

# NEWSLETTER

**Inherited retinal disease are leading causes for blindness....both inherited photoreceptor diseases and glaucoma are also major causes for vision loss in dogs**

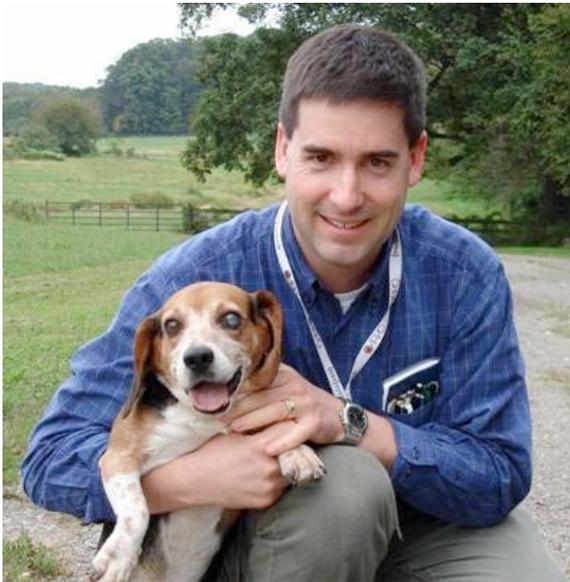


Figure 1: Dr. Komáromy with one of his glaucoma patients.

**Dr. András M. Komáromy** is a clinician scientist at the Department of Clinical Studies – Philadelphia; joining as a post-doctoral fellow in 2003 and becoming an Assistant Professor – Tenure Track in 2004. He received his veterinary degree from the University of Zurich in Switzerland, was an intern in small animal medicine and surgery at the

Michigan State University, and obtained his PhD and veterinary ophthalmology training at the University of Florida. Dr. Komáromy is a board-certified veterinary ophthalmologist. As a clinician, he has a strong interest in comparative ophthalmology, diagnosing and treating eye diseases in various animal species.

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You have just witnessed the birth of a new species: our newsletter. You may ask, "Why do we need another newsletter?" The answer is that we felt it would be informative, helpful, collaborative and community-building. This newsletter is yours to share current research, campus happenings, and important information that requires more than a one line twitter. In Darwinian fashion, we hope that this creature will evolve and grow stronger with your participation. Occasionally unusual mutations may delight or annoy, so please let us know what you think.



Send ideas, suggestions, and tips to:

[resnews@vet.upenn.edu](mailto:resnews@vet.upenn.edu)

**MANY SPECIES. ONE MEDICINE™ 125th Anniversary Research Symposium**

On Wednesday, June 17, 2009, Penn Vet will celebrate a proud tradition going back to 1884 with a 125th Anniversary Faculty Research Symposium at the School of Medicine’s BRB II/III Auditorium. As many of you know, a rich history led to the establishment of a School of Veterinary Medicine during the 19th century. Penn Vet will commemorate its early beginnings in concert with the School of

Medicine with the symposium: “**Animal Diseases and Translational Research**”. Dr. John Wolfe, Professor of Pathology and Medical Genetics in the Department of Pathobiology is this year’s chair of the organizing committee which includes Drs. Rose Nolen-Walston, Kurt Hankenson, Meg Sleeper, and Bruce Freedman, Phillip Scott, and Dean Joan Hendricks.

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## Veterinary Center for Infectious Disease Research

Funding opportunity: Research Initiative Funds. Potential applicants are encouraged to read the new instructions carefully, since they are extensively modified for 2009. The Funds are to support research in Infectious Disease and Food Safety that encompasses collaboration between laboratories in a clinical department (Clinical Studies - Philadelphia, Clinical Studies - NBC) and laboratories in a basic science department (Animal Biology, Pathobiology). Proposals matching intra-departmental laboratories that are clearly focused on clinical or basic research will also be considered. Funds are intended to foster translational research by promoting collaborations between basic and clinical research laboratories. Applications up to \$100,000 (full-cost budget) will be entertained.

<http://www.vet.upenn.edu/> (under Research Centers)

Please contact Louisa Dowling ([dowling@vet.upenn.edu](mailto:dowling@vet.upenn.edu)) for more information.

## Dr. Komáromy's research continued from page 1

Dr. Komáromy is a member and intermittent chief of the Ophthalmology Service at the Matthew J. Ryan Veterinary Hospital at the University of Pennsylvania, where he also directs the veterinary ophthalmology residency program. Before receiving his first NIH R01 grant from the National Eye Institute (NEI) in 2009, he was enrolled in the Penn Vision Clinical Scientist Program (NEI-supported K12 program) at the Scheie Eye Institute; the first and only veterinarian to date going through this program designed for MD ophthalmologists. His primary research and clinical interests are determining the molecular causes of inherited retinal diseases in the dog and developing treatment approaches to ameliorate sight degeneration.

**Inherited retinal and optic nerve diseases are leading causes for blindness:** Two of the most common diseases responsible for vision loss, especially in individuals over 50-years of age, are age-related macular

degeneration (AMD) and glaucoma. Both diseases are multifactorial with a strong genetic predisposition, and they are some of the most common neuro-degenerative diseases in man. In outer retinal diseases such as AMD, the loss of the cone photoreceptors is responsible for the deterioration of eye sight. In contrast, in glaucoma it is the loss of the retinal ganglion cells located in the inner retina and their axons in the optic nerve which are primarily damaged. Despite the high disease prevalence, the mechanistic basis of AMD and glaucoma are not well understood and a cure is currently not available.

**Why the dog?** The Komáromy laboratory, in collaboration with other investigators, takes advantage of the fact that inherited photoreceptor diseases and glaucoma are also major causes for vision loss in dogs. The morphology of the canine and human retina is very similar, with a cone-rich central region and a well developed retinal vasculature. *continued on page 3*



Figure 2: A scene as it might be viewed by a healthy person (a), a patient with AMD (b), and a patient with glaucoma (c). Note that with AMD the initial loss of sight occurs in the central visual field, mediated by the cone-dense macula, while with glaucoma the initial visual field loss occurs typically in the periphery (“tunnel vision”). Simulations were provided by the National Eye Institute.

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Furthermore, the dog eye is similar in size to the human eye, which becomes important when new therapies are translated from one species to the other. The research done in the dog complements the work done in other animal species and will ultimately benefit both dog and man.



**Understanding disease mechanisms in cone photoreceptors – the example of achromatopsia or total color blindness:** In order to obtain a better understanding about complex outer retinal diseases such as AMD, the Komáromy laboratory, together with collaborators at the University of Pennsylvania (Dr. Gustavo Aguirre), Cornell University (Dr. Gregory Acland), and Temple University (Dr. Jacqueline Tanaka), are focusing on achromatopsia, a congenital primary disease of the cone photoreceptors. Children that are born with this disease suffer from day blindness, increased light sensitivity (photophobia), complete color blindness, and a loss of central visual acuity. In order to cope with their disability, many achromatopsia patients must wear dense sunglasses during the day, to prevent light-induced discomfort, and they must use magnifying glasses to read standard size print.

Dr. Komáromy and his collaborators study achromatopsia in two dog breeds. In these canine patients and about 75% of human achromatopsia patients, the underlying genetic defect affects the function of the cone cyclic nucleotide-gated ion channels, which are crucial for the normal functioning of the cone photoreceptor. The goal of the research is to determine the molecular disease pathways that lead from the mutation to the clinical disease phenotype. Ultimately, the investigators would like to discover means by which to reverse the disease process and restore cone function.

**Rescue of cone function with viral-mediated gene therapy – achromatopsia as a test case:**

For most investigators, the ultimate goal of studying and understanding disease processes is to find a cure. In collaboration with other investigators, such as Dr. William Hauswirth at the University of Florida, Dr. Komáromy has recently been able to successfully restore cone function by viral-mediated gene therapy in both forms of canine achromatopsia. The virus being used is a recombinant adeno-associated virus (rAAV), a human parvovirus that so far has not been shown to cause disease. Preliminary results in the achromatopsia-affected dogs are very encouraging, with long-term restoration of day vision. The NIH has provided 5-years of additional funding to evaluate and refine this treatment for subsequent use in human patients with cone photoreceptor diseases. The work is also supported by the Foundation Fighting Blindness

(FFB). Retinal gene therapy using rAAV for a childhood blindness, Leber congenital amaurosis, has recently entered phase 1 clinical trials at the University of Pennsylvania and other institutions, and so far the results have been very promising. This raises hope that future gene therapy for human achromatopsia patients may also be effective.

**Glaucomatous optic neuropathy – it is not just about the pressure!**

Glaucoma is a group of progressive optic neuropathies characterized by a slow progressive degeneration of retinal ganglion cells and their axons, resulting in visual loss. Without treatment, glaucoma causes visual degeneration and eventual blindness. Elevation in intraocular pressure (IOP) is the only proven treatable risk factor for glaucoma. Consequently, currently approved glaucoma medications and surgical therapies are directed at lowering IOP to attenuate the progressive visual field loss. However, some patients continue to suffer from an ongoing visual field loss even after their IOP is effectively controlled. These observations indicate the possible contribution of IOP-independent mechanisms to disease progression.

Primary open-angle glaucoma (POAG) is the most common type of glaucoma in humans, particularly in populations of European and African ancestry. Glaucoma is also a leading cause of blindness in dogs, but in contrast to man, the POAG form is extremely rare. Therefore, it was a big breakthrough when Dr. Komáromy identified a number of

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Dr. Komáromy's research continued from page 3

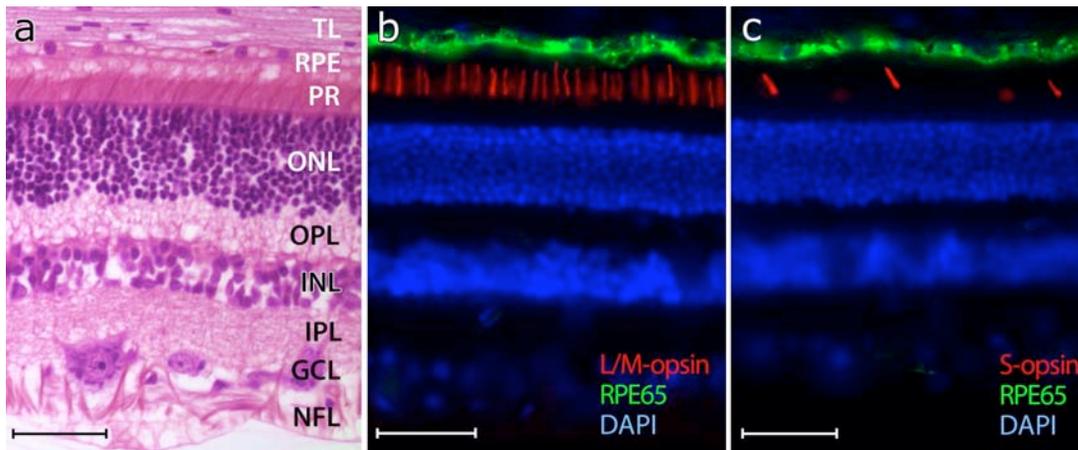


Figure 3: Photomicrographs of normal canine retinas. (a) The outer retina contains the rod and cone photoreceptors (PR), while the retinal ganglion cells (GCL) are located in the inner retina. (b) Labeling of red/green-sensitive cone outer segments in red. (c) Labeling of the blue-sensitive cone outer segments in red. The retinal pigment epithelium (green) is labeled with an RPE65 antibody, and the cell nuclei are shown in blue with DAPI (b, c). The following layers are identified in (a): Tapetum lucidum (TL), retinal pigment epithelium (RPE), photoreceptors (PR), outer nuclear layer (ONL), outer plexiform layer (OPL), inner nuclear layer (INL), inner plexiform layer (IPL), ganglion cell layer (GCL), and nerve fiber layer (NFL). Calibration marker = 40  $\mu$ m.

POAG-affected dogs. Together with collaborators at the University of Pennsylvania (Dr. Gustavo Aguirre), Cornell University (Dr. Gregory Acland), and Vanderbilt University (Dr. Rachel Kuchtey), and with support of the University Research Foundation, he is working on the identification of the disease-causing genetic defect. Furthermore, in order to continue the work of his former mentor Dr. Kirk Gelatt at the University of Florida, Dr. Komáromy is planning to establish a colony of POAG dogs at the University of Pennsylvania for eventual translational studies. Such studies should clearly shed some light on the mechanisms responsible for disease and provide a valuable model in which to test translational therapies to improve vision in human glaucoma patients. ❖

Dr. Komáromy's laboratory is located in Ryan 2024 and his office in Ryan 3006 .



### Veterinary Library Search Tools & Training

There are 30 minute training classes offered both here and at New Bolton Center for a variety of search tools—**pubmed**, ISI citation index, Scopus (multidisciplinary and strong scientific abstract and citation database), Ovid Multi-file (such as CAB Abstracts, Medline, Agricola, Biosis, and Global Health). Over the next several weeks, the Veterinary Libraries will be offering 30 minute training sessions on a number of key resources and tools available at Penn. These sessions will give you a general introduction to each database and the knowledge to construct basic search strategies. Feel free to attend any or all of the sessions. Sessions are scheduled for 12 noon and will be held either in the **Atwood Library** or the **NBC Library**. Feel free to bring your lunch to the sessions! Registration is not required, but if possible, please send us email at [vetlib@pobox.upenn.edu](mailto:vetlib@pobox.upenn.edu) and let us know which sessions you plan to attend, so we can estimate total attendance.

[http://gethelp.library.upenn.edu/guides/vet/lecture\\_series.html](http://gethelp.library.upenn.edu/guides/vet/lecture_series.html)

Frank Campbell [campbell@pobox.upenn.edu](mailto:campbell@pobox.upenn.edu)

## ANNIVERSARY RESEARCH SYMPOSIUM *continued from page one*

The day-long event will highlight contributions of research on animal diseases, that have, or may, facilitate translation from bench-to-bedside or cage-to-stall. Presentations will focus on naturally occurring animal diseases in the domestic animal species, including both captive and clinical populations. There will be studies presented on clinical diseases applicable to advance medical research for all species.

Speakers will include Penn Vet's **Gustavo Aguirre V.M.D., Ph.D.** (*From gene discovery to treatment in canine models of human blindness*); **Steven Walkley, D.V.M., Ph.D.**, Albert Einstein College of Medicine (*The Pathobiology of Lysosomal Disease in Large Animal Models*); **Francis Golder, D.V.M., Ph.D.**, Penn Vet (*Phrenic motorneuron facilitation and potential translation to spinal cord injuries*); **Andrew Lackner D.V.M., Ph.D.**, Tulane University (*Non-human primate models of neuroAIDS*); **Thomas Parsons, V.M.D., Ph.D.**, Penn Vet (*Temporal coding by the chick auditory nerve: Implications for human cochlear prostheses?*); **Dennis D. Hickstein, M.D.**, Center for Cancer Research, NCI/NIH (*Gene therapy for leukocyte adhesion deficiency- the road from Irish Settlers to children*); **Dorothy Cimino Brown, D.V.M., M.S.C.E.**, Penn Vet (*Translational potential of clinical trials in animal patient populations*); **Randall S. Prather, Ph.D.**, University of Missouri and the Natl. Swine Resource and Research Center (*Transgenic and cloned pig models of cystic fibrosis*); **Kurt Hankenson, D.V.M., Ph.D.**, Penn Vet (*The potential for skeletal regeneration using mesenchymal stem cell-based therapy*); **Margaret M. Sleeper, V.M.D.**, Penn Vet (*Canine familial dilated cardiomyopathy and potential treatment approaches*); and **Rainer Storb, M.D.**, Fred Hutchinson Cancer Research Center (*Dog models for organ trans-plantation and gene therapy of muscular dystrophies*). The anniversary symposium is co-sponsored by the **Walter Flato Goodman Center for Comparative Medical Genetics; Institute for Translational Medicine and Therapeutics (ITMAT)**; and training programs in comparative medical and molecular genetics and gene therapy/cystic fibrosis and genetic diseases. Register online at <http://www.vet.upenn.edu/2009symposium> to enjoy the presentations and join with us in honoring our ongoing partnerships campus-wide.



### PENN VET Student Research

*Morris Animal Foundation Veterinary Student Scholar Project*—Four Penn Vet students were awarded Student Scholar stipends for their research projects. They were: **Lizette Durand** (mentor: Thierry Work) “Isolate CFPHV, the herpes virus associated with marine turtle fibropapillomatosis”; **Angela Fusello** (mentor: Craig Bassing) “Characterization of the DNA Damage Response Pathway in Canine Lymphoma and Assessment of PARP1 Inhibitors as Novel Chemotherapeutic Agents”; **Alexandra O’Keefe** (mentor: Urs Giger) “Studies on Immune-mediated Hemolytic Anemia Focusing on American Cocker Spaniels”; and **Sana Ahmed** (mentor: James Serpell) “Dog Bites: An Assessment of Veterinary and Pediatric Professionals Understanding, Attitudes, and Practice”.



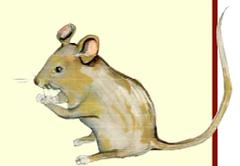
**NIH updates**—In response to the **NIH Stimulus Package** approximately 45 Penn Vet applications were submitted to NIH in the form of ARRA administrative supplements, competitive supplements and challenge grants as well as shared equipment and renovation applications. Penn Vet Business Administrators and the Office of Research Services were very supportive and helpful to the principal investigators.

Beginning with the summer 2009 review cycle/September Council, the **review criteria by which NIH applications are scored** has been substantially revised. This new scoring system is geared at evaluating the overall **IMPACT** of the proposal and addressing its **MAJOR** strengths and weaknesses. As such, an emphasis on the impact and significance of your proposal on a human health issue is essential. The new scoring system will utilize a 9-point rating for the impact/priority score.

For more information please go to: <http://enhancing-peer-review.nih.gov/> .

**ULAR updates:** New staff veterinarians have now joined ULAR, Drs. Christin L. Veeder and Janlee A. Jensen. Dr. James O. Marx has been appointed Assistant Professor Clinician Educator in Laboratory Animal Medicine of the Department of Pathobiology. On the services side, ULAR have just completed an electronic survey of users, are comparing the data with our 2006 electronic survey and will be presenting these data to Penn's the Animal Program Advisory Committee (APAC). The Clinical Research Building (CRB) mouse colonies, that were moved temporarily to Hill Vivarium for upgrades to the CRB environmental monitoring systems, are just about to move back to CRB.

<http://www.upenn.edu/research/rcr/animals.htm>



**Check-out: INSIDE.Vet** <http://inside-wlbs.vet.upenn.edu/>



The 'Research' silo on **INSIDE.VET** provides information on funding opportunities (both external and here at Penn); guidelines and policies for faculty; core facilities; grant-writing tips; seminar series announcements; NIH information; authorship guidelines; Penn Vet's internal mini-study section guidelines; center and institute information; research events; and a variety of resources and tools for faculty and laboratory staff. A selection of Penn Vet faculty publications over the last three years may be found on INSIDE.VET (Research).



## **125th ANNIVERSARY RESEARCH SYMPOSIUM**

WEDNESDAY, JUNE 17, 2009 LOCATION: BRB II/III AUDITORIUM

8:00 AM TO 6:30 PM

Online registration: <http://www.vet.upenn.edu/2009symposium>

Poster guidelines: posters should be no larger than 4 ft x 4 ft and pins will be provided.

## Some recent grants awarded:

G. Aguirre, CoP I:W. Beltran, B. Zangerl  
Foundation Fighting Blindness  
Title: Large animal translational & research facility  
Dates: 4/1/09-3/31/14  
\$1,150,000

Paula Henthorn  
AKC  
Title: Molecular basis of tricuspid valve dysplasia  
Dates: 1/1/09-12/31/10  
\$98,930

Andras Komaromy  
NIH  
Title: Achromatopsia - Disease Mechanisms and  
Cone-Directed Gene Therapy  
Dates: 2/1/09-1/31/14  
\$2,322,847

Nicola Mason  
AKC  
Title: Immune targeting of canine  
hemangiosarcoma using a canine single chain  
antibody approach  
Dates: 1/1/09-12/31/10  
\$123,126

K. Sorenmo  
OASMI Pharmaceutical  
Title: Efficacy and Safety of Paclical Vet vs  
Lomustine in Canine Mast Cell Tumors  
Dates: 2/09-12/10  
\$61,009

T Schaer/D Richardson  
Synthes  
In vivo porcine model for trochanteric fixation in  
femoral neck/trochanteric fractures  
1/1/2009--12/31/2009  
\$1,598,621

T Schaer/D Richardson  
Synthes  
Evaluation of porous PEEK in vertebral bone  
1/1/2009--12/31/2009  
\$461,096

Narayan Avadhani  
NIH  
Role of Mitochondria Targeted CYP2I and HO-1  
in Alcohol Mediated Tissue Injury  
8/1/08--7/31/2013  
\$1,711,875

Narayan Avadhani  
NIH  
Mechanisms and Functions of Biomodally  
Targeted Cytochrome P450s to Mitochondria  
7/1/2009--6/30/2014  
\$1,575,000

Narayan Avadhani  
NIH  
Role of Mitochondrial Respiratory Stress  
Signalling in Cancer Progression  
7/1/2009--6/30/2014  
\$1,968,750

Kendra Bence  
NIH  
Neuronal Protein Tyrosine Phosphatases in  
Metabolism  
7/1/2009--6/30/2014  
\$1,968,750

Leszek Kubin  
NIH  
A Rodent Model of Compromised Upper Airway  
4/1/2009--3/31/2011

Dan Yee  
NIH R01  
Central Actions of Angiotensin II in the Control  
of Fluid Balance  
1/1/2009--11/30/2013  
\$1,968,750

Dieter Schifferli, R2I (NIH)  
The PSA Fibriae of *Yersinia pestis*, as adhesin with  
protective immunogenic properties  
02/15/09-01/31/11  
\$449,076

Phil Scott, R01 (NIH)  
Initiation of Immune Response in Chronic  
Leishmaniasis  
2/15/09-1/31/14  
\$1,968,750

Hannah Galantino  
The Bernice Barbour Foundation  
Laminitis Discovery Database  
1/2/2009--1/1/2010  
\$132,000

Robert Whitlock  
Grayson Jockey Club  
Botulism: A New Diagnostic Approach-Real Time  
PCR Test  
1/1/2009--12/31/2009  
\$21,600

T Schaer/D Richardson  
Synthes  
Evaluation of *in vivo* performance of IPS  
biomaterial in ovine model  
1/1/2009--12/31/2009  
\$520,022

T Schaer/D Richardson  
Synthes  
Validation of efficacy of Synthes Collagen Putty  
1/1/2009--12/31/2009  
\$437,076

Robert Greenberg  
NIH R2I  
Transformation of *C. elegans* with a novel  
schistosome calcium channel subunit  
5/15/2009--3/31/2011  
\$433,111

See more faculty publications on <http://inside-wlbs.vet.upenn.edu/> under *Research*.

## Recent Publications



Influence of Sex and CRF Pathways as Determinants in 5-HT Sensitivity. McEuen JG, Semsar KA, Lim MA, Bale TL. *Endocrinology*. Apr 2. [Epub ahead of print] PMID: 19342454 (2009)



Sweeney RW, Whitlock RH, Bowersock TL, Cleary DL, Meinert TR, Habecker PL, Pruitt GW. Effect of subcutaneous administration of a killed *Mycobacterium avium* subsp. *paratuberculosis* vaccine on colonization of tissues following

oral exposure to the organism in calves. *Am J Vet Res* (2009) 70:493-498.



MHC class II-dependent basophil-CD4<sup>+</sup> T cell interactions promote Th2 cytokine-dependent immunity. Perrigoue JG, Saenz SA, Siracusa M, Allenspach EJ, Taylor BC, Giacomini PR, Nair MG, Du Y, Zaph C, van Rooijen N, Comeau MR, Pearce EJ, Laufer TM, and Artis D. (2009) *Nature Immunology* In press.



Virus-Induced Unfolded Protein Response Attenuates Antiviral Defenses via Phosphorylation-Dependent Degradation of the Type I Interferon Receptor. Jianghuai Liu, Wei-

Chun HuangFu, K.G. Suresh Kumar, Juan Qian, James P. Casey, Robert B. Hamanaka, Christina Grigoriadou, Rafael Aldabe, Alan Diehl, and Serge Y. Fuchs. *Cell Host Microbe* 5, 72-83 (2009)

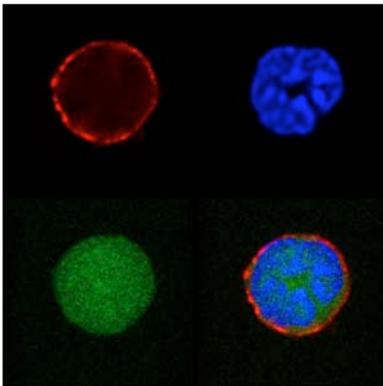


Female Mice Delay Reproductive Aging in Males. Jonathan A Schmidt, Jon M Oatley, and Ralph Brinster. *Biology of Reproduction* 80: 1009-1014 (2009)



B. Zangerl, J. L. Johnson, J. Pillardy, Q. Sun, C. André, F. Galibert, G.M. Acland, G.D. Aguirre. Comparative genomic mapping of uncharacterized canine retinal ESTs to identify novel candidate genes for hereditary retinal disorders

*Molecular Vision* 15:927-936 (2009)



A research paper soon to appear in *Nature Immunology* entitled "MHC class II-dependent basophil-CD4 + T cell interactions promote Th2 cytokine-dependent immunity" by Perrigoue JG, Saenz SA, Siracusa M, Allenspach EJ, Taylor BC, Giacomini PR, Nair MG, Du Y, Zaph C, van Rooijen N, Comeau MR, Pearce EJ, Laufer TM, and David Artis identifies basophils (pictured here) as novel initiators of

type 2 immunity. Type 2 inflammatory responses are required for immunity and tissue repair following exposure to helminth parasites. However, Th2 cytokine responses can also promote asthma and allergic disease pathology. Although dendritic cells (DCs) are thought to drive Th2 responses, the Artis' lab demonstrated that antigen presentation by DCs alone is insufficient, and that basophils are required to initiate CD4+ Th2 cell responses and type 2 inflammation at mucosal surfaces. These results suggest new mechanisms by which immunity to parasites and the potential pathologic effects that accompany type 2 immunity can be regulated. The original images, featured on the cover of *Nature Immunology*, were generated by Jacqueline Perrigoue and Lingli Zhang. Dr. Zhang, director of Penn Vet's Imaging Core Facility, may be

contacted at (215) 746-0471. The core houses a new (4 laser) two-photon/cofocal laser scanning spectral imaging Leica SP5 system on a DM6000 microscope and a (2 laser) Yokagawa CSX-1 spinning disk confocal configured with a Leica DMI4000 microscope. The Artis Lab is funded by NIH, Crohn's & Colitis Foundation, Burroughs Wellcome Fund, UPenn Pilot funds from the University Research Foundation, Penn Genome Frontiers Institute, and the Veterinary Center for Infectious Disease Research.

The **Penn Vet Research Newsletter** will be distributed quarterly. Suggestions, requests, comments, and story ideas should be directed to: [resnews@vet.upenn.edu](mailto:resnews@vet.upenn.edu).

Office of the Associate Dean for Research, Phillip Scott, Ph.D.



TO: