



Annual Faculty Research Retreat on June 8 page 6



Dr. David Galligan receives Distinguished Service Award—page 6

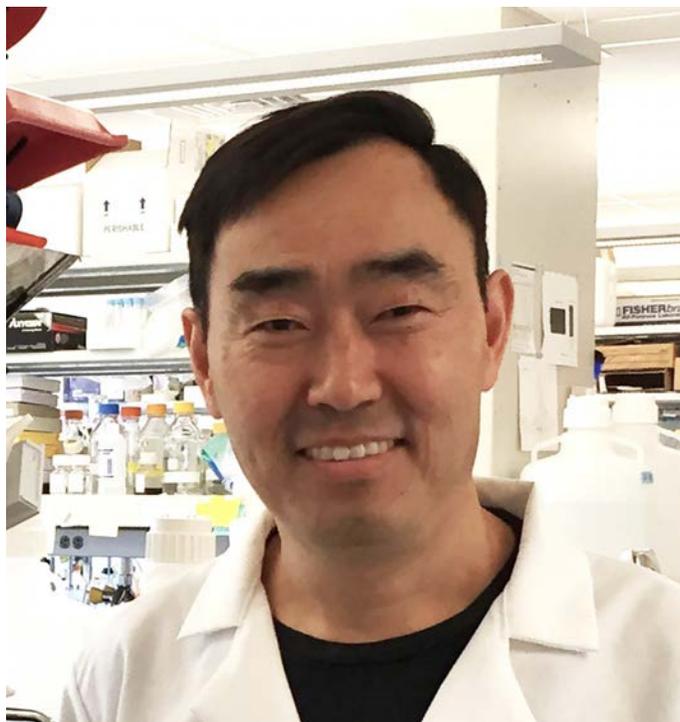


Dr. Nicola Mason awarded Zoetis Prize for research excellence—page 6



The Joan C Hendricks Arch named for her exemplary service to Penn Vet

NEWSLETTER



Meiosis and Fertility

Dr. Jeremy Wang is professor of developmental biology in the Department of Biomedical Sciences and director of the Center for Animal Transgenesis and Germ Cell Research. Dr. Wang received his MD from Peking University Health Sciences Center in 1990. After receiving his Ph.D. in biochemistry, cell and molecular biology from Cornell University in 1997, he worked as a post-doctoral fellow in the Laboratory of Dr. David Page at the Whitehead Institute/Massachusetts Institute of Technology (M.I.T.) before joining Penn Vet as an assistant professor in 2002. Dr. Wang’s research interests are centered on the genetic regulation

of germ cells in mice and humans, focusing on meiosis, transposon silencing, maternal factors, sperm motility, male infertility, and male contraception.

In the past 16 years, Dr. Wang has sought to understand the regulation of spermatogenesis by assessing the function of dozens of novel germ cell-specific proteins that he and his lab identified using two innovative cost-effective genome-wide screens. In the first screen, which Dr. Wang carried out as a postdoc at the Whitehead Institute, he developed a cDNA subtraction approach (in the pre-microarray era) and identified 36 germ cell-specific genes, 24 of which were novel (1). Since then, his laboratory has



Continued on page 2

published genetic studies on more than 10 of these genes. In the second genome-wide screen, Wang and coworkers undertook a proteomics approach and identified 51 meiotic chromatin-associated proteins in mouse, 32 of which were uncharacterized (2). To date, the Wang laboratory has published functional studies of four proteins (MEIOB, SCML2, UTF1, and YTHDC1) identified in the proteomics screen. These two genome-wide screens represent significant contributions to the field of mammalian reproduction, since study of these genes has provided unique molecular insights into spermatogenesis in mice. Moreover, the results of these studies have important implications for understanding the genetic causes of male infertility in humans and identifying novel targets for male contraception.

Meiosis and Fertility Meiosis, a cell division unique to germ cells, allows the reciprocal exchange of genetic materials between paternal and maternal genomes through meiotic recombination. Thus, meiosis generates the genetic diversity necessary for species evolution. Importantly, abnormalities in meiosis and aberrant recombination are a leading cause of birth defects and infertility.

During meiosis, homologous chromosomes undergo synapsis and recombination. Meiotic recombination begins with generation of programmed DNA double-strand breaks (~300 DSBs per germ cell). This process relies on the complex interplay of DNA repair proteins.

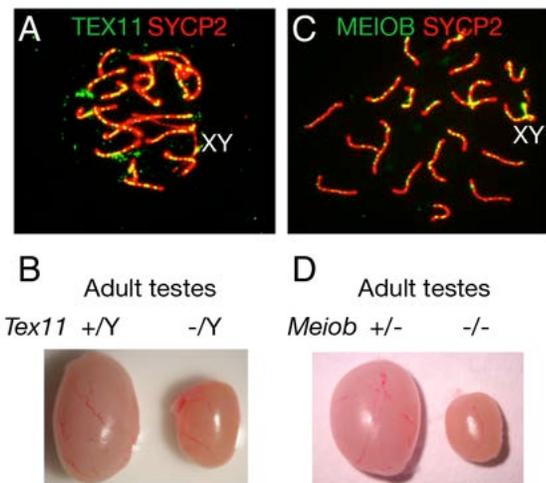


Figure 1. Two essential meiosis-specific factors. (A, C) Localization of meiotic recombination proteins (A, TEX11; C, MEIOB) as foci on the meiotic chromosomal axes in spermatocytes. SYCP2 is an SC component. The foci are where the meiotic DSBs are being repaired. (B, D) Inactivation of *Tex11* or *MeioB* causes meiotic arrest, leading to dramatically reduced testis size and sterility.

However, as meiotic recombination occurs between non-sister chromatids (homologues) rather than sister chromatids as in somatic cells, many DNA repair proteins have evolved to function specifically during meiosis. The Wang laboratory has identified and studied a number of such meiosis-specific factors, including SYCP2, TEX11,

Continued on page 3

Welcome



M. Andrés Blanco joined the Department of Biomedical Sciences as an assistant professor on January 1, 2018. Dr. Blanco received his Bachelor's degree from Cornell University where he double-majored in Biological Sciences and Philosophy. He received his PhD from the Department of Molecular Biology at Princeton University where he studied the molecular and genomic basis of breast cancer metastasis. Dr. Blanco then moved to Harvard Medical School for his postdoctoral training, where he studied chromatin and epigenetics using the nematode *C. elegans* and mice as model organisms. With K22 funding from the National Cancer Institute (NCI), Dr. Blanco came to Penn to start up his laboratory with an aim of understanding how chromatin-based epigenetic programs regulate cellular identity in normal and cancerous cells. By learning more about how healthy cells orchestrate differentiation programs, the Blanco lab aims to find ways to induce differentiation in cancer cells to halt their growth. This understudied therapeutic approach has great promise, but will require a greater knowledge of the fundamental mechanisms by which cell identity is regulated.

and MEIOB (Figure 1) and have found that SYCP2 is an integral component of the synaptonemal complex (SC), which physically connects the homologous chromosomes (Fig. 1). They also find that TEX11 interacts with SYCP2 and is a novel factor involved in recombination (Fig. 1A). TEX11 promotes both synapsis and recombination (3). Notably, inactivation of *Tex11*, an X-linked gene, causes meiotic defects and sterility in males (Fig. 1B). By screening hundreds of infertile men, the Wang laboratory have shown that mutations in the *TEX11* gene alone account for 1% of cases of azoospermia (infertile men with no sperm in semen) (4). Thus, our study on *Tex11* in mice provides a strong rationale for screening for *TEX11* mutations in infertile men to further inform genetic consultations with couples seeking infertility treatment.

Dr. Wang's group also identified MEIOB, a meiosis-specific protein, in the aforementioned proteomics screen (2). MEIOB binds to ssDNA and localizes to DSBs in meiotic germ cells (Fig. 1C). *Meiob*-null mice exhibit a failure in meiosis and sterility in both sexes (Fig. 1D). MEIOB forms a heterodimer with SPATA22, another meiosis-specific protein. Disruption of the interaction between MEIOB and SPATA22 destabilizes both proteins (5), raising the intriguing possibility that small molecule inhibitors of the MEIOB-SPATA22 interaction could be further developed for male contraception.

Transposon Silencing and Genome Evolution—

Repetitive elements, term “junk DNA”, occupy ~40% of the mammalian genome and include retrotransposons such as LINES, SINEs, and endogenous retroviruses. Retrotransposons have an enormous capacity to metastasize throughout the genome using a “copy and paste” mechanism involving reverse transcription. While retrotransposons play an important role in genome evolution, their mobilization can be detrimental to genome integrity, particularly in germ cells. In most species, the inability to silence retrotransposons in the germline is often associated with sterility. To protect genome integrity, germ cells employ multiple mechanisms to suppress retrotransposon activity, including small non-coding piRNAs, DNA methylation, and repressive histone modifications.

Piwi-interacting RNAs (piRNAs) are a diverse class of small non-coding RNAs required for the silencing of retrotransposons and the safeguarding of genome integrity. In mammals, piRNAs are only present in male germ cells. In collaboration with Dr. Zissimos Mourelatos' laboratory at Perelman School of Medicine, Dr. Wang and colleagues find that MOV10L1, a putative RNA helicase

Continued on Page 4

Welcome



In July, Dr. Laurel Redding, assistant professor of Epidemiology, joined the Department of Clinical Studies, New Bolton Center. Dr. Redding received her PhD and VMD from the University of Pennsylvania in 2014 and 2015, respectively. Her dissertation research at Penn examined the use of antibiotics on small dairy farms in rural Peru, and she received the Saul Winegrad Award for Outstanding Dissertation for this work. She is also a recipient of a Penn Vet Inspiration Award. Prior to returning to Penn Vet, she was a small animal general practitioner in Springfield, PA, and an adjunct assistant professor at the University of North Texas Health Sciences Center, where she taught classes on Zoonotic Disease and Global Food Security. Her chief research interests involve the use of antimicrobials in veterinary settings and the animal reservoir of zoonotic pathogens, with a current focus on *Clostridium difficile*, the primary cause of nosocomial diarrhea in people and an important enteric pathogen in several animal species.

identified in the genomic screen described above (1), binds to piRNA precursors to initiate piRNA biogenesis. This result identified MOV10L1 as a master regulator of the piRNA pathway in mammals (6). Loss of Mov10l1 results in absence of piRNAs, activation of retrotransposons, and male sterility. In the future, the Wang laboratory will continue to investigate the genetic and epigenetic mechanisms of retrotransposon silencing in germ cells.

Dr. Wang’s research is funded by the NIH/NIGMS MIRA award (R35GM118052) and NIH/NICHD grants (R01HD069592, R01HD084007, and P50 Center Grant HD068157). His laboratory is located at 304 Rosenthal and his office is at 390EC Rosenthal/Old Vet.

References

1. Wang PJ, McCarrey JR, Yang F, Page DC. (2001) An abundance of X-linked genes expressed in spermatogonia. *Nat Genet* 27:422-426.
2. Mengcheng Luo, Fang Yang, N. Adrian Leu, Jessica Landaiche, Mary Ann Handel, Ricardo Benavente, Sophie La Salle & P. Jeremy Wang (2013) MEIOB exhibits single-stranded DNA-binding and exonuclease activities and is essential for meiotic recombination. *Nat Commun* 4:2788.
3. Yang F, Gell, K van der Heijden GW, Eckardt S, Leu NA, Page DC, Benavente R Her C, Hoog, C, McLaughlin KJ, and Wang PJ. (2008) Meiotic failure in male mice lacking an X-linked factor. *Genes Dev* 22:682-691.
4. Yang F, Silber S, Leu NA, Oates RD, Marszalek JD, Skaletsky H, Brown LG, Rozen S, Page DC, Wang PJ. (2015) TEX11 is mutated in infertile men with azoospermia and regulates genome-wide recombination rates in mouse. *EMBO Mol Med* 7:1198-1210.
5. Xu Y, Greenberg RA, Schonbrunn E, Wang PJ. (2017) Meiosis-specific proteins MEIOB and SPATA22 cooperatively associate with the ssDNA-binding RPA complex and DNA double-strand breaks. *Biol Reprod* 96:1096-1104.
6. Vourekas A, Zheng K, Fu Q, Maragkakis M, Alexiou P, Ma J, Pillai RS, Mourelatos Z, Wang PJ (2015) The RNA helicase MOV10L1 binds piRNA precursors to initiate piRNA processing. *Genes Dev* 29(6):617-629.



The Wang research group—Emma Lipschutz, Jessica Chotiner, Fang Yang, Yongjuan Guan, Baolu Shi, Jeremy Wang, & Seth Kasowitz—notice the unique tie-dye lab coats in the Wang Laboratory

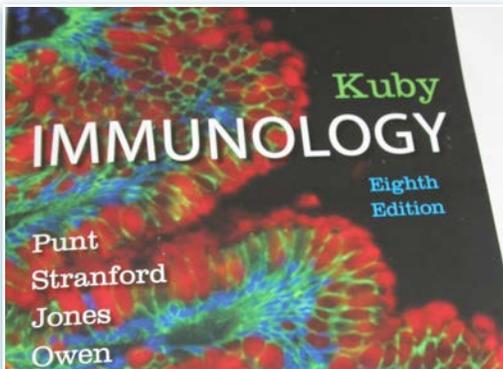


K99 award

Postdoctoral fellow, **Adam Sateriale**, a member of the **Boris Striepen Laboratory**, has been awarded K99 funding. The purpose of the NIH Pathway to Independence Award (K99/R00) program is to increase and maintain a strong cohort of new and talented, NIH-supported, independent investigators in order to help awardees to launch competitive, independent research careers. The K99/R00 award will provide up to 5 years of support in two phases. The initial (K99) phase will provide support for up to 2 years of mentored postdoctoral research training and career development. The second (R00) phase will provide up to 3 years of independent research support, which is contingent on satisfactory progress during the K99 phase and an approved, independent, tenure-track (or equivalent) faculty position. The two award phases are intended to be continuous in time. The Striepen laboratory is on the 3rd floor of Hill Pavilion. The title of Adam’s project is ‘Investigation of subtelomeric gene families in *Cryptosporidium*’.



Jennifer PuntVMD, PhD, Associate Dean of One Health, is co-author of the 8th edition of the textbook entitled “Kuby Immunology” published by W. H. Freeman (2018). The current group of authors took over from the original author, Janis Kuby, who died of breast cancer in 1996. All the authors have taught immunology at the undergraduate level: Haverford College (J Punt and J Owen), Pomona and Mt. Holyoke (S Stranford), Stanford (P Jones), Columbia (J Punt). They have designed the book with a nod to Janis Kuby’s original intention—to introduce students, not just to information, but to the research and the recognition that learning begins with the discoveries!



Publications

Bais S, Berry CT, Liu X, Ruthel G, Freedman BD, **Greenberg RM** (2018) Atypical pharmacology of schistosome TRPA1-like ion channels. *PLoS Neglected Tropical Diseases* 12: e0006495.



Chakrabarti R (2018) Notch ligand DLL1 mediates cross-talk between mammary stem cells and the macrophageal niche. *Science* 17 May 2018: eaan4153
Link to Press release: [Penn Today](#)



Pesato ME, Boyle AG, Fecteau ME, Hamberg A, Smith BI. (2018) Gastrointestinal spindle cell tumor of the rumen with metastasis to the liver in a goat. *J Vet Diagn Invest.*:30(3):451-454



Hung LY, Oniskey TK, Sen D, Krummel MF, Vaughan AE, Cohen NA, **Herbert DR**. (2018) Trefoil Factor 2 Promotes Type 2 Immunity and Lung Repair through Intrinsic Roles in Hematopoietic and Nonhematopoietic Cells *Am J Path* 188(5):1161-1170.



Patel NN, Kohanski MA, Maina IV, Triantafyllou V, Workman AD, Tong CCL, Kuan EC, Bosso JV, Adappa ND, Palmer JN, **Herbert DR**, Cohen NA (2018) Solitary chemosensory cells producing interleukin-25 and group-2 innate lymphoid cells are enriched in chronic rhinosinusitis with nasal polyps. *Int Forum Allergy Rhinol*. Epub ahead of print.

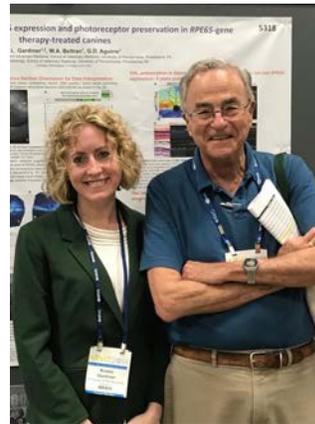


Annual Faculty Research Retreat—

A very large crowd of faculty, postdocs, residents, students, and staff gathered at New Bolton Center for the annual research retreat symposium on June 8. The theme, *Centers of Excellence*, was presented by speakers from four centers—Penn Vet Cancer Center (Ellen Puré, Sue Volk and Christopher Lengner); Center for Host-Microbial Interactions (Dan Beiting and Christine Cain); Center for Animal Health and Productivity (David Galligan, Zhengxia Dou, Dipti Pitta and Tom Parsons); and the Center for Animal Transgenesis and Germ Cell Research (Jeremy Wang, Charles Vite and Andrew Vaughn). Dean Joan Hendricks and former Dean Robert Marshak made an inspiring presentation of a **Distinguished Service Award to David Galligan**. Oliver Garden, chair of the Clinical Sciences and Advanced Medicine presented the annual **Zoetis Prize** for research excellence in veterinary medicine to **Nicola Mason**. Of interest to all was the Marshak Lecture, given by Paul Offit, professor of vaccinology at the Children’s Hospital of Philadelphia. His talk, “*The Rotavirus Vaccine: From Bench to Bedside*” was particularly interesting in that the vaccine was made in part using a strain that was isolated at New Bolton Center from a calf. The very *Best Poster* prizes were awarded to Kristin Gardiner (1st); William Beltran (2nd); and David Holt (3rd).



Dean Joan Hendricks and Dr. David Galligan



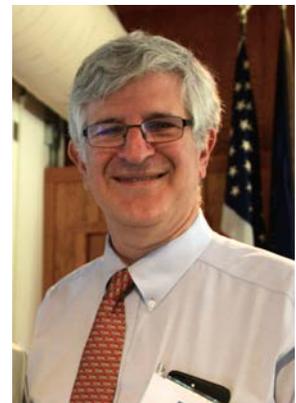
Drs Kristin Gardiner & Gus Aguirre



Drs Oliver Garden & Nicola Mason



Former Dean Robert Marshak attends retreat



Dr. Paul Offit



An enjoyable day for all at New Bolton Center for the 2018 Annual Faculty Research Retreat



Student Sabina Hlavaty



Dr. David Holt

Recent Awards (direct costs)

William Beltran

OPHTHOTECH
Gene therapy for treatment of rhodopsin-mediated
autosomal-dominant Retinitis Pigmentosa (adRP)
6/1/18 – 5/31/2021 \$2,887,683

Brittany Tisa

MADDIE'S FUND - The Pet Rescue Foundation
Maddie's Shelter Medicine Internship Grant
7/1/18- 8/31/19 \$50,000

Oliver Garden

Center for Host-Microbial Interactions PILOT
The intestinal microbiome of dogs with idiopathic
immune-mediated hemolytic anemia: an occult
trigger for pathogenic autoimmunity?
6/1/2018—5/31/19 \$50,000

Deborah Silverstein

NOVA Biomedical
Method Comparison and Precision Study Evaluation
of the NOVA StatSensor® and the StatSensor®
Xpress? Hand Held Creatinine Monitor in Dogs
4/1/18 – 3/31/19 \$ 7,271

Igor Brodsky

NIH R21
Novel role of CARD19 in cell death and anti-
bacterial host defense
6/8/18-5/31/20 \$442,750

Igor Brodsky

Burroughs Wellcome Fund
Lab Retreat Travel-August 2018
5/1/18-9/30/18 \$6,000

John Cain (mentor, Michael Povelones)

Morris Animal Foundation
Molecular Dissection of Mosquito Resistance to
Heartworm Infection
6/1/18-9/1/18 \$5,000

Adam Sateriale (mentor, B. Striepen)

NIH K99
Investigation of subtelomeric gene families in
Cryptosporidium
5/5/18-4/30/20. \$216,000 (for the first phase of
program)

Amy Durham

NIH S10
Aperio VERSA Digital Slide Scanner; eSlide
Manager Database, and Advanced Image
Analysis Software
5/1/18-4/30/19 \$329,186

Laurel Redding

Center for Host-Microbial Interactions PILOT
Clostridium difficile in canine fecal samples
6/1/18-5/31/19 \$23,450—Plus \$29,478 from the
PennCHOP Pilot opportunity

Thomas Schaer

NIH/NIAMSK (with University of Connecticut
Health Center) A Translational Approach Towards
Ligament Regeneration
5/1/18 – 1/31/19 \$135,056

Ron Harty

Fox Chase Chemical Diversity Center
Development of Small Molecule Therapeutics
Targeting Hemorrhagic Fever Viruses
6/1/18-5/31/19 \$50,000

James Marx

American Society for Laboratory Animal
Practitioners 2018 ASLAP Foundation Summer
Fellowship Program
6/1/18-8/31/18 \$5,000

Nicola Mason

(with Karin Eisinger, PSOM) Abramson Cancer
Center Pilot—Evaluation of constitutive
canonical NF-κB activity as the Achilles Heel of Soft
Tissue Sarcoma.— Funds will support a pilot clinical trial
using local administration of an NF-κB inhibitor in dogs
with soft tissue sarcomas. 7/1/18—6/30/19 \$250,000

Nate Sotuyo

NIH/NINDS F31
VMD/PhD program (mentors Stewart Anderson, MD
& Ethan Goldberg, MD PhD)
Treatment of epilepsy and associated comorbidities
using stem cell-derived interneurons to correct
circuit dysfunction in an animal model of Dravet
syndrome \$44,524

Andrew Vaughan

Center for Host-Microbial Interactions PILOT
*Transcriptional programming by Notch controls
regenerative outcomes following influenza injury*
6/1/18-5/31/19 \$30,000

Andres Blanco

McCabe Fund Pilot Grant
Screen for FDA-approved inhibitors that synergize with GSK-LSD1 to
induce therapeutic differentiation in non-APL acute myeloid leukemia
8/1/18-7/31/19 \$21,047

Rumela Chakrabarti

Emerson Collective Cancer Research Fund
Understanding function of Notch signaling in
Tamoxifen resistant breast cancer
8/1/18-7/31/20 \$170,000

Montserrat Anguera and Michael Atchison

University Research Foundation (URF)
Influence of altered X-linked gene dosage on
the microbiome during autoimmunity
8/1/18-7/31/19 \$50,000

Montserrat Anguera

NIH/ NIAID
Gene regulation from the inactive X in activated B
cells
6/1/18-5/31/19 \$314,945

Preprint Journal Club

Our preprint journal club is open to all—faculty, postdocs, veterinary and PhD students. The idea is based on the addition of a new [NIH notice](#) that encourages investigators to use interim research products, such as preprints, to speed the dissemination and enhance the rigor of their work. This notice clarifies reporting instructions to allow investigators to cite their interim research products and claim them as products of NIH funding. A common form is the preprint, which is a complete and public draft of a scientific document. Preprints are typically unreviewed manuscripts written in the style of a peer-reviewed journal article. Scientists issue preprints to speed dissemination, establish priority, obtain feedback, and offset publication bias. The Penn Vet preprint journal club is focused on host pathogen interactions and microbiome papers posted to @biorxivpreprint Each Journal Club meeting will produce a review via @PREreview. For more information contact Dr. Dan Beiting at beiting@upenn.edu

EMBO Fellowship Awarded—Amandine Guerin, postdoctoral fellow in the laboratory of Dr. Boris Striepen has been awarded a prestigious EMBO fellowship for her work on the topic of *Cryptosporidium* invasion and host cell manipulation. Her award is for \$90,265 beginning January 1, 2019—December 31, 2020. EMBO stands for excellence in the life sciences



Amandine Guerin

with a goal of helping young scientists advance their research, promote their international reputations and ensure their mobility.

Some of the faculty speakers at the June 8 research retreat



Andrew Vaughan



Christine Cain



Daniel Beiting

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

Phillip Scott, PhD
Vice Dean for Research & Academic Resources

Editor:
Gayle Joseph
University of Pennsylvania
School of Veterinary Medicine
(215) 898-9793

