



**FEATURE ARTICLE**  
**BORIS STRIEPEN**  
DEPARTMENT OF  
PATHOBIOLOGY



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AAAS FELLOW  
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# NEWSLETTER



## Diseases caused by parasites

Dr. **Boris Striepen** recently joined Penn Vet as a professor in the Department of Pathobiology. Boris studied biology in Bonn and Marburg, Germany and conducted undergrad research on liver flukes in Bonn and cattle trypanosomes in Bobo Dioulasso, Burkina Faso. After earning his Ph.D. with Ralph Schwarz in Marburg, Boris was a postdoc with David Roos at the University of Pennsylvania, after which he joined the faculty of the Center for Tropical & Emerging Global

*Cryptosporidium, an important but challenging problem*

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Diseases at the University of Georgia (UGA), where he last served as a Distinguished Research Professor. In addition, Boris has been an instructor at the Marine Biological Laboratory (MBL) Biology of Parasitism summer research course since 2001 and served as course director.

**Toxoplasma—a somewhat surprising model organism**

When Boris considered graduate projects, his mentor suggested focusing on *Toxoplasma gondii*, a pathogen that was relatively obscure at the time and was studied by only a tiny research community. Boris had spent time in West-Africa and was much more taken with parasites that caused ‘tropical’ diseases like malaria or sleeping sickness. However, the *Toxoplasma* project was a collaboration with Jean-François Dubremetz, so Dr. Schwarz was able to entice Boris by cleverly offering to send him to France to learn from the world’s leading *Toxoplasma* biologists. *Toxoplasma* infection in humans is very common, but is largely asymptomatic unless the patient is immunosuppressed or infected *in utero*, in which case it can have devastating consequences. In his dissertation studies, Boris discovered that an important antigen used to differentiate acute infection in pregnant women (which threatens the fetus) from chronic infection (which does not), is not a protein, but actually from a family of glycolipids. He resolved their molecular structures, mapped the epitopes, and delineated the biosynthetic pathways leading to their assembly [1, 2].

Boris’ decision to study *Toxoplasma* turned out to be timely, as at the time of his thesis defense, the laboratories of Drs. J. Boothroyd, D. Roos, and L. Sibley established genetic manipulation for *Toxoplasma*. This made *Toxoplasma* the first genetically tractable apicomplexan parasite and allowed the field to take off. Boris joined Dr. David Roos’s lab to learn how to transfect parasites, and developed the first *Toxoplasma* expressing fluorescent proteins. He used this model to determine how the parasite sorts and targets its proteins to a variety of critical organelles. In his own laboratory at UGA he built a program that expanded and harnessed the genetic *Toxoplasma* model to dissect fundamental aspects of parasite biology, addressing such questions



Alexis Gibson and Rina Matsuda, PhD graduate students in the Striepen Laboratory

**Publications & Honors**



Dr. Gus Aguirre has been named a fellow of the American Association for the Advancement of Science (AAAS).



Schoenle LA, Schoepf I, Weinstein NM, Moore IT, Bonier F (2018) Higher plasma corticosterone is associated with

reduced costs of infection in red-winged blackbirds *Gen Comp Endocr* 256:89-98.



Luethy D, Stefanovski D, Salber R, Sweeney RW. (2017)

Prediction of packed cell volume after whole blood transfusion in small ruminants and South American camelids: 80 cases (2006 to 2016). *J Vet Int Med* 2031:1900-1904.



Xu J, Sun Y, Li Y, Ruthel G, Weiss SR, Raj A, Beiting D, & López CB. (2017)

Replication defective viral genomes exploit a cellular pro-survival mechanism to establish paramyxovirus persistence. *Nature Communications* 8(1):799.

Dr. Carolina López was selected for a Fulbright US Scholar Award to support a 6-month sabbatical at the Pasteur Institute in Paris where she will study virus dynamics and evolution.



as: How are parasites built and assembled? What are the mechanistic nuts and bolts of organelle biogenesis and parasite replication [3, 4] and how does parasite metabolism feed these processes?

*Cryptosporidium, an important but challenging problem*—The current focus of the Striepen group is *Cryptosporidium*. This parasite related to *Toxoplasma* is an important cause of diarrheal disease in the US. The incidence of *Cryptosporidium* in the US is rising and the Center for Disease Control (CDC) is estimating 750,000 annual cases and implicating the parasite in >50% of waterborne outbreaks. *Cryptosporidium* is resistant to water chlorination and listed as a category B bioterrorism agent. Globally, *Cryptosporidium* is the second leading cause of severe diarrheal disease in small children, second only to Rotavirus and an important contributor of child mortality (-10% of under-five mortality is due to diarrhea). There is no fully effective treatment and no vaccine. A main block to such advances has been the poor tractability of the parasite system with significant limitations in culture, animal model and genetics [5].

*Molecular genetics to enable drug development and fundamental biology*—Following a decade-long effort, the Striepen lab pioneered molecular genetics in *Cryptosporidium* in 2015 [6] by engineering reporter parasites expressing luciferases and fluorescent proteins. These tools enabled a collaboration with the Novartis Institute for Tropical Diseases to screen a library of anti-malaria compounds for potential activity against *Cryptosporidium*. Importantly, these studies led to the discovery and development of a PI4K inhibitor that cures cryptosporidiosis in mice and calves [7]. This candidate is now slated for first in man clinical studies. However, while the last three years have seen unprecedented progress in *Cryptosporidium* drug development, critical knowledge of their mode of action remains scant. As part of the Bill & Melinda Gates Foundation funded *Cryptosporidium* Drug Accelerator program the Striepen laboratory uses molecular genetics to validate targets, link targets to compounds, and further understanding of parasite metabolism to identify vulnerabilities that could be targeted for drug development.

*Cryptosporidium* has a single host life cycle, with both asexual and sexual processes occurring sequentially in the intestinal epithelium of the same host. Completion of this developmental program is required for continued infection, severe disease, and spread of the pathogen. Despite the fundamental importance of the lifecycle for drug and vaccine development, current understanding of the mechanism is rudimentary. The Striepen laboratory dissects the parasite’s lifecycle at the molecular and cellular level, attempting to answer important questions such as How do gametes develop and find each other within the cells of their host and how could one genetically interrupt the process? Identification of such mutants will not only drive fundamental insight but could also be starting points for attenuation.

*Drugs are terrific—a vaccine could be better*—Although epidemiological and experimental studies support the likely development of immune-mediated resistance to *Cryptosporidium*, single exposure does not consistently produce sterilizing immunity and host nutritional status, and host and parasite genetic diversity likely modulate resistance. Moreover, the immunological mechanisms required for control and protection are not well defined, as rodent studies have been challenged by the fact that only severely immune-compromised mice are susceptible to infection with common *Cryptosporidium* strains. To remedy this situation, the Striepen laboratory derived a natural mouse model for



Dr. Striepen with postdoctoral researcher, Dr. Adam Sateriale

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*Cryptosporidium* infection from parasites isolated from ‘wild’ mice. These parasites are genetically tractable and produce self-limiting infection of the small intestine in immunocompetent mice. Importantly, these mice are protected from reinfection and immunity is transferable. This has opened *Cryptosporidium* immunology to rigorous experimentation and it is the group’s hope that this may close critical knowledge gaps towards vaccination

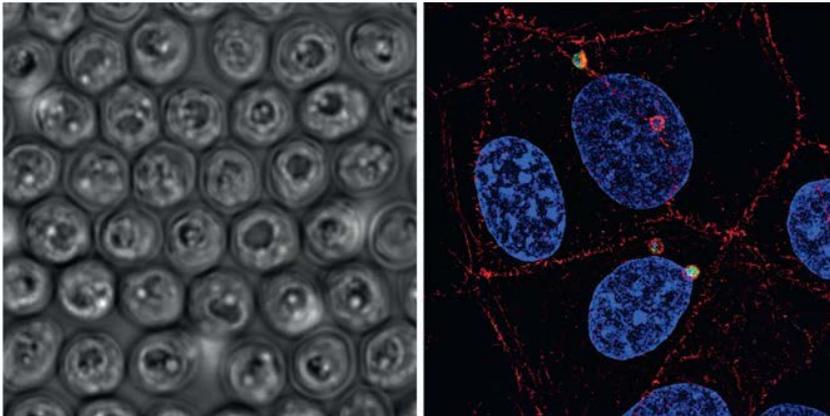


Figure 1. The apicomplexan parasite *Cryptosporidium parvum*. (A) Infection occurs by ingestion of oocysts, meiotic spores that contain four invasive parasites and are resistant to water chlorination. (B) Crypto (green) induces actin polymerization (red, phalloidin) in the host cell at the site of infection. Blue, DNA. Images: Kandasmay and B. Striepen.

Dr. Striepen’s laboratory is located on the 3<sup>rd</sup> Floor, Hill Pavilion and his office is found at 317 Hill Pavilion. Research in the Striepen laboratory is supported by the National Institutes of Health (NIH): R01AI12427, R01AI27798, R01AI25362, F32AI124518, and the Bill & Melinda Gates Foundation: OPP1183177 and OPP1161001.

References

1. Striepen, B., Zinecker, C.F., Damm, J.B., Melgers, P.A., Gerwig, G.J., Koolen, M., Vliegthart, J.F., Dubremetz, J.F., and Schwarz, R.T. (1997). Molecular structure of the "low molecular weight antigen" of *Toxoplasma gondii*: a glucose alpha 1-4 N-acetylgalactosamine makes free glycosyl- phosphatidylinositols highly immunogenic. *J Mol Biol* 266, 797-813.
2. Striepen, B., Dubremetz, J.F., and Schwarz, R.T. (1999). Glucosylation of glycosylphosphatidylinositol membrane anchors: identification of uridine diphosphate-glucose as the direct donor for side chain modification in *Toxoplasma gondii* using carbohydrate analogues. *Biochemistry* 38, 1478-1487.
3. Francia, M.E. and Striepen, B. (2014). Cell division in apicomplexan parasites. *Nat Rev Microbiol* 12, 125-136.
4. van Dooren, G.G. and Striepen, B. (2013). The algal past and parasite present of the apicoplast. *Annu Rev Microbiol* 67, 271-289.
5. Striepen, B. (2013). Parasitic infections: Time to tackle cryptosporidiosis. *Nature* 503, 189-191.
6. Vinayak, S., Pawlowic, M.C., Sateriale, A., Brooks, C.F., Studstill, C.J., Bar-Peled, Y., Cipriano, M.J., and Striepen, B. (2015). Genetic modification of the diarrhoeal pathogen *Cryptosporidium parvum*. *Nature* 523, 477-480.
7. Manjunatha, U.H., Vinayak, S., Zambriski, J.A., Chao, A.T., Sy, T., Noble, C.G., Bonamy, G.M.C., Kondreddi, R.R., Zou, B., Gedeck, P., et al. (2017). A *Cryptosporidium* PI(4)K inhibitor is a drug candidate for cryptosporidiosis. *Nature* 546, 376-380.

Positive atmosphere found in Hill Pavilion research laboratories

Every day the researchers on the 3<sup>rd</sup> Floor of Hill Pavilion are greeted with a different cartoon art and a positive message on the white board in the break room. Dr. Farima Zahedi is the creator of this daily treat. Dr. Zahedi, postdoctoral fellow in the laboratory of Dr. Serge Fuchs, came to Penn Vet after earning her Ph.D. at the Ludwig-Maximilian University of Munich, Germany. She hails from Tehran, Iran. Dr. Zahedi works on the mechanisms of cancer metastasis with a focus on prostate cancer. If you need to start your day with a happy message—stop by the 3 Hill break room.



Recent Awards

**Sue Volk**

AKC Canine Health Foundation  
Tumor permissive collagen signatures in canine mammary gland tumors: Development of Prognostic markers and targeted Therapies for Improved Outcomes  
3/1/18 to 2/29/20 \$162,700

**Boris Striepen (feature article)** received a \$1.8-million, three-year grant from the Bill & Melinda Gates Foundation to enable the development of drugs for cryptosporidiosis, a diarrheal disease caused by microscopic parasites.  
Bill and Melinda Gates Foundation  
*Cryptosporidium*: Tools for target identification and validation  
11/29/17—10/1/20 \$1,851,258

**Bruce Freedman**

NIH/ NIAID R21  
The Membrane Repair Channel TRPML1 Regulates Ebola Virus Budding  
12/21/17—11/30/19 \$275,000

**Robert Greenberg**

NIH/ NIAID R21  
Are schistosome micro-exon genes (MEGs) upregulated as an immune evasion response to the antischistosomal drug praziquantel?  
12/21/17—11/30/19 \$275,000

**Ronald N. Harty**

NIAID/NIH  
Modular Domains of Host Proteins Regulate Filovirus Maturation  
4/1/18 - 3/31/20 \$275,000

**Ronald N. Harty**

The Wellcome Trust  
Development of Host-Oriented Therapeutics Against Hemorrhagic Fever Viruses  
2/10/18 - 2/9/20 \$682,000

**Ronald N. Harty**

University Research Foundation  
Regulation of Tight Junction Integrity by Ebola Virus VP40  
3/1/18 - 2/28/19 \$45,000

**Magi Casal**

AKC-Canine Health FDN.  
Microphthalmia and Delayed Growth Syndrome in the Portuguese Water Dog 11/1/17-10/31/19 \$12,960

**Nicola Mason**

Leidos Biomedical research Inc.  
Preserving Cancer Stem Cells In Canine Blood Specimens  
12/1/17-6/30/18 \$297,300

**Nicola Mason**

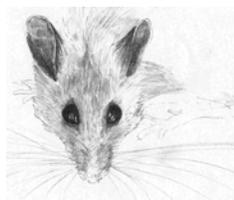
AKC Canine Health Foundation  
Immune Targeting of the V600E B-Raf neo-Antigen in Canine Urothelial Carcinoma  
2/1/18—1/31/20 \$183,146

**Nicola Mason & Amy Durham**

AKC Canine Health Foundation  
Precision Medicine for Canine Lymphoma  
3/1/18—2/29/20 \$86,400

**Carlo Siracusa**

Zoetis  
Sileo (dexmedetomidine oromucosal gel) for Veterinary Visit Anxiety In Dogs: a randomized, doubleblind, placebo controlled pilot study  
12/6/17-12/5/18 \$29,940



**Brittany Watson**

Petsmart Charities  
Student Ambassador Program  
9/1/17-9/1/18  
\$15,000

**Brittany Watson**

Petsmart Charities  
Second Annual Shelter Medicine Educator's Meeting  
10/1/17-12/31/17 \$10,000

**Charles Vite**

BioMarin Pharmaceuticals Inc.  
BioMarin MPSIIIA research project  
12/6/17-12/31/18 \$397,503

**Charles Vite**

Leidos Biomedical Research Inc.  
Creation of Feline NPC2 Using CRISPR/Cas9 genome editing  
9/25/17-8/31/18 \$807,263

**Sue McDonnell**

Dorothy Russell Havemeyer FDN  
Reproductive Behavior and Physiology of Horses  
11/1/17-10/31/18 \$34,748

**Dipti Pitta**

Ikena  
Influence of Valkalor AL 881 on Milk Production in Holstein Cows  
10/1/17-9/30/18 \$72,719

**Dipti Pitta**

USDA NIFA  
Deciphering the crosstalk between bacteria – archaea interactions in the rumen and methane-yield phenotype of dairy cows  
1/1/2018-12/31/20 \$499,739

**Dipti Pitta**

DSM Nutritional Products AG  
The effects of 3-nitrooxypropional (3NOP), a persistent methane inhibitor, on ruminal microbial gene expression profiles in dairy cows  
12/15/17-6/15/19 \$86,091

**Tom Parsons**

National Pork Board  
Impact of duration of farrowing crate closure on sow welfare and piglet mortality  
12/1/17-11/30/18 \$72,509

**Ann Kashina**

NIH/GM R35  
Protein Arginylation as a Key Regulator of Cell Migration  
8/31/18-8/31/2022 \$513,453

**Anna Kashina**

Abzyme Therapeutics, LLC  
Development of Arginine Linkage-Specific Antibodies  
11/27/17-08/31/18 \$50,633

**Gus Aguirre**

American Spaniel Club Health & Rescue Foundation  
Molecular Genetic Studies of Inherited Cataracts in the American Cocker Spaniel  
1/1/18—12/31/21 \$163,389

More Publications



Nelson, FE, Hollingworth S, Marx JO, Baylor SM, and Rome LC (2018) Small Ca<sup>2+</sup> releases enable hour-long high-frequency contractions in midshipman swimbladder muscle *J Gen Physiol* 150: 127-143.



Cain CL, Bradley CW, & Mauldin EA (2017) Clinical and histologic features of acute-onset erythroderma in dogs with gastrointestinal disease: 18 cases (2005–2015) *J Am Vet Med A* 251: 1439-1449



Dou Z, Toth JD, Westendorf ML. (2018) Food waste for livestock feeding: Feasibility, safety, and sustainability implications. *Glob Food Secur*, in press

Li, T, W. Zhang, D. Powlson, X. Liu, X. Chen, F. Zhang, Z. Dou. (2017) Enhanced-efficiency fertilizers are not a panacea for resolving the nitrogen problem. *Glob Change Biol*. gcb.13918. Epub ahead of print

Mason JB, Gurda BL, Hankenson KD, Harper LR, Carlson CS, Wilson JM, Richardson DW. (2017) Wnt10b and Dkk-1 gene therapy differentially influenced trabecular bone architecture, soft tissue integrity, and osteophytosis in a skeletally mature rat model of osteoarthritis. *Connect Tissue Res*. 58(6):542-552.



Pitta DW, Indugu N, Vecchiarelli B, Rico DE, and Harvatine KJ (2018) Alterations in ruminal bacterial populations at induction and recovery from diet-induced milk fat depression in dairy cows *J Dairy Sci* 101: 295-309.



Jacobs CC, Levine DG, & Richardson DW (2017) Use of locking compression plates in ulnar fractures of 18 horses. *Vet Surg* 46(2): 242-248.



Kubin L and Mann GL (2018) Hypoglossal motoneurons are endogenously activated by serotonin during the active period of circadian cycle. *Resp Physiol Neurobi* 248: 17-24



Guha M, Srinivasan S, Raman P, Jiang Y, Kaufman BA, Taylor D, Dong D, Chakrabarti R, Picard M, Carstens RP, Kijima Y, Feldman M, Avadhani NG. (2018) Aggressive triple negative breast cancers have unique molecular signature on the basis of mitochondrial genetic and functional defects *Biochim Biophys Acta* S0925-4439(18)30003-6. Epub ahead of print



Wang G, Wu M, Maloneyhuss MA, Wojcik J, Durham AC, Mason NJ and Roth DB (2017) Actionable mutations in canine hemangiosarcoma. *PLoS One* 12(11):e0188667.



Lo A, Li CP, Buza EL, Blomberg R, Govindaraju P, Avery D, Monslow J, Hsiao M, & Puré, E (2017) Fibroblast activation protein augments progression and metastasis of pancreatic ductal adenocarcinoma *JCI Insight* 2(19): Epub ahead of print.

**A successful Penn Vet Cancer Center Symposium**—the inaugural Penn Vet Cancer



Penn Vet's Nicola Mason

Center symposium was held on November 30—December 1, 2017, to discuss “How Man’s Best Friend Could Help Us Cure Cancer”. Under the leadership of Dr. Ellen Puré a conference was held to address basic discoveries and more effective ways to treat cancer in all species. Speakers included Elaine Ostrander, PhD (chief, Cancer Genetics and Comparative Genomics branch at the National Institutes of Health); Kristy Weber, MD (director of the Penn Sarcoma Program); Jaime Modiano, VMD., PhD (Perlman professor of oncology and comparative medicine at the University of Minnesota School of Veterinary Medicine); Rodney Page, DVM

(director, Flint Animal Cancer Center, Colorado State University); Amy Leblanc,

DVM (director, Comparative Oncology Program, National Cancer Institute [NIH]); Robert Vonderheide, MD, DPhil (director, Abramson Cancer Center; The John H. Glick, MD Abramson Cancer Center Director’s Professor); and Andrew Ewald, PhD (Johns Hopkins School of Medicine). Read more in Arthur Brodsky’s blog about newly developed cancer treatments that were highlighted at the symposium and the inspiring aspects on how we can more reliably translate breakthroughs between our two species and better sustain innovation in the long run—to ensure continued advances for both of us for the foreseeable future.



Robert Vonderheide and Ellen Puré

<https://www.cancerresearch.org/blog/january-2018/dogs-cure-cancer-penn-vet-symposium>

**2018 Student Research Day on March 20<sup>th</sup>**



Students and faculty will gather on Tuesday, **March 20, 2018** for the annual **Student Research Day**. The

keynote address will be given by Patricia Conrad, DVM, PhD, who is recognized for her research and contributions to the veterinary profession, taking a One Health approach that address the interconnectedness of humans, animals and the environment. An expert



Patricia Conrad

on how disease-causing single-celled parasites are transmitted, Conrad is known worldwide for her new insights on babesiosis, a tick-transmitted parasitic disease that afflicts humans, domestic animals and wildlife. VMD and VMD/PhD students will present talks and posters on their research projects carried out in Penn Vet laboratories as well as laboratories across campus. Register here: <http://surveyvet.upenn.edu/index.php?sid=69374&lang=en>

**PENN VET RESEARCH CLUB**

**PennVet Research Club** is a new student organization that launched during the fall semester of 2017. The mission of the club is to provide an opportunity for veterinary students to discuss current research, meet new faculty mentors, and immerse themselves in exciting research projects across Penn’s campus. Thanks to the hard work of the club’s inaugural board (president **Sabina Hlavaty**, vice president **Philip Hicks**, secretary **Ariel Shepley-McTaggart**, treasurer **Dani Mitchell**, seminar coordinator **Sara Jastrebski**, and club coordinator **Greta Niedermeyer**) and its two faculty advisors (**Drs. Jennifer Punt and Christopher Lengner**) the group succeeded in organizing an elective journal club seminar course where students present and discuss an article of their choice. The course met every two weeks during the fall of 2017 and is slated to follow a similar schedule in the spring. Though registration to receive credit has closed, all interested students and faculty are invited to attend. The club is also hard at work planning student lunch talks that will be announced as their details are finalized. For further information contact Philip Hicks at [hicksph@vet.upenn.edu](mailto:hicksph@vet.upenn.edu)



**Charles W. Bradley**, VMD, of the School of Veterinary Medicine (Penn Vet), and **Elizabeth A. Grice**, PhD, of the Perelman School of Medicine (Penn Medicine), were named the 2017 recipients of **Penn’s One Health Award**, recognizing their exemplary interdisciplinary collaboration in improving health care for the benefit of humans, animals, and the environment. Research conducted by Bradley and Grice has uncovered important insights about the skin microbiome of atopic dermatitis (AD) in dogs compared to humans. Canine AD shares important features with the human disorder, making dogs an excellent clinical model.



Charles Bradley, Elizabeth Grice and Dean Joan Hendricks

The **Penn Vet Research Newsletter** is distributed quarterly. Suggestions, comments, requests and story ideas may be directed to: [resnews@vet.upenn.edu](mailto:resnews@vet.upenn.edu)

**Phillip Scott, PhD**  
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