

NEWSLETTER

The pathogenesis and treatment of *inherited brain diseases in feline and canine models of human disease...*

Dr. Charles H. Vite is an Assistant Professor of Veterinary Neurology (tenure-track) in the Department of Clinical Studies – Philadelphia. He received a B.S. in Biology from Cornell University in 1986 and his D.V.M. at Purdue University in 1990. He worked nights as an emergency veterinarian at Veterinary Emergency Service, Inc. in Fresno, California until 1992 when he came to Penn Vet for residency training in veterinary neurology. He remained at Penn as a neurology lecturer, obtained a Ph.D. in Cell and Molecular Biology (Gene Therapy), and joined the faculty in 2004. Dr. Vite’s research interest is the study of the pathogenesis and treatment of inherited brain diseases in feline and canine models of human diseases. This work involves 1) identification of ante mortem and post mortem surrogate markers of disease progression and severity; 2) development and application of experimental therapies; 3) evaluation of therapeutic efficacy in these large animal models using validated surrogate markers; and 4) use of these experimental therapies



and surrogate markers to further understand disease pathogenesis.

Cholesterol and the cat brain
Niemann-Pick type C (NPC) disease is a progressive neurological disorder characterized by dementia and ataxia, hepatic and pulmonary disease, and death typically within the first or second decade. Over 300 disease-causing mutations have been identified in the lysosomally-localized proteins NPC1 and NPC2 which result in altered regulation of cholesterol homeostasis;

2011 Faculty Research Retreat

The **Translational and Collaborative Partnerships** theme of the annual research retreat was carried out in five paired presentations by Penn Vet Faculty in a multi-disciplinary forum held on Friday, June 10, 2011 at New Bolton Center in Kennett Square, Pennsylvania. Over 125 faculty, postdocs, and students attended the talks and poster session followed by a reception at the Allam House. The Annual Pfizer Award for Research Excellence was presented to **Dr. Kendra Bence**, Department of Animal Biology. Read more about the event on page 6.



lysosomal storage of cholesterol, gangliosides, and sphingosine; and neurodegeneration. Despite the identification of causative mutations, the pathogenesis is not clear and therapies to successfully

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Pathogenesis and treatment of inherited brain diseases in feline and canine models--continued

treat NPC disease have been ineffective to date.

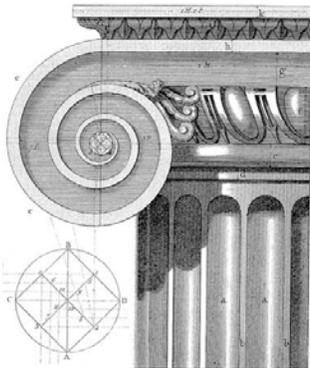
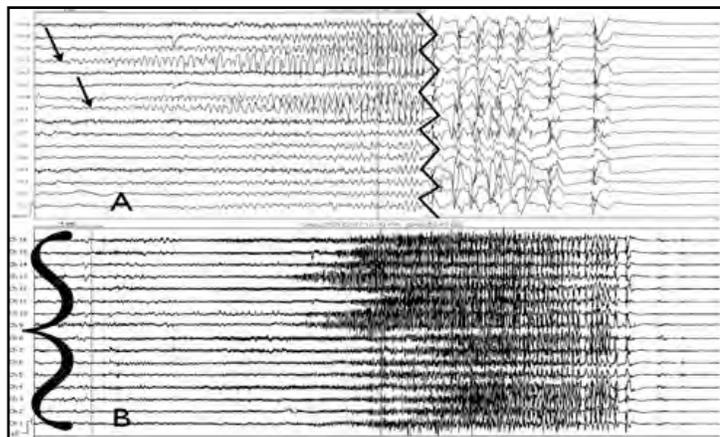
The critical barriers to developing effective treatment for Niemann-Pick type C (NPC) disease are 1) the lack of natural history studies due to the relatively low incidence and the heterogeneity of disease in human patients, 2) an insufficient understanding of how the defect in cholesterol transport results in the phenotype, 3) the paucity of validated surrogate markers of

brain disease that can be monitored as secondary clinical endpoints, and 4) the dearth of candidate compounds which substantially improve neurological disease in animal models. Dr. Vite's laboratory addresses these barriers first by utilizing a unique large animal model of NPC disease for which a breeding colony and natural history data exist. Second, the

well-characterized feline model allows for the identification and validation of biochemical and nuclear magnetic resonance surrogate makers of neurological disease due to its large size and its accurate recapitulation of human disease. These biochemical markers provide insight into CNS disease pathogenesis. Third, recent studies in both the feline and

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Figure 1. (A) Focal onset right occipital seizure (arrows) with secondary generalization in a dog on intracranial EEG, onset and termination. Jagged vertical line denotes intervening portion of record (removed) showing secondarily generalization. (B) Regional onset seizure (sharp wave to left of red line defines onset time, bracket denotes channels involved). Event begins with diffuse electrodecrement and widespread low voltage fast activity prominent in channels 15, 16, 7,8, 4 and 1, among others.



New website to Help Researchers Collaborate—A new [Collaboration Opportunities website](#), sponsored by the Clinical and Translational Science Awards (CTSA) Consortium, is designed to help researchers post requests for needed collaborators and search for opportunities to collaborate with others. Those who post and respond do not need to be affiliated with a CTSA institution. Projects should address an interesting question in clinical or translational science. If you want to be notified when colleagues post projects, please subscribe at [CollabOppNotice](#). The NIH National Center for Research Resources administers the [CTSA program](#), which supports a cooperative network of institutions focused on advancing clinical and translational research.

Podcasts—Writing your Vertebrate Animal Section Podcast. There are helpful podcasts on grant writing to explain [what must be included in your grant application](#) if you use vertebrate animals in your research. The Office of Extramural Research --all about grants podcasts may be found at this [site: http://grants.nih.gov/podcasts/All_About_Grants/](http://grants.nih.gov/podcasts/All_About_Grants/)



New publications.....

Eroshin VE, Reiter AM, Rosenthal K, Fordham M, Latney L, Brown S, **Lewis JR.** Oral disease in a population of rescued ferrets: clinical examination findings. *J Vet Dent*, 2011, 28: 8-15.

NEMO Binding Domain peptide inhibits constitutive NF- κ B activity and reduces tumor burden in a canine model of relapsed, refractory Diffuse Large B-Cell Lymphoma. Gaurnier-Hausser A, Patel R, Baldwin AS, May MJ, **Mason, N.** *Clin Cancer Res.* 2011 May 24. [Epub ahead of print]



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murine models have revealed substantial therapeutic benefit of 2-hydroxypropyl- β -cyclodextrin (HP β CD) on NPC disease.

Dr. Vite is funded by an RO1 (NIH) to rigorously evaluate the mechanistic, pharmacologic, and toxicity issues associated with HP β CD therapy in NPC disease. His laboratory discovered that intrathecal administration of HP β CD ameliorates all clinical aspects of neurological disease at least up to a year of age (untreated cats need to be euthanized at 24 weeks of age for the neurological disease) and that neuronal storage of cholesterol was substantially reduced. They also identified a dose-related toxic effect of HP β CD on hearing threshold. The remarkable therapeutic effect of HP β CD in affected cats has led to its use as an FDA-designated orphan drug and to plan for a controlled clinical trial in NPC patients. The availability of effective intrathecal therapy also allows for the identification and validation of biochemical markers of disease severity and therapeutic effect and to further understand the mechanism of action of cholesterol storage in CNS disease. In collaboration with Washington University in St Louis, Dr. Vite has evaluated the effect of cyclodextrin therapy on serum oxysterol concentrations in treated cats, to help validate oxysterol concentrations as the first blood test available for diagnosing NPC in newborns. His laboratory has also identified altered beta-amyloid processing in the spinal fluid of treated cats compared to untreated cats in collaboration

with the University of Gothenburg. Their ongoing work is focused on identifying the mechanism of action of cyclodextrin in CNS therapy as well as on hair cell function of the inner ear.

Predicting seizures in dogs

Idiopathic canine epilepsy is the most common neurological disorder seen in the neurology clinic and the prevalence, age of onset, and signs of the naturally occurring canine disease are similar to those observed in humans. The majority of dogs with recurrent seizures have no intracranial structural defect, no demonstrable serum or spinal fluid abnormalities, and no interictal neurological deficits, consequently, the disease is "idiopathic". Affected dogs usually have their first seizure during the first three years of life (approximating adolescence to early adulthood), and exhibit recurring motor, autonomic, and/or behavioral signs throughout life. Electroencephalographic studies reveal focal spikes and spike/wave discharges in canine epilepsy, but are technically difficult to document due to the need for behavioral training or sedation to minimize recording artifacts.

Despite spending as little as 0.01% of their lives having seizures, dogs and people with epilepsy take antiepileptic drugs (AEDs) on a daily basis for years to decades. Many experience significant AED-related side effects, and approximately 1/3 of patients continue to have seizures despite treatment. To reduce exposure to AED, epilepsy could be more

effectively treated by responsively delivering AEDs only during periods of increased seizure likelihood. Dr. Vite is funded by a grant from NeuroVista Corporation to implant cortical electrodes and to use mathematical electroencephalogram-based algorithms to detect (and develop ways to predict) the onset of seizures in dogs. Preliminary data from these studies have resulted in a well-scored UoI grant (14 percentile) that includes co-investigators at the Mayo Clinic, University of Minnesota, and University of Pennsylvania and for which Dr. Vite, at the Veterinary School and Dr. Litt, at the School of Medicine, are co-investigators. Their expectation is that this novel investigation will enable the development of a seizure prediction device for human and animal patients which will limit the requirement for AEDs to those times when a seizure is expected. It is also anticipated that the ability to record continuous intracranial activity in dogs via telemetry will aid in developing evidence-based methods to treat better both status epilepticus and epilepsy.

Dr. Vite's research is funded by the NIH (1RO1NS073661-PI Vite), NCRP P40 grant (RR02512 - PI Mark Haskins), Ara Parseghian Medical Research Foundation, Johnson and Johnson, and NeuroVista Corporation. His office is located in the Rosenthal Building, room 208. ☞



NEW ONLINE TOOLS FOR AUTHORS:

AMA Manual of Style and PubsHub

New Penn Libraries subscriptions to the American Medical Association's (AMA) **Manual of Style and PubsHub Journals & Congresses** should help authors to polish their manuscripts, then to choose a suitable journal in which to publish.

JAVMA refers authors to the **AMA Manual** for questions of style. Search and link to it from FindIt or Franklin, or access it directly at <http://hdl.library.upenn.edu/1017/95780>

PubsHub is a database of Submission Criteria for journals and conferences:

- For more than 3,600 biomedical journals, PubsHub provides journal impact factors, links to author guidelines, circulation numbers, acceptance rates, and publication turnaround times, where this information is available. Advanced search features indicate the types of article accepted (case reports, rapid communication, etc.)
- For nearly 2400 conferences, search or browse by subject to find information on the number of attendees, upcoming deadlines, dates and locations of conferences, and whether and where abstracts are published.

Limited Veterinary outlets....

PubsHub will be of most use to Penn Vet authors planning to publish or present in human medicine venues. It includes only three of the top ten veterinary journals (ranked by ISI impact factor). Veterinary titles included in PubsHub are:

American Journal of Veterinary Research, Australian Veterinary Journal, BMC Veterinary Research, Comparative Immunology Microbiology And Infectious Diseases, Equine Veterinary Journal, Medical Mycology, Veterinary Clinics of North America: Small Animal Practice and Veterinary Research.

Veterinary associations and/or conferences described in PubsHub are: Australian Veterinary Association (AVA), World Association for Veterinary Dermatology (WAVD), and World Small Animal Veterinary Association (WSAVA).

Access PubsHub directly at: <http://hdl.library.upenn.edu/1017/94538> or visit the Veterinary Library homepage at: <http://www.library.upenn.edu/vet>

Follow Penn Vet library news at <http://pennvetlib.blogspot.com/>

The Penn Vet Student Inspiration Awards

The Penn Vet Student Inspiration Awards are given annually to current Penn Vet students. The award is designed to inspire ambition and reward – for enterprise, creativity, vision and talent. The 2011 Student Inspiration Award is **Jonathan Lustgarten**, Class of 2013, for his vision in creating a state-of-the-art, easily deployed veterinary health record system to help veterinarians and staff in caring for animals during disaster relief efforts.

Biomedical Postdoctoral Programs

The **10th Annual Biomedical Postdoctoral Research Symposium** will feature a keynote lecture by the incoming dean of the School of Medicine, Dr. J. Larry Jameson on Wednesday, **October 12, 2011**. Abstracts are due July 22nd. Go to the [Postdoc Research Symposium](http://PostdocResearchSymposium) website for more information or call 215 573-4332.

The Office of Biomedical Postdoctoral Programs (BPP) works to provide biomedical postdocs in the Schools of Medicine, Veterinary Medicine, Dental Medicine, Nursing, Children's Hospital and the Monell Chemical Senses Center with the highest quality **training in and outside of the laboratories. Responsible Conduct of Research classes; Bioethics sessions; and career planning programs** are offered periodically. Go to their site to learn more about their programs offered throughout the year.

<http://www.med.upenn.edu/postdoc/>



Aronson LR, Stumhofer J, Drobatz KJ, Hunter CR. Affect of Cyclosporine, dexamethasone and CTLA4-Ig on production of

cytokines in normal cats and those undergoing renal transplantation.

Am J Vet Res 72(4):541-9, 2011

RECENT AWARDS....funding our research

James Marx

Grants For Laboratory Animal Science which is sponsored by AALAS. "Effects of Blood Collection on Clinically Ill Mice in Biomedical Research".

6/2011 - 5/2012 \$28,200

James Marx

ACLAM Foundation "The Oral Administration of Antibiotics to Research Mice".

7/1/2011-6/30/2012 \$10,800

Diane J. Gaertner

NIH/NCRR 1-R25-RR-032017-01 "Translational Research and Laboratory Animal Medicine Education for Veterinarians"

05/01/11 - 02/28/16 \$371,490.00

Tajie Harris and Chris Hunter

NIH R21 "Role of chemokines in the T cell response to ocular toxoplasmosis"

5/1/11-4/30/13 \$275,000

Brett Kaufman

United Mitochondrial Disease Foundation (UMDF) "Regulatory mechanisms governing TFAM-mediated mtDNA copy number control"

8/1/2011-7/31/2012 \$20,000

Lauren Wiley

(G Smith Laboratory) Nestle Purina Canine Hip Dysplasia Study: Lifelong Assessment of the Metric Value of the PennHIP Distraction Index and the Norberg Angle. 5/1/11-12/31/11 \$6,795

Pete Felsburg

NIH R01-AI-043745 Gene Therapy for Canine X-linked SCID

6/1/11-5/31/12 \$626,059

Lillian Aronson

Cephalon, Inc. Comparative Study to Evaluate Delivery of Treanda/Celator Probenda 17(PB17) in Tumor-Bearing Dogs

5/10/11-5/9/12 \$25,180

Gustavo Aguirre

Foundation Fighting Blindness Large Animal Translational and Research Facility (Period 3)

4/1/11-3/31/12 \$230,000

Ronald Harty

Pilot Grant, Comprehensive Neuroscience Ctr., "Novel FLIM based approach to study HSV-1 entry into neurons"

7/1/2011-6/30/2012 \$43,500

Carolyn Gray

(May Laboratory) American Heart Association Novel Mechanisms of non-canonical NF-kappB regulation

7/1/2011-6/30/2013 \$46,000

Christopher Lengner

NIH Center Grant P30-DK050306 Control of stem cell-driven intestinal tumorigenesis by Musashi RNA binding proteins

7/1/2011-6/30/2012 \$20,000

Gudrun Debes

Skin Disease Research Center Pilot & Feasibility grant: "Migration of antibody secreting cells in skin"

7/1/2011-6/30/2012 \$42,500

Thomas Parsons

Kansas State U (sub from USDA) Project Pennsylvania: Delineating different strategies for area control of PRRS in different geographic regions

9/15/2010-9/14/2011 \$25,000

Thomas Schaer

Synthes In vivo evaluation of an antimicrobial plate sleeve (APS) for local delivery of an antimicrobial/anti-infective compound at the surface of an osteosynthesis plate

2/1/2011-1/31/2012 \$956,047

Thomas Schaer

Synthes Evaluation of porous peek in vertebral bone

2/1/2011-1/31/2012 \$820,276

Raymond Sweeney

Penn State U (sub from USDA) Johne's Disease Diagnostic Test Evaluation

4/1/2011-12/14/2011 \$42,569



Penn Vet Imaging Core

Thursday, July 21, 2011

Andrea L Stout, Ph.D.

Director, Microscopy Core Facility
Department of Cell and Developmental Biology
School of Medicine
Title: Introduction to Digital Image Processing with Image J.

Thursday, August 11, 2011

Julia Lonchar, M.B.

(Biotechnology)

From Ralph Meyer's Laboratory
Department of Animal Biology
School of Veterinary Medicine
Title: Imaging and comparing 3D nuclear architecture of sperm: Influence of altered poly(ADP-ribose) metabolism.

Call for more information:

215-746-0471 or 215-573-8218

Seminar location: 220 Hill pavilion,
380 S. University Avenue.

12 noon--Pizza lunch at 11:50 AM

Recent Publications

Lee Y-H. and Saint-Jeannet J-P.

(2011). Cardiac neural crest is dispensable for outflow tract septation in *Xenopus*. (2011) *Development*. 138: 2025-2034. Also featured in Science Daily April 23, 2011



Okumura, A. and Harty, R. N.

Rabies Virus Assembly and Budding. In: Research Advances in Rabies (Alan Jackson, Ed.), *Advances in Virus Research*, Elsevier, Vol. 79, pgs 23-32, 2011.



Kuznetsova, T., Zangerl, B., Goldstein, O., Acland, G.M., Aguirre, G.D.

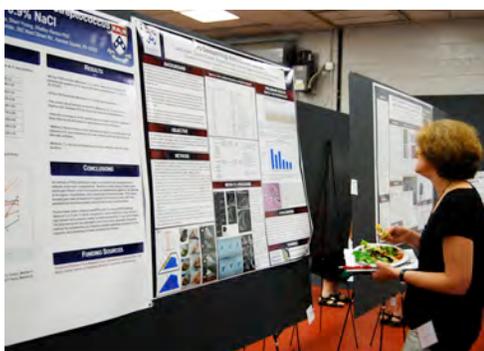
Structural organization and expression pattern of the canine *RPGRIP1* isoforms in retinal tissue

Invest Ophthalmol Vis Sci 52:2989-2998, 2011.



2011 ANNUAL FACULTY RESEARCH RETREAT

Faculty, postdocs, and students gathered at the New Bolton Center on Friday, June 10th for the **Annual Faculty Research Retreat**, chaired by Nicola Mason and Kendra Bence. In carrying out the theme of “Translational and Collaborative Partnerships”, Sue Volk and Kurt Hankenson spoke on “Optimizing Adult Stem Cell Therapies for Veterinary Regenerative Medicine”; Louise Southwood and Ralph Meyer spoke on the “Potential for a Protective Role of PARP Inhibitors in Equine Colic”; Charles Vite and Mark Haskins talked on the “Challenges of Therapy for Lysosomal Storage Diseases”; Julie Engiles and Hannah Galantino-Homer spoke on “Equine Laminitis: From Post Room, to Bench, to Stallside”; and Karin Sorenmo presented her work on the “Molecular Study of Canine Mammary Tumor Development and Progression: From Genome to Clinical Outcome”. Dr. Colin Parrish, College of Veterinary Medicine, Cornell University gave the Marshak Lecture on “The Emergence of New Epidemic Viruses by Host Shifting: Mechanisms and the Co-evolution of the Viruses and Their Hosts”.



FROM A PI'S POINT OF VIEW...part 2. Roselyn Eisenberg, Ph.D.

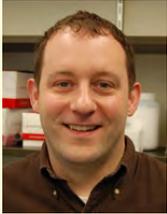
I have seen this from both sides - as an applicant (supplicant) and as a reviewer). If you did not see the January '2011 Penn Vet Research Newsletter, get it--pages 7-8! What I am writing about now will make more sense. This time I want to make suggestions on how to interpret a review (*when you do not get funded*) and what to do next.

- Within 2 days after the review, call your program officer (PO) – not the chair of the study section or its administrator. The PO will have notes and a memory of the conversation in the room.
- If your score is >25 (which usually translates to 10th % or so) you will likely not get funded. And that is not going to change anytime soon.
- It is all about the money. BUT – Don't rush back. First, look at the Summary Statement (pink sheets) to consider your options. Second, you need time to think – with only one more shot at it – the second one has to be substantially better, regardless of score.
- Even with a close score - when you do go back (of course you will), you may get different reviewers. They are not obliged to give you a better score.
- Let's assume your pink sheets are less than glowing. You will be angry, hurt, in mourning. All understandable. Give yourself time to feel angry, hurt, etc. Frame your response (you get a page to do that for resubmission). Remember, the worst thing you can do is to insult a reviewer – THEY CONTROL THE \$\$\$.
- Get someone to read the pink sheets, preferably someone who has served on study section. Make certain they give you *honest* feedback. Show your critique to several people. Oftentimes, reviewers disguise the fact that they hate an aim or an approach with phrases like “dampened enthusiasm” – a euphemism for “I hate this – it is awful”. “Ambitious or very ambitious” means *there ain't no way* this can get done in 5 years.
- The most important items that make a grant go up or down are scores for Innovation and Approach (significance is third in my mind – everything can be made to sound significant). The overall impact score will be most reflected by the scores in those categories with one exception: productivity (if this is an R01 renewal). If you have not published at least 4-5 papers (in decent journals) or 3 if they are all blockbusters - that is a killer and it will come out in “Investigator and Approach”.
- If productivity is a major issue, then publish before you go back in!!
- Pay attention to what the summary points out, at the very beginning, as the weakest link. If you cannot fix it – delete it - even if it is a whole aim. If it is a whole aim, think of a new one – or cut an aim out. A grant can survive with two aims instead of three.
- Start early on the resubmission and get in touch with Leslie King, Grant Editor, as rapidly as possible. Do not do this as a rush job.
- In a resubmission – a reviewer will look first at at the pink sheets, then at your response and only then at your aims. Your response becomes the most important page you will write. You have to re-write this several times. If you have new preliminary data and publications – make sure they know that. After the reviewer gets done with that page, they will already be forming an opinion. The next most important pages are Specific Aims, Significance and Innovation.
- Of course the rest of the grant has to be well written. Short, clear sentences are preferable to long ones. Too many commas are a death-knell.
- It must be hypothesis driven. Another code phrase for “I don't like this grant” is that “it is not hypothesis driven”. And often they have a good point. If you don't know *why* you are doing it, don't expect the reviewer to figure it out for you.
- You may or may not want to go back to the same Study Section. However, the new study section will still get those pink sheets as well as your proposal.
- As before: Good Luck! Stay in the game, even if you don't make it in two rounds. Take the best parts, change the direction to a grant with a new perspective.



Special honors and awards.....

Research Grants Awarded at Symposium--The United Mitochondrial Disease Foundation



(UMDF) has awarded a half of a million dollars to five researchers whose projects may lead to a cure or better treatments for those who battle a mitochondrial disease. The research grant awards were presented at the UMDF's annual symposium "**Mitochondrial Medicine 2011: Chicago.**" The "Chairman's Award" recipient for the top-rated grant was **Brett Kaufman, Ph.D.** of the Department of Animal Biology. He was awarded \$120,000 for his project entitled: "*Regulatory mechanisms governing TFAM-mediated mtDNA copy number control*". His research could lead to therapies that would increase the number of copies of normal mitochondrial DNA in patients with specific types of mitochondrial disease.

The **Comprehensive Neuroscience Center (CNC) at the University of Pennsylvania** awarded **Dr. Ronald Harty**, Department of Pathobiology, School of Veterinary Medicine, a pilot grant of \$43,500 for July 1, 2011. CNC selected 10 pilots out of fifty-nine applications in an effort to support as many meritorious pilot projects as possible. The pilot project entitled "Novel FLIM based approach to study HSV-1 entry into neurons" is a collaborative project and Dr. Harty shares this honor with Dr. **Roselyn Eisenberg** (Pathobiology); Dr. **Bruce Freedman** (Pathobiology), Dr. **Gary Cohen** (Dental School; and Dr. **Paul Bates** (School of Medicine) as co-investigators.



Students & Postdocs with Children

The **Family Center** is closed in the summer; however, they are opening a Play Room and Lactation Space in the Graduate Student Center (on the third floor, 3615 Locust Walk) on Monday open 12 - 4 PM each weekday through August 26. Stop by with your little ones for play time, nap time, or feeding time. Be aware, however, the Locust Walk is closed due to construction. You need to enter the Grad Student Center from the [alternate route behind the building](#).

Also, a reminder that the University's **Emergency Backup Child Care pilot program** for students and post-doctoral fellows will begin July 1. **All full-time Penn students and Penn post-doctoral fellows** who have dependent children are eligible. Students and post-docs who wish to

use backup child care must first [join the Family Resource Center](#). This program will be piloted for six months, from July 1-December 31, 2011.

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kids@gsc.upenn.edu



The **Penn Vet Research Newsletter** is distributed quarterly. Suggestions, requests, comments, and story ideas should be directed to:

resnews@vet.upenn.edu

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