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# NEWSLETTER



## Female-bias in autoimmune disorders

Dr. Montserrat C. Anguera is an assistant professor (tenure-track) in the Department of Biomedical Sciences. Dr. Anguera received a B.A. in Environmental Chemistry from the University of California, San Diego in 1998. As an undergraduate, she worked at the Scripps Institute for Oceanography where she investigated secondary metabolites from marine fungi. She completed a Ph.D. in Biochemistry, Molecular and Cellular Biology from Cornell University in 2005, where she worked on one-carbon metabolism. During her post-doctoral fellowship at Harvard Medical School/Massachusetts General Hospital, Dr. Anguera became interested in both the mechanistic role of long noncoding RNAs (lncRNAs) and the

female-specific epigenetic phenomenon of X-chromosome Inactivation. Since joining Penn Vet in 2013, she has expanded these studies to investigate the role of X-chromosome Inactivation in female-biased disease and the biological role of lncRNAs in early human development

**Female-bias in autoimmune disorders: multiple Xs matter**

Systemic lupus erythematosus (SLE) is a severe autoimmune disease that affects people of every race, age, and socio-economic status, with females at the highest risk of disease. The observed sex disparity in SLE likely originates with the X-chromosome, as it contains the greatest absolute number of immunity-related genes of any chromosome, and disease is frequently associated with abnormal expression of X-linked genes [1]. Moreover, individuals with multiple X chromosomes, including females (XX), Klinefelter syndrome patients (XXY), and polysomy X patients (XXX) are at higher risk of developing SLE. There is no cure for SLE, and current treatments primarily focus on reducing the associated symptoms. Thus, the Anguera lab focuses on understanding mechanisms that control the expression and function of genes encoded on the X-chromosome, thereby providing critical new insights into pathogenesis and, perhaps treatment of female-biased autoimmune diseases.

Female mammals, who have 2 X chromosomes (XX), silence one in a process called X-Chromosome Inactivation (XCI), thereby equalizing X-linked gene expression with males (XY) [2]. XCI is initiated by the X-linked long noncoding RNA XIST, which localizes as an RNA ‘cloud’ on the inactive X and recruits heterochromatin complexes for persistent chromosome-wide silencing [3]. This silencing is abrogated when the XIST gene is deleted or silenced, thereby increasing the expression of normally silenced genes [4, 5]. Notably, Dr. Anguera and colleagues discovered that, unlike all other somatic cells examined to date, the inactive X-chromosome in mature naïve peripheral T and B cells from females lacks XIST RNA clouds and a variety of heterochromatic marks [6]. Following antigenic activation of these lymphocytes, they also found that XIST RNA transcripts returned to the inactive X,

**Tracy Bale  
receives NIH  
MERIT Award**



MERIT awards are designed to give productive and creative scientists long-term support, without the burden of constantly devoting time and staff resources to applying for new grants to fund their research. NIH created the MERIT award program in 1986, to support investigators whose research skills and productivity are "distinctly superior" and who are highly likely to continue to perform in an outstanding manner. Tracy Bale's MERIT award is for her recently funded R01 MH108286 on Paternal Stress Epigenetics. This award converts a five year grant into a ten year grant. MERIT awardees cannot apply for the award; they are nominated by the funding NIH institute from a large pool of competing award recipients and then endorsed by an institutes' advisory council.

# Penn Vet Student Research Day

On March 23, the scholarly achievements of Penn Vet Students were presented at the Annual Student Research Day conference. Penn Vet faculty, alumni, students and mentors heard oral presentations and enjoyed poster sessions where students presented their research projects carried out during the last year. The Class of 66 Keynote Address was delivered by **Alexander Travis VMD, PhD**, on “*Following your Science—from Sperm to Stroke and from Basic to Bedside*”. Awards were given to Bailey Baumann—*The effect of Muller Cell Dysfunction on Iron Transport Across the Neurosensory Retina* (1<sup>st</sup> place in dual degree category); Feini Qu—*A Low-cost, Wearable Magnet-based Detection System to Assess Joint Kinematics in Humans and Large Animals* (2<sup>nd</sup> Place); Elinor Willis—*Neonates Generate Long-lived Protective Immune Response in the Presence of Maternal Antibodies* (3<sup>rd</sup> place). In the VMD category, 1<sup>st</sup> place was awarded to Yukwah Kwok—*Activation of Aedes aegypti Mosquito Immune Signaling Reduces Infection by Heartworm Dirofilaria immitis*; Kathryn Short—*Re-directed T Cell Therapy in Canine B Cell Lymphoma* (2<sup>nd</sup> Place); and Jonathan Nagel—*Soluble AXL Decoy Receptor (S6-1) Improves Therapeutic Outcome in Mouse Model of Acute Myeloid Leukemia* (3<sup>rd</sup> Place). Faculty judges called a tie for first place in the Best Poster Awards: Talia Wong—*Role of Endothelial Specific NF-κB During Acute Infection with Toxoplasma Gondii* and Martina Jackson—*Mitochondrial Retrograde Signaling-induced Transcription Reprogramming in Canine Osteosarcoma Tumor Model*. 2<sup>nd</sup> Place Best Poster went to Jonathan Ferrari—*Production of an Anti-canine Programmed Death 1(cPD-1) Monoclonal Antibody for Immune Checkpoint Blockade*; and 3<sup>rd</sup> Place Best Poster was awarded to Sara Davenport—*Use of Topical Spray Containing Lidocaine to Mitigate Pain in Pigs Undergoing Castration*.



Yukwah Kwok & Dr. Michael Povelones

*continued on page 4*



Feini Qu



Jonathan Nagel



Talia Wong



Feini Qu

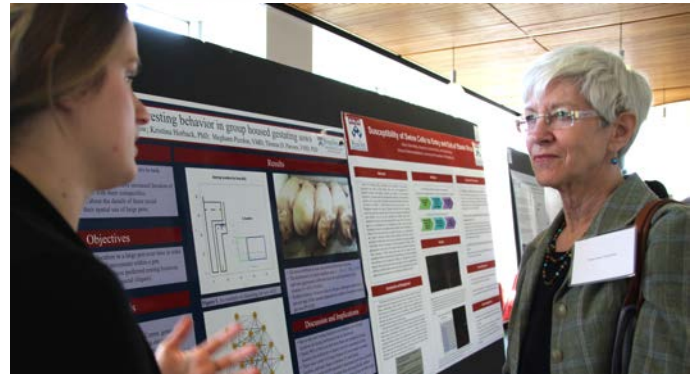




Sophie Eiger describes her poster to Dr. K Michel



Martina Jackson



Dean Joan Hendricks



Jonathan Ferrari introduces the keynote speaker

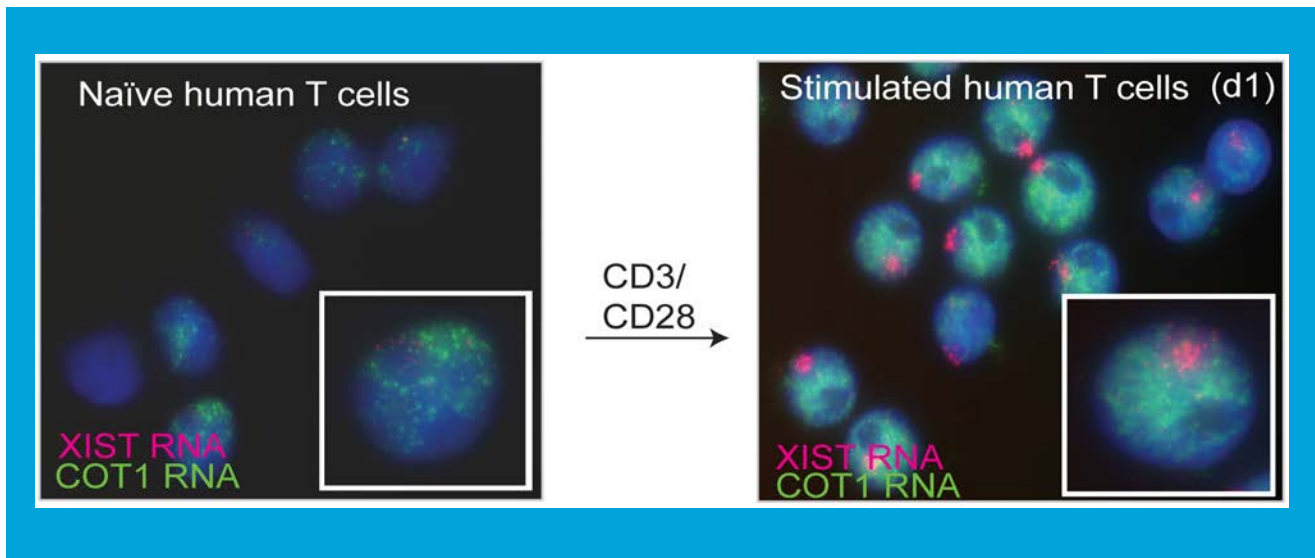


Jessica Piergiovanni, Emma LeBlanc, Sara Davenport, & Anna Martin



Sherrie Xie, Nathaniel Sotuyo, M. Noelle Knight, Jonathan Madara & Abigail Shearin

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along with some, but not all, heterochromatin modifications (Figure 1). These findings suggest that the inactive X could be more prone to partial reactivation in female lymphocytes. In support, using single-cell RNA fluorescence in situ hybridization, the Anguera lab found that autoimmunity-related X-linked genes are expressed from the inactive X in a subset of healthy female lymphocytes. These findings are the first to demonstrate gender-specific differences in gene dosage from the X chromosome and that female lymphocytes express higher levels of X-linked immunity-related genes, thus providing a potential mechanistic basis for enhanced female susceptibility to autoimmune disorders.

Looking ahead, Anguera and colleagues are investigating the location and level of transcriptional expression arising specifically from the inactive X in female B and T cells. Dr. Anguera is also working in collaboration with Dr. Michael Atchison in the Department of Biomedical Sciences to examine the mechanisms that bring XIST RNA transcripts back to the inactive X in activated lymphocytes. They found that deletion of YY1, a transcription factor that also has RNA binding activity, impairs the return of the XIST RNA transcript to the inactive X [6]. This work highlights a new role for YY1 in lymphocyte function, and offers new clues about how transcriptional silencing of the inactive X is maintained.



Dr. Montserrat with Jianle Wang and Camille Syrett.

Continued on page 6

***The X-linked long noncoding RNA lncRHOXF1 regulates the viral response in human placental progenitors***

The Anguera laboratory also investigates the physiologic role of lncRNAs important for early human development, which they model using human pluripotent stem cells. They have recently discovered a novel human-specific X-linked lncRNA, which they have named lncRHOXF1, that is abundantly expressed in human trophoblasts, the progenitor cells that form the placenta (Penkala, et al, under revision for *MCB*). Using gain and loss of function approaches with *in vitro* derived trophoblast cells, Dr. Anguera and colleagues were surprised to see that lncRHOXF1 knockdown in human trophoblast progenitors increased expression of viral response genes, and induced a type I interferon response. Working together with Dr. Carolina Lopez from the Department of Pathobiology at Penn Vet, they discovered that lncRHOXF1 RNA is the first example of a lncRNA that regulates the host response to viral infections in the early human placenta. Future studies will examine the molecular mechanisms of gene repression mediated by lncRHOXF1 RNA in human trophoblasts, and will shed light on novel host-pathogen interactions required during early human development.

Dr. Anguera's research is funded by an NIH/NICHHD (K12) award, McCabe Foundation, Pennsylvania Health Research Formula Fund, and the University Research Foundation. Her laboratory is located in Rosenthal 304 and her office is in Old Vet 390EB.

## REFERENCES

1. Zhou Y, Yuan J, Pan Y, Fei Y, Qiu X, Hu N, Luo Y, Lei W, Li Y, Long H, et al: T cell CD40LG gene expression and the production of IgG by autologous B cells in systemic lupus erythematosus. *Clinical immunology* 2009, 132:362-370.
2. Lee JT, Bartolomei MS: X-Inactivation, Imprinting, and Long Noncoding RNAs in Health and Disease. *Cell* 2013, 152:1308-1323.
3. Payer B, Lee JT: X chromosome dosage compensation: how mammals keep the balance. *Annu Rev Genet* 2008, 42:733-772.
4. Anguera MC, Sadreyev R, Zhang Z, Szanto A, Payer B, Sheridan SD, Kwok S, Haggarty SJ, Sur M, Alvarez J, et al: Molecular signatures of human induced pluripotent stem cells highlight sex differences and cancer genes. *Cell Stem Cell* 2012, 11:75-90.
5. Yildirim E, Kirby JE, Brown DE, Mercier FE, Sadreyev RI, Scadden DT, Lee JT: Xist RNA is a potent suppressor of hematologic cancer in mice. *Cell* 2013, 152:727-742.
6. Wang J, Syrett CM, Kramer MC, Basu A, Atchison ML, Anguera MC: Unusual maintenance of X chromosome inactivation predisposes female lymphocytes for increased expression from the inactive X. *Proc Natl Acad Sci U S A* 2016.



*Publications & Honors*



Xu Z, Takizawa F, Parra D, Gomez D, von Gersdorff Jorgensen L, LaPatra SE, & **Sunyer JO** (2016) Mucosal Immunoglobulins at respiratory surfaces mark an ancient association that predates the emergence of tetrapods. *Nat Commun.* 2016 Feb 12;7:10728

**Keynote speaker** at the 2016 Veterinary Vaccinology Network Conference, Manchester, UK, "Recent advances in fish mucosal immunity: Implications for the development of effective fish vaccines"



Hunt VL, Tsai JJ, Coghlan A, Reid AJ, Holroyd N, Foth BJ, **Lok JB** et al. The genomic basis of parasitism in the *Strongyloides* clade of nematodes. *Nat Genet.* (2016);48:299-307

Albarqi MM, Stoltzfus JD, Pilgrim AA, Nolan TJ, Wang Z, Kliever SA, Mangelsdorf DJ & **Lok JB**. Regulation of life cycle checkpoints and developmental activation of infective larvae in *Strongyloides stercoralis* by dafa-chronic acid. *PLoS Pathog.* (2016) 12(1):e1005358.

**Dr. Lok** was also featured in a **cover story**: The Developmental Biology of Parasitic Nematodes *PLOS Pathogens* 12(3): e1005328. March 10, 2016



**DW Pitta**, N Indugu, S Kumar, B Vecchiarelli, R Sinha, LD Baker, B Bhukya, Ferguson JD (2016): Metagenomic assessment of the functional potential of the rumen microbiome in Holstein dairy cows. *Anaerobe.* 201638:50-60.

**DW Pitta**, **Dou Z**, Kumar S, Indugu N, Toth JD, Vecchiarelli B, and Bhukya B (2016) Metagenomic evidence of the prevalence and distribution patterns of antimicrobial resistance genes in dairy agroecosystems *Foodborne Pathog Dis.* April 5 Epub ahead of print.



T Ruane, **Mark Haskins**, A Cheng, P Wang, **G Aguirre**, VW Knox IV, Y Qi, T Tompkins, CA O'Neill, Pharmacodynamics, pharmacokinetics and biodistribution of recombinant human Nacetyl galactosamine 4-sulfatase after 6 months of therapy in cats using different IV infusion durations, *Mol Gen Metab* 117 (2016) 157-163

Pang, B, Yee, KK, Lischak, FW, Rawson, NE, **Haskins, ME**, Wysocki, CJ, Craven, BA, Van Valkenburgh, B The influence of nasal airflow on respiratory and olfactory epithelial distribution in felids. (2016) *J Exp Biol.* 2016 Apr 4. pii: jeb.131482. [Epub ahead of print]



**Gustavo Aguirre VMD, PhD**, professor in the Department of Clinical Studies and head of the **Ophthalmology Research Group** at Penn Vet has been awarded the prestigious **2016 Louis Braille Award** for his pioneering work in the treatment for vision disorders. Dr. Aguirre is a professor of medical genetics and ophthalmology. He has investigated the genetic basis of a wide variety of inherited blinding diseases and even restored the vision in dogs.

Photoreceptor proliferation and dysregulation of cell cycle genes in early onset inherited retinal degenerations. KL Gardiner, Downs L, Berta-Antalics AI, Santana E, Aguirre, GD, & Genini S. *BMC Genomics* 2016 17(1) 221.



Kristin Gardiner

*Awards*

**Dipti Pitta**

Purina Animal Health  
Honey Bee Gut Microbiome Project  
3/1/2016-2/28/2019  
\$300,000

**Ashley Boyle**

Grayson Jockey Club  
Validation of stall-side strangles diagnosis using LAMP  
4/1/2016-3/31/2017  
\$22,330

**Angelica Ortiz**

NIH/NCI F32-CA-206431  
IFNARI downregulation in melanoma cells and stromal cells promotes melanoma progression and pulmonary metastasis  
9/1/16 – 8/31/18 \$110,412

**Sophie Eiger**

Morris Animal Foundation  
Veterinary Student Scholar  
Developing novel stromal cell-targeted approaches to treat canine mammary gland tumors  
5/15/16-8/15/16 \$5,000

**Shelley Rankin and Stephen Cole**

ACVD:A Molecular Bead-Based Assay for Molecular Detection of Cutaneous Infectious Organisms  
7/1/16-6/30/17 \$16,500

**Dieter Schifferli**

NIH R21  
Genetic detminants of systemic host-adapted Salmonella  
2/15/16-1/31/18 \$275,000

**Charles Vite**

ITMAT Pilot Program in Comparative Animal Biology  
Cell based therapy for seizures by transplantation of human stem cell derived inhibitory interneurons modified for rapid maturation-study in dogs  
2/1/2016-1/31/2017 \$45,000

**Manti Guha,**

University Research FDN  
Establishing the Contribution of mtDNA Depletion Towards Metastasis Using a Novel PDX Model. 3/1/16-2/1/28/16 \$50,000

**Oriol Sunyer**

USDA NIFA award  
Collaborative Immune Reagent Network: Aquacultured Species to generate antibody reagents  
5/1/16-4/30/19 \$500,000

**James Serpell**

Tufts University  
Animal Ownership Interaction Study.  
1/1/16-10/31/17 \$20,356

**Keiko Miyadera**

University Research FDN  
Molecular Characterization of a Multigenic Canine Model of Retinal Degeneration. 3/1/16-2/1/28/16  
\$50,000



**Morris Student Scholar Award**

The Morris Animal Foundation selected **Sophie Eiger, V'18** to receive the **Veterinary Student Scholar Award**. Sophie's award winning project is for her study on determining if targeting of surrounding non-malignant cells that support the growth and spread of tumor cells is effective as a novel approach to treating canine mammary gland tumors.

Dr. Ellen Puré, chair of the Department of Biomedical Sciences is her mentor.



A Beautiful Friendship—and an interest in canine cancer research

Modern Eye, the hip optical boutique and full-service optometrist's office at 3419 Walnut Street, a campus fixture for over 24 years, has forged a very special relationship with Penn Vet. Pet-loving owner/optometrist Dr. Chris Anastasiou and his team have collected donations for Penn Vet canine cancer research on a daily basis, encouraging contributions to a prominently displayed piggy bank in exchange for eyeglass adjustments and other services; as well as having staged several day-long trunk shows of fashion eyewear, with a percentage of the sales donated to Penn Vet and then matched by Modern Eye. In appreciation of this special bond a discount of **25%** towards one or more complete pair of eyeglasses will be offered to those faculty, students, and support staff of the Penn Vet School who can produce a valid PENN I.D. Some restrictions apply.

**Penn Vet Research Newsletter**

Phillip Scott, PhD

**Office of the Vice Dean for Research and Academic Resources**

Gayle Joseph, Editor  
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