9TH GREAT LAKES NUCLEAR RECEPTOR CONFERENCE

OCTOBER 19 – 20, 2023

ROSWELL PARK COMPREHENSIVE CANCER CENTER
665 CARLTON STREET, BUFFALO, NY 14263
RESEARCH STUDIES CENTER BUILDING
(Across the street from the main hospital)
HOHN AUDITORIUM

SPONSORED BY:

9th Great Lakes Nuclear Receptor Conference Program

October 19-20, 2023, Buffalo, NY

Organizers: Subhamoy Dasgupta, PhD; Pamela Hershberger, PhD; and Erik Knudsen, PhD

Thursday, October 19th

2:00 PM	Check in and poster set up	**Research Studies Center 1st Floor Lobby**
4:00-4:15 PM	Welcome and opening remarks	**Hohn Auditorium**
4:20-5:20 PM	**Opening Keynote:** Speaker Introduction: Pamela Sung, MD, PhD, Roswell Park, NY *Evolution of endocrine therapies for Breast and Prostate cancer* **Donald McDonnell, PhD** **Glaxo-Wellcome Distinguished Professor of Molecular Cancer Biology** **Duke University School of Medicine, NC**	
5:30-6:45 PM	**Talks in Hot Topics** (chosen from abstracts) Session chairs: Diane Robins, PhD, University of Michigan Medical School, MI Ania Woloszynska, PhD, Roswell Park, NY	**Zebro Family Conference Room**
5:30-5:42 PM	*Androgen receptor-targeted molecules induce altered protein-complex assembly* Sarah Kohrt, Case Western Reserve University	
5:42-5:54 PM	*Targeting Human Breast Cancer with a CARM1 Proteolysis Targeting Chimera* Megan Bacabac, University of Wisconsin-Madison	
5:54-6:06 PM	*Developing a method to quantify the 49 mouse nuclear receptors in vivo by mass spectrometry* Michael Saikali, University of Toronto	
6:06-6:18 PM	*The Epigenetic Role of Nuclear Receptor Co-Repressor 2 (NCOR2) in Neuroendocrine Prostate Cancer Progression* Justine Jacobi, Roswell Park	
6:18-6:30 PM	*Estrogen and progesterone signaling modulate extravillous trophoblast function* Adrian Kocinski, Case Western Reserve University	
6:30-6:42 PM	*Targeting AR-coregulator interactions for treatment of castration-resistant prostate cancer* Ujjwal Dahiya, Lerner Research Institute, Cleveland Clinic	
6:45- 8:15 PM	**DINNER ON SITE**	**Zebro Family Conference Room**

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Friday, October 20th

7:30-8:30 AM — Breakfast and poster set up — **Research Studies Center 1st Floor Lobby**

Session 1: Hormone driven cancers — **Hohn Auditorium**

8:30-8:35 AM — Session chairs:
Julie Ostrander, PhD, University of Minnesota, MN
David Goodrich, PhD Roswell Park, NY

8:35-9:00 AM — *AR alterations and genetic plasticity in castration-resistant prostate cancers*
Scott Dehm, PhD, University of Minnesota Medical School, MN

9:05-9:20 AM — *Liver cancer: Interplay between nuclear receptor signaling, metabolism and sex*
Sayeepriyadarshini Anakk, PhD, University of Illinois, IL

9:25-9:40 AM — *Novel mechanisms of AR action contribute to prostate cancer progression*
Hannelore Heemers, PhD, Cleveland Clinic, OH

9:45-10:00 AM — The combination of YAP-TEAD-inhibitor in conjunction with endocrine therapy on refractory bone metastatic breast cancer
Hai Wang, PhD, Roswell Park, NY

10:00-10:15 AM — **COFFEE BREAK & DINNER SIGN UP** — **Gaylord Cary Conference Room**

Session 2: Nuclear Receptors and Coregulator Signaling — **Hohn Auditorium**

10:15 AM — Session chairs:
Marja Nevalainen, MD, PhD, Thomas Jefferson University, PA
Dominic Smiraglia, PhD, Roswell Park, NY

10:20-10:40 AM — *Policing Nuclear Receptor Playmates: Tracking ER/PR complexes in Breast Cancer*
Carol Lange, PhD, University of Minnesota Medical School, MN

10:45-11:00 AM — *Allosteric mechanisms of transcriptional control in FXR*
C. Denise Okafor, PhD, Penn State University, PA

11:05-11:20 AM — *Discovery of a mammalian 12h ultradian oscillator regulated by an XBP1/SRC-3/SON axis*
Bokai Zhu, PhD University of Pittsburgh, PA

Session 3: Nuclear receptors in development and disease — **Hohn Auditorium**

11:25 AM — Session chairs:
Gokul Das, PhD, Roswell Park, NY
Olga Astapova, MD PhD University of Rochester, NY

11:30-11:50 AM — *Understanding and small molecule targeting of Chromatin-MYC-AR- axis in prostate cancer*
Debabrata “Debu” Chakravarti, PhD, Northwestern University, IL

11:55-12:10 PM — *The Intersection Between Steroids, Innate Immunity, and Lymphangioleiomyomatosis (LAM).*
Stephen R. Hammes, MD, PhD, University of Rochester, NY

12:15-12:30 PM — *Chemotherapy resistant CSC populations upregulate PR-activated pathways in ER+ breast cancer*
Thu Truong, PhD, University of Minnesota, MN

12:30-1:30 PM **LUNCH ON SITE** **Gaylord Cary Conference Room**

Session 4: Nuclear receptors in metabolism and immunity **Hohn Auditorium**

1:30-1:35PM Session chairs:
Carolyn Cummins, PhD, University of Toronto, ON, Canada
Hemn Mohammadpour DVM, PhD, Roswell Park, NY

1:35-1:50 PM *Leveraging nuclear receptors involved in cholesterol homeostasis to re-educate tumor associated myeloid immune cells*
Erik Nelson, PhD, University of Illinois Urbana-Champaign, IL

1:55-2:10 PM *Immunomodulatory roles for estrogen receptor signaling in T cells*
Wendy Goodman, PhD, Case Western Reserve University, OH

2:15-2:30 PM *FXR mediates macrophage intrinsic responses to suppress colon cancer progression*
Ting Fu, PhD, University of Wisconsin-Madison, WI

2:30-3:45 PM **POSTER SESSION & REFRESHMENTS** **Research Studies Center 1st Floor Lobby**

Nuclear metabolic pathway drives epigenetic rewiring in tumors
Abhisha Sawant Dessai, PhD, Roswell Park, NY

Transcriptional adaptations under hypoxic stress promote breast cancer progression
Tao Dai, Roswell Park, NY

Repurposing Tamoxifen to Treat Triple Negative Breast Cancer Based on a Novel ERβ-p53-p73 Signaling Axis
Chetan Oturkar, PhD, Roswell Park, NY

TRPS1 modulates chromatin accessibility to regulate estrogen receptor (ER) binding and ER target gene expression in luminal breast cancer cells
Thomas Scott, University of Virginia, VA

Paxillin Regulates Androgen Receptor in Granulosa Cells
Anna Roy, University of Rochester, NY

Characterizing the Structure-Activity Relationship and the Mechanism of Structural Selectivity for Liver X Receptor β Antagonists
Jin Shi, University of Toronto, ON, Canada

The role of Liver Receptor Homolog 1 (LRH-1) in regulating breast cancer progression by modulating the immune response
Yu Wang, University of Illinois, IL

Evaluation of a novel selective glucocorticoid receptor modulator: Des-Ciclesonide and its therapeutic potential in bronchopulmonary dysplasia
Nathalie El Khoury, University of Pittsburgh School of Medicine, PA

Estrogen dependent and independent metabolic maladaptations contributing to BPH
Mia Cararrini, University of Pittsburgh School of Medicine, PA

Integration of Glucocorticoid and Mineralocorticoid receptor signaling in triple-negative breast cancer models
Sai Harshita Posani, University of Minnesota, MN

Therapeutic targeting of mitochondrial metabolism by P2X4 receptor inhibition and amino acid restriction in renal carcinoma models
Sabrina Orsi, University at Buffalo, NY

Murine CD4+ T cells exhibit sexually dimorphic responses to estrogen signaling
Sarah McNeer, Case Western Reserve University School of Medicine, OH

PKN1 engages UPF1 as a mediator of AR- and SRF-dependent transcription in prostate cancer
Gaurav Chauhan, Cleveland Clinic, OH

Screening proteins secreted by endothelial progenitor cells as mediators of liver X receptor-dependent anti-atherosclerotic activity
Sarah Shawky, University of Toronto, ON, Canada

Examining the importance of LXRβ in brown fat vs white fat in the modulation of glucocorticoid-mediated adipose tissue dysfunction
Hetvi Shah, University of Toronto, ON, Canada

Liver-Specific Loss of the Nuclear Receptor Co-Regulator ARGLU1 Protects Against Diet-Induced Obesity in Female Mice
Sarah Cash, University of Toronto, ON, Canada

Sex differences in bile acid composition in a murine model of hepatocellular carcinoma promotes dysbiosis
Angela Dean, University of Illinois at Urbana-Champaign, IL

Role of ER/PR/IRS-1 Transcriptional Complexes in Endocrine Resistant Breast Cancer
Susan Schmidt, University of Minnesota, MN

Androgen receptor mediated transcriptional repression of SIRT3 drives prostate cancer progression
Zoe Lawler, Roswell Park, NY

Coregulator SRC-2 dependent increased lipid metabolism induces an immunosuppressive prostate tumor microenvironment
Alphonse Dimeck, Roswell Park, NY

Re-sensitizing the Refractory Breast Cancer Bone Metastasis to Endocrine Therapies
Anindita Das, Roswell Park, NY

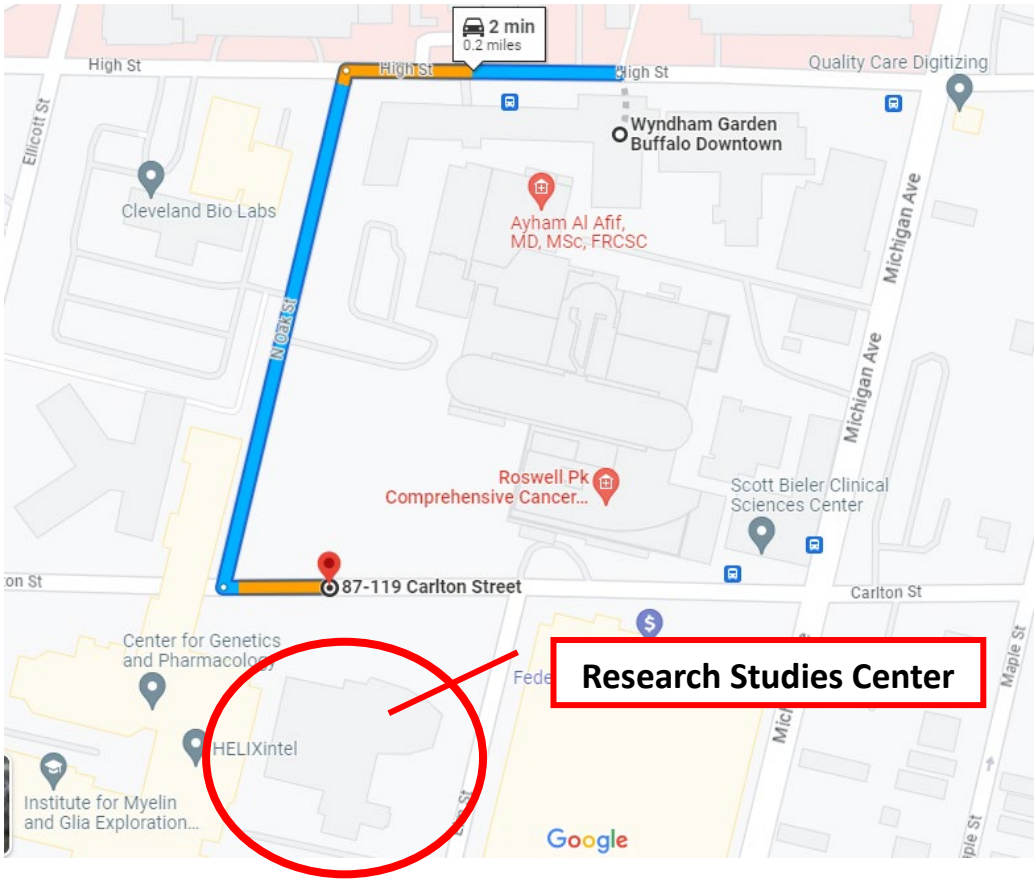
3:45-4:45 PM **<u>Closing Keynote:</u>** **Hohn Auditorium**
Speaker Introduction: Qiang (John) Li, MD, PhD, Roswell Park

Targeting Transcription Factor Neo-Enhancesomes in Cancer
Arul M. Chinnaiyan, MD, PhD
Director, Michigan Center for Translational Pathology
S.P. Hicks Endowed Professor of Pathology and Urology
American Cancer Society Research Professor
Investigator, Howard Hughes Medical Institute
University of Michigan Medical School, MI

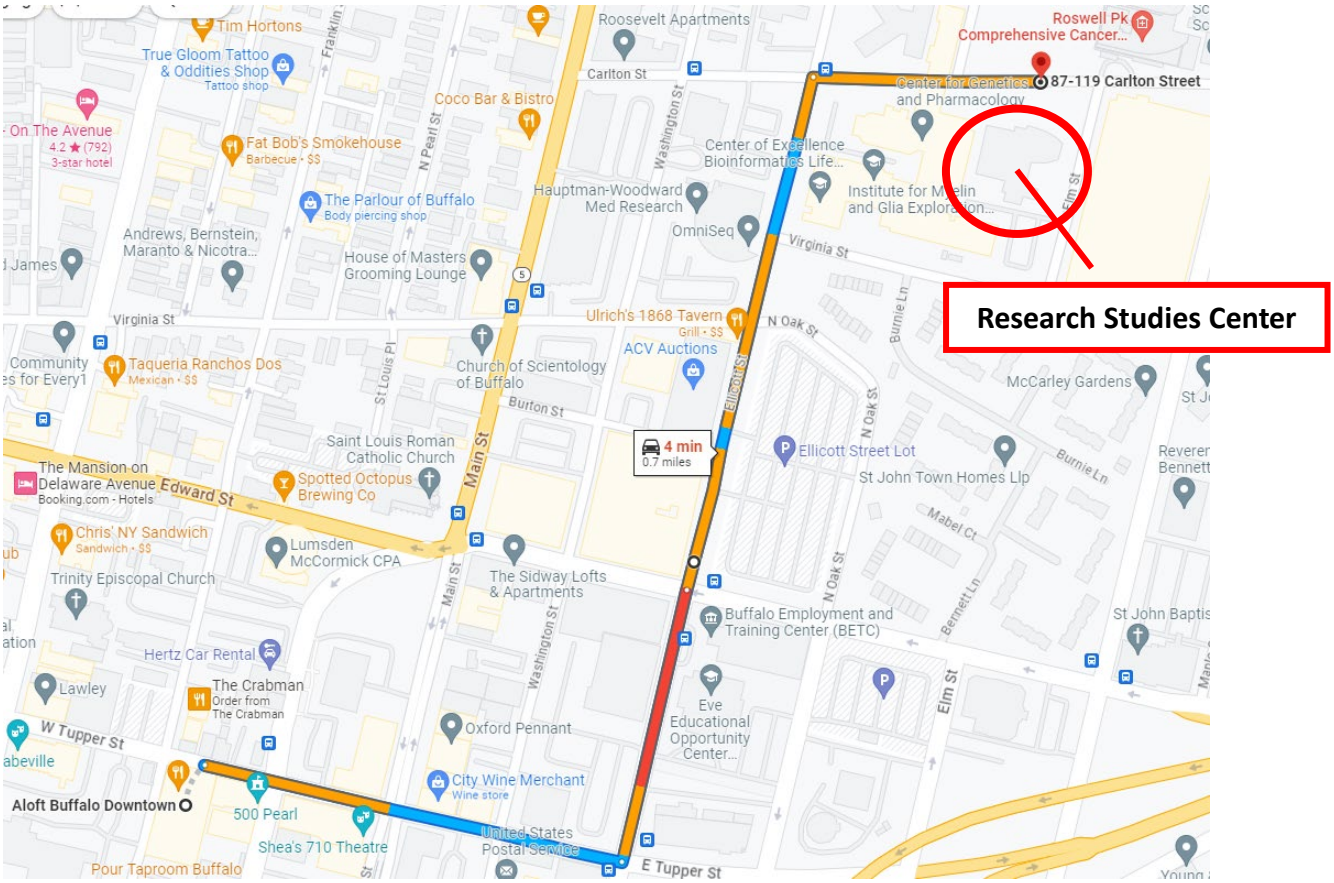
5:00 PM Closing remarks, awards, and reception **Hohn Auditorium**

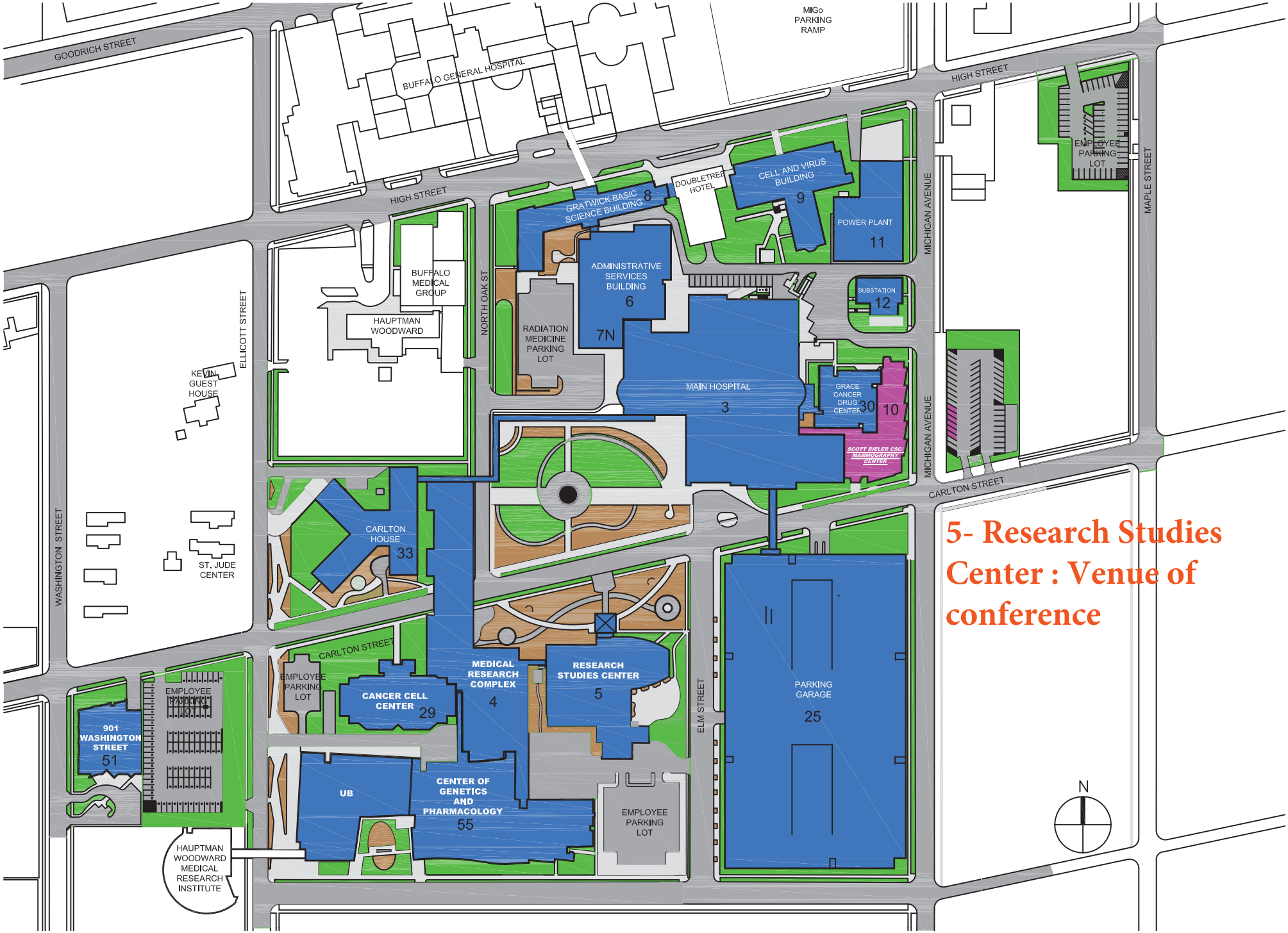
6:30 PM Depart for dinner with small groups (optional)

Directions from Wyndham Garden Buffalo to Roswell Park Research Studies Center



Directions from Aloft Hotel to Roswell Park Research Studies Center





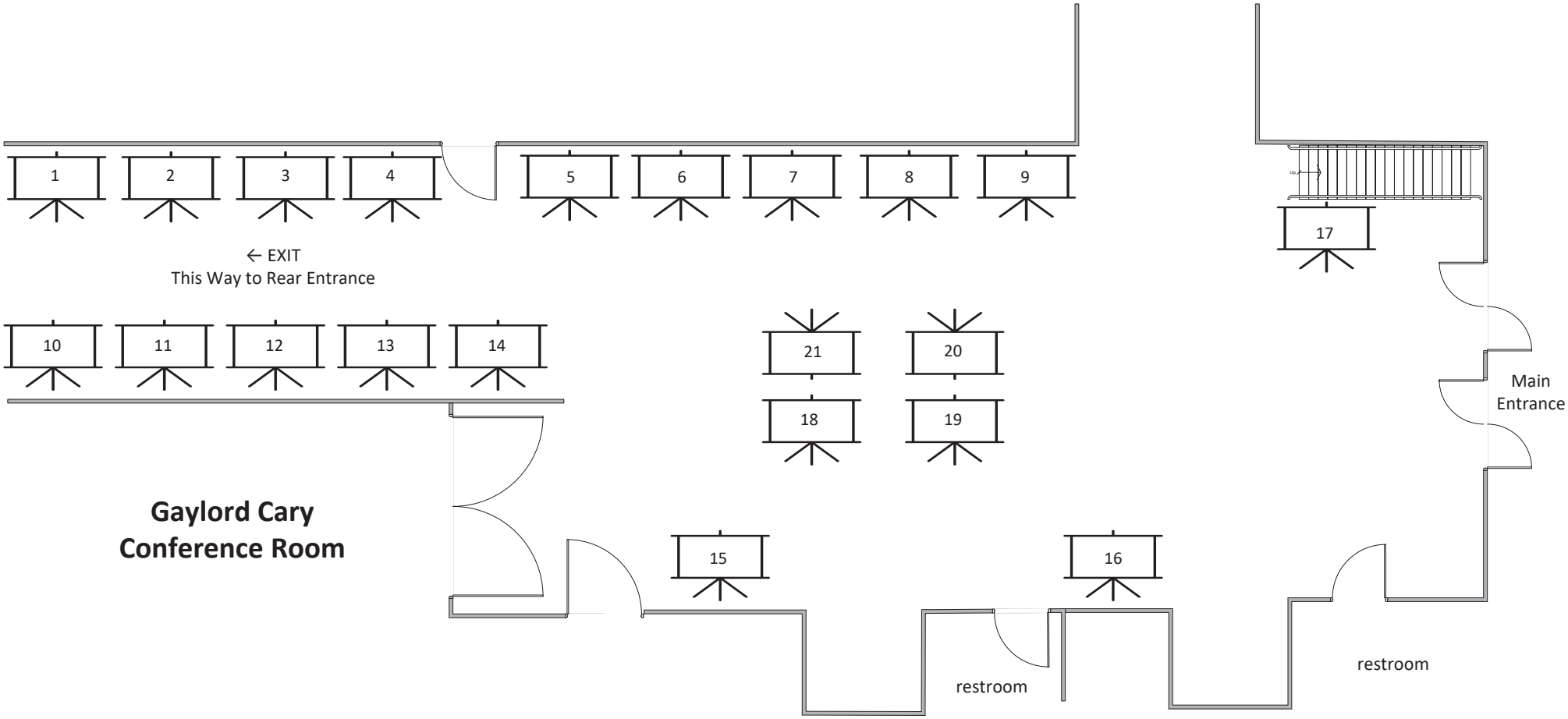
5- Research Studies Center : Venue of conference

CAMPUS BUILDING MAP

9th Great Lakes Nuclear Receptor Conference
October 20, 2023

Sponsored by: ENDOCRINE SOCIETY

POSTER LAYOUT



Abstracts Selected for "Talks in Hot Topics"

Developing a method to quantify the 49 mouse nuclear receptors in vivo by mass spectrometry.

Michael F. Saikali[1], Carolyn L. Cummins[1]

[1]Department of Pharmaceutical Science, Leslie Dan Faculty of Pharmacy, University of Toronto

The nuclear receptor (NR) family of transcription factors control the expression of genes involved in a wide range of physiological processes. The ability to study NRs quantitatively at the protein level has been hindered by the poor quality of available antibodies, as well as the lack of available high throughput methods to study more than a few receptors at a time. We have developed a mass spectrometry (MS) based targeted proteomic assay to quantify the absolute amounts of NR protein in mouse livers. An in silico pipeline was developed for the identification of tryptic peptides from both mouse and human NRs that are between 7-20 amino acids long. 1002 peptides were identified, with only 382 peptides conserved across species. NR1H5 (only in mouse) and NR0B1 (low sequence homology) were processed through the pipeline manually. Only 284 peptides were identified as having no post translational modifications and were subsequently searched within the Global Proteome Machine (GPM) database. We identified 169 candidate peptides for the 47 NRs and purchased the top ranked peptides as synthetic isotopes. The identity and spectra were validated by overexpressing each NR in HEK293 cells and spiking in the synthetic heavy labelled peptides. Analysis is conducted on an EASY-Spray C18 column (75 um x 50 cm, 3Å), and analyzed on a Thermo QExactive HF mass spectrometer in parallel reaction monitoring mode. The assay is currently in use to quantify the circadian expression of NRs in mouse livers, as well as their changes in expression during fasting and re-feeding.

Targeting AR-coregulator interactions for treatment of castration-resistant prostate cancer

Ujjwal R. Dahiya[1], Sangeeta Kumari[1], Babal Kant Jha[2], Tao Liu[3], Song Liu[3] and Hannelore V. Heemers[1]

[1]Department of Cancer Biology and [2]Center for ImmunoTherapy and Immunooncology, Cleveland Clinic; [3]Department of Biostatistics and Bioinformatics, Roswell Park Comprehensive Cancer Center

Androgen receptor (AR) drives prostate cancer (CaP) even after androgen deprivation therapy (ADT) failed. Inhibiting AR's transcription factor function to overcome resistance to ADT is an attractive therapeutic avenue. However, which AR-coregulator interaction to target is not clear, AR-coregulator complex higher order structures are unknown, and how manipulating AR-coregulator interactions impacts AR cistromes is not understood.
We explore the feasibility of targeting interactions between AR and WD repeat 77 (WDR77, non-catalytic component of the methylosome complex), which are enriched after ADT-resistance and mediate CaP cell survival.

AR and WDR77 cistromes overlapped considerably and the AR cistrome was reduced after WDR77 loss, suggesting that WDR77 controls AR complex formation at target genes. WDR77 overexpression induced CaP cell proliferation before and after ADT. WDR77 silencing decreased cell proliferation, and delayed growth of ADT-naïve and -resistant CaP xenografts. Cell-free co-IPs and BioLayer Interferometry (BLI) assays showed that WDR77 directly interacts with AR and isolated a central WDR77 domain critical for AR binding and complex formation. CoIP and BLI assays using peptides spanning the central WDR77 domain narrowed down the AR-WDR77 interaction site to a 21 aa region. Overexpression of the central WDR77 domain and 21 aa region altered AR-WDR77 interactions and AR complex composition in CoIP studies. A rationally designed WDR77 inhibitor similarly interfered with AR-WDR77 interactions and AR transcription complex formation.

Our studies confirm the importance of WDR77 for ADT-resistant CaP growth, AR complex formation and AR cistrome. Disrupting AR-WDR77 interplay is feasible and may be a novel CaP treatment strategy.

Estrogen and progesterone signaling modulate extravillous trophoblast function

Adrian D. Kocinski[1], Tamara Tilburgs[2], and Wendy A. Goodman[1]

[1]Department of Pathology, Case Western Reserve University School of Medicine
[2]Division of Immunobiology, Center for Inflammation and Tolerance, Cincinnati Children's Hospital

The complex interplay of hormones during pregnancy is crucial for successful implantation, invasion, placentation, and normal fetal development. 17β-estradiol (estrogen, "E2"), and progesterone ("P4") increase steadily throughout the course of human pregnancy and peak prior to parturition. E2 signals through its nuclear receptors ERα and ERβ, while P4 signals through PR-A and PR-B, leading to transcriptional changes in decidual immune cells, stromal cells, and trophoblasts. These hormones influence placental and fetal development by regulating angiogenesis, decidualization, and orchestrate a tolerogenic immune state.
Here, we investigated the role of E2 and P4 signaling on extravillous trophoblast (EVT) phenotype and function. EVTs are fetal-derived cells that play an active role in spiral artery remodeling, placental anchoring, and tolerogenic responses. Prior studies have demonstrated that hormonal signaling is dysregulated in abnormal placentae and trophoblasts. Although EVTs are a primary source of P4 during pregnancy, their capacity to respond to hormone signaling represents a key knowledge gap. We used EVT-like cell lines, derived from primary term EVTs, to test functional responses to signaling downstream of nuclear ERs and PRs. We found that treatment of EVTs with Fulvestrant (ICI 182,780), an ERα antagonist, and Mifepristone (RU486), PR antagonist, increases gene expression of TNF-α and IL-6. Furthermore, we observed differences in expression of EVT surface markers including HLA-C,-E, and -G in response to E2 and P4 treatment. Further studies will elucidate the role that estrogens and progesterone play in regulating EVT phenotype and function with respect to immune and developmental functions.

Targeting Human Breast Cancer with a CARM1 Proteolysis Targeting Chimera

Haibo Xie,[1‡] Megan S Bacabac,[2‡] Min Ma,[1] Eui-Jun Kim,[2] Yidan Wang,[2] Wenxin Wu,[3] Lingjun Li,[1,3] Wei Xu [2*] and Weiping Tang[1,3*]

[1]Lachman Institute for Pharmaceutical Development, School of Pharmacy, University of Wisconsin-Madison, Madison, Wisconsin 53705, United States
[2]McArdle Laboratory for Cancer Research, University of Wisconsin-Madison, Madison, Wisconsin 53705, United States
[3]Department of Chemistry, University of Wisconsin-Madison, Madison, Wisconsin 53706, United States
[‡]These authors contributed equally.

Coactivator-associated arginine methyltransferase 1 (CARM1) asymmetrically dimethylates proteins on arginine residues. Methylation of BAF155 by CARM1 in triple-negative breast cancer (TNBC) drives cancer metastasis. Amplification and overexpression of CARM1 has been observed in a variety of cancers, including breast cancer, and its overexpression correlates with poor prognosis. Potent small molecule inhibitors for CARM1 have been developed but the effects of inhibiting CARM1 differ from the effects of knocking out (KO) CARM1 in cancer cells using single-cell RNA-seq analyses. CARM1 KO, but not CARM1 inhibition, decreases cancer cell proliferation. This implies that CARM1 also has non-enzymatic roles in driving cancer progression which necessitates the development of small molecule degraders of CARM1. We have developed CARM1-specific proteolysis targeting chimeras (PROTACs), which contain a CARM1 ligand (TP-064), a linker, and an E3 ligase ligand (von-Hippel Lindau) to target CARM1 for proteasomal degradation. We tested the activity of 23 compounds with different linkers by immunoblotting in MCF7 cells and identified four compounds that potently degrade CARM1 by two hours. We characterized the degradation activity of the best compound, **3b**, which has a DC50 of 8.1 nM and a Dmax of 97%. Proteomic analysis revealed specific CARM1 degradation with minimal off-target effects. **3b** is not cytotoxic but does inhibit methylation of CARM1-specific substrates and migration of a TNBC cell line. **3b** does not inhibit growth of MCF10A, a non-tumorigenic mammary cell line. Our results showed that CARM1 PROTACs can potentially be developed as therapeutic agents for targeting CARM1-driven cancers more effectively than currently available inhibitors.

The Epigenetic Role of Nuclear Receptor Co-Repressor 2 (NCOR2) in Neuroendocrine Prostate Cancer Progression

Jacobi JJ[1], Long MD[2], Rowsam AM[1], Rosario SR[2], Campbell MJ[3], and Smiraglia DJ[1]

[1]Department of Cell Stress Biology, Roswell Park Comprehensive Cancer Center, Buffalo, NY
[2]Department of Biostatistics and Bioinformatics, Roswell Park Comprehensive Cancer Center, Buffalo, NY
[3]Department of Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA

In prostate cancer, most patients develop androgen-driven luminal-like adenocarcinoma. Patients presenting with, or progress to, advanced metastatic disease are treated with androgen deprivation therapy (ADT). While initially highly effective, nearly all patients recur with castration-resistant prostate cancer (CRPC) and a subset transform into the aggressive, androgen-independent Neuroendocrine Prostate Cancer (NEPC). NEPC exhibits heterogeneous morphology and limited treatment options, resulting in poor survival. This transition to NEPC may involve clonal divergence from a CRPC precursor, facilitated by aberrant epigenetic reprogramming. We investigated the role of nuclear receptor co-repressor, NCOR2, in this process. We previously found that reduced NCOR2 expression correlates with shorter time to biochemical recurrence, neuronal-like characteristics, and epigenetic changes driving NEPC progression. NCOR2 is well-known to recruit histone deacetylases, establishing a repressive chromatin state. We hypothesized that NCOR2 serves as an epigenetic barrier at lineage-specific enhancer regions, constraining the activation of developmental programs thereby inhibiting transdifferentiation to NEPC. NCOR2 loss would enhance lineage plasticity under ADT pressure by eliminating the epigenetic barriers at lineage-specific enhancer regions. Utilizing Multiome single cell-seq, we identified gene expression and genome accessibility changes that drive NCOR2-dependent transdifferentiation to NEPC occurring as early as seven days following castration in the CWR22 prostate cancer xenograft mouse model. Using CUT&RUN-seq for the active enhancer mark, H3K27ac, we found that NCOR2 knockdown triggers earlier activation of neuronal super enhancers compared to control CRPC cells under androgen withdrawal. Our study highlights the potential of targeting NCOR2-dependent epigenetic plasticity as complementary therapeutic approach to the androgen receptor signaling axis.

Androgen receptor-targeted molecules induce altered protein-complex assembly

Kohrt SE[1,2], Asante Y[2], Kim H[2], Adelaiye-Ogala R[3], Corey E[4], Oyelere AK[5], Gryder BE2,[6]

[1]Department of Pharmacology, Case Western Reserve University, Cleveland, OH, [2]Case Comprehensive Cancer Center, Cleveland, OH, [3]School of Medicine and Biomedical Sciences, University at Buffalo, SUNY, Buffalo, NY; [4]Department of Urology, University of Washington, Seattle, [5]Parker H. Petit Institute for Bioengineering & Biosciences, Department of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA, [6]Department of Genetics and Genome Sciences, Case Western Reserve University, Cleveland, OH

Castration-resistant prostate cancer (CRPC) is a lethal disease driven by amplified androgen receptor (AR) expression and activity. The AR antagonist enzalutamide is an effective treatment, but tumors inevitably become resistant, largely by AR-driven mechanisms. Using structure-guided medicinal chemistry we developed enzalutamide analogs, BG-15a and BG-15n, and designed for higher efficacy in CRPC models. Our studies indicate BG-15a/n binds to AR with a higher potency than enzalutamide. BG15a/n also result in greater efficacy in a number of CRPC models including cell lines, patient-derived xenografts, and *in vivo* models. Like enzalutamide, BG-15a/n treatment resulted in downregulation of androgen response pathway genes by RNA-seq and geneset enrichment analysis. Interestingly, however, BG-15a/n promoted localization of the AR into the nucleus similar to AR agonists (e.g., testosterone). We further hypothesized BG-15a/n altered transcriptional activity by altering the binding-partner recruitment preferences of the AR. ChIP-seq data indicated increased AR binding in BG-15n treated cells at early times points, yet this binding decreases over time. AQuA-HiChIP for AR and H3K27ac was performed to show the 3D folding of chromatin, and these studies demonstrate acetylation and 3D connectivity are lost with BG-15n treatment. AR IP-mass spec and RIME data show changes in AR binding partners at these different time points. Furthermore, immunofluorescent puncta are observed in drug treated cells and suggest AR aggregation within the nucleus drives the loss of AR signaling and transcriptomic function. These studies warrant further development of BG-15a/n as effective therapeutics for the treatment of CRPC with a novel mechanism of action.

Abstracts for Poster Session

Poster #1

Nuclear metabolic pathway drives epigenetic rewiring in tumors

Abhisha Sawant Dessai[1], Nadya Elhalawany[1], Tao Dai[1], Eriko Katsuta[1], Justine Jacobi[1], Tao Liu[2], Nagireddy Putluri[3], Sung Yun Jung[3], Subhamoy Dasgupta[1]

[1]Roswell Park Comprehensive Cancer Center, Department of Cell Stress Biology, Buffalo, NY, [2]Roswell Park Comprehensive Cancer Center, Department of Biostatistics & Bioinformatics, Buffalo, NY, [3]Baylor College of Medicine, Department of Molecular and Cellular Biology, Houston, TX

During evolution, cells have acquired the ability to sense and adapt to varying conditions of extracellular nutrient availability. Mitochondria remain at the core of cellular metabolism generating energy, whereas the nucleus integrates cellular and environmental signals to activate genes that alter function and cell fate. However, it remains largely unexplored how mitochondrial metabolism and nuclear transcription communicate to drive gene expression in response to nutrient stress. To investigate the metabolic signals that may promote gene expression, we performed a biochemical screen and identified mitochondrial enzymes regulating citrate synthesis such as citrate synthase (CS), aconitase 2 (ACO2), and isocitrate dehydrogenase 2 (IDH2) to be present in the nucleus. Nuclear localization of IDH2 and ACO2 along with ACLY were found to be driving nuclear acetyl CoA synthesis using alpha-ketoglutarate derived from glutamine, and ablation of ACO2 or IDH2 significantly reduced several histone H3 acetylation marks. Interestingly, in an isolated functional nucleus, addition of alpha-ketoglutarate enhanced histone acetylation marks and increased chromatin accessibility, however, the loss of ACO2 or IDH2 abrogated this effect, implying these enzymes are required for nuclear acetyl CoA synthesis independent of their mitochondrial function. ATAC-seq analysis confirmed reduced chromatin accessibility in ACO2 ablated cells compared to control, specifically impacting chromatin profile of pioneering factors and master regulators such as FOXA1, JUN and AR. Our findings indicate the existence of a potential nuclear metabolic pathway regulating chromatin accessibility and defining cell fate.

This work is supported by the funds from NIH (R01CA252092 and DP2CA260421) to S.D.

Poster #2

Transcriptional adaptations under hypoxic stress promote breast cancer progression

Tao Dai[1], Abhisha Sawant Dessai[1], Spencer Rosario[2], Subhamoy Dasgupta[1]

[1]Department of Cell Stress Biology, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263.
[2]Department of Biostatistics and Bioinformatics, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263

To sustain energy production for survival under hypoxic conditions, tumor cells undergo metabolic rewiring predominantly by accentuating glucose metabolism through hypoxia-driven enhanced expression of glycolytic enzymes. 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 4 (PFKFB4) is one of the hypoxia response glycolytic enzymes which regulate glucose metabolism and its highly expressed in breast cancer. However, the function of PFKFB4 under hypoxia is still poorly understood. Previously, from an unbiased RNAi-screen, we identified PFKFB4 as a major regulator of steroid receptor coactivator-3 (SRC-3) through SRC-3 phosphorylation at Ser857. We next sought to understand how PFKFB4-SRC-3 axis is regulated under hypoxic stress and how that contributes to breast cancer progression. RNA sequencing revealed focal adhesion genes including ITGB3 as downstream targets of PFKFB4. ITGB3 expression was induced under hypoxia but was completely abrogated in the absence of PFKFB4. ITGB3 has been implicated in promoting invasive properties in tumor cells; indeed, we found that PFKFB4 ablation inhibited tumor cell migration while ectopic expression of ITGB3 rescued this migratory defect. We observed high occupancy of SRC-3 on ITGB3 promoter, and SRC-3 depletion reduced ITGB3 expression, suggesting that ITGB3 may be regulated by PFKFB4-SRC-3 axis. Next, we asked whether PFKFB4-SRC-3 axis has broader effects in regulating hypoxia target genes besides ITGB3. Using HIF reporter assay, we found that PFKFB4 or SRC-3 depletion alone suppressed HIF signaling, while depletion of both did not yield any additional effects compared to SRC-3 deletion alone. This suggests a novel mechanism that PFKFB4 potentially regulates HIF signaling through SRC-3 activation under hypoxic stress in breast cancer.

[Supported by NIH Common Fund 1DP2CA260421-01, Susan G. Komen Foundation and Roswell Park Alliance Foundation grants to S.D., and Breast Cancer Coalition of Rochester Pre-doctoral grant to T.D.]

Poster #3

Repurposing Tamoxifen to Treat Triple Negative Breast Cancer Based on a Novel ERβ-p53-p73 Signaling Axis

Oturkar CC[1], Park J[2], Adams C[1], Mukhopadhyay UK[1], Ijaz I[1], Dolan M[1], Mastri M[1], Caradori A[1], Oshi M[1], Tokumaru Y[1], Abha K[2], Mishra R[2], Jung KH[2], Yang S[2], Ebos J[1], Wang J[1], Takabe K[1], Attwood K[1], Kaipparettu BA[2], Das GM[1]

[1]Roswell Park Comprehensive Cancer Center, Buffalo, NY; [2]Baylor College of Medicine, Houston, TX.

Triple-negative breast cancer (TNBC) is an aggressive subtype without any effective targeted therapies and rapidly become resistant to generic chemotherapy. Therefore, there is an urgent need to develop new therapeutic strategies. While these cancers do not express estrogen receptor alpha (ERα), estrogen receptor beta (ERβ) is expressed in TNBCs. Recent reports including the Cancer Genome Atlas show that about 80% of TNBC express mutant p53 and it is the most predominant driver in these cancers. We have previously reported (JNCI, 2019, 111:1202-1215) that ERβ binds p53 and exerts proliferative versus anti-proliferative/tumor suppressive functions depending on the wild type and mutant p53 status in TNBC, respectively. In the current work we used multiple approaches such as immunoprecipitation, in situ proximity ligation assay, and gene expression analysis by quantitative real-time PCR to show that tamoxifen (Tam) increases ERβ-mutant p53 interaction thereby sequestering mutant p53 away from p73 resulting in de-repression of p73 and upregulation of anti-proliferation genes leading to cell cycle arrest and apoptosis in TNBC cells. Importantly, Tam synergized with doxorubicin (Doxo) in killing the tumor cells, and importantly, in p53-dependent manner. Furthermore, Tam, besides increasing ERβ-mutant p53 interaction in the nucleus, in combination with Doxo, it promoted localization of ERβ and mutant p53 in mitochondria leading to cytochrome C release and caspase activation in the TNBC cells. RNA-seq analysis of tamoxifen and Doxo treated isogenic TNBC cells revealed that these agents impacted various cellular pathways in a mutant p53-dependent manner. We also validated the increased anti-tumor activity TNBC cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) tumors. Consistent with our observations in the in- vitro models, combination therapy inhibited progression of both CDX and PDX tumors more effectively compared to monotherapies. Furthermore, the antitumor effect was dependent on expression of mutant p53 in tumors. Our study has revealed a novel ERβ-mutant p53-p73 axis that could be targeted by Tam in combination with chemotherapy, raising the possibility of repurposing Tam to treat molecularly stratified TNBC. Besides the potential for relatively faster entry of a safe and less expensive therapy to the clinic, our discovery can be exploited to reduce toxic adverse effects by reducing the dose of Doxo in treatment regimens

Poster #4

TRPS1 modulates chromatin accessibility to regulate estrogen receptor (ER) binding and ER target gene expression in luminal breast cancer cells

Thomas G. Scott[a], Kizhakke Mattada Sathyan[b,c], Daniel Gioeli[d,e], Michael J. Guertin[b,c]

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Common genetic variants in the repressive GATA-family transcription factor (TF) TRPS1 locus are associated with breast cancer risk, and luminal breast cancer cell lines are particularly sensitive to TRPS1 knockout. We introduced an inducible degron tag into the native TRPS1 locus within a luminal breast cancer cell line to identify the direct targets of TRPS1 and determine how TRPS1 mechanistically regulates gene expression. We acutely deplete over 80 percent of TRPS1 from chromatin within 30 minutes of inducing degradation. We find that TRPS1 regulates transcription of hundreds of genes, including those related to estrogen signaling. TRPS1 directly regulates chromatin structure, which causes the estrogen receptor (ER) to redistribute in the genome. ER redistribution leads to both repression and activation of dozens of ER target genes. Downstream from these primary effects, TRPS1 depletion represses cell cycle-related gene sets and reduces cell doubling rate. Finally, we show that high TRPS1 activity, calculated using a gene expression signature defined by primary TRPS1-

regulated genes, is associated with worse breast cancer patient prognosis. Taken together, these data suggest a model in which TRPS1 modulates the activity of other TFs, both activating and repressing transcription of genes related to cancer cell fitness.

Poser #5

Paxillin Regulates Androgen Receptor in Granulosa Cells

Anna Roy, Adelaide E. Weidner, Kenji Vann and Olga Astapova

Paxillin is a ubiquitously-expressed adaptor protein integral in focal adhesions, cell motility, apoptosis, and mediation of pro-tumorigenic androgen signaling in prostate cancer cells, where it is necessary for rapid cytoplasmic kinase signaling triggered by activation of membranebound androgen receptor (AR). We sought to investigate paxillin and AR in granulosa cells (GC), where androgen actions, apoptosis and focal adhesions are of known importance, but the role of paxillin is understudied. We found that GC-specific paxillin knockout in mice results in reduced AR protein, but not mRNA expression. We then created paxillin-null KGN cell lines using

CRISPR-Cas9 gene editing which showed reduced AR protein expression early on, but this effect disappeared after weeks of clonal expansion. Expanded clones exhibited normal AR protein expression, but increased mRNA expression, suggesting that an adaptive increase in transcription compensated for reduced AR protein levels in cells that survived paxillin deletion. Additionally, the half-life of AR decreased from 6.7 to 4.5 hours (approximately 33%) with paxillin deletion, indicating accelerated AR protein degradation. To investigate the physiological significance of this, we exposed our mouse models to chronic postnatal dihydrotestosterone to induce anovulation. As expected, 0 out of 6 control mice had estrous cycles. However, 2 out of 6 paxillin knockout

mice resumed cycling, indicating that paxillin deletion may decrease activity in androgenresponsive pathways, which could be compensating for the negative effects of androgen excess. Thus, paxillin may be a novel target in the management of androgen-related disorders in women, such as polycystic ovary syndrome.

Poster #6

Characterizing the Structure-Activity Relationship and the Mechanism of Structural Selectivity for Liver X Receptor β Antagonists

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Glucocorticoids (GCs) are powerful anti-inflammatory and immunosuppressive drugs that have revolutionized the treatment of acute and chronic inflammatory diseases. However, long-term glucocorticoid therapy results in metabolic side effects, such as increased liver glucose production and insulin resistance, causing type 2 diabetes. Our previous studies have revealed that the inhibition of liver X receptor β (LXRβ) can preserve the beneficial effects of glucocorticoids while minimizing their metabolic complications. We identified the small molecule LO-520 as a selective LXRβ antagonist with an IC50 of 215 nM. To continue to advance an LXRβ antagonist to pre-clinical status, we aim to achieve a molecule with a potency <100 nM, *in vitro* metabolic stability in microsomes >200 min and selectivity of LXRβ/LXRα >100 fold. Therefore, we performed SAR studies on LO-520 and were able to increase the potency of our LXRβ antagonists from over 200 nM to less than 10 nM while maintaining the metabolic stability of the most promising compounds. Within the compounds tested, we identified a subset that exhibited more than 10-fold selectivity for LXRβ over LXRα. Mechanistic characterization of the structural basis for the selectivity of LXRβ antagonists was initiated, and validation of a direct interaction between LO-520 and the LXRβ ligand binding domain was achieved using affinity selection-mass spectrometry. These results lay the groundwork for developing a metabolically stable and orally bioavailable selective LXRβ antagonist for the treatment and prevention of glucocorticoid-induced diabetes.

[Note that structures will not be shown to protect a patent filing in the near future].

Poster #7

The role of Liver Receptor Homolog 1 (LRH-1) in regulating breast cancer progression by modulating the immune response

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Breast cancer remains the second leading cause of death among American women. Thus, it is imperative to develop novel therapeutic targets facilitating the engagement of immune system in cancer therapies.

Since cholesterol metabolism is important for myeloid immune cell function, we launched studies to identify proteins involved in cholesterol homeostasis that are amenable to small molecule intervention. Liver Receptor Homolog 1 (LRH-1/NR5A2) is highly expressed in myeloid cells, particularly neutrophils. We have found that elevated LRH-1 expression in breast tumors is associated with increased survival rate. Thus, we hypothesized that LRH-1 acts as a cancer immunity modulator in myeloid cells, which subsequently impacts breast cancer progression.

Neutrophil NETosis has previously been implicated in reemergence from breast cancer dormancy and metastatic recurrence. Neutrophils treated with an LRH-1 antagonist demonstrated an increased in NETosis, while an agonist decreased NETosis. Neutrophil phagocytosis is an important neutrophil functiomn. LRH-1 antagonist treatment strongly decreased the phagocytotic ability, while treatment with an agonist did not significantly impact this process. We also found that LRH-1 inhibits neutrophil migration towards cancer cells, a finding that may have important implications regarding infiltration of immune-suppressive myeloid cells. Finally, we find that LRH-1 expressed in neutrophils can inhibit T cell expansion.

Collectively, our data indicate that LRH-1 plays important roles in regulating neutrophils functions, including NETosis, phagocytosis, migration and T cell activation. Overall, these findings suggest that LRH-1 in neutrophils regulates the immune response, and therefore can be a potential therapeutic target for cancer patients.

Poster #8

Evaluation of a novel selective glucocorticoid receptor modulator: Des-Ciclesonide and its therapeutic potential in bronchopulmonary dysplasia

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Des-ciclesonide (DesCIC), the metabolite of ciclesonide (CIC), is a potent glucocorticoid receptor (GR) agonist with tissue-specific metabolism and a higher safety profile, compared to dexamethasone (Dex), making it a promising pharmacotherapy for BPD.

Sprague-Dawley P0 pups were given five daily s.c. injections of vehicle, 0.5 mg/kg Dex, 0.5 or 1.25 mg/kg DesCIC. Systemic effects were assessed by measuring weight gain, brain weight, blood glucose and serum levels of insulin-like growth factor-1 (IGF-1).

Dex was associated with delayed weight gain and reduced IGF-1; Des-CIC did not trigger growth suppression or reductions in IGF-1. Hyperglycemia was evident in Dex-treated pups at 4 and 24 hours but absent in 0.5 mg/kg DesCIC with only a modest transient elevation after 1.25 mg/kg DesCIC. Pups treated with high but not low dose DesCIC had a modest reduction in brain weight that was significantly different than that observed with Dex. RNAseq of lung and liver tissue revealed a greater number and higher level of gene induction in Dex compared to the DesCIC group with unique pathways defined by the transcriptome in each tissue. qRTPCR of lung tissue confirmed the repression of pro-inflammatory GR target gene, TNF-α, by DesCIC.

DesCIC may be anti-inflammatory without producing the detrimental growth and hyperglycemic effects of Dex in neonatal rats. The potential enhanced safety profile of the prodrug CIC to treat BPD may be influenced by its tissue-selective conversion to a novel selective GR modulator, whose unique transcriptional responses may limit adverse systemic effects typically triggered by therapeutic sGCs in neonates.

Poster #9

Estrogen dependent and independent metabolic maladaptations contributing to BPH

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Background: While androgens and estrogens are likely to impact the development and progression of benign prostatic hyperplasia (BPH), the role of metabolic maladaptation driven by steroid receptors or other signaling pathways in disease remains unresolved.

Methods: The impact of ERß on prostatic mitochondrial function was assessed in aged global ERß knockout mice. Mechanistic studies to assess the impact of mitochondrial dysfunction utilized the BHPrS1 benign human prostate stromal cell line. Glucose-deprivation forces BHPrS1 cells to rely predominantly on oxidative phosphorylation (OXPHOS) for ATP production and maintaining metabolic homeostasis, sensitizing them to disruptions in OXPHOS. We tested the impact of glucose deprivation on cell growth, fibrosis-related gene expression and mitochondrial respiration via cell growth assays, qPCR and Oroboros analyses. Expression of anoikis resistance markers was assayed using qPCR and immunofluorescent staining.

Results: Aged but not young ERß knockout mice displayed reduced activity of mitochondrial electron transport chain (ETC) complex I and II. Under glucose-deprivation conditions, BHPrS1 proliferation was significantly but reversibly inhibited and fibrosis-related gene expression was increased. Glucose deprivation sensitized cells to mitochondrial stress induced by rotenone, further reducing proliferation as well as loss of cellular adhesion. Anoikis resistance markers (ZC3H4 and TrkB) were up-regulated.

Conclusions: ERß may play a protective effect in aging prostate to maintain mitochondrial ETC activity and metabolic homeostasis. Metabolic maladaptations resulting from reduced glycolytic ATP production may promote fibrosis in prostate stromal cells. Prostate stromal cells appear to be sensitive to complex I inhibition and may adapt to mitochondrial dysfunction through promotion of anoikis resistance.

Poster #10

Integration of Glucocorticoid and Mineralocorticoid receptor signaling in triple-negative breast cancer models.

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Glucocorticoid receptors (GR) sense a convergence of host and cellular stress signaling to orchestrate an array of advanced cancer phenotypes associated with triple-negative breast cancer (TNBC) progression. The Lange lab reported p38 MAP kinase mediated phosphorylation of GR at serine 134 (Ser134) in response to tumor microenvironment-derived cytokines, such as TGF-beta-1. Phospho-Ser134-GR (p-Ser134-GR) upregulated gene sets that promote cancer cell survival, chemoresistance, and migratory/invasive behavior in TNBC models. In addition to acting as ligands for GR, glucocorticoids also bind to and activate another closely related steroid hormone receptor - the mineralocorticoid receptor (MR). The elucidation of functional responses upon activation

of MR remains an untapped area in breast cancer. Our probe into public datasets (METABRIC, and TCGA) demonstrated significantly higher expression of MR transcripts in TNBC relative to luminal breast cancer. High expression of MR predicted worse overall survival in ERα-negative breast cancer patients compared to the low expressing cohort. Silencing of MR was carried out by siRNA-mediated knockdown and treatment with spironolactone, a competitive MR inhibitor. Interestingly, MR knockdown significantly reduced the TGF-beta-1 induced migratory capacity of breast cancer cells compared to the wild-type cells. This biological phenotype of decreased TGF-beta-1 induced migration upon MR knockdown parallels the reduced migration we observed when the Ser 134 site on GR was mutated to alanine in TNBC models. We therefore hypothesized that MR and GR may cooperate under the influence of growth factors and cytokines abundantly present in the tumor-microenvironment. Preliminary data suggest that cytoplasmic GR/MR complexes associate upon TGF-beta-1 treatment. The overarching goal of this study is to elucidate if MR is a required GR binding-partner and a potential therapeutic target in GR- and cytokine-driven metastatic processes in TNBC.

Poster #11

Therapeutic targeting of mitochondrial metabolism by P2X4 receptor inhibition and amino acid restriction in renal carcinoma models

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Background. Large-scale metabolomic data have associated metabolic alterations with the pathogenesis and progression of renal carcinoma and have correlated mitochondrial activity with poor survival in a subset of patients. Lysosomes are intracellular Ca^{2+} hubs that are essential for membrane trafficking and signaling. The lysosomal purinergic receptor 4 (P2XR4), an ATP/Ca^{2+} pump, plays a key role in energy flux. Furthermore, dietary restrictions have been reported to potentially modulate tumor metabolism. In this study, we investigated the role of P2XR4 inhibition and amino acid (AA) restriction in metabolic and energy dynamics in clear cell and translocation RCC models.

Methods. Seahorse, immunofluorescence and fluorescence cell sorting, genetic silencing and pharmacological inhibition were utilized to assess the role of P2X4R and AA in regulating mitochondrial function. Patient-derived organoids and murine xenograft models were used to demonstrate the impact of P2XR4 inhibition and AA restriction.

Results. Our data suggest that oxo-phosphorylation is the main source of tumor-derived ATP in a subset of ccRCC cells but in all the tRCC cells assessed. Mitochondrial function inhibition failure induced by pharmacological inhibition or P2XR4 silencing was associated with increased oxygen radical species, changes in mitochondrial permeability. Amino acid restriction was associated in decreased oxidative phosphorylation in RCC models with baseline elevated mitochondrial function. The results from combining amino acid restriction and P2X4R inhibition are ongoing and will be presented.

Conclusion: Overall, our preliminary results suggest that the perturbed mitochondrial activity induced by P2XR4 inhibition and amino acid restriction may represent a new therapeutic strategy for a subset of RCC patients.

Poster #12

Murine CD4+ T cells exhibit sexually dimorphic responses to estrogen signaling

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Many autoimmune diseases exhibit sexual dimorphism. 17β-estradiol (estrogen, “E2”), a steroid sex hormone primarily known for its reproductive roles, has also been shown to modulate the phenotype and function of CD4+ T cells. E2 signals through two nuclear receptors, ERα and ERβ, which regulate gene transcription through direct DNA binding and other non-genomic mechanisms. We previously showed that in the SAMP/YitFC model of Crohn’s-like ileitis, loss of ERβ enhanced inflammation selectively in female mice. Additionally, our previous studies showed that loss of ERβ resulted in decreased expression of Foxp3 in CD4+ T cells, together suggesting a pro-inflammatory role for ERα and anti-inflammatory role for ERβ, potentially in a sex-specific manner.

Using the CD45RB T cell transfer model of colitis, we tested the pathogenicity of CD4+ T cells lacking expression of ERα vs. ERβ. Based on prior findings supporting a proinflammatory role for ERα in T cells, we hypothesized that skewing signaling in favor of ERβ (through deletion of ERα) would prevent or improve experimental colitis. However, recipients of ERα-KO cells developed more severe disease compared to recipients of WT or ERβ-KO cells, indicating that deletion of ERα was not protective. Further, recipients of male ERα-KO and male ERβ-KO cells developed comparable disease, suggesting a sex-specific functional redundancy for ERα and ERβ in CD4+ T cells. Future studies will identify the contributions of ERα vs. ERβ-specific signaling in effector and regulatory T cell subsets and the functional impact of these signaling pathways in males versus females.

Poster #13

PKN1 engages UPF1 as a mediator of AR- and SRF-dependent transcription in prostate cancer.

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The ligand-activated androgen receptor (AR) is a transcription factor that controls prostate cancer (CaP) progression. Androgen deprivation therapy (ADT) that prevents AR-androgen interaction is the default treatment for metastatic CaP. Despite initial remissions, ADT invariably fails and CaP progresses to castration-recurrent CaP (CRPC), which still relies on aberrantly activated AR. Alternative approaches are needed to inhibit AR action in CaP that has failed ADT. Our laboratory has been exploring the therapeutic potential of a non-canonical AR signaling mechanism wherein AR stimulates another transcription factor, Serum Response Factor (SRF). AR-SRF action correlates with CaP progression and is enriched in CRPC. Inhibiting SRF-dependent AR action may be an effective treatment strategy following failure of ADT but remains poorly understood.

Previously, we determined that the Rho effector Protein Kinase N1 (PKN1) transduces signaling from AR to SRF. This signaling was mediated by PKN1 and SRF interaction at AR-SRF target genes, whose transcription relied on PKN1's kinase moiety. In Co-IP, ChIP and qRT-PCR assays, kinase-dead PKN1 prevented SRF-PKN1 interaction, recruitment of PKN1 to SRF target genes and AR-SRF target gene expression. Here, we performed biotin-based Turbo-ID-mediated proximity labeling coupled with mass spectrometry (PLA-MS) to elucidate SRF-PKN1 complex function. We isolated 26 significant and mostly novel PKN1 interactors with preferential roles in transcription, RNA binding and DNA repair. The majority had not previously linked to AR or SRF action or CaP progression. PLA-MS studies which we combined with SRF IP, androgen treatment or nuclear localization independently returned several of these PKN1 interactors. A prominent hit was the RNA helicase UPF1, involved in mRNA surveillance and nonsense-mediated mRNA decay (NMD). Co-IP assays confirmed that both SRF and PKN1 interacted with UPF1 and showed wild-type PKN1 increased while kinase-dead PKN1 decreased UPF1-SRF interactions. Moreover, silencing of UPF1 decreased CRPC cell viability, consistent with effects of SRF and PKN1 loss. UPF1 protein sequence contained 3 putative PKN1 consensus phosphorylation motifs, 2 of which were confirmed in in vitro kinase assays. RNA-seq studies combined with pathway analyses revealed considerable overlap between AR-dependent UPF1- and PKN1-dependent gene signatures and cell functions. Confirming clinical relevance of the UPF1-SRF-PKN1 interaction, we found overlap in gene expression profiles of CaP specimens that showed high PKN1, high SRF and high UPF1 expression, which was enriched in CRPC cases and associated with functions in cell proliferation and cell division.

Collectively, our findings establish UPF1, which represents a druggable target, as a novel regulator of clinically relevant AR-SRF-PKN1 signaling in CaP growth. Additionally, our results suggest an unrecognized role for NMD in CaP progression.

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Poster #14

Screening proteins secreted by endothelial progenitor cells as mediators of liver X receptor-dependent anti-atherosclerotic activity

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Early atherosclerosis is characterized by endothelial dysfunction and monocyte-endothelial cell adhesion (MEA). The liver X receptors (LXRs) are known to be anti-atherogenic in part by promoting macrophage reverse cholesterol transport. However, LXRs have also been shown to mediate vasoreparation independent of cholesterol efflux gene expression, implicating additional cell types. We found that LXR activation by the synthetic ligand GW3965 in bone marrow-derived endothelial progenitor cells (EPCs) generates a secretome that decreases MEA in 2D culture and 3D organ-on-chip models, as well as aortic sinus lesion area in *Ldlr-/-* mice. Our goal is to identify and characterize protein(s) from the LXR-activated EPC secretome as potential therapeutic targets. Conditioned media (CM) was generated from EPCs treated in the presence of GW or vehicle. Human aortic endothelial cells (HAECs) were treated with GW- or vehicle-treated EPC CM, or one of 10 candidate recombinant proteins at their estimated concentrations in the GW-treated EPC CM before co-treatment with TNFα. HAECs were cocultured with labelled THP-1 monocytes to assess MEA or analyzed by RT-qPCR to measure the expression of inflammatory (*Il1b*, *Il6*), cell adhesion (*Icam1*, *Vcam1*, *Sele*) and cholesterol efflux (*Abca1*, *Abcg1*) genes. Four candidates (IL18-BP, CD5L, PPT1 and soluble TREM2 (sTREM2)) decreased MEA with comparable efficacy to the GW-treated EPC secretome alone. sTREM2 shows greatest promise as it decreases MEA dose-dependently and drives an anti-atherogenic gene expression profile in activated HAECs. Thus far, sTREM2 demonstrates the most promising anti-atherogenic potential. Next, we will assess its protective effects through AAV-mediated expression in an *Ldlr*-/- mouse model.

Poster #15

Examining the importance of LXRβ in brown fat vs white fat in the modulation of glucocorticoid-mediated adipose tissue dysfunction

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Synthetic glucocorticoids (GC) are used therapeutically as potent and effective anti-inflammatory drugs. However, long-term exposure to GCs increases the incidence of obesity in part through suppressing thermogenesis function of brown adipose tissue (BAT) and disrupting white adipose tissue (WAT) lipogenesis and lipolysis. We have recently found that loss of LXRβ in both WAT and BAT depots [LXRβ$^{fl/fl,Adipoq\text{-}Cre,}$ WBKO] prevents GC-induced adipose tissue dysfunction seen in WT mice. To address the specific contribution of LXRβ in BAT, we generated BAT-specific LXRβ KO mice [LXRβ$^{fl/fl,Ucp1\text{-}Cre}$, BKO], treated them with GC for 5 days (Dexamethasone, 5 mg/kg, b.i.d), and compared their GC response to WT and WBKO mice. Body weight, adipose tissue depot weight and gene expression were analyzed. As observed previously, GC-treated WBKO were resistant to BAT whitening and the development of fatty liver (from reduced shuttling of fatty acids). In contrast, BKO mice were not protected again GCinduced BAT whitening. WT and BKO showed GC-mediated increases in the mRNA expression of *de novo* lipogenesis genes (*Fasn, Acaca*) (P<0.05) and triglyceride synthesis gene (*Lpin1*) (P<0.05) in epididymal, inguinal, and mesenteric WAT. Thus, GC-induced adipose tissue dysfunction is largely dependent on the expression of LXRβ in WAT and promotes the shuttling of fatty acids to BAT causing whitening, and functional impairment. This study improved our understanding of the interplay between GR and LXRβ in inter-organ communication in response to GCs and defined LXRβ in WAT as a therapeutic target to allow the anti-inflammatory benefit of GCs without the detrimental metabolic side effects.

Poster #16

Liver-Specific Loss of the Nuclear Receptor Co-Regulator ARGLU1 Protects Against Diet-Induced Obesity in Female Mice

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Arginine and glutamate rich 1 (ARGLU1) is a co-regulator for several nuclear receptors that are key modulators of nutrient metabolism. Herein, we assessed the importance of ARGLU1 in lipid and carbohydrate metabolism. Aged (11-month-old) female wildtype *Arglu1*$^{fl/fl}$ mice (WT) and liver-specific *Arglu1*$^{fl/fl,AlbCre}$ (LKO) were fed a high-fat, high-cholesterol diet (HFD, TD.88137 Envigo) for 12-weeks (N=6-13). Mice were housed in Promethion Metabolic Cages (Sable Systems) at thermoneutrality for 5 days to measure energy balance by indirect calorimetry (N=5-7). Mice were also subjected to glucose tolerance and insulin tolerance tests (N=4-8). LKO mice were resistant to diet-induced obesity with final body weights compared to HFD-fed WT mice of 30.6±0.9g vs 35±1g (P≤0.05). This coincided with decreased white and brown adipose tissue weight in LKO mice vs WT mice. In addition, LKO mice were more glucose tolerant and insulin tolerant compared to HFD-fed WT mice. Interestingly, metabolic cage data showed no change in food intake, locomotor activity or energy expenditure between HFD-fed WT and LKO mice when accounting for body mass as a covariate (ANCOVA, CalR). The respiratory exchange ratio suggested that LKO mice preferentially used fat as their energy source compared to WT mice (P≤0.0082). Compared to WT mice, LKO mice absorbed less lipid from the diet, and contained elevated fecal cholesterol and triglycerides (P≤0.01). These data suggest that liver ARGLU1 modulates intestinal lipid absorption. Future studies will examine bile acid levels and use RNA-seq and ATAC-seq of livers from WT and LKO mice to understand mechanisms of resistance to diet-induced obesity.

Poster #17

Sex differences in bile acid composition in a murine model of hepatocellular carcinoma promotes dysbiosis

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Hepatocellular carcinoma (HCC), a primary liver cancer with high incidence and mortality, displays increased prevalence in men than women. Bile acid metabolism is changed during hepatocarcinogenesis, and bile acids have been indicated as potential prognostic markers for HCC.

Primary bile acids, cholic acid and chenodeoxycholic acid, are made in the liver and conjugated to either taurine or glycine by bile acid-CoA: amino acid N-acyltransferase (BAAT). To aid in fat digestion, bile acids are secreted into the intestine and can interact with resident microbes, which remove the amino acid residue via bile salt hydrolase (BSH) and further modify them into secondary bile acids, deoxycholic acid and lithocholic acid. From the intestine, bile acids are reabsorbed and circulated back to the liver. If during enterohepatic circulation, bile acids are not transported into the liver, they enter systemic circulation. During hepatocarcinogenesis, increased systemic bile acids have been observed.

We have a mouse model, where the bile acid-related nuclear receptors, farnesoid X receptor (*Fxr*) and small heterodimer partner (*Shp*), are knocked out, resulting in increased circulating bile acids. This double knockout (DKO) model mimics the liver cancer incidence observed in humans, including the sex differences. The circulating bile acid composition of the DKO male mice consists of a higher proportion of unconjugated cholic acid that does not appear to stem from lack of conjugation in the liver.

Thus, understanding sex differences in microbial composition during bile acid dysregulation will enable us to develop a signature that may aid in HCC surveillance.

Poster #18

Role of ER/PR/IRS-1 Transcriptional Complexes in Endocrine Resistant Breast Cancer

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In the United States, 1 in 8 women will develop invasive BC within their lifetime. For Luminal breast cancer expressing steroid hormone receptors (SRs) for estrogen and progesterone (ER+/PR+), current standard of care targets ER with antagonists, such as tamoxifen, or blocks estrogen synthesis using aromatase inhibitors. Unfortunately, these endocrine therapies ultimately fail in up to 40% of patients with node positive status. Most endocrine resistant breast cancers retain expression of ER and PR, *PGR* being a key ER target gene. Two common mechanisms of resistance are ESR1 gene mutations, providing ligand-independent activation of ER, high expression of PR, and activation of oncogenic signaling pathways that circumvent therapies. These pathways include mitogen- and stress-induced signaling pathways (MAPKs, CDKs, PI3K/AKT) as well as those driven by PR, such as ErbB family members and their ligands. Interestingly, PR can act as a repressor of ER-driven proliferation in hormone-sensitive breast cancer models. However, tumor-promoting actions of PR have been identified by the Lange lab and others. Constitutive ER/PR complexes cooperate at cancer-relevant target genes and anti-progestins block estrogen-driven proliferation and survival. The Lange lab has demonstrated that MAPK-activated phospho-PRs drive tamoxifen resistance and cancer stem cell expansion. Tumor heterogeneity underscores the need to target both hormone sensitive proliferating cells and cancer stem cells to avoid recurrence of newly resistant BC. A cytoplasmic adaptor molecule in the IGF/insulin signaling pathway, insulin receptor substrate-one (IRS-1), has been identified as a new possible target. The Lange lab reported that IRS-1 forms a complex with ER/PR and is required for novel nuclear functions driving breast cancer stemness properties. *IRS-1* is a ligand-independent phospho-PR target gene. We hypothesize that the transcriptional regulation of target genes by phosphorylated PRs in p-PR/ER/IRS-1 complexes promotes increased insulin sensitivity, endocrine resistance, and stemness phenotypes in ER+ breast cancer. Characterization of the mechanisms by which PR contributes to endocrine resistance may lead to new therapeutic targets for improved outcomes for women with endocrine resistant ER+ breast cancer.

Poster #19

Androgen receptor mediated transcriptional repression of SIRT3 drives prostate cancer progression.

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Prostate cancer (PCa) progression to lethal castration resistant metastatic disease is a continual challenge in treatment. Androgen receptor (AR) signaling is a critical component of PCa development and progression, and although treatment with AR signaling inhibitors (ARSIs) is clinically very effective it often results in resistance and relapse. Therefore, a distinct need exists to uncover novel therapeutic targets addressing aggressive metastatic PCa. Recent studies from our laboratory identified that mitochondrial deacetylase sirtuin-3 (SIRT3) is transcriptionally repressed by AR and its coregulator steroid receptor coactivator-2 (SRC-2). SIRT3 is known to regulate activity of various mitochondrial metabolic enzymes and clinical transcriptomic data analysis revealed SIRT3 expression is significantly diminished in metastatic lesions compared to benign/localized tumors. To understand the biology, we re-expressed SIRT3 in mouse PCa lines using inducible constructs, and Seahorse metabolic assays revealed significantly decreased maximal oxygen consumption rate (OCR) in SIRT3 tumors compared to control. Implantation of SIRT3-prostate tumor cells in syngeneic mice resulted in significantly reduced tumor growth, and bulk RNA-sequencing analysis identified aspartate metabolism significantly activated in SIRT3 tumors. Our ongoing experiments with a genetic mouse model with prostate specific SIRT3 deletion is also showing a significant increase in tumor weight compared to wild type animals at multiple timepoints. Together, these findings suggest that SIRT3 has tumor suppressive function in PCa through metabolic reprogramming, and SIRT3 repression by AR and SRC-2 drives prostate tumor progression.

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Poster #20

Coregulator SRC-2 dependent increased lipid metabolism induces an immunosuppressive prostate tumor microenvironment.

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Dysregulated lipid metabolism, and an immunosuppressive tumor microenvironment (TME) are hallmarks of prostate cancer progression. However, the mechanisms by which dysregulated lipid metabolism influences immune response in the TME remains relatively unexplored. We have demonstrated that steroid receptor coactivator 2 (SRC-2) drives glutamine dependent *de novo* lipogenesis, which leads to the development of aggressive metastatic prostate cancer. Mechanistically, we found that mitochondrial citrate biosynthesis was significantly increased to support the increased demand for lipids. This was mediated by activation of aconitase enzyme (ACO2), which was post-translationally regulated by acetylation. Coregulator SRC-2 along with AR increases ACO2 activity by repressing mitochondrial deacetylase SIRT3 favoring lipogenesis. Genetic inhibition of ACO2 significantly reduced *de novo* lipogenesis and eventually regressed tumor growth in syngeneic mouse models. We performed single-cell RNA sequencing (scRNASeq) using wildtype (WT) and ACO2 depleted prostate tumors to investigate the effects on TME. Macrophages were significantly polarized, with pro-inflammatory M1-like macrophages being associated with the ACO2 depleted tumors, compared to WT tumors which displayed increased enrichment of pro-tumorigenic M2-like. By incubating bone marrow derived macrophages with tumor conditioned media, we observed a similar shift to a more M1 like population when incubated with ACO2 depleted media compared to WT. Our observations indicate that secreted factor/metabolite due to dysregulated lipid metabolism may be responsible for the polarization. Current studies are directed towards identifying the secreted factors to define the mechanisms involved in macrophage polarization. Our studies will identify whether modulating dysregulated lipid metabolism will alter immunosuppressive prostate TME.

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Poster #21

Re-sensitizing the Refractory Breast Cancer Bone Metastasis to Endocrine Therapies

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Approximately 90% of Breast Cancer (BrCa) related deaths are caused by metastasis and bone is the first and most frequent site of breast cancer metastatic expansion, which can lead to severe pain, immobility, fractures, and nerve damage, as well as the development of metastases in other organs, hence; a poor quality of life in patients. Currently, treatment options for these bone metastases (BoM) are limited because most patients with BoM shows reduced ER dependency which leads to resistance to standard endocrine or hormonal therapies for estrogen receptor-positive (ER+) BrCa. The long-term goal of the proposed research is to develop a strategy where metastatic cancer cells in bone can be dependent on ER signaling again thereby restoring their sensitivity to endocrine therapies. We observed a transient loss of ER expression in concert with enhanced transcriptional activity of the transcriptional coactivators YAP/TAZ - the downstream effectors of the Hippo pathway (responsible for regulating cell proliferation and death) during bone colonization by BrCa cells. We hypothesize that the interaction between cancer cells and osteoblasts in the bone microenvironment leads to the activation of calcium signaling in cancer cells, resulting in the dephosphorylation and nuclear localization of YAP/TAZ which subsequently suppresses the transcription of the estrogen receptor gene (ESR).

Our research strategy is as presented below. First, we will employ a combination of 2D/3D co-culture models of BoM along with a mechanical loading system and determine the molecular mechanism driving the dynamical activation of YAP/TAZ in BCa BoM. Using a unique ex vivo BM model called Bone In Culture Array (BICA) which replicates the in-vivo conditions, we will determine if verteporfin, a YAP/TAZ antagonist, can synergize and possibly enhance the effects of fulvestrant, an ER antagonist in current use for certain types of BrCa in preventing BoM outgrowths and treating established BoM in mice. This research could ultimately lead to a favorable combination strategy to treat endocrine-resistant BoM in BrCa patients and prolong their survival.

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