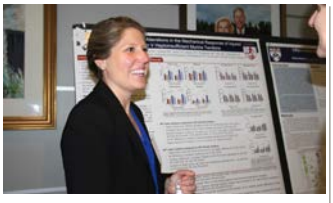
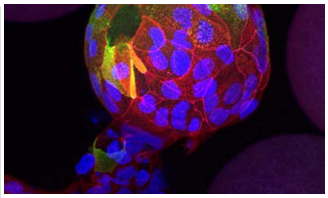
Paratuberculosis in cattle
NEW BOLTON CENTER
PAGE 1



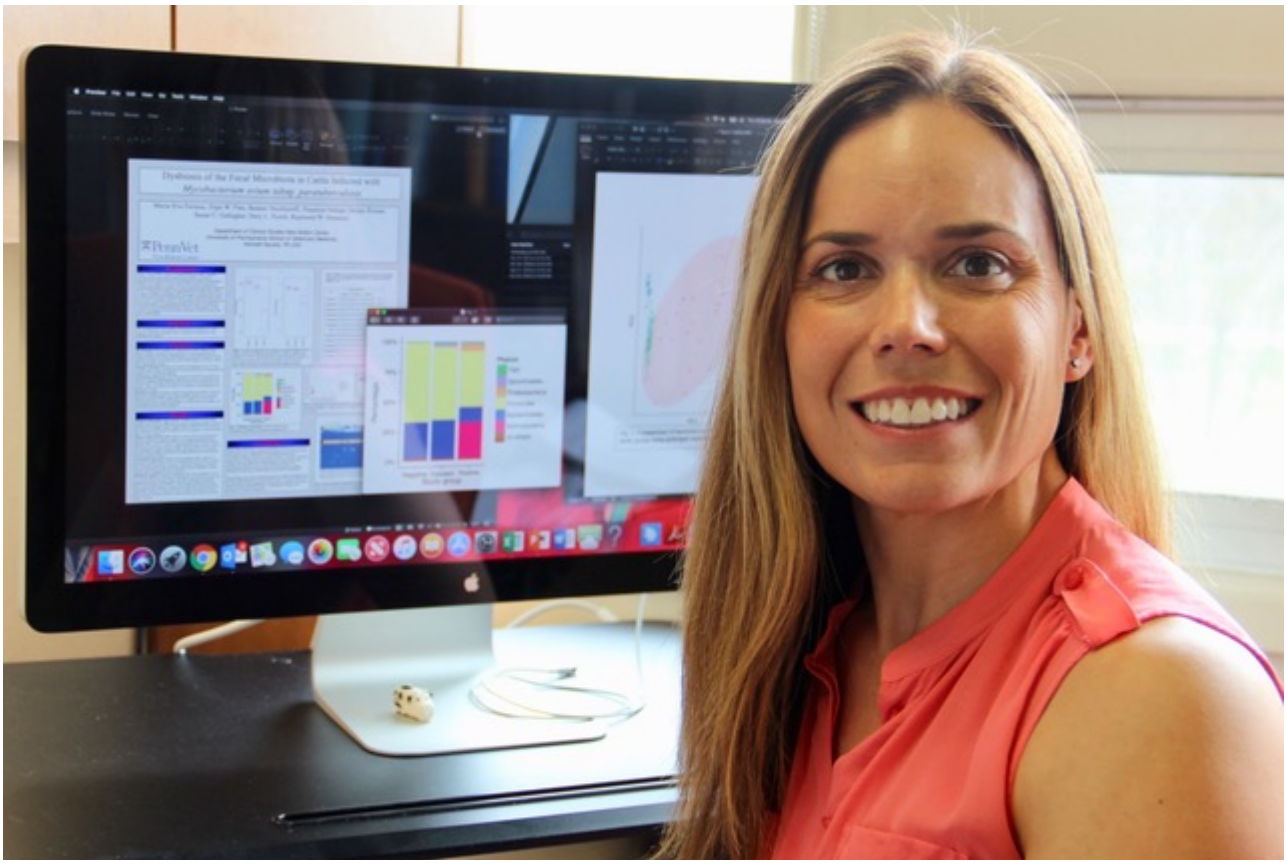
STUDENT RESEARCH DAY
PAGE 7

50TH ANNIVERSARY DUAL DEGREE
PAGE 7



6TH ANNUAL JOINT MICROBIOME SYMPOSIUM PAGE 6

NEWSLETTER



Johne's Disease and the enteric microbiome

Dr. **Marie-Eve Fecteau** is an associate professor of Farm Animal Medicine and Surgery (Clinician Educator track) in the Department of Clinical Studies-New Bolton Center. Dr. Fecteau received her veterinary degree from the Université de Montréal in 1999 and subsequently completed a large animal rotating internship at the same institution. Following her internship, she continued to work there for one year as a staff clinician in their farm animal ambulatory service, practicing mostly on

the pathophysiology and prevention of *paratuberculosis* in cattle

Continued on page 2

dairy cattle. Dr. Fecteau then entered a Large Animal Internal Medicine-Food Animal Emphasis residency program at the School of Veterinary Medicine of the University of California-Davis and became a diplomate of the college in 2004. Later that same year, Dr. Fecteau joined the PennVet Faculty as an Assistant Professor of Farm Animal Medicine and Surgery, and subsequently joined the Johne's Laboratory under the mentorship of Drs. Robert Whitlock and Raymond Sweeney. Dr. Fecteau's research interests are centered on the pathophysiology and prevention of paratuberculosis in cattle, and the pathogen's influence on the host's intestinal microbiome.

Background

Paratuberculosis (or Johne's Disease (JD)) is a chronic gastrointestinal disease of cattle caused by an infection with *Mycobacterium avium* subsp. *paratuberculosis* (MAP). Infection with MAP results in inflammation of the intestinal lining, chronic diarrhea, weight loss, and is ultimately fatal. Most animals become infected during the neonatal period but due to a long incubation period (up to 5-7 years), the majority (95%) of infected animals do not show signs of illness. The absence of clinical signs in the early stages of infection, along with the lack of completely reliable diagnostic methods in the preclinical stages of the disease, and the extreme resistance of the organism in the environment, make prevention and control of MAP infection very difficult. Moreover, there are no drugs currently approved for the prevention or treatment of paratuberculosis in cattle in the United States, and vaccination is not fully protective.

Protecting the calf

As most calves become infected with MAP very early in life, current control programs focus on preventing transmission from adult cattle shedding MAP organisms in feces to young replacement stock on the farm. However, when a herd is heavily infected with MAP, preventing exposure of young stock to the MAP organisms is nearly impossible. Some of Dr. Fecteau's earlier work focused on the chemoprophylaxis of MAP infection in neonatal calves, using gallium (Ga) compounds. Ga is a trivalent semi-metal that shares many similarities with ferric iron and functions as an iron mimic. In susceptible organisms, Ga substitutes for ferric iron in many cellular metabolic pathways and disrupts them. Fecteau initially demonstrated the antimicrobial efficacy of Ga against 10 different MAP isolates *in vitro*.[1] In a follow up experiment, Fecteau and colleagues demonstrated the safety of two Ga compounds (Ga nitrate and Ga maltolate) and compared the

Continued on page 3

WELCOME

In February, Dr. Elizabeth Lennon, assistant professor of Medicine, joined the Department of Clinical Sciences and Advanced Medicine, Philadelphia. Dr. Lennon received her DVM from North Carolina State University in 2007, completed an internship in small animal medicine and surgery at the University of Pennsylvania in 2008, and then entered the Clinician Scientist Training Program at North Carolina State University, combining an internal medicine residency with a PhD, which she completed in 2015. She received the AVMA/AVMF Young Investigator Award, Phi Zeta National Research Manuscript Award, and a Career Development Award from the National Institutes of Health. She was a Research Assistant Professor at North Carolina State University and then joined the University of Tennessee as an assistant professor in late 2015. Dr. Lennon's research is focused on investigating novel anti-inflammatory mechanisms of mast cells in inflammatory bowel disease (IBD) and investigating IBD pathogenesis in dogs and cats to improve treatment for veterinary patients and also to serve as a model of human IBD.

serum and tissue concentrations of the two compounds following oral administration.[2] Lastly, they demonstrated that in experimentally infected neonatal calves, Ga treatment was associated with a significant reduction in MAP tissue burden when compared to control calves.[3] Based on her results, Fecteau proposed that Ga compounds could be used as a potential feed additive (such as in milk replacers) in MAP-infected herds, and that their use during the period of high susceptibility and high exposure, when coupled with rigorous control measures, could reduce the incidence of JD in those herds.

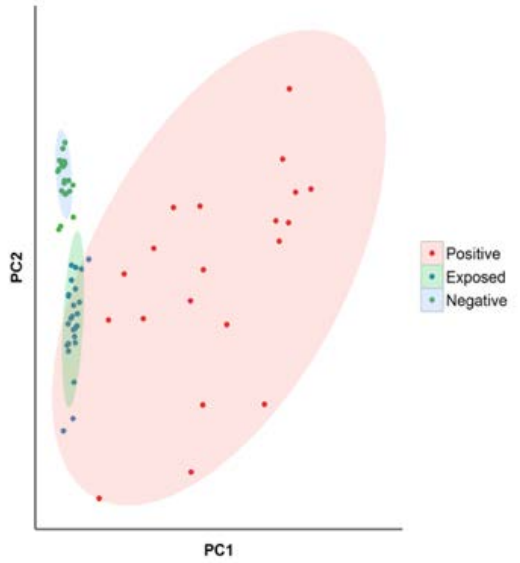


Figure 1. Comparison of bacterial community composition by study group using principal coordinate analysis.

MAP's effect on the microbiome: a possible key to prevention?

The gastrointestinal microbiome is fundamental to the overall health and production performance of most mammals. This diverse community of gastrointestinal bacteria exists in a delicate balance with the host. Disruption of this balance, termed "dysbiosis" can result in gastrointestinal dysfunction, including inflammation of the intestinal lining. Based on the inflammatory nature of JD, Dr. Fecteau next asked if MAP infection impacted the intestinal microbiome of infected cattle. With the help of her colleagues, Drs. Dipti Pitta and Raymond Sweeney from the Department of Clinical Studies-New Bolton Center, she investigated the diversity patterns of fecal bacterial populations in adult cattle infected with MAP, compared to those of uninfected-exposed cattle and uninfected-unexposed cattle using phylogenomic analysis. They demonstrated that fecal bacterial communities of MAP-positive cows varied significantly from those of cows from the exposed and negative groups (Figures 1 and 2).[4] In collaboration with Dr. Daniel Beiting from the PennVet Center for Host Microbial Interactions, Fecteau investigated the impact of early MAP infection on the fecal bacterial populations of neonatal calves following experimental infection. Using a metagenomic analysis, they were able to conclude that the dysbiosis observed in MAP-infected calves (Figure 3) is a direct consequence of MAP infection, and that dysbiosis is likely to play a role in the intestinal inflammation observed in the affected animals. Notably, these findings may provide potential biomarkers for early detection and/or therapeutic probiotic agents designed to restore the microbiome to its proper balance, thereby reducing intestinal inflammation in MAP-infected animals.

One Medicine

Crohn's disease (CD), an inflammatory gastrointestinal disease of humans, has many clinical and pathologic similarities to JD. The definitive cause of CD remains elusive and it is

Continued on page 4

thought to result from a complex interaction of host susceptibility factors and an intense immune response to bacteria or other antigens in the intestines.[5] Numerous studies investigating the role of MAP in CD have shown conclusively that MAP can be isolated from intestinal tissue of Crohn's patients (significantly more than controls), but the medical community still debates whether MAP causes the intestinal inflammation, or merely is able to colonize already-compromised intestinal tissues of afflicted individuals.[6-7] In collaboration with Dr. Robert Baldassano and colleagues at the Children Hospital of Philadelphia, Drs. Fecteau, Sweeney and Beiting have turned their focus on improving MAP detection methods in pediatric CD patients to directly address this issue.

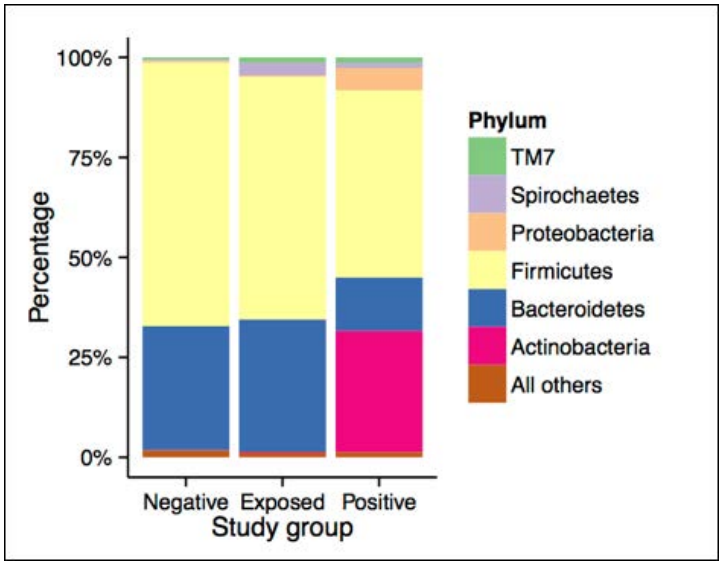
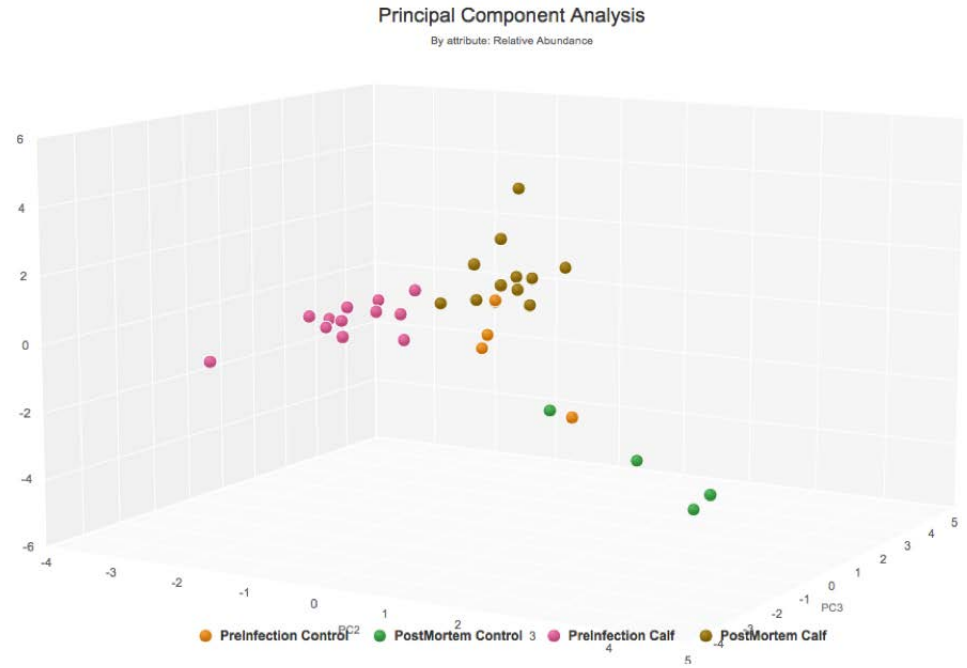


Figure 2. Phylogenic distribution. Stack bar plot showing phylogenetic distribution of bacteria at the phylum level.

Figure 3 Principal component analysis between MAP-infected and negative control calves at 2 time periods (Pre-infection and Post-mortem).



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Recent Awards (direct costs)

Jorge Alvarez
ITMAT Pilot Grant— T cell based therapy to target B cells within the central nervous system $150,000 2/1/19—1/31/20

Jorge Alvarez
EMD Serono
Defining the role of anti-B cell therapies in meningeal inflammation
$90,000 2/4/19—2/3/20

Igor Brodsky
NIH R01 —Defining the mechanisms and functions of RIPK1-induced cell death in anti-bacterial defense $1,715,450 2/1/19—1/1/24

Karina Guziewicz
NIH/NEI R21
The role of a novel scaffold protein in mediating RPE phagocytosis of photoreceptor outer segment
$275,000 3/1/19—2/28/21

Chris Hunter
Surface Oncology
Role of anti IL-27p28 antibody during toxoplasmosis
$69,650 3/19/19—9/19/20

David Christian & Chris Hunter
NIH R21 Novel role of DC1 in vaccine induced CD8 T cell responses
$275,000 1/4/19—12/31/20

C Konradt & Chris Hunter
NIH R21 The role of endothelial and T cells during infection of the vascular compartment
$275,000 1/08/19—12/31/20

Phil Scott/Elizabeth Grice
NIH R01 Skin microbiome contributions to the pathogenesis of cutaneous leishmaniasis
$2,249,075 3/4/19—2/29/24

Charles Vite
Biomarin Pharmaceutical
Biomarker development in canine MPSIIIA
$111,506 1-14-19—1/13/22

Charles Vite
NIH Referral CTR. Animal models of human genetic disease
$2,336,040 1/18/19—12/31/23

Dieter Schifferli & Igor Brodsky
NIH R21 Outer Membrane Vesicle Production by Salmonella PhoPQ and Inflammasome Activation
$275,000 2/5/19—1/31/21

Raimon Duran-Struuck
PICAB pilot grant—Development of clinically relevant swine tumor model through genetic modification of porcine lymphohematopoietic cancers
$45,000 3/1/19—2/28/20

Ron Harty
Intervir LLC/Welcome Trust
Development of host-oriented therapeutics against hemorrhagic fever viruses $196,932 1/1/19—12/31/20

DeBroski Herbert & James Lok
NIH Using transgenic parasitic nematodes to investigate Type 2 immunity
$150,000 1/15/19—12/31/20

James Lok
University Research Foundation
Regulatable CRISPR/Cas9 mutagenesis in parasitic nematodes
$50,000 3/1/19—2/28/20

Jennifer Punt
Center for Undergrad Research and Fellowships—Team grants for inter-disciplinary activities
$24,715 5/1/19—8/31/19

Boris Striepen
NIH R01 Genetic Analysis of Cryptosporidium
$1,250,000 5/1/19—4/30/24

Oriol Sunyer
NIH R01 —Primordially conserved principles governing mucosal immune responses to pathogens and microbiota
$982,795 3/4/19—12/31/22

Dan Morris/Peter Canning
Longitudinal evaluation of the atopic feline clinical and immunological response to allergen-specific immunotherapy: a randomized clinical trial
$4,583 1/1/19—12/31/19

Dan Morris/Bailey Brame
Clinical Trial to assess the utility of serological and skin prick allergen testing for cutaneous food sensitivity in cats
$9,950 1/1/19—12/31/19

Anna Kashina
NIH/NINDS—Role of arginylation in prevention of alpha synuclein driven neurodegeneration
$522,269 4/15/19-3/31/24

continued on page 8

Publications

Patton JB, Bonne-Annee S, Deckman J, Hess JA, Torigian A, Nolan TJ, Wang Z, Kliewer SA, Durham AC, Lee JJ, Eberhard ML, Mangelsdorf DJ, Lok JB, Abraham D. Methylprednisolone acetate induces, and Delta7-dafachronic acid suppresses, Strongyloides stercoralis hyperinfection in NSG mice. *Proc Natl Acad Sci U S A.* 2018;115(1):204-209.

Rane CK, Jackson SR, Pastore CF, Zhao G, Weiner AI, Patel NN, Herbert DR, Cohen NA, & Vaughan AE. Development of solitary chemosensory cells in the distal lung after severe influenza injury (2019) *Am J Physiol Lung Cell Mol Physiol.* Mar 25 [Epub ahead of print]

Park H, Oh J, Shim G, Cho B, Chang Y, KimS, Baek S, Kim H, Shin J, Choi H, Yoo J, Kim J, Jun W, Lee M, Lengner CJ, Oh Y-K, & Kim J (2019) In vivo neuronal gene editing via CRISPR–Cas9 amphiphilic nanocomplexes alleviates deficits in mouse models of Alzheimer's disease. *Nat Neurosci* 22(4): 524-528.

Shi B, Xue J, Yin H, Guo R, Luo M, Ye L, Shi Q, Huang X, Liu M, Sha J, Wang PJ. Dual functions for the ssDNA-binding protein RPA in meiotic recombination. *PLoS Genetics.* 2019;15(2):e1007952.

Continued from page 4

Dr. Fecteau's office is located in the New Bolton Center Hospital for Large Animals, Room 227.

References

1. Fecteau ME, Fyock, TL, McAdams SC, Boston RC, Whitlock RH, Sweeney RW: Evaluation of the in vitro activity of gallium nitrate against *Mycobacterium avium* subsp. *paratuberculosis*. *Am J Vet Re*s 2011; 72: 1243-1246.
2.Monk CS, Sweeney RW, Bernstein LR, Fecteau ME. Serum and tissue concentration of gallium following oral administration of gallium nitrate and gallium maltolate in neonatal calves. *Am J Vet Res* 2016; 77: 151-155.78
3.Fecteau ME, Whitlock RH, Fyock TL, McAdams SC, Boston RC, Sweeney RW: Antimicrobial activity of gallium nitrate against Mycobacterium avium subsp. *paratuberculosis* in neonatal calves. *J Vet Intern Med* 2011; 25: 1152-1155.
4.Fecteau ME, Pitta DW, Vecchiarelli B, Indugu N, Kumar S, Gallagher SC, Fyock TL, Sweeney RW. Dysbiosis of the fecal microbiota in cattle infected with *Mycobacterium avium* subsp. *paratuberculosis. PLOS ONE* 2016; 11(8) e0160353.
5.Marks DJ, Rahman FZ, Sewel GW, Segal AW. Crohn's disease: an immune deficiency state. *Clin Rev Allergy Immunol* 2010; 3: 20-31.
6.Abubakar I, Myhill D, Aliyu SH, Hunter PR. Detection of *Mycobacterium avium* subspecies *paratuberculosis* from patients with Crohn's disease using nucleic acid-base techniques: a systematic review and meta-analysis. *Inflamm Bowel Dis* 2008; 14: 401-410.
7.Liverani E, Scaioli E, Cardamone C, Dal Monte P, Belluzzi A. *Mycobacterium avium* subspecies *paratuberculosis* in the etiology of Crohn's disease, cause or epiphenomenon? *World J Gastroenterol* 2014; 20: 13060-13070.

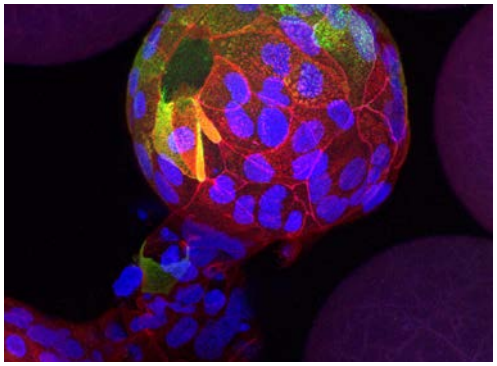
Sixth Annual Microbiome Symposium

(Jointly organized by PennCHOP/PennVet/PennMedicine)

The Impact of the Microbiome on Cancer Progression and Therapy—October 2-3, 2019. The Keynote presentation will be delivered by Laurence Zitvogel, MD, PhD, Research Director, Department of Clinical Biology/ Laboratory of Clinical Immunology, Gustave Roussy Cancer Center, Villejuif, France. Stay tuned for more announcements on this exciting event!

Co-Organizers: Drs. Robert Baldassano, Daniel Beiting, Frederick Bushman, Andrea Facciabene, Costas Koumenis, Ellen Puré, and Gary Wu.

Location: BRB II-III Auditorium, Perelman School of Medicine.



Intestinal cells in 3D culture

MARCH 21-22, 2019— Penn Vet's Student Research Day and a 50th Anniversary of the Combined Degree Program

In commemoration of the unique and outstanding success of the VMD-PhD program, Penn Vet faculty, students, alumni and mentors gathered to showcase their academic achievements over the course of two chock-full days. Penn Vet alum, Dr. Steven Bensinger (UCLA) delivered the first day's Class of 66 keynote lecture entitled: "Towards Understanding How Lipid Metabolism Influences Immunity". The student winners of the day included Rebecca Rosenthal, Mariel Covo, John Cain, Ian Penkala, Katherine Neupauer, Robyn Allen, Monica Jimenez, Pierce Nathanson, and Philip Hicks. The second day featured a commemoration of the 50th anniversary of the dual degree program, alumni talks, networking sessions, and a celebratory dinner. We were privileged to have Dr. Ralph Brinster as the keynote speaker. His talk was on "Understanding and Modifying the Mammalian Genome". Noteworthy was the presence of four esteemed Penn Vet Deans—Robert Marshak, Alan Kelly, Joan Hendricks and Andrew Hoffman.

Back row: Rebecca Rosenthal, John Cain, Mariel Covo, Ian Penkala, Philip Hicks and *front row*: Katherine Neupauer, Robyn Allen, Pierce Nathanson and Monica Jimenez

Major NIH Resource Center (P40) Grant—Charles Vite, DVM, PhD, and his team (Drs. Jessica Bagel, Patricia O'Donnell, Caitlyn Molony, Christian Cross, Allison Bradbury, Magi Casal, Urs Giger, Paula Henthorn, Chris Lengner, Kai Wang, Adrian Leu, Victor Stora, Ping Wang, Susan Volk, Nicola Mason, Meg Sleeper, Dana Clarke, Jeff Runge, Keiko Miyadera, Wil Mai, Beth Callan, Rebecka Hess, Carlo Siracusa, Mariah Gentry, and Carol Margolis) have been awarded a multimillion dollar P40 grant to continue their fantastic work as the Referral Center for Animal Models of Human Disease (RCAM), an incredible resource for which Penn Vet is known the world over. The recognition of the excellent work the RCAM is a milestone in its illustrious history.

Online Course for Credit—Penn Vet will launch a four-course, for-credit Certificate Program in **Animal Welfare Science and Animal Behavior** designed for individuals working with animals in research, industry, and the nonprofit sector, as well as for those who are interested in developing careers in animal health and welfare. Taught by nationally and internationally renowned Penn Vet faculty, it prepares students to understand how animal welfare and behavior are understood and assessed. The course follows UPenn's semester schedule and includes both asynchronous and weekly synchronous components, allowing students direct contact with multiple faculty members who have unique expertise in large and small animal health, welfare, and behavior. For more information contact Jennifer Punt, VMD, PhD at punt@vet.upenn.edu

Meaghan Hogan is the new Vice Dean of Institutional Advancement

Meaghan Hogan earned her Bachelor of Arts degree in English from Vassar College; her Juris Doctor from Emory University; and her Master of Laws in Taxation from Temple University. Quoted from Penn Vet's website—"I'm delighted to support Penn Vet and fulfill its aspirations for *The Power of Penn Vet* Campaign and beyond", Hogan said. "The School's mission to advance health and science for the betterment of animals, humans, and the environment is more relevant and urgent than ever. We have a wonderful story to tell".

Continued from page 5

Awards (direct costs)

Ellen Puré
Subaward NIH/NHLBI
Atherosclerosis, Prostaglandin Inhibition and Checkpoint Blockade
$75,759 1/1/19-11/30/22

Michael May
University Research Foundation
VMD Symposium
$20,000 3/1/19-2/28/20

Rumela Chakrabarti
American Cancer Society
DLL1 Mediated Notch Signaling in Tamoxifen Resistance of Breast Cancer
$792,000 7/1/19-6/30/23

More upcoming events.....

Penn Vet's Annual Faculty Research Retreat on Friday, June 14, 2019 at the Inn at Swarthmore. https://www.vet.upenn.edu/research/news-events-conferences/annual-faculty-research-retreatThe Marshak Lecture "A genome-first approach to understanding biology, disease, and therapeutic targets" will be delivered by Dr. Dan Rader (Perelman School of Medicine)

IRM/Penn Vet Frontiers of Germ Cell Research —the Brinster SSC Transplantation 25th Anniversary Symposium at Penn Vet's Hill Pavilion on Wednesday August 14, 2019 https://spark.adobe.com/page/jS0cDLzLHvOiJ/

Publications

Goulart MR, Hlavaty SI, Chang Y-M, Polton G, Stell A, Perry J, Wu Y, Sharma E, Broxholm J, Lee AC, Szladovits B, Turmaine M, Gribben J, Xia D, and **Garden OA** (2019)Phenotypic and transcriptomic characterization of canine myeloid-derived suppressor cells *Sci. Rep* Volume 9 (1) 3574.

Syrett CM, Paneru B, Sandoval-Heglund D, Wang J, Banerjee, S, Sindhava V, Behrens EM, **Atchison M and Anguera MC.** (2019) Altered X-chromosome inactivation in T cells may promote sex-biased autoimmune diseases. *JCI Insight* 4(7):e126751

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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