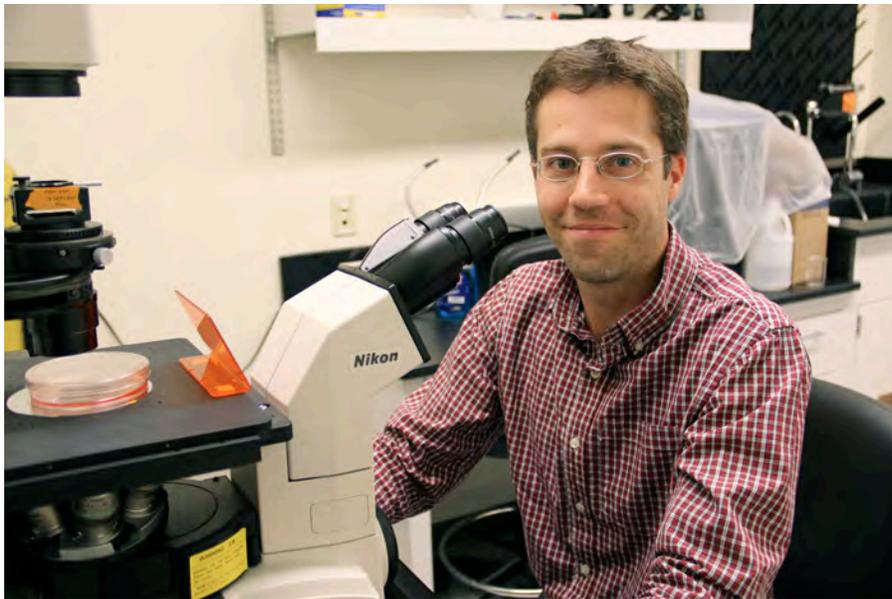


NEWSLETTER

Harnessing stem cell control mechanisms *for application in cancer therapy and regenerative medicine*



Chris Lengner is an assistant professor in the Department of Animal Biology and is also a member of the Penn Institute for Regenerative Medicine. Chris began his research career as an undergraduate studying applied biotechnology at the Worcester Polytechnic Institute, from which he received his B.S in 1998. He went on to study the transcriptional control of cell fate deter-

mination in mesenchymal stem cells (the precursors of muscle, bone, cartilage, and fat) at the University of Massachusetts Medical School³. It was here that Chris became focused on understanding how mechanisms governing stem cell fate determination and self-renewal could directly contribute to tumorigenesis when deregulated⁴.

continued on page 2

A Fish Immunologist at Penn Vet

A recent story in [Penn Current](#) (June 7, 2012) focuses on Penn Vet's fish immunologist, professor Oriol



Sunyer, and his studies on the immune system of rainbow trout to develop vaccines. The article, entitled *Studying Fish Immunology for the Greater Good*, written by

Katherine Unger Baillie, brings to the forefront Dr.

Sunyer's paradigm-shifting research on the immune system of fish. A professor in the Department of Pathobiology, Dr. Sunyer's work is of global importance. "We study the fish immune system so that we can learn from a so-called 'primitive' organism," says Sunyer. "Because the immune system of mammals is so complex, sometimes you find things in fish that escaped notice in mice."

Translational & Collaborative Partnerships

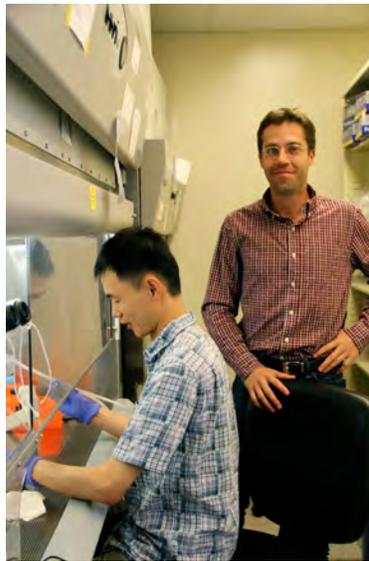
Penn Vet celebrated the wide range of research projects carried out at both campuses and beyond with presentations at the annual research retreat on June 8th. Faculty and collaborators presented their work and the Marshak keynote address delivered by Dean J. Larry Jameson of the Perelman School of Medicine emphasized the importance of interdisciplinary research. Below is a picture of Dean Jameson's dog Bella, lying on a blanket presented to Dean Jameson! See more about the retreat on Page 7.



DR. CHRIS LENGNER continued from Page 1

After completing his Ph.D. in 2005, Chris moved to the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology where he was a Ruth L. Kirschstein Postdoctoral Fellow in the laboratory of renowned stem cell biologist Rudolf Jaenisch. While at the Whitehead, Chris demonstrated that the regulatory networks that maintain pluripotency (the ability of a stem cell to differentiate into *any* other cell type in an organism) in embryonic stem cells are, in fact, entirely dispensable for stem cell function in the adult⁵. This study suggested that true pluripotent cells do not exist in adult tissue⁶. As technical and ethical issues limit the use of embryonic stem cells for therapeutic purposes, the search for a robust source of pluripotent cells for regenerative medicine applications continued. Importantly, the advent of direct epigenetic reprogramming, in which ectopic expression of just four transcription factors in differentiated adult cells generates pluripotent stem (iPS) cells with the characteristics of embryonic stem cells, made this goal a reality. Chris made seminal contributions to this burgeoning field, demonstrating that all adult cell types are susceptible to epigenetic reprogramming. Moreover, he helped generate and apply reprogramming systems that yield iPS cells with high efficiency⁷ and is an inventor on a patent for direct reprogram-

ming technology that is now being applied broadly to hundreds of diseases in thousands of laboratories across the world.



Dr. Lengner and postdoc Ning Li

Working with a team at the Whitehead Institute and Harvard University, Chris also studied the epigenetic stability of human embryonic stem cells by deriving human ES cell lines under physiological oxygen concentrations (5%O₂) rather than the traditional atmospheric oxygen concentrations (20%O₂) that can produce oxidative stress in cultured cells. Using this system, he was the first to derive and maintain female human embryonic stem cell lines without triggering X chromosome inactivation, a process critical for dosage compensation of X-linked genes to normalize their expression between the sexes⁸. Prior to this study, the

process of X chromosome inactivation could be studied only in the mouse. This study revealed that X inactivation occurs in humans much the same way as in mice, and paved the way for subsequent investigation into mechanisms underlying human dosage compensation and how these mechanisms are affected during the generation of iPS cells by direct epigenetic reprogramming.

At the start of 2011, Chris established his laboratory in the Department of Animal Biology here at the School of Veterinary Medicine. Currently, his laboratory is focusing on identifying mechanisms that maintain stem cell potency in adult stem cell compartments and determining how their deregulation contributes to oncogenic transformation. Through a close collaboration with Michael Kharas at the Memorial Sloan Kettering Cancer Center, they have identified a family of RNA binding proteins that regulate adult stem cell maintenance and serve as potential oncogenes. Michael and Chris initially reported that one of the family members, MSI2, is a potent cooperative oncogene that confers a stem cell-like phenotype to transformed cells in a variety of leukemias, including both chronic and acute myelogenous leukemias (CML and AML).

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WHERE TO FIND SAMPLE APPLICATIONS AND SUMMARY STATEMENTS

Several investigators have graciously agreed to post their exceptional applications online. See the NIAID/NIH website for this information:

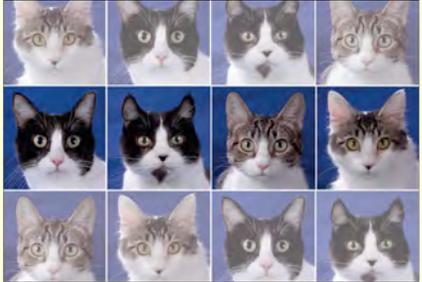
<http://www.niaid.nih.gov/researchfunding/grant/Pages/appsamples.aspx>

FINANCIAL CONFLICTS OF INTEREST (FCOI)

There is new federal regulation governing financial conflicts of interest (FCOI) applicable to all NIH/PHS awards or contracts with Notice of Awards (NOAs) issued after August 24, 2012 (including noncompeting continuations). The immediate impact will be that at the time of **each NIH (and/or PHS) proposal submission**, anyone listed as principal investigator **OR** key personnel (Investigators) on the proposal must disclose his/her external financial interests and relationships for the past 12 months, *regardless of whether they are related to the research proposed*, and also disclose all travel that was reimbursed to the investigator or paid on the investigator's behalf, with limited exceptions (e.g. travel paid by Penn, other institutions of higher education, or any federal, state, or local government agency). This disclosure obligation is completely distinct from the required annual school-based extramural reporting. Faculty receiving PHS/NIH funding will be expected to participate in training that will occur every four years. The training program has not yet been implemented and investigators will be on the look out for communications going forward related to the interim disclosure process and training requirements, as well as specific requests for information relative to proposals.

FUTURE EXPERTS IN COMPARATIVE MEDICINE

Drs. **Emily Miedel** (left front) and **Holly Habbershon** (right front) were congratulated at a celebration on June 15th for successfully completing their 3-year residency training in Laboratory Animal Medicine in the Department of Pathobiology's Division of Laboratory Animal Medicine and University Laboratory Animal Resources (ULAR). Completion of the LAM residency, which is a recognized residency program with the American College of Laboratory Animal Medicine (ACLAM), is a key step in qualifying to sit for the ACLAM boards and become a specialist in the care and use of laboratory animals. Dr. Miedel joined the laboratory of Dr. Kurt Hankenson, Department of Animal Biology, School of Veterinary Medicine, for her 3rd research immersion year and Dr. Habbershon joined the laboratory of Dr. Yale Cohen in Otorhinolaryngology, Perelman School of Medicine (UPENN). This residency is co-directed by Drs. Diane J. Gaertner (left rear) and F. Claire Hankenson (right rear) who are faculty members in the Department of Pathobiology, University of Pennsylvania School of Veterinary Medicine.



the international journal of molecular and cellular therapeutics
Molecular Therapy
 official journal of the American Society of Gene & Cell Therapy
 vol. 20 no. 5 May 2012 www.moltherapypub.org

Neonatal gene therapy with a γ retroviral vector
 Modified mRNA as a gene therapeutic
 Targeting CD20 in melanoma patients

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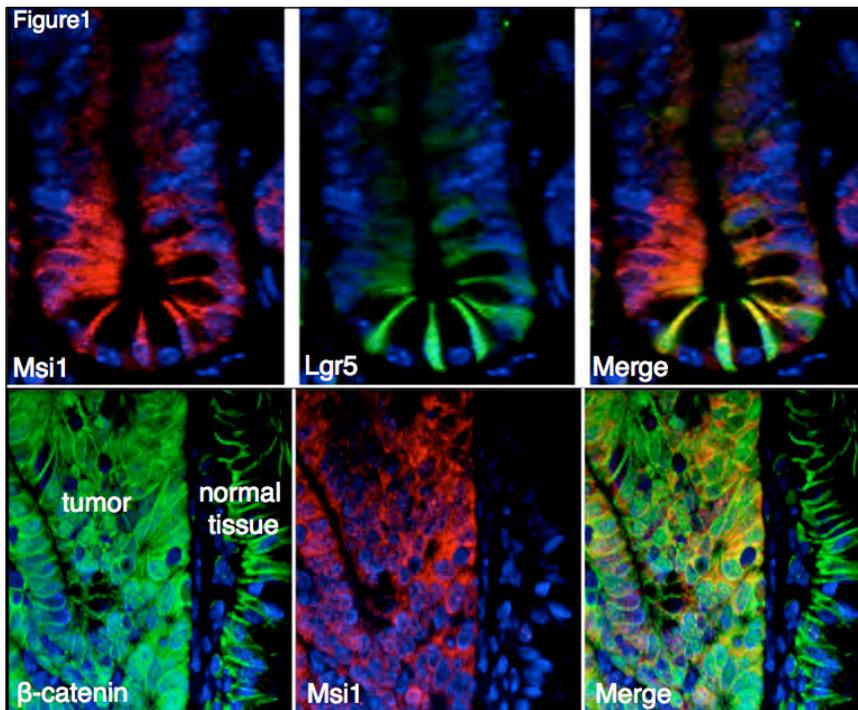
Ponder, KP, O'Malley, TM, **Wang, P**, O'Donnell, PA, Traas, A, Knoz, VW, **Aguirre**, GA, Ellinwood, NM, Metcalf, JA, Wang, B, Parkinson-Lawrence, E, **Sleeper**, M, Brooks, D, Hopwood, JJ, **Haskins**, ME (2011) Neonatal Gene Therapy with a Gamma Retroviral Vector in Mucopolysaccharidosis VI Cats. *Molec Therapy* 20:898-907 (2012)



University Laboratory Animal Resources (ULAR) is responsible for the procurement, care, and use of all University-owned animals used for teaching and research. The main office is located at 3800 Spruce Street, Suite 177E, Philadelphia PA 19104-6009

CONTINUED FROM PAGE 2

MSI2 expression in these cancers is negatively correlated with survival, and depletion of MSI2 in leukemic cells is sufficient to induce their differentiation, inhibit their proliferation, and promote cell death, making MSI2 an attractive therapeutic target in these deadly diseases ⁹.



Expression of the Msi1 protein in normal stem cells of the intestinal crypt (top panels, marked by Lgr5). Upon loss of the APC tumor suppressor, intestinal stem cells inappropriately express β -catenin and initiate tumor formation (bottom panels). These tumors express high levels of Msi1

The Lengner lab has recently extended the work on MSI RNA binding proteins to the gastrointestinal system, where both family members (MSI1 and MSI2) are expressed in the intestinal stem cell compartment and are inappropriately upregulated in a variety of cancers, including colorectal adenocarcinoma, the third leading cause of cancer-related deaths globally (Figure 1). Using a combination of gain- and loss-of-function approaches in the mouse as well as human patient samples and genomic approaches, the Lengner lab is unraveling the mechanisms by which MSI proteins contribute to maintenance and oncogenic transformation of intestinal stem cells with the long term goals of 1) identifying novel points of intervention for cancer therapy and 2) harnessing stem cell control mechanisms for application in regenerative medicine.

Research in the Lengner Lab is funded by grants from the State of Pennsylvania Health Research Formula, the W.W. Smith Charitable Trust, the University of Pennsylvania Institute for Regenerative

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Cross disciplinary research at Penn Vet

A research team at Penn has arrived at a surprising finding: T cells, which comprise a key part of the immune system, track down parasites using a movement strategy similar to those used by predators such as sharks,



Tajie Harris

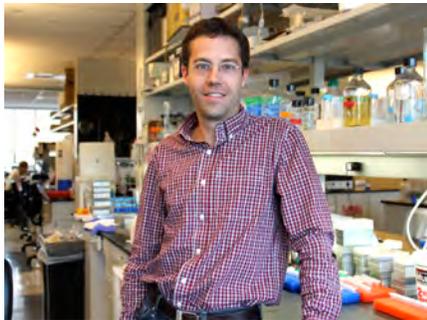
monkeys, and blue-fin tuna to hunt prey. The research, published in the journal *Nature*, involved a unique collaboration between

the laboratories of senior authors Christopher Hunter, professor and chair of the Pathobiology Department at [Penn Vet](#), and Andrea Liu, the Hepburn Professor of Physics in the Department of Physics and Astronomy in the [School of Arts and Sciences](#). Penn Vet post-doctoral researcher Tajie Harris and physics graduate student Edward Banigan played leading roles in the research. The study was conducted in mice infected with the parasite *Toxoplasma gondii*. Using a powerful microscope that can display living tissues in three dimensions in real time, the researchers tracked the movements of T cells.

“Generalized Lévy walks and the role of chemokines in migration of effector CD8⁺ T cells.” Tajie H. Harris, Edward J. Banigan, David A. Christian, Christoph Konradt, Elia D. Tait Wojno, + et al. *Nature* doi:10.1038/nature11098, Published online 27 May 2012

CONTINUED FROM PAGE 4

Medicine and Center for Molecular Studies in Digestive and Liver Diseases, and the NIH/National Cancer Institute. Dr. Lengner's laboratory is located on the 3rd Floor of the Rosenthal Building.



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1. Lengner CJ, Drissi H, Choi JY, van Wijnen AJ, Stein JL, Stein GS, Lian JB. Activation of the bone-related Runx2/Cbfa1 promoter in mesenchymal condensations and developing chondrocytes of the axial skeleton. *Mech Dev* 2002;114:167-70.
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development are regulated by Mdm2-p53 signaling. *J Cell Biol* 2006;172:909-21.

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Lectures

Gustavo Aguirre, VMD, PhD, spoke on May 30, 2012 at the Centre for Brain Repair, Addenbrooke's Hospital, Cambridge University, UK. His lecture was on "Photoreceptor directed gene therapy-restoring function and structure, and reversing inner retinal remodeling."



Recent Publications

Hermesh, T, Moran TM, Jain D, and **Carolina Lopez.**



Granulocyte Colony-Stimulating Factor Protects Mice during Respiratory Virus Infections. *PLoS ONE* 7(5): e37334. (2012)



Roselyn Eisenberg et al.

Herpes Virus Fusion and Entry: A Story with Many Characters. *Viruses* 4(5): 800-832 (2012)
A special issue:

Virus-induced membrane fusion.



Stein VM, Crooks A, Ding W, Prociuk M, O'Donnell P, Bryan C, Sikora T, Dingemans J, Vanier MT, Walkley SU, & **Charles Vite.** Miglustat improve purkinje cell survival

and alters microglial phenotype in feline Niemann-Pick disease type C. *J Neuropathol Exp Neurol* 71(5): 434-48 (2012).



Smith GK et al. Chronology of Hip Dysplasia Development in a Cohort of 48 Labrador Retrievers Followed for Life. *Vet Surg* 2012 41(1): 20-33



Drs. H Galantino-Homer, J Engles and N Mason at June 8th Research Retreat.

RECENT AWARDS

Gus Aguirre (PI)

Macula Vision Research Foundation Grant -Gene Replacement Therapy in Bestrophin 1 Model: Implications for Recessive and Dominant Human BEST1-Disorders
2012-2015 \$300,000

Mark Haskins (PI) UPenn pilot grant The Pathophysiology and the effect of treatments on cardiovascular disease in Mucopolysaccharidosis I in Dogs. The goal of the grant is to test simvastatin in combination with enzyme therapy in dogs with MPS I. 2011-2013 \$149,831.

Mark Haskins (PI) UPenn pilot grant Pre-Clinical Evaluation of TNF- α Antagonists For the Treatment of MPS I in Combination With Enzyme Replacement Therapy. The goal of the grant is to test a cat-based anti-inflammatory drug in combination with enzyme therapy in cats with MPS I. 2011-2013 \$164,686.

Regina Turner (PI) Grayson Jockey Club Towards an Understanding of Testicular Degeneration 4/1/2012-3/31/2014 \$109,732



Ron Harty (PI)

Bruce Freedman (Co-PI)
R21 AI102104 NIH
Host-Oriented Therapeutics Targeting Filovirus Budding
7/1/12-6/30/14 \$275,000

Tracy Bale (PI)

NIH/NIMH
Prepubertal Stress: Windows of Risk and Sex Bias for Affective Disturbance
P50 SCOR (Specialized Centers of Research) grant
2012-2017 \$3,750,000

Penn Vet Imaging Core Facility

The online scheduler for the Imaging Facility Management System allows you to book time on the



core instruments and microscopes. It serves the entire Penn research community with *state-of-the-art* optical imaging technology. You will need to be registered in the software to access the scheduler. Please contact the core manager, Gordon Ruthel at

goruthel@vet.upenn.edu.

HONORS

Erika Crosby, a graduate student in the laboratory of Phil Scott, received a travel award from BGS (Biomedical Graduate Studies) to attend the 2012 Woods Hole Immunoparasitology Meeting where she received the AAI (American Association of Immunologists) Young Investigator award for Best Oral Presentation on the Influence of viral specific memory cells on *Leishmania major* infection.



Erika Crosby



Mark Haskins, VMD, MS, PhD, was appointed to Chair of the Scientific Advisory Committee of the National Tay-Sachs and Allied Diseases.



Student **Bridget Lyons** was awarded a Morris Animal Foundation Veterinary Student Scholar award for her

research project entitled: Development of a point-of-care isothermal nucleic acid amplification reactor for the rapid diagnosis of bacteremia in septic dogs and cats. Deborah Silverstein & Shelley Rankin are her mentors.

ANNUAL FACULTY RESEARCH RETREAT AT NEW BOLTON CENTER ON JUNE 8TH



Perelman School of Medicine Dean J. Larry Jameson with Harvey Crumm of Pfizer and Penn Vet Dean Joan Hendricks.

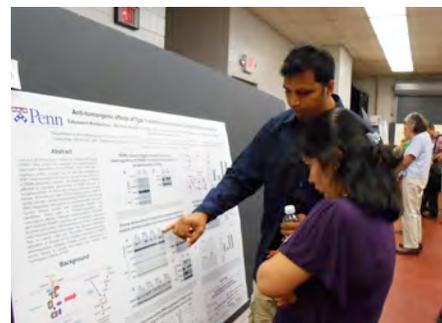
“What a great way to end the school year and what a tribute to the interest of our school's scholars in science” said Professor Roselyn Eisenberg after the Annual Faculty Research Retreat held recently on the campus of New Bolton Center (NBC). Perelman School of Medicine Dean J. Larry Jameson delivered the Marshak Lecture on “Shaping the Future of Penn Medicine”. Serge Fuchs, Nicola Mason, Michael May and John Lewis organized a program of paired faculty presentations based on collaborative research at Penn Vet. William Beltran won first place for his poster on “AAV2/5 Mediated Gene Augmentation corrects RPGR Ciliopathy in Two Canine Models of X-Linked Retinitis Pigmentosa”. Second Place winners were Chris Carbone (Fuchs Lab) and Hannah Galantino-Homer (Laminitis Institute). Four third place poster winners were: Claudia Gonzalez (Scott Lab); Xiomara Mercado-Lopez (Lopez Lab); Deepika Jain (Lopez Lab); and Louise Southwood Parente.



Winner of the 2012 Pfizer Award for Research Excellence, Dr. Eric Parente, Department of Clinical Studies NBC and daughter Kylie.



Ron Harty & Dieter Schifferli relaxing at the faculty retreat.



Sabyasachi Bhattacharya & Seema Bansal discuss poster



Faculty and staff enjoying the day.



Rebecka Hess & Dean Robert Marshak



Dean Hendricks, John Lewis & William Beltran.



Amy Johnson, Elizabeth Davidson & Mary Robinson.

The Medtronic Prize



The 7th annual Society for Women's Health Research Medtronic Prize for Scientific Contributions to Women's Health was presented to **Dr. Tracy L. Bale** from the University of Pennsylvania School of Veterinary Medicine, at the Society for Women's Health Research (SWHR) 19th Annual Gala Dinner on May 10, 2012. The

[Medtronic Prize](#) is major prize given to a

female scientist in her early to mid-career who has devoted a significant part of her work to sex differences research and has served as a role model and mentor for both colleagues and students. Tracy Bale is an associate professor in the Department of Animal Biology. "I am incredibly honored and deeply humbled to be named the recipient of the 2012 SWHR Medtronic Prize. "Through our research we hope to uncover the neurobiology behind how stress impacts mental health disorders and women's overall health," said Bale.

The Penn Vet
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is distributed quarterly.

Suggestions, requests,
comments, and story ideas
should be directed to:

resnews@vet.upenn.edu

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