

NEWSLETTER

Congestive heart failure accounts for half a million *deaths per year in the United States.....*



Meg on her horse Shyrocco Troilus

Dr. **Meg M. Sleeper** is an associate professor of cardiology (clinician educator track) in the Department of Clinical Studies-Philadelphia. Dr. Sleeper received a B.S. in Biology from Ursinus College in 1989 and her V.M.D. from the University of Pennsylvania in 1993. She completed an equine medicine/surgery internship at Mid-Atlantic Equine Medical Center in Ringoes, New Jersey and returned to the University of Pennsylvania in 1995 for a cardiology residency. Other than a year in private practice (Idexx-Vet Referral Center) she has worked in the section of cardiology since 1995. Dr.

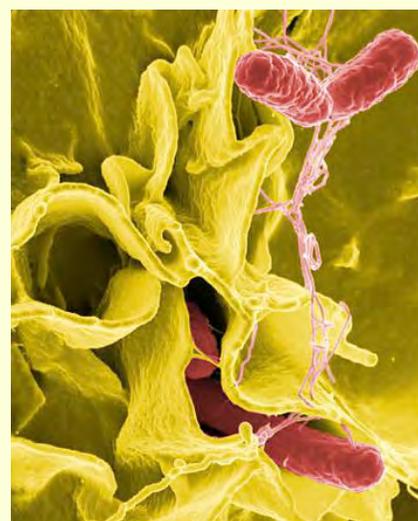
Sleeper's primary research projects are centered on myocardial gene delivery to normalize cardiac dysfunction and evaluation of cardiac disease and therapy in lysosomal storage diseases. She is also interested in cardiovascular disease in non-human primates, particularly chimpanzees.

Therapeutic gene delivery

Congestive heart failure (CHF) accounts for half a million deaths per year in the United States. Despite the high level of morbidity associated with CHF, current pharmacological and mechanical remedies only slow disease progression and there are few therapeutic modalities

Center for Host-Microbe Interactions

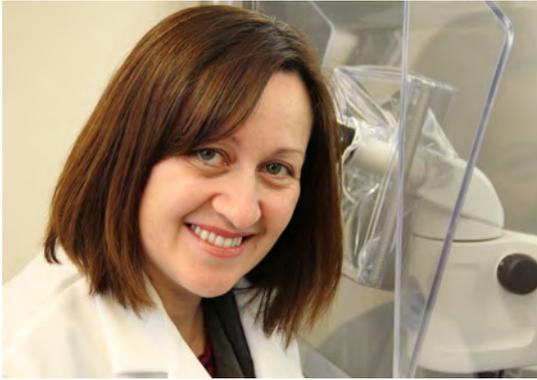
Dean Joan Hendricks has announced the establishment of a Center for Host-Microbe Interactions in an effort to advance genomics research throughout the Penn Vet research community. To kick off this initiative, a **Request for Applications** has been posted for projects of up to \$50,000. Clinical and basic science investigators are invited to submit proposals that leverage 'omic approaches to investigate host-microbe interactions. The deadline is May 1st. For application guidelines, faculty may contact Dan Beiting at beiting@vet.upenn.edu The 2013 Faculty Research Retreat on June 7th will focus on 'omic approaches in research at Penn Vet.



Salmonella

Continued on page 3

NEW ASSISTANT PROFESSOR IN ANIMAL BIOLOGY



Montserrat C. Anguera

Dr. Montserrat C. Anguera has joined the Department of Animal Biology. She received her undergraduate degree from the University of California, San Diego and her PhD from Cornell University, Ithaca, NY. Dr. Anguera carried out her postdoctoral studies at the Howard Hughes Medical Institute, Massachusetts General Hospital/Harvard Medical School. She is interested in the function and mechanisms of long noncoding RNAs important for early development in humans and mice, and how these long noncoding RNAs become mis-regulated in disease. Her research laboratory is located on the third floor Rosenthal Building and her office is at 390 EB. Stop by and say hello.

PENN VET BIOMATHEMATICIAN/BIOSTATISTICIAN RAY BOSTON RETIRES

In 1991 Dr. Raymond Boston moved to the United States from Australia to become professor of applied biomathematics at the University of Pennsylvania School of Veterinary Medicine. As a biomathematician, Dr. Boston applied mathematics to biology in collaboration with a broad range of researchers. As a faculty member at the large animal campus, New Bolton Center, Dr. Boston focused on 1) the application of mathematical modeling to the analysis and interpretation of biomedical and agricultural data, 2) the application of statistics to the design and investigation of clinical trials, and field experiments, and 3) the development of new computer methods for the management, processing and analysis of biomedical data, and for the instruction of students (particularly veterinary students) in clinical methods,

epidemiological techniques, and disease pathologies. Dr. Boston was funded by NIH from 1978 to 2004 to develop ideas and methods for the investigation of health and disease issues using computer-based statistical and mathematical methods.

A prolific scholar, Dr. Boston published 303 peer-reviewed articles and among those several were highly cited. He also published 20 book chapters and three books during his academic career. His published work represents a wide range of disciplines including agricultural science, allergies and immunology, analytical chemistry, cancer, cardiology, diabetes, and various topics in veterinary medicine resulting from his collaborative research over the years at New Bolton Center. Thankfully, Dr. Boston will not leave New Bolton Center abruptly in July; he will work on a shortened schedule for the next couple of years.



Raymond Boston

Selected publications

Boston RC et al (2000) CPM Dairy: Dairy cow ration formulation software. The conversion of a scientific model describing dairy cow nutrition and production to an industry tool: the CPM Dairy Project. Modeling nutrient utilization in farm animals. J.F. McNamara, D. Beever (eds.). Page: 361-377.

Boston RC, Stefanovski D, Moate PJ, Sumner AE, Watanabe RM, Bergman RN (2003) MinMod Millennium: Software for the estimation of Insulin Resistance. MinMod Millennium (Computer Software) MINMOD Millennium: a computer program to calculate glucose effectiveness and insulin sensitivity from the frequently sampled intravenous glucose tolerance test. Diabetes Technology & Therapeutics 5: 1003-1015.

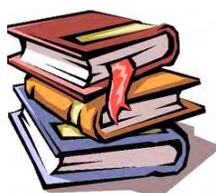
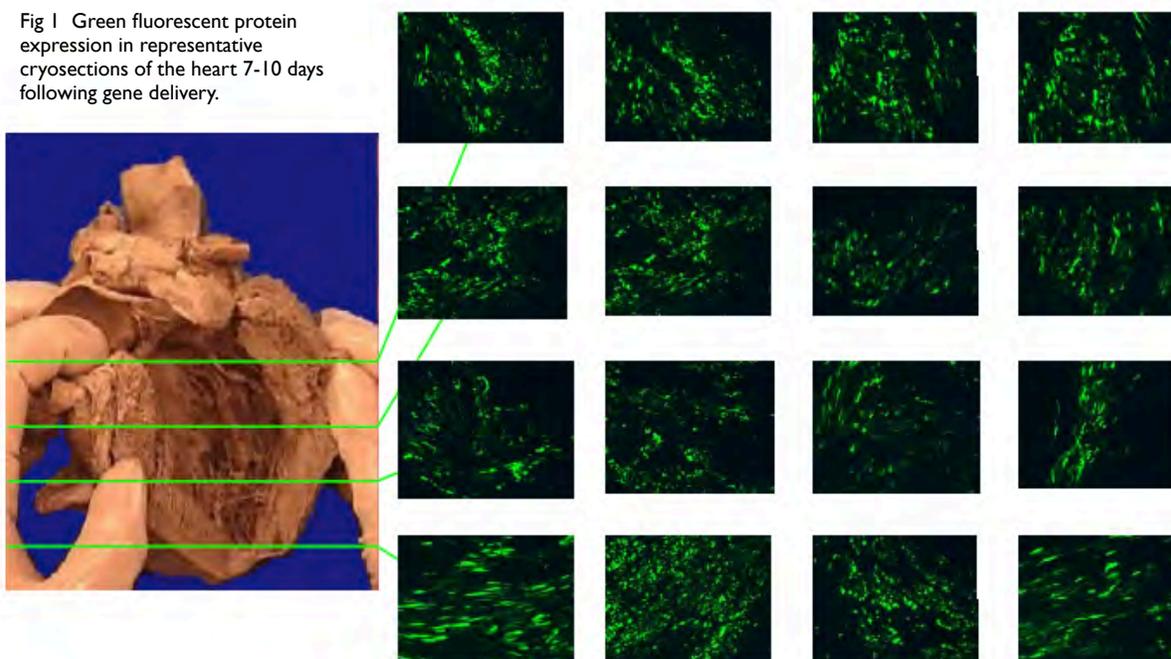
Meg Sleeper continued from page 1.

available for patients with advanced heart failure. An analogous disease, dilated cardiomyopathy (DCM), is the second most common cause of acquired heart disease in dogs, mainly affecting large breed dogs such as Doberman Pinschers, Great Danes and Irish Wolfhounds. Therapeutic options are even more limited for canines, with medical management of signs associated with heart failure being the only recourse. Thus, there is a critical need to explore new therapeutic approaches in heart failure for both humans and dogs. Notably, recent advances in our understanding of the molecular basis of myocardial dysfunction, together with the evolution of increasingly efficient gene transfer technology, have placed heart failure within reach of gene-based therapy.

To further explore this exciting possibility, Dr. Sleeper has collaborated with Dr. Lee Sweeney from the department of physiology at the Perelman School of Medicine at the University of Pennsylvania, to develop an efficient cardiac gene transfer strategy using a minimally invasive approach in dogs. Utilizing an injection catheter inserted into the carotid artery and advanced into the left ventricle, multiple injections of adeno-associated virus serotype 6 (AAV6) result in transduction of greater than 60% of the myocardium (see Figure 1).¹ Dr. Sleeper and colleagues have been using this technique in dogs affected with golden retriever X-linked muscular dystrophy (GRMD), a large animal model for Duchenne muscular dystrophy, the most common inherited disease affecting humans.

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Fig 1 Green fluorescent protein expression in representative cryosections of the heart 7-10 days following gene delivery.



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<http://appsontap.wordpress.com/2013/03/22/working-off-campus-access-e-resources-with-this-browser-button/>

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This disease occurs due to a mutation in the gene encoding dystrophin, and human patients often succumb to cardiomyopathy. To test the potential therapeutic efficacy, Dr. Sleeper and colleagues used their gene delivery technique to restore cardiac dystrophin expression in dogs affected with GRMD. Encouragingly, restoration of cardiac dystrophin expression at 13 months was confirmed and was accompanied by improved cardiac function as assessed by cardiac magnetic resonance imaging.² Further safety studies are currently underway in advance of taking this powerful approach to a human clinical trial.

Based on the promising results above, Dr. Sleeper and her colleagues believe that a similar technique may eventually be utilized for canine and human patients with acquired heart disease. As the molecular basis for acquired heart disease is less clear, therapy using cardiac rAAV gene delivery of several regulatory proteins involved in calcium cycling within the myocardial cell, most notably a pseudophosphorylated mutant of phospholamban and $Sl00A1$, are currently being explored. Indeed, this technique has been successfully utilized to suppress heart failure in several small animal models as well as in an ovine model of heart disease. A clinical trial to deliver these transgenes to client owned dogs affected with DCM is scheduled to begin in 2013. This therapy will

allow veterinarians to directly modify the molecular changes that occur with canine heart disease, hopefully improving their prognosis.

Finally, as the genetic basis for many inherited human diseases has now been identified, animals with orthologous genetic diseases provide invaluable models in which to test new therapeutic strategies for both animal and human patients. Working with Dr. Mark Haskins from the Department of Pathobiology and Dr. Kathy Ponder from Washington University School of Medicine, Dr. Sleeper has described the cardiovascular abnormalities that occur in dogs and cats with several inherited lysosomal storage diseases. Furthermore, they have described the cardiovascular response to therapeutic gene delivery as well as enzyme replacement therapy and anti-inflammatory approaches in dogs with mucopolysaccharidoses (MPS)³, one type of lysosomal storage disease. As progressive cardiac involvement is observed in many human patients with MPS, translation of these therapies to the clinic is now underway based on these results.

Therapies for inherited cardiovascular disease Additional therapies to address GRMD and Duchenne muscular dystrophy (DMD) have also been investigated by Dr. Sleeper and colleagues. Specifically, a systemic gene delivery approach *see page 5*

Calendar

Friday, June 7

Annual Faculty Research Retreat

8:30 am to 5 pm

New Bolton Center, Kennett Square, PA.

Registration will open soon online.

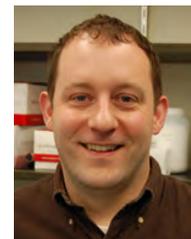
David Roos, Department of Biology University of Pennsylvania will deliver the Marshak Lecture: "Mining Omics Datasets: The Systems Biology of Host-Pathogen Interactions"

Publications

J. Oriol Sunyer was invited to write a review in the first issue of a new journal of the "Annual Review" series called "Annual Review of Animal Biosciences" devoted to publishing reviews relevant to veterinary medicine and biosciences. The review is entitled "Evolution of B Cell Immunity" by David Parra, Fumio Takizawa, and J. Oriol Sunyer. Available online at <http://www.annualreviews.org/doi/abs/10.1146/annurev-animal-031412-103651>



J E Kolesar, C Y Wang, Y V Taguchi, S-H Chou & **Brett A Kaufman**. Two-dimensional intact mitochondrial DNA agarose electrophoresis reveals the structural complexity of the mammalian mitochondrial genome. *Nucleic Acids Res* (2012) 1-14.



Continued from page 4

was utilized in GRMD using a dominant negative mutant of myostatin. Myostatin is a negative regulator of skeletal muscle mass that may also promote fibrosis. Treated dogs were followed for 13 months and systemic myostatin inhibition resulted in increased muscle mass as assessed by MRI and confirmed at tissue harvest. Hypertrophy of type IIA fibers was largely responsible for the increased muscle mass. Reductions in serum creatine kinase and muscle fibrosis were associated with long-term myostatin inhibition in GRMD.⁴ Based on these promising results, long term studies are underway.

Finally, nitric oxide (NO)-cGMP signaling pathways also provide a new potential target for therapeutic intervention in GRMD and DMD. Loss of dystrophin prevents normal nNOS expression and/or signaling in all (skeletal, smooth, and cardiac) muscle and reduced NO-GMP signaling appears to be a key contributor to DMD cardiac pathogenesis. Restoration of nNOS signaling, particularly increased cGMP second messenger levels, may therefore provide therapeutic benefit to dystrophic hearts. Phosphodiesterase 5 inhibitors (PDE5I), which block cGMP breakdown, have been shown to ameliorate cardiac dysfunction in mdx mice (a murine model of DMD). In a short-term study Dr. Sleeper and colleagues compared two PDE5Is

in affected GRMD dogs and based on these results, a long-term trial is currently under way to further evaluate therapeutic efficacy.

Chimpanzee heart health

Nearly 10 years ago, Dr. Sleeper consulted on a case of DCM and CHF in an adult chimpanzee.⁵ Since that time, she has performed echocardiograms on nearly 200 chimpanzees, recommended treatment for approximately 30 with various forms of heart disease and has published reports describing cardiovascular disease in this species. Because cardiovascular disease is a leading cause of death in captive great apes, the Great Ape Heart Project was founded 3 years ago to improve the understanding, diagnosis, and treatment for the four non-human great ape taxa (gorillas, orangutans, chimpanzees, and bonobos). The project now involves more than 50 participants from over 30 institutions and Dr. Sleeper is the cardiac advisor for chimpanzees.

Endurance racing Dr. Sleeper is also an international equine endurance equestrienne with a long list of accomplishments including the 2011 North American Endurance Championship 100 mile ride individual silver medal and team bronze, and 2011 Pan American Championship, Chile team silver medal. In 2011 Dr. Sleeper received the prestigious Maggie Price Award in Endurance in recognition of her equestrian endurance achievements and commitment to the discipline.

Dr. Sleeper's research has funded by the NIH (P40 OD012095 and U54-AR-052646-06) and the Canine Health Foundation. Her office is in RYAN, Room 1120.



Meg Sleeper

Selected publications

Bish, L.T., *et al.*, Long-term restoration of cardiac dystrophin expression in golden retriever muscular dystrophy following rAAV6-mediated exon skipping. *Mol Ther* 2012. 20(3): p.580-9.

Ponder, K.P., *et al.*, Neonatal gene therapy with a gamma retroviral vector in mucopolysaccharidosis VI cats. *Mol Ther*. 2012 20:898-907.

Bell, P., Gao, G., Haskins, M.E., Wang, L., Sleeper, M., Wang, H., Calcedo, R., Vandenberghe, L.H., Chen, S.-J., Weisse, C., Withnall, E., Wilson, J.M. (2011) Evaluation of adeno-associated viral vectors for liver-directed gene transfer in dogs. *Human Gene Therapy*. 2011 22:985-997.

Bish, L.T., *et al.*, Long-term systemic myostatin inhibition via liver-targeted gene transfer in golden retriever muscular dystrophy. *Hum Gene Ther*. 2011. 22(12): p. 499-509.

Bish, L.T., *et al.*, Percutaneous transendocardial delivery of self-complementary adeno-associated virus 6 achieves global cardiac gene transfer in canines. *Mol Ther* 2008. 16(12): 1953-9.

Sleeper, M.M., *et al.*, Successful treatment of idiopathic dilated cardiomyopathy in an adult chimpanzee (Pan troglodytes). *Comp Med*. 2005. 55(1): 80-4.

Sleeper, M.M., *et al.*, Gene therapy ameliorates cardiovascular disease in dogs with mucopolysaccharidosis VII. *Circulation*.. 2004. 110(7): 815-20.

CANINE CANCER RESEARCH PIGGYBANK



Dale Gaumer, Dr. Chris Anastasiou, Kate Goughary, and Brooke Morris

Dr. Christopher Anastasiou, Optometrist at Modern Eye (3419 Walnut Street) recently collected **\$1894** for Penn Vet. In addition to Dr. Anastasiou's gracious donations to Penn Vet, he keeps a very large piggy bank on the counter in his office. Patients of "Modern Eye" happily fill this piggy bank up with coins and paper money to support the **Lucky & Buddy Fund for Canine Cancer Research** at Penn Vet. Dr. Anastasiou supports research at Penn Vet in memory of his two dogs treated at the Matthew J. Ryan Veterinary Hospital. Stop by and meet his friendly staff. Periodically, when the piggy is full, we count the coins for research.

RECENT AWARDS (DIRECT COSTS)

Igor Brodsky

University Research FDN
Role of Calcium signaling in
inflammasome activation
3/1/13-2/28/14 \$25,000

Igor Brodsky

NIH R21
Mechanisms of Inflammasome
Inhibition by Salmonella
2/15/13-1/31/15 \$275,000

Robert Greenberg

NIH R21
Role of schistosome ABC
transporters in modulation of host
immune responses
3/1/13-2/28/15 \$275,000

Mark Haskins

NIH P40
Referral Center: Animal Models of
Human Genetic Disease
3/1/13-2/28/18 \$2.5 million

James Lok

NIH R21
Mechanisms and Treatment of
Chronic, Latent Human
Strongyloidiasis
3/1/13-2/28/15 \$342,517

Lisa Murphy

Commonwealth of PA
Development of a Fast and Sensitive
LC/MS Screening Method for the
Detection of Seizure-Causing
Toxicants 1/1/13-6/30/13 \$9,500

Daljit Vudathala

Commonwealth of PA
Fast and accurate detection of
freshwater algal toxins in animal
tissues using LC/MS
1/1/13-6/30/13 \$13,700

Shelley Rankin

Commonwealth of PA
Evaluation of a Molecular Serotyping
Assay for *Salmonella enterica*
1/1/13-6/30/13 \$21,793

Michael Atchison

NIH Office of the Director: T35
Short-term training: Students in
health professional schools
\$524,640 4/1/13-3/31/18

Michael Atchison

NIH NIAID T32
VMD-PhD training in infectious
disease-related research.
\$964,640 7/1/13-6/30/18

Recent Publications



Greenberg RM.

New approaches for
understanding
mechanisms of drug
resistance in
schistosomes. (2013)
Parasitology. Apr 3:
1-13 [Epub ahead of
print]



C Gonzalez-
Lombana, C
Gimblet, O Bacellar,
W W. Oliveira, S
Passos, LP Carvalho,
M Gold-schmidt, EM
Carvalho, & **Phillip
Scott** (2013) IL-17
Mediates Immuno-
pathology in the

Absence of IL-10 Following Leishmania
major Infection. *PLOS Pathogens* Epub
2013 Mar 21



Pan X, Papasani
M, Hao Y,
Calamito M, Wei
F, Quinn III, WJ,
Basu A, Wang J,
Hodawadekar S,
Zapranzna K, Liu
H, Shi Y, Allman D,
Cancro M,
Atchison ML
(2013) YY1

controls Igk repertoire and B-cell
development, and localizes with
condensin on the Igk locus. *EMBO Epub
ahead of print*



Keynote speaker, Dr Mark Haskins

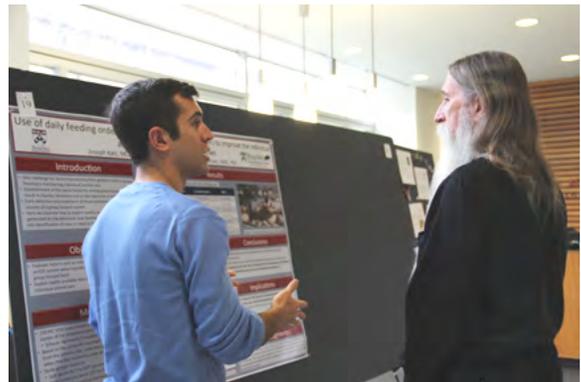
Winners at Phi Zeta Student Research Day on March 25

Neither rain nor snow kept the Penn Vet students from participating in their annual Phi Zeta Student Research Day. Dean Joan Hendricks opened the symposium and Mark Haskins, VMD, PhD, professor in the Department of Pathobiology, delivered the keynote address entitled “Genetic Disease: Translational Medicine-- Yesterday, Today, Tomorrow”. Phil Scott, Associate Dean for Research, awarded **Abigail Shearin 1st place** in the VMD/PhD oral presentations on “Metabolic changes in mice with adipocyte specific deletion of Akt” and **Marc Myers was awarded 1st place** in the VMD oral presentations on “Thrombospondin-2 influences revascularization and bone volume in ischemic fracture”. Other award winners were **Feini Qu, Robyn Allen, Lauren Harris, and Chelsea del Alcazar**. Forty-three abstracts were submitted.

Joseph Katz won 1st prize in the Best Poster Competition on “Use of Daily Feeding Order at an Electronic Sow Feeder (ESF) to Improve the Individual Animal Care of Group Housed Sows”. **Pierce Nathanson won 2nd prize** for his poster on “The DNA-Binding Properties of TDP-43 in Health and Disease” and **Peri Rosenstein won 3rd prize** for her poster on “Mechanisms for the Persistence of the Rabies Virus in Feral Cat Populations in Pennsylvania: Endemicity or Repeated Reintroduction?” Members were inducted into the veterinary medicine honor society, Phi Zeta, *Beta Chapter*.



Marc Myers



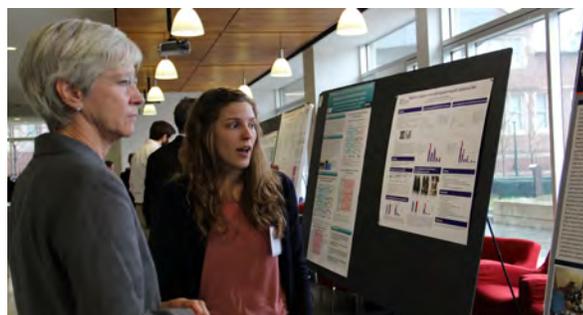
Joseph Katz talks with Mark Haskins



Ray Stock, VMD, looks at Pierce Nathanson's poster



Abigail Shearin

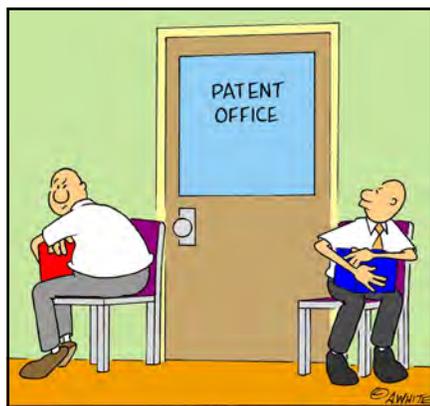


Dean Joan Hendricks at poster session



Feini Qu

Patents--a switch from “first to invent” to “first to file”



On March 16 the United States made a change in patent policy. A major overhaul of patent law has taken place. In the former “first-to-invent” system, patents were granted based on when an

invention was conceived, not when a patent was filed. Under the new system, the person who files first gets the patent, regardless of whether he or she was the first one to conceive of the idea. Moreover, there is no one-year grace period as in the previous policy. Penn's Center for Technology Transfer (CTT), the organization that helps faculty commercialize inventions, file for patent protection, and incubate spin-off businesses, will be handling these changes. A full article by Evan Lerner may be found in *Penn Current*. For more information you may email CTT info@ctt.upenn.edu.

The **Penn Vet Research Newsletter** is distributed quarterly. Suggestions, requests, comments, and story ideas may be directed to: resnews@vet.upenn.edu

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for Research

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Gayle Joseph, Editor

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NIH renews a Penn Vet P40 grant for years 29-33

\$2.5 million in direct costs was approved. The grant, “Referral Center: Animal Models of Human Genetic Disease”, was originated by Donald Patterson DVM, DSc, the founder of the Section of Veterinary Medical Genetics. Since Dr. Patterson’s retirement in 1998, the PI has been Mark Haskins VMD, PhD. Co-investigators include Drs. Margret Casal, Peter Felsburg, Urs Giger, Paula Henthorn, Meg Sleeper, Charles Vite, and John Wolfe. The Referral Center finds, characterizes, and makes available dog and cat gene-homologous models of human genetic disorders for the study of the pathogenesis of disease and the development of effective, safe therapies for human patients. **The genetic dog and cat models under study include dilated cardiomyopathy, ectodermal dysplasia, cutaneous lupus erythematosus, lethal acrodermatitis, 10 lysosomal storage diseases, four clotting factor deficiencies, two porphyrias, X-linked severe combined immunodeficiency, Duchenne muscular dystrophy, cystinuria, tricuspid valve dysplasia, congenital hypothyroidism, epilepsy, and leukocyte adhesion deficiency.** The grant application included 72 supporting letters from colleagues at Penn, and from across the U.S., Canada, Europe, Australia, and South America. The Referral Center contributed to 23 grants and in the previous four years of support was acknowledged in 131 published papers.

Gustavo Aguirre receives the Kennel Club Award

Gustavo Aguirre, VMD, PhD, professor in the Department of Clinical Studies Philadelphia was awarded the International Canine Health Award from the Kennel Club Charitable Trust and Metro Bank at Crufts, the club’s dog show recently held in Birmingham, England. Dr. Aguirre leads the way in research relating to the inheritance of retinal degenerations in dogs, humans, and other mammals.