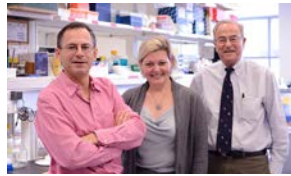
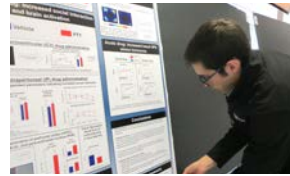


Mast Cells in Chronic Inflammatory Disease: More than just Histamine and IgE—

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PENN CENTER FOR INNOVATION AWARDS
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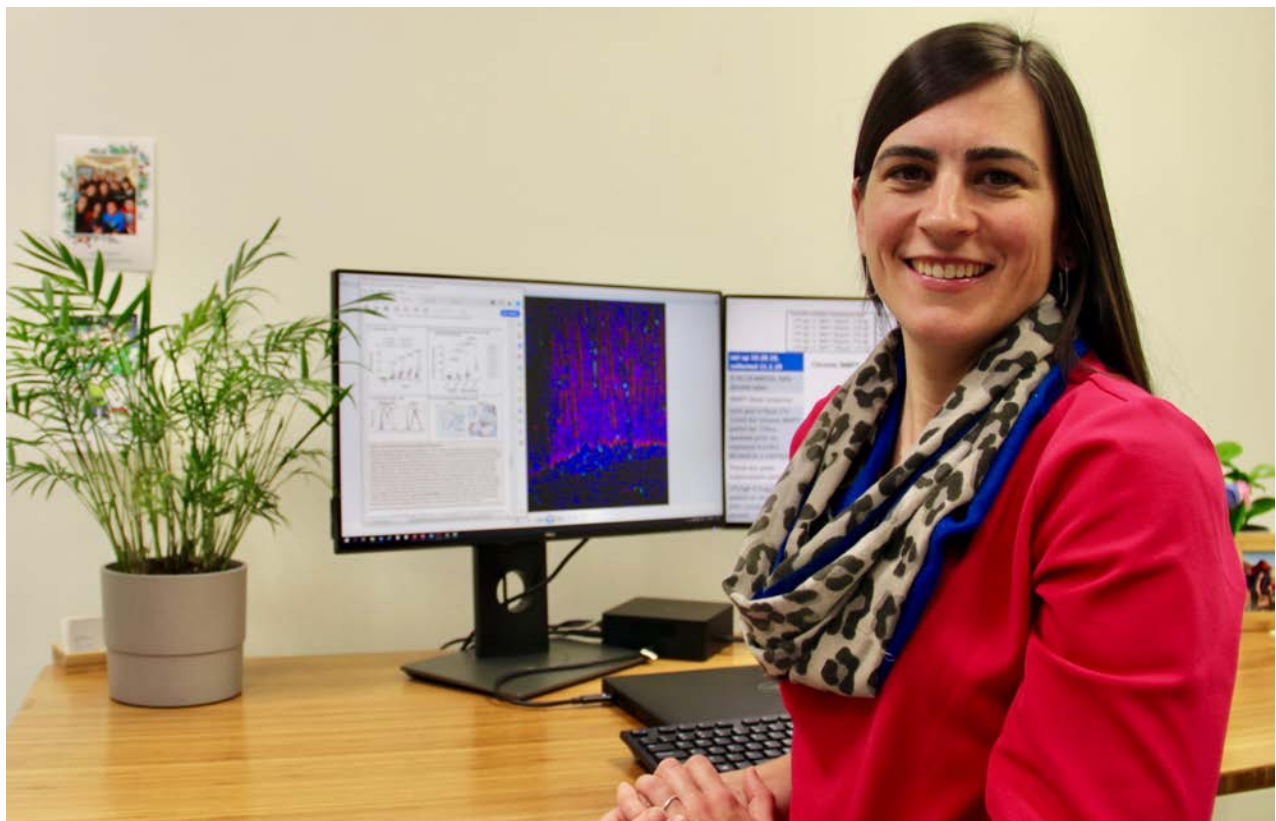


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NEWSLETTER



Chronic Inflammatory Disease

Dr. Elizabeth Lennon is the Pamela Cole assistant professor of Internal Medicine (tenure-track) in the Department of Clinical Sciences and Advanced Medicine. Dr. Lennon is a veterinary internal medicine specialist and her research focuses on immunoregulatory roles of mast cells in inflammatory diseases, particularly in inflammatory bowel disease (IBD). Dr. Lennon received her veterinary degree from North Carolina State University, and pursued a rotating internship in small animal medicine and surgery at the University of Pennsylvania from 2007-2008. She then was recruited by North Carolina State University to train in their Clinician

Inflammatory Bowel Disease and Mast Cells

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Investigator program, which combines a small animal internal medicine residency with a PhD training program. During her residency, Dr. Lennon developed a clinical interest in IBD, and her passion for treating this condition led her to focus her research on the pathophysiology of IBD. Following the completion of her PhD, Dr. Lennon received a K award from the National Institutes of Health, and joined the faculty at North Carolina State University as a Research Assistant Professor. Dr. Lennon then moved to the University of Tennessee as an Assistant Professor in 2015, and finally joined the Department of Clinical Sciences and Advanced Medicine



at Penn in February 2019. Dr. Lennon’s research interests are in anti-inflammatory and tissue repair mechanisms of mast cells in chronic inflammatory diseases, especially IBD.

Inflammatory Bowel Disease and mast cells—

IBD has become increasingly common in the last 50 years and now affects more than 3 million people in the United States. IBD is a debilitating, incurable disease; patients are frequently hospitalized and require lifelong treatment with immunosuppressive medications. Despite medical therapy, affected individuals can also develop fibrosis, resulting in intestinal strictures that often require surgical treatment. IBD is thought to result from a complex interaction between genetic predisposition, environmental factors, an altered intestinal microbiome, and immune dysregulation. The importance of the innate immune system in the pathogenesis of IBD has become increasingly clear over the last 10 years.

Mast cells are innate immune cells that are involved in IBD. Most people associate mast cells with allergy, asthma, and anaphylaxis. Indeed, mast cells are powerful “first responder” cells that can initiate inflammatory responses and exacerbate acute inflammation. However, mast cells are highly influenced by their microenvironment and may have divergent functions in acute compared to chronic inflammation. Indeed, Dr. Lennon made a surprising discovery when she found that IBD-prone mice that are deficient in mast cells

Continued on page 3

Honors



Christopher A. Hunter, PhD, Mindy Halikman Heyer Distinguished Professor of Pathobiology at the School of Veterinary Medicine of the University of Pennsylvania (Penn Vet), has been elected President-elect of the International Cytokine and Interferon Society. Hunter began his term in November and will take office as President in October 2021.



Dr. Camille Syrett in Dr. Montserrat Anguera’s laboratory was a 2019 Penn Med’s Department of Genetics Tom Kadesch Prize recipient—for excellence in research and citizenship.

actually had worse disease, indicating an anti-inflammatory, protective function for mast cells. In support, reconstitution of mast cells in mast cell-deficient IBD-prone mice reduced inflammation.¹ This discovery was echoed by other studies in chronic asthma models, in which mast cells were found to play anti-inflammatory roles² and additional studies highlighting the integral roles of mast cells in initiating and driving tissue repair, limiting inflammation, and regulating intestinal barrier function.

While the anti-inflammatory effects of mast cells have been ascribed to their ability to recruit T-regulatory cells and synthesize anti-inflammatory prostaglandins and lipid mediators, Dr. Lennon's laboratory discovered that mast cells control the intestinal levels of bone morphogenetic proteins (BMPs), stabilizing their levels during tissue recovery and repair following cycles of inflammatory flares. BMPs are members of the transforming growth factor- β (TGF- β) cytokine superfamily, and have both anti-inflammatory and anti-fibrotic activities in the intestine. As intestinal fibrosis is a major complication of IBD, the dual anti-inflammatory and anti-fibrotic role of BMPs suggest that they play a particularly important role in the control of IBD. Unfortunately, BMPs cannot be administered directly to patients due to their expense and short half-life, so Dr. Lennon is currently studying the signaling mechanisms that control BMP concentrations in the intestine in hopes of therapeutically manipulating these pathways to increase BMP levels in IBD patients, thereby reducing pathology.

Effects of psychological stress on mast cells as a trigger for IBD flares—

Psychological stress can induce flares of IBD and, compared to the general population, IBD patients have a higher incidence of psychological disorders, including anxiety and depression, which often precede the IBD diagnosis.³ Furthermore, stressful life events are associated with IBD onset as well as disease flares. The “gut-brain axis” which is used to describe neural circuitry that facilitates bi-directional interactions between the central nervous system, the enteric nervous system, and the intestinal microbiota, has been implicated in the association between psychological disorders and IBD, but the exact mechanisms that contribute to increased disease risk are not understood. Mast cells are essential mediators of the crosstalk between the enteric nervous system and the immune system. Therefore, Dr. Lennon is currently investigating the mechanisms by which alterations in neuropeptide production by central and enteric neurons influence mast cell phenotype and function in her newly generated murine model that recapitulates increased susceptibility to IBD in response to psychological stress⁴.

IBD research and clinical gastroenterology—

Dr. Lennon is a part of the incredible team of small animal internal medicine veterinarians in the Ryan Hospital. Her clinical work combines her passion for helping veterinary patients and their humans with her desire to answer basic questions about disease mechanisms. Indeed, her clinical

Dr. Lennon continued from page 3

curiosity about her IBD patients drives her research questions, and vice versa. Dr. Lennon believes that by studying mechanisms of mast cells in clinical patients (both veterinary and human) she can better understand how these cells limit inflammation. Moreover, because mast cells behave differently in acute compared to chronic inflammation and are highly influenced by their microenvironment, her assessment of mast cell function in naturally occurring disease provides a more accurate real-life picture of their role in inflammatory diseases.

Dr. Lennon has ongoing clinical studies to investigate mast cell phenotypes in inflammatory diseases. Supported by a Morris Animal Foundation grant, she and her graduate student Jane Woodrow, who is a large animal internal medicine specialist, have recently described alterations in mast cell phenotypes and BMP expression in equine asthma. She also has documented alterations in fat-soluble vitamin concentrations in dogs and cats with IBD. With the resources of the high caseload of the Ryan Hospital, the support of research infrastructure to collaborate with the Gastroenterology Division at the Perelman School of Medicine, and the Veterinary Clinical Investigations Center, Dr. Lennon is excited to harness the translational potential of evaluating mast cell function in the immunoregulation of inflammatory disorders across species and across veterinary and human medicine.

Dr. Lennon’s laboratory is funded by the National Institutes of Health/Office of Research Infrastructure Programs (K01 OD019729 and R03 OD026599). Her laboratory is in the Old Vet Building, 204E and her office is located at 298E.

References

1. Lennon EM, Borst LB, Edwards LL, et al. Mast Cells Exert Anti-Inflammatory Effects in an IL10^{-/-} Model of Spontaneous Colitis. *Mediators Inflamm* 2018;2018:7817360 PMID: 29849494.
2. Morita H, Arae K, Unno H, et al. An Interleukin-33-Mast Cell-Interleukin-2 Axis Suppresses Papain-Induced Allergic Inflammation by Promoting Regulatory T Cell Numbers. *Immunity* 2015;43:175-86 PMID: 26200013.
3. Walker JR, Ediger JP, Graff LA, et al. The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *Am J Gastroenterol* 2008;103:1989-97 PMID: 18796096.
4. Lennon EM, Maharshak N, Elloumi H, et al. Early life stress triggers persistent colonic barrier dysfunction and exacerbates colitis in adult IL-10^{-/-} mice. *Inflamm Bowel Dis* 2013;19:712-9 PMID: 23446335.



PhD student Jane Woodrow, DVM, DACVIM, is a large animal internal medicine specialist

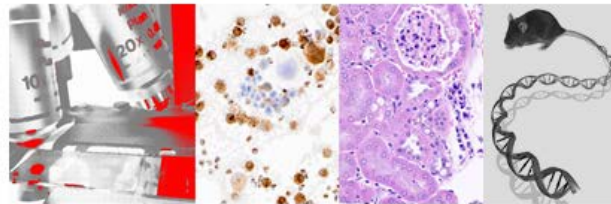
Awards and Honors



William Beltran, Melissa Kelly, Phil Scott, Susan Volk, Dean Andrew Hoffman, Gustavo Aguirre & Lydia Melnyk

Penn Vet faculty were recipients of the **Penn Center for Innovation’s Celebration of Innovation awards** in December. **Susan Volk**, Department of Clinical Sciences and Advanced Medicine (CSAM) was selected as Emerging Inventor of the Year for her novel method of suppressing breast cancer metastasis. As Inventors of the Year, **William Beltran and Gustavo Aguirre** (CSAM) were selected for their unparalleled approach to developing novel therapies for the treatment of inherited retinal disorders.

 PennVet
**Mouse
 Pathology
 Workshop**



The **Comparative Pathology Core** at the University of Pennsylvania School of Veterinary Medicine is hosting its first "Mouse Pathology Workshop" this year. The workshop is organized on four consecutive Fridays with interactive lectures in the morning and hands-on labs in the afternoon. It is primarily aimed at graduate students, post-doctoral fellows and laboratory technicians wanting to enhance their understanding of the mouse as a model of disease as well as improve their dissection and tissue handling skills. The lectures and labs are given by board-certified veterinary pathologists specialized in comparative pathology and more specifically in the use of mice in research. The first session of the workshop took place on Friday January 17th 2020.

Some recent awards (direct costs)

Chris Hunter/Boris Striepen

NIH R01 Immunity to Cryptosporidium
12/1/19—11/30/24 \$ 2,279,502

Nicola Mason

NIH U54 Engineering the next generation of T cells
9/25/19—8/31/24 \$ 595,950

Chris Lengner

Helmsley Charitable Trust through CHOP
A Crohn's Disease Epithelial Stem Cell Atlas: Pediatric to Adult Continuum
12/1/2019-11/30/2022 \$255,951

Chris Lengner/Andrew Vaughan

NIH R01 Identification and Preclinical Evaluation of Novel Therapeutic Approaches to Dyskeratosis Congenital. 7/1/2019-6/30/2023 \$853,675

Brittany W. Tisa

ASPCA Establishing a Penn Vet Collaboration for Studies in Accessible High Quality Clinical Medicine with a Research Project Examining Metronidazole Treatment in Dogs with Diarrhea 11/1/19-10/31/20 \$49,300

Gus Aguirre

NIH/NEI R01 Models for therapy of hereditary retinal degeneration
12/18/19—11/30/24 \$2,316,910

Wm Beltran

Iveric bio. Efficacy study with GMP grade AAV2/5-RHO820-shRNA820 prior to onset of retinal degeneration in mutant canines 12/5/19—12/31/20 \$ 516,281

Enrico Radaelli

DOD/Childrens Res Inst. Development of therapeutic strategies for NF1-associated optic pathway glioma 9/30/19—9/29/21 \$17,018

Enrico Radaelli

Univ Research FDN Dissecting the Role of Mitochondrial Dysfunction and Ferroptosis in the Pathogenesis of Impaired Spermatogenesis in Par-deficient Mice 3/1/20—2/28/21 \$30,917

Dan Beiting

ITMAT Pilot A High-throughput Screen to Identify Metabolic Modulators of Intestinal Innate Immune Signaling During Infection 2/1/20—1/31/21 \$30,000

Shelley Rankin

Univ Research FDN Community Population Prevalence of Carbapenem Resistant Enterobacteriaceae (CRE) in Dogs and Cats
3/1/20—2/18/21 \$49,558

Phil Scott

NIH R01 Host and Parasite Factors Promoting Disease and Treatment Failure in Leishmania braziliensis Patients
12/01/19-11/30/23 \$626,175

Publications



Effector-triggered immunity and pathogen sensing in metazoans (Review—2020) Lopes Fischer N, Naseer N, Shin S, and **Brodsky IE**. *Nat Microbiol.* 5(1):14-26.

JAK-ing into M1/M2 Polarization SteErs Salmonella-containing Macrophages Awar from Immune Attack to Promote Bacterial Persistence (2020) **Brodsky IE**. *Cell Host Microbe* 27(1) 3-5.



Near-infrared imaging and optical coherence tomography for intraoperative visualization of tumors (Review)(2020) **Holt, D**, Singhal S, and Selmic LE. *Vet Surg* 49: 1, Pages 33-43

Evaluation of Aminolevulinic Acid-Derived Tumor Fluorescence Yields Disparate Results in Murine and Spontaneous Large Animal Models of Lung Cancer (2019) Predina, JD, Runge JB, Newton A, **Mison M**, Xia L, Corbett C, Shin M, Sulyok L, **Durham A**, Nie S, Singhal S, and **Holt D**. *Sci. Rep.* 9(1): 7629

International Partners in Research—The Office of the Vice Provost for Research, in collaboration with Penn Global, has created a new website to help faculty navigate compliance



requirements and other issues related to international collaboration and global engagement activities in the current environment. The website can be found at: <https://research.upenn.edu/resources/international-partners/>. We

will be updating the site as new agency guidance is issued related to what must be reported in grant applications and progress reports regarding international appointments and activities.



Dr. Ellen Puré has been named a **Fellow of the American Association for the Advancement of Science (AAAS)** and will be honored at the 2020 AAAS Annual Meeting in Seattle on Feb. 15. She is the Grace Lambert Professor of Biomedical Science and chair of the Department of Biomedical Sciences at Penn Vet. She serves as director of

the [Penn Vet Cancer Center](#), which integrates research and cancer care, speeding the translation of science to the clinic. She is an expert in the cellular and molecular mechanisms underlying diseases associated with chronic inflammation and fibrosis, including cancer. Among other key discoveries, Puré's work has uncovered new ways that inflammation and fibrosis contribute to the development, growth, and spread of cancer. She's helping pioneer therapeutic strategies that target the tumor microenvironment as a way of slowing or stopping cancer's spread, and working to understand how tumors might "seed" distant tissues to promote metastasis.



Publications



Association of a functional Claudin-5 variant with schizophrenia in female patients with the 22q11.2 deletion syndrome. (2019) Guo Y, Singh LN, Zhu Y, Gur RE, Resnick A, Anderson SA, and **Alvarez JI**. *Schizophr Res.* (19) 30424-4. [Epub ahead of print]



Inducible knockout of $\Delta Np63$ alters cell polarity and metabolism during pubertal mammary gland development. (2019) Kumar S, Nandi A, Mahesh A, Sinha S, Flores E, and **Chakrabarti R**. *FEBS Lett* Dec 3. [Epub ahead of print]



Clinical and histopathological classification of feline intraocular lymphoma (2020) Musciano AR, Lanza MR, Dubielzig RR, Teixeira LBC, and **Durham AC**. *Vet Ophthalmol* 23(1): 77-89.

Lupus Research Alliance Invests More Than \$3.5 Million in Grants to Spark New Treatments

The Lupus Research Alliance announced the recipients of its *Target Identification in Lupus* Grants that are designed to accelerate development of promising new discoveries into potential therapies as well as enable scientists to address fundamental questions in lupus research and remove the barriers to advanced and innovative studies. Penn Vet’s **Montserrat Anguera, PhD**, in the Department of Biomedical Sciences is one of the six 2019 recipients. She plans to test whether genes that normally shut off in women’s cells, turn back on in lupus, causing the immune system to malfunction.



Annual Student Research Day—March 19, 2020—

The The Martin M. Kaplan V’40 Keynote address will be delivered by Theresa Alenghat, VMD, PhD, an associate professor, University of Cincinnati School of Medicine/Cincinnati Children’s Hospital in the Department of Immunobiology, and Center for Inflammation and Tolerance. Her laboratory investigates epithelial and immune cell homeostasis in intestinal health and disease. The goals of the Alenghat laboratory are to provide insight into molecular mechanisms that mediate the host-microbiota relationship, and to examine how this regulation affects innate immunity, metabolism, and chronic conditions, such as Inflammatory Bowel Disease.

Register here: <https://www.vet.upenn.edu/research/news-events-conferences/student-research-day>



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