

WHIP 2021

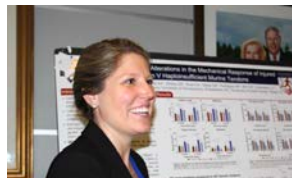
IMMUNOPARASITOLOGY

WOODS HOLE
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NIH BIOSKETCH
& OTHER SUPPORT

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STUDENT
RESEARCH DAY

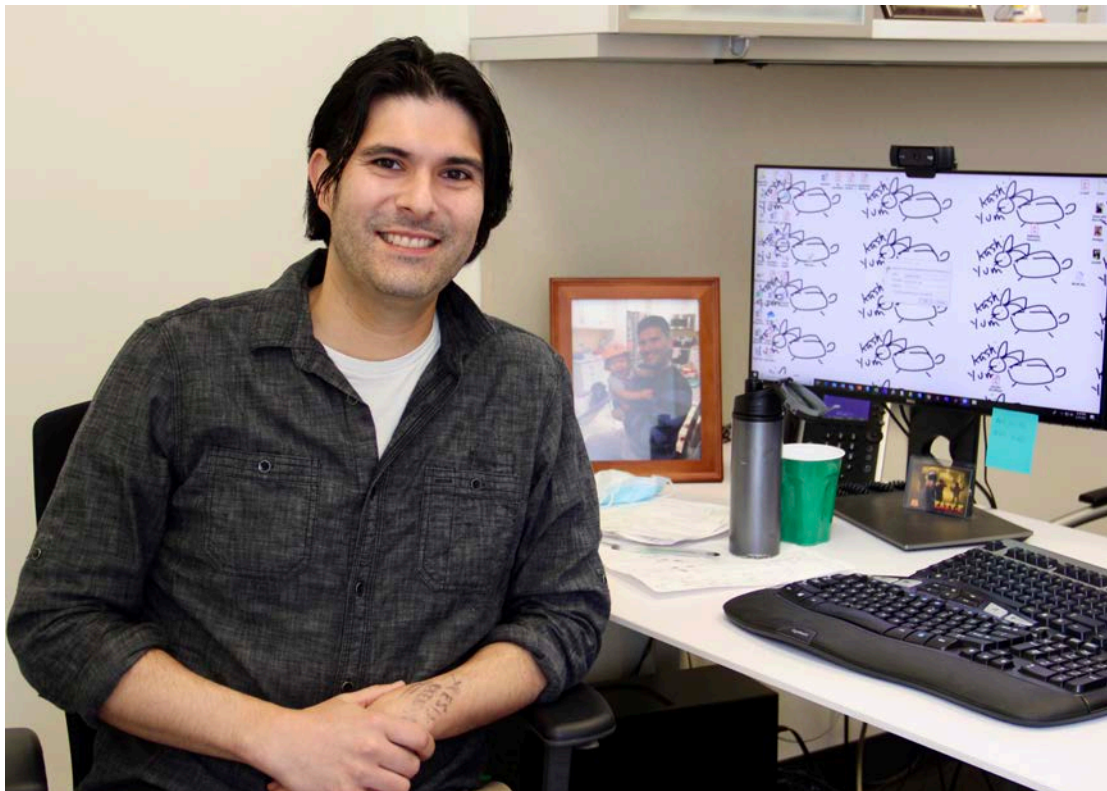
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NEW
FLOW CYTOMETER

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NEWSLETTER



Chromatin Biology and Cancer

Dr. M. Andrés Blanco is an assistant professor in the Department of Biomedical Sciences who was recruited to Penn Vet in 2018. Dr. Blanco received a B.A. from Cornell University with a double major in Biological Sciences and Philosophy. It was here that Dr. Blanco developed his passion for research, performing an undergraduate thesis project on the evolutionary basis of aging and longevity under the mentorship of Dr. Paul Sherman. Dr. Blanco then earned his Ph.D. in Molecular Biology from Princeton University, where he studied the molecular and genomic mechanisms of breast cancer metastasis in the lab of Dr. Yibin Kang. Here Dr. Blanco expanded his knowledge of

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molecular cancer biology, and also acquired expertise in bioinformatics and statistical analysis of genome-scale datasets. Dr. Blanco then moved to Harvard Medical School for his postdoctoral research at in the laboratory of Dr. Yang Shi, a leader in epigenetics and chromatin biology.

As a postdoc, Dr. Blanco's research in basic chromatin biology led to the discovery of a novel metazoan chemical modification of DNA – N6-methyladenine (6mA) – present in the genome of *C. elegans*. This finding challenged the widely accepted dogma that 5-methylcytosine (5mC) is the sole DNA modification in metazoan organisms, opening up a new area of investigation in epigenetic chromatin modifications. After completing this study, Dr. Blanco merged his training in chromatin biology with his background in cancer biology to initiate studies in cancer epigenetics, focusing on the (dys)regulation of cellular identity decisions in oncogenic transformation and progression.

Acute myeloid leukemia: a case of mistaken identity

Acute myeloid leukemia (AML) is a prominent example of the ramifications of improper cell fate control. AMLs are universally characterized by a "differentiation block" – an inability to execute normal myeloid maturation programs that leaves AML blasts stuck in a highly proliferative, stem cell-like state. A breakthrough in AML therapeutics came with the development of "differentiation therapy" in which treatment with all *trans* retinoic acid (ATRA) induces terminal myeloid differentiation, thereby promoting cell cycle exit and eventual death by apoptosis. Remarkably, this low-toxicity treatment is almost universally curative in the promyelocytic (APL) AML subtype. Unfortunately, differentiation therapy has not been successful in other AML subtypes thus far. However, the possibility of achieving differentiation therapy in non-APL AML has gained recent traction due to the emergent theme that epigenetic regulators are especially important in sustaining the differentiation block. A greater understanding of this process will be crucial for designing pro-differentiation-based therapeutic strategies in non-APL AML.

To identify novel regulators of the non-APL AML differentiation block, Dr. Blanco's laboratory turned to one of their most commonly used discovery tools: CRISPR-Cas9-based genetic screening. Utilizing chromatin-focused sgRNA libraries, they devised a screening system to identify genes whose knockout induces myeloid differentiation in AML cells. Through these screens, Dr. Blanco's group identified the histone acetyltransferase KAT6A as a novel driver of AML differentiation arrest. They found that KAT6A

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Aguirre GD, Cideciyan AV, Dufour VL, Ripolles-García A, Sudharsan R, Swider M, Nikonov R, Iwabe S, Boye SL, Hauswirth WW, Jacobson SG, and **Beltran WA** (2021) Gene therapy reforms photoreceptor structure and restores vision in NPHP5-associated Leber congenital amaurosis. *Mol. Ther.* <https://doi.org/10.1016/j.ymthe.2021.03.021>



JL Rokhsar JL, **J Canino**, K Raj, S Yuhnke, J Slutsky, U Giger. (2021) Web resource on available DNA variant tests for hereditary diseases and genetic predispositions in dogs and cats: An Update. *Hum Genet.* doi: 10.1007/s00439-021-02256-5.



DW Pitta, A Melgar, N Indugu, C Pappalardo, ML Hennessy, B Vecchiarelli, V Shabtai, M Kindermann, N Walker, AN Hristov (2021). Temporal changes in total and metabolically active ruminal methanogens induced by 3-nitrooxypropanol in dairy cows. *J Dairy Sci (In Press)*.

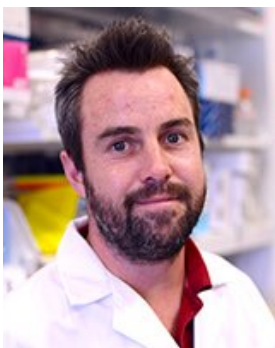


NIH News—reminders of changes—NIH has updated the guidance for the new [Biosketch](#) and [Other Support](#) forms. The new effective date is January 25, 2022. All Biosketch and Other Support forms submitted as part of proposal applications, JIT requests, and RPPRs should be in the current format until January 25, 2022. **However, the requirement to disclose all sources of research support, including support to the individual PI/PD or key personnel as well as in-kind support remains effective May 25, 2021 in compliance with [NOT-OD-21-073](#).**

The **Annual Woods Hole Immunoparasitology Meeting** was held on April 11-14, 2021. This year’s all-virtual program featured cutting edge science from colleagues across the globe. Penn Vet’s Phil Scott, Christopher Hunter and De’Broski Herbert served on the Advisory Committee. The image used on the program cover is from our own Dr. David Christian—an image of a milky spot from a mouse omentum containing cells infected with *Toxoplasma gondii*. “This conference has no equal for attendees to learn cutting-edge concepts in basic immunology and host-parasite interactions,” said Dr. Herbert.



Awards and Honors:

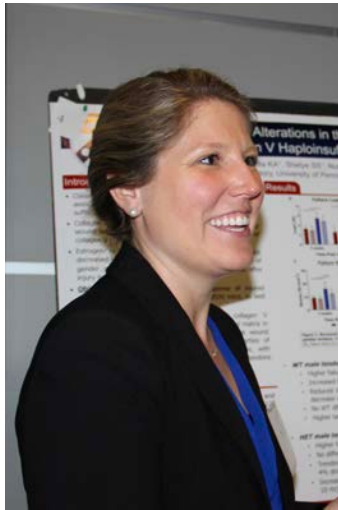


Matt Atherton BVS, PhD, DECVIM(oncology), Shuman Translational Research Fellow in the Department of Biomedical Sciences has received a NIH/NCI Ko8 Mentored Clinical Scientist Research Career Development Award. It is entitled "Prognostic and Therapeutic Implications of IFNAR1 Signaling on CAR T Cell Therapy for Cancer". Congratulations!

Ashley Vanderbeck V’24 is a VMD/PhD student with expected graduation of Spring 2024 and her mentor is Dr. Ivan Maillard (Perelman School of Medicine). As part of the [UPENN COVID-19 Processing Unit](#), Ashley was a co-author in an observational study in *SCIENCE* entitled “Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications” (<https://pubmed.ncbi.nlm.nih.gov/32669297/>). She has already received a NIH F31 Predoctoral Fellowship, and in 2021 Ashley won two poster prizes at the Institute for Regenerative Medicine Symposium and the 2nd Annual Symposium on Epigenetics, Immunity & Cancer.



ANNUAL STUDENT RESEARCH DAY



Jaclyn Carlson

Under pandemic conditions, the Penn Vet **Annual Student Research Day** was held virtually on Friday, March 19, 2021. Over 200 students, faculty, postdocs and mentors attended the event. 43 Abstracts were submitted and six students (VMD and VMD/PhD) were competitively selected to give oral presentations on their research projects. Additionally, Research Club students presented a poster video.

Jaclyn Carlson: Collagen V Haploinsufficiency Results in Delayed Healing and Altered Wound Matrix Post-Injury in Murine Tendons (mentor: Dr. L. J. Soslowsky)

Megan Clark: Remodeling the Electron Transport Chain in Macrophages by a Peptide-miRNA Axis (mentor: Dr. Jorge Henao-Mejia)

Martha Stone: Chemogenetic Activation of Orexin Neurons Accelerates Emergence from Isoflurane Anesthesia (mentor: Dr. M. Kelz)

Justine Cianci: Qualitative Assessment of Fracture Configuration and Subchondral Bone Pathology in Horses with Lateral Condylar Fractures of MC/MT₃ (mentor: Dr. K. Ortved)

Victoria Kranz: Sow Familiarity and Aggression at Post-gestation Mixing (mentor: Dr. M. K. Pierdon)

Julianne Nolte: Non-canonical NF- κ B Signaling in Lymphatic Vessels Regulates Immune Homeostasis in the Lung (mentor: Dr. M. May).

Faculty judges selected the following posters as “Best Posters”:

Matthew Boulanger: Identifying Sow Lameness Utilizing Time-of-Flight Cameras (mentor: Dr. Thomas Parsons)

Eli Braun: Development of a RT-LAMP Assay for the Detection of SARS-CoV-2 in Companion Animal Samples at Ryan Veterinary Hospital (mentors: Drs. Stephen Cole and Shelley Rankin)

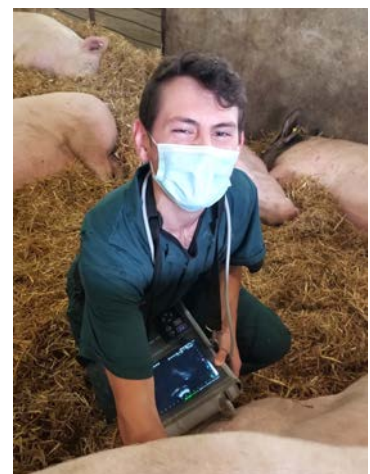
Brinkley Raynor: The impact of the COVID-19 pandemic on rabies reemergence in Latin America (mentor: Dr. Ricardo Castillo-Neyra)



Justine Cianci

Ariel Shepley-McTaggart: Identification of a SARS-CoV-2 E/Host ZO-1 Interaction: Implications for Tight Junction Damage in Human Lung Epithelial Cells (mentor: Dr. Ronald Harty).

A gift from the Martin M Kaplan V⁴⁰ Lectureship enabled support of the keynote lecture given by Theresa Alenghat VMD, PhD, from University of Cincinnati, School of Medicine, Cincinnati Children’s Hospital. Dr. Alenghat spoke on “Epigenetic Regulation of the Host-Microbiota Relationship”.



Matthew Boulanger

cooperates with ENL, an associated chromatin-binding protein, to drive high expression of AML oncogenes such as *MYC*, *MYB*, and *FLT3*. According to their mechanistic model, KAT6A localizes to oncogene promoters where it catalyzes histone H3K9 acetylation (H3K9ac); this recruits ENL, which binds H3K9ac with high affinity. ENL, in turn, recruits transcriptional elongation machinery that stimulates high levels of RNA Pol III transcription. Phenotypically, Dr. Blanco's group found that loss of KAT6A depletes the "stemness" of AML cells, leading to de-repression of differentiation programs and reduced proliferation both *in vitro* and in AML mouse models (Figure 1). Accordingly, they propose that KAT6A may represent a new, high-potential therapeutic target for non-APL AML.

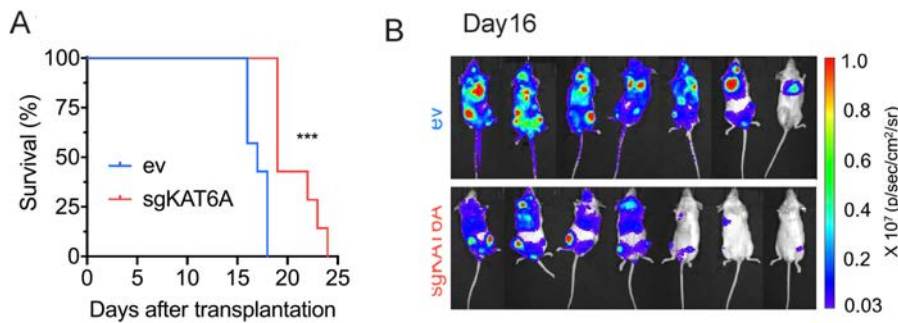


Figure 1. (A) CRISPR knockout (KO) of KAT6A extends the survival of mice in an AML transplant experiment (left). (B) Representative bioluminescent imaging of AML disease burden in control (top) and KAT6A KO (bottom) mice.

The point of no return

To understand how cell fate regulation is corrupted in cancer cells, it is critical to understand the mechanisms that govern cell identity decisions in normal cells. Accordingly, Dr. Blanco's lab pairs their AML studies with investigations into the normal myeloid cell differentiation program. In a study Dr. Blanco initiated as a postdoc and completed as a PI, he investigated one of the most fundamental aspects of cellular differentiation: its unidirectionality. To understand how this irreversibility is achieved, Dr. Blanco used a primary cell model of myeloid differentiation in which inducible expression of the transcription factor *Hoxa9* determines whether cells will remain in the progenitor state (*Hoxa9* ON) or terminally differentiate (*Hoxa9* OFF). By toggling *Hoxa9* on, off, and on again, Dr. Blanco found that the myeloid differentiation program is reversible via reactivation of *Hoxa9* for up to 72 hours. However, after 72 hours, the cells pass an epigenetic "point of no return," after

Microbiome Webinar



Dan Beiting co-hosted a webinar with NIH/NIAID on Thursday, May 6, 2021. The webinar demonstrated how researchers can use web-based tools to analyze microbiome data. This was a great opportunity for researchers starting out in microbiome analyses or those with more experience who are planning to investigate new, more streamlined tools and features. The webinar focused on using web resources for the analysis of 16S rRNA microbiome

Publication



Han Z, Ye H, Liang J, Shepley-McTaggart A, Wrobel JE, Reitz AB, Whigham A, Kavelish KN, Saporito MS, **Freedman BD**, Shtanko O, and **Harty RN**. Compound FC-10696 Inhibits Egress of Marburg Virus. *Antimicrob Agents Chemother.* 2021. doi: 10.1128/AAC.00086-21. Epub ahead of print. PMID: 33846137.

which reactivation of Hoxa9 fails to bring cells back to the progenitor state.

Via in-depth epigenomic profiling of the differentiation program, Dr. Blanco derived a molecular model of the "point of no return" based on transcription factor (TF)-chromatin interactions. In this model, the chromatin configuration of progenitor state cells is relatively "open" – regulatory elements such as enhancers are active and accessible. As cells differentiate, progenitor state enhancers start to close as their TFs get silenced. If Hoxa9 is re-activated before the commitment point, its enhancers remain sufficiently open to permit its binding and consequent restarting of the progenitor state transcriptional program. However, after the commitment point, these enhancers are almost completely closed, preventing Hoxa9 chromatin binding and reactivation of progenitor gene expression programs. This model contrasts with most proposed – but generally untested – models of differentiation commitment, and it will be of interest to determine which models apply in other cell types and developmental stages.

Looking forward

As Dr. Blanco's laboratory grows, he aims to expand his studies on the epigenetic regulation of cell fate decisions and how this process breaks down in cancer. In AML, he will continue his studies on KAT6A and, more generally, how regulatory chromatin complexes cooperate with TFs to regulate gene expression programs driving the differentiation block. Additionally, in close collaboration with Dr. Chris Lengner at Penn Vet, he will study cell fate regulation in solid tumor contexts such as colorectal cancer. Ultimately, the Blanco laboratory aims to help unlock the remarkable potential of differentiation therapy in a wide range of oncogenic contexts.

Dr. Blanco's office is located on the 4th Floor Hill Pavilion, room 414.

Reference

EL Greer, MA Blanco, L Gu, E Sendinc, J Liu, D Aristizabal-Corrales, C-H Hsu, L Aravind, C He, and Y Shi (2015) DNA Methylation on N6-Adenine in *C. Elegans* *Cell* 161(4):868-78.

MA Blanco, D Sykes, L Gu, M Wu, R Petroni, R Karnik, M Wawer, J Rico, H Li, W Jacobus, A Jambhekar, S Cheloufi, A Meissner, K Hochedlinger, D Scadden, Y Shi (2021) Chromatin state barriers enforce an irreversible mammalian cell fate decision. *bioRxiv* 2021.05.12.443709 (2021) doi:10.1101/2021.05.12.443709.

Theriogenologist of the Year

Dr. Gary Althouse, Department of Clinical Studies, New Bolton Center, has been named Theriogenologist of the Year by the American College of Theriogenologists!! This is in honor of Gary's work in andrology; both clinical work for the porcine producers nationally for whom his laboratory serves as the major reference laboratory for quality control; and for his research on semen extender diluents, evaluation of sperm functional markers, and development of new methodologies in the analysis of semen and sperm quality.



NBC Research in the News!



Congratulations to **Mary Robinson, PhD, VMD**, the Pennsylvania Equine Toxicology & Research Center, and authors Joanne Haughan, Zibin Jiang, Darko Stefanovski, Kaitlyn Moss and Kyla Ortved for having their paper, “Detection of Intra-articular Gene Therapy in Horses using Quantitative Real Time PCR in Synovial Fluid and Plasma” (*Drug Test Anal.* 2020 12(6): 743-751), featured in *Horsetalk* (March 12, 2021). The paper describes an effective method to detect gene doping (administering gene-like molecules to make the horse’s own tissues produce the desired performance-affecting compounds) in racehorses.

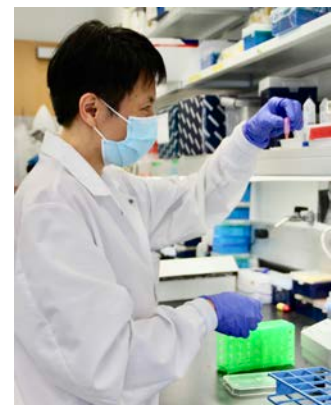
Congratulations also to **Drs. Catie Torcivia** and **Sue McDonnell** on the AMAZING response to their paper, “Equine Discomfort Ethogram,” in which they describe and illustrate, including videos, a catalog of behaviors (an ethogram) associated with equine physical discomfort related to different body systems. This paper (<https://www.mdpi.com/2076-2615/11/2/580>) has over 8000 full paper views. and downloads in 12 days!

The **Breast Cancer Alliance** has awarded **Dr. Rumela Chakrabarti**, Department of Biomedical Sciences, \$100,000, as an Exceptional Project Grant for her project entitled: A novel combination immunotherapy to improve treatment of metastatic triple negative breast cancer. Her recent Nature Communications article is entitled Dll1+ quiescent tumor stem cells drive chemoresistance in breast cancer through NF-κB survival pathway. *Nat Commun* 12:432(2021).



Stephen Cole VMD, assistant professor of clinical microbiology in the Department of Pathobiology, presented on teaching disaster preparedness and interdisciplinary teamwork in a virtual environment at the Pandemic Pedagogy Research Symposium on May 5, 2021. The Covid-19 global pandemic brought many challenges; the symposium focused on how higher education leaders have been at the forefront of research and innovation in determining how universities should modify their teaching strategies to optimize student learning.

PENN’s **Research Facilities Development Fund**: To meet the needs of expanding research requiring sophisticated flow cytometers, Phillip Scott, Vice Dean for Research and Academic Resources, announced an award of \$200,000 for the acquisition of a new flow cytometer. The **BD Symphony A3 Lite Flow Cytometer** is a state-of-the-art flow cytometer equipped with 5 lasers, superior optics, and low-noise electronics, allowing the detection of up to 23 distinct fluorescent signals. The cytometer is a fully enclosed system that allows analysis of normal or infectious materials and is a next-generation instrument that will enhance the capabilities of the Penn School of Veterinary Medicine beyond what is currently possible for investigators.



Qun Fang

THE PENN RESEARCH PORTAL— A new personalized homepage is announced. Faculty can engage with the research information systems that they are currently using in an environment that uses single site sign-on (SSO) so they will not have to continually re-enter their Penn credentials to access each system. In addition, the homepage includes a Current Funding financial widget that will provide faculty with easy access to the grants on which they are currently principal investigator so that they can easily see information regarding budget spent, budget encumbered, budget remaining, time remaining, and a high-level recent 30-day expense breakdown on each of their grants.

<https://portal.research.upenn.edu>



MARK YOUR CALENDARS The annual Cores Day will be held on Thursday, September 20, 2021. The event showcases the many outstanding biomedical research resources and services available throughout the campus. It is an opportunity for students, faculty, and staff to interface with a multitude of research core facilities. Stay tuned for more details.



Publications



Eman A Anis

Anis E, Turner G, **Ellis JC**, Di Salvo A, Barnard A, Carroll S, **Murphy L**. Evaluation of a real-time RT-PCR panel for detection of SARS-CoV-2 in bat guano. *J. Vet. Diagn. Invest.* 2021 Mar;33(2):331-5.

Hennessy M, Indugu N, Vecchiarelli B, **Bender J**, Pappalardo C, Leibstein M, Toth J, **Stefanovski D**, Katepalli A, Garapati S & **Pitta D** (2021) Short communication: Comparison of the fecal bacterial communities in diarrheic and nondiarrheic dairy calves from multiple farms in Southeastern Pennsylvania. *J Dairy Sci* (In Press).



Joseph Bender

Recent Awards (direct costs)

Anna Kraus Gelzer

ACVIM Foundation
 Characterization of buccal mucosal cells from boxers with ARVC
 \$14,933. 1/1/21—1/1/23

Cynthia Otto

Dept of Agriculture
 A proof of concept: are detection dogs a useful tool to screen White-tailed deer (*Odocoileus virginianus*) feces for CWD?
 \$220,224. 3/1/21—2/28/23

Mark Oyama

Nestle Purina Petcare
 Targeted Metabolomics in Dogs with Mitral Valve Disease
 \$11,813. 2/1/21—1/31/22

Charles Vite

StrideBio, Inc
 Biodistribution study in normal cats and Intracisternal administration of novel AAV-fNPC1 to restore expression and treat cerebellar ataxia in feline NPC1
 \$298,018. 2/11/21—12/31/22

Gus Aguirre

Amer. Spaniel Club Health & Rescue Foundation
 Molecular Genetic Studies of Inherited Cataracts in the American Cocker Spaniel
 \$87,173.00 1/1/21—6/30/22

Sue Volk

AKC Canine Health Foundation
 Tumor-permissive collagen signatures in canine mammary gland tumors: development of prognostic markers and targeted therapies for improved outcomes
 \$182,845. 3/1/21—2/28/23

Swarna Bais/Robert Greenberg

NIH R21—Oncolytic virus targeting Schistosomes
 \$275,000. 3/16/21—2/28/23

Raimon Duran-Struuck

ITMAT-TAPIMAT UPENN grant
 CAR Treg technology for immune tolerance to skin allografts—a pre-clinical model of skin grafting and vascular tissue allotransplantation
 \$150,000. 3/1/2021 – 02/28/2023

Ron Harty

NIH R21
 Role of Host Angiotensin as a Central Regulator of Filovirus Egress and Dissemination
 \$275,000 3/31/21— 2/28/23.

De'Broski Herbert

NIH U01 Supplement Award
 Trefoil Factor Proteins Regulate Inflammation and Immunity Importance of Trefoil factor 3-LINTO2 interactions during infection of human nasal epithelial cells w/ SARS-Cov-2.
 \$343,891 11/25/20—7/31/21

Matthew Atherton

NIH NCI K08—Prognostic and Therapeutic Implications of IFNAR1 Signaling on CAR T Cell Therapy for Cancer
 \$711,345. 7/1/21-6/30/2026

Ellen Puré

ITMAT Pilot Grant Translational Biomedical Imaging Center Companion diagnostic and therapeutic biomarker imaging tools for understanding CAR T cell efficacy
 \$50,000. 03/01/21—2/28/2022

Chris Hunter

NIH U01 (sub to University of Colorado)
 Mechanisms of combined CD40/TLR adjuvant-elicited cellular immunity
 \$799,998. 3/25/21—2/28/26

Andrew van Eps

Grayson Jockey Club Research Foundation
 Understanding and preventing supporting limb laminitis
 \$148,185 4/1/21—3/31/23

Dr. Ashley Boyle

Boehringer Ingelheim Vetmedica
 Guttural Pouch Microbiome in Health and Disease
 \$15,000.00. 1/1/21-12/31/21

Dr. Joseph Bender

Pennsylvania Department of Agriculture
 Evaluation of reproductive efficiency on Pennsylvania dairy farms. \$10,000.00. 1/1/21-6/30/21

Dr. Katrin Hinrichs

American Quarter Horse Foundation
 Effect of Day Estrus Cycle at TVA on Rates of *in vitro* Oocyte Maturation and Blastocyst Production after ICSI
 \$68,590.67. 10/1/21-9/30/22

Dr. Katrin Hinrichs

National Institute of Food and Agriculture/Department of Agriculture
 PENV-FY2021 Capacity Grant
 \$68,371.00. 10/1/2020-9/30/22

Dr. Michaela Kristula

Pennsylvania Department of Agriculture
 Novel implementation of FARM on a Pennsylvania Dairy Farm pilot project
 \$9,348.00. 1/1/21-6/30/21



Blanco Laboratory: Josh Rico, Maria Carrera, Yumi Yan, and Dr. Andres Blanco



The Penn Vet Research Newsletter—a digital edition during the COVID-19 pandemic. 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

[Research News Link](#)

University of Pennsylvania School of Veterinary Medicine