

MAJOR PENN VET RESEARCH SYMPOSIA

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DEAN JOAN HENDRICKS' PORTRAIT UNVEILED

PAGE 8



JAMES (SPARKY) LOK HONORED BY THE AMERICAN SOCIETY OF PARASITOLOGISTS PAGE 5



STUDENT RESEARCH DAY SEE PAGE 4

NEWSLETTER



Cancer and Autoimmune Disease

Oliver A. Garden, BVetMed, PhD, joined Penn Vet in 2016 as chair of the Department of Clinical Studies and Advanced Medicine. He was named as the Corinne R. and Henry Bower Professor of Medicine. Garden graduated from the Royal Veterinary College (1993) after earning his Bachelor of Science degree from King's College London (1990). Following a rotating internship in small animal medicine and surgery, he completed a Wellcome Trust Clinical PhD program in small animal gastroenterology and immunology at the Royal Veterinary College

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(1998), followed by a Wellcome Trust Research training fellowship at the School of Medicine at the University of South Carolina. He held a residency in small animal internal medicine at Cornell University.

Current research in the Garden laboratory focuses on the role of regulatory cells of lymphoid and myeloid origin in the pathogenesis of cancer and autoimmune disease. While early studies were carried out in murine models, more recent studies embrace the over-arching ethos of [One Health, One Medicine](#) at Penn Vet and focus on natural canine diseases. Importantly, these canine diseases can provide critical insight for a plethora of human diseases—and studying canine disease clearly benefits both canine and human patients.

Immunosuppression by regulatory T cells—the key to reducing some autoimmune diseases—Regulatory T cells

(Tregs) play a critical role in immunosuppression and therefore have the potential to reduce or prevent harmful autoimmune and inflammatory immune responses. Using Tregs from mice, humans and, most recently dogs, the Garden laboratory has identified the critical role of several signaling cascades, including phosphoinositide 3-kinase $\text{p110}\delta$, cytokines utilizing the common gamma chain, and microRNA-155 -15b/16 in the induction, function, and development of Tregs. The Garden laboratory was also the first to document a key defect in the ability of conventional (non-regulatory) T cells to be regulated by Tregs in a murine model of systemic lupus erythematosus (SLE)¹, a pathomechanism subsequently demonstrated in other murine models and T cells from human patients. Moreover, they showed that reduced T cell receptor α chain diversity of Tregs in NOD mice, a murine model of type 1 diabetes mellitus, compromised peripheral tolerance and enhanced disease. By discovering these mechanisms, their work has highlighted pathways that may underlie defects of Treg function in disease, potentially identifying novel targets by which these cells may be manipulated for therapeutic gain.

Suppressive immune cells promote “tolerance” of cancer in dogs—Dr. Garden’s laboratory is also interested in the role that Tregs

and myeloid-derived suppressor cells (MDSCs) play in the development and progression of cancer in dogs. Dogs make excellent large animal models of various human cancers, recapitulating the human disease in a spontaneous manner that cannot be captured in genetically modified murine models. The Garden laboratory is first focusing on the role of Tregs and MDSCs in dogs with multicentric B cell lymphoma, a model of human non-Hodgkin lymphoma. They found that the frequency of Tregs in the affected lymph nodes of dogs with multicentric B cell lymphoma predicts survival in dogs undergoing chemotherapy² and that

THREE *in a* ROW

Howard Hughes Medical Institute- Burroughs Wellcome Fund Medical Research Fellows



Megan Clark



Anna Martin



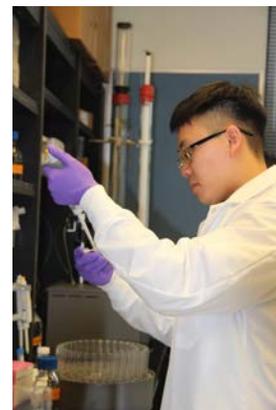
Sabina Hlavaty

From 2016 through 2018 three Penn Vet Students have been awarded Howard Hughes Medical Institute- Burroughs Wellcome Fund Medical Research Fellowships. More information about these students may be found on page 7.

hypoxic changes in tumors appears to promote infiltration by FoxP3⁺ Tregs. In studies carried out by former post-doc Dr. Michelle Goulart, and currently carried out by Sabina Hlavaty, the Garden laboratory is phenotypically and functionally defining canine monocytic (M) and polymorphonuclear (PMN) MDSCs, and determining how the increased frequency of PMN-MDSCs in the peripheral blood of dogs with larger tumor burdens contributes to disease progression. Notably, their studies to date also demonstrate that the phenotypic and functional properties of both canine Tregs and MDSCs closely resemble their human counterparts, further demonstrating that natural canine models will be invaluable for determining if immunotherapies targeting these cells can revolutionize cancer treatment.

Studying immune-mediated disease in dogs may permit refinement of therapeutic treatments

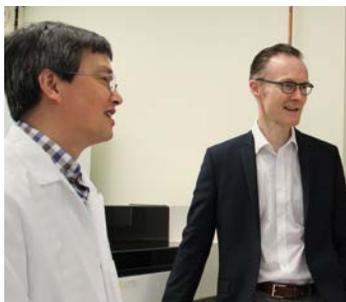
—Current therapies for autoimmune and other immune-mediated diseases often rely on inelegant blanket immunosuppressive treatments that can elicit a number of intolerable side effects in treated patients. To identify means to avoid the use of immunosuppressive “sledgehammers”, the Garden laboratory is currently elucidating the pathogenic mechanisms that drive the onset and progression of immune-mediated hemolytic anemia (IMHA), the most common autoimmune disease in dogs. Interestingly, while dogs with IMHA have increased serum concentrations of pro-inflammatory cytokines, their frequency of Tregs did not differ from healthy dogs, suggesting that a deficiency of Tregs is not responsible for development of disease³. Further expansion of studies such as these that incorporate detailed phenotypic and functional data will allow for development of novel approaches that permit earlier diagnosis and more effective, targeted treatment for IMHA, and presumably other autoimmune and immune-mediated diseases.



Andrew Phan

Attacking Myasthenia Gravis from the Inside Out

—The Garden laboratory is also focused on understanding pathological mechanism driving myasthenia gravis (MG), an autoimmune disease in which the acetylcholine receptor (AChR) is targeted, disrupting neuromuscular transmission and causing characteristic weakness and fatigue. Previous studies in experimental autoimmune myasthenia gravis (EAMG) models utilized disease-inducing epitopes derived from the extracellular portion of the AChR in an attempt to induce antigen-specific immunosuppression. However, the use of such therapeutic antigens proved to be tricky and dangerous. Notably, autoantibodies generated during EAMG induce complement-dependent focal lysis and the subsequent shedding of AChR-rich fragments of the postsynaptic membrane stimulates an antibody response to the normally concealed cytoplasmic domain of the AChR. Dr. Jie Luo, a Senior Research Investigator in the Garden laboratory, exploited this finding and has successfully tested a novel vaccine consisting of the cytoplasmic domains of human muscle AChR subunits in rats⁴. This approach provided safe and effective immunosuppression, highlighting a new path towards antigen-specific immunotherapies for autoimmune diseases targeting transmembrane proteins. Ongoing work



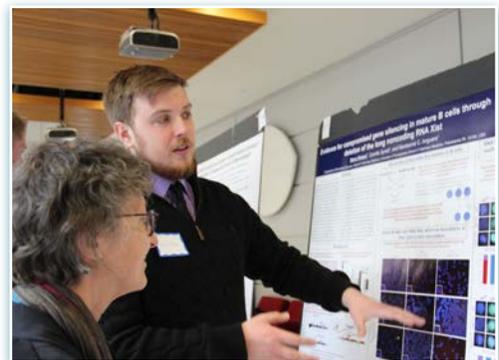
Jie Luo and Oliver Garden

addresses the mechanistic basis for this therapy. Moreover, translating these rodent studies into a spontaneous large animal model that recapitulates the human disease will provide proof-of-principle studies that will inform and accelerate human clinical trials.

2018 STUDENT RESEARCH DAY

Penn Vet’s annual **Student Research Day** was held on Tuesday, March 20, 2018 in the Hill Pavilion. VMD and VMD/PhD students gave research talks and 39 research posters were presented. Faculty judges for the presentations and posters included Drs. Narayan Avadhani, Charles Bradley, Igor Brodsky, Amy Durham, William Feeney (GlaxoSmithKline), Olena Jacenko, Carolina Lopez, Elizabeth Mauldin, Kathryn Michel, Kyla Ortved, Nathaneal Oster (Merial/Boehringer Ingelheim), Jennifer Punt, Pascale Salah, and Andrew Vaughan. **Patricia Conrad, DVM, PhD**, from the University of California Davis delivered an inspiring keynote address entitled “Challenge the Dogma and be Amazed by Your Discoveries”.

Academic prizes were awarded to **Bailey Baumann** (1st place dual degree) and **Anna Martin** (1st place VMD); **Greg Sousa** (2nd place dual degree), **Megan McGeehan** (2nd place VMD), **Amanda Samuels** (3rd place dual degree) and **Alexandra Sanz** (3rd place VMD). Best Poster prizes were awarded to **Sabina Hlavaty** (1st place), **Mary Jane Drake** (2nd place) and **Alycia Frampton** (3rd place).



Recent *Awards* (direct costs)

Amy Durham
National Center for Advancing Translational Sciences/NIH
Institutional Clinical and Translational Science Award
2/1/18-1/31/19 \$45,000

De'Broski Herbert
Burroughs Wellcome Fund
22nd Annual Woods Hole Immunoparasitology (WHIP)
Meeting 3/1/18-8/31/18 \$6,000

Boris Striepen
Bill and Melinda Gates Foundation
Forward Genetic Technology for Cryptosporidium
6/1/17-5/31/18 \$200,535

Meghan Wynosky-Dolfi
National Center for Advancing Translational Sciences/NIH
Institutional Clinical and Translational Science Award
2/1/18-1/31/19 \$25,000

Tom Schaer
NIH ROI (with Thomas Jefferson University)
Synovial Fluid and Joint Sepsis
08/01/17 - 05/31/18 \$144,940

Oliver Garden/Ciera Barr
AKC-CHF
The impact of intravenous anesthetic agents on canine natural
killer cell cytotoxic function: the Achilles heel in cancer
diagnosis and surgery?
1/1/18-12/31/18 \$14,945

Nicola Mason
Petco Foundation Pet Cancer Support
**Clinical Advancement of CAR T cell therapy for dogs with
B cell malignancies**
4/1/18-3/31/20 \$300,000

Keiko Miyadera
UNC Chapel Hill/Tamid Biomed Inc.
AAV Gene Therapy for Muscular and Ocular Diseases
1/1/18-11/30/18 \$60,775

Keiko Miyadera
UNC Chapel Hill/MPS Society
Safe and Effective Therapy for Vision Loss in MPS1 Patients
7/1/17-6/30/18 \$48,687

Sabina Hlavaty (Oliver Garden's Laboratory)
Howard Hughes Medical Institute —Research Fellowship
Award 8/1/18-7/31/19 \$43,000

Olivia Nathanson/Dana Clarke
Nestle Purina—Evaluation of procedural & maintenance data
when esophagostomy tubes are used for nutritional support
during acute and chronic illness and identify risk factors
for short and long term complications
4/1/18-3/31/19 \$13,978

Serge Fuchs
NIH R01/Wistar
Negative regulation of myeloid-derived suppressive cells in cancer
12/18/17-11/30/18 \$193,764

Christopher Lengner
Institutional Clinical and Translational Science Award (ITMAT)
Developing novel immunotherapy for metastatic colorectal cancer
2/1/18-1/31/19 \$21,955



Mariel Covo, Class of 2020 has won the 2018 **Parasitology Award**—The Schad Prize in Parasitology is named in honor of our late Penn colleague, the eminent parasitologist Gerhard Schad. The Schad Prize goes each year to the student achieving the highest academic standing in the core Veterinary Parasitology course.

Dr. James (Sparky) Lok, shown in the photograph with Mariel Covo, has been named by the **American Society of Parasitologists as the Bueding and von Brand Lecturer for 2018**. He will receive his award and deliver the lecture at the June society meeting. The **Bueding and von Brand Lectureship** honors someone who has made major research contributions to the field of biochemistry, molecular biology, and/or pharmacology of parasitic helminths.



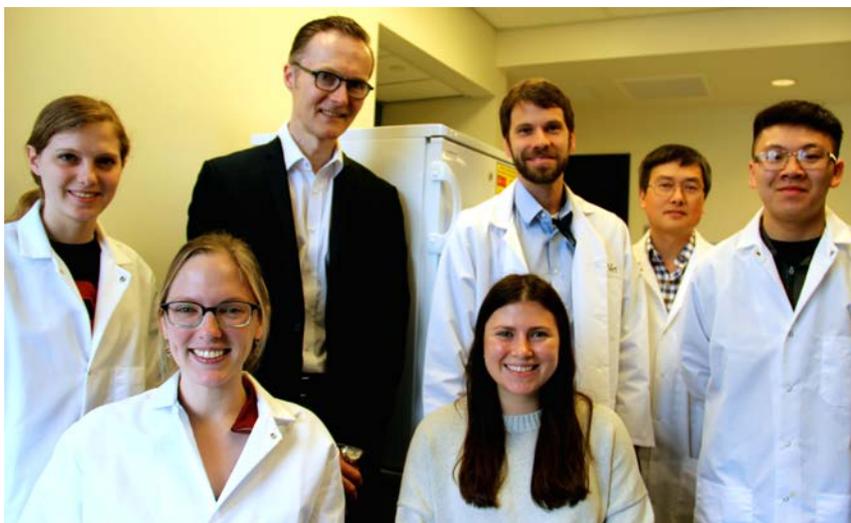
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What is bugging the immune system?—There is increasing recognition that the “exposome”, environmental factors that include the patient’s mucosal microbiome, impacts the manifestation of autoimmune disease in human patients. The Garden laboratory is currently testing the hypothesis that alterations in intestinal microbiome are an etiological factor for IMHA and that idiopathic IMHA patients showing a poor response to immunosuppressive therapy will exhibit persistent disease-associated changes in their microbiome. Positive results would imply that strategies to address proximal pathological changes in microbiota, including prebiotics, probiotics, or focused antimicrobial agents, could complement immunosuppressive therapeutic regimens in non-responsive or relapsing patients to improve outcome. Moreover, signatures of microbiota associated with refractory disease may also be used in a predictive manner to stratify patients to particular treatment regimens and to provide important prognostic information.

Dr. Garden’s laboratory is located in 201E OVQ Building and his office is at 2011 Ryan.

Selected References

1. Monk, C, Spachidou, M, Rovis, F, Botto, M, Lechler, RI and **Garden, OA** (2005) MRL/Mp CD4⁺CD25⁻ T cells resist suppression by CD4⁺CD25⁺ Tregs *in vitro*: a novel defect of T cell regulation in systemic lupus erythematosus. *Arthritis and Rheumatism* 52(4): 1180-1184
2. Pinheiro, D, Chang, YM, Bryant, H, Szladovits, B, Dalessandri, T, Davison, LJ, Yallop, E, Mills, E, Leo, C, Lara, A, Stell, A, Polton, G and **Garden, OA** (2014) Dissecting the regulatory microenvironment of a large animal model of non-Hodgkin lymphoma: evidence of a negative prognostic impact of FOXP3⁺ T cells in canine B cell lymphoma. *PLOS ONE* 9(8): e105027
3. Swann, JW, Woods, K, Wu, Y, Glanemann, B and **Garden, OA** (2016) Characterisation of the immunophenotype of dogs with primary immune-mediated haemolytic anaemia, *PLOS ONE* 11(12): e0168296
4. Luo, J and Lindstrom J (2015) AChR-specific immunosuppressive therapy of myasthenia gravis. *Biochem Pharmacol.* 97(4):609-619



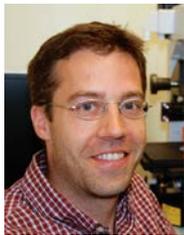
Top left to right: Lauren Olenick, Oliver Garden Jim Perry, Jie Luo, Andrew Phan; seated left to right: Sabina Hlavaty and Julia Barnard

Selected Publications



Guan F and Robinson MA. (2017) Comprehensive solid-phase extraction of multitudinous exogenous peptides from equine plasma and urine for doping detection. *Anal Chim Acta* 985:79-90

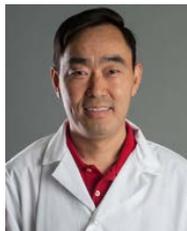
Guan F, You Y, Li X, and Robinson MA (2018) Detection and confirmation of α -cobra-toxin in equine plasma by solid-phase extraction and liquid chromatography coupled to mass spectrometry. *J Chromatogr A*: 1533: 38-48.



Yousefi M, Nakauka-Ddamba A, Berry CT, Li N, Schoenberger J, Simeonov KP, Cedeno RJ, Yu Z, Lengner CJ. (2018) Calorie Restriction Governs Intestinal Epithelial Regener-

ation through Cell-Autonomous Regulation of mTORC1 in Reserve Stem Cells. *Stem Cell Reports* 10(3):703-711.

Shi B, Xue J, Zhou J, Kasowitz SD, Zhang Y, Liang G, Guan Y, Shi Q, Liu M, Sha J, Huang X, Wang PJ. (2018) MORC2B is essential for meiotic progression and fertility. *PLoS Genet*. 14(1):e1007175.



Guziewicz KE, Cideciyan AV, Beltran WA, Komáromy AM, Dufour VL, Swider M, Iwabe S, Sumaroka A, Kendrick BT, Ruthel G, Chiodo VA, Héon E, Hauswirth WW, Jacobson SG, Aguirre GD (2018) Best1 gene therapy corrects a diffuse retina-wide microdetachment modulated by light exposure. *Proc Natl Acad Sci U S A*. 115(12): E2839-E2848.



Honors

John Cain, V'20 is the 2018 recipient of a Morris Animal Foundation (MAF) Veterinary Student Scholar award for his summer research project entitled: Molecular Dissection of Mosquito Resistance to Heartworm Infection. John will carry out his project in the laboratory of Dr. Michael Povelones, Department of Pathobiology. This competitive program, open to veterinary students enrolled in an AVMA accredited school, provides the opportunity to become involved in mentored research.



Dr. Urs Giger, Department of Clinical Sciences & Advanced Medicine is the 2018 recipient of the Distinguished Lecture Ramsey Award from Iowa State University (ISU) for his outstanding research contributions in veterinary medicine. He is pictured aside the Good Doctor statue at ISU's College of Veterinary Medicine.

Continued from page 2—**Three HHMI-BWF awards in a row at Penn Vet.....**In 2016 **Megan Clark**, V'18, was named a medical research fellow by the Howard Hughes Medical Institute—Burroughs Wellcome Fund (HHMI-BWF). Megan's research project involved examining the role of skin-resident memory T cells and their migration into non-inflamed skin sites during infection with the skin disease in the tropics called Leishmaniasis (mentor, Dr. Phil Scott). Then an award in 2017 was given to **Anna Martin**, V'19 for her project: partial X chromosome inactivation of B cells: mechanisms contributing to the development and severity of systemic Lupus Erythematosus (mentors—Drs Michael Atchison and Montserrat Anguera). **Sabina Hlavaty**, in the laboratory of Dr. Oliver Garden, was named an HHMI-BWF fellow for the period of August 1, 2018 – July 31, 2019. Her project is on: “antimicrobial peptides as myeloid-derived suppressor cell effector molecules in cancer: harnessing the power of evolution to shift innate immune paradigms”. HHMI-BWF funding enables a student to spend a year in a laboratory with a mentor on a project proposed by the student.

Research Symposia

On **March 5, 2018** Penn Vet faculty, Drs. De’Broski Herbert, Igor Brodsky, Montserrat Anguera, and Carolina López, were speakers at a meeting called “**From Bench to Bedside at the Mucosal Interface**”. The Institute for Immunology Symposium was held at the Smilow Center for Translational Research. The symposium was a joint effort between Penn Vet and Penn Perelman School of Medicine.

On **March 12, 2018**, a symposium on **Intestinal Infection and Immunity** was held at Penn Vet, organized by Dr. Boris Striepen with the Department of Pathobiology. Global advancements in science to tackle diarrheal disease in children were presented and discussed by researchers. Targeting emerging challenges, such as the protozoan parasite *Cryptosporidium*, was at the forefront of this meeting. Research presentations were given by Drs. Yasmine Belkaid, NIH; Carol Gilchrist, University of Virginia; Paul Offit, Childrens’ Hospital of Philadelphia, William Petri, University of Virginia; Eline Luning Prak, University of Pennsylvania; Boris Striepen, School of Veterinary Medicine, University of Pennsylvania; Christoph Thaiss and John Wherry, Perelman School of Medicine, University of Pennsylvania.



Drs. De’Broski Herbert, Igor Brodsky, Montserrat Anguera, Carolina López, and Boris Striepen



Joan C. Hendricks, VMD, PhD, Gilbert S. Kahn Dean of the School of Veterinary Medicine (Penn Vet), was honored at her portrait unveiling on April 11, 2018. The portrait was painted by artist Peter Schaumann. Dean Hendricks, a faculty member at Penn Vet for more than 30 years was the recipient of the Trustees’ Council of Penn Women (TCPW) Provost Award for exceptional contributions to the lives of women at the University of Pennsylvania and the wider academic community. on April 12th.

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

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