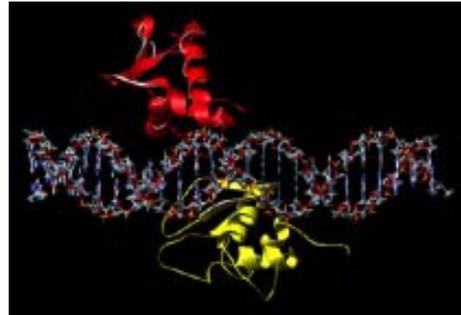


Spring 2011

www.vet.upenn.edu/research/programs/vmstp

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Dear VMD-PhD Alumni,

Greetings from Penn! Much has happened in the past six months. We have gone through another admissions season, the VMD-PhD Program was evaluated by an internal/external review committee, we had a dinner party at the Program Director's home, we participated in the Annual Student Research Day, and our current students have generated an impressive list of publications. Our applicant pool this year was exceptionally strong and three new student offers have been made. The profiles of new students will be provided in the Fall 2011 Newsletter. Three students will also join the alumni ranks this spring as they graduate and move on to the next stage in their careers and lives. Their information is presented here, along with some updates on other alumni and notable awards. Be sure to check out your alumni listing on our website. We hope this will enable our current students to learn more about those who completed the Program ahead of them, and will serve as a way for them to seek out advice on science, medicine, and career.

Wishing you the best in 2011,
Michael Atchison, Ph.D.
Director, VMD-PhD Program



Alumni are Online!

Check out:

www.vet.upenn.edu/Research/ResearchTrainingOpportunities/VMDPhDProgram/OurAlumni/

Find your profile, and send us feedback!

Admissions for Fall, 2011

This year we receive 32 applications to the VMD-PhD Program. Eight students were interviewed and three were offered admission (9.4% of the admission pool). This year's applicant pool represented the strongest our admissions committee has ever seen. Details of incoming students will be provided in the Fall Newsletter.

The 2011 Phi Zeta Student Research Day, March 25, 2011

Pictured below are Associate Dean for Research Phillip Scott and Dr. Kenneth Simpson



Keynote Speaker: Kenneth Simpson, BVM&S, Ph.D.

Chief, Section of Small Animal Medicine
Cornell University, College of Veterinary Medicine

Dr. Kenneth Simpson, is Professor and Chief of the Section of Small Animal Medicine at Cornell University, College of Veterinary Medicine. Dr. Simpson earned his BVM&S from the University of Edinburgh, Scotland in 1984. In 1988 he received his PhD degree at the University of Leicester in England and completed a rotating internship in Small Animal Medicine and Surgery at the University of Pennsylvania School of Veterinary Medicine in 1989. Dr. Simpson completed his

residency in Small Animal Internal Medicine at The Ohio State University in 1991 and is board certified in small animal internal medicine.

Dr. Simpson's overall goal is to understand the interplay between enteric bacteria and the host that leads to inflammatory bowel disease (IBD), and to effectively translate laboratory based studies to improve detection, therapy and ultimately prophylaxis. IBD is a major cause of morbidity in the United States. Methodologically, he applies contemporary culture independent and molecular microbiological approaches to study host bacterial interactions in animals, humans and *in vitro* systems to achieve these goals. His laboratory has discovered that Adherent and invasive *E. coli* (AIEC) are associated with IBD across species (people, dogs and mice). Current studies are focused on determining what genes make an AIEC an AIEC, defining the selection pressures in the enteric microenvironment that drive the proliferation of AIEC, and elucidating bacterial and host attributes that enable adherence, invasion and intracellular survival. Dr. Simpson gave the Keynote Address at the 2011 Phi Zeta Student Research Day with a talk entitled: ***Host-bacterial interactions in the gastrointestinal tract: A cross species approach.***

Current VMD-PhD students also submitted posters and abstracts, and competed for awards based on oral presentations.



This years' VMD-PhD student presentation winners were:

First Place VMD-PhD Award: Gregory Rak

NK Cell Lytic Granule Secretion through the Actin Network at the Immunological Synapse.

Greg is a 5th year VMD-PhD student in the laboratory of Jordan Orange. His thesis work focuses on the NK cell response and dendritic cell interactions. Greg studies the actin network at the human natural killer cell immunological synapse (IS) and how lytic granules are secreted in the context of this network. Using the advanced fluorescent imaging technique, total internal reflection fluorescence microscopy, he demonstrated that filamentous actin (f-actin) is present throughout the IS. To image secretion and the actin network in real

time, he generated and imaged cells expressing fluorescently tagged actin and a novel secretory indicator. These image sequences, along with quantitative image analysis, demonstrated that secretion occurs in areas where actin is present. How was it possible that granules were being secreted in an area where there were filaments? Since fluorescence microscopy is limited in its resolution, he also imaged the synaptic f-actin network using an ultra-resolution technique called platinum replica electron microscopy. This technique showed that there are clearances in the network that are small enough to be undetectable by fluorescence microscopy, but are sufficient in size to accommodate lytic granules. Thus he identified potential granule access points in the actin network. Finally, Greg showed that three functionally different chemical inhibitors of actin all affect the ability of NK cells to secrete granule contents; and thus he proposed that the dynamics of the actin network must be intact for secretion to occur. Ultimately, these findings present a novel paradigm for secretion in lymphocytes and highlight the importance of the actin network in the NK cell cytotoxic process.

Second Place VMD-PhD Award: Brittany Gregory

Regulation of Gene Expression by Lysine Specific Demethylase 4C.

Brittany is a 5th year VMD-PhD student in the laboratory of Vivian Cheung. Her thesis work focuses on determining how sequence variants affect gene expression differences among individuals. A genetics of gene expression study performed by the lab identified KDM4C as a polymorphic regulator of gene expression for seven genes, six of which are involved in transcriptional regulation or transcript processing. KDM4C functions as a histone demethylase, which removes a transcriptionally repressive mark, so Brittany first confirmed that KDM4C is a direct regulator of gene expression for these genes by showing that KDM4C knockdown decreased target expression and that KDM4C localized to the target gene promoters. She also found that KDM4C abundance differed among individuals from the study, both at the gene expression and protein level, so she performed association analysis on KDM4C gene expression levels and found a region of the KDM4C gene that is associated with its expression level, indicating cis-regulation. Individuals with high KDM4C expression had statistically greater expression of the seven target genes than low expressing individuals. Brittany's research indicates that KDM4C sequence variants affect KDM4C abundance, and thus affects the downstream expression level of the seven target genes that she confirmed to be regulated by KDM4C. Her future work will focus on identifying and determining the consequences of the KDM4C sequence variants on downstream cellular processes.



Third Place VMD-PhD Award: Irene Bukh

Increased Mucosal CD4+ T Cell Activation Following Vaccination with a Species-specific Adenovirus Vector in Rhesus Macaques.

Irene is a 4th year VMD-PhD student in the laboratory of Michael R. Betts. Her presentation focused on a potential explanation for why the STEP Study, a clinical trial that aimed to test the efficacy of an HIV-1 vaccine, failed. Individuals who received the vaccine and had high neutralizing antibody responses to Human Adenovirus -5 (which was also used as the vaccine vector) had increased rates of HIV-1 acquisition compared to the placebo group. One explanation for this is that vaccination with Adenoviral vectors increased mucosal CD4+ T-cell activation, leading to increased targets for HIV infection. Irene used a rhesus macaque as a model to examine the results of the STEP Study, in which vaccinated macaques with a Simian Adenovirus-based vector were examined for CD4+ T cell activation in the peripheral blood and rectal mucosa. Irene saw that there was increased activation in the rectal mucosa, but not in the blood. These results indicate that peripheral vaccination with an Adenovirus vector can increase the activation state of mucosal CD4+ T-cells providing an experimental model in which to

further evaluate the role of host-vector interactions on increased HIV acquisition.

VMD-PhD Program Review Outcome

The full report of the review committee is not yet completed. Details will be provided in the Fall newsletter.

Graduating VMD-PHD Students

Susan Bender

Mentor: Dr. Susan Weiss

Graduate Group: CAMB MVP



Susan performed her thesis entitled "Receptor utilization and antiviral CD8 T cell responses during central nervous system infection with a murine coronavirus" in the laboratory of Dr. Susan Weiss. She is nearing completion of all her clinical rotations and will graduate in May, 2011. Post-graduation, Susan will begin a residency in Anatomic Pathology at the University of Pennsylvania School of Veterinary Medicine starting July 1, 2011. She currently envisions a career in academia incorporating diagnostic pathology, teaching, and research.

Michelle Cook Sanger

Mentor: Narayan Avadhani

Graduate Group: Pharmacology

Michelle's thesis is entitled "The role of mitochondrial-targeted human Cytochrome P450 2D6 in drug metabolism and toxicity" and was performed in the laboratory of Dr. Narayan Avadhani. She has completed all VMD and PhD requirements and will receive her diplomas in May 2011. Post-graduation, Michelle is pursuing a residency in veterinary clinical pharmacology at the University of Illinois Urbana-Champaign. She will also pursue post-doctoral research in conjunction with the residency. The residency will prepare her for both a career in academic research as well as in industry. Michelle is still weighing her options for her future career path



LaTasha Crawford

Mentor: Sheryl Beck

Graduate Group: Neurosciences



Last year, LaTasha successfully defended her thesis entitled "Probing the neurophysiology of anxiety: Social stress alters the modulation of serotonin neurons" under the mentorship of Dr. Sheryl Beck. Though anxiety disorders are the most prevalent of all mental disorders, little is known about the neural changes that cause anxiety, although the serotonin system is suspected to play a key role. LaTasha's thesis project characterized 2 subpopulations of serotonin cells and revealed that those 2 subpopulations are regulated differently in a social stress-based model of anxiety. She will complete her clinical rotations and graduate in May 2011. LaTasha's post-graduation plans

include an anatomical pathology residency and post-doctoral research position at Johns Hopkins University beginning this summer. She is looking forward to gaining a more substantial background in comparative neuropathology and she is especially excited about learning how the central nervous system interacts with body organ systems. Ultimately, LaTasha would like to pursue a career in research examining the links between mental disease and somatic diseases (such as cardiovascular disease or urinary tract disease) that are often comorbid in human and veterinary medicine. Outside of the lab/classroom/clinic, LaTasha likes to live an active lifestyle and enjoys taking muay thai kickboxing classes and playing volleyball when she has time.

Alumni Awards, Accomplishments, and Honors



Mark J. Pykett, VMD/PhD (1994) Executive Vice President and Chief Development Officer at Neoprobe Corporation

We congratulate Dr. Mark Pykett who recently accepted a new position as Executive Vice President and Chief Development Officer at Neoprobe Corporation. Mark is a premier leader of public and private biotechnology companies with more than 15 years of successful product and business development. Mark has held President or Director roles at a number of companies including Alseres Pharmaceuticals, CyGenics, Adventrx Pharmaceuticals, Cordlife, Pte., Ltd., Cell Science Therapeutics, Oramax, LLC, and Cytomatrix, LLC. We congratulate Mark in his new endeavors with Neoprobe Corporation.

Sarah Ralson VMD/PhD (1982) Associate Professor, Rutgers University

We congratulate Dr. Sarah Ralson for being awarded the Rutgers Academic Professional Excellence Award for Academic Innovation in 2010. She was also invited to be an Independent Observer for the American Horse Protection Association Wild Horse Gather Pilot Program in August 2010. Recently Dr. Ralson has published five book chapters, one refereed publication, two invited reviews at International meetings and one abstract. Dr. Ralson was an invited speaker at the Australian Equine Society Meetings in June 2010 and the Dorothy C. Havemeyer Geriatric Horse Workshop at Tufts University in October 2010.



James Thomson, VMD/PhD (1988) Director of Regenerative Biology at the Morgridge Institute for Research and Professor at the University of Wisconsin

We congratulate Dr. James Thomson for winning the 2011 King Faisal International Prize and also the 2011 Albany Medical Center Prize in Medicine and Biomedical Research. An excerpt from the University of Wisconsin announcement about these awards stated "The King Faisal Foundation noted that his continuing work to advance stem cell science, which led to his 2007 success in genetically reprogramming adult skin cells to an embryonic state, revitalized interest in stem cell biology, with many laboratories re-investigating the possible use of these cells in the modeling and treatment of human disease." In the Wisconsin State Journal Dr. Robert Golden, Dean of the UW Medical School, said "Dr. Thomson's stem cell research, dating back nearly 20 years, has been characterized by one significant breakthrough after another," Golden said. "Hundreds of researchers around the world are able to use these cells to advance both understanding and progress towards cures and treatments."





Alexander J. Travis, VMD/PhD (1999) Associate Professor, Cornell University

A late congratulations to Dr. Alexander Travis for winning a 2009 NIH Pioneer Award. These awards are highly coveted and selective awards are given to a very small number of scientists doing cutting edge research. The NIH website states, "His research investigates the design and function of mammalian sperm, particularly the organization of their energy-producing pathways. With his Pioneer Award, Dr. Travis is harnessing this design to develop very small energy sources for implantable medical devices that could carry out a variety of diagnostic and therapeutic functions." Dr. Travis is also Co-editing a Special Feature on Poverty Traps and Biodiversity Conservation for PNAS. Papers will be out soon.

We want to know....

New position, promotion, patent, publication, etc.? Please share your news!
vmstp@vet.upenn.edu

Student Publications

2010

Bender, S.J., Phillips, J.M., Scott, E.P., and Weiss, S.R. Murine coronavirus receptors are differentially expressed in the central nervous system and play virus strain-dependent roles in neuronal spread. *J. Virol.* 84:11030-11044 (2010) PMID: 20739537

Bender, S.J. and Weiss, S.R. Pathogenesis of murine coronavirus in the central nervous system. *J. Neuroimmune Pharmacol.* 5:336-354 (2010). PMID: 20369302

Shah, P.P., Zheng, X., Epshtein, A., **Carey, J.N.**, Bishop, D.K., & Klein, H.L. Swi2/Snf2-Related Translocases Prevent Accumulation of Toxic Rad51 Complexes during Mitotic Growth. *Mol. Cell* 39: 862-872 (2010). PMID: 20864034

Cook Sangar, M., Anandatheerthavarada, H.K., Martin, M.V., Guengerich, F.P., and Avadhani, N.G. Identification of genetic variants of human cytochrome P450 2D6 with impaired mitochondrial targeting. *Mol. Genet. Metab.* 99:90-97 (2010). PMID: 19781968

Cook Sangar, M., Bansal, S., and Avadhani, N.G. Bimodal targeting of microsomal cytochrome P450s to mitochondria: implications in drug metabolism and toxicity. *Expert Opin. Drug Metab. Toxicol.* 6:1231-1251 (2010). PMID: 20629582

Crawford, L.K., Craige, C.P., and Beck, S.G. Increased intrinsic excitability of lateral wing serotonin neurons of the dorsal raphe: a mechanism for selective activation in stress circuits. *Journal of Neurophysiology* 103:2652-2663 (2010). PMID: 20237311

Phoenix, K.N., Vumbaca, F., Fox, M.M., **Evans, R.**, and Claffey, K.P. Dietary energy availability affects primary and metastatic breast cancer and metformin efficiency. *Breast Cancer Research and Treatment.* 123:333-344 (2010). PMID: 20204498

Solyom, S., **Patterson-Fortin, J.**, Pylkas, K., Greenberg, R.A., and Winqvist, R. Mutation screening of the MERIT40 gene encoding a novel BRCA1 and RAP80 interacting protein in breast cancer families. *Breast Cancer Research and Treatment* 120:165-168 (2010). PMID: 19572197

Patterson-Fortin, J., Shao, G., Bretscher, H., Messick, T.E., and Greenberg, R.A. Differential regulation of JAMM domain deubiquitinating enzyme activity within the RAP80 complex. *J. Biol. Chem.* 285:30971-30981 (2010). PMID: 20656689

Sanborn, K.B., **Rak, G.D.**, Mentlik, A.N., Banerjee, P.P., and Orange, J.S. Analysis of the NK cell immunological synapse. *Methods Mol Biol.* 612:127-48 (2010). PMID: 20033638

Shearin, A.L. and Ostrander E.A. Leading the way: canine models of genomics and disease. *Dis. Model Mech.* 3:27-34 (2010). PMID: 20075379

Shearin, A.L. and Ostrander, E.A. Canine morphology: hunting for genes and tracking mutations. *PLoS Biol.* 2010 Mar 2;8(3):e1000310. PMID: 20209140

Parker, H.G., **Shearin, A.L.**, and Ostrander, E.A. Man's best friend becomes biology's best in show: genome analyses in the domestic dog. *Ann. Rev Genet.* 44:309-336 (2010). PMID: 21047261

2011

Mongroo, P.S., Noubissi, F.K., Cuatrecasas, M., Kalabis, J., **King, C.E.**, Johnstone, C.N., Bowser, M.J., Castells, A., Spiegelman, V.S., and Rustgi, A.K. IMP-1 Displays Cross-Talk with K-Ras and Modulates Colon Cancer Cell Survival through the Novel Proapoptotic Protein CYFIP2. *Cancer Res.* 71(6):2172-2182 (2011) PMID: 21252116

King, C., Wang, L., Winograd, R., Madison, B., Mongroo, P., Johnstone, C., and Rustgi, A.K. LIN28B fosters colon cancer migration, invasion, and transformation through let-7 dependent and independent mechanisms, (To be published by *Oncogene* April 2011)

Orange, J.S., Roy-Ghanta, S., Mace, E.M., Maru, S., **Rak, G.D.**, Sanborn, K.B., Fath, A., Saltzman, R., Paisley, A., Monaco-Shawver, L., Banerjee, P.P., Pandey, R. IL-2 induces a WAVE2-dependent pathway for actin reorganization that enables WASp-independent human NK cell function. *J Clin Invest.* 2011 Mar 7. pii: 44862. doi: 10.1172/JCI44862. [Epub ahead of print] PMID: 21383498

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