2025
Est. 2019

OCMF

Ovarian Cancer Midwest Focus Conference

November 10 - 11, 2025

Graduate Hotel

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Department of OBGYN &
Women's Health

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Welcome!

Welcome to the 7th annual Minnesota-based Ovarian Cancer Midwest Focus (OCMF) Conference!

PROGRAM CHAIRS

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University of Minnesota - School of Medicine

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University of Pennsylvania - Perelman School of Medicine

Andrew K. Godwin, PhD
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Boris Winterhoff, MD, MS
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2025 OCMF Est. 2019 Ovarian Cancer Midwest Focus Conference

2025 Keynotes

Ethel N. Ruvelson Keynote Speaker

Joan Brugge, PhD

Professor, Department of Cell Biology
Harvard Medical School

Dr. Brugge is currently a Professor of Cell Biology at HMS. She has held full professorships at the SUNY, Stony Brook, and the University of Pennsylvania, where she was also an investigator of the Howard Hughes Medical Institute. From 1992-1997, she was a founder and scientific director of the biotechnology company ARIAD. She then joined Harvard in 1997 and was Chair of Cell Biology from 2004-2014. She is the co-founder and co-director of the Ludwig Center at Harvard, where investigators across Harvard develop strategies to overcome barriers limiting the efficacy of current and emerging cancer therapies.

The **Ethel N. Ruvelson Memorial Lectureship in Ovarian Cancer fund** helps us continue to fund vital research lectureships and provide educational programs for our faculty and clinical researchers at the University of Minnesota.

John L. McKelvey Keynote Speaker

Ernst Lengyel, MD, PhD

Chair, Department of Obstetrics and Gynecology
University of Chicago

Dr. Lengyel is a translational scientist and gynecologic oncologist currently working with the University of Chicago, where he has established a clinical practice focused on ovarian cancer and oversees a translational research laboratory investigating the biology of the disease. Dr. Lengyel has received the NCI R35 Outstanding Investigator Award and multiple foundation grants, currently mentors two NIH K-awardees, and regularly serves as an ad hoc member of NIH study sections. Dr. Lengyel is a member of the U.S. National Academy of Medicine and the Association of American Physicians (AAP).

The **John L. McKelvey Lectureship fund** provides support for annual events that bring together leading experts who share knowledge with our faculty, researchers, and conference attendees.

Day 1 November 10, 2025

2025 Est. 2019 CMF Ovarian Cancer Midwest Focus Conference

Breakfast: 7:15 - 8:00 AM

Opening Remarks & Welcome: 8:00 - 8:10 AM

SESSION 1: CANCER CHROMOSOMES

MODERATORS: ALEX MAIA, PHD & ANDREW K. GODWIN, PHD

TIME	TITLE	PRESENTER
8:10 - 9:00 AM	Single Cell Approaches to Define Ovarian Cancer Cell Populations that Survive Chemotherapy	**Ethel N. Ruvelson Keynote Speaker** **Joan Brugge, PhD** Harvard Medical School
9:00 - 9:10 AM	Question & Answer Session	
9:10 - 9:30 AM	Activating Anti-Cancer Immunity with Beta-Radioligand Therapy and Isoform-Selective Targeting of 4Ig-B7-H3	**David Piwnica-Worms, MD, PhD** University of Texas - MD Anderson Cancer Center
9:30 - 9:35 AM	Question & Answer Session	
9:35 - 9:55 AM	PARP Inhibitor Resistance: Mutation, Adaptation, and Survival	**Annapoorna Venkatachalam, PhD, MS** Mayo Clinic
9:55 - 10:00 AM	Question & Answer Session	
10:00 - 10:20 AM	3D Genomic Analysis of Human Pancreatic Precancer	**Laura Wood, MD, PhD** Johns Hopkins University School of Medicine
10:20 - 10:25 AM	Question & Answer Session	

Day 1 November 10, 2025

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SESSION 1: CANCER CHROMOSOMES

MODERATORS: ALEX MAIA, PHD & ANDREW K. GODWIN, PHD

TIME	TITLE	PRESENTER
10:25 - 10:40 AM	Break	
10:40 - 11:25 AM	**Flash Talks**	
	FOXK2–KANSL1 Axis Sustains ROS Homeostasis and Drives Cisplatin Resistance in Ovarian Cancer	**Junzui Li, PhD** Northwestern University Feinberg School of Medicine
	Small Extracellular Vesicle Proteomics Reveal Potential Early Biomarkers for High-Grade Serous Ovarian Cancer	**Bidii Ngala, MS, PhD** University of Kansas Medical Center
	STAR (Stroma-Tumor AI Risk) Assessment: Association of AI-Derived Tumor-Stroma Proportion with Patient Survival Provides Added Prognostic Value Beyond KELIM in Epithelial Ovarian Cancer	**Morgann Madill, MD** University of Minnesota School of Medicine
11:25 - 11:35 AM	Transition	
11:35 - 12:00 PM	**Community Awards**	
	Award for Outstanding Support for Ovarian Cancer Research	The Amy Krouse Rosenthal Foundation **Presented to: Ernst Lengyel**
	Inspiration and Philanthropy Award	Gilda's Club Minnesota **Presented to: Katherine Todd**
	Lifetime Achievement Award for Excellence in Community Outreach	**Presented to: Kathleen Gavin**

Day 1 November 10, 2025

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SESSION 2: OVARIAN CANCER MICRO ENVIRONMENT

MODERATORS: RONNY DRAPKIN, MD, PHD & BORIS WINTERHOFF, MD, MS

TIME	TITLE	PRESENTER
12:00 - 1:15 PM	Lunch & Poster Session	
1:20 - 1:30 PM	Natera Sponsor Presentation	
1:30 - 1:50 PM	Targeting the COP9 Signalsome Overcomes Platinum Resistance in Ovarian Cancer Through Two Distinct Genome Stability Mechanisms	**Maggie Mullen, MD, MSCI** Washington University in St. Louis
1:50 - 1:55 PM	Question & Answer Session	
1:55 - 2:15 PM	Contributions of Chronic Viral Mimicry Towards Ovarian High Grade Serous Carcinoma Initiation	**Charles Ishak, PhD** University of Texas - MD Anderson Cancer Center
2:15 - 2:20 PM	Question & Answer Session	
2:20 - 2:40 PM	A Th17 Dendritic Cell Vaccine for Ovarian Cancer Patients	**Matt Block, MD, PhD** Mayo Clinic
2:40 - 2:45 PM	Question & Answer Session	
2:45 - 3:00 PM	Break	
3:00 - 3:20 PM	Engineering Microbes to Target and Reshape the Ovarian Tumor Metabolic Landscape	**Mohammed Dwidar, PhD** Cleveland Clinic Foundation

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2025 CMF Est. 2019 Ovarian Cancer Midwest Focus Conference

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MODERATORS: RONNY DRAPKIN, MD, PHD & BORIS WINTERHOFF, MD, MS

TIME	TITLE	PRESENTER
3:20 - 3:25 PM	Question & Answer Session	
3:25 - 3:45 PM	Developing Consensus on the Management of STIC Lesions to Plan for a Clinical Trial	**Joan Walker, MD** University of Oklahoma Health Sciences College of Medicine
3:45 - 3:50 PM	Question & Answer Session	
3:50 - 4:10 PM	Development of a Claudin 6 Targeting Antibody Drug Conjugate: From Bench to Bedside and Back	**Gottfried Konecny, MD** University of California Los Angeles
4:10 - 4:15 PM	Question & Answer Session	
4:15 - 4:20 PM	Closing Remarks	
4:20 - 6:00 PM	Poster Session	

Reception

Join Us for Dinner, Drinks, and Games!
6:00pm - 9:00pm

Topgolf Lounge - located on the first floor of the Graduate Hotel
Sign up for our Air Hockey Tournament at registration.

Day 2 November 11, 2025

2025 Est. 2019 OCMF Ovarian Cancer Midwest Focus Conference

Breakfast: 7:15 - 8:00 AM
Welcome: 8:00 AM

SESSION 3: TRANSLATING INNOVATION TO THE CLINIC

MODERATORS: GOTTFRIED KONECNY, MD & PAOLA VERMEER, PHD

TIME	TITLE	PRESENTER
8:05 - 8:40 AM	Patient Advocate Stories	
8:40 - 9:30 AM	Role of the Tumor Microenvironment in Ovarian Cancer	**John L. McKelvey Keynote Speaker** **Ernst Lengyel, MD, PhD** University of Chicago
9:30 - 9:40 AM	Question & Answer Session	
9:40 - 10:00 AM	Hematopoietic Stem Cell Derived Adipocytes Influence the Ovarian Cancer Microenvironment	**Zachary Watson, PhD** University of Colorado Anschutz Medical Campus
10:00 - 10:05 AM	Question & Answer Session	
10:05 - 10:15 AM	Break	
10:15 - 11:00 AM	**Flash Talks**	
	Targeting Early Adaptive Survival to PARP Inhibitors in High-grade Serous Ovarian Cancer	**Julie Duffield, PhD Candidate** Mayo Clinic
	AXL-Expressing Cancer-Associated Fibroblasts Suppress NK Cell Function in Vitro	**Manon Miller, PhD Candidate** University of California San Francisco
	A Rare Multipotent Peg-like Epithelial Cell is a Candidate Cell-of-Origin for High-Grade Serous Ovarian Cancer	**Megan Ritting, PhD Candidate** Mayo Clinic

Day 2 November 11, 2025

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SESSION 3: TRANSLATING INNOVATION TO THE CLINIC

MODERATORS: GOTTFRIED KONECNY, MD & PAOLA VERMEER, PHD

TIME	TITLE	PRESENTER
11:00 - 11:10 AM	Transition	
11:10 - 11:30 AM	Ovarian Cancer Prevention: Moving from Paradigm Shift to a National Standard of Care	**Becky Stone, MD, MS** Johns Hopkins School of Medicine
11:30 - 11:35 AM	Question & Answer Session	
11:35 - 11:55 AM	Personal Perspective on Advances in Ovarian Cancer Care and Research	**Dineo Khabele, MD** Washington University in St. Louis
11:55 - 12:00 PM	Question & Answer Session	
12:00 - 12:20 PM	"Nervous in the Service" TRPV1+ Tumor Innervation as a Novel Driver of Ovarian Cancer Progression	**Matt Knarr, PhD** University of Pennsylvania Perelman School of Medicine
12:20 - 12:25 PM	Question & Answer Session	
12:30 PM	Flash Talk & Poster Awards Closing Remarks	
Grab-and-Go Lunch		

On behalf of the OCMF Program Chairs, we would like to express our sincere gratitude to this year's sponsors, speakers, and participants. As we continue the fight against ovarian cancer, your contributions and collaboration are vital in our effort to expand education for those involved at all levels of research.

Join us in 2026 for the 8th annual OCMF Conference at the Mayo Clinic in Rochester, Minnesota.

Flash Talk Presenters

Junzui Li, PhD
Postdoctoral Fellow, Northwestern University

FOXK2–KANSL1 Axis Sustains ROS Homeostasis and Drives Cisplatin Resistance in Ovarian Cancer

Junzui Li is a Postdoctoral Fellow in Dr. Daniela Matei's laboratory at Northwestern University. His research focuses on the molecular mechanisms of ovarian cancer chemoresistance, particularly the transcriptional and epigenetic regulation of redox homeostasis.

Bidii Ngala, PhD
Postdoctoral Fellow, University of Kansas

Small Extracellular Vesicle Proteomics Reveal Potential Early Biomarkers for High-Grade Serous Ovarian Cancer

Bidii Ngala is a Postdoctoral Fellow in Dr. Andrew Godwin's lab at the University of Kansas. His research focuses on development and validation of small extracellular vesicles (sEVs) based detection systems for cancer early detection and disease monitoring with initial focus in ovarian cancer.

Morgann Madill, MD
Gyn Onc Fellow, University of Minnesota

STAR (Stroma-Tumor AI Risk) Assessment: Association of AI-Derived Tumor-Stroma Proportion with Patient Survival Provides Added Prognostic Value Beyond KELIM in Epithelial Ovarian Cancer

Morgann Madill is a second-year Gynecologic Oncology fellow at the University of Minnesota. Originally from Kansas City, Missouri, Morgann earned her medical degree and completed her OB/GYN residency at Saint Louis University.

Julie Duffield
PhD Candidate, Mayo Clinic

Targeting Early Adaptive Survival to PARP Inhibitors in High-grade Serous Ovarian Cancer

Julie Duffield is a third-year Molecular Pharmacology Ph.D. candidate under the mentorship of Dr. Arun Kanakkanthara at the Mayo Clinic. Her research focuses on novel biomarker-driven therapeutic strategies for ovarian cancer, and her work was recently recognized with an invitation to present orally at the 2025 AACR Advances in Ovarian Cancer Research.

Manon Miller
PhD Candidate, University of California San Franscisco

AXL-expressing Cancer-associated Fibroblasts Suppress NK Cell Function in Vitro

Manon Miller is a forth-year biomedical science Ph.D. student at UCSF where she is co-mentored by Dr. Katherine Fuh and Dr. Alan Ashworth. Her thesis focuses on the role of the TME on ovarian cancer metastasis, therapeutic resistance, and immune suppression.

Megan Ritting
PhD Candidate, Mayo Clinic

A Rare Multipotent Peg-like Epithelial Cell is a Candidate Cell-of-Origin for High-Grade Serous Ovarian Cancer

Megan Ritting is a fifth-year Ph.D. candidate in the Molecular Pharmacology and Experimental Therapeutics program at Mayo Clinic. Working under the mentorship of Dr. Nagarajan Kannan in the Stem Cell and Cancer Biology Laboratory, her research focuses on understanding the cellular origins and early molecular events driving ovarian cancer development.

FOXK2–KANSL1 Axis Sustains ROS Homeostasis and Drives Cisplatin Resistance in Ovarian Cancer

Junzui Li
Northwestern University Feinberg School of Medicine

Cisplatin resistance remains a major obstacle in ovarian cancer therapy. By integrating patient cohorts, single-cell/spatial transcriptomics, and functional assays, we identify FOXK2 as a central driver of chemoresistance through maintenance of redox balance. In TCGA-OC and independent datasets, FOXK2 expression is elevated in resistant tumors and associates with poorer progression-free survival. Single-cell analyses reveal enrichment of FOXK2-high cancer cells within resistant clusters, and spatial maps confirm FOXK2-high regions with low ROS signatures in recurrent specimens. Genetic FOXK2 knockdown/knockout across SKOV3, OVCAR5/8, and OVCAR5-cisR cells reduces cisplatin IC50, increases Annexin-V positivity and cleaved caspase-3, elevates cellular ROS (DCFDA), lowers mitochondrial spare/maximum respiration, and enhances glycolytic reliance; the antioxidant NAC reverses these phenotypes and rescues drug sensitivity. RNA-seq of FOXK2-KO cells shows coordinated down-regulation of antioxidant/ROS-metabolic programs (e.g., AP4B1, GPX2, PGC1A, SOD2), corroborated by qPCR/Western and increased sensitivity to H2O2 that is mitigated by NAC. CUT&Tag/ChIP tracks and ATAC profiles indicate FOXK2 occupancy and permissive chromatin at target promoters. IP-MS and reciprocal co-IP demonstrate that FOXK2 associates with the KANSL1/MOF/NCOR1 chromatin complex; spatial co-expression of FOXK2 and KANSL1 in tumors, and KANSL1 perturbation, support a functional complex that maintains H4K16ac and antioxidant gene expression. Collectively, these data define a FOXK2–KANSL1 epigenetic module that buffers ROS to sustain survival under cisplatin stress. Targeting this axis, alone or combined with redox modulation, offers a rational strategy to overcome chemoresistance in ovarian cancer.

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Small Extracellular Vesicle Proteomics Reveal Potential Early Biomarkers for High-Grade Serous Ovarian Cancer

Bidii Ngala, Sagar Rayamajhi, Jared Sipes, Leonidas E. Bantis, Samuel G. Mackintosh, Ricky D. Edmondson, Harsh Pathak, Ronny Dapkin, Andrew K. Godwin

Department of Pathology and Laboratory Medicine, University of Kansas Medical Center; Department of Biostatistics and Data Science, University of Kansas Medical Center; University of Arkansas For Medical Sciences, IDeA National Resource for Quantitative Proteomics; Department of Obstetrics and Gynecology, University of Pennsylvania; Kansas Institute of Precision Medicine, University of Kansas Medical Center

Background: High grade serous ovarian cancer (HGSOC), the most lethal Ovarian cancer subtype, is diagnosed at advanced stages due to nonspecific early symptoms. HGSOC is believed to originate in the fallopian tube (FT). Small extracellular vesicles (sEVs) released by cells into bodily fluids, are promising liquid biopsy biomarkers reflecting the molecular status of their cells of origin.

Hypothesis: We hypothesize that specific stage-based EV biomarkers can serve as clinically relevant analytes for the early detection of STIC, prior to its progression to early-stage (ES) HGSOC, at a time when the disease remains confined to the FT and curative interventions are still feasible.

Methods: To investigate this hypothesis, we used immortalized non-malignant FT epithelial cell model which were genetically modified to mimic the progression of p53 signatures to STIC lesions to ES-HGSOC, alongside a case-control study cohort plasma samples of 10 ES and 20 late-stage (LS) HGSOC and 40 healthy controls (HC). sEVs were isolated using ultracentrifugation, exoRneasy and size exclusion chromatography. EV- proteomic profiles were established via mass spectrometry.

Results: 52 of 1078 EV proteins were significantly upregulated in ES-HGSOC compared to HC, while 59 EV-proteins were upregulated in LS- HGSOC versus HC (log fold change >1, $p < 0.05$). Commonly upregulated EV-protein shared between the cell line models and ES-HGSOC include GSTP1, PRDX1/6, CS, CLU, B2M and SLC16A3. Additionally, p53 emerged as the top disease associated protein in the cell line model. Moreover, HGSOC had MYL6, MUC1, MYH14 and PTGS1 upregulation. Candidate EV-protein biomarkers were validated through immunohistochemistry, western capillary blotting and immunoassays. MUC1 EV-proteins showed strong diagnostic performance with an AUC of 0.840 for ES-HGSOC versus HC, and 0.860 for LS HGSOC versus HC. The p53 protein demonstrated an AUC of 0.889 in parental FT194 versus FT194 YAP-expression cells and an AUC of 0.779 in both parental FT282 versus FT282 CCNE1 and parental FT 194 versus FT194 MYC.

Conclusions: The presence of common upregulated plasma and FT progression cell model sEV proteins indicates their association with early lesions in the FT. This finding suggests that sEV cargo profiles can serve as effective early detection biomarkers for HGSOC, potentially improving diagnosis before cancer spreads.

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STAR (Stroma-Tumor AI Risk) Assessment: Association of AI-Derived Tumor-Stroma Proportion with Patient Survival Provides Added Prognostic Value Beyond KELIM in Epithelial Ovarian Cancer

Arpit Aggarwal, **Morgann Madill**, Mayukhmala Jana, Tilak Pathak, Timothy K. Starr, Boris Winterhoff, Katelyn M. Tessier, Britt K. Erickson, Andrew C. Nelson, Emil Lou, Anant Madabhushi, Martina Bazzaro.

Department of Biomedical Engineering, Emory University and Georgia Institute of Technology; Masonic Cancer Center and Department of Obstetrics, Gynecology and Women's Health, University of Minnesota; Masonic Cancer Center, Biostatistics Core; Department of Laboratory Medicine & Pathology, University of Minnesota; Division of Hematology, Oncology, and Transplantation, Department of Medicine, University of Minnesota; Atlanta Veterans Administration Medical Center; Department of Biomedical and Clinical Sciences (BKV), Linköping University, 58183 Linköping, Sweden

Background: There remains a critical need for prognostic biomarkers of treatment response in epithelial ovarian cancer (EOC). The KELIM score, derived from the rate of CA-125 elimination during the first 100 days of treatment, is a clinically available biomarker of treatment response to platinum-based chemotherapy; its utility is limited by the need for post-treatment data. Tumor–stroma proportion (TSP) has emerged as a prognostic biomarker across several malignancies. Studies from our group have shown that high TSP (≥50% stroma content assessed by pathologist evaluation, TSPmanual) is associated with platinum resistance and poor survival in EOC at diagnosis and before treatment.

Methods: We compared the prognostic value of TSP and KELIM by analyzing manual pathologist (TSPmanual) and artificial intelligence–derived assessments (TSPauto) on digitized images from a cohort of EOC specimens.

Results: In this cohort, we showed the prognostic significance of TSPmanual, confirming prior findings. Furthermore, TSPauto and TSPmanual assessments were highly concordant (94% agreement, Cohen's Kappa 0.89, $p<0.001$), providing a highly reproducible, automated approach. Unlike KELIM, which was only associated with platinum resistance but not survival outcomes, high TSPauto was significantly associated with poor survival (HR 1.99, $p=0.02$).

Conclusion: These findings support AI-derived TSP as a pre-treatment prognostic biomarker for EOC that complements KELIM.

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Targeting Early Adaptive Survival to PARP Inhibitors in High-grade Serous Ovarian Cancer

Julie R. Duffield, Xiaonan Hou, Benjamin W. Wilson, Anjali Prasad, Iman K. McKeon-Makki, Amelia M. Huehls, Xinyan Wu2, Scott H. Kaufmann, Larry M. Karnitz, S. John Weroha, Arun Kanakkanthara

Department of Oncology, Mayo Clinic; Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic

PARP inhibitors (PARPis) are an important therapy for high-grade serous ovarian cancer (HGSOC), especially those with defects in homologous recombination (HR) DNA repair. However, resistance to these drugs poses a significant concern, necessitating the exploration of novel treatment strategies. Here, we demonstrate that targeting an early PARPi-induced adaptive survival response represents an effective approach to enhance PARPi efficacy in HGSOC. Specifically, we found that brigatinib, an FDA-approved anaplastic lymphoma kinase (ALK) inhibitor, can be repurposed to disrupt a PARPi-induced adaptive mechanism mediated by the transcription factor FRA1, thereby sensitizing HGSOC cells to PARP inhibition.

Clonogenic cell survival assays revealed that brigatinib synergizes with PARPis in HR-proficient, -deficient, and PARPi-resistant HGSOC cell lines. In subsequent proteomics approaches and cell-based confirmatory studies, we found that brigatinib induces a dual blockade of FAK and EPHA2 tyrosine kinases, leading to the suppression of AKT and ERK signaling accompanied by a decrease in FRA1 protein levels. Contrastingly, PARPis were revealed to increase the abundance of FRA1 in HGSOC cells at early timepoints, with FRA1 depletion resensitizing cells to PARPi-mediated apoptosis. Additionally, in HGSOC patient-derived xenograft (PDX) models, the brigatinib and PARPi combination therapy induced tumor regression and improved overall survival, particularly in models with high FAK and EPHA2. These findings support dual targeting of FAK and EPHA2 as a strategy to achieve effective and durable PARPi responses and identify a promising biomarker-based combinatorial approach utilizing brigatinib and PARPi for HGSOC.

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AXL-expressing cancer-associated fibroblasts suppress NK cell function in vitro

Manon Miller, Xia Wang, Huadong Chen, Junhao Lu, Alan Ashworth, Katherine Fuh
University of California, San Francisco

High-grade serous ovarian cancer (HGSC) is often characterized by an immunosuppressive tumor microenvironment (TME) with several mechanisms of escape including downregulation of MHC I. However, natural killer (NK) cells can recognize and kill independent of MHC I, making them a compelling therapy. Both translational and clinical evidence support their use, but not much is known on the immunosuppression that hinders therapeutic potential. We identified that cancer associated fibroblasts (CAFs) express high levels of receptor tyrosine kinase AXL and were associated with lower survival. Additionally, stromal-high OC has shown to correlate with lower NK cell infiltration and activation. The objective of this study is to investigate how AXL expressing (AXL+) CAFs contribute to immunosuppression.

Several cytokines were found differentially secreted between AXL+ CAFs and their AXL CRISPR-knockout (AXL-) derivatives. Specifically, AXL- CAFs showed an increase in promotive (IL-2, 2.35 fold-change (FC); IL-15, 2.09FC; INF-γ, 1.98FC) and decrease in suppressive (TGF-β, 0.47FC; VEGF 0.30FC) cytokines. Based on the IL-15 change, we asked whether AXL affects NK cells. When AXL+ CAF conditioned media (CM) was used either as a treatment or chemoattractant, we found lower NK-92 migration compared to AXL- CAF CM (0.45FC, $p=0.0072$; 0.67FC, $p=0.002$) and controls (0.35FC, $p=0.002$; 0.42FC, $p<0.001$), suggesting AXL+ CAFs suppress NK migration. In addition, killing assays using primary NK cells cultured with AXL+ CAFs showed higher OVCAR8 and PEO1 cell counts, suggesting decreased killing compared to those cultured with AXL- CAFs (2.27FC, $p<0.0001$; 1.71FC, $p=0.019$). Overall, data supports the role of AXL+ CAFs in NK cell suppression.

An AXL-CAR-NK-92 was created to target OC and decrease AXL+ cells' influence on the TME. We found selective targeting of AXL+ vs AXL- OVCAR8 and CAFs with fewer viable cells (0.48FC, $p=0.0002$; 0.15FC, $p<0.0001$). We also found it led to fewer viable cells than NK-92s (0.31FC, $p<0.0001$; 0.18FC, $p<0.0001$). This suggests an enhanced ability to target tumor and stromal compartments. Additionally, AXL-CAR-NK-92 in vivo injection showed reduction of OVCAR8 tumors compared to NK-92 (0.288FC, $p=0.017$).

The data suggests OC AXL+ CAFs suppress NK cell function and developing an AXL-targeted NK cell immunotherapy can overcome the immunosuppressive OC TME.

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A Rare Multipotent Peg-like Epithelial Cell is a Candidate Cell-of-Origin for High-Grade Serous Ovarian Cancer

Megan L. Ritting, Wenmei Yang, Syed Mohammed Musheer Aalam, Hui Zhao, Liang Feng, Jianning Song, Mihai G. Dumbrava, Wazim M. Ismail, Kenneth Schaufelberger, David J. H. F. Knapp, Chen Wang, Alexandre Gaspar-Maia, Mark E. Sherman, Jamie N. Bakkum-Gamez, Nagarajan Kannan
Mayo Clinic; Institut de recherche en immunologie et en cancérologie (IRIC)

High-grade serous ovarian cancer (HGSOC), the most prevalent and lethal ovarian cancer subtype, is typically diagnosed at an advanced stage due to the absence of effective early detection strategies. Mounting evidence indicates that HGSOC originates from the fallopian tube (FT), particularly from secretory epithelial cells in the fimbria. However, incomplete understanding of the cellular and molecular origins of HGSOC continues to hinder early interception efforts.

To address this, we established a clinically and genetically annotated living FT organoid biobank at Mayo Clinic, representing over 200 patient donors. Using optimized enrichment protocols, we isolated FT epithelial stem/progenitor cells from tissue and Tao brushings, generating organoids independent of anatomical site or laterality that recapitulate native FT epithelial architecture and lineage differentiation.

We applied integrated multi-omic analyses—including single-cell RNA sequencing, single-nucleus RNA/ATAC sequencing, and bulk RNA-seq—across fresh cells and organoids. Integration with public datasets produced the largest single-cell atlas of normal and high-risk FTs to date. This analysis defined high-specificity gene signatures for secretory and multiciliated lineages that outperform canonical lineage markers (e.g. PAX8, FOXJ1), identified lineage-defining transcription factors and regulatory networks, and showed concordant protein expression in the human FT epithelium.

Notably, subcluster-level analysis revealed a rare hybrid epithelial–mesenchymal population transcriptionally and proteomically aligned with the mesenchymal-like subtype of HGSOC. Spatial immunoprofiling demonstrated that these cells express multiple defining markers and reside above the basement membrane, intercalated between epithelial cells and lack luminal contact—reminiscent of the histologically described peg cell population. Comparative analyses with fetal mesonephric tissues uncovered developmental parallels, and this population was stably maintained in 3D organoid cultures, providing a robust ex-vivo model to study early transformation.

Together, our findings identify a rare, multipotent epithelial population with mesenchymal features as a candidate origin for mesenchymal-like HGSOC and establish the FT organoid biobank as a powerful platform for mechanistic and translational studies in ovarian carcinogenesis.

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Poster Session Abstracts

Poster Session Abstracts

Poster Session Abstracts

Poster Session Abstracts

Vote on Poster Awards for OCMF 2025!

Use the QR code survey to vote on your top choices for posters in the 2025 session. The survey is anonymous and you can submit as many votes as you choose.

The three posters with the most votes will each win $250.

Hydrophobic Tagging as a Novel Strategy to Therapeutically Target FOXM1 in High-Grade Serous Ovarian Cancer (HGSOC)

Tania Aguilera-Pineda, C. Martin, S. Kumar, A. Natarajan, A. R. Karpf.
University of Nebraska Medical Center; University of Cincinnati

High-grade serous ovarian carcinoma (HGSOC) is a deadly disease frequently driven by the aberrant activation of FOXM1. Current strategies to inhibit FOXM1 with small molecules are limited by poor selectivity and incomplete target engagement. To address this, we developed a novel therapeutic approach using Hydrophobic Tag Degraders (HyTDs) to induce targeted degradation of FOXM1. To do this, we synthesized FDI-6-based HyTDs designed to bind to FOXM1 and selectively trigger its degradation by the cellular protein quality control machinery. The binding moiety, FDI-6, is an established binder of the FOXM1 DNA binding domain (DBD). As hydrophobic moieties, we utilized adamantane or norbornene and conjugated these to FDI-6 through PEG or amide linkages. A series of FDI-6-based HyTDs was synthesized and evaluated, and treatment of HGSOC cells with these HyTDs resulted in a significant, dose-dependent reduction in cell viability. Additionally, target engagement studies showed a decrease in FOXM1 protein levels as well as the expression of FOXM1 target genes. Amongst the tested compounds, HyTDs with an amide linker showed the highest efficacy. In summary, we report a novel approach to therapeutically target FOXM1. FDI-6 HyTDs offer a new path for the future development of FOXM1-targeted therapies for HGSOC and other human cancers.

Molecular Insights from Spatial Transcriptomics of Ovarian Tissue from BRCA1/2 Mutation Patients

Jocelyn Baquier, Noelle Gillis, Laura J. Mauro, Carol Lange
Masonic Cancer Center, University of Minnesota; Larner College of Medicine, University of Vermont, Department of Pharmacology

Hereditary breast and ovarian cancer (HBOC) syndrome confers high risk of breast and ovarian cancer development due to BRCA1/2 gene mutations (mBRCA1/2). These mutations lead to DNA damage and genomic instability, with steroid signaling playing a role in cancer development in sex hormone-regulated tissues. The fallopian tube (FT) and breast tissues of healthy mBRCA1/2 carriers exhibit distinct cellular and molecular characteristics that likely predispose them to higher cancer risk. However, the impact of these mutations in the ovary remains unknown, even though the ovarian-FT microenvironment is key to tumor cell survival. We hypothesize there are distinct molecular signatures expressed in the ovaries of mBRCA1/2 patients that could provide novel insights into the etiology of ovarian cancer in persons with HBOC. Tissue samples were collected from patients with known pathogenic variants of the BRCA1/2 genes and those presumed to be noncarriers (WT). Three cases (mBRCA1, mBRCA2, WT) were selected for pilot spatial transcriptomics based on age, RNA quality and histology. Regions of interest (ROIs) encompassing distinct ovarian structures (cortex, stroma, corpus luteum, and corpus albicans) were collected and RNA library construction and sequencing performed. Analysis revealed unique genetic profiles for each patient group, with distinct differentially expressed genes (DEGs) and pathways. Principal component analysis revealed strong separation among patient groups, with variance in gene expression of 63% due to differences between BRCA1 and WT and 12% due to BRCA2 and WT. Functional enrichment analysis for mBRCA1 revealed modulation of cell adhesion functions with upregulated DEGs, while cytoplasmic translation functions were downregulated. Similar analysis in mBRCA2 samples revealed that immune response functions were upregulated, while DNA-binding transcription factor activity was downregulated. Furthermore, when examining ovarian cortex, stroma, and follicular structures for genes indicative of ovarian function, many genes were either downregulated or not expressed in mBRCA1/2 patients. This implies there are distinct differences in ovarian function among these patient groups. Future work will expand the spatial transcriptomics study and explore the ovarian proteomic landscape to reveal critical signaling pathways that predispose patients to ovarian cancer.

The Role of Glycosaminoglycans in Ovarian Cancer Progression and Platinum Resistance

Ava R.S. Beaudin, Erica J. Peterson, Jaiden Murray, Jennifer E. Koblinski, Ryan J. Weiss, Thomas Clausen, Sharanya P. Deshmukh, Amrita Basu, Nicholas P. Farrell, Larisa Litovchick

Massey Cancer Center, Virginia Commonwealth University (VCU); Dept. of Internal Medicine, VCU; BioPlatinum Technologies LLC; Dept. of Biochemistry and Molecular Biology, VCU; Complex Carbohydrate Research Center, UGA; Thomas Clausen, VAR2 Pharmaceuticals ApS

Ovarian cancer is a lethal gynecologic malignancy, usually diagnosed at advanced stages, marked by frequent recurrence following platinum-based chemotherapy. Approximately 30% of cases are classified as platinum-resistant or refractory, with aggressive forms recurring within six months of initial treatment. Emerging evidence implicates glycosaminoglycans (GAGs) as key modulators of tumor progression, metastatic potential, and chemotherapy resistance. This study aimed to determine how GAGs influence ovarian tumor biology and response to carboplatin treatment. To characterize GAG-related gene expression and identify their cellular sources within the tumor microenvironment, we analyzed single-cell RNA sequencing datasets from normal ovarian tissue, primary ovarian/fallopian tube tumors, and metastatic lesions involving the abdomen and colon. To further evaluate the relationship between GAG levels and platinum sensitivity, glycan reductive isotope labeling mass spectrometry (GRIL-MS) was performed on ovarian cancer patient-derived xenografts with known carboplatin sensitivity profiles. GAG depletion was achieved in ES2-luc ovarian cancer cells through CRISPR/Cas9-mediated knockout of XYLT1/2. Wild-type (WT) and knockout (KO) cells were compared in vitro for proliferation rates, morphological characteristics, and carboplatin sensitivity. WT and KO cells were injected intraperitoneally into NSG mice to establish xenograft models, with tumor burden monitored longitudinally via bioluminescence imaging. Endpoint analyses assessed body weight, tumor distribution, and ascites formation. Single-cell RNA sequencing revealed that fibroblasts in the tumor microenvironment are a predominant source of GAG gene expression. GRIL-MS identified chondroitin-4-sulfate (C4S) as the most abundant GAG disaccharide, with high C4S expression correlated to reduced carboplatin sensitivity. In vivo, WT cells produced tumor dissemination and ascites in all animals, whereas GAG-deficient KO cells formed more localized tumors and did not develop ascites. Our findings demonstrate that glycosaminoglycans, particularly C4S, play a crucial role in ovarian cancer progression and platinum resistance. These findings support using C4S as a predictive tool to guide targeted chemotherapy in ovarian cancer and other C4S-expressing malignancies and potentially improve treatment precision and outcomes.

NRF2: A Barrier to Atovaquone Efficacy in the Treatment of Ovarian Cancer?

Michael Berube, Nicha Boonpattrawong, Rob Schultz, Arvinder Kapur, Mayra Betancourt Ponce, Manish Patankar, Maria Virumbrales-Munoz, Lisa Barroilhet

Department of Obstetrics and Gynecology, School of Medicine and Public Health, University of Wisconsin, Madison; Department of Biology, University of Wisconsin, Oshkosh

Atovaquone, an FDA-approved oxidative phosphorylation (OXPHOS) inhibitor used for malaria treatment, has shown promise as a potential therapeutic agent for ovarian cancer. However, a well-described resistance mechanism driven by the transcription factor NRF2, which mediates cellular responses to oxidative stress, may limit atovaquone's efficacy. This project aims to evaluate the role of NRF2 in resistance to atovaquone treatment in ovarian cancer cell lines and to determine whether pharmacological inhibition of NRF2 with brusatol can enhance atovaquone's antitumor effects.

Ovarian cancer cell lines OVCAR3, OVCAR5, and ID8 were seeded in 96-well plates at 80% confluency and treated with increasing concentrations of atovaquone or brusatol to determine IC_{50} values. The IC_{50} range was 13–30 μM for atovaquone and 18–22 nM for brusatol. Subsequently, cells were treated with atovaquone in a time-dependent manner to assess NRF2 activation and expression of its target genes CAT, NQO1, and SOD1, measured by RT-qPCR and Western blot. To counteract this resistance mechanism, cells were co-treated with brusatol and atovaquone for 72 hours, and cell viability was measured using the MTT assay. Statistical significance was determined by one-way or two-way ANOVA ($P < 0.05$).

Results showed an increase in NRF2 expression 24 hours after atovaquone treatment. Expression of CAT, NQO1, and SOD1 also increased during the 72-hour post-treatment window in OVCAR3 and ID8, but not in OVCAR5. RNA-seq analysis of atovaquone-treated OVCAR3 cells was compared with datasets from NRF2-overexpressing cancer cell lines, revealing an overlap of 36 NRF2 target genes. Functional enrichment analysis using DAVID linked these genes to oxidative stress resistance and apoptotic pathways. Co-treatment with brusatol reduced cell viability, and this effect was modestly enhanced when combined with atovaquone in OVCAR3. This combination also suppressed the upregulation of NRF2 target genes typically induced by atovaquone.

In conclusion, combining atovaquone with brusatol partially overcomes NRF2-mediated resistance and enhances cytotoxicity in ovarian cancer cells, particularly in OVCAR3. Ongoing Seahorse metabolic flux assays will provide further insights into how this combination affects mitochondrial respiration and glycolysis, supporting its potential as a therapeutic strategy for ovarian cancer.

Engineering an Omentum-on-a-Chip for Studying Adiposopathy in Ovarian Cancer Metastasis

Amrita Bhagia, Simona Plesselova, Kadance Coughlin, Mazzi Moore, Pilar de la Puente
University of South Dakota Sanford School of Medicine; Sanford Research

Introduction: Considered a silent killer in women, ovarian cancer (OC) is often diagnosed after metastasis has already occurred. OC preferentially metastasizes to the omentum, after which 5-year survival drops by 50%. The omentum has a complex microenvironment, composed of vascularized adipose tissue overlaid with mesothelial cells. It is thought that adiposopathy, or dysfunctional adipose tissue found in cases of clinical obesity, may act as a catalyst for OC metastasis to the omentum. A novel, biologically and functionally accurate model of the omentum can help us understand how adipose tissue and adiposopathy contribute to metastatic burden in OC patients. Therefore, our overall objective is to recapitulate the OC metastatic microenvironment by creating an omentum-on-a-chip model with relevant biological and physical parameters to study conditions related to metabolically dysfunctional adipose tissue.

Materials and Methods: A tri-compartmentalized omentum-on-a-chip was designed using K-Layout and manufactured using SU-8 photolithography and polydimethylsiloxane (PDMS). The central chamber of the device was filled with adipocytes (VNPAD or NPAD) and human umbilical vein endothelial cells (HUVECs) in a patient-derived 3D matrix; Met5a mesothelial cells were then seeded into the top chamber of the device. Adiposopathic cells were engineered by exposing mature adipocytes to Tumor Necrosis Factor-α for 24 hours following differentiation.

Results/Discussion: Adipocytes, HUVECs, and mesothelial cells were successfully cultured to create an omentum-on-a-chip. qPCR demonstrated decreased expression of SLC2A (GLUT4) and adiponectin genes in adiposopathic adipocytes compared to control, confirming reprogramming to align with classical presentations of clinical obesity. Significant phenotypic changes were seen in the adiposopathic multi-culture model, with increased accumulation of lipid droplets and lipid peroxidation as well as downstream effects on HUVECs and cancer cells, resulting in changes in cell morphology and increased expression of markers associated with metastatic potential, respectively. Overall, our physiologically relevant model reveals that adiposopathy transforms the omental microenvironment, possibly creating a pro-tumor niche; further study will allow us to identify therapeutic targets unique to metastatic OC under these conditions.

Secreted CD55 traffics into chemo naïve ovarian cancer cells, conferring cisplatin resistance

Rashmi Bharti, Goutam Dey, Akankshya Nayak, Michelle S. Longworth, Ofer Reizes
Department of Cardiovascular and Metabolic Sciences, Lerner Research Institute, Cleveland Clinic Foundation; Case Comprehensive Cancer Center; Department of Immunity and Inflammation, Lerner Research Institute, Cleveland Clinic

Platinum resistance is the primary cause of poor survival in ovarian cancer (OC) patients. Targeted therapies and biomarkers of chemoresistance are critical for the treatment of OC patients. We recently found that the membrane complement regulatory protein, CD55, can localize to the nucleus in OC and induce chemoresistance. Nuclear localization is driven by a nuclear trafficking code within the serine/threonine (S/T) domain of CD55. Nuclear CD55 is necessary for cisplatin resistance, stemness, and cell proliferation in ovarian cancer cells in vitro and in vivo. In the nucleus, CD55 binds and attenuates the epigenetic reader and tumor suppressor ZMYND8 with a parallel increase in H3K27 trimethylation and members of the Polycombs Repressive Complex 2 (PRC2). Our studies identify a therapeutic mechanism for treating platinum-resistant ovarian cancer by blocking CD55 nuclear entry.

CD55 is tethered to the outer membrane via a glycerol phosphatidyl inositol (GPI) anchor. In our current study, we observed that membrane localization is not necessary for nuclear entry of the CD55 protein. Our study further demonstrated that deletion of the GPI anchor leads to elevated secretion of CD55 in the conditioned media. Next, this condition media was added to CD55 knockout cells. Interestingly, the CD55 protein from the conditioned media entered the CD55-knockout cells and accumulated in the nucleus. In the nucleus, CD55 accumulation caused suppression of ZMYND8 tumor suppressor and an increase in EZH2 complex member of PRC2 cell identity proteins. We next show that CD55 is secreted from chemoresistant OC cells compared to naïve OC cells. Collectively, these findings indicate that CD55 can behave in a paracrine manner to expand the chemoresistant population of ovarian cancer.

The Unseen Cost: A Comprehensive Look at Cancer-Related Time Burdens

Sarah Boyle, Helen Parsons, Patricia Jewett, Katherine Brown, Alyssa Pecoraro, Indya Starks, BS, Stacey Ingram, Zuofu Huang, Arjun Gupta, Deanna Teoh, Yingling Fan, Anne Blaes, Rebecca Arend, Gabrielle Rocque, Julian Wolfson, Rachel I. Vogel
University of Minnesota; University of Alabama at Birmingham

Background: Cancer treatment imposes significant burdens on patients including physical, emotional, and financial, which can impact quality of life. Time burdens related to cancer care can be substantial, however the time costs from administrative and at-home tasks are often overlooked. Our objective was to measure the time spent on multiple aspects of cancer care.

Methods: We enrolled individuals receiving treatment for advanced-stage ovarian or metastatic breast cancer at the University of Minnesota and the University of Alabama-Birmingham. Participants used a mobile application for 28 days to identify time spent related to cancer care including appointments, travel time, and at-home and administrative tasks such as scheduling, billing, symptom management, and taking medications. Participants also reported daily symptoms of distress. We used descriptive statistics to summarize the time spent on direct care, indirect care, and at-home and administrative tasks.

Results: 60 participants were included in the analysis; 28 with ovarian cancer and 32 with breast cancer. The median age was 59 years, 42% were employed, and 57% were undergoing treatment for recurrent or progressive disease. Participants spent a median of 401 (Q1-Q3: 266-605) minutes per week on cancer-related activities. Time spent on direct clinical care varied greatly in both frequency and duration of episodes among participants, but time spent traveling and waiting often exceeded time spent receiving care. The median time spent on at-home cancer-related activities was 209 (Q1-Q3: 121-355) minutes per week, and participants engaged in these activities on 80% of study days. Participants spent a median of 13 (Q1-Q3: 3-57) minutes per week specifically on administrative tasks, including scheduling, managing medical bills, and arranging help and transportation. While not necessarily time-consuming, participants reported significantly higher distress on days that included completing administrative tasks compared to days without administrative tasks (3.5 vs 3.0 on 0 to 10-point Likert scale, $p<0.0001$).

Conclusions: Cancer care puts significant time burdens on patients with advanced cancer, with a large proportion of this time occurring outside of direct clinical care. These findings suggest the need to develop interventions to alleviate demands on patients' time at home to improve well-being.

Activating Tumor-Infiltrating Immune Cells to Enhance Anti-Tumor Immunity and Prolong Survival in Metastatic Ovarian Cancer Models

Yifan Emily Chang, Manon Miller, Jaidev Bapat, Sofia Ruau, Wanda Gan, Leah Wormack, Atip Lawanprasert, Rohit Sharma, Dengpan Liang, Alan Ashworth, Niren Murthy, Katherine Fuh.
University of California San Francisco; University of California Berkeley

Activating tumor-infiltrating immune cells in ovarian cancer (OC) has been challenging. To achieve tumoral immune activation while limiting systemic toxicity, we developed a new strategy of using lipid nanoparticles (LNP) to deliver IL-2 mRNA via intraperitoneal (IP) administration using OC models. We aimed to demonstrate an increase in tumor-infiltrating immune cells and an increase in survival.

Two syngeneic C57Bl/6 mouse models were used: ID8Trp53-/-Brca2-/- (ID8TB) and p53−/−R172HCcne1OEAkt2OEKRASG12V (KPCA). Two candidate LNPs: L46 and E92, were tested for specificity of delivery to tumors. At 40 days (ID8TB) or 8 days (KPCA) post tumor cell injection, the mice received 5 daily IP injections of vehicle (phosphate buffered solution/saline), LNP encapsulating control mRNA (luciferase mRNA), or human IL-2 mRNA. Bioluminescence imaging (BLI) was used to track tumor growth. Mice were observed for overall survival. For immune profiling: omental tumors were harvested from mice 48h after last treatment, dissociated, stained for immune markers, and analyzed via spectral flow cytometry. Statistical analysis (One-way ANOVA; Kaplan-Meier curve for survival) was conducted using GraphPad Prism (10.6.0).

An increase in granzyme B positive immune activating CD8+ T cells was seen in models receiving L46 IL2-mRNA compared to models receiving L46 luc-mRNA control (49.9% vs 5.4%, $p < 0.0001$). This increase in immune activating CD8+ T cells was again observed in models receiving E92 IL2-mRNA compared to E92 luc-mRNA control (76.1% vs 10.5%, $p < 0.0001$). Additionally, L46 IL-2 mRNA treated KPCA model also showed significantly less tumor growth compared to groups treated with control mRNA (6.6e+006 vs 7.8e+007 p/sec/cm2/sr, $p = 0.031$). Lastly, an increase in survival was also observed in L46/E92 IL-2 mRNA treated models: E92 IL-2 mRNA treatment prolonged the survival of ID8TB mice from an average of 8 weeks in vehicle/control mRNA mice to over 11 weeks in treated mice.

Intraperitoneal LNP delivery of IL-2 mRNA demonstrated pre-clinical efficacy with significant reduction of tumor growth and prolonged survival in OC murine models, likely via increased cytotoxic T cell infiltration and activation. These findings suggest that LNP delivery of IL-2 mRNA is a potentially promising treatment for metastatic OC, supporting its further evaluation in clinical studies

The Role of Obesity in Metastatic Dissemination of High Grade Serous Ovarian Cancer

Larkin Clem, Christian Sacia Garcia, Ning Yang, Pamela K. Kreeger
University of Wisconsin, Madison

Background: High grade serous ovarian cancer (HGSOC) is the most lethal gynecologic malignancy, with a 5-year survival rate of 50%. Over 40% of women in the United States are classified as obese, and the prevalence of obesity has been steadily increasing. Obesity has been linked to an increased risk of developing HGSOC, and patients with obesity have worse overall survival. The mechanisms driving these poor outcomes are not fully understood, but obesity is linked to changes in adipose immune populations and fatty acid uptake. As HGSOC metastasizes to visceral adipose depots such as the omentum, these changes have the potential to promote cancer growth and progression. Using a diet-based intervention, we are examining the role of obesity in HGSOC metastasis.

Methods: To evaluate the role of obesity in HGSOC metastasis, three week-old female mice were fed a high fat diet (HFD) or control chow for 16 weeks, injected interperitoneally (i.p.) with FTE cells and monitored for up to 45 days. Metastatic tumor burden was characterized at various time points and histology was used to examine the tumor microenvironment.

Results: Beginning at 13 weeks on the diet, HFD mice weighed significantly more compared to chow controls and by 16 weeks on HFD, the mass of mesentery and omentum adipose tissues was significantly increased. Adipocyte diameter was also significantly larger in these tissues compared to chow mice. The overall survival of tumor-bearing HFD mice was unchanged relative to chow mice controls (average of 44 days versus 43 days, respectively). Despite this, the masses of tumors on the omentum and mesentery were significantly greater for HFD mice.

To determine when these differences arose in tumor progression, tumors were characterized at 20 days. While omentum and mesentery tumor mass were not impacted by obesity, significantly more adipocytes remained in obese mice at this timepoint, which suggests a higher potential for future growth that may contribute to the finding of larger endpoint tumors. Future work will characterize tumor cell behavior in response to obese adipocytes through measuring lipid uptake via BODIPY staining and analyzing fatty acid transfer proteins.

Prussian Blue Nanoparticle Photothermal Therapy (PBNP-PTT) improves allogeneic T cell therapy and antitumor cytotoxicity in ovarian cancer

Jose A. Colina, Abigail V. Lee, Erin E. Grundy, Elizabeth Sweeney, Rohan Fernandes, Conrad R. Cruz, Katherine B. Chiappinelli
The George Washington University; Children's National Research Hospital, Washington, DC

Immunotherapy has revolutionized cancer treatment across a range of malignancies, yet its efficacy in ovarian cancer (OC) has remained limited due to low tumor mutational burden and limited neoantigen expression. While current Immunotherapy strategies have struggled to achieve durable responses, adoptive T cell therapy (ATT) presents a promising avenue to overcome the inherent challenges of immune resistance in OC. ATT, involves the ex vivo modification or expansion of T cells that are subsequently reintroduced into the patient to mediate anti-tumor immunity. Utilizing Prussian blue nanoparticle based photothermal therapy (PBNP-PTT) our team has established a novel manufacturing process that encourages robust T cell expansion and specificity for OC target cells. Here we demonstrate that PBNP-PTT induces robust immunogenic cell death ex vivo compared to other cancer cell lysis methods. These PBNP-PTT treated ovarian cancer lines were then used to train allogeneic T cells from HLA matched donors. These PBNP-PTT trained T cells had improved IFNγ secretion when co-cultured with cancer cells compared to non-PBNP-PTT or untrained T cells. Importantly, PBNP-PTT trained T cells demonstrated robust cancer cell cytotoxicity across all three cell lines tested with 2 of the 3 showing significant improvement over T cells trained against un-lysed cells. Given these encouraging results our team will be apply this novel PBNP-PTT based manufacturing process to patient derived tumor samples isolated from patient ascites.

Extracellular Vesicle-based Organic Nanotherapeutics and Heavy-Atom-Free Nanophotosensitizers for Enhanced Photodynamic Cancer Therapy

Thuy Nguyen Thi Dao, Van-Nghia Nguyen, HyoJoo Lee, Yeju Lee, Yong Shin, Juyoung Yoon
Department of Biotechnology, College of Life Science and Biotechnology, Yonsei University, Seoul 03722, Republic of Korea, Department of Pathology and Laboratory Medicine, University of Kansas Medical Center; School of Chemistry and Life Sciences, Hanoi University of Science and Technology, 1 Dai Co Viet Road, Hanoi 100000, Vietnam; Department of Biotechnology, College of Life Science and Biotechnology, Yonsei University, Seoul 03722, Republic of Korea; Department of Chemistry and Nanoscience, Ewha Womans University, Seoul 03760, Republic of Korea, Graduate Program in Innovative Biomaterials Convergence, Ewha Womans University, Seoul 03760, Republic of Korea; Department of Biotechnology, College of Life Science and Biotechnology, Yonsei University, Seoul 03722, Republic of Korea; Department of Chemistry and Nanoscience, Ewha Womans University, Seoul 03760, Republic of Korea, Graduate Program in Innovative Biomaterials Convergence, Ewha Womans University, Seoul 03760, Republic of Korea

Traditional antitumor therapies often face significant limitations, including poor targeting specificity, severe systemic side effects, and the development of drug resistance, which collectively hinder their clinical efficacy. These challenges have stimulated extensive research into drug delivery systems capable of improving therapeutic outcomes. Among the emerging strategies, extracellular vesicles (EVs), which are membrane-bound vesicles secreted by various human cell types, have gained considerable attention due to their intrinsic biocompatibility, ability to cross biological barriers, and potential for targeted delivery in cancer treatment and other biomedical fields. Simultaneously, sulfur-substituted carbonyl fluorophores have shown promise as heavy-atom-free photosensitizers for photodynamic cancer therapy (PDT), offering key advantages such as red-shifted absorption, which penetrates deep into mammalian tissues, and highly efficient intersystem crossing, which enhances production of reactive oxygen species (ROS). Despite these benefits, their clinical potential is limited by poor water solubility, low bioavailability, and inadequate tumor-targeting efficiency. In this study, we developed a biocompatible EV-based thio-courmarin nanophotosensitizer (CMS2@EVs) designed to overcome these limitations and enable safe, efficient PDT. The resulting CMS2@EVs exhibited a particle size distribution from 50–200 nm, slightly larger than the free EVs, which measured between 30–100 nm. The UV-Vis absorption spectrum of CMS2@EVs displayed a distinct peak at 500 nm, consistent with the absorption profile of free CMS2, indicting successful loading of CMS2 into the vesicles and confirming the retention of its photophysical properties upon encapsulation. Cellular update studies demonstrated that CMS2@EVs were efficiently internalized by cancer cells within 4 hours. Upon irradiation with 520 nm LED light (green), CMS2@EVs showed enhanced phototoxic effects against cancer cells compared to free CMS2, with an IC50 value of 5 μM across concentrations from 1 to 20 μM. Furthermore, fluorescence imaging assays confirmed the generation of ROS following cellular uptake and light activation of CMS2@EV, underscoring the pivotal role of ROS-mediated cytotoxicity in the observed anticancer effect.

Optimal Evaluation of NK cell Immunotherapy in Novel Humanized Mouse Models of Ovarian Cancer

Elise L. Femino, Philippa R. Kennedy, Laura Bendzick, Quinlan M. Kile, Anna Weis, Behiye Kodal, Mihir Shetty, Riley Lyons, Peter Hinderlie, Brian Soper, Peter Deng, Melissa Geller, Jeffery S. Miller, Martin Felices

Masonic Cancer Research Center, University of Minnesota; Division of Hematology, Oncology and Transplantation, University of Minnesota; Division of Obstetrics, Gynecology and Women's Health, University of Minnesota; The Jackson Laboratory

Natural Killer (NK) cell immunotherapies are being implemented in the clinic for treatment of hematologic malignancies and solid tumors; however, our ability to discern which of these immunotherapies will work best is hindered by the rudimentary in vivo systems we currently employ in pre-clinical studies. To address this issue, we generated an Ovarian Cancer (OC) model using three different mouse strains, with different immune complexity through use of humanization and transgene expression, and evaluated efficacy of our Tri-specific Killer Engager (TriKE) platform in said strains. Mouse models employed in our studies included NSG mice engrafted with enriched human NK cells (xeno-NSG; least complex), CD34 humanized standard NSG mice (huNSG; intermediate complexity), and CD34 humanized NSG-FLT3-IL15 (F15; highest complexity). OVCAR8-luciferase cells were injected intraperitoneally. In xeno-NSG models, enriched NK cells were injected 4 days after tumor engraftment. Mice were treated 3x/week with a B7H3-targeting TriKE, and tumor bioluminescence (BLI) was evaluated weekly. Fluids and tissues from different compartments were harvested for a 42 marker cytometry by time-of-flight (CyTOF) analysis (Standard Biotools Helios system) and multiplex-immunofluorescence imaging on the phenocycler-fusion system (Akoya Biosciences) at different time points. Bioluminescence (BLI) confirmed the greatest tumor control in the F15 groups by TriKE treatment. Blood harvested for flow cytometry and CyTOF demonstrated increased NK cell and immune complexity in the F15 groups. Multiplex immunofluorescence imaging of NSG, HuNSG, and F15 spleens visually confirmed greater immune complexity in the F15 group. The responses seen in the F15 models, compared to the other models, indicate that immune complexity is a key factor in evaluating NK cell therapeutics. We postulate that this more complex approach is necessary to better elucidate how patients will respond to NK cell immunotherapies and gives us a tool to understand why certain immunotherapies succeed or fail. Future work will involve comparing correlates within these systems to ongoing clinical trials in order to fully evaluate the value of these strains.

Anti-OSMR antibodies inhibit tumor growth and metastasis of ovarian cancer

Anjali Geethadevi, Zhiqiang Ku, Sunila Pradeep, Ningyan Zhang, Zhiqiang An and Pradeep Chaluvally-Raghavan
Medical College of Wisconsin

Oncostatin M (OSM) is a member of the IL-6 subfamily of cytokines that binds Oncostatin M receptor (OSMR) and activates JAK/STAT mediated oncogenic signaling. Compared to other IL6 family ligands OSM induced activation of STAT3 signaling resulted into sustained activation for prolonged period, which suggest that OSM signaling could serve as a critical mediator of oncogenesis in cancer cells. In conjunction, OSM induced high level of cellular invasion, migration and tumor growth. To block OSM-mediated signaling, we developed a fully human OSMR-specific monoclonal antibody clones named 'B14' and 'B21' that bind to the extracellular domain of OSMR, which in turn abrogate OSM-induced heterodimerization of OSMR with IL6ST (a.k.a. GP130). We also observed that our antibody resulted into the internalization and degradation of OSMR and subsequent reduction in STAT3 activation, tumor cell invasion, tumor growth and metastasis. Transcriptome-based further analysis along with in vitro and functional assays identified that cisplatin-resistant ovarian cancer cells express high levels of OSMR compared to cisplatin sensitive cells, and those cells rely on OSMR for cisplatin resistant tumor growth. Strikingly, we found that the treatment of anti-OSMR antibodies sensitized cisplatin treatment in cancer cells in vitro and in vivo. Taken together, our studies demonstrate a previously understudied mechanism of OSMR-driven oncogenesis in ovarian and other cancers where the use of our anti-OSMR antibodies provides unprecedented opportunities to treat highly aggressive tumors and sensitize them towards chemotherapy.

Therapeutic Targeting of FXR1 Expressing Tumors Using LNA form of siRNA

Jasmine George, Xiaolong Ma, Ishaque Pulikkal Kadamberi, Sonam Mittal, Elaheh Hashemi, Anjali Geethadevi, Anupama Nair, Subramaniam Malarkannan, Chien-Wei Lin, Sunila Pradeep, Pradeep Chaluvally-Raghavan

Department of Obstetrics and Gynecology, Medical College of Wisconsin; Division of Biostatistics, Data Science Institute; Versiti Blood Research Institute

Ovarian cancer remains a major contributor to cancer-related deaths in women, underscoring the urgent need for novel therapeutic strategies. Fragile X-related protein 1 (FXR1), frequently amplified and overexpressed in ovarian and other malignancies, plays a central role in driving oncogenesis through translational regulation of multiple cancer-promoting genes. Here, we demonstrate that RNA interference of FXR1 using a locked nucleic acid–modified siRNA (siFXR1-LNA) markedly suppresses ovarian tumor progression. Compared with unmodified siRNA, siFXR1-LNA displayed enhanced stability against RNase-mediated degradation, improved tumor uptake, and stronger target mRNA inhibition in vivo, leading to significant reductions in tumor growth, ascites accumulation, and metastatic spread. Single-cell RNA sequencing of malignant ascites further revealed that FXR1 silencing not only impaired tumor cell proliferation but also reshaped the tumor microenvironment by reducing immunosuppressive M2-like macrophages and enriching for cytotoxic T cells, NK cells, and dendritic cells with anti-tumor activity. Collectively, these findings establish FXR1 as a critical oncogenic driver and highlight FXR1 silencing via siFXR1-LNA as a promising therapeutic strategy for ovarian cancers characterized by high FXR1 expression.

Mechanisms of UNC-45A-Mediated Microtubule Destabilization: Implications for Paclitaxel Resistance and Neuropathic Pain

Asumi Hoshino, Brian Castle, Mihir Shetty, Hannah Khan, David Odde, Martina Bazzaro.
Department of Biomedical Engineering, University of Minnesota

Background: Paclitaxel is a widely used chemotherapy drug for treating ovarian cancer. As a microtubule (MT)-stabilizing agent, paclitaxel exerts its cytotoxic effects by disrupting cell division and inducing cell death. However, its effectiveness is often limited by two major challenges: the development of drug resistance and the onset of neuropathy caused by nerve degeneration. In our laboratories, we identified UNC-45A as a MT-destabilizing protein that promotes paclitaxel resistance by counteracting its stabilizing effects. Our findings have been published in several peer-reviewed studies (Hoshino A. et al., JBC, 2023; Habicht J., Mooneyham A., Hoshino A., et al., J Cell Sci, 2021, Editor's Pick and First-Author Interview; Clemente V. et al., Cells, 2020; Mooneyham A. et al., Mol Cancer Res, 2019, Cover Art; Habicht J. et al., Cancer Biol Ther, 2019).

Objective: This study investigates the impact of UNC-45A on neuronal damage and the mechanisms through which it may exacerbate paclitaxel-induced neuropathy, aiming to evaluate UNC-45A as a dual therapeutic target in paclitaxel-resistance and neurotoxicity. Methods: We employed biochemical and biophysical techniques, including cell-free reconstituted MT assays, high-resolution fluorescence imaging, purified recombinant UNC-45A protein, and both mouse primary neuronal cultures and neuronal cell lines.

Results: In neurons, UNC-45A localizes to subcellular regions exhibiting swelling, a hallmark of early degeneration. Its overexpression worsens this phenotype and contributes to neurite loss, which is further intensified by paclitaxel treatment. Mechanistically, UNC-45A binds to paclitaxel-induced defects in MTs, blocks repair and leads to MT mass loss.

Conclusion: UNC-45A destabilizes paclitaxel-treated MTs by binding to fragile regions and preventing their repair, promoting MT mass loss. These findings suggest that UNC-45A contributes to both chemoresistance and paclitaxel-induced neuropathy. Targeting UNC-45A could restore drug sensitivity and reduce neurotoxicity.

RHNO1 promotes ovarian cancer cell survival under DNA replication stress via a positive feedback loop with the ATR/Chk1 pathway

Niphat Jirapongwattana, C. M. Conover, C. Trujillo Jaramillo, Adam R. Karpf
Eppley Institute for Cancer Research and Fred & Pamela Buffett Cancer Center, University of Nebraska Medical Center

Ovarian cancer (OVC) is characterized by elevated DNA replication stress (RS), which fuels genomic instability and cancer progression. To survive, OVC cells become highly dependent on the ATR/Chk1 pathway, creating a therapeutic vulnerability. Rad9-Hus1-Rad1 interacting nuclear orphan 1 (RHNO1) is a component in the ATR/Chk1 pathway and is often overexpressed in OVC and contributes to chemotherapy resistance. However, the precise functions of RHNO1 on the RS response are still largely unknown. Here, we investigated the effect of RHNO1 depletion on RS response in OVC, and we generated an endogenously HiBiT-tagged RHNO1 cell line to dissect the molecular functions of RHNO1. The effect of RHNO1 depletion on cell proliferation and RS response after hydroxyurea (HU) treatment was evaluated in stable RHNO1 knockdown OVC cell lines using cell viability and colony formation assays, and micronuclei formation by immunofluorescence. The effect of RHNO1 depletion was further examined by an in vivo xenograft study. A HiBiT-tagged RHNO1 HEK293T cell line was generated by CRISPR-Cas9 knock-in and used to investigate protein localization, colocalization, and phosphorylation via immunofluorescence, western blotting, and kinase inhibitor treatments. Depletion of RHNO1 significantly reduces proliferation rate, clonogenicity, and in vivo OVC tumor growth, while extending host mouse survival. RHNO1 knockdown sensitized cells to HU, increasing cell death and micronuclei formation. Mechanistically, RHNO1 was upregulated in response to the HU, formed nuclear foci, and was colocalized with phosphorylated RPA32, a marker of RS and DNA damage. We also found that RHNO1 was phosphorylated by ATR/Chk1 under RS conditions, and this phosphorylation stabilizes the RHNO1 protein. Furthermore, RHNO1 localization in chromatin under RS conditions was found to be phosphorylation dependent. Surprisingly, this chromatin recruitment of RHNO1 appeared to be independent of 9-1-1, a DNA clamp complex previously known to bind RHNO1. These findings highlight the potential of RHNO1 as a target for OVC treatment and encourage further investigation on the molecular biology of RHNO1 under RS conditions, which are highly elevated in OVC.

A self-assembled killer engager complex that targets B7H3 enhances NK cell anti-tumor function against ovarian cancer

Melissa Khaw, Philippa Kennedy, Laura Bendzick, Yvette Soignier, Anna Weis, Mihir Shetty, Terran Stenger, Marieke van Breukelen, Emma Krienke, Jeffrey Miller, Melissa Geller, Martin Felices
Masonic Cancer Center, University of Minnesota

Natural killer (NK) cells mediate antibody-dependent cellular cytotoxicity (ADCC) through their Fc receptor, CD16 - the only receptor capable of independently triggering NK cell activation without additional co-stimulatory signals. However, CD16 is rapidly cleaved by 'a disintegrin and metalloprotease17' (ADAM17) in the solid tumor microenvironment, undermining the efficacy of ADCC-based immunotherapies and limiting ovarian tumor control. To overcome this limitation, we developed a multi-functional Tri-specific Killer Engager Poly-Antigen Cytokine Complex (TriKE-PACC) molecule that is designed to preserve CD16 and sustain ADCC while delivering activation and proliferation signals to the NK cells. The TriKE consists of a CD16-binding nanobody, an interleukin (IL)15 moiety, and a nanobody arm binding B7H3, an antigen highly expressed on ovarian cancer. The PACC consists of an ADAM17-blocking antibody fragment arm linked to an interleukin-15 receptor alpha (IL15Rα) that noncovalently binds IL15 in the TriKE to form the self-assembled TriKE-PACC molecule. Upon tumor or phorbol 12-myristate 13-acetate stimulation, the TriKE-PACC retained CD16 expression on the NK cells at levels comparable to unstimulated NK cells, whereas the control TriKE-treated NK cells exhibited substantial CD16 shedding. The IL15-IL15Rα component in the TriKE-PACC induced stronger pSTAT5 signaling and with the anti-ADAM17 component, robustly increased NK cell proliferation throughout 7-days. The TriKE-PACC-treated NK cells also showed markedly enhanced cytotoxicity when challenged with tumor spheroids over a prolonged period of time (5-days). When co-cultured with immunosuppressive ascites fluid from ovarian cancer patients, the TriKE-PACC-treated NK cells retained CD16, showed increased proliferative capability and mediated enhanced cytotoxicity against tumor cells compared to the TriKE-treated NK cells. These in vitro results translated to significantly better tumor control and improved survival of xenogeneic mice engrafted with human ovarian cancer cells, with higher NK cell counts observed in both the blood and intraperitoneal space of the TriKE-PACC-treated mice. Evaluations of the TriKE-PACC in additional solid cancer models show equally promising results, highlighting its potential for enhancing NK cell immunotherapies in solid tumor settings where ADCC is impaired by CD16 clipping.

Engineering CAR NK Cells for Translation: Addressing Persistence, Allogeneic Rejection, and the Suppressive TME

Joshua B. Krueger, Jae-Woong Chang, Kylie Buchanan, Timothy D. Folsom, Joseph G. Skeate, Melissa Geller, Beau R. Webber, Branden S. Moriarity

Department of Pediatrics, Center for Genome Engineering, Masonic Cancer Center, Stem Cell Institute, University of Minnesota; Department of Obstetrics, Gynecology and Women's Health (OBGYN), Division of Gynecologic Oncology, University of Minnesota

Ovarian cancer is often diagnosed late, making traditional treatments less effective, and prone to relapse. Cellular immunotherapies such as CAR T cell therapy have made great strides in treating leukemias, but have struggled to address solid tumors like ovarian cancer. Additionally CAR-T cells suffer from high cost of production, systemic toxicities, and antigen escape. Natural kill (NK) cells are an attractive alternative to T cells as they can mediate killing through multiple innate receptors reducing antigen escape, allogeneic production allows for quick and robust scale up, and NK cells have had less reported toxicities in early testing. In order to utilize genetically modified NK cells for ovarian cancer there are three major hurdles that need to be addressed; low persistence of NK cells in pre-clinical models, allogeneic rejection of NK cells, and overcoming the suppressive microenvironment. Here we showcase the use of transposon engineered chimeric antigen receptor (CAR) NK cells that have been "imprinted" with TGFb (TGFBi) and secrete IL15 (slIL15) which are able to robustly kill ovarian cancer in many challenging models. Although potent, these TGFBi-CAR-sl15-NK cells will still be rapidly depleted when given in the proposed allogeneic setting. That is why the addition of Bi-specific T-cell engagers (BiTE) are also being investigated in conjunction. BiTEs are a synthetic protein which contains two binding sites, one for CD3, and another for the target antigen on ovarian cancer. BiTEs are able to bring T-cells into proximity with ovarian cancer and form an immunological synapse for the activation of T-cells and killing of ovarian cancer. If BiTEs can be secreted by TGFBi-CAR-sl15-NK cells it may help prolong the therapeutic response even after the TGFbi-CAR-sl15-NK cells are rejected by producing BiTEs which activate the patients CD3+ T-cells. This approach leverages the advantages of engineering NK cells while also gaining the use of autologous T cells.

Figure 1: A: Schematic design of engineered TGFBi-CAR-sl15-NK cells. B: Validation of engineered NK cells via flow cytometry and ELISA. C: Serial killing assay of TGFBi-CAR-sl15-NK cells vs OVCAR8 (ovarian cancer). D. In-vivo validation of TGFBi-CAR-sl15-NK cells in NSG mice engrafted with OVCAR8. E: Killing assay of T-Cells with BiTE media on OVCAR8.

NMNAT1 promotes homologous recombination and PARP inhibitor resistance in high-grade serous ovarian cancer

Ajay Kumar Raj
Mayo Clinic

High-grade serous ovarian cancer (HGSOC) is the most lethal subtype of ovarian cancer. PARP inhibitors (PARPis) have emerged as an effective therapy for HGSOC, particularly in tumors with defects in homologous recombination (HR) DNA repair. However, the development of PARPi resistance remains a major clinical challenge, and the underlying mechanisms are not fully understood. Here, we identify NMNAT1, a key enzyme in nuclear NAD^+ biosynthesis, as a novel mediator of PARPi resistance in HGSOC. We found that NMNAT1 is upregulated in HR-defective HGSOC cells with acquired PARPi resistance. Functional studies reveal that NMNAT1 promotes resistance by restoring HR. Mechanistically, NMNAT1 enhances MRE11 activity through NAD-driven, SIRT1-mediated deacetylation, facilitating efficient DNA end resection and HR. Together, our findings uncover a previously unrecognized NMNAT1–SIRT1–MRE11 axis that drives PARPi resistance and highlight NMNAT1 as a potential therapeutic target to overcome resistance in HGSOC.

Performance of gene expression-based homologous recombination DNA repair deficiency (HRD) prediction tools in high-grade serous carcinoma (HGSC)

Samantha Lopez Alvarez, Katherine A Lawson-Michod, Courtney E Johnson, Lindsay J Collin, Xintian Song, David A Nix, Chad D Huff, Andrew Berchuck, Lucas A Salas, Casey S Greene, Jeffrey R Marks, Lauren C Peres, Joellen M Schildkraut, Jennifer Anne Doherty, Natalie R. Davidson

Department of Obstetrics and Gynecology, University of Colorado Anschutz; Department of Biomedical Informatics, University of Colorado Anschutz; Division of Public Health Sciences, Fred Hutchinson Cancer Center; Department of Epidemiology, University of Washington Department of Epidemiology, Rollins School of Public Health, Emory University; Huntsman Cancer Institute; MD Anderson Cancer Center; Division of Gynecologic Oncology, Duke University School of Medicine; Department of Epidemiology, Geisel School of Medicine at Dartmouth, Dartmouth Cancer Center; Department of Surgery, Duke University School of Medicine; Department of Cancer Epidemiology, Moffitt Cancer Center; Department of Population Health Sciences and Huntsman Cancer Institute, University of Utah

Homologous recombination deficiency (HRD) influences tumor behavior and treatment response in ovarian high-grade serous carcinoma (HGSC). Clinical HRD tests quantify genomic scarring or homologous recombination (HR) pathway alterations to guide PARP inhibitors and platinum therapy use. However, these are often missing in publicly available datasets, limiting research on HRD in HGSC across populations. Fortunately, transcriptome-based predictors, such as IdentifiHR and ExpHRD, offer functional insight into the HR pathway but their performance remains underexplored. We evaluated IdentifiHR and ExpHRD in HGSC tumors from self-identified Black (n=273) and White (n=317) participants in the African American Cancer Epidemiology Study (AACES) and North Carolina Ovarian Cancer Study (NCOCS), integrating clinical variables, SBS3 mutational signature, HR pathway mutations, and transcriptomic subtype (mesenchymal, proliferative, immunoreactive, differentiated). Differential expression analysis (DESeq2) identified 1406 significantly differentially expressed genes (FDR<0.05, |log2FC|>1) between the two populations, with minimal overlap with HRD model gene lists, suggesting little population-level bias. IdentifiHR and ExpHRD produced moderately correlated HRD scores (Pearson r=0.47), though ExpHRD classified considerably more tumors as HRD (416 ExpHRD, 123 IdentifiHR). Comparing transcriptomic and genomic indicators, IdentifiHR showed the strongest overlap with mutation-based (ASCO prioritized genes) predictors (59 IdentifiHR, 62 mutation-based; χ^2 (1) = 21.07, p = 4.4×10^{-6}), while ExpHRD generated numerous false positives (84 HRD without genomic scarring). HRD prevalence varied by HGSC subtype, with most tumors identified as HRP. Immunoreactive tumors had the highest mismatch between IdentifiHR and mutation-based calls (31.4%), and mesenchymal tumors the lowest (21.8%), indicating subtype-related confounding. Overall, IdentifiHR reliably reflected genomic scarring, whereas ExpHRD frequently overestimated HRD. Our work identified that population differences were minimal but emphasized the importance of equitable HRD classification for accurate research and fair cancer diagnostics and treatment.

Multiomic approaches to characterize ovarian cancer chemoresistance

Amelia Mazzone, Wazim Mohammed Ismail, L. Assad Maia Sandoval, L. Pham, Y. Yan, K.Y. Song, X. Hou, S.J. Weroha, J.A. Fernandez, M. Patnaik, Alexndre Gaspar-Maia,

Division of Experimental Pathology, Department of Lab Medicine and Pathology; Center for Individualized Medicine, Epigenomics program; Department of Physiology and Biomedical Engineering; Division of OncologyDivision of Hematology, Mayo Clinic

Recent technological advances have made it possible to analyze heterogeneous cell populations with different omics approaches at the single-cell level and with long-read technologies. scRNA-seq enables genome-wide transcription profiling, while scATAC-seq maps accessible chromatin regions in individual cells. The scMultiome platform integrates scRNA-seq and scATAC-seq, capturing multiple regulatory layers within the same cell. Generating high-quality single-nuclei suspensions is essential for reliable scMultiome results, requiring careful optimization for each sample. Two tissue dissociation methods for ovarian cancer samples were compared, with NP-40 yielding better nuclei quality and improved clustering over collagenase, especially for frozen samples. Additional evaluations showed that FACS sorting didn't enhance sequencing results. For older clinical samples, such as OCT-embedded tissues, RNA-based analysis and RNA integrity values rather than visual inspection alone were required beforehand. We also performed a comparison of snRNA-seq and scRNA-seq data from PBMCs, examining differences in cell type detection. The results showed high consistency, especially with regard to cell-specific markers and highly expressed genes. Long-read sequencing technologies have revolutionized the field of epigenomics by enabling the direct detection of DNA modifications without the need for chemical conversion or enrichment steps in addition to the identification of genetic variants and single-molecule resolution analysis of chromatin states. The use of 6mA-modifying enzymes with long-read sequencing enhances epigenomic studies by enabling detection of open chromatin regions, offering a complete view of genome regulation, advancing insights into epigenetic mechanisms in health and disease. Overall, our findings demonstrate that integrating transcriptional and chromatin accessibility data from the same cells offers a more comprehensive view of cell identity and function. Furthermore, optimizing single-nuclei isolation enhances data quality and ensures efficient use of valuable tissue specimens, particularly in scMultiome workflows. These improvements are key to achieving accurate biological insights and maximizing the utility of integrated single-cell approaches in both fresh and archived clinical samples.

Single cell multiomic analysis of high-grade serous ovarian carcinoma reveals an intrinsic epigenetic program that primes chemotherapy tolerance in persister cells

Mihai Gabriel Dumbrava, **Wazim Mohammed Ismail**, Leticia Sandoval, Amelia Mazzone, Syed Mohammed Musheer Aalam, Megan L. Ritting, Xiaonan Hou, Yiwen Xie, Sierra Hamernick, Chunling Hu, Fergus J. Couch, Shariska P. Harrington, Scott H. Kaufmann, Nagarajan Kannan, S. John Weroha, Alexandre Gaspar-Maia
Mayo Clinic

Cancer can recur when a subset of tumor cells, termed persister cells, survive therapy and re-enter the cell cycle. The cellular lineages that give rise to persister cells and the mechanisms that confer the persister state remain poorly understood. Through single-cell multiomic profiling (snRNA-seq and snATAC-seq) on a cohort of (1) non-malignant fallopian tube, (2) treatment-naïve, and (3) neoadjuvant chemotherapy (NACT)-treated high-grade serous ovarian cancer (HGSOC) patient samples, we identified an epigenetic signature that defines the chemotherapy-tolerant persister state. The changes in chromatin accessibility characterizing the signature were identified in residual NACT tumors and in treatment-naive samples from patients who later developed resistance. Further, this epigenetic signature independently predicted chemotherapy response in patient-derived xenograft models of HGSOC and in a patient cohort of metastatic ovarian cancer. Cells enriched in the persister state arose from multiple lineages and displayed activation of oncogenic pathways, including altered stress responses and changes to the cell cycle promoting quiescence. Finally, we identified a subset of genes that are epigenetically primed for expression before treatment. These findings suggest that an intrinsic epigenetic program primes tumor cells towards chemotherapy tolerance and reveal new vulnerabilities of the persister state that could be exploited to delay or prevent cancer recurrence.

In Vitro Characterization of Acquired PARP Inhibitor Resistance in High-Grade Serous Ovarian Cancer Cells

Trudy J Philips, Alanis PM Hernandez, Zoe M Mulvihill, Stefani N Thomas
University of Minnesota; University of Puerto Rico de Ponce; Amherst College

Background: High-grade serous ovarian cancer (HGSOC) is the most common and aggressive subtype of epithelial ovarian cancer. Approximately 50% of HGSOC tumors have BRCA1/2 mutations and are sensitive to PARP inhibitors (PARPi), which block DNA repair and induce cell death through a process known as synthetic lethality. However, about 40% of HGSOC patients with BRCA1/2 mutation relapse after PARPi treatment due to acquired resistance. The mechanism behind this acquired resistance remains unclear. This study aims to establish and characterize Niraparib (PARPi)-resistant HGSOC cells as a model for investigating and understanding the mechanisms of acquired PARPi resistance in HGSOC.

Method: PEO1 and PEO16 parental HGSOC cells (PEO1S, PEO16S) with BRCA2 mutations were exposed to increasing concentrations of Niraparib to develop acquired resistance (PEO16R, PEO1R). To evaluate resistance, sensitivity to Niraparib was measured using Sulforhodamine B (SRB) and Growth Rate (GR) assays. The DNA damage response (DDR) was analyzed by measuring the expression of gamma-H2AX (DNA damage marker), RAD51 (DNA damage repair marker), and cleaved PARP (apoptotic marker) through Western blot analysis. Proteins comprising adaptive pathways of acquired Niraparib resistance were assessed using a targeted mass spectrometry-based proteomic approach, Parallel Reaction Monitoring (PRM).

Results: PEO16R and PEO1R cells exhibited decreased sensitivity, with IC_{50} values of 145.2 µM and 117.6 µM, respectively, compared to IC_{50} values of 2.0 µM and 68.9 µM for the parental cells (n=4). The GR_{50} values were 47.1µM and 49.3µM for the PEO16R and PEO1R cells, respectively, compared to 2.31µM and 7.4µM for the parental cells (n=3). PEO16R cells had increased gamma-H2AX and RAD51 expression, and decreased cleaved PARP expression. PEO16R showed an increased abundance of DNA damage repair proteins, including ARID1A, BRCA1, TDG, and XRCC5 ($p < 0.0001$), as well as ATM ($p < 0.05$), compared to PEO16S. PEO1R showed increased abundance of BRCA1, BRCA2, RAD50, and RAD51C; however, this was not statistically significant.

Conclusion: Niraparib-resistant HGSOC cells exhibit decreased sensitivity to Niraparib and enhanced DDR. Altered DDR has a potential role in the mechanism of acquired PARPi resistance in HGSOC.

ZC3H18 Controls NAD⁺ Metabolism in HGSOC by Driving NMNAT1 Expression

Sophie L. Robison, Benjamin Wilson, Ajay Kumar Raj, Natalie Wilson, Xianfeng Chen, Larry M. Karnitz, Arun Kanakkanthara

Department of Oncology, Mayo Clinic; Quantitative Health Sciences; Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic

ZC3H18 is a multifunctional regulator of gene expression that is lost in a subset of high-grade serous ovarian cancers (HGSOC). While our prior studies have shown that ZC3H18 loss reduces BRCA1 levels, impairing homologous recombination DNA repair, we now reveal an additional role for ZC3H18 in energy metabolism. Specifically, ZC3H18 depletion lowers mRNA and protein levels of the NAD⁺-biosynthetic enzyme NMNAT1 in HGSOC cells. Mechanistically, ZC3H18 binds the NMNAT1 promoter and recruits CDK12 to drive NMNAT1 transcription. Loss of ZC3H18 reduces CDK12 occupancy at the promoter, decreasing NMNAT1 expression and cellular NAD⁺ levels. These findings uncover a previously unrecognized function of ZC3H18 in metabolic regulation and highlight potential therapeutic opportunities that exploit the metabolic vulnerabilities associated with ZC3H18 deficiency.

Unravelling the Ambiguous Role of MECOM Transcription Factor as a Tumor Suppressor and Oncogene in Endometrial Cancer

Jacqueline Romani, Shariska Harrington, David Chen, Alexandre Maia
Graduate School of Biomedical Sciences, Mayo Clinic Comprehensive Cancer Center; Department of Biochemistry and Molecular Biology; Department of Laboratory Medicine and Pathology

Copy number high (CNH) is an aggressive molecular subtype of endometrial cancer (EC) characterized by frequent TP53 mutations and relative chemoresistance in advanced or recurrent stages. Notably, serous endometrial carcinomas are the prototype CNH EC and exhibit molecular features similar to high grade serous ovarian cancers. Previously, we have performed single cell multiomic profiling of ovarian tumors from high grade serous carcinomas (HGSC). Our analysis reveals an epigenetic signature of around 100 transcription factors that are high in patients treated with neoadjuvant chemotherapy and are also associated with chemotherapy resistance in naïve tumors. Amongst these regulators, we have identified MECOM, and showed it cooperates with other master regulators of HGSC and cancer stem cell factors upon chemotherapy treatment. The rationale for extending this investigation to CNH ECs include the molecular similarities between CNH ECs and HGSOCs and the high prevalence of MECOM amplification in CNH EC. Analysis of TCGA data from 523 EC samples identified MECOM as the most amplified gene in endometrial cancer, present in 12% of tumors overall and among 507 ECs profiled by molecular subtype, MECOM amplification was found in 35% of CNH tumors. Given its high prevalence in CNH EC and the aggressive nature of this subtype, our central hypothesis is that MECOM amplification promotes tumorigenesis and poor prognosis in CNH EC. MECOM (also known as PRDM3) is a transcriptional regulator that has been described both as a tumor suppressor and as an oncogene. This functional complexity is frequently seen in other members of the PRDM family, which are defined by an N-terminal PR domain and frequently altered in cancer. Most PRDMs produce multiple isoforms, and growing evidence suggests that in several cases, the full-length isoforms function as tumor suppressors, whereas shorter isoforms lacking the PR domain exhibit oncogenic activity. To address the ambiguity surrounding MECOM's seemingly contradictory roles, we sought to determine if MECOM overexpression is associated with poor prognosis in clinically annotated biospecimens and elucidate its context-dependent role by characterizing the role of MECOM in endometrial cancer

Unbiased examination of ctDNA methylomics as predictors of platinum sensitivity in high grade serous ovarian cancer

Peter Rosen, Jessica Linford, Andrew Lu, Breanna Yang, Andrew Chen, Aaron Wang, Irfan Alahi, Rikki Drexler, Pradeep Chauhan, Mary Mullen, Aadel Chaudhuri
Mayo Clinic; Washington University in St. Louis

Circulating tumor DNA (ctDNA) is cell-free DNA of tumor origin shed into the blood plasma of cancer patients. In the ovarian cancer context, prior ctDNA studies have shown promise in diagnosis and predicting patient outcomes. However, ctDNA methylation-based treatment response studies have been limited in scope, focusing only on specific genes or targeted gene panels. Our goal is to adopt an unbiased approach to identify novel noninvasive markers of therapeutic response in high grade serous ovarian cancer (HGSOC), which is critically important because development of resistance to front line platinum therapy is almost universal. In this study, we take a whole genome approach using enzymatic methyl sequencing (EM-seq) on DNA isolated from pretreatment plasma samples of HGSOC patients. This study included primary stage II (n=3), III (n=31), and IV (n=5) patients for a total cohort of 39 patients. Drug response outcomes of these patients were abstracted, with 12 platinum sensitive patients, 19 platinum resistant patients, and 8 platinum refractory patients. Macroscopic bioinformatic analysis of cfDNA methylomes showed no significant differences between refractory vs sensitive patients in tumor fraction or short to long fragment ratios. Deeper analysis of methylation and fragmentomic patterns between the platinum sensitive and resistant groups is underway. Prior work has identified that resistance is driven by distinct molecular changes at specific genomic loci, and thus, we hypothesize more granular bioinformatic analyses will reveal significant differences. Our long-term goals are to identify differential molecular features, functionalize them into clinically useful biomarkers, and integrate them with the current knowledge base of ovarian cancer drug resistance so that we can move forward scientific and clinical understanding of platinum resistance in HGSOC.

Tracing the Early Origins of Ovarian Cancer: The Emerging Role of Extracellular Vesicles

Jared Sipes, Didi Zha, Sagar Rayamajhi, Leonidas E. Bantis, Rashna Madan, Amrita Mitra, Rajni V. Puri, Mohammod Mahmudur Rahman, Foyez Ahmmed, Harsh B. Pathak, Angela Russo, Mihaela Sardiu, Brett C. Isenberg, Brian P. Cain, Jonathan Coppeta, Pamoda M. Galhenage, Shailja Pathania, Shannon MacLaughlan David, Courtney A. Marsh, Lane K. Christenson, Joanna E. Burdette, and Andrew K. Godwin

Department of Pathology and Laboratory Medicine, University of Kansas Medical Center; Bioengineering Program, The University of Kansas; Department of Pharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago; Department of Biostatistics and Data Science, University of Kansas Medical Center; The Kansas Institute for Precision Medicine, University of Kansas Medical Center; Department of Statistics, Comilla University, Cumilla, Bangladesh; Charles Stark Draper Laboratory; Center for Personalized Cancer Therapy, University of Massachusetts; Department of Biology, University of Massachusetts Boston; Translational Oncology Program, University of Illinois Cancer Center, University of Illinois at Chicago; Department of Obstetrics and Gynecology, University of Kansas Medical Center; Department of Cell Biology and Physiology, University of Kansas Medical Center; The University of Kansas Cancer Center, University of Kansas Medical Center

High-grade serous ovarian cancer originates in the fallopian tube (FT), and risk correlates with lifetime ovulation events; however, the mechanisms underlying this association remain unclear. Follicular fluid (FF), released during ovulation, induces inflammation, DNA damage, and phenotypic shifts in the FT epithelium that resemble early preneoplastic lesions. FF contains extracellular vesicles (EVs), which play essential roles in reproductive processes, but their effects on the FT epithelium remain poorly understood. Previously, we reported the use of a microfluidic culture system (PREDICT-MOS) to model complex EV-tissue interactions in the FT and demonstrated that EVs derived from ovarian cancer cells can remodel the FT microenvironment (PMID: 40689422). Here, we extend this approach to investigate preneoplastic changes induced by FF-derived EVs (FF-EVs). In a pilot study, we used size exclusion chromatography to purified FF-EVs from follicular fluid samples (n= 10) collected from women undergoing ultrasound–guided oocyte retrieval. Isolated FF-EVs displayed characteristic size, morphology, and surface biomarkers (e.g., CD81), and yielded sufficient protein and particle counts for downstream applications. We then performed mass spectrophotometry to characterize EV cargo and the corresponding EV-depleted FF fractions. Gene Ontology analysis of these data identified distinct, functionally enriched pathways in FF-EVs. To assess FF-EV effects on FT epithelium, we exposed ex vivo FT explants (n=5) cultured in the PREDICT-MOS to varying concentrations of FF-EVs (0 µg, 1.5 µg, 3 µg, and 6 µg). Using the GeoMx Whole Transcriptome Atlas, we analyzed ~18,000 protein-coding transcripts to evaluate spatial transcriptomic changes in both epithelium and stromal compartments. This study provides the first transcriptomic characterization of FT responses to FF-EVs and identifies key genes and pathways potentially involved in preneoplastic transformation.

A Novel Dual-Targeting NK Cell Engager Strategy to Prevent Relapse in Ovarian Cancer

Terran Stenger, Yvette Soignier, Joshua T. Walked, Tumpa TD. Dasgupta, Emma M. Eungard, Melissa J. Khaw, Madison Shackelford, Melissa A. Geller, Jeffrey Miller, Martin Felices
Masonic Cancer Center

Natural Killer (NK) cell infiltration correlates with improved prognosis in ovarian cancer, highlighting their potential for immunotherapy. Our group previously demonstrated efficacy using a Tri-Specific Killer Engager (TriKE) to direct NK cell activity against ovarian tumors. However, the marked heterogeneity of ovarian cancer, along with evidence from CAR T studies, indicates that targeting a single antigen may promote antigen escape and therapeutic resistance. To overcome this, we developed a dual-targeting NK cell engager, the TriKE-PACC (poly-antigen targeting cytokine-receptor complex). The core TriKE structure includes an anti-CD16 domain to activate NK cells, an IL-15 moiety to promote proliferation, and an anti-CD133 domain to eliminate cancer stem cells. We further incorporated an IL-15 receptor alpha (IL-15Rα) domain to stabilize and potentiate IL-15 signaling, while a second targeting arm directed against B7H3 broadens activity against bulk tumor cells.

Following production and purification of the TriKE-PACC, we confirmed construct formation and proper binding of the antibody domains. Using CRISPR-edited ovarian cancer cell lines expressing either B7H3 alone, CD133 alone, neither antigen, or both, we demonstrated that the TriKE-PACC enhances NK cell activation and proliferation. It significantly increased CD107a expression, IFNγ, and TNFα production, and promoted NK expansion compared to single-targeting constructs. Cytotoxicity assays showed that the TriKE-PACC outperformed both B7H3- and CD133-specific TriKEs, mediating superior killing of tumor populations expressing either or both antigens. We also observed that tumor cells exposed to the TriKE-PACC exhibited slower regrowth after treatment cessation compared to cells treated with the CD133-TriKE alone, which poorly kills bulk tumor cells, or the B7-H3-TriKE alone, which does not target cancer stem cells. Ongoing studies are extending these findings to ovarian cancer mouse models to evaluate the TriKE-PACC's therapeutic potential and its ability to prevent antigen escape and relapse. By combining dual antigen and stem cell targeting with NK cell activation, the TriKE-PACC represents a promising approach that may help reduce relapse and improve outcomes in ovarian cancer, potentially supporting future clinical translation for patients in critical need of durable therapies.

Evaluation of apoptosis- and senescence-driven therapeutic vulnerabilities in PARP inhibitor-resistant ovarian cancer

Annapoorna Venkatachalam, **Annabella Strathman**, Xianon Hou, Cordelia McGehee, Emily Balczewski, Haiming Dai, Cristina Correia, Rachel M. Hurley, Jill M. Wagner, Karen S. Flatten, Kevin L. Peterson, Paula A. Schneider, Laura N. Duffield, Silvana DeLorenzo, Andrea Wahner E. Hendrickson, Ann Oberg, Hu Li., S. John Weroha and and Scott H. Kaufmann
Mayo Clinic Alix School of Medicine

Background: PARP inhibitors (PARPis) significantly improve progression-free survival (PFS), with maximal benefit in BRCA1/2-mutated tumors. However, drug resistance remains a challenge. Despite growing insight into PARPi efficacy, the apoptotic processes driving PARPi cytotoxicity remain unclear. Recent data link PARPi-induced DNA damage to senescence, complicating distinctions between cell death and therapy resistance. This study aims to characterize cell fate outcomes following acute and long-term PARPi exposure.

Methods: Using three different PARPis (olaparib, veliparib, and niraparib), we evaluated cell fate dynamics in two genetically distinct ovarian cancer cell lines and two isogenic high-grade serous ovarian cancer (HGSOC) patient-derived xenografts (PDXs) selected for PARPi resistance. Immunofluorescence and flow cytometry assessed cellular phenotypes, while proteomics, immunoblotting, and survival assays identified and validated pathway vulnerabilities.

Results: In parental PEO1 (BRCA2m) and COV362 (BRCA1m) cell lines, continuous PARPi treatment induced both apoptosis and senescence, with apoptosis plateauing at day 6 and senescence persisting to day 12 via a sustained SASP profile. Apoptosis occurred through the intrinsic pathway involving BCL2 family members. In vivo, RNAseq and IHC confirmed SASP-associated changes. Comparing isogenic PARPi-sensitive and -resistant lines revealed increased BCLXL and cell cycle proteins, prompting testing of combinations with checkpoint modulators and BH3 mimetics. Adavosertib and ceralasertib modestly enhanced PARPi sensitivity, while BCLXL inhibitor A1155463 strongly resensitized resistant lines. Although this combination did not significantly shrink PARPi-resistant PDX tumors, it slowed tumor growth (p=0.06).

Conclusions: PARPi exposure induces dual cell fates of apoptosis and senescence. Persistence of senescent, multinucleated, pro-survival cells represents a vulnerability that can be exploited with BCLXL inhibition. These findings support further investigation of PARPi–BCLXL inhibitor combinations as a rational strategy to overcome PARPi resistance in ovarian cancer.

Investigating the interplay between BRCA status and WT1-CD200 axis in stromal regulation of TLS formation in HGSOC

Swathi Suresh, Erika Lampert, Grace Gorecki, Ian P. MacFawn, Huda Atiya, Tullia C. Bruno, Lan Coffman

University of Pittsburgh School of Medicine, Department of Medicine; Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh; Internal Medicine, Allegheny Health Network; Grove City College, Department of Biology; Division of Hematology/Oncology; Division of Gynecologic Oncology, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh; Department of Immunology, University of Pittsburgh; Division of Hematology/Oncology; Division of Gynecologic Oncology, Department of Obstetrics,; Gynecology, and Reproductive Sciences; Department of Pathology, University of Pittsburgh, Magee-Womens Research Institute

High-grade serous ovarian cancer (HGSOC) is the most lethal subtype of ovarian cancer, with more than 70% of patients presenting with metastatic disease at the time of diagnosis. While germline BRCA1/2 mutations carry a 30-40-fold higher risk of HGSOC, paradoxically, patients with BRCA mutations have improved responses to treatment and overall survival benefit compared to BRCA-wildtype patients. This study aimed to investigate how BRCA status alters the tumor microenvironment (TME), particularly the stromal compartment, to support anti-tumor immunity. Our lab has previously demonstrated that ovarian cancer cells epigenetically reprogram their resident tissue mesenchymal stromal/stem cells (MSCs) to develop a cancer-supportive phenotype. These cancer-associated mesenchymal stem cells (CA-MSCs) express high levels of WT1, a transcription factor associated with protumorigenic functions and immune evasion. Using our mRNA seq data, we identified a positive correlation between WT1 and CD200, an immune-modulatory protein, in CA-MSCs. With the help of multispectral flow analysis, we found that elevated CD200 expression in CA-MSCs impairs their differentiation into follicular dendritic cells (fDCs), a stromal subtype essential for the development and active function of tertiary lymphoid structures (TLS). These are ectopic lymphoid aggregates that develop in the TME and serve as a hub with multiple immune cells, including B cells and T cells, associated with enhanced anti-tumor immunity and a favorable response to immunotherapy. To investigate whether BRCA status influences this stromal differentiation axis, we isolated CA-MSCs from primary HGSOC tumors with known germline BRCA status and analyzed CD200 expression by qPCR and flow cytometry. We observed that CA-MSCs derived from germline BRCA-mutant tumors express significantly lower levels of CD200 compared to those from BRCA-wildtype tumors. Functionally, MSCs with reduced CD200 expression exhibit an enhanced capacity to differentiate into fDCs in vitro. Therefore, these results suggest that BRCA mutations may downregulate the WT1-CD200 axis in CA-MSCs, promoting stromal reprogramming that supports TLS formation and antitumor immune responses. Overall, our findings reveal a novel mechanism that highlights the stromal WT1-CD200 axis as a potential target for enhancing TLS formation and anti-tumor immune responses.

Proteomic profiling of HGSOC cells treated with NB compounds identifies FOXM1 and MYC pathway downregulation and unfolded protein response activation as mechanisms of action

Makenzie Vorderbruggen, S. H. Kim, B.S. Katzenellenbogen, J.A. Katzenellenbogen, M. Naldrett, S. Alvarez, N.T. Woods, A. R. Karpf
University of Nebraska Medical Center

1,1-diarylethylene based drugs, also known as NB compounds, were recently identified from a chemical library screen as Forkhead Box M1 (FOXM1) inhibitors. Activation of the FOXM1 transcription factor and its network is the second most common molecular alteration in high-grade serous ovarian cancer (HGSOC). We have previously shown that two NB compounds, NB-73 and NB-115, promote proteasomal degradation of FOXM1 and disrupt its transcriptional pathway in HGSOC cells. Importantly, both compounds potently, efficaciously, and selectively inhibit cell viability, induce apoptosis, and decrease clonogenic growth of HGSOC cell models. To better understand the mechanism of action of NB-73 and NB-115 in HGSOC, we performed unbiased proteomic profiling using tandem mass tag (TMT) mass spectrometry. Bioinformatic analysis validated NB compounds as FOXM1 inhibitors in addition to alterations in other pathways relevant to HGSOC, including downregulation of MYC transcriptional targets and upregulation of unfolded protein response (UPR) proteins. MYC is a well-established oncoprotein in HGSOC. We employed RT-qPCR and western blotting to confirm downregulation of both MYC and its transcriptional targets. We further conducted a time course experiment to compare the kinetics of FOXM1 and MYC loss and observed decreases in FOXM1 protein prior to MYC following NB-73 treatment, while treatment with NB-115 diminished both proteins at similar times. Experiments are currently underway to better understand how NB compounds mediate loss of MYC. The UPR is another important pathway in cancer due to higher rates of proliferation, which result in a greater unfolded protein burden. This necessitates higher basal UPR activation to stay below the apoptotic threshold and maintain cell viability. Western blotting validated UPR activation following NB compound treatment in a panel of HGSOC cells and this response was less pronounced in non-transformed fallopian tube epithelial cells. We employed a time course study to better understand the kinetics of FOXM1 loss and UPR activation and observed both alterations at similar times and occurring by 6-9 hours post-treatment. Overall, our data reveals new mechanisms of action of NB compounds in HGSOC cells and suggests potential synergistic combination approaches using agents that target the MYC or UPR pathways.

Exploiting CTPS1 dependency for the treatment of ovarian cancer

Xiyin Wang, Michael Emch, Lauren Voll, Rebecca Epp, Esther Rodman, Noa Odell, Nicole Pearson, Xiaonan Hou, Ya Li, Taro Hitosugi, Matthew P. Goetz, Scott Kaufmann, S. John Weroha, Philip Beer, John R. Hawse

Graduate School of Biomedical Sciences, Mayo Clinic; Department of Biochemistry and Molecular Biology, Mayo Clinic; College of Saint Benedict & Saint John's University; Case Western Reserve University; Department of Oncology, Mayo Clinic; Step Pharma, Saint-Genis-Pouilly, France

Despite therapeutic advances, ovarian cancer (OC) recurrence remains common and outcomes for advanced disease are poor, highlighting the need for novel therapeutic targets. We identified CTPS1 as a highly expressed and essential gene for survival in OC cell lines. CTPS1 and CTPS2 are enzymes responsible for de novo synthesis of cytidine triphosphate (CTP), a critical nucleotide for DNA and phospholipid biosynthesis. CTPS1 is the predominant isoform expressed in OC cells, with significantly higher levels in advanced and resistant disease compared to normal tissue, benign lesions, and treatment naïve cancers. Notably, 25% of OC samples completely lacked CTPS2 protein expression, suggesting near complete reliance on CTPS1 for survival.

Using CTPS1 siRNAs and genetically engineered OC cells with a degradation tag (dTAG) fused to endogenous CTPS1, we showed that CTPS1 knockdown or degradation induces S-phase arrest followed by apoptosis. Leveraging a first-in-class, highly selective, orally bioavailable CTPS1 inhibitor (STP938) developed by Step Pharma, we found nanomolar IC50 values across 20+ OC cell lines and validated anti-tumor activity in ex vivo patient-derived xenograft (PDX) models. STP938 synergized with standard chemotherapy and PARP inhibitors, even in resistant models, supporting clinical potential.

To elucidate STP938's mechanism, multi-omic profiling (bulk RNAseq, phospho- and total proteomics) of sensitive and resistant OC lines, and single-cell RNAseq of an OC PDX tumor post-treatment, revealed dysregulation of DNA replication, cell cycle, and metabolic pathways. STP938 rapidly depleted CTP levels for 72 hours, indicating insufficient salvage pathway compensation, compromising cancer cell viability. Since CTP is a precursor for activated intermediates in phospholipid biosynthesis, mass-spectrometry lipidomics and metabolomics revealed multiple changes. To uncover resistance mechanisms and therapeutic vulnerabilities, genome-wide CRISPR knockout screens in vehicle and STP938-treatment models were performed.

In collaboration with Step Pharma, a Phase 1a/b trial of STP938 is enrolling patients with advanced solid tumors, including an expansion cohort for CTPS2-null OC patients (NCT06297525). These findings and clinical efforts aim to broaden uptake of this novel therapy to improve outcomes in CTPS1-dependent disease.

AXL Receptor Tyrosine Kinase Promotes Ovarian Tumor Initiation and Progression: Evidence from Clinical Cohorts and Transgenic Mouse Models

Li Wang, Lingrui Li, Md Kamrul Hasan Khan, Yali Zhai, Jidong Wang, Yajue Huang, Nanlin Hu, Hunter J. Atkinson, Melissa C. Larson, Sun-Hee Lee, Xiaonan Hou, Akhilesh Pandey, Jamie N. Bakkum-Gamez, Ann L. Oberg, John S. Weroha, Scott H. Kaufmann, Kathleen R Cho, Xinyan Wu

Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic; Department of Pathology, University of Michigan Medical School; Department of Laboratory Medicine and Pathology, Mayo Clinic; Department of Quantitative Health Sciences, Mayo Clinic; Department of Oncology, Mayo Clinic

AXL, a receptor tyrosine kinase, has been implicated in tumor progression and therapeutic resistance, emerging as a promising biomarker and therapeutic target. To elucidate the role of AXL in ovarian cancer, we analyzed its expression in a tissue microarray comprising 576 ovarian cancer specimens. AXL positivity was observed in approximately 90% of high-grade serous (HGSOC), 60% of endometrioid, and 60% of clear cell ovarian cancers. High AXL expression predicted poor progression-free survival ($p = 0.009$) and overall survival ($p = 0.010$), underscoring its clinical significance.

We further identified that elevated plasma soluble AXL (sAXL), a proteolytically cleaved form of the AXL extracellular domain, were associated with suboptimal tumor debulking ($p = 0.002$), shorter overall survival ($p = 0.002$), reduced progression-free survival ($p = 0.009$), and poorer therapeutic response, suggesting its potential as a prognostic and minimally invasive biomarker for ovarian cancer.

To investigate AXL's oncogenic function, we established inducible AXL knockout (KO) and overexpression (OE) models using the HGSOC cell line OVCAR8. These cell line models demonstrated that AXL expression was required for promoting cell proliferation and colony formation in vitro. In vivo, AXL OE accelerated tumor growth, whereas AXL KO markedly suppressed it. Consistently, AXL siRNA and inhibitors effectively reduced viability in AXL-positive cell lines.

Given that many ovarian cancers, particularly HGSOC, originate in the fallopian tubes, we generated an inducible AXL transgenic mouse model with fallopian tube–specific expression. Crossbreeding this model with well characterized ovarian cancer models, BPRN (Brca1, Trp53, Rb1, Nf1 knockout) and PA (Pten, Apc knockout), revealed that AXL OE significantly accelerated tumor initiation. Large tumors appeared as early as 2.5 months post–tamoxifen induction, while controls showed no visible tumors. HGSOC was yielded in the iCre;AXL^{+};BPRN model and endometrioid or clear cell carcinomas were detected in the iCre;AXL^{+};PA model.

Collectively, our findings demonstrate that AXL drive ovarian cancer initiation and progression and highlight its potential as a therapeutic target. The AXL transgenic mouse models established here provide valuable tools for mechanistic studies of ovarian tumorigenesis and for preclinical evaluation of anti-AXL therapies.

A Comparative Evaluation of Intraperitoneal vs Subcutaneous Delivery of TriKE Molecules in Ovarian Cancer

Anna J. Weis, Laura Bendzick, Mihir Shetty, Behiye Kodal, Zhenya Ni, Martin Felices, Melissa Geller
University of Minnesota Medical School

Despite profound in vivo expansion and activation of endogenous NK cells, IL-15 alone has minimal anti-tumor activity due to a lack of antigen specificity of NK cells (NKc). To overcome this limitation, we developed a Tri-specific Killer Engager (TriKE) that binds and ligates a single activating receptor on NKc (CD16), directs tumor antigen targeting against B7H3, and provides co-stimulation with IL-15 to support NK cell proliferation, priming, and survival. This study evaluates whether intraperitoneal (IP) or subcutaneous (SQ) administration of TriKEs, in combination with human NKc, provides superior anti-tumor activity against ovarian cancer (OC) in xenogeneic mouse models. OVCAR8-GFP-Luc+ OC cells were engrafted intraperitoneally into female NSG-IL15 mice. Four days after tumor engraftment, enriched (CD3/19 depleted) NKc were delivered IP along with the first dose (IP or SQ) of a B7-H3 TriKE. TriKE was dosed at 50 µg three times weekly. Additional groups included tumor alone and NK alone controls. At day 14, mice with the highest and lowest tumor burdens were harvested for flow cytometric analysis of the IP compartment. Tumor progression was monitored weekly by BLI through day 70. Flow cytometry revealed greater NKc accumulation within the peritoneal wash of IP-treated mice compared with SQ-treated and NK-alone mice. Additionally, proportions of CD16+ and CD69+ NK subsets were comparable across groups, suggesting that TriKE treatment did not impact the profile of NKc, but rather, enhanced local persistence and proliferation of NKc when treated IP. BLI revealed that IP TriKE significantly suppressed tumor growth through day 42 ($p = 0.0022$) compared to SQ delivery. Median survival was 92 days for IP TriKE, vs. 44 days for SQ TriKE, 47 days for tumor-alone, and 48 days for NK-alone controls ($p = 0.0005$). In this model of OC, the route of TriKE administration profoundly influenced therapeutic efficacy. IP delivery enhanced NKc persistence, achieved superior tumor control, and more than doubled survival relative to SQ dosing. These findings highlight the potential of local TriKE delivery as an immunotherapeutic strategy to combat the highly suppressive intraperitoneal microenvironment of OC, providing strong rationale for advancing IP TriKE administration into clinical testing for OC.

Characterization of Transposable Elements Regulation in High-grade Serous Ovarian Cancer

Yiwen Xie, Wazim Mohammed Ismail, Amelia Mazzone, Leticia Sandoval, Megan Ritting, Musheer Alam, Nagarajan Kannan, Saravut (John) Weroha, Katherine Chiappinelli, Alexandre Gaspar-Maia
Mayo Clinic Graduate School BMB Track; Division of Experimental Pathology and Laboratory Medicine, Department of Laboratory Medicine and Pathology, Mayo Clinic; Mayo Clinic Graduate School MPET Track; Division of Hematology, Department of Medical Oncology, Mayo Clinic; Department of Microbiology, Immunology, and Tropical Medicine, George Washington University

Late-stage diagnosis of the high-grade serous ovarian cancer (HGSOC) is one of the major clinical challenges contributing to the high mortality and poor survival rate of the disease. Previous research has shown that transposable elements (TEs) are abnormally enriched in multiple cancers including HGSOC while being mostly silenced in healthy adult tissues. Recent studies in HGSOC further point out that, specifically, the LINE1 element is not only significantly enriched in the late stage of the cancer, but also detectable in serous tubal intraepithelial carcinoma (STIC), a precursor lesion associated with HGSOC. However, how TEs become reactivated has remained mysterious, which prompts the aim of this project to understand the regulations of TEs during HGSOC progression. In this study, we have first applied a TE-specific algorithm to the single cell multi-omics sequencing (snATAC-seq and snRNA-seq from the same cells) dataset performed on a patient cohort including both the HGSOC patients and the non-malignant fallopian tube (FT) donors and revealed the unique TE features specific to the cell subtypes. We then incorporated the differential methylation data from an oncogenic transformation model and found that the loss of DNA methylation is associated with the LINE1 and ERV1 subfamilies transcription. Interestingly, by running the TE-locus specific motif analysis, we additionally discovered a unique positive correlation between the upregulated TEs and the enrichment of the FOX transcription factors (TFs) family at those hypomethylated and more accessible TEs loci in HGSOC epithelia, which is not observed in FT. To validate TEs transcriptional dependencies in HGSOC, we are generating a FACS sorting-based over-expression screening platform in both the human HGSOC as well as immortalized FT cell lines using a multiplexed-overexpression regulatory factors (MORF) library covering the comprehensive collection of all human TF isoforms. Altogether, our studies identified previously unreported TFs association of the TEs activation beyond DNA methylation and chromatin accessibility patterns, potentially leveraging the role of the TEs regulators in characterizing the progression of HGSOC.

Development of microfluidic explant cultures to model ovarian cancer minimal residual disease

Mihai Dumbrava, Daheui Choi, Min Ji Kim, Jose M. de Hoyos Vega, Rafaela Mayumi Simoes Torigoe, Alan Gonzalez-Suarez, Saravut (John) Weroha, Gulnaz Stybayeva, Alexandre Gaspar-Maia, Alexander Revzin,

Mayo Clinic, Medical Scientist Training Program; Mayo Clinic, Department of Physiology and Biomedical Engineering; Mayo Clinic, Department of Pathology and Laboratory Medicine; Mayo Clinic, Department of Medical Oncology

Introduction: Despite advances in surgical debulking and targeted therapy, patients with ovarian cancer (OC) have poor outcomes due to high rates of cancer recurrence. Chemoresistant cancer cells comprising minimal residual disease (MRD) have various adaptations, including altered communication with the tumor microenvironment (TME), that has rendered approaches such as immunotherapy ineffective to date. However, 3D models that recapitulate the TME of treatment-naïve OC and MRD ex vivo are lacking. Our objective is to develop a clinically relevant model of OC to characterize the features of resistant disease and identify new therapeutic vulnerabilities.

Methods: Using poly-dimethysiloxane-based (PDMS) microfluidic devices (μFDs) fabricated with soft-lithography approaches, we cultured OC tissue explants from therapy-naïve and chemotherapy-treated tumors. OC tissue cores from debulking surgeries were embedded in collagen within μFDs or large volume well controls and maintained in media optimized for OC organoid formation. μFDs enable secretome concentration, precise control of microenviornmental conditions, oxygenation through PDMS, and require only a small amount of tissue. Viability was assessed by Live/Dead staining, H&E histology, and CA-125 secretion, while TME composition was evaluated by immunostaining for epithelial, immune and stromal markers.

Results: Long-term culture (2 weeks) of OC explants showed improved viability and epithelial outgrowths in μFDs compared to large volume controls. Explants in μFDs retained vasculature, epithelial architecture, and TME compartments resembling fresh tissue. By contrast, explants cultured in a large volume under identical conditions showed declining tissue architecture with loss of epithelial markers. Chemotherapy treatment of μFD explants with clinical-grade carboplatin produced a therapeutic dose response and allowed for assessment of interpatient variability in chemotherapy resistance.

Conclusions: We have developed a μFDs tissue explant model that recapitulates the characteristics of OC including the tumor epithelium, surrounding TME, and tissue architecture. Our platform represents a more clinically relevant model to study OC MRD, evaluate therapeutic responses, and identify patient-specific mechanisms of chemotherapy resistance.

Epigenetic Regulation of Cancer Stem Cells in High Grade Serous Ovarian Carcinoma

Sierra Hamernick, Amelia Mazzone, Wazim Mohammed Ismail, Mihai Dumbrava, Xiaonan Hou, John Weroha, Ann Oberg, Alexandre Gaspar-Maia

Department of Laboratory Medicine and Pathology; Department of Medical Oncology; Division of Computational Biology; Department of Laboratory Medicine and Pathology; Mayo Clinic Graduate School of Biomedical Sciences-Regenerative Sciences

Therapeutic resistance is a common and critical challenge in the treatment of high-grade serous ovarian cancer (HGSC), as it drives frequent tumor recurrence and significantly contributes to the disease's lethality. In many cancers, including HGSC, cancer stem cells (CSCs) are implicated in treatment resistance, tumor recurrence, and tumor propagation, making them a promising target for therapeutic intervention in HGSC. However, CSCs remain poorly characterized, and effective therapeutic targets are limited. Our work has aimed to explore trends in patient multiomic data to identify potential CSC-related transcriptomic signatures. Preliminary results suggest SOX2 expression correlation with chemo-treatment resistance, highlighting it as a promising candidate for further investigation.

Notably, preliminary analysis of immunohistochemistry in HGSC patient tissue microarrays also indicates a significant correlation between SOX2 expression and decreased survival rates. SOX2 is known to support pluripotency and self-renewal, and it is under investigation for similar roles in CSCs in different tumor types, but its specific role in HGSC and drug resistance remains elusive. To explore this further, we utilized ovarian cancer cell lines to model SOX2 expression. Gain of function and loss of function of SOX2 revealed changes in sensitivity to chemotherapy. Investigation into the role of SOX2 may further elucidate the mechanisms of treatment resistance and role in defining cancer stem cell's function. Ongoing studies aim to clarify the mechanisms by which SOX2 contributes to the regulation of CSC characteristics, metastasis, and therapeutic resistance in HGSC. Ultimately, this work will contribute to a better understanding of the epigenetic regulation underlying CSC behavior and its implications for improving treatment strategies in HGSC.

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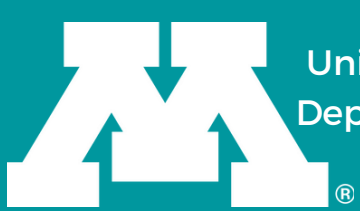

University of Minnesota
Department of OBGYN &
Women's Health