Can mosquitoes teach us how to stop disease transmission?

Michael Povelones is an assistant professor of Parasitology (tenure-track) in the Department of Pathobiology. Dr. Povelones received a B.A. in Chemistry from Columbia University in 1995. As an undergraduate and after a two-year period as a research assistant at the Columbia University Medical Center, Dr. Povelones studied nerve injury signals in the marine mollusk, *Aplysia californica*. Dr. Povelones received a Ph.D. in Developmental Biology from Stanford University in 2005 where he studied Wnt signaling in *Drosophila*. He was a postdoctoral fellow at Imperial College London before joining Penn Vet’s Department of Pathobiology in 2014. Continued on page 5
The Center for Host-Microbial Interactions announces the 2nd Annual Microbiome Symposium—2015

Wednesday, October 28, 2015, 6pm-7pm. A public lecture at Penn Vet will be given by Dr. Jo Handelsman, associate director for science at the White House Office of Science and Technology Policy, appointed by President Barack Obama. The talk will be given in the Marookian Auditorium, 130 Hill Pavilion, School of Veterinary Medicine. The organizers are: Drs. Gary Wu (Perelman School of Medicine) and Daniel Beiting (School of Veterinary Medicine)  On Thursday, October 29—The Keynote address and symposium begins at 8am to 7pm in the BRB II/III Auditorium, Perelman School of Medicine. The keynote address will be given by David A. Relman, MD, Stanford University, Chief of Infectious Diseases at the Veterans Affairs Health Care System in Palo Alto, California. For more information contact: April Weakley (aweakley@mail.med.upenn.edu) and register at: https://somapps.med.upenn.edu/apps/form/molecular/view.php?id=4998
Students to watch—they are on the move—veterinary students, medical students, undergraduates, high school students inspired to choose a career in research—basic, clinical or translational medicine

Matt Boyle, Peddie High School student worked with Dr. Nicola Mason on immunotherapy as a cancer treatment for canine osteosarcoma and hopes to do further research on an equine vaccine for lymphoma.

Martina Jackson V’18, Merial Scholar, worked in Narayan Avadhani’s laboratory on mitochondrial retrograde signaling-induced transcription reprograming in canine osteosarcoma.

Shreya Nahata, Indian Institute of Technology Roorkee and visiting Khorana Scholar in Dr. Avadhani’s laboratory working on the role of mitochondrial DNA reduction in the induction of cancer stem-like cells in esophageal squamous cell carcinoma.

Ishan Datt, student at Syosset High School, worked with Dr. Dan Beiting on “Blooming in the gut”—how intestinal inflammation is linked to microbiome diversity and composition.

Amber Shi, Peddie High School student assisted in a study in Dr. Carolina Lopez’ laboratory on the characterization of SeV defective viral genomes.

Jonathan Ferrari V’17 a Merial Scholar, worked with Dr. Nicola Mason on generation of an anti-canine PD-1 (cPD-1) monoclonal antibody for checkpoint blockage in immune therapy.

Brandi Steady, an undergraduate at the University of Delaware worked in the Scott laboratory on testing for mediators of vascular endothelial growth factor during a Leishmania major infection.
Emma LeBlanc, V’18, a Merial Scholar carried out her project in Dr. Narayan Avadhani’s laboratory—investigating whether mitochondrial stress plays a role in the mechanism by which a ‘smoke’ carcinogen induces macrophages to form osteoclasts.

Lauren Johnson, a Wellesley College undergrad worked with Dr. Hannah Gallantino-Homer’s group studying equine foot morphometry and laminitis pathology.

Leonardo Maronne, medical student from Brazil (Fed. University of Mato Grosso) worked in Dr. Phil Scott’s laboratory on determining how IL-1 affects CD8+ T cell response.

Kristin Derfus V’19, carried out her project in the laboratory of Dr. Michael Povelones investigating the genetics of susceptibility of Aedes aegypti mosquitoes to infection by canine heart worm (Dirofilaria immitis).

Jenny Kwok V’17, Merial Scholar worked in Dr. Michael Povelones’ lab investigating how activation of the mosquito’s immune signaling affects infection by canine heart worm (Dirofilaria immitis).

William Chung V’18, Merial Scholar worked in the laboratory of Dr. Jeremy Wang on the topic of protein interactions in meiotic recombination.

Talia Wong V’18, a Merial Scholar worked in the laboratories of Drs. Michael May and Chris Hunter on a project defining the role of NF-κB in the endothelium during an acute Toxoplasma gondii infection.

Megan Clark, V’18, a Merial Scholar studied the role of metabolism on CD8+ T cell function in the laboratory of Dr. Phil Scott.

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Can mosquitoes teach us how to stop disease transmission?

Mosquitoes transmit diseases that threaten over half the world's population and are responsible for approximately one million deaths annually (1). There are no licensed vaccines for many of the diseases mosquitoes transmit. In addition, mosquito insecticide resistance and, in the case of malaria, parasite drug resistance threaten our current control measures. Disease transmission requires that mosquitoes must first become infected themselves. However, mosquitoes have powerful defenses protecting them from infection and work in the Povelones lab focuses on understanding and manipulating these natural defense reactions to provide novel avenues to control disease transmission. Dr. Povelones is addressing fundamental questions concerning innate recognition and neutralization of pathogens. The ultimate goal is to transform one of mankind’s deadliest enemies into an ally in combating the spread of mosquito borne illness.

**PennVet Insectary**

Dr. Povelones has established a mosquito insectary in the Old Vet building. The facility currently houses 4 mosquito colonies: two strains of the arboviral and heartworm model vector, *Aedes aegypti* (Fig. 1) as well as the African and Asian malaria vectors, *Anopheles gambiae* and *An. stephensi*, respectively. Approximately 10,000 mosquitoes are produced per week. A separate containment suite within the facility is used when infecting mosquitoes with human pathogens, such as malaria parasites, *Plasmodium falciparum* and dengue virus.

**Mosquito complement pathway**

Malaria is caused by *Plasmodium* parasites that enter female anopheline mosquitoes during blood feeding (Fig. 2).

Ingested parasites traverse gut epithelial cells. Upon entering the body cavity (hemocoel), ookinetes become exposed to the mosquito blood (hemolymph) and are rapidly attacked by the immune system. Although the majority of parasites are eliminated, surviving ookinetes transform into oocysts, each producing thousands of sporozoites capable of reinfecting humans. The transition from ookinete to oocyst in the hemocoel is one of the major bottlenecks parasites face in their lifecycle (2). Using the recently established *An. gambiae* as a valuable model for studying innate immunity, Dr. Povelones has contributed to work that identifies mosquito complement as the most potent immune mechanism contributing to this bottleneck (3, 4). Dr. Povelones is particularly interested in fundamental questions concerning how (i) parasites are recognized by complement (ii) how recognition is coupled to killing (iii) how the response is regulated and (iv) how some parasites evade the mosquito immune system.

Characterization of the LRIM family: a novel family of putative innate receptors

Insects lack an adaptive immune response and therefore must rely on innate pathogen recognition proteins for immune protection.
Little is known about how *An. gambiae* recognizes and targets *Plasmodium* parasites and other pathogens for elimination. Dr. Povelones identified a family of 24 putative innate receptors named Leucine-rich repeat Immune Proteins (LRIMs) in *An. gambiae* that may help solve this conundrum (5-7). Two members of LRIM family are required for activation of the mosquito complement pathway but the function of the other family members is not known. Dr. Povelones is currently testing the hypothesis that LRIMs are specialized to recognize the different pathogens mosquitoes encounter.

**Heartworm transmission**

Using methods developed to study malaria, Dr. Povelones has begun to examine in more detail mosquito transmission of canine heartworm. Heartworm is transmitted via the bite of an infected mosquito (Fig. 3). It is present in all 50 states and roughly one million dogs in the U.S. have heartworm disease (8). This disease poses a constant threat to dogs and cats and requires regular monthly treatment with protective drugs. Worryingly, there is emerging evidence of drug resistance in heartworm populations.

Despite being in contact with the parasites, not all mosquitoes are capable of heartworm transmission (9). Dr. Povelones is making use of two strains of *Ae. aegypti*, one susceptible to infection by heartworm, and one that is resistant (Fig. 4) to study the differences between these mosquitoes. By comparing genetic and cell biological experiments with state-of-the-art sequencing, imaging and other technologies available at Penn Vet, Dr. Povelones will compare these mosquitoes to address key questions in the disease transmission cycle, such as: How are the worms recognized by the mosquito immune system? What molecules mediate worm killing? How do some worms survive this attack?

The goal of this work is to provide a better understanding of heartworm transmission by mosquitoes. This knowledge could ultimately translate into novel strategies for preventing heartworm transmission at a time when new approaches are urgently needed. From a OneHealth perspective, what we learn about heartworm may aid in our understanding of mosquito transmission of parasitic nematodes infecting humans.

**Figure 2.** Mosquito midgut invasion is a bottleneck in the *Plasmodium* lifecycle.

**Figure 3.** Photomicrograph of two heartworm larvae developing in a susceptible mosquito host.
Dr. Povelones’ laboratory is located in Rosenthal 304. The insectary is Old Vet Quad, suite 246.

References:


Surface Oncology has been named as one of Fierce Biotech’s “Fierce 15”, designating it as one of the most promising private biotechnology companies in the industry. What sets the company apart is their brain trust that includes Penn Vet’s Christopher Hunter, chair, in the Department of Pathobiology.

Search for more articles by Penn Vet Faculty at http://www.library.upenn.edu/vet/ at the Penn Vet Library Page
Dr. Rumela Chakrabarti is joining the faculty of the Department of Biomedical Sciences as an assistant professor. She received her MS from Pune University, India and a PhD from Kent State University, Ohio. Dr. Chakrabarti carried out her postdoctoral research in the Department of Biochemistry, State University of New York, Buffalo (2007-10) and the Department of Molecular Biology at Princeton (2010-15). Stem cells represent an exciting area of research and medicine because it offers great prospects for therapeutic applications. Research in Dr. Chakrabarti’s laboratory will aim to understand how cell intrinsic and cell extrinsic factors control the fate of normal mammary stem cells and cancer stem cells during breast cancer initiation and progression. Her office and laboratory are located on the 4th floor of Hill Pavilion.

Meet Rumela Chakrabarti, MS, PhD

Dr. Rumela Chakrabarti is joining the faculty of the Department of Biomedical Sciences as an assistant professor. She received her MS from Pune University, India and a PhD from Kent State University, Ohio. Dr. Chakrabarti carried out her postdoctoral research in the Department of Biochemistry, State University of New York, Buffalo (2007-10) and the Department of Molecular Biology at Princeton (2010-15). Stem cells represent an exciting area of research and medicine because it offers great prospects for therapeutic applications. Research in Dr. Chakrabarti’s laboratory will aim to understand how cell intrinsic and cell extrinsic factors control the fate of normal mammary stem cells and cancer stem cells during breast cancer initiation and progression. Her office and laboratory are located on the 4th floor of Hill Pavilion.

Awards (direct costs)

**Deborah Silverstein**
Frankie’s Friends
Comparison of Two Methods of Blood Sampling and Two Anesthetics on Extended Database Values
$5,000  8/1/15-7/31/17

**Charles Vite**
ARA Parsegian Medical Research Foundation
Postsymptomatic cyclodextrin therapy in the NPC1 cat
$100,000  7/1/15-6/30/17

**Charles Vite**
Biomarin: Intrathecal recombinant GALC administration to treat canine Krabbe disease
$791,300  7/30/15-7/30/20

**Charles Vite**
Biomarin: Twenty-Six Week or Longer Intracerebroventricular (ICV) Infusion Study of BMN 250 Administered Biweekly in a Canine Model of Mucopolysaccharidosis type IIIB (MPS IIIB).
$38,013  8/25/15-8/24/16

**Michael May,**
NIH/NHLBI Targeting NF-kB in Atherosclerosis (R56)
$269,501  9/15/15 – 8/31/16

**Tracy L. Bale**
NIH/NIMH Paternal Stress epigenetic programming of offspring neuro-development (R01)
$1,731,398  8/1/15 – 5/31/20

**Christopher Lengner**
Mari Lowe Pilot award Identifying markers for the prospective
$30,000  7/1/15-5/31/16

**Dan Beiting**
Margaret Q. Landenberger Research Foundation
The role of the microbiome in treatment and remission of inflammatory bowel disease
$200,000  7/1/15-6/30/17

**Chris Hunter**
NIH/NIAID Immunopathogenesis of Toxoplasmonic encephalitis (R01)
$1,125,000  9/2/15-2/29/17

**David Holt**
Mari Lowe Pilot Award —Near-Infrared Imaging of Spontaneous Canine Tumors Accurately Delineates Tumor Margins and Detects Lymph Node Metastases
$30,000  7/1/15—5/31/16

**Zhengxia Dou**
University Research Foundation
Household food waste composition and recovery assessment
$44,930  8/1/2015-7/31/2016

**Gary Althouse**
Merck Animal Health
ReproPig Continuing Education Course
$10,253  10/12/2015-10/11/2016

**Reg Turner/Victor Absalon-Medina**
Irvine Scientific—Evaluation & Optimization of Media for In Vitro Maturatiion (IVM) of Mammalian Oocytes and Culture Media for Embryos. $84,000  7/24/2015-7/23/2016

**Karina Guziewicz**
Foundation for Fighting Blindness
Leading the collaboration as PD/PI AAV-mediated therapy for Best Vitelliform Macular Dystrophy
$959,074  9/30/15-9/29/17

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