

March 23

**PHI ZETA STUDENT
RESEARCH DAY**

Keynote speaker:
Alexander Travis VMD, PhD



NIH UPDATES
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**GUT-BRAIN LINK—
TRACY BALE IN NATURE
NEWS PAGE 6**



NEWSLETTER



Chris Hunter with Jonathan DeLong and Gretchen Harms

Understanding immunity to infection

Dr. Christopher Hunter is a professor of parasitology, chair of the Department of Pathobiology, director of the “Center for Host Microbial Interactions” and the inaugural Mindy Halikman Heyer President’s Distinguished Professor (*see page 3*). He was awarded his BSc in Zoology (1985) and a PhD in Parasite Biochemistry (1989) from the University of Glasgow. He performed additional research on the immune response to parasitic infections as a post-doctoral fellow at Glasgow University School of Veterinary Medicine, as a student at the Woods Hole Biology of Parasitism

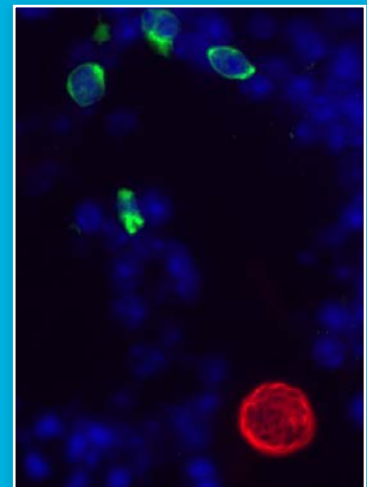
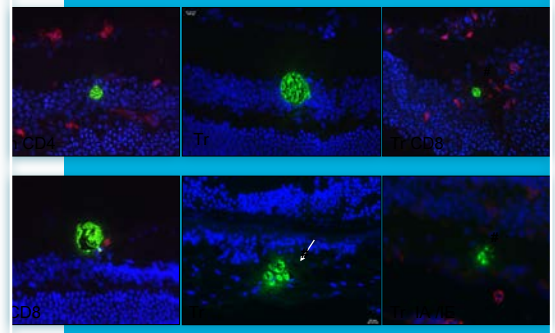
Course in 1991, and at Stanford University before joining the Pathobiology Department at Penn Vet in 1996. In particular, the Hunter laboratory studies the parasite *Toxoplasma gondii*, a pathogen that affects animals and humans and can cause severe disease in newborns, infants, and patients with immune deficiencies. This parasite is a significant cause of disease in livestock and small animals and as a zoonotic organism is readily transmitted to humans. According to the Centers for Disease Control and Prevention, this foodborne parasite infects more than 60 million people in the U.S. and approximately one-third of the world's population.

Basic parasitology since 1984

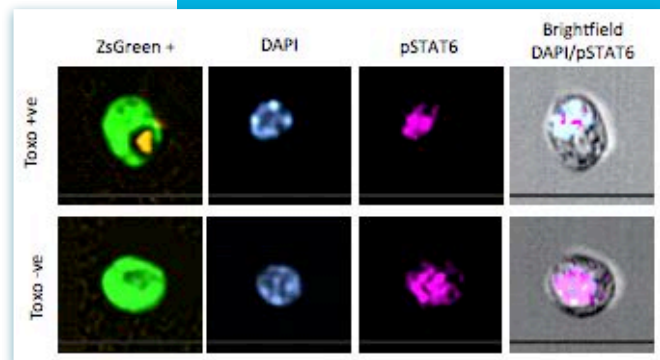
Dr. Hunter has been working on various aspects of basic parasitology since 1984. For the last 20 years, his laboratory at Penn Vet has been dedicated to further understanding how the immune response controls infection but at the same time can lead to collateral damage and aberrant inflammation. As a post-doctoral fellow, Dr. Hunter's work focused on trypanosomes, the single celled parasites that cause African sleeping sickness in humans and cattle. Trypanosomes invade the central nervous system (CNS) and promote chronic neuro-inflammation that is lethal unless treated. Dr. Hunter demonstrated an important role for the immune system in causing this lethal pathology, thus fundamentally changing how we think about the pathogenesis of this disease and how it should be managed(1). This work stimulated a long-term interest in infectious diseases that affect the brain and how the immune system controls infections in this unique setting, previously considered to be immune privileged. Current studies focus on the application of real time imaging of different immune populations in the CNS to understand how protective T cell responses operate in the brain and recent work has focused on visualizing how *Toxoplasma* can cross the blood brain barrier(2). Working with his longtime collaborator Dr. David Roos (Department of Biology, Penn Arts and Sciences) and others in the *Toxoplasma* scientific community, Dr. Hunter's laboratory has used a reductionist approach to determine how immune populations interact with genetically modified parasites that express fluorescent markers (3). As part of these latter studies he has worked closely with Dr. Andrea Liu in the Department of Physics and Astronomy, University of Pennsylvania, to develop better ways to analyze and describe how lymphocytes migrate in tissues and how

How immune cells behave in settings of infection and cancer

T. gondii in the retina



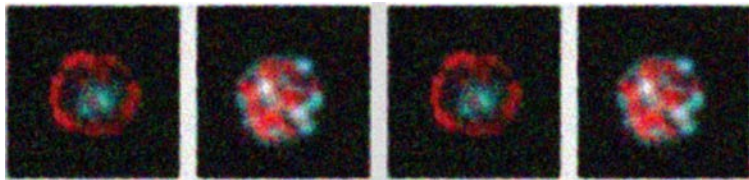
Toxoplasma cyst GFP+T cells



STAT6 activation in cells from infected mice

their behavior may be optimized to find pathogens(4). The laboratory is committed to the continued development of these models to understand how immune cells behave in settings of infection and cancer.

In studies carried out at the height of the HIV pandemic, Dr. Hunter also began to study toxoplasmic encephalitis (TE), a disease in which latent *Toxoplasma gondii* infections are reactivated in immunocompromised patients, including those with AIDS. Such studies led to the development of severe combined immunodeficient (SCID) mouse models that mimicked this disease in AIDS patients as well as in Hyper IgM patients (the bubble boys). While patients infected with HIV highlighted the important role of T cells for long term control of *Toxoplasma*, during his fellowship at Stanford, Dr. Hunter also became interested in understanding how other cells can be harnessed to promote resistance to this pathogen. Dr. Hunter’s studies contributed to the recognition that the cytokine IL-12 has a central node in stimulating Natural Killer (NK) cells to help control this opportunistic infection, but his studies also uniquely determined how other cytokines and immune pathways such as CD28 and the aryl hydrocarbon receptor impacted on NK cell activities and the relevant innate interactions that lead to IL-12 production (5). In addition, as part of efforts to understand how other IL-12 family members promote immunity to *T. gondii*, the Hunter laboratory provided the first evidence that IL-27 played a critical role in limiting infection-induced inflammation. Subsequently, the laboratory delineated the mechanisms by which IL-27 influences the immune system. This seminal work provided a basis for numerous studies examining inflammatory processes in multiple experimental systems, including other viral, bacterial and parasitic infections as well as models of auto-immune inflammation, asthma and cancer, thus establishing IL-27 as an endogenous inhibitor of inflammatory cytokine production, as well as a critical regulator of mechanisms that limit inflammation(6). Continued on Page 5



Stylized images of CD8+ T cells looking at differential localization of the transcription factor T-bet in mouse cells after infection with the parasite *Toxoplasma gondii*, using the Amnis ImageStream. In the cell in the first and third box, T-bet (red) does not co-localize with DAPI (blue), indicating that it is cytoplasmic, whereas in the cell in the second and fourth box, T-bet does co-localize with DAPI, indicating that it is nuclear. Gretchen Harms and David Christian provided these images.



Mindy and Andrew Heyer Endow President’s Distinguished Professorship to Dr. Christopher Hunter

Christopher Hunter, BSc, PhD, professor and chair of the Department of Pathobiology, University of Pennsylvania School of Veterinary Medicine, has been named the inaugural Mindy Halikman Heyer President’s Distinguished Professor. Established by Penn alumni Mindy and Andrew Heyer, the \$3 million endowment will advance Hunter’s research on how the immune system protects animals and humans from infectious disease. Dr. Hunter studies the parasite

Toxoplasma gondii, a pathogen that affects animals and humans and can cause severe disease in newborns, infants, and patients with immune deficiencies.

Recent Awards (*total direct costs*)

- Michael Atchison**
NIH/NIAID/R01
Control of B Cell Development by YY1
12/1/15-11/30/20 \$1,401,161
- Montserrat Anguera**
Research Careers in Women's Health
K12 BIRCHWH Scholars
1/1/16 to 12/31/18 \$250,000
- Manti Guha**
Breast Cancer Alliance
Reduced mitochondrial DNA copy number is a determinant of breast cancer metastasis
2/1/16 to 1/31/18 \$125,000
- Allison Bradbury**
Legacy of Angels Foundation
Lentiviral-mediated Hematopoietic Stem Cell Gene Therapy for Canine Globoid Cell Leukodystrophy
11/1/15-12/31/18 \$226,800
- Erika Krick**
Cytosorbents Corp.
Effects of hemoabsorption on cytokine removal and quality of life in cats with cancer
9/15/15-9/14/16 \$5,000
- Erika Krick**
Morris Animal Foundation
A Contemporaneous Controlled Study of the Standard of Care (SOC) in dogs with Appendicular Osteosarcoma
\$Payment based on enrollment 1/1/16-12/31/17
- Erika Krick**
Morris Animal Foundation
Evaluation of Orally Administered mTOR inhibitor Rapamycin in Dogs in the Adjuvant Setting with Osteosarcoma
\$Payment based on enrollment 1/1/16-12/31/17
- Oriol Sunyer**
NSF IOS-1457282
Evolution of Mucosal B Cell Immunity: Novel Roles of IgT+ B Cells in the Control of Host-pathogen Interactions
8/15/15—7/31/18 \$420,665
- Nicola Mason**
Richard Lichter Charity for Dogs
Re-Directed T Cell Therapy in Dogs with B Cell Lymphoma
12/1/15-11/30/16 \$186,219
- Keiko Miyadera**
Burrows Enterprises
Clinical & Safety Evaluation of Burr-I Drops for the Treatment of Dogs with Cataracts
11/9/15-11/8/16 \$69,934
- Cynthia Otto**
AKC-CHF
Medical Surveillance of Dogs Deployed to the World Trade Center and the Pentagon 2015-Completion
12/1/15-11/30/16 \$11,340
- Brittany Watson (Tisa)**
PetSmart Charities
Penn Vet Shelter Medicine Surgical Program
12/1/15-11/30/16 \$206,422
- Charles Vite**
University of Pitt (Legacy of Angels flowdown)
Treatment of Krabbe Disease Using Intravenous Adeno-Associated Virus Gene Therapy
12/1/15-11/30/16 \$8000
- Charles Vite**
Million Dollar Bike Ride Program
Targeted AAV gene therapy for vertical supranuclear gaze palsy and dysphagia
1/1/2016—12/31/2016 \$53,500
- Charles Vite**
Million Dollar Bike Ride Program
Natural history study and biomarker development in the large animal model of mucopolipidosis II
1/1/2026-12/31/2016 \$50,500
- Phil Scott**
U01 AI088650
The role of innate cells in the pathogenesis of Leishmania braziliensis infection
1/1/16-12/31/19 \$1,166,248
- Victor Absalon Medina**
Li Animal Health
Evaluation and optimization of culture media for in vitro embryo purposes using mammalian eggs
1/1/2016—12/31/2018 \$1,749,448
- David Galligan**
Wharton China Center
Penn Vet & Wharton Dairy Training Program
12/1/2015—11/30/2018 \$339,750
- Ashley Boyle**
Boehringer Ingelheim
Validation of a point-of-care self-heating, microfluidic cartridge for isothermal nucleic acid amplification of *Streptococcus equi subsp equi*
12/1/2015—11/30/2016 \$15,000
- Tom Schaer**
Orthopaedic Association
Evaluation of Local Tissue Concentrations and Bioactivity of Vancomycin Eluted from PMMA Implants in an Ovine Fracture Healing Model
1/1/2016—12/31/2017 \$49,800
- Sue McDonnell**
Merck
Merck 2015 IN Applicator Behavior Clinical Trial
1/1/2016—6/30/2016 \$12,500
- Sue Volk & Karin Sorenmo (Co-PI's)**
Greater Good Foundation
The role of collagen in directing canine mammary tumor progression
1/1/16-12/31/16 \$28,235



Continued from Page 3

By studying how the immune system can control infectious disease, Dr. Hunter’s research is relevant to many inflammatory processes, including those involved in cancer, asthma, lupus, multiple sclerosis, and arthritis. The broad impact of his research is illustrated by his roles as a Senior Investigator for the American Asthma Foundation and as a Scientific Founder and member of the Scientific Advisory Board for Surface Oncology, a Cambridge, MA-based Company focused on cancer immunotherapies. Hunter is a Fellow of the American Academy of Microbiology and a Fellow of the Royal Society of Edinburgh. He is the recipient of the Cormie Prize in Neurology, and was selected as an Irvington Research Scholar. Support for these studies has been provided by the NIH, Genzyme, Amgen, Medimmune, Janssen, American Asthma Foundation, and the Burroughs Wellcome Young Investigator Award.

Dr. Hunter’s office and laboratory are located on the 3rd Floor Hill Pavilion.

References

1. Hunter CA, Jennings FW, Adams JH, Murray M, Kennedy PGE. 1992. Subcurative chemotherapy and fatal post-treatment reactive encephalopathies in African trypanosomiasis. *Lancet* 339: 956-8
2. Konradt C, Ueno N, Christian DA, DeLong J, Harms Pritchard G, Herz J, Bzik DJ, Koshy AA, McGavern DB, Lodoen MB, CA H. 2016. Endothelial cells are a replicative niche for entry *Toxoplasma gondii* to the central nervous system. . *Nature Microbiology (In Press)*.
3. Christian DA, Koshy AA, Reuter MA, Betts MR, Boothroyd JC, Hunter CA. 2014. Use of Transgenic Parasites and Host Reporters To Dissect Events That Promote Interleukin-12 Production during Toxoplasmosis. *Infection and immunity* 82: 4056-67
4. Harris TH, Banigan EJ, Christian DA, Konradt C, Tait Wojno ED, Norose K, Wilson EH, John B, Weninger W, Luster AD, Liu AJ, Hunter CA. 2012. Generalized Levy walks and the role of chemokines in migration of effector CD8+ T cells. *Nature* 486: 545-8
5. Hunter CA, Sibley LD. 2012. Modulation of innate immunity by *Toxoplasma gondii* virulence effectors. *Nat Rev Microbiol* 10: 766-78
6. Yoshida H, Hunter CA. 2015. The immunobiology of interleukin-27. *Annual review of immunology* 33: 417-43



William Beltran DVM, PhD, Artur Cideciyan, PhD, Gustavo Aguirre, VMD, PhD, and Samuel Jacobson, MD, PhD

Successful collaboration across the Penn Campus —

Successful arrest of photoreceptor and vision loss expands the therapeutic window of retinal gene therapy to later stages of disease. **Beltran WA**, Cideciyan AV, Iwabe S, Swider M, Kosyk MS, McDaid K, Martynyuk I, Ying GS, Shaffer J, Deng WT, Boye SL, Lewin AS, Hauswirth WW, Jacobson SG, **Aguirre GD**. *Proc Natl Acad Sci U S A*. 2015 Oct 27;112(43):E5844-53. pnas.1509914112. Epub 2015 Oct 12.

Awards and Honors—Mark Haskins, VMD, PhD, professor in the Department of Pathobiology (pathology and medical genetics) received an award from the International Society for Mannosidosis and Related Diseases (ISMRD) at the Glycoproteinases: Fourth International Conference on Advances in Pathogenesis and Therapy in St. Louis, Missouri. Dr. Haskins was recognized for his lifetime of service and knowledge of lysosomal storage diseases.



Mark Haskins



Urs Giger

Urs Giger, PD, DVM, MS, professor in the Department of Clinical Studies Philadelphia was the recipient of the 2015 Winn/AVMF (American Veterinary Medical Foundation) Excellence in Feline Research Award. Dr. Giger has held the endowed Charlotte Newton Sheppard Professor of Medicine Chair at the University of Pennsylvania in Philadelphia since 1997.



Tracy Bale

Tracy Bale, PhD, professor in the Department of Biomedical Sciences was featured with neuroscientists who are probing the connections between intestinal microbes and brain development in “Brain, Meet Gut”, *Nature* 526: 312-314, 2015

Bale TL and Epperson CN (2015) Sex differences and stress across the lifespan. *Nature Neurosci* 18(10): 1413-20.

Register Now!

2016 Phi Zeta Student Research Day

Wednesday, March 23, 2016

12 noon —6 pm

Main Floor Hill Pavilion



Keynote Speaker

*“Following your science—
from sperm to stroke and
from basic to bedside”*

Alexander J Travis, VMD, PhD

Associate Professor of
Reproductive Biology

Cornell University College of
Veterinary Medicine

Registration Link:

[http://survey.vet.upenn.edu/
index.php?sid=22515&lang=en](http://survey.vet.upenn.edu/index.php?sid=22515&lang=en)

Publications



Song, J., Liu, C., Bais, S., Mauk, M.G., Bau, H.H., **Greenberg, R.M.** (2015) Molecular detection of schistosome infections with a disposable microfluidic cassette. *PLoS Neglected Tropical Diseases* 9, e0004318.

Bais, S., Churgin, M.A., Fang-Yen, C., **Greenberg, R.M.** (2015) Evidence for novel pharmacological sensitivities of transient receptor potential (TRP) channels in *Schistosoma mansoni*. *PLoS Neglected Tropical Diseases* 9, e0004295.



Alvarez JI, Kébir H, Cheslow L, Chabarati M, Larochelle C, and Prat A (2015) JAML mediates monocyte and CD8 Tcell migration across the brain endothelium *Ann Clin Transl Neurol* 2(11): 1032-1037

Cheslow L and **Alvarez JI** (2015) Glial-endothelial crosstalk regulates blood-brain barrier function. *Curr Opin Pharmacol* 26: 39-46



Xu J, Mercado-López X, Grier JT, Kim WK, Chun LF, Irvine EB, Del Toro Duany Y, Kell A, Hur S, Gale M Jr, Raj A, **López CB.** (2015) Identification of a Natural Viral RNA Motif That Optimizes Sensing of Viral RNA by RIG-I. *Mbio* 6(5):e01265-15.

Sun Y, Jain D, Koziol-White CJ, Genoyer E, Gilbert M, Tapia K, Panettieri RA Jr, Hodinka RL, & **Lopez CB** (2015) Immunostimulatory Defective Viral Genomes from Respiratory Syncytial Virus Promote a Strong Innate Antiviral Response during Infection in Mice and Humans. *PLoS Pathog.* 2015 Sep 3;11(9):e1005122



Fonseca DM, Hand TW, Han SJ, Gerner MY, Glatman Zaretsky A, Byrd AL, Harrison OJ, Ortiz AM, Quinones M, Trinchieri G, Brenchley JM, **Brodsky IE**, Germain RN, Randolph GJ, Belkaid Y. (2015) Microbiota-dependent sequelae of acute infection compromise tissue-specific immunity *Cell* 163(2):354-66.

Rosadini CV, Zandoni I, Odendall C, Green ER, Paczosa MK, Philip NH, **Brodsky IE**, Meccas J, Kagan JC. (2015) A Single Bacterial Immune Evasion Strategy Dismantles Both MyD88 and TRIF Signaling Pathways Downstream of TLR4. *Cell Host Microbe* 18(6): 682-93



Yue M, Han X, Masi LD, Zhu C, Ma X, Zhang J, Wu R, Schmieder R, Kaushik RS, Fraser GP, Zhao S, McDermott PF, Weill FX, Mainil JG, Arze C, Fricke WF, Edwards RA, Brisson D, Zhang NR, **Rankin SC, Schifferli DM.** (2015) Allelic variation contributes to bacterial host specificity. *Nature Commun.* 6:8754

Zoobiquity Conference in Philadelphia Connecting Health and Medicine in Animals and Humans

April 2, 2016 Saturday

Arthur H. Rubenstein Auditorium, Smilow Center for Translational Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Registration Link:

<http://zoobiquity2016.com>

Registration is limited to the first 240 healthcare professionals and 70 students.

Jointly presented by Penn Vet, Penn Medicine and the Pennsylvania Veterinary Medical Association



The featured manuscript for the cover photo "Evaluation of Presurgical Skin Preparation Agents in African Clawed Frogs (*Xenopus laevis*) is from Dr. Blythe Phillips, former resident and now a staff veterinarian.



NIH updates—For grant applications due on January 25, 2016, and beyond, revised application instructions and review criteria will focus on four areas important for enhancing rigor and transparency. A website has been established (<http://grants.nih.gov/reproducibility/index.htm>) and excerpts presented below.

1. The **scientific premise** that forms the basis for the proposed research question(s) must be supported and include the general strengths, weaknesses, and rigor of the previous experimental designs, as well as their incorporation of relevant biological variables and authentication of key resources. **Reviewers will evaluate scientific premise as part of the significance criteria as well as overall impact.** In contrast to Significance, which indicates how the field will change if the aims are achieved, scientific premise includes a retrospective consideration of the foundation for the application.
2. **Scientific rigor** is the strict application of the scientific method to ensure robust and unbiased experimental design, methodology, analysis, interpretation and reporting of results. This includes full transparency in reporting experimental details so that others may reproduce and

- extend the findings. **Rigor and biological variables will be judged as part of the approach criteria as well as overall impact.** Applicants should consider methods to reduce bias, such as having multiple individuals recording assessments, defining terminology in advance, using independent, blinded assessors, etc. "Robust" and "unbiased" results are goals, not absolute standards to be met, and may vary across scientific disciplines.
3. **Biological variables**- NIH expects that sex as a biological variable will be factored into research designs, analyses, and reporting in vertebrate animal and human studies. Strong justification from the scientific literature, preliminary data or other relevant considerations must be provided if proposing to study only one sex. **Considering the possible role of sex early in the research continuum may save money by revealing differences or similarities that need to be taken into consideration in subsequent phases of study.** Age, weight, and underlying health conditions should be considered where applicable.
 4. **Key biological and/or chemical resources** including cell lines, specialty chemicals, antibodies and other biologics must be authenticated in a **new PDF attachment.** Each investigator will have to determine which resources fit these criteria. As per current requirements in many journals, information regarding *the source of the cell lines, their authentication, their*

*mycoplasma status will likely be required. Commonly misidentified cell lines (<http://iclac.org/databases/cross-contaminations/>) will clearly receive the most scrutiny. Actual data demonstrating authenticated resources will not needed. While Reviewers' concerns will not influence the overall impact score, they must be addressed prior to award. **Applications identified as non-compliant with this limitation will be withdrawn from the review process!!!!!!***

Leslie King, PhD



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

resnews@vet.upenn.edu

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Research and Academic
Resources

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