Penn Vet Autumn Events

To kick off the fall season at Penn Vet, an event was held to celebrate the brilliant career of Ralph Brinster with over 300 in attendance (p. 4); the Penn Vet Working Dog Center opened on September 11 (p. 8); students brought their summer research projects to closure in our laboratories (p. 7), and the school year began. Assistant professors will be attending an annual faculty orientation on November 1st to get acquainted with colleagues and key resource individuals at Penn. The University Research Foundation pilot grant deadline approaches on October 26—offered competitively to junior faculty undertaking pilot projects to launch their investigative careers and to established faculty developing preliminary data on novel or pioneering ideas.

Cell suicide - in the service of immunity

Dr. Igor Brodsky is an Assistant Professor in the Department of Pathobiology and a member of the Penn Institute for Immunology. Igor began his research career as an undergraduate at Princeton University studying Alpha Herpes-viruses in the laboratory of Lynn Enquist, and obtained his B.A. in Molecular Biology in 1997. His undergraduate studies on viruses sparked an interest in host-pathogen interactions, so Igor went on to pursue graduate studies at Stanford University in the laboratory of Stanley Falkow, a pioneer in the field of microbial pathogenesis.

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CONFERENCE ON THE INTEGRITY OF RACING

Lawrence Soma, V.M.D., Marilyn M. Simpson professor of anesthesia in the Department of Clinical Studies New Bolton Center led the organizing committee for the International Conference of Racing Analysts and Veterinarians held in Philadelphia on September 15-22 to discuss horse and greyhound racing as a multi-billion dollar industry throughout the world. The primary focus was on efforts to prevent the misuse of medications that may affect the performance and health of racing animals. Dr. Soma, co-chaired the event with Cornelius Uboh, PhD, director of the Pennsylvania Equine Toxicology and Research Laboratory. Dean Richardson, James Serpell, Eric Parente and Michael Ross were invited speakers from Penn Vet.
Igor Brodsky continued from page 1

Igor’s Ph.D. studies focused on using the foodborne pathogen Salmonella to understand how bacterial pathogens evade key host immune effector mechanisms, such as the antimicrobial peptides produced by macrophages and mucosal tissues [1,2]. At the end of his Ph.D. studies, Igor became fascinated with understanding how the host innate immune system initially detects and responds to microbial infection. After obtaining his Ph.D. in 2004, Igor undertook post-doctoral studies at Yale University as a National Research Service Award (NRSA) Ruth Kirchstein Postdoctoral Fellow in the laboratory of Ruslan Medzhitov, who, with Charles Janeway, was one of the early innovators of modern innate immunity and defined many of the fundamental principles behind innate immune recognition and signaling [3].

In the Medzhitov lab, Igor continued his work on host-pathogen interactions, and developed a number of model systems using Yersinia pseudotuberculosis, a bacterial pathogen closely related to Salmonella and to Yersinia pestis, the causative agent of plague. Igor’s studies in the Medzhitov laboratory focused on the regulation of cell death during bacterial infection, and how different forms of cell death might contribute to immune responses against bacterial pathogens. Using mouse models of infection and a number of newly generated genetic tools, Igor’s studies revealed that cell death was an important immune defense mechanism that could promote bacterial clearance and enhance survival of the infected host in the context of Yersinia infection [4]. In addition, collaborative studies performed with the laboratory of Sankar Ghosh revealed that pattern recognition receptors, evolutionarily conserved receptors that recognize critical structural motifs present on microbes but not host cells [5], played a critical role in triggering production of mitochondrial reactive oxygen species (ROS), and that this mitochondrial ROS contributed to killing of intracellular bacteria [6]. However, a conceptual challenge for the field of innate immunity at this time was to understand how pattern recognition receptors that recognized broadly conserved bacterial structures could be unresponsive to the trillions of commensal bacteria normally present in mucosal tissues and surfaces, but simultaneously capable of mounting a robust immune response against infection by closely related pathogenic bacteria. Studies conducted by Igor in the Medzhitov lab contributed to further insight into this paradox by demonstrating that sensing of pore forming activities of pathogenic bacterial secretion systems [7,8] promoted activation of caspase-1 dependent cell death and release of caspase-1 dependent inflammatory signals, providing an additional layer of innate immune recognition for invading organisms. Finally, Igor’s studies revealed that bacterial pathogens such as Yersinia had evolved sophisticated ways to evade this additional layer of immune detection, and were able to avoid immune clearance by preventing caspase-1 activation [8]. Such evasion strategies are likely to be employed by many different types of infectious organisms, and identifying the molecular players involved may lead to development of improved antimicrobial therapies.

The current research in the Brodsky lab continues this line of investigation and focuses on innate immune recognition of bacterial pathogens and corresponding evasion strategies used by bacterial pathogens to subvert the innate immune response. One of the laboratory’s research projects, undertaken by Erin Zwack, a second year Ph.D. student in the Microbiology-Virology-Parasitology (MVP) graduate program, involves defining the signaling pathways by which pore-forming bacterial secretion systems are sensed by infected cells and activate caspase-1 dependent immune responses. A second project in the laboratory addresses how related pathogens, specifically Salmonella, subvert this type of innate inflammatory response to establish chronic infection.

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Although *Salmonella* can cause severe food poisoning in infected individuals, it can also persist asymptomatically in important farm animal populations, particularly pigs, chickens, and cows, which results in long-term shedding of the bacteria into the environment. Thus chronically infected animals perpetuate this pathogen in the human food supply chain, as evidenced by recurring *Salmonella* food poisoning outbreaks. New studies in the Brodsky lab conducted by Meghan Wynosky-Dolfi, a post-doctoral fellow, and Annelise Snyder, a Research Specialist, have identified *Salmonella* genes that enable *Salmonella* to evade innate immune responses. Future studies may provide new methods to target these bacterial genes and could potentially reduce the burden of persistent *Salmonella* in agricultural animal populations.

Finally, additional projects in the Brodsky lab focus on the signaling pathways that regulate macrophage cell death and inflammatory responses to infection by *Yersinia* (see Figure 1). Recent studies conducted by Naomi Philip, a second year Ph.D. student in the Immunology Graduate Group program, are revealing an unexpected interplay between distinct signaling pathways that control cell death. Control of cell death and the signals associated with dying cells play a critical role in shaping the pathology and immune response to infection, and understanding how these signals are regulated may enable future interventions that could protect tissues and organ systems from the pathological consequences of inflammatory responses. Naomi’s studies have uncovered a new link between activation of caspase-8.

*Figure 1. Live imaging of cell death in real time.* Murine macrophages were loaded with a vital dye, CellTracker Green, and infected with Yersinia pseudotuberculosis. The cell impermeable dye, Propidium Iodide (PI) was added following infection. The left panel shows cells at 1 hour post-infection, while the right panel shows the same visual field 4 hours post-infection. Red cells have lost membrane integrity and taken up the PI dye, while the live cells remain green. (Images were collected by Naomi Philip using the Penn Vet Imaging Core Leica DMI4000 spinning disk confocal microscope).

**Recent papers**


SYMPOSIUM TO HONOR PROFESSOR RALPH BRINSTER

This year marks 50 years of Ralph Brinster's association with the University of Pennsylvania and the School of Veterinary Medicine where he began as a veterinary student in 1956. Dr. Brinster became an instructor in physiology in 1961 and a faculty member in 1965. As a tribute to Dr. Brinster's break-through scientific accomplishments in reproductive biology, transgenesis, and stem cell biology, a two-day symposium was held on August 24-25. Dr. Brinster's has received many awards over the years. Most recently he was awarded the prestigious National Medal of Science for his life's work by President Barack Obama. To celebrate Ralph Brinster's illustrious career notable scientists were invited from around the globe, including Nobel Laureat Michael S. Brown who spoke on “Genetically engineered mouse strains: models for human disease”. In addition, speakers for the event were: Richard Behringer, Allan Bradley, Ina Dobrinski, John Gurdon, Robert Hammer, Kathy High, Rudolf Jaenisch, Richard Palmiter, Janet Rossant, Hans Schöler, Richard Schultz, Takashi Shinozuka, Jamie Thomson, and Kenneth Zaret. 300 guests attended the event.

NEW FACULTY

Christine Cain, DVM, Dip. ACVD, has joined the Department of Clinical Studies Philadelphia as an assistant professor of dermatology. Her main clinical interests within the field of veterinary dermatology include infectious disease, dermatopathology, and allergy/immunology. Her primary research interests are staphylococcal infections, particularly the pathogenesis and treatment of recurrent pyoderma, immunologic response to staphylococcal infections, antimicrobial resistance (including methicillin resistance), and the implications of antimicrobial resistance for clinical practice of veterinary dermatology. Dr. Cain’s office is located at 2067 Ryan.


A TIP FOR NIH GRANT SUBMISSIONS

If you are preparing a proposal for submission through Grants.gov, attachment filenames will now be validated by them for allowable characters. The characters that can be used are as follows: A-Z, a-z, 0-9, Underscore _, Hyphen -, Space, Period.
and caspase-1, and have revealed that disruption of NF-kB and MAPK signaling by certain bacterial virulence factors leads to a non-canonical pathway of caspase-1 activation that appears to require caspase-8. A key area of research focus in the lab is to understand the basis for this link, and to define the immunological and pathological consequences for this unusual pathway of caspase-1 activation.

Research in the Brodsky laboratory is funded by pilot project awards from the University Research Foundation, McCabe Fund, Center for Molecular Studies in Digestive and Liver Disease, and the Office of the Vice Provost for Research. Dr. Brodsky’s laboratory is located on the third floor of the Rosenthal Building, and his office is in Old Vet Quad (390EE).

References


Grant Writing Workshop

Learn tips and strategies for NIH grant writing success, such as selecting the best funding institute and/or study section to review your proposal and techniques for selling your scientific ideas to reviewers.

Wednesday, Nov. 28, 2012
3:30 - 5:00 pm
1311 Blockley Hall
Instructors: Michael Marks, PhD (Perelman School of Med) and Leslie King, PhD (Penn Vet).
Course enrollment site (under COURSES): http://www.med.upenn.edu/fapd/ADVANCEResearchResourcePage.shtml

PUBLICATIONS


ENLISTING DOGS IN BATTLING CANCER

The work of Dr. Nicola Mason, B.VetMed. Ph.D., assistant professor of medicine, Department of Clinical Studies Philadelphia and the Department of Pathobiology was featured in a recent Philadelphia Inquirer article that reported the first canine patient vaccinated with recombinant *Listeria monocytogenes* at the University of Pennsylvania’s School of Veterinary Medicine. Yvonne Paterson, Ph.D. Professor of Microbiology originally developed the innovative technology that capitalizes on the inherent capacity of *Listeria* to induce potent immune responses. By genetically modifying this bacteria to express various tumor antigens, the immune system can be strongly stimulated against cancer cells. To determine the safety and efficacy of this approach in the treatment of her2/neu expressing cancers such as osteosarcoma, Dr. Nicola Mason is now conducting a clinical trial in which dogs with osteosarcoma are being vaccinated after standard of care amputation and chemotherapy. Given the similarity of pediatric and canine osteosarcoma at both the biological and genetic levels, positive results in this clinical trial are likely to hold great promise for the treatment of osteosarcoma in people. The response from veterinarians, dog breed clubs and owners across the nation has been overwhelming—calls have come from the UK and Spain for possible enrollments. Pivotal in this translational effort at Penn Vet have been the cardiologists, radiologists, surgeons, veterinary criticalists, nurses, and veterinary students.

RECENT AWARDS

**Robert M. Greenberg**  
NIH (NIAID)  
Schistosome TRP ion channels as potential drug targets  
$275,000 7/1/12–6/30/14

**Christopher Hunter**  
American Asthma FDN  
Clinical and basic aspects of IL-27 and asthma  
$750,000 7/1/12–6/30/15

**Christopher Lengner**  
NIH/NCI  
Deregulation of MSI RNA-binding proteins promotes intestinal tumorigenesis  
$1,660,000 8/7/12–5/31/13

**Christopher Lengner**  
Penn IRM  
Single cell characterization of quiescent and cycling intestinal stem cell dynamics  
$500,000 4/1/2012–3/31/13

**Christopher Lengner**  
NIH Anil Rustgi Center Grant  
The contribution of Mitochondrial DNA organization to liver disease progression  
$31,500 7/1/2012–6/30/13

**Keiko Miyadera**  
Foundation Fighting Blindness  
Career Development Award  
$86,490 2/1/2015

**G. Aguirre/Wm Beltran**  
FDN Fighting Blindness  
Retinal remodeling in canine models of LCA/Early onset retinal degeneration.  
$350,000 8/1/12–7/31/17

**Gus Aguirre**  
NEI/NIH Translational Research for Retinal Degeneration Therapies  
$3,176,035 2012–2013

**William Beltran**  
University of California at Berkeley NEI/NIH Sub-award  
$275,000 2012–2013

**Paul Wilson**  
NIH  
Migration of Skin Antibody Secreting Cells  
$103,156 7/1/12–6/30/14

**Sherrill Davison**  
USDA–Maintenance Laboratory Requirements  
$50,000 4/1/2012–3/31/13

**Dieter Schifferli**  
NIH  
Allelic variants of Salmonella fimbrial adhesins  
$275,000 7/25/12–6/30/14

**Claude Krummenacher**  
NIH  
Effects of saliva on herpes simplex virus infection of oral cells  
$250,000 8/1/12–7/31/13

**Robert Greenberg**  
NIH Schistosome TRP ion channels as potential drug targets  
$275,000 7/1/12–6/30/14

**Igor Brodsky**  
UPENN Pilot Mechanisms of Salmonella Innate Immune Evasion  
$20,000 7/1/12–6/30/14

**Charles Vite**  
Janssen Research & Dev.  
Niemann-Pick type C (NPC) disease  
$49,500 8/8/12–7/31/13

**Ralph Brinster**  
NIH R01  
MicroRNA regulation of spermatogonial stem cells and spermatogenesis  
$480,000, 8/16/2012–7/31/2014

**Parsons, Thomas**  
ASPCA Research fellowship and welfare training at Swine Ctr.  
$80,000 6/1/2012–6/1/2013

**Linardi, Renata/ Galantino-Homer, Hannah**  
USDA—Equine lamellar organotypic culture system: A tool for laminitis research & regenerative medicine  
$105,000 9/1/2012–8/31/2014

**Parsons, Thos./A Blaustein**  
American Humane Society  
Assessment of swine personalities in gestation pens  
$4,000 6/1/2012–10/1/2012

**Nicola Mason**  
AKC Canine Health Fdn.  
Clinical advancement of RNA-transfected CD40-B cell vaccine technology for cancer therapy  
$96,660 10/1/12–9/30/14
Summer training programs provide mentorship and infrastructure for veterinary students, high school students, visiting scholars, undergraduates and graduate students to attain specific technical and conceptual skills to perform hypothesis-based research involving faculty supervised projects at PENN VET. In addition, during the summer months, Penn Vet hosts a National Institutes of Health (NIH)/Merial Summer Scholars Program, directed by Dr. Michael Atchison. Shown below are the Merial participants and their faculty mentors.

**Student**
- Michelle Acierno
- Robyn Allen
- Elizabeth Golden
- Stephen Cole
- Chelsea del Alcazar
- Kreig Embriano
- Kristin Gardiner
- Samuel Gilbert
- Lauren Harris
- Rebecca King
- Britt Levy
- Austin Luskin
- Bridget Lyons
- Katelyn MacGillivray
- Andrea Moffit
- Marc Myers
- Shannon Palermo
- Diana Richerson
- Peri Rosenstein
- John Spronyi

**Faculty**
- Urs Giger
- Brett Kaufman
- Phil Scott
- Dieter Schifferli
- Mark Haskins
- Olena Jacenko
- Gus Aguirre
- Gail Smith
- Sue Volk
- Ron Harty
- Margret Casal
- Dustin Brisson
- Shelley Rankin
- Bruce Freedman
- Joseph Baur
- Kurt Hankenson
- Cynthia Otto
- Michael May
- Gary Smith
- Tracy Bale

**Nick Croy** is an undergraduate from Tulane University who worked on transcriptional analysis of cells subjected to mitochondrial stress in Dr. Narayan Avadhani’s Laboratory.

**Betsy Golden** is a veterinary student who worked in Dr. Phil Scott’s laboratory on the question: “Do Wound-healing Macrophages Promote Lesion Resolution in Leishmaniasis?”

**Seleeke Flingai** is a summer rotation graduate student in Dr. Gudrun Debes’ laboratory, who worked on the role of lymphatic endothelial cells in regulating tissue exit (and accumulation) of T cells and other lymphocytes.

**Allison Putterman** is a veterinary student who worked on “Avascular Osteonecrosis in Perlecan Hypomorph Mice” in Dr. Olena Jacenko’s laboratory.
Research Supplements to Promote Diversity

Funds are available for administrative supplements to improve the diversity of the research workforce by supporting and recruiting students, postdoctoral researchers, and eligible investigators from groups that have been shown to be underrepresented in health-related research. This supplement opportunity is also available to PD(s)/PI(s) of research grants who become disabled and need additional support to accommodate their disability in order to continue to work on the research project. Administrative supplements must support work within the scope of the original project. A parent grant may support more than one individual on a supplement; however, each request must be strongly justified and include assurances that each candidate will receive appropriate mentoring.

Program announcement: http://grants.nih.gov/grants/guide/pa-files/PA-12-149.html

The Penn Vet Working Dog Center celebrated its grand opening on Tuesday, September 11th at Penn’s new South Bank site in Grays Ferry. The Center highlights the culmination of Dr. Cynthia Otto’s research interests in the health, genetic and behavioral aspects of performance in detection dogs. Dr. Otto, associate professor, Department of Clinical Studies Philadelphia, has studied the complex behavior in detection dogs as a result of her interest in the “9/11” response. She and her group have a funded project on the effect of different hydration strategies on performance, hydration, and inflammation in detection dogs. The Penn Vet Working Dog Center will integrate the science and field experience to breed, select, raise and train dogs to use their noses to detect things (e.g. explosives, drugs, people, and even cancer and infectious diseases). Penn Vet’s Working Dog Center will be a prime resource for behavioral, nutrition, development and conditioning studies in dogs being trained for detection work. For more information Call: 215 989 - 2200 or email: griff@vet.upenn.edu

Craig Carnaroli, Penn’s executive vice president, will foster ‘Socks’ a working dog in training.