6th Annual CU MSTP Retreat

Celebrating 30 years of NIH funding and 40 years as an MD-PhD program

Saturday April 20th, 2024

Krugman Hall, RC2

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Cancer Center

NCI-DESIGNATED COMPREHENSIVE CANCER CENTER

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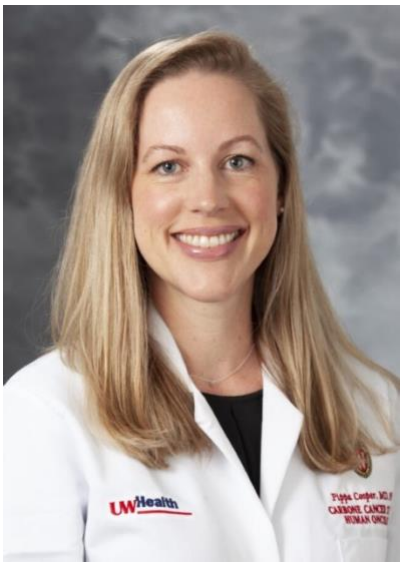
DEPARTMENT OF MEDICINE

Retreat Schedule

Time	Session
9:00-9:30 AM	**Registration, Breakfast, & Welcome** *Cara Wilson, MD*
9:30-10:30 AM	**Career Panel**
10:30-11:30 AM	**Keynote I** *Pippa Cosper, MD, PhD*
11:30-11:40 AM	**Break**
11:40-12:30 PM	**Student Oral Presentations I** *Kelsey Kines* *Thomas Forman*
12:30-1:30 PM	**Lunch & Program Address** *Arthur Gutierrez-Hartmann, MD* *Excellence in Service Award*
1:30-2:30 PM	**Keynote II** *Taraz Samandari, MD, PhD*
2:30-3:20 PM	**Student Oral Presentations II** *Lily Nyugen* *Bruce Kirkpatrick*
3:20-3:30 PM	**Break**
3:30-4:30 PM	**Keynote III** *Craig van Horne, MD, PhD*
4:30-4:45 PM	**Flash Talks** *Hei-Yong (“Grant”) Lo* *Ashlyn Stahly*
4:45-5:45 PM	**Poster Session & Refreshments**

Keynote Speakers



Pippa Cosper, MD, PhD

Assistant Professor of Radiation Oncology at the University of Wisconsin-Madison

Dr. Cosper received her B.S. in Biochemistry from the University of Texas at Austin. After taking 2 years off to coordinate clinical trials, she enrolled in the Medical Scientist Training Program at the University of Colorado where she joined the lab of Dr. Leslie Leinwand, an HHMI Professor in the Department of Molecular, Cellular, and Developmental Biology at the University of Colorado, Boulder. During this time, she studied the mechanisms underlying cardiac muscle atrophy due to cancer and was the first to establish and describe a murine model of this specific type of cachexia. Following medical school, Dr. Cosper started her residency in Radiation Oncology at Washington University in St. Louis. She was admitted to the B. Leonard Holman Research Pathway from the American Board of Radiology which provided 18 months of fully protected research time during residency. During this time, she studied gene expression differences in paired cervical tumor biopsies before and during chemoradiation to determine genes associated with radiation resistance. This work revealed that maintenance of human papillomavirus (HPV) oncogene expression and a reduced local immune response were associated with a decreased response to chemoradiation and poor patient outcomes. This work led to an interest in how HPV modulates tumor biology and therapeutic response. Following residency, Dr. Cosper pursued further post-doctoral training at the University of Wisconsin-Madison, where she was able to continue her studies on HPV but was also introduced to the field of chromosomal instability (CIN) under Drs. Beth Weaver and Paul Lambert. There, she characterized a novel mechanism of HPV-induced chromosomal instability. She found that the E6 oncoprotein selectively degrades the mitotic kinesin CENP-E, which results in polar chromosomes and ultimately CIN and aneuploidy, which likely plays a role in tumorigenesis.

During her post-doctoral studies, she also studied how CIN, a continuous rate of chromosome missegregation over the course of multiple cell divisions, affects radiation sensitivity in head and neck cancer. Using engineered isogenic CIN and non-CIN cell lines, she showed that cells with higher levels of CIN at baseline are more sensitive to radiation because they are closer to their maximally tolerated threshold of chromosome loss. This was also shown to be true in patients: patients with laryngeal cancers with higher CIN have a better response to radiation therapy and have decreased local recurrence. The goal is to establish CIN as a biomarker to enable dose de-escalation in some patients or to inform that escalation of therapy will likely be necessary. Within this body of work, she has also shown that docetaxel, a microtubule stabilizing drug, radiosensitizes tumors by inducing multipolar spindles (a form of CIN) rather than causing mitotic arrest, challenging the dogma of the last 35 years.

Dr. Cosper became an Assistant Professor at the University of Wisconsin-Madison in 2022. Her lab currently focuses on utilizing errors in mitosis, or CIN, as an Achilles heel to promote radiation induced cell death. Her life-long goal is to have a deeper understanding of the tumor biology that drives radiation sensitivity and overall treatment response such that we can provide more personalized radiation therapy to improve patient outcomes and decrease treatment related toxicities. She treats cancer patients one day per week at a satellite clinic near Madison.

Dr. Cosper has received numerous early career awards including the ASCO Young Investigator Award, Fellowship awards from the Radiological Society of North America (RSNA), as well as a K08 award from the NCI during her post-doctoral studies. She was named a Forbeck Scholar from the William Guy Forbeck Foundation, which brings together “the most brilliant minds in cancer research” to advance the field. She is an Associate Senior Editor of Biology for Advances in Radiation Oncology, is committed to service with the American Society of Therapeutic Radiation Oncology (ASTRO) and participates in various foundation study sections. She is a frequent guest lecturer for the UW-Madison Radiobiology course, a Clinical skills course for MD students, and assorted virology classes.

Taraz Samandari, MD, PhD

Medical Epidemiologist
US Public Health Service (CDC), Captain (retired)

Dr. Samandari was trained at University of Colorado’s Medical Scientist Training Program, completing his PhD in Biochemistry in 1991 and his MD in 1993. From Denver, he left to serve as a resident in internal medicine at Vanderbilt University in Nashville, Tennessee, and as a fellow in infectious diseases in Baltimore at University of Maryland’s Center for Vaccine Development where he investigated the human immune response to Shigella vaccines.

Seeking to improve the lives of large populations, particularly those in developing countries, Dr. Samandari began his career at the Centers for Disease Control and Prevention (CDC) in 2001. For the duration of his tenure at the CDC, he remained within the National Center for HIV Viral Hepatitis STD and Tuberculosis Prevention as an officer of the US Public Health Service. During this period, he conducted research in medical epidemiology, participated in outbreak investigations, the immune response to vaccines and infectious diseases and conducted clinical trials for prevention of disease. Infectious diseases he studied with his colleagues included viral hepatitis A and B, anthrax during the 2001 attacks, tuberculosis, HIV and COVID-19. He has worked in countries and territories as far flung as Palau in the western Pacific, Alaska, Thailand, Kenya, Botswana and the United States. Dr. Samandari established collaborative projects with academia, government and donor organizations and throughout his career has had supervisory and financial responsibilities. He has held academic

positions with the University of Maryland and Emory University and served as an expert panelist at the World Health Organization.

Dr. Samandari has over 50 publications in peer-reviewed journals and served as a reviewer for 16 journals. Topics of his publications range from the human immune response to viruses and vaccines, to clinical trials for the prevention of TB, HIV and COVID-19, public health policy statements, outbreak investigations and large-scale health systems research for the prevention of HIV.

Craig G. van Horne, MD, PhD

Professor of Neurosurgery and Neuroscience
Co-Director of the Neurorestoration Center
Virginia T. Barrow Endowed Chair of Neurosurgery
University of Kentucky, College of Medicine

Dr. van Horne grew up in Colorado then graduated with a B.A. from Williams College where he authored an undergraduate thesis on nerve grafting in goldfish. Subsequently, he returned to the University of Colorado where he received an M.D. and Ph.D. from the department of Pharmacology under Professor Barry Hoffer. He completed his residency in Neurological Surgery from Brigham and Women's Hospital. After completing his residency, he remained in Boston at The Brigham becoming the Co-Director of the Neurosurgical Movement Disorders Program then the Chief of Neurological Surgery at St. Elizabeth's Medical Center before moving to the University of Kentucky where he is now Professor and Chair of the Department of Neurosurgery.

Dr. van Horne has been at the forefront of using deep brain stimulation (DBS) as a therapy for movement disorders and has over 20 years of experience implanting this therapy. However, from his time as an undergraduate, he has steadily advanced the concept of using cell-based therapies for repair of neurodegenerative diseases of the central nervous system. During his doctoral work and residency, his research concentrated on tissue grafting and transplantation strategies in animal models of Parkinson's disease before serving as the local implanting neurosurgeon for a trial investigating the xenografting of fetal porcine cells for Huntington's disease.

Since arriving at Kentucky, he has assembled a multi-disciplinary team that has made advances through multiple clinical trials including stem cell therapy for patients with chronic stroke symptoms and a series of three different trials to use reparative autologous peripheral nerve tissue as a source for altering neurodegenerative disease progression. This last set of trials involved a first-of-its-kind combination of DBS and cell therapy in what has been termed DBS-Plus. Dr. van Horne has designed, established and executed three different DBS-Plus trials beginning first with a pilot study, then a safety and feasibility study, and currently a Phase I trial to guide future efficacy studies. While the predominant focus of these studies has been on movement disorders, he has also expanded to

examining strategies for altering cognitive decline by targeting the nucleus basalis of Meynert. These trials have involved over 80 participants with PD thus making the University of Kentucky a leader in neurosurgical interventional cell-therapy.

An indirect benefit of the DBS-Plus trials is that Dr. van Horne has enabled the study of human peripheral nerve injury in a way that has not been previously possible because naïve and regenerative sural nerve tissue is collected from the same participant. His lab has established the only human peripheral nerve regeneration transcriptomic and proteomic database.

Dr. van Horne is an active artist whose works are displayed at the UK hospitals and clinics and has recently developed an interest in the potential of merging art with AI.

Career Panel

Jeffrey Bennett, MD, PhD
Professor, Neurology
Professor, Ophthalmology

Enrique Alvarez, MD, PhD
Associate Professor, Neurology
Assistant Medical Director, Neurology

Pippa Cosper, MD, PhD
Assistant Professor, Radiation Oncology, University of Wisconsin-Madison

Craig G. van Horne, MD, PhD
Professor, Neurosurgery and Neuroscience
Co-Director, Neurorestoration Center
Virginia T. Barrow Endowed Chair of Neurosurgery

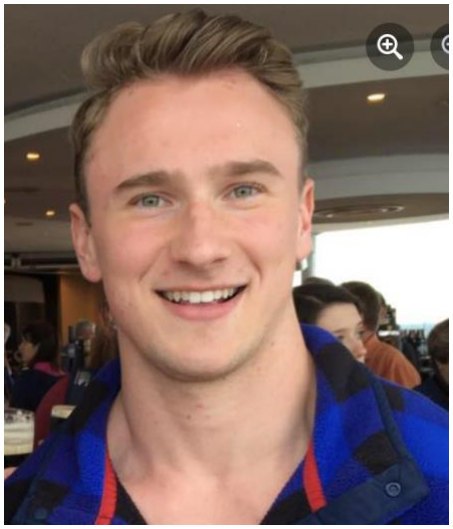
Taraz Samandari, MD, PhD
Medical Epidemiologist
US Public Health Service (CDC)
Captain (retired)

Student Oral Presentations

Aging-associated changes in the mammary gland and breast cancer reveal a role for TGFβ1-mediated upregulation of Semaphorin 7A.

Kelsey T Kines, Heather R Fairchild, Alan M Elder, Veronica Wessels, Zachary P Strugar, Sarah E Tarullo, Virginia F Borges, Traci R Lyons

Breast cancer risk is heightened in the postpartum period, and this transient risk lasts longer in women whose first childbirth occurs after age 30. However, research is lacking to unveil targetable mechanisms that may contribute to the increased breast cancer risk and tumorigenesis in these women. We observed that semaphorin 7A (SEMA7A), an integrin signaling molecule, is elevated in tissue samples from postpartum breast cancer patients aged >30 compared to those aged <30. Via in vivo flow cytometry, SEAM7A is upregulated in the aged (9-12 months) murine mammary gland, especially on transforming growth factor beta (TGFβ) positive cells, compared to young (6-8 weeks) mice, regardless of parity status. In two murine mammary carcinoma models, we also observed accelerated tumor growth and metastases, increased tumoral SEMA7A and TGFβ expression, and promotion of epithelial-to-mesenchymal plasticity (EMP) in aged mice. Additionally, SEMA7A knockout mice and heterozygous littermates reveal that these phenotypes depend on host SEMA7A expression but can be mimicked by SEMA7A overexpressing tumor cells. In vitro, TGFβ1 induces SEMA7A expression in triple-negative breast cancer cells via canonical (SMAD3) and non-canonical (MAPK) pathways, which depend on EMP cellular state. Furthermore, a novel monoclonal antibody targeting SEMA7A can significantly reduce tumor growth and metastatic spread of SEMA7A+ tumors. Collectively, these results highlight the impact aging has on the mammary gland and in breast cancer tumorigenesis, revealing potential targets for breast cancer patients.



PDGFRα signaling regulates Srsf3 transcript binding to affect PI3K signaling and endosomal trafficking

Thomas E. Forman, Marcin Sajek, Eric D. Larson, Neelanjan Mukherjee, and Katherine A. Fantauzzo

Signaling through the platelet-derived growth factor receptor alpha (PDGFRα) plays a critical role in craniofacial development, as mutations in PDGFRα are associated with cleft lip/palate in humans and PDGFRα mutant mouse models display varying degrees of facial clefting. Phosphatidylinositol 3-kinase (PI3K)/Akt is the primary effector of PDGFRα signaling during skeletal development in the mouse. We previously demonstrated that Akt phosphorylates the RNA-binding protein serine/arginine-rich splicing factor 3 (Srsf3) downstream of PI3K-mediated PDGFRα signaling in mouse embryonic palatal mesenchyme (MEPM) cells, leading to its nuclear translocation. We further showed that ablation of Srsf3 in the murine neural crest lineage results in severe midline facial clefting, due to defects in proliferation and survival of cranial neural crest cells, and widespread alternative RNA splicing (AS) changes. Here, we sought to determine the molecular mechanisms by which Srsf3 activity is regulated downstream of PDGFRα signaling to control AS of transcripts necessary for craniofacial development. We demonstrated via enhanced crosslinking and immunoprecipitation (eCLIP)-seq of MEPM cells that PDGF-AA stimulation leads to preferential binding of Srsf3 to exons and loss of binding to canonical Srsf3 CA-rich motifs. Through the analysis of complementary RNA-seq data, we showed that Srsf3 activity results in the preferential inclusion of exons with increased GC content and shorter intron to exon length ratio. Moreover, we found that the subset of transcripts that are bound by Srsf3 and undergo AS upon PDGFRα signaling commonly encode regulators of PI3K signaling and early endosomal trafficking. Functional validation studies further confirmed that Srsf3 activity downstream of PDGFRα signaling leads to retention of the receptor in early endosomes and increases in downstream PI3K-mediated Akt signaling. Finally, we generated an Srsf3 phosphomutant knock-in allele (Srsf3A7) through mutagenesis of the seven Akt consensus motifs in Srsf3 and demonstrated that trans-heterozygous Srsf3A7/fl;Wnt1-Cre+/Tg embryos develop severe midline facial clefting. Taken together, our findings reveal that growth factor-mediated phosphorylation of an RNA-binding protein underlies gene expression regulation necessary for mammalian craniofacial development.

Transposable element derived enhancers in ovarian cancer

Lily L. Nguyen, Atma Ivancevic, Francis To, Abigail Jeong, Benjamin G. Bitler, Edward B. Chuong

There is global epigenetic dysregulation during transformation from normal to cancerous cells. One of the many consequences of this global epigenetic dysregulation is the reactivation of transposable elements (TEs). TEs compose roughly half of the human genome and are normally repressed through epigenetic mechanisms such as DNA methylation and histone modifications. Endogenous retroviruses (ERVs) are a class of TEs that contain long terminal repeats (LTRs) with putative gene regulatory motifs. LTRs can be co-opted to be pro-tumorigenic by becoming non-canonical promotors for oncogenic genes. While several examples of TE-derived promotors have been reported in cancer, the potential significance of TE-derived enhancers remains largely unexplored. Here, we utilized publicly available multi-omics datasets (bulk and single-cell ATAC-seq, bulk and single-cell RNA-seq, and chromatin profiling) in the context of ovarian cancer to determine if there are tumor specific, TE-derived-enhancers that have gene regulatory function. We used CRISPRi technology to functionally validate a putative TE-derived enhancer and gene regulatory axis. We discovered that on the bulk tissue level, several TE families are enriched at open chromatin sites and sites marked by H3K27Ac (enhancer mark) of ovarian tumors, suggesting the presence of tumor specific, TE-derived enhancers. On the single-cell level, we discovered that ovarian cells have the highest expression of these TE transcripts compared to stromal and immune cells in the tumor microenvironment, suggesting that the increased TE-derived enhancer activity observed on the bulk level are specific to ovarian cells. Lastly, when we silenced a specific LTR18 locus upstream of a gene, TIPARP, TIPARP gene expression was also repressed, suggesting that these putative TE-derived enhancers have gene regulatory function. Determining the regulatory role of these TE-derived enhancers will provide novel insights into cancer-related transcriptomes.

Photoinduced transformations in extracellular matrix properties drive intestinal organoid morphogenesis in synthetic hydrogels

Bruce E. Kirkpatrick, F. Max Yavitt, Kaustav Bera, Ella A. Hushka, Lea Pearl Hibbard, Grace K. Hach, Ana Santos, Alex Khang, Michael R. Blatchley, Yongdoo Park, Peter J. Dempsey, Kristi S. Anseth

Intestinal organoids replicate the structure and cellularity of the native crypt-villus axis, providing an exciting bioengineering platform for disease modeling and drug testing. These microtissues offer unique insights into gut biology and are a potential replacement for some animal models with fewer ethical concerns and the ability to use patient-derived cells. However, typical organoid culture suffers from inter-organoid heterogeneity and batch-to-batch variability in the extracellular matrix scaffolding (Matrigel) used in this process. To address these issues, we have developed several novel chemical strategies for exerting spatiotemporal control over intestinal organoid structure and function in synthetic poly(ethylene glycol) hydrogels. Using photoresponsive matrix properties, we control local epithelial curvature and subsequent crypt growth, enabling construction of highly homogenous arrays of geometrically templated organoids. Further, we elucidate early mechanisms of intestinal stem cell mechanotransduction and symmetry breaking through membrane tension-mediated ion channel activity upstream of metabolic reprogramming and YAP signaling. We demonstrate that our photopatterning approach is easily extended to other organoid systems, and show that multiple chemistries can facilitate guided morphogenesis, offering flexibility in our material design to facilitate applications including light-based biofabrication. Our results have implications for tissue engineering, mechanobiology, stem cell signaling, and gut homeostasis, and chart a course towards next-generation personalized medicine for identifying patient-specific responses to drugs and other biochemical stimuli in scalable and physiologically relevant in vitro systems.

Flash Talks

Quantification of subcellular RNA localization through direct detection of RNA oxidation
Hei-Yong G. Lo, Raeann Goering#, Agnese Kocere, Megan C. Pockalny, Laura K. White, Haydee Ramirez, Abraham Martinez, Seth Jacobson, Robert C. Spitale, Chad G. Pearson, Marino J. E. Resendiz, Christian Mosimann, and J. Matthew Taliaferro*

The Orchid Whisperer: My Black Thumb's Best-Kept Secret"
*Ashlyn Stahly**

Poster Session

Cancer Biology

1. **The role of inflammation in myelodysplastic syndrome therapy response**
   Daniel Moskop, Sweta Patel, Brett Stevens, Austin Gillen, Craig Jordan, Eric Pietras*

2. **Dependence of PAX3-FOXO1 Chromatin Occupancy on ETS1 Exposes New Targetable Vulnerability in Fusion-Positive Rhabdomyosarcoma**
   Joseph Hsieh, Etienne Danis, Nathan Nowling, and Paul Jedlicka*

Cell, Stem Cell and Developmental Biology

3. **Placental endothelial cell mechanosensation in severe, early-onset fetal growth restriction**
   Stefano Ginocchio, Taylor Hord, Amanda Flockton, Emily J Su*

Chemical & Biological Engineering

4. **Photothermal Actuation of Thick 3D-Printed Liquid Crystalline Elastomer Nanocomposites**
   Nathaniel P. Skillin, Grant E. Bauman, Bruce E. Kirkpatrick, Joselle M. McCracken, Kyoungweon Park, Richard A. Vaia, Kristi S. Anseth, Timothy J. White*

Immunology

5. **Elucidating the Role of Autoreactive BND2 Cells in Type 1 Diabetes (T1D)**
   Brandon Hilliard, Zachary Stensland, Mia Smith*
6. **Unveiling HIF mediated IFNg responses in the intestinal epithelium**
   Rachel Cohen, Ian Cartwright, Liheng Zhou, and Sean Colgan*
7. **Antibody blockade of cis PD-L1 and CD80 interactions on dendritic cells dictates chemokine-driven migration during inflammation**
   Uma Kantheti, Erin Lucas and Beth Tamburini*
8. **Determining the Fate of Pulmonary iILC2s in Helminth Infection**
   Amita Kashyap, Mindy M Miller, R. Lee Reinhardt*
9. **Pulmonary macrophage programming is conserved in healthy repair and fibrosis**
   Emily M. King, Yifan Zhao, Alexandra L. McCubbrey, Kelsey C. Anderson, Benjamin Steinhart, Camille Moore, Brian Vestal, Peter M. Henson, William J. Janssen*

10. **Bacterial catabolism of dietary tryptophan into indole enhances DC-mediated proinflammatory responses in autoimmunity**
    Brenda Seymour, Brendan Allen, Kristine Kuhn*

Microbiology

11. **Defining Mechanisms that Influence Dengue Virus Viremia**
    Erin R. Fish, Katherine S. Carpentier, Bennett J Davenport, and Thomas E. Morrison*

Molecular Biology

12. **Interferon-responsive lymphatic endothelial cells (LECs) acquire high levels of foreign protein antigenein antigen**
    Ira Fleming, Tadg Forward, Beth Tamburini, Jay Hesselberth*
13. **Layered regulation of the Drosophila CTLH complex during the maternal-to-zygotic transition controls maternally-deposited RNA binding protein clearance**
    Chloe Briney, Jesslyn Henriksen*, Olivia Rissland*
14. **Investigating SIX1 as a master epigenetic regulator in myogenesis and FN-RMS**
    Gustafson, A.L., Hsu, J.Y., Artinger, K.B., and Ford, H.L.*

Molecular, Cellular and Developmental Biology

15. **Elucidating the effect of PARP inhibitors on MMEJ-mediated DNA repair**
    Raquel Ortega, Sophie Whitehead, Benjamin Bitler, Nausica Arnoult*
16. **Nucleus accumbens interneurons orchestrate social attachment**
    El-Kalliny MM, Winther K, Maker M, Donaldson ZR.*
17. **Hippocampal contributions to dynamic social memory in prairie voles.**
    William Sheeran, Kelly Winther, Jayme Temple, & Zoe Donaldson*

Neuroscience

18. **Towards the development of a cerebellar prosthetic**
    Jackson H. Stocking & Abigail L. Person*
19. **Distribution of Chromatic Tuning in Mouse Early Visual System**
    Juan Santiago Moreno, Daniel J. Denman*
20. **Stress increases sperm respiration and motility in mice and men**
    Nickole Moon, Christopher Morgan, PhD, Alyssa Jeng, Neill Epperson, MD, and Tracy L Bale, PhD*

Pharmacology

21. **TRPM2 signaling drives excessive GABAergic synaptic inhibition after brain ischemia**

Amelia Burch, Joshua D. Garcia, Heather O'Leary, Ami Haas, James E. Orfila, Erika Tiemeier, Nicholas Chalmers, Katharine R. Smith, Nidia Quillinan, Paco Herson*

22. **Acute stress causes sexually dimorphic changes to ventral subiculum synapses and behavior**
Carley Miller, Yuan Li, Kevin T. Beier, Jason Aoto*

Thank you to the 2024 Retreat Planning Committee!

*Carley Miller**

*Kelsey Kines**

Sarah Zych

Bruce Kirkpatrick

Alex Camai

Frances Li

Brandon Hilliard

Yvonne Cui

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