professor (CE) of Pathology & Dermatology in the Department of Pathobiology, University of Pennsylvania School of Veterinary Medicine. She obtained her Doctor of Veterinary Medicine degree from North Carolina State University in 1993. As head of Penn Vet’s **histopathology** laboratory, she directs the histology service at Penn Vet for both clinical and basic researchers. Dr. Mauldin is a veterinary dermatopathologist and works as both a pathologist, focused on skin biopsy interpretation, and a clinical dermatologist in the Matthew J. Ryan Hospital. The Penn Vet histology lab provides a range of services from tissue trimming, embedding and processing to histochemical staining which can be tailored to meet the needs of researchers. The lab has a busy **surgical biopsy service**, led by Dr. Michael Goldschmidt and supported by Drs. Amy Durham and Melissa Sanchez. The service is used by veterinary practices across the United States spanning Alaska to Puerto Rico.

Dr. Goldschmidt established the biopsy service 34 years ago and it now ranks as the largest and most respected academic surgical biopsy service in the United States. Case material from this service has been used to train 43 board certified anatomic pathologists and this activity has resulted in scientific publications advancing clinical veterinary medicine. The case material from the surgical biopsy service also supports studies in the Veterinary Clinical Investigations Center and Oncology Service.

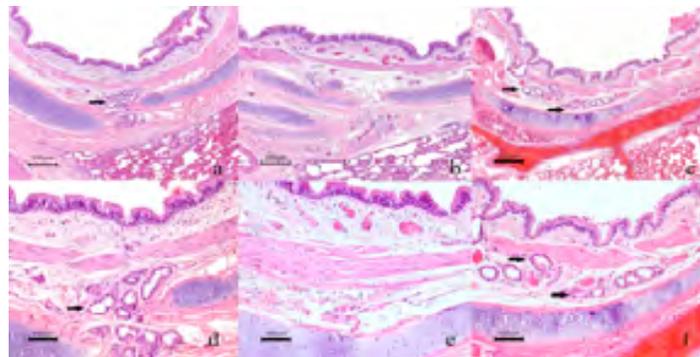
Dr. Mauldin’s research interests focus on the recognition, pathogenesis and treatment of skin disorders in companion animals. Dr. Mauldin, in collaboration with Dr. Margret Casal from the Medical Genetics section, is investigating the pathogenesis of several hereditary canine skin diseases to increase understanding of the disorders, with the goal of ultimately developing a screening test to identify carrier animals. These include

cutaneous exfoliative lupus erythematosus of the German short-haired pointer, Ehlers Danlos disease and nonepidermolytic ichthyosis (fish-scale disease) affecting the Golden retriever and American bulldog. Furthermore, extensive collaborative investigations are underway into the morphologic manifestations of canine X-linked hypohidrotic ectodermal dysplasia and response to interventional treatment as this disorder in dogs is identical to that seen in humans. A

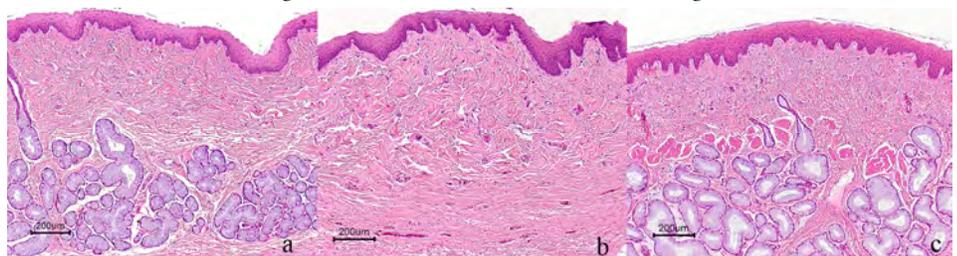


Dr. Michael Goldschmidt

recent publication on X-linked ectodermal dysplasia treatment in dogs was showcased by the *American Journal of Medical Genetics* (September issue) (Vol 149A (9): 2045-2049 (2009).



Bronchial glands in XLHED treated and untreated dogs.



Esophageal glands in XHLED treated and untreated dogs

Histology Service Request forms are found at INSIDE.VET under 'Research'
<http://inside-wlbs.vet.upenn.edu/>
 Histopathology Laboratory 215 898-7874

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can be curative in some cases, cats rarely show symptoms until the cancer has advanced to an inoperable size. In addition, oral SCC has historically been minimally responsive to radiation therapy and current chemotherapy options. Based on his interest in SCC, Dr. Lewis jumped at the chance to join a residency program at Penn Vet to further explore surgical and non-surgical options for improving the outcome for SCC patients.

Treatment of oral SSC in feline patients- room for improvement

SCC is the most common feline oral tumor, representing 70% of feline oral tumors.¹ As the median survival time from diagnosis to death or euthanasia is approximately 60 days², there is much room for improvement. While Dr. Lewis was eager to hone his surgical skills for treatment of feline SCC patients from established experts like Colin Harvey and Alexander Reiter at Penn Vet, he also saw an opportunity to improve treatment options for patients who were not surgical candidates. In conjunction with Dr. Tom O'Brien's group at Lankenau Institute for Medical Research, Dr. Lewis and colleagues in Penn Vet's Oncology Section and Dentistry and Oral Surgery Service embarked on a Phase I/II clinical trial of polyamine inhibitor therapy for cats with spontaneously occurring oral SSC. Dr. O'Brien, renowned for his work on the role of polyamines in cancer cell growth and successful polyamine-based therapy in experimentally induced murine models of SCC³, was anxious to evaluate this therapy in a

spontaneous feline model, so the collaboration was initiated.

Polyamine inhibitors

Polyamines are ubiquitous amino acid derived compounds that have been widely implicated in the growth and development of many mammalian tissues. When cellular polyamine synthesis is inhibited, cell growth is stopped or severely retarded. Providing exogenous polyamines restores the growth of cells. Polyamine synthesis is increased in many types of cancers and expression levels of the rate limiting synthetic enzyme, ornithine decarboxylase (ODC), are often increased as well.⁴ As Dr. O'Brien's original studies indicated that the ODC inhibitor difluoromethylornithine (DFMO) was effective in treating experimentally induced murine SCC⁵, a Phase I/II study was carried out to determine whether cats tolerate DFMO. Results of this study will soon be submitted for publication, but the relatively minimal side effects seen with DFMO protocols suggest that further studies are justified for use in a clinical setting.

Although targeting polyamine synthesis with ODC inhibitors can be effective for cancer cell growth inhibition, most eukaryotic cells have a polyamine transport system in their cell membrane that facilitates internalization of extracellular polyamines. Thus, polyamine synthesis inhibitors will only fight half the battle in reducing intracellular polyamine levels. To overcome this limitation, Dr. Lewis' latest study focuses on treating cats affected by oral SCC with a combination therapy

utilizing DFMO and a polyamine transport inhibitor developed by MBF Therapeutics. The Veterinary Clinical Investigation Center (VCIC) has greatly facilitated all phases of this second combination study, and Dr. Lewis further credits the team effort put forth between Dr. Karin Sorenmo, Dr. Erika Krick, Dr. Nicola Mason, members of the Dentistry and Oral Surgery Service, Sections of Radiology and Pathology, and practitioners who have shown interest in referring cases. While this study is still ongoing, it is the hope that such combined therapy will halt cancer growth but not significantly diminish other important quality of life aspects.

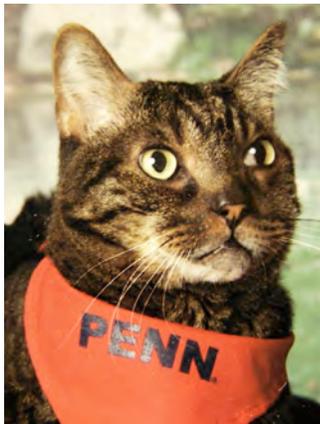
Pets- man's best friends provide hope for the future

Feline oral SCC is a frustrating disease for pet owners, and there is an overt willingness of pet owners to help find better treatment options. Clients from near and far have inquired about ongoing SCC studies for treatment of their cats. Indeed, one family from Chicago, the Dehertoghs, traveled to Penn for treatment of their cat, Tiger. Within a year, the Dehertoghs' other cat, Elsa, developed oral SCC and was also enrolled in the study. Most notably, Ms. Kathleen Jack created the Feline Oral SCC Research Fund to support Dr. Lewis' research when her cat, Bud, was diagnosed with the disease. While increased research on feline oral SCC will undoubtedly benefit feline patients, it is Dr. Lewis' hope that such research will also have important implications for human patients.

Dr. Lewis' belief that spontaneous companion animal cancer models

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are invaluable for identifying and evaluating therapeutics for species-specific use as well as for eventual use in human patients led him to co-found the Comparative Oncology Working Group to further potential collaborations between veterinarians at Penn Vet and clinicians at the School of Medicine. He believes that such Spontaneous Parallel Reciprocal Models (SPAREDELS), a term coined by a member of Penn's Comparative Oncology Working Group and recently discussed in JAVMA⁶, are extremely valuable to researchers attempting to span the gap from bench to bedside. Indeed, spontaneous companion animal models often more closely resemble human disease conditions than do experimentally induced rodent models. In addition, since pets and people are exposed to common environmental influences that could predispose to disease, these models provide a unique opportunity for obtaining insight into the comparable human cancers. As many clinicians are unaware of currently existing spontaneous animal models in their research area, Dr. Lewis is dedicated to increasing awareness of the

importance of comparative analysis of spontaneous diseases in companion animals and humans for the mutual benefit of all species. Dr. Lewis' research is funded by the Squamous Cell Carcinoma Research Fund (created by a donation from Ms. Kathleen Jack), and subcontracting through projects funded at Lankenau Institute for Medical Research.

Dr. Lewis' office is in Ryan, room 3109.

References

1. Lewis JR. Oral neoplasia-malignant. In: Cote, E, ed. *Clinical Veterinary Advisor*. Philadelphia: Mosby Elsevier, 2007; 771-773.
2. Reeves NCP, Turrel JM, Withrow SJ. Oral squamous cell carcinoma in the cat. *J Am Anim Hosp Assoc* 1993, 29: 438-441.
3. Chen Y, Hu J, Boorman D, Klein-Szanto A, and O'Brien TG, Therapy of murine squamous cell carcinomas with 2-diflouromethylornithine. *J Carcinogenesis* 2004, 3: 1-10.
4. Duda L, Lewis JR, Kagan SH, Evans SM. Letter to the editor: SPAREDEL-Spontaneous parallel reciprocal model. *JAVMA* 2009, 235 (8): 933.



Secretary of Agriculture launches National Institute of Food and Agriculture: science and research at USDA—Agricultural Science poised to make major contributions to health, environmental challenges

In October 2009 Agriculture Secretary Tom Vilsack announced the National Institute of Food and Agriculture (NIFA). He outlined his vision for global challenges we face over the next decades. Secretary Vilsack sees a need for the USDA science to focus its resources on accomplishing a few, bold outcomes to improve human health and protect our environment.

- Keep American agriculture competitive and end world hunger
- Improve nutrition and end child obesity
- USDA science will support efforts to improve food safety—studies on the impact of food-borne diseases
- USDA science will secure American's energy—by rapidly improving the quality of plant-based feed-stocks that will be a source of biofuel
- Animal agriculture research will strive for positive contributions to environmental, human, and animal health
- USDA science to make us better stewards of the environment and identify agricultural operations that will be net carbon sinks

In launching a new paradigm for the science that underpins our food, agriculture, and natural resources systems research, a new promise for Schools of Veterinary Medicine comes into view. Visit: <http://www.nifa.usda.gov/> and search NIFA.



Figure 1: Oral squamous cell carcinoma is the most common oral cancer in humans and cats. (Human photo courtesy of The Merck Manual Online Medical Library).

**PENN VET'S
NEUROSCIENCE CENTER**

Neuroscience research at Penn Vet focuses on clinical and basic studies to improve our understanding of the central nervous system and its involvement in diseases ranging from neurodegenerative disorders to obesity. Core areas of emphasis and expertise include feeding behavior/metabolism (**Tracy Bale, Kendra Bence, Narayan Avadhani, and Dan Yee labs**), sleep (**Leszek Kubin lab**), stress and neuro-psychiatric diseases (**Tracy Bale, Adrian Morrison labs**), neuro-transmission (**Tom Parsons lab**) and neuro-immunology (**Chris Hunter lab**). In these studies, the generation of important animal models of disease provides valuable information that aids in the development of new drug targets and therapies in disease prevention and treatment. As one of the key focuses within Penn Vet research, the neuroscience of obesity focuses on understanding the underlying causes of the recent escalation in overweight and obese humans and domestic pets. Basic research is examining the signal transduction pathways involved in regulation of feeding behavior (Bence lab) and the neuroplasticity and stress related to dietary changes that may promote long-term weight gain (Bale lab). The goal of the clinical neuroscience research at Penn Vet is to improve the characterization and treatment of nervous system disease in animal patients. Studies focus on naturally occurring neurodegenerative diseases in dogs and cats including lysosomal storage diseases (Niemann-Pick type C, alpha-mannosidosis, globoid cell leuko-dystrophy, and mucopolysaccharidoses) (**Charles Vite lab**). Current treatment emphasis is centered on the development of therapies for these diseases using pharmaceuticals and gene transfer technologies.

This spring, the Neuroscience Center will co-host two invited speakers in concert with the School of Medicine (SOM). The first seminar is the Vice Provost Special Seminar in Neuroscience co-sponsored by Penn's Mahoney Institute of Neurological Sciences, Genetics, and the Intellectual and Developmental Disabilities Research Center. **Eric Nestler, Ph.D.**, professor and chair of Neuroscience at Mt. Sinai School of Medicine, will be the speaker on March 22, 2010 in the BRB auditorium. Dr. Nestler's research crosses many areas and levels of neuroscience including the neurobiology of addiction and affective disorders and epigenetics. The second joint seminar will be the Neuroscience of Obesity Special Seminar with the SOM Institute for Diabetes, Obesity and Metabolism on May 11, 2010 in Hill Pavilion, Room 130. The speaker will be **Martin Myers Jr, M.D., Ph.D.**, from the University of Michigan. Dr. Myers' research focuses on the molecular mechanisms contributing to obesity and diabetes. There will be a catered reception following both seminars. More details including seminar titles will be available in early 2010.



Tracy L. Bale, Ph.D., Director

Recent Awards

Mark A. Oyama, DVM and Associate Professor in the Department of Clinical Studies - Philadelphia, received the Cardiology American Kennel Club-Canine Health Foundation Asa Mays, DVM, Excellence in Canine Health Research Award at the National Parent Club Canine Health Conference in St. Louis, MO.

F. Claire Hankenson, DVM, Assistant Professor in Pathobiology, and Senior Associate Director in University Laboratory Animal Resources, was the recipient of the 2009 Pravin N. Bhatt Young Investigator Award from the the American Association for Laboratory Animal Science recognizing outstanding young scientist who has made significant contributions to the fields of laboratory animal science or comparative medicine.

Recent Publications

Neonatal treatment with recombinant ectodysplasin prevents respiratory disease in dogs with X-linked ectodermal dysplasia. (2009) Mauldin EA, Gaide O, Schneider P, **Casal ML.** *Am. J. Med. Genet.* 149A(9): 2045-9.



Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolp, MS, Mackay F, **Artis, D.**, Xavier RJ, Teixeira MM, & Mackay CR. (2009) *Nature* 461:1282-6.



Interaction Between Ebola Virus Glycoprotein and Host TLR-4 Leads to Induction of Pro-Inflammatory Cytokines and SOCS1. Okumura A, Pitha PM, Yoshimura A, **Harty RN.** *J Virol.* 2009 Oct 21. [Epub ahead of print]



New policies for Public Access--*you have to play to get paid!!*



Are you in compliance with the NIH Public Access Policy (<http://publicaccess.nih.gov/>)? Your award money is dependent on it!! The policy requires NIH-funded investigators to 1) submit final peer-reviewed manuscripts to PubMed Central (PMC) and 2) to cite NIH-funded research using the PMC-supplied reference number (PMCID) in all NIH applications and progress reports. As many investigators are failing to complete the submission process, the NIH is now requiring PMCID numbers **within 3 months of publication** (<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-136.html>). Program officer are monitoring awards; as **non-compliance can result in withholding of funds**, submit your manuscripts to PMC **upon final acceptance for publication** don't wait until applications/ progress reports are due!

How do I submit my accepted manuscript to PMC? Before signing any publication and/or copyright transfer agreement, make sure that it **allows the paper to be posted to PMC**. If not, check with your institutional official and/or legal counsel to ensure compliance. If the journal is not submitting the published article to PMC on your

behalf, you must submit the **final peer-reviewed manuscript** (including all suggested modifications, figure and table files, and supplementary materials) to the NIH Manuscript Submissions (NIHMS). Complete instructions can be obtained at http://publicaccess.nih.gov/submit_process.htm and FAQs are at: <http://www.nihms.nih.gov/faq.html>. Following submission, you will receive an NIHMSID that can be used as a temporary measure to cite papers **within 3 months of publication**. The NIHMS will email the author for approval of the converted files and a PMCID will be provided following final approval.

How do I cite public access articles? When citing a paper in NIH applications and progress reports, you must include either the NIHMSID (within 3 months of publication) or the PMCID. Such citations should be included in your Bibliography, Progress Report, and Biosketch. For further directions, see <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-119.html>. Check your eRA Commons profile regularly to see which manuscripts are linked with your award in the NIHMS.

What do I do if I'm not compliant? First, determine if your manuscripts HAVE an assigned PMCID. The PMCID is a 7 digit number preceded by PMC located under the right hand side of a PubMed abstract. If your manuscripts do NOT have a PMCID, submit the final version of the manuscript to NIHMS (see above) after making sure that

copyright transfer agreement allow you to do so. Be aware that if a paper is 3 months beyond publication, an NIHMSID will **NOT** be issued. As a PMCID is required for compliance and will not be issued for several weeks, submit your manuscripts **NOW** before your applications/ progress reports are due!!

Some recent awards....

Gary Smith, D.Phil, Model Hierarchies Working Group within RAPIDD Program-- Fogarty International CTR/NIH. 7/1/2009 - 6/30/2011 \$93,060

Brett Kaufman, Ph.D., Identification and characterization of genes affecting mitochondrial myopathies, Muscular Dystrophy Assoc. 1/1/09 --12/1/2010, \$81,800

Brett Kaufman, Ph.D., The contribution of mitochondrial DNA organization to the mitochondrial dysfunction induced by high glucose levels in cancer. Pilot grant from Mari Lowe Center for Comparative Oncology 5/01/09-04/31/2010, \$20,000

Gustavo Aguirre, VMD. PhD, NIH Supplement to Translational Research for Retinal Degeneration Therapies, \$140,375.

Dorothy Brown, DVM, MSCE, Development of a canine Model of Radiotherapy Induced Oral Mucositis. NIH 9/25/09-8/31/11, \$275,000

Chris Hunter, Ph.D. "What is the effect of IL-27 on Treg expansion and homeostasis?" Centocor, 8/3/09-8/2/10, \$100,000.

Chris Hunter, Ph.D. Molecular & Cellular Regulation of Tolerance, project in a NIH program project grant, 7/22/09 - 6/30/2011, \$501,676

Chris Hunter, Ph.D., Supplement to Immunopathogenesis of toxoplasmic encephalitis, 9/22/09 - 9/21/2011, NIH, \$130,582.

Michael Atchison, PhD, NIH Supplement to PcG Function of YY1 in Transcription and Development. \$71,509

Coins for Canine Cancer Research



Phillip Scott, Associate Dean for Research receives a gift of a piggy bank from Dr. Chris Anastasiou of Modern Eye optical shop in University City in support of canine cancer research.

Dr. Christopher Anastasiou, Optometrist of the **Modern Eye**, located at 3419 Walnut Street at the Shops at Penn in University City, has been collecting donations in a blue piggy bank at his office in memory of his two dogs, Lucky and Buddy, who were treated at the Matthew J Ryan Veterinary Hospital of the University of Pennsylvania School of Veterinary Medicine. He recently presented the piggy bank tightly packed with \$1289.58 in coins and dollar bills. In addition, Dr. Anastasiou graciously presented Penn Vet with a check for \$1000 and he has a new piggy bank set up and ready to continue collecting for the Lucky & Buddy Fund for Canine Cancer Research. Stop in and see him.



The **Penn Vet Research Newsletter** will be distributed quarterly. Suggestions, requests, comments, and story ideas should be directed to: resnews@vet.upenn.edu.
Office of the Associate Dean
for Research
Phillip Scott, Ph.D.



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Art by Nancy Norman

TO: