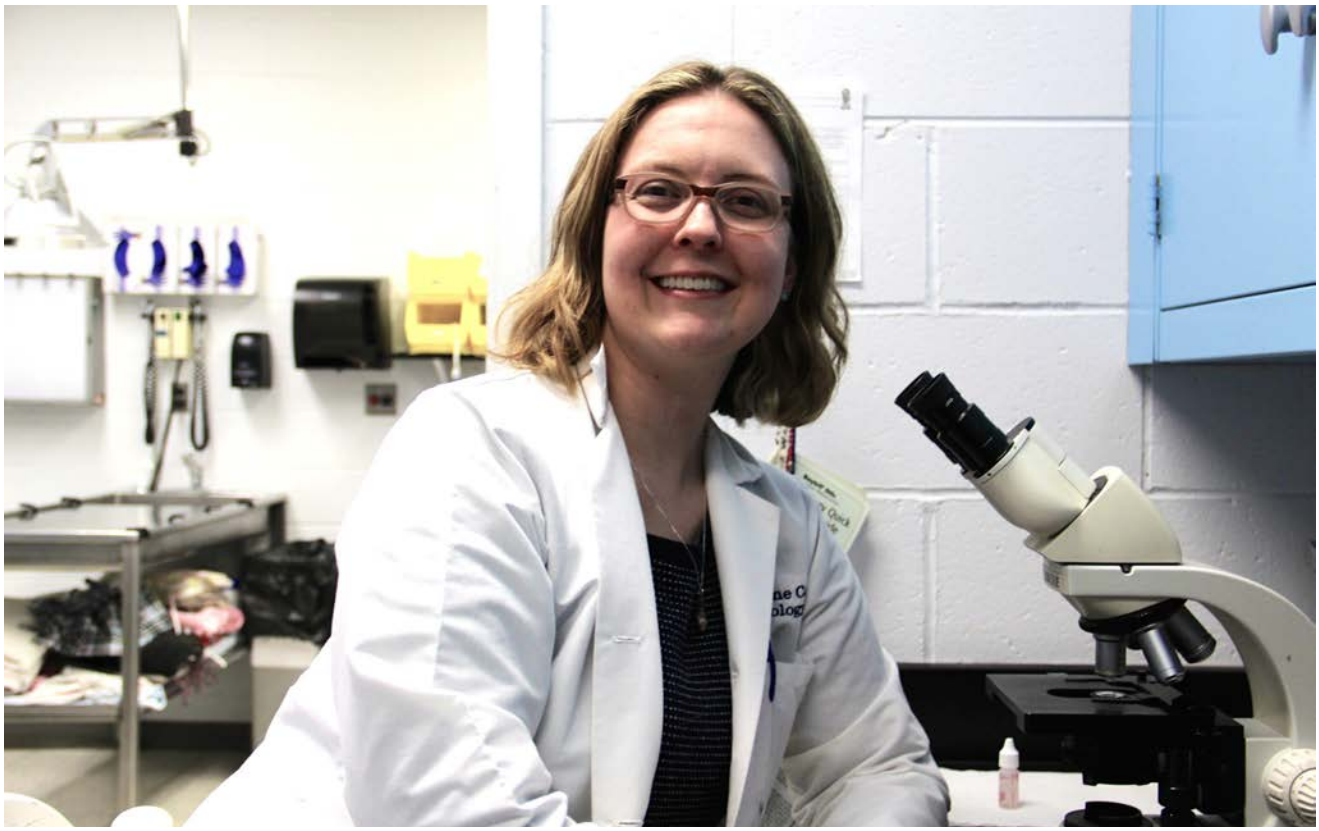
STEVEN HANES RECEIVES MORRIS VET STUDENT SCHOLAR **PRIZE**
PAGE 6

2017 STUDENT RESEARCH DAY
WINNERS PAGE 4

NEW CLINICAL TRIAL
PAGE 6

RALPH L. BRINSTER
NAMED PRESIDENT'S DISTINGUISHED PROFESSORSHIP PAGE 6

NEWSLETTER



From the laboratory to the clinic

Manipulation of microbial populations may yield promising new therapeutic approaches

Dr. Christine Cain is an assistant professor of veterinary dermatology and allergy (clinician educator track) in the Department of Clinical Studies – Philadelphia. Dr. Cain received a BS in Biological Sciences from Cornell University in 2003 and a DVM from the Ohio State University, College of Veterinary Medicine in 2006. She completed a one-year rotating internship in small animal medicine and surgery at Red Bank Veterinary Hospital in Tinton

Continued on page 2

Falls, New Jersey, followed by a residency in veterinary dermatology and allergy at the University of Pennsylvania, School of Veterinary Medicine. Dr. Cain was board certified by the American College of Veterinary Dermatology in 2010. She worked as an assistant professor at the University of Tennessee, College of Veterinary Medicine prior to joining the Department of Clinical Studies – Philadelphia in 2012. Dr. Cain's clinical research centers on the pathogenesis, epidemiology, and treatment of canine skin and ear infections, as well as characterization of the cutaneous microbiome in health and disease.

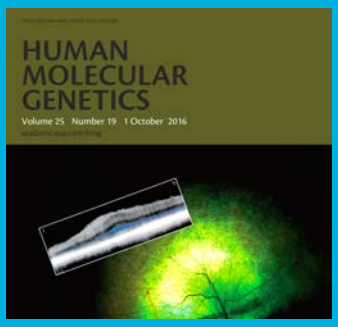
From the laboratory to the clinic – the journey to a potential new therapy for staphylococcal infections in dogs—

The increasing prevalence of antimicrobial resistance in both human and veterinary medicine presents a major challenge to clinicians attempting to successfully manage infections and raises concerns for transfer of resistance genes between bacteria harbored by humans and their pets. Thus, there is a distinct need to identify new therapies for antibiotic resistant bacteria in companion animals, to both improve veterinary care and to minimize their potential spread to humans. In veterinary dermatology, canine skin and ear infections, most commonly caused by *Staphylococcus* sp., are encountered on a daily basis. Research by Dr. Cain and colleagues initially focused on *Staphylococcus schleiferi*, an emerging pathogen in both humans and companion animals that exhibits high rates of methicillin resistance (resistance to all β-lactam antimicrobials) in clinical isolates [1,2]. This work has provided an exciting opportunity for collaboration across departments and for translation of bacterial genomics into a potential new therapy for staphylococcal infections in companion animals.

Like other staphylococcal species, particularly *S. aureus*, methicillin resistant *S. schleiferi* isolates are more clonally related than are methicillin susceptible isolates and these methicillin resistant clones have expanded and disseminated across the United States in recent years [1,3]. These findings, coupled with the increasing prevalence of multi-drug resistance in *S. schleiferi* isolates, emphasized the need for further investigation of the genetic fingerprint of *S. schleiferi.* Dr. Cain and colleagues collaborated with Drs. Daniel Beiting and Ana Misic in the Department of Pathobiology, who sequenced the first complete genome of *S. schleiferi*[4]. Surprisingly, comparative genomic analysis demonstrated that staphylococci, including *S. schleiferi*, that commonly colonize companion animals utilize an isoprenoid biosynthetic pathway that is distinct from that used by staphylococci that more commonly colonize humans, including *S. aureus*. Specifically, isoprenoids, which are essential for

continued on page 3

Penn Vet Research



Dr. Gus Aguirre's work featured on the cover of *Human Molecular Genetics*—a retinal photograph of the right eye of an NPHP5 mutant dog with advanced retinal degeneration. The original article is entitled Overlap of abnormal photoreceptor development and progressive degeneration in Leber congenital amaurosis caused by NPHP5 mutation *Hum Mol Gen* (2016) 25(19): 4211-4226.

Guziewicz KE, Sinha D, Gómez NM, Zorych K, Dutrow EV, Dhingra A, Mullins RF, Stone EM, Gamm DM, Boesze-Battaglia K, Aguirre GD. (2017) Bestrophinopathy: An RPE-photoreceptor interface disease. *Prog Retin Eye Res:* epub ahead of print

Novais FO, Carvalho AM, Clark ML, Carvalho LP, **Beiting DP, Brodsky** IE, Carvalho EM, & **Scott P.** (2017) CD8+ T cell cytotoxicity mediates pathology in the skin by inflammasome activation and IL-1β production. *PLoS Pathog* 13(2): e1006196

bacteria survival, are generated by a non-mevalonate pathway in staphylococci that commonly colonize companion animals while they are generated by the mevalonate pathway in those that more typically colonize humans[5]. Moreover, fosmidomycin, an anti-malarial agent and antibiotic that targets the non-mevalonate pathway, was effective *in vitro* against canine clinical staphylococcal isolates but had no effect on the growth or survival of *S. aureus*[5]. Dr. Cain and colleagues are now hoping to translate this work in the laboratory into a new therapy for staphylococcal infections of the skin and ear canal in companion animals. Favorable tolerability of fosmidomycin applied as a topical formulation to the ear canals of healthy dogs has been demonstrated, and Dr. Cain and colleagues are moving forward with clinical trials using fosmidomycin as a topical treatment for canine skin and ear canal infections. Notably, antibiotics such as fosmidomycin that are effective in companion and livestock animals but not in humans may reduce cross-species transfer of drug resistance genes.

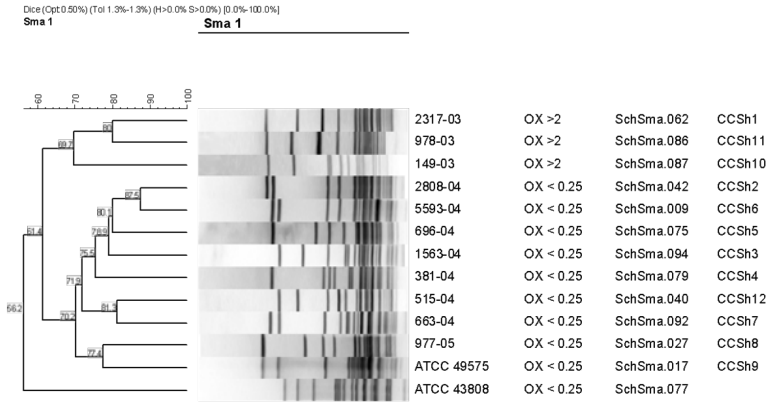


Figure 1. Results of pulsed-field gel electrophoresis of 11 *Staphylococcus schleiferi* isolates derived from clinical samples obtained from dogs and 2 ATCC *S. schleiferi* type strains, each representative of a different clonal cluster (CC). The predominant oxacillin (methicillin) susceptibility result (OX) for each of the *S. schleiferi* clonal clusters is indicated [1].

The big picture – investigating the cutaneous and rectal microbiome of dogs with perianal fistulas—Characterization of microbial populations ('the microbiome') using next-generation sequencing techniques, as well as the role of shifts in these populations in disease flares and remissions, has been a major focus in human medical research over the past several years. Investigation of the cutaneous microbiome in companion animals is an emerging area of research that may ultimately yield potential therapeutic targets in both veterinary and human patients with homologous diseases. Perianal fistulas are painful sinus tracts that develop in the perianal skin of dogs, most commonly in German shepherd dogs. As in humans with inflammatory bowel disease, particularly Crohn's disease, affected dogs often experience diarrhea concurrent with flares in skin lesions, suggesting that canine perianal fistulas may serve as a spontaneous model of human fistulizing Crohn's disease. The current mainstay of therapy for canine perianal fistulas is immunosuppressive therapy. However, retrospective data analyzed by Dr. Cain and colleagues has shown that long-term administration is typically required and that relapses are common with cessation of therapy [Cain *et al*, unpublished data]. Given the frequent need for lifelong immunosuppression in these patients, as well as the unknown role of microbiota in the onset and maintenance of fistulas, there is a need for further studies to investigate the role that cutaneous and intestinal microbial populations play in this disease. In collaboration with Dr. Charles Bradley in the Department of Pathobiology, Dr. Cain is currently enrolling German shepherd dogs with perianal fistulas (as well as healthy German shepherd dogs) in a study to track longitudinal changes in the cutaneous and rectal microbiome in dogs treated with standard-of-care

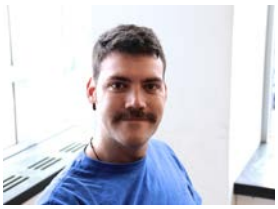
continued on page 5

2017 Annual Student Research Day

On March 22, 2017, the scholarly achievements of Penn Vet Students were presented at the Annual Student Research Day. Faculty, alumni, students and mentors heard oral presentations and enjoyed poster sessions on a wide range of research projects carried out by students at Penn Vet. The *Class of 66* keynote address was delivered by **Amy LeBlanc, DVM**, a board certified veterinary oncologist and director of the Comparative Oncology Program at the National Cancer Institute (NCI), National Institutes of Health. She spoke on the NCI Comparative Oncology Program: **One Health in Action**. Those who received awards for their scholarly presentations were: **Nathaniel Sotuyo** (1st place combined degree)—Stem cell-derived interneuron transplants as a treatment for Dravet syndrome; **Jeffrey N. Carey** (2nd place combined degree)—Regulated stochasticity in a bacterial signaling network permits tolerance of a rapid environmental change; and **Ian Penkala** (3rd place combined degree)—Transcriptional regulation of alveolar epithelial cell fate and plasticity during lung development; **Megan L. Clark** (1st place VMD students)—Leishmania-specific skin resident CD4 T cells are formed from recently activated effector T cells; **Jonah Binstock** (2nd place VMD students)—The role of type III collagen in the fibrotic response: therapeutic strategies to engineer regenerative and tumor micro environments; and **Jenna Schoenberger** (3rd place VMD students)—The cellular basis of enhanced intestinal regeneration through calorie restriction. The 'Best Poster' awards went to: **Megan McGeehan** (1st place)—Tertiary lymphoid organs in a natural model of multiple sclerosis ; **Meghan Ramos** (2nd place)—Biosensing of biofilm: detecting the volatile organic compounds (VOC) of biofilm using a dogs nose; and **Ariel M. Aguiar** (3rd place—Characterizing immune regulation of canine heart worm *Dirofilaria immitis* infection in *Aedes aegypti* mosquitoes. **Talia Wong, Molly Klores, Corey Spies, and Brianna Parsons** received **Inspiration Awards**.

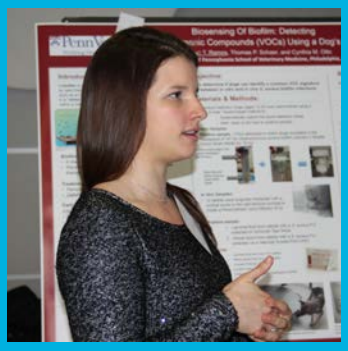
Nathaniel Sotuyo

Inspiration Awardees: Corey Spies, Brianna Parsons, Talia Wong and Molly Klores



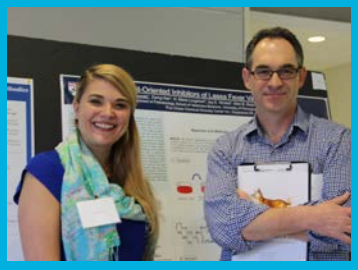
George McClung

Phil Scott congratulates Jonah Binstock



Meghan Ramos

Dr. Amy LeBlanc, NCI/NIH



Sarah Wronski & Dr. Michael May

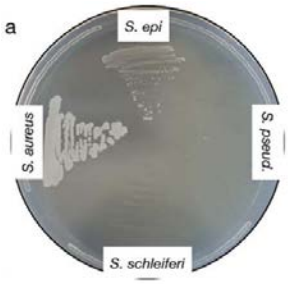
Jenna Schoenberger

Dr. Phil Scott congratulates Jeff Carey

immunosuppressive therapy. The goals of this work are to examine the effects of immunosuppressive therapy on cutaneous and enteric microflora, as well as to investigate whether shifts in the cutaneous and rectal microbiome are associated with clinical remission of perianal fistulas. Manipulation of microbial populations may ultimately yield promising new therapeutic approaches for alleviation of skin diseases in humans and companion animals alike.

Dr. Cain's research has been funded by the American College of Veterinary Dermatology, the Morris Animal Foundation, the American Kennel Club, and the Penn Vet Center for Host-Microbial Interactions. Her office is located at 2065 Ryan.

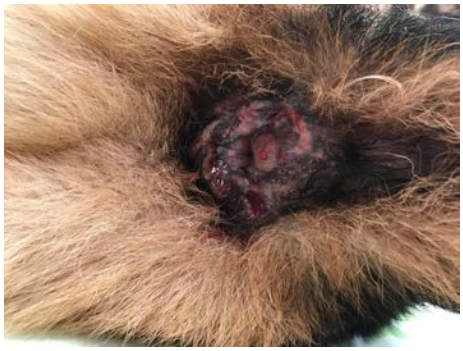
a



b

Species (strain)	MIC (µg/ml)	MBC (µg/ml)
S. schleiferi (1360-13)	1	16
S. schleiferi (2142-05)	1	4
S. schleiferi (2317-03)	0.5	128
S. schleiferi (5909-02)	8	128
S. pseudintermedius (11680P)	1	64
S. pseudintermedius (5317)	0.5	32
S. aureus (3964)	no inhibition	no killing
S. aureus (3899)	no inhibition	no killing
S. epidermidis (1151OP-12)	no inhibition	no killing
S. lugdenensis (F36680)	no inhibition	no killing

Figure 2a. Mueller-Hinton agar plate containing 50 µg/ml fosmidomycin streaked with overnight cultures of *S. aureus, S. epidermidis*, *S. pseudintermedius*, and *S. schleiferi*, demonstrating selective inhibition of *S. pseudintermedius* and *S. schleiferi* (*Staphylococcus* sp. most commonly associated with infections in companion animals). **b.** Minimum inhibitory concentrations (MIC) and minimum bactericidal concentrations (MBC) of fosmidomycin for 10 *Staphylococcus* strains [5].



Dr. Cain and 4th year student Caroline Maguire

Figure 3. Perianal fistulas in a German shepherd dog enrolled in a study to track longitudinal changes in the cutaneous and rectal microbiome in dogs treated with standard-of-care immunosuppressive therapy (photo taken prior to initiating therapy).

References

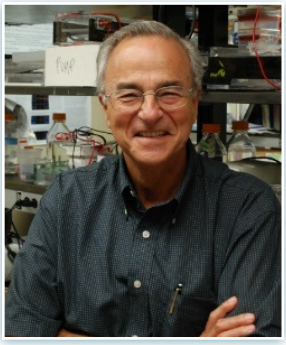
1. Cain CL, Morris DO, O'Shea K, Rankin SC. Genotypic relatedness and phenotypic characterization of *Staphylococcus schleiferi* subspecies in clinical samples from dogs. *Am J Vet Res* 2011; 72 (1): 96-102.

2. Cain CL, Morris DO, Rankin SC. Clinical characterization of *Staphylococcus schleiferi* infections and identification of risk factors for acquisition of oxacillin-resistant strains in dogs: 225 cases (2003-2009). *J Am Vet Med Assoc* 2011; 239 (12): 1566-73.

3. Kunder DA, Cain CL, O'Shea K, Cole SD, Rankin SC. Genotypic relatedness and antimicrobial resistance of *Staphylococcus schleiferi* in clinical samples from dogs in different geographic regions of the United States. *Vet Dermatol* 2015; **26** (6): 406-10.

4. Misic AM, Cain CL, Morris DO, Rankin SC, Beiting DP. Complete genome sequence and methylome of *Staphylococcus schleiferi,* an important cause of skin and ear infections in veterinary medicine. *Genome Announc* 2015; **3** (5): e01011-15.

5. Misic AM, Cain CL, Morris DO, Rankin SC, Beiting DP. Divergent isoprenoid biosynthesis pathways in *Staphylococcus* species constitute a drug target for treating infections in companion animals. *mSphere* 2016; **1** (5): e00258-16.



Penn Vet's **Gustavo Aguirre,** VMD, PhD, FARVO (RC) is the **first veterinarian** to win the prestigious **Proctor Medal** that will be presented on May 8 in Baltimore at the annual meeting of the Association for Research in Vision and Ophthalmology (ARVO). The Proctor Medal is awarded for outstanding research in the basic or clinical sciences as applied to ophthalmology. Dr. Aguirre's unique canine models of retinal degeneration have given us invaluable basic information about their counterpart human diseases. Moreover, this preclinical work has established safety and efficacy for most of the clinical trial work in progress on neurotrophic factors (CNTF) as well as gene therapy (RPE65).His most recent work on XLRP demonstrates that gene therapy can successfully arrest advanced photoreceptor and vision loss, dramatically expanding the therapeutic window to late stages of disease.

Nicola J. Mason, PhD, BVetMed, Department of Clinical Studies Philadelphia will launch a **new clinical trial** will be opening in **May/June of 2017** to evaluate the safety and effectiveness of a listeria based vaccine in targeting a very common mutation that occurs in up to 87% of dogs with transitional cell carcinoma (bladder cancer). Dr Mason is working with Dr. Dana Clarke (Department of Clinical Studies Philadelphia) on this study. This trial will provide patients with the opportunity to receive immunotherapy that aims to target and control local and metastatic disease.

William Beltran, DVM, PhD, has been elected into the Fellowship of The College of Physicians of Philadelphia. His formal induction ceremony, will take place on Friday, May 19, 2017, as he will be asked to sign the historic membership register and have his name added to the distinguished roster of Fellows that commenced in 1787 with the founders of American Medicine.

Penn Vet, through the generosity of Henrietta Alexander, established the Ralph L. Brinster, **President's Distinguished Professorship.** Dr. Brinster's groundbreaking research in the development of techniques for manipulating the cellular and genetic composition of early mouse embryos made him the first and only veterinarian to be awarded the National Medal of Science in 2010. His transformational work has set global standards in research and innovation in animal and human health."

Steven Hanes, V'19, has received a Morris Animal Foundation Student Scholar award for his application entitled "Induction of X-reactivation in B cells through deletion of the long non-coding RNA Xist". **Dr. Montserrat Anguera**, Department of Biomedical Sciences, will be Steven's mentor for his summer research project. Steven presented a poster at the March Student Research Day.

Awards (direct costs)

Tom Parsons
PA Department of Agriculture
Best Practices for Loose Housed Sows: A Field Study
1/1/17-6/30/17 $22,000

Zhenzhia Dou
PA Department of Agriculture
Mitigating antibiotic resistance risks through a holistic approach
1/1/17-6/30/17 $28,826

Serge Fuchs
NIH/NCI
2R01-CA-092900-15
Role of HOS in cell transformation and apoptosis
12/02/16 – 11/30/21 $1,068,750

Chakrabarti, Rumela
Abramson Cancer Center: Breakthrough Bike Challenge-Cooper Scholar Award
Crosstalk between ΔNP63+ cancer stem cells and myeloid derived suppressor cells in triple negative breast cancer.
01/01/17-12/31/17 $55,000

Christopher Lengner
NIH/NCI
R01-CA-168654-06
Cell type and molecular determinants of colorectal cancer initiation downstream of APC inactivation
06/01/17 – 05/31/22 $1,187,500

Igor Brodsky
NIH R01 AI-128530
Defining the role of Caspase-8 activity in anti-bacterial immune defense
3/1/17–2/28/22 $1,012,377

Robert Greenberg
NIH R01 AI-123173
Physiological roles of schistosome TRP ion channels with atypical pharmacology
1/1/17–12/31/20 $750,000

Chris Hunter
Surface Oncology
To test the impact of antibodies specific for the IL-27 and IL-27 receptor complex on infection-induced responses
2/1/17-1/31/19 $125,940

Carolina Lopez
NIH R21 AI-127832
Mechanism for virus persistence after acute infections
12/15/16-11/30/18 $275,000

Donna Kelly/Lisa Murphy
Commonwealth of Pennsylvania
Determination of the Prevalence of MRSA in Poultry meat in Pennsylvania
1/1/17-6/30/17 $18,000

Shelley Rankin
American College Veterinary Dermatology
Evaluation of the CosmosID Software Platform for Rapid Microbial Identification and Pathogen Characterization from Canine Skin
7/1/17-6/30/18 $27,756

Oriol Sunyer
USDA/NIFA
Fish mucosal CD4+ T cells and their association with B cells: Implications for the induction of mucosal immune responses
5/1/17—4/30/20 $490,000

David Holt
Penn Translational Biomed. Imaging Center
Near-infrared Fluorophores for Intraoperative Detection of Lung Tumor Margins, Co PI S. Singhal.
1/1/17-12/31/17 $50,000

David Holt and co PI Dana Clarke
New York University Medical Center
Evaluation of a Laryngeal Stent to Treat Idiopathic Laryngeal Paralysis
1/1/17-12/31/17 $70,000

Gus Aguirre
Poodle Club of North America
Optic Nerve Hypoplasia Micropapillae and Juvenile Cataracts in Poodles
2/15/17-2/14/20 $163,439

Keiko Miyadera
Landenberger Research Foundation
Canine model of night blindness to target retinal bipolar cells for new therapies
1/1/17-12/31/19 $200,000

A Beautiful Friendship—and an interest in **canine cancer** research—Modern Eye, the optical boutique and optometrist's office at 3419 Walnut Street, has forged a very special relationship with Penn Vet.. Pet-loving owner/optometrist Dr. Chris Anastasiou and his team have collected donations for Penn Vet canine cancer research on a daily basis, encouraging contributions to a prominently displayed piggy bank in exchange for eyeglass adjustments and other services. This month the piggy was emptied and the total collected was $1262 and donated to the canine cancer research fund.

Penn Vet Publications

JJ Keating, **JJ Runge**, S Singhal, S Nims, O Venegas, **AC Durham,** G Swain. S Nie, PS Low, and **DE Holt (2017)** Intraoperative near-infrared fluorescence imaging targeting folate receptors identifies lung cancer in a large animal model. ***Cancer*** 123(6):1051-1060

David Holt

Kathryn Michel

Latney, LV, Toddes, BD., Wyre, NR., **Brown, DC**, **Michel, KE**, Briscoe, JA. (2017) Effects of various diets on the calcium & phosphorous composition of mealworms (Tenebrio molitor larvae) and superworms (Zophobas morio larvae). ***Am J Vet Res*** 78 (2): 178-185.

Christopher Hunter

Glatman Zaretsky A, Konradt C, Dépis F, Wing JB, Goenka R, Atria DG, Silver JS, Cho S, Wolf AI, Quinn WJ, **Engiles JB, Brown DC, Beiting D,** Erikson J, Allman D, Cancro MP, Sakaguchi S, Lu LF, Benoist CO, & **Hunter CA**.(2017) T regulatory cells support plasma cell populations in the bone marrow. ***Cell Rep***.21;18(8):1906-1916.

Narayan Avadhani

Chowdhury AR, Long A, Fuchs SY, Rustgi A, and **Avadhani NG**. (2017) Mitochondrial stress-induced p53 attenuates HIF-1α activity by physical association and enhanced ubiquitination. ***Oncogene*** 36(3): 397-409

M Guha, S Srinivasan, K Guja, E Mejia, M Garcia-Diaz, F B Johnson, G Ruthel, BA Kaufman, EF Rappaport, MR Glineburg, J-Kang Fang, A Klein S, H Nakagawa, J Basha, T Kundu and **NG Avadhani** (2016) HnRNPA2 is a novel histone acetyltransferase that mediates mitochondrial stress-induced nuclear gene expression.***Cell Discov*** 2: 16045.

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The Penn Vet Research Newsletter is distributed quarterly. Suggestions, requests and comments may be directed to:

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Phillip Scott, PhD

Office of the Vice Dean for Research and Academic Resources

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